

**ELUCIDATION OF THE VARIOUS MECHANISMS OF ANTIOXIDANT ACTIVITY OF
ORGANOSULFUR COMPOUNDS**

By

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Abstract

Polysulfides, produced from olefin sulfurization, are common additives to various petroleum-derived products such as engine oils, hydraulic fluids, rubbers and polymeric materials in an effort to protect these materials from oxidative degradation. The mechanisms by which organosulfur compounds act as antioxidants are often described as ‘secondary antioxidants’ since it is believed that they slow the rate of radical initiation by decomposing hydroperoxides. Organosulfurs also figure in various natural products from the genus *Allium*, of which garlic is a prominent species. Our group previously shown that thiosulfonates (RS(O)SR), key components of garlic, are potent radical-trapping antioxidants (RTAs) through the intermediacy of sulfenic acids (RSOH).

In an effort to shed light on the antioxidant mechanisms of other organosulfur constituents of garlic and sulfurized olefins, in Chapter 2, we reported on the antioxidant activity of trisulfide-1-oxides (RS(O)SSR) at 37 °C. In that study, we found these moieties to be effective RTAs, equal in potency to hindered phenols, the industry standard. Trisulfide-1-oxides were shown to react with peroxy radicals via a concerted bimolecular homolytic substitution reaction, forming a perthiyl radical as product. In Chapter 3, inspired by the findings at 37 °C, we investigated the RTA activity of polysulfides at elevated temperatures, from 100 °C to 160 °C, and found that tetrasulfides were surprisingly potent RTAs at and above 100 °C. Paralleling the reactivity of trisulfide-1-oxides, tetrasulfides were found to react with peroxy radicals via a concerted bimolecular homolytic substitution reaction, also forming a perthiyl radical as an initial product.

Perthiyl radicals are formed in multiple reactions described in the abovementioned studies and although they were shown to rapidly recombine, their apparent stability, as well as preliminary computational investigations into the S-H bond strength in hydropersulfides (RSSH), prompted us to investigate hydrogen-atom transfers from hydropersulfides. As reported in Chapter 4, we found that hydropersulfides (RSSH) are very potent hydrogen-atom donors, making them highly effective RTAs in organic and aqueous media, even besting thiols in many H-atom transfer reactions with alkyl,

alkoxyl and peroxy radicals. The one-electron oxidation exhibited by hydropersulfides parallels the one we previously reported for sulfenic acids (RSOH).

Previous successful studies on the one-electron oxidation of sulfenic acids prompted us to make use of the persistence imparted by a triptycene backbone to study two-electron processes, namely - thiol oxidation by hydrogen peroxide (H_2O_2). Indeed, the reaction of thiols with H_2O_2 is central to many processes essential to life, from protein folding to redox signaling. However, kinetic and mechanistic characterization of their subsequent reactions had not been reported due to the instability of the sulfenic acid intermediate under study. Gratifyingly, as reported in Chapter 5, using our triptycene model with an appended fluorine atom, we were able to investigate the complete series of consecutive reactions with hydrogen peroxide, from thiol to sulfenic acid to sulfinic acid to sulfonic acid, which has hitherto not been possible, and found that the reaction is specific base-catalyzed.

Sulfinic acids (RSO_2H), the primary product of sulfenic acid oxidation, have been used increasingly in recent years in many synthetic applications such as sulfonylation reactions. As described in Chapter 6, using a similar approach to previous studies, we synthesized a triptycene sulfinic acid and demonstrated that the triptycene backbone is also effective at rendering the sulfinic acid and sulfonyl radical ($\text{RSO}_2^\bullet$) persistent enough to study H-atom transfer reactions. We showed that sulfinic acids are good H-atom donors to alkyl and alkoxyl radicals but they are not effective RTAs due to the propensity of sulfinic acids to autoxidize through the reaction of sulfonyl radicals with oxygen.

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Statement of Originality

I hereby certify that all of the work described in this thesis is the original work of the author, with exceptions for work performed by collaborators noted in the preface to each chapter. The work in this thesis draws upon a great deal of published research. Any published (or unpublished) work by others is cited and fully acknowledged within the references.

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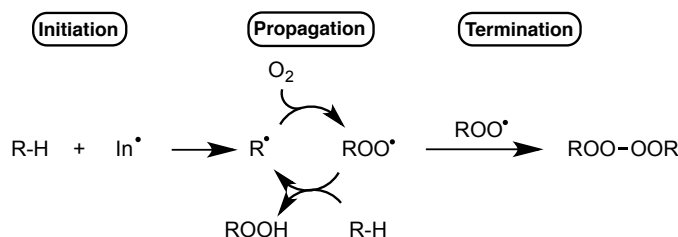
α -TOC	α -tocopherol
AAPH	2,2'-azobis-(2-amidinopropane) monohydrochloride
AIBN	azobisisobutyronitrile
BDE	bond dissociation enthalpy
BHT	butylated hydroxytoluene (2,6-di- <i>t</i> -butyl-4-methylphenol)
DCP	dicumylperoxide
DKIE	deuterium kinetic isotope effect
DPA	diphenylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
E_a	activation energy
EDG	electron donating group
EI	electron impact
EPR	electron paramagnetic resonance
ESI	electrospray ionization
GC	gas chromatography
H-atom	hydrogen atoms
HAT	hydrogen atom transfer
HOMO	highest occupied molecular orbital
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrometry
KSE	kinetic solvent effect
LFP	laser flash photolysis
LUMO	lowest unoccupied molecular orbital
MeO-AMVN	2,2'-Azobis(4-methoxy-2,4-dimethylvaleronitrile)

NBO	natural bond orbital
NMBHA	<i>N</i> -methylbenzohydroxamic acid
NMR	nuclear magnetic resonance
PCET	proton coupled electron transfer
PET	photoinduced electron transfer
PMC	2,2,5,7,8-pentamethyl-6-chromanol
REqEPR	radical equilibrium EPR spectroscopy
ROS	reactive oxygen species
RTA	radical trapping antioxidant
SOMO	singly occupied molecular orbital
SPLET	sequential proton-loss electron transfer
<i>t</i> -Bu ₂ DPA	4,4'-di- <i>tert</i> -butyldiphenylamine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
THF	tetrahydrofuran
TOCO	thiol-olefin cooxidation
TS	transition state

CHAPTER 1: Background and Significance

1.1 Hydrocarbon autoxidation

All hydrocarbons (R-H) undergo spontaneous reactions with atmospheric oxygen; a process termed autoxidation.¹ This radical-mediated process is responsible for the irreversible oxidative degradation of all hydrocarbon based materials, from lubricating oils to biological phospholipid membranes.^{2,3} The accepted mechanism constitutes the archetype free radical chain reaction and therefore consists of initiation, propagation and termination steps – generally depicted as in Scheme 1.1.



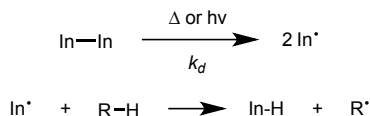
Scheme 1.1. Hydrocarbon autoxidation.

Hydrocarbon autoxidation usually initially produces hydroperoxides (ROOH) that can further decompose to yield alcohols, aldehydes, ketones, esters, and carboxylic acids, some or all of which can lead to deleterious changes to hydrocarbon-based products or toxicity to a cell/tissue/organism.^{4,5}

Given the importance of preserving hydrocarbons that comprise petroleum-derived products, efforts were made in the 1950s to further our understanding of hydrocarbon autoxidation and what could be done to control and/or prevent it. Today, our understanding of such processes led to important commercial applications and a recognition of their contribution in biological contexts. Indeed, despite deleterious repercussions, autoxidations are done on industrial scale to produce commodity chemicals such as phenol and acetone via the autoxidation of cumene, termed the Hock process.⁶ Hydrocarbon autoxidation has also been applied in the total synthesis of natural products.⁷ Our current understanding of the autoxidation of hydrocarbons is introduced in more detail in the sections below.

1.1.1 Initiation

Hydrocarbon autoxidation commences when an initiating radical species ($\text{In}^\bullet$) is produced from a thermally or photochemically labile precursor containing a weak bond. As shown in Scheme 1.2, this initiating radical will abstract hydrogen from hydrocarbons (RH) to form carbon centered radicals.

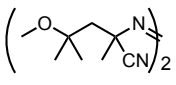
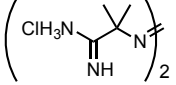
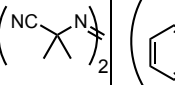
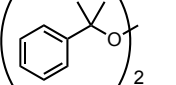
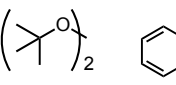
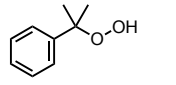


Scheme 1.2. Initiation of hydrocarbon autoxidation

Commonly, (hydro)peroxides undergo O-O bond homolysis, yielding highly reactive alkoxy radicals ($\text{RO}^\bullet$) and hydroxyl radicals ($\text{HO}^\bullet$) that will initiate chain reactions by abstracting hydrogen atoms (H-atoms). Those high energy oxygen-centered radicals abstract H-atoms high rates, forming strong O-H bonds. For example, H-atom abstraction from cumene and 1-octene by the cumyloxy radical occurs at $k = 2.3 \times 10^6$ and $4.6 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, respectively.⁸

Other common synthetic initiators of hydrocarbon autoxidation are azo initiators, $\text{R}-\text{N}=\text{N}-\text{R}$, which decompose at known rates upon thermal or photochemical activation to form 2 equivalents of alkyl radicals ($\text{R}^\bullet$) and N_2 . Physico-chemical properties of common initiators are shown in Table 1.1.

Table 1.1. Half-life and activation energy of common radical-chain initiators.⁹

	$\text{R}-\text{N}=\text{N}-\text{R} \xrightarrow[k_d]{\Delta \text{ or } h\nu} 2 \text{R}^\bullet + \text{N}_2$			$\text{R}-\text{O}-\text{O}-\text{R} \xrightarrow[k_d]{\Delta \text{ or } h\nu} 2 \text{R}-\text{O}^\bullet$		
	 MeO-AMVN	 AAPH	 AIBN	 DCP	 tBuOOtBu	 CumylOOH
10 $t_{1/2}$ (°C)	30	56	65	115	125	140
E_a (kcal/mol)	22.5	29.5	31.1	35.4	36.5	31.7

The half-life of initiators depend on the solvent they are measured in since the viscosity of the solvent will impact the ability of the initiating radicals to escape the solvent cage. This is accounted

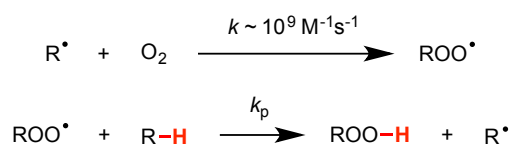
for in the equation describing the rate of initiation, R_i (eq. 1.1), where ‘ e ’ is a cage-escape efficiency coefficient, k_d , the dissociation rate constant and $[In]$ is the concentration of the initiator:

$$R_i = 2ek_d[In] \quad (1.1)$$

Given that the dissociation of initiators has a high activation energy (E_a), the half-life of the initiators is also strongly dependent on the temperature at which the autoxidation is carried out.

1.1.2 Propagation

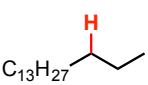
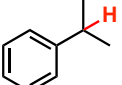
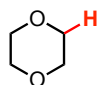
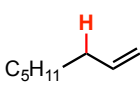
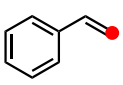
The majority of the (hydro)peroxides produced in an autoxidation are formed during propagation steps, as depicted in Scheme 1.3. First, alkyl radicals react with oxygen at extremely high rates ($\sim 10^9 \text{ M}^{-1}\text{s}^{-1}$)¹⁰ to form the chain carrying species, peroxy radicals ($\text{ROO}^\bullet$). Next, peroxy radicals abstract H-atoms to form hydroperoxides and alkyl radicals, the latter of which go through the same reaction pathway and continue the chain process.



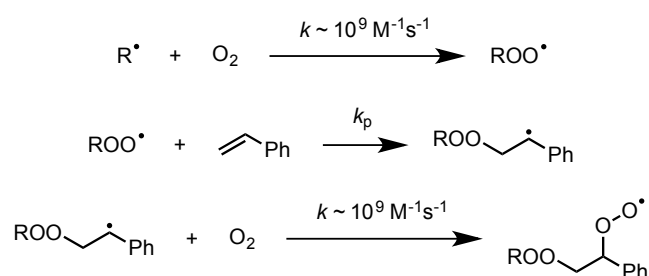
Scheme 1.3. Chain propagation in alkyl hydrocarbon autoxidation.

The propagation rate constant, k_p , is unique to each oxidizable substrate and will vary based on the structure of the substrate and the temperature of the autoxidation. More specifically, the bond dissociation enthalpy of the C-H bond being broken (Table 1.2, in red) will influence the magnitude of k_p as the stronger the C-H bond, the lower the k_p will be, in general.

Table 1.2. C-H BDE's (red) and propagation rate constant (k_p) for hydrocarbon autoxidation at 30 °C.

						
	<i>n</i> -hexadecane	cumene	1,4-dioxane ¹¹	1-octene	THF ¹¹	styrene
k_p (M ⁻¹ s ⁻¹) ¹²	0.01	0.18	0.5	1.0	4.3	41
BDE _{C-H} (kcal/mol) ¹³	98.0	84.5	96.0	83.4	92.0	-

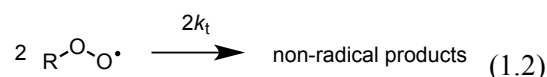
Alternatively to H-atom abstraction, peroxy radicals can add to activated alkenes, such as styrene, in which case k_p is determined from the rate of addition onto the alkene.¹² This reaction sequence is commonly utilized in polymerization chain reactions for which an example of the propagation steps for the autoxidation of styrene are depicted in Scheme 1.4 and produce co-polymers of oxygen and styrene.



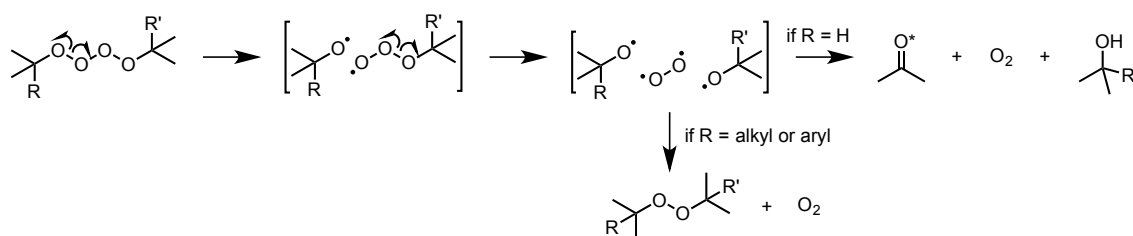
Scheme 1.4. Chain propagation in styrene autoxidation.

1.1.3 Termination

Apart from participating in H-atom abstraction, peroxy radicals can combine to yield non-radical products, thus terminating two chains. The termination of two peroxy radicals (eq. 1.2) is by far the most predominant termination event during an autoxidation. The rapid addition of O₂ to alkyl radicals, the other propagating radical species, ensures that the steady state concentration of alkyl radicals is kept very low over the course of the autoxidations.



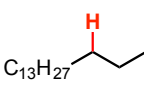
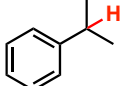
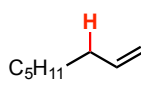
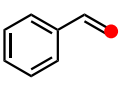
In general, the more substituted the alkyl group on the peroxy, the slower it will terminate (k_t) because of the increasing steric effects.¹⁴ Moreover, the structure of the peroxy radical will dictate the mechanism by which it terminates. Tertiary peroxy radicals react with other peroxy radicals very slowly compared to primary alkylperoxy radicals,¹⁵ and will form di-*tert*-alkyl peroxides. The Russell mechanism, proposed in 1957, is believed to take place for primary and secondary peroxy radicals. It involves decomposition of a tetroxide through a cyclic transition state where an α -H-atom is transferred. The Russell mechanism is a plausible explanation as to why secondary peroxy radicals have a faster termination reaction than tertiary peroxy radicals.¹⁶ More recently, Coote and co-workers showed computationally that secondary peroxy radicals terminate via a similar intermediate to tertiary peroxy radicals, as shown in Scheme 1.5.¹⁷



Scheme 1.5. Termination of alkylperoxy radicals.

The rate at which peroxy radicals terminate is an important consideration when looking at the overall kinetics of autoxidations since the oxidizability of the hydrocarbon is defined as a ratio of: $k_p/\sqrt{2k_t}$. As shown in Table 1.3, a hydrocarbon with a high k_p and low k_t (e.g. styrene) will be more oxidizable than a hydrocarbon with a low k_p and high k_t (e.g. hexadecane) since at high k_t the steady state concentration of peroxy radicals is low, thus slowing the oxidation of the substrate.

Table 1.3. Termination rate constants (k_t) for hydrocarbon autoxidations at 30 °C and oxidizability of the hydrocarbon.¹²

						
	<i>n</i> -hexadecane	cumene	1,4-dioxane ¹¹	1-octene	THF ¹¹	styrene
$k_t \times 10^6 \text{ (M}^{-1}\text{s}^{-1}\text{)}$	13	0.0075	25	130	16	21
$k_p/\sqrt{(2k_t)} \times 10^{-3} \text{ (M}^{-1/2}\text{s}^{-1/2}\text{)}$	0.0020	1.5	0.069	0.062	0.76	8.9

Chain reactions are often characterized by their chain length - the number of propagation cycles per initiating events. Therefore for an autoxidation to be considered a chain reaction, the rate of propagation must be greater than the rate of initiation ($R_p > R_i$).

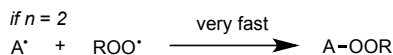
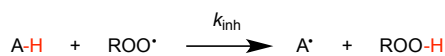
The production of hydroperoxide during an autoxidation follows first order kinetics for concentration of substrate (RH) and one-half order in the rate of chain initiation, R_i . The rate of hydroperoxide formation over the course of an uninhibited autoxidation can be determined using eq. 1.3, assuming a steady state concentration of peroxy radicals.

$$\frac{d[\text{ROOH}]}{dt} = \frac{k_p[\text{RH}]\sqrt{R_i}}{\sqrt{2k_t}} \quad (1.3)$$

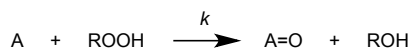
1.1.4 Inhibition

Given the importance of hydrocarbon autoxidation in biology and industry, a great deal of research has been carried out to understand how to inhibit the autoxidation process.^{2,3} Compounds capable of inhibiting autoxidation by stopping chain propagation are called radical-trapping antioxidants (RTAs), or primary antioxidants (Scheme 1.6A), while those preventing initiation events are called preventative antioxidants, or secondary antioxidants (Scheme 1.6B).^{2,3} Most commonly, RTAs react directly with peroxy radicals (propagating radicals) via H-atom transfer (HAT) or proton-coupled electron transfer (PCET) to form species that do not propagate chain reactions. On the other hand, preventative antioxidants such as phosphines and sulfides reduce (hydro)peroxides, preventing the initiation of new chain reactions.^{2,3}

A) Primary antioxidants (RTAs)



B) Secondary antioxidants

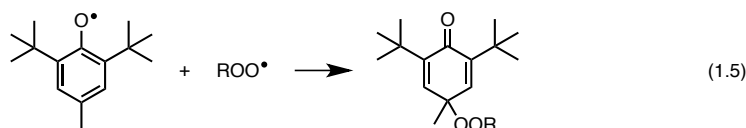
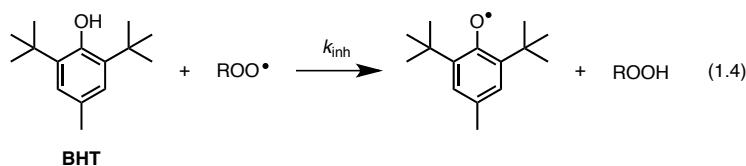


Scheme 1.6. Mechanisms of antioxidant action.

When considering the activity of RTAs, two factors must be considered. The rate constant at which they react with peroxy radicals, k_{inh} , and the stoichiometry, n , of the inhibition (i.e. the number of chain reactions halted per molecule of RTA).^{2,3} In general, the most effective RTAs will have both high k_{inh} and n .

1.2 Phenolic antioxidants

Phenols are the most widely used antioxidant in industry and biology. Their antioxidant activity stems from their ability to transfer their phenolic H-atom to a propagating radical yielding a phenoxyl radical that is incapable of carrying on the chain (Eq. 1.4 in Scheme 1.7). Instead, the phenoxyl radical persists until it reacts with another radical to yield non-radical products (Eq. 1.5); thus, one phenolic RTA halts two chain reactions ($n = 2$).

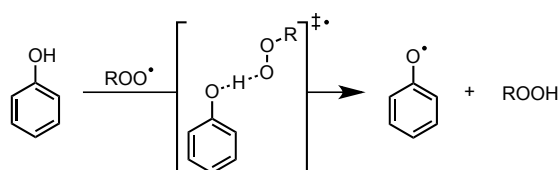


Scheme 1.7. Phenolic radical-trapping antioxidants trap two peroxy radicals, as exemplified by 2,6-di-tert-butyl-4-methylphenol (BHT).

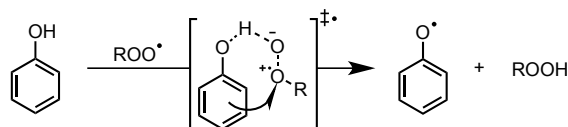
Several factors influence the antioxidant properties of phenols: their O-H BDEs, steric hinderance, and solvent interactions.^{2,3} The impact of those three factors can be rationalized by considering the three (non-exclusive) mechanisms of formal H-atom transfer from phenols to propagating radicals, as depicted in Scheme 1.8: hydrogen atom transfer (HAT), proton-coupled electron transfer (PCET), and sequential proton-loss electron transfer (SPLET).¹⁸ The interplay of the three mechanisms depend on the structure of the antioxidant (steric hinderance) and the environment (solvent effects).

Conceptually, HAT and PCET are very different mechanisms, although it is difficult to distinguish between HAT and PCET mechanism experimentally.¹⁹ HAT from phenols to peroxy radicals go through a one proton and three electron transition state whereas in PCET, the transition state involves one proton and five electrons. PCET, first proposed by Mayer *et al*,²⁰ involves a hydrogen-bonded complex between the peroxy radical lone pair on the oxygen and the phenol O-H before the hydrogen is transferred from the phenol to the peroxy radical. Simultaneously, an electron is transferred from the π system (HOMO) of the phenol to the SOMO of the peroxy radical.

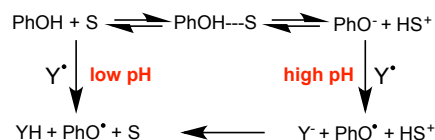
A. hydrogen-atom transfer (HAT)



B. proton-coupled electron transfer (PCET)



C. sequential proton-loss electron transfer (SPLET)

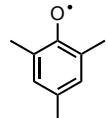
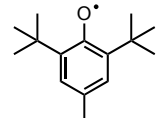


Scheme 1.8. Reaction of phenolic antioxidants with peroxy radicals.

The O-H BDE in phenols is a major contributor to its antioxidant efficacy. Moreover, the substituents on the aromatic ring have a direct influence on the BDE. The resulting phenoxyl radical is electron poor, therefore phenols bearing electron donating substituents (e.g. 4-OMe) have lower O-H BDEs than phenols substituted with electron withdrawing groups (e.g. 4-NO₂).²¹ The BDEs of phenols are often measured by radical equilibrium EPR spectroscopy (REqEPR).²² This method determines the equilibrium constants between two phenol/phenoxyl radical couples, one of whose O-H BDE is known, allowing the derivation of the unknown O-H BDE.²²

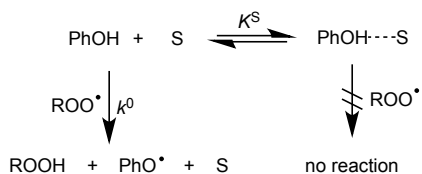
Steric hinderance has great influence on the reactivity of phenols. Indeed, a phenol is most effective as an antioxidant when the resulting phenoxyl radical is both stable and persistent. Stability is a thermodynamic parameter and the stability of the phenoxyl radical is enhanced with improved delocalization. Persistence is a kinetic parameter and the persistence of the phenoxyl radical depends on steric effects around the radical preventing a reaction with another molecule. An example of a persistent radical is the phenoxyl radical derived from BHT. The steric crowding around the phenoxyl radical is responsible for the lower BDE and lower rate of termination between two phenoxyl radicals, $2k_t$. As shown in Table 1.4, the addition of the two tert-butyl groups decreases the O-H BDE of BHT by more than 7 kcal/mol compared to phenol. Moreover, self-termination between two phenoxyl radicals derived from BHT is 6 orders of magnitude lower than the same reaction for phenoxyl radicals derived from phenol.

Table 1.4. BDE and termination rate constants ($2k_t$) of para-substituted phenols.

			
O-H BDE (kcal/mol) ²²	88.3	82.7	81.0
$2k_t$ (M ⁻¹ s ⁻¹)	2.6×10^9	4.5×10^7	8.6×10^3

As mentioned previously, kinetic solvent effects can influence the efficacy of phenolic antioxidants. In general terms, any hydrogen bond accepting solvent capable of forming hydrogen

bonds with the phenolic O-H group will decrease k_{inh} .²³ The kinetic solvent effect model proposed by Ingold *et al* is depicted in Scheme 1.9.²³ The model assumes that any phenolic antioxidant hydrogen bonded to the solvent is unreactive to HAT due to sterics and that only free PhOH can react.²³



Scheme 1.9. Kinetic solvent effects in HAT of phenolic antioxidants.

From Scheme 1.9, the experimental rate constant (k^S) for HAT between PhOH and $\text{ROO}^\bullet$ in a given solvent, S, is depicted by Eq 1.6,¹⁸ where k^0 is the rate constant of HAT in a hydrocarbon (i.e in the absence of hydrogen bonding):

$$k^S = \frac{k^0}{(1 + K^S)} \quad (1.6)$$

The hydrogen bond accepting ability of a solvent is represented by β_2^H , a relative scale of solute basicities in CCl_4 ranging from 0.0 for alkanes to 1.00 for HMPA.²⁴ On the other hand, the hydrogen bond donating ability of a substrate is represented by α_2^H , a relative scale of substrate acidities in CCl_4 .²⁵ The linear free energy relationship between the rate constant of HAT, the α_2^H of the antioxidant, and the β_2^H of the solvent is represented by Eq. 1.7.²³ The approach brought forth by Ingold allows the kinetic solvent effects for various HAT reactions to be quantitatively described.

$$\log k_{inh}^S = -8.3\alpha_2^H\beta_2^H + \log k_{inh}^0 \quad (1.7)$$

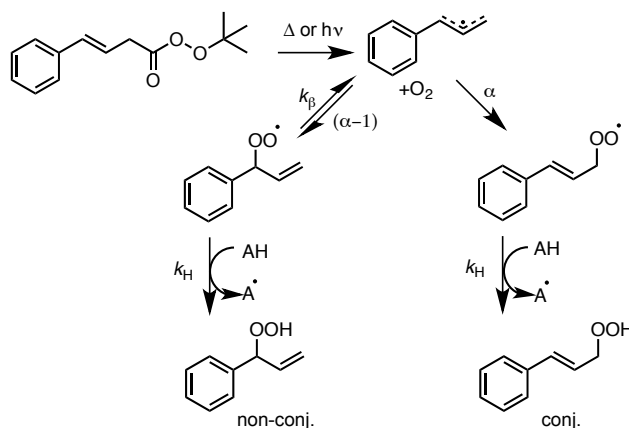
In cases where the antioxidant is highly ionizable, such as an electron rich phenol, hydrogen bonding might not fully explain the observed rate constant. As depicted in Scheme 1.8C, in a polar solvent, a phenolic antioxidant can react via a combination of HAT and sequential proton-loss electron transfer (SPLET) wherein the phenol is ionized to the phenoxide and then undergoes electron transfer to a peroxy radical.¹⁸

1.3 Methods to measure antioxidant activity

Several methods exist to measure the kinetics of reactivity of antioxidants with peroxy radicals and have been recently reviewed.²⁶ They include direct approaches such as laser flash photolysis²⁷ and electron paramagnetic resonance (EPR)²⁸ - all of which necessitate the use of specialized equipment, and indirect approaches, such as peroxy radical clocks and inhibited autooxidations.

1.3.1 Peroxyl radical clocks

Peroxyl radical clock methods,²⁹⁻³¹ as shown in Scheme 1.10, involve a competition between the β -fragmentation of a non-conjugated peroxy radical (k_β) and a bimolecular reaction that will trap the peroxy radical with an unknown rate constant, k_H , forming a hydroperoxide.



Scheme 1.10. Peroxyl radical clock based on the product distribution resulting from the thermal or photolytical decomposition of peroxyesters in the presence of an antioxidant (AH).

Using this competitive kinetic method, it is relatively simple to determine the rate constants for reactions between peroxy radicals and antioxidants since it requires no specialized equipment other than a GC or HPLC for product analysis. Once the ratio of the two products is known, the rate constant between a peroxy radical and an antioxidant (AH) can be determined using Eq. 1.8, where α is the oxygen partition coefficient.²⁹

$$\frac{[\text{conj.}]}{[\text{non-conj.}]} = \frac{k_{\beta}}{k_{\text{H}}[\text{AH}]} \left(\frac{1-\alpha}{\alpha} \right) + \left(\frac{1-\alpha}{\alpha} \right) \quad (1.8)$$

Although peroxy radical clocks offer a convenient way to determine the inhibition rate constant of an antioxidant, the stoichiometry of the antioxidant itself cannot be obtained via this method because the inhibition time is not monitored, only the product distribution at pre-determined time points.

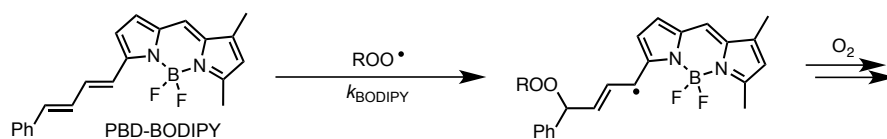
1.3.2 Inhibited autoxidations

Inhibited autoxidations allow the determination of both the inhibition rate constant and the stoichiometry of RTAs.³ By adding an antioxidant to the autoxidation the rate of autoxidation, or production of ROOH, is slowed. The rate of oxidation can be monitored by oxygen consumption³² or by quantifying the hydroperoxides formed over time during the autoxidation. This can be easily done for oxidizable substrate such as cumene or tetralin that produce a single hydroperoxide product, cumene hydroperoxide and tetralin hydroperoxide, respectively.¹² However, for styrene, the formation of styrene-oxygen co-polymers over the course of the autoxidation precludes the analysis of the products by GC or HPLC and necessitate other techniques such as oxygen consumption.³²

Recently, our group reported on the use of a continuous spectrophotometric approach to monitor autoxidations by UV-vis spectroscopy.³³ The treatment of the kinetic data is comparable to the one performed for oxygen consumption experiments and is described below.

In the presence of an oxidizable hydrocarbon (e.g. cumene, styrene, etc), the method makes use of a BODIPY core conjugated to a phenyl-butadiene moiety (PBD-BODIPY) or styrene moiety (STY-BODIPY) that co-oxidizes in a similar fashion to styrene. The propagation rate constant (k_{BODIPY}) refers to peroxy radical addition onto the butadiene or styrene core, as shown in Figure 1.1A for PBD-BODIPY.

A.



B.

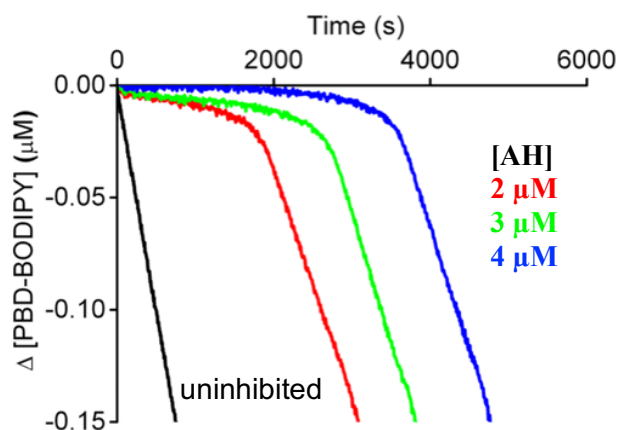


Figure 1.1. PBD-BODIPY acts as a signal carrier in inhibited autoxidations. (A) Autoxidation of PBD-BODIPY inhibited by 2-4 μM of antioxidant. (B)

As the autoxidation progresses, the small amount of PBD-BODIPY present in solution (i.e. 10 μM) is consumed in competition with the substrate, which is less reactive, but present in significant excess (Figure 1.1B, black trace). Upon addition of an antioxidant, the rate of oxidation of PBD-BODIPY is retarded until the antioxidant is fully consumed, after which the slope parallels the one of the uninhibited trace. The slope of the inhibited period represents the rate of the inhibited autoxidation and can be expressed as in Eq. 1.9, where k_{BODIPY} is the rate constant of peroxy radical addition onto BODIPY, $[\text{RH}]$ and $[\text{AH}]$ are the concentration of oxidizable substrate and antioxidant, respectively, and n is the stoichiometric factor.

$$\frac{d[\text{ROOH}]}{dt} = \frac{k_{\text{BODIPY}}[\text{RH}]R_1}{nk_{\text{inh}}[\text{AH}]} \quad (1.9)$$

The stoichiometry of the antioxidant (n) is determined from Eq. 1.10 by extrapolating the time of inhibition, t_{inh} , from the kinetic traces. That is, the intersection of the inhibited and the uninhibited slope.

$$n = \frac{t_{\text{inh}} R_i}{[\text{AH}]} \quad (1.10)$$

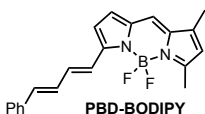
This method offers great advantages compared to more classic approaches; both k_{inh} and n can be determined without requiring the use of specialized equipment or aliquot collection. Moreover, two kinetic parameters necessary to determine k_{inh} of an antioxidant via Eq. 1.9 can be easily determined for various substrate/solvent systems. R_i is determined from Eq. 1.10 by using a standard antioxidant with an established stoichiometry of $n = 2$, such as PMC.³⁴

k_{BODIPY} is determined by measuring the rate of dye consumption in uninhibited autoxidations at various dye concentrations, while keeping a constant initiator loading.³³ The slope of the uninhibited line plotted as a function of dye concentration yields a line where the slope relates to k_{BODIPY} , $\sqrt{R_i}$, and $\sqrt{2k_t}$, as described by eq. 1.11.

$$-\frac{\delta[\text{BODIPY}]}{\delta t} = \frac{k_{\text{BODIPY}}}{\sqrt{2k_t}} \sqrt{R_i} [\text{BODIPY}] \quad (1.11)$$

Representative k_{BODIPY} and physicochemical properties are presented in Table 1.5 for PBD-BODIPY and STY-BODIPY.

Table 1.5. k_p and physicochemical properties of PBD-BODIPY and STY-BODIPY in various substrate/solvent compositions at 37 °C.

	substrate/solvent	k_{BODIPY} ($\text{M}^{-1}\text{s}^{-1}$)	λ_{max} (nm)	ϵ ($\text{M}^{-1}\text{cm}^{-1}$)
 PBD-BODIPY	THF/PhCl (1:4) ³⁵	2240	588	128 100
	Styrene/PhCl (1:1) ³³	2720	591	139 000
	Dioxane/DMSO/PhCl (1:1:2) ³⁵	5900	587	118 200
	Hexadecene/PhCl (5:1) ³⁵	3790	588	148 700
	Hexadecene/PhCl (5:1, 100 °C) ³⁶	17 800	587	119 200
 STY-BODIPY	Cumene/PhCl (1:1) ³³	141	571	128 000
	THF/H ₂ O (1:4) ³³	7900	562	147 000

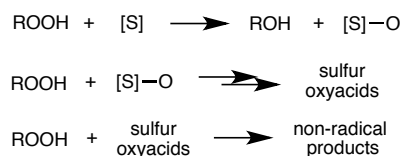
From Table 1.5, both λ_{max} and ϵ are solvent and temperature dependent and must be determined under the same conditions as the autoxidations of interest.

The value of k_t in Eq. 1.11 is obtained from literature values since it is influenced in majority by the rate constant of termination of two substrate derived peroxy radical (Substrate-OO• + Substrate-OO•).¹² That is because the termination of peroxy radicals from the BODIPY dye can be ignored given that the substrate is present in much greater concentration than the dye (M vs μ M).³³

The versatility of the aforementioned spectrophotometric approach will be demonstrated throughout the work presented in this thesis.

1.4 Organosulfur antioxidants*

Sulfur is the most abundant element in crude petroleum after carbon and hydrogen.¹ In the 1940's, Denison and Condit³⁷ observed that the removal of natural organosulfur compounds from petroleum renders the hydrocarbons much more oxidizable. In fact, although sulfur is removed from petroleum feedstocks in refining processes, it is generally added back to the finished products. It is widely believed that organosulfur compounds act as secondary antioxidants by decomposing hydroperoxides,³⁸ the primary products of hydrocarbon autoxidation, as shown in Scheme 1.11. By decomposing the product hydroperoxides, organosulfur compounds and sulfur oxyacids slow the rate at which new chain reactions are initiated.



Scheme 1.11. Organosulfur antioxidants decompose hydroperoxides.

Organosulfur compounds are often used as secondary antioxidants to inhibit hydrocarbon autoxidation in tandem with primary radical-trapping antioxidants² such as BHT and α -tocopherol (α -TOH, the most biologically-active form of vitamin E).³⁹

* This section is presented in large part as it was published in the Canadian Journal of Chemistry (Chauvin, J.-P. R.; Zielinski, Z. A. M.; Pratt, D. A. *Can. J. Chem.* **2016**, *94*, 1–8.) with permission from Canadian Science Publishing (license # 467277066926).

Thiols are both primary and secondary antioxidants. They react as primary antioxidants with peroxy radicals via H-atom abstraction of their S-H bond ($k_{\text{inh}} \sim 10^3 \text{ M}^{-1}\text{s}^{-1}$ for thiophenols).^{40,41} They can also react as secondary antioxidants by reducing hydroperoxides to alcohols, a reactivity common to the alkylhydroperoxide reductase family of enzymes.⁴² The disulfide formed as the end product of thiol oxidation by hydroperoxides can react as a secondary antioxidant to form a thiosulfinate.

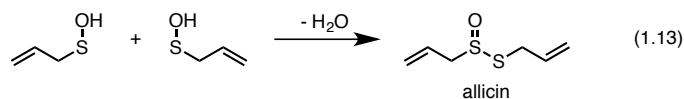
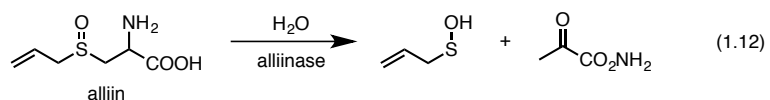
In the early 1950's Bateman and coworkers showed that the reaction of cyclohexyl methyl sulfide with *t*-butylhydroperoxide is bimolecular in hydroperoxide in hydrocarbon solvents and unimolecular in hydroperoxide in alcoholic solvents.⁴³ This observation suggests that the reaction proceeds through an ionic mechanism since a radical mechanism would not be as sensitive to solvent effects. Additionally, the reaction of hydroperoxides with sulfides was found to be insensitive to molecular oxygen, further supporting an ionic mechanism of secondary antioxidant action.

Hydrocarbon autoxidations conducted in the presence of sulfides and disulfides showed a small, but significant, delay in the inhibition period. This delay was attributed to the oxidation of sulfides and disulfides to sulfoxides (RS(O)R) and thiosulfonates (RS(O)SR), respectively.⁴⁴ It was then concluded that a large part of the antioxidant activity of (di)sulfides comes from their immediate oxidation products, sulfoxides and thiosulfonates.

1.4.1 Hindered sulfoxides and thiosulfonates

Organosulfur compounds are featured prominently in natural product chemistry,⁴⁵ medicinal chemistry, and biological chemistry.⁴⁶ Among the richest organosulfur chemistry in Nature is found in the genus *Allium*, of which garlic is the most prolific species.⁴⁶ Used as a medicinal agent for millennia, garlic has proven to be a treasure trove of compounds whose study has contributed greatly to our understanding of organosulfur chemistry.⁴⁷ One well-known property of garlic is its antibacterial activity; Cavallito was the first to ascribe this property to Allicin, one of the many organosulfur constituents garlic.⁴⁸ Allicin is formed from the nonproteinogenic amino acid alliin by the C-S lyase

alliinase upon physical stress to the plant and is believed to be garlic's primary defense against pathogens (Scheme 1.12).⁴⁶

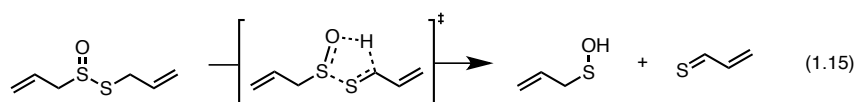


Scheme 1.12. The transformation of alliin to allicin.

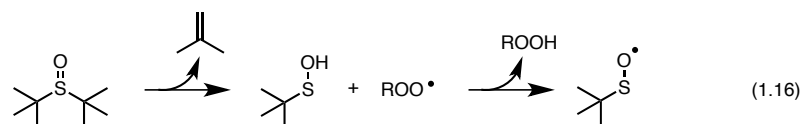
Allicin's biological activity has been the focus of many studies - some of which have suggested that allicin is a potent RTA.^{49–52} Structurally, allicin is devoid of any of the typical functionalities that are found in good RTAs (e.g., a weak O–H bond, as in phenols). Okada *et al* originally proposed a mechanism involving a HAT from an allylic C–H bond to a peroxy radical (Eq. 1.14):⁵²



This mechanism was later revoked as Amorati and Pedulli⁵³ demonstrated unambiguously that hydrogen atom donation from a methylene group flanked by a double bond and a sulfur atom (in diallyl disulfide) cannot be responsible for the RTA activity of allicin. In fact, they measured a rate constant for the reaction of cumene-derived peroxy radicals and diallyl disulfide of $\sim 1.6 \text{ M}^{-1} \text{ s}^{-1}$, which is indistinguishable to the rate constant for the propagation of cumene autoxidation.⁵³ The introduction of an oxygen atom on one of the sulfur atoms in diallyl disulfide — as in allicin — does not change the lability of the hydrogen atom on the distal methylene unit (the calculated C–H BDEs, determined using the eminently reliable CBS-QB3 methodology are 82.4 and 81.8 kcal/mol, respectively).⁵⁴ However, oxygenation of one of the sulfur atoms enables the highly favorable Cope-type elimination of a sulfenic acid from the thiosulfinate (Eq. 1.15):⁴⁶



The 2-propenesulfenic acid derived from allicin was found to be an excellent hydrogen atom donor.⁵⁵ In fact, this was not the first suggestion that a sulfenic acid would react rapidly with peroxy radicals; in 1972, Koelwijn and Berger invoked the Cope-type elimination of *tert*-butylsulfenic acid from di-*tert*-butylsulfoxide (Eq. 1.16) to explain the RTA activity of the latter.⁵⁶



1.4.2. Sulfenic acids

Sulfenic acids are notoriously unstable⁵⁷ and readily self-condense to yield a thiosulfinate (among other possible reaction pathways). Computations have revealed that sulfenic acids have among the weakest O–H bonds known (~69 kcal/mol, roughly the same as those in hydroxylamines).⁵⁵ Moreover, sulfenic acids undergo barrierless reactions with peroxy radicals via a transition state (TS) with significant overlap between orbitals on the sulfur atom of the sulfenic acid and the inner oxygen atom of the peroxy radical (a *syn* TS, Figure 1.2A).⁵⁵ This secondary orbital interaction (Figure 1.2B) appears to be key to the tremendous reactivity of sulfenic acids with peroxy radicals, since the TS structure that minimizes the interaction between the groups on the reacting moieties (*anti* TS, Figure 1.2A) is significantly higher in energy (up to 5 kcal/mol).⁶⁹

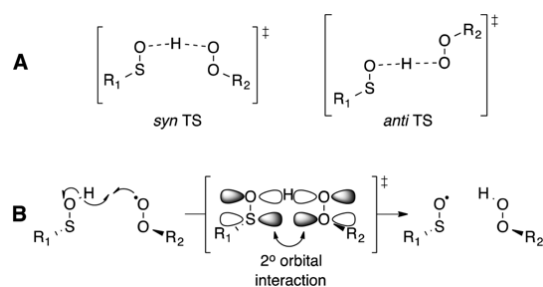
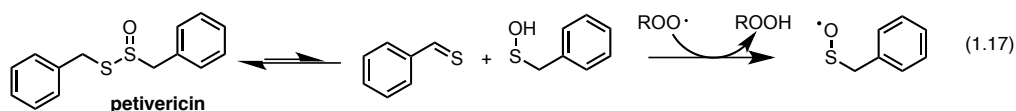


Figure 1.2. (A) Schematic depiction of the reaction of a sulfenic acid with a peroxy radical with either a *syn* or an *anti* transition state geometry. (B) Schematic representation of the secondary orbital interaction that leads to a preference for the *syn* TS.⁵⁸

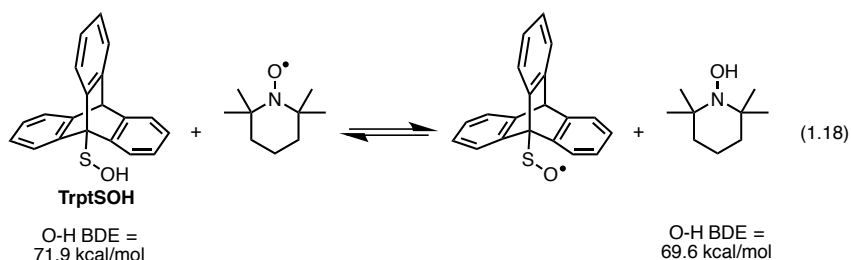
The dibenzyl analog of allicin (petivericin), which derives from garlic's relative *Petiveria alliaca*, is commonly used in the South and Central Americas in many of the same medicinal applications wherein garlic has been used in Asia.^{59,60} Although petivericin has indistinguishable RTA activity from allicin — including the abolishment of this activity in the presence of strong H-bond donating solvents that slow Cope elimination - it is of far greater relative stability because sulfenic acid formation is reversible, presumably due the greater stability of thiobenzaldehyde compared to thioacrolein.⁵⁴



Due to the reversibility of the Cope elimination from petivericin, the inhibited autoxidation data can be fit to the standard kinetic scheme for RTA-inhibited autoxidations to estimate a rate constant for the reaction of α -toluenesulfenic acid with peroxy radicals, revealing $k_{\text{inh}} = 3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.⁶¹ This rate constant, which agrees well with computations, is 10-fold greater than that for the reaction of α -TOH with peroxy radicals and is among the largest ever reported for an RTA.⁵⁵

The clearest demonstration of the intervention of sulfenic acids in the RTA activity of allicin and petivericin would be the direct determination of the radical reactivity of the sulfenic acids derived therefrom. However, unhindered sulfenic acids self-condense to thiosulfonates too rapidly to be observed.⁵⁷ In fact, only a handful of sulfenic acids that are sufficiently persistent to study have been prepared. The first report of a persistent sulfenic acid was in 1912 by Fries where he made use of intramolecular hydrogen bonding to impart persistence to an anthraquinone sulfenic acid.⁶² Steric hindrance is another approach to render sulfenic acids persistent by preventing the access of nucleophiles to the $\sigma_{\text{S-O}}^*$ orbital of the sulfenic acid. For example, Nakamura reported a 9-triptycenesulfenic acid (**TrptSOH**)⁶³ and Goto and co-workers made use of large molecular cavities to provide stability to the sulfenic acid.^{64–66} More recently, the Liu group made use of electronic effects to prepare solution-stable perfluoroalkylsulfenic acids.⁶⁷

Thermodynamic support for the RTA reactivity of sulfenic acids and confirmation of the weak O-H BDE computed for them in earlier work (~ 69 kcal/mol) were obtained by EPR equilibration experiments with **TrptSOH** and the persistent nitroxide TEMPO (eq. 1.18) and yielded an experimental O-H BDE of 71.9 ± 0.3 kcal/mol.⁶⁸ The use of persistent radicals is necessary to maintain a constant concentration of radicals during the time scale of the experiment. The very weak O-H bond - roughly 14 kcal/mol weaker than that in valence isoelectronic hydroperoxides (~ 86 kcal/mol) - was ascribed to the significant spin delocalization onto the internal sulfur atom (50%) in the sulfinyl radical.⁶⁸



TrptSOH has also been used to inhibit the AIBN-initiated autoxidation of styrene, enabling the derivation of a rate constant for its reaction with chain-carrying peroxy radicals, $k_{\text{inh}} = 3.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ (in chlorobenzene)⁶¹ - essentially the same as that of α -TOH ($3.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$).³⁹ While this value is an order of magnitude slower than the value determined for the α -toluenesulfenic acid derived from petivericin ($3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$),⁶¹ kinetic solvent effects and kinetic isotope effects are consistent with the same hydrogen atom transfer mechanism for both sulfenic acids. The difference in rate constants was attributed to the steric bulkiness of the triptycyl moiety relative to benzyl, which should hinder formation of the preferred *syn* TS for the formal hydrogen atom transfer.

It should be pointed out that the schematic representation of the reaction of a sulfenic acid and a peroxy radical in Figure 1.2B is an oversimplification. In fact, the calculated TS structures display characteristics of both the ideal hydrogen atom transfer mechanism shown in Figure 1.2B and the ideal proton-coupled electron transfer mechanism represented schematically in Figure 1.3.^{61,69}

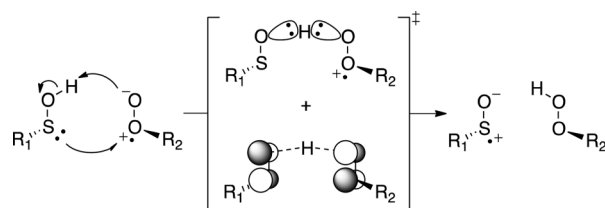


Figure 1.3. Schematic representation of the pairs of interacting orbitals in the proton-coupled electron transfer reaction between a sulfenic acid and a peroxy radical.⁵⁸

In the proton-coupled electron transfer mechanism, the proton is transferred between nonbonding orbitals (lone pairs) in the plane of the local molecular framework, while the electron is transferred between the π^* -HOMO of the sulfenic acid and the π^* -SOMO of the peroxy radical, which are nominally orthogonal to the local molecular framework.

The foregoing studies presented an interesting paradox: the oxidation of a thiol to a sulfenic acid yields a more potent antioxidant.

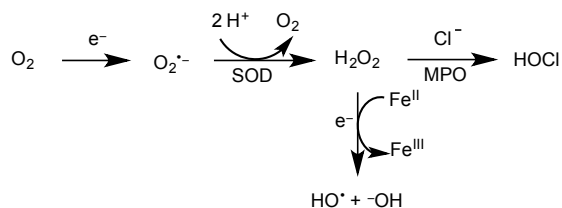
1.5. Thiol oxidation in biology

Thiols are ubiquitous in Nature and are major contributors to protein structure and function.⁷⁰ They maintain the cellular redox balance and participate in redox signaling,⁷¹ usually through their reduction and oxidation chemistry via disulfide bond formation and reduction. The archetype example of this reactivity is elegantly demonstrated in the redox responsive transcription factor OxyR in *E. coli*.⁷² Upon exposure with hydrogen peroxide (H_2O_2), two cysteine residues in OxyR are oxidized to a disulfide, activating the OxyR transcription factor which induces the expression of antioxidant genes.^{72,73} Through tedious derivatization and protein mutation, the mechanism of the OxyR activation was shown to occur through a sulfenic acid intermediate.⁷⁴ The hardship associated with characterizing the mechanism of cysteine oxidation highlights the need to establish molecular models that are representative of protein reactivity *in vivo*.

Among the most prevalent biomolecules containing thiol moieties include cysteine, homocysteine, and glutathione; some present in millimolar concentrations in cells.⁷⁵ Thiols have lower

pK_a values and are stronger nucleophiles than their corresponding alcohols; for example, the pK_a values for cysteine and serine are 8.2 and 9.2, respectively. These are key features when considering the reactivity of thiols in biological systems.

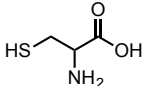
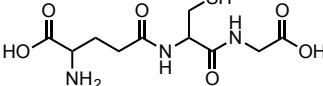
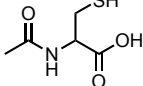
Thiols are oxidized by small molecule oxidants (so-called reactive oxygen species, ROS),⁷⁶ whose progenitor is superoxide ($O_2^{\bullet-}$). Superoxide is formed through triplet oxygen reduction in the electron transport chain of mitochondria.⁷⁷ Hydrogen peroxide (H_2O_2), produced from superoxide by the superoxide dismutase (SOD),⁷⁸ can undergo further reactions to yield other oxidants such as hypochlorous acid through myeloperoxidase (Scheme 1.13).⁷⁹



Scheme 1.13 Production of hydrogen peroxide from superoxide.

The oxidation of biologically relevant thiols to their corresponding disulfide has been studied in detail and it was shown that the rate constant for the oxidation of cysteine and glutathione by H_2O_2 increases with increasing pH.^{80,81} Rate constants for the oxidation of various biologically relevant thiols by ROS are presented in Table 1.6.

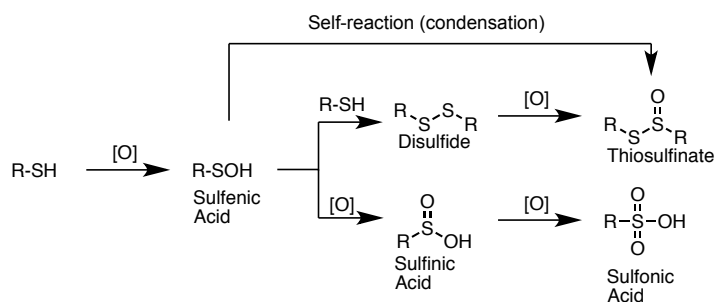
Table 1.6. Bimolecular rate constants ($M^{-1}s^{-1}$) for the oxidation of biologically relevant thiols at 37 °C and pH 7.4.

			
	Cysteine (8.2)	Glutathione (8.8)	N-acetylcysteine (9.5)
Oxidant (pK_a)			
H_2O_2 ⁸¹	2.9	0.87	0.16
HOCl ⁸²	3.6×10^8	1.2×10^8	0.29×10^8
HOONO ⁷⁶	4.5×10^3	1.4×10^3	0.41×10^3

The differences in rate constants between the three thiols shown above is rationalized based on their pK_a values. Cysteine, having the most acidic thiol group (i.e. highest concentration of thiolate at pH 7.4), is the most reactive, followed by glutathione and *N*-acetylcysteine.⁷⁶ Furthermore, both hypochlorous acid (HOCl) and peroxyxynitrite (HOONO) are stronger oxidants towards thiols than H_2O_2 , HOCl reacting at over 5 orders of magnitude faster with thiols than H_2O_2 .

In most studies to date, the kinetics of thiol oxidation were measured by monitoring the consumption of thiol and not the production of the first oxidation product, sulfenic acids, given the instability of the latter. As such, the intermediate sulfenic acid is often trapped by derivatization to detect its formation.^{83–87}

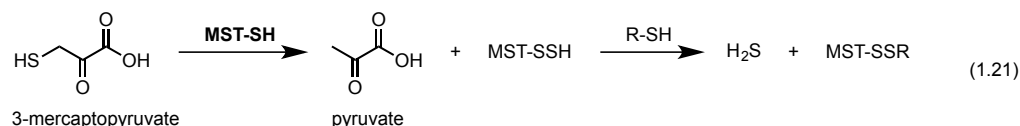
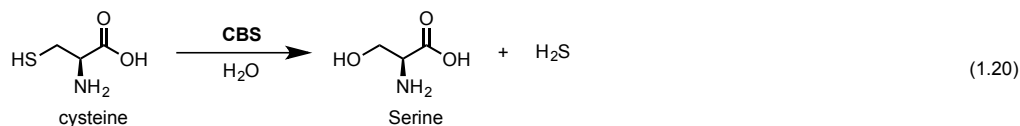
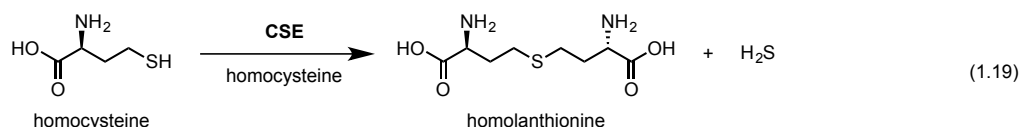
As mentioned earlier, sulfenic acids are labile groups that can rapidly react with another equivalent of thiol to form the corresponding disulfide or they can self-react to form a thiosulfinate (Scheme 1.14).⁸⁸ In the presence of excess thiols and a low concentration of oxidant, sulfenic and sulfonic acids are rarely formed.



Scheme 1.14. Competing pathways in thiol oxidation.

1.6. Hydropersulfides (RSSH) are H_2S storage units *in vivo*

Hydrogen sulfide (H_2S) is a biological signaling molecule that impacts various physiological pathways.^{89,90} Previously known only as a toxic gas, H_2S more recently emerged as an important gasotransmitter formed endogenously by cystathionine β -synthase (CBS),^{91,92} cystathionine γ -lyase (CSE),⁹³ and 3-mercaptopyruvate sulfurtransferase (MST)^{94,95} (Scheme 1.15).

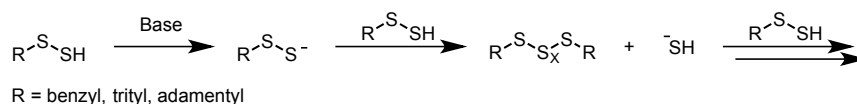


Scheme 1.15. Endogenous enzymatic production of H₂S.

H₂S plays a role in multiple biological functions, including circulation regulation,^{96,97} energy production,⁹⁸ apoptotic gene regulation,⁹⁵ and protection from oxidative stress.^{99–101} The ability to detect H₂S in vivo enables our understanding of the role of H₂S in biology and various methods now exist to image H₂S.^{102–104}

It is proposed that H₂S regulates biological functions by reacting with oxidized protein thiols (sulfenic acids or disulfides) to form hydropersulfides.^{105–107} Protein and small molecule hydropersulfides are detected using chemical probes such as cycloalkynes and iodoacetates.^{108–111} The role of protein hydropersulfides as H₂S storage units prompted the investigation of other small molecules as potential H₂S storage units.^{112–114} Indeed, polysulfides such as alkyl trisulfides and tetrasulfides release H₂S upon reaction with thiols.^{115,116}

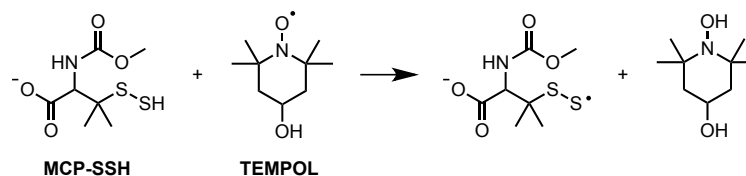
Similar to thiols, hydropersulfides are oxidized by iodine to polysulfides and reduced by triphenylphosphine to the corresponding thiols.¹¹³ They are more easily oxidized and reduced compared to thiols.¹¹⁷ On the other hand, contrary to thiols, hydropersulfides are base sensitive as the persulfide anion reacts with hydropersulfides to form polysulfides, as shown in Scheme 1.16.¹¹³ The base sensitivity of hydropersulfides have precluded accurate pK_a measurements (pK_a ~ 6–7) via classic potentiometric titrations - their pK_a are usually estimated based on reactivity profiles.¹¹⁸



Scheme 1.16. Base-catalyzed decomposition of hydropersulfides.

Hydropersulfides are electron rich and are primed to undergo various redox processes.^{119,120} Fukuto *et al* recently showed that cellular hydropersulfides protect cellular thiols from irreversible modifications by reacting with oxidizing agents and electrophiles faster than thiols.¹¹⁷ The protein sulhydration ($\text{RSH} \rightleftharpoons \text{RSSH}$) is reversible, making this process an ideal protective event for cellular thiols.¹¹⁷

Making use of an *in situ* generated hydropersulfide, MCP-SSH, the same group investigated the redox couple between a hydropersulfide and a perthiyl radical ($\text{RSS}\cdot$) by reacting a hydropersulfide with a nitroxide (Scheme 1.17).¹²¹



Scheme 1.17. Reaction of MCP-SSH and nitroxide (TEMPOL)

These results suggested that hydropersulfides have very weak bonds and that the perthiyl radical is more stable than thiyl radicals. Even if perthiyl radicals are known to recombine at extremely fast rates ($k \sim 10^9 \text{ M}^{-1}\text{s}^{-1}$), the $\text{RSSH}/\text{RSS}\cdot$ equilibrium is significant in a biological context since the localized concentration of perthiyl radical is low.¹²¹ Moreover, the perthiyl radical does not react with oxygen or nitrous oxide, making it an even more attractive moiety in biology.¹²¹

Pleased with our current understanding of the antioxidant activity of thiols, sulfoxides, thiosulfinates, and sulfenic acids, we wondered if other constituents of garlic could also be RTAs. Indeed, trisulfides are major components of garlic extracts and sulfurized olefins, which are used as industrial antioxidants.

1.7 Research Objectives

1.7.1 The Antioxidant Activity of Trisulfides and their Corresponding 1-Oxides

The antioxidant activity of garlic and *Petiveria* derived thiosulfinates is well documented.^{54,55,61} We wondered if the biological activity of garlic and other *Alliums* could be governed by other predominant organosulfur constituents, such as trisulfides and their 1-oxides, which have previously been identified in similar concentrations as thiosulfinates.⁴⁶ Primary trisulfides have been subject to many biological studies, in particular diallyltrisulfide - revealing promising activities similar to the thiosulfinates.⁴⁶

Trisulfides have also been highly utilized as sulfur carriers, key additives in the oil and lubricant industry. They are mainly manufactured in high-pressure sulfurized isobutylene processes and can be used as lubricants to prevent wear by forming iron sulfide films on the metal surfaces. They have also been reported to have good antioxidant and anti-corrosion behavior.^{4,122} Could trisulfides and trisulfide-1-oxides decompose in similar fashion to thiosulfinates yielding potent RTAs?

The objectives of this project were to:

1. Synthesize model trisulfides and their corresponding 1-oxides containing similar structures to previously studied thiosulfinates.
2. Measure the antioxidant activity of the trisulfides and their corresponding 1-oxides in cumene and styrene autoxidations at ambient temperatures (37 °C) and compare their activity to thiosulfinate RTAs previously studied.
3. Perform mechanistic studies (solvent effects, KIEs) concomitantly with computations to elucidate the mechanism through which trisulfide-1-oxides react with peroxy radicals.

1.7.2 The Antioxidant Activity of Polysulfides

Sulfurized olefins (polysulfides) are common additives to various petroleum-derived products, such as engine oils, hydraulic fluids, rubbers and various polymeric materials.¹²² Moreover, phenolic and/or diarylamine radical-trapping antioxidants are often substituted with sulfur-containing alkyl moieties in order to maximize their efficacies. The mechanisms of organosulfur antioxidants are often presented

as ‘complex’, but it is acknowledged that they must first be oxidized to render them effective as antioxidants.¹²² In general, they are described as ‘secondary antioxidants’ since it is believed that they slow the rate of initiation by decomposing hydroperoxides.³⁸ Even though it is believed that all polysulfides are effective antioxidants, we wondered if some polysulfides are better RTAs than others, or are they all equally potent RTAs? Would there be a temperature dependence on the RTA activity? The objectives of this project were to:

1. Synthesize model poly(sulfide) substrates (sulfides to tetrasulfides) and their corresponding 1-oxides to measure their activity as RTAs in 1-hexadecene autoxidation at 100 °C.
2. Perform decomposition studies to put forth a mechanism explaining the observed RTA activity of polysulfides.
3. Perform *n*-hexadecane autoxidations at 160 °C to investigate if the observed antioxidant activity at 100 °C translates to 160 °C.

1.7.3 The Hydrogen Atom Transfer Reactivity of Hydropersulfides

The formation of protein hydropersulfides (RSSH) as H₂S storage units have prompted the investigation of other small molecules as potential H₂S storage units.^{102,112,114} The ability to detect H₂S in vivo is of great importance to further our understanding of the role of H₂S, to that extent, various methods now exist to image H₂S.^{103,104,123}

Hydropersulfides are primed to undergo various redox reactions and they have been implicated in various redox active processes.^{119,120} Fukuto et al recently showed that hydropersulfide protect protein thiols from irreversible modifications by reacting with oxidizing agents and electrophiles faster than thiols. They also point out the reversibility of the protein sulphydration, making this process an ideal protective event for cellular thiols.¹¹⁷ Moreover, the same group investigated the redox couple between a hydropersulfide and a perthiyl radical (RSS’) and have shown

that the stability of the perthiyl radical makes the process more significant than the equivalent thiol/thiyl radical redox process.¹²¹

Although much is known about the H-atom transfer chemistry of thiols, to our knowledge, H-atom transfer from hydropersulfides had not been investigated. We wondered if hydropersulfides could potentially be good H-atom donors in various chemical transformations? How would they compare to thiols?

The objectives of this project were to:

1. Synthesize model hydropersulfides using known chemistry developed by Pluth and co-workers.
2. Investigate the peroxy radical-trapping activity of hydropersulfides in organic and aqueous solutions as well as in lipid bilayers.
3. Investigate the potency of hydropersulfides as hydrogen atom transfer agents to alkyl, alkoxyl, and thiyl radicals, both experimentally and computationally.

1.7.4 On the Reactions of Thiols, Sulfenic Acids, and Sulfinic Acids with Hydrogen Peroxide

The primary oxidation product of thiol oxidation by hydrogen peroxide is believed to be a sulfenic acid (R-SOH), but it is generally not observed since it readily undergoes condensation with another equivalent of thiol to form a disulfide. This reaction, as well as the self-condensation of two sulfenic acids to yield a thiosulfinate, can be slowed by steric hindrance, which we have previously taken advantage of to study the radical reactivity of sulfenic acids using 9-triptycenesulfenic acid.^{61,68,69}

Given the persistence of this sulfenic acid, we wondered if we could use the triptycene backbone to investigate the series of reactions of thiol to sulfenic acid, sulfenic acid to sulfinic acid, and sulfinic acid to sulfonic acid, which has hitherto not been possible because of the lability of the sulfenic acid. We also hypothesized that installing a fluorine atom in the bridgehead position of the triptycene backbone would allow us to use ¹⁹F NMR to investigate the kinetics of thiol, sulfenic acid and sulfinic acid oxidation by hydrogen peroxide in various buffered methanol solutions. The ¹⁹F NMR

methodology could also circumvent the use of expensive deuterated solvents and enables greater flexibility in the mechanistic investigations and answering questions such as: Is the reaction general or specific base catalyzed? Are thiols more or less oxidizable than sulfinic acids? What is the pH dependence on the reactivity?

The objectives of this project were to:

1. Synthesize the model substrates, that is; 9-fluorotriptycenethiol, 9-fluorotriptycenesulfinic acid, 9-fluorotriptycenesulfinic acid, and 9-fluorotriptycenesulfonic acid.
2. Determine the kinetics of the reaction of each substrate with H_2O_2 by monitoring the reaction progress in situ by ^{19}F NMR in buffered methanol of varying pH.
3. Determine the kinetics of the reaction of 9-Fluorotriptycenethiol with various organic hydroperoxides.

1.7.5 The Hydrogen Atom Transfer Reactivity of Sulfinic Acids

Sulfinic acids (RSO_2H), secondary products of thiol oxidation, have been used in sulfonylation of alkenes¹²⁴ and as H-atom donors in alkene functionalizations.¹²⁵ The radical chain reaction taking place in both of these examples involve a key H-atom transfer propagation step from sulfinic acids to either an alkyl or peroxy radical. To date, no rate constants are known in the literature for those H-atom transfer reaction, information that would enable further use of sulfinic acids in organic synthesis.

Given our previous success utilizing a triptycene backbone to enable the study of the redox chemistry of sulfinic acids^{61,68} and selenenic acids,⁶⁹ we wondered if we could make use of the triptycene backbone to investigate the H-atom transfer chemistry of sulfinic acids. How will sulfinic acids compare to thiols and sulfinic acids in regards to their H-atom transfer chemistry?

The objectives of this project were to:

1. Synthesize a model 9-triptycenesulfinic acid using a similar approach to the one previously used to make 9-fluorotriptycenesulfinic acid.

2. Investigate the potency of sulfinic acids as hydrogen atom transfer agents to alkyl, alkoxy and peroxy radicals, both experimentally and computationally.
3. Compare the reactivity of sulfinic acids and sulfenic acids as H-atom donors and investigate the O-H bond dissociation energy of sulfinic acid using EPR spectroscopy.

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CHAPTER 2: Polysulfide-1-Oxides React with Peroxyl Radicals as Quickly As Hindered Phenolic Antioxidants and do so by a Surprising Concerted Homolytic Substitution*

2.1 Preface

Polysulfides are important additives to a wide variety of industrial and consumer products and figure prominently in the chemistry and biology of garlic and related medicinal plants. Although their antioxidant activity in biological contexts has received only recent attention, they have long been ascribed ‘secondary antioxidant’ activity in the chemical industry, where they are believed to react with the hydroperoxide products of autoxidation to slow the auto-initiation of new autoxidative chain reactions. Herein we demonstrate that the initial products of trisulfide oxidation, trisulfide-1-oxides, are surprisingly reactive ‘primary antioxidants’, which slow autoxidation by trapping chain-carrying peroxyl radicals. In fact, they do so with rate constants ($k \sim 1\text{--}2 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ at 37 °C) that are indistinguishable from those of the most common primary antioxidants, i.e. hindered phenols, such as BHT. Experimental and computational studies demonstrate that the reaction occurs by a concerted bimolecular homolytic substitution (S_H^2), liberating a perthiyl radical – which is ca. 16 kcal mol⁻¹ more stable than a peroxyl radical. Interestingly, the (electrophilic) peroxyl radical nominally reacts as a nucleophile – attacking the $\sigma_{\text{S1-S2}}^*$ of the trisulfide-1-oxide – a role hitherto suspected only for its reactions at metal atoms. The analogous reactions of trisulfides are readily reversible and not kinetically competent to inhibit hydrocarbon autoxidation, consistent with the longstanding view that organosulfur compounds must be oxidized to afford significant antioxidant activity. The reactivity of trisulfides and their oxides are contrasted with what is known of their shorter cousins and predictions

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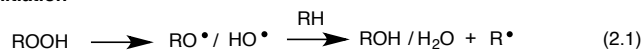
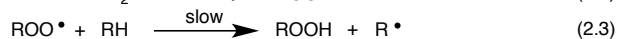
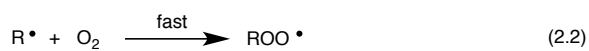
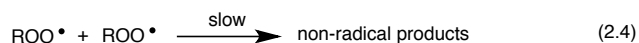
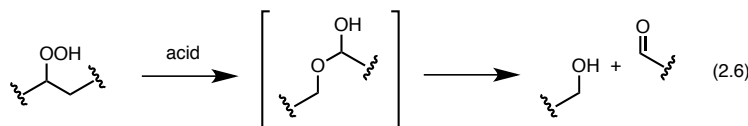
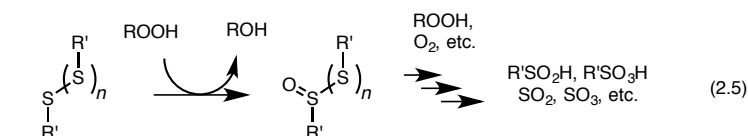
are made and tested with regards to the reactivity of higher polysulfides and their 1-oxides – the insights from which may be exploited in the design of future antioxidants.

2.2 Introduction

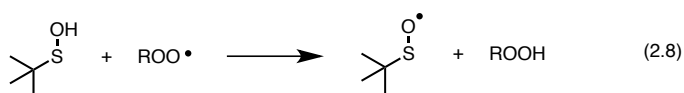
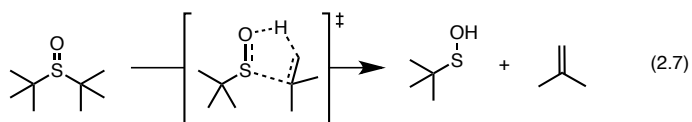
Organosulfur compounds have long been recognized to slow hydrocarbon autoxidation, the deleterious free radical chain reaction depicted in Scheme 2.1.¹ In fact, it was the pioneering work of Denison and Condit² in the 1940s that led to the conclusion that *"the oxidation stability of refined petroleum lubricating oils is the result of small quantities of natural sulfur compounds and not of any inherent stability of the hydrocarbon fraction itself. In the absence of the natural sulfur compounds the hydrocarbon fraction oxidizes rapidly and, in the initial stages of the reaction, autocatalytically."* Hence, although naturally-occurring organosulfur compounds are removed from crude oil in its refinement, organosulfur compounds comprise important additives to finished products.³

The antioxidant mechanisms of organosulfur compounds are often presented as complex. However, it is generally acknowledged that they must first be oxidized to render them effective.⁴ Organosulfur compounds are ascribed ‘secondary antioxidant’ activity since it is believed that they slow the rate of initiation (Eq. 2.1) by decomposing hydroperoxides.⁵ Two mechanisms are particularly important in this context: the direct reduction of hydroperoxides (Eq. 2.5) and the production of Bronsted or Lewis acids, which catalytically decompose hydroperoxides (Eq. 2.6).

Secondary antioxidants can be contrasted with ‘primary antioxidants’, which are radical-trapping antioxidants (RTAs) such as phenols and diarylamines.⁶ These additives inhibit autoxidation directly via reaction with chain-propagating peroxy radicals.^{7,8}

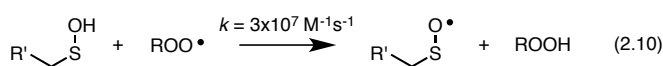
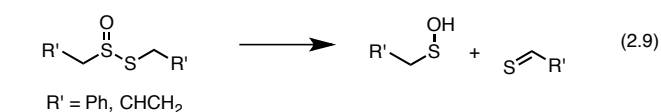
Initiation**Propagation****Termination****Scheme 2.1.** Hydrocarbon autoxidation.**Scheme 2.2.** Key reactions of organosulfur antioxidants.

Organosulfur compounds may also act as primary antioxidants.^{7,9} Koelewijn and Berger¹⁰ showed that sulfides, upon oxidation to sulfoxides, undergo Cope-type elimination to yield a sulfenic acid (Eq. 2.7), which they surmised would undergo fast reactions with peroxy radicals (Eq. 2.8). Since sulfenic acids are transient species that rapidly undergo self-reaction to yield thiosulfonates, they were unable to directly determine the kinetics of reaction (2.8), but estimated a rate constant of ca. $10^7 \text{ M}^{-1} \text{ s}^{-1}$ based on inhibited autoxidations of tetralin with *in situ* formation of *t*-BuSOH from thermolysis of di-*tert*-butyl sulfoxide at 60 °C.¹⁰



Using a persistent sulfenic acid, 9-triptycenesulfenic acid,¹¹ we recently determined the kinetics and thermodynamics of the reaction of a sulfenic acid with peroxy radicals directly. The weak O-H bond in the sulfenic acid (71.9 kcal/mol)¹² gives way to highly favourable reaction thermodynamics with peroxy radicals (ca. 14 kcal/mol), and the presence of the sulfur atom α to the reactive O-H drives a very fast proton-coupled electron transfer reaction with peroxy radicals ($k = 3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$) – despite the steric demand of the triptyceny moiety.^{13,14}

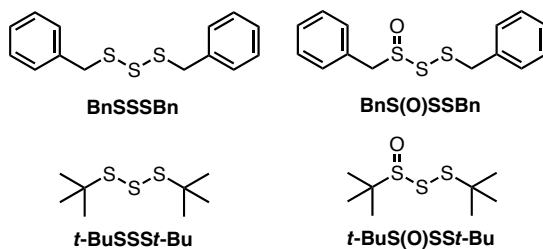
Our studies of the radical chemistry of sulfenic acids were motivated by the widely reported antioxidant activity of allicin, the odorous thiosulfinate found in garlic, and petivericin, the analogous thiosulfinate from the medicinal plant *Petiveria alliaca*. We demonstrated^{15,16} that the antioxidant activity of both thiosulfonates was dependent on the Cope-type elimination of a sulfenic acid, which proceeds readily for both compounds at ambient temperature owing to the activated β C-H bond.¹⁷



Since trisulfides and their oxides are among the most prevalent organosulfur compounds in allium species (e.g., diallyltrisulfide and diallyltrisulfide-1-oxide from garlic)^{18,19} and are predominant among the mixtures of sulfurized materials added to protect petroleum-derived products from autoxidation,^{4,20} we wondered if they would possess analogous ‘primary antioxidant’ chemistry to hindered sulfoxides and activated thiosulfonates. Herein we report an investigation of the RTA activities of some trisulfides and their 1-oxides in an attempt to extend the foregoing knowledge to a more comprehensive view of the primary antioxidant activity of polysulfides and their 1-oxides, in general.²¹

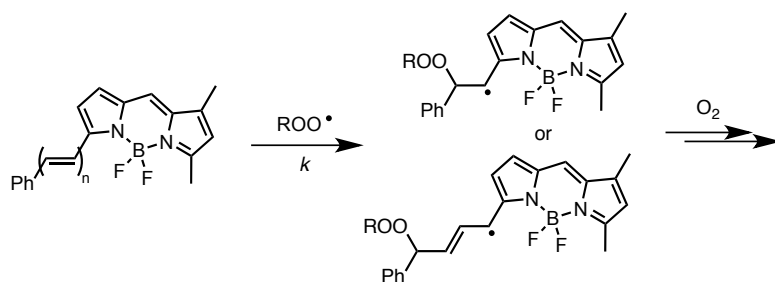
2.3 Results

Given both the volatility and lability of diallyl trisulfide and its 1-oxide, their benzyl analogs, dibenzyl trisulfide (BnSSSBn) and dibenzyltrisulfide-1-oxide (BnS(O)SSBn), were investigated.²² These compounds, synthesized as described by Harpp²³ and Stensaas,²⁴ respectively, are solids at ambient temperature and allow direct comparison with petivericin (BnS(O)SBn) and its corresponding disulfide (BnSSBn). The reactivities of di-*tert*-butyltrisulfide (*t*-BuSSSt-Bu)²³ and its 1-oxide (*t*-BuS(O)SS*t*-Bu)²⁵ – also synthesized as described by Harpp – were also explored. These derivatives lack the activated β C-H in the allyl and benzyl moieties found in the garlic- and petiveria-derived allicin and petivericin, respectively.



2.3.1 Inhibited Autoxidations

The efficacies of the trisulfide-1-oxides as inhibitors of hydrocarbon autoxidation were investigated using styrene and cumene as model substrates. Although autoxidations are conventionally monitored by O₂ consumption, the recently developed method based on the competitive autoxidation of either PBD-BODIPY (with styrene) or STY-BODIPY (with cumene) was instead employed (Scheme 2.3).²⁶ Representative results are shown in Figures 2.1A and B for varying amounts of BnS(O)SSBn and *t*-BuS(O)SS*t*-Bu.



Scheme 2.3. The absorbance of STY-BODIPY and PBD-BODIPY decrease as they are co-oxidized with cumene and styrene, respectively. STY-BODIPY: $n = 1$, $\lambda_{\text{max}} = 591 \text{ nm}$, $k = 141 \text{ M}^{-1}\text{s}^{-1}$; PBD-BODIPY: $n = 2$, $\lambda_{\text{max}} = 571 \text{ nm}$, $k = 2720 \text{ M}^{-1}\text{s}^{-1}$.

The data in Figures 2.1A and B clearly demonstrate the ability of both trisulfide-1-oxides to retard the oxidation – and to a similar extent. From the rates of the retarded reactions, and assuming a stoichiometric factor of $n = 1$ (*vide infra*), the inhibition rate constants for BnS(O)SSBn and *t*-BuS(O)SS*t*-Bu were calculated using Eq. 2.11 to be $k_{\text{inh}} = (1.5 \pm 0.4) \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ and $(1.1 \pm 0.3) \times 10^4 \text{ M}^{-1}\text{s}^{-1}$, respectively. The corresponding disulfides and trisulfides had no effect on the rate of PBD-BODIPY oxidation.

$$-\frac{d[\text{PBD-BODIPY}]}{dt} = \frac{k_p[\text{PBD-BODIPY}]R_i}{nk_{\text{inh}}[\text{antioxidant}]} \quad (2.11)$$

The lack of clear inhibited periods for the trisulfide-1-oxides in the foregoing styrene autoxidations precluded a determination of the stoichiometry for their reaction with peroxy radicals. Therefore, co-oxidations of cumene and STY-BODIPY were also carried out. These less oxidizable substrates generally provide greater resolution between inhibited and uninhibited phases of the autoxidation.²⁶ The results are shown for *t*-BuS(O)SS*t*-Bu and BnS(O)SSBn in Figures 2.1C and 2.1D, respectively.

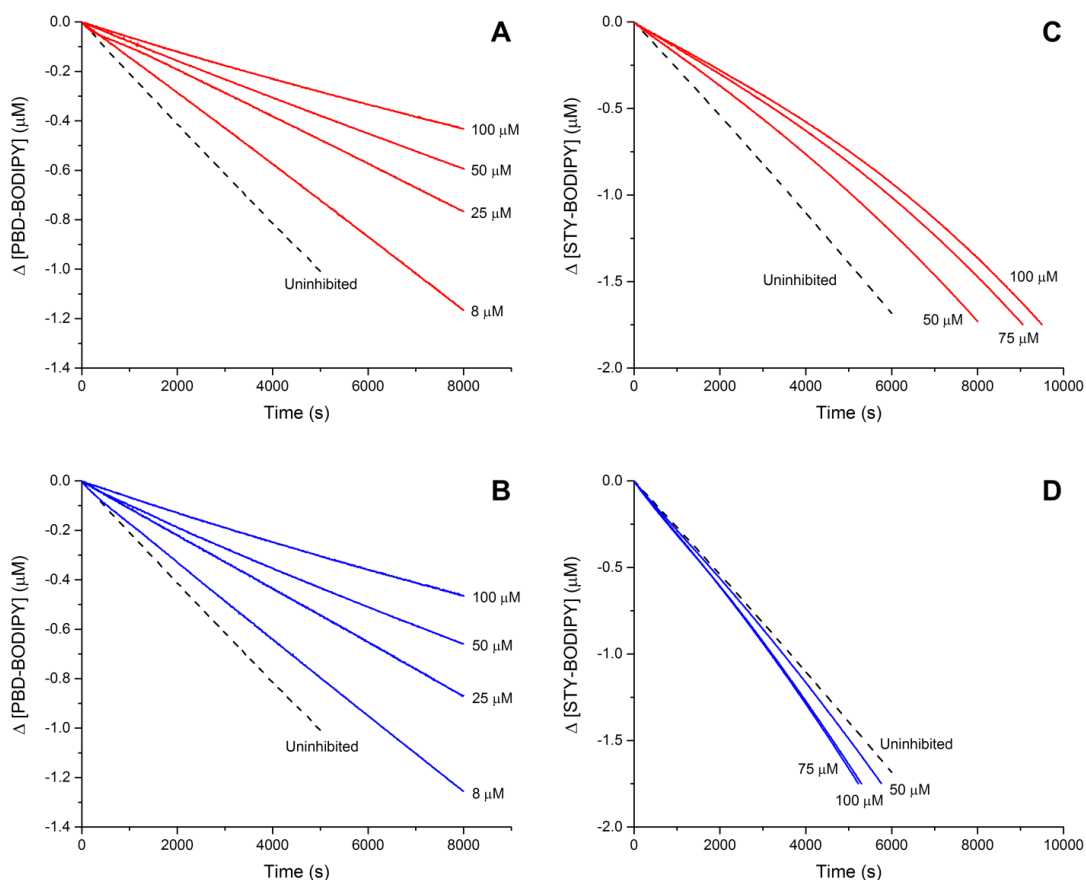


Figure 2.1. Thermally-initiated (AIBN, 6 mM) co-oxidation of styrene (4.35 M) and PBD-BODIPY (10 μM) at 37 $^{\circ}\text{C}$ in chlorobenzene in the presence of either BnS(O)SSBn (A) or *t*-BuS(O)SS*t*-Bu (B). Corresponding data is shown alongside for the AIBN-initiated (40 mM) co-oxidation of cumene (3.6 M) and STY-BODIPY (10 μM) in the presence of BnS(O)SSBn (C) or *t*-BuS(O)SS*t*-Bu (D).

The STY-BODIPY/cumene co-oxidations were less well inhibited by the trisulfide-1-oxides compared to the PBD-BODIPY/styrene co-oxidations; in fact, *t*-BuS(O)SS*t*-Bu was unable to inhibit the autoxidation at all, displaying instead a slight, but reproducible, acceleration of the autoxidation.²⁷ This was particularly surprising given the greater propagation rate constants of PBD-BODIPY (2720 $\text{M}^{-1}\text{s}^{-1}$) and styrene (41 $\text{M}^{-1}\text{s}^{-1}$) compared to STY-BODIPY (141 $\text{M}^{-1}\text{s}^{-1}$) and cumene (0.34 $\text{M}^{-1}\text{s}^{-1}$). Kinetic analysis of the initial rates of the BnS(O)SSBn-inhibited autoxidations (i.e. Eq.

