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MECHANISMS OF BASE-CATALYSED H-D EXCHANGE REACTIONS

by

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Thesis presented to the School of
Graduate Studies of the University
of Ottawa as partial fulfillment
of the requirements for the degree
of Doctor of Philosophy in
Chemistry

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ABSTRACT

Part I

Two sulfoxides were chosen for the study of internal return.

- a) The conformationally rigid biaryl sulfoxide 3 in t-butanol and methanol and b) the conformationally mobile benzyl methyl sulfoxide in water.

The effect of dicyclohexyl-18-crown-6, a cyclic polyether known to complex potassium ion effectively, on the selectivity of potassium alkoxide-catalyzed exchanges of the four α protons in 3 in t-butanol and methanol was investigated. The stereoselectivity was altered in both solvents on the addition of crown ether, indicating the involvement of potassium ion in designing the stereoselectivity. Crown ether also affected the rate of exchange of a particular proton in a different way in different solvents, indicating a variable involvement of solvent in the exchange process. The primary kinetic isotope effects k^H/k^T and k^H/k^D involving exchanges of the α protons were measured in t-butanol and methanol respectively. The presence of internal return was revealed by the low isotope effects. Both the investigation of the effects of potassium ion complexing agent and the primary isotope effects showed that the relative rates of exchange do not reflect 'pure' carbanion stability. A mechanistic scheme has been postulated for the exchange reactions of the α protons.

A quantitative assessment of the amount of internal return was made for the exchanges of each diastereotopic methylene proton of benzyl methyl sulfoxide. The amount of internal return was found to be small having a virtually negligible effect on the experimental relative rates. Thus, information obtained from kinetics regarding the stability of the anionic intermediates is reliable in the case of benzyl methyl sulfoxide exchanging in aqueous medium.

Part II

Measurements of the rates of exchange of the four benzylic protons of the conformationally rigid nitrosamine, N-nitroso-6,7-dihydro-1,11-dimethyl-5H-dibenz[c,e]azepine, were made in t-butanol-O-d containing potassium t-butoxide at several base concentrations. Each pseudo-axial proton exchanged one hundred fold faster than its geminal partner (pseudo-equatorial), likely as a result of a stereo-electronic effect. Each syn proton exchanged one thousand fold faster than the anti proton in the same biaryl environment. The lack of any significant effect of added potassium ion complexing agent and the similar syn selectivity observed with tetramethylammonium hydroxide as a base indicate lack of involvement of the counterion. The preferential syn exchange was rationalized with the symmetry properties of the highest occupied molecular orbital (HOMO) of the anionic intermediate for which an attractive interaction exists between the terminal atoms of the four atom π system, in resemblance to the butadiene dianion. This explanation is similar to that derived by Epiotis and by Hoffman and Olofson to account for the greater stability of many cis over trans dihalo- and diacyloxy-olefins.

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PART I

INVESTIGATION OF THE EXCHANGES OF 1,11-DIMETHYL-
5,7-DIHYDRODIBENZ[c,e]THIEPIN S-OXIDE AND
BENZYL METHYL SULFOXIDE

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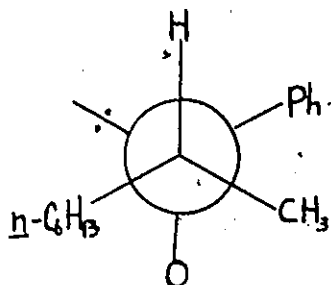
INTRODUCTION

A. Historical Development

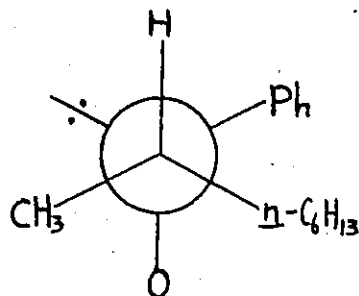
Studies of α -sulfinyl carbanions received little attention until 1965 when Wolfe and co-workers¹ reported a stereoselective hydrogen-deuterium exchange reaction of benzyl methyl sulfoxide. The benzylic methylene protons were found to differ in their relative rates of base-catalyzed exchange by 16:1 in D₂O at 15°C. This, of course, inferred that the molecule had given rise to an asymmetric carbanion which contradicted the conclusion previously presented by Cram and Pine² that α -sulfinyl carbanions were intrinsically symmetric. Cram and Pine based their conclusion on the base-catalyzed exchanges of optically active 2-octyl phenyl sulfoxide by studying the relative rates of exchange (k_e) vs racemization (k_α) at the 2 position of the sulfoxide and the stereochemical results were expressed in terms of a k_e/k_α ratio. In a proton exchange reaction, k_e/k_α approaching infinity indicates retention, complete racemization is expressed by a ratio equal to one, whereas complete inversion requires a ratio of 0.5. In *t*-butanol-0-d with potassium *t*-butoxide as base, the sulfoxide 1 (R,S) had $k_e/k_\alpha = 1.2$ and 2 (S,S) had $k_e/k_\alpha = 3.6$.* In dimethyl sulfoxide 1.2M in methanol-0-d with potassium methoxide as base, 1 had $k_e/k_\alpha = 0.6$ and 2 had $k_e/k_\alpha = 1.4$. Based on the low values of k_e/k_α observed, Cram therefore concluded that the sulfinyl sulfur provided only a slight tendency to maintain asymmetry at the carbanion. The contrasting behaviour of benzyl

*The structural assignments for 1 and 2 result from the work of Mislow et al (J. Amer. Chem. Soc., 87, 1958 (1965)).

methyl sulfoxide thus stimulated further work.



1 (R,S)



2 (S,S)

Following the report by Wolfe and co-workers, several other reports describing stereoselective exchanges in acyclic sulfoxides also appeared³. In order to gain further insight as to the stereochemical behaviours of α -sulfinyl carbanions, Rauk, Wolfe and Csizmadia⁴ carried out extensive ab initio MO calculations on the hypothetical hydrogen methyl sulfinyl carbanion ($\overline{\text{C}}\text{H}_2\text{-S(O)H}$). Calculation of the energy of this species as a function of rotation about the C-S bond showed two maxima and two minima (see Figure 1). The most stable conformation was found to be the one in which the carbanion is gauche to both the S-O bond and the sulfur lone-pair and maintains considerable pyramidal character (the H-C-H angle was 115°).

The predictions of this theory were tested in several conformationally fixed sulfoxides by analysis of the kinetic data as a function of stereochemistry. In the studies of the bridged

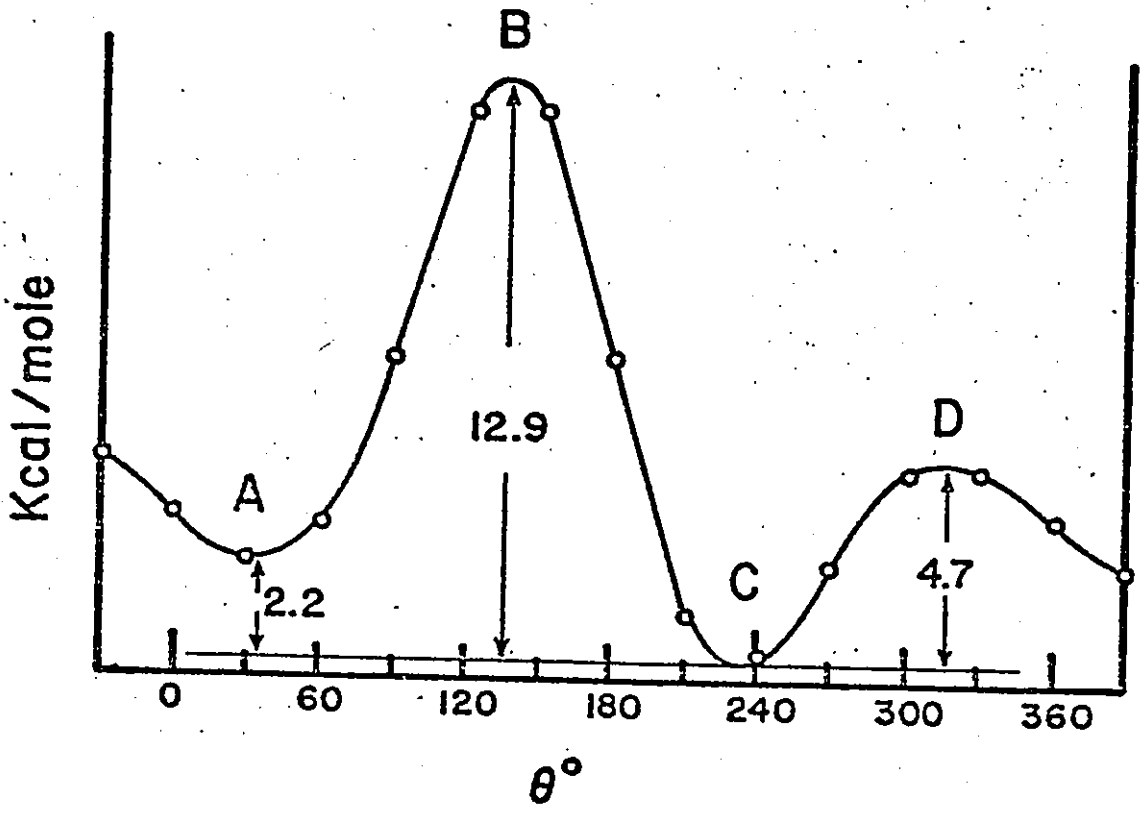
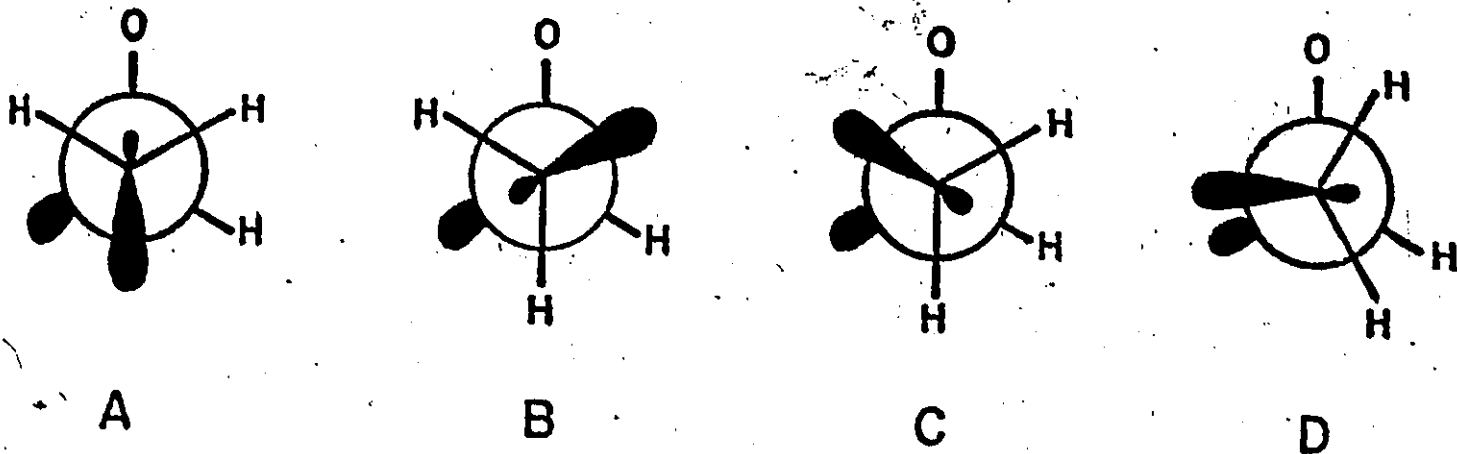


Figure 1. The variation in carbanion stability as a function of θ , the rotational angle about the C-S bond.