(2.11)) afforded $k_{\text{inh}} = (2.4 \pm 0.6) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$; *ca.* 6-fold smaller than the rate constant derived from the styrene co-autoxidations. Nevertheless, the presence of a distinct inhibited period followed by reaction progress at the same rate as in the uninhibited reaction enabled the determination of the stoichiometric number from the length of the inhibited period, τ (as in Eq. 2.12). The result was $n = 0.9 \pm 0.2$, thereby validating the assumption made in the styrene autoxidations (*vide supra*).

$$\tau = \frac{n[\text{antioxidant}]}{R_i} \quad (2.12)$$

To probe whether the benzylic H-atoms in BnS(O)SSBn play a role in its radical-trapping antioxidant activity, d_4 -BnS(O)SSBn was synthesized in a manner similar to that used to prepare d_4 -BnS(O)SBn in our previous work (see Experimental Section),¹³ and its RTA activity was evaluated in styrene/PBD-BODIPY co-autoxidations. Experiments were also carried out wherein a small volume of a protic/deuteric solvent was added to determine if an exchangeable H-atom/D-atom is involved in the radical-trapping reaction. The results are given in Table 2.1 (see Supporting Information for the inhibited autoxidation traces). For comparison, $k_{\text{H}}/k_{\text{D}}$ values of 16 and 18 were determined from d_4 -BnS(O)SBn-inhibited autoxidations carried out in the presence of D_2O .¹³

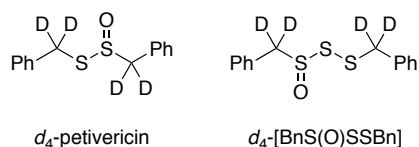


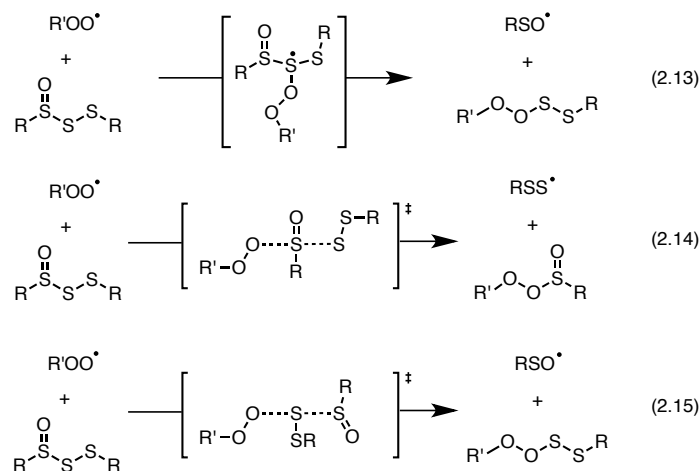
Table 2.1. Inhibition rate constants determined from thermally-initiated co-autoxidation of styrene and PBD-BODIPY in chlorobenzene at 37 °C in the presence of either BnS(O)SSBn or d_4 -BnS(O)SSBn and MeOH or MeOD.

Trisulfide-1-oxide/additive	$k_{\text{inh}} (\text{M}^{-1} \text{s}^{-1})$	$k_{\text{H}}/k_{\text{D}}$
BnS(O)SSBn	$(1.5 \pm 0.4) \times 10^4$	--
BnS(O)SSBn/MeOH (1%)	$(1.5 \pm 0.4) \times 10^4$	--
BnS(O)SSBn/MeOD (1%)	$(1.3 \pm 0.4) \times 10^4$	1.2
d_4 -BnS(O)SSBn/MeOD (1%)	$(1.1 \pm 0.2) \times 10^4$	1.4

Analogous co-autoxidations inhibited by *t*-BuS(O)SS*t*-Bu in the presence of either 1% MeOH or MeOD yielded indistinguishable results from co-autoxidations carried out in their absence.

2.3.2 Computational Studies

Since the similar reactivity of BnS(O)SSBn and *t*-BuS(O)SS*t*-Bu toward styrene-derived peroxy radicals suggested no role for the substituents on the trisulfide-1-oxide, computational studies focused on the direct interaction of peroxy radicals and trisulfide-1-oxide moiety. Three possible mechanisms were considered, which are shown in Scheme 2.4. The first was a step-wise addition/fragmentation mechanism, which liberates a sulfinyl radical along with formation of a peroxydisulfane (Eq. 2.13). The second and third mechanisms are concerted homolytic substitutions occurring on either the sulfinyl sulfur (S1), to liberate a perthiyl radical (Eq. 2.14), or on the adjacent sulfur atom (S2), to liberate a sulfinyl radical (Eq. 2.15, the concerted analog of Eq. 2.13).



Scheme 2.4. Mechanistic possibilities for the reaction of trisulfide-1-oxides with peroxy radicals.

CBS-QB3 calculations²⁸ were carried out on model compounds wherein the substituents on the trisulfide-1-oxide and peroxy radical (R and R', respectively) were methyl groups. Despite extensive effort, a minimum energy structure for the intermediate in the step-wise reaction (Eq. 2.13) could not be located. However, transition states for both concerted homolytic substitutions were

readily located, and are shown in Figure 2A. The structures are 15.1 and 18.5 kcal/mol, respectively, higher in free energy than the separated reactants. Application of transition state theory affords rate constants of 3.8×10^3 and $14 \text{ M}^{-1}\text{s}^{-1}$, respectively – the former in good agreement with the experimental data for BnS(O)SSBn of $(1.5 \pm 0.4) \times 10^4$. Replacement of the methyl substituents on the trisulfide-1-oxide and methylperoxyl radical with *t*-butyl groups increases the barrier by 3.7 kcal/mol - consistent with the fact that *t*-BuS(O)SS*t*-Bu does not inhibit cumene autoxidation.²⁹

Both substitutions are predicted to be thermodynamically favourable: $\Delta G^0 = -9.3$ kcal/mol for reaction at S1 (the sulfinyl sulfur) and $\Delta G^0 = -7.1$ kcal/mol for reaction at S2. Much of the energetic benefit derives from exchange of the peroxy radical for either of the more stabilized perthiyl or sulfinyl radicals – which is clear when one considers the X-H BDEs (calculated by CBS-QB3) in MeSS-H (70.8 kcal/mol) and MeSO-H (68.4 kcal/mol) compared to MeOO-H (86.2 kcal/mol) – as well as the stronger S-O bonds in the products (40.1 and 37.2 kcal/mol in MeOOS(O)Me and MeOOSSMe compared to 30.6 kcal/mol for the S1-S2 bond in MeS(O)SSMe). In the reaction at S1, the sulfinyl S-O bond length (1.480 Å) contracts ever so slightly from the starting material (1.487 Å), whereas in the reaction at S2, the sulfinyl S-O lengthens slightly (1.496 Å) on its way to becoming a free sulfinyl radical (1.511 Å). Consideration of the transition state structure suggests that the lone pair on the S1 sulfur does not participate directly in the reaction. In fact, the electronic structure of the transition state can essentially be viewed as interacting peroxy, sulfinyl and perthiyl radicals (Figure 2.3).

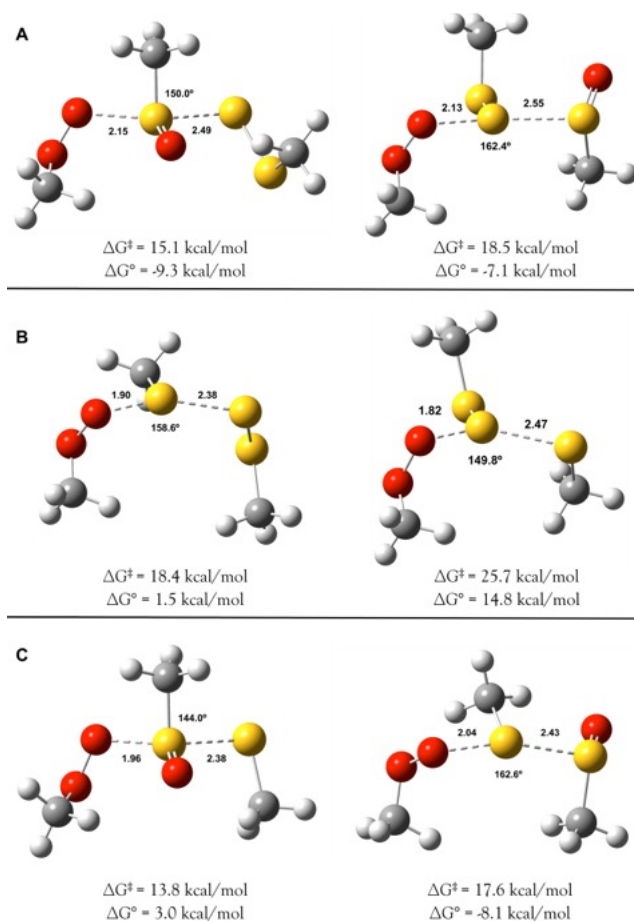


Figure 2.2. Transition state structures for the reaction of MeOO• with MeS(O)SSMe at either the sulfinyl sulfur (S1, left) or S2 (**A**), MeSSSMe at either S1 (left) or S2 (**B**) and MeS(O)SMe at either the sulfinyl sulfur (S1, left) or S2 (**C**). Bond lengths (in Å) are shown for the forming O-S and breaking S-S bonds. The angle between these bonds is also indicated.

This view is reinforced by the results of natural bond orbital (NBO) analyses³⁰ of the corresponding wavefunction, which is dominated by peroxy π^* (SOMO) $\rightarrow \sigma_{S1-S2}^*$ and perthiyl π^* (SOMO) $\rightarrow \sigma_{S1-O}^*$ interactions – worth a total of 73.5 kcal/mol. Interestingly, the NBO analyses also reveal strong interactions between the lone pairs on the sulfinyl oxygen and the σ_{S-S}^* and σ_{S1-O}^* orbitals – worth a total of 60.2 kcal/mol – consistent with the fact that the transition state is stabilized by oxidation of S1.

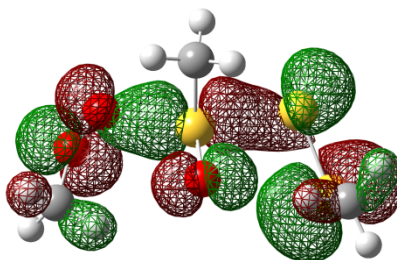


Figure 2.3. The highest occupied molecular orbital for the lowest energy transition state structure for the reaction of $\text{MeOO}\bullet$ and MeS(O)SSMe illustrates the key interactions between the π^* orbitals of the peroxy (left), sulfinyl (centre) and perthiyl (right) moieties.

For comparison, the analogous transition states for the reaction of a trisulfide with a peroxy radical were determined and are shown in Figure 2.2B. These structures are 18.4 and 25.7 kcal/mol, respectively, higher in energy than the separated reactants. The corresponding rate constants determined by transition state theory are 17 and $1.2 \times 10^{-4} \text{ M}^{-1}\text{s}^{-1}$, respectively - consistent with the fact that no inhibition of styrene or cumene autoxidation was observed in the presence of the trisulfides. Both of these reactions are endergonic, with reaction at S1 being far less unfavourable ($\Delta G^0 = +1.5$ kcal/mol), than that at S2 ($\Delta G^0 = +14.8$ kcal/mol). This is largely due to the greater stability of the perthiyl radical leaving group in the former reaction relative to the thiyl radical leaving group in the latter reaction (the CBS-QB3-calculated MeS-H and MeSS-H BDEs are 87.1 and 70.8 kcal/mol, respectively).

Although analogous transition state structures could not be located for the reaction of a disulfide with a peroxy radical, transition state structures were again readily located for the reaction of a peroxy radical with a thiosulfinate, and are shown in Figure 2.2C. These structures are 13.8 and 17.6 kcal/mol, respectively, higher in energy than the separated reactants. Interestingly, the barrier for reaction at S1 is even lower than that determined for the reaction of peroxy radicals with the trisulfide-1-oxide. However, this reaction is endergonic by 3.0 kcal/mol – implying that it is readily reversible – while the reaction of the trisulfide-1-oxide is exergonic by 9.3 kcal/mol. This difference arises largely

since the reaction of the thiosulfinate produces a thiyl radical, which is far less stable than the perthiyl radical (by 16.3 kcal/mol, *vide supra*). Although the reaction of the thiosulfinate at S2 is significantly exergonic ($\Delta G^0 = -8.1$ kcal/mol), it has a higher barrier. The rate constant calculated for substitution at S2 is $61 \text{ M}^{-1}\text{s}^{-1}$, in reasonable agreement with rate constants determined for unactivated thiosulfonates (e.g. *n*-propyl *n*-propanethiosulfinate, for which $k_{\text{inh}} = (244 \pm 31) \text{ M}^{-1}\text{s}^{-1}$).³¹

2.3.3 Peroxyl Radical-Trapping by Hydropersulfides

The foregoing computational results imply that the preferred reaction path between trisulfide-1-oxide and peroxyl radical yields a perthiyl radical. The stoichiometry observed in the inhibited autoxidations ($n = 1$, *vide supra*) implies that the perthiyl radical is unreactive under the autoxidation conditions. To confirm this point, benzyl hydropersulfide (BnSSH) was synthesized³² and its radical-trapping antioxidant activity investigated using the same STY-BODIPY/cumene co-autoxidation as for BnS(O)SSBn (*cf.* Figure 2.1C). The results are shown in Figure 2.4.

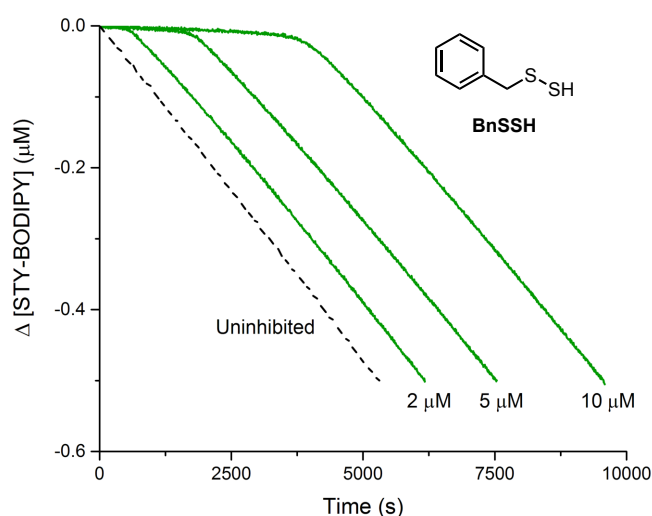


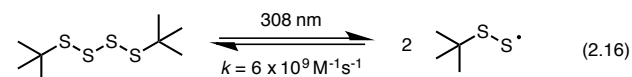
Figure 2.4. Thermally-initiated (AIBN, 6 mM) co-autoxidation of cumene (3.6 M) and STY-BODIPY (10 μM) at 37 $^{\circ}\text{C}$ in chlorobenzene in the presence of various concentrations of BnSSH.

The stoichiometry of the reaction of BnSSH with peroxy radicals was determined to be $n = 1.0 \pm 0.2$ from this data, consistent with a mechanism involving initial H-atom transfer from the hydropersulfide to a chain-carrying peroxy radical and then no involvement of the resultant perthiyl radical in the reaction. It should be noted that hydropersulfides are evidently very potent radical-trapping antioxidants – similar in reactivity to α -tocopherol, Nature’s premier lipid-soluble radical-trapping antioxidant^{33,34} – a result we will follow up on in subsequent work.

2.3.4 Direct Measurements of the Fate of Perthiyl Radicals

The reaction of perthiyl radicals with O₂ has been reported in aqueous solution to occur with $k = 5.1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.³⁵ We initially expected that the resulting RSSOO• may participate in the ensuing radical chemistry in the autoxidations inhibited by the trisulfide-1-oxide (and hydropersulfide). However, the foregoing results imply that RSSOO•, if formed, does not participate. The other possibility is, of course, that it is either not formed under the reaction conditions or that the reaction is readily reversible.

To provide insight on these possibilities, the reactivity of perthiyl radicals towards oxygen was investigated in chlorobenzene by laser flash photolysis. Di-*tert*-butyl tetrasulfide was used as a model compound, since it is known to give a pair of perthiyl radicals upon UV irradiation.³⁶



Photolysis of the tetrasulfide at 308 nm yielded a transient species with a pronounced absorption at 375 nm corresponding to the perthiyl radical (Figure 2.5A). This transient absorption decayed rapidly (Figure 2.5B) with concomitant reformation of the tetrasulfide at 340 nm (Figure 2.5A).

The second order rate constant for the recombination of perthiyl radicals to the tetrasulfide was determined to be $(6.0 \pm 0.5) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ at 25 °C (assuming $\epsilon_{390\text{nm}} = 1600 \text{ M}^{-1} \text{ cm}^{-1}$ based on pulse

radiolysis studies of similar compounds^{35,37,38}). This is *ca.* 4-fold larger than the reported values in water (1.5 and $1.9 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$, respectively). Importantly, as is clear in Figure 2.5B, no difference in the decay kinetics of the perthiyl radical could be detected in the presence or absence of O_2 .

We also carried out a series of computations to probe the plausibility of the reaction of a perthiyl radical with O_2 (Eq. 2.17). It was not possible to find a bound perthiyl- O_2 adduct using the CBS-QB3 approach that we employed above (where geometries are obtained at the B3LYP/CBSB7 level of theory). However, when the calculations were carried out with basis sets that included diffuse functions on the heavy atoms, bound structures were located. The corresponding CBS-QB3(+)³⁹ ΔG° was 12.9 kcal/mol with an associated barrier of $\Delta G^\ddagger = 14.2 \text{ kcal/mol}$ – consistent with the lack of reactivity determined experimentally.

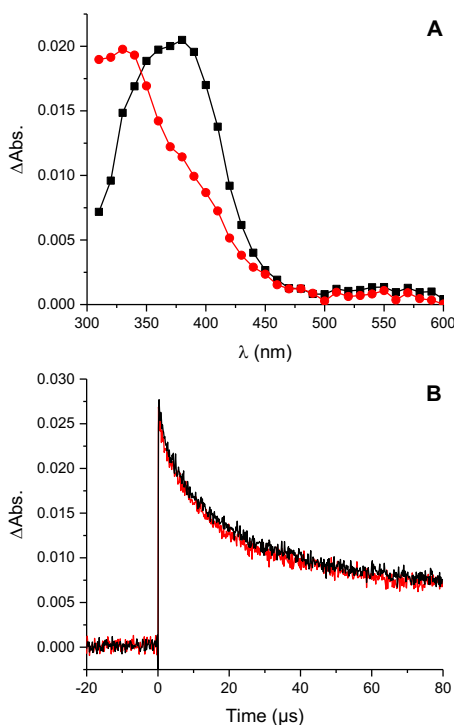
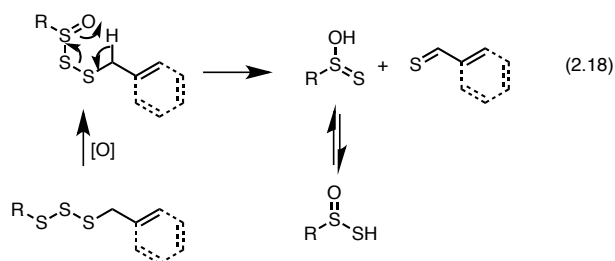


Figure 2.5. Transient absorption spectra obtained either $1 \mu\text{s}$ (■) or $30 \mu\text{s}$ (●) after photolysis of a 0.2 mM solution of di-*tert*-butyl tetrasulfide in chlorobenzene (A) and decay of the absorption at 390 nm in the presence (black) and absence (red) of O_2 (B).



2.4 Discussion

In line with the dogma that organosulfur compounds must be oxidized to afford antioxidant activity, trisulfides do not react at an appreciable rate with peroxy radicals, while their 1-oxides are as reactive as hindered phenols, e.g., $k_{\text{inh}} = 1.5 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ for BnS(O)SSBn and $1.4 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ for 2,6-di-*tert*-butyl-4-methylphenol (BHT).⁴⁰ Given the similar structure and reactivity of BnS(O)SSBn to petivericin, we initially wondered if it could undergo an analogous Cope-type elimination (Eq. 2.18) to afford a good H-atom donor. This would account for both its need to be oxygenated and its relatively high k_{inh} – which is too high for H-atom transfer from a benzylic C-H position ($\sim 1 \text{ M}^{-1}\text{s}^{-1}$).⁴¹



While a transition state for this process was readily located in CBS-QB3 calculations on the corresponding allylic trisulfide-1-oxide (the benzyl groups were exchanged for allyl groups for computational expediency), the structure was a prohibitive 40.9 kcal/mol higher in energy than the starting material. For comparison, the transition state structure for Cope-type elimination of 2-propenesulfenic acid from allicin is calculated to have $\Delta H^\ddagger = 19.5 \text{ kcal/mol}$ (CBS-QB3), in good agreement with experimental observations.^{15,16}

Of course, the fact that *t*-BuS(O)SS*t*-Bu reacts with styrylperoxyl radicals with essentially the same rate constant as BnS(O)SSBn implies that the mechanism involves direct reaction at the trisulfide-1-oxide moiety. We initially surmised that this could take place by an addition/fragmentation mechanism, where the peroxy radical would add to a lone pair on the sulfur atom to form an intermediate sulfur-centered radical that would be captodatively stabilized by the sulfur atom on one

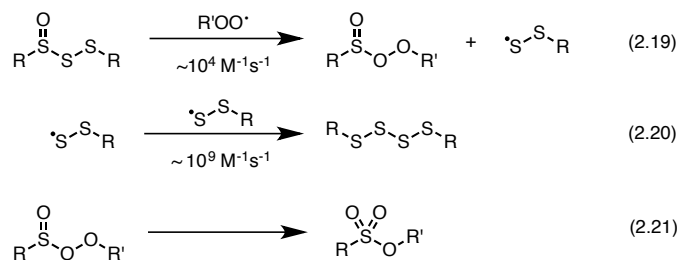
side and the sulfinyl group on the other (Eq. 2.13). Subsequent α -cleavage would yield either of two potential pairs of formal substitution products. However, computational efforts to provide evidence for this intermediate were unsuccessful.

Since computations indicated that the S(O)-SS bonds in trisulfide-1-oxides are weak (i.e. 29.8 kcal/mol in *t*-BuS(O)SS*t*-Bu by CBS-QB3 – see Supporting Information), a concerted substitution was considered next. This seemed unlikely since it requires that the peroxy radical serve nominally as the nucleophile. Nevertheless, transition state structures were readily located for substitution at each of the sulfinyl sulfur atom (S1) and S2. Substitution at S1 was predicted to take place with a lower barrier (15.1 kcal/mol vs. 18.5 kcal/mol for substitution at S2) and the corresponding rate constant obtained from application of transition state theory was in good agreement with our experiments. This mechanism is also consistent with the lack of deuterium kinetic isotope effects on peroxy radical-trapping by either *t*-BuS(O)SS*t*-Bu ($k_H/k_D = 1.0$) or BnS(O)SSBn ($k_H/k_D = 1.4$). This is in sharp contrast with the large KIEs observed for petivericin ($k_H/k_D = 16$ or 18.2, depending on experimental approach) – whose mechanism involves two isotope-sensitive steps: C-H bond cleavage in the Cope-type elimination and O-H bond cleavage in the formal H-atom transfer from the sulfenic acid to the peroxy radical.¹³

The rates of reactions of peroxy radicals with RTAs are generally independent of the structure of the peroxy radical; that is, inhibited autoxidations of styrene or cumene, where the chain reaction is carried by styrylperoxy or cumylperoxy radicals, respectively, usually yield the same inhibition rate constant.⁴⁰ The fact that the trisulfide-1-oxides react at different rates with these peroxy radicals, and that the steric demand of the substituents on the trisulfide-1-oxide have a greater impact on the rate when the peroxy radical is also hindered (cumylperoxy), further support that these reactions take place by a homolytic substitution mechanism at the sulfinyl sulfur atom.

Thus, the RTA activity of the trisulfide-1-oxides in organic solution can be ascribed to the reactions in Scheme 2.5. The substitution products are a perthiyl radical and a peroxysulfinate ester

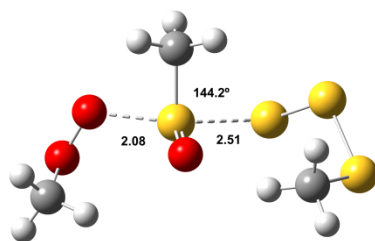
(Eq. 2.19). Interestingly, in contrast with the literature precedent (in aqueous solution), our flash photolysis experiments indicate that the perthiyl radical rapidly combines with another of itself to form a tetrasulfide (Eq. 2.20) *even in the presence of O₂*. The peroxyulfinate ester is the same product that is formed upon reaction of a sulfinyl radical with a peroxy radical, and is believed to rapidly rearrange to a sulfonate ester (Eq. 2.21) – possibly by O-O cleavage and in-cage recombination.^{13,16} This reaction mechanism is consistent with all of the foregoing data, including the fact that a trisulfide-1-oxide traps a single peroxy radical under ambient conditions, unlike activated thiosulfonates and sulfoxides, which trap 2.



Scheme 2.5. Proposed reaction mechanism for the trapping of peroxy radicals by trisulfide-1-oxides.

The reactions of peroxy radicals at metal centers (e.g. magnesium, zinc, aluminum and tin) have been proposed to occur via an S_H^2 mechanism,⁴² but to the best of our knowledge, this mechanism does not seem to be operative on non-metal centers. Substitution of an alkyl substituent for a peroxy radical substituent is commonly invoked in the autoxidation of trialkylboranes (e.g. in the common Et₃B/O₂ radical initiator system),⁴³ but this is likely to be mechanistically distinct owing to the initial formation of a Lewis acid-base complex between a lone-pair on the peroxy radical and the vacant boron *2p* orbital that precedes homolytic boron-carbon bond cleavage.⁴⁴ The substitutions of peroxy radicals at centres that have non-bonded electron pairs, such as in phosphines and sulfides, are believed to proceed via addition-fragmentation sequences in non-polar solvents⁴⁵ and by electron transfer in polar solvents when the peroxy is highly electrophilic (i.e. halogenated methylperoxyls),^{46,47} respectively.

In light of the mechanism in Scheme 2.5, the foregoing investigations were extended to include the next polysulfide-1-oxide. Initial CBS-QB3 calculations predicted $\Delta G^\circ = -8.2$ kcal/mol for $\text{MeOO}\bullet + \text{MeS(O)SSSMe}$ – little different from the -9.3 kcal/mol calculated for $\text{MeOO}\bullet + \text{MeS(O)SSMe}$. This is explained simply on the basis that the leaving groups ($\text{MeSSS}\bullet$ and $\text{MeSS}\bullet$) are similarly stabilized (CBS-QB3 BDEs in MeSS-H and MeSSS-H are 70.8 and 72.7 kcal/mol, respectively). Moreover, the transition state for the S_H^2 reaction of the tetrasulfide-1-oxide was readily located (*cf.* Figure 2.6), and its associated $\Delta G^\ddagger = 14.7$ kcal/mol was essentially the same as that which was calculated for the corresponding trisulfide-1-oxide (15.1 kcal/mol).



$$\Delta G^\ddagger = 14.7 \text{ kcal/mol}$$

$$\Delta G^\circ = -8.2 \text{ kcal/mol}$$

Figure 2.6. Transition state structure for the reaction of $\text{MeOO}\bullet$ with MeS(O)SSSMe . Bond lengths (in Å) are shown for the forming O-S and breaking S-S bonds. The angle between these bonds is also indicated.

The reactivity was subsequently confirmed in styrene autoxidations inhibited by *t*-BuS(O)SSS*t*-Bu, which yielded data that were indistinguishable from those wherein *t*-BuS(O)SS*t*-Bu was used the inhibitor of (*cf.* Figure 2.7), and characterized by a $k_{\text{inh}} = (1.0 \pm 0.3) \times 10^4 \text{ M}^{-1}\text{s}^{-1}$. Although no stoichiometric information could be gleaned from the styrene autoxidations inhibited by *t*-BuS(O)SSS*t*-Bu (as was the case with *t*-BuS(O)SS*t*-Bu, *vide supra*), it is highly likely based on the foregoing that it also traps a single peroxy radical by a mechanism analogous to that shown in Scheme 2.5. Similarly to the trisulfide, the tetrasulfide displayed no such RTA activity.

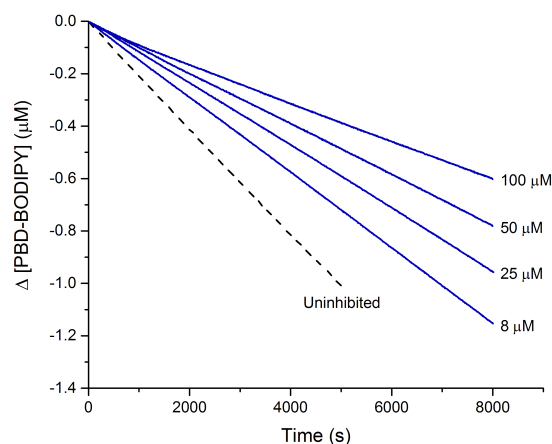


Figure 2.7. Thermally-initiated (AIBN, 6 mM) co-oxidation of styrene (4.35 M) and PBD-BODIPY (10 μ M) at 37 $^{\circ}$ C in chlorobenzene in the presence of various concentrations of *t*-BuS(O)SSSt-Bu.

It seems reasonable to suggest that the reactivity of trisulfide-1-oxides and tetrasulfide-1-oxides extends to higher polysulfide-1-oxides, since the S-S bond strength in higher polysulfides is essentially independent of the number of sulfur atoms.⁴⁸ The generality of this reactivity is in sharp contrast to that of the lower thiosulfinates and sulfoxides, whose activities require appropriate substitution to promote Cope-type elimination of a sulfenic acid.

2.5 Conclusions

The RTA activity of trisulfides, tetrasulfides and their corresponding 1-oxides were determined by inhibited autoxidations. In each case, the polysulfides were inactive, while their 1-oxides were as reactive as hindered phenols – the most common type of primary antioxidant – with $k_{\text{inh}} \sim 1$ to 2×10^4 $\text{M}^{-1}\text{s}^{-1}$. The results of kinetic isotope effects, steric effects and high level computations are consistent with a bimolecular homolytic substitution mechanism wherein the peroxy radical is the nominal nucleophile, attacking the $\sigma_{\text{S1-S}}^*$ of the polysulfide-1-oxide. The stoichiometry of the reaction of the

trisulfide-1-oxides with peroxy radicals was determined to be $n \sim 1$, indicating that the peroxysulfinate ester initially formed rearranges to a sulfonate ester instead of cleaving to yield an alkoxyl radical that would propagate the chain. The other substitution product, the perthiyl radical, simply combines with another of itself to form a tetrasulfide. It is anticipated that higher polysulfide-1-oxides undergo the same rapid bimolecular homolytic substitution reactions with peroxy radicals. This chemistry may contribute to the antioxidant activity of allium-derived polysulfides, such as garlic's diallyltrisulfide, as well as that of sulfurized olefins that are added as secondary antioxidants to petroleum-derived products. Results of further investigations along these lines are reported in Chapter 3.

2.6 Experimental Section

2.6.1 General

All chemicals and solvents were purchased from commercial suppliers and used without further purification unless otherwise indicated. PBD-BODIPY and STY-BODIPY were synthesized following our previously reported procedure.²⁶ Styrene and cumene were extracted three times with NaOH (1 M), washed with water, dried with MgSO₄, filtered, distilled under reduced pressure and percolated through a silica column. They could be kept at -20 °C under nitrogen for up to 5 days. Immediately before use, the distilled material was percolated again through a silica/basic alumina (1:4) column. Chlorobenzene was dried over 3 Å molecular sieves before use. SCl₂ was distilled in the presence of PCl₅ and used within 2 hours. BnSSSBn, *t*-BuSSSt-Bu and *t*-BuSSSS*t*-Bu were prepared according to a previously reported procedure.²³ Similarly, BnS(O)SBn,¹⁶ BnS(O)SSBn,²⁴ *t*-BuS(O)SS*t*-Bu²⁵, BnSSH³² and *t*-BuS(O)SSSt-Bu⁴⁹ were prepared according to previously reported procedures. UV-visible spectra were measured with a spectrophotometer equipped with a thermostatted 6 x 6 multi cell holder.

2.6.2 Synthesis

***d*₄-BnSSSBn.** Potassium carbonate (2.35 g, 17.0 mmol) was added portion-wise to a stirred solution of *d*₂-BnSAc¹³ (2.35 g, 14.0 mmol) in methanol (40.0 mL). After 1 hour, it was extracted with ether. The organic layer was then washed with water and brine, dried with MgSO₄, filtered and the solvent removed under reduced pressure to yield crude *d*₂-BnSH as a pale yellow oil (1.66 g, 94%), which was used without purification. Freshly distilled SCl₂ (411 mg, 4.00 mmol) was added to dry ether (20.0 mL) and cooled to -78 °C under argon. One equivalent of *d*₂-BnSH (504 mg, 4.00 mmol) and triethylamine (404 mg, 4.00 mmol) in ether (10.0 mL) were added dropwise to the cooled SCl₂ solution over a period of 30 minutes. The solution was stirred for another 30 minutes after the addition was completed. A second equivalent of *d*₂-BnSH and triethylamine (404 mg, 4.00 mmol) in ether (10.0 mL) were then added dropwise to the cooled solution over a period of 30 minutes. The solution was stirred for another 30 minutes after the addition was completed. After completion of the reaction (as judged by TLC analysis), the reaction mixture was diluted with ether, washed with water, saturated aqueous NaHCO₃ and water until the pH of the organic phase was *ca.* 7. The organic layer was dried with MgSO₄, filtered and was removed under reduced pressure. The crude dark orange oil was recrystallized from ethanol to afford the final product as white crystals (767 mg, 68%). ¹H NMR (400 MHz; *d*₆-acetone): δ 7.38-7.28 (m, 10H). ¹³C NMR (100 MHz; acetone-*d*₆): δ 137.67, 130.31, 129.41, 128.35. HRMS EI: *m/z* calc. for C₁₄H₁₀D₄S₃ 282.05087, Found: 282.05220.

***d*₄-BnS(O)SSBn.** A solution of m-CPBA (155 mg, 0.90 mmol) in CH₂Cl₂ (2.00 mL) was added dropwise to a solution of *d*₄-BnSSSBn (282 mg, 1.00 mmol) in CH₂Cl₂ (1.50 mL) at 0 °C. The solution was stirred at 0 °C for 20 minutes after which all the trisulfide was consumed (as judged by TLC). The reaction mixture was diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃, water and brine. The organic layer was dried over MgSO₄ and removed under reduced pressure. The crude white solid was recrystallized from hexanes and ether to afford the final product as white crystals (229 mg, 77%) ¹H NMR (400 MHz; CDCl₃): δ 7.38-7.27 (m, 10H). ¹³C NMR (100 MHz; CDCl₃): 136.60,

130.45, 129.96, 129.23, 128.94, 128.84, 127.90. HRMS ESI $[M + Na]^+$: m/z calc. for $C_{14}H_{10}D_4OS_3Na$ 321.03555, Found: 321.03790.

2.6.3 Inhibited co-autoxidations

The inhibited autoxidations were carried out following our recently published procedure.²⁶ To a 3.5 mL quartz cuvette was added styrene or cumene (1.25 mL) along with PhCl, such that the final reaction volume is 2.50 mL. The cuvette was then pre-heated in a thermostatted sample holder of a UV-vis spectrophotometer and allowed to equilibrate to 37 °C for approximately 15 minutes. A small volume (12.5 μ L) of a 2.00 mM solution of the BODIPY probe in 1,2,4-trichlorobenzene was added, followed by the appropriate amount of 0.300 M solution of AIBN in PhCl to achieve the required rate of initiation (typically 50 μ L, where $R_i = 2.2 \times 10^{-9} \text{ M s}^{-1}$). The solution was thoroughly mixed. The absorbance at either 591 nm (PBD-BODIPY) or 571 nm (STY-BODIPY) was monitored for 30–45 min to ensure that the reaction was proceeding at a constant rate, after which 10.0 μ L of a solution of the test antioxidant was added. The solution was thoroughly mixed and the absorbance readings resumed. The resulting data was processed as previously reported.²⁶ The rate of initiation ($R_i = 1.1 \times 10^{-8} \text{ M s}^{-1}$) and $2ek_d = 2.8 \times 10^{-7} \text{ M}^{-1}\text{s}^{-1}$ for this system, necessary to derive stoichiometric data, was determined using PMC as a standard, which has an established stoichiometry of 2.⁴⁰

2.6.4 Laser Flash Photolysis

Nanosecond transient absorption experiments were performed on an LFP-112 spectrometer (Luzchem, Canada). Excitation was performed using an EX10 (GAM Laser, USA) XeCl Excimer laser (308 nm, *ca.* 10 mJ/pulse, *ca.* 12 ns pulse width). The transient absorption spectra were recorded in a quartz cuvette (1 cm $\times$ 1 cm) equipped with a septum and samples were bubbled with nitrogen or oxygen for 10 minutes before measurement.

2.6.5 Calculations

Calculations were carried out using CBS-QB3²⁸ complete basis set method as it is implemented in the Gaussian 09⁵⁰ suite of programs. CBS-QB3(+) calculations³⁹ were performed for the perthiyl-O₂ adduct, wherein the geometry of the adduct was optimized at the B3LYP/6-311+G(2d,d,p) level of theory and the resulting frequencies read into the CBS-QB3 calculation of Gaussian 09 without further modifications. Due to the large size of the structure, calculations for the transition states of the reactions of trisulfide-1-oxide and peroxy radicals with *t*-butyl substituents were carried out with only the first two steps of the CBS-QB3 calculation (B3LYP/CBSB7).

Optimized structures and energies (Gaussian 09) of the computationally calculated structures are provided in the Supporting Information section of the publication in Chemical Science (Chauvin, J.-P. R.; Haidasz, E. A.; Griesser, M.; Pratt, D. A. *Chem. Sci.* **2016**, 7, 6347–6356.)

2.7 Supporting Information

2.7.1 Deuterium Kinetic Isotope Effects

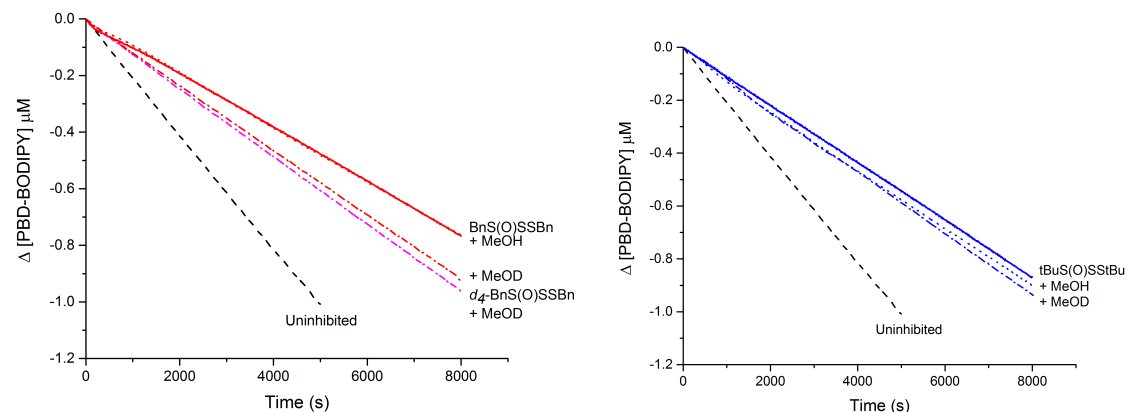


Figure 2.8. Thermally initiated (AIBN, 6 mM) co-oxidations of styrene (4.35 M) and PBD-BODIPY (10 μM) at 37 $^{\circ}\text{C}$ in chlorobenzene inhibited by either (d_4 -)BnS(O)SSBn (left) or *t*-BuS(O)SSi-Bu (right) in the presence of 1% (v/v) MeOH or MeOD.

2.7.2 Laser Flash Photolysis of *t*-BuSSSS*t*-Bu

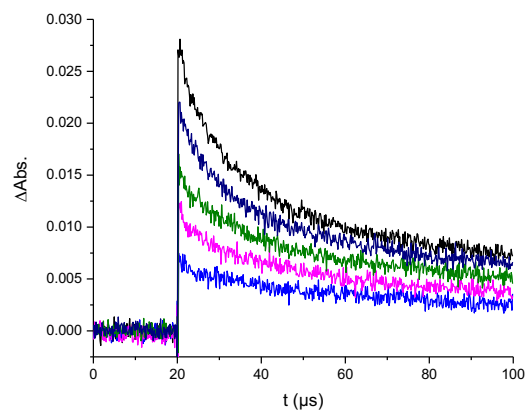


Figure 2.9. Transient absorption decays at 390 nm following laser flash photolysis at 308 nm of a 0.2 mM solution of di-*tert*-butyltetrasulfide in chlorobenzene at different laser energies (6-12 mJ).

2.7.3 Dependence of k_{inh} on the Rate of Initiation

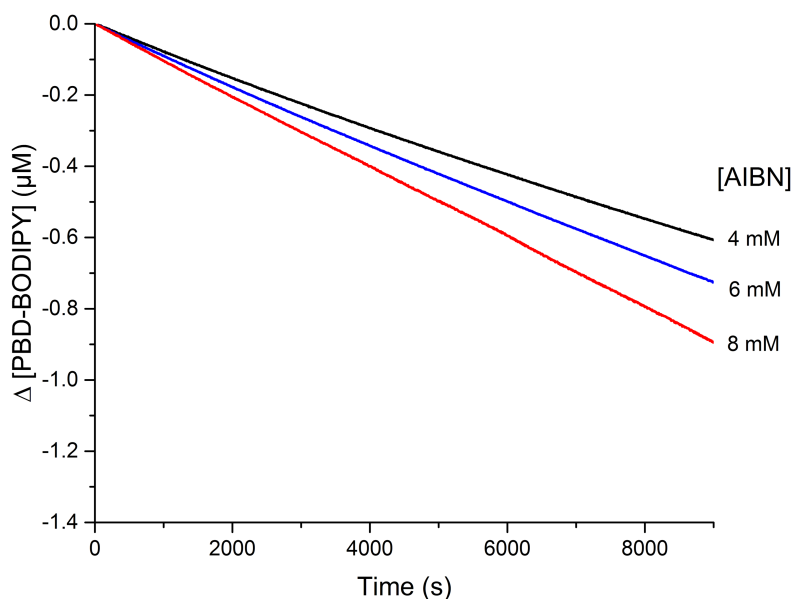


Figure 2.10. Thermally initiated (AIBN, 4, 6 or 8 mM) co-oxidations of styrene (4.35 M) and PBD-BODIPY (10 μ M) at 37 $^{\circ}$ C in chlorobenzene inhibited by *t*-BuS(O)SS*t*-Bu (50 μ M). The k_{inh} values obtained from these data are $1.4 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$, $1.3 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ and $1.6 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$, for the AIBN concentrations of 4 mM, 6 mM and 8 mM, respectively.

2.7.4. Background Reaction of STY-BODIPY and PBD-BODIPY with Polysulfides

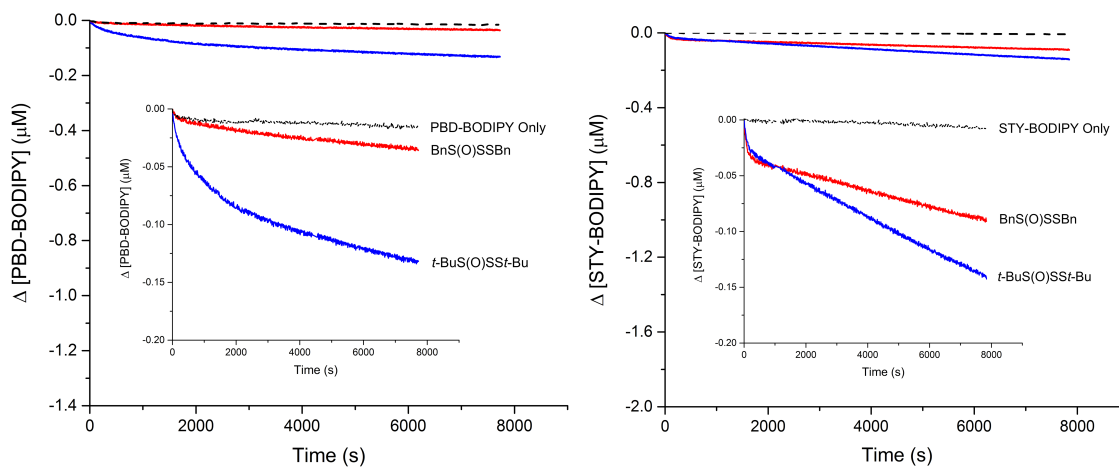


Figure 2.11. Decay of PBD-BODIPY (10 μ M, left) and STY-BODIPY (10 μ M, right) at 37 $^{\circ}$ C in the presence of various polysulfides (50 μ M) in the absence of initiator.

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CHAPTER 3: The Antioxidant Activity of Polysulfides: It's Radical!*

3.1 Preface

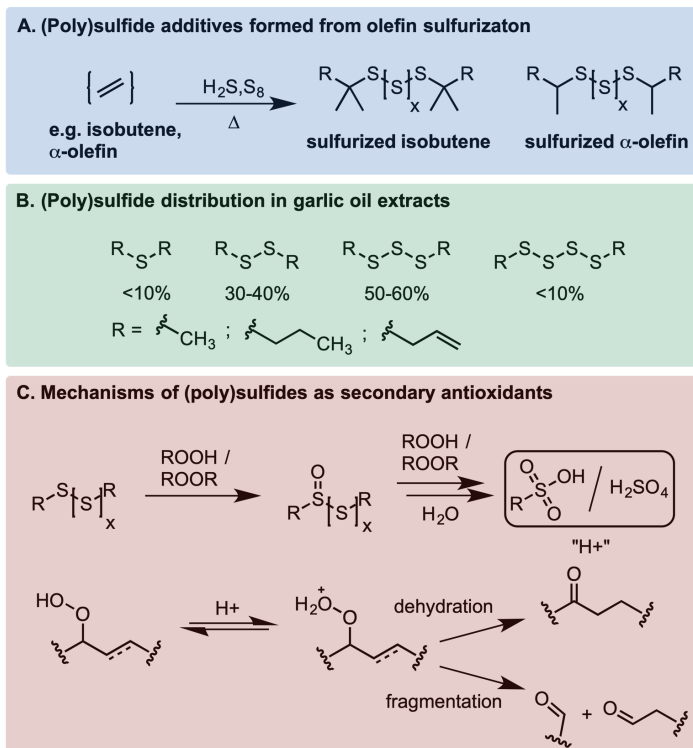
Olefin sulfurization, wherein alkenes and sulfur are heated together at high temperatures, produces branched polysulfides. Due to their anti-wear properties, they are indispensable additives to lubricants, but are also added to other petroleum-derived products as oxidation inhibitors. Polysulfides also figure prominently in the chemistry and biology of garlic and other plants of the *Allium* species. We previously reported that trisulfides, upon oxidation to their corresponding 1-oxides, are surprisingly effective radical-trapping antioxidants (RTAs) at ambient temperatures. Herein, we show that the homolytic substitution mechanism responsible also operates for tetrasulfides, but not trisulfides, disulfides or sulfides. Moreover, we show that this reactivity persists at elevated temperature (160 °C), enabling tetrasulfides to not only eclipse their 1-oxides as RTAs, but also hindered phenols and alkylated diphenylamines – the most common industrial antioxidant additives. The reactivity is unique to higher polysulfides ($n \geq 4$), since homolytic substitution upon them at S2 yields stabilized perthiyl radicals. The persistence of perthiyl radicals also underlies the greater reactivity of polysulfides at elevated temperatures relative to their 1-oxides, since homolytic S–S bond cleavage is reversible in the former, but not in the latter. These results suggest that olefin sulfurization processes optimized for tetrasulfide production will afford materials that impart significantly better oxidation stability to hydrocarbon-based products to which polysulfides are added. Moreover, it suggests that RTA activity may contribute to the biological activity of plant-derived polysulfides.

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3.2 Introduction

It was well recognized before the mid-20th century that the oxidative stability of normally refined petroleum used for the production of lubricants and other products was largely the result of the small quantities of organosulfur compounds naturally present and not the inherent stability of the hydrocarbon fraction itself.^{1,2} However, great efforts were made to remove the organosulfur compounds during the refining process due to their propensity to form corrosion-inducing acids. Over time, synthetic organosulfur compounds were introduced into lubricants (and some other petroleum-derived products) because of their excellent anti-wear properties, particularly at extreme pressures,³⁻⁵ and those compounds with the best balance of maximum anti-wear properties and minimum corrosive effects were identified, developed, and incorporated into commercial products.

Sulfurized olefins (polysulfides), obtained by the treatment of alkenes with elemental sulfur at elevated temperatures (Scheme 3.1A), are among the most common organosulfur additives to petroleum-derived products.^{6,7} Polysulfides also figure prominently in the chemistry and biology of *Allium* species, which include garlic and petiveria (Scheme 3.1B).^{8,9} Their medicinal properties are well recognized, but the mechanism(s) responsible – often linked to their ability to inhibit oxidative stress – are poorly understood.^{10,11} In an industrial context, polysulfides are described as ‘secondary antioxidants’ since they are known to react with hydroperoxides to produce alcohols, inhibiting the auto-initiation of autooxidation chain reactions that degrade hydrocarbons (Scheme 3.1C).^{2,12,13} Moreover, the oxidation of polysulfides eventually leads to the formation of sulfur oxyacids, which catalyze the decomposition of hydroperoxides by either dehydration or Hock fragmentation to carbonyl compounds (Scheme 3.1C).^{14,15} This is in contrast with ‘primary’ antioxidants, such as hindered phenols (e.g. BHT) and alkylated diphenylamines, which react with chain-carrying peroxy radicals to interrupt chain propagation (leading to their classification as radical-trapping antioxidants – RTAs).^{4,5}

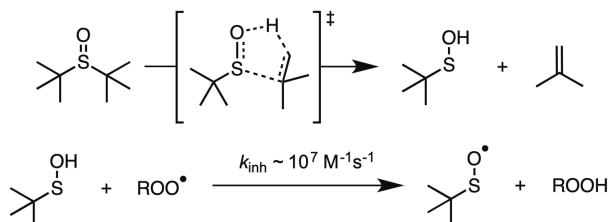


Scheme 3.1.

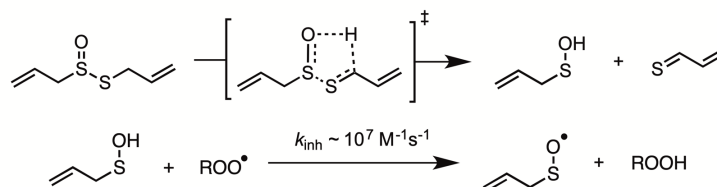
In 1974, Koelewijn and Berger¹⁶ provided evidence that organosulfur compounds can act as RTAs. They showed that di-*tert*-butylsulfide, upon oxidation to the corresponding sulfoxide, is a good RTA. They proposed that the sulfoxide undergoes a Cope-type elimination to yield a sulfenic acid (Scheme 3.2A), which they surmised would undergo fast reactions with peroxy radicals. Since sulfenic acids are transient species that rapidly undergo self-condensation to yield thiosulfinates, they were unable to directly determine the kinetics of the reaction, but estimated a rate constant of $\sim 10^7 \text{ M}^{-1} \text{ s}^{-1}$ based on the rates of inhibited autoxidations of tetralin and sulfoxide thermolysis (to produce *t*-BuSOH) at 60 °C. Several years later, we showed that this sequence of reactions is also responsible for the RTA activity of allicin and petivericin, the odorous thiosulfinates derived from garlic and petiveria, respectively (Scheme 3.2B).¹⁷⁻¹⁹ Unactivated thiosulfinates were unreactive as RTAs under the same conditions (37 °C).

Mechanisms of organosulfur compounds as primary antioxidants (RTAs)

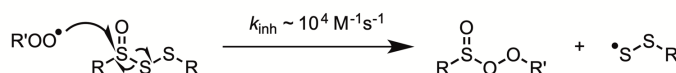
A. Hindered sulfoxides



B. Activated thiosulfinates



C. Trisulfide-1-oxides



Scheme 3.2.

We recently reported that trisulfide-1-oxides react with peroxy radicals with $k_{\text{inh}} = 1\text{--}2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ at 37 °C (Scheme 3.2C).²⁰ As such, they are similarly reactive to the most common industrial RTA (hindered phenols) and suggests that the antioxidant activity of sulfurized olefins may not stem solely from secondary antioxidant reactions, but also from their reactivity as RTAs. Experimental and computational investigations suggested that the reaction proceeds via a concerted bimolecular homolytic substitution by the peroxy radical at the oxidized sulfur center, liberating a highly-stabilized perthiyl radical. The corresponding trisulfides were unreactive under the same conditions. We have since wondered if higher polysulfides would be amenable to direct substitution by peroxy radicals. The rationale is straightforward; on going from the trisulfide to tetrasulfide (and higher), the S-S bond strength weakens considerably (53.4 to 36.3 kcal/mol, respectively),²¹ such that it approaches the RS(O)-SSR bond strength (29.8 kcal/mol).²⁰ Moreover, we wondered how this reactivity would translate from the biologically-relevant temperatures at which we have studied the reactions of the activated thiosulfinates and trisulfide-1-oxides to more industrially-relevant (elevated) temperatures. Would the polysulfides and/or their 1-oxides be too labile to be effective in this capacity? Herein we

address these questions as part of a comprehensive study of the RTA activity of polysulfides ($n = 1-4$) and their corresponding 1-oxides at 37, 100, and 160 °C.

3.3 Results

tert-Butylated (poly)sulfides were chosen as model substrates because of their structural similarity to the common sulfurized olefin, sulfurized di(isobutylene) (see Chart 1). These compounds were either obtained from commercial sources (**3.1** and **3.2**) or prepared in one step from *tert*-butylthiol and SCl_2 (**3.3**) or S_2Cl_2 (**3.4**). The corresponding 1-oxides **3.5-3.8** were obtained by treating the parent (poly)sulfide with one equivalent of *m*-CPBA. Details are available in the Supporting Information.

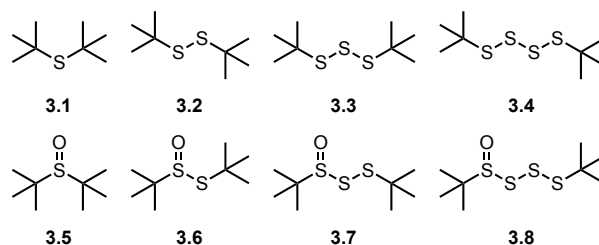


Chart 3.1.

3.3.1 Inhibited autoxidation of 1-hexadecene

The reactivity of the *tert*-butyl polysulfides (**3.1-3.4**) and their corresponding 1-oxides (**3.5-3.8**) as inhibitors of hydrocarbon autoxidation was first evaluated in 1-hexadecene at 100 °C using the PBD-BODIPY co-autoxidation approach.^{22,23} This method, which is illustrated in Figures 3.1A and 3.1B, utilizes the highly-absorbing and highly-autoxidizable PBD-BODIPY to enable monitoring of the autoxidation by conventional spectrophotometry. The reactivity of the polysulfides and their 1-oxides to peroxy radicals can be derived from their ability to suppress the initial rate of PBD-BODIPY consumption using Eq. (3.1) and the stoichiometry of the reaction determined from the length of the inhibited period of the autoxidation using Eq. (3.2). Representative data for the polysulfides and their corresponding 1-oxides are given in Figures 3.1C and 3.1D, respectively. Corresponding data obtained at 37 °C are shown in Figures 3.1E and 3.1F, respectively.

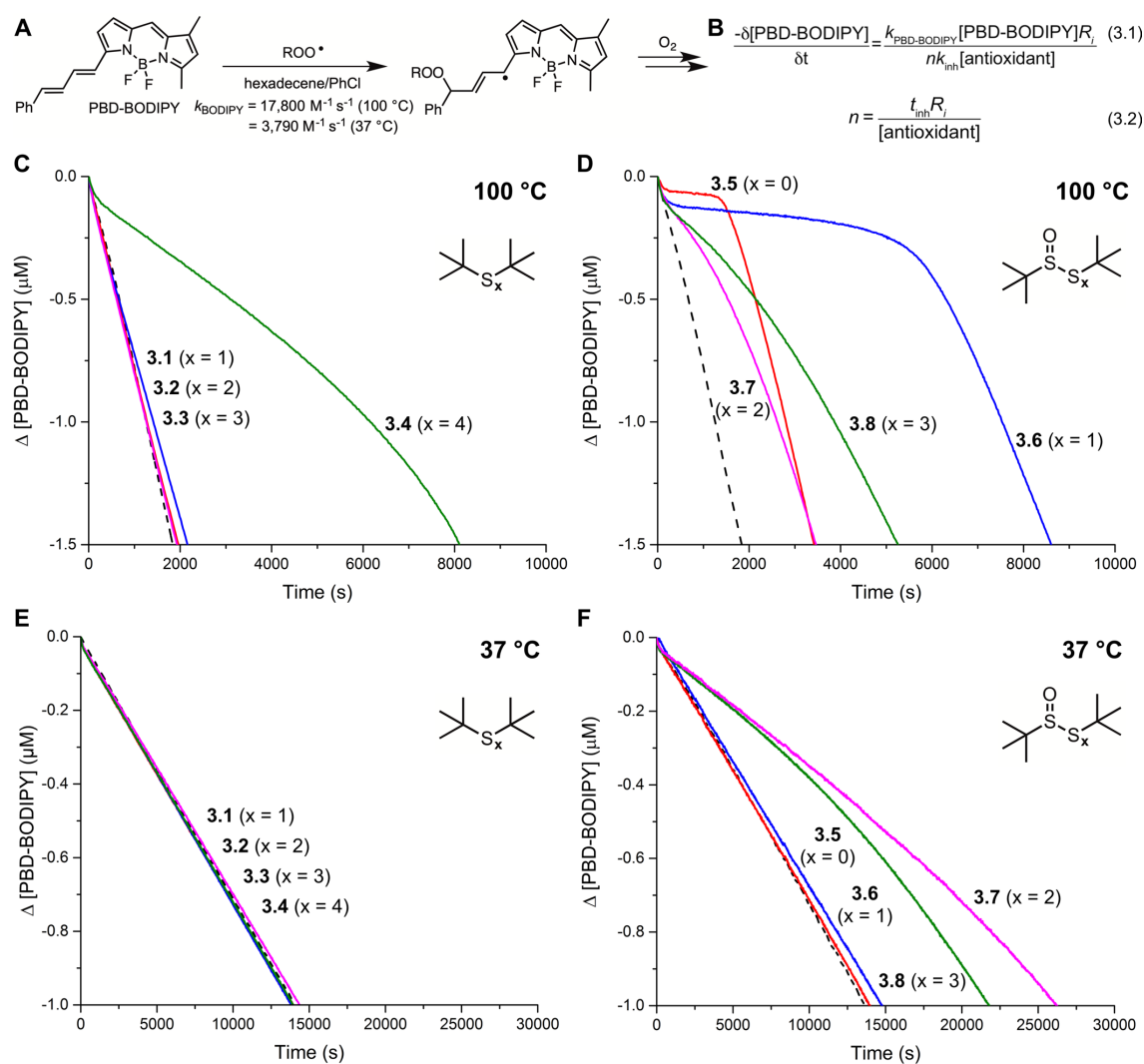


Figure 3.1. PBD-BODIPY is the signal carrier in 1-hexadecene autoxidations (A), enabling determination of rate constants (k_{inh}) and stoichiometries (n) for reactions of inhibitors with chain-carrying peroxy radicals (B). Co-autoxidations of 1-hexadecene (2.8 M) and PBD-BODIPY (10 μM) initiated with dicumylperoxide (1 mM) in chlorobenzene at 100 $^{\circ}\text{C}$ (dashed black trace) and inhibited by 50 μM of organosulfur compounds **3.1-3.4** (C) and **3.5-3.8** (D). Reaction progress was monitored by absorbance at 587 nm ($\epsilon = 119\,166\text{ M}^{-1}\text{ cm}^{-1}$). Co-autoxidations of 1-hexadecene (2.8 M) and PBD-BODIPY (10 μM) initiated with AIBN (6 mM) in chlorobenzene at 37 $^{\circ}\text{C}$ (dashed black trace) and inhibited by 50 μM of organosulfur compounds **3.1-3.4** (E) and **3.5-3.8** (F). Reaction progress was monitored by absorbance at 588 nm ($\epsilon = 148\,700\text{ M}^{-1}\text{ cm}^{-1}$).

Of the polysulfides, only the tetrasulfide (**3.4**) inhibited PBD-BODIPY oxidation, with the initial rate giving rise to $k_{\text{inh}} = (2.3 \pm 0.4) \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ at 100 °C. The stoichiometry of peroxy radical trapping was determined to be $n = 1.4 \pm 0.2$, indicating that each molecule of tetrasulfide halts between one and two chain reactions. The sulfide (**3.1**), disulfide (**3.2**), and trisulfide (**3.3**) were unable to suppress the rate of autoxidation. In contrast, each of the polysulfide-1-oxides were inhibitors, albeit with differing activity. The sulfoxide (**3.5**) and thiosulfinate (**3.6**) were the most reactive compounds, with $k_{\text{inh}} = (1.4 \pm 0.6) \times 10^6$ and $(2.8 \pm 0.6) \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, respectively, but they had significantly different stoichiometries of $n = 0.4 \pm 0.1$ and 1.0 ± 0.1 , respectively. The trisulfide-1-oxide (**3.7**) and tetrasulfide-1-oxide (**3.8**) were significantly slower to react with peroxy radicals, yielding $k_{\text{inh}} = (1.3 \pm 0.4) \times 10^5$ and $(1.6 \pm 0.5) \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, while their stoichiometries were similar to that of the sulfoxide, with $n = 0.4 \pm 0.1$ and 0.5 ± 0.1 respectively. None of the polysulfides were able to inhibit the autoxidations carried out at 37 °C, whereas the trisulfide-1-oxide and tetrasulfide-1-oxide were effective, yielding $k_{\text{inh}} = (5.6 \pm 0.9) \times 10^4$ and $(3.1 \pm 0.8) \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ with $n = 0.7 \pm 0.1$ and 0.6 ± 0.1 , respectively – fully consistent with previous observations.²⁰ For comparison, under the same conditions, BHT and an alkylated diphenylamine have $k_{\text{inh}} = 3.0 \times 10^4$ and $1.7 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ at 37 °C and 2.0×10^5 and $9.9 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ at 100 °C, respectively (see Supporting Information for the data).

3.3.2 Mechanism of polysulfide reactivity

Since the tetrasulfide lacks labile H-atoms and there is no obvious reaction by which it could form a good H-atom donor *in situ*, there are limited mechanisms that may account for their good RTA activity. Each possibility must be consistent with the observation that the tetrasulfide is a good RTA under conditions where the trisulfide is not. Three possibilities were identified: 1) the tetrasulfide reacts with the dicumyl peroxide initiator (as a secondary antioxidant), and therefore only appears to be an RTA, 2) the tetrasulfide undergoes homolysis to yield two perthiyl radicals, which can combine with chain-carrying peroxy radicals to yield stable products, and 3) the tetrasulfide undergoes a homolytic

substitution reaction with a peroxy radical similarly to the reaction of trisulfide-1-oxides and tetrasulfide-1-oxides at lower temperatures (i.e. Scheme 3.2C).²⁰

It has been reported that the rate of reaction of polysulfides with peroxides is proportional to the number of sulfur atoms in the polysulfide.²⁴ On this basis, it is expected that the tetrasulfide would react with either the initiating peroxide – or product hydroperoxides – faster than the trisulfide. To probe the intervention of any secondary antioxidant behaviour by the polysulfides under the reaction conditions, we heated compounds **3.3** and **3.4** (1 equiv.) with a model hydroperoxide (tetralin hydroperoxide) (5 equiv.) at 100 °C (see Supporting Information). No significant change was observed in the rate of peroxide decomposition over three hours in each case (as determined by HPLC; data not shown), excluding a role for peroxide decomposition in the antioxidant activity of the tetrasulfide under these conditions.

As mentioned in the Introduction, the central S-S bond in a tetrasulfide is 17 kcal/mol weaker than the S-S bond in a trisulfide due to the greater stability of perthiyl radicals over thiyl radicals. To establish whether S-S homolysis is efficient under the conditions of the autoxidation, an equimolar solution of di-*iso*-propyltetrasulfide (**3.9**) and di-*tert*-butyltetrasulfide (**3.8**) was heated at 100 °C under air and monitored by GC. After *ca.* 2 hours, roughly equimolar amounts of di-*tert*-butyltetrasulfide, di-*iso*-propyltetrasulfide and *tert*-butyl-*iso*-propyltetrasulfide were observed, supporting the equilibrium in Figure 3.2A. It is important to note that the reaction progress was essentially identical in the presence/absence of air, consistent with our previous observations that perthiyl radicals do not react with O₂.^{20,23} (When analogous experiments were carried out with the corresponding trisulfides, no scrambling was observed – consistent with its significantly stronger S-S bond.) The data were fit to a kinetic model depicting the reactions shown in Figure 3.2A, where input of the concentrations of the starting symmetrical tetrasulfides and the known recombination rate constant ($k_{\text{rec}} = 6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$),²⁰ yielded a homolysis rate constant for the tetrasulfides of $2.9 \times 10^{-4} \text{ s}^{-1}$ at 100 °C, in reasonably good agreement with an estimated rate constant of $4.5 \times 10^{-5} \text{ s}^{-1}$ derived from the calculated S-S BDE

(at 25 °C). Thus, although homolysis of the tetrasulfide may be competitive with chain propagation, the highly-reversible nature of the reaction suggests that insufficient perthiyl radical will accumulate to intercept a chain-carrying peroxy radical.

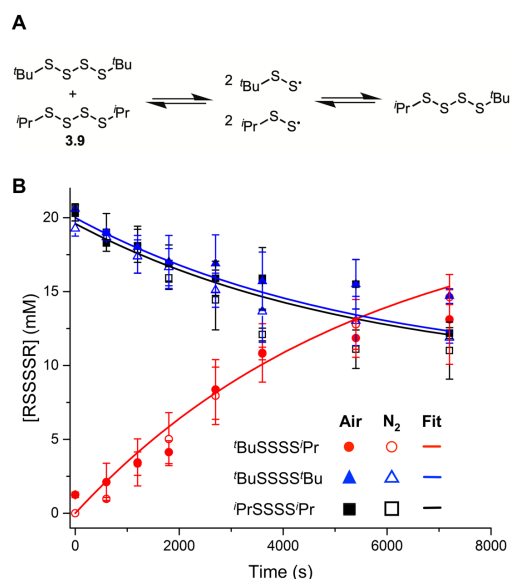


Figure 3.2. Thermal equilibration of tetrasulfides. (A) Scrambling experiment of **3.4** (20 mM) and **3.9** (20 mM) in PhCl at 100 °C under an atmosphere of air (solid symbols) or nitrogen (empty symbols). Solid lines are from numerical fitting of the data obtained under nitrogen to the reaction mechanism shown above given the known rate constant of perthiyl radical recombination of $k_r = 6 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$. (B)

The remaining possibility – homolytic substitution – can occur at either S1 or S2 of the tetrasulfide, which yield similarly stabilized perthiyl radicals ($\text{RSSS}\cdot$ and $\text{RSS}\cdot$, respectively).²⁰ As such, the reaction at S2 may be expected on steric grounds. In contrast, reactions of the trisulfide at S1 and S2 yield perthiyl and thiyl radicals, respectively. Given the far greater stability of the former than the latter ($\sim 17 \text{ kcal/mol}$),²³ substitution at S1 is expected to be the preferred path on thermodynamic grounds, but because of steric hindrance of the adjacent *t*-butyl group, chemistry may be directed to S2. Indeed, in our previous work, we found substitution at the sulfinyl (S1) sulfur atom of the

trisulfide-1-oxides can be subject to profound steric effects.²⁰ This may explain why the tetrasulfide displays good RTA activity in the foregoing experiments while the trisulfide does not: the substitution on the most accessible sulfur atom yields radicals of significantly different stability.

To probe the regioselectivity of substitution, we examined the reactivity of a less hindered tetrasulfide (di-*iso*-propyl tetrasulfide **3.9**) and found it to be a slightly poorer inhibitor than di-*tert*-butyl tetrasulfide (compare $k_{\text{inh}} = 1.3 \pm 0.2$ to $2.3 \pm 0.4 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$). If substitution at S1 were the mechanism, it is expected that the di-*iso*-propyl tetrasulfide would be far more reactive.²⁵ To provide some corroboration for homolytic substitution at S2 being operative in the reaction of tetrasulfides with peroxy radicals, we turned to computations – the results of which are summarized in Figure 3.3. Fully consistent with the above considerations, peroxy radical attack is predicted to be most favourable at S2 of the tetrasulfide (compare $\Delta G^\ddagger = 19.9 \text{ kcal/mol}$ to 22.4 kcal/mol for substitution at S1 at 25 °C) and S1 of the trisulfide (compare $\Delta G^\ddagger = 21.2 \text{ kcal/mol}$ to 26.4 kcal/mol for substitution at S2 at 25 °C).²⁶

The difference in calculated free energy barriers to substitution at S2 of the tetrasulfide and S1 of the trisulfide (1.3 kcal/mol) corresponds to a difference in rate constant of a factor of 7 at 100 °C, implying that retardation of the autoxidations inhibited by the trisulfide should be observed. In fact, retardation was observed, but only at much higher concentrations of trisulfide (~1 mM), yielding $k_{\text{inh}} \sim 2 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$ (see Supporting Information). The larger difference in reactivity between trisulfides and tetrasulfides determined experimentally (~100-fold) may result from greater steric hindrance in the experimental system (wherein hexadecenylperoxy radicals carry the autoxidation chain) as compared to the computational model (which employs methylperoxy radicals for computational expediency).

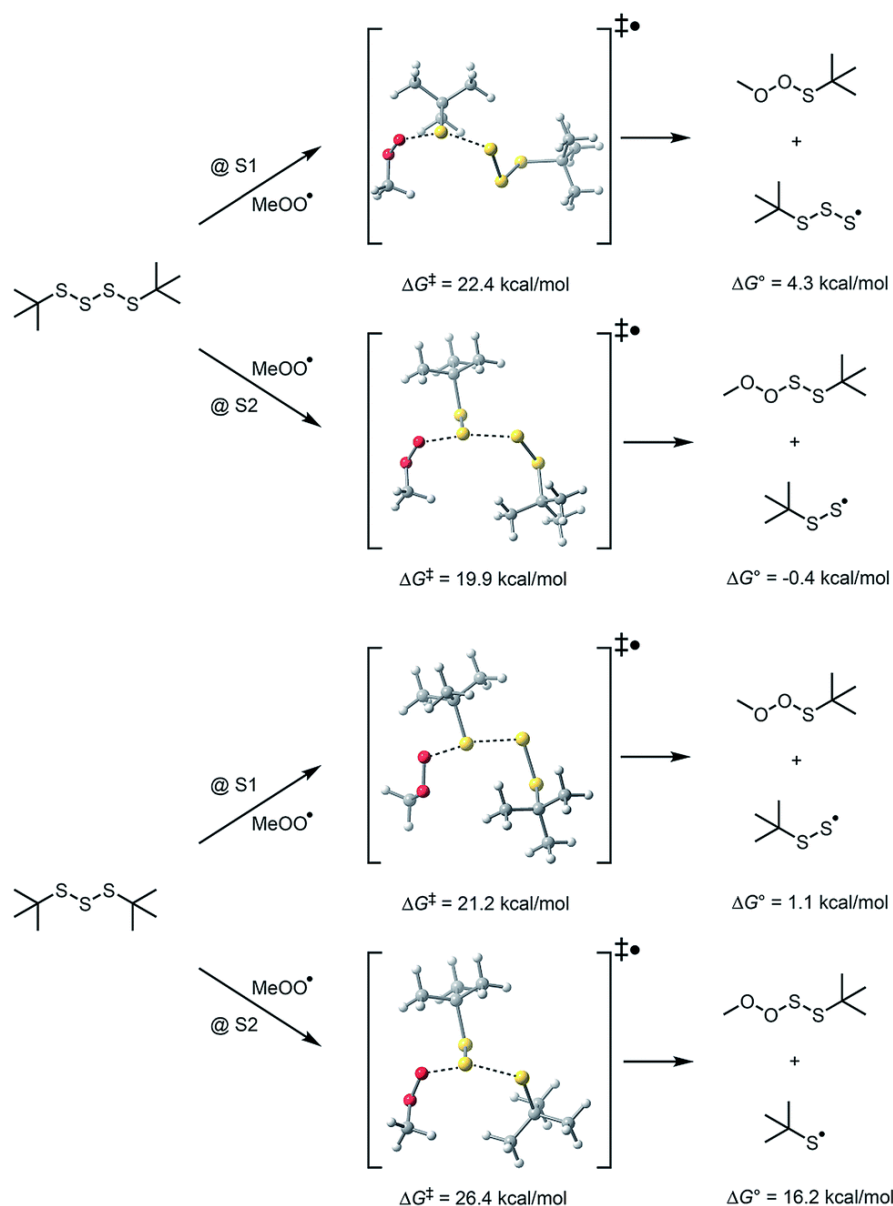


Figure 3.3. Computational insight on the regioselectivity of homolytic substitution of peroxy radicals on trisulfides and tetrasulfides at 25 °C.

3.3.3 Mechanisms of polysulfide-1-oxide reactivity

Although the RTA mechanisms of the hindered sulfoxides and thiosulfinates (Cope elimination followed by H-atom transfer to peroxy radicals) and the trisulfide-1-oxides and tetrasulfide-1-oxides (homolytic substitution by peroxy radicals) are established, the data in Figures 3.1D and 3.1F

underscore that their relevance is highly temperature-dependent. At 37 °C, the sulfoxide and thiosulfinate show no activity, while the trisulfide-1-oxide and tetrasulfide-1-oxide are effective inhibitors. At 100 °C, the opposite is observed. Since Cope elimination from the sulfoxide ($k = 6.8 \times 10^{-6} \text{ s}^{-1}$ at 96 °C) is faster than from the thiosulfinate ($1.9 \times 10^{-6} \text{ s}^{-1}$ at 96 °C),²⁷ sulfenic acid may build up that does not trap peroxy radicals, but instead undergoes other reactions, such as self-condensation or oxidation. When the autoxidation is inhibited by the persistent sulfenic acid, TrptSOH,^{28,29} similar $k_{\text{inh}} = (2.0 \pm 0.6) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ and $n = 0.5 \pm 0.1$ are observed, suggesting that oxidation depletes the sulfenic acid, since TrptSOH cannot undergo self-condensation. The importance of the competition between radical-trapping and oxidation is highlighted when autoxidations are carried out at varying rates of initiation. At a higher rate of initiation (R_i) (dicumylperoxide concentration was doubled) the stoichiometry of the sulfoxide increased slightly from $n = 0.4$ to $n = 0.5$. Conversely, at a lower R_i (dicumylperoxide concentration was halved) the stoichiometry decreased slightly from $n = 0.4$ to $n = 0.3$. The thiosulfinate presumably has a larger n because it produces sulfenic acid more slowly. Accordingly, its k_{inh} increased from 1.5 to $3.5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ when R_i was halved ($n = 1$ in both cases), but eroded when R_i was doubled. In contrast, the RTA activity of tetrasulfide **3.4** was independent of the R_i . Please consult the Supporting Information for all of the data for the results given above.

In principle, at elevated temperatures the trisulfide-1-oxide and tetrasulfide-1-oxide could undergo β -elimination in a manner similar to the thiosulfinate and sulfoxide (*cf.* Scheme 3.2). Since the propensity of polysulfide 1-oxides to undergo β -elimination has not been reported beyond thiosulfinates,²⁷ we calculated the barriers for this process for the trisulfide-1-oxide and tetrasulfide-1-oxide using CBS-QB3 and compared them to the sulfoxide and thiosulfinate. The results are summarized in Figure 3.4.

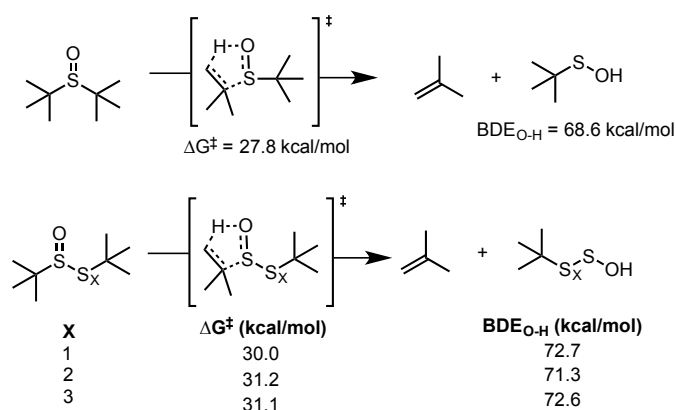


Figure 3.4. Free energy barriers for β -elimination of excellent H-atom donors from sulfoxides, thiosulfinates and polysulfide-1-oxides at 25 °C.

The calculations predict $\Delta G^\ddagger = 31.2$ and 31.1 kcal/mol for the elimination of (perthio)sulfenic from the trisulfide- and tetrasulfide-1-oxides, respectively – scarcely different from the thiosulfinate ($\Delta G^\ddagger = 30.0$ kcal/mol). Confidence in these data can be gleaned from the good agreement between rate constants derived from the computed barriers for elimination from the thiosulfinate ($1.9 \times 10^{-5} \text{ s}^{-1}$) at 100 °C with experimental data determined by Block at 96 °C ($1.9 \times 10^{-6} \text{ s}^{-1}$).²⁷ However, the S-S bond dissociation free energies of the trisulfide- and tetrasulfide-1-oxide are only 12.9 and 16.1 kcal/mol, respectively, at 100 °C, suggesting that they will homolyze faster than they undergo Cope elimination to produce a good H-atom donor. Indeed, when we attempted to fit the experimental data from the polysulfide-1-oxide-inhibited autoxidations to a kinetic model involving initial elimination of (perthio)sulfenic acid followed by H-atom transfer, only the sulfoxide- and thiosulfinate-inhibited autoxidation data could be fit – yielding inhibition rate constants of 2.0×10^7 and $1.2 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, in excellent agreement with previous estimates of the reactivity of unhindered sulfenic acids to peroxy radicals.¹⁹

The foregoing suggests that the facile bond homolysis of the higher polysulfide-1-oxides may explain their lower reactivity at elevated temperatures. In lieu of simply returning the starting compound (as is the case of the tetrasulfide, see Figure 3.2), homolysis of the weak S-S bond in the

polysulfide-1-oxides is expected to yield redox inactive thiosulfonates from dimerization of two sulfinyl radicals.^{18a} Fortunately, the other product, a polysulfide, would still be reactive via homolytic substitution. To support these expectations, the trisulfide-1-oxide was injected onto a gas chromatograph (inlet temperature set to 100 °C), which revealed only the tetrasulfide ('BuSSSS'Bu) and thiosulfonate ($\text{'BuSO}_2\text{S'Bu}$) in the chromatogram. When the decomposition products of 'BuS(O)SS'Bu we monitored over (Figure 3.5), the concentration of tetrasulfide was steady at about half of the initial concentration of trisulfide-1-oxide whereas the thiosulfonate concentration dropped to zero within 5 minutes under an air atmosphere or within 15 minutes under a nitrogen atmosphere. These observations suggest that the sulfinyl radical formed from the homolysis of the trisulfide-1-oxide reacts with O_2 , preventing the formation of thiosulfonate. Initially, most of the mass balance is thiosulfonate, and corresponds to the loss in thiosulfonate, but arises from an unknown mechanism that is accelerated in air. Although we cannot exclude a role for the sulfenic acids formed by elimination from the trisulfide- and tetrasulfide-1-oxides based on the calculated energy barriers in Figure 3.4, overall, these data suggest that the RTA activity of the trisulfide-1-oxide and tetrasulfide-1-oxide at 100 °C results primarily from homolytic substitution on the polysulfide derived therefrom and not the 1-oxides themselves, which are unstable.

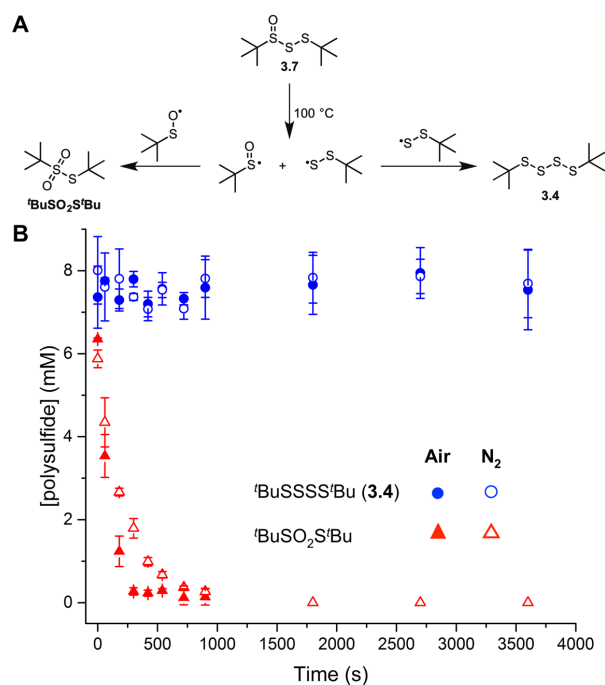


Figure 3.5. Decomposition of di-*tert*-butyl trisulfide-1-oxide **3.7** (20 mM) at 100 °C in chlorobenzene yields di-*tert*-butyl thiosulfonate and **3.4** (A). Product formation from the decomposition of **3.7** under air or nitrogen atmosphere as a function of time (B).

3.3.4 Inhibited autoxidation of hexadecane at 160°C

Given the substantial temperature dependence of the reactivity of both the tetrasulfides and the polysulfide-1-oxides, and the fact that sulfurized olefins are often used in applications at elevated temperatures, we also carried out inhibited autoxidations at 160 °C. *n*-Hexadecane was selected as the autoxidizable hydrocarbon for these experiments, which were carried out under a continuous flow of O_2 to prevent mass transfer from limiting reaction progress.^{30,31} Product hydroperoxides were determined over the course of the autoxidation using a pro-fluorescent coumarin probe, which exhibits substantial fluorescence enhancement upon oxidation (Figure 3.6A).^{15,38} Representative data sets are shown in Figures 3.6B and 3.6C.

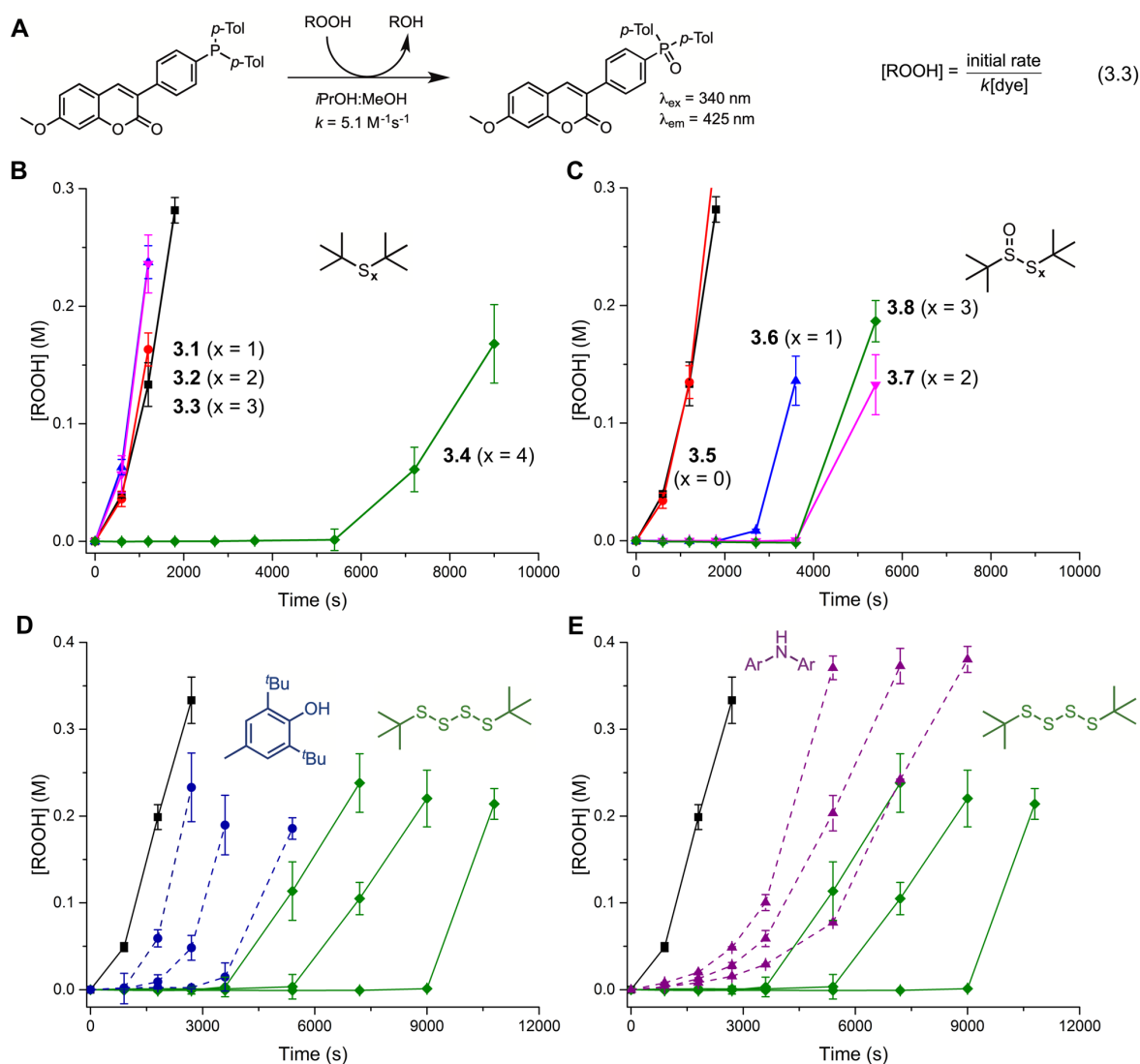


Figure 3.6. A phosphine-coumarin conjugate (A) enables the quantification of hydroperoxides formed during inhibited *n*-hexadecane autoxidation at 160°C (black squares) inhibited by 500 μM organosulfur compound (B and C). Hydroperoxide production over the course of a *n*-hexadecane autoxidation (5 mM tetralin hydroperoxide) at 160 °C (black square) inhibited by 250, 500 and 1000 μM BHT (blue circle) and **3.4** (green diamond) (D). Hydroperoxide production over the course of a *n*-hexadecane autoxidation (5 mM tetralin hydroperoxide) at 160 °C (black square) inhibited by 250, 500 and 1000 μM $t\text{Bu}_2\text{DPA}$ (purple triangle) and **3.4** (green diamond) (E).

Again, of the polysulfides, only the tetrasulfide was an efficient inhibitor, producing an inhibited period lasting for $t_{\text{inh}} \sim 6000 \text{ s}$. It is important to note that autoxidations carried out at these

temperatures are autocatalytic, precluding accurate determination of the RTA stoichiometry from t_{inh} as in equation 2 since R_i is not constant, but increasing with the formation of product peroxides. Interestingly, and in contrast with the results at 100 °C, the trisulfide-1-oxide and tetrasulfide-1-oxide were most effective of the polysulfide-1-oxides ($t_{\text{inh}} \sim 3600$ s), followed by the thiosulfinate ($t_{\text{inh}} \sim 2700$ s). The sulfoxide was completely ineffective at this temperature, suggesting that Cope elimination to sulfenic acid is so rapid that it is consumed immediately, precluding efficient RTA activity. Evidently, the slower Cope elimination from the thiosulfinate is slightly better matched to the rate of the autoxidation, enabling it to inhibit. However, it is clear that the higher polysulfide-1-oxides are best. Nevertheless, they remain less reactive than the tetrasulfide, presumably since half of the 1-oxides are used to produce polysulfides that trap peroxy radicals – analogous to what was observed at 100 °C. Similar results were obtained with analogous higher molecular weight polysulfides and their 1-oxides, confirming that the lack of activity for some of the small chain analogues is not due to their volatility at 160 °C (see Supporting Information for further details).

Lastly, we sought to compare the reactivity of the tetrasulfide to that of the common primary antioxidants: a hindered phenol (BHT) and an alkylated diphenylamine (4,4'-di-*tert*-butyldiphenylamine, 'Bu₂DPA). Representative results are presented in Figures 3.6D and 3.6E, respectively. Interestingly, we found that the tetrasulfide was a better inhibitor of *n*-hexadecane autoxidation at 160 °C than either BHT or 'Bu₂DPA. This contrasts the order of reactivity seen at 37 °C, where 'Bu₂DPA > BHT >> tetrasulfide and 100 °C, where 'Bu₂DPA > BHT ~ tetrasulfide (see the Supporting Information for the data).

3.4 Discussion

The antioxidant mechanisms of organosulfur compounds are generally believed to be ionic 'secondary antioxidant' processes, where they react with (hydro)peroxides directly or via the eventual formation of sulfur dioxide or sulfur oxyacids.³ Moreover, it is generally accepted that all polysulfides are equally competent at inhibiting the oxidation of hydrocarbons when normalized to the number of sulfur atoms

in the chain (i.e. a tetrasulfide reacts as quickly as 2 eq of disulfide). This dogma appears to stem from the work of Bridgewater and Sexton, who studied the rates of reaction between polysulfides derived from para-sulfurization of a hindered phenol and cumene hydroperoxide.²⁴ Thus, our observations that the tetrasulfide is a much better inhibitor of autoxidation than the corresponding trisulfide, disulfide and sulfide initially provided a very strong indication that a different mechanism was operative. In fact, tetrasulfides are shown to be potent radical-trapping antioxidants ($k = 2.3 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ at 100 °C) under conditions where they are unreactive toward either hydroperoxides or initiating peroxides, and our experimental and computational results suggest that a homolytic substitution mechanism, which yields a stable and persistent perthiyl radical, is responsible.

Similarly to the lower polysulfides, the lower 1-oxides (i.e. sulfoxide and thiosulfinate) are not activated to substitution due to their stronger S-S bonds. Nonetheless, they *can be* effective RTAs under certain conditions. Since their reactivity relies on the irreversible elimination of a sulfenic acid, and the sulfenic acid is not persistent under most conditions, the rate of the elimination must be similar to the rate of radical generation. With careful manipulation of laboratory conditions this is easily achieved – particularly for the sulfoxide at 100°C, as the free energy barrier for elimination of the sulfenic acid therefrom (30.0 kcal/mol) is almost indistinguishable from that of O-O bond homolysis of an initiating species (e.g. 30.9 kcal/mol for ^tPrO-O^tPr). However, this similarity is unlikely to consistently manifest itself in real-world contexts, which is likely why sulfides and their sulfoxides are not commonly employed as RTAs.

The higher polysulfide-1-oxides are, like the tetrasulfide, activated to substitution by peroxy radicals. This mechanism is clearly favoured over the elimination of sulfenic acid since they are effective throughout the temperature range that was investigated. If their RTA activity relied on sulfenic acid formation – which is predicted to take place at a similar rate to the thiosulfinate – we would expect it to be effective only at 100 °C under these conditions. However, for the same reason they are activated to substitution (weak S1-S2 bonds), the higher polysulfide 1-oxides decompose

readily. Although the tetrasulfide has a similarly weak bond,³⁶ its homolysis is reversible. When the polysulfide-1-oxides homolyze, the reaction is irreversible. Instead, two sulfinyl radicals combine to initially afford an unreactive thiosulfonate and the perthiyls combine to give a polysulfide (exemplified above in the decomposition of the trisulfide-1-oxide).^{‡18a} Thus, they are only roughly 50% as effective as an authentic polysulfide (Figure 3.6).

Homolytic substitution of a peroxy radical on a tetrasulfide produces a peroxy-perthiyl adduct. The fact that this reaction is predicted to be essentially thermoneutral implies that the adduct must undergo a rapid subsequent reaction with some driving force. Moreover, given that the observed stoichiometry of radical-trapping reactivity of the tetrasulfide is close to the stoichiometry of 1.5 associated with the mechanism, the product must be relatively innocuous (*i.e.* it does not propagate the autoxidation). Given the structural similarity of the adduct to the tetroxide intermediate invoked when two peroxy radicals combine to terminate an autoxidation chain, we considered an analogous fate for the peroxy-perthiyl adduct: cleavage of the O-O bond, subsequent loss of sulfur monoxide and then in-cage disproportionation of the thiyl and alkoxyl radicals to yield a thiol and carbonyl (Figure 3.7). CBS-QB3 calculations indicate that although the initial O-O bond cleavage is very likely, and the overall reaction is 70 kcal/mol exergonic, the fragmentation of sulfur monoxide from the alkylthiosulfinyl radical is not a particularly good reaction (requiring ca. 37 kcal/mol). This suggests that the alkoxyl radical would have plenty of time to escape the solvent (substrate) cage and abstract an H-atom to initiate a new chain reaction. However, explorations of the potential energy surface near the O-O cleavage coordinate generally converged on combination of the alkoxyl and alkylthiosulfinyl radical fragments to yield a thiosulfurous acid diester, which was 47.5 kcal/mol exergonic relative to the perthiyl-peroxy adduct. Moreover, we were able to identify a transition state structure for the concerted rearrangement, which has a predicted barrier of $\Delta G^\ddagger = 12.4$ kcal/mol.³⁷ Thus, it seems reasonable to suggest that the perthiyl-peroxy adduct rearranges to a thiosulfurous acid diester – by either step-wise bond homolysis and in-cage radical recombination or concerted (1,2-) alkoxyl migration – nicely accounting for the observed stoichiometry of radical-trapping.

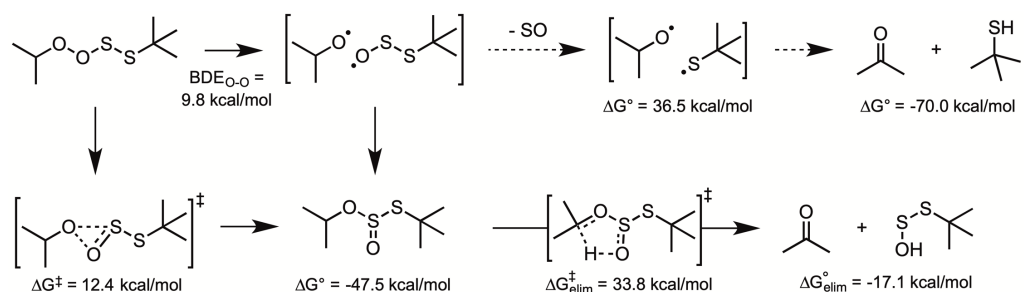


Figure 3.7. Possible fates of the peroxy-perthiyl adduct formed from homolytic substitution of a (model) peroxy radical on di-*tert*-butyltetrasulfide.

Interestingly, we found that elemental sulfur (S_8) did not inhibit the autoxidations we carried out (see Supporting Information), even though an analogous substitution reaction between it and a peroxy radical could be envisioned. Although a transition state for peroxy radical substitution on octahedral sulfur was readily identified using the same CBS-QB3 calculations that were carried out on the polysulfides (Figure 3.8), the barrier for the reaction was predicted to be higher than that for the tetrasulfide ($\Delta G^\ddagger = 22.9$ kcal/mol versus 19.9 kcal/mol).³⁵ In contrast with the thermoneutral reaction of the peroxy radical with the tetrasulfide ($\Delta G^\circ = -0.4$ kcal/mol), the substitution on S_8 is endergonic ($\Delta G^\circ = 8.5$ kcal/mol) due to the increased entropic cost of the reaction (essentially an addition rather than substitution). Moreover, while the facile rearrangement of the peroxy-perthiyl adduct to the thiosulfurous acid diester appears to drive the reaction of the peroxy radical and tetrasulfide forward, there is no obvious corresponding follow-up reaction of the peroxy- S_8 adduct to compete with the reverse reaction. Thus, it would appear that olefin sulfurization is not only a means to better solubilize sulfur for use in hydrocarbon-based products, but also to activate it to interception of peroxy radicals.

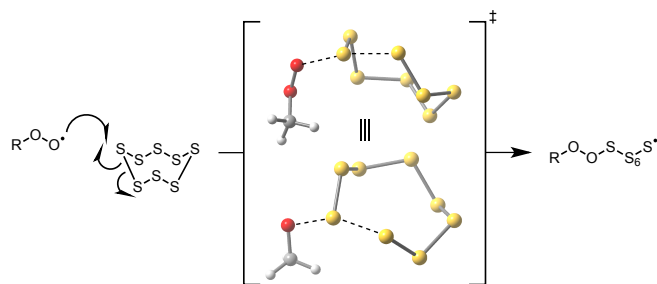


Figure 3.8. Computed transition state for homolytic substitution of a (model) peroxy radical on the most common allotrope of elemental sulfur (S₈).

The impressive RTA activity of the tetrasulfide is maintained at elevated temperatures (160 °C), where it is a more effective inhibitor of *n*-hexadecane autoxidation than either the quintessential hindered phenolic antioxidant (BHT) or a representative alkylated diphenylamine ('Bu₂DPA). At first glance, this result is perplexing given that the tetrasulfide is less reactive than both BHT and 'Bu₂DPA at 37 °C. However, the reactivity gap narrows upon increasing the temperature to 100 °C – fully consistent with the trends in E_a , viz. 0.8 kcal/mol (BHT)³² 2.5 kcal/mol (diarylamine),³³ and 9.9 kcal/mol (tetrasulfide, computed).³⁴ Of course, the length of the inhibited period is dictated by the radical-trapping stoichiometry and not simply the kinetics. BHT and related hindered phenols are generally considered to trap a single radical at elevated temperatures, whereas the stoichiometry of alkylated diphenylamines vary wildly depending on reaction conditions. The data in Figure 3.6D suggest that the tetrasulfide has an elevated stoichiometry relative to the hindered phenol – and more so than the 1.5 quantified at 100 °C. An explanation for this enhanced stoichiometry arises upon consideration of the fate of the initially formed peroxy-perthiyl adduct discussed above. The product thiosulfurous acid diester can be expected to undergo a 5-centre Cope-type elimination to produce the thiosulfenic acid which is responsible for the RTA activity of the corresponding thiosulfinate. We readily identified a transition state for this reaction using CBS-QB3 which suggests that it has a higher barrier ($\Delta G^\ddagger = 33.8$ kcal/mol) than the elimination from the corresponding thiosulfinate ($\Delta G^\ddagger = 30.0$ kcal/mol), but still easily accessible at 160 °C. This also accounts for why the tetrasulfide has a higher stoichiometry than the thiosulfinate at 160 °C, despite a similar stoichiometry at 100 °C.

The foregoing results suggest that preparations of polysulfides enriched in tetrasulfide will impart greater oxidative stability to lubricants and other hydrocarbon-based products to which sulfurized olefins are added. Of course, this must be balanced against any negative impact this would have on the extreme pressure anti-wear properties of the material, which tend to be best exhibited by low order polysulfides ($n \leq 4$) due to their increased stability. It would appear that 4 is the ‘magic’ number.

3.5 Conclusions

Inhibited autoxidations have revealed that the radical-trapping antioxidant activity of (poly)sulfides varies significantly with chain length. Of the first four members of the series of di-*tert*-butyl polysulfide, only the tetrasulfide is sufficiently reactive towards peroxy radicals to inhibit the autoxidation of 1-hexadecene and *n*-hexadecane at 100 and 160 °C, respectively. The rate constant for the reaction of the tetrasulfide with peroxy radicals was measured to be $2 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ at 100 °C, similar to hindered phenols, the most common industrial antioxidant. Moreover, the tetrasulfide also bested both hindered phenols and alkylated diphenylamines at 160 °C. Computation and experiment point to a homolytic substitution of peroxy radicals on the central sulfur atom(s) of the tetrasulfide, which liberates a highly stabilized and persistent perthiyl radical which simply combines with another to reform a tetrasulfide. Based on the stoichiometry observed at 100 °C (ca. 1.5), the other product, a perthiyl-peroxy adduct, must decompose to other non-radical products, which we have proposed to be a thiosulfurous acid diester. By comparison, trisulfide-1-oxide and tetrasulfide-1-oxide are better RTAs at ambient temperatures since they are further activated to analogous homolytic substitution (at the sulfinyl sulfur atom), but their activity erodes at elevated temperatures due to the irreversible cleavage of the S1-S2 bond. Still, they retain activity, since this bond cleavage results in formation of reactive polysulfides (tetrasulfide and hexasulfide, respectively). It is anticipated that these findings will prompt researchers to develop olefin sulfurization processes which enrich the product in

tetrasulfide, and will result in an expanded role of sulfurized olefins in industrial and/or commercial applications.

3.6 Experimental Section

3.6.1 General

All chemicals obtained from commercial suppliers were used as received unless indicated otherwise. 1-Hexadecene and *n*-hexadecane were percolated through a column of basic alumina and silica (3:1) twice before use. Column chromatography was carried out with 40–63 μm , 230–400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE spectrometer at 400 and 101 MHz, respectively, unless indicated otherwise. High-resolution mass spectra were obtained on a Kratos Concept tandem mass spectrometer (EI) and Micromass Q-TOF (ESI). PBD-BODIPY was synthesized according to our previously reported procedure.²² The hydroperoxide probe³⁸ and the acid probe¹⁵ were also synthesized as previously reported. Chlorobenzene was dried over 4 Å molecular sieves before use. UV–visible spectra were measured with a Cary 100 spectrophotometer equipped with a thermostated 6 $\times$ 6 multicell holder. Unless otherwise indicated, the errors that are reported were obtained from the standard deviation of at least three independent experimental trials.

3.6.2 Inhibited Autoxidations

1-Hexadecene autoxidations at 37 °C and 100 °C. These experiments were carried out in a manner similar to those which we have previously reported.^{23,39} Briefly, a 3.5 mL cuvette was loaded with hexadecene (2.00 mL) and PhCl (440 μL) and placed in a preheated thermostatted sample holder of a spectrophotometer set to 37 °C or 100 °C. After 15 min, 12.5 μL of a solution of PBD-BODIPY (2.00 mM in 1,2,4-trichlorobenzene) was added followed by 50 μL of a solution of either AIBN (37 °C, 300 mM in PhCl) or dicumylperoxide (100 °C, 50 mM in PhCl). The solution was mixed thoroughly and the absorbance at either 588 nm (37 °C) or 587 nm (100 °C) was monitored for 5 min after which 10 μL of a solution of the test antioxidant was added, the solution was thoroughly mixed and the

absorbance readings continued until roughly 20% of the PBD-BODIPY was consumed. The data were processed as previously reported.²² The rate of initiation ($R_i = 1.3 \times 10^{-9}$ and 9.2×10^{-9} M/s at 37 °C and 100 °C, respectively) were determined using PMC as a standard, which has an established stoichiometry of 2.⁴⁰

n-Hexadecane autoxidation at 160 °C. These experiments were carried out in a manner similar to those which we have previously reported.¹⁵ Briefly, *n*-hexadecane (10 mL) was loaded into test tubes placed within the pre-drilled holes of an aluminum block and each tube was purged with nitrogen via capillary tubes. While under the atmosphere of nitrogen, the block was heated to 160 °C, at which point, the test compounds were added to individual tubes (100 µL of a 50 mM solution in dioxane). The initiator (tetralin hydroperoxide) was added to the tubes (100 µL of a 0.5 M solution in dioxane) and the flow of nitrogen was replaced with oxygen. Aliquots (~0.5 mL) were removed at regular intervals and cooled to room temperature for analysis. A small volume (5 µL) of each sample was loaded into the wells of a 96-well microplate and diluted with 2-propanol and methanol (1:4, 215 µL) using the automated reagent dispenser of the microplate reader. Next, 30 µL of a solution containing the fluorogenic coumarin phosphine dye (100 µM) and BODIPY acid probe (100 µM) in acetonitrile was added to each well again using the automated reagent dispenser. The plate, incubated at 37 °C, was stirred for 30 seconds, and after a 5 second delay, the fluorescence of each well was measured every second for 60 seconds (coumarin phosphine dye: absorption 340 nm, emission 425 nm; BODIPY acid probe: absorption 475 nm, emission 515 nm). The concentration of hydroperoxide in each well was determined from the rate of phosphine oxidation using the rate constant for the reaction of the dye with secondary hydroperoxides ($k = 5.1 \text{ M}^{-1}\text{s}^{-1}$), assuming pseudo-first-order kinetics.¹⁵ The acid concentration in each well was determined from the average fluorescence reading over 10 s ($\text{RFU} = 359[\text{Acid}] + 34925$).¹⁵

3.6.3 Product Studies

Tetrasulfide scrambling at 100 °C. A solution of $^i\text{PrSSSS}^i\text{Pr}$ (**3.9**) and $^t\text{BuSSSS}^t\text{Bu}$ (**3.4**) (20 mM each) in chlorobenzene was heated at 100 °C in a screw cap vial under an air or nitrogen atmosphere. Aliquots (50 μL) were removed every 15 minutes and diluted to 1 mL in a GC autosampler vial containing 900 μL of hexanes and 50 μL of a hexylbenzene stock solution (20 mM). The samples were analyzed by GC–FID (3 μL injections, split 50:1, flow = 125 mL min⁻¹, inlet temperature of 100 °C) on an instrument equipped with an Agilent HP-5 column (30 m $\times$ 0.320 mm $\times$ 0.25 μm) with a constant Helium flow of 2.5 mL min⁻¹ according to the following temperature profile: 100 °C, hold 0 min, 3 °C min⁻¹ to 145 °C, hold 0 min, 34 °C min⁻¹ to 297 °C, hold 0 min, 35 °C min⁻¹ to 100 °C. The detector temperature was set to 300 °C. The method yielded retention times of 2.0, 10.2, 11.5 and 12.6 minutes for hexylbenzene, $^i\text{PrSSSS}^i\text{Pr}$, $^i\text{PrSSSS}^t\text{Bu}$ and $^t\text{BuSSSS}^t\text{Bu}$, respectively.

Trisulfide-1-oxide decomposition at 100 °C. A solution of $^t\text{BuSOSS}^t\text{Bu}$ (**3.7**) (20 mM) in chlorobenzene was heated at 100 °C in a screw cap vial under an air or nitrogen atmosphere. Aliquots (50 μL) were removed over at regular intervals and diluted to 1 mL in a GC autosampler vial containing 900 μL of hexanes and 50 μL of a hexylbenzene stock solution (20 mM). The samples were analyzed by a GC–FID (3 μL injections, split 50:1, flow = 125 mL min⁻¹, inlet temperature of 100 °C), on an instrument equipped with an Agilent HP-5 column (30 m $\times$ 0.320 mm $\times$ 0.25 μm) with a constant Helium flow of 2.5 mL min⁻¹ according to the following temperature profile: 100 °C, hold 0 min, 3 °C min⁻¹ to 145 °C, hold 0 min, 34 °C min⁻¹ to 297 °C, hold 0 min, 35 °C min⁻¹ to 100 °C. The detector temperature was set to 300 °C. The method yielded retention times of 1.5, 7.1 and 12.7 minutes for hexylbenzene, $^t\text{BuSO}_2\text{S}^t\text{Bu}$ and $^t\text{BuSSSS}^t\text{Bu}$, respectively.

3.6.4 Computations

Calculations were carried out using the CBS-QB3⁴¹ complete basis set method as implemented in the Gaussian 16 suite of programs.⁴² Unless indicated otherwise, the calculations were performed at

standard conditions.

Optimized structures and energies (Gaussian 09) of the computationally calculated structures are provided in the Supporting Information section of the publication in Chemical Science (Chauvin, J.-P. R.; Griesser, M.; Pratt, D. A. *Chem. Sci.* **2019**, *10*, 4999–5010.)

3.7 Supporting Information

3.7.1 Synthetic Procedures

Di-octylsulfide was obtained from commercial suppliers and used as received. *t*-BuS(O)S*t*-Bu (**3.6**),⁴³ *t*-BuS(O)SS*t*-Bu (**3.7**),⁴⁴ C₁₂H₂₅SSC₁₂H₂₅,⁴⁵ C₁₂H₂₅SOSC₁₂H₂₅,⁴⁵ cumyl-SSH⁴⁶ and *tert*-dodecyl-SSH⁴⁶ were prepared as previously reported by our group.

Di-*tert*-butyltrisulfide⁴⁷ (3.3). *tert*-Butylthiol (3.00 g, 33.3 mmol) and Et₃N (3.34 g, 33.3 mmol) were added dropwise as a solution in dry ether (40 mL) to a solution of freshly distilled SCl₂ (1.71 g, 16.6 mmol) in dry ether (40 mL) cooled to -78°C in a dry ice/acetone bath. After the addition is complete, the solution was stirred at -78°C for an additional 30 minutes, after which it was diluted with ether (100 mL) and washed with water, Na₂CO₃ (sat.) and brine. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude oil was purified by column chromatography using 5% EtOAc in Hexanes to obtain the product as a beige oil (3.1 g, 88%). ¹H NMR (400 MHz; CDCl₃): δ 1.37 (s, 18H). ¹³C NMR (101 MHz; CDCl₃): δ 49.1, 30.0. HRMS (EI, [M⁺]): m/z calcd for C₈H₁₈S₃ 210.0571, found 210.0581.

Di-*tert*-butyltetrasulfide⁴⁷ (3.4). A solution of S₂Cl₂ (2.21 mL, 27.7 mmol) in dry ether (70 mL) is cooled to -78°C in a dry ice/acetone bath. A solution of *tert*-butylthiol (6.25 mL, 55.4 mmol) and Et₃N (7.68 mL, 55.4 mmol) in dry ether (70 mL) was added dropwise over 1 hour. After the addition was complete, the solution was stirred at -78°C for an additional 30 minutes after which it was warmed to room temperature and quenched with water. The organic layer was separated and washed with water, Na₂CO₃ (sat.) and brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude yellow oil was purified by column chromatography using hexanes as the eluent to yield the product as a yellow

oil (5.20 g, 78%). ^1H -NMR (400 MHz; CDCl_3): δ 1.40 (s, 18H). ^{13}C NMR (101 MHz; CDCl_3): δ 49.3, 30.4. HRMS (EI, $[\text{M}^+]$): m/z calcd for $\text{C}_8\text{H}_{18}\text{S}_4$ 242.0291, found 242.0298.

Di-*tert*-butylsulfoxide⁴⁸ (3.5). To a solution of di-*tert*-butylsulfide (1.25 g, 8.55 mmol) in dry DCM (20 mL) at 0°C was added m-CPBA (2.00 g, 9.95 mmol) dropwise as a solution in DCM (10 mL). The resulting white suspension was stirred at 0°C for 2 hours after which Na_2CO_3 (0.50 g) was added and the organic layer was washed with water and brine, dried over MgSO_4 , filtered and concentrated in vacuo. The crude white solid was purified by column chromatography using 10% EtOAc in Hexanes to yield the product as a white solid (1.10 g, 79%). ^1H -NMR (400 MHz; CDCl_3): δ 1.33 (s, 18H). ^{13}C NMR (101 MHz; CDCl_3): δ 57.3, 25.7. HRMS (EI, $[\text{M}^+]$): m/z calcd for $\text{C}_8\text{H}_{18}\text{S}$ 162.1078, found 162.1090.

Di-*tert*-butyltetrasulfide-1-oxide⁴⁹ (3.8). To a solution of di-*tert*-butyltetrasulfide (0.500 g, 2.10 mmol) in dry DCM (8.0 mL) at 0°C was added m-CPBA (0.470 g, 2.10 mmol) dropwise as a solution in DCM (2.0 mL). The resulting white suspension was stirred at 0°C for 1 hour after which Na_2CO_3 (0.20 g) was added and the organic layer was washed with water and brine, dried over MgSO_4 , filtered and concentrated in vacuo. The crude oil was purified by column chromatography using 10% EtOAc in Hexanes to yield the product as a white solid (0.340 g, 63%). ^1H -NMR (400 MHz; CDCl_3): δ 1.41 (s, 9H), 1.39 (s, 9H). ^{13}C NMR (76 MHz; CDCl_3): δ 60.8, 50.0, 30.0, 24.1. HRMS (ESI, $[\text{M} + \text{Na}^+]$): m/z calcd for $\text{C}_8\text{H}_{18}\text{OS}_4\text{Na}$ 281.0138, found 281.0130.

Di-isopropyltetrasulfide⁵⁰ (3.9). Synthesized following the same procedure as 3.4 starting from 2-propanethiol and obtained as a yellow oil (1.85 g, 70%). ^1H NMR (400 MHz; CDCl_3): δ 3.31 (7, J = 6.8 Hz, 2H), 1.39 (d, J = 6.8 Hz, 12H). ^{13}C NMR (101 MHz; CDCl_3): δ 42.3, 22.8. HRMS (EI, $[\text{M}^+]$): m/z calcd for $\text{C}_6\text{H}_{14}\text{S}_4$ 213.9978, found 213.9968.

Di-*tert*-dodecyltrisulfide (3.12): 2,2'-thiobis(isoindoline-1,3-dione)⁵¹ (0.200 g, 0.620 mmol) was dissolved in DCM (4.0 mL) and purged with N_2 in a 25 mL RBF. *t*-Dodecylthiol⁴⁶ (0.250 g, 1.23 mmol) and Et_3N (170 μL , 1.23 mmol) were added dropwise as a solution in DCM (2.2 mL) and the solution was stirred at room temperature for 2 hours. Upon completion of the reaction as determined

by thin layer chromatography, the solution was diluted with DCM (30 mL) and the organic layer was washed with Na₂CO₃ (sat.), water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude oil was purified by column chromatography using hexanes as the eluent to yield the product as a colourless oil (0.205 g, 74%). ¹H NMR (400 MHz; CDCl₃): δ 1.60-1.56 (m, 4H), 1.36-1.27 (m, 40H), 0.88 (t, *J* = 6.9 Hz, 6H). ¹³C NMR (101 MHz; CDCl₃): δ 52.4, 41.5, 32.1, 30.1, 29.8, 29.8, 29.5, 27.9, 24.8, 22.9, 14.3. HRMS (EI, [M⁺]): *m/z* calcd for C₂₄H₅₀S₃ 434.3075, found 434.3049.

Di-2-octyltetrasulfide (3.13). Synthesized following the same procedure as **3.4** starting from 2-octanethiol⁵² and obtained as a yellow oil (0.359 g, 74%). ¹H NMR (600 MHz; CDCl₃): δ 3.11 (qd, *J* = 6.8, 3.0 Hz, 2H), 1.74 (ddt, *J* = 13.7, 8.8, 6.8 Hz, 2H), 1.58-1.52 (m, 2H), 1.43-1.38 (m, 10H), 1.32-1.29 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 6H). ¹³C NMR (151 MHz; CDCl₃): δ 47.6, 36.3, 31.9, 29.2, 27.1, 22.8, 21.0, 14.2.

Di-octylsulfoxide (3.14): To a solution of di-octylsulfide (1.00 g, 3.87 mmol) in dry DCM (15 mL) at 0 °C was added m-CPBA (0.908 g, 4.06 mmol) dropwise as a solution in DCM (5 mL). The resulting white suspension was stirred at 0 °C for 2 hours after which Na₂CO₃ (0.50 g) was added and the organic layer was washed with water, brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude white solid was purified by column chromatography using 10% EtOAc in hexanes to obtain the product as a white solid (0.950 g, 90%). ¹H NMR (400 MHz; CDCl₃): δ 2.72-2.57 (m, 4H), 1.79-1.71 (m, 4H), 1.49-1.39 (m, 4H), 1.33-1.27 (m, 16H), 0.87 (t, *J* = 7.0 Hz, 6H). ¹³C NMR (101 MHz; CDCl₃): δ 52.6, 31.9, 29.3, 29.2, 29.0, 22.7, 14.2. HRMS (ESI, [M+Na⁺]): *m/z* calcd for C₁₆H₃₄OSNa 297.2228, found 297.2246.

Di-*tert*-dodecyltrisulfide-1-oxide (3.16): To a solution of di-*tert*-dodecyltrisulfide (0.200 g, 0.460 mmol) in dry DCM (1.5 mL) at 0 °C was added m-CPBA (0.110 g, 0.480 mmol) dropwise as a solution in DCM (0.8 mL). The resulting white suspension was stirred at 0 °C for 2 hours after which Na₂CO₃ (0.10 g) was added and the organic layer was washed with water, brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude white solid was purified by column chromatography using 10% EtOAc in hexanes to yield the product as a white solid (0.127 g, 61%). ¹H NMR (600 MHz; CDCl₃):

δ 1.80 (m, 1H), 1.65-1.59 (m, 3H), 1.39-1.33 (m, 15H), 1.28 (m, 25H), 0.88 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (151 MHz; CDCl_3): δ 64.2, 52.4, 41.5, 37.1, 32.1, 32.0, 30.2, 30.1, 29.7, 29.7, 29.6, 29.5, 29.4, 27.9, 27.7, 24.9, 23.9, 22.8, 22.8, 21.5, 21.3, 14.3, 14.3. HRMS (ESI, $[\text{M}+\text{Na}^+]$): m/z calcd for $\text{C}_{24}\text{H}_{50}\text{OS}_3\text{Na}$ 473.2922, found 473.2929.

3.7.2 Inhibited Co-Autoxidation of 1-Hexadecene at 100 °C

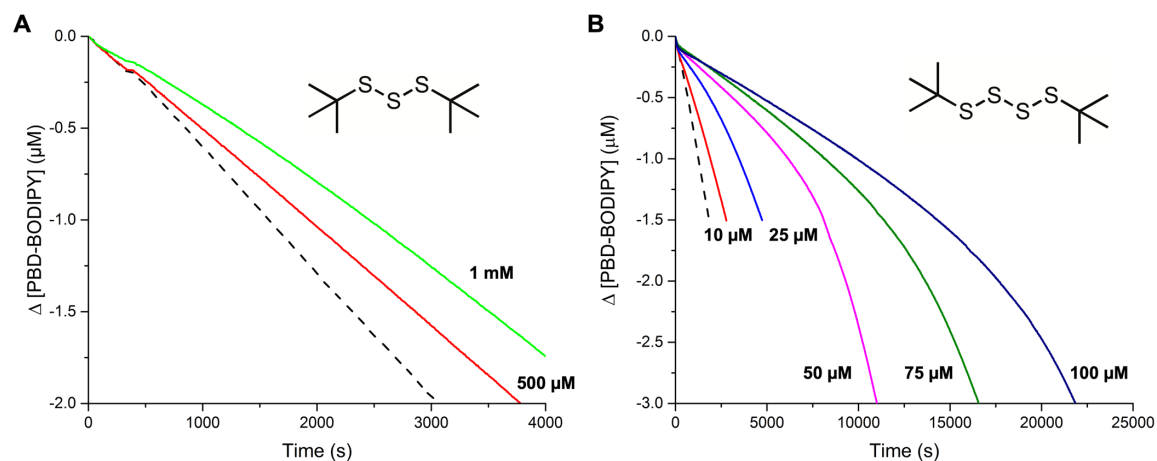


Figure 3.9. Co-autoxidations of 1-hexadecene (2.8 M) and PBD-BODIPY (10 μM) initiated by dicumylperoxide (1 mM) in chlorobenzene at 100 °C (dashed black trace) and inhibited by 10-100 μM of organosulfur **3.3** (A) and **3.4** (B). Reaction progress was monitored by absorbance at 587 nm ($\epsilon = 119\,166\text{ M}^{-1}\text{ cm}^{-1}$).

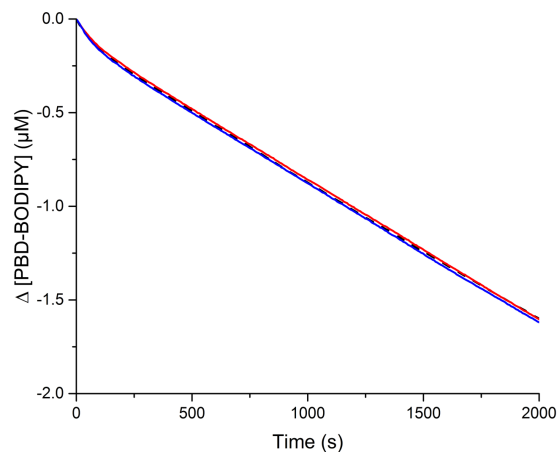


Figure 3.10. Co-oxidations of 1-hexadecene (2.8 M) and PBD-BODIPY (10 μM) initiated by dicumylperoxide (1 mM) in chlorobenzene at 100 $^{\circ}\text{C}$ (dashed black trace) and inhibited by 50 μM (red) and 100 μM (blue) of sulfur. Reaction progress was monitored by absorbance at 587 nm ($\epsilon = 119\,166\,\text{M}^{-1}\,\text{cm}^{-1}$).

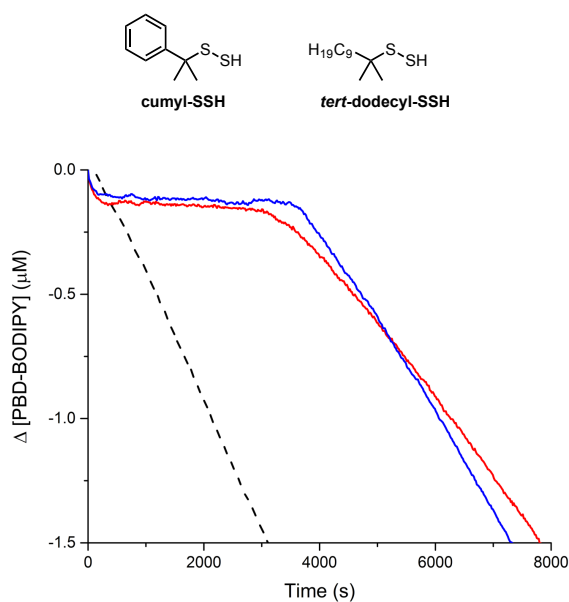


Figure 3.11. Co-oxidations of 1-hexadecene (2.8 M) and PBD-BODIPY (10 μM) initiated by dicumylperoxide (1 mM) in chlorobenzene at 100 $^{\circ}\text{C}$ (dashed black trace) and inhibited by 50 μM of cumyl-SSH (red) and *tert*-dodecyl-SSH (blue). Reaction progress was monitored by absorbance at 587 nm ($\epsilon = 119\,166\,\text{M}^{-1}\,\text{cm}^{-1}$).

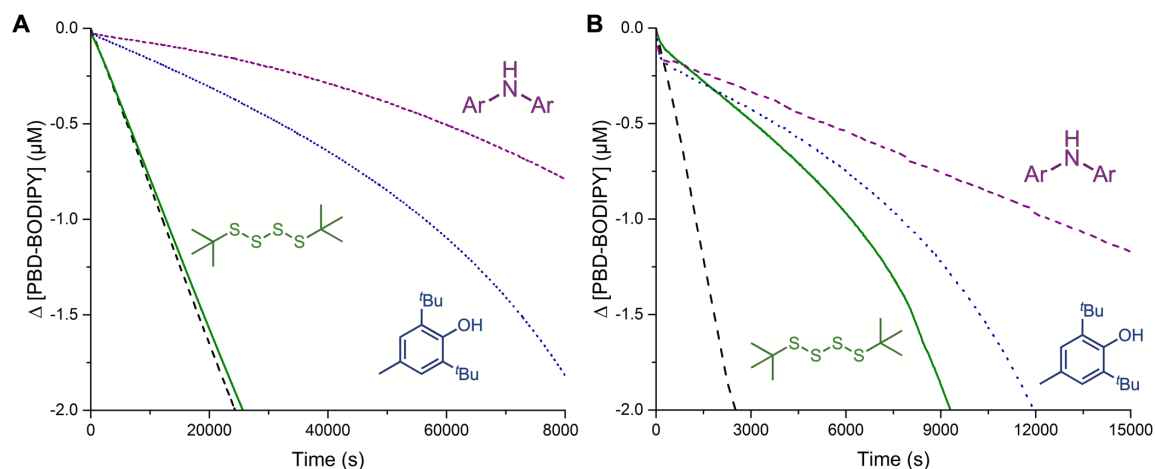


Figure 3.12. Co-oxidation of 1-hexadecene (2.8 M) and PBD-BODIPY (10 μM) initiated with AIBN (6 mM) in chlorobenzene at 37 $^{\circ}\text{C}$ (dashed black trace) and inhibited by 50 μM of 50 μM of **3.4** (green), BHT (blue) and $t\text{Bu}$ -DPA (purple) (A). Reaction progress was monitored by absorbance at 588 nm ($\epsilon = 148\,700\text{ M}^{-1}\text{ cm}^{-1}$). Co-oxidation of 1-hexadecene (2.8 M) and PBD-BODIPY (10 μM) initiated by dicumylperoxide (1 mM) in chlorobenzene at 100 $^{\circ}\text{C}$ (dashed black trace) and inhibited by 50 μM of **3.4** (green), BHT (blue) and $t\text{Bu}$ -DPA (purple). Reaction progress was monitored by absorbance at 587 nm ($\epsilon = 119\,166\text{ M}^{-1}\text{ cm}^{-1}$) (B).

3.7.3 Variation of R_i in 1-Hexadecene Autoxidation at 100 $^{\circ}\text{C}$

Table 3.1. Inhibition rate constants and stoichiometries obtained from thermally-initiated (0.5-2 mM dicumylperoxide, DCP) co-oxidation of 1-hexadecene and PBD-BODIPY in chlorobenzene at 100 $^{\circ}\text{C}$ in the presence of 50 μM of organosulfur.

[DCP] (mM)	0.5		1		2	
Substrate	$k_{\text{inh}} (10^6\text{ M}^{-1}\text{ s}^{-1})$	n	$k_{\text{inh}} (10^6\text{ M}^{-1}\text{ s}^{-1})$	n	$k_{\text{inh}} (10^6\text{ M}^{-1}\text{ s}^{-1})$	n
4	(0.15 ± 0.02)	1.2 ± 0.2	(0.23 ± 0.04)	1.4 ± 0.3	(1.7 ± 0.2)	1.1 ± 0.1
5	(2.1 ± 0.5)	0.3 ± 0.1	(1.4 ± 0.2)	0.4 ± 0.1	(2.4 ± 0.2)	0.5 ± 0.1
6	(3.5 ± 0.9)	1.0 ± 0.1	(1.5 ± 0.5)	1.0 ± 0.1	(1.4 ± 0.5)	0.5 ± 0.1

3.7.4 Tetralin Hydroperoxide Decomposition by Polysulfides

Tetralin hydroperoxide (1 mM) was loaded in a screw cap vial containing either $t\text{BuSSSS}t\text{Bu}$ or $t\text{BuSSSSS}t\text{Bu}$ (0.2 mM) in PhCl and heated at 100 °C under air. Aliquots (100 μL) were taken every 15 minutes and diluted to 500 μL in an autosampler vial containing 350 μL of hexanes and 50 μL of a benzyl alcohol stock solution (2 mM). The samples (10 μL injections) were separated using a Waters Acquity UPLC (1.5% 2-propanol in hexanes, 1.2 mL min^{-1} ; Sunfire Silica column (5 μm , 4.6 $\text{mm} \times 250 \text{ mm}$)) and analyzed by UV absorbance at 215 nm.

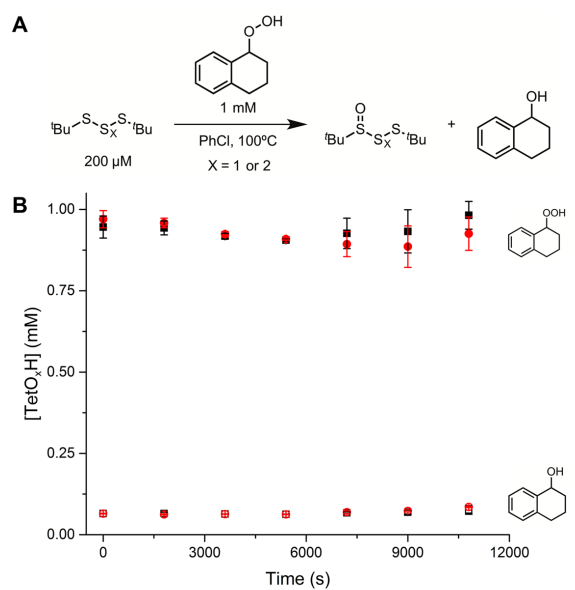


Figure 3.13. Tetralin hydroperoxide (full) decomposition to tetralin alcohol (empty) by **3.3** (square, black) or **3.4** (circle, red) in PhCl at 100 °C.

3.7.5 Inhibited *n*-Hexadecane Autoxidation

Acid Formation

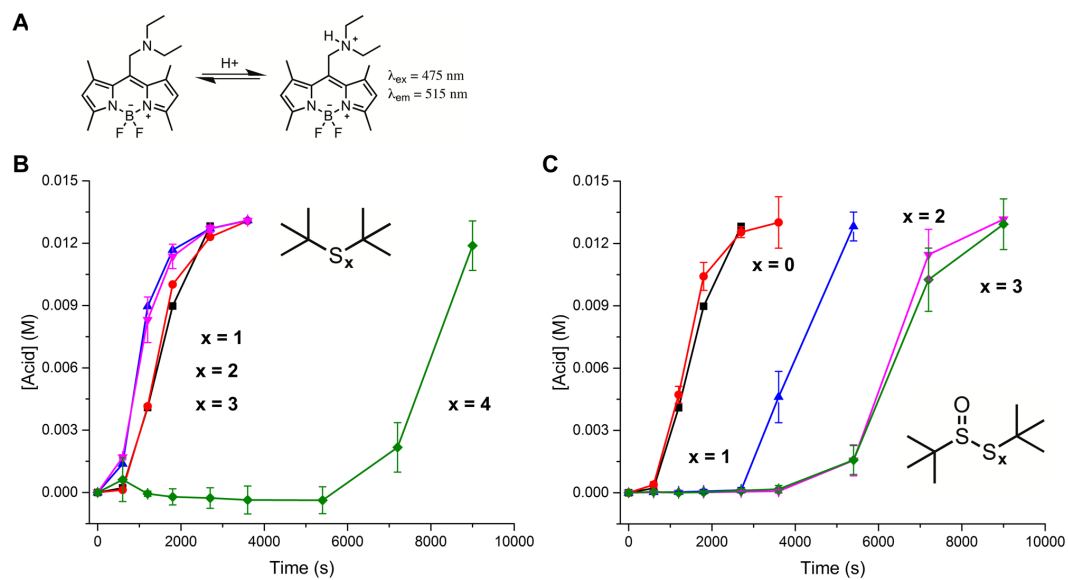


Figure 3.14. BODIPY probe (A) allows the quantification of acids formed during *n*-hexadecane autoxidation at 160 °C inhibited by polysulfides (B) and their corresponding 1-oxides (C).

Long Chain Analogues

Since the autoxidation of *n*-hexadecane was conducted at 160 °C, one should consider the boiling points of compounds **3.1-3.8** to exclude that the absence of activity of some compounds may be due to their volatility at 160 °C. Therefore, we performed inhibited *n*-hexadecane autoxidation at 160 °C inhibited by long chain (poly)sulfides **3.10-3.17** (Figure 3.15) and found that their inhibition, or lack of, corresponded well to their shorter chain analogues.

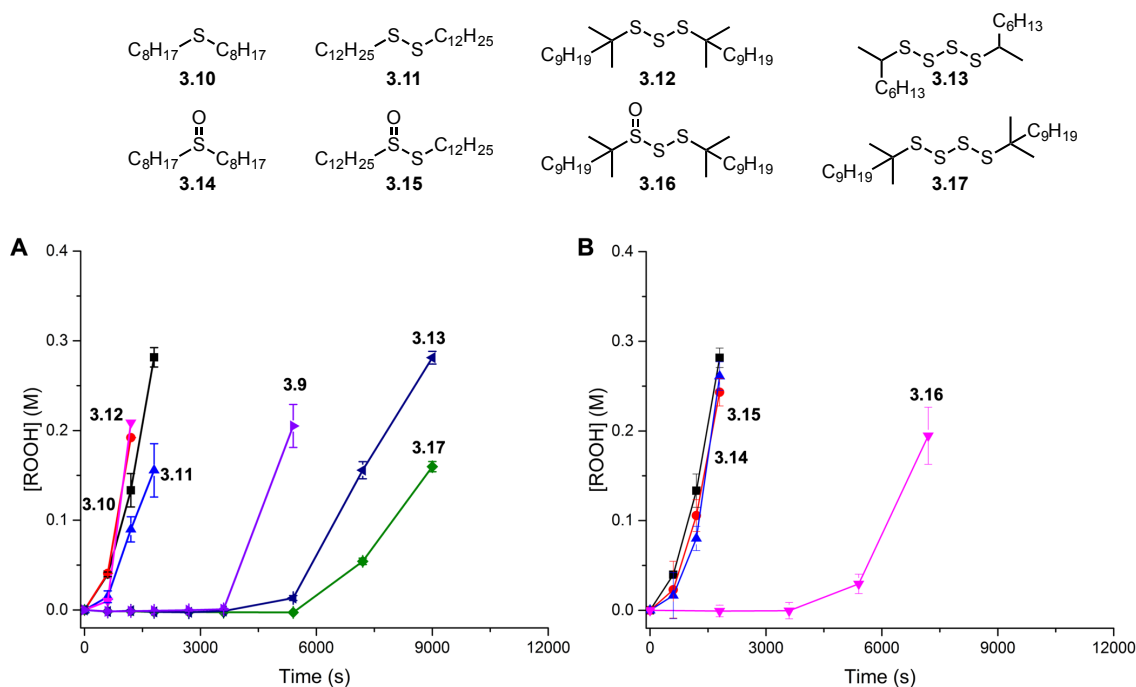


Figure 3.15. Hydroperoxide production over the course of a *n*-hexadecane autoxidation at 160 °C (black square) inhibited by 500 μ M polysulfides (A) and their corresponding oxides (B).

The synthesis of long chain analogues also highlights the effect of the side chain substituent on the RTA activity of tetrasulfides. The *tert*-butyl group is not necessary for the activity of those compounds as both **3.9** and **3.13** are potent RTA at 160 °C. (Figure 3.15A).

3.8 References

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- (26) Alas, application of transition state theory affords a corresponding rate constant of $290 \text{ M}^{-1}\text{s}^{-1}$ at 100°C , thereby significantly underestimating the observed k_{inh} . Changing the peroxy radical to a secondary peroxy radical ('PrOO•) to better represent the peroxy radical which propagates 1-hexadecene autoxidations decreased the $\Delta G^\ddagger$ and afforded a three-fold increase in the calculated rate constant of $909 \text{ M}^{-1}\text{s}^{-1}$ at 100°C , but this remains two orders of magnitude lower than the experimental value.
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CHAPTER 4: Hydropersulfides: H-Atom Transfer Agents Par Excellence*

4.1 Preface

Hydropersulfides (RSSH) are formed endogenously via the reaction of the gaseous biotransmitter hydrogen sulfide (H_2S) and disulfides (RSSR) and/or sulfenic acids (RSOH). RSSH have been investigated for their ability to store H_2S in vivo and as a line of defense against oxidative stress, from which it is clear that RSSH are much more reactive to two-electron oxidants than thiols. Herein we describe the results of our investigations into the H-atom transfer chemistry of RSSH, contrasting it with the well-known H-atom transfer chemistry of thiols. In fact, RSSH are excellent H-atom donors to alkyl ($k \sim 5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$), alkoxy ($k \sim 1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$), peroxy ($k \sim 2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$), and thiyl ($k > 1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$) radicals, besting thiols by as little as 1 order and as much as 4 orders of magnitude. The inherently high reactivity of RSSH to H-atom transfer is based largely on thermodynamic factors; the weak RSS–H bond dissociation enthalpy ($\sim 70 \text{ kcal/mol}$) and the associated high stability of the perthiyl radical make the foregoing reactions exothermic by 15–34 kcal/mol. Of particular relevance in the context of oxidative stress is the reactivity of RSSH to peroxy radicals, where favorable thermodynamics are bolstered by a secondary orbital interaction in the transition state of the formal H-atom transfer that drives the inherent reactivity of RSSH to match that of α -tocopherol (α -TOH), nature's premier radical-trapping antioxidant. Significantly, the reactivity of RSSH eclipses that of α -TOH in H-bond-accepting media because of their low H-bond acidity ($\alpha_2^H \sim 0.1$). This affords RSSH a unique versatility compared to other highly reactive radical-trapping antioxidants (e.g., phenols, diarylamines, hydroxylamines, sulfenic acids), which tend to have high H-bond acidities. Moreover,

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the perthiyl radicals that result are highly persistent under autoxidation conditions and undergo very rapid dimerization ($k = 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) in lieu of reacting with O_2 or autoxidizable substrates.

4.2 Introduction

Considerable interest in hydropersulfides (RSSH) has emerged in recent years owing to their identification at significant levels in mammalian tissues.¹⁻³ They, and other polysulfide ($\text{RS}_n\text{R}'$) species, have been proposed to be responsible for the cell signaling and/or redox modulatory effects of H_2S ,^{1,4} which is produced by cystathionine β -synthase (CBS),^{5,6} cystathionine γ -lyase (CSE)⁷ and 3-mercaptopyruvate sulfurtransferase (MST)^{8,9} in response to various stimuli. Indeed, multiple biological functions have been ascribed to H_2S , including circulatory regulation,^{10,11} energy production,¹² apoptotic gene regulation,¹³ and protection from oxidative stress.¹⁴⁻¹⁶

It is widely believed that the various functions of H_2S are mediated by RSSH, which arise from its reaction with disulfides or other sulfur electrophiles.^{9,17,18} Protein persulfides have been detected using various chemical probes such as cycloalkynes and iodoacetates.^{2,3,19-23} Nevertheless, the chemical basis of the putative physiological effects of RSSH is unclear.^{24,25} Recent work by Fukuto and co-workers²⁶ has provided insight into the ionic reactivity of RSSH toward oxidants and electrophiles, revealing that these are more reactive than the thiols from which RSSH are derived. This provides some support for the suggestion that H_2S is produced to augment the abilities of thiols to sense oxidants and electrophiles. Given these observations, it figures that the homolytic reactivity of RSSH may also be enhanced relative to that of thiols.

Thiols are well known to be useful H-atom donors in synthetic contexts, perhaps most prominently in the thiol-ene reaction and as polarity-reversal catalysts.²⁷ There is a widespread misconception that thiols are also useful as radical-trapping antioxidants (RTAs), which react with autoxidation chain-carrying peroxy radicals by formal H-atom transfer (HAT). In fact, thiols react

slowly with peroxy radicals ($<10^3 \text{ M}^{-1} \text{ s}^{-1}$)²⁸ relative to good RTAs, such as α -tocopherol (α -TOH), the most biologically active form of Vitamin E ($k > 10^6 \text{ M}^{-1} \text{ s}^{-1}$).²⁹ On the other hand, despite their apparently weak S-H BDEs (estimated to be ca. 70 kcal/mol – compare to thiols at 87 kcal/mol),^{30,31} little is known of the H-atom transfer (HAT) reactivity of RSSH.³² Herein we describe the results of our efforts to fill this void, and present data for the reactivity of RSSH toward a variety of oxidants, including peroxy (ROO•), alkoxyl (RO•), alkyl (R•) and thiyl (RS•) radicals. In line with the trends in their ionic reactivity, we find the HAT reactivity of RSSH to be analogous – but greatly accelerated – relative to thiols.

4.3 Results

Cumylhydropersulfide (cumyl-SSH) and 2-methylundecan-2-persulfide (*t*-dodecyl-SSH) were chosen for study owing to the greater persistence of hydropersulfides adjacent to tertiary centres, which slow their self-reaction to trisulfide and H₂S.³³ Both compounds (Figure 4.1) were synthesized by acidic methanolysis of the corresponding *S*-acetylalkyldisulfide, which was synthesized from the corresponding thiol and acetylsulfenyl chloride.³³

4.3.1 Hydropersulfides Are Excellent Radical-Trapping Antioxidants

The reactivity of the hydropersulfides toward peroxy radicals was determined using the venerable inhibited autoxidation approach.³⁴ The addition of PBD-BODIPY as co-substrate enables reaction monitoring simply by loss of the absorbance at 588 nm due to the addition of peroxy radicals to the 1-phenylbutadiene moiety (Figure 4.1A).³⁵ THF is present in order to maintain a radical chain reaction, ensuring a steady-state concentration of peroxy radicals and enabling derivation of the rate constant for the reaction of the hydropersulfide with peroxy radicals (k_{inh}) from the initial rate of the inhibited reaction (Figure 4.1B). The stoichiometry (n) of the RTA-peroxy reaction is determined from the

duration of the inhibited period (t_{inh} , also in Figure 4.1B).³⁵ Representative results are shown for cumyl-SSH and *t*-dodecyl-SSH in Figures 4.1C and 4.1D, respectively.

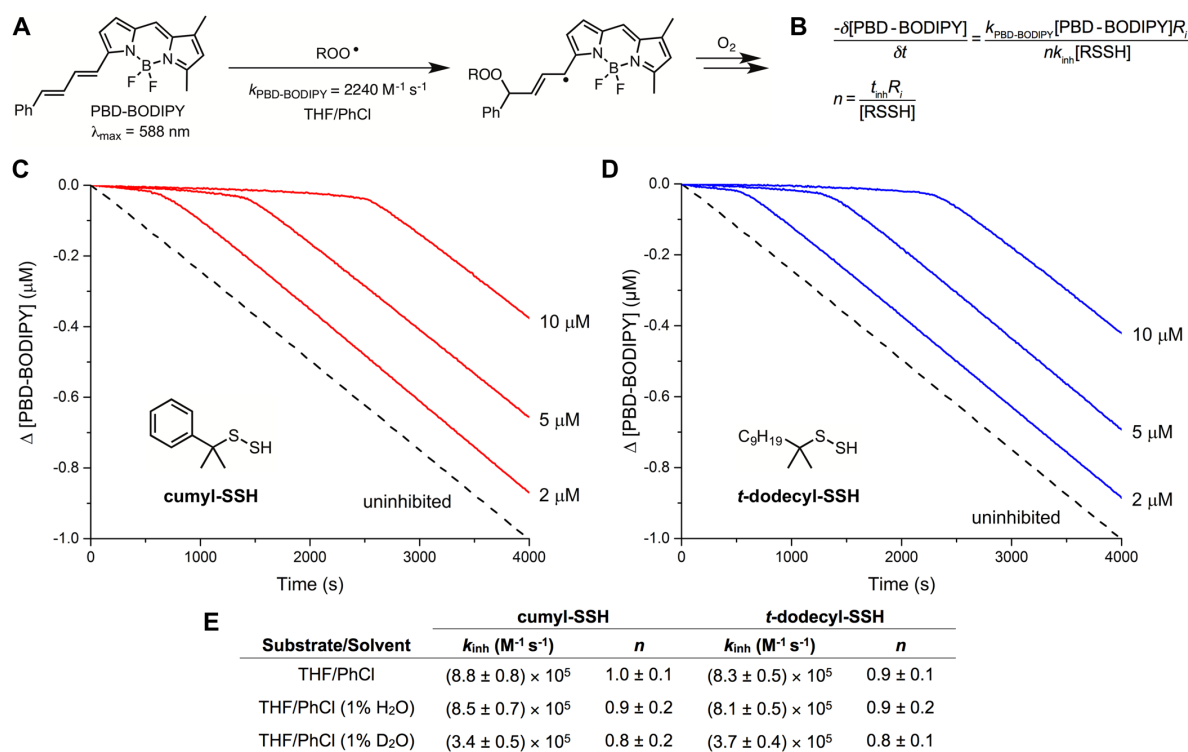


Figure 4.1. PBD-BODIPY serves as the signal carrier in THF autoxidations (A), enabling determination of rate constants (k_{inh}) and reaction stoichiometries (n) for reactions of inhibitors with chain-carrying peroxy radicals (B). Co-autoxidations of THF (3.1 M) and PBD-BODIPY (10 μM) initiated by AIBN (6 mM) in chlorobenzene at 37 °C (dashed black trace) and inhibited by 2 μM , 5 μM and 10 μM of cumyl-SSH (C) and *t*-dodecyl-SSH (D). Average inhibition rate constants and stoichiometry summarized in (E). Reaction progress was monitored by absorbance at 588 nm ($\epsilon = 128,100 \text{ M}^{-1} \text{ cm}^{-1}$).

The traces in Figures 4.1C and 4.1D clearly indicate that hydropersulfides are excellent inhibitors of autoxidation. The inhibition rate constants derived from the initial rates in the presence of each compound are essentially indistinguishable, with $k_{\text{inh}} = (8.0 \pm 0.8) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ and $(8.3 \pm 0.5) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for cumyl-SSH and *t*-dodecyl-SSH, respectively. For comparison, α -TOH is characterized

by $k_{\text{inh}} = 7.1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ under the exact same conditions (see Supporting Information for the data). The observed inhibition periods correspond to stoichiometries of $n = 1.0 \pm 0.1$ and $n = 0.9 \pm 0.1$ for the reactions of cumyl-SSH and *t*-dodecyl-SSH, respectively, suggesting that following H-atom transfer to peroxy radicals, the resultant perthiyl radicals do not contribute to either chain-propagating or chain-breaking events. Indeed, we have previously shown that perthiyl radicals combine to give tetrasulfides with $k = 6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, and tetrasulfides are unreactive to peroxy radicals under these conditions.³⁶

In order to provide direct evidence that the reaction between the hydropersulfides and peroxy radicals is a HAT process, corresponding inhibited autoxidations were carried out in the presence of 1% H₂O or 1% D₂O. Whilst the kinetic data in the presence of water were indistinguishable from those obtained in its absence, in the presence of D₂O the rate constants were 2.2 to 2.5-fold lower. This primary kinetic isotope effect suggests that an (exchangeable) H-atom is transferred in the reaction of the hydropersulfides with peroxy radicals.

4.3.2 H-Atom Transfer from Hydropersulfides is Relatively Insensitive to H-Bonding Interactions

The kinetics of HAT reactions are known to vary systematically as a function of the H-bond donating ability of the H-atom donor and the H-bond accepting ability of the solvent according to the scheme in Figure 4.2A and associated kinetics in Figure 4.2B.³⁷ Given that thiols are poor H-bond donors whose HAT kinetics are insensitive to changes in reaction medium,³⁸ we wondered if hydropersulfides would be similarly poor H-bond donors with corresponding medium-independent HAT kinetics.

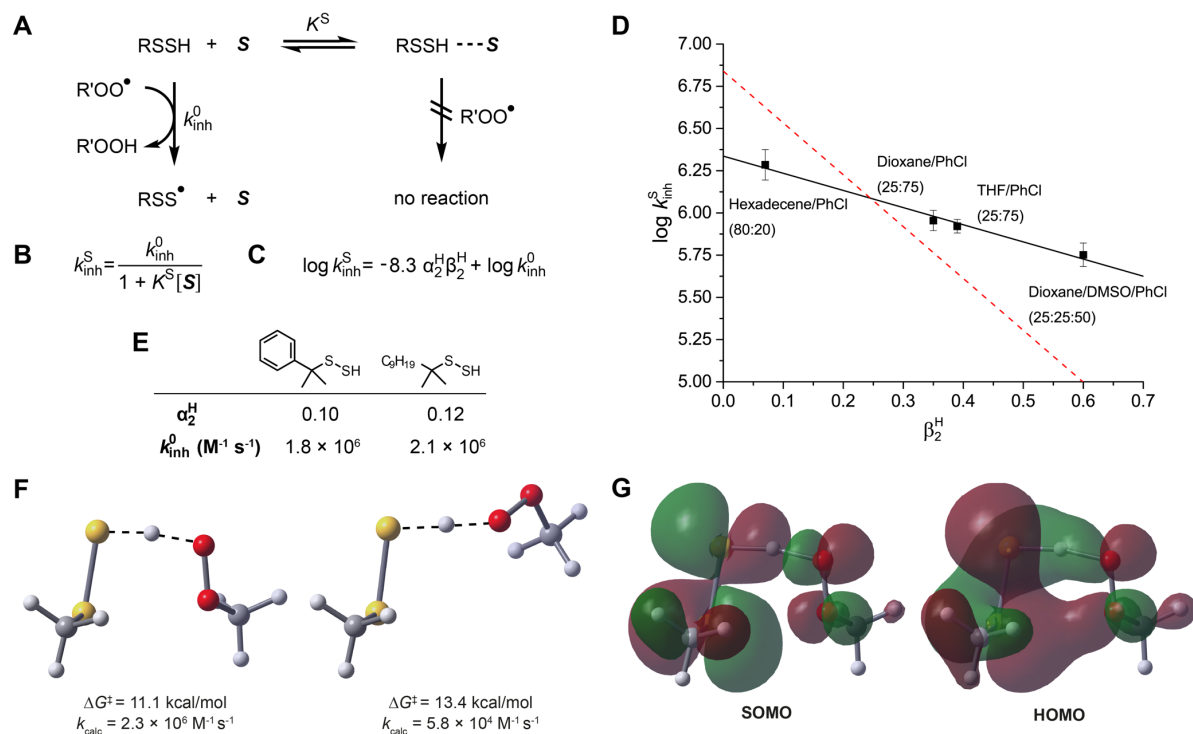


Figure 4.2. The kinetics of H-atom transfer reactions are slowed by H-bonding interactions with solvent, illustrated for hydropersulfides in (A), which can be quantified according to the expression in (B). The H-bonding equilibrium can be expressed in terms of Abraham's H-bond acidity and basicity parameters α_2^{H} and β_2^{H} as in (C). The inhibition rate constants for *t*-dodecyl-SSH, determined as in Figure 4.1 (see Supporting Information for the raw data) plotted as a function of medium β_2^{H} ; the corresponding relationship for α -TOH is represented by the dashed red line (D). The H-bond acidity parameters for cumyl-SSH and *t*-dodecyl-SSH determined from the line of best fit of the data in (D) fit to the expression in (C), and estimated rate constants for the reaction in the absence of any H-bonding interactions (E). The calculated (CBS-QB3) transition state structures for HAT between a model hydropersulfide (MeSSH) and model peroxy radical (MeOO•) and associated free energy barriers and rate constants estimated using transition state theory (F). The SOMO and HOMO of the *syn* transition state structure (G).

Using Abraham's NMR method,³⁹ we determined the H-bond acidities (on the α_2^H scale) of cumyl-SSH and *t*-dodecyl-SSH to be 0.10 and 0.09, respectively – slightly larger than those determined for the corresponding thiols (0.02 and 0.08, respectively) determined under identical conditions. For comparison, alcohols have α_2^H values that range from 0.4 to 0.8.⁴⁰ Even a somewhat hindered and electron rich phenol such as α -TOH has an α_2^H value of 0.37,⁴¹ and since there is a logarithmic relationship between this parameter and the HAT kinetics (Figure 4.2C), its k_{inh} varies considerably with the H-bond accepting basicity of the solvent. For example, on going from pure chlorobenzene ($\beta_2^H = 0.09$) to 3:1 chlorobenzene:THF ($\beta_2^H = 0.39$), k_{inh} drops from $3.6 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $7.1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$. In sharp contrast, and consistent with the values of α_2^H for cumyl-SSH and *t*-dodecyl-SSH we determined by NMR, autoxidations inhibited by the hydropersulfides were much less affected by changes in medium, as shown for *t*-dodecyl-SSH in Figure 4.2D. The slope of the correlation between $\log k_{inh}$ and the β_2^H of the media yielded an α_2^H value of 0.12 for *t*-dodecyl-SSH – in excellent agreement with the NMR data. Thus, while α -TOH is a better radical-trapping antioxidant than the hydropersulfides in simple hydrocarbons, the trend is reversed once H-bond acceptors are introduced to the medium.

Previous work by our group has revealed the importance of secondary orbital interactions in reactions between H-atom donors and peroxy radicals. CBS-QB3 calculations indicate that this contributes to the reactivity of hydropersulfides as well. As is the case with phenols,⁴² diphenylamines,⁴³ and the more structurally-related sulfenic (RSOH)⁴⁴ and selenenic acids (RSeOH)⁴⁵, the lowest energy transition state (TS) structure for the reaction of hydropersulfides with peroxy radicals is characterized by a *syn* relationship between the substituents on the atoms between which the H-atom is being transferred (Figure 4.2F). This maximizes overlap between the singly-occupied π^* of the peroxy radical and the lone-pair of the 'outer' sulfur atom of the hydropersulfide, as illustrated in Figure 4.2G. The free energy barrier calculated at this level of theory is 11.1 kcal/mol, which corresponds to a rate constant of $k = 2.3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 37 °C upon application of TS theory.

This value is in excellent agreement with the experimental values derived in the absence of H-bonding ($k^0 = 1.8\text{--}2.1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 37 °C). The barrier to reaction via the *anti* TS structure is 2.3 kcal/mol higher. The reaction has a significant thermodynamic driving force ($\Delta G^\circ = -15.4 \text{ kcal/mol}$) owing to the difference in the MeSS-H and MeOO-H bond dissociation enthalpies (BDEs), which were calculated to be 70.8 and 86.2 kcal/mol, respectively.

4.3.3 Hydropersulfides React with Peroxyl Radicals via Two Distinct Mechanisms in Water

The HAT reactivity of the hydropersulfides was also investigated in aqueous solution. THF has been shown to be a useful autoxidizable substrate for monitoring peroxyl radical reactions in buffered solutions (pH 2-12),⁴⁶ and we have shown that STY-BODIPY, the more slowly oxidized analogue of PBD-BODIPY, is an effective signal carrier for monitoring reaction progress under these conditions (Figure 4.3A,B).³⁵ Representative results from co-autoxidations of THF and STY-BODIPY carried out at pH 7.4 are shown in Figure 4.3C.

Following the trend established in the previous section, the hydropersulfides were significantly more reactive to peroxyl radicals than α -TOH – or at least Trolox, a water-soluble version of α -TOH in which the phytyl sidechain has been replaced with a carboxylic acid. The inhibition rate constants determined for cumyl-SSH and *t*-dodecyl-SSH were 3.7×10^6 and $3.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, respectively – almost an order of magnitude larger than that determined for Trolox ($4.1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$).⁴⁶ Despite this exciting reactivity, the hydropersulfides suffer from poor stability in water, which facilitates their self-reactions (to mixtures of polysulfides and thiols). As such, the inhibition periods were much shorter than those observed in organic solution, corresponding to much smaller reaction stoichiometries of $n = 0.15 \pm 0.03$ and 0.12 ± 0.05 for cumyl-SSH and *t*-dodecyl-SSH, respectively, as opposed to $n \sim 1$ as below.

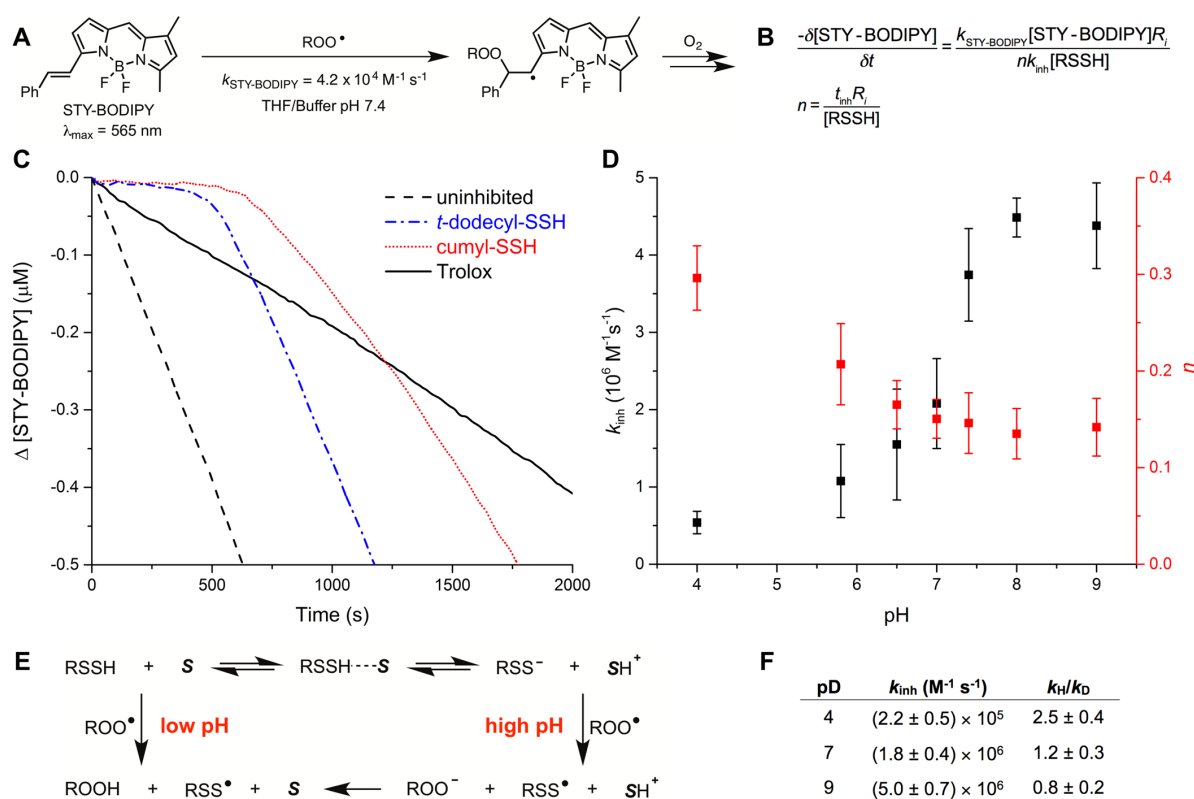


Figure 4.3. STY-BODIPY serves as the signal carrier in THF autoxidations (A), enabling determination of rate constants (k_{inh}) and reaction stoichiometries (n) for reactions of inhibitors with chain-carrying peroxy radicals (B). Co-autoxidations of THF (3.1 M) and STY-BODIPY (10 μM) initiated by AAPH (1 mM) in phosphate-buffered saline (pH 7.4, 100 mM) at 37 $^\circ\text{C}$ (dashed black trace) and inhibited by 10 μM of cumyl-SSH (red), *t*-dodecyl-SSH (blue) and 4 μM of Trolox (black) (C). Inhibition rate constants and reaction stoichiometries determined as a function of pH (D). Reaction scheme illustrating the change in mechanism of the hydropersulfide/peroxyl radical reaction from H-atom transfer to sequential proton loss electron transfer (SPLET) as a function of pH (E). Inhibition rate constants determined as a function of pD and corresponding deuterium kinetic isotope effects (F).

Since cumyl-SSH has slightly better stability in aqueous solution than *t*-dodecyl-SSH, we expanded our studies with it to include inhibited autoxidations in buffers of varying pH ranging from 4 to 9. Interestingly, not only were the k_{inh} values dependent on pH, but a sigmoidal relationship was

observed (Figure 4.3D). The reaction stoichiometries were also pH-dependent, increasing at lower pH presumably due to a slowing of their self-reactions, which are known to be faster at basic pH.³³ The sigmoidal curve was fit using a Boltzmann function, yielding a pK_a value of 7.0 corresponding to the inflection point at pH = 7, strikingly similar to pK_{as} estimated for hydropersulfides.^{47,48}

Accordingly, we wondered if the pH dependence of k_{inh} could be attributed to a change in mechanism: as the pH of the medium increases and the concentration of the persulfide anion increases, the reactions takes place by electron transfer as opposed to the HAT that takes place from the hydropersulfide at lower pH (Figure 4.3E). This mechanism is sometimes referred to as sequential proton loss electron transfer or SPLET.³⁷ To provide additional insight on this apparent change in mechanism, deuterium kinetic isotope effects were determined at acidic pH (4), neutral pH (7) and basic pH (9) by running the inhibited autoxidations in buffers made in D₂O as opposed to H₂O (Figure 4.3F). In the event, the DKIE decreased from 2.5 at pH 4 (similar to the value obtained in chlorobenzene, *vide supra*) to 1.8 at pH 7, and then vanished at pH 9 (0.8 ± 0.2). These trends are fully consistent with an increasing contribution of the SPLET mechanism in the reaction of the hydropersulfide with peroxy radicals on going from pH 4 to 7 and this mechanism operating exclusively at basic pH.

4.3.4 Hydropersulfides Have Enhanced Reactivity to Alkyl, Alkoxy and Thiyl Radicals Compared to Thiols

The H-atom transfer chemistry of hydropersulfides was further investigated with alkyl, alkoxy and thiyl radicals. Alkyl radicals were considered first, as they are known to react very quickly with thiols ($k \sim 10^6 \text{ M}^{-1} \text{ s}^{-1}$)^{38,49} in one of the two propagating steps in the thiol-ene reaction. To do so, a classic alkyl radical clock approach was employed which utilized the 5-exo *trig* cyclization of the 6,6-diphenylhexenyl radical ($k_c = 5.0 \times 10^7 \text{ s}^{-1}$) as the reference reaction (Figure 4.4A).⁵⁰ The PTOC ester precursor to this radical was synthesized as described by Newcomb,^{50,51} who had used it to ‘clock’ the

reactions of selenols with alkyl radicals. Similarly, we photolyzed the ester (at 25 °C in benzene) and determined the ratio of the linear and cyclized hydrocarbons (by GC) as a function of hydropersulfide concentration in order to obtain the second order rate constant for trapping the primary alkyl radical (Figure 4.4B) using Eq. (4.1):

$$\frac{[\text{Linear}]}{[\text{Cyclized}]} = \frac{k_H}{k_C} [\text{RSSH}] \quad (4.1)$$

The reactions of the two hydropersulfides yielded essentially indistinguishable rate constants, *viz.* $k_H = (5.2 \pm 0.9) \times 10^8$ and $(5.6 \pm 2.0) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, for cumyl-SSH and *t*-dodecyl-SSH, respectively. Corresponding calculations of the HAT transition state (Figure 4.4G) yielded a free energy barrier of 7.8 kcal/mol, which corresponds to a rate constant of $3.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, in excellent agreement with experiment. Once again, the driving force for HAT is considerable ($\Delta G^0 = -30.2 \text{ kcal/mol}$), as a result of the weak RSS-H bond.

H-atom transfer kinetics to alkoxy radicals were determined by transient absorption spectroscopy. Cumyloxy radicals were generated by photolysis of dicumylperoxide (Figure 4.4C) with the 308 nm emission of a nanosecond-pulsed XeCl excimer laser and the rates of decay of their absorbance at 485 nm were determined as a function of hydropersulfide concentration (Figure 4.4D). The rate constants were expectedly greater than those measured above, at $(8.3 \pm 0.4) \times 10^8$ and $(1.1 \pm 0.1) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for cumyl-SSH and *t*-dodecyl-SSH, respectively, consistent with the greater driving force for the H-atom transfer of -33.9 kcal/mol (calculated by CBS-QB3, Figure 4.4H). Again, computation predicts a barrier to reaction ($\Delta G^\ddagger = 7.1 \text{ kcal/mol}$) that yields a calculated rate constant in excellent agreement with experiment ($9.5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$). These rate constants are all significantly faster than those reported for the reactions of thiols with tertiary alkoxy radicals (e.g. $6.5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for *t*-BuO• + *n*-C₆H₁₃SH).⁵²

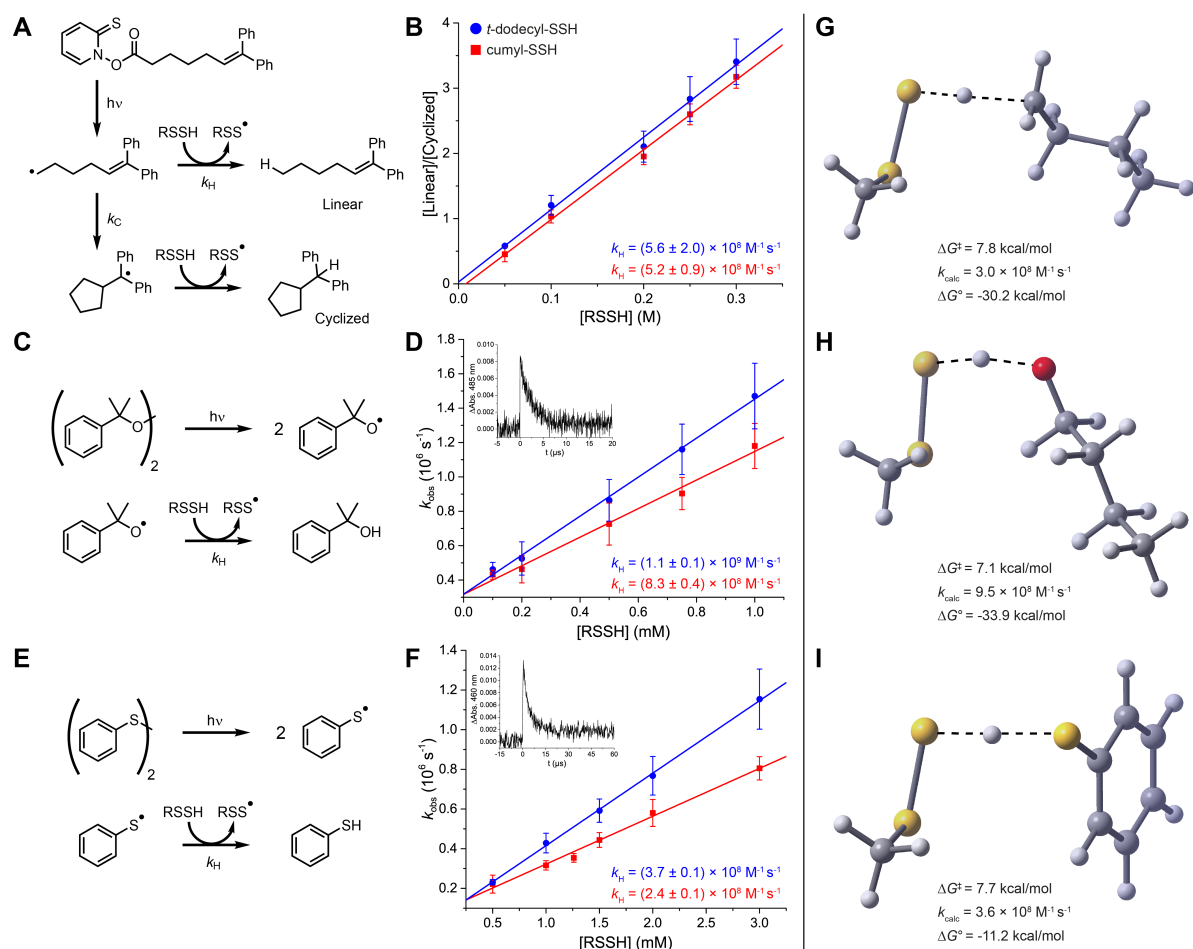


Figure 4.4. Photolytic generation of the 6,6-diphenylhexenyl radical and its use as a radical clock to obtain the rate constant for HAT from hydropersulfides to alkyl radicals (**A**). Ratio of linear and cyclized products as a function of the concentration of cumyl-SSH (red) or *t*-dodecyl-SSH (blue) during photocleavage of the radical precursor in benzene at 25 °C (**B**). Photolytic generation of cumyloxyl radicals from dicumylperoxide (**C**). Dependence of the pseudo-first order rate on the concentration of cumyl-SSH (red) or *t*-dodecyl-SSH (blue) upon photolysis of dicumylperoxide in benzene at 25 °C; inset: example decay of the cumyloxyl radical (**D**). Photolytic generation of phenylthiyl radicals from diphenyldisulfide (**E**). Dependence of the pseudo-first order rate on the concentration of cumyl-SSH (red) or *t*-dodecyl-SSH (blue) upon photolysis of diphenyldisulfide in benzene at 25 °C; inset: example decay of the phenylthiyl radical (**F**). Calculated (CBS-QB3) transition

state structures and associated free energy barriers, estimated rate constants and reaction free energies for HAT between a model hydropersulfide (MeSSH) and a model alkyl radical (*n*-Bu●) (**G**), a model alkoxy radical (*n*-BuO●) (**H**), and phenylthiyl radical (**I**).

Transient absorption spectroscopy was also used to obtain kinetics for the reaction of the hydropersulfides with the triplet state of benzophenone (corresponding data can be found in the Supporting Information). We expected similar results to those obtained with cumyloxyl radicals since the $n \rightarrow \pi^*$ state of the carbonyl group has an effectively unpaired electron on the oxygen atom. As for the reaction with cumyloxyl radicals, the experiment was performed under pseudo-first order conditions and the benzophenone triplet state monitored at 530 nm following photolysis at 308 nm. The resulting rate constants were determined to be $(1.1 \pm 0.1) \times 10^9$ and $(1.5 \pm 0.1) \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ for cumyl-SSH and *t*-dodecyl-SSH, respectively. Once again, the results of CBS-QB3 calculations are in excellent agreement with experiment, predicting a slightly faster reaction than with alkoxy radicals ($k = 1.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, $\Delta G^\ddagger = 6.9 \text{ kcal/mol}$) and a driving force of $\Delta G^0 = -36.5 \text{ kcal/mol}$. For comparison, thiols are reported to react with the benzophenone triplet much more slowly (e.g. $8.8 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for *n*-C₅H₁₂SH).⁵³

HAT between thiols and thiyl radicals, despite being a thermoneutral process, is a fast reaction. Literature reports offer rate constants that span 10^4 to $10^7 \text{ M}^{-1} \text{ s}^{-1}$, and our own CBS-QB3 calculations suggest a rate constant of $2.2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for the reaction between *n*-butylthiyl radical and *n*-butylthiol.⁵⁴ Thus, the analogous reaction between hydropersulfides and thiyl radicals, which would have a considerable driving force, could be diffusion-controlled. Despite the fact that thiyl radicals are quite easily generated (by photolysis of disulfides), they are challenging species to follow by optical spectroscopy due to their lack of absorbance $> 300 \text{ nm}$ (aromatic thiyls being the exception, *vide infra*). Fortunately, the perthiyl radical has an absorbance at 375 nm – enabling monitoring of the reaction by growth of this signal rather than consumption of the thiyl. Regardless, when *n*-butyl disulfide was photolyzed in the presence of cumyl-SSH or *t*-dodecyl-SSH, we were unable to fully resolve the

growth of the corresponding perthiyl radical. Considering the experimental conditions and the time resolution of our instrument, we estimate a lower-bound for the rate constant of $1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$. Efforts to compute a rate constant using the same CBS-QB3 approach that has yielded highly accurate predictions with peroxy, alkyl and alkoxy radicals gave inconsistent results. Initially, when MeSSH was used as a simplified model, a predicted rate constant of $4.2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ was obtained, but the larger *t*-BuSSH yielded $k_{\text{H}} = 1.2 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ ($\Delta G^\ddagger = 5.6 \text{ kcal/mol}$). The origins of this difference are unclear. Nevertheless, it seems reasonable to suggest that these reactions are indeed diffusion-controlled.

Phenyldisulfide was also used as a thiyl radical precursor (Figure 4.4E). We reasoned that the lower S-H BDE in thiophenol (83 kcal/mol)⁵⁵ would render the reaction of phenylthiyl radicals with the hydropersulfides less exergonic and this may afford the opportunity to measure its kinetics. Moreover, the phenylthiyl radical is characterized by a broad absorption band centered around 460 nm such that its decay in the presence of hydropersulfides could be followed directly by LFP (Figure 4.4F). Indeed, the rate constants for HAT could be determined as $(2.4 \pm 0.1) \times 10^8$ and $(3.7 \pm 0.1) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for cumyl-SSH and *t*-dodecyl-SSH, respectively. (Similar data were obtained for reactions of the hydropersulfides with 2-pyridinethiyl radicals, see the Supporting Information for the data). In this case it is difficult to compare these results to the kinetics of the corresponding reaction of a thiol since it would be endothermic. Interestingly, the calculated transition state structure for the reaction between the model hydropersulfide (MeSSH) and phenylthiyl radical (Figure 4.4I) suggests some interaction between the SOMO of the phenylthiyl radical and the HOMO of the hydropersulfide – a secondary orbital interaction not unlike that seen in the reaction with peroxy radicals (*cf.* Figure 4.2G). The associated free energy barrier is computed to be $\Delta G^\ddagger = 7.7 \text{ kcal/mol}$, equivalent to a rate constant of $3.6 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, in excellent agreement with experiment. Expectedly, the driving force for HAT from the hydropersulfide to phenylthiyl ($\Delta G^0 = -11.2 \text{ kcal/mol}$) is predicted to be smaller than to *n*-butylthiyl ($\Delta G^0 = -15.4 \text{ kcal/mol}$).