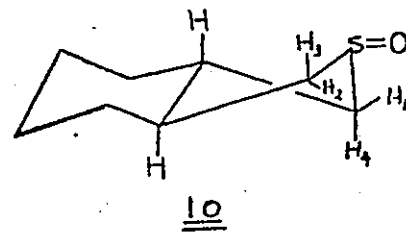
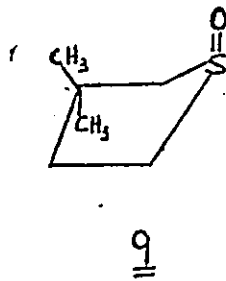
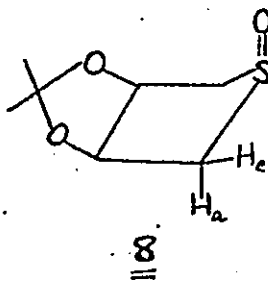
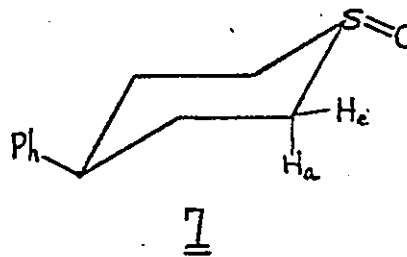
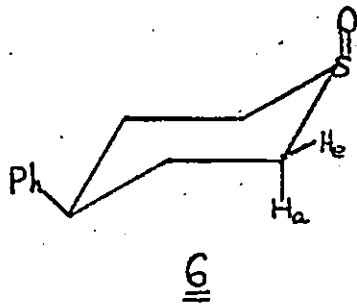
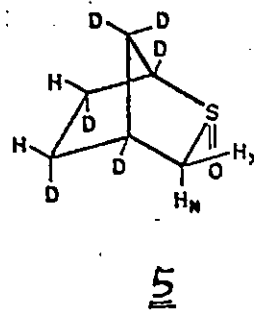
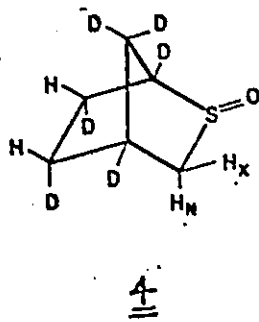
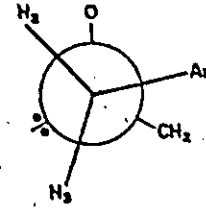
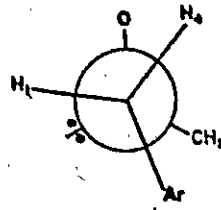
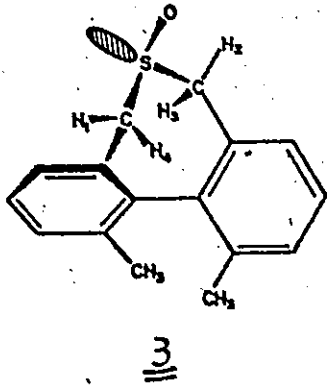


Figure 2

Some conformationally fixed cyclic sulfoxides 3-5 and biased sulfoxides 6-10.

biaryl sulfoxide 3 and the 4-phenylthiane S-oxides 6 and 7, appreciable solvent effects were noted. For example, in sulfoxide 3, the two protons (i.e., H₁ and H₂) which differ by only 40° in their dihedral angular orientation with respect to the sulfoxide group had their rates differ by 200 fold in methanolic sodium methoxide but by 1100 fold in t-butanol-0-d-potassium t-butoxide. Moreover, the proton trans to the lone-pair on sulfur (H₄) exchanged four times faster than that trans to the S-O bond (H₃) in t-butanol-0-d, but 250 times slower in methanol-d₄^{5b}. In 6 and 7, considerable stereoselectivity was found in water and methanol but not in t-butanol⁶.

Studies on the exo and endo isomers of 2-thiabicyclo [2.2.1]heptane S-oxide, i.e., 4 and 5, showed that formation of the carbanion eclipsed with the lone-pair on sulfur was much slower than that eclipsed with oxygen. This result together with the ratio H₁/H₂ in 3 indicated that selectivity was very sensitive to a change in θ .

Inspection of the data collected in Table 1 showed that the orders of carbanion stability were in severe contrast to the theoretical predictions based on the ab initio MO calculations. The lack of agreement was concluded^{5b} to be due to the strong solvation effects which were not included in the calculations. In other words, the relative stabilities of α -sulfinyl carbanions in solution are greatly dependent on environmental factors other than the orientation of the developing anion with respect to the asymmetric sulfur atom.

A more striking solvent effect on the stereochemical course of the carbanion was observed with benzyl methyl sulfoxide⁷.

Table 1

Rates of Exchange of α Protons in Conformationally Rigid Sulfoxides

Compound	Solvent, M^+	Result	Order of carbanion stability	Ref
3	\underline{t} -BuOD, K^+	$H_1/H_2 = 1/1100$ $H_3/H_4 = 1/4$	$B > A$	5
3	CD_3OD , Na^+	$H_1/H_2 = 1/200$ $H_3/H_4 = 250/1$	$A > B$	5
4	CD_3OD , Na^+	$H_X/H_N \geq 12/1$		5
5	CD_3OD , Na^+	$H_X/H_N = 1/2.5$		5
6 and 7	D_2O , Na^+ or MeOD, Na^+		$A > C > B$	6
6 and 7	\underline{t} -BuOD, Na^+		$A \sim C \sim B$	6
10	D_2O , Na^+	$H_2 > H_1$ $H_3 > H_4$		11
theory	gas phase		$C > A > B$	4

The relative rates of exchange of the diastereotopic methylene protons were found to vary from 14:1 ($D_2O/NaOD$) to 0.5:1 ($t\text{-BuOD}/t\text{BuONa}$). Experiments on quenching α -lithio benzyl methyl sulfoxide with D_2O gave the same diastereomers in ratio ranging from 1.7:1 (DMSO) to 0.0651 (T.H.F.).

Apart from the strong solvation effect, ion-pairing has also been shown to be an important factor in determining stereoselectivity⁸. For example, quenching of the lithium derivative of benzyl methyl sulfoxide with methyl iodide in THF gave a product of diastereomeric ratio of 19:1^{8b}; on the addition of the macrobicyclic diamine polyether 21, a reagent known to complex with Li^+ effectively, the selectivity dropped to 5:1. The lithio derivative, which existed as intimate ion-pairs or aggregates in T.H.F., was changed to cryptate separated ion-pairs in the presence of polyether (2,2,2), each of the two species of the lithio compound had different stereoselectivity towards a common electrophile.

Up to the present stage it has thus become obvious that the solvent and the ion-pairing effects should be included along with any consideration of conformational effects on the stability of α -sulfinyl carbanions.

B. Aim of This Research

Most of the above experimental investigations into the structure of α -sulfinyl carbanions have utilized base-catalyzed hydrogen exchange of diastereotopic methylene protons adjacent to a

sulfinyl group as the principal technique. Recently⁹ Wolfe and co-workers pointed out that this technique involved a kinetic model which assumed retention of configuration in all subsequent steps after abstraction of proton. Since exchange with inversion of configuration¹⁰ is known, a knowledge of the stereochemical fate of the carbanion is necessary for a proper analysis of the kinetic data in terms of carbanion stability. However, Fraser⁵ was able to show by logical arguments that lack of such knowledge in no way invalidated the kinetic method of determining the relative carbanion stabilities. The argument was based on the Brønsted linear free-energy relationship which requires each transition state free energy to resemble that of the carbanion being formed. For the more rapidly exchanging hydrogen, a carbanion is formed and consumed with high selectivity. The only reasonable process for this exchange is one involving retention of configuration; if inversion were the course, no stereoselectivity could be observed. For the slower proton, although the stereochemistry of the exchange cannot be determined, it was proved by consideration of steady-state rate equations that the relative amounts of deuterated products of the two diastereomers will be determined solely by the relative heights of the two corresponding transition states. However, if for the faster proton the rate of solvent reorganization for exchange (k_e) is very slow, two consequences could result and thus invalidate the above analysis: (1) inversion to a less stable carbanion (k_{α}) followed by deuteration could be a favoured path, this would cause the exchange rates for both protons to be equal in spite of unequal carbanion

stabilities, (2) collapse of the carbanion back to the starting material (called internal return) could be present thus leading to a slower rate of deuteration and giving rise to a false selectivity. It is interesting to note that this false selectivity would arise only if the amounts of internal return differ markedly for the two diastereotopic proton exchange processes.

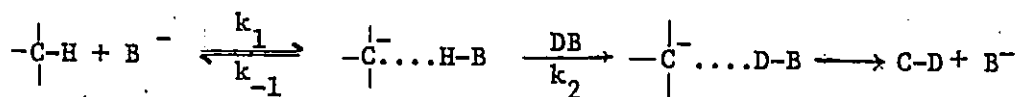
In a recent study of several cyclic-S-oxide¹¹ derivatives, the sulfoxides 6, 8 and 9 which have the same angular relation of the α -methylene H's to the S-O bond were compared for their H-D exchange in D₂O. It was found that considerable selectivity of the same order was observed in 6 and 8 in which the axial proton (trans to oxygen) reacted faster than the equatorial one (gauche to oxygen and lone pair). No selectivity, however, was observed with 9. For the sulfoxide 10 in D₂O, the proton cis to oxygen was found to be more reactive within the equatorial pair ($H_1 < H_2$) but the reverse is found in the axial pair ($H_3 > H_4$). These results showed that pairs of diastereotopic protons of the same orientation with respect to the sulfur function exhibited different selectivity patterns even in the same solvent, D₂O, which minimizes ion-pairing. These ambiguous data added to that previously accumulated on the H-D exchanges in other sulfoxide systems are summarized in Table 1 and emphasize the need to test for the presence of internal return in an exchange reaction. In order to achieve the aim, we have chosen for studies of internal return (a) the base-catalyzed exchange of each methylene proton of the conformationally mobile benzyl methyl sulfoxide in water and for comparison (b) the

exchange of the conformationally rigid biaryl sulfoxide 3 in *t*-butanol and methanol. It was our hope that these studies would contribute to a better understanding of the general problem of stereoselectivity in isotopic exchanges alpha to the sulfinyl group.

C. Methods of Detecting Internal Return

1. Introduction

Based on the Brønsted free-energy relationship between the kinetic and thermodynamic acidities, it has become a common practice to use the rates of hydrogen isotope exchange as a measure of carbanion stability. It has been clear for some time, however, that interpretation of the kinetic data can be made difficult by the existence of internal return. The pioneering research of Cram and co-workers¹² first established the presence of internal return in an isotopic exchange reaction involving carbanion intermediates. For an isotopic exchange process formulated in Scheme 1, the step of carbanion formation, k_1 , which involves cleavage of a covalent bond is undoubtedly much lower valued than k_{-1} or k_2 which is a



Scheme 1

diffusion type of step, therefore the carbanion formed is consumed as soon as it is formed and the steady-state approximation applies, $k_{\text{expt}} = k_1 k_2 / (k_{-1} + k_2)$ where k_{expt} is the observed rate constant. If the rate of the back reaction governed by k_{-1} is very slow,

i.e., $k_2 \gg k_{-1}$, then $k_{\text{expt.}} = k_1$ and the observed rate reflects the ease of carbanion formation. In this case the Brønsted correlation between kinetic and thermodynamic acidities should hold. When the rate of solvent reorganization necessary for exchange (k_2) is very slow, then reprotonation of the carbanion back to the starting material (k_{-1}) becomes highly favored and $k_{\text{expt.}} = k_2 k_1 / k_{-1} = k_2 K$ where $K = k_1 / k_{-1}$, in which case the rate-determining step is not the rate of carbanion formation but rather the rate of exchange of solvent molecules at the carbanion site. The kinetic acidity therefore fails to be a measure of carbanion stability.