4.4 Discussion

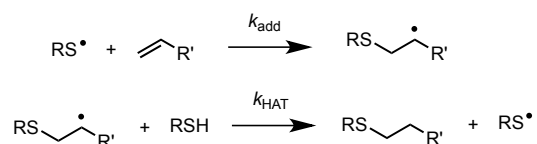
Thiols are often described as ‘antioxidants’, but this can be misleading. Their ionic reactions with H_2O_2 and hydroperoxides are not particularly fast ($k \sim 1 \text{ M}^{-1} \text{ s}^{-1}$ at neutral pH),⁵⁶ so they are used instead as reducing co-factors for enzymes (e.g. glutathione peroxidases) that catalyze reactions with these oxidants with kinetics that are greater by several orders of magnitude. Likewise, HAT from thiols to peroxy radicals, the key chain-carrying radicals in lipid peroxidation, are quite slow ($<10^3 \text{ M}^{-1} \text{ s}^{-1}$),^{28,57} making it impossible for them to compete with propagation of the peroxidation chain reaction. In a biological context, this task is largely the responsibility of α -tocopherol (α -TOH), owing to its much greater reactivity to peroxy radicals ($> 10^6 \text{ M}^{-1} \text{ s}^{-1}$).²⁹

According to the Evans-Polanyi principle and estimates of the RSS-H bond strength (70 kcal/mol),³⁰ hydropersulfides should undergo HAT reactions more readily than thiols (87 kcal/mol).³¹ The foregoing results establish that this is indeed true for HAT to peroxy radicals as well as alkyl, alkoxy and thiyl radicals. The inherent reactivity of hydropersulfides to peroxy radicals is particularly striking because it is 4 orders of magnitude greater than for thiols, and essentially the same as that of α -TOH, long considered the gold-standard against which other radical-trapping antioxidants are measured.^{58,59} In fact, upon transitioning from hydrocarbons to media containing H-bond accepting functionality, hydropersulfides become superior to α -TOH, owing to the fact that they do not engage in strong H-bonds. The weak H-bond donating acidities of hydropersulfides ($\alpha_2^H \sim 0.1$) make them ideal HAT agents to peroxy radicals, as all other classes that have similarly high reactivity ($k_{\text{inh}} > 10^6 \text{ M}^{-1} \text{ s}^{-1}$), which include some phenols,⁴² diarylamines,⁶⁰ sulfenic acids^{45,61} and hydroxylamines⁶² are characterized by significantly higher H-bond acidities (generally $\alpha_2^H \geq 0.4$). Moreover, the perthiyl radicals that arise upon HAT from hydropersulfides persist until they encounter another perthiyl radical with which they form tetrasulfides rather than carry on the oxidation via reactions with either O_2 or the substrate. These results suggest that unlike thiols, hydropersulfides, produced when cells synthesize H_2S , prevent lipid peroxidation.

In order to operate effectively in this capacity, the disulfides or other electrophilic thiol derivatives from which the hydropersulfides are produced should be relatively lipophilic. This ensures they have access to lipid regions where they are more likely to encounter lipid-derived peroxy radicals, and because the hydropersulfides are much less effective as H-atom donors in aqueous media. It is important to make the distinction between *effective* and *reactive*, since the hydropersulfides are highly reactive to peroxy radicals in aqueous solution. In fact, over a range of pH from 4 to 10, k_{inh} varied from 0.5 to $4.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ – greatly exceeding the corresponding rate constants obtained with Trolox, a water-soluble derivative of α -TOH ($k = 4.1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$), which varies little in the same pH range ($k = 2.1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ and $k = 6.8 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ at pH 4 and 9, respectively).⁴⁶ The pH dependence of hydropersulfide reactivity results from the increasing contribution of a faster electron transfer reaction between the persulfide anion and a peroxy radical as the pH approaches – and then exceeds – the estimated pK_{a} of the hydropersulfide (ca. 7).^{47,48} It is noteworthy that the position of the inflection point in the sigmoidal relationship between the inhibition rate constant and the pH nicely corroborate the pK_{a} value obtained by fitting the sigmoidal curve using a Boltzmann function and the values reported in the literature.

The difficulty associated with measuring a reliable pK_{a} value for hydropersulfides underlies why they are relatively ineffective radical-trapping antioxidants in aqueous solutions: they decompose too readily. As such, where the hydropersulfides each cleanly trap one peroxy radical by HAT in organic solution, the reaction stoichiometry decreases sharply in aqueous solution (0.3 at pH 4) and is further eroded with increasing pH where decomposition is accelerated.³³ Hydropersulfides are known to decompose to yield mixtures of polysulfides and thiols,³³ which are unreactive to peroxy radicals.³⁶

In contrast to the insignificant role of HAT reactions between thiols and peroxy radicals, thiols are important reagents in a variety of alkyl radical-mediated reactions, perhaps most importantly in the thiol-ene reaction (Scheme 4.1).



Scheme 4.1. The radical chain propagation steps of a generalized thiol-ene reaction.

A corresponding hydropersulfide-ene reaction would, in principle, provide a route to unsymmetric disulfides. Although hydropersulfides are two orders of magnitude more reactive to (primary) alkyl radicals than thiols, and it is often the HAT step that is rate-controlling in the propagation sequence, it is likely that the perthiyl addition would be too thermodynamically unfavourable (CBS-QB3 predicts the reaction with styrene to have $\Delta G^\circ = +9.4$ kcal/mol). Indeed, while we have estimated that styrene reacts with *t*-butylperthiyl radicals generated by laser flash photolysis of *t*-BuSSSS*t*-Bu with $k = 1.1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ (see Supporting Information) this was only observed in the presence of O_2 , which presumably trapped the intermediate benzylic radical precluding the reverse reaction (fragmentation).⁶³ This can be compared to the addition of thiyl radicals to styrene, which proceeds 200-fold faster, and is slightly exothermic (CBS-QB3 predicts the reaction to have $\Delta G^\circ = -4.5$ kcal/mol).⁶⁴ Although it seems unlikely that disulfides can be prepared via a hydropersulfide-ene reaction, hydropersulfides may yet find use in place of thiols for other transformations.

Our expectations for the greater HAT reactivity of hydropersulfides compared to thiols are based on the S-H BDE estimates that were made on the basis of Benson's group additivity scheme.^{30,47,65} These estimates have been corroborated by the high accuracy quantum chemical calculations (CBS-QB3) we have made use of here, which suggest BDEs of 70.8, 70.4 and 70.4 kcal/mol in MeSSH, *t*-BuSSH and cumyl-SSH, respectively. Given the similarity of the hydropersulfide S-H BDE with that of the hydroxylamine derived from the persistent nitroxide TEMPO (69.6 kcal/mol),⁶⁶ we attempted experimental confirmation of a hydropersulfide S-H BDE by

measuring the equilibrium constant for eq 4.2 by EPR – an approach used to obtain many X-H BDEs (making the reasonable assumption that $\Delta S \sim 0$ for the HAT process).^{67,68}



Sadly, despite extensive efforts, we were unable to resolve a signal for the perthiyl radical. Expecting that this may be due to its rapid dimerization to the tetrasulfide ($k = 6.0 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$),⁶⁹ we also carried out the reaction under continuous photolysis, but to no avail (see Supporting Information). It is important to note that Fukuto, Toscano and co-workers recently reported similar results.⁷⁰ This led us to suspect that the nitroxide and perthiyl may react with each other. Indeed, perthiyl radicals generated by laser flash photolysis of solutions of di-*tert*-butyl tetrasulfide gave clean pseudo-first order decay kinetics in the presence of TEMPO that afforded a second order rate constant of $(1.9 \pm 0.1) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$. The formation of the perthiyl-TEMPO adduct is readily reversible since the central S-O bond is very weak ($\Delta G^\circ = 6.0 \text{ kcal/mol}$, by CBS-QB3), but competitive N-O bond cleavage of the adduct (which requires only 4.2 kcal/mol more free energy, by CBS-QB3) leads to reactive products, precluding the reverse reaction. This would account for the inability to observe the perthiyl radical in the radical equilibration experiment.⁷¹

4.5 Conclusion

Hydropersulfides are excellent H-atom donors towards alkyl ($k \sim 5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$), alkoxyl ($k \sim 1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$), peroxy ($k \sim 2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$) and thiyl ($k > 1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$) radicals – besting thiols in all cases by at least one, and up to four, orders of magnitude. The inherently high reactivity of hydropersulfides to H-atom transfer is based largely on thermodynamic factors; the weak RSS-H BDE ($\sim 70 \text{ kcal/mol}$) and associated high stability of the perthiyl radical makes the foregoing reactions exothermic by 15 to 34 kcal/mol. Given the implication of hydropersulfides in redox biology, their (peroxy) radical-trapping antioxidant activity may be the most relevant reactivity studied here. The favourable

thermodynamics of the reaction are bolstered by secondary orbital interactions in the HAT transition state that enhance the kinetics. Furthermore, the persistence of the product perthiyl radicals – toward both O₂ and the substrate undergoing autoxidation – is key, as is their near-diffusion-controlled combination to give innocuous tetrasulfide products. A highly unique attribute of hydropersulfides as radical-trapping antioxidants is their low H-bond acidity, which makes their reactivity relatively insensitive to changes in solvent/medium. The reactivity of well-established radical-trapping antioxidants, such as phenols and diarylamines, are highly medium-dependent owing to strong H-bond interactions of the H-atom undergoing HAT. The radical-trapping antioxidant activity of hydropersulfides may be exploited by amphiphilic disulfides (thiols) in small molecules and/or proteins exposed to exogenous H₂S, which is known to readily transverse and accumulate in lipid bilayers.⁷²⁻⁷⁴ Whether this reactivity could be exploited in the design of small molecule preventive and/or therapeutic agents for diseases wherein lipid peroxidation (ferroptosis)⁷⁵⁻⁷⁷ has been implicated remains to be explored.

4.6 Experimental Section

4.6.1 General

Reagents were obtained from commercial suppliers and used as is, unless indicated otherwise. Column chromatography was carried out with 40-63 μ m, 230-400 mesh silica gel. ¹H and ¹³C NMR spectra were recorded on a Bruker AVANCE spectrometer at 400 MHz and 101 MHz, respectively, unless indicated otherwise. High-resolution mass spectra were obtained on a Kratos Concept Tandem mass spectrometer (EI) and Micromass Q-TOF (ESI). PBD-BODIPY and STY-BODIPY were synthesized following our previously reported procedure.³⁵ Chlorobenzene was dried over 3 Å molecular sieves before use. UV-visible spectra were measured with a Cary 100 spectrophotometer equipped with a thermostatted 6 x 6 multi-cell holder. pH measurements were carried out using an Accumet Electrode referenced to Ag/AgCl. pD were measured by adding a correction factor of 0.4 to the pH readings (pD

= $\text{pH}_{\text{read}} + 0.4$).⁷⁸ Unless otherwise indicated, the reported error bars were obtained from the standard deviation of at least three experimental trials.

4.6.2 Synthetic Procedures

The syntheses of cumyl-SSH and *t*-dodecyl-SSH have been achieved following a similar approach to Pluth's reported methods.³³ For the complete synthetic procedure of the intermediates see supporting information.

Cumylhydropersulfide (cumyl-SSH). Cumylacetyl disulfide (0.10 g, 0.44 mmol) was dissolved in methanol under nitrogen at 0 °C. In a separate flask, a 5 M methanolic solution of HCl was made by the addition of acetyl chloride (0.89 mL) to methanol (1.61 mL) at 0 °C. The HCl solution (0.30 mL, 1.50 mmol) was added dropwise to the cumylacetyl disulfide solution after which the flask was equipped with a nitrogen balloon directly on the septum, without the use of a needle to avoid any metal from making contact in the flask. The reaction was stirred overnight at room temperature and the solvent was evaporated by rotary evaporation with a water bath at room temperature to yield the product as a clear colorless oil (67 mg, 83%). ¹H NMR (400 MHz; CDCl₃): δ 7.52-7.49 (m, 2H), 7.38-7.33 (m, 2H), 7.28-7.23 (m, 1H), 2.62 (s, 1H), 1.76 (s, 6H). ¹³C NMR (101 MHz; CDCl₃): δ 144.4, 128.4, 127.2, 126.8, 51.3, 28.0. HRMS (ESI, [M-H⁺]): *m/z* calc. for C₉H₁₁S₂: 183.0307, found 183.0302.

***t*-Dodecylhydropersulfide (*t*-dodecyl-SSH).** *t*-Dodecylacetyl disulfide (0.10 g, 0.36 mmol) was dissolved in isopropanol under nitrogen at 0 °C. In a separate flask, a 5 M methanolic solution of HCl was made by the addition of acetyl chloride (0.89 mL) to methanol (1.61 mL) at 0 °C. The HCl solution (0.25 mL, 1.24 mmol) was added dropwise to the *t*-butyldodecylacetyl disulfide solution after which the flask was equipped with a nitrogen balloon directly on the septum, without the use of a needle to avoid any metal from making contact in the flask. The reaction was stirred overnight at room

temperature and the solvent was evaporated by rotary evaporation with a water bath at room temperature to yield the product as a clear colorless oil (74 mg, 87%). ^1H NMR (300 MHz; CDCl_3): δ 2.63 (s, 1H), 1.57-1.52 (m, 2H), 1.37-1.32 (m, 3H), 1.27 (br s, 17H), 0.88 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR (76 MHz; CDCl_3): δ 48.9, 40.5, 32.0, 30.2, 29.8, 29.5, 26.8, 24.8, 22.8, 14.3. HRMS (ESI, $[\text{M}-\text{H}^+]$): m/z calc. for $\text{C}_{12}\text{H}_{25}\text{S}_2$: 233.1398, found 233.1394.

4.6.3 General Procedure for Inhibited Autoxidations

Inhibited autoxidations were carried out following our recently published method.³⁵ Similar procedures were used for all autoxidations reported herein, the procedure for THF autoxidation in chlorobenzene is given as an example. For detailed autoxidation procedures of other substrates in various solvents, see supporting information. A 3.5 mL quartz cuvette was loaded with unstabilized THF (0.625 mL) along with PhCl (1.805 mL), such that the final reaction volume is 2.50 mL. The cuvette was then pre-heated in a thermostatted sample holder of a UV-vis spectrophotometer and allowed to equilibrate to 37 °C for approximately 15 minutes. A small volume (12.5 μL) of a 2.00 mM solution of the PBD-BODIPY probe in 1,2,4-trichlorobenzene was added, followed by 50 μL of a 300 mM solution of AIBN in PhCl. The solution was thoroughly mixed and the absorbance at 588 nm was monitored for 10 minutes to ensure that the reaction was proceeding at a constant rate, after which 10.0 μL of a solution of the test antioxidant was added. The solution was thoroughly mixed and the absorbance readings resumed. The resulting data was processed as previously reported.³⁵ The rate of initiation ($R_i = 3.2 \times 10^{-9} \text{ M s}^{-1}$) and propagation rate constant for the dye ($k_{\text{PBD-BODIPY}} = 2240 \text{ M}^{-1} \text{ s}^{-1}$) necessary to derive stoichiometric data and inhibition rate constants, were determined using PMC as a standard, which has an established stoichiometry of 2.⁷⁹

4.6.4 Alkyl Radical Clock Kinetics

Alkyl radical clock kinetics were determined using a previously reported procedure by Newcomb.^{50,51} The PTOC ester and the standards were synthesized according to the procedures described therein. Briefly, vials equipped with a septum and wrapped in aluminum foil were loaded with the appropriate amount of hydropersulfides (50-300 mM) and PTOC ester clock (20 mM) in THF (1 mL). The vials were thoroughly purged with nitrogen for 10 minutes before the aluminum foil was removed and the vials exposed to a high pressure sodium lamp (400 W) at a distance of 50 cm for 1 h. A 50 μ L aliquot was taken from each vial and added to a GC vial containing 50 μ L of a hexylbenzene standard solution (40 mM). The solution was diluted by adding 900 μ L of benzene for a total volume of 1 mL per vial. The samples (4 μ L splitless injections) were analyzed by GC-MS equipped with an Agilent HP-5 ms column (30 m x 0.25 mm x 0.25 μ m) with a constant He flow of 1.2 mL min⁻¹ using the following temperature profile (inlet temperature was set at 260 °C): 100 °C hold 3 min, 8 °C min⁻¹ to 260 °C, hold 12 min. The method yielded retention times of 7.1, 15.9, and 16.7 min for hexylbenzene, linear and cyclized products, respectively.

4.6.5 Laser Flash Photolysis

Nanosecond transient absorption experiments were performed on an LFP-112 spectrometer (Luzchem, Canada). Irradiation source was an EX10 (GAM Laser, USA) XeCl Excimer laser (308 nm, ca. 10 mJ/pulse, ca. 12 ns pulse width). The transient absorption data were recorded in a quartz cuvette (1 cm x 1 cm) equipped with a septum. Sample concentrations in benzene/PhCl were adjusted to yield an absorbance of 0.2-0.3 at 308 nm and the solutions were bubbled with nitrogen for 10 minutes before measurement. The rate constants for hydrogen abstraction (k_H) were determined in pseudo-first-order according to the following equation $k_{\text{obs}} = k_0 + k_H[\text{RSSH}]$.

4.6.6 Calculations

Calculations were carried out using the CBS-QB3⁸⁰ complete basis set method as implemented in the Gaussian 09⁸¹ suite of programs. Rate constants were calculated via transition state theory at 25 °C, except for peroxy (37 °C).

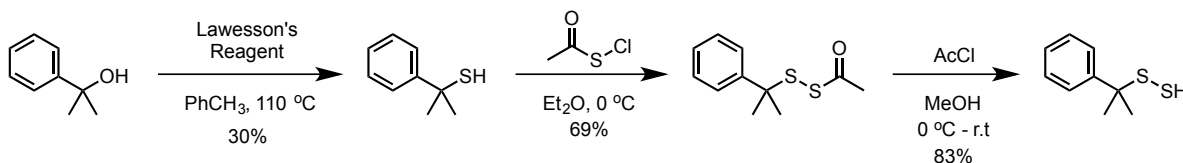
Optimized structures and energies (Gaussian 09) of the computationally calculated structures are provided in the Supporting Information section of the publication in the Journal of the American Chemical Society (Chauvin, J.-P. R.; Griesser, M.; Pratt, D. A. *J. Am. Chem. Soc.* **2017**, *139*, 6484–6493.)

4.7 Supporting Information

4.7.1 General

Cumene was extracted three times with NaOH (1 M), washed with water, dried with MgSO₄, filtered, distilled under reduced pressure and percolated through a silica column. The purified material could be kept at -20 °C under nitrogen for up to 5 days. Immediately before use, the distilled material was percolated again through a column with silica/basic alumina (1:4). 2-Methylundecene,⁸² acetylsulfonyl chloride,^{83,84} and di-*tert*-butyl tetrasulfide⁸⁵ were synthesized according to previously reported procedures. pH measurements were carried out using an Accumet Electrode referenced to Ag/AgCl. pD values were measured by adding a correction factor of 0.4 to the pH readings ($pD = pH_{\text{read}} + 0.4$).⁸⁶ For pH 4.0 buffer, 100 mM sodium acetate/acetic acid was made in milli Q water and the pH was adjusted with 1 M NaOH or 1 M HCl. For pH 5.8 - 9.0 buffers, 100 mM phosphate buffers were made in Milli-Q water and the pH adjusted with 1 M NaOH or 1M HCl. The buffers in D₂O were made following the same procedure, using DCl and NaOD (1M in D₂O) to adjust the pH. Electron paramagnetic resonance (EPR) spectra were recorded on a Bruker EMXplus (X-band) spectrometer equipped with an ER 4119HS cavity. The radical concentration was determined using the quantitative EPR package of the Bruker Xenon software.

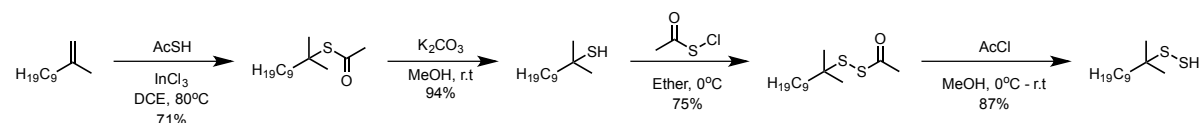
4.7.2 Synthetic Procedures



Cumylthiol.⁸⁷ 2-Phenyl-2-propanol (5.00 g, 36.7 mmol) was dissolved in toluene (360 mL) under nitrogen. After stirring for 5 minutes, Lawesson's reagent (14.8 g, 36.7 mmol) was added and the solution was heated at reflux (110 °C) for 3 hours. The solvents were removed under reduced pressure

and the crude solid was purified by column chromatography using hexanes as the eluent to yield the product as a clear pale yellow oil (1.67 g, 30%). ^1H NMR (300 MHz; CDCl_3): δ 7.59-7.56 (m, 2H), 7.36-7.30 (m, 2H), 7.25-7.19 (m, 1H), 2.25 (s, 1H), 1.84 (d, $J = 0.4$ Hz, 6H). ^{13}C NMR (101 MHz; CDCl_3): δ 148.6, 128.4, 126.8, 125.5, 46.0, 34.6. HRMS (ESI, $[\text{M}-\text{H}^+]$): m/z calcd for $\text{C}_9\text{H}_{11}\text{S}$: 151.0581, found 151.0567.

Cumylacetyl disulfide. Cumylthiol (0.60 g, 3.90 mmol) was dissolved in ether (2.2 mL) and cooled to 0 °C under nitrogen. Acetyl sulfenyl chloride (0.47 g, 4.29 mmol) in ether (2.2 mL) was added dropwise and the mixture was warmed to room temperature and stirred for 2 hours. The solvent was removed and the crude oil was purified by column chromatography using hexanes as the eluent to yield the product as a clear colorless oil (0.61 g, 69%). ^1H NMR (400 MHz; CDCl_3): δ 7.55-7.52 (m, 2H), 7.37-7.32 (m, 2H), 7.28-7.24 (m, 1H), 2.30 (s, 3H), 1.72 (s, 6H). ^{13}C NMR (101 MHz; CDCl_3): δ 195.5, 144.0, 128.4, 127.6, 126.8, 53.9, 28.6, 28.5. No molecular ion was obtained during mass spectral analysis due to its decomposition to the cumyl (radical) cation.



tert-Dodecylthiol. 2-Methylundecene (5.00 g, 30.0 mmol) and InCl_3 (0.33 g, 1.50 mmol) were dissolved in 1,2-dichloroethane (30.0 mL) in a round bottom flask equipped with a reflux condenser and the solution was purged with nitrogen. Thioacetic acid (2.14 mL, 30.0 mmol) was added dropwise through the condenser and the solution was refluxed at 80 °C for 2 hours. After cooling to room temperature, ether was added and the organic layer extracted with 1 M HCl_{aq} , water and brine. The resulting organic phase was dried with magnesium sulfate, filtered through a pad of celite and solvents removed under reduced pressure to yield crude *tert*-dodecyl thioacetate as a clear pale yellow oil that was used in the next step without further purification.⁸⁸ Potassium carbonate (3.60 g, 26.1 mmol) was added to a solution of *tert*-dodecyl thioacetate (5.80 g, 23.8 mmol) in methanol (70.0 mL). The resulting solution was stirred at room temperature for 3 hours after which it was poured into ether and

extracted with water and brine. The resulting organic phase was dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The crude oil was purified by column chromatography using pet ether as the eluent yield the product as a clear colorless oil (4.50 g, 94%). ^1H NMR (400 MHz; CDCl_3): δ 1.67 (s, 1H), 1.57-1.53 (m, 2H), 1.42-1.38 (m, 2H), 1.37 (d, $J = 0.4$ Hz, 6H), 1.28 (br, 12H), 0.88 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (101 MHz; CDCl_3): δ 46.8, 45.0, 33.0, 32.0, 30.2, 29.8, 29.5, 25.5, 22.8, 14.3. HRMS (ESI, $[\text{M}-\text{H}^+]$): m/z calcd for $\text{C}_{12}\text{H}_{25}\text{S}$: 201.1677, found 201.1670.

tert-Dodecylacetyl disulfide. *tert*-Dodecylthiol (0.40 g, 1.98 mmol) was dissolved in ether (1.1 mL) and cooled to 0 °C under nitrogen. Acetyl sulfenyl chloride (0.24 g, 2.18 mmol) in ether (1.1 mL) was added dropwise and the mixture was warmed to room temperature and stirred for 2 hours. The solvent was removed and the crude oil was purified by column chromatography using hexanes as the eluent to yield the product as a clear colorless oil (0.41 g, 75%). ^1H NMR (300 MHz; CDCl_3): δ 2.45 (s, 3H), 1.55-1.50 (m, 2H), 1.46-1.30 (m, 3H), 1.27 (br s, 11H), 1.25 (s, 6H), 0.88 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR (101 MHz; CDCl_3): δ 195.6, 52.5, 41.8, 32.0, 30.2, 29.72, 29.69, 29.5, 28.9, 27.5, 24.9, 22.8, 14.3. HRMS (EI, $[\text{M}]^+$): m/z calcd for $\text{C}_{14}\text{H}_{28}\text{OS}_2$: 276.1582, found 276.1584.

4.7.3 Deuterium Kinetic Isotope Effects

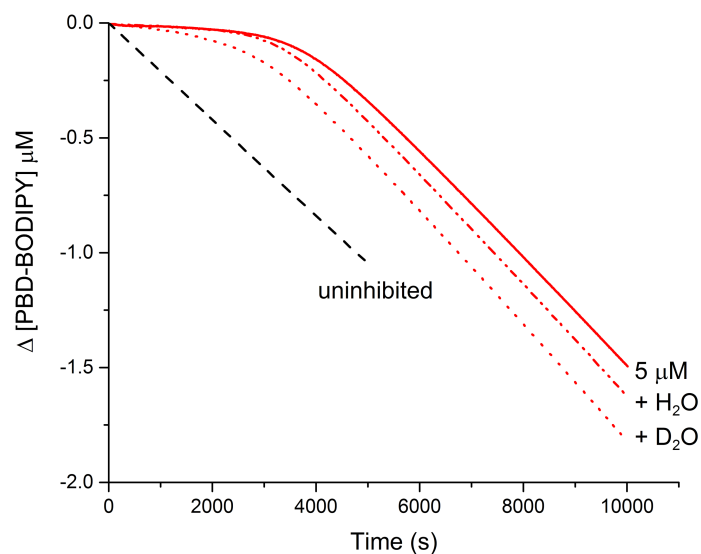


Figure 4.5. Thermally initiated (AIBN, 6 mM) co-oxidations of THF (3.1 M) and PBD-BODIPY (10 μ M) at 37 $^{\circ}$ C in PhCl inhibited by cumyl-SSH (5 μ M) and in the presence of H₂O or D₂O (1%, v/v).

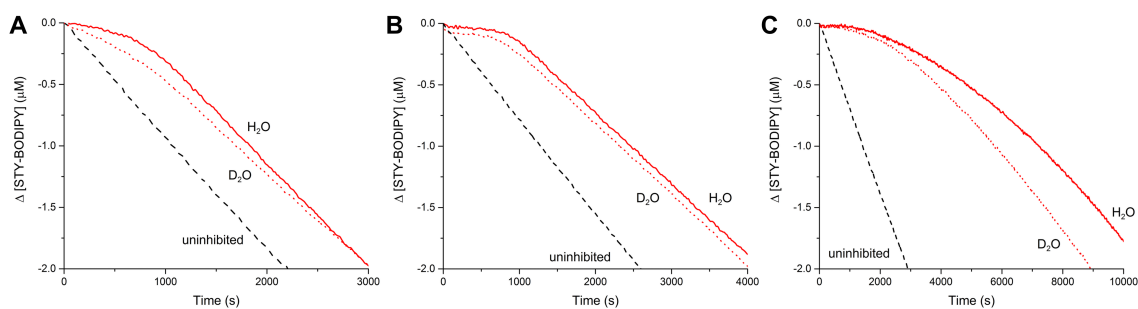


Figure 4.6. Thermally initiated (AAPH, 1 mM) co-oxidations of THF (3.1 M) and STY-BODIPY (10 μ M) at 37 $^{\circ}$ C in buffer inhibited by cumyl-SSH (5 μ M) at pH (or pD) 4.0 (**A**), 7.0 (**B**), or 9.0 (**C**).

4.7.4 Standardization of Co-autoxidations in Organic Solutions

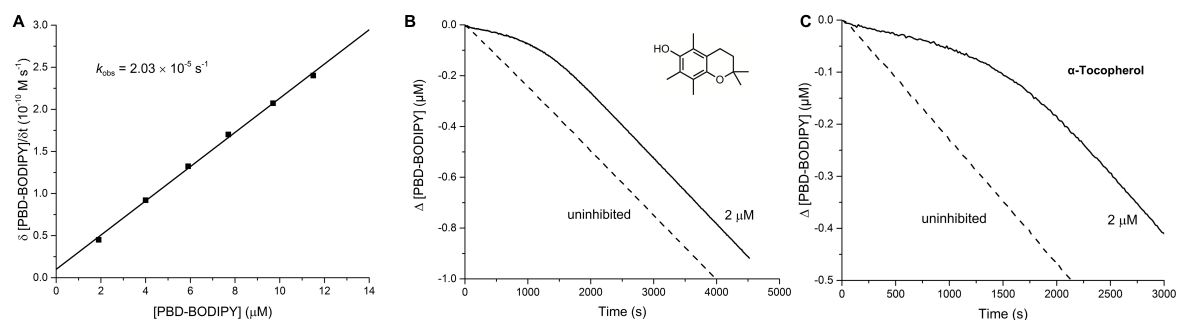


Figure 4.7. Rate of PBD-BODIPY consumption as a function of its concentration in AIBN-initiated (6 mM) co-autoxidations with THF (3.1 M) in PhCl at 37 °C (A). Thermally initiated (AIBN, 6 mM) co-autoxidations of THF (3.1 M) and PBD-BODIPY (10 μM) at 37 °C in PhCl inhibited by 2 μM of PMC (B) or α -TOC (C). Reaction progress was monitored via absorbance at 588 nm ($\epsilon = 128\,100 \text{ M}^{-1} \text{ cm}^{-1}$). See Figure 4.1 for co-autoxidations inhibited by cumyl-SSH and *t*-dodecyl-SSH.

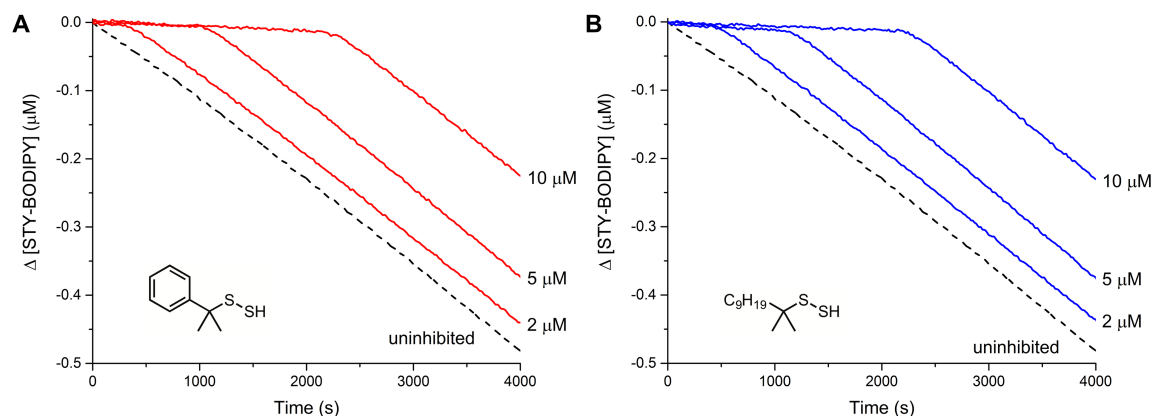


Figure 4.8. Thermally initiated (AIBN, 6 mM) co-autoxidations of cumene (3.6 M) and STY-BODIPY (10 μM) in PhCl at 37 °C inhibited by 2, 5, and 10 μM of cumyl-SSH (A) or *t*-dodecyl-SSH (B). Reaction progress was monitored via absorbance at 571 nm ($\epsilon = 128\,000 \text{ M}^{-1} \text{ cm}^{-1}$).⁸⁹

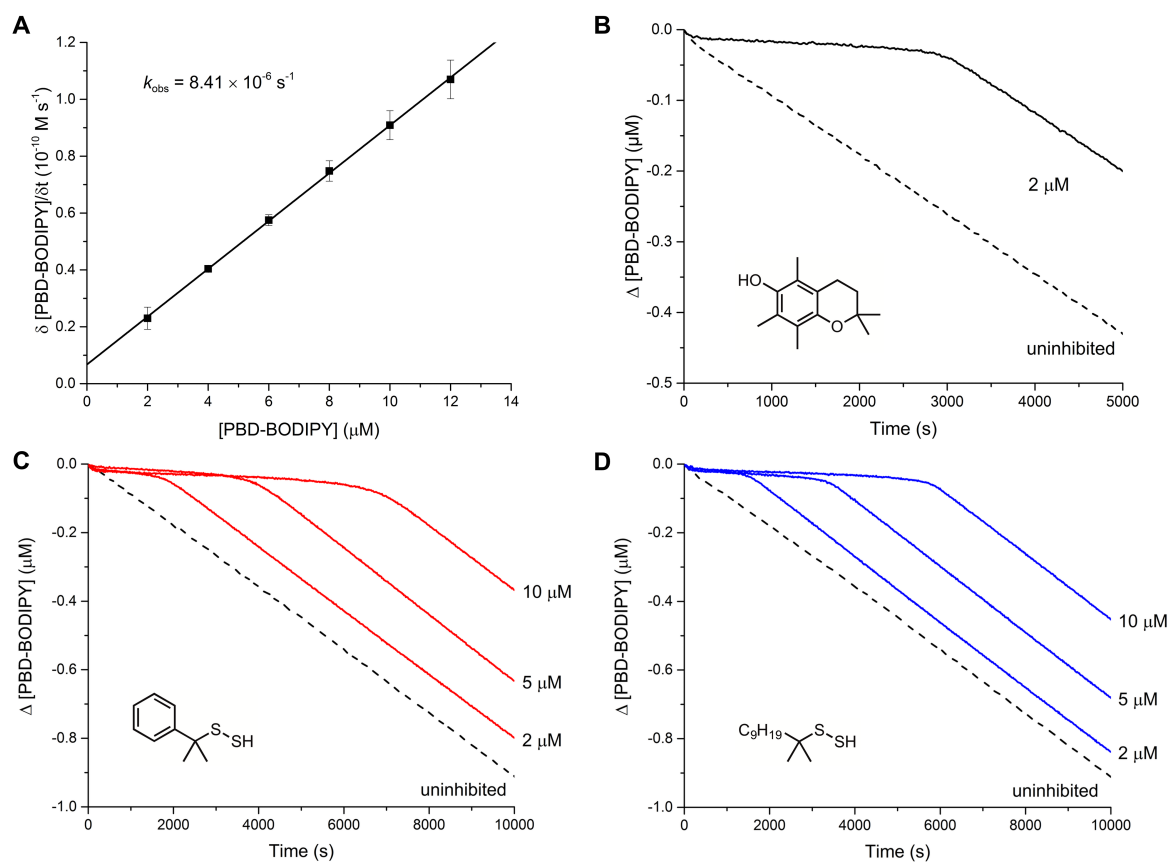


Figure 4.9. Rate of PBD-BODIPY consumption as a function of its concentration in AIBN-initiated (6 mM) co-oxidations with hexadecene (2.8 M) in PhCl at 37 °C (A). Thermally initiated (AIBN, 6 mM) co-oxidations of hexadecene (2.8 M) and PBD-BODIPY (10 μM) at 37 °C in PhCl inhibited by 2 μM of PMC (B), or 2, 5, and 10 μM of cumyl-SSH (C), and *t*-dodecyl-SSH (D). Reaction progress was monitored via absorbance at 588 nm ($\epsilon = 148\,700 \text{ M}^{-1} \text{ cm}^{-1}$).

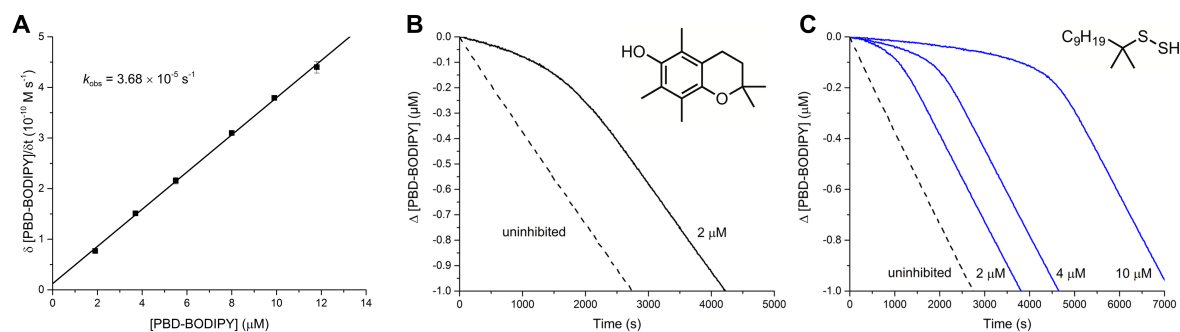


Figure 4.10. Rate of PBD-BODIPY consumption as a function of its concentration in AIBN-initiated (6 mM) co-oxidations with dioxane (2.9 M) in PhCl at 37 °C (A). Thermally initiated (AIBN, 6 mM) co-oxidations of dioxane (2.9 M) and PBD-BODIPY (10 μM) at 37 °C in PhCl inhibited by 2 μM of PMC (B) or 2, 4, and 10 μM of *t*-dodecyl-SSH (C). Reaction progress was monitored via absorbance at 587 nm ($\epsilon = 123\,000 \text{ M}^{-1} \text{ cm}^{-1}$).

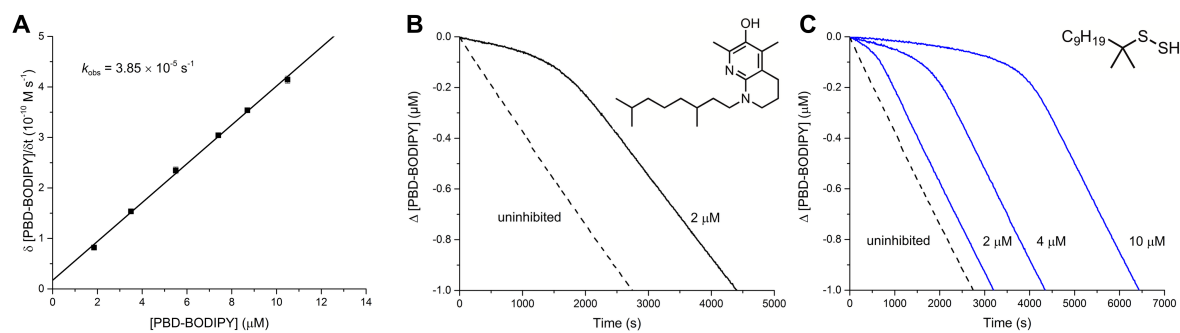


Figure 4.11. Rate of PBD-BODIPY consumption as a function of its concentration in AIBN-initiated (6 mM) co-oxidations with dioxane (2.9 M, 25% v/v) in DMSO (25% v/v) and PhCl (50% v/v) at 37 °C (A). Thermally initiated (AIBN, 6 mM) co-oxidations of dioxane (2.9 M, 25% v/v) and PBD-BODIPY (10 μM) in DMSO (25% v/v) and PhCl (50% v/v) at 37 °C inhibited by 2 μM of C₁₀-THN (B) or 2, 4, and 10 μM of *t*-dodecyl-SSH (C). Reaction progress was monitored via absorbance at 587 nm ($\epsilon = 118\,200 \text{ M}^{-1} \text{ cm}^{-1}$).

4.7.5 Summary of Rate Constants in Organic Solutions

Table 4.1. Summary of rate constants (k_{inh}) and stoichiometry (n) during inhibited co-autoxidations of various substrates (6 mM AIBN) at 37 °C.

Substrate/Solvent	cumyl-SSH		<i>t</i> -dodecyl-SSH	
	k_{inh} ($\text{M}^{-1} \text{s}^{-1}$)	n	k_{inh} ($\text{M}^{-1} \text{s}^{-1}$)	n
Cumene/PhCl	nd^a	0.9 ± 0.1	nd^a	0.9 ± 0.1
Dioxane/PhCl	-	-	$(7.2 \pm 0.7) \times 10^5$	1.0 ± 0.1
Dioxane/DMSO/PhCl	-	-	$(5.7 \pm 0.7) \times 10^5$	0.7 ± 0.1
Hexadecene/PhCl	$(1.5 \pm 0.5) \times 10^6$	0.9 ± 0.1	$(1.6 \pm 0.3) \times 10^6$	0.9 ± 0.1

^a nd = not determined; propagation was not sufficiently competitive to yield a sufficient slope to reliably determine k_{inh} .

Table 4.2. Summary of parameters for the standardization of co-autoxidations of PBD-BODIPY in various solvents at 37 °C.

Substrate/Solvent	λ_{max}	ϵ	$k_{\text{PBD-BODIPY}}$	R_i
	(nm)	($\text{M}^{-1} \text{cm}^{-1}$)	($\text{M}^{-1} \text{s}^{-1}$)	($\times 10^{-9} \text{M s}^{-1}$)
Dioxane/PhCl	587	123 000	5300	2.4
Dioxane/DMSO/PhCl	587	118 200	5900	2.1
Hexadecene/PhCl	588	148 700	3790	1.3
THF/PhCl	588	128 100	2240	3.2

4.7.6 Standardization of Co-autoxidations in Aqueous Solutions

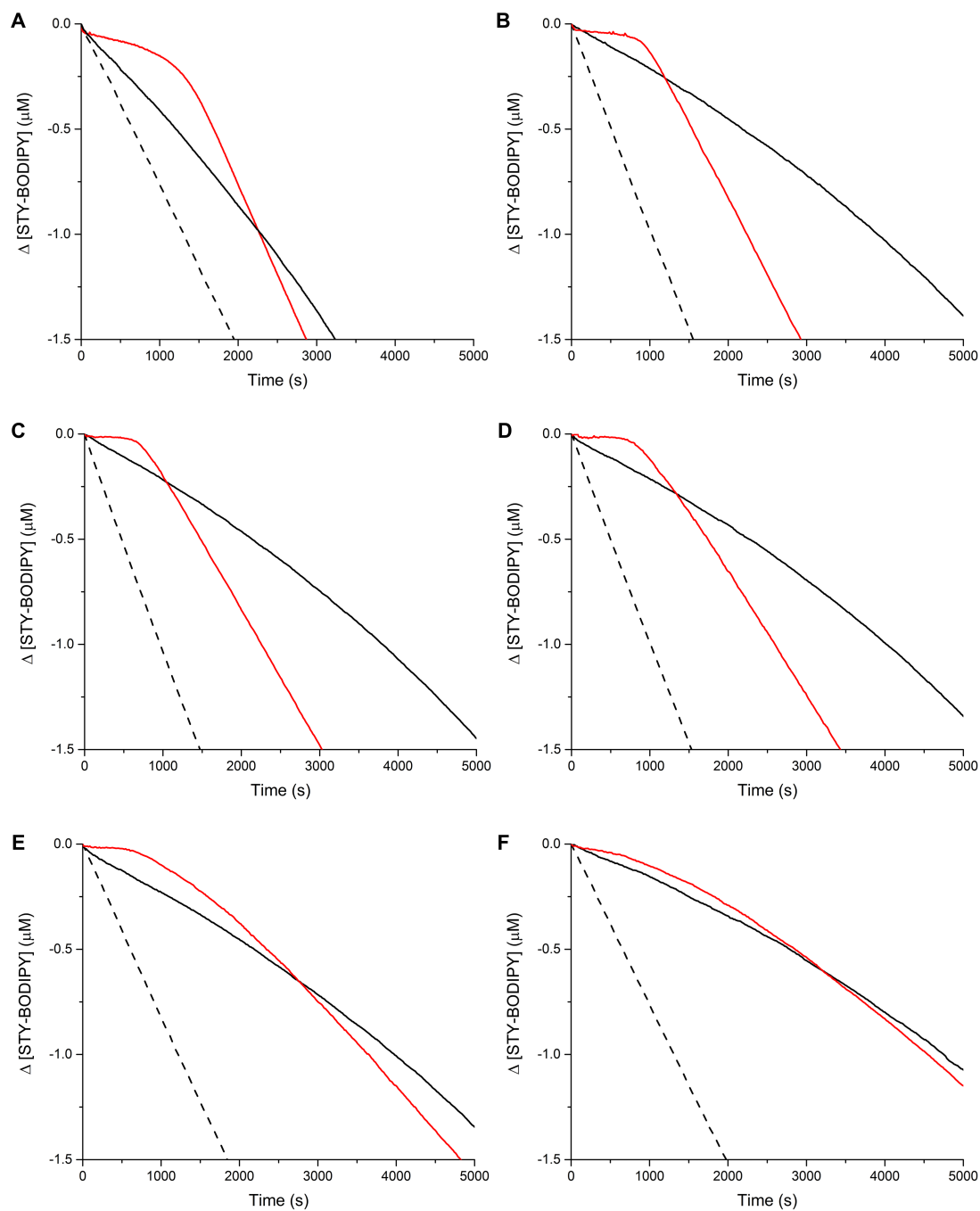


Figure 4.12. Thermally initiated (AAPH, 1 mM) co-autoxidations of THF (3.1 M) and STY-BODIPY (10 μM) at 37 $^{\circ}\text{C}$ in buffer (dashes) or inhibited by Trolox (4 μM , black) or cumyl-SSH (10 μM , red) at pH 4 (A), pH 5.8 (B), pH 6.5 (C), pH 7.0 (D), pH 8.0 (E), and pH 9.0 (F). Reaction progress was monitored via absorbance at 565 nm ($\epsilon = 132\,300 \text{ M}^{-1} \text{ cm}^{-1}$).

4.7.7 Summary of Rate Constants in Aqueous Solutions

Table 4.3. Summary of parameters for the standardization of co-autoxidations of STY-BODIPY in various buffers at 37 °C.

	$k_{\text{STY-BODIPY}}$	R_i	k_{inh}^a
pH	($\times 10^4 \text{ M}^{-1} \text{ s}^{-1}$)	($\times 10^{-9} \text{ M s}^{-1}$)	($\times 10^5 \text{ M}^{-1} \text{ s}^{-1}$)
4.0	2.2	1.74	2.1
5.8	3.3	1.45	3.2
6.5	4.2	1.56	3.8
7.0	4.2	1.31	4.1
7.4	4.4	1.50	4.2
8.0	5.3	1.30	5.4
9.0	6.2	1.25	6.8

^a The k_{inh} values for Trolox, used to determine $k_{\text{STY-BODIPY}}$, were obtained from the slope of k_{inh} vs pH for Trolox measured by oxygen consumption.⁹⁰

4.7.8 Hydrogen Atom Abstraction by the Benzophenone Triplet

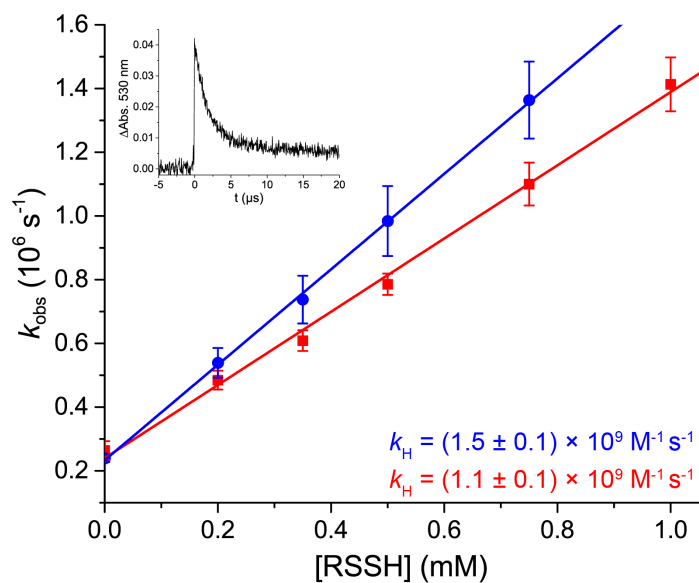


Figure 4.13. Dependence of the pseudo-first order rate on the concentration of cumyl-SSH (red) or *t*-dodecyl-SSH (blue) upon photolysis of benzophenone (BP) in benzene at 25 °C; where the inset shows an example decay of the BP triplet.

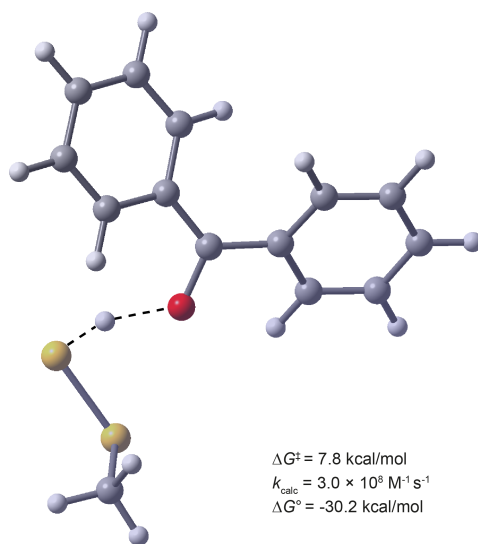


Figure 4.14. Calculated (CBS-QB3) transition state structures and associated free energy barriers, estimated rate constants, and reaction free energies for HAT between a model hydropersulfide (MeSSH) and the excited triplet state of benzophenone (BP).

4.7.9 Hydrogen Atom Abstraction by the *n*-Butylthiyl Radical

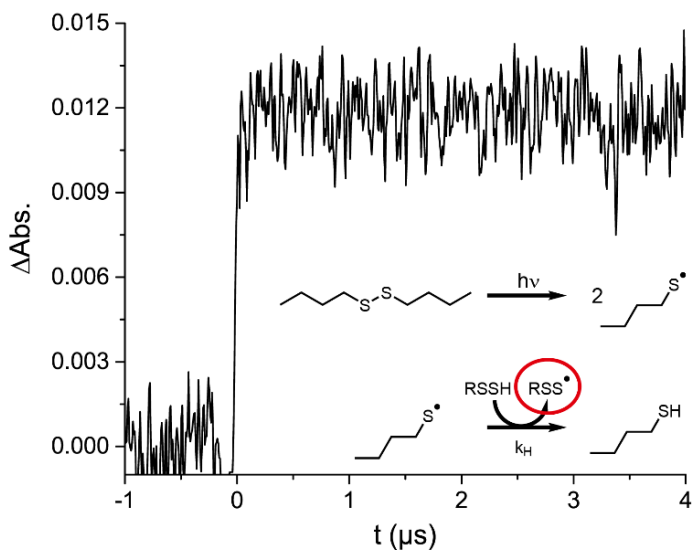


Figure 4.15. Transient absorption trace (375 nm) of a solution of 0.1 mM butyl disulfide and 0.1 mM *t*-dodecyl-SSH in benzene. The monitored species is the generated perthiyl radical (see inset).

4.7.10 Hydrogen Atom Abstraction by the 2-Pyridylthiyl Radical

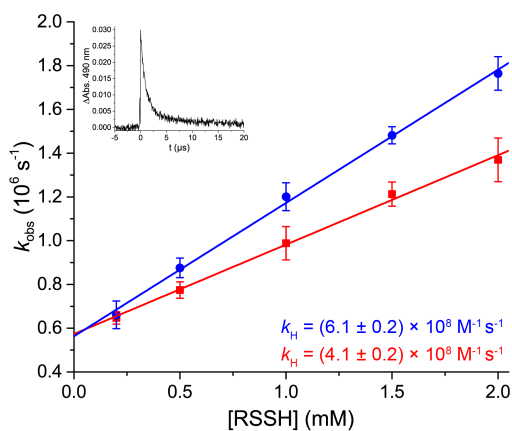


Figure 4.16. Dependence of the pseudo-first order rate on the concentration of cumyl-SSH (red) or *t*-dodecyl-SSH (blue) upon photolysis of the radical precursor (PTOC-ester, see Figure 4A) in benzene at 25 °C; where the inset shows an example decay of the 2-pyridylthiyl radical.

4.7.11 Estimation of the Kinetics of Addition of the *t*-Butylperthiyl Radical to Styrene

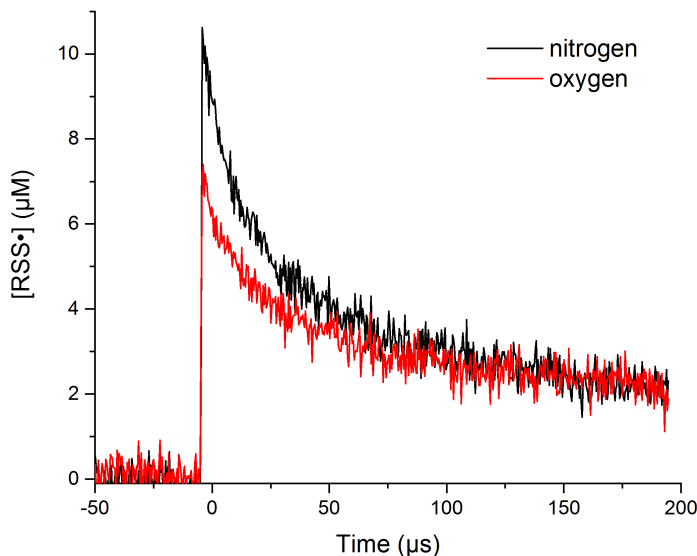


Figure 4.17. Decays for the *t*-butylperthiyl radical (390 nm , $\varepsilon = 1600\text{ M}^{-1}\text{ cm}^{-1}$)⁹¹ under nitrogen (black) and oxygen (red) generated from di-*tert*-butyl tetrasulfide in a solution of styrene (1 M) in PhCl at 25 °C.

The following rate constants were determined for the (apparent) recombination reaction:

nitrogen: $k_{\text{RSS}} = (5.6 \pm 0.3) \times 10^9\text{ M}^{-1}\text{ s}^{-1}$

oxygen: $k_{\text{obs}} = (7.1 \pm 0.5) \times 10^9\text{ M}^{-1}\text{ s}^{-1}$

Under the assumption that the difference in second order rate is caused by the (trapped) reaction with styrene the following equation can be constructed:

$$k_{\text{obs}}[\text{RSS}]^2 = k_{\text{RSS}}[\text{RSS}]^2 + k_{\text{sty}}[\text{RSS}][\text{styrene}]$$

As $[\text{RSS}\cdot]$ is $\sim 7\text{ }\mu\text{M}$ at the beginning of the decay $k_{\text{sty}} = (1.1 \pm 0.5) \times 10^4\text{ M}^{-1}\text{ s}^{-1}$.

In contrast the calculated rate (CBS-QB3) for the reaction is $k_{\text{calc}} = 2.0 \times 10^2\text{ M}^{-1}\text{ s}^{-1}$.

4.7.12 Reaction of the *t*-Butylperthiyl Radical with TEMPO

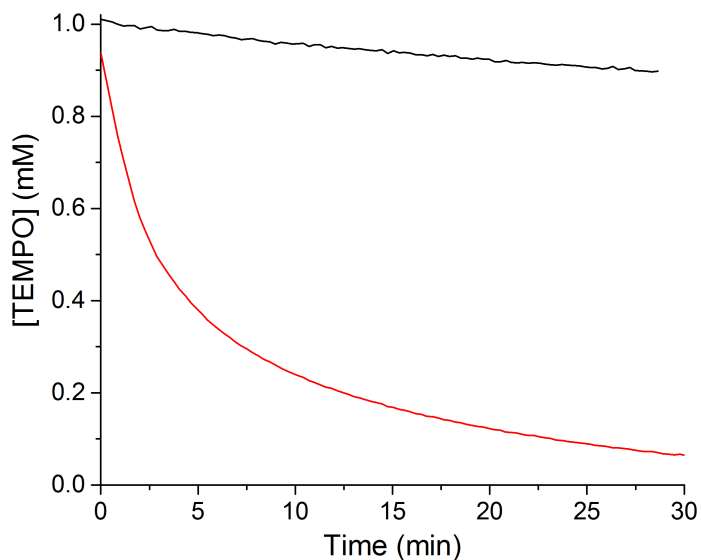


Figure 4.18. Concentration of TEMPO, determined by EPR, upon photolysis using a Hg-Xe lamp, in the presence (red) or absence (black) di-*tert*-butyl tetrasulfide (1 mM) in benzene at 25 °C.

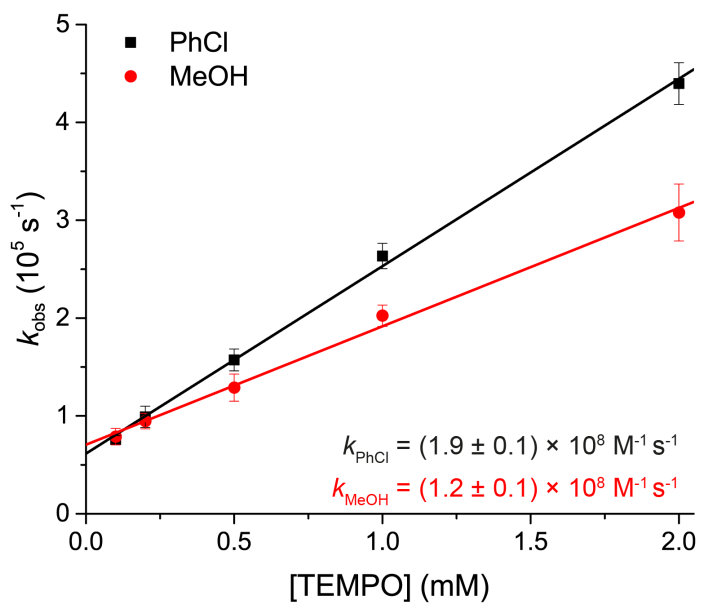
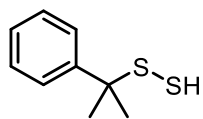
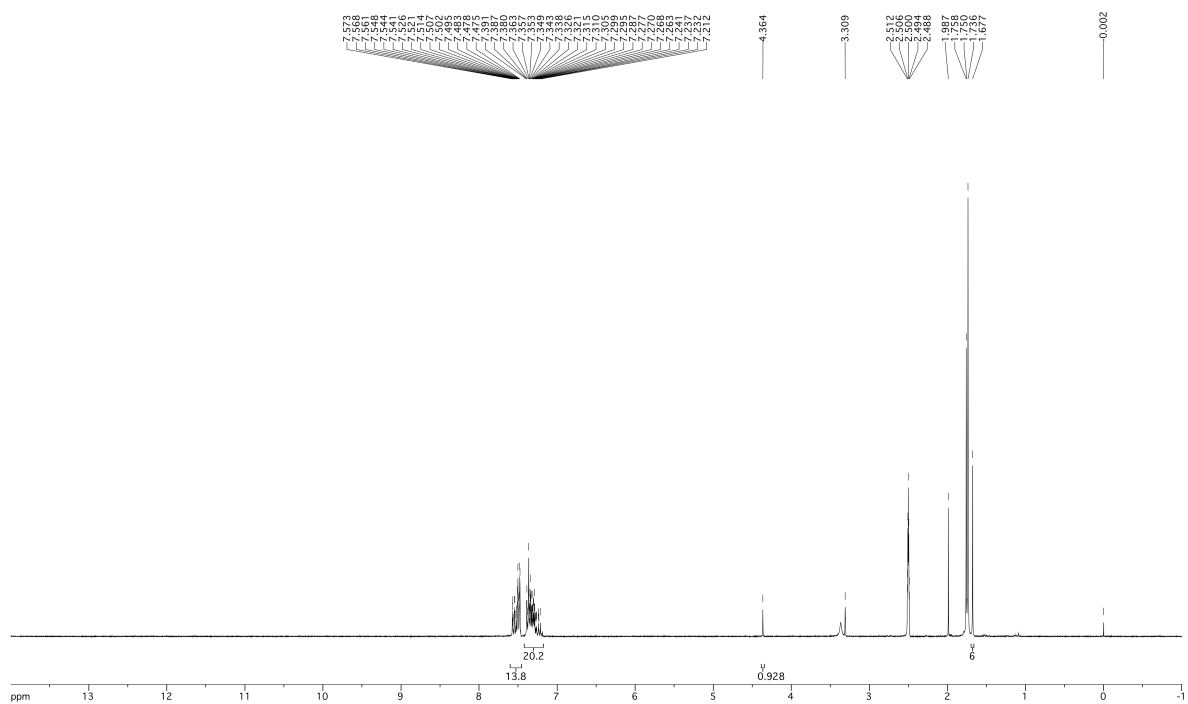


Figure 4.19. Dependence of the pseudo-first order rate (monitored at 390 nm) on the concentration of TEMPO upon photolysis of di-*tert*-butyl tetrasulfide in PhCl (black) and MeOH (red) at 25 °C.

4.7.13 α_2^H Determination by ^1H NMR⁹²



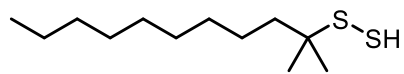
in $\text{DMSO-}d_6$ (significant decomposition to cumylthiol and other polysulfides is observed).



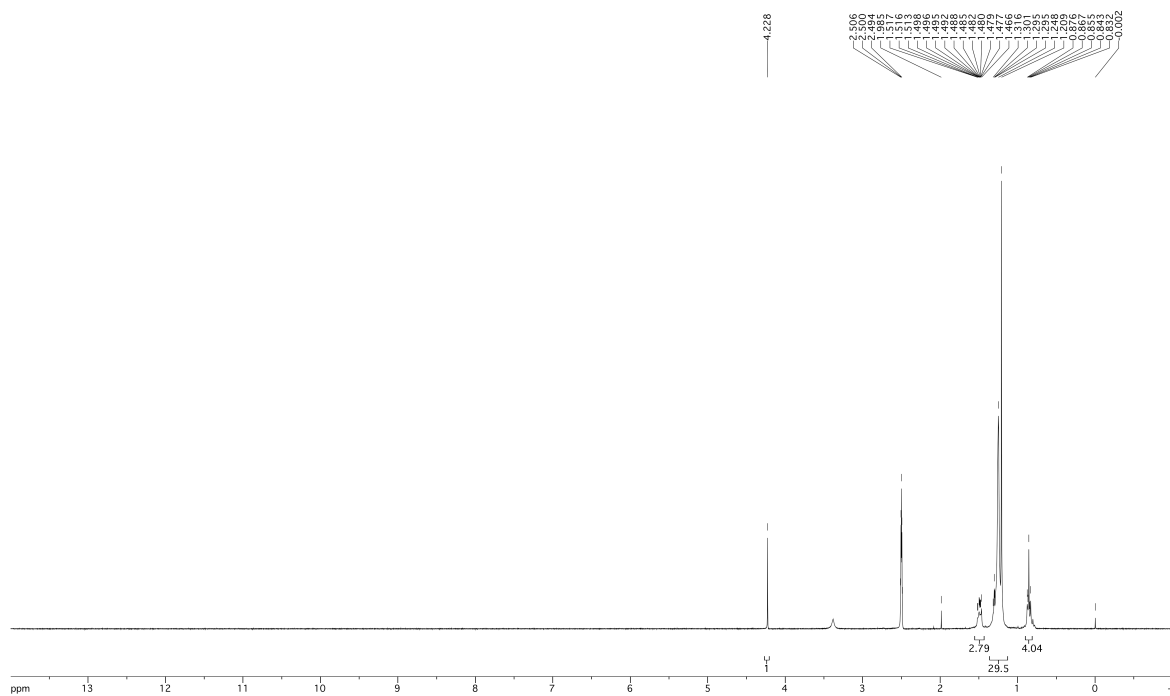
$$\alpha_2^H = 0.0066 - 0.128 + 0.133(\delta_{\text{DMSO}} - \delta_{\text{CDCl}_3})$$

$$\alpha_2^H = 0.0066 - 0.128 + 0.133(4.36 \text{ ppm} - 2.62 \text{ ppm})$$

$$\alpha_2^H = 0.10$$



in DMSO- d_6 (decomposition to *t*-dodecylthiol and other polysulfides is observed).



$$\alpha_2^H = 0.0066 - 0.128 + 0.133(\delta_{\text{DMSO}} - \delta_{\text{CDCl}_3})$$

$$\alpha_2^H = 0.0066 - 0.128 + 0.133(4.23 \text{ ppm} - 2.64 \text{ ppm})$$

$$\alpha_2^H = 0.09$$

4.8 References

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Chapter 2, 3, and 4 highlight that perthiyl radicals are persistent under autoxidation conditions and that they are unreactive towards molecular oxygen - which makes them ideal substrates in an oxidative environment. The calculated S-H BDE of hydropersulfides and the formation of perthiyl radicals as by-products of peroxy radical substitution onto polysulfides led us to investigate one-electron oxidation processes (e.g. H-atom transfer) of hydropersulfides. We next explored a two-electron oxidation of organosulfur antioxidants wherein we studied the oxidation of thiols, sulfenic acids, and sulfinic acids with hydrogen peroxide, the details of which are reported in Chapter 5.

Chapter 5: On the Reactions of Thiols, Sulfenic Acids, and Sulfinic Acids with Hydrogen Peroxide*

5.1. Preface

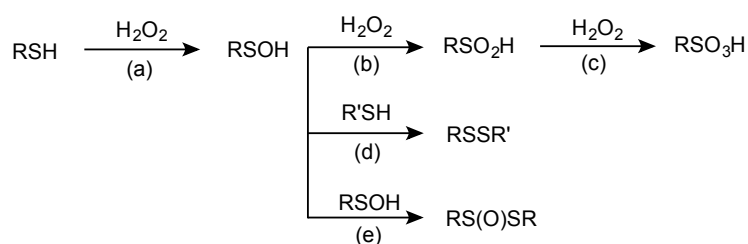
The reaction of thiols with H_2O_2 is central to many processes essential to life, from protein folding to redox signalling. The initial products are assumed to be sulfenic acids, but their observation, and the kinetic and mechanistic characterization of their subsequent reactions, has proven challenging due to the high reactivity of sulfenic acids. Indeed, sulfenic acids can react with thiols to form disulfides, or they can self-react via a condensation reaction to form thiosulfonates. We previously made use of a triptycene backbone to render sulfenic acids persistent enough to study one-electron oxidation processes. We thought of using a similar approach to study two-electron oxidation processes of various biologically-relevant organosulfur moieties. To facilitate the kinetics studies, we found that the introduction of a 9-fluorotriptycene substituent enabled the use of ^{19}F NMR to directly monitor the reaction of a thiol with H_2O_2 to yield a sulfenic acid, and its subsequent oxidation to sulfinic and sulfonic acids. The oxidations are specific base catalyzed, as revealed by the lack of isotope effects and the dependence of the kinetics on pH but not buffer concentration.

5.2 Introduction

Thiol oxidation is among the most ubiquitous reactions in biology, playing key roles in protein folding,¹ redox homeostasis,² signal transduction,³ and the regulation of gene expression.⁴ Of particular interest are oxidations by H_2O_2 , the pervasive “reactive oxygen species” that is believed to reflect the global redox state of the cell.⁵ The reaction of cysteine and other thiols with H_2O_2 has been extensively studied.⁶ Despite the common assumption that the immediate product is a sulfenic acid (Scheme 5.1 a), to our knowledge, there are no examples in which this has been directly demonstrated. Instead, sulfenic

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acid intermediates are indirectly identified following derivatization.⁷ As such, kinetic and mechanistic studies of thiol oxidation have generally been carried out by monitoring the loss of the thiol in the presence of excess H₂O₂ - reaction profiles that could not be corroborated by monitoring concomitant formation of the corresponding sulfenic acid.⁸ The persistence of sulfenic acids is limited by their oxidation to sulfinic and sulfonic acids (Scheme 5.1 b,c), reaction with thiols to yield disulfides (Scheme 5.1 d), and self-condensation to yield thiosulfonates (Scheme 5.1 e).⁹



Scheme 5.1. Competing fates of putative sulfenic acid intermediates formed upon the oxidation of thiols with H₂O₂.

Sulfenic acids can be rendered persistent with bulky substituents that prevent access for nucleophiles to its low-lying $\sigma_{\text{S-O}}^*$ orbital.¹⁰ We recently used Nakamura's 9-triptycenesulfenic acid^{10a,d} to characterize the radical chemistry of the sulfenic acid moiety,¹¹ as well as that of the corresponding selenenic acid.¹² Emboldened by this success, we wondered whether the triptycene backbone would enable direct monitoring of the oxidation of a thiol to a sulfenic acid, and subsequent oxidations to the sulfinic and sulfonic acids, thereby permitting rigorous kinetic and mechanistic characterization of each of these reactions.

5.3 Results and Discussion

Early efforts to monitor the oxidation of 9-triptycenethiol to 9-triptycenesulfenic, sulfinic, and sulfonic acids were complicated by difficulties with their reproducible separation and quantitation. We surmised that the introduction of a fluorine atom at the other bridgehead position would enable direct monitoring of the reaction since it was likely that the ¹⁹F chemical shifts would depend on the oxidation

state of the transannular sulfur atom. Indeed, when the fluorinated 9-triptycenethiol (**5.1**) was treated with H_2O_2 in buffered methanol, four signals were clearly visible in the ^{19}F NMR spectra (Figure 5.1). Moreover, these signals evolved in a predictable way, with the thiol giving way to two successively formed intermediates (the presumed sulfenic and sulfinic acids) that eventually gave way to a single product (the presumed sulfonic acid).

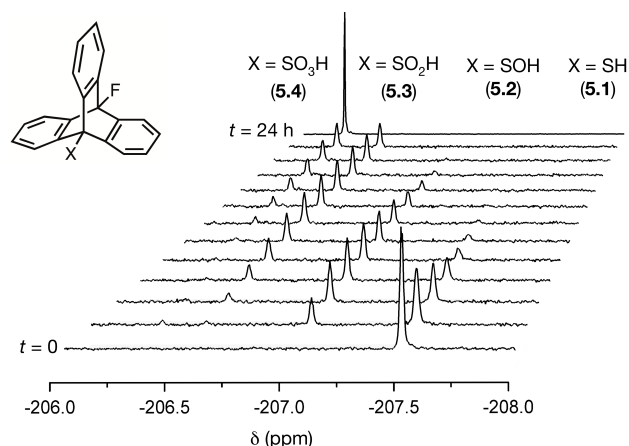


Figure 5.1. Representative ^{19}F NMR spectra recorded during the reaction of 9-fluoro-10-triptycenethiol (5 mM) with H_2O_2 (50 mM) in buffered methanol at pH 12.1 (20 mM 2,2,6,6-tetramethylpiperidine) at 20°C .

A representative reaction profile obtained over 1 h at 20°C is shown in Figure 5.2. This data could be fit to a simple kinetic model for successive bimolecular reactions with H_2O_2 , from which rate constants of 0.033, 0.013 and $0.00050\text{ M}^{-1}\text{s}^{-1}$ were derived for the reactions of thiol, sulfenic acid, and sulfinic acid, respectively. These results suggest that the thiol is most easily oxidized, followed by sulfenic acid and sulfinic acid.

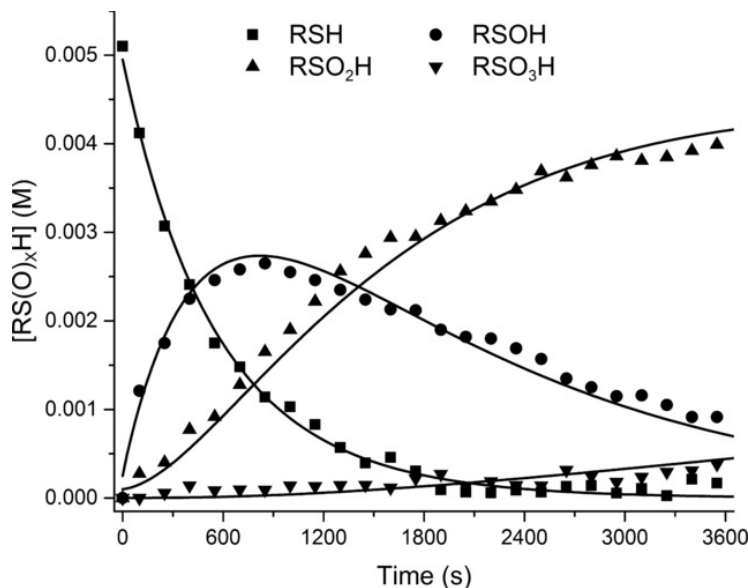
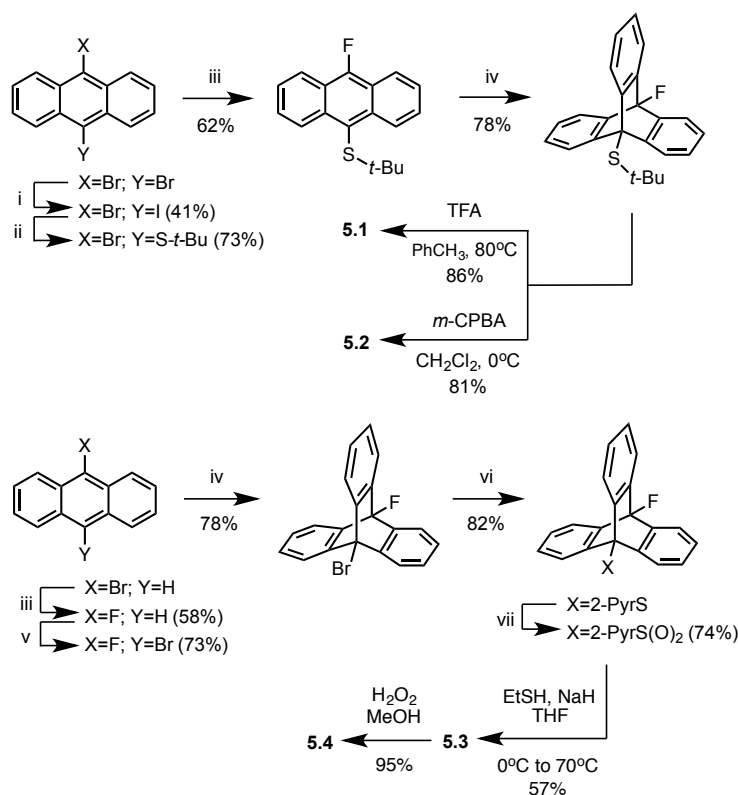


Figure 5.2. Representative reaction profile for the oxidation of 9-fluoro-10-triptycenethiol (5 mM) by H_2O_2 (50 mM) in buffered methanol at pH 11.5 (20 mM 2,2,6,6-tetramethylpiperidine) at 20 °C. Concentrations were determined directly by ^{19}F NMR relative to an internal standard (PhCF_3). Solid lines are from numerical fitting of the data to a simple kinetic scheme for consecutive bimolecular reactions of the thiol, sulfenic acid, and sulfinic acid with H_2O_2 .

Given these results, we independently synthesized the fluorinated 9-triptycenesulfenic (**5.2**), sulfinic (**5.3**),¹³ and sulfonic (**5.4**) acids (Scheme 5.2) and confirmed that they correspond to the two intermediates and final product, respectively, observed in the oxidations (see Figure 5.2).



Scheme 5.2. Synthesis of fluorinated 9-triptycenethiol (**5.1**), sulfenic acid (**5.2**), sulfinic acid (**5.3**), and sulfonic acid (**5.4**). i) BuLi, THF, -78 °C, then I₂. ii) *t*BuSH, CuI, *t*BuOK, 1,10-phen, 110 °C, PhCH₃. iii) BuLi, THF, -78 °C, then NFSI. iv) Anthralinic acid, isoamyl nitrite, TCA, THF. v) NBS, DMF, 0 °C. vi) BuLi, PhH/MTBE, -20 °C, then (2-PyrS)₂. vii) RuCl₃, NaIO₄, H₂O/EtOAc. THF = tetrahydrofuran, phen = 1,10-phenanthroline, TCA = trichloroacetic acid, NBS = *N*-bromosuccinimide, DMF = *N,N*-dimethylformamide, TFA = trifluoroacetic acid, *m*CPBA = *m*-chloroperbenzoic acid, Pyr = pyridine, NFSI = *N*-fluorobenzenesulfonimide, MTBE = methyl *tert*-butyl ether.

With the authentic reaction intermediates in hand, we also determined the rate constants for each reaction step independently (Figure 5.3), obtaining essentially indistinguishable results from those obtained by fitting the data in Figure 5.2, that is, $k_{\text{obs}} = 0.029$, 0.014, and 0.00058 M⁻¹s⁻¹ for the oxidation of the thiol, sulfenic acid, and sulfinic acid, respectively.

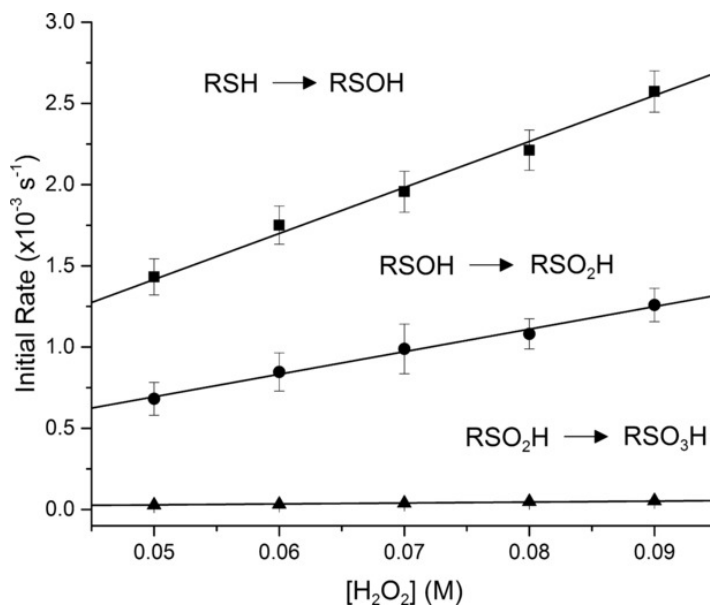


Figure 5.3. Initial rates of reaction of 9-fluoro-10-triptycenethiol (■), 9-fluoro-10-triptycenesulfenic acid (●), and 9-fluoro-10-triptycenesulfinic acid (▲) as a function of H₂O₂ concentration in buffered methanol at pH 11.5 (20 mM 2,2,6,6-tetramethylpiperidine) at 20 °C. Reaction progress was determined directly by ¹⁹F NMR on 5 mM of substrate.

The role of a thiol/thiolate pre-equilibrium in the oxidation of thiols by H₂O₂ has been demonstrated.^{6h} We sought to both confirm that this was also the case for the current system, and also investigate its role in the reactions of the sulfenic and sulfinic acids with H₂O₂. Results of reactions carried out in buffered methanol at pH ¹⁴ 6.6 to 13.5 are shown in Figure 5.4.

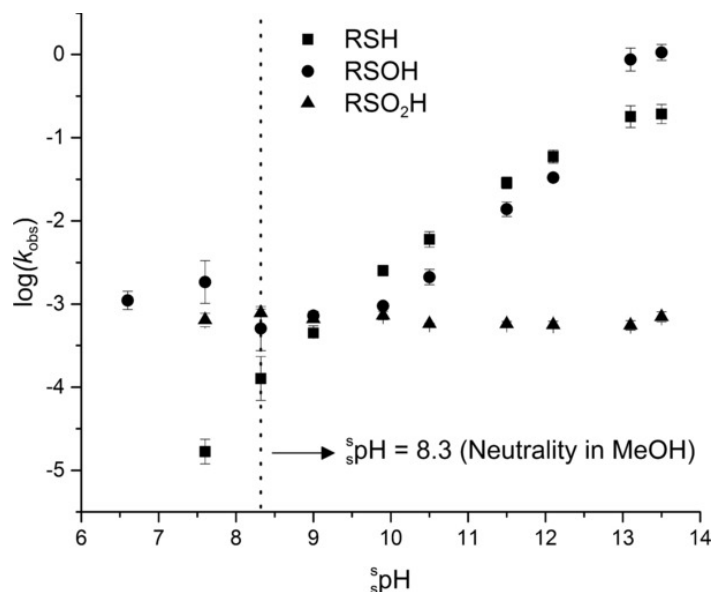
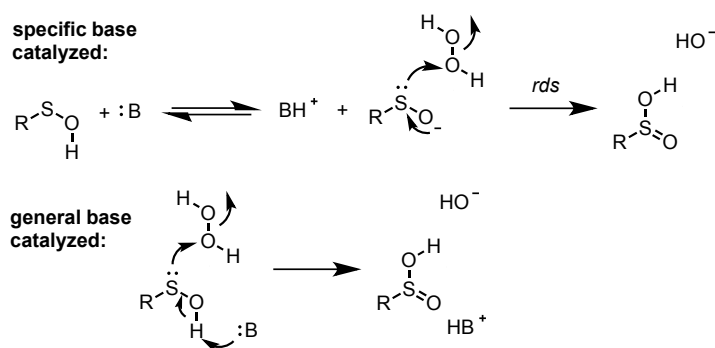


Figure 5.4. pH-Dependence of the kinetics of oxidation of 9-fluoro-10-triptycenethiol (■), 9-fluoro-10-triptycenesulfenic acid (●), and 9-fluoro-10-triptycenesulfonic acid (▲) by H₂O₂ in methanol at 20 °C.

The observed rate constants for thiol and sulfenic acid oxidation were dependent on the pH of the medium, reaching a maximum at around $s\text{pH} \approx 12$ and 13, respectively, which roughly correspond to the pK_a values of the thiol and sulfenic acids (determined independently to be 11.6 and 12.8 under the same conditions, see the Supporting Information).¹⁵ The plateau at $s\text{pH}$ values above the pK_a indicate that the inherent reactivity of the sulfenate anion is greater than of the thiolate. The rate of sulfenic acid oxidation was independent of pH in the range that was studied, which is expected since it exists as the sulfinate throughout this pH range ($pK_a = 4.3$, see the Supporting Information). Interestingly, the rates of oxidation of the thiol, sulfenic acid, and sulfenic acid converge around neutral pH; in fact, the reactivity increases slightly as the oxidation state of the sulfur increases. At neutral pH, the sulfenic acid is fully ionized and the sulfinate anion is evidently more reactive than the sulfenic acid, which is not ionized at neutral pH. Moreover, it would appear that the sulfenic acid is more reactive than the thiol, which is consistent with the computed reactivities of simple thiols and sulfenic acids with H₂O₂.¹⁶

These results establish that base catalysis enhances the reactivity of both thiols and sulfenic acids to oxidation. To learn whether the mechanism is specific or general base catalysis (illustrated for the reaction of the sulfenic acid in Scheme 3), we carried out corresponding reactions in methanol-*d* (at $\text{s pH} = 9.9$). These yielded negligible kinetic isotope effects of 1.1 ± 0.1 and 1.2 ± 0.2 for oxidations of the thiol and sulfenic acid, respectively (corresponding experiments with the sulfinic acid yielded $k_{\text{H}}/k_{\text{D}} = 1.1 \pm 0.2$), thus implying that no acidic proton is transferred in the rate-determining step of the reaction. This rules out a general base catalyzed reaction, as well as concerted transfer of the thiol proton to the departing hydroxide ion during the substitution - a suggestion that has been made based on computations.¹⁷



Scheme 5.3. Base catalysis in the oxidation of a sulfenic acid by H_2O_2 .

A specific base catalysis mechanism was corroborated by experiments carried out at constant pH and varying buffer concentration, which yielded small changes in rate for reactions of thiol and essentially no change in rate for reactions of either sulfenic or sulfinic acids (see the Supporting Information). The weak dependence of the rate of reaction of thiol on buffer concentration is proposed to arise from H-bonding between the conjugate acid of the buffer and H_2O_2 (which increases its electrophilicity), since switching the buffer from amine to borate yielded rates that were invariant with buffer concentration.

The reactivity of the thiol towards alkyl hydroperoxides was also assessed using this approach (Figure 5.5). One each of a primary (benzyl), secondary (tetralyl), and tertiary (cumyl) hydroperoxide were examined. The reactions cleanly yielded sulfenic, then sulfinic, and finally, sulfonic acids. The

relative rates decreased with increasing substitution, as expected owing to both electronic and steric factors, but the differences were actually quite small (i.e., $k_{\text{obs}} = 0.0031$, 0.0019 , and $0.0012 \text{ M}^{-1}\text{s}^{-1}$ for benzyl, tetralyl, and cumyl hydroperoxides, respectively). Associated KIE values and pH/buffer dependence suggest that the mechanism of thiol oxidation by hydroperoxides is also specific base catalyzed (see the Supporting Information).

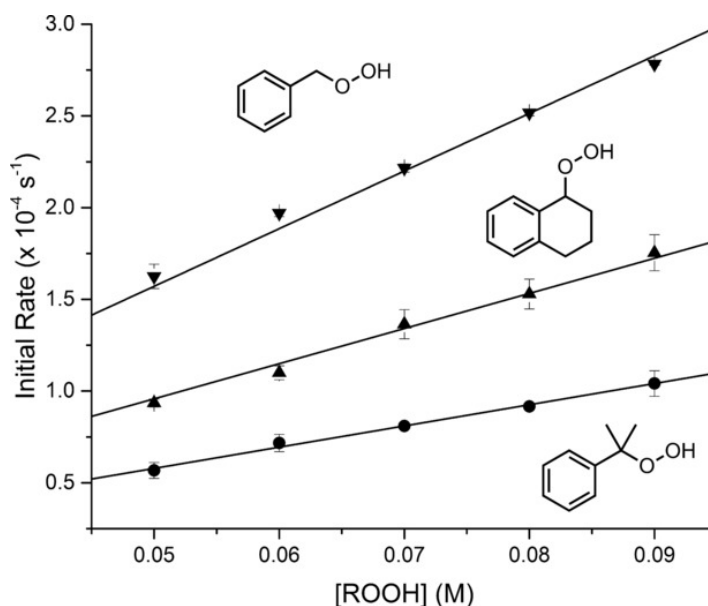


Figure 5.5. Initial rates of reaction of 9-fluoro-10-triptycenethiol (5 mM) with benzyl hydroperoxide (▼), tetralin hydroperoxide (▲), and cumyl hydroperoxide (●) in buffered methanol of $\text{pH } 9.9$ (20 mM *N*-methylpiperidine) at 20°C . Reaction progress was determined directly by ^{19}F NMR.

5.4 Conclusion

It is well known that the reactivity of a protein thiol can be modulated significantly by the immediate environment of the cysteine residue. It has long been recognized that proximal basic residues lead to significant rate enhancements for reactions with H_2O_2 .¹⁸ Moreover, work on peroxiredoxins, thiol-containing enzymes responsible for the detoxification (reduction) of H_2O_2 and alkyl hydroperoxides, has clearly shown the role of activating the peroxide to nucleophilic attack by the thiol.¹⁹ Our work provides a baseline for comparison of the inherent chemical reactivity of thiol, sulfenic acid, and

sulfinic acid toward hydrogen peroxide (and hydroperoxides), which may aid in the interpretation of trends that are observed in peroxiredoxins and other protein thiols, in general. Indeed, it would appear that the thiol microenvironment must be very carefully controlled and nucleophiles carefully juxtaposed to avoid overoxidation of the intermediate sulfenic acid to the sulfinic acid, given that outside the vicinity of pH neutrality, the sulfenic acid and sulfenate anion are more reactive than the thiol and thiolate anion, respectively.

5.5 Supporting Information

5.5.1 General

Reagents were obtained from commercial suppliers and used as is, unless indicated otherwise. Benzyl hydroperoxide^{20,21} and tetralin hydroperoxide²² were synthesized according to previously reported procedures. Column chromatography was carried out with 40-63 μm , 230-400 mesh silica gel. ^1H , ^{19}F and ^{13}C NMR spectra were recorded on a Bruker AVANCE spectrometer at 400 MHz, 377 Hz and 101 MHz, respectively, unless indicated otherwise. ^{19}F chemical shifts were referenced to PhCF_3 (-63.72 ppm). High-resolution mass spectra were obtained on a Kratos Concept Tandem mass spectrometer (EI) and Micromass Q-TOF (ESI). pH measurements were carried out using an Accumet Electrode referenced to Ag/AgCl .

5.5.2 The σ_{S-O}^* orbital of 9-triptycenesulfenic acid

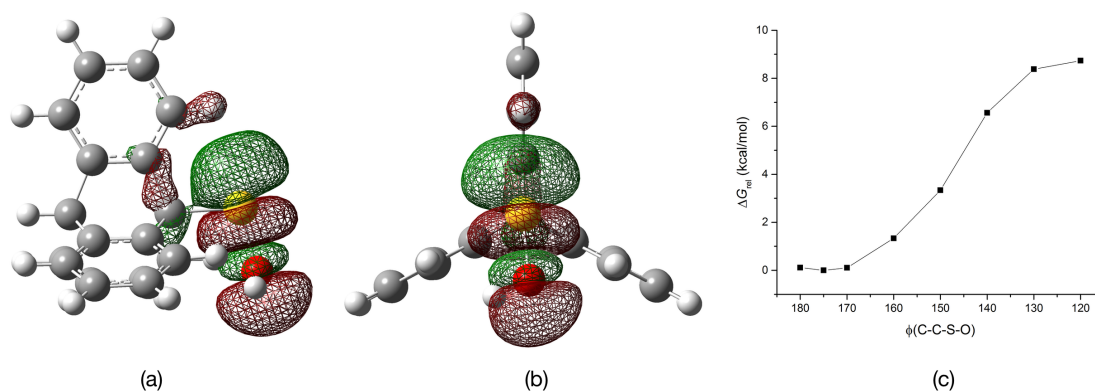


Figure 5.6. The σ_{S-O}^* orbital of the sulfenic acid moiety in the minimum energy structure of 9-triptycenesulfenic acid (a – side view; b – front view) is not accessible to nucleophiles. The structure wherein the σ_{S-O}^* orbital is accessible requires rotation by 60° about the C-S bond, but corresponds to a transition state structure – not an equilibrium structure. Calculated at the B3LYP/6-31+G(2d,2p) level of theory including DiLabio’s dispersion corrections.²³

5.5.3 Synthetic Procedures

9-Bromo-10-iodoanthracene.²⁴ 9,10-Dibromoanthracene (3.36 g, 10.0 mmol) was dissolved in THF (60 mL) and cooled to -78°C under nitrogen. After stirring for 10 minutes, BuLi (11.0 mmol, 4.40 mL) was added dropwise as a solution in hexanes (2.5 M). The dark red solution was stirred for 3 hours at -78°C to ensure complete halogen exchange. I_2 (11 mmol, 2.79 g) was dissolved in THF (7.00 mL) and added dropwise to the stirring mixture. After the addition was completed, the reaction was stirred for another 2 hours at -78°C and then room temperature overnight. The reaction mixture was quenched with water (200 mL) and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The resulting organic phase was washed with brine, dried over magnesium sulfate, filtered and the solvents removed under reduced pressure. The crude solid was recrystallized from toluene to yield the product as yellow needles (1.76 g, 41%). $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.57-8.55 (m, 4H), 7.64-7.60 (m,

4H). ^{13}C NMR (101 MHz; CDCl_3): δ 134.4, 134.2, 131.1, 128.7, 128.1, 127.6, 125.6, 106.6. HRMS (EI, $[\text{M}]^+$): m/z calculated for $\text{C}_{14}\text{H}_8\text{BrI}$: 381.8854, found 381.8851.

9-Bromo-10-tert-butylthioanthracene. 9-Bromo-10-iodoanthracene (1.15 g, 3.00 mmol), CuI (116 mg, 0.60 mmol), 1,10 phenanthroline (110 mg, 0.60 mmol) and KO^tBu (511 mg, 4.55 mmol) were added to toluene (6.0 mL) in a thick-walled glass tube under nitrogen. $^t\text{BuSH}$ (376 μL , 3.30 mmol) was then added and the tube was quickly sealed. The reaction mixture was heated at 120°C for 19 hours. The reaction mixture was then cooled, filtered through a pad of celite and diluted with ethyl acetate and washed with water three times. The resulting organic phase was rinsed with brine, dried over magnesium sulfate, filtered and the solvents removed under reduced pressure. The crude solid was purified by column chromatography using hexanes as the eluent to yield the product as a yellow solid (764 mg, 73%). ^1H -NMR (400 MHz; CDCl_3): δ 9.18 (m, 2H), 8.61 (m, 2H), 7.58-7.62 (m, J = 8.2, 1.7 Hz, 4H), 1.25 (s, 9H). ^{13}C NMR (101 MHz; CDCl_3): δ 137.3, 130.9, 129.8, 129.3, 128.3, 127.2, 126.4, 126.2, 50.7, 32.0. HRMS (EI, $[\text{M}]^+$): m/z calculated for $\text{C}_{18}\text{H}_{17}\text{BrS}$: 344.0234, found 344.0220.

9-tert-Butylthio-10-fluoroanthracene. 9-Bromo-10-tert-butylthioanthracene (700 mg, 2.00 mmol) was dissolved in THF (6.75 mL) and cooled to -78°C under nitrogen. After stirring for 10 minutes, BuLi (1.20 mL, 3.00 mmol) was added dropwise as a solution in hexanes (2.5 M). The dark red solution was stirred for 3 hours at -78°C to ensure complete halogen exchange. NFSI (960 mg, 3.00 mmol) was added all at once to the stirring mixture. After the addition was completed, the reaction was stirred for another 2 hours at -78°C and then warmed to room temperature overnight. The reaction mixture was quenched with water (50 mL) and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The resulting organic phase was washed with brine, dried over magnesium sulfate, filtered and the solvents removed under reduced pressure. The crude solid was purified by column chromatography using hexanes as the eluent to yield the product as a yellow solid (354 mg, 62%). ^1H -NMR (400 MHz;

CDCl₃): δ 9.08-9.06 (m, 2H), 8.31 (dt, J = 8.4, 0.7 Hz, 2H), 7.61-7.52 (m, 4H), 1.26 (s, 9H). ¹³C NMR (101 MHz; CDCl₃): δ 156.8, 154.2, 137.3, 137.2, 128.6, 128.5, 126.7, 126.7, 125.6, 125.6, 120.9, 120.8, 119.7, 119.5, 50.5, 50.4, 31.9. ¹⁹F NMR (377 MHz; CDCl₃): δ -127.9. HRMS (EI, [M]⁺): m/z calculated for C₁₈H₁₇FS: 284.1035, found 284.1040.

9-tert-Butylthio-10-fluorotriptycene. Isoamyl nitrite (0.645 mL, 4.80 mmol) was added to a suspension of anthranilic acid (398 mg, 2.91 mmol) and trichloroacetic acid (24 mg, 0.15 mmol) in THF (3.00 mL) under nitrogen at 0°C. The resulting tan suspension was stirred for 2 hours at room temperature after which a tan precipitate formed. The benzenediazonium-2-carboxylate was filtered through a fritted funnel, rinsed with cold THF until the washings were colorless and washed with cold 1,2-dichloroethane. (note: care must be taken not to let the salt dry out as diazonium salts can explode when heated or shocked). The wet salt was transferred into a round-bottom flask containing 9-tert-butylthio-10-fluoroanthracene (200 mg, 0.70 mmol) and DCE (5.00 mL) equipped with a reflux condenser. The solution was heated slowly to 60°C at which point an exothermic reaction took place, liberating gas and the solution became black. The solution was stirred at 60°C overnight after which it was concentrated under reduced pressure. The crude material was purified by column chromatography using 2% CH₂Cl₂/hexanes as the eluent to yield the product as a yellow solid (197 mg, 78%). ¹H-NMR (400 MHz; CDCl₃): δ 7.84-7.82 (m, 3H), 7.60-7.57 (m, 3H), 7.14-7.08 (m, 6H), 1.74 (s, 9H). ¹³C NMR (101 MHz; CDCl₃): δ 143.8, 143.7, 143.7, 143.5, 125.7, 125.4, 123.6, 123.6, 118.5, 118.4, 98.7, 96.6, 64.3, 64.2, 47.6, 34.4. ¹⁹F NMR (377 MHz; CDCl₃): δ -207.1. HRMS (EI, [M]⁺): m/z calculated for C₂₄H₂₁FS: 360.1348, found 360.1326.

9-Fluoro-10-triptycenethiol. (5.1) To a solution of 9-tert-butylthio-10-fluorotriptycene (100 mg, 0.28 mmol) in toluene (25 mL) under nitrogen was added triflic acid (51 μ L, 0.57 mmol) and trifluoroacetic acid (38 μ L, 0.50 mmol). The solution was stirred at 80°C overnight and then concentrated under

reduced pressure. The crude material was purified by column chromatography using hexanes as the eluent to yield the product as a white solid (72 mg, 86%). ^1H -NMR (400 MHz; CDCl_3): δ 7.71-7.61 (m, 6H), 7.12-7.16 (m, 6H), 2.44 (s, 1H). ^{13}C NMR (101 MHz; CDCl_3): δ 143.4, 143.2, 143.1, 143.0, 126.1, 125.9, 121.5, 121.5, 118.7, 118.6, 98.7, 96.7, 57.7, 57.6. ^{19}F NMR (377 MHz; CD_3OD): δ -207.4. m.p. 232-234 °C (decomp). HRMS (EI, $[\text{M}]^+$): m/z calculated for $\text{C}_{20}\text{H}_{13}\text{FS}$: 304.0722, found 304.0718.

9-Fluoro-10-triptycenesulfenic acid. (5.2) A stirred solution of 9-tert-butylthio-10-fluorotriptycene (250 mg, 0.69 mmol) in CH_2Cl_2 (12.0 mL) was cooled to 0°C and mCPBA (158 mg, 0.70 mmol) was added dropwise as a solution in CH_2Cl_2 . The solution was stirred at room temperature overnight and then concentrated under reduced pressure. The crude material was purified by column chromatography using 2:1 CH_2Cl_2 : hexanes with 1% acetic acid as the eluent to yield the product as a white solid (179 mg, 81%). ^1H -NMR (400 MHz; CD_3OD): δ 7.60-7.53 (m, 6H), 7.14-7.07 (m, 6H). ^{13}C NMR (76 MHz; CD_3OD): δ 145.5, 145.3, 143.0, 142.9, 126.8, 126.5, 123.4, 119.2, 119.1, 100.5, 97.7, 64.6, 64.6. ^{19}F NMR (377 MHz; CD_3OD): δ -207.2. m.p. 228-230 °C (decomp). HRMS (ESI, $[\text{M}-\text{H}]^+$): m/z calculated for $\text{C}_{20}\text{H}_{12}\text{FOS}$: 319.0598, found 319.0593.

9-Fluoroanthracene.²⁴ 9-Bromoanthracene (4.00 g, 15.6 mmol) was dissolved in THF (52.0 mL) and cooled to -78°C under nitrogen. After stirring for 10 minutes, BuLi (9.36 mL, 23.4 mmol) was added dropwise as a solution in hexanes (2.5 M). The dark red solution was stirred for 3 hours at -78°C to ensure complete halogen exchange. NFSI (7.38 g, 23.4 mmol) was added all at once and the reaction was stirred for another 2 hours at -78°C and then warmed to room temperature overnight. The reaction mixture was quenched with water (200 mL) and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The resulting organic phase was washed with brine, dried over magnesium sulfate, filtered and the solvents removed under reduced pressure. The crude solid was recrystallized from toluene to

yield the product as yellow needles (1.78 g, 58%). ¹H-NMR (300 MHz; CDCl₃): δ 8.38 (d, *J* = 8.2 Hz, 2H), 8.17 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.56 (quintet, *J* = 7.0 Hz, 4H). ¹³C NMR (76 MHz; CDCl₃): δ 155.7, 152.3, 132.0, 131.9, 127.8, 127.8, 125.8, 125.5, 125.5, 121.3, 121.2, 120.6, 120.6, 119.2, 119.0. ¹⁹F NMR (377 MHz; CDCl₃): δ -132.1. HRMS (ESI, [M-H⁺]): *m/z* calculated for C₁₄H₉F: 196.0688, found 196.0683.

9-Bromo-10-fluoroanthracene.²⁵ *N*-Bromosuccinimide (1.98 g, 11.2 mmol) was added portion-wise to a stirred solution of 9-fluoroanthracene (2.00 g, 10.2 mmol) in DMF (12.0 mL) at 0°C. The suspension was stirred for 5 hours after which it was diluted with ether (100 mL) and extracted with water (3 x 50 mL). The resulting organic phase was washed with brine, dried over magnesium sulfate, filtered and the solvents removed under reduced pressure. The crude solid was recrystallized from toluene to yield the product as yellow needles (2.05 g, 73%). ¹H NMR (300 MHz; CDCl₃): δ 8.52-8.48 (m, 2H), 8.31-8.27 (m, 2H), 7.66-7.53 (m, 4H). ¹³C NMR (76 MHz; CDCl₃): δ 155.9, 152.5, 130.7, 130.7, 127.9, 127.6, 127.5, 126.0, 126.0, 121.1, 121.0, 120.1, 119.9, 116.2, 116.1. ¹⁹F NMR (377 MHz; CDCl₃): δ -131.0. HRMS (EI, [M]⁺): *m/z* calculated for C₁₄H₈BrF: 273.9793, found 273.9783.

9-Bromo-10-fluorotrypticene. Isoamyl nitrite (8.87 mL, 66.0 mmol) was added to a suspension of anthralinic acid (5.48 g, 40.0 mmol) and trichloroacetic acid (327 mg, 2.00 mmol) in THF (40.0 mL) under nitrogen at 0°C. The resulting tan suspension was stirred for 2 hours at room temperature after which a tan precipitate formed. The benzenediazonium-2-carboxylate was filtered through a fritted funnel, rinsed with cold THF until the washings were colorless and washed with cold 1,2-dichloroethane. (note: care must be taken not to let the salt dry out as diazonium salts can explode when heated or shocked). The wet salt was transferred into a round-bottom flask containing 9-bromo-10-fluoroanthracene (2.70 g, 9.78 mmol) and DCE (65.00 mL) equipped with a reflux condenser. The solution was heated slowly to 60°C at which point an exothermic reaction took place, liberating gas

and the solution became black. The solution was stirred at 60°C overnight and then concentrated under reduced pressure. The crude material was purified by column chromatography using 2% CH₂Cl₂/hexanes as the eluent to yield the product as a white solid (2.59 g, 78%). ¹H-NMR (400 MHz; CDCl₃): δ 7.80-7.78 (m, 3H), 7.59 (dd, *J* = 7.2, 1.4 Hz, 3H), 7.19-7.11 (m, 6H). ¹³C NMR (101 MHz; CDCl₃): δ 151.5, 142.1, 141.9, 141.7, 141.7, 128.4, 126.5, 126.2, 123.5, 123.5, 118.5, 118.4, 117.5, 98.6, 96.5, 68.9, 68.9. ¹⁹F NMR (377 MHz; CDCl₃): δ -207.4. HRMS (EI, [M]⁺): *m/z* calculated for C₂₀H₁₂BrF: 350.0106, found 350.0123.

2-((10-Fluoro-9,10-[1,2]benzenoanthracen-9(10*H*)-yl)thio)pyridine. 9-Bromo-10-fluorotriptycene (1.70 g, 4.81 mmol) was dissolved in benzene (55.0 mL) and MTBE (40.0 mL) and cooled to -20°C under nitrogen. After stirring for 10 minutes, BuLi (2.90 mL, 7.22 mmol) was added dropwise as a solution in hexanes (2.5 M). The solution was stirred for 15 minutes at -20°C and 2,2'-dipyridyldisulfide (1.59 g, 7.22 mmol) was added as a solution in benzene. The reaction was stirred at room temperature overnight and then quenched with water (200 mL) and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The resulting organic phase was washed with brine, dried over magnesium sulfate, filtered and the solvents removed under reduced pressure. The crude material was purified by column chromatography using 10% ethyl acetate/hexanes as the eluent to yield the product as a white solid (1.51 g, 82%). ¹H-NMR (400 MHz; CDCl₃): δ 8.47 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.65 (dd, *J* = 7.4, 0.9 Hz, 3H), 7.51-7.49 (m, 3H), 7.32 (ddd, *J* = 8.1, 7.5, 1.9 Hz, 1H), 7.17-7.12 (m, 3H), 7.04-7.00 (m, 4H), 6.73 (d, *J* = 8.2 Hz, 1H). ¹³C NMR (101 MHz; CDCl₃): δ 157.8, 149.4, 143.6, 143.4, 140.4, 140.3, 135.8, 125.9, 125.6, 124.2, 123.3, 119.8, 118.8, 118.7, 98.7, 96.7, 60.6, 60.6. ¹⁹F NMR (377 MHz; CDCl₃): δ -207.1. HRMS (EI, [M]⁺): *m/z* calculated for C₂₅H₁₆FNS : 381.0988, found 381.0959.

2-((10-Fluoro-9,10-[1,2]benzenoanthracen-9(10*H*)-yl)sulfonyl)pyridine. RuCl₃ (38 mg, 0.183

mmol) was added to a suspension of 2-((10-fluoro-9,10-[1,2]benzenoanthracen-9(10*H*)-yl)thio)pyridine (1.40 g, 3.67 mmol) in ethyl acetate (7.0 mL) and water (7.0 mL). The solution was stirred for 10 minutes and sodium periodate (4.71 g, 22.02 mmol) was added portion-wise. The resulting black suspension was stirred overnight. The solution was then diluted with ethyl acetate and washed with water. The organic layer was washed with brine, dried with magnesium sulfate and evaporated under reduced pressure. The crude material was purified by column chromatography using 10-20% ethyl acetate/hexanes as the eluent to yield the product as a white solid (1.12 g, 74%). ¹H-NMR (300 MHz; CDCl₃): δ 8.45-8.39 (m, 2H), 8.37-8.33 (m, 1H), 8.08 (td, *J* = 7.9, 1.8 Hz, 1H), 7.85 (dt, *J* = 7.9, 0.8 Hz, 2H), 7.65-7.60 (m, 3H), 7.52 (ddd, *J* = 7.6, 4.7, 1.0 Hz, 1H), 7.18-7.13 (m, 4H), 6.98 (td, *J* = 7.7, 1.3 Hz, 2H). ¹³C NMR (151 MHz; CDCl₃): δ 161.3, 149.2, 144.1, 143.9, 143.2, 143.1, 138.6, 137.5, 137.5, 137.4, 137.3, 127.5, 126.2, 126.1, 126.0, 125.8, 125.8, 125.3, 124.0, 124.0, 123.4, 121.8, 119.3, 119.2, 118.6, 118.5, 98.0, 96.6, 76.4, 76.4. ¹⁹F NMR (377 MHz; CDCl₃): δ -205.7. HRMS (EI, [M]⁺): *m/z* calculated for C₂₅H₁₆FNO₂S : 413.0886, found 413.0868.

Sodium 10-fluoro-9-triptycenesulfinate. (5.3) 2-((10-Fluoro-9,10-[1,2]benzenoanthracen-9(10*H*)-yl)sulfonyl)pyridine (750 mg, 1.81 mmol) was dissolved in THF (9.0 mL) purged with nitrogen in a tube at 0°C. NaH (217 mg, 5.44 mmol) was added portion-wise to the sealed tube followed by ethanethiol (1.34 mL, 18.12 mmol) and the tube was quickly sealed. The reaction was heated at 70°C for 12 hours after which the solvent was removed under reduced pressure. The crude material was purified by column chromatography using 20% CH₂Cl₂/methanol as the eluent to yield the product as a white solid (0.369 g, 57%). ¹H-NMR (400 MHz; MeOD): δ 8.30 (br, 3H), 7.52-7.49 (m, 3H), 7.11-7.06 (m, 6H). ¹³C NMR (101 MHz; CD₃OD): δ 147.2, 147.0, 142.5, 126.1, 125.8, 125.6, 119.1, 119.0, 100.3, 98.2, 71.3. ¹⁹F NMR (377 MHz; CD₃OD): δ -206.7. HRMS (ESI, [M-H]⁺): *m/z* calculated for C₂₀H₁₂FO₂S: 335.0548, found 335.0542.

Sodium 10-fluoro-9-triptycenesulfonate. (5.4) Sodium 10-fluoro-9-triptycenesulfinate (10 mg, 0.03 mmol) was dissolved in methanol (150 μ L) and hydrogen peroxide (30 μ L, 0.30 mmol) was added as a 30 % solution in water. The solution was stirred for 24 hours after which the solvent was removed under reduced pressure to yield the product as a white solid (10.5 mg, 95%). ^1H -NMR (400 MHz; MeOD): δ 8.27-8.23 (m, 3H), 7.52-7.49 (m, 3H), 7.14-7.07 (m, 6H). ^{13}C NMR (101 MHz; CD_3OD): δ 145.8, 145.5, 141.3, 141.2, 126.4, 126.3, 126.13, 126.1, 118.6, 118.5, 100.2, 97.5, 74.1, 74.0. ^{19}F NMR (377 MHz; CD_3OD): δ -206.4. HRMS (ESI, $[\text{M}-\text{H}^+]$): m/z calculated for $\text{C}_{20}\text{H}_{12}\text{FO}_3\text{S}$: 351.0497, found 351.0491.

5.5.4 Standard Oxidation Procedure

The following amine bases were used to buffer methanol to the desired s°pH : 2-picoline (s°pH = 6.6), 2,6-lutidine (s°pH = 7.6), *N*-methylmorpholine (s°pH = 8.3 - 9.0), *N*-methylpiperidine (s°pH = 9.9), triethylamine (s°pH = 10.5), 2,2,6,6-tetramethylpiperidine (s°pH = 11.5 - 12.1), (L)-proline (s°pH = 13.1-13.5). Methanolic solutions of the amine (20 mM) were acidified to the desired s°pH by addition of a 3:1 methanol: HCl_{conc} solution. The s°pH in methanol was calculated by subtracting -2.24 from the value measured by pH meter with an aqueous electrode.¹⁴ Solutions of substrate (thiol, sulfenic acid or sulfinic acid) and standard (trifluorotoluene, 10 mM) were made up in buffer and added to NMR tubes containing a sealed capillary filled with benzene- d_6 to enable locking of the sample. The appropriate volume of a 30% hydrogen peroxide solution in water were added to the NMR tube immediately before starting the acquisition. NMR spectra were acquired as a function of time and the peaks corresponding to the fluorine atoms on each of the thiol, sulfenic acid, sulfinic acid and sulfonic acid were integrated relative to the internal standard.

5.5.5 Base Dependence on the Kinetics of Oxidation by H₂O₂

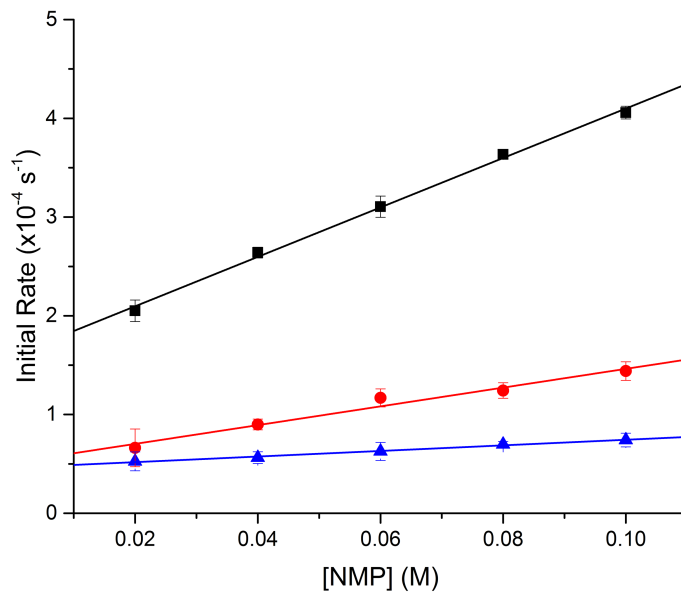


Figure 5.7. Oxidation of 9-fluoro-10-triptycenesethiol (■), 9-fluoro-10-triptycenesulfenic acid (●) and 9-fluoro-10-triptycenesulfenic acid (▲) by H₂O₂ (60 mM) with increasing concentration of n-methylpiperidine in buffered methanol at ^spH 9.9 at 20°C.

5.5.6 Deuterium Kinetic Isotope Effects

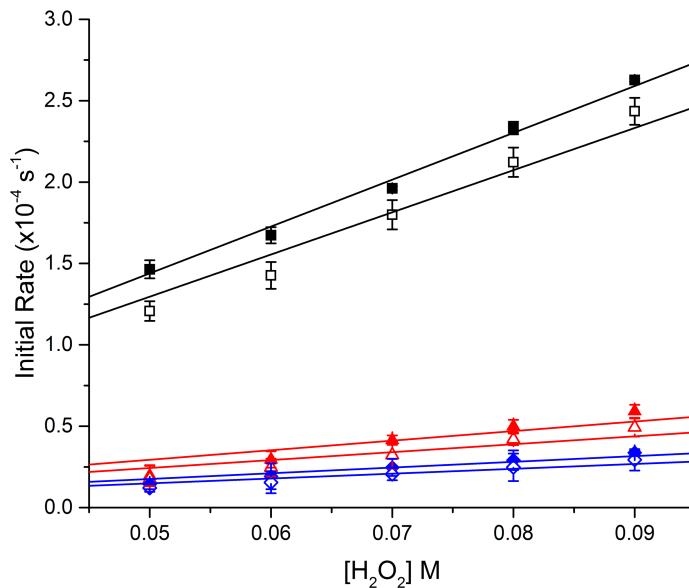


Figure 5.8. Oxidation of 5 mM of 9-fluoro-10-triptycenethiol (■), 9-fluoro-10-triptycenesulfenic acid (●) and 9-fluoro-10-triptycenesulfinic acid (▲) by H₂O₂ in buffered methanol (full) or methanol-*d* (hollow) at δ pH 9.9 (20 mM N-methylpiperidine) at 20°C.

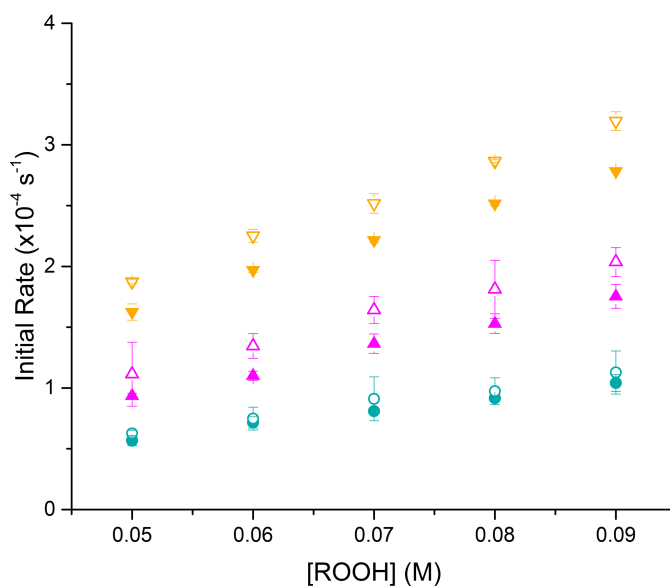


Figure 5.9. Oxidation of F-TrpSH (5 mM) by benzylhydroperoxide (▼), tetralin hydroperoxide (▲) and cumene hydroperoxide (●) in buffered methanol (full) or MeOD (hollow) at δ pH 9.9 (20 mM n-methylpiperidine) at 20°C.

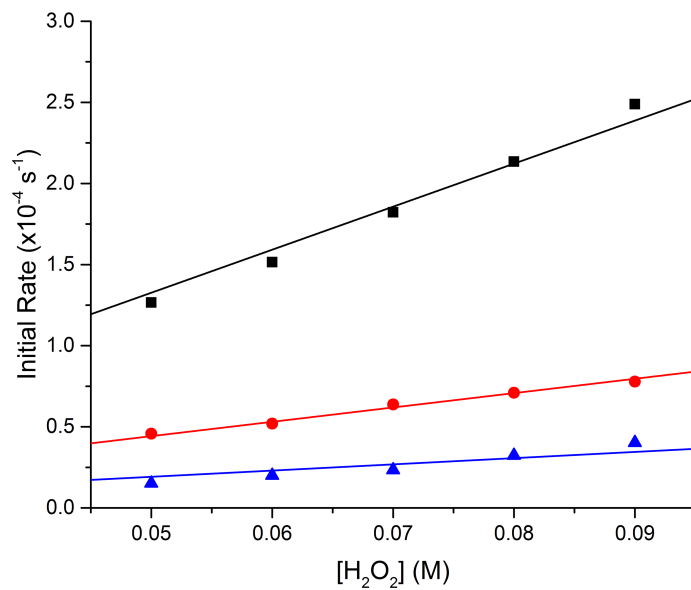


Figure 5.10. Oxidation of 5 mM of 9-fluoro-10-triptycenesulfenic acid (■), 9-fluoro-10-triptycenesulfenic acid (●) or 9-fluoro-10-triptycenesulfenic acid (▲) by H₂O₂ in buffered methanol (20 mM sodium borate) at ^spH 9.9 at 20°C.

5.5.7 Summary of Rate Constants, k_{obs}

Table 5.1. Second order rate constants ($\text{M}^{-1}\text{s}^{-1}$) for the oxidation of thiol, sulfenic acid and sulfinic acid by hydrogen peroxide in buffered methanol at 20°C.

pH	RSH	RSOH	RSO ₂ H
6.6	-	1.11×10^{-3}	-
7.6	1.68×10^{-5}	1.85×10^{-3}	6.44×10^{-4}
8.3	1.27×10^{-4}	5.08×10^{-4}	7.83×10^{-4}
9.0	4.49×10^{-4}	7.26×10^{-4}	6.64×10^{-4}
9.9	2.52×10^{-3}	9.50×10^{-4}	7.29×10^{-4}
10.5	6.00×10^{-3}	2.11×10^{-3}	5.78×10^{-4}
11.5	2.86×10^{-2}	1.38×10^{-2}	5.75×10^{-4}
12.1	5.92×10^{-2}	3.30×10^{-2}	5.62×10^{-4}
13.1	1.79×10^{-1}	8.70×10^{-1}	5.55×10^{-4}
13.5	1.92×10^{-1}	1.06	7.02×10^{-4}

Table 5.2. Second order rate constants ($\text{M}^{-1}\text{s}^{-1}$) for the oxidation of thiol, sulfenic acid and sulfinic acid by hydrogen peroxide in methanol-*d* at pH 9.9 (20 mM *N*-methylpiperidine) at 20°C.

Solvent	F-TrpSH	F-TrpSOH	F-TrpSO ₂ H
MeOD	2.28×10^{-3}	7.91×10^{-4}	6.61×10^{-4}

Table 5.3. Second order rate constants ($\text{M}^{-1}\text{s}^{-1}$) for the oxidation of thiol, sulfenic acid and sulfinic acid by hydrogen peroxide in methanol at pH 9.9 (20 mM sodium borate) at 20°C .

Buffer	F-TrpSH	F-TrpSOH	F-TrpSO ₂ H
Sodium Borate	2.45×10^{-3}	8.85×10^{-4}	6.83×10^{-4}

Table 5.4. Second order rate constants ($\text{M}^{-1}\text{s}^{-1}$) for the oxidation of thiol by alkyl hydroperoxides in methanol at pH 9.9 (20 mM *N*-methylpiperidine) at 20°C .

ROOH	F-TrpSH
BnOOH	3.14×10^{-3}
TetOOH	1.92×10^{-3}
CumylOOH	1.16×10^{-3}

5.5.8 pK_a Measurements

The pK_a s of thiol, sulfenic acid and sulfinic acid were measured in methanol using a pH meter equipped with standard aqueous electrodes. Solutions of the thiol or sulfenic acid (1 mM) were made in methanol (3.0 mL) and the pH was measured as a function of added volumes of either 20 mM NaOH (for thiol and sulfenic acid) or 20 mM HCl (for sulfinic acid). The s_pH in methanol was calculated by 2.24 to the measured value.¹⁴ The pK_a s correspond to the measured pH when 0.5 equivalents of NaOH or HCl were added to the solution.

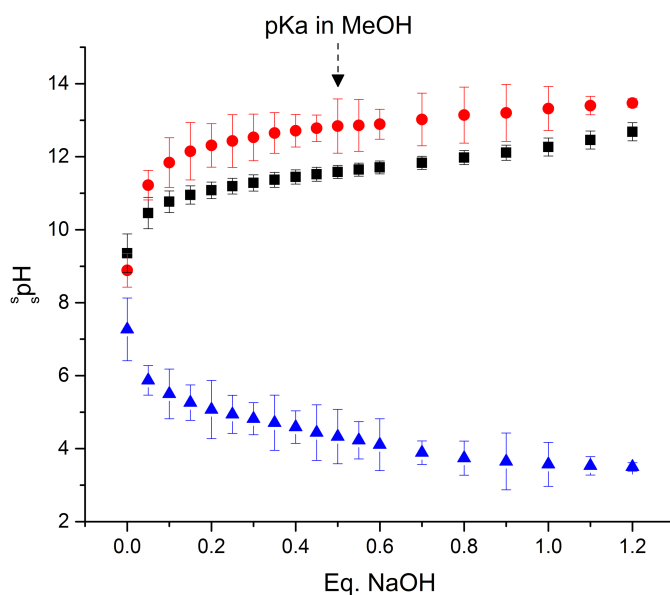


Figure 5.11. Titration of a 1 mM solution of 9-fluoro-10-triptycenethiol (■), 9-fluoro-10-triptycenesulfenic acid (●), and 9-fluoro-10-triptycenesulfinic acid (▲) at 22°C in methanol with 20 mM NaOH or 20 mM HCl.

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CHAPTER 6: The Hydrogen Atom Transfer Reactivity of Sulfinic Acids*

6.1 Preface

Sulfinic acids (RSO_2H) have a reputation for being difficult reagents to handle due to their facile autoxidation. Nevertheless, they have recently been employed as key reagents in a variety of useful radical chain reactions. To account for this paradox and enable further development of radical reactions employing sulfinic acids, we have characterized the thermodynamics and kinetics of their H-atom transfer reactions for the first time. The O–H bond dissociation enthalpy (BDE) of sulfinic acids was determined by radical equilibration to be ~ 78 kcal/mol; roughly halfway between the RS-H BDE in thiols (~ 87 kcal/mol) and RSO-H BDE in sulfenic acids (~ 70 kcal/mol). Regardless, RSH, RSOH and RSO_2H have relatively similar inherent H-atom transfer reactivity to alkyl radicals ($\sim 10^6 \text{ M}^{-1} \text{ s}^{-1}$). Counter-intuitively, the trend in rate constants with more reactive alkoxyl radicals follows the reaction energetics: $\sim 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for RSO_2H , midway between thiols ($\sim 10^7 \text{ M}^{-1} \text{ s}^{-1}$) and sulfenic acids ($\sim 10^9 \text{ M}^{-1} \text{ s}^{-1}$). Importantly, since sulfinic and sulfenic acids are very strong H-bond donors ($a_2^H \sim 0.63$ and 0.55 , respectively), their reactivity is greatly attenuated in H-bond accepting solvents, whereas the reactivity of thiols is largely solvent-independent. Efforts to measure rate constants for the reactions of sulfinic acids with alkylperoxyl radicals were unsuccessful. Computations predict these reactions to be surprisingly slow; ~ 1000 -times slower than for thiols and $\sim 10\,000\,000$ -times slower than for sulfenic acids. On the other hand, the reaction of sulfinic acids with sulfonylperoxyl radicals – which propagate sulfinic acid autoxidation – is predicted to be almost diffusion-controlled. In fact, the rate-

* This chapter is reproduced from [Griesser, M.; Chauvin, J.-P. R.; Pratt, D. A. *Chem. Sci.* **2018**, *9*, 7218–7229.] with permission from the Royal Society of Chemistry. This work was performed in conjunction with Dr. Markus Griesser. I was responsible for the synthesis of the sulfinic acid substrates as well as performing the inhibited autoxidations (reactions with peroxyl radical) and the alkyl radical clocking experiments (reactions with alkyl radicals).

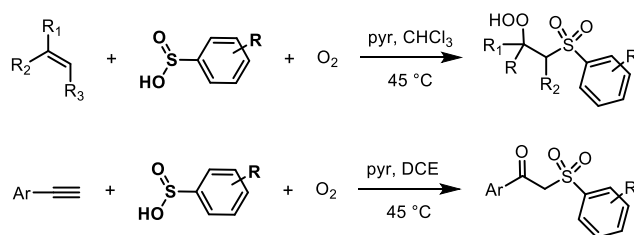
determining step in sulfinic acid autoxidation, and the reason they can be used for productive chemistry, is the relatively slow reaction of propagating sulfonyl radicals with O₂ ($\sim 10^6 \text{ M}^{-1} \text{ s}^{-1}$).

6.2 Introduction

Sulfinic acids (RSO₂H) are trivalent sulfur oxyacids isoelectronic with carboxylic acids. Although they are less prominent than the thiols from which they are derived, and the sulfonic acids to which they are oxidized, they are useful Brønsted acids and as precursors to various sulfonate derivatives. One-electron oxidation of sulfinic acids (or their conjugated bases) yields sulfonyl radicals,^{1,2} important intermediates in industrial processes (e.g. sulfoxidation to produce surfactants)³ and synthetic transformations where they often give way to sulfones via radical additions to double and triple bonds.^{4–11} Sulfonyl radicals are most commonly generated from sulfonyl halides,⁵ pseudohalides⁸ or azides⁹ by photolysis or atom/group transfer reactions as part of chain reactions.

Despite the fact that sulfinic acids are widely considered to be difficult to work with due to their facile autoxidation, the direct use of sulfinic acids in organic synthesis has recently gained popularity.^{12–21} Particularly noteworthy are Lei's reports of the use of sulfinic acids for sulfonylation of alkenes¹² and alkynes,¹³ and Nicewicz's use of sulfinic acids as catalytic H-atom donors in photocatalytic anti-Markovnikov alkene functionalizations (e.g. Figure 6.1).¹⁵ Central to these radical chain reactions are chain-propagating steps which involve H-atom transfer (HAT) from a sulfinic acid to a peroxy radical (top, Figure 6.1), to a peroxy radical and alkoxy radical (middle, Figure 6.1) or alkyl radical (bottom, Figure 6.1). Rate constants for these key reactions are unknown,²² data which would greatly enable further development of reactions utilizing sulfinic acids for organic synthesis.

Lei's aerobic sulfinylation of alkenes and alkynes (2013)



Nicewicz's photocatalytic anti-Markovnikov alkene hydroacyloxylation (2013)

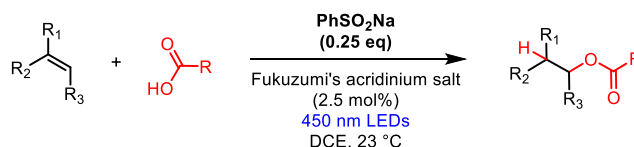


Figure 6.1. Examples of recently reported transformations employing sulfinic acids for group transfer/radical additions.

Likewise, surprisingly little is known of the stability of sulfonyl radicals relative to other commonly utilized reagents for addition and/or H-atom transfer in organic synthesis, such as thiols. The stability of a given radical (e.g. $\text{X}^\bullet$) relative to another (e.g. $\text{Y}^\bullet$) is generally estimated by comparing the X-H bond dissociation enthalpy (BDE) to that of Y-H. No definitive sulfinic acid O-H BDE has been reported. To the best of our knowledge, the first suggestion was made in 1971 (111 kcal/mol),²³ but was shortly thereafter revised to be at most 104 kcal/mol.²⁴ Benson later estimated that the phenylsulfonyl radical should have a similar stability to the benzyl radical (and therefore a BDE of ca. 90 kcal/mol).²⁵ A subsequent estimate put the BDE at 73 kcal/mol,²⁶ and a recent calculation suggested 77 kcal/mol.²⁷ Given the central importance of the $\text{RSO}_2^\bullet \rightleftharpoons \text{R}^\bullet + \text{SO}_2$ equilibrium to the chemistry of sulfonyl radicals, knowledge of the inherent stability of $\text{RSO}_2^\bullet$ is highly desirable.

Herein we provide the first experimental determination of the O-H BDE in sulfinic acids, and report on the kinetics of their H-atom transfer to alkyl, alkoxy, and peroxy radicals. We compare these results to corresponding data for the structurally-related sulfenic acids, which have among the weakest O-H bonds²⁸ and some of the fastest HAT reactions^{29,30} ever reported. We also study the

solvent effects on these reactions, and demonstrate that sulfinic (and sulfenic) acid(s) engage in strong H-bonding interactions that slow HAT.

Our results provide key information for the development of synthetic methodology employing sulfonyl radicals and/or sulfinic acids and offer unique insights on the role of secondary orbital interactions in the reactions of peroxy radicals, which are quite significant for sulfenic acids and virtually non-existent for sulfinic acids.

6.3 Results

Kinetic and thermochemical experiments were carried out with phenylsulfinic acid (PhSO_2H) (generated from its commercially-available sodium sulfinate salt) and/or 9-triptycenesulfinic acid (TrptSO_2H), which enables direct comparison with the analogous 9-triptycenesulfenic acid (TrptSOH).^{28,31} The 9-triptycenesulfinic acid was prepared as described in the Supporting Information, in a manner similar to that we recently described for the synthesis of a fluorinated analog.³²

6.3.1 O-H Bond Dissociation Enthalpies of Sulfinic Acids

The radical equilibration EPR (REqEPR) technique³³ was employed to establish a reliable O-H BDE for sulfinic acids. The approach, depicted in Figure 6.2A, relies on the equilibration of persistent radicals – one derived from a precursor whose X-H BDE is known (the reference compound) and one from the compound for which the Y-H BDE is desired. The difference in the X-H and Y-H BDEs can be estimated directly from the equilibrium constant determined by double integration of the EPR signals of the two equilibrated radicals $\text{X}^\bullet$ and $\text{Y}^\bullet$, assuming the entropy of the H-atom exchange is negligible.

Previous EPR studies of sulfonyl radicals^{24,34,35} have been challenging owing to their rapid disproportionation (e.g. $k = 8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for *p*-tosylsulfonyl)³⁵ to sulfinyl and sulfonyloxyl radicals.

As such, it was hoped that the triptycene substituent in TrptSO₂H would impart sufficient persistence to the sulfonyl radical to enable the REqEPR experiment. Indeed, the room temperature photolysis of a solution of 9-triptycenesulfinic acid containing *t*-BuOO*t*-Bu yielded a broad signal which could be ascribed to the 9-triptycenesulfonyl radical (Figure 6.2B). Within seconds, a significantly sharper signal appeared at slightly lower field. Assuming that the latter signal corresponded to the 9-triptycenesulfinyl radical, which we had previously characterized to have $g = 2.0114$,²⁸ the former signal was centered at $g = 2.0053$ in good agreement with previously reported values for sulfonyl radicals.^{24,36}

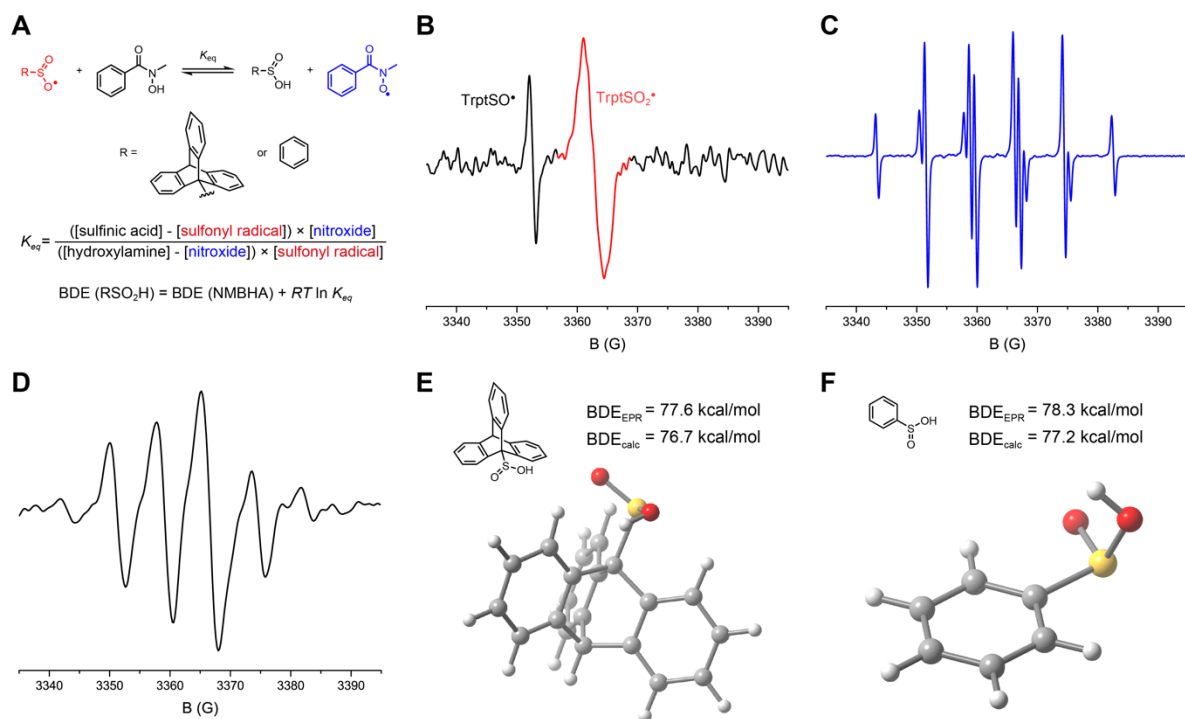


Figure 6.2. (A) The equilibration of the sulfonyl and nitroxyl radicals derived from TrptSO₂H/PhSO₂H and N-methylbenzhydroxamic acid (NMBHA) enables the derivation of an O-H BDE for the sulfinic acid. (B) EPR spectrum obtained during the irradiation of a mixture of TrptSO₂H and di-*tert*-butylperoxide in benzene at 298 K. (C) EPR spectrum of the nitroxide derived from NMBHA. (D) Representative EPR spectrum of the equilibrated radical mixture. (E,F) CBS-QB3-calculated and experimental BDEs for TrpSO₂H and PhSO₂H.

To identify an appropriate reference compound for the REqEPR experiment, CBS-QB3 calculations were carried out to predict the O-H BDEs of each of the phenylsulfenic acid (77.2 kcal/mol) and 9-triptycenesulfenic acid (76.7 kcal/mol).³⁷ We also calculated an O-H BDE of 71.0 kcal/mol for 9-triptycenesulfenic acid using the same methodology, which is in excellent agreement with the experimental value of 71.9 kcal/mol we previously determined using the REqEPR technique,^{28,38} suggesting that oxidation of the sulfur atom has a relatively modest (~5 kcal/mol) effect on the O-H BDE. *N*-Methylbenzohydroxamic acid (NMBHA) was therefore chosen as the reference compound since its O-H BDE (78 kcal/mol)³⁹ is similar to the predicted values for the sulfenic acids and the *N*-oxyl radical produced upon H-atom abstraction therefrom is persistent (Figure 6.2C).

Photolysis of a solution of 9-triptycenesulfenic acid and NMBHA containing *t*-BuOO*t*-Bu yielded spectra consistent with the superposition of the sulfonyl and *N*-oxyl radical spectra (Figure 6.2D). The equilibrium constant was readily determined from these data, but estimation of the sulfenic acid O-H BDE first required correction of the equilibrium constant for the H-bonding interactions between the sulfenic acid/NMBHA and the *t*-BuOH used to help solubilize them in benzene (10% v/v) – see Supporting Information for the details. The resultant value of 77.6 kcal/mol is in excellent agreement with the CBS-QB3 calculations, and confirms that oxidation of the sulfur atom in a sulfenic acid raises the O-H BDE by 5 to 6 kcal/mol. Analogous experiments were carried out with phenylsulfenic acid in benzene, which yielded an O-H BDE of 78.3 kcal/mol, again consistent with the predictions by CBS-QB3. By comparison, alkylthiols and arylthiols have S-H BDEs of 87 and 79 kcal/mol, respectively.

6.3.2 Reactions with Alkyl Radicals

The kinetics of H-atom transfer from PhSO₂H and TrptSO₂H to alkyl radicals were determined using the radical clock approach employing the 1,2-aryl migration in the (naphthyl)neophyl radical as the reference reaction ($k_r = 1.4 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ at 25 °C).⁴⁰ The radicals were generated by photolysis of the

corresponding Barton ester, and the reduced and rearranged products were quantified by GC/MS as a function of sulfinic acid concentration to yield the H-atom transfer rate constant (Figure 6.3A). Initial experiments in THF yielded $k_H = (5.2 \pm 0.7) \times 10^4$ and $(8.7 \pm 1.8) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ for PhSO_2H and TrptSO_2H , respectively (Figure 6.3B) – the order of reactivity being consistent with the slightly weaker O-H bond in TrptSO_2H compared to PhSO_2H . Given the acidity of the O-H bond in sulfinic acids, we anticipated a significant solvent effect on the H-atom transfer kinetics and therefore sought to determine rate constants in a range of H-bond accepting solvents. Unfortunately, the limited solubility of the sulfinic acids at the concentrations necessary to afford reliable kinetics by the competition method precluded such an endeavor.

Therefore, we also performed direct kinetic experiments by laser flash photolysis. Cumyl radicals were generated by the photolysis of dicumylketone with the 308 nm emission of a nanosecond-pulsed XeCl excimer laser. The rate of decay of the 330 nm absorption of the cumyl radicals was determined as a function of sulfinic acid concentration to yield the H-atom transfer rate constant (Figure 6.3C). Initial experiments in benzene yielded a rate constant of $(1.0 \pm 0.2) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for PhSO_2H (Figure 6.3D) – consistent with a substantial kinetic solvent effect when comparing to the data in THF. Additional experiments were carried out in isooctane, chlorobenzene, and anisole, which revealed a dramatic drop in the HAT rate constant with increasing hydrogen bond basicity (Figure 6.3G). Plotting the data according to the Ingold-Abraham equation⁴¹ that relates H-atom transfer kinetics to solvent H-bond basicity (β_2^H),

$$\log k_{\text{inh}}^S = -8.32\alpha_2^H\beta_2^H + \log k_{\text{inh}}^0$$

suggests an H-bond acidity of the sulfinic acid of $\alpha_2^H = 0.61$. The deviation of the data points obtained by competition kinetics (empty symbols) from the correlation comprised of data points obtained by LFP is consistent with the increased reactivity of primary over tertiary alkyl radicals (*ca.* 10 x).

Corresponding experiments carried out with the sulfenic acid (in isooctane, chlorobenzene, benzene, and anisole) yielded rate constants that were systematically *ca.* 3-fold greater than those of the sulfinic acids (e.g. $(2.9 \pm 0.4) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for TrptSOH in benzene). Plotting these data according to the Ingold-Abraham equation yields $\alpha_2^{\text{H}} = 0.57$ for the sulfenic acid, in excellent agreement with previous reports ($\alpha_2^{\text{H}} = 0.54$).³¹ The modest difference in the H-atom transfer kinetics of sulfinic and sulfenic acids is surprising given the *ca.* 5-6 kcal/mol difference in the experimental O-H BDEs, and may reflect a more favorable polarization of the H-atom transfer TS in the case of the sulfinic acid compared to the sulfenic acid, consistent with their pK_{as} (~ 1.9 vs. 12.5, respectively).³²

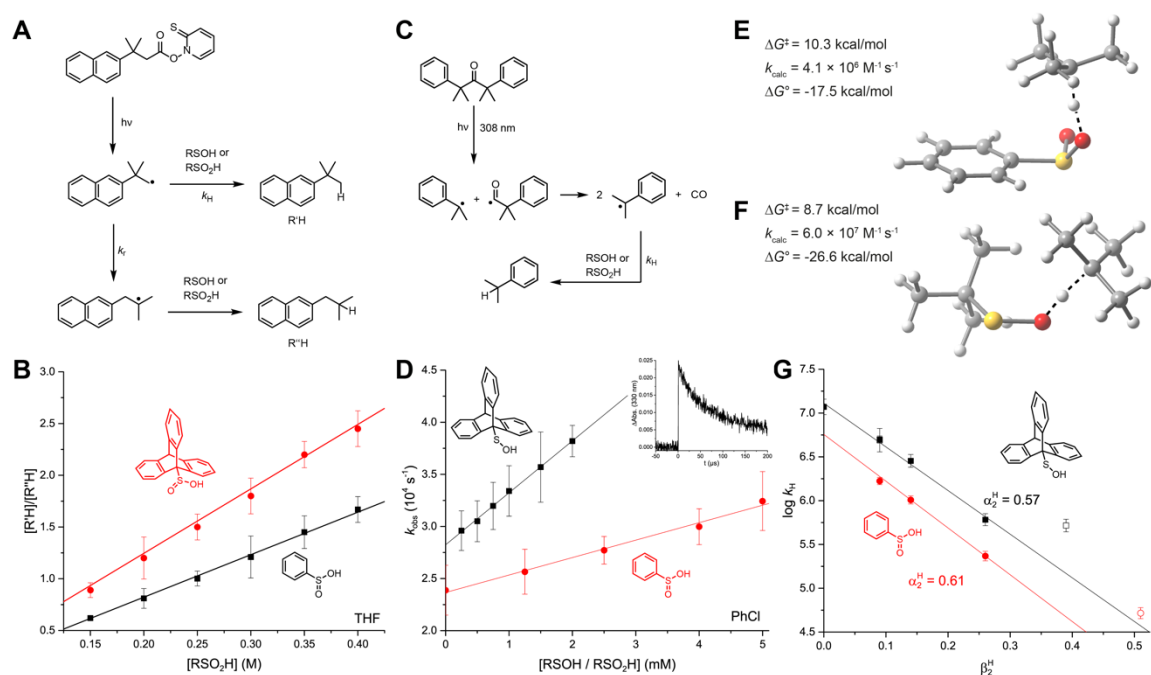


Figure 6.3. (A) Photolytic generation of the 2-methyl-2-(2-naphthyl)-1-propyl radical and its use as a radical clock to obtain the rate constant for HAT from sulfenic and sulfinic acids to alkyl radicals. (B) Ratio of reduced ($\text{R}'\text{H}$) to rearranged and reduced ($\text{R}''\text{H}$) products as a function of the concentration of TrptSO₂H (red) or PhSO₂H (blue) during photocleavage of the radical precursor in THF at 25 °C. (C) Photolytic generation of cumyl radicals from dicumylketone. (D) Dependence of the pseudo-first order rate on the concentration of PhSO₂H (red) and TrptSOH (black) upon photolysis of

dicumylketone in PhCl at 25 °C; inset: example decay of the cumyl radical. (E,F) Calculated (CBS-QB3) transition state structures and associated free energy barriers, estimated rate constants and reaction free energies for HAT between a model alkyl radical (*t*-Bu•) and either PhSO₂H or *t*-BuSOH (model for TrptSOH). (G) The HAT rate constants for PhSO₂H (red) and TrptSOH (black), determined via LFP (full symbol) and radical clock (empty symbol) plotted as a function of medium β_2^H .

The HAT transition states (TS) for the reactions of representative sulfinic and sulfenic acids are shown in Figure 6.3EF. The results are fully consistent with the experimental trends. That is, CBS-QB3 predicts a barrier of $\Delta G^\ddagger = 10.3$ kcal/mol for PhSO₂H (corresponding to $k = 4.1 \times 10^6$ M⁻¹ s⁻¹) and $\Delta G^\ddagger = 8.7$ kcal/mol for *t*-BuSOH (corresponding to $k = 6.0 \times 10^7$ M⁻¹ s⁻¹). Again, the difference in the kinetics (ca. 15-fold) is relatively modest given the significant difference in the driving force ($\Delta\Delta G^\circ = 9.1$ kcal/mol).

6.3.3 Reactions with Alkoxy Radicals

The reaction of sulfinic acids with *t*-butoxy radicals has been used to generate sulfonyl radicals for low-temperature EPR studies²⁴ (as above for our REqEPR experiments), but the kinetics of this reaction have never been reported.⁴² To provide insight to this reactivity, we chose cumyloxy radicals as model species since they possess an absorption at 485 nm. The cumyloxy radicals were generated from dicumylperoxide via laser flash photolysis, and their decay monitored as a function of sulfinic acid concentration to obtain the desired rate constants. In addition, kinetics for the reactions of the sulfinic acids with the triplet state of benzophenone (monitored at 530 nm) were also determined (Figure 6.4A). The benzophenone triplet state has a much higher extinction coefficient than the cumyloxy radical, greatly improving the signal quality. The results are comparable to those obtained with cumyloxy radicals since the $n \rightarrow \pi^*$ state of the carbonyl has a similar electronic structure as alkoxy radicals. Representative results of initial measurements of the reactivity of PhSO₂H with the

benzophenone triplet (^3BP) are shown in Figure 6.4C. Interestingly, the pseudo first order rate constants from the decay traces yielded a non-linear relationship with sulfinic acid concentration. This suggested that self-association of the sulfinic acid in H-bonded dimers may retard the rate by precluding access to the labile H-atom. Indeed, the data could be easily fit to a non-linear equation accounting for the contribution of the competing equilibrium that defines the amount of sulfinic acid available for reaction (Figure 6.4D). Doing so for the data in Figure 6.4C yielded $k_{\text{H}} = (1.7 \pm 0.3) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and $K_{\text{d}} = (6.4 \pm 2.2) \times 10^{-3} \text{ M}$. Corresponding data obtained with cumyloxyl radicals under otherwise identical conditions was ca. 2-fold slower, yielding $k_{\text{H}} = (6.9 \pm 1.3) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$.

Given the retardation of the H-atom transfer from PhSO_2H to ^3BP and cumyloxyl by self-association and the foregoing results with alkyl radicals, it was expected that the H-atom transfer kinetics would again be highly solvent dependent. Therefore, our investigations were expanded to include more (CH_3CN , EtOAc) and less (PhCl) H-bond accepting solvents, the results of which are summarized in Figure 6.4E. Plotting these data according to the Ingold-Abraham equation yields $\alpha_2^{\text{H}} = 0.65$, in good agreement with the value of 0.61 derived from the alkyl radical kinetic data. The rate constant for the reaction of TrptSO_2H with ^3BP was also determined for comparison. In CH_3CN , where self-association does not contribute, $k_{\text{H}} = (1.8 \pm 0.1) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, a factor of ~ 3 greater than that measured for PhSO_2H ($k_{\text{H}} = 6.5 \pm 0.2) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, consistent with its slightly lower O-H BDE, and implying that the triptycene moiety imparts little to no steric effect on its fast HAT activity.

For comparison, the kinetics of HAT from TrptSOH to ^3BP and cumyloxyl were also determined. In benzene, $k_{\text{H}} = (2.3 \pm 0.1) \times 10^9$ and $(1.4 \pm 0.2) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for ^3BP and cumyloxyl, respectively. Consistent with the foregoing observations with the sulfinic acids, and trends in HAT reactions in general, the rate constant for HAT to ^3BP is slightly greater than for cumyloxyl. These kinetics were also explored in different solvents, revealing a significantly smaller effect than for the sulfinic acids (see Figures 6.4E and 6.4B as well as the Supporting Information) – a surprising result given the similarity in H-bond acidity of the sulfenic and sulfinic acids (*vide supra*). In fact, when the

rate constants for reactions with ^3BP and cumyloxyl are plotted against the solvent H-bond basicity, the Ingold-Abraham equation predicts $\alpha_2^{\text{H}} = 0.23$ and 0.26 , respectively – less than half the value measured directly by IR spectroscopy ($\alpha_2^{\text{H}} = 0.54$)³¹ or determined above from the kinetics of reactions with alkyl radicals ($\alpha_2^{\text{H}} = 0.57$). We surmise that a competing electron transfer reaction is enabled by the more polar (H-bond accepting) solvents.⁴³

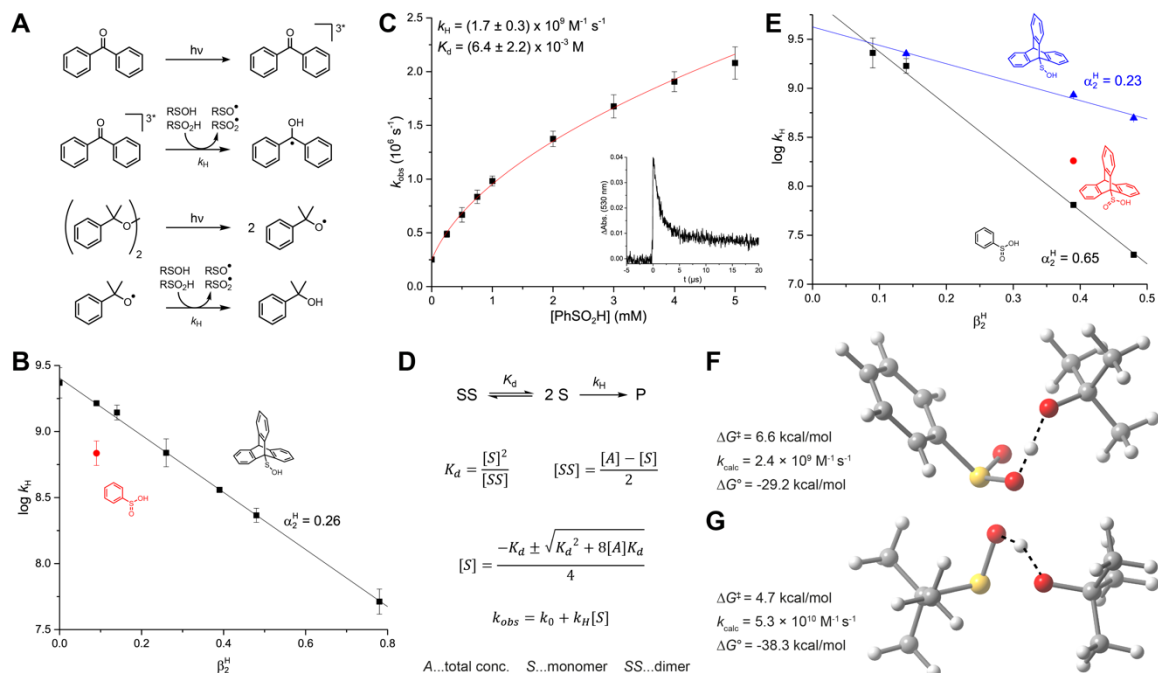


Figure 6.4. (A) Excitation of benzophenone to its triplet state and photolytic generation of cumyloxyl radicals from dicumylperoxide. (B) The HAT rate constants for PhSO_2H (red) and TrptSOH (black) with cumyloxyl radicals plotted as a function of medium β_2^{H} . (C) Dependence of the pseudo-first order rate on the concentration of PhSO_2H upon excitation of BP in benzene at 25°C and non-linear fit; inset: example decay of ^3BP . (D) Contribution of sulfinic acid dimerization to the observed HAT rate constant. (E) The HAT rate constants for PhSO_2H (black), TrptSO_2H (red) and TrptSOH (blue), with ^3BP , plotted as a function of medium β_2^{H} . (F) Calculated (CBS-QB3) transition state structures and associated free energy barrier, estimated rate constant and reaction free energy for HAT between a model alkoxy radical ($t\text{-BuO}^\bullet$) and PhSO_2H and $t\text{-BuSOH}$.

The CBS-QB3-calculated TS structures for HAT from PhSO₂H and *t*-BuSOH to a model alkoxyl radical (t-butyloxyl) is shown in Figures 6.4F. Consistent with experiment, the calculated free energy barriers are very close; $\Delta G^\ddagger = 6.6$ and 4.7 kcal/mol for PhSO₂H and *t*-BuSOH, respectively, corresponding to $k = 2.4 \times 10^9$ and $5.3 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$, respectively. Obviously, the exergonicity of these reactions is so great ($\Delta G^0 = -29.2$ and -38.3 kcal/mol, respectively) that the kinetics have converged to be essentially diffusion-controlled.

6.3.4 Reactions with Peroxyl Radicals

The reactivity of sulfinic acids to peroxyl radicals was explored via inhibited co-oxidation of PBD-BODIPY (Figure 6.5A).⁴⁴ PBD-BODIPY reports on the reaction progress of the autoxidation and its consumption is conveniently monitored by conventional spectrophotometry. Since its reactivity toward peroxyl radicals has been independently determined (e.g. $k_{\text{PBD-BODIPY}} = 3790 \text{ M}^{-1} \text{ s}^{-1}$ in 1-hexadecene/chlorobenzene at 37 °C, see Supporting Information), the inhibition rate constant (k_{inh}) of an added peroxyl radical-trapping antioxidant and the stoichiometry of the inhibition reactions (n) can be easily derived from the data as in Figure 6.5B.

Despite extensive experimentation under various conditions and co-substrates, such as 1-hexadecene and styrene, we were unable to see any inhibition of autoxidation by the sulfinic acids, suggesting that they do not efficiently react with the chain-carrying peroxyl radicals. Representative data are shown in Figure 6.5C, where co-oxidations carried out in the presence of PhSO₂H and TrptSO₂H can be compared to TrptSOH, which has previously been shown to undergo very fast reactions with peroxyl radicals ($k = 3.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$).³⁰ Since sulfonyl radicals are known to readily add to alkenes (e.g. $k = 7 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for 2-vinylnaphthalene),⁴⁵ which would afford an alkyl radical that could carry the autoxidation chain, inhibited autoxidations of substrates lacking a double bond (THF and dioxane) were also carried out, but yielded similar results. As expected, the peroxyl radical-

trapping kinetics of the sulfenic acid was highly solvent-dependent, yielding $\alpha_2^H = 0.46$ when the data was plotted according to the Ingold-Abraham relationship (Figure 6.5D), consistent with previous reports.³¹

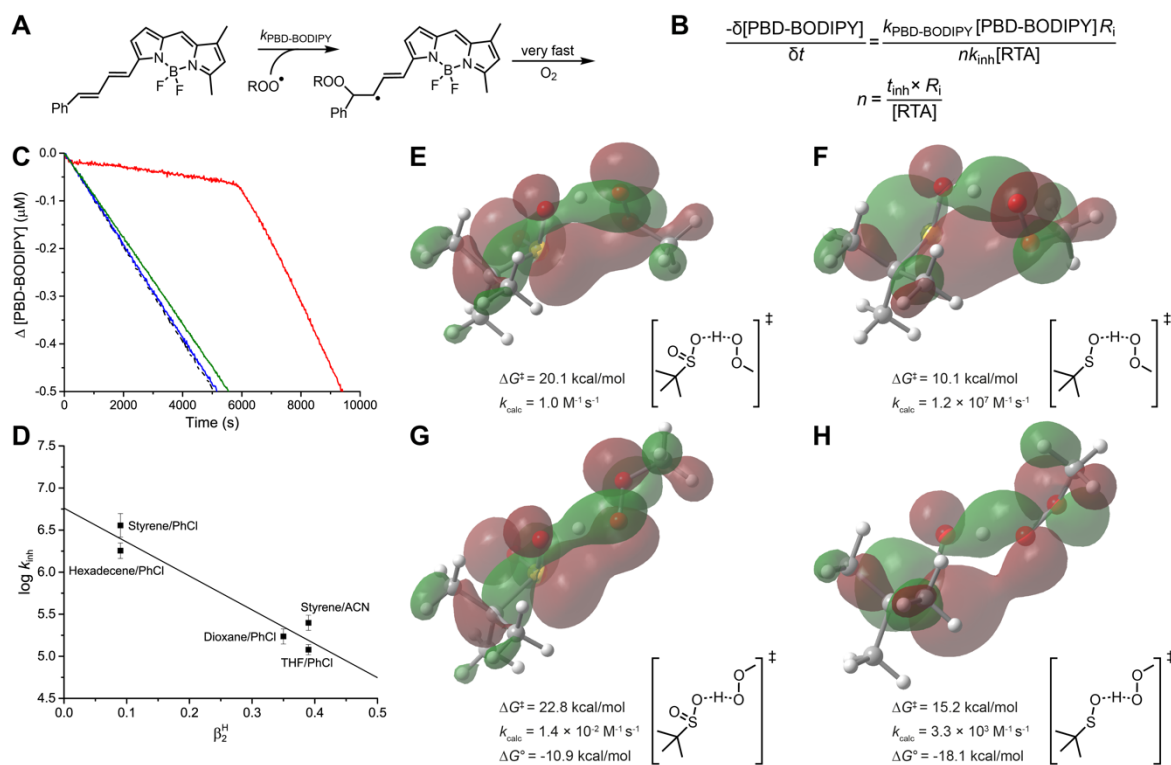


Figure 6.5. (A, B) PBD-BODIPY serves as the signal carrier in hydrocarbon autoxidations, enabling determination of rate constants (k_{inh}) and reaction stoichiometries (n) for reactions of inhibitors with chain-carrying peroxy radicals. (C) Co-autoxidations of 1-hexadecene (2.8 M) and PBD-BODIPY (10 μM) initiated by AIBN (6 mM) at 37 °C (dashed black trace) and inhibited by 10 μM of TrpSOH (red), TrpSO₂H (blue) PhSO₂H (green). (D) The inhibition rate constants for TrpSOH, plotted as a function of medium β_2^H . (E-H) Calculated (CBS-QB3) TS structures for HAT between model sulfenic and sulfinic acid and model peroxy radical (MeOO•) and associated free energy barriers and rate constants estimated using transition state theory, HOMO visualized. TS structures were confirmed to link H-bonded pre- and post-reaction complexes by intrinsic reaction coordinate calculations (see Supporting Information).

To provide insight on the lack of reactivity of the sulfinic acids to peroxy radicals, we calculated the transition state structures for the reactions of *t*-BuSO₂H and *t*-BuSOH with a model peroxy radical (methylperoxy). Two structures were identified for each system (Figures 6.5E-H), one wherein the substituents on the oxygen atoms between which the H-atom is transferred are oriented *anti* with respect to one another, and the other wherein they are *syn*. The *syn* TS structures were significantly lower in energy in both cases and, consistent with the experimental observations, the predicted barriers for the reaction of *t*-BuSO₂H were much higher than those for *t*-BuSOH. These results suggest that the inhibition rate constants for sulfinic acids are roughly seven orders of magnitude lower than for corresponding sulfenic acids, and as such, consistent with our observations that the sulfinic acids are incapable of inhibiting the co-oxidations that were carried out.

Insight to the stark contrast in reactivity of the sulfinic and sulfenic acids is provided upon consideration of the HOMO of the transition states which are shown in Figures 6.5E and F for the preferred *syn* TS and in Figures 6.5G and H for the *anti* TS. Although there is clearly overlap between the π^* of the peroxy radical and the lone pair of the sulfur atom that leads to the preference for the *syn* TS in the reactions of both the sulfinic and sulfenic acids, this interaction is smaller in the sulfinic acid ($\Delta\Delta G^\ddagger = 2.7$ kcal/mol) compared to the sulfenic acid ($\Delta\Delta G^\ddagger = 5.1$ kcal/mol), presumably due to the lower sulfur lone pair energy in the sulfinic acid. Indeed, natural bond orbital analyses indicate that the interaction energy of the sulfur lone pair and peroxy radical π^* drops from 3 kcal/mol in the *syn* TS of the sulfenic acid reaction to 0.4 kcal/mol in the *syn* TS of the sulfinic acid reaction.

In addition to the foregoing efforts, we performed transient absorption spectroscopic experiments to directly monitor the reaction of peroxy radicals with sulfinic acids. The cumyl radicals generated from photolysis of dicumylketone (see above) were used to produce cumylperoxy radicals simply by carrying out the photolysis under an atmosphere of O₂. Although cumylperoxy radicals do not exhibit a visible absorption – precluding observation of their decay in the presence of sulfinic acids – the product sulfonyl radicals absorb at 350 nm. Nevertheless, the data acquired over a wide range of

concentrations (validated through comparing with the equivalent alkyl radicals – see Supporting Information for conditions), suggested no sulfonyl radical formation on the timescale of the experiment.

6.4 Discussion

Thiols, the precursors to both sulfenic and sulfinic acids,^{32,46,47} are eminently useful H-atom transfer agents,⁴⁸ serving as terminal (stoichiometric) reductants in a number of transformations, including the thiol-ene coupling^{49,50} and its aerobic counterpart, the TOCO reaction.^{51,52} We recently showed that the oxidation of a thiol to a sulfenic acid³² renders it a better H-atom donor – on thermodynamic grounds (i.e. alkyl sulfenic acid SO-H BDE ~70 kcal/mol vs. alkyl thiol S-H BDE ~87 kcal/mol)³¹ and kinetic grounds (e.g. $k \sim 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for reactions of alkyl sulfenic acids with peroxy radicals vs. $<10^3 \text{ M}^{-1} \text{ s}^{-1}$ for alkyl thiols).³⁰ However, the greater stability of the sulfinyl radicals precludes useful chemistry. To the best of our knowledge, there is no equivalent of the thiol-ene coupling or TOCO reaction with a sulfenic acid, although these could be very useful reactions! In the preceding pages we have expanded our previous studies to show that, despite their significantly weaker bonds, sulfenic acids are only slightly more inherently reactive towards alkyl and alkoxy radicals compared to thiols. Moreover, because sulfenic acids are such good H-bond donors ($\alpha_2^{\text{H}} \sim 0.55$) they react more slowly than thiols ($\alpha_2^{\text{H}} \sim 0-0.1$)⁵³ in good H-bond accepting solvents.

Further oxidation of the sulfenic acid to a sulfinic acid enables production of the more reactive sulfonyl radical that can be used for productive chemistry. Indeed, Lei and co-workers recently demonstrated the sulfinic acid equivalent of a TOCO reaction,¹² in another example that sulfinic acids are gaining in popularity. The foregoing results enable us to place the reactivity of sulfinic acids into proper context; the alkyl sulfinic S(O)O-H BDE ~78 kcal/mol infers that the stability of the sulfonyl radical is roughly midway between that of thiyl and sulfinyl radicals. Nevertheless, sulfinic acids are

similarly inherently reactive to both alkyl and alkoxy radicals as sulfenic acids and thiols. Importantly, like sulfenic acids, sulfinic acids are excellent H-bond donors ($\alpha_2^H \sim 0.63$), and as such, they are comparatively poor H-atom donors to thiols in good H-bonding solvents. Thus, sulfinic acids are expected to be useful as H-atom transfer agents only in non-H-bonding solvents;⁵⁴ otherwise, thiols are likely to be a much better choice. Indeed, Lei's TOCO-like reaction and Nicewicz's use of sulfinic acids as catalytic H-atom donors in photocatalytic alkene functionalizations are optimal in weak H-bond accepting chlorinated hydrocarbons ($\beta_2^H \sim 0.15$).⁵⁵

To complete the sulfur oxyacid series, we used CBS-QB3 to predict the O-H BDE in a sulfonic acid. The computed result of 107.4 kcal/mol for *t*-BuSO₃H underscores why these compounds are unreactive to any of the radicals we have investigated here. For ease of reference, a summary of our results is presented in Figure 6.6.

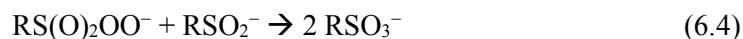
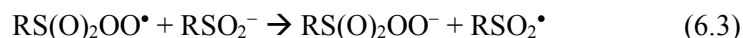
	$\text{R-S-H} \xrightarrow{[\text{O}]} \text{R-S-O-H} \xrightarrow{[\text{O}]} \text{R-S(=O)-O-H} \xrightarrow{[\text{O}]} \text{R-S(=O)}_2\text{-O-H}$				
	thiol	sulfenic acid	sulfinic acid	sulfonic acid	
BDE	~87	~70	~78	~107	BDEs in kcal/mol
$k_H (+ R^\bullet)$	high 10^6	high 10^6	low 10^6	unreactive	rate constants in $M^{-1}s^{-1}$
$k_H (+ RO^\bullet)$	high 10^7	low 10^9	mid 10^8	unreactive	previously reported
$k_H (+ ROO^\bullet)$	$<10^3$	$\sim 10^7$	$<10^3$	unreactive	this work

Figure 6.6. Comparison of H-atom transfer thermochemistry and kinetics for thiols and each of the thiol-derived sulfur oxyacids.

In light of the similar inherent reactivity of thiols, sulfenic acids and sulfinic acids to alkyl and alkoxy radicals, the difference in the peroxy radical reactivity between thiols and sulfenic acids (> 4 orders of magnitude) is quite significant. In one sense, this is intuitive given that the reactions are far less exergonic (e.g. compare $\Delta G^\circ \sim -16$ and ~ 0 kcal/mol for reactions of sulfenic acids and thiols with peroxy radicals versus $\Delta G^\circ = -34$ and -18 kcal/mol for reactions of sulfenic acids and thiols with primary alkyl or alkoxy radicals). However, previous work from our group^{31,56,57} suggests that there

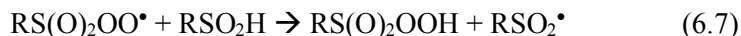
is more to it; specifically, that HAT to peroxy radicals is enabled by secondary orbital interactions, wherein filled π or non-bonding orbitals on the group attached to the atom from which the H-atom is being transferred interact with the proximal end of the peroxy radical π^* MO.⁵⁹ Upon oxidation of the electron-rich sulfur atom in the sulfenic acid to a sulfinic acid, this secondary orbital interaction is expected to be significantly reduced. Indeed, our calculations predict that the sulfinic acid is not only less reactive to peroxy radicals than the sulfenic acid, but is even less reactive than thiols, despite significantly more favourable reaction energetics (of *ca.* 10 kcal/mol). Moreover, both PhSO₂H and TrptSO₂H were incapable of inhibiting the autoxidation of styrene and 1-hexadecene, substrates whose autoxidation is propagated by peroxy radicals.⁵⁸

At first glance, the poor HAT reactivity of sulfinic acids toward peroxy radicals would seem to be the best evidence to date that secondary orbital interactions contribute to the reactivity of good peroxy radical-trapping agents (i.e. antioxidants). However, it must be acknowledged that there is another explanation for the lack of inhibition of the autoxidation: the sulfinic acids themselves autoxidize. This has been noted to be particularly facile in water,⁶⁰ where it is likely to be initiated and propagated by electron transfer reactions, eventually producing a sulfonate:



There is also precedence for sulfinic acid autoxidation in non-polar organic solvents,⁶¹ which presumably propagates via H-atom transfer in lieu of electron transfer (In[•] is an arbitrary initiating radical):





Presented in this way, sulfinic acid autoxidation is analogous to aldehyde autoxidation, which eventually yields carboxylic acid via Baeyer-Villiger oxidation of aldehyde with the autoxidation product peracid.

The increasing popularity of sulfinic acids (and/or their corresponding sulfinate salts) to carry out sulfonylations of multiple bonds or serve as a terminal reducing agent is surprising in light of their purported facile autoxidation. The autoxidation depends on the rate and equilibrium position of Eq 6.6 as well as the follow-up H-atom transfer reaction (Eq 6.7). The rate constant for the reaction of sulfonyl radicals with O_2 has been reported to be $1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ in water/MeOH.⁶² If the reaction were this fast in organic solvent, reactions involving sulfonyl radicals would be impossible under aerobic conditions.^{12,13,17} For example, under the reaction conditions developed by the Lei group for oxidative functionalization of alkynes,¹³ both the addition of sulfonyl radicals and the addition of oxygen would have effective rates of around $1 \times 10^7 \text{ s}^{-1}$. Therefore, yields of 80% would be impossible, since the sulfinic acid (present in excess) would simply autoxidize. Surprisingly, there is no data for the reaction of sulfonyl radicals with O_2 in the non-aqueous solvents in which synthetic organic transformations are generally carried out. Moreover, there are no data on the position of the $\text{RSO}_2^\bullet/\text{O}_2$ equilibrium and the H-atom abstraction from a sulfinic acid by a sulfonylperoxyl radical.

To provide some insight on the rate and equilibrium position of $\text{RSO}_2^\bullet/\text{O}_2$ in organic solvents, we carried out additional CBS-QB3 calculations. The addition of oxygen to $\text{MeSO}_2^\bullet$ and $\text{PhSO}_2^\bullet$ is predicted to be exergonic by 2.9 kcal/mol, with barriers of $\Delta G^\ddagger = 11.0$ and 10.0 kcal/mol, corresponding to rate constants of $k = 2.8 \times 10^6$ and $1.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, respectively, at 37 °C.⁶³ These results suggest that water and/or protic solvents accelerate the reaction and increase the driving force

– perhaps due to stronger H-bonding interactions in the product sulfonylperoxyl than the starting sulfonyl.

Interestingly, if the sulfonylperoxyl radical forms, it is predicted to be extremely reactive; the calculated barrier for H-atom abstraction from MeSO₂H by MeS(O)₂OO• is predicted to be $\Delta G^\ddagger = 7.0$ kcal/mol, corresponding to a rate constant of $1.9 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. This would lead to very fast consumption of sulfinic acid.⁶⁴ Recall, the predicted barrier for H-atom abstraction from MeSO₂H by MeOO• is nine orders of magnitude slower!

To corroborate these predictions, we photolyzed *p*-toluenesulfonyl iodide in benzene and monitored the decay of the *p*-toluenesulfonyl radical at 350 nm in the presence and absence of O₂. Under an atmosphere of N₂, the tosyl radicals decayed with $k = (7.3 \pm 0.5) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, consistent with the kinetics of their disproportionation to sulfinyl and sulfonyloxyl radicals obtained by EPR.³⁵ The tosyl radicals decayed at a greater rate when analogous experiments were carried out under an air atmosphere, yielding an apparent rate constant of $k = (1.0 \pm 0.2) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. Assuming this rate constant is the superposition of the disproportionation and O₂ addition reactions, a rate constant for the latter can be estimated to be $k = (9 \pm 4) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, in remarkably good agreement with the value predicted by CBS-QB3, and most importantly, >1000-fold slower than in aqueous solution.⁶⁵ With a rate constant in this range, typical propagating reactions of sulfonyl radicals (e.g. addition to double and triple bonds, $k = 10^7 - 10^9 \text{ M}^{-1} \text{ s}^{-1}$)⁴⁵ can compete effectively with oxygen addition, which under typical synthetic conditions⁶⁶ translates to a difference of 3 – 3.5 orders of magnitude in reaction rates.⁶⁷ An indication that optimized synthetic procedures depend strongly on these kinetics is highlighted by the significant drop in yield (>50%) that is observed upon switching from an air atmosphere to exclusively O₂.¹³

6.5 Conclusions

Sulfinic acids are very good H-atom donors leading to highly reactive sulfonyl radicals which have a wide range of synthetic applications. This activity is quite similar to sulfenic acids although because of their increased BDE of ~ 78 (vs. 70) kcal/mol they are typically slightly slower at $2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ vs. alkyl and $5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ vs. alkoxy radicals. A surprising property is the slow reaction of sulfinic acids with peroxy radicals, which could not be measured but calculated at $< 10^3 \text{ M}^{-1} \text{ s}^{-1}$, displaying the effect a change in orbital electronics can have on reactions that are enhanced via secondary orbital interactions. An additional disadvantage of sulfinic acids is their tendency to autoxidize, facilitate via the addition of oxygen to sulfonyl radicals. Although this has not deterred recent synthetic endeavours as the reaction seems to be greatly enhanced in water (polar solvents) and thus is slow enough in organic solvents (at $\sim 1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$) to enable these reactions to proceed. Similar to sulfenic acids, the more oxidized sulfinic acids also show high H-bond acidity and therefore a very large modulation of their HAT activity in different solvents. This should be taken into account when employing them in catalytic and/or chain reactions.

6.6 Experimental Section

6.6.1 General

Reagents were obtained from commercial suppliers and used as is, unless indicated otherwise. Column chromatography was carried out with 40-63 μm , 230-400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE spectrometer at 400 MHz and 101 MHz, respectively, unless indicated otherwise. High-resolution mass spectra were obtained on a Kratos Concept Tandem mass spectrometer (EI) and Micromass Q-TOF (ESI). TrptSO₂H, PhSO₂H and dicumylketone were synthesized as described in the Supporting Information. TrptSOH,²⁸ PBD-BODIPY and STY-BODIPY,⁴⁴ NMBHA,⁶⁸ tosyl iodide,⁶⁹ as well as the GC standards for the alkyl radical clock kinetics⁷⁰

were synthesized following previously reported procedures. Chlorobenzene was dried over 3 Å molecular sieves before use. Solvents for kinetics experiments were of anhydrous or HPLC quality. UV-visible spectra were measured with a Cary 100 spectrophotometer equipped with a thermostatted 6 x 6 multi-cell holder.