2. Qualitative Test for Internal Return

For a hydrogen isotopic exchange reaction, the difference in rates between the breaking of a C-H bond and a C-D bond, where C, H and D are carbon, hydrogen and deuterium, respectively, is determined by the difference in the activation energy ΔE^\ddagger of the two ionization reactions and the kinetic isotope effect is expressed as $k^H/k^D = \exp\{\Delta(\Delta E^\ddagger)/RT\}$. The stretching vibration of a C-H bond is quantized with a frequency ν_H and an associated zero-point vibrational energy of $1/2 h\nu_H$. Since the frequency ν depends upon the isotopic mass, the difference in zero-point energy of the two isotopic bonds is $1/2 h(\nu_H - \nu_D)$. In the case of the transfer of the hydrogen isotopic atom L from C-L to another atom B via a linear transition state ^{13a} $\overset{+}{\text{C}} \text{---} \overset{+}{\text{L}} \text{---} \overset{+}{\text{B}}$, the symmetrical stretching vibration does not involve any movement of L. Consequently the symmetrical vibration frequency ν^\ddagger does not depend on the mass of L and

$1/2 h\nu_H^\ddagger - 1/2 h\nu_D^\ddagger = 0$. Only $1/2 h(\nu_H - \nu_D)$, the net difference in activation energy $\Delta(\Delta E^\ddagger)$, is reflected in the isotope effect (Figure 3a). The isotope effect k^H/k^D for a reaction involving cleavage of an aliphatic C-H bond was calculated to be 6.2^{13b} at 298°K .

The isotope effect of an exchange reaction in which $k_{-1} \gg k_2$ is expressed by the equation

$$k^H/k^D = k_2^H/k_2^D \times K^H/K^D$$

The term k_2^H/k_2^D deals with processes in which no covalent bonds are made or broken, and value close to unity is expected. The term K^H/K^D should also be close to unity since the isotope effect of k_1 is substantially equal to k_{-1} . Thus an observed k^H/k^D close to 1 indicates an appreciable amount of internal return.

Several examples of low isotope effects are collected in Table 2 and were interpreted on the basis of $k_{-1} \gg k_2$.

3. Quantitative Assessment of Internal Return

In the linear transition state C---L---B for a proton transfer process, if L is attached to one of the two atoms C or B more strongly than the other, then the 'symmetric' stretching vibration involves motion of the L atom and the stretching frequency will be dependent on the mass L. This will give rise to a difference in

Table 2
 Low Primary Isotope Effects due to the Presence of
 Internal Return

Substrate	Base	Solvent	Primary Isotope Effect	Ref
toluene	<i>t</i> -BuOK	BMSO	0.6 (k^H/k^D)	14
thiophene	<i>t</i> -BuOK	DMSO	0.8 (k^D/k^T)	15
triphenylmethane	MeONa	MeOH	1.77 (k^H/k^T)	16
2-octyl phenyl sulfone	<i>t</i> -BuOK	<i>t</i> -BuOD	~ 1 (k^H/k^D)	17

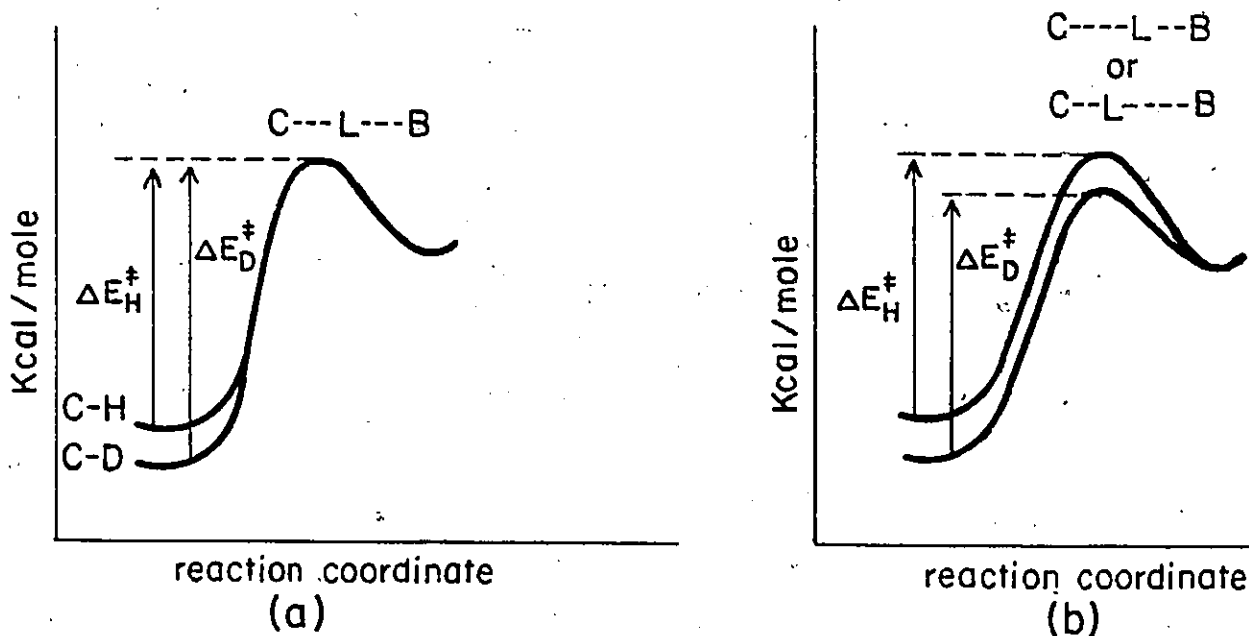


Figure 3. Zero-point energies and hydrogen-isotope effect for a proton-transfer reaction (a) for a symmetrical transition state and (b) for an unsymmetrical transition state.

the zero-point energies of the two transition states for the two isotopes, which may partly or completely balance that of the reactants (Figure 3b). Consequently the kinetic isotope effect will be lower than the maximum value of 6.2 even though no internal return is involved. The possibility that a low primary isotope effect may result from an unsymmetrical transition state rather than from the incursion of substantial internal return emphasizes the need for a quantitative assessment of the amount of internal return involved in an exchange reaction.

In the absence of internal return, the tritium, deuterium and hydrogen isotope effects of a base-catalyzed exchange reaction are interrelated by the equation 1 developed by Swain et.al. The value of x is 2.26 by Swain-Schaad treatment¹⁸ and 2.344 by Streitweiser treatment¹⁹ in which the assumption by Swain that reduced masses can be approximated by the masses of the hydrogen isotopes were no longer made and instead the reduced masses were calculated for the carbon-isotope bonds involved.

$$k^H/k^D = (k^D/k^T)^x \tag{1}$$
$$k^H/k^T = (k^D/k^T)^{x+1} = (k^H/k^D)^{(x+1)/x}$$

When by use of equation 1, the experimental isotope effects k^H/k^T and k^D/k^T for an exchange reaction give rise to an x value smaller than 2.344, the presence of internal return is indicated.

A quantitative determination of internal return has recently been achieved by Streitweiser's group¹⁶ for several base-

catalyzed exchange reactions. Assuming the solvent isotope effect on the primary kinetic isotope effect is negligible, equation 2 is derived in which a^T which is the ratio k_{-1}^T/k_2 can be determined from the experimentally determined quantities A and B

$$A + (A-B)a^T = [1 - (B^{1/(x+1)} - 1)a^T]^{x+1} \quad (2)$$

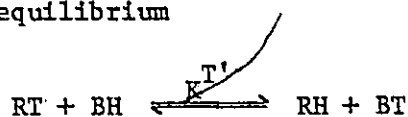
where

$$A = (k_{\text{expt}}^D/k_{\text{expt}}^T)^{x+1} / (k_{\text{expt}}^H/k_{\text{expt}}^T)$$

and

$$B = (k_{\text{expt}}^D/k_{\text{expt}}^T)^{x+1} K^T/K^H$$

That k_2 is a diffusion step and therefore has no isotope effect implies that the carbanion is only hydrogen-bonded to the solvent molecule BH (Scheme 1), and thus the equilibrium $K^H = k_1^H/k_{-1}^H$ is determined by the relative energies of B-H and C-H. Therefore, $K^T/K^H = K^{T'}$ for the equilibrium



where $K^{T'}$ is experimentally determinable by measuring the relative amount of tritium content in the solvent and that incorporated in the substrate at equilibrium.

With a^T and $K^{T'}$ determined as described above, one can now correct for internal return and find the isotope effect for the primary step by equation 3

$$k_1^T/k_1^H = k_{\text{expt}}^T/k_{\text{expt}}^H + a^T (k_{\text{expt}}^T/k_{\text{expt}}^H - K^{T'}) \quad (3)$$

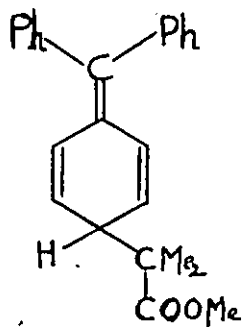
which is derived from the experimental isotope effect given by

$$k_{\text{expt}}^T / k_{\text{expt}}^H = \frac{k_1^T (k_{-1}^H + k_2)}{k_1^H (k_{-1}^T + k_2)}$$

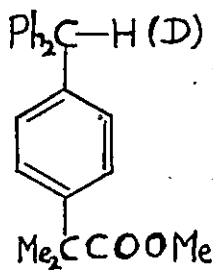
according to Scheme 1. Other isotope effects for the primary step, i.e., k_1^H/k_1^D and k_1^D/k_1^T , are obtained from the determined k_1^T/k_1^H by using equation 1.

a^H is derived from a^T by the relation $a^H = a^T K^T k_1^H / k_1^T$ which is obtained from $K^{T'} = K^T / K^H = (k_1^T / k_{-1}^T) / (k_1^H / k_{-1}^H)$ and $a^T / a^H = k_{-1}^T / k_{-1}^H$. Similarly a^D can be obtained from a^T .

The consistency of Streitweiser's results in several cases indicates the approach to be reliable. For example, $a^{H^{16}}$ was found to have a value of 1.44 (i.e., 59% internal return for hydrogen exchange) in the exchange of triphenylmethane in methanolic sodium methoxide, the result is comparable with the 46-7% intramolecularity found in the rearrangement of 11 to 12²⁰ in the same solvent-base system. In both cases the triarylmethyl anion is involved as an intermediate.




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Another example is given by the base-catalyzed exchange of fluorene in methanolic sodium methoxide. The H, D and T exchanges for fluorene and 9-methylfluorene agreed approximately with expectation from a Swain-Schaad type of treatment. The x values were found to be $2.0 \pm .2^{19}$ for the fluorene at 25° and 9-methylfluorene at 45° , indicating that internal return was of minor importance. When equation 3 derived by Streitweiser was applied to deduce a^T for these compounds, the isotope effects reported previously yielded a^T values of 0.016 ± 0.006 for fluorene at 25°C and $0.024 \pm .022^{16}$ for methylfluorene at 45°C . The results obtained from both treatments are virtually consistent with each other. Moreover, their k^H/k^D of values 6.3 obtained from k^D/k^T by equation 1 are in the normal high range for substantial proton transfer at the transition state, which will minimize internal return^{13b}.

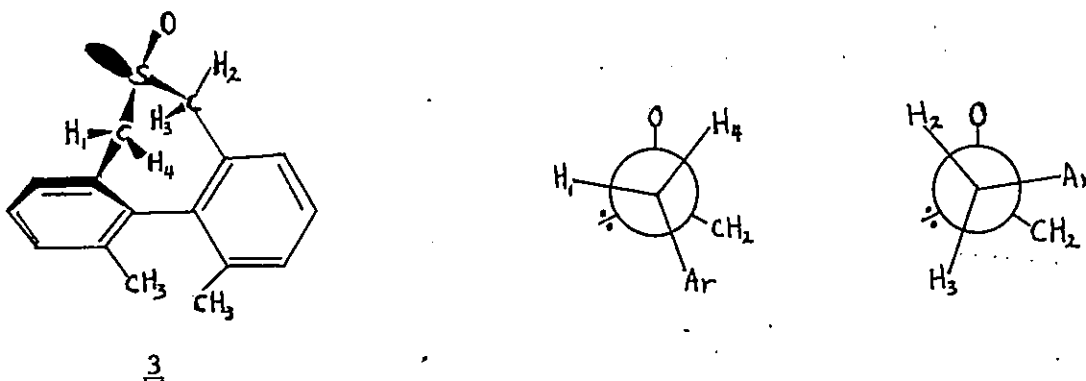


STUDIES OF ISOTOPIC EXCHANGES IN THE BRIDGED BIARYL
SULFOXIDE 3 AND BENZYL METHYL SULFOXIDE

A. Stereochemical Assignments

1. The Bridged Biaryl Sulfoxide 3

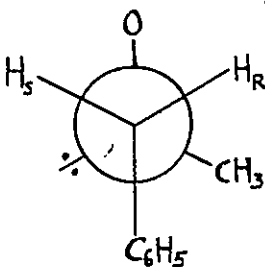
The sulfoxide 3 possesses four magnetically nonequivalent benzylic protons owing to the restricted rotation about the central biaryl bond and the presence of the pseudo asymmetric sulfoxide group. In the 100 MHz n.m.r. spectrum of 3 in CDCl_3 , four doublets appear for the four alpha protons at δ 4.119 (H_1), 3.629 (H_2), 3.289 (H_3) and 2.776 (H_4). The inequality in germinal coupling constants $J_{1,4} = -11.4$ Hz and $J_{2,3} = -13.7$ Hz identified the diastereotopic pairs. Individual proton assignments have been previously determined by nuclear Overhauser effects²¹ in conjunction with the known correlation between the configuration at sulfur and geminal coupling constant between the α protons²². The dihedral angular relationships of the four benzylic protons with respect to the sulfoxide group, as measured on a Dreiding model, are depicted in Figure 2.



(taken from Figure 2)

2. Benzyl Methyl Sulfoxide

Benzyl methyl sulfoxide gives well-resolved AB spectra (n.m.r.) for the diastereotopic protons in DMSO-d₆ or CDCl₃. In CDCl₃, $\delta_R = 3.91$, $\delta_S = 4.05$, $J_{RS} = 13$ Hz; in DMSO-d₆, $\delta_S = 3.92$, $\delta_R = 4.08$, $J_{RS} = 12.6$ Hz where the subscripts R and S refer to the pro-R in S and pro-S in S protons respectively. For simplification purposes we will hereafter refer to the pro-R in S proton as H_R proton and the pro S in S proton as H_S. The assignments of these two protons have been established previously²³.



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B. Preparation of Labelled Substrates for the Studies of Primary Isotope Effects

1. Preparation of Samples Containing Tritium in Place of H₁ and H₂ in the Bridged Biary Sulfoxide 3

Because of the extreme inertness of H₁ in t-butanol-0-d-potassium t-butoxide medium (relative rates are 1:1100:300:1300^{5b} for H₁:H₂:H₃:H₄), tritiation in place of H₁ was achieved in the following manner: complete tritiation in place of all four α protons to the

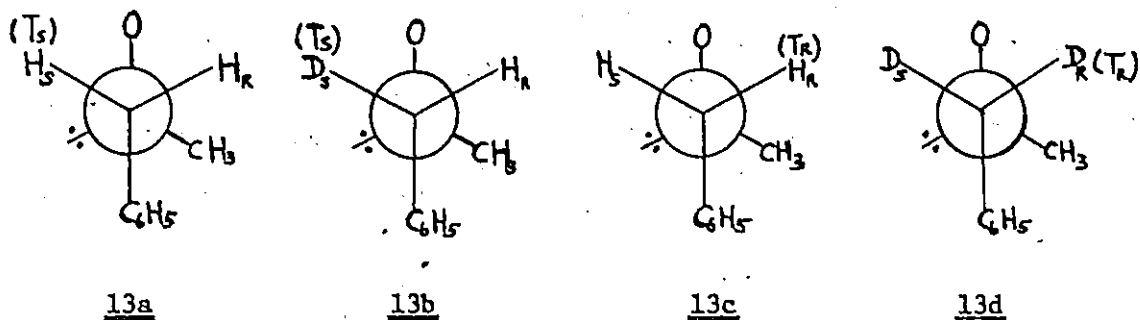
equilibrium isotopic distribution, (the equilibrium distribution constant K^T was approximately 1.2 with the tritium content more concentrated in the solvent than in the sulfoxide (see Experimental)), followed by detritiation at the three more labile sites.

Tritiation in place of H_2 was achieved by transferring tritium from position 1 to 2 by inversion of the configuration of the sulfur. The inversion was achieved by reaction of the sulfoxide with Meerwein's reagent, followed by hydrolysis of the ethoxysulfonium salts²⁴. The sulfoxide containing tritium in place of H_1 was mixed with the sulfoxide specifically deuterated in place of H_3 in a 1.8:1 proportion. From careful n.m.r. measurements of the deuterium content at H_3 and H_4 before and after the inversion, the percent of inversion was estimated to be $89 \pm 3\%$.

2. Specific Labelling of the Diastereotopic Protons in Benzyl Methyl Sulfoxide

In order to determine the amount of internal return in the exchanges of the two diastereotopic protons in benzyl methyl sulfoxide in water, four samples, i.e., 13a, 13b, 13c and 13d in which brackets indicate the site of the tritium, were prepared for kinetic runs in which the primary isotope effects k^H/k^T and k^D/k^T were determined.

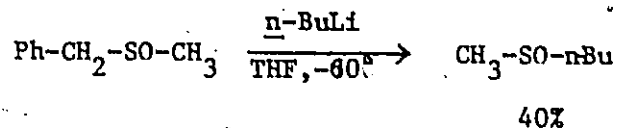
All four samples were labelled with tritiated water, the tritium content of which was adjusted in each case to provide a specific activity of 10^5 dpm/mole in the resultant sample.



a) Preparation of Samples 13a and 13b

Previous results have shown that specific labelling in place of H_S can be achieved by quenching the α -lithio derivative in T.H.F. at -60°C with water containing the desired label. When D_2O was used as the quenching agent, the SS (RR) diastereomer was formed in large excess (94:6) relative to the RS (SR) diastereomer⁷. However, this high stereoselectivity was obtained only when $F-CH_3Li$ (prepared from CH_3Cl by Foote Mineral Co.) was used to generate the lithio derivative. When $V-CH_3Li$ (prepared from CH_3Br by Ventron Corporation, 2M in ether) was used, the diastereomeric ratio dropped to 3:1. The large difference in the stereoselectivity was reported by Durst and Molin^{8a} to be due to the presence of $LiBr$ in $V-CH_3Li$. $F-CH_3Li$ is made from CH_3Cl and was thus free of any lithium salt ($LiCl$ is insoluble in ether). Since $F-CH_3Li$ was no longer commercially available, we had decided to use $n-BuLi$ in hexane from Ventron. This solution should not contain any lithium salts because of their insolubility in hexane. However, previous experience²⁵ has shown that when $n-BuLi$ was used as a base

and the lithiosulfoxide was quenched after one minute with excess water, displacement reactions at the sulfur competed effectively with the formation of the lithio sulfoxide.



We felt that if lithium diisopropyl amide (LDA, formed by reaction of n-BuLi and diisopropylamide) which is a bulkier and weaker base than n-BuLi was used to generate the lithio derivative, the displacement reaction in which Ph-CH₂ is expelled would be minimized. Actually, when the reaction was carried out at -95°C* in T.H.F. using LDA as the base and the lithiosulfoxide was quenched after 1 minute, the yield of the purified $\phi\text{CH}_2\text{SOCH}_3$ rose to 90%. When D₂O was used for quenching, the diastereoisomer ratio, measured by n.m.r., was >94:6.

Sample 13a, containing tritium in place of H₃ was produced by quenching the lithiosulfoxide with tritiated water. The kinetics of detritiation for this sample indicated 1.9% tritium had been

* In view of the increased selectivity with lower reaction temperature⁷, we decided to generate the lithiosulfoxide at -95°C. The anionic species, however, were allowed to equilibrate at higher temperature (-78°C) to speed up the equilibration before being cooled down to -95°C for further equilibration. Viau²⁵ noted that the lithio sulfoxide precipitated out of solution at -78°C, the sulfoxide concentration he used was 1 mole/35 ml T.H.F. We used a lower concentration of 1 mmole/20 ml, at this concentration the reaction mixture remained homogeneous even at -95°C.

incorporated into the methyl group (see Results of Kinetic Measurements). Sample 13b was deuterated and tritiated in place of H_S by using D₂O containing 0.3% of tritiated water as the quenching solution. The kinetic behavior of the detritiation of this sample showed 4% tritium at the methyl group (see Results of Kinetic Measurements). The lower amount of tritium residue in sample 13a than in 13b was ascribed to the shorter time of carbanion equilibration in the preparation of 13b (10 minutes at -78°C and 10 minutes at -95°C) than for 13a (15 minutes at -78°C and 15 minutes at -95°C), such that the carbanion formed by initial abstraction of hydrogen from the methyl group did not equilibrate as effectively with the benzylic carbanions. This interpretation was proven correct by two additional experiments. Under the same reaction conditions, if the lithiosulfoxide was quenched with D₂O after an equilibration for 45 minutes at -78°C and for 15 minutes at -95°C, the product showed no detectable deuteration at the methyl group while 2% of one deuterium at the methyl group was detected (both analyses by n.m.r.) if the carbanion equilibration at -78°C was shortened to 15 minutes. Therefore, in order to maintain a minimum deuteration at this unfavorable site, a longer time for carbanion equilibration is necessary and for this reason the amount of LDA used was chosen to be less than 1 equivalent (.92 equivalent) for each mole of sulfoxide used in the reaction. This conclusion which was reached only after completion of kinetic measurements on 13a and 13b has been applied to the preparation of the dideuterated sample 13d in the following section. Viau²⁵ observed that a 50% decomposition occurred when the lithio derivatives of benzyl methyl sulfoxide was

quenched with water after 4 hours at -60°C in T.H.F. Similarly we have suffered a lower yield (72%) of the labelled sulfoxide (purified by column chromatography only) for an equilibration time of 1 hour at -78°C and 15 minutes at -95°C .

b) Preparation of Samples 13c and 13d

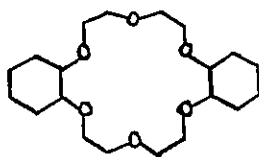
Previous experience¹ showed that isotopic labelling in place of H_R can be achieved in a highly stereoselective manner. By conducting base-catalyzed hydrogen-deuterium exchange in D_2O , the RS(SR) diastereomeric α -deuterobenzyl methyl sulfoxide was produced 16 times faster than the SS(RR) isomer. Since the relative amounts of the RS(SR) and the SS(RR) isomers become more nearly equal as the exchange proceeds, the exchange was allowed to proceed to 3% completion in the labelling procedure for preparing samples 13c and 13d.