6.6.2 Laser Flash Photolysis

Nanosecond transient absorption experiments were performed on an LFP-112 spectrometer (Luzchem, Canada). Irradiation source was an EX10 (GAM Laser, USA) XeCl Excimer laser (308 nm, ca. 10 mJ/pulse, ca. 12 ns pulse width). The transient absorption data were recorded in a quartz cuvette (1 cm x 1 cm) equipped with a septum. Sample concentrations were adjusted to yield an absorbance of 0.2-0.3 at 308 nm and the solutions were bubbled with nitrogen for 10 minutes before measurement. The rate constants for hydrogen abstraction (k_H) were determined in pseudo-first-order according to the following equation $k_{\text{obs}} = k_0 + k_H[\text{H-Donor}]$.

6.6.3 Competition Kinetics

Alkyl radical clock kinetics was determined using a previously reported procedure by Valgimigli and co-workers.⁴⁰ The PTOC ester synthesis is described in the Supporting Information and the standards were synthesized as described previously.⁷⁰ Briefly, vials were loaded with the appropriate amount of sulfinic acid (150-400 mM) and capped with a septum. THF (950 µL) was added followed by 1 eq of methanesulfonic acid and the vials were wrapped in aluminum foil before adding the PTOC ester clock (20 mM). The vials were purged with nitrogen and the aluminum foil was removed before the vials were exposed to a sodium lamp (400 W) at a distance of 40 cm for 1 h at room temperature (ca. 25 °C). Aliquots of 50 µL were taken from each vial and added to a GC vial containing hexylbenzene standard solution (50 µL, 40 mM). The solution was diluted by adding 900 µL of acetonitrile for a

total volume of 1 mL per vial. The samples (4 μL splitless injections) were analyzed by a GC–MS equipped with an Agilent HP-5 ms column (30 m $\times$ 0.25 mm $\times$ 0.25 μm) with a constant He flow of 1.1 mL min^{-1} using the following temperature profile (inlet temperature was set at 150 $^{\circ}\text{C}$): 90 $^{\circ}\text{C}$, hold 1 min, 2 $^{\circ}\text{C min}^{-1}$ to 120 $^{\circ}\text{C}$, hold 1 min, 5 $^{\circ}\text{C min}^{-1}$ to 165 $^{\circ}\text{C}$, hold 1 min, 20 $^{\circ}\text{C min}^{-1}$ to 300, hold 5 min. The method yielded retention times of 10.9, 22.9, 23.4, and 25.4 min for hexylbenzene, 2-tert-butyl-naphthalene, 2-isobutyl-naphthalene, 2-(2-methylallyl)-naphthalene and 2-(2-methylprop-1-en-1-yl)-naphthalene, respectively.

6.6.4 Inhibited Autoxidations

Inhibited autoxidations were performed as previously described.⁵⁶ The procedure for 1-hexadecene autoxidation in chlorobenzene is transcribed below. 1-Hexadecene (2.00 mL) was added in a 3.5 mL quartz cuvette along with PhCl (0.44 mL). The cuvette was then placed in a thermostated sample holder of a UV–vis spectrophotometer and allowed to equilibrate to 37 $^{\circ}\text{C}$ for approximately 10 min. The PBD-BODIPY probe (12.5 μL , 2.00 mM solution in 1,2,4-trichlorobenzene) was added followed by AIBN (50 μL , 300 mM in chlorobenzene) and the solution was thoroughly mixed. The absorbance at 588 nm was monitored for 10 min after which 10.0 μL of a solution of the test antioxidant was added. The solution was mixed and the absorbance readings resumed. The resulting data were processed as previously reported.^{44,56} PMC, which has an established stoichiometry of 2,⁷¹ was used as a standard to derive the rate of initiation ($R_i = 1.3 \times 10^{-9} \text{ M s}^{-1}$) and propagation rate constant for the dye ($k_{\text{PBD-BODIPY}} = 3790 \text{ M}^{-1} \text{ s}^{-1}$).

6.6.5 Calculations

Calculations were carried out using the CBS-QB3 complete basis set method⁷² as implemented in the Gaussian 16 suite of programs.⁷³ Stationary points were identified as minima or maxima by calculation

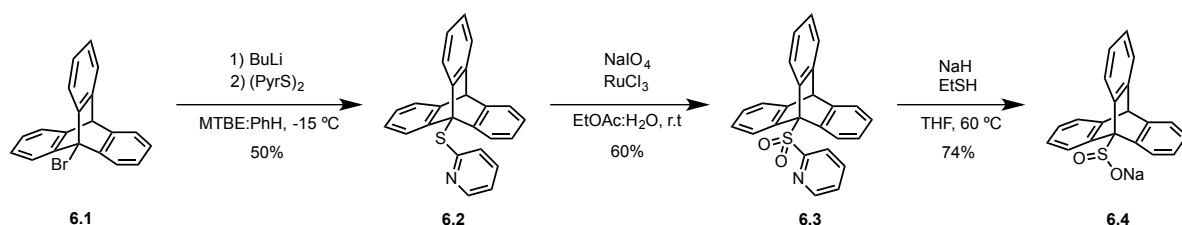
of second derivatives. Maxima were verified to be transition states for the relevant H-atom transfer reactions by carrying out intrinsic reaction coordinate calculations in both the forward and reverse directions. Rate constants were calculated via transition state theory at 25 °C, except for peroxy (37 °C, for comparison with experiment).

Optimized structures and energies (Gaussian 09) of the computationally calculated structures are provided in the Supporting Information section of the publication in Chemical Science (Griesser, M.; Chauvin, J.-P. R.; Pratt, D. A. *Chem. Sci.* **2018**, *9*, 7218–7229.)

6.7 Supporting Information

6.7.1 Synthetic Procedures

Synthesis of 9-triptycenesulfinic acid



2-(9,10-[1,2]Benzenoanthracen-9(10H)-ylthio)pyridine. (6.2)

9-Bromotriptycene (**6.1**) (4.0 g, 12.0 mmol) was dissolved in dry MTBE (95 mL) and benzene (145 mL) and cooled to -15 °C under nitrogen. After stirring for 15 minutes, BuLi (5.8 mL, 14.5 mmol) was added dropwise. The solution was warmed to 0 °C over 30 minutes and 2,2'-dithiopyridine was added all at once and the resulting yellow solution was stirred overnight. The reaction was quenched with water (100 mL) and added to EtOAc (150 mL) in a separatory funnel. The organic phase was washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by column chromatography using 10% EtOAc/hexanes as the eluent to yield the product as a white solid (2.10 g, 50%). ¹H NMR (400 MHz; CDCl₃): δ 8.49 (ddd, *J* = 4.8, 1.8, 0.8 Hz, 1H),

7.51-7.43 (m, 6H), 7.29-7.25 (m, 1H), 7.07-6.94 (m, 7H), 6.67 (d, $J = 8.2$ Hz, 1H), 5.46 (s, 1H). ^{13}C NMR (101 MHz; CDCl_3): δ 158.5, 149.3, 145.4, 142.9, 135.8, 125.9, 125.0, 124.6, 123.8, 123.6, 119.7, 62.1, 54.1. HRMS (EI, $[\text{M}^+]$): m/z calcd for $\text{C}_{25}\text{H}_{17}\text{NS}$: 363.1082, found 363.1079.

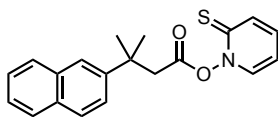
2-(9,10-[1,2]benzenoanthracen-9(10H)-ylsulfonyl)pyridine. (6.3)

2-(9,10-[1,2]benzenoanthracen-9(10H)-ylthio)pyridine (1.50 g, 4.30 mmol) was added to a 1:1 mixture of EtOAc and water (16 mL) and cooled to 0 °C under N_2 . RuCl_3 (44.4 mg, 0.21 mmol) was added and the solution was stirred for 10 minutes before NaIO_4 (5.50 g, 26.0 mmol) was added portion wise and the mixture was vigorously stirred at room temperature overnight. The solution was diluted with ethyl acetate (100 mL) and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The crude yellow solid was purified by column chromatography using a gradient of 10-20% EtOAc/hexanes as the eluent to yield the product as a white solid (1.10 g, 60%). ^1H NMR (400 MHz; CD_3CN): δ 8.41 (dt, $J = 8.1, 1.0$ Hz, 1H), 8.36 (ddd, $J = 4.7, 1.7, 0.9$ Hz, 1H), 8.24-8.18 (m, 2H), 7.80 (dt, $J = 7.9, 0.5$ Hz, 2H), 7.64 (ddd, $J = 7.7, 4.7, 1.1$ Hz, 1H), 7.53-7.49 (m, 3H), 7.13-7.08 (m, 4H), 6.97-6.93 (m, 2H), 5.60 (s, 1H). ^{13}C NMR (101 MHz; acetone- d_6): δ 162.4, 149.8, 147.3, 146.4, 141.6, 140.8, 140.2, 128.8, 127.2, 126.85, 126.66, 125.35, 125.24, 124.99, 124.91, 124.2, 122.8, 78.8, 54.9. HRMS (EI, $[\text{M}^+]$): m/z calcd for $\text{C}_{25}\text{H}_{17}\text{NO}_2\text{S}$: 395.0980, found 395.0985.

Sodium 9,10-[1,2]benzenoanthracene-9(10H)-sulfinate (6.4)

2-(9,10-[1,2]benzenoanthracen-9(10H)-ylsulfonyl)pyridine (1.00 g, 2.53 mmol) was dissolved in dry THF (12 mL), cooled to 0 °C and purged with N_2 in a sealed tube. NaH (30.4 mg, 7.59 mmol) was added portion wise followed by EtSH (violent gas evolution) and the tube was sealed quickly. The solution was stirred at 70 °C overnight after which the reaction was quenched with methanol (5 mL) and concentrated. The crude product was purified by column chromatography using a gradient of 10-20% MeOH:DCM to yield the product as a off white solid (63.0 mg, 74%). ^1H NMR (400 MHz; CD_3OD): δ 8.26 (br, 3H), 7.36-7.34 (m, 3H), 7.01-6.94 (m, 6H), 5.32 (s, 1H). ^{13}C NMR (151 MHz;

CD₃OD): δ 148.1, 143.9, 126.5, 126.2, 125.5, 123.8, 75.9, 55.8. HRMS (ESI, [M-H⁺]): m/z calculated for C₂₀H₁₃O₂S: 317.0642, found 317.0652.



2-thioxopyridin-1(2H)-yl-3-methyl-3-(naphthalen-2-yl)butanoate. 3-Methyl-3-(naphthalen-2-yl)butanoic acid⁷⁴⁻⁷⁵ (0.600 g, 2.60 mmol) was dissolved in dry benzene (15 mL) in an over-dried round bottom flask and purged with N₂ for 5 minutes. DMF (1 drop) and thionyl chloride (0.283 mL, 3.9 mmol) were added dropwise and the solution was heated at reflux for 2 hours. Excess thionyl chloride was removed by rotary evaporation and the crude acyl chloride was dissolved in benzene (2 mL) and added dropwise to a stirred suspension of 2-mercaptopyridine sodium salt (0.500 g, 3.38 mmol) and DMAP (0.050 g, 0.40 mmol) in benzene (10 mL). The solution was stirred at room temperature for 1 hour in the dark after which it was concentrated and the crude yellow solid was purified by column chromatography using 50% EtOAc/hexanes as the eluent to yield the product as a yellow solid (0.53 g, 61%). ¹H NMR (600 MHz; CDCl₃): δ 7.86-7.81 (m, 4H), 7.60 (ddd, J = 8.7, 4.8, 1.8 Hz, 2H), 7.50-7.45 (m, 2H), 7.07 (ddd, J = 8.7, 7.0, 1.6 Hz, 1H), 6.75 (d, J = 7.0 Hz, 1H), 6.34 (td, J = 6.9, 1.7 Hz, 1H), 3.15 (s, 2H), 1.68 (s, 6H). ¹³C NMR (151 MHz; CDCl₃): δ 175.9, 166.6, 144.2, 137.5, 137.3, 133.5, 133.3, 132.1, 128.2, 128.2, 127.5, 126.4, 126.0, 124.5, 124.2, 112.5, 45.2, 37.9, 29.1.

***N*-Hydroxy-*N*-methylbenzamide.**⁷⁶ A suspension of *N*-methylhydroxylamine hydrochloride (2.02 g, 24 mmol) in THF/H₂O (40 mL, 10:1) at 0 °C was treated with NaHCO₃ (4.06 g, 48 mmol) and stirred for 10 min, then benzoyl chloride (2.81 mL, 24 mmol) was added dropwise over 10 min. The reaction was stirred overnight without cooling. After dilution with 50 mL of DCM and H₂O the solution was extracted three times with DCM and washed with brine. The yellow oil was purified by column

chromatography (20% EtOAc/hexanes to 100% EtOAc) to give a pale yellow oil (2.50 g, 69%). ¹H NMR (400 MHz; DMSO-d₆): δ 9.99 (s, 1H), 7.63-7.56 (m, 2H), 7.48-7.37 (m, 3H), 3.24 (s, 3H).

2,4-Dimethyl-2,4-diphenyl-3-pentanone.⁷⁷ 1,3-diphenylpropan-2-one (2.00 g, 9.5 mmol), dissolved in 30 mL of dry THF was added dropwise over 15 min to a suspension of NaH (2.28 g, 95 mmol) in 30 mL of dry THF under N₂ at 0 °C. After 30 min of stirring, MeI (14.2 g, 100 mmol) was added dropwise and after 30 min the reaction was heated to reflux for 3 h. After cooling and addition of water the mixture was extracted three times with EtOAc, washed with brine, and dried over MgSO₄ and concentrated in vacuo. To also convert remaining trimethylated product the procedure was repeated once more with a third of the reagents. Finally the product was recrystallized from hexanes to give white needles (1.18 g, 46%). ¹H NMR (400 MHz; CDCl₃): δ 7.30-7.27 (m, 2H), 7.26-7.24 (m, 2H), 7.23-7.17 (m, 6H), 1.29 (s, 12H).

6.7.2 Procedure to Determine BDEs Through REqEPR

Electron paramagnetic resonance (EPR) spectra were recorded on a Bruker EMXplus (X-band) spectrometer equipped with an ER 4119HS cavity. The (composite) spectra were fitted and the radical concentration was determined using the quantitative EPR package of the Bruker Xenon software. To generate the radicals 5% (v/v) di-*tert*-butyl peroxide was added to the solutions in benzene (with or without 10% v/v *t*-BuOH) under nitrogen and the EPR cavity irradiated with a Hamamatsu LC5 Hg–Xe lamp (150 W) via a 3.5 mm quartz light guide. REqEPR experiments with sulfonyl radicals were performed under continuous irradiation.

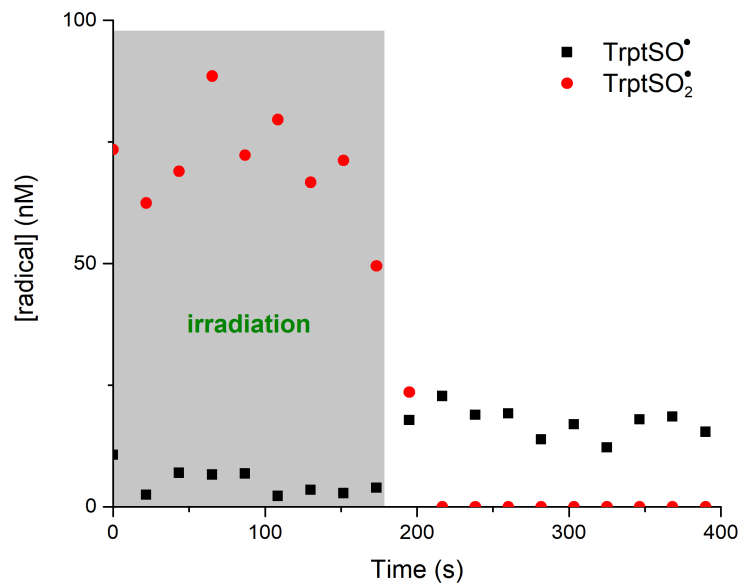


Figure 6.7. Concentrations of sulfinyl and sulfonyl radicals, determined during and after the irradiation of TrptSO₂H (4 mM) and 5% (v/v) di-*tert*-butyl peroxide in benzene with 10% (v/v) *t*-BuOH at 25 °C.

During the REqEPR experiments the concentrations of nitroxide and sulfonyl radical were recorded over time under continuous irradiation, which was necessary due to the decay of the sulfonyl radicals. Data after reaching “stable” conditions were processed and averaged. In total 5 concentrations (54 data points) were averaged for TrptSO₂H and 4 concentrations (75 data points) were averaged for PhSO₂H.

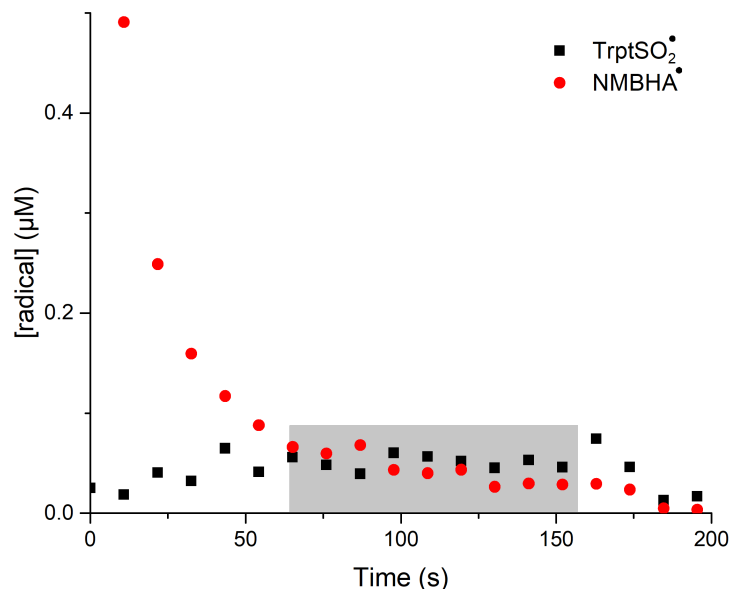


Figure 6.8. Concentrations of nitroxide and sulfonyl radical, determined during the irradiation of TrptSO₂H (4 mM) and NMBHA (0.5 mM) and 5% (v/v) di-*tert*-butyl peroxide in benzene with 10% (v/v) *t*-BuOH at 25 °C. The grey area represents the region of useful data.

Assuming a negligible reaction entropy for the H-atom exchange and given the known BDE of NMBHA, the BDE for sulfinic acid can be determined. As all involved compounds are relative strong hydrogen bond donors it is important to take this influence on the apparent BDE into account. For this purpose we also re-examined the BDE of NMBHA as at the time no correction had been made.⁷⁸ The important properties to know is the hydrogen bond acidity α_2^H of the analytes as well as the hydrogen bond basicity β_2^H of the solvent system. This influence has been quantified previously⁷⁹ and can be expressed by the following equation:

$$\Delta H \left(\frac{kcal}{mol} \right) = -20.56 \alpha_2^H \beta_2^H + 0.59$$

The β_2^H for benzene is 0.14 and for the mixture of benzene/*t*-BuOH 9:1, which was necessary to solubilize NMBHA and TrptSO₂H, was determined as 0.34. This was achieved via the ¹⁹F NMR method we have described previously.⁸⁰ The α_2^H values for phenols have been studied previously.⁸⁰ We employed a value of $\alpha_2^H = 0.24$ for BHT,⁸¹ while NMBHA was determined to have $\alpha_2^H = 0.45$ (via ¹H NMR shifts in CDCl₃ and DMSO-d₆).⁸²

Using these values we obtained a new, solvent corrected, BDE for NMBHA of 78.0 ± 0.2 kcal/mol. Referencing this value and employing an $\alpha_2^H = 0.64$ for sulfinic acid (see manuscript) we can determine an O-H BDE of 77.6 kcal/mol for 9-triptycenesulfinic acid. For phenylsulfinic acid a similar correction (in benzene) is necessary, finally yielding a BDE of 78.3 kcal/mol. Both values are in very good agreement with the CBS-QB3 calculations. The direct experimental error from the processed data is 0.2 kcal/mol, although including the error for the reference NMBHA and the solvent effect a more appropriate error is ± 1.0 kcal/mol.

6.7.3 LFP – Details and Results

Table 6.1. Summary of rate constants (k_H) for HAT by cumyl radicals, determined via photolysis of dicumylketone.

Solvent	k_H (M ⁻¹ s ⁻¹)	
	PhSO ₂ H	TrptSOH
isooctane	-	$(1.2 \pm 0.2) \times 10^7$
chlorobenzene	$(1.7 \pm 0.2) \times 10^6$	$(5.0 \pm 0.4) \times 10^6$
benzene	$(1.0 \pm 0.2) \times 10^6$	$(2.9 \pm 0.4) \times 10^6$
anisole	$(2.3 \pm 0.3) \times 10^5$	$(6.1 \pm 0.8) \times 10^5$

Table 6.2. Summary of rate constants (k_H) for HAT by benzophenone triplet.

Solvent	k_H ($M^{-1} s^{-1}$)		
	PhSO ₂ H	TrptSO ₂ H	TrptSOH
chlorobenzene	$(2.3 \pm 0.6) \times 10^9$	-	-
benzene	$(1.7 \pm 0.3) \times 10^9$	-	$(2.3 \pm 0.1) \times 10^9$
acetonitrile	$(6.5 \pm 0.1) \times 10^7$	$(1.8 \pm 0.1) \times 10^8$	$(8.6 \pm 0.1) \times 10^8$
ethyl acetate	$(2.0 \pm 0.1) \times 10^7$	-	$(5.0 \pm 0.1) \times 10^8$

Table 6.3. Summary of rate constants (k_H) for HAT by cumyloxyl radicals, determined via photolysis of dicumylperoxide.

Solvent	k_H ($M^{-1} s^{-1}$)	
	PhSO ₂ H	TrptSOH
isooctane	-	$(2.3 \pm 0.5) \times 10^9$
chlorobenzene	-	$(1.6 \pm 0.1) \times 10^9$
benzene	$(6.9 \pm 1.3) \times 10^8$	$(1.4 \pm 0.2) \times 10^9$
anisole	-	$(6.9 \pm 0.2) \times 10^8$
acetonitrile	-	$(3.6 \pm 0.1) \times 10^8$
ethyl acetate	-	$(2.3 \pm 0.3) \times 10^8$
dimethyl sulfoxide	-	$(5.2 \pm 1.0) \times 10^7$

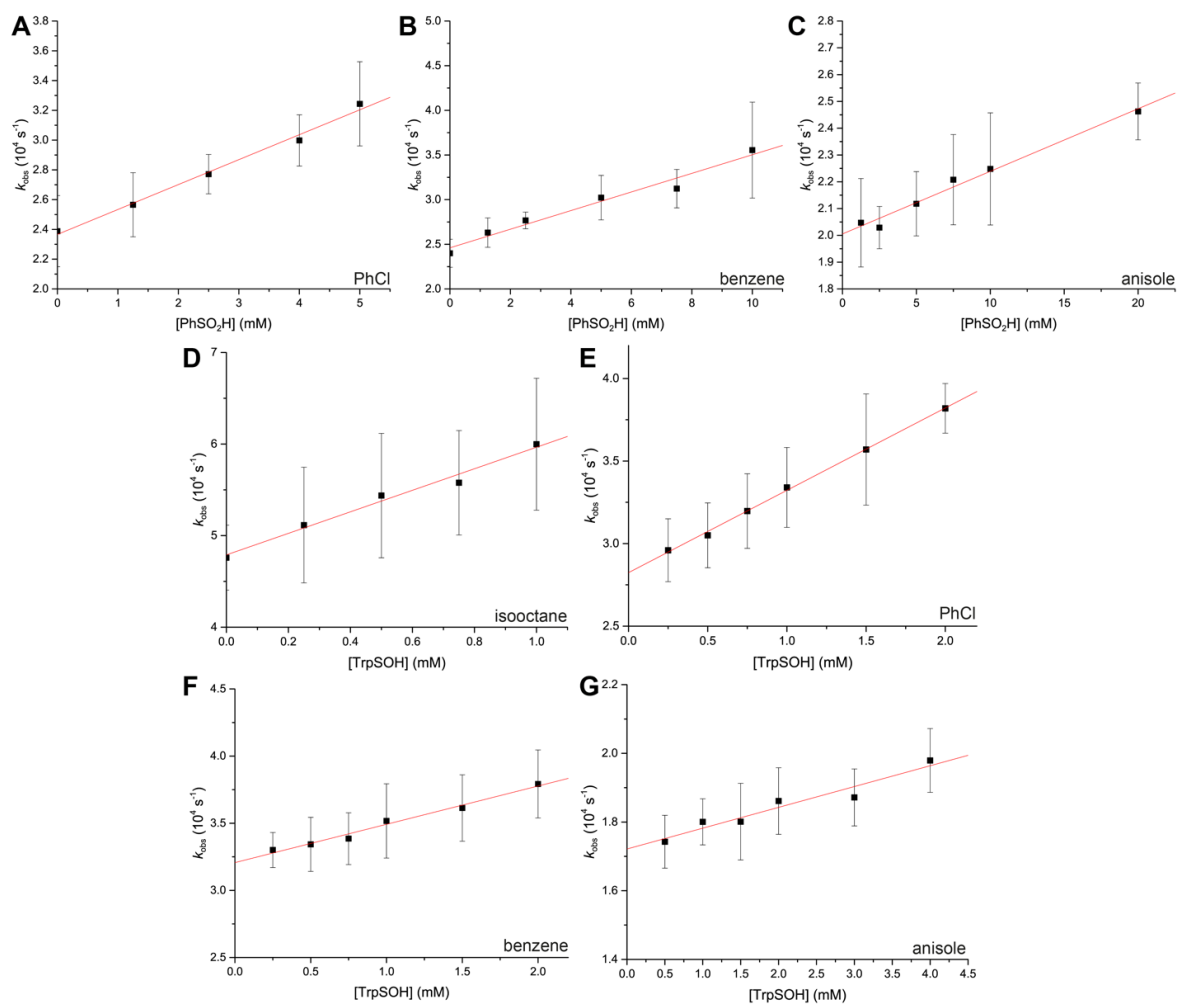


Figure 6.9. Dependence of the pseudo-first-order rate on the concentration of PhSO_2H (A-C) and TrpSOH (D-G) upon photolysis of dicumylketone (2 mM) at 25 °C in PhCl (A, E), benzene (B, F), anisole (C, G), and isooctane (D).

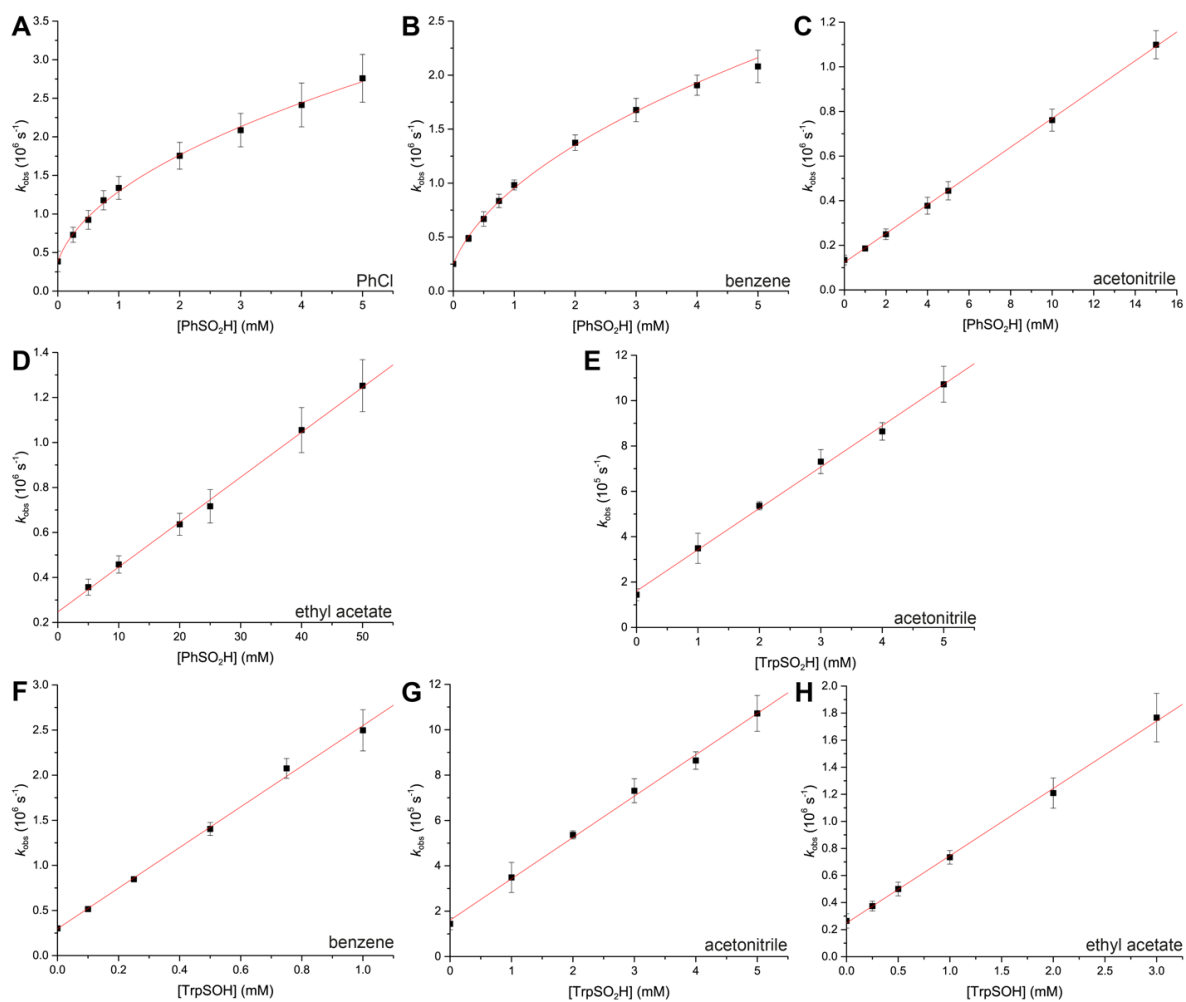


Figure 6.10. Dependence of the pseudo-first-order rate on the concentration of PhSO_2H (A-D), TrpSO_2H (E), and TrpSOH (F-H) upon photolysis of benzophenone (2 mM) at 25 °C in chlorobenzene (A), benzene (B, F), acetonitrile (C, E, G), and ethyl acetate (D, H).

6.7.4 Generation of cumylperoxyl radicals

LFP experiments (308 nm) were performed under oxygen atmosphere in benzene with between 1 and 3 mM of dicumylketone and the appearance of sulfonyl radical (from sulfinic acid) was monitored at 350 nm. The concentration of PhSO_2H was varied between 1 and 20 mM. No appearance of signal could be observed (also at longer timescales eg. 250 μs). A higher concentration of dicumylketone led to a decrease in radical production because of optical density.

Performing equivalent experiments under nitrogen atmosphere were successful in determining HAT kinetics of cumyl radicals indirectly in a concentration range of 1-5 mM of PhSO_2H .

6.7.5 Transient Absorption Experiments with PhSSPh

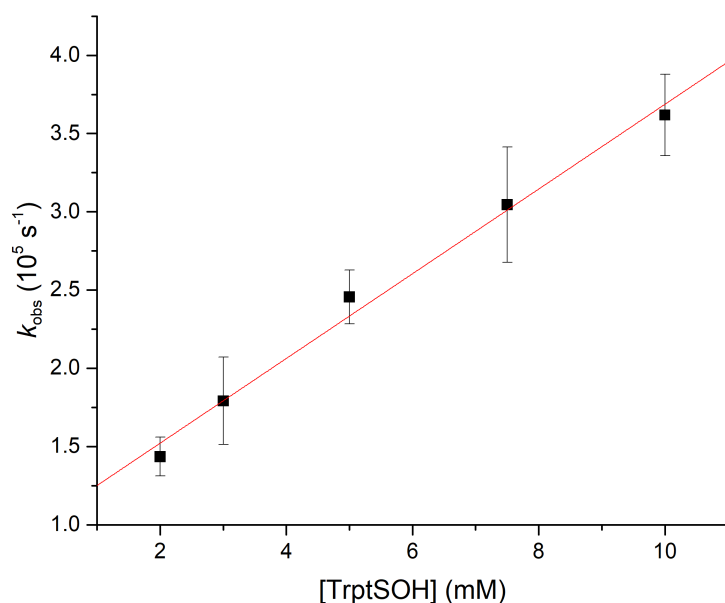


Figure 6.11. Dependence of the pseudo-first-order rate on the concentration of TrptSOH upon photolysis of diphenyl disulfide in acetonitrile at 25 °C.

As the phenylthiyl radical has a visible absorption (observed at 460 nm) and is easily produced by photolysis of diphenyldisulfide (0.2 mM), it is a convenient probing molecule. While for TrptSOH HAT activity with PhS[•] can be observed ($k = (2.7 \pm 0.4) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ in acetonitrile – single experiment), no reactivity could be discerned for PhSO₂H. This is also corroborated when calculating the corresponding TS via CBS-QB3. For PhSO₂H $\Delta G^\ddagger = 15.1 \text{ kcal/mol}$ corresponding to a rate constant of $k = 1.2 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, in addition the reaction is only exergonic by 4.6 kcal/mol. In contrast for sulfenic acids $\Delta G^\circ \sim -14 \text{ kcal/mol}$ and the rate constant predicted near the diffusion limit.

6.7.6 Estimation of the Kinetics of Addition of the Tosyl Radical to Oxygen

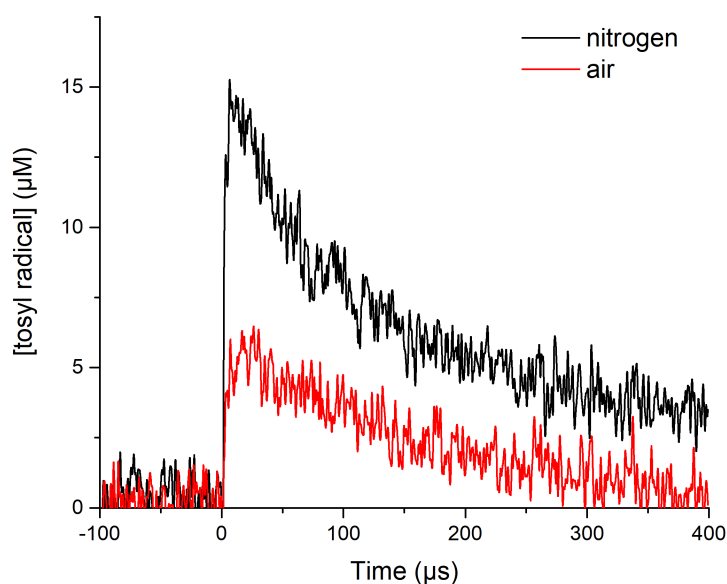


Figure 6.12. Decays for the tosyl radical (335 nm , $\epsilon = 1200 \text{ M}^{-1} \text{ cm}^{-1}$)⁸³ under nitrogen (black) and air (red) generated from a solution of 0.2 mM p-toluenesulphonyl iodide⁸⁴ in benzene at 25 °C.

The following rate constants were determined for the (apparent) disproportionation reaction in second order:

nitrogen: $k_{\text{RSO}_2} = (7.3 \pm 0.5) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$

air: $k_{\text{obs}} = (1.0 \pm 0.2) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$

Under the assumption that the difference in second order rate is caused by the reaction with oxygen the following equation can be constructed:

$$k_{\text{obs}}[\text{RSO}_2]^2 = k_{\text{RSO}_2}[\text{RSO}_2]^2 + k_{\text{O}_2}[\text{RSO}_2][\text{O}_2]$$

As $[\text{RSO}_2^*]$ is $\sim 6 \mu\text{M}$ at the begin of the decay we can estimate the rate constant $k_{\text{O}_2} = (9 \pm 4) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.

6.7.7 Co-oxidations in Organic Solutions

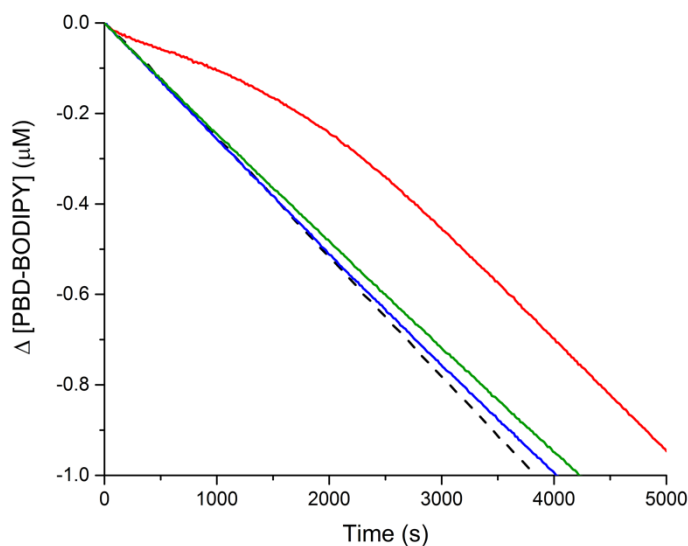


Figure 6.13. Thermally initiated (AIBN, 6 mM) co-oxidations of THF (3.1 M) and PBD-BODIPY (10 μM) at 37 °C in PhCl inhibited by 10 μM of TrptSOH (red), TrptSO₂H (blue) or PhSO₂H (green). Reaction progress was monitored via absorbance at 588 nm ($\epsilon = 128\,100 \text{ M}^{-1} \text{ cm}^{-1}$).⁸⁵

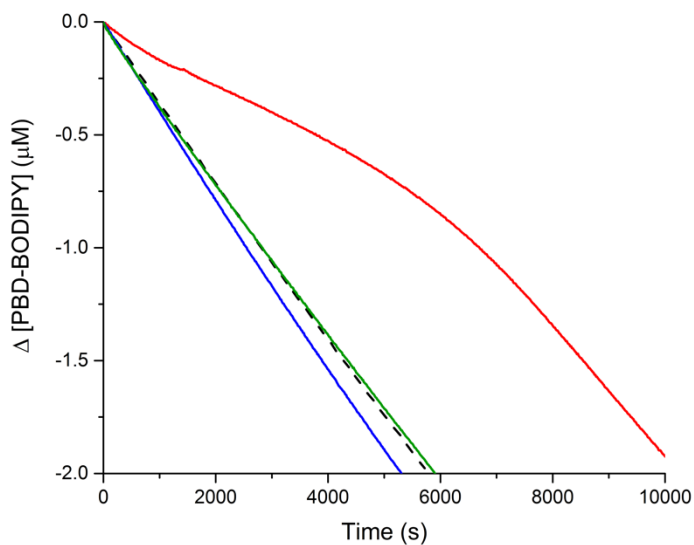


Figure 6.14. Thermally initiated (AIBN, 6 mM) co-oxidations of dioxane (2.9 M) and PBD-BODIPY (10 μM) at 37 $^{\circ}\text{C}$ in PhCl inhibited by 10 μM of TrptSOH (red), TrptSO₂H (blue) or PhSO₂H (green). Reaction progress was monitored via absorbance at 587 nm ($\epsilon = 123\,000\text{ M}^{-1}\text{ cm}^{-1}$).⁸⁵

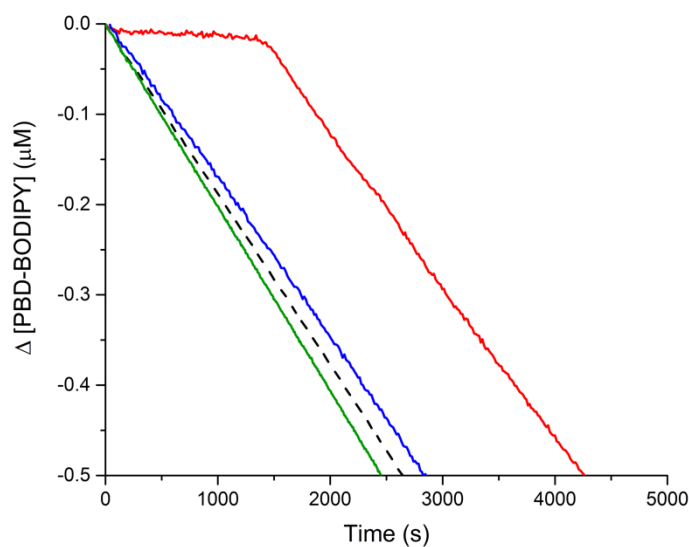


Figure 6.15. Thermally initiated (AIBN, 6 mM) co-oxidations of styrene (4.3 M) and PBD-BODIPY (10 μM) in PhCl at 37 $^{\circ}\text{C}$ inhibited by 10 μM of TrptSOH (red), TrptSO₂H (blue) or PhSO₂H (green). Reaction progress was monitored via absorbance at 591 nm ($\epsilon = 139\,000\text{ M}^{-1}\text{ cm}^{-1}$).⁸⁶

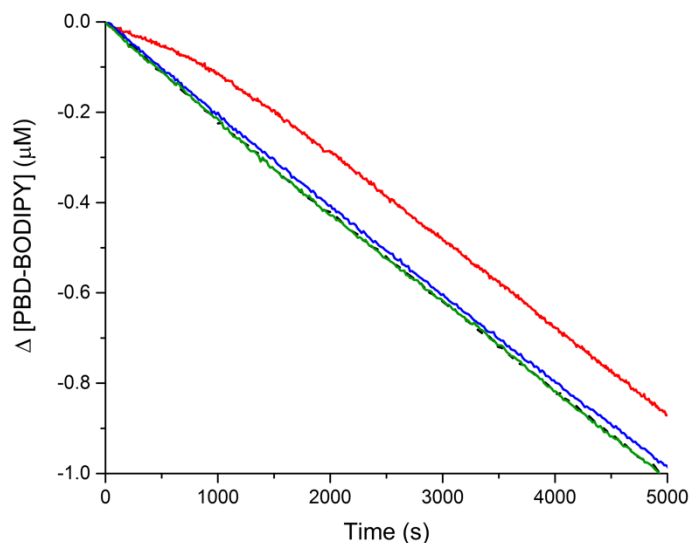


Figure 6.16. Thermally initiated (AIBN, 6 mM) co-oxidations of styrene (4.3 M) and PBD-BODIPY (10 μM) in MeCN at 37 $^{\circ}\text{C}$ inhibited by 10 μM of TrptSOH (red), TrptSO₂H (blue) or PhSO₂H (green). Reaction progress was monitored via absorbance at 585 nm ($\epsilon = 127\,860\,\text{M}^{-1}\,\text{cm}^{-1}$).⁸⁶

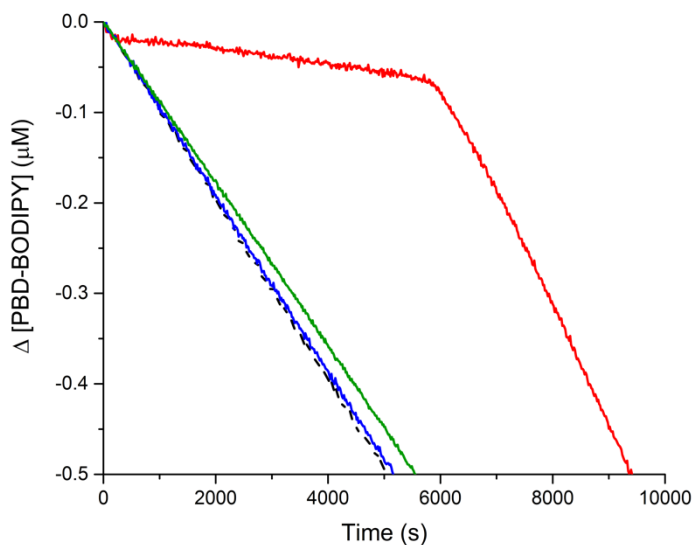


Figure 6.17. Thermally initiated (AIBN, 6 mM) co-oxidations of hexadecene (2.8 M) and PBD-BODIPY (10 μM) at 37 $^{\circ}\text{C}$ in PhCl inhibited by 10 μM of TrptSOH (red), TrptSO₂H (blue) or PhSO₂H (green). Reaction progress was monitored via absorbance at 588 nm ($\epsilon = 148\,700\,\text{M}^{-1}\,\text{cm}^{-1}$).⁸⁵

6.7.8 Summary of Rate Constants for Peroxyl Radicals

Table 6.4. Summary of rate constants (k_{inh}) and stoichiometry (n) during inhibited co-autoxidations (6 mM AIBN) at 37 °C.

Substrate/Solvent	TrptSOH	
	k_{inh} ($\text{M}^{-1} \text{s}^{-1}$)	n
THF/PhCl	$(1.2 \pm 0.2) \times 10^5$	0.6 ± 0.1
Dioxane/PhCl	$(2.7 \pm 0.4) \times 10^5$	0.7 ± 0.1
Styrene/PhCl	$(3.6 \pm 0.7) \times 10^6$	0.5 ± 0.05
Styrene/MeCN	$(2.5 \pm 0.6) \times 10^5$	0.5 ± 0.03
Hexadecene/PhCl	$(1.8 \pm 0.4) \times 10^6$	0.7 ± 0.1

6.7.9 Naphthyl-Neophyl Clock to Measure Alkyl Radical Kinetics

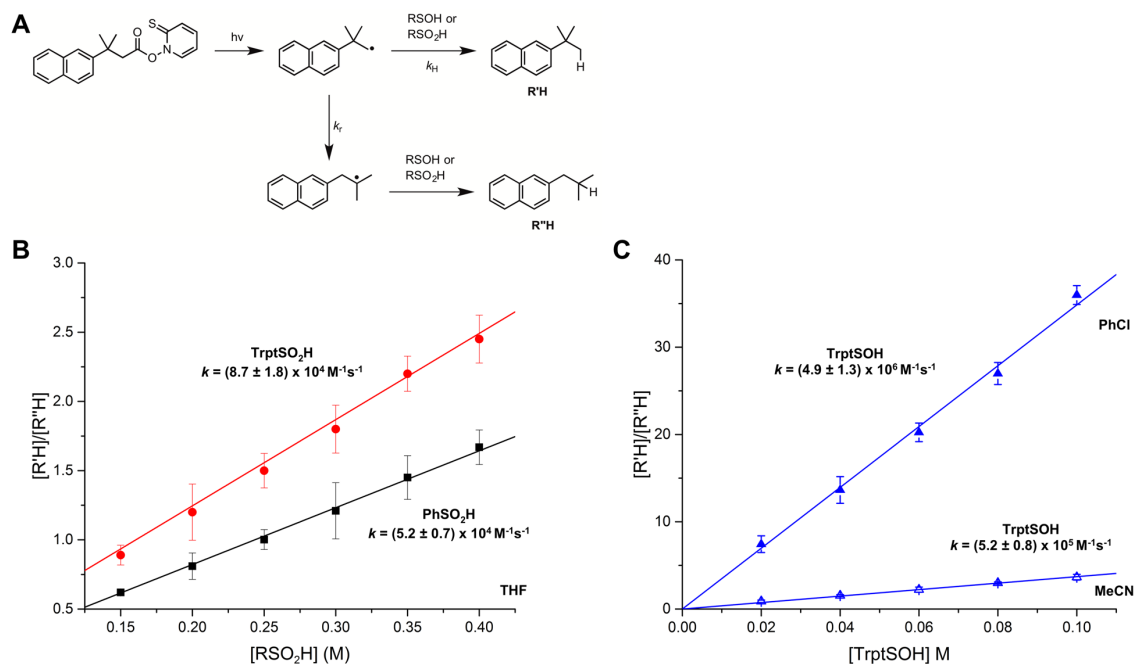


Figure 6.18. Photolytic generation of the 2-methyl-2-(2-naphthyl)-1-propyl radical as a radical clock to obtain the rate constant for HAT from sulfenic acids and sulfinic to alkyl radicals (A). Ratio of reduced (R'H) to rearranged and reduced (R''H) products as a function of the concentration of TrptSO₂H (red) or PhSO₂H (blue) during photocleavage of the radical precursor in THF at 25 °C (B). Ratio of reduced (R'H) to rearranged and reduced (R''H) products as a function of the concentration of TrptSOH during photocleavage of the radical precursor in chlorobenzene or acetonitrile at 25 °C (C).

6.7.10 Computational Data

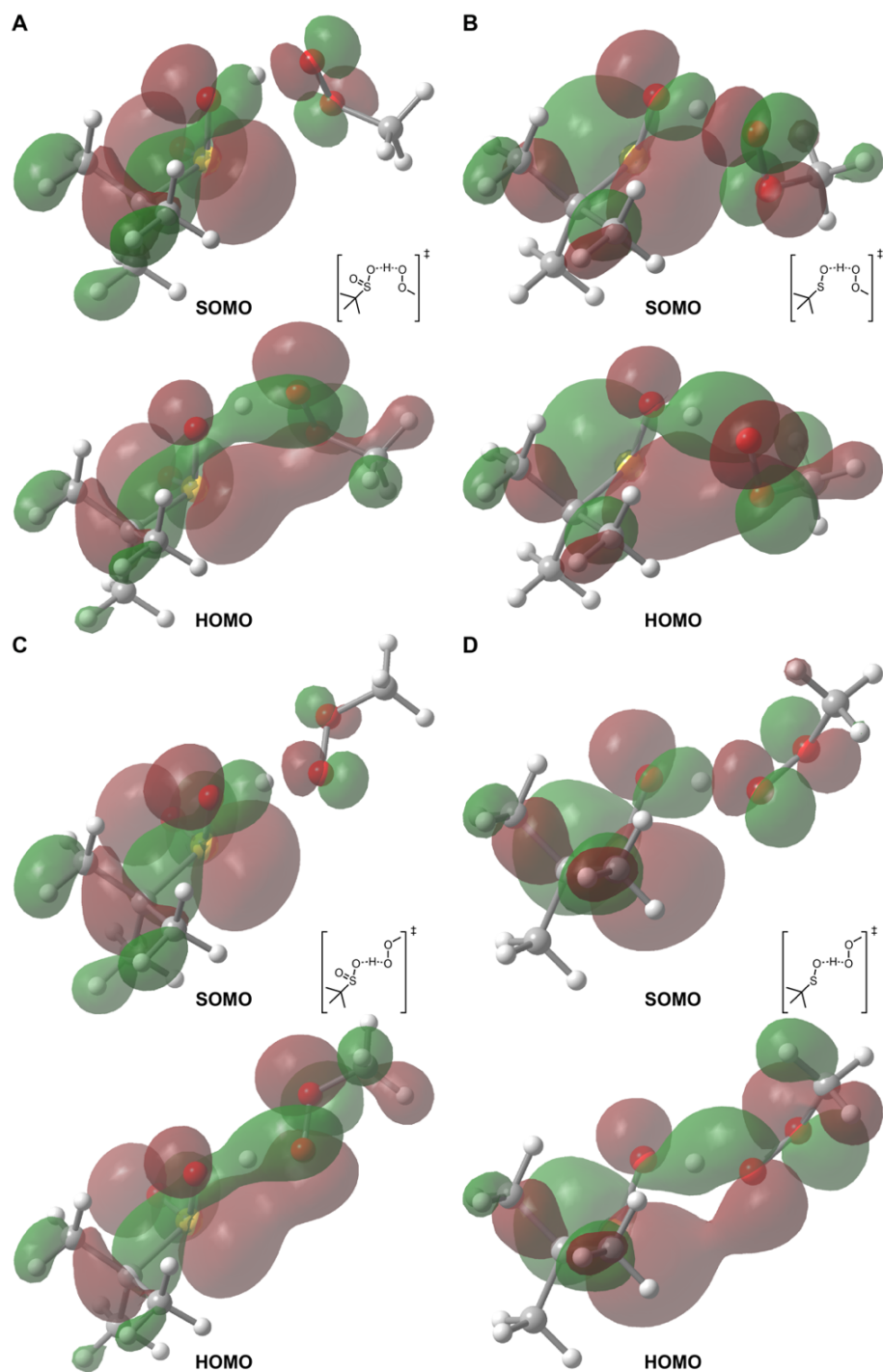


Figure 6.19. Calculated (CBS-QB3) TS structures for HAT between model sulfenic and sulfinic acid and model peroxy radical ($\text{MeOO}^\bullet$) and associated free energy barriers and rate constants estimated using transition state theory, SOMO and HOMO visualized.

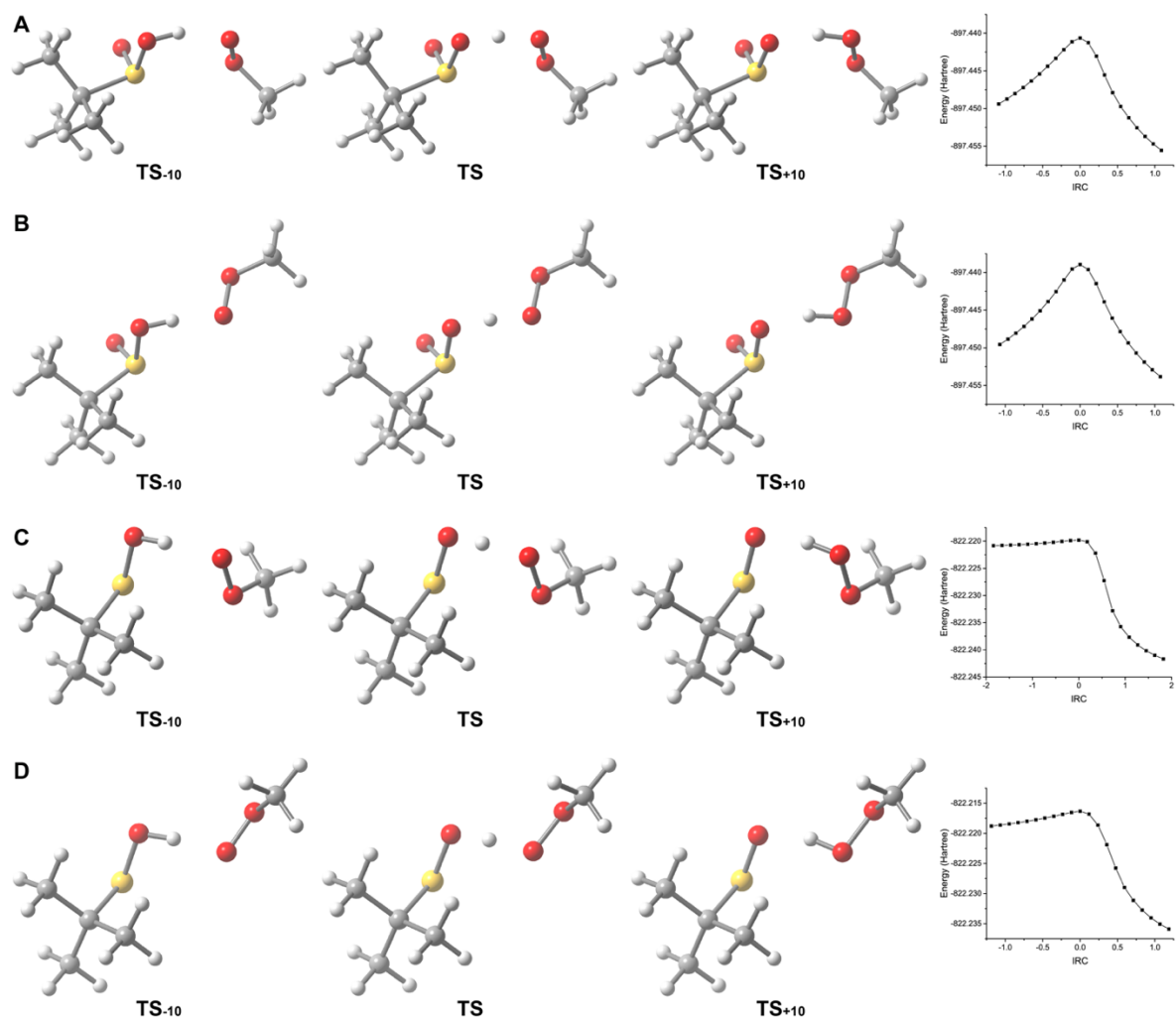


Figure 6.20. Calculated (CBS-QB3) structures for HAT between model sulfenic and sulfinic acid and model peroxy radical (MeOO•) as well as corresponding IRC energy diagrams. Visualized are the TS as well as structures preceding and following the TS by 10 steps (stepsize = 0.1 Bohr).

6.8 References

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- (59) It is very difficult to definitively tease out whether these types of reactions should be described as a HAT or proton-coupled electron transfer (PCET). However, simply considering the TS geometries in Figure. 6.5, the authors are inclined to describe them as HAT-like. Since both the sulfinyl/sulfonyl and peroxy radicals are π radicals, a HAT TS would feature the H-atom moving along a coordinate that is orthogonal to the planes made up by the carbon, sulfur and oxygen of the sulfinyl/sulfonyl radical and the carbon, oxygen and oxygen of the peroxy

radical. In contrast, in a purely PCET process, the proton and electron are, by definition, transferred between different pairs of (nominally orthogonal) orbitals; the proton between the lone pairs on the terminal oxygen atoms of the sulfinyl/sulfonyl and peroxy radicals and the unpaired electron is delocalized across both p^* orbitals. The predicted structures are more consistent with the former description than the latter. This is perhaps easiest to see in the SOMOs, where there is a node on the H-atom (see Supporting Information).

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- (63) The corresponding reaction of $\text{MeSO}\cdot$ is 12.2 kcal/mol endergonic.
- (64) To test this assumption, we attempted to monitor the sulfinic acid during the autoxidation. To do so, we employed a 9-triptycenesulfinic acid featuring a fluorine atom at the other bridgehead position such that the reaction could be followed directly by ^{19}F NMR. We recently showed that the sulfinic and sulfonic acids of this fluorinated triptycene have distinct chemical shifts.³² Although the concentration of the sulfinic acid was increased up to 10 mM in order to facilitate detection by NMR, the experiment revealed rapid consumption of the sulfinic acid on the time-scale of the experiment, which would prevent them to inhibit the autoxidation.
- (65) This indicates that the formation of sulfonyl radicals should be visible in LFP experiments with cumyloxyl radicals if they would react at rates similar to sulfenic acid ($10^7 \text{ M}^{-1} \text{ s}^{-1}$) or other comparable antioxidants (such as α -tocopherol, which has a comparable BDE and reacts at $10^6 \text{ M}^{-1} \text{ s}^{-1}$). Therefore, the LFP results strongly suggest that the reaction of alkylperoxyl radicals with sulfinic acids are as slow as predicted by calculations ($< 10^3 \text{ M}^{-1} \text{ s}^{-1}$).
- (66) [Substrate (alkene or alkyne)] = 50 mM and [oxygen] = 2–7 mM.

- (67) Of course, the additions must also compete with the disproportionation of sulfonyl radicals, but this is quite slow in comparison due to the very low concentrations of these transient intermediates compared to the alkene/alkyne substrate.
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CHAPTER 7: Summary and Perspective

7.1 Summary and Future Work

The work described herein addresses several fundamental questions regarding the antioxidant activity of organosulfur compounds. Building off of previous work on the mechanisms of the characteristic thiosulfates found in the *Allium* species,¹⁻⁴ and enabled by our recent development of a vastly more efficient inhibited autoxidation methodology,⁵ we have investigated the mechanisms by which many types of organosulfur compounds react with peroxy radicals. The insights acquired through these studies shed light on best practices in the use of various organosulfur compounds in industrial, synthetic, and biological contexts.

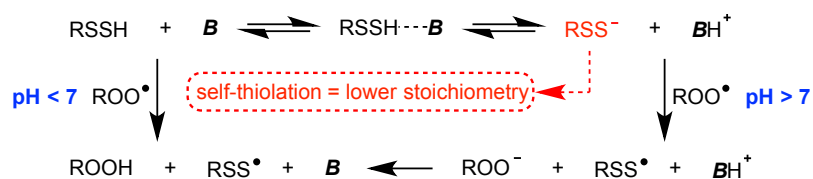
Firstly, trisulfide-1-oxides (RS(O)SSR), the primary oxidation products of trisulfides and also prominent components of *Alliums*, were shown to be surprisingly potent radical-trapping antioxidants. Mechanistic studies revealed that trisulfide-1-oxides react with peroxy radicals via a homolytic substitution reaction (S_H^2), roughly equaling hindered phenolic antioxidants in their reactivity toward peroxy radicals ($k_{inh} = 1-2 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$).⁶ The driving force for this reaction was determined to be the formation of a persistent perthiyl radical (RSS•), which were demonstrated to be unreactive to O_2 in contrast with previous reports.

Motivated by our discoveries, we explored the antioxidant activity of various polysulfides and their oxidized derivatives, some of which we anticipated may undergo analogous S_H^2 reactions to produce perthiyl radicals. We also extended our investigations to include temperatures relevant in industrial applications. From the series of polysulfides tested, we found that tetrasulfides are superior at inhibiting high temperature hydrocarbon autoxidations. This was especially evident in hexadecane autoxidations at 160 °C, wherein tetrasulfides bested hindered phenols and aromatic amines (standard industrial antioxidants).⁷ The next steps currently under investigation involve the antioxidant activity of tetrasulfides in base stock oils and various formulated oils – in an effort to translate our fundamental insights to commercial applications. The cumulative understanding imparted by these findings may

guide the design of better and industrially relevant organosulfur antioxidants by optimizing olefin sulfurization processes to target tetrasulfides.

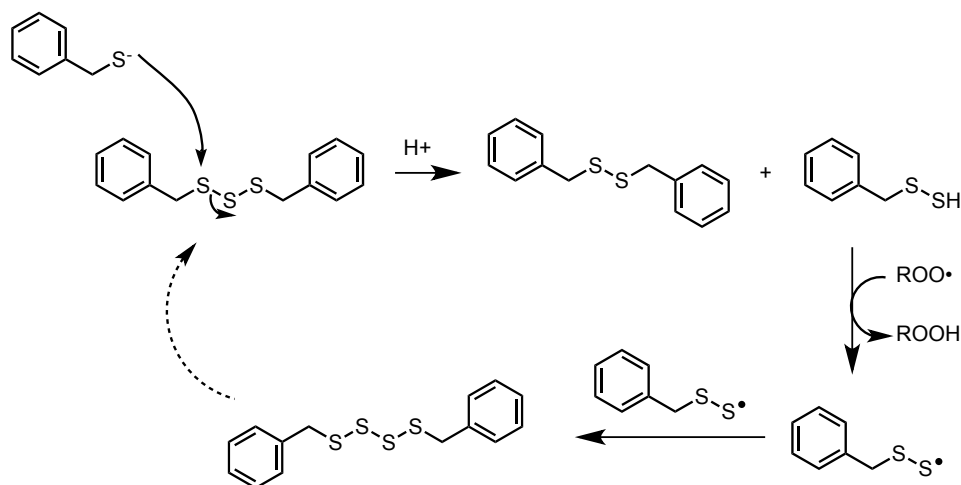
Our efforts to rationalize the persistence of perthiyl radicals prompted us to calculate the S-H BDE in hydropersulfides (RSSH), the reduced form of perthiyl radical. The BDE was predicted to be very low, ~ 71 kcal/mol, comparable to the O-H BDE of sulfenic acids. These computational results prompted our investigation of the hydrogen atom transfer reactivity of hydropersulfides (RSSH).⁸ Due to the stability of thiyl radicals, thiols have synthetic utility as H-atom donors in various applications such as the thiol-ene reaction and as chain transfer agents in polymerization reactions. Given the structural similarity between thiols and hydropersulfides, we aimed to compare their ability to donate an H-atom to various oxidants. In those studies, we found that hydropersulfides are potent H-atom transfer agents toward peroxy, alkyl, alkoxy, and thiyl radicals, reacting between 1 and 4 orders of magnitude faster than thiols. Furthermore, investigations into solvent effects revealed that hydropersulfides are very poor H-bond donors, similar to thiols, making them highly potent RTAs even in strongly H-bonding environments. Taken together, these results revealed hydropersulfides might have promising synthetic utility. However, the enhanced stability of the perthiyl radical renders them unusable in thiol-ene type chemistry due to the reversible elimination pathway.

Hydropersulfides have been of particular interest in recent years as they are purportedly important hydrogen sulfide (H_2S) carriers in vivo. As revealed by autoxidation in buffered aqueous solutions, hydropersulfides surpassed Trolox, a water-soluble analogue of α -tocopherol, by an order of magnitude, showing promise as potent RTAs under biologically-relevant conditions.⁸ However, in aqueous solutions, the stoichiometry of hydropersulfides decreased significantly ($n \sim 0.2$ - 0.3) from that observed in organic solutions ($n \sim 1$). This is due to the ionization of hydropersulfides to the persulfide anion, which favors side reactions (e.g. self-thiolation, oxidation) and consumes hydropersulfides before they can inhibit the autoxidation.



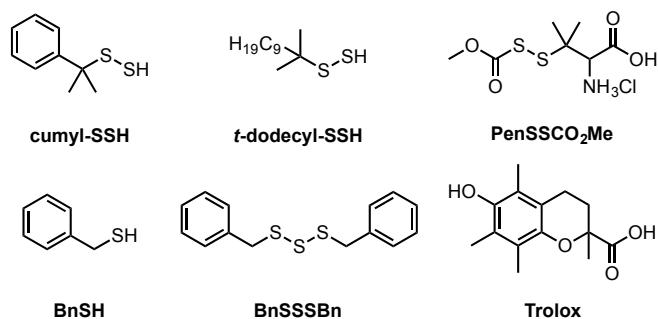
Scheme 7.1. Reaction pathways depicting the change in mechanism in the reaction of hydropersulfides and peroxy radicals from H-atom transfer to sequential proton loss electron transfer (SPLET) as a function of pH.

Given the low stoichiometries observed in aqueous solutions, we wondered if hydropersulfides generated *in situ* over the course of the autoxidation would improve their potency as radical-trapping antioxidants. We therefore attempted to generate hydropersulfides *in situ* by the reactions of H₂S or thiols with organosulfur electrophiles such as disulfides, trisulfides and their 1-oxides. An example using dibenzyltrisulfide (**BnSSSBn**) and benzyl mercaptan (**BnSH**) are shown in Scheme 7.2.



Scheme 7.2. *In situ* generation of benzylhydropersulfide from the reaction of BnSSSBn and BnSH.

For comparison, cumylhydropersulfide (**cumyl-SSH**) and 2-methylundecan-2-persulfide (**t-dodecyl-SSH**) were chosen as authentic hydropersulfides.⁸ S-(methoxycarbonyl)penicillamine hydrochloride (**PenSSCO₂Me**) was chosen as a model precursor to persulfides owing to its ability to generate a hydropersulfide by intramolecular rearrangement at pH 7.4.⁹



Preliminary results are shown below (Figure 7.1) wherein the activation of **BnSSSBn** by **BnSH** is clearly demonstrated. That is, as the concentration of **BnSH** increases, the inhibition time increases (Figure 7.1C) due to the in situ production of **BnSSH**. The generation of H₂S from dibenzylpolysulfides (RS_xR) has been reported in aqueous media,¹⁰ a process that generates hydropersulfides. Moreover, the higher order polysulfides (tri- and tetrasulfides) were shown to be potent persulfide/H₂S donors when treated with cysteine or glutathione.¹⁰ Thus, the preliminary results presented below are in good agreement with those studies.

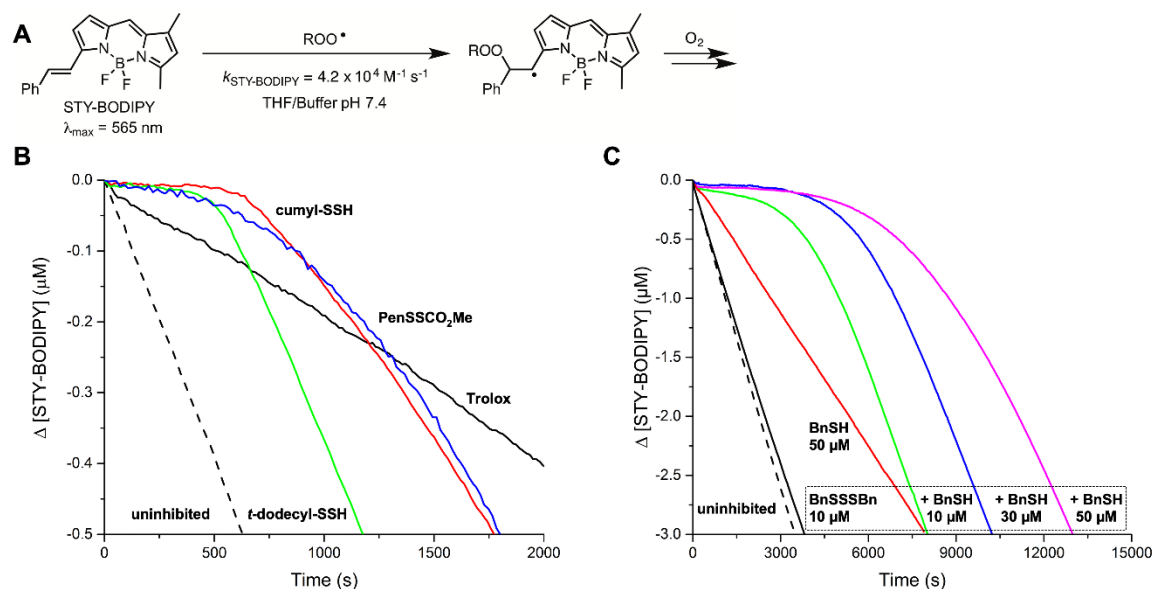


Figure 7.1. STY-BODIPY serves as the signal carrier in THF autoxidations (A). Co-autoxidations of THF (3.1 M) and STY-BODIPY (10 μM) initiated by AAPH (1 mM) in phosphate-buffered saline (pH 7.4, 100 mM) at 37 °C (dashed black trace) and inhibited by 10 μM of **cumyl-SSH** (red), **t-**

dodecyl-SSH (green), 10 μM of PenSSCO₂Me and 4 μM of Trolox (black) (B). Co-autoxidations of THF (3.1 M) and STY-BODIPY (10 μM) initiated by AAPH (1 mM) in phosphate-buffered saline (pH 7.4, 100 mM) at 37 °C (dashed black trace) and inhibited by 10 μM of **BnSSSBn** (black) and 10-50 μM **BnSH** (C).

The reported production of H₂S from the reaction of **BnSSSBn** and **BnSH** motivated us to look at the activation of **BnSSSBn** by H₂S under the conditions presented above. Inhibited autoxidations with **BnSSSBn** and increasing amounts of H₂S were conducted in buffered THF solutions (Figure 7.2).

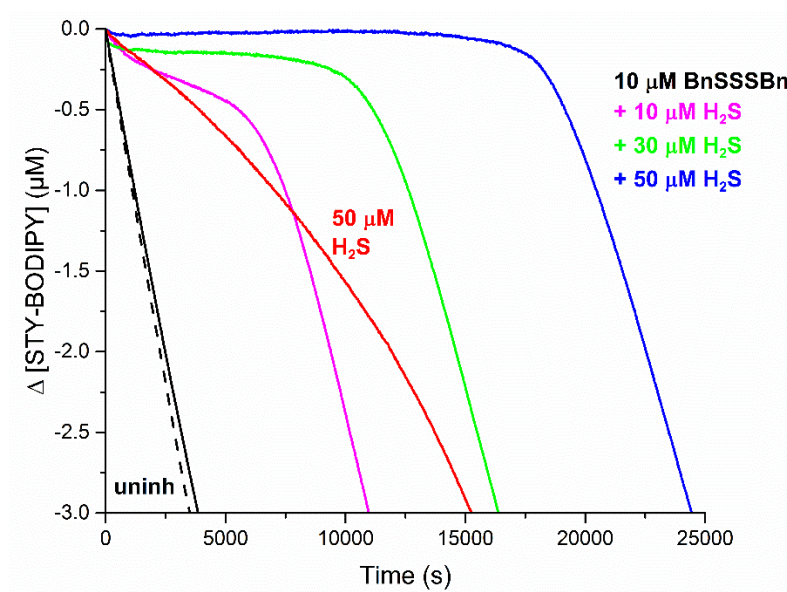
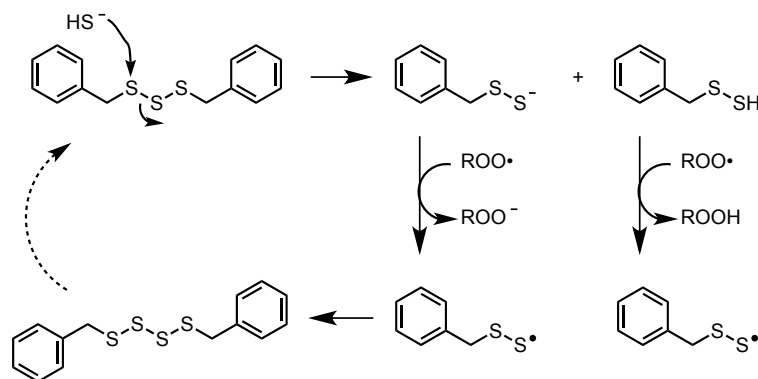


Figure 7.2. Co-autoxidations of THF (3.1 M) and STY-BODIPY (10 μM) initiated by AAPH (1 mM) in phosphate-buffered saline (pH 7.4, 100 mM) at 37 °C (dashed black trace) and inhibited by 10 μM **BnSSSBn** (black), 50 μM H₂S (red) or by **BnSSSBn** (10 μM) with increasing amounts of H₂S (10-50 μM).

Preliminary results show that H₂S activates **BnSSSBn** more efficiently than **BnSH**, presumably because the initial reaction produces two equivalents of **BnSSH** (see Scheme 7.3). Furthermore, H₂S is more acidic than **BnSH**, pK_a ~ 7 vs 9 for H₂S and **BnSH**, respectively, indicating a greater

concentration of hydrosulfide anion than thiolate at pH 7.4.



Scheme 7.3. *In situ* generation of benzylhydropersulfide from the reaction of **BnSSSBn** and H₂S.

Unfortunately, corresponding experiments in lipid-bilayers (egg PC liposomes) did not yield any observable activation from the reaction of **BnSSSBn** and **BnSH**, most likely due to the localization of both substrates within the lipid domain, which prevents **BnSH** to be ionized in order to substitute onto **BnSSSBn** (Scheme 7.2). A full mechanistic characterization (pH dependence, isotope effects, etc.) of the activation of polysulfides by thiols and hydrogen sulfide will be the focus of future studies.

Hydropersulfides can be formed *in vivo* from the reaction of H₂S and thiol oxidation products such as sulfenic acids or disulfides.¹¹ This is yet another example of thiol oxidation products being involved in redox processes. Indeed, thiols are ubiquitous in biology and represent a major contributor to redox signaling, usually achieved through their oxidation and reduction chemistry. Nevertheless, the kinetics and mechanisms of thiol oxidation processes are notoriously difficult to study. To date, the primary oxidation product of thiol oxidation by hydrogen peroxide, the ubiquitous reactive oxygen species, was believed to be a sulfenic acid, but it was generally not observed since it readily underwent condensation with another equivalent of thiol to form a disulfide. We utilized a triptycene backbone to impart persistence on the sulfenic acid which allowed us to fully characterize the following series of consecutive oxidation reactions: thiol to sulfenic acid, sulfenic acid to sulfinic acid, and sulfinic acid to sulfonic acid.¹² The fluorine atom appended to the bridgehead position of the triptycene served as a handle to monitor the reaction progress *in situ* by ¹⁹F NMR in buffered methanol solutions. This

work has laid the foundation for future studies on thiol oxidation. We plan to extend these initial studies by investigating the kinetics of thiol oxidation by hydrogen peroxide and other oxidants such as sodium hypochlorite (NaOCl), peroxyxynitrite (ONOO⁻), triplet and singlet oxygen, and ozone in aqueous media, bridging the gap between organic solution and biological conditions.

The triptycene backbone imparts persistence to the sulfinic acid produced from the oxidation of triptycene thiol. The second reaction product of this sequential oxidation is the corresponding sulfinic acid; this moiety has seen increasing use in synthetic chemistry in recent years. We demonstrated that the triptycene backbone is also effective at rendering the sulfinic acid and sulfonyl radical (RSO₂•) persistent enough to allow the measurement of the reactivity of the former with alkyl and alkoxy radicals as well as enabling the determination of an experimental O-H BDE of the latter (78 kcal/mol, half-way between the S-H BDE of thiols (87 kcal/mol) and the O-H BDE in sulfinic acids (70 kcal/mol)).¹³

Sulfinic acids are known to autoxidize, a reaction that is accelerated in aqueous media. Our experimental and computational findings provide a clear indication that the reaction of sulfinic acid with sulfonylperoxy radical is the main propagating event. The results from these studies suggest that careful manipulation of reaction conditions is necessary to ensure that sulfinic acids can be effectively used in catalytic or chain reaction applications. That is, to be productive, reactions involving sulfinic acids must be performed in aprotic organic solvents in the absence (or presence of a limited amount) of molecular oxygen to slow the consumption of sulfinic acids and sulfonyl radicals via autoxidation.

7.2 Perspective

Taken together, the work described in this thesis sheds light on the underlying radical and ionic mechanisms responsible for the great antioxidant potential of organosulfur compounds. This body of work may serve as a foundation for the optimization and design of future generations of organosulfur antioxidants with potential medicinal and industrial applications.

The majority of the work described in this thesis stemmed from the reported antioxidant activity of allicin, the medicinal thiosulfinate found in garlic. Medicinal thiosulfonates are potent RTA in organic solutions but their potency decreased significantly in model lipid bilayer due to the localization of the sulfenic acids in the aqueous environment, outside of the lipid bilayers. In comparison, it is expected that other constituents of garlic, such as trisulfides and tetrasulfides, would be located in the lipid-bilayers where they could react with lipid peroxy radicals, albeit at slower rate constants than the reaction between sulfenic acids and peroxy radicals. Perhaps more significant in a biological context is the electrophilic nature of polysulfides such as diallyl trisulfide. As mentioned earlier, the reaction of thiols with trisulfides and tetrasulfides yields highly reactive RTA such as hydropersulfides. Due to their reactive nature, hydropersulfides are not likely to be present in a cellular environment at high concentrations but could still be a major contributor to the purported antioxidant activity of garlic derived organosulfur compounds *in vivo*. Moreover, as H₂S storage units, hydropersulfides are likely to be involved in many H₂S signaling pathways.

Given the complexity of cellular environments, common approaches to study cellular processes usually involve the use of model reactions in biologically relevant conditions. Even though many factors can be controlled in a laboratory setting (e.g. temperature, pressure, pH, concentration, etc.), certain components are harder to model (e.g. cellular microenvironment, H-bonding, enzyme catalysis, etc). For instance, our studies of thiol oxidation by hydrogen peroxide were conducted using 9-triptycenethiol in buffered methanol due to the limited solubility of the triptycene substrates in aqueous solutions. Although the temperature, concentration, and pH were well controlled, the rate constants gleaned from the aforementioned studies are most likely not quantitatively representative of the reactivity of biological thiols. Nonetheless, the studies using the triptycene model allowed for an improved mechanistic understanding of the reaction differences between thiols, sulfenic acids, and sulfinic acids with hydrogen peroxide.

As we deepen our fundamental understanding of organosulfur reactivity, it becomes clear that this class of compounds has a high degree of applicability in industrial, polymer, biological, and medicinal contexts which must be carefully and thoroughly explored. This work is a case-in-point that a careful exploration of the reactivity of organosulfur compounds (in the context of oxidation chemistry) is a necessary and productive step toward developing new technologies despite the commonly-held notion that such reactivity is ‘unpredictable and complex’. Moreover, with an increasing understanding of their chemistry, organosulfur compounds could be optimized for specific operating temperatures and conditions in a wide range of specific applications.

The ever increasing demand for reusable and biodegradable polymers is an area where organosulfur chemistry could play a pivotal role moving forward. The ability to engineer enzymes capable of degrading polymers through the chemistry one of nature’s strongest nucleophile, thiols, is a promising venue and highlights the necessity to understand the reactivity of thiols and other organosulfur compounds. Another approach to polymer recyclability is often to engineer their composition to make them easily reusable or depolymerized. This is an interesting concept since sulfur, obtained as an unwanted by-product of petroleum refinement, is an inexpensive commodity chemical that could be valued in several industrial polymer applications, such as inverse vulcanization.¹⁴ Given our current understanding of polysulfide chemistry, a high degree of polysulfides in a polymer could be an interesting path forward for predictable and controlled degradation of polymers.

Furthermore, recent investigations into the reactivity of organosulfur compounds continue to demonstrate their broad applicability among diverse fields including oxidation chemistry,^{15,16} chemical biology,¹⁷ computational mechanistic investigations,¹⁸ industrial scale chemical production,¹⁹ synthetic methodology,^{20,21} and polymer synthesis.²² In all, these reports indicate that an ever-deepening understanding of organosulfur reactivity continues to expand the development of tools in a range of scientific applications.

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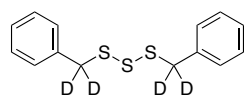
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Annexe A: Publication List

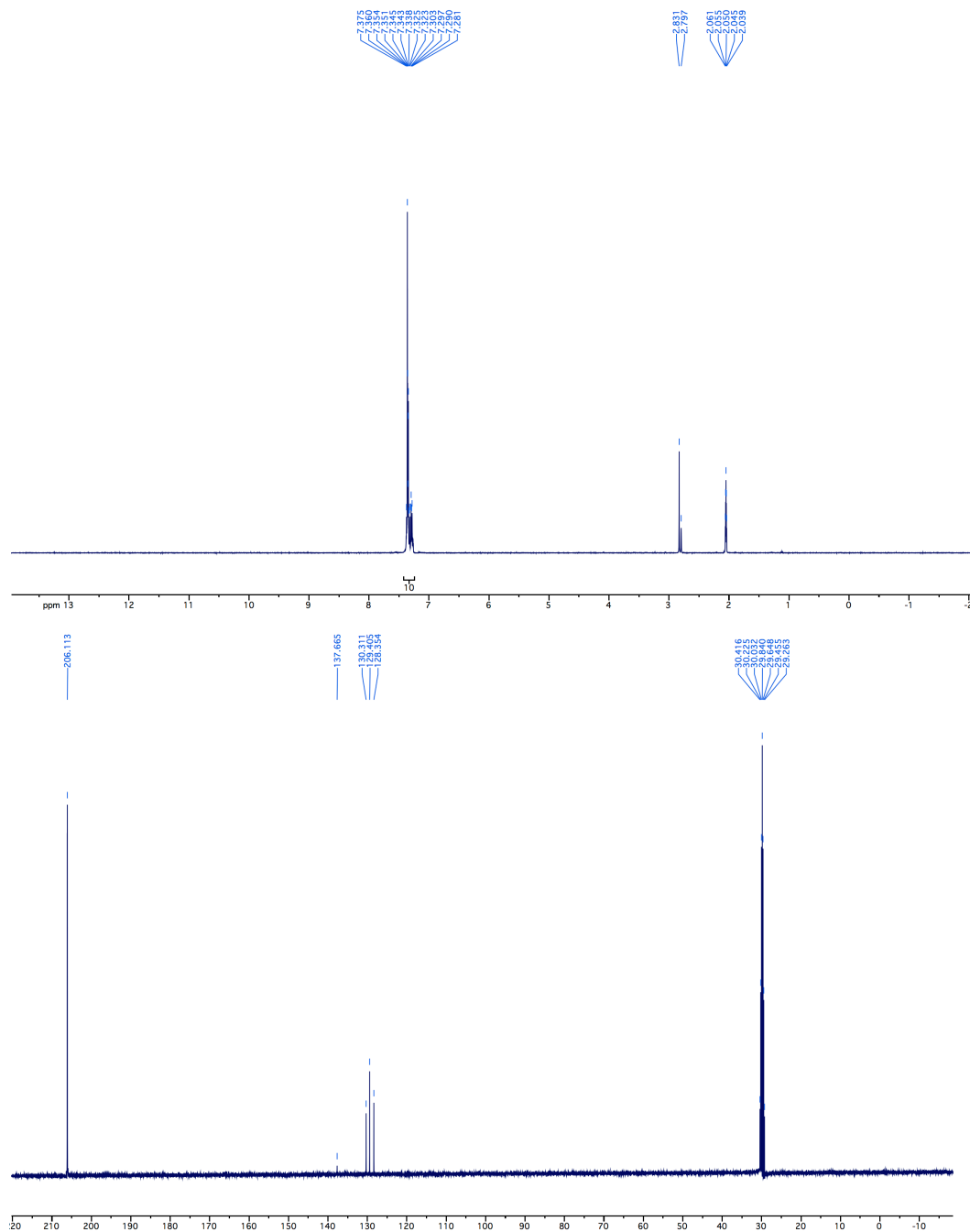
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6. **Hydropersulfides: H-atom transfer agents par excellence**
 - Chauvin, J.-P. R.; Griesser, M.; Pratt, D. A. *J. Am. Chem. Soc.* **2017**, 139, 6484–6493.
7. **The hydrogen atom transfer reactivity of sulfinic acids**
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8. **Electrochemical dimerization of phenylpropenoids and the surprising antioxidant activity of the resultant quinone methide dimers.**
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9. **The antioxidant activity of polysulfides: it's radical!**
 - Chauvin, J.-P. R.; Griesser, M.; Pratt, D. A. *Chem. Sci.* **2019**, 10, 4999–5010.