Accordingly, sample 13c in which tritium was introduced in place of H_R was produced by exchange of benzyl methyl sulfoxide in tritiated water to proceed to only 3.3% of reaction. Sample 13d required for measurement of $k^{\text{D}}/k^{\text{T}}$ for H_R was produced by complete deuteration of the methylene group followed by back exchange in tritiated water to 3% of reaction. Complete deuteration of the methylene group by base-catalyzed exchange would lead to incorporation of deuterium at the methyl group, thus complicating any rate determination by m.s. analysis. For this reason the dideuterated species was prepared by first introducing the deuterium in place of H_S by addition of D_2O to the lithiosulfoxide generated by using LDA as a base, followed by deuteration in place of H_R by base-catalyzed exchange to six half-lives.

C. Results of Kinetic Measurements

1. Potassium Alkoxide-Catalyzed Isotopic Exchange in the Bridged Biaryl Sulfoxide 3

In the studies on the potassium alkoxide-catalyzed isotopic exchange of the α protons in 3 in t-butanol- $O-d$ and methanol- d_4 , we have examined the effects of dicyclohexyl-18-crown-6 which is the cyclic polyether 14, a compound known to complex potassium ion effectively²⁶, on the relative reactivities of exchanges. We have also measured the primary isotope effects in two ways: a) by comparison of the rates of deuteration in CH_3OD with rates of protonation of $\underline{3-d_4}$ in CH_3OH , and b) by measuring k^H/k^T in t-butanol- $O-d$. In all kinetic runs, good first-order plots were obtained for at least five kinetic points (unless otherwise stated) at appropriate time intervals. Generally data were taken to two half-lives (unless otherwise stated). Results are summarized in Tables 3 and 4.



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The isotope effect k^H/k^D for the exchange of H_1 in methanol was not determined because of the inertness of this proton under the reaction conditions used. At higher temperature where exchange of H_1 can be followed conveniently, H_2 and H_3 are too reactive to allow an

Table 3

Effects of Crown Ether on the Rates of Exchange of α Protons in 3

Run #	Temp (°C)	Crown Ether <u>14</u> (M)	Base/Solvent	$10^5 k \text{ sec}^{-1}$ ^a			
				H ₁	H ₂	H ₃	H ₄
1 ^b	30		t-BuOK/t-BuOD	0.27		82	
2	27	0.02M	t-BuOK/t-BuOD	(12.6)	87.2	27.3	133
3	27	0.02M	t-BuOK/t-BuOD				relative rates
				1	1100	300	1500
4	27	0.0028	t-BuOK/t-BuOD	1.45	(12.5)	288	18
					1.7	36.6	2.6
5	27	1N	CD ₃ OK/CD ₃ OD				relative rates
				1	8.7	200	12.4
6 ^c	27	1.1	CD ₃ OK/CD ₃ OD		.31	2.3	.089
					1.18	1.85	.69

^a Rate constants in t-butanol-O-d and methanol-d₄ measured on our Varian HA-100 n.m.r. spectrometer were determined with an accuracy of $\pm 10\%$ and $\pm 6\%$, respectively. Rate constants in brackets were calculated from relative rates.

^b Results of this run were obtained from ref. 5b.

^c Rate constants were determined from one-point kinetics.

Table 4
 Primary Isotope Effects of α Proton Exchanges in 3

Run #	Base/Solvent	Temp (°C)	$10^5 k \text{ sec}^{-1a}$			
			H ₁	H ₂	H ₃	H ₄
7	2M CH ₃ OK/CH ₃ OD	26±.5		.78±.04(0.9986)	8.02 ^b	.44±.04(0.9967)
8	2M CH ₃ OK/CH ₃ OH	27.6±.5		.44±.04(0.9975)	1.61 ^b	.28±.02(0.9959)
			k^H/k^D	1.8	5	1.6
			$k^H = 1.91^b$			
			$k^T = 1.57±.04(0.9960)$			
			$k^H/k^T = 1.21$			
10	0.002M <u>t</u> -BuOK/ <u>t</u> -BuOD	29±.1		$k^H = 11.27±.61(0.9987)$		
				$k^T = 8.01±.14(0.9997)$		
				$k^H/k^T = 1.41$		

^aRate constants obtained by least squares analysis²⁷ are quoted with the uncertainty in accuracy equal to the standard deviation. Correlation coefficients, in brackets, follow.

^bThese values obtained from only two kinetic points (see Experimental).

accurate determination. For comparison purpose, the primary isotope effects involving the exchanges of the four α protons should be determined at the same temperature since isotope effect is temperature-dependent^{13b}.

The isotope effects k^H/k^T in t-butanol-0-d were determined for the exchanges of H_1 and H_2 but not H_3 and H_4 because tritiation in place of H_3 could not be achieved in a highly stereoselective manner. Although in the previous work^{5b}, H_3 and H_2 (the next fastest proton) were reported to exchange in methanol with a relative rate of 38:1, we found a reproducible relative rate of 10:1 on repeating the kinetics. We therefore decided that this stereoselectivity was not sufficiently high for preparing a sample containing tritium in place of H_3 for the k^H/k^T study in t-butanol.

2. Sodium Hydroxide-Catalyzed Exchange of Benzyl Methyl Sulfoxide

For the exchanges of the methylene protons in benzyl methyl sulfoxide, Streitweiser's method (see equation 2 in Introduction) was applied to derive the values of internal return for these two α protons.

In determining the isotope effects k^H/k^T and k^D/k^T for each proton, rate constants were determined by monitoring the gain or loss of deuterium using mass spectrometry, loss of tritium was measured by scintillation counting. The simultaneous measurements of exchanges of two isotopes (H and T or D and T) during a single run minimizes the sources of systematic error and solvent isotope effect.

A sample of mass spectrometric analysis of deuterium content in benzyl methyl sulfoxide follows: The parent benzyl methyl sulfoxide was found to have the isotopic ratio of the $(M)^+$, $(M+1)^+$, $(M+2)^+$ and $(M+3)^+$ peaks as 100, 10, 5.5 and 0.4. This then gives the empirical correction factors for the $(M+1)^+$, $(M+2)^+$ and $(M+3)^+$ ions. One aliquot of the exchanged molecule showed that the ratios of the peaks to be 114 $(M)^+$, 81.3 $(M+1)^+$, 15.2 $(M+2)^+$ and 5 $(M+3)^+$ in which the $(M+1)^+$, $(M+2)^+$ and $(M+3)^+$ peaks have to be corrected for the isotopic natural abundance. The higher isotopes of the $(M)^+$ peak in the $(M+1)^+$ peak would contribute $(114 \times 10)\%$ to the intensity found for the $(M+1)^+$ peak. Similarly the contribution to the intensity of the $(M+2)^+$ peak would be $(114 \times 5.5)\%$ and to the intensity of the $(M+3)^+$ peak would be $(114 \times .4)\%$. Corrections were then made in a similar manner for the higher isotopes of the $(M+1)^+$ peak in the intensities of the $(M+2)^+$ and $(M+3)^+$ peaks and so on. From the corrected relative intensities then, the proportions of undeuterated, monodeuterated and dideuterated sulfoxides could be determined.

Two sample first-order plots for dedeuteration (loss of the dideuterated species d_2) and detritiation of sample 13d are given in Figures 4 and 5 respectively. The experimental data for the kinetics are summarized in Tables 5 and 6.

The pseudo-first-order rate constant for loss of d_2 was obtained directly from the slope of the plot multiplied by 2.303: $k = 0.231$ (before least-square treatment). The rate constant obtained was corrected to give the rate constant of dedeuteration of H_R (see

Table 5
Dedeuteration Kinetics of Sample 13d

Time (hr)	d_2^a (mole fraction)	$\log C_0/C^b$
0	.731	0
1	.585	.098
1.85	.482	.182
2.7	.394	.269
3.5	.327	.350
4.3	.268	.436
6.5	.164	.650

^aThe dideuterated species in mass spectra.

^b C_0 and C 's are the mole fractions of d_2 at time = 0 and for the aliquots respectively.

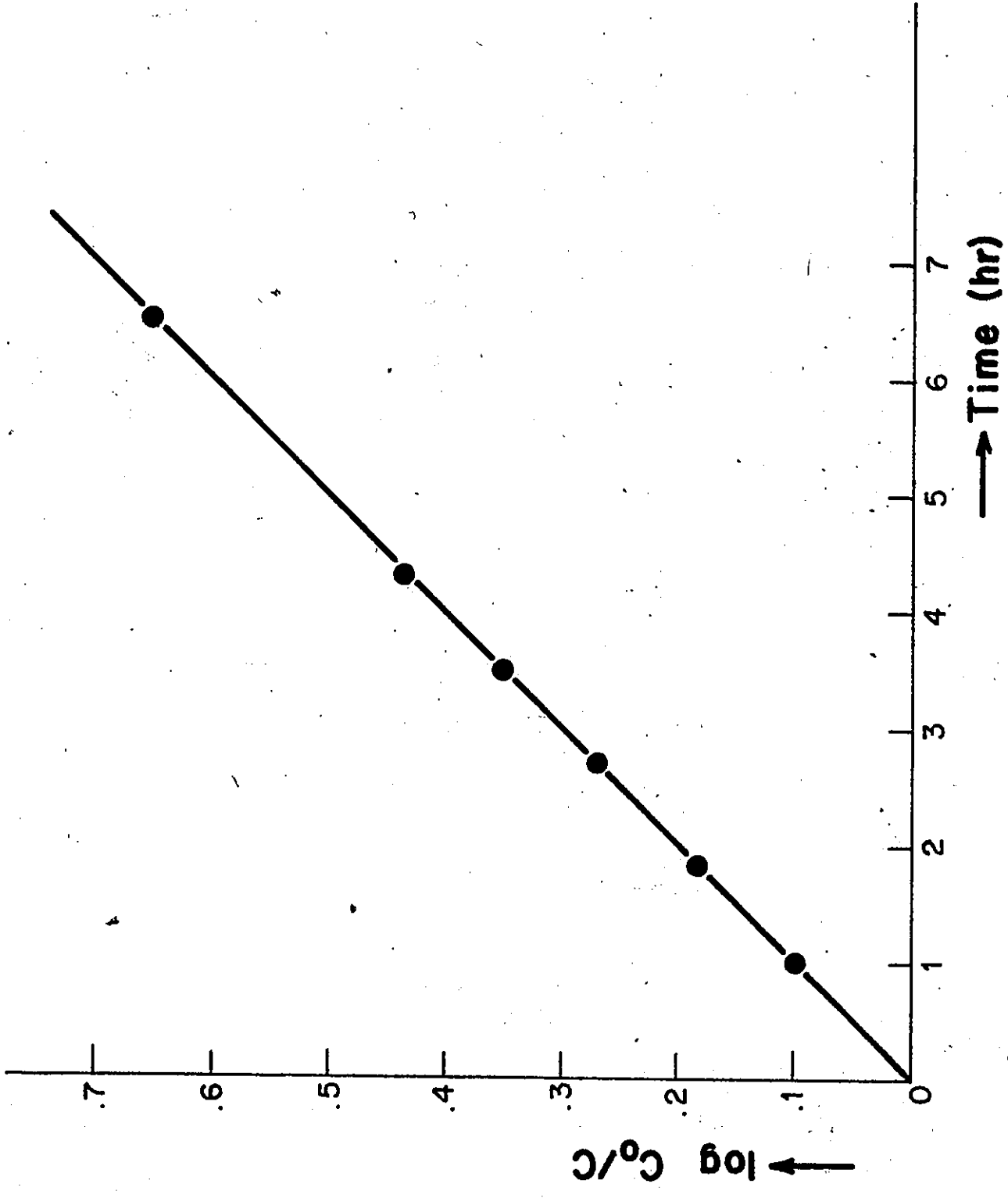


Figure 4. First-order plot of $\log C_0/C$ versus time for the dedeuteration kinetics of sample 13d

Table 6
Detritiation Kinetics of Sample 13d

Time (hr)	dpm/mgx10 ³ ^a	log C ₀ /C	dpm/mgx10 ³ ^b	log C ₀ /C
0	3.39	0	3.16	.03
.5	3.19	.027	2.96	.030
1.0	2.95	.060	2.72	.065
1.85	2.60	.116	2.37	.125
2.7	2.33	.164	2.10	.178
3.5	2.08	.215	1.85	.234
4.3	1.86	.258	1.65	.282
5.4	1.59	.332	1.36	.365
6.4	1.40	.389	1.17	.434
7.4	1.23	.444	1.00	.499
8.8	1.04	.519	0.81	.590

^a Specific activity in dpm/mg (disintegration per minute per mg) of aliquots before correction for tritium residue in place of H₂ was made.

^b After correction for 7% T₂.

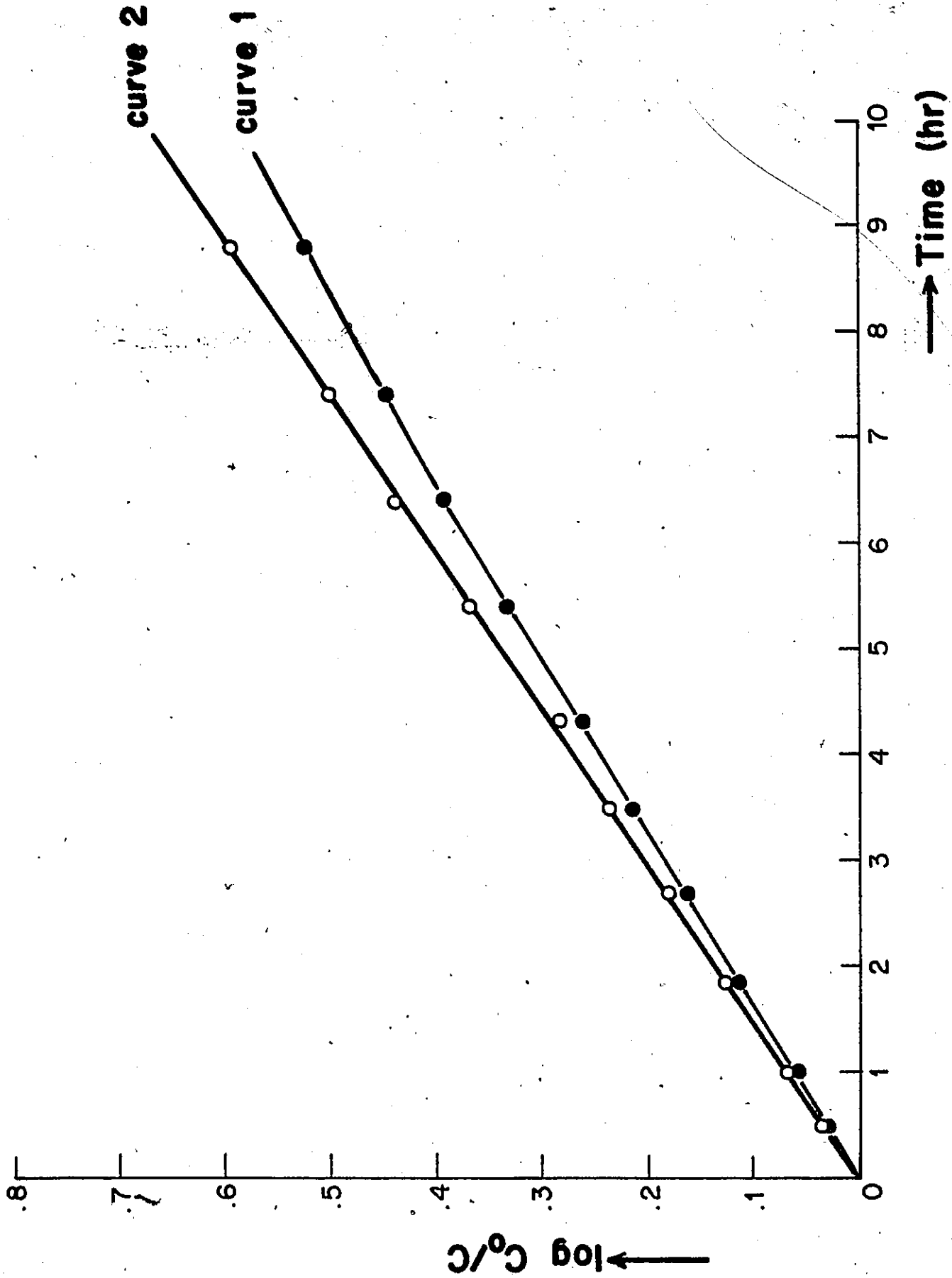


Figure 5. First-order plot of $\log C_0/C$ vs time for the detritiation kinetics of sample 13d. Curves 1 and 2 are plotted before and after correction for residual tritium in place of H_2O was made for each aliquot respectively

Determination of k_R^D/k_R^T in H_2O)⁴ The first-order plot for detritiation showed a slight curvature at the end of the kinetics (curve 1 in Figure 5). The curvature was removed after correction for residual tritium: in place of H_S was made for each aliquot (curve 2 in Figure 5) (see Determination of k_R^D/k_R^T in H_2O).

All of the data were treated assuming a pseudo first-order reaction using a least-squares program. The substrate concentration (0.065 M or 10 mg/ml) used and the small molecular weight of water are such that at equilibrium only a negligible amount of hydrogen isotope (.1%) remained in the hydrocarbon. Thus a simple pseudo first-order kinetic treatment suffices. The experimental first-order rate constant was converted to the second-order rate constant by dividing by the concentration of sodium hydroxide, which remained constant throughout the kinetic run. Table 7 summarizes the results.

Since the rate determination differs somewhat for each kinetic run, descriptions of salient factors for each case follow.

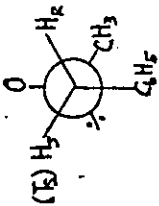
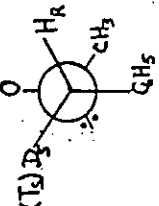
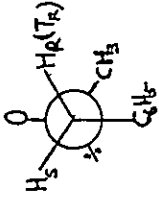
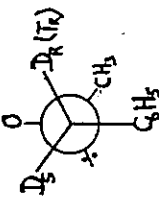
a) Determination of k_S^H/k_S^T in D_2O

The aliquots for the measurements of detritiation and deuteration of H_S were taken after H_R has been completely deuterated. This was done to insure a constant secondary isotope effect throughout the kinetic run. Thus deuteration was measured as $-d[d_1]/dt$ (the rate of decrease of the monodeuterated peak d_1 in the mass spectra).

The substrate, i.e., sample 13a, prepared from quenching the α -lithio derivatives with tritiated water in T.H.F., was assumed to

Table 7

Isotopic Exchange Rates of Methylene Protons of Benzyl Methyl Sulfoxide^a

Substrate	Base/Solvent	k^2 standard deviation $M^{-1} \text{ hr}^{-1}$	I Effect	Internal Return $\frac{H}{a}$
<u>13a</u> 	NaOD (0.48M) in D ₂ O	$k_S^H = 0.945 \pm 0.01$ $k_S^T = 0.33 \pm 0.004$	$\frac{H}{k_S^T} = 2.86$	0.14
<u>13b</u> 	NaOH (0.48M) in H ₂ O	$k_S^D = 0.545 \pm 0.006$ $k_S^T = 0.392 \pm 0.004$	$\frac{D}{k_S^T} = 1.39$	
<u>13c</u> 	NaOD (0.04M) in D ₂ O	$k_R^H = 21.6 \pm 0.3$ $k_R^T = 7.22 \pm 0.06$	$\frac{H}{k_R^T} = 2.99$	0.03
<u>13d</u> 	NaOH (0.04M) in H ₂ O	$k_R^D = 5.41 \pm 0.08$ $k_R^T = 3.90 \pm 0.03$	$\frac{D}{k_R^T} = 1.39$	

^aAll rate constants expressed as second order rate constants measured at 29.8 ± 0.1°C and derived from least-squares treatment of the data. All correlation coefficients were 0.9998 or better.

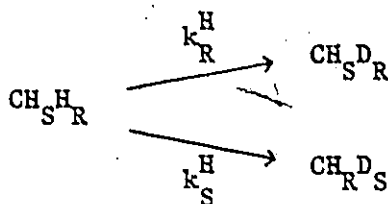
contain 6% T_R according to a labelling selectivity of 17:1. This tritium label was estimated to be removed by 94% (4 half-lives) before points used for the determination of detritiation rate for H_S were taken. The first-order plot, however, showed a slight curvature at the end of the kinetics (3 half-lives). An aliquot at 7 half-lives indicated the presence of residual tritium (1.9% of the total incorporation) which is likely to have been incorporated at the methyl group when the carbanion formed by initial abstraction of hydrogen from the methyl group was quenched with tritiated water during the preparation of the substrate (sample 13a). After correcting each aliquot for this residual amount, the curvature of the first-order plot was removed.

b) Determination of k_S^D/k_S^T in H_2O

Sample 13b obtained from quenching the lithiosulfoxide with tritiated water containing D_2O was also assumed to contain 94% D_S and T_S . Loss of tritium and deuterium were measured for kinetics after 25% of the total tritium had been lost (4 half-lives for the exchange of T_R). Again to obtain the accurate rate constants, it was necessary to correct for the tritium (and deuterium) content incorporated at the methyl group. The amount, determined in a similar way described in the preceding section (a), was found to be 4%. The mass spectra of the starting material indicated $5.4 \pm 1.7\%$ of the d_2 species. Both values agreed within experimental error. Good first-order plots for detritiation and dedeuteration kinetics (rate measured as $d[d_0]/dt$) were obtained after correcting each aliquot for this residual amount of label (4%).

c) Determination of k_R^H/k_R^T in D_2O

The rate of deuteration, k_R^H , was obtained from the rate of disappearance of the undeuterated parent peak in mass spectra. The observed rate is the sum of the rates of exchange of the two methylene protons, i.e., observed rate = $k_{obs}^H [H_R H_S] = k_R^H [H_R H_S] + k_S^H [H_R H_S]$ or $k_{obs}^H = k_R^H + k_S^H$ as envisaged by Scheme 2.



Scheme 2

The relative rate, i.e., k_R^H/k_S^H has been found to be 14.4 by Swingle²⁸ using mass spectral analysis to follow the exchange in D_2O at 24°C. Thus $k_{obs}^H = 15.4/14.4 k_R^H$ which leads to $k_R^H = .935 k_{obs}^H$.