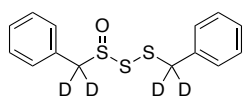
Annexe B: Collected Spectral Data

B.1 Polysulfide-1-Oxides React with Peroxyl Radicals as Quickly As Hindered Phenolic Antioxidants and do so by a Surprising Concerted Homolytic Substitution

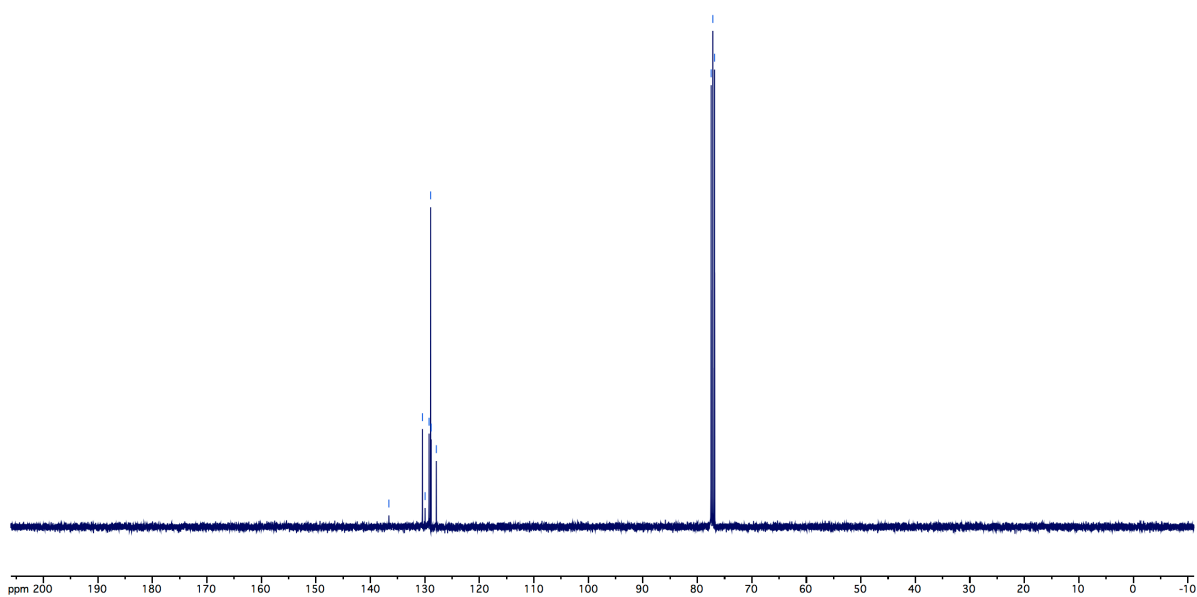
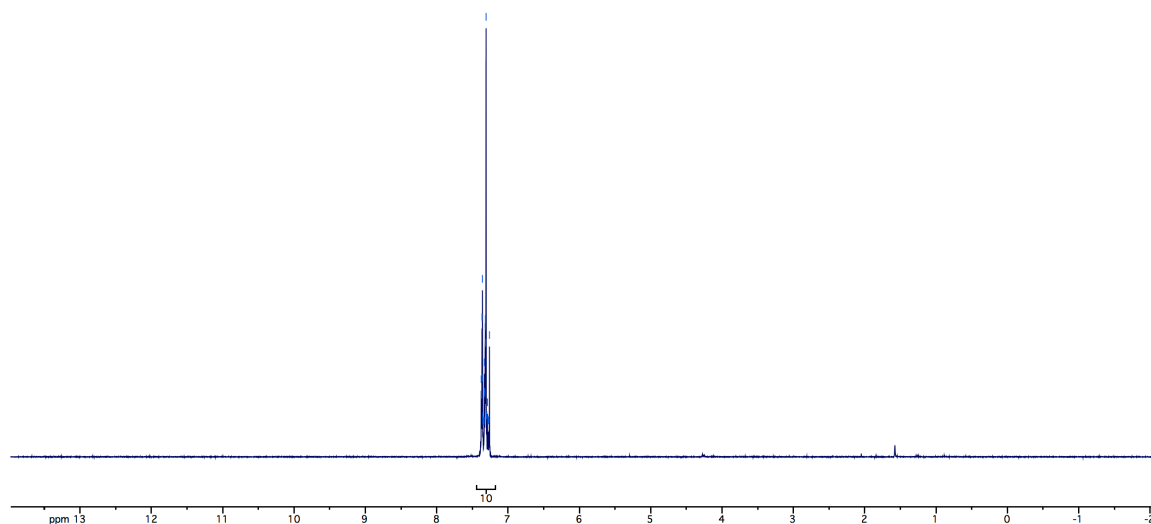


(*d*₄-BnSSSBn) in *d*₆-acetone

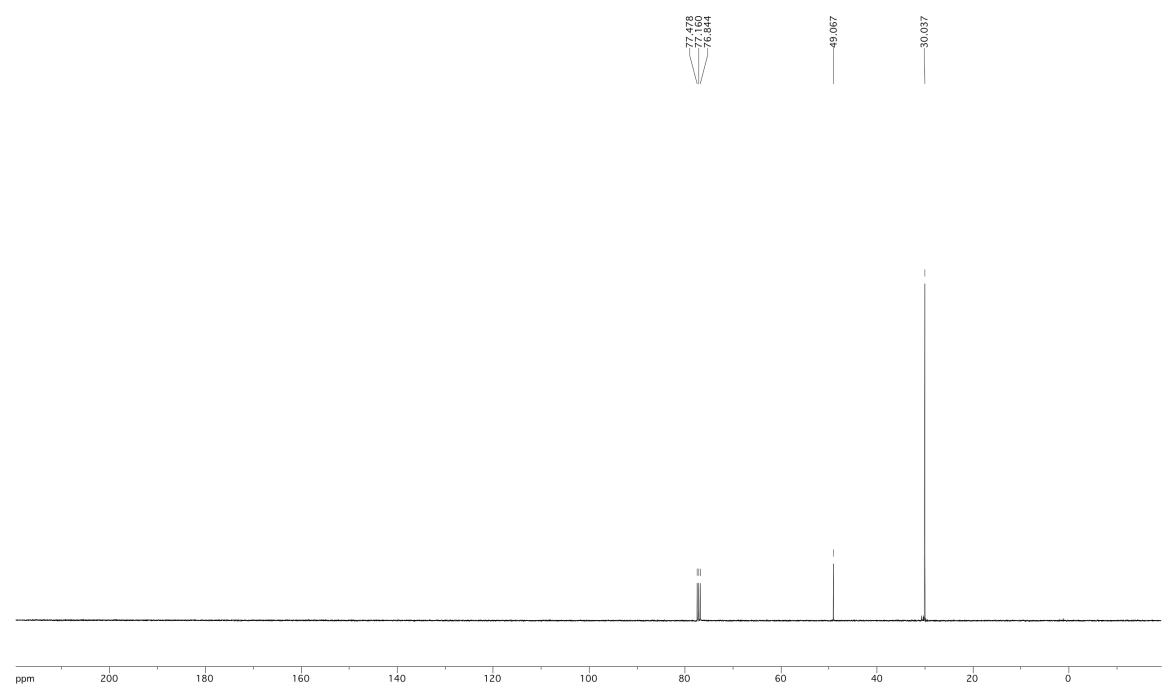
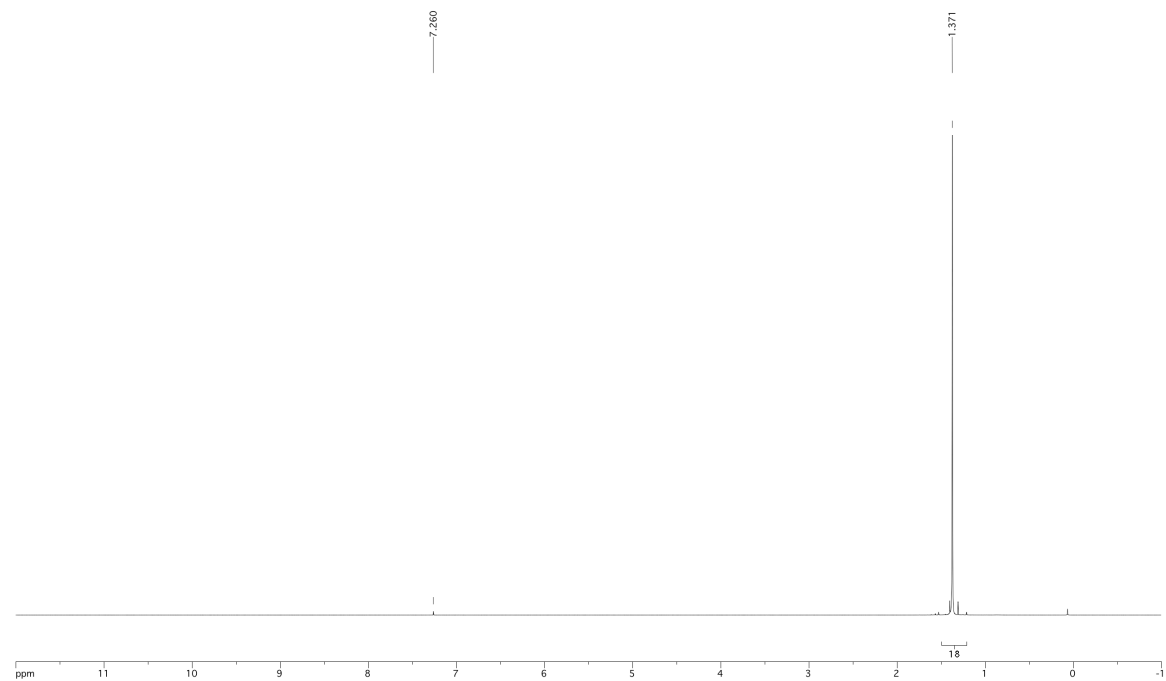
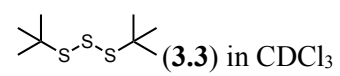


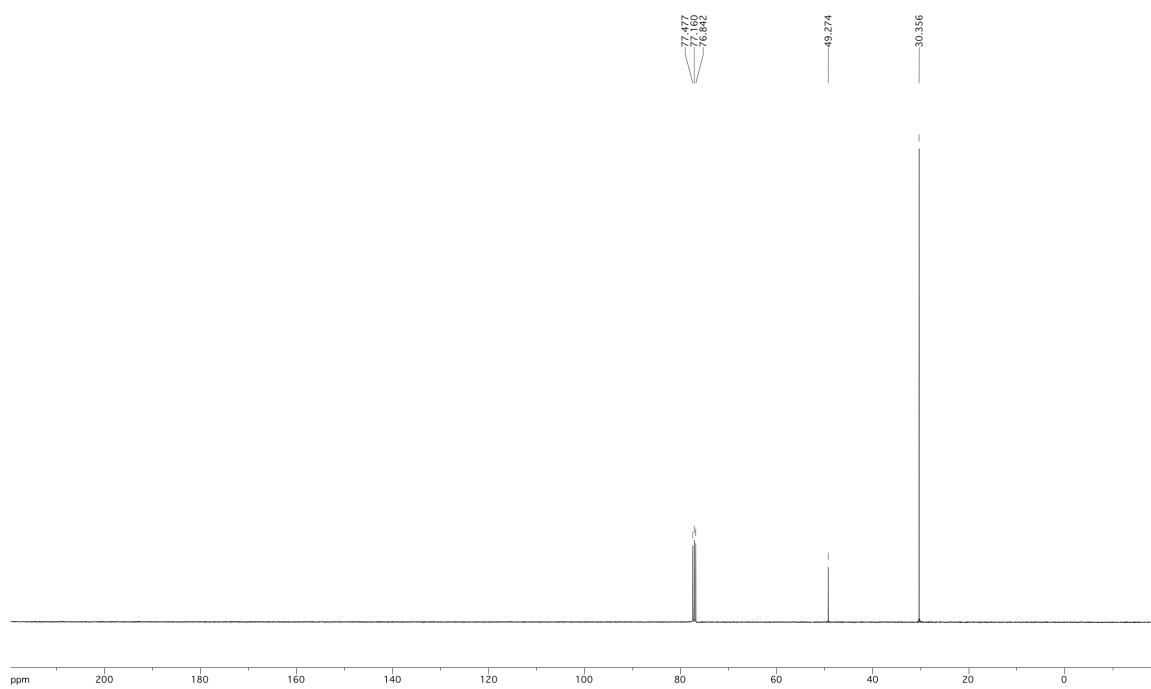
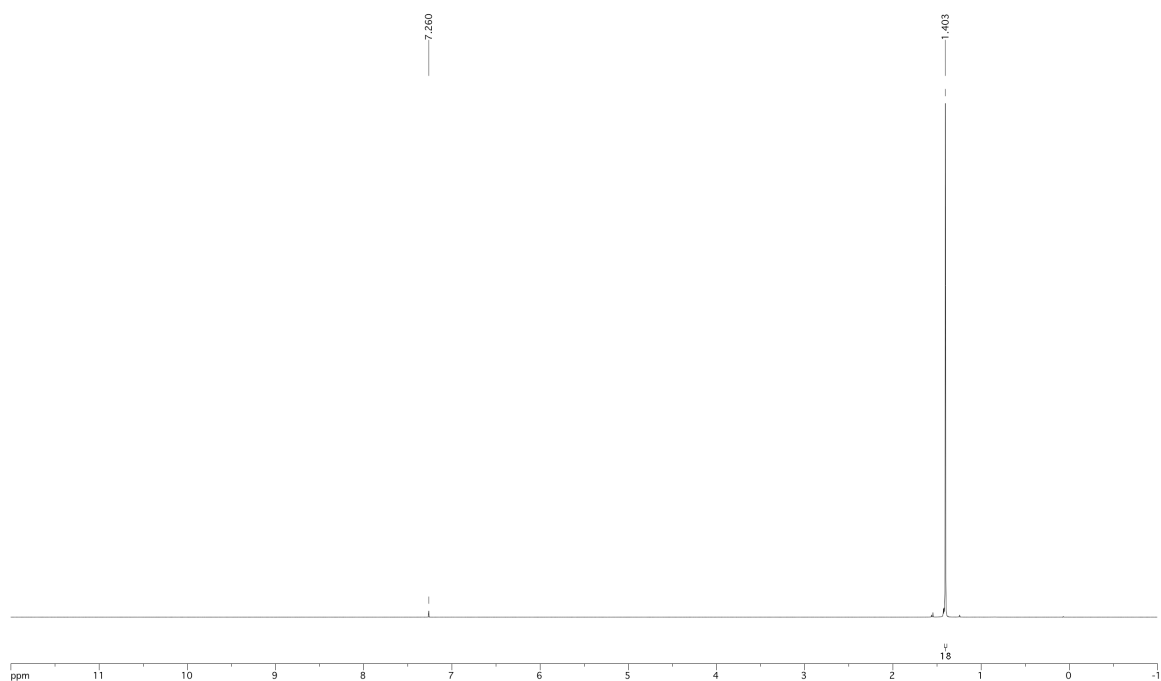
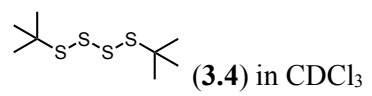


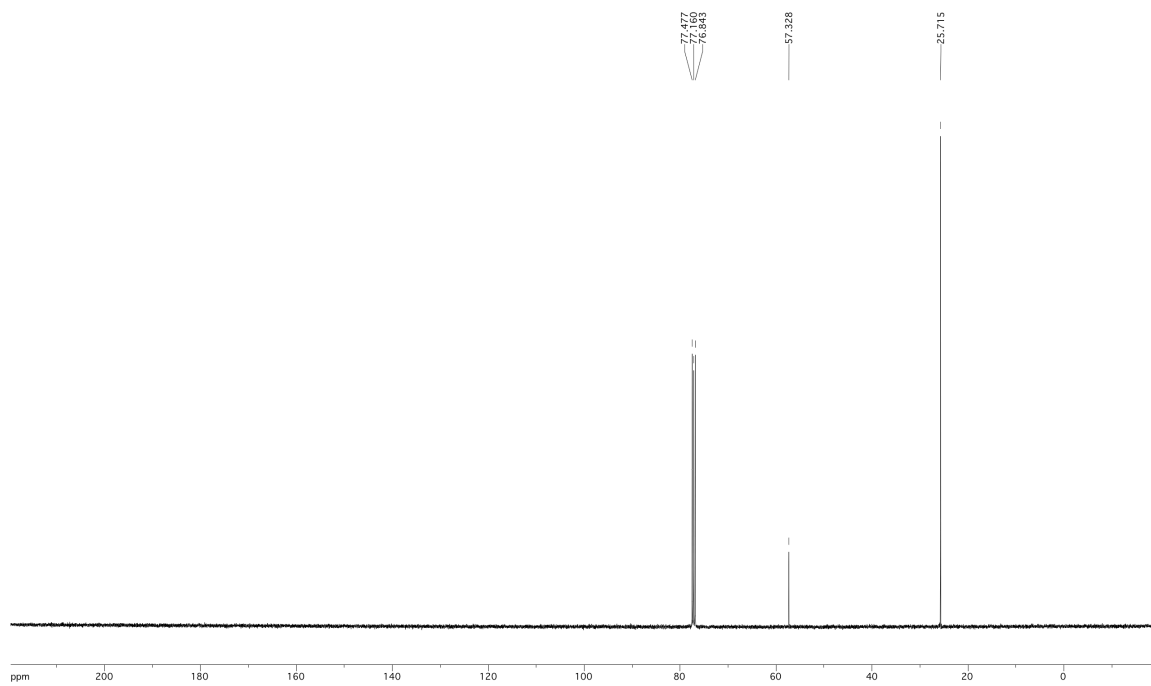
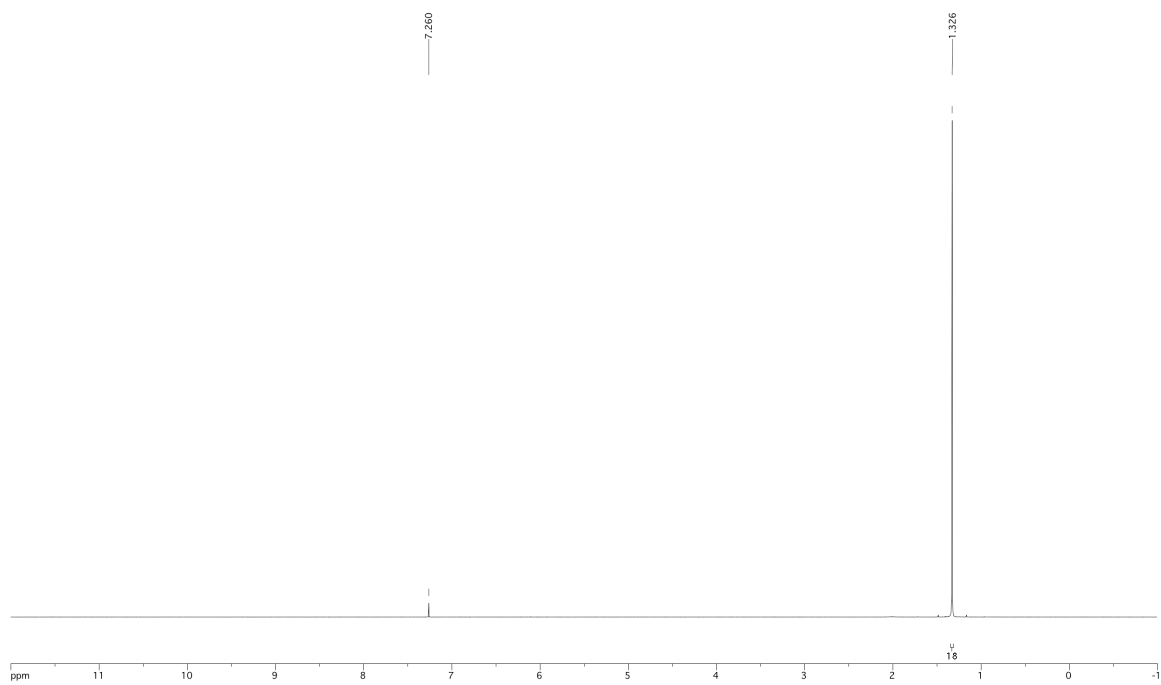
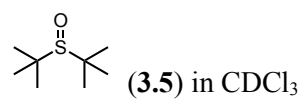
(*d*₄-BnS(O)SSBn) in CDCl₃

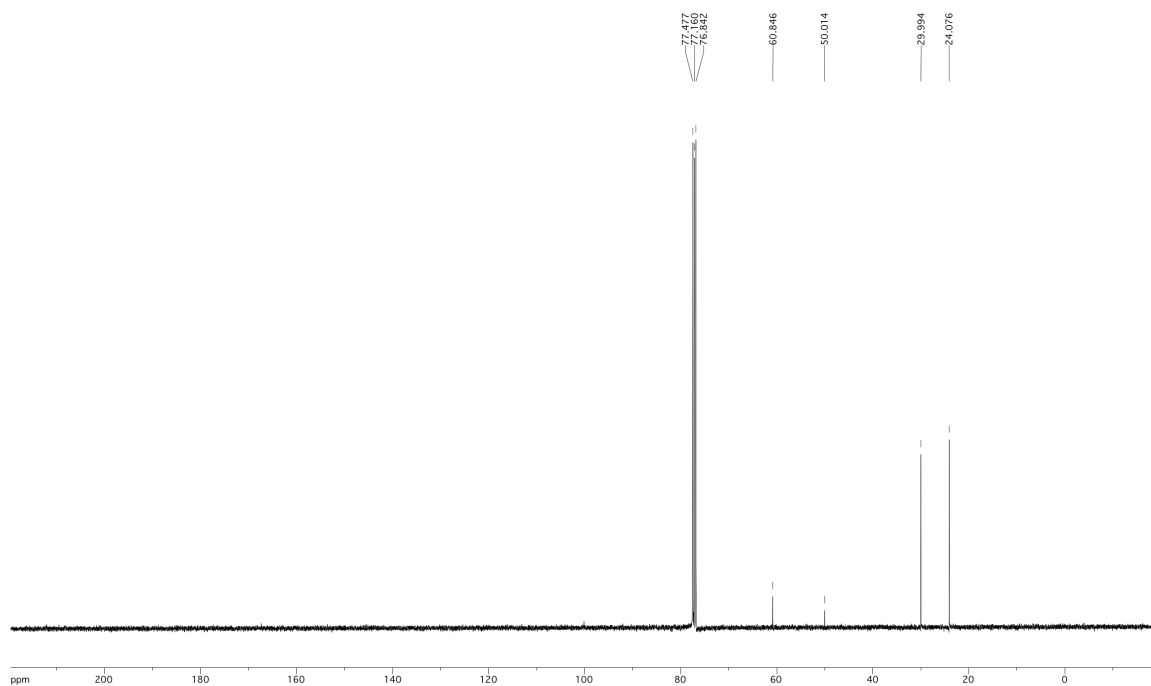
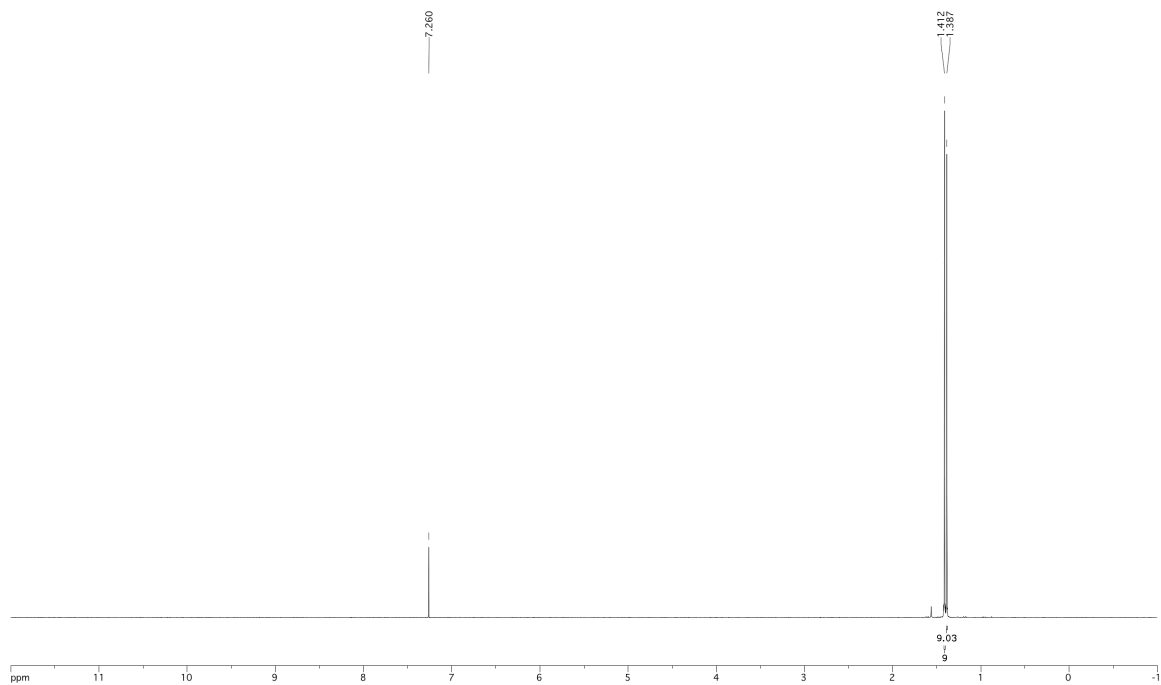
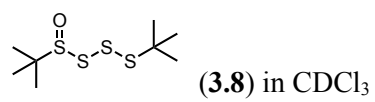


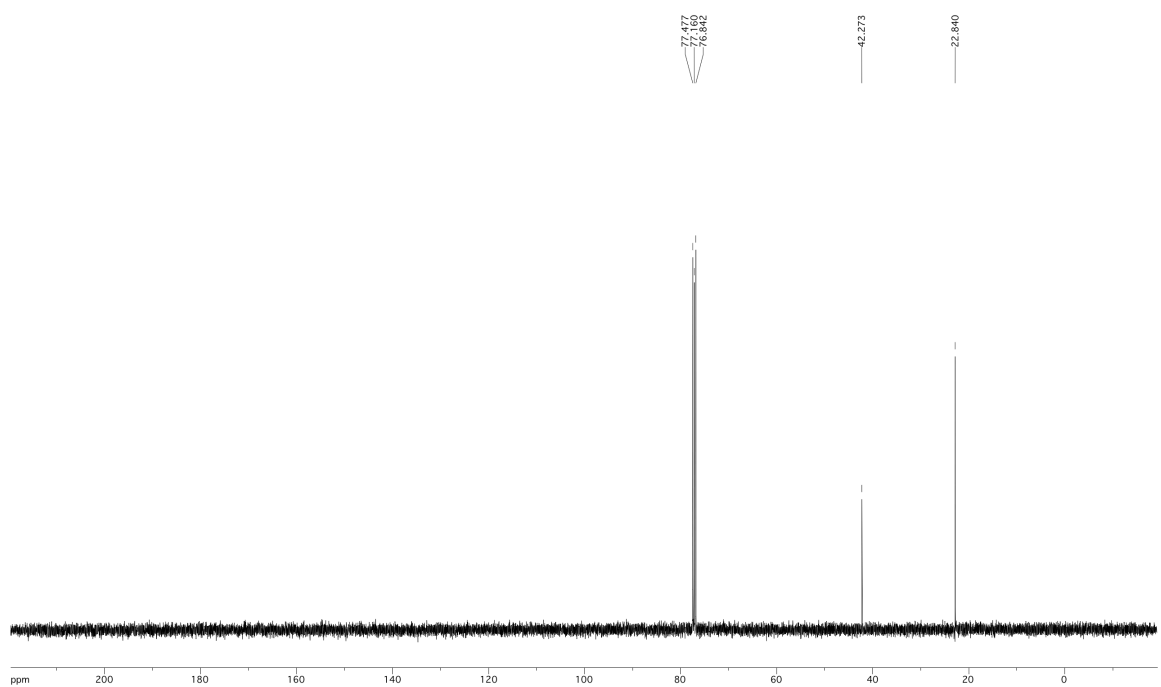
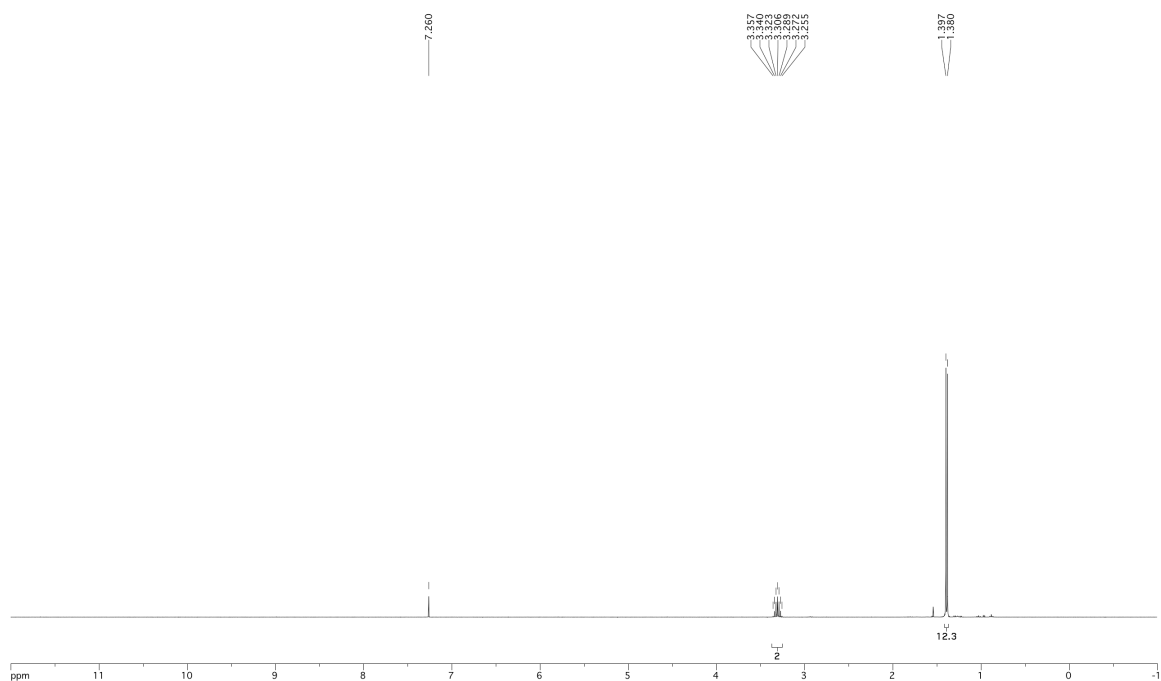
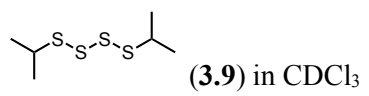
B.2 The Antioxidant Activity of Polysulfides: It's Radical!

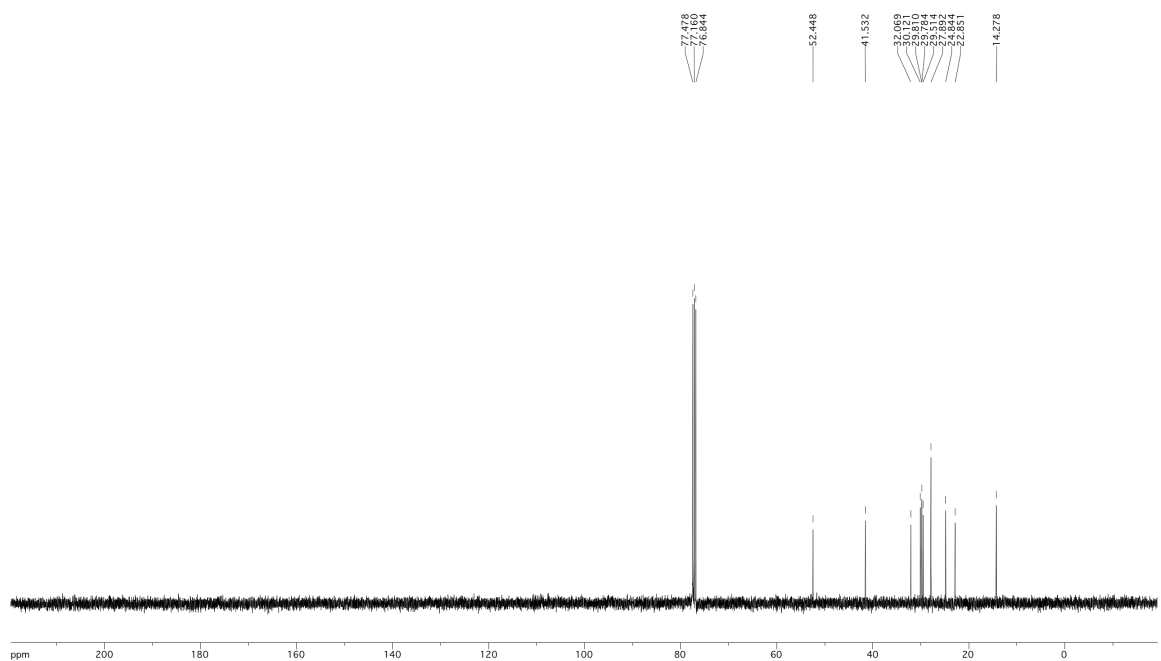
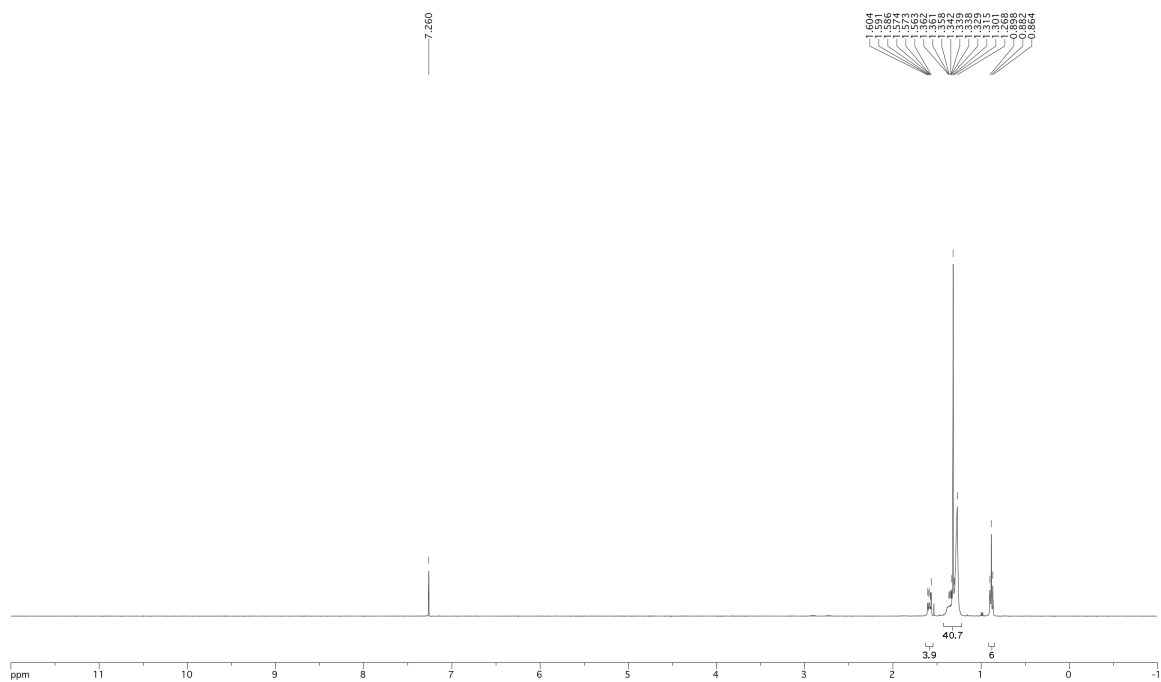
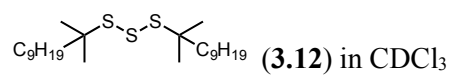


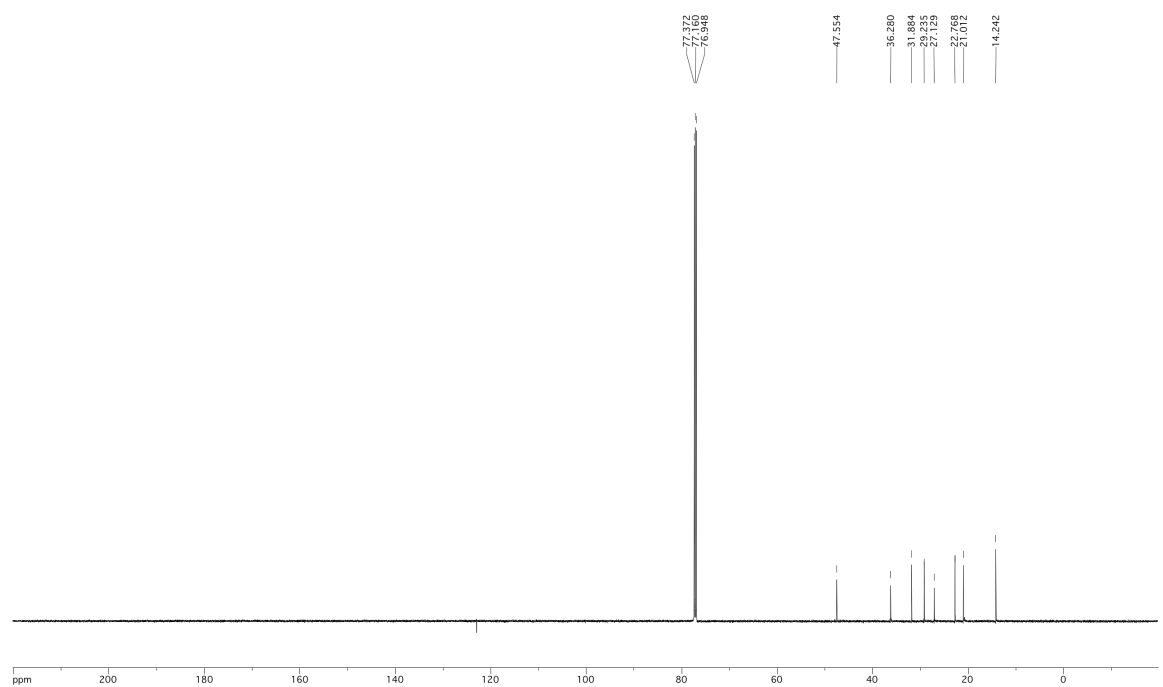
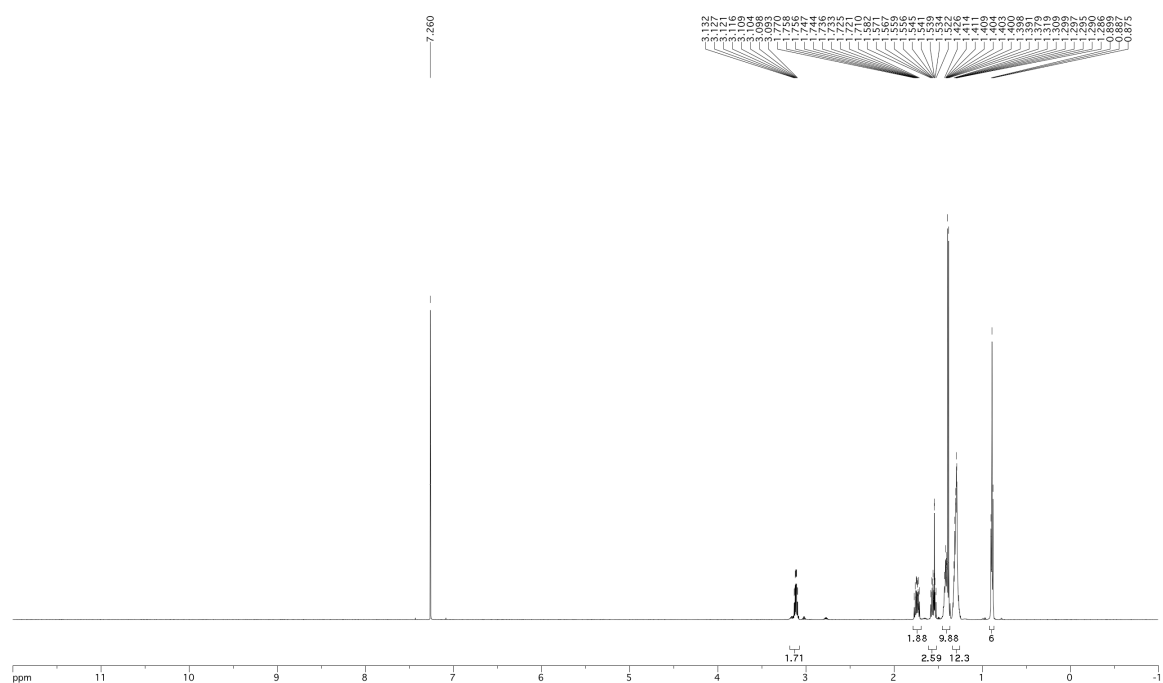
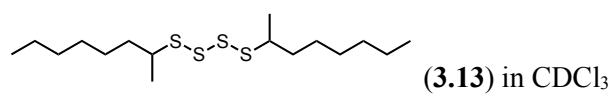


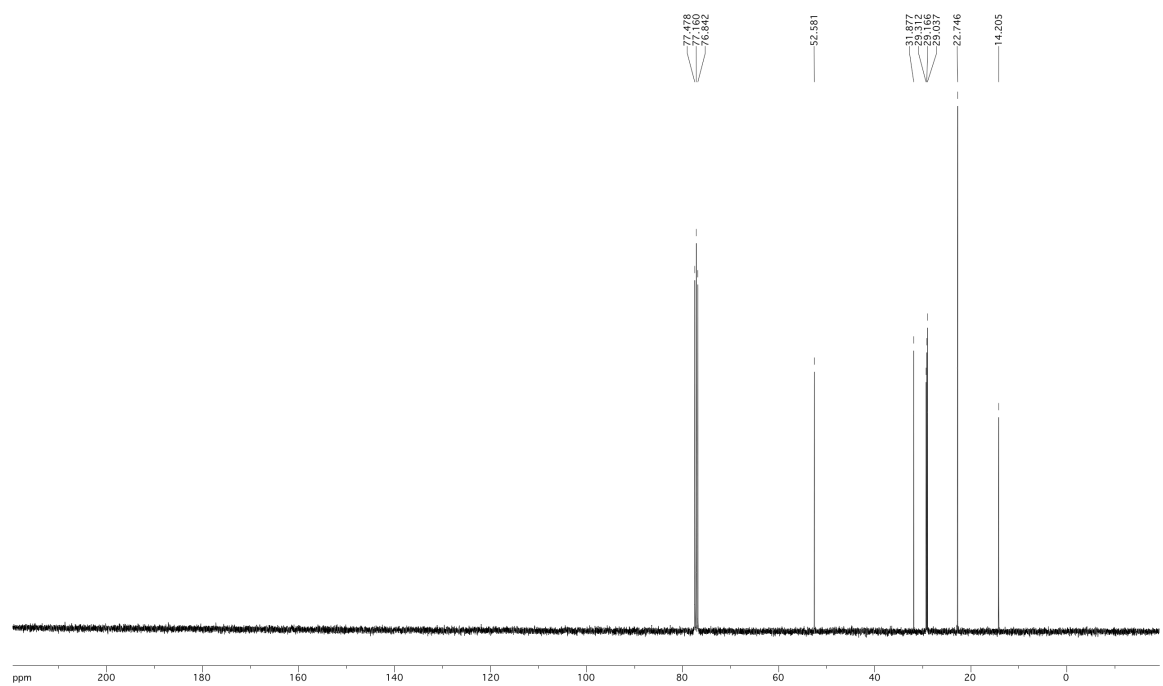
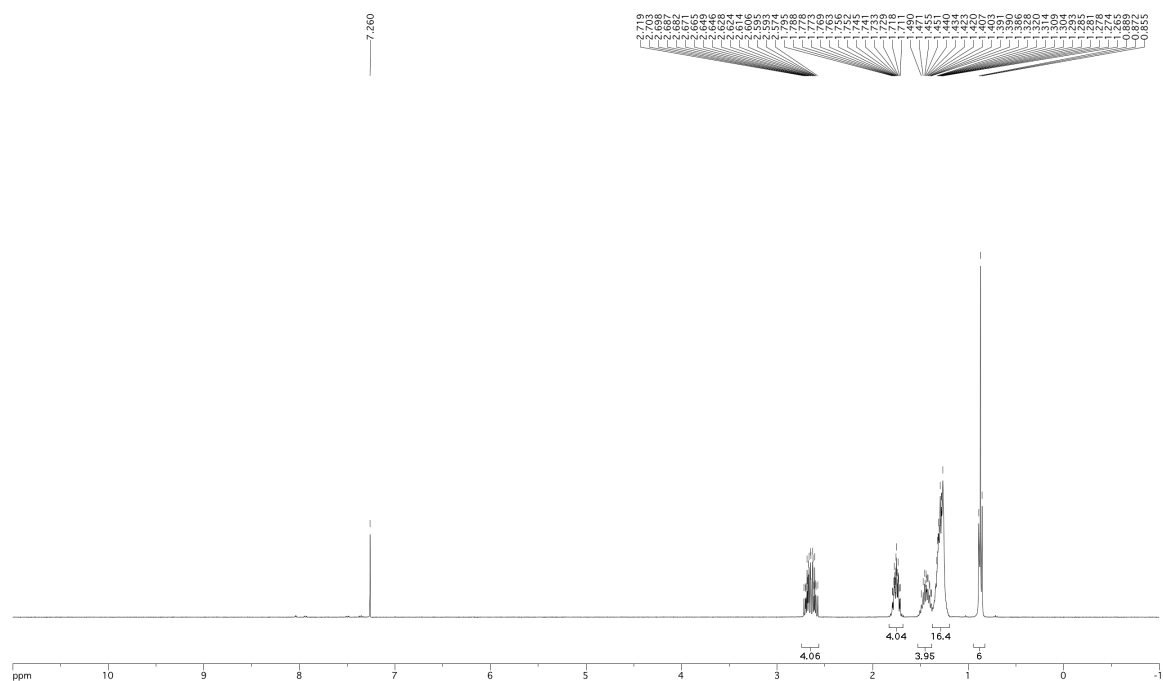
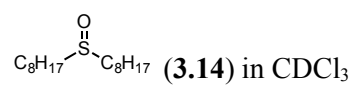


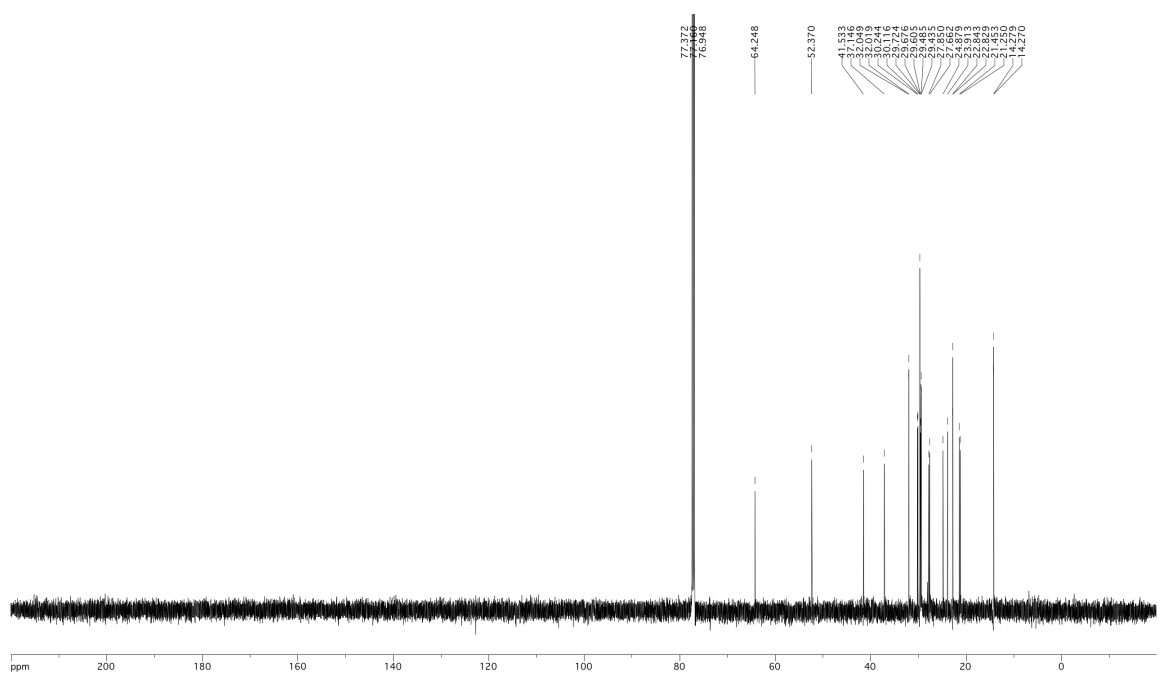
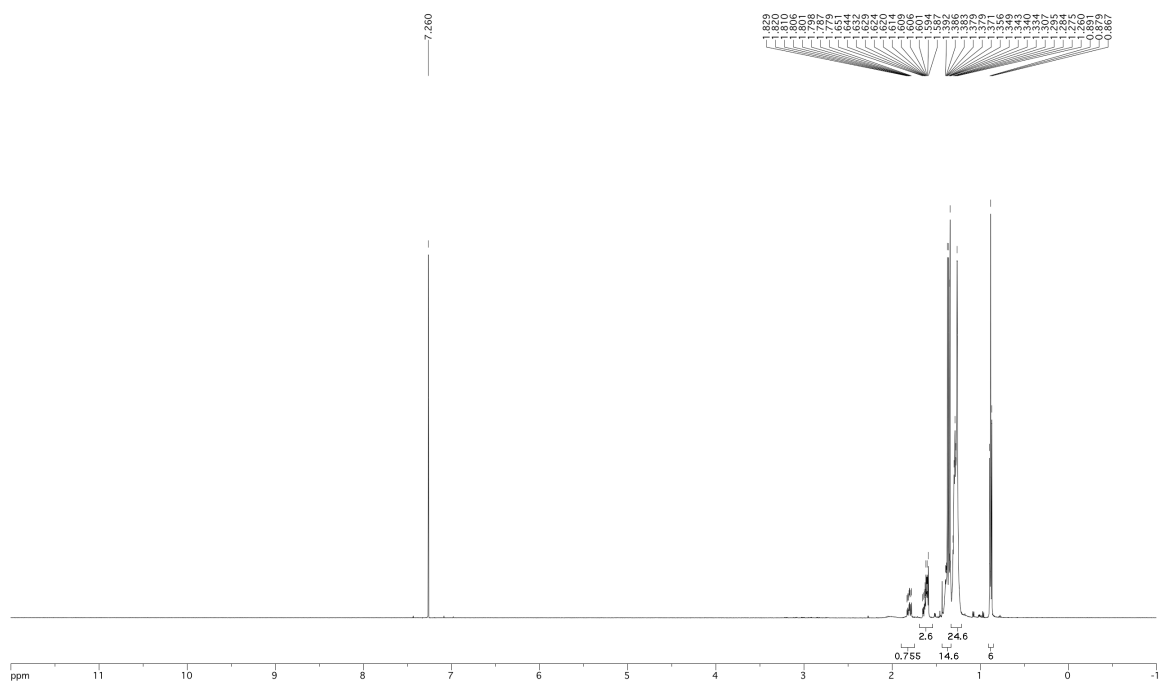
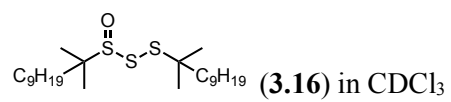




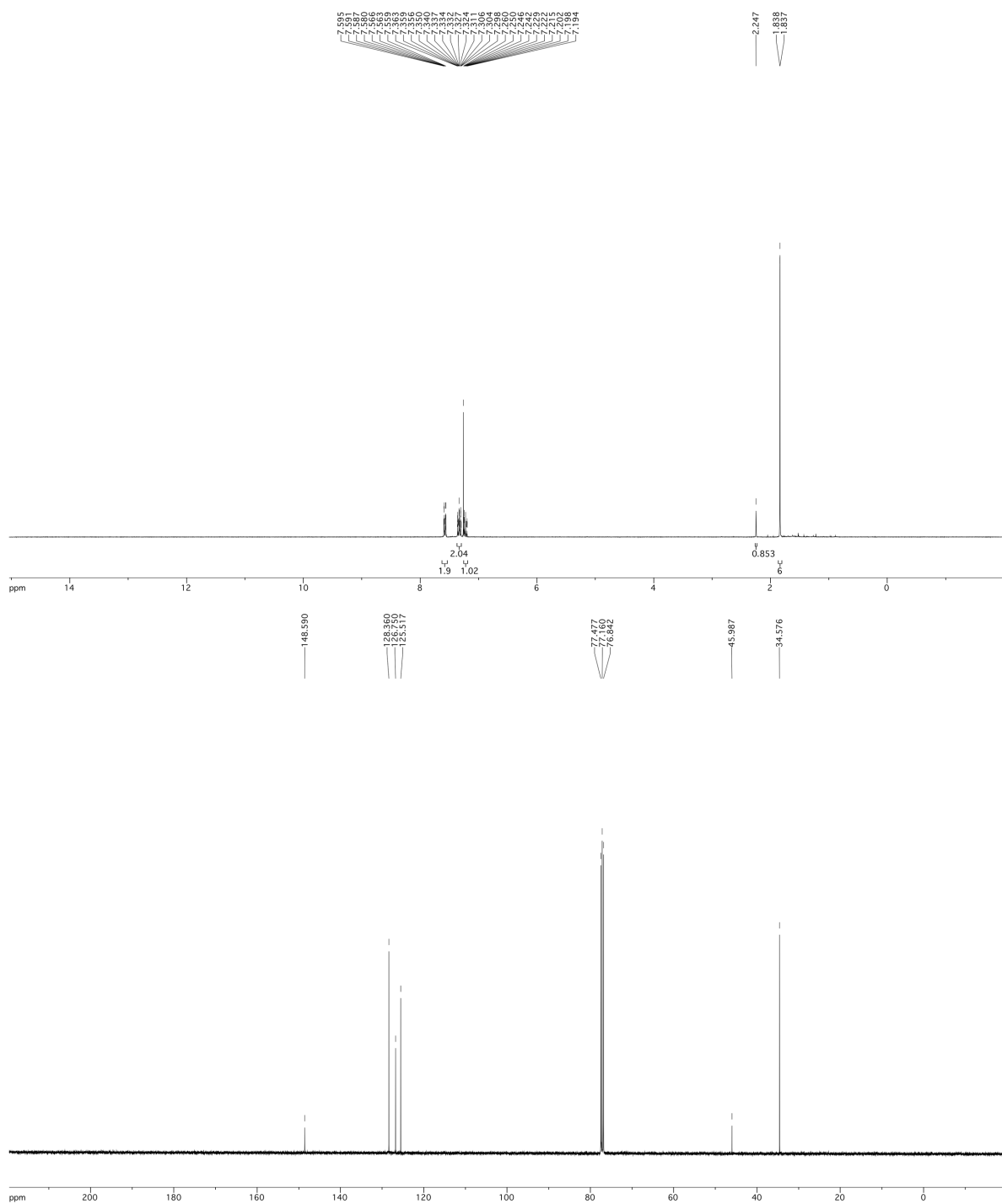
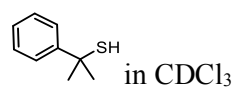


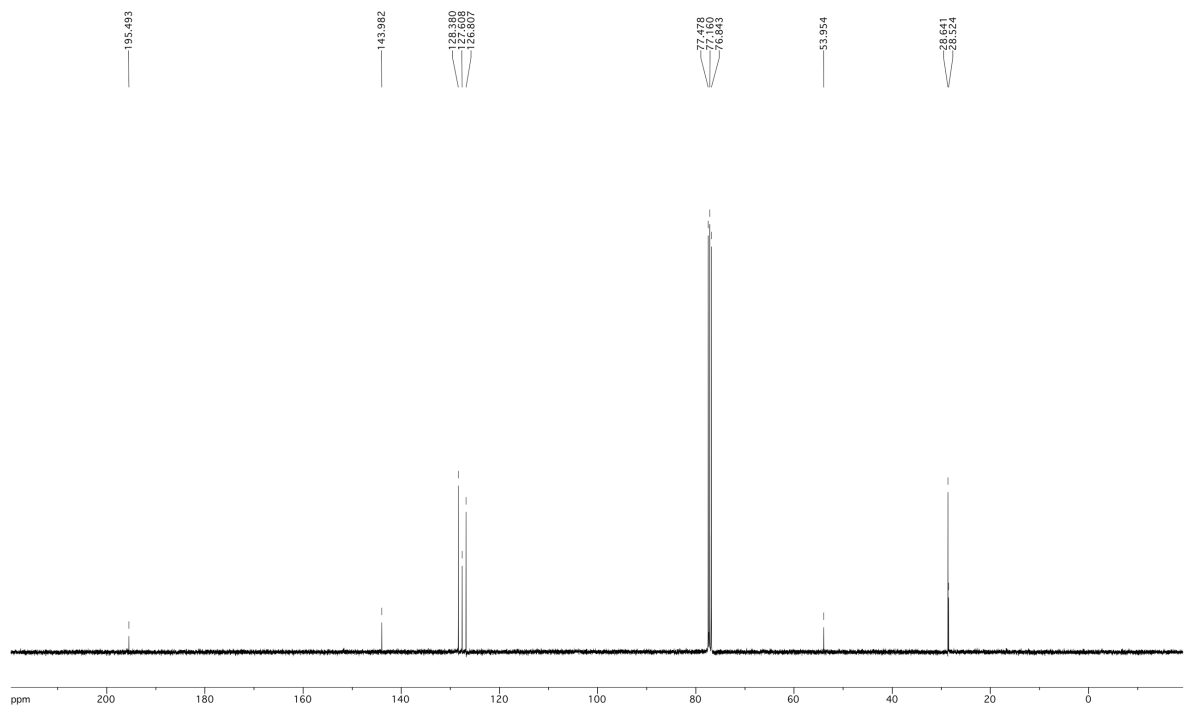
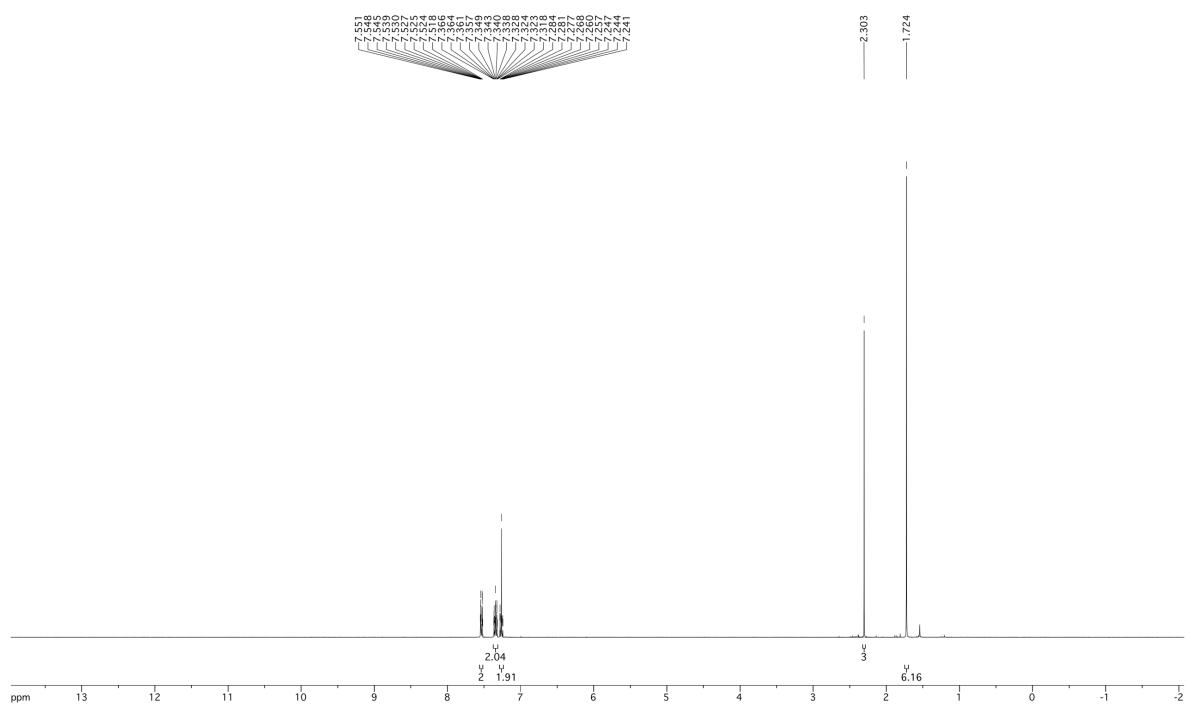
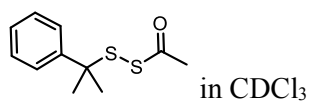


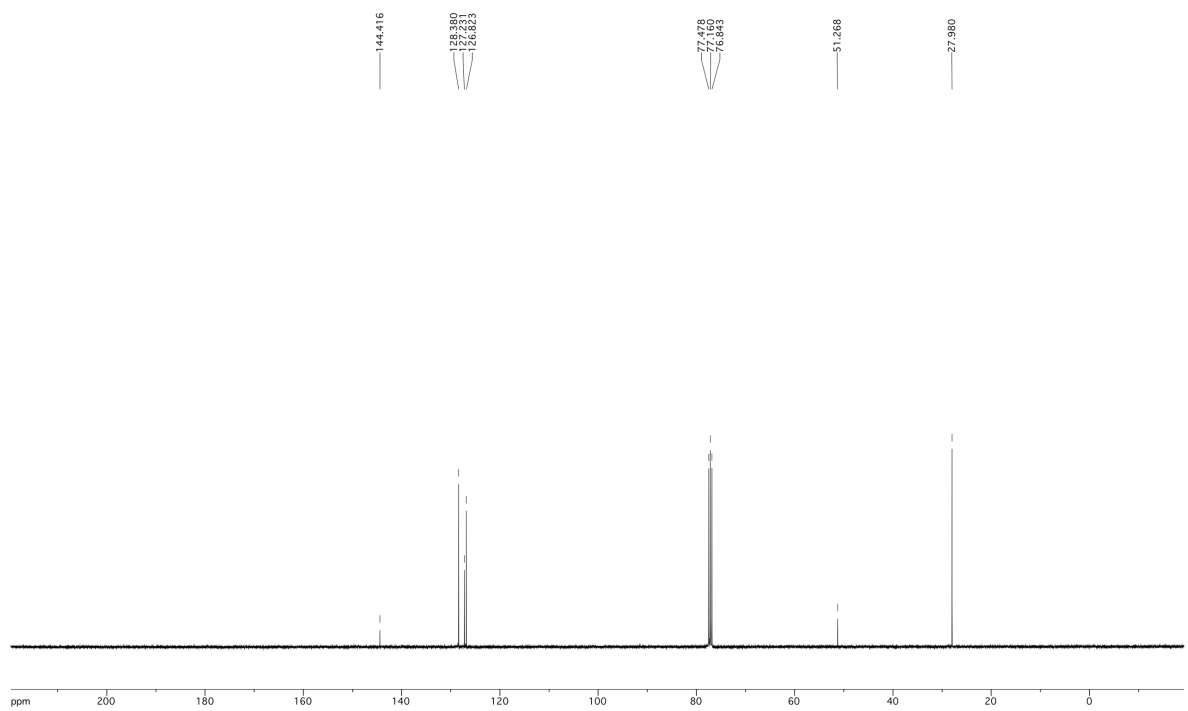
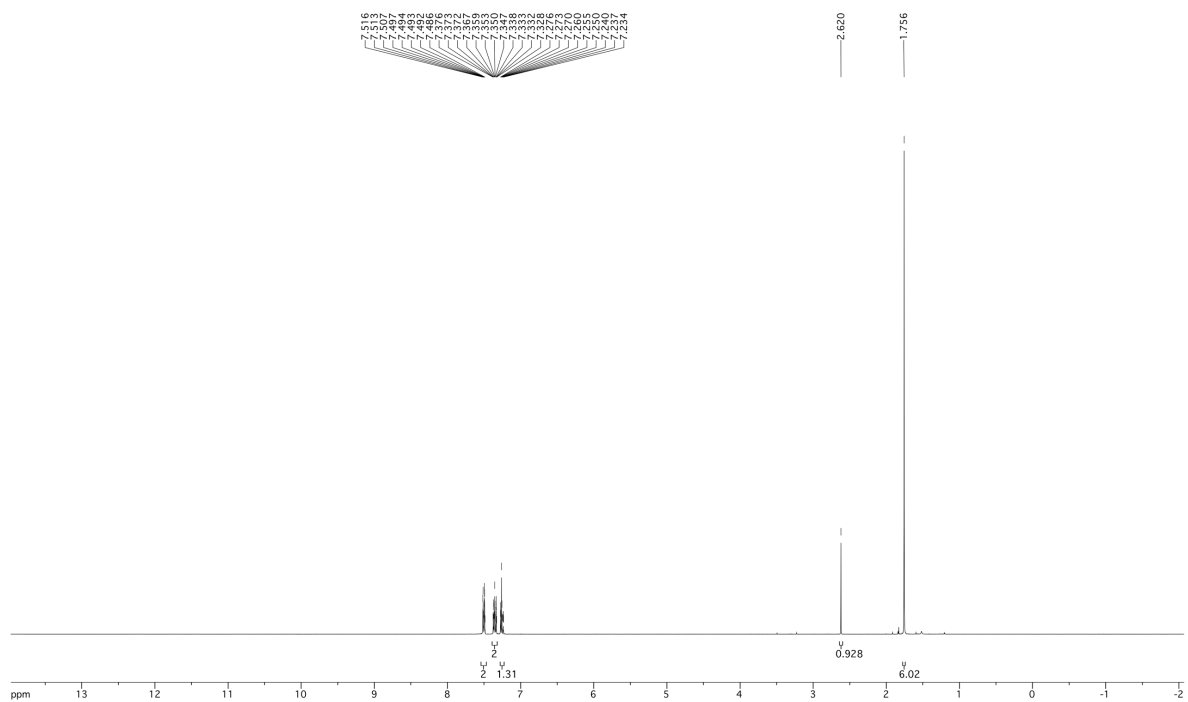


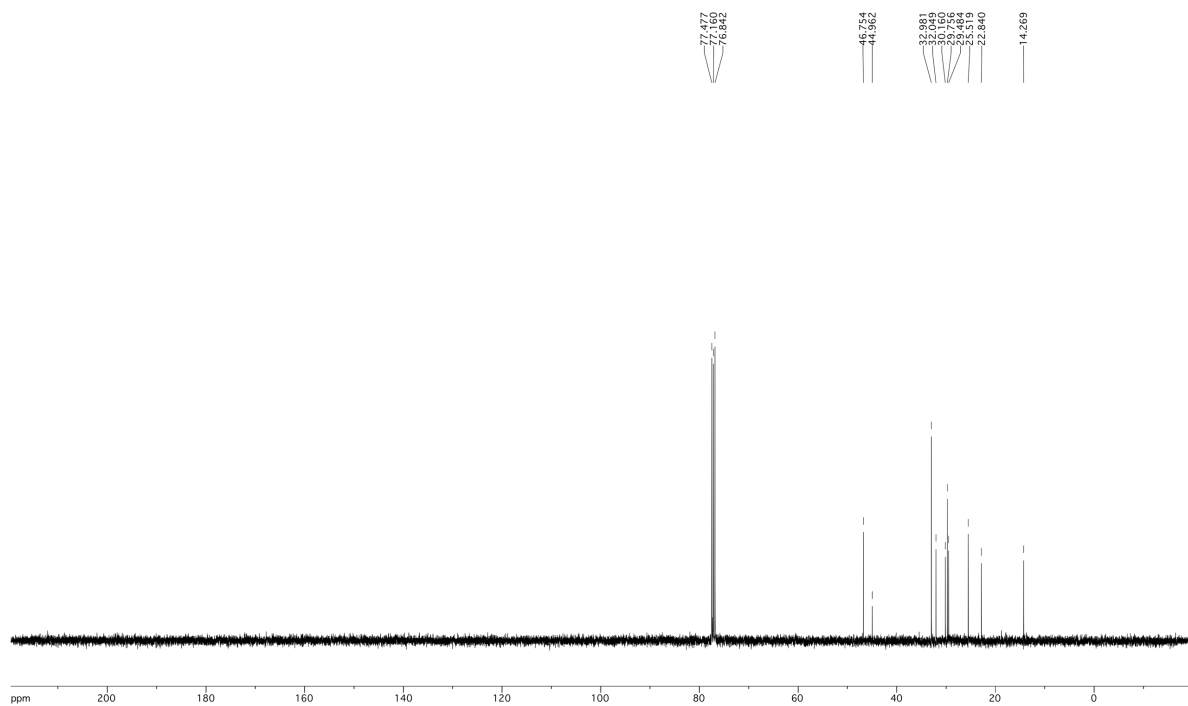
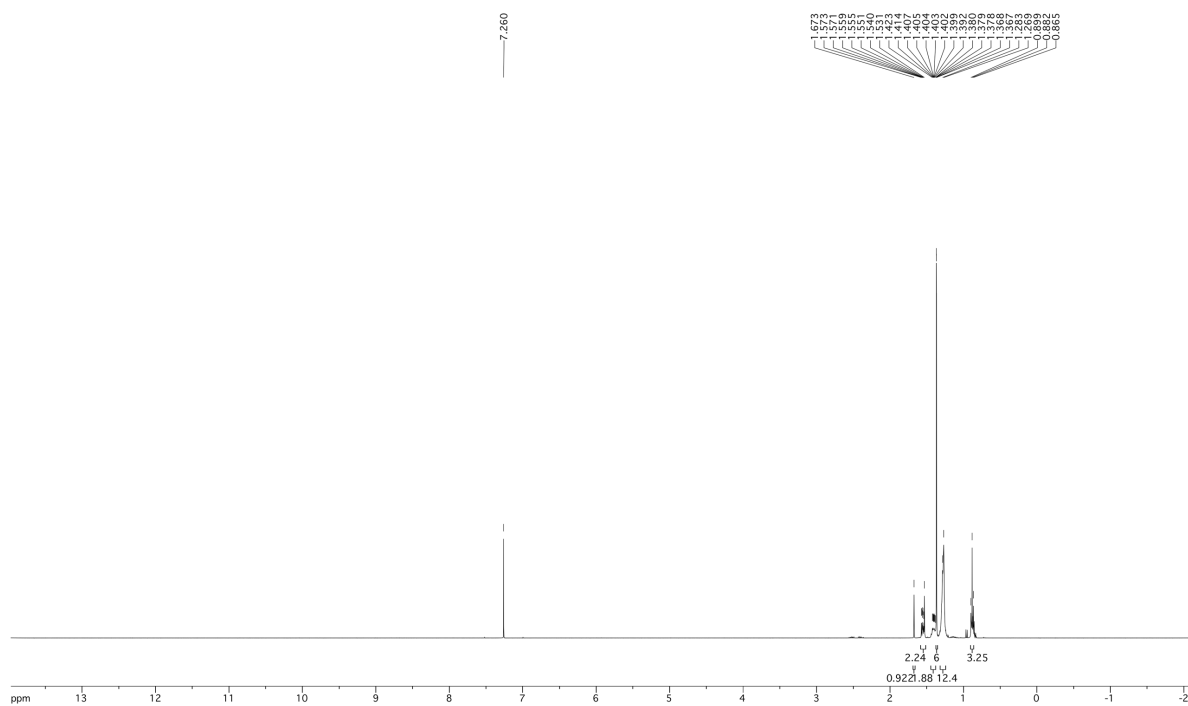
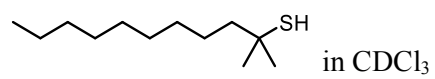


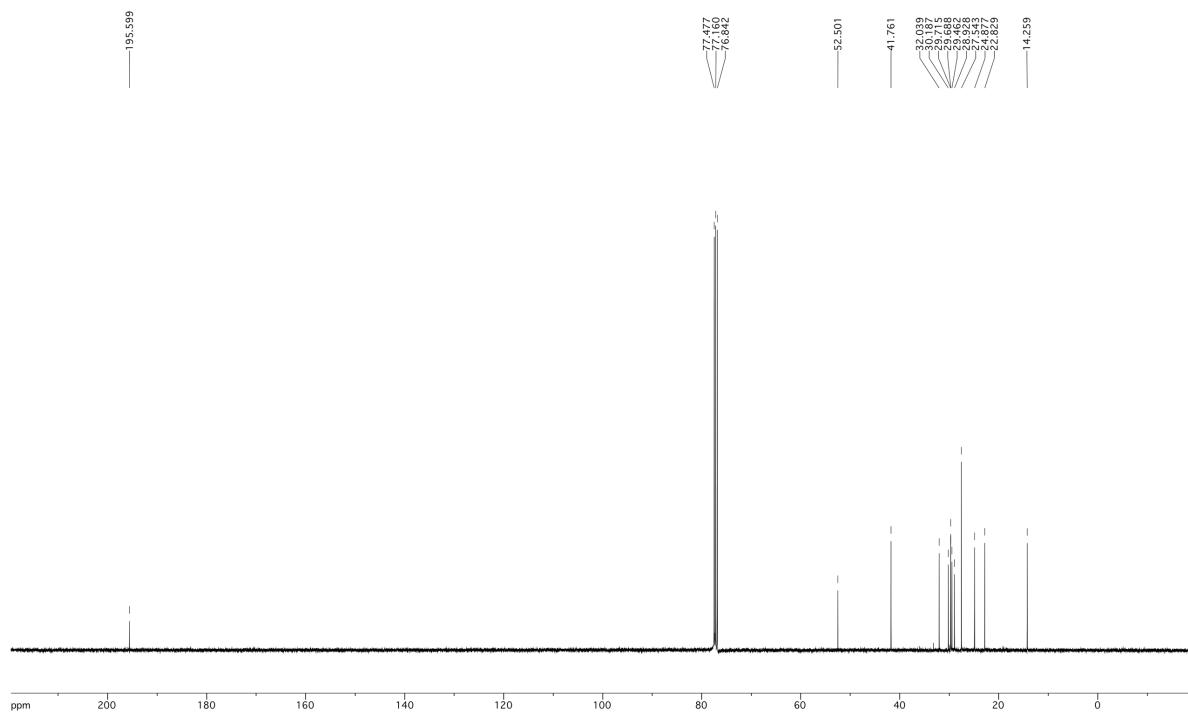
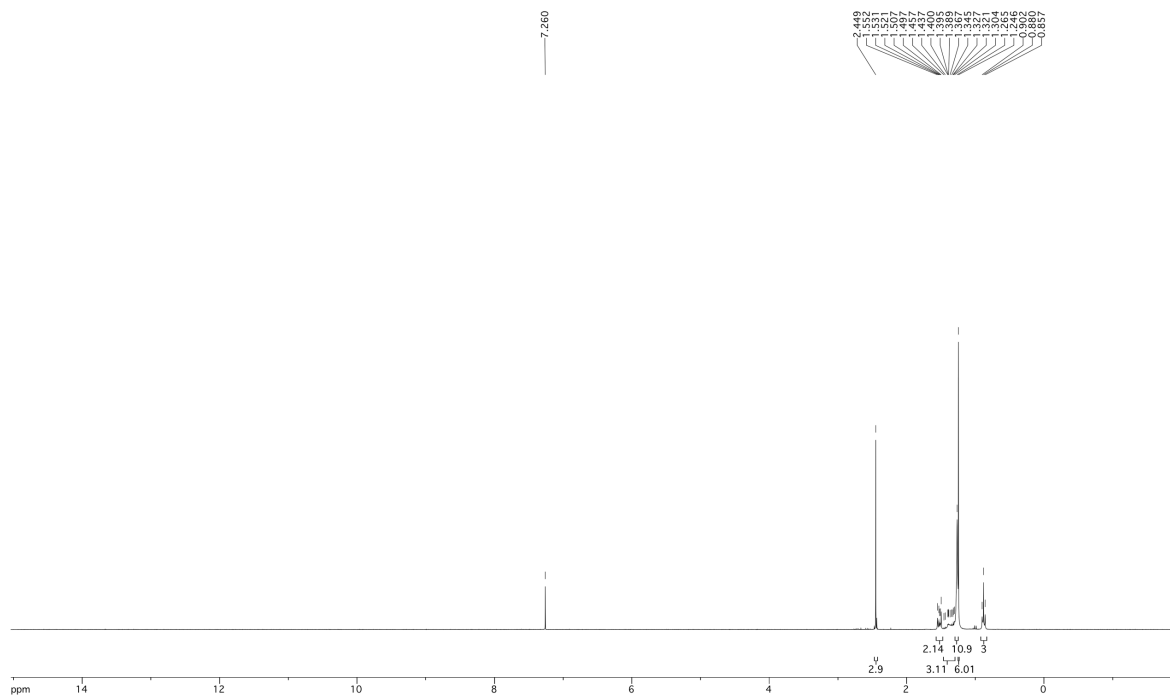
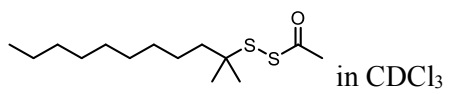
B.3 Hydropersulfides: H-Atom Transfer Agents Par Excellence

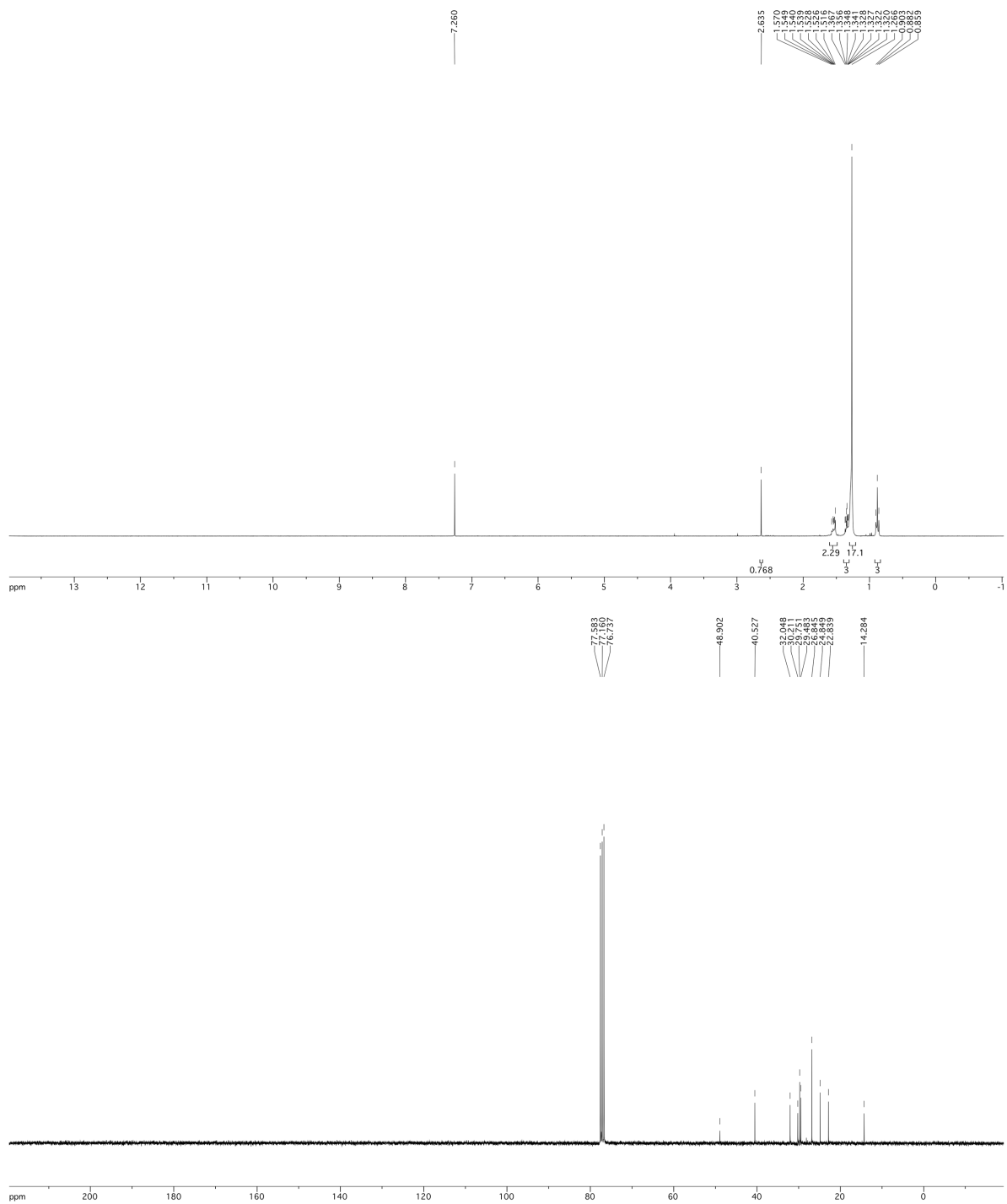


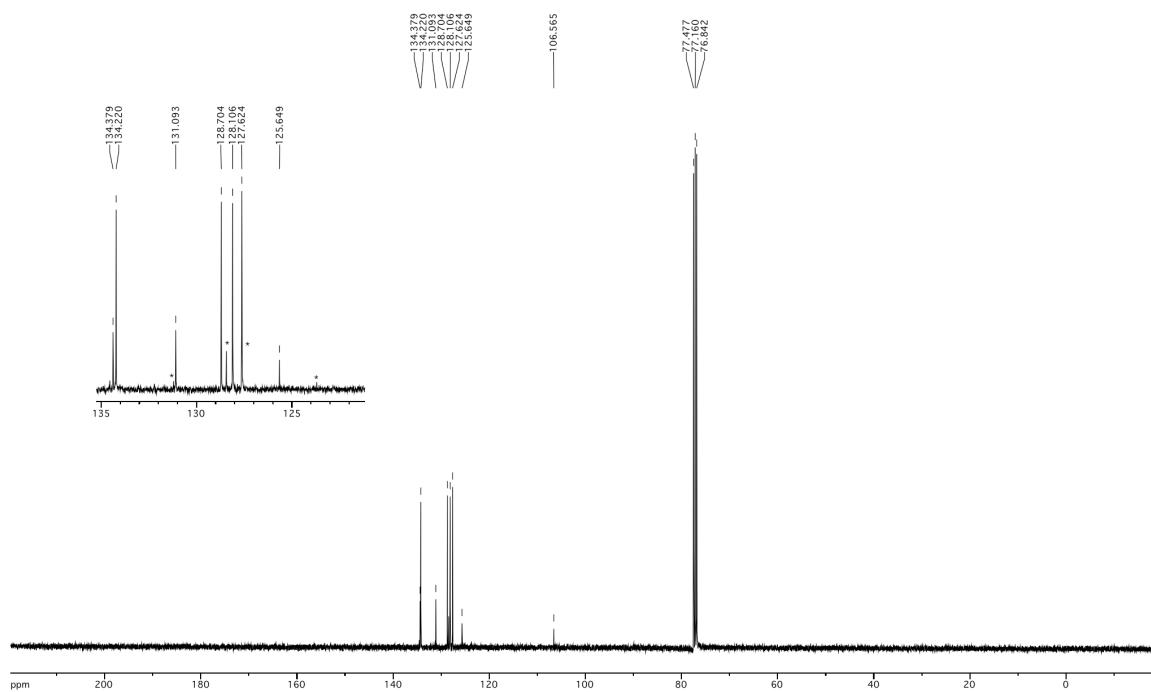
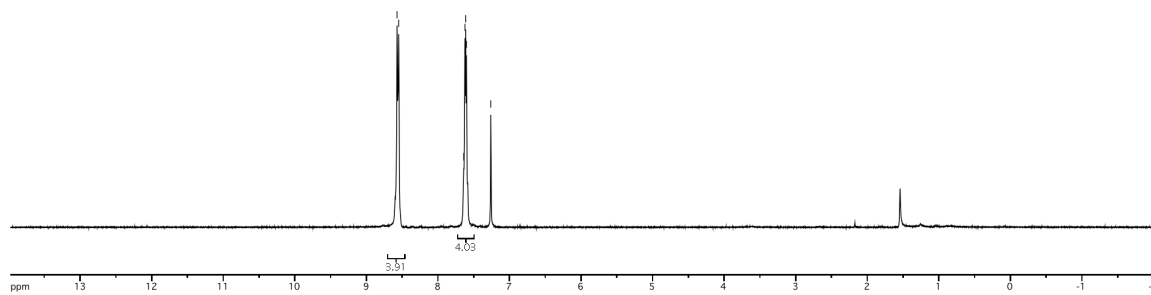


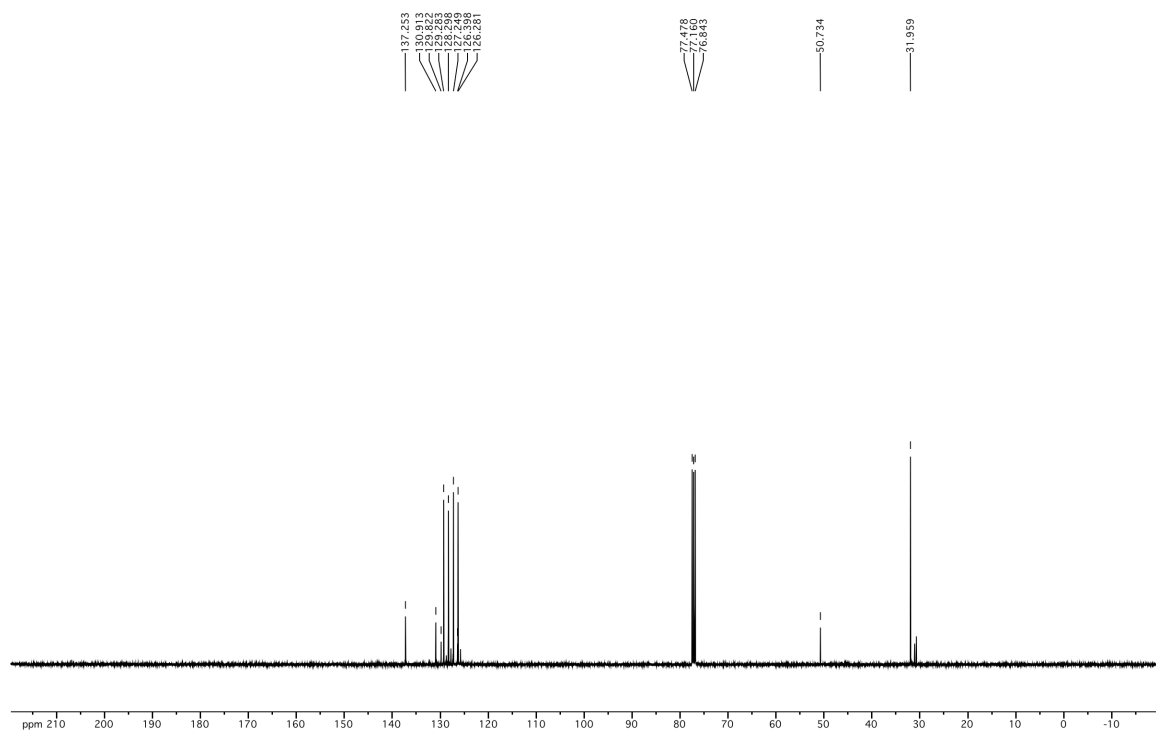
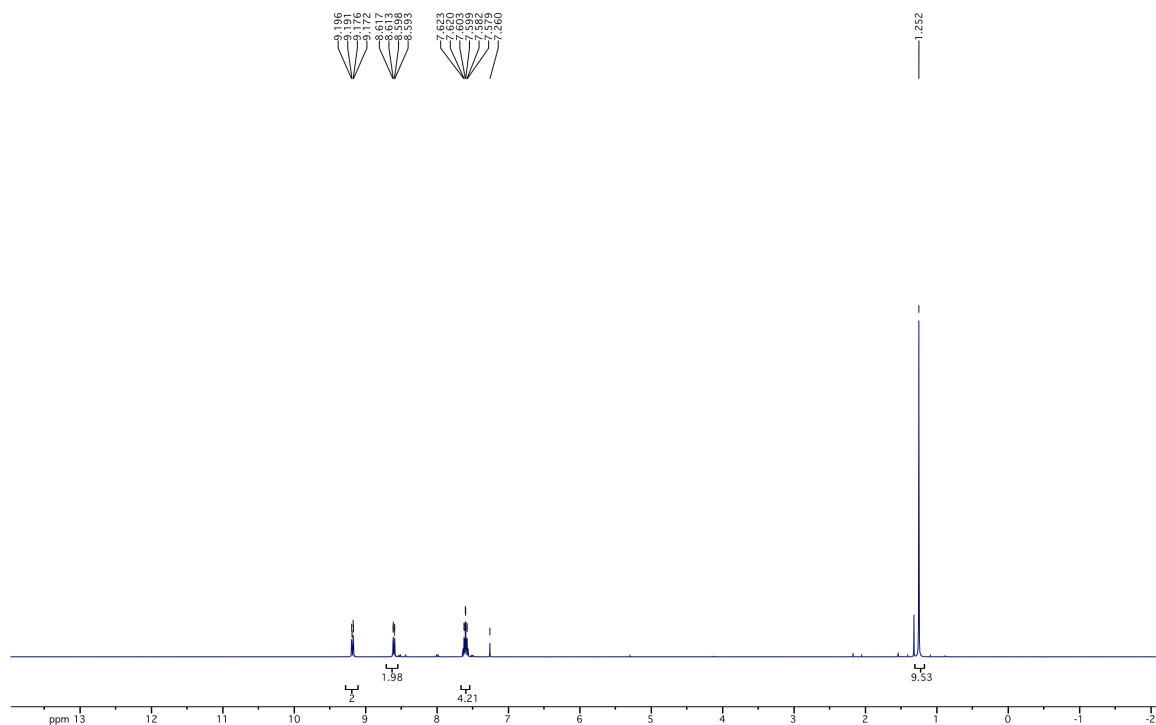
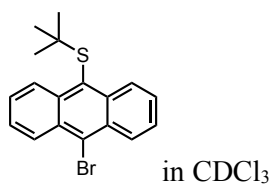


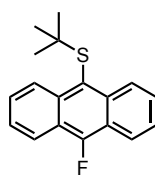




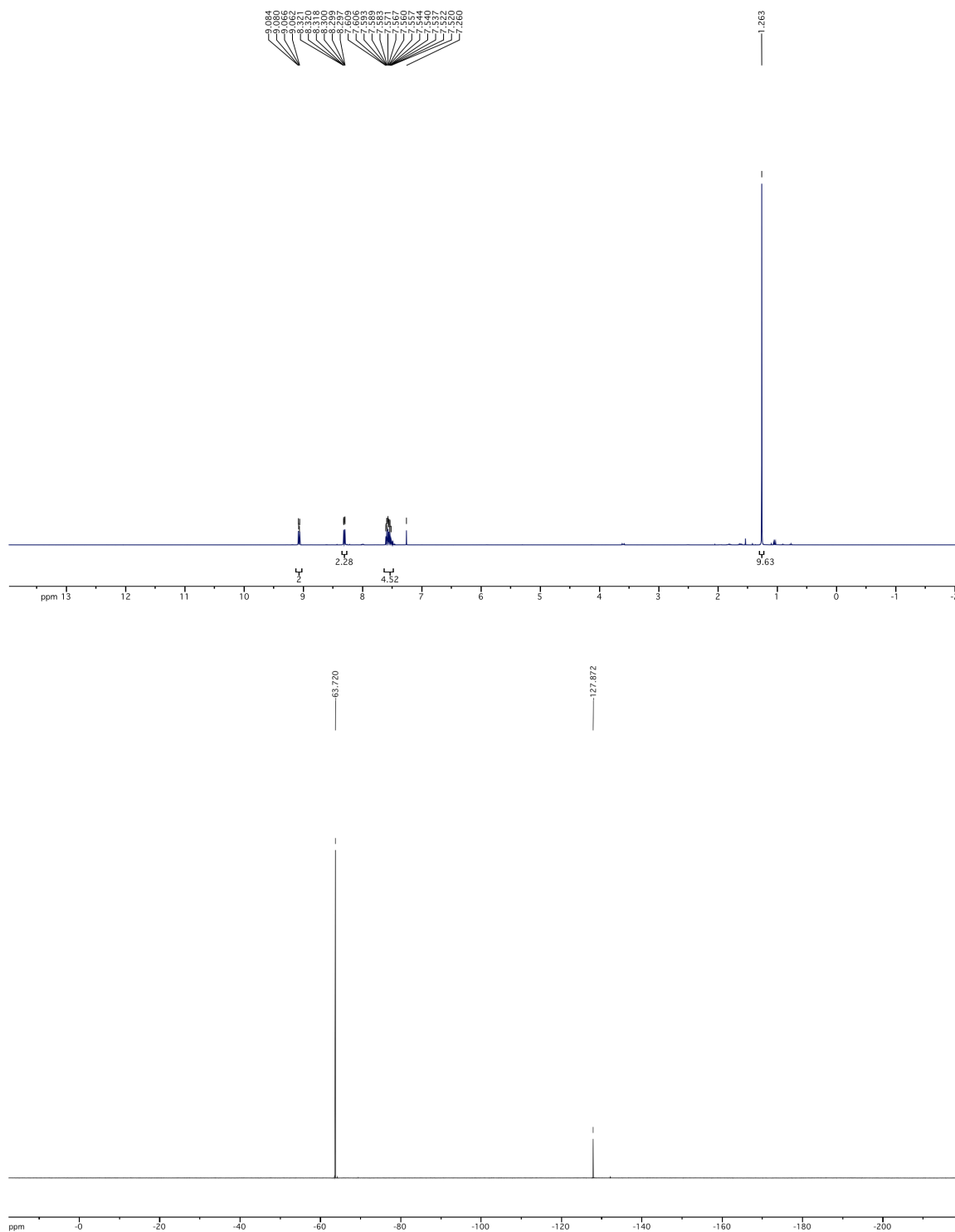




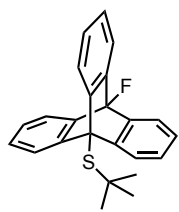




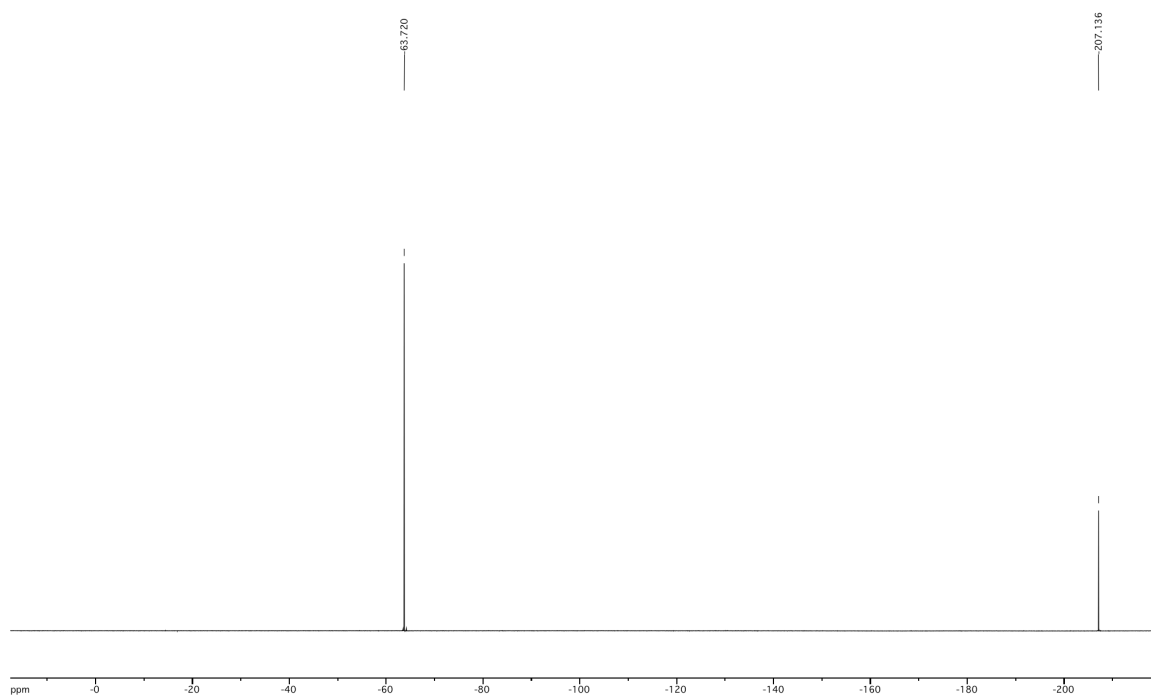
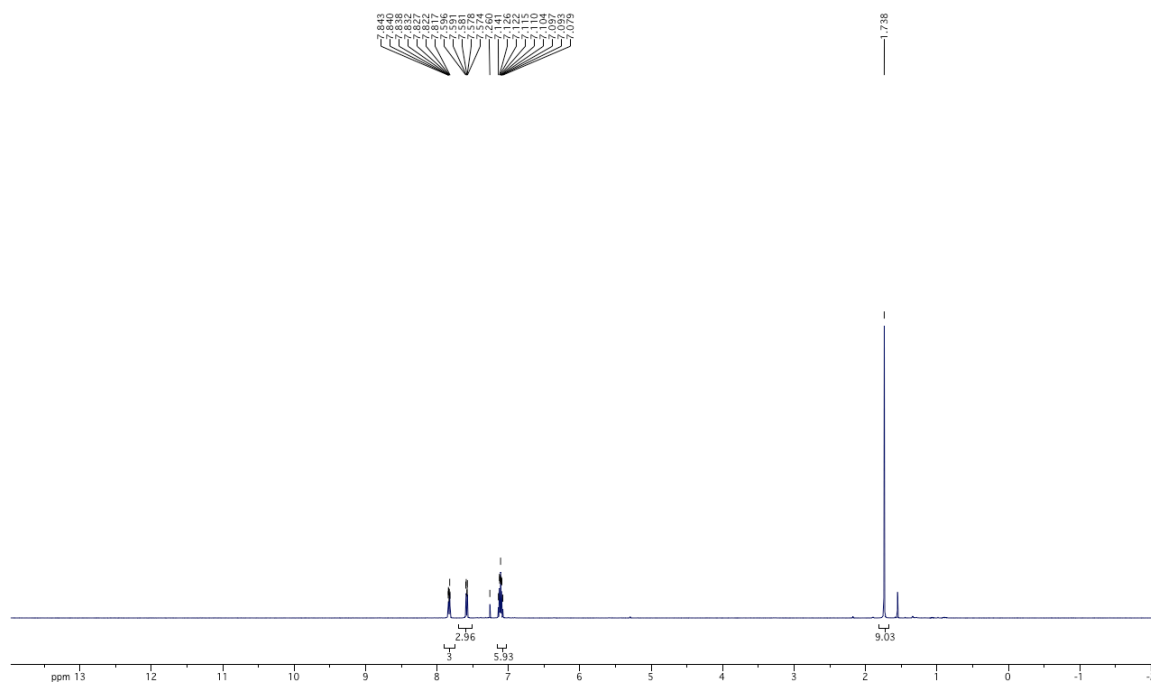
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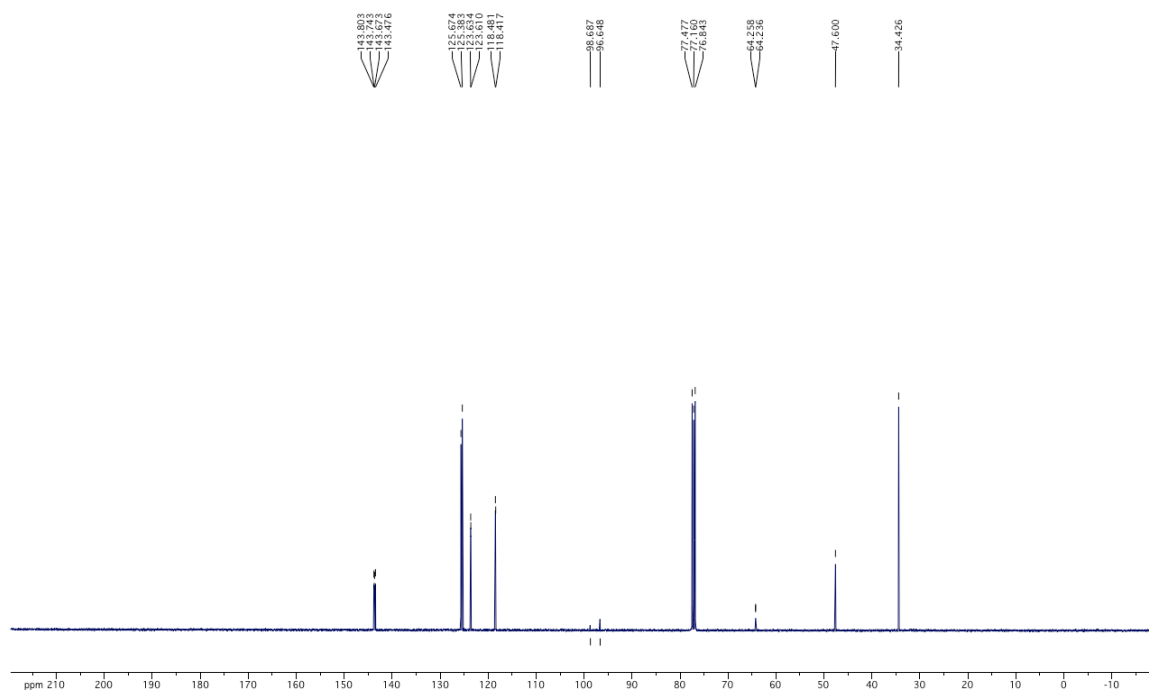


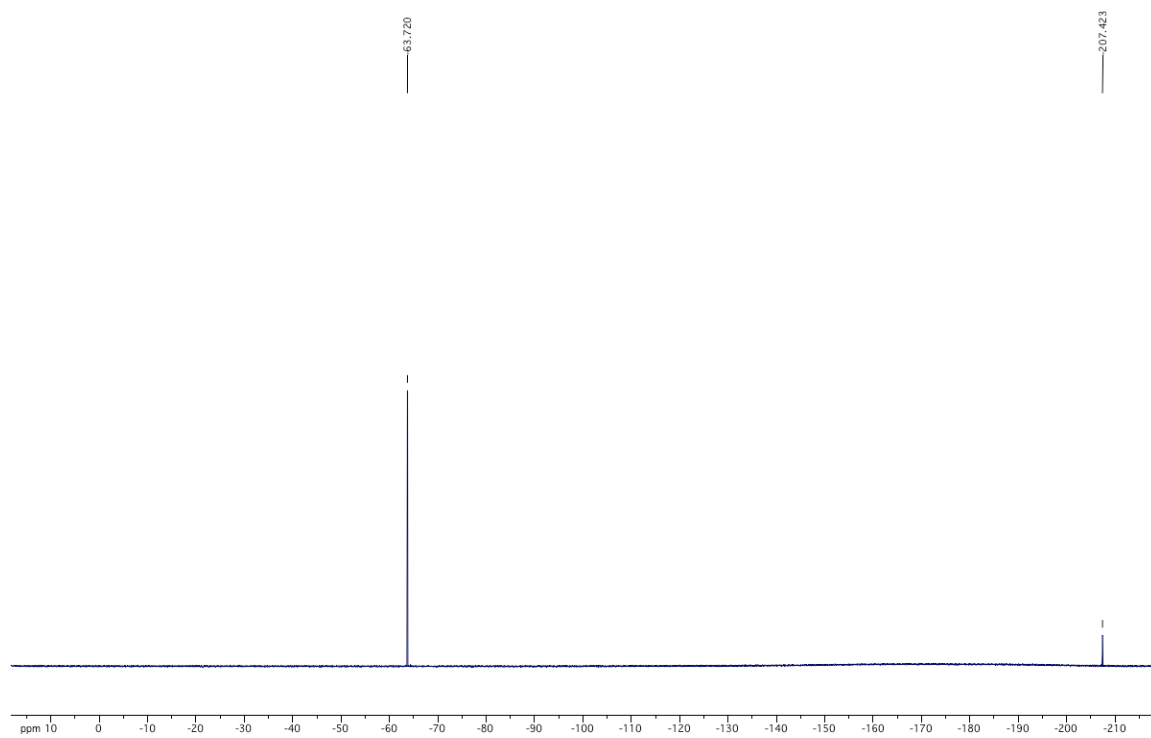
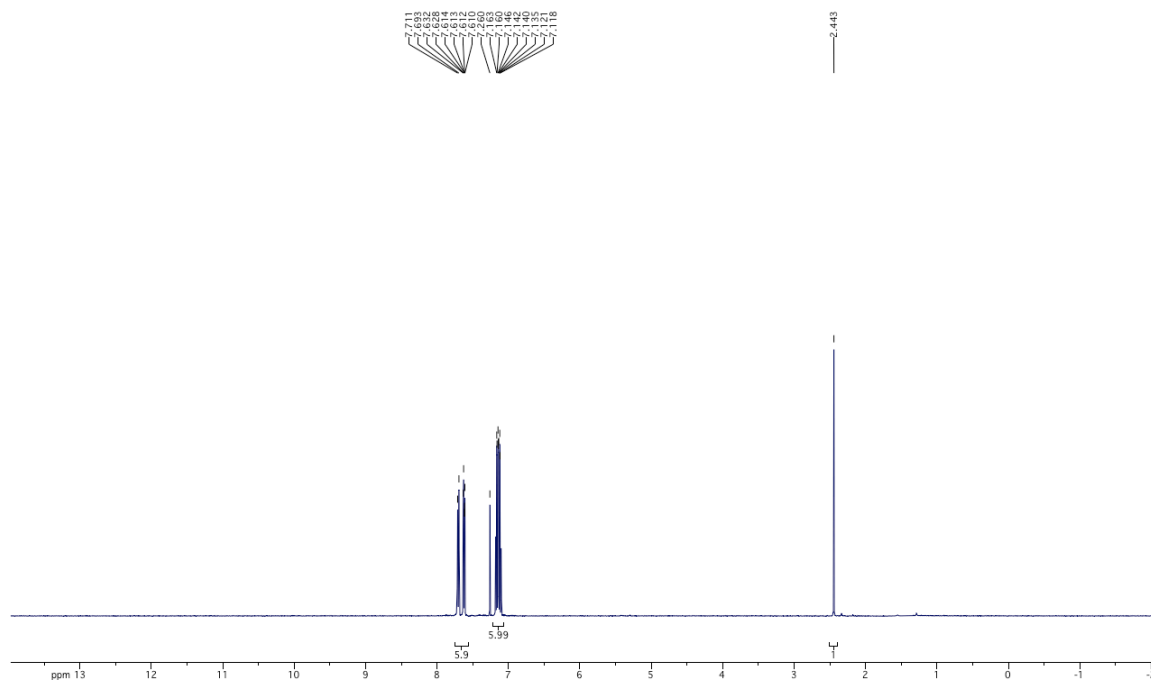
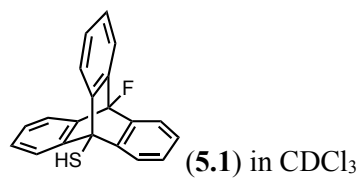


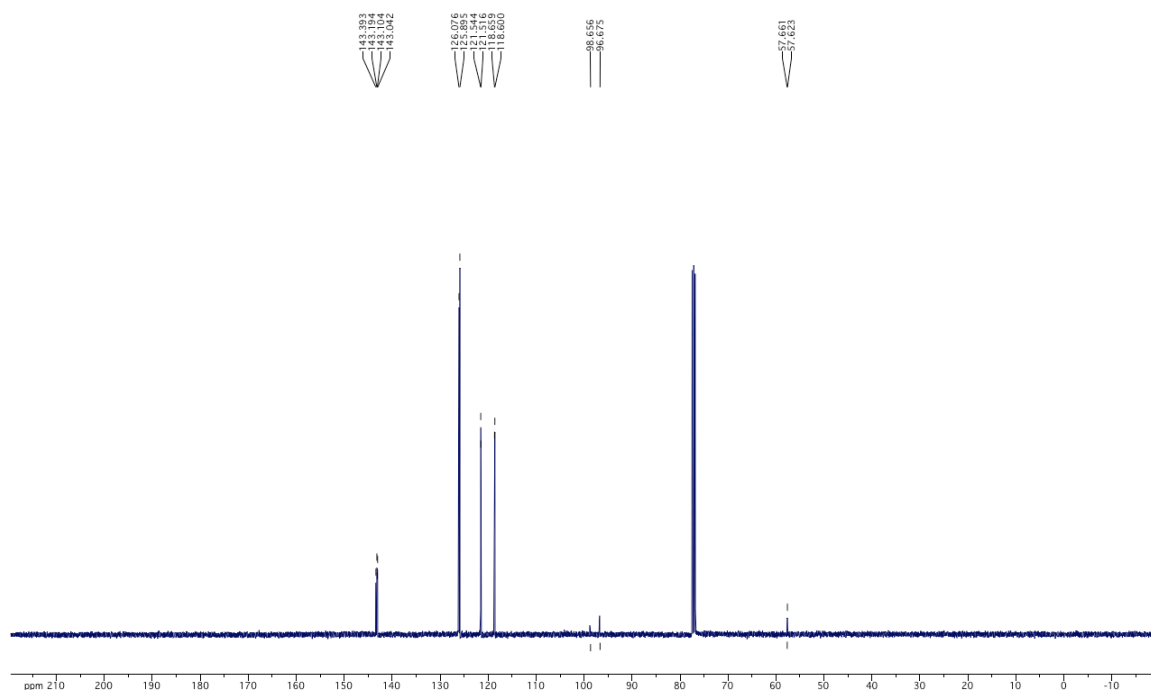


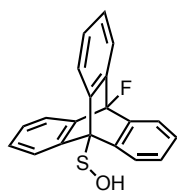
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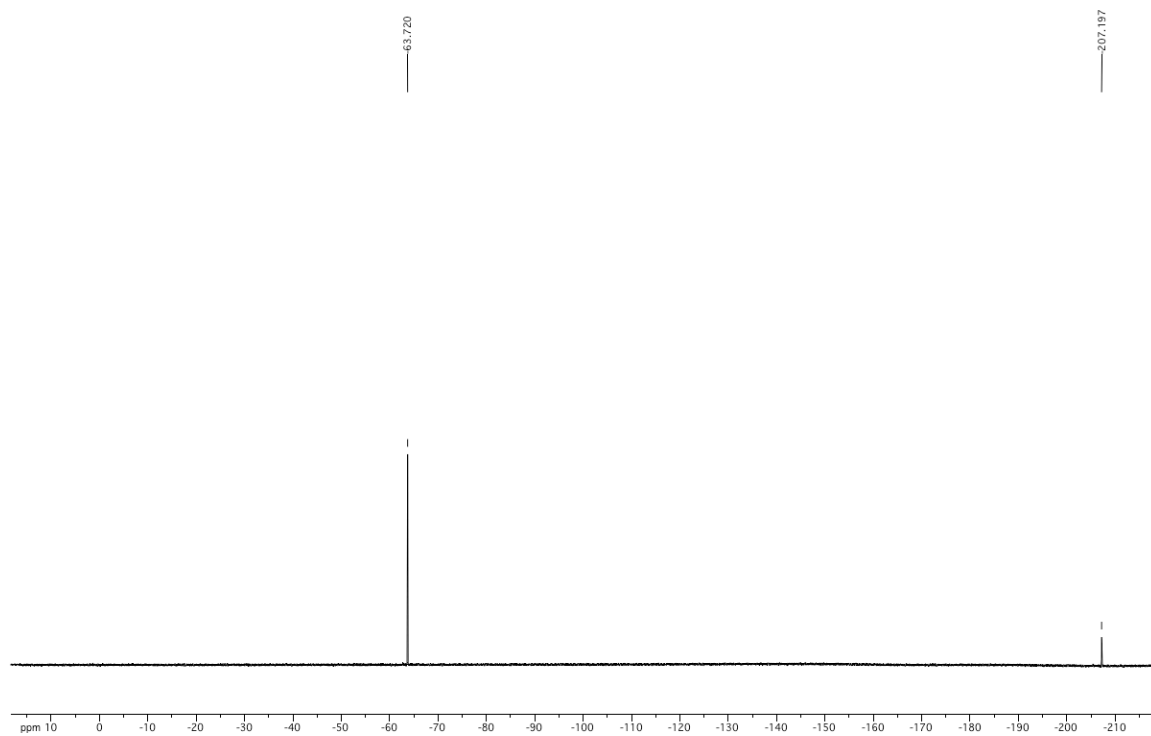
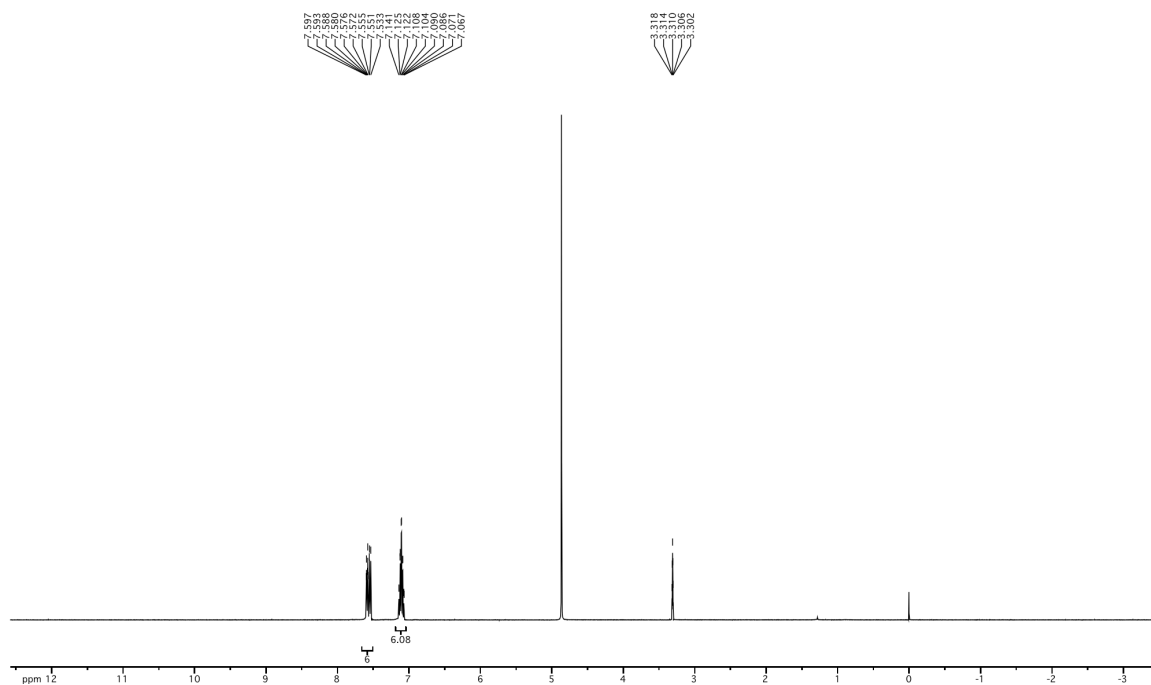




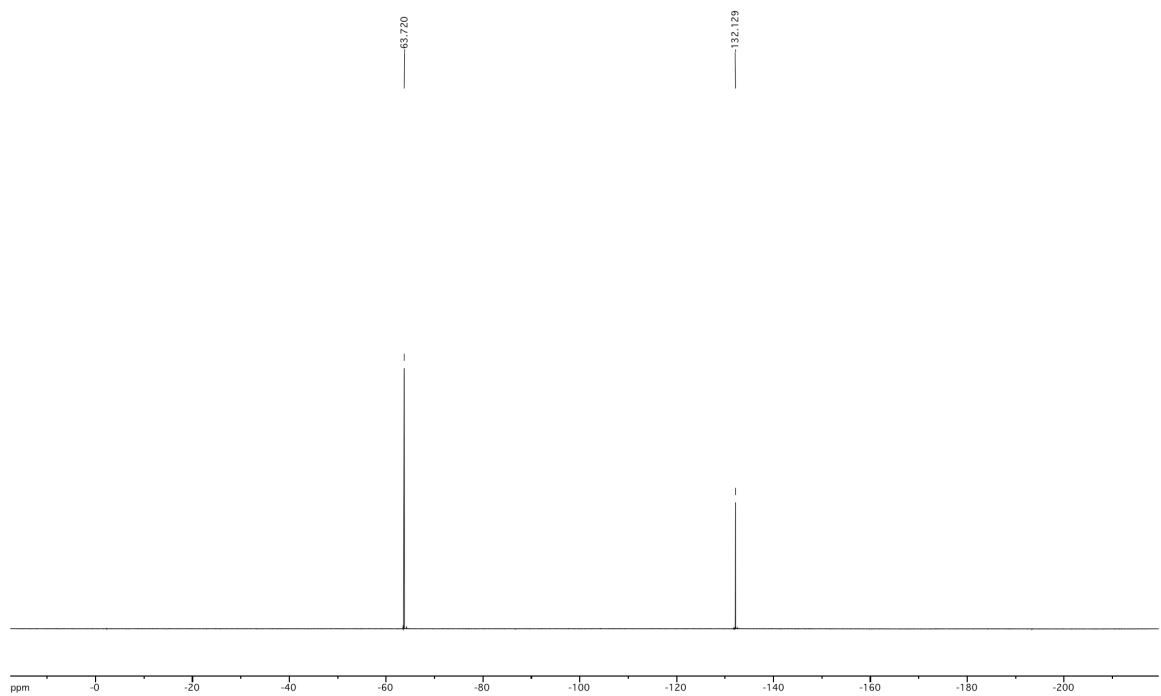
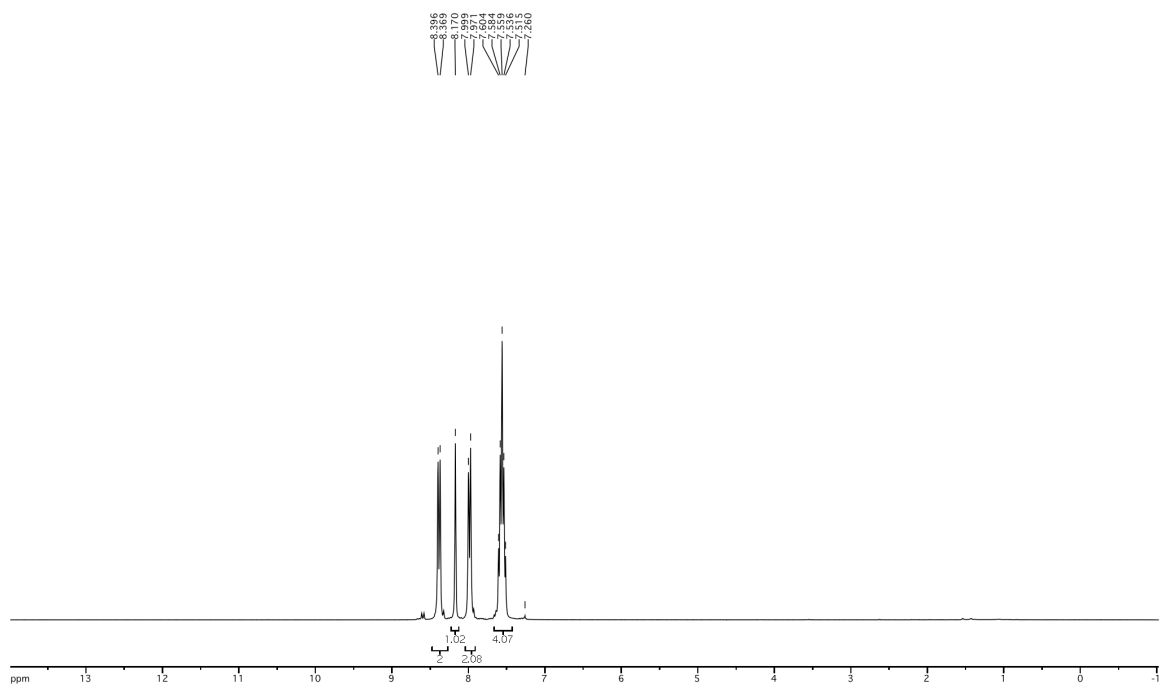
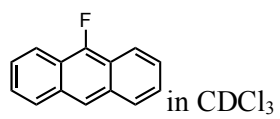


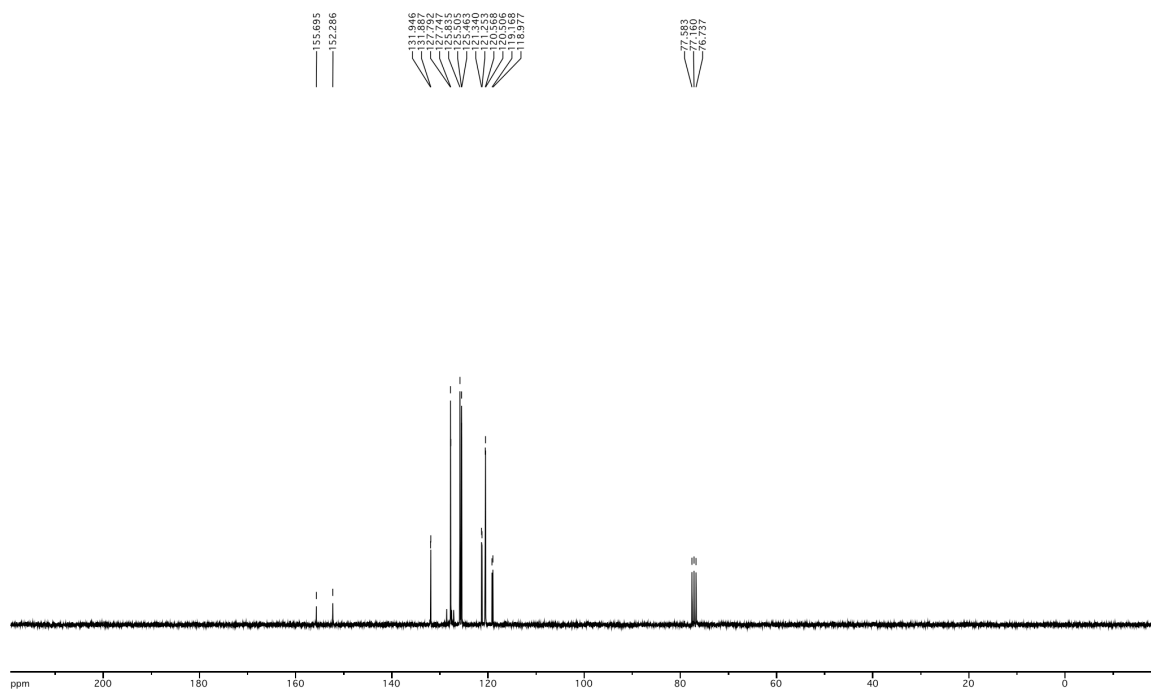


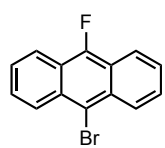
(5.2) in CD₃OD



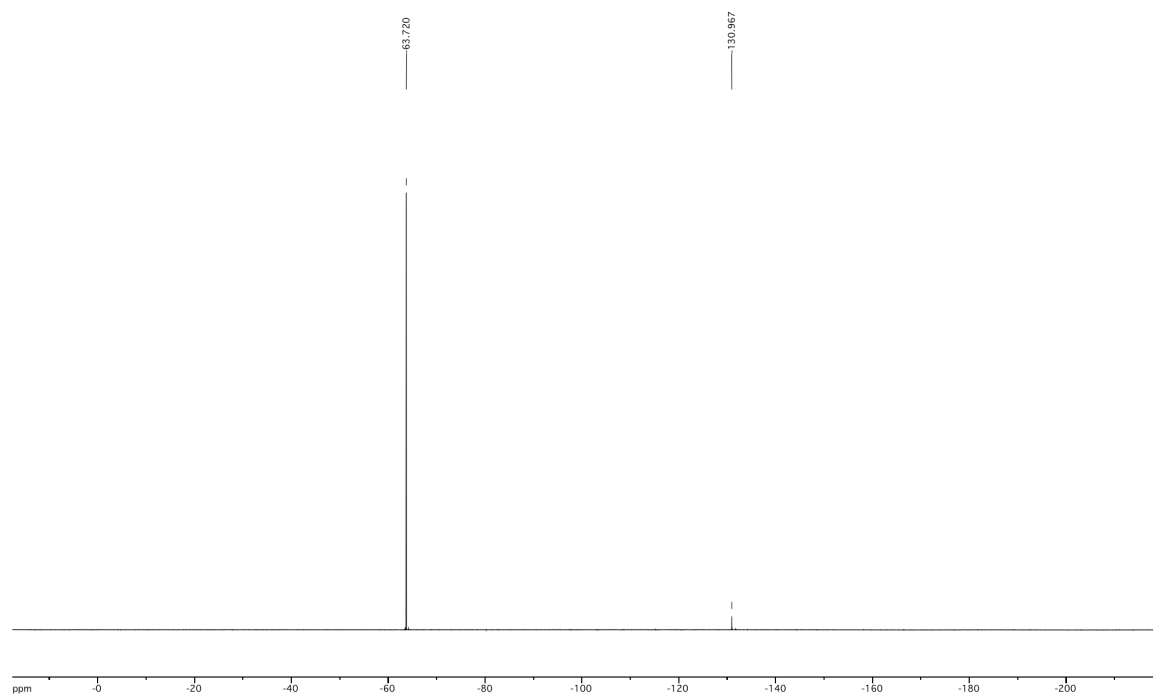
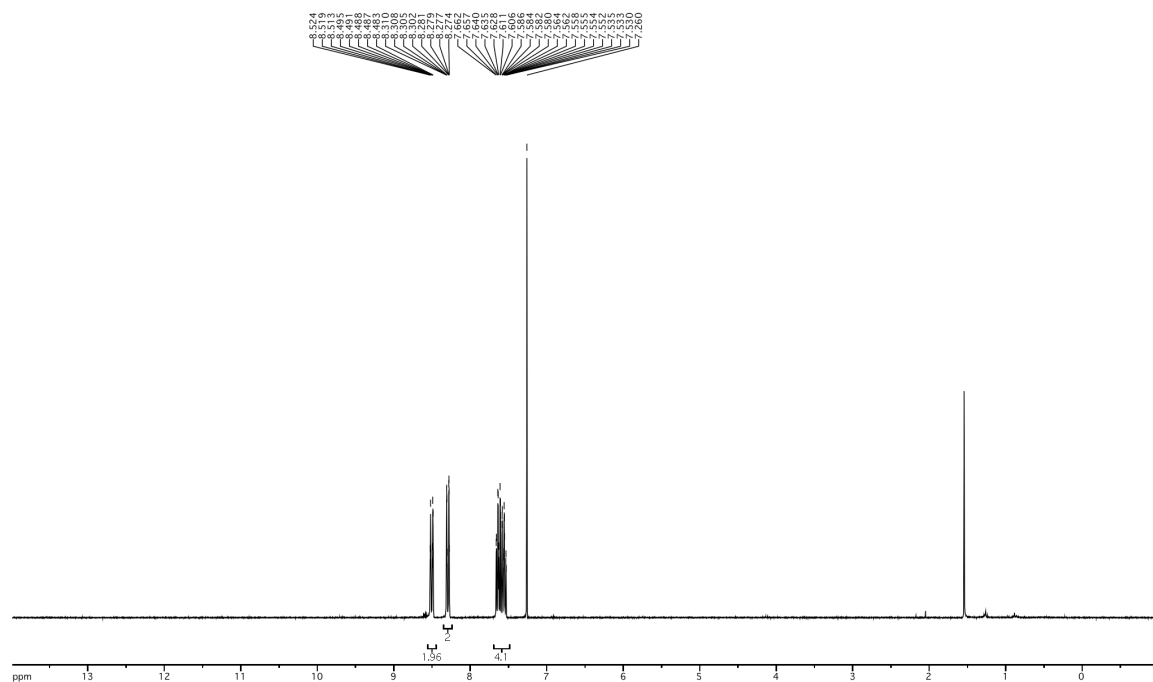


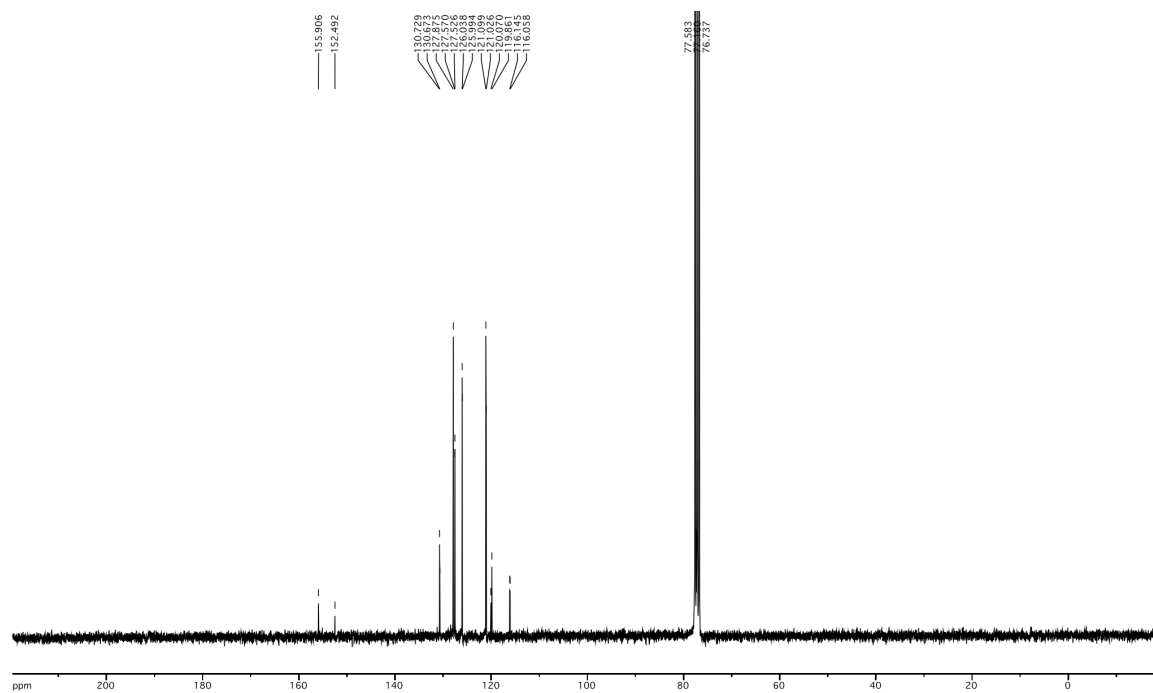


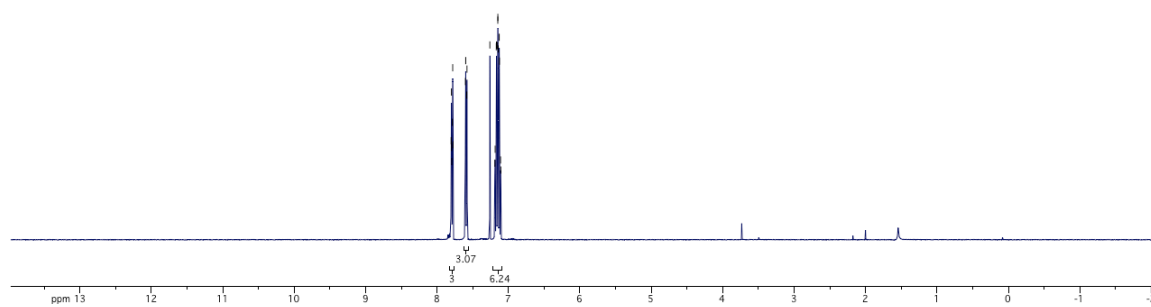
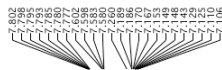
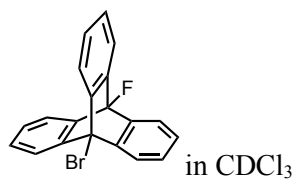




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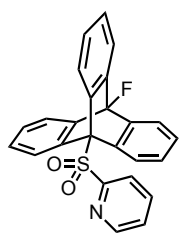




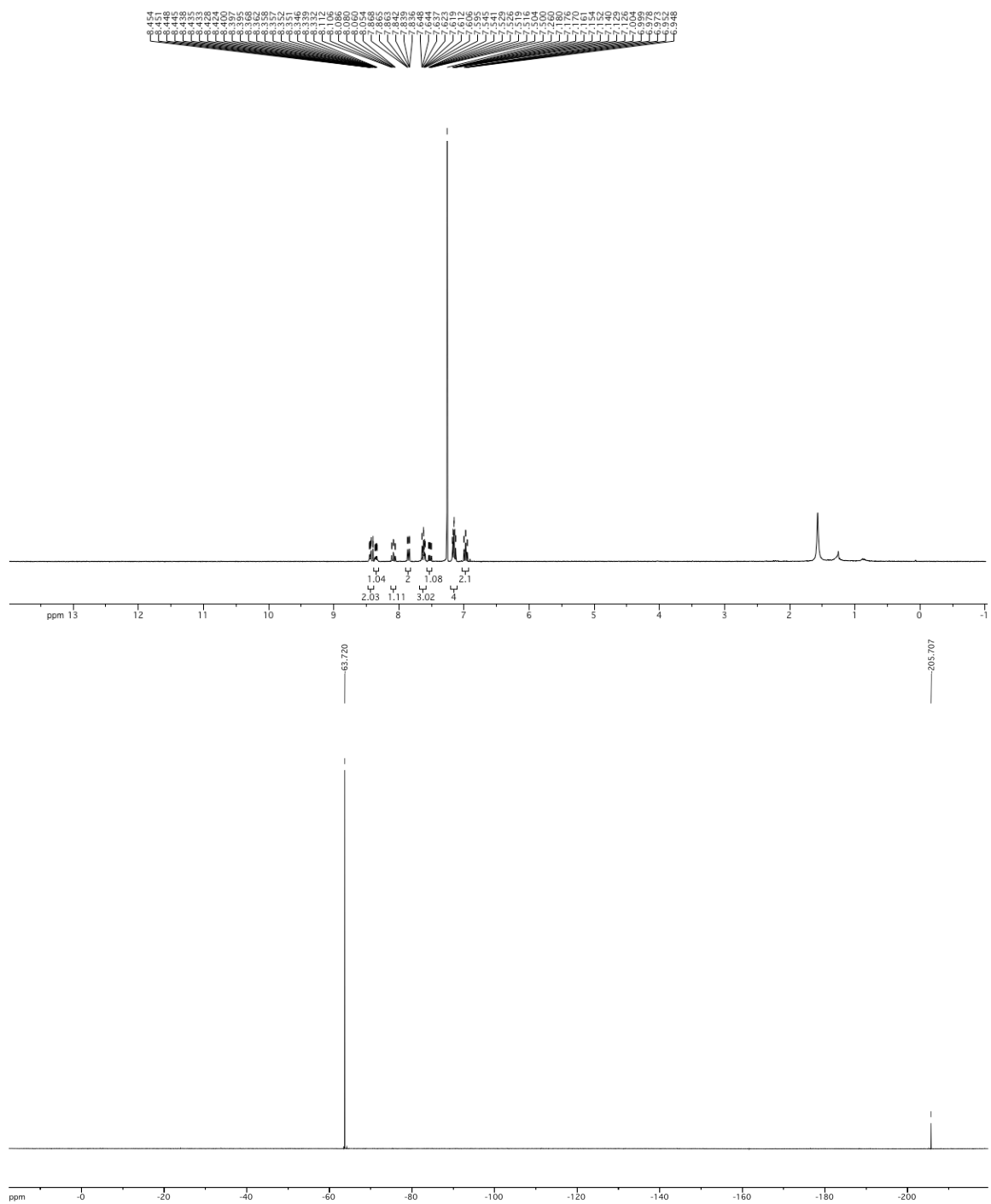


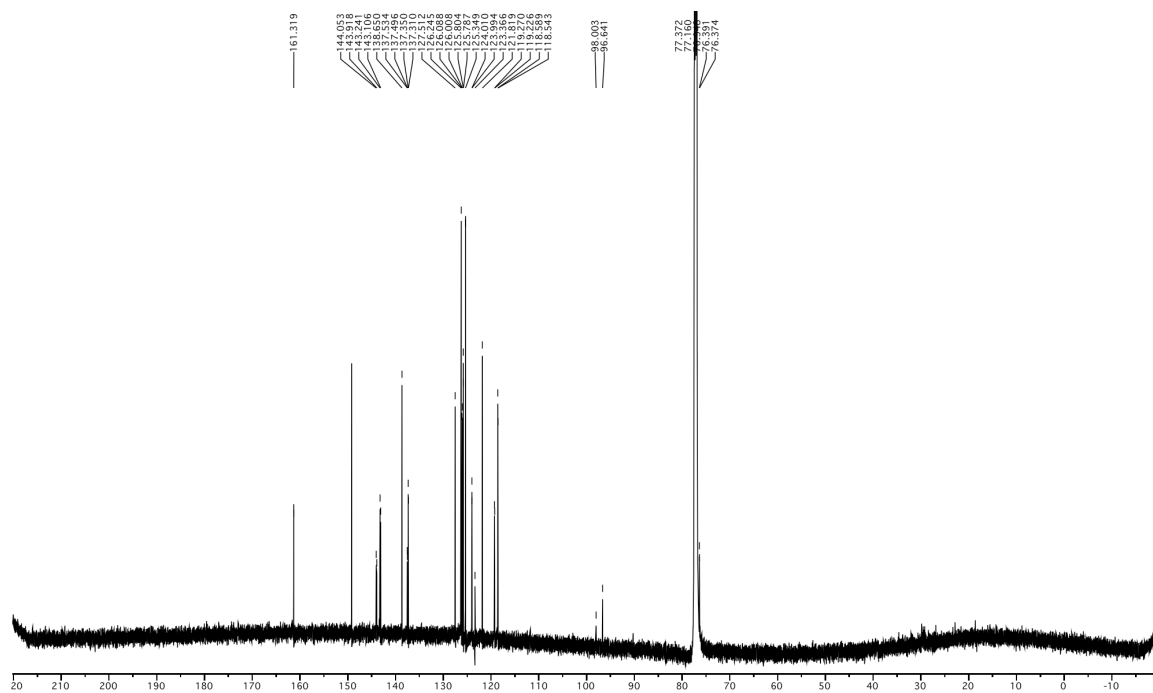


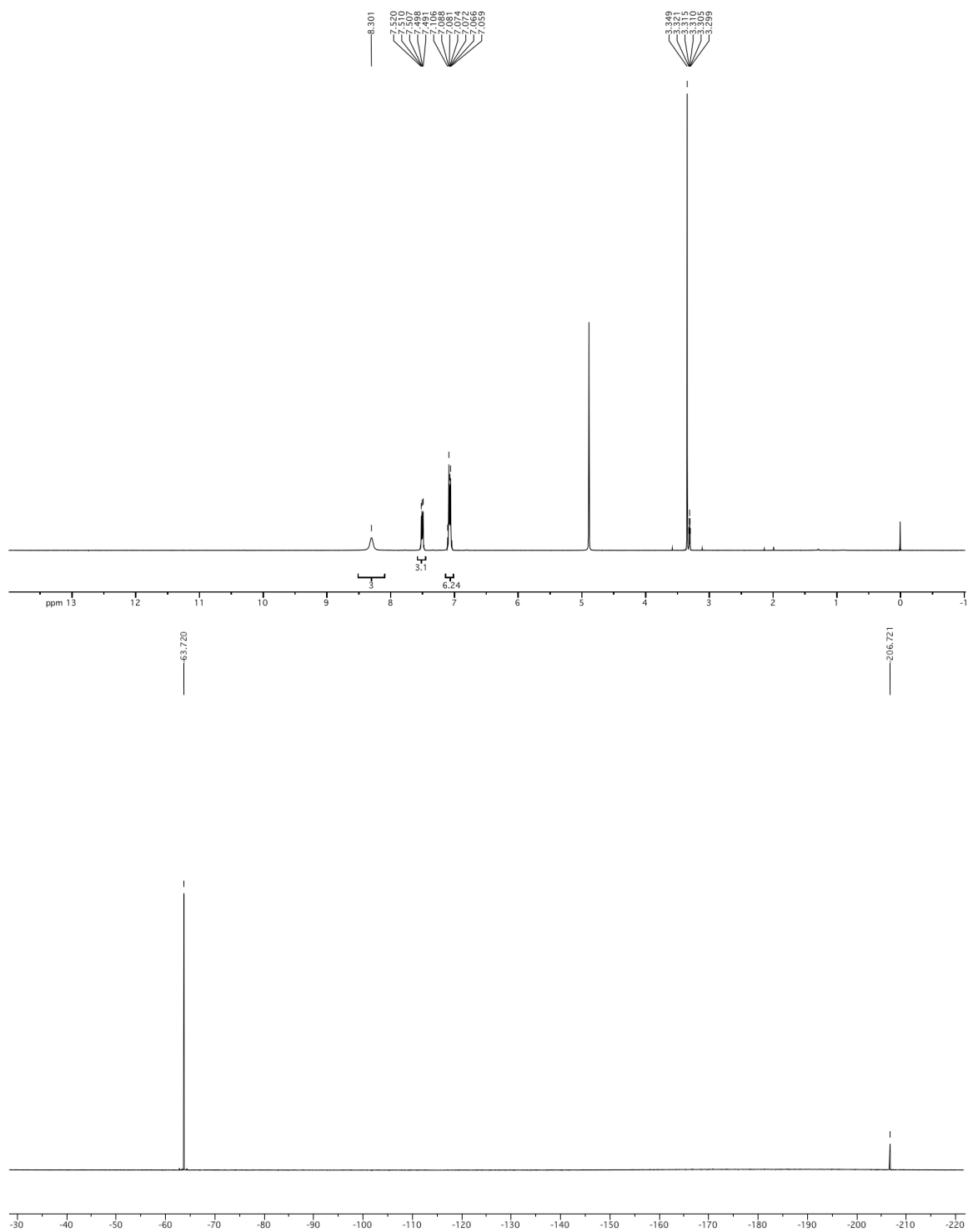


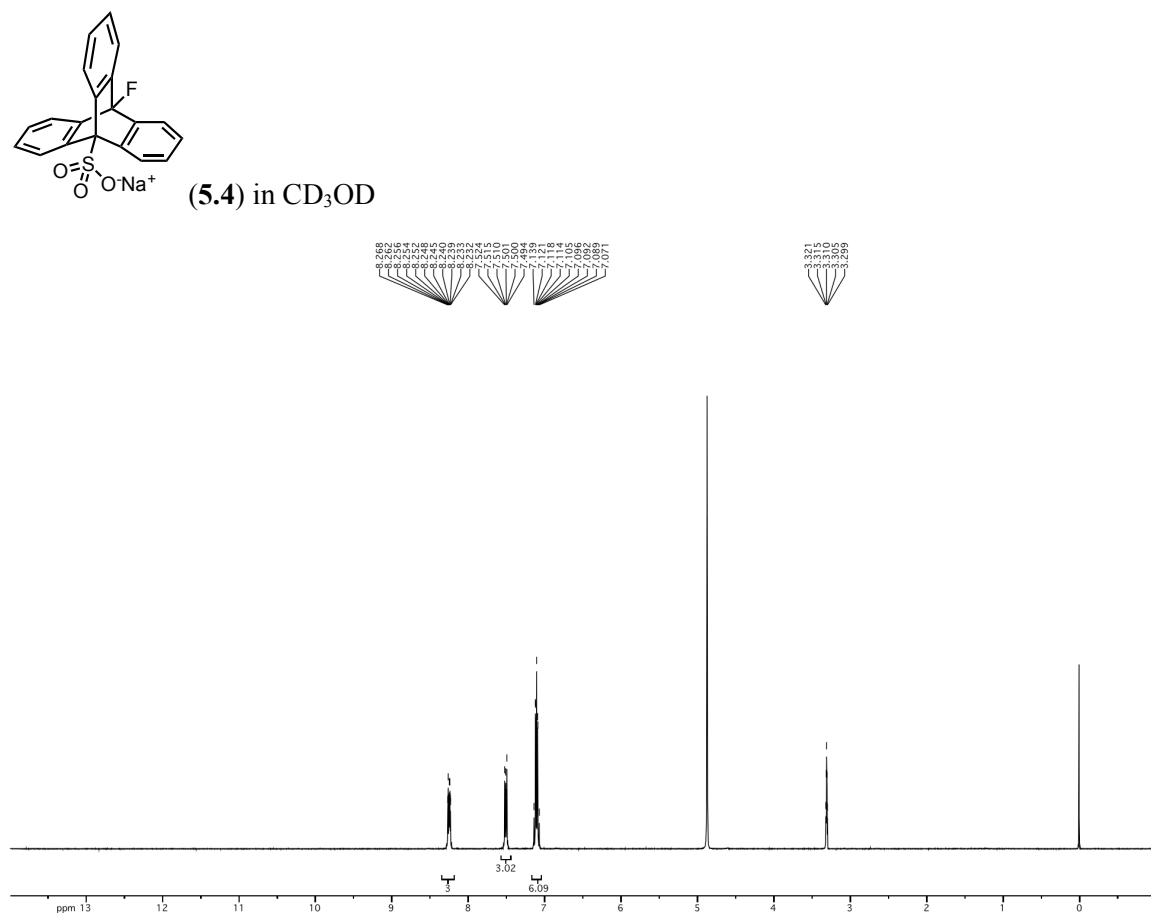
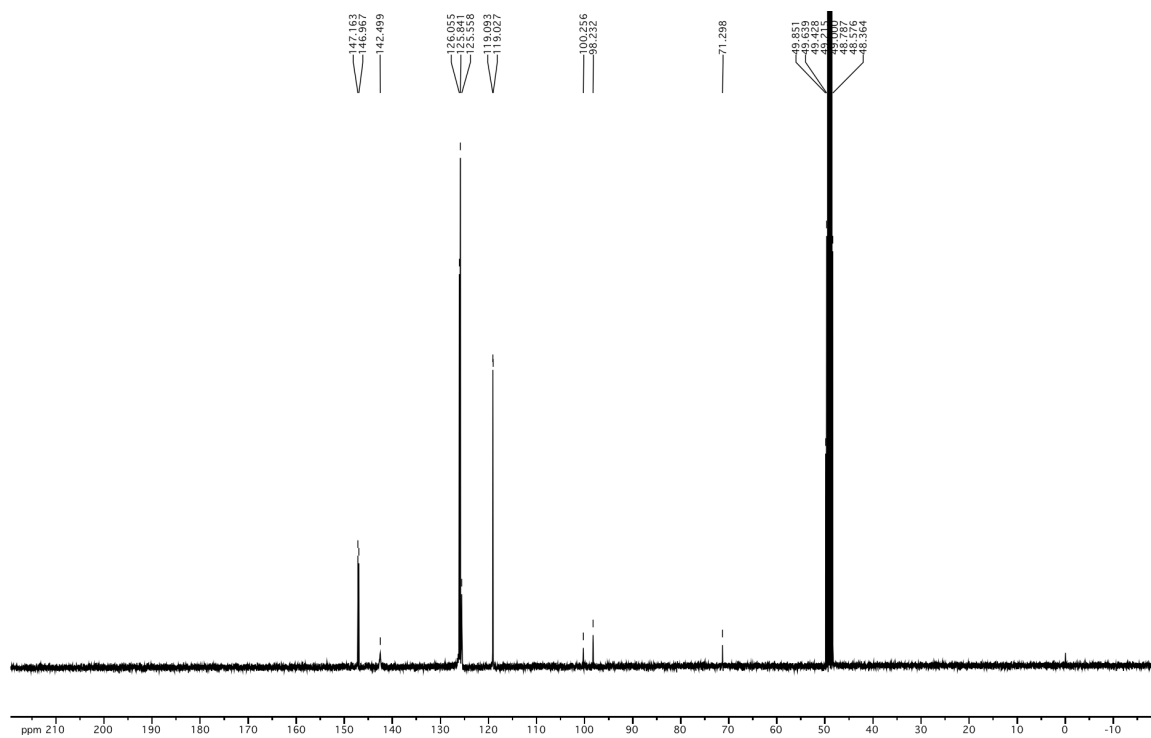


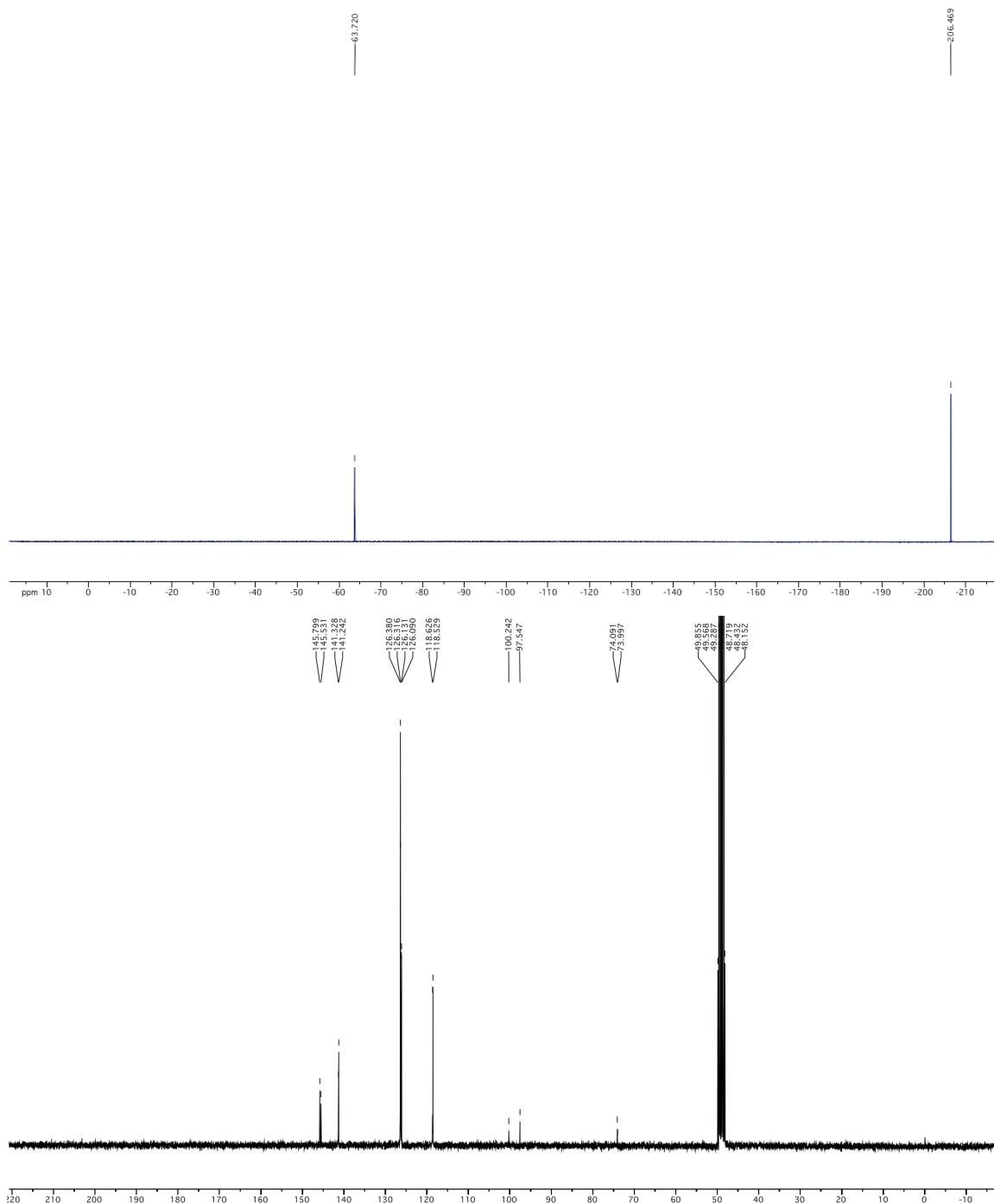
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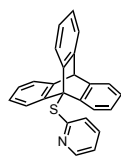




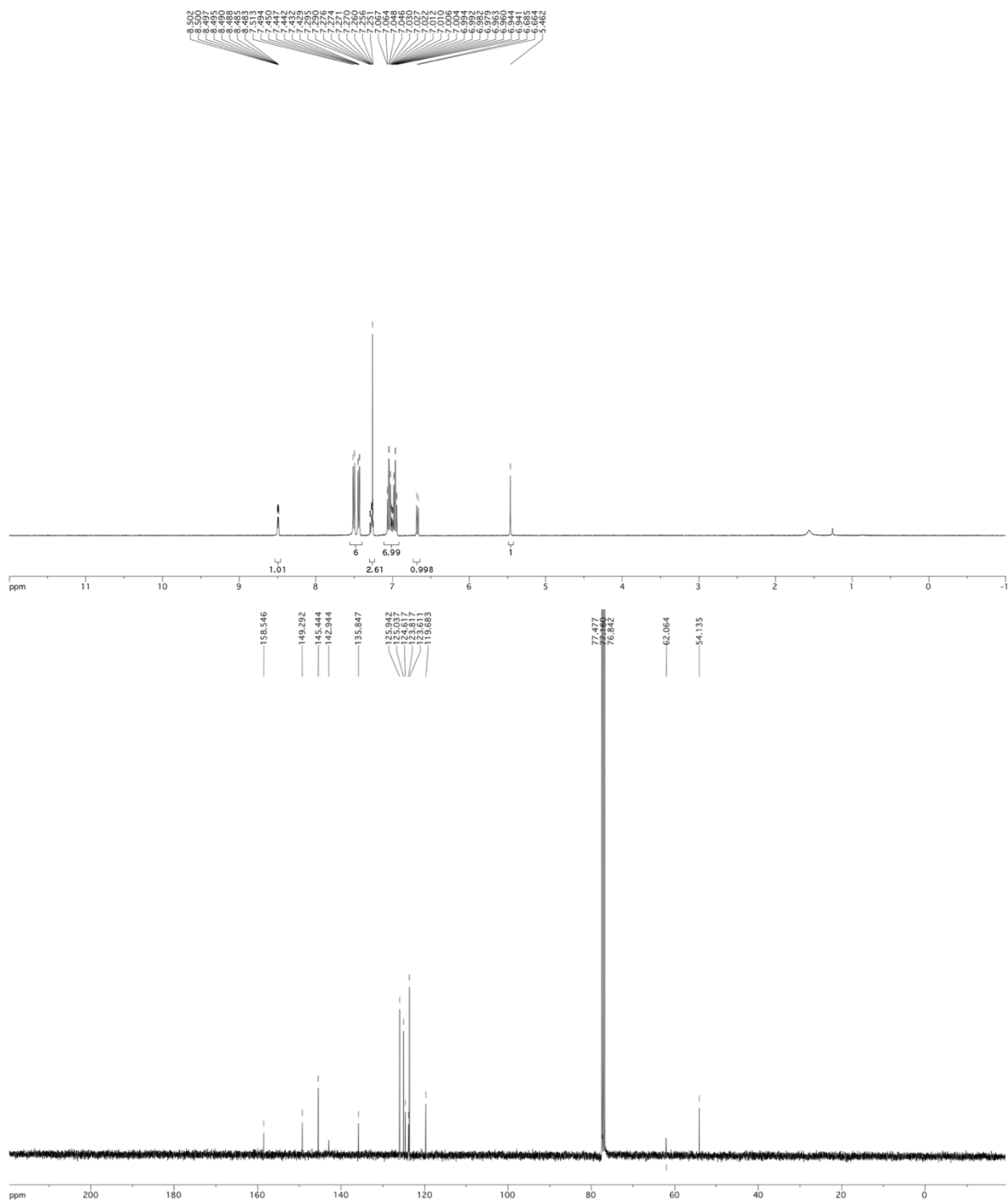


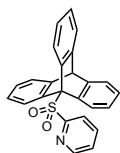


B.5 The hydrogen atom transfer reactivity of sulfinic acids

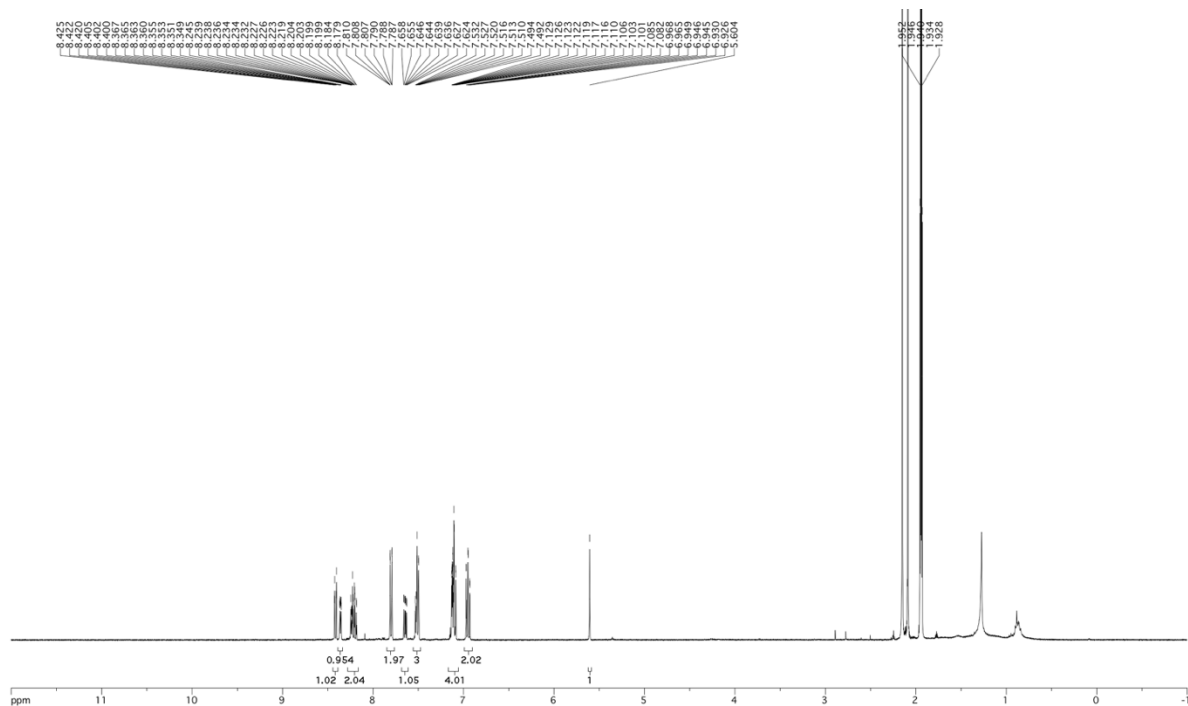


in CDCl_3

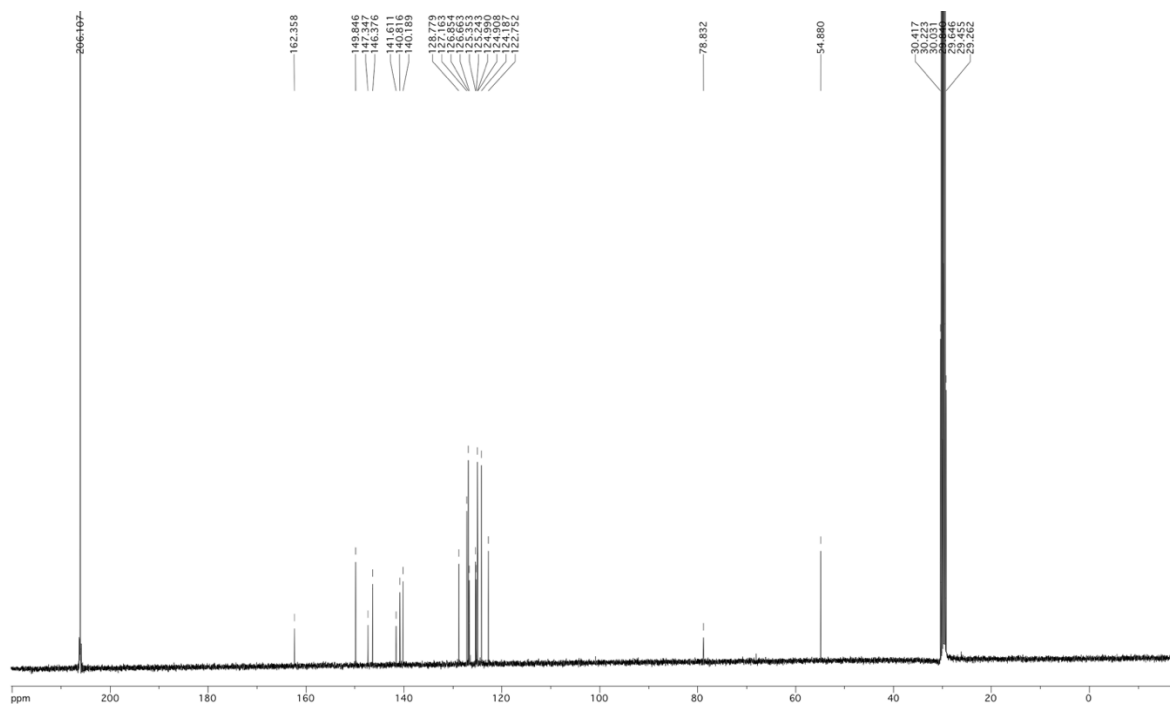


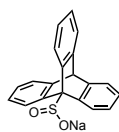


in CD_3CN

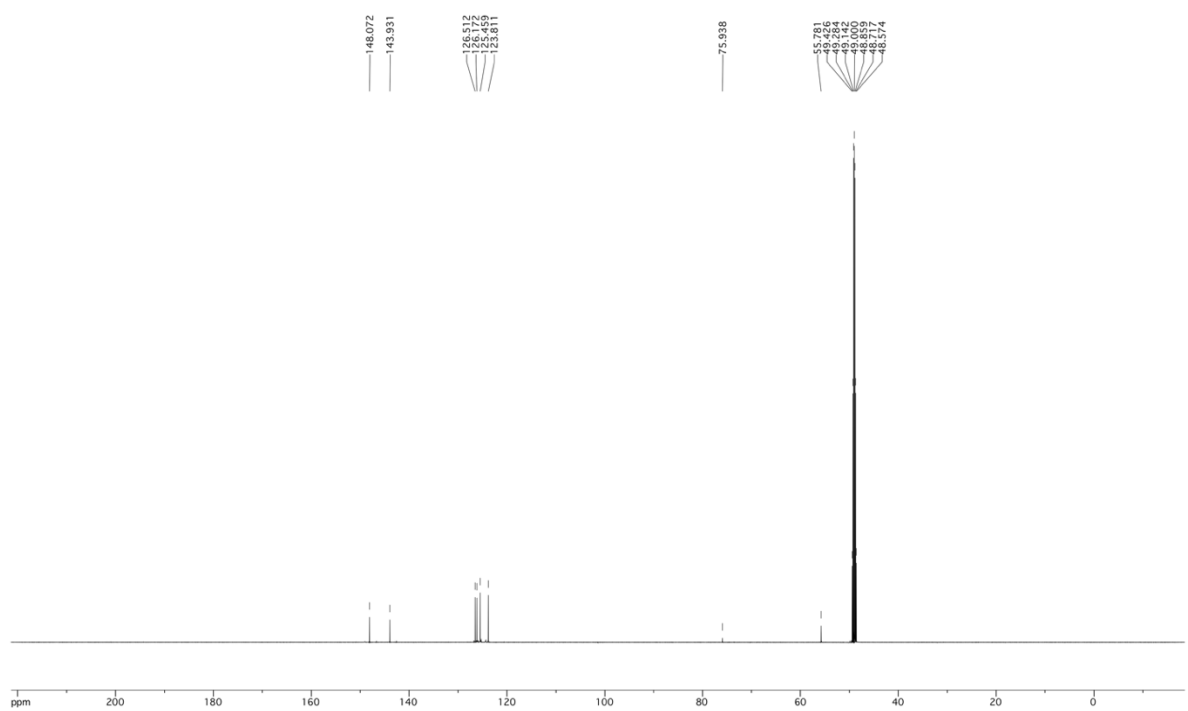
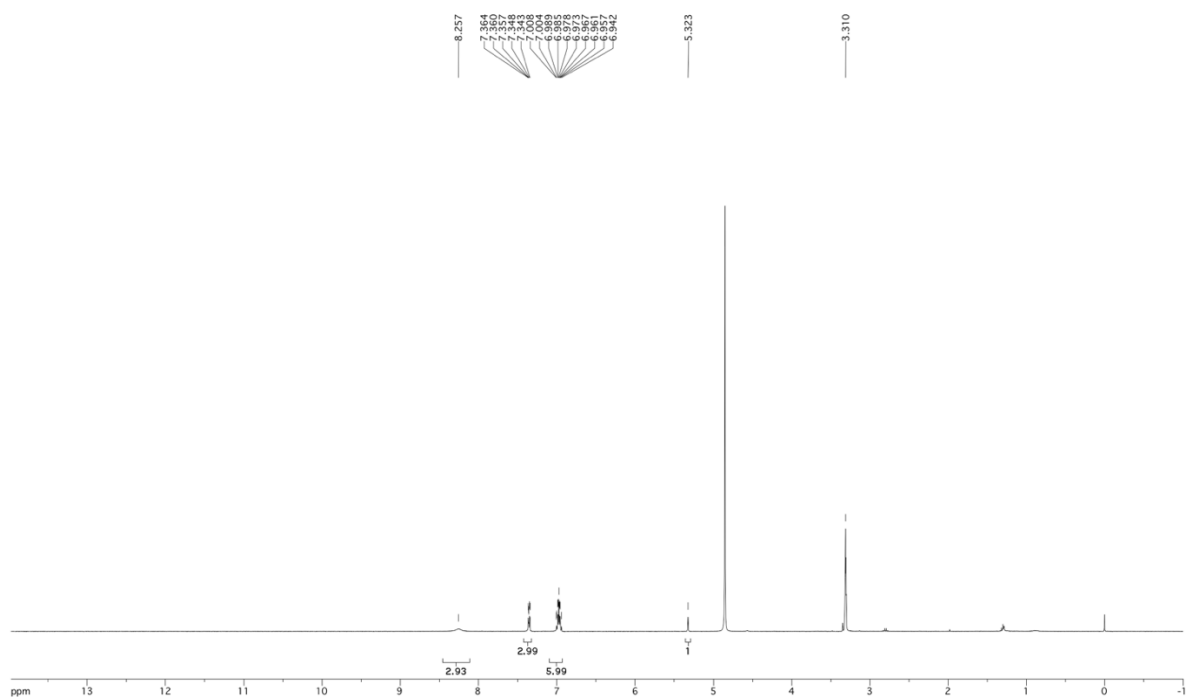


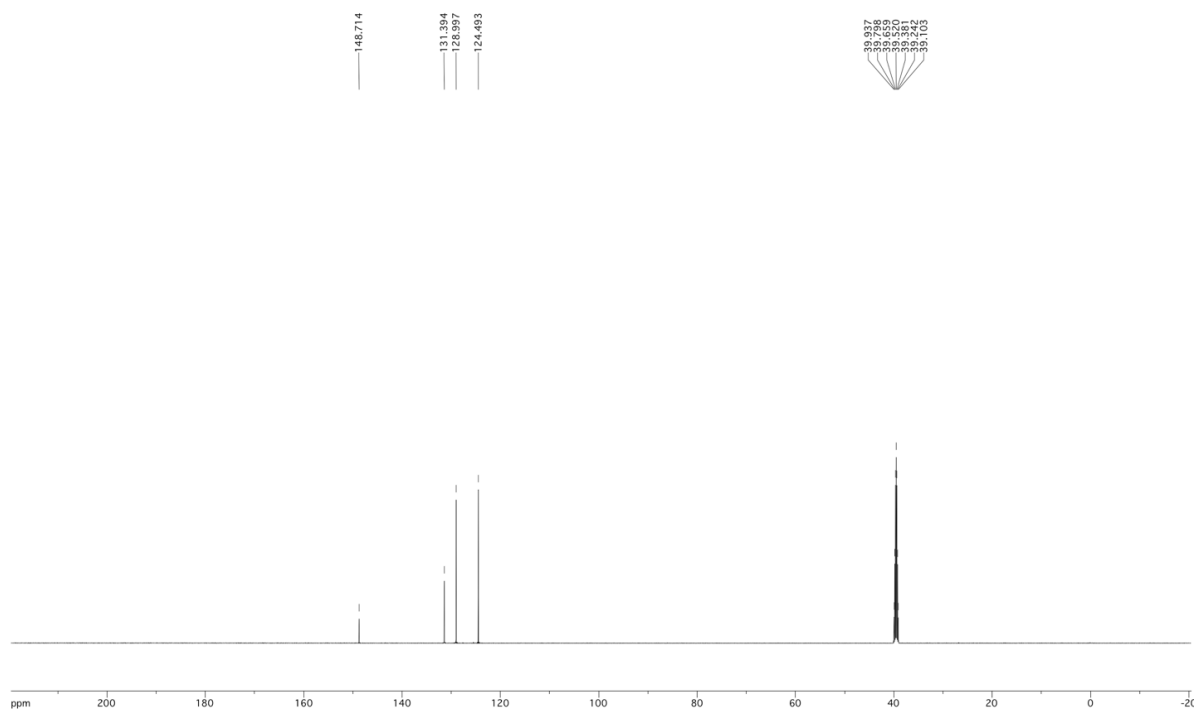
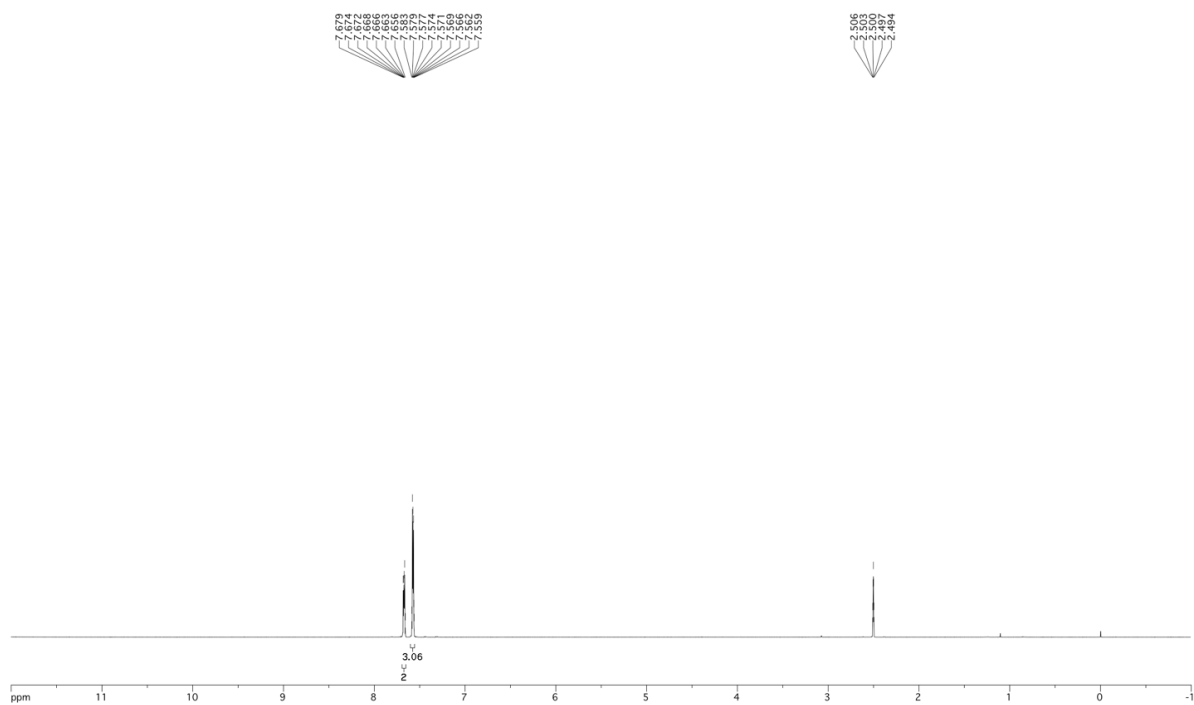
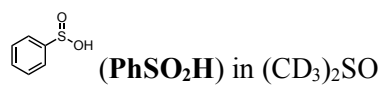
in $(\text{CD}_3)_2\text{CO}$

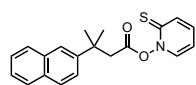




(TrpSO₂Na) in CD₃OD







in CDCl₃