During the base-catalyzed tritiation of H_R , a certain amount of tritium was incorporated in place of H_S . Since no direct method for the determination of the tritium label is available, we must assume the selectivity in tritiation to be the same as in deuteration. Therefore, according to the relative rates of 14.4²⁸ for the hydrogen-deuterium exchanges of H_R and H_S , the sample should contain 7% T_S for a 3.3% reaction. Detritiation kinetics were measured to two half-lives of T_R assuming no change in $[T_S]$.

The loss of tritium was monitored over two half-lives and the tritium content was corrected for the presence of 7% T_S by assuming a tritiation selectivity of 14 : 1 for a 3% reaction (Figure 5 contains the plotted data).

D. Discussion

1. Effects of Crown Ether on Stereoselectivity of Exchange in 3

In the conformationally rigid³⁰ bridged biaryl sulfoxide 3, the carbanions derived from abstraction of protons H₁ to H₄ have been classified as A (H₃), B (H₄) and C (H₁ and H₂) in Figure 6 depending upon the conformations of the α sulfinyl carbanions depicted in Figure 1.

The 3 dimensional model of the sulfoxide 3 shows that H₁ and H₂ are protons which reside in identical environments with respect to the asymmetric biaryl system, as are H₃ and H₄. Thus the steric and electronic influences of the benzene ring on the rate of exchange of the protons within each pair will be equal. A proper evaluation of the influence of the sulfoxide group on the stability of the transition state resulting from proton abstraction, therefore, requires a comparison of H₁ vs H₂ and H₃ vs H₄ only. This comparison will reflect the stereochemically dependent stabilizing effect of the sulfoxide group on an α carbanion.

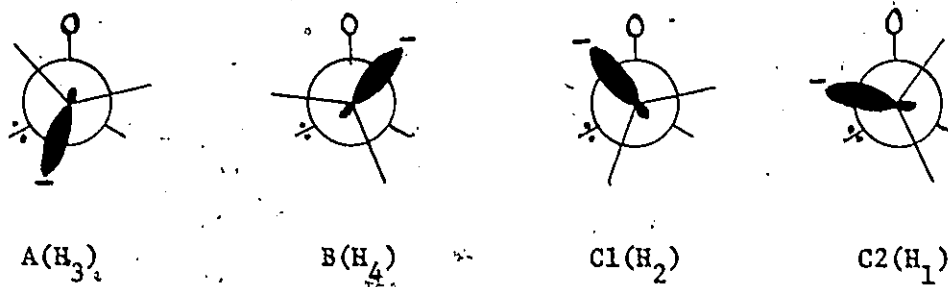


Figure 6. The Newman projection formulas representing the conformations of the four α -sulfinyl carbanions resulted from the abstraction of H_1 , H_2 , H_3 and H_4 in 3.

A previous report by Fraser and co-workers^{5b} on the hydrogen-deuterium exchange of the α protons in 3 showed that a switch from t-butanol to methanol as solvent changes the relative rates of $H_1:H_2:H_3:H_4$ from 1:1100:300:1300 to 1:200:7600:30*. Surprisingly, the relative reactivities of H_3 and H_4 were completely reversed. The result was ascribed to the effects of solvation. Since potassium

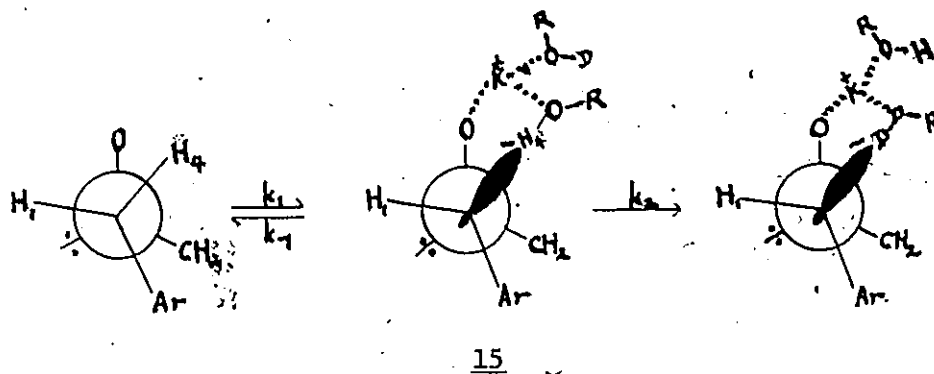
*This figure was found to be in error and was corrected to 1:194:2300:30. (see Results of Kinetic Measurements section (1)).

alkoxide has been known to exist as an ion pair in the nondissociating solvent such as t-butanol, and has been known to participate in carbanion-forming hydrogen abstraction^{12,31}, it seems likely that the potassium ion might be playing an important role in determining the stereoselectivity^{8b}. In a case where internal return is known to occur as detected in acyclic system and called isoinversion³², the addition of crown ether was found to alter the stereochemical course by, decreasing the amount of internal return. Thus an observed effect of crown ether on the stereoselectivity in proton exchanges could be an indication of the existence of internal return in the exchange.

In the isotopic exchanges of the α protons in 3 in t-butanol- $O-d$ containing potassium t-butoxide, the addition of crown ether 14 changed the relative rates of the four α protons, i.e., $H_1:H_2:H_3:H_4$, from 1:1100:300:1300 to 1:8.7:200:12.4 in which the rates of exchange of H_1 and H_3 were increased by 10 fold whereas those of H_2 and H_4 were retarded by 7 fold (see runs 2 and 3 in Table 3). Effectively the addition of crown ether reversed the relative rates of H_3 and H_4 and narrowed the spread between the rates of exchange of H_1 and H_2 .

Based on the recent work which successfully demonstrated the ability of crown ether 14 to complex with the potassium ion in t-butanol^{32,33} and methanol²⁶, the observed sensitivity of the rates of exchanges of the α protons to the cation indicates that this cation is present in the intermediate responsible for hydrogen-deuterium exchange. The following explanation, though not unique, accounts for the influence of added crown ether.

For H_2 and H_4 which are closer to the oxygen of the sulfur group (see the Newman projection in Figure 6), the intermediates are those in which the cation is bonded to the sulfoxide oxygen of the substrate (see structure 15). This bonding interaction between the substrate oxygen and the cation is absent in the intermediates for H_1 and H_3 exchanges because the oxygen is remote from the corresponding incipient carbanion sites while the proximate lone pair is less capable of coordinating with the potassium ion owing to the slight positive character of the sulfur in the S-O bond.



Scheme 4

If an internally coordinated metal ion is present as in 15, then this coordination would serve to lower the activation energies for the solvent reorganization process (k_2) more than for the back reaction (k_{-1}) (see scheme 4). If one compares the k^H/k^T values of 1.21 and 1.41 for H_1 and H_2 respectively, they do indicate less internal return in the exchange of H_2 (will be discussed later in more detail). A similar model has been postulated for the preferential cis exchange in 1-methoxyacenaphthalene³⁴.

In the presence of crown ether, the species that abstracts the proton is the crown ether-separated ion pair in which the coordination sites of potassium ion are neither occupied by the alkoxide nor the solvent molecules. This species resembles in properties the ordinary solvent-separated ion pair³⁵ (see Figure 7). The capture of

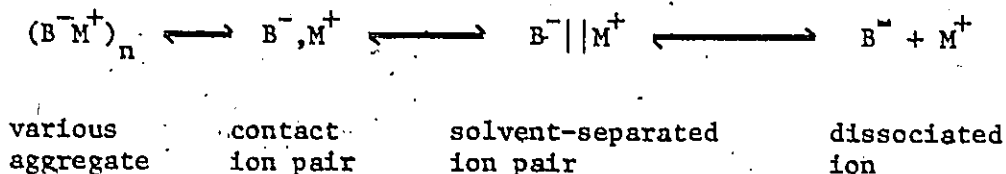


Figure 7. Possible equilibria for metal alkoxide in alcohol media potassium ion by crown ether essentially removes the stabilization due to the bonding between the substrate and the cation in 15. This would result in more internal return and accounts for the decreased rates of exchange of H₂ and H₄. Although it has been found in several cases that the rates of exchanges were dramatically increased by 30-1000 fold³⁶ on the addition of an equivalent of crown ether due to the increased basicity of the t-butoxide ion, the rates of exchange of H₁ and H₃, however, were only accelerated 10 fold. Possibly some preferential internal return induced by the effect of added crown ether is of influence here too.

In contrast, the addition of crown ether to the methanolic solution of 3 containing potassium methoxide as base retarded the exchange of H₃ slightly while the rates of exchange for H₂ and H₄ were increased by 4 and 8 fold respectively. At the high base concentration (1N) employed, potassium methoxide exists substantially as

intimate ion pairs³⁷, thus the intermediate for H₄ exchange is very likely to be one with structure 15. Since methanol forms a more strongly hydrogen-bonded solvent pool than t-butanol, it is less easy to remove a methanol molecule from its solvent pool for solvent reorganization at the carbanion site to occur. In this case the internal chelation in 15 serves to hold the abstracted H₄ in the vicinity of the carbanion rather than to assist the solvent reorganization, and the back reaction governed by k₋₁ is favored. The higher k^H/k^D for H₃ (5) than H₄ (1.6) and thus the smaller amount of internal return for H₃ than H₄ is consistent with this picture. The effect of crown ether in destroying 15 is therefore expected to be opposite to that in t-butanol. The addition of crown ether removes the potassium ion from the metal carbanide ion pair, effectively decreases the rate governed by k₋₁ and thus leads to a rate increment for the H₂ and H₄ exchanges. For the exchange of H₃, no enhancement in rate was observed in methanol as in t-butanol because the activity of methoxide ion in methanol is not increased as that of t-butoxide ion in t-butanol on the addition of crown ether. In the presence of crown ether, the methoxide ion is highly solvated and is thus in a sense "buffered" by solvent in methanol. The t-butoxide ion, when separated from the counterion, is relatively poorly solvated in t-butanol, a solvent of low dielectric constant, and is therefore more reactive.

In the above rationalization, the effect of crown ether was interpreted in terms of a retention mechanism in the presence and absence of crown ether. For base-catalyzed exchanges in t-butanol-potassium t-butoxide medium, generally the retention mechanism is

operating^{12,31,38}. Although the presence of crown ether has been known to result in an increased possibility of inversion³⁶, it would seem highly improbable for inversion to take place in the geometrically restrained biaryl sulfoxide 3³⁹.

From the studies on the effects of crown ether, it has become quite obvious that ion pairing between the carbanion and counterion plays an important role in designing the stereoselectivity of the exchange reactions of sulfoxide 3 in t-butanol and methanol. It is noticeable that ion-pairing affects the internal return and stereoselectivity in different ways in different solvents. This implies that discussion of carbanion stability must be extended to include not only the carbanion itself and the perturbing influence of the counterion but also perturbation by the surrounding solvent molecule. In other words, the stereoselectivity of the exchange reactions does not reflect the preferential stability of the α -sulfinyl carbanions in the potassium alkoxide-catalyzed isotopic exchanges in t-butanol or methanol.

2. Internal Return

a) Benzyl Methyl Sulfoxide

Derivation of the internal return values, a^H , from the experimental primary isotope effects involving the exchanges of the methylene protons in benzyl methyl sulfoxide using Streitweiser's method (see Introduction) requires a value for the equilibrium distribution constant, k^T , which was found to be 1.27 (see Experimental).

The derived internal return values a^H 's, using $x = 2.344$, were 0.3 and 0.14 for H_R and H_S respectively, both at $29.8 \pm 1^\circ\text{C}$. For an internal return mechanism (see scheme 1 in Introduction), the experimental rate of exchange of a hydrogen isotope is $k_{\text{expt}} = k_1 k_2 / (k_{-1} + k_2) = k_1 / (a+1)$. The experimental relative rates for the two methylene protons in the benzyl methyl sulfoxide is therefore $k_{\text{expt}}^R / k_{\text{expt}}^S = k_1^R (a_S+1) / k_1^S (a_R+1)$ or $k_1^R / k_1^S = k_{\text{expt}}^R (a_R+1) / k_{\text{expt}}^S (a_S+1)$. Using $k_{\text{expt}}^R / k_{\text{expt}}^S = 14.4$ for the hydrogen-deuterium exchange found by Swingle²⁸ at 24°C , the actual relative rate for the primary step, k_1^R / k_1^S , is $14.4 \times 1.03 / 1.14 = 13$. Obviously the small amount of internal return has a virtually negligible effect on the calculated relative stabilities of the two transition states leading to anion formation. With these values we can now correct for internal return and find the isotope effect for the primary step; the values of k_1^H / k_1^T are 3.1 and 3.2 for the H_R and H_S exchanges respectively. Note especially that the derived primary isotope effects for the proton transfer processes hardly differ from the experimental values (29). When converted to hydrogen-deuterium isotope effects by the equation of Swain and co-workers (see equation 1 in Introduction), the value of 1.39 for k^D / k^T leads to a value of k^H / k^D of 2.2. This low value of primary isotope effect with negligible amount of internal return is indicative of an unsymmetrical transition state in which the hydrogen isotope is more strongly attached to the base than the α carbon, i.e., the transition state resembles the carbanion in the endothermic proton abstraction process⁴⁰.

b) The Bridged Biaryl Sulfoxide 3

Although information obtained from kinetics regarding the stability of an anion intermediate is reliable in the case of benzyl methyl sulfoxide in aqueous media, the same cannot be said for the exchange of 3 in t-butanol-O-d. Values of k^H/k^T of 1.21 and 1.41 were found for the isotopic exchanges at H_1 and H_2 using stereoselectivity tritiated samples of 3. In the previous work, both the phenomenon of internal return⁴¹ and the unsymmetrical transition state⁴² have been used to explain low primary isotope effects in carbanion-forming hydrogen abstractions. However, such low primary isotope effects for the H_1 and H_2 exchanges in 3 cannot possibly reflect values for k_1^H/k_1^T (the isotope effect of the proton abstraction step). For example, k_1^H/k_1^T in benzyl methyl sulfoxide in water was calculated to be 3.2. Moreover, high intramolecularity which provides unambiguous evidence for the phenomenon of internal return has been generally observed in t-butanol-O-d-potassium t-butoxide medium^{41a,43}. In the present work, both effects of unsymmetrical transition states and internal return might be responsible for the low isotope effect. Although the individual contribution of each effect is not known, we can assume that the primary isotope effect k_1^H/k_1^T of this sulfoxide exchange is the same as for benzyl methyl sulfoxide, i.e., $k_1^H/k_1^T = 3.2$. From this value for k_1^H/k_1^T and the experimental k^H/k^T , the percent internal return is calculated to be 80 ± 15 and $70 \pm 15\%$ for H_1 and H_2 respectively.

In methanol, the resulting isotope effects listed in Table 4 for the exchange of 3 includes a solvent isotope effect. This solvent isotope effect $k_{\text{CH}_3\text{OD}}/k_{\text{CH}_3\text{OH}}$ was found to be 1.5^{42c} and 2.2¹⁹ in the base-catalyzed exchanges of monohydrofluorocarbon and methylfluorene respectively. If we arbitrarily take 1.8 for the solvent isotope effect $k_{\text{CH}_3\text{OD}}/k_{\text{CH}_3\text{OH}}$ for the exchange of the sulfoxide 3, the corrected values for $k^{\text{H}}/k^{\text{D}}$ become 1, 2.8 and 0.7 for H_2 , H_3 and H_4 respectively. These estimated values of $k^{\text{H}}/k^{\text{D}}$ for H_2 and H_4 exchanges strongly indicate the existence of a great deal of internal return. The value for H_3 , being close to the $k_1^{\text{H}}/k_1^{\text{D}}$ (2.2) for benzyl methyl sulfoxide in aqueous media implies a negligible amount of internal return in this case. Since variation of the primary isotope effect with solvent⁴⁴ has been observed as a general phenomenon in which the very high isotope effects found in non-polar solvents are much reduced on passing to polar solvents, we should be careful in concluding the absence of internal return in the exchange of H_3 in 3 since the $k_1^{\text{H}}/k_1^{\text{D}}$ in methanol is likely to be much greater than that in the more polar water.

The results obtained from the investigation of internal return in sulfoxides 3 and 13 were in good agreement with Bell's prediction^{13b} which generalizes that internal return in proton transfer reactions usually occur in media of low dielectric constant such as *t*-butanol and methanol. For exchanges in water, which is a solvent of high dielectric constant, internal return is less probable. The results are also consistent with the summary of Hunter⁴⁵ that in alkoxide-alcohol media, exchange rates may give a close but not

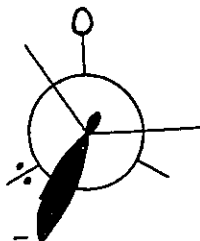
complete measure of carbanion stability since intramolecularity is usually observed.

The origin of the phenomenon of internal return could be visualized in the following way: the sulfinyl anion formed is a strong base compared to the base $^{\ominus}\text{OR}$ (R can be H, CH_3 or t-Bu), and the carbanion is undoubtedly hydrogen bonded to the solvent molecule formed in the transfer of hydrogen isotope from the carbon acid to the oxygen of the base, $^{\ominus}\text{OR}$. Consequently, the reverse transfer of the same atom of hydrogen isotope back to carbon (rate governed by k_{-1} in Scheme 1) might be competitive with the exchange of solvent molecule at the carbanion site (rate governed by k_2). In methanol and t-butanol , the carbanion is suggested to be singly bonded to the solvent molecule⁴⁶ in order to account for the intramolecularity and isoinversion observed in the hydrogen-deuterium exchange between several carbon acids and t-butanol or methanol. The energetic factor preventing strong association of the carbanion with more than one solvent molecule at a time is most likely steric as the R group in the base occurs in a trimeric or a more highly-associated species. Therefore, in these two solvents, the hydrogen isotope from the substrate, being strongly hydrogen-bonded to the carbanion site, must be unique from those in the bulk solvent and thus $k_{-1} > k_2$, resulting in internal return. But water, due to its small size and high solvating ability, is able to associate with the carbanion to form a highly associated species. The ready access of the solvent molecules from the solvent pool to the carbanion site retards the back reaction governed by k_{-1} , thus diminishes the amount of carbanion formation without isotopic exchange (internal return).

3. Conclusion

From the effect of crown ether on the exchange of the α protons in sulfoxide 3, we have seen that in t-butanol and methanol, relative rates of exchange (H_3 vs H_4 and H_1 vs H_2) did not reflect "pure" carbanion stabilities. This was further confirmed by the observed low isotope effect in the exchange reaction, indicating the presence of an appreciable amount of internal return. These findings may account for the divergence of the early accumulated data on the proton exchange α to a sulfoxide group in these solvents from the predictions made on the basis of ab initio M.O. calculations⁴ which did not include the perturbation of the environments on the carbanion stability.

Although it would appear that assignment of the relative stabilities of α -sulfinyl carbanion should be made with caution in both t-butanol and methanol. The α proton exchanges of benzyl methyl sulfoxide in water proceed with negligible internal return and thereby provide significant data regarding anion stabilities. For this system the rationale that anion 16 likely is most stable^{5b} still stands. In this case predictions by M.O. theory again are not strictly comparable.



EXPERIMENTAL

Heavy water (99.9 atom %D), methanol-0-d (99 atom %D) and methyl alcohol-d₄ (99.5 atom %D) were obtained from Merck, Sharp and Dohme Canada Ltd. Tritiated water (25 mC/ml and 5 mC/ml) and standard tritiated toluene were obtained from New England Nuclear. Solutions of lower specific activity were prepared by volumetric dilution. Tritiated t-butanol was prepared by about 200 fold dilution of tritiated water with t-butanol. Dicyclohexyl-18-crown-6 cyclic polyether obtained from Aldrich was used without further purification. The silical gel used for T.L.C. and preparative T.L.C. was MN Kieselgel N/UV254, supplier Markey, Nagel & Co., silica gel 60, used for column chromatography, was supplied by Brinkmann Instruments Canada Ltd. 2,5-Diphenyloxazole (PPO) and 2,2'-p-phenylene-bis (5-phenyloxazole) (POPOP), liquid scintillation counter grade, were obtained from Baker Co. Bio-Solv. solubilizer (Formula BB5-3) was supplied by Beckmann Instrument Inc. Scintanalyzed toluene was obtained from Fisher Scientific Company.

Benzyl methyl sulfoxide²⁸ and 5,7-dihydro-1,11-dimethyl-dibenzo[c,e]thiepin 6-oxide 3²¹ were prepared as described previously. Diisopropylamine was distilled from calcium hydride before use. Dry T.H.F. was obtained by distillation from lithium aluminum hydride just prior to use. Methanol was dried by heating the material under reflux over magnesium turnings for 4 hours, followed by distillation into a dried receiver. t-Butanol-0-d was prepared by the procedure of Cram and Nielsen⁴⁷. The deuterium content was assayed by comparison of the OH signal's integral with that of the ¹³C side band of the t-

butyl hydrogens. The alcohol contained 97.5% d and was stored in a serum-capped flask in a desiccator.

Base solutions of potassium and sodium methoxide in methanol or methanol-d₄ and solutions of sodium deuterioxide in D₂O were prepared by adding a carefully weighed amount of the clean metal to a measured volume of solvent cooled in an ice-bath. Concentrated (1M) stock solution of potassium t-butoxide in t-butanol was prepared by heating under reflux freshly cut potassium metal with t-butanol-0-d. Base solutions containing dicyclohexyl-18-crown-6 cyclic polyether 14 were prepared by adding a calculated quantity of base solution to an accurately weighed amount of crown ether to ensure 10% molar excess of 14. Concentration of each base solution was measured by titrating with standard hydrochloric acid and the solution stored in a serum-capped flask.

Toluene scintillation liquid was prepared by dissolving 4 gm of PPO and 1 gm of POPOP in 1 liter of scintanalyzed toluene. The water miscible scintillation liquid was made up of 0.3 gm POPOP, 5 gm PPO, 130 ml spectroscopic methanol and 100 ml of Bio-solv. solubilizer.

All weighings were done on an E. Mettler Zurich Type H-16 balance. All n.m.r. spectra were taken in deuteriochloroform solution (unless otherwise noted) on our Varian HA-100 MHz spectrometer equipped with an SD-100 deuterium spin decoupler. Tritium counting was performed in a Beckmann LS-150 scintillation counter equipped with an external standard channel ratio operation. Deuterium content of each

kinetic sample was analyzed using an AEI MS-902 mass spectrometer. All kinetic data were treated as pseudo-first-order using a least squares program²⁷ on an IBM 360. Standard deviations quoted for rate constants in Tables 4 and 7 were taken as two times the slope standard deviations.

Sample Isolation: For each sulfoxide, the same method of isolation and purification of the sulfoxide was employed in all labelling experiments and kinetic runs. An example for each sulfoxide is given below. The reaction mixture of the bridged biaryl sulfoxide 3 in t-butanol or methanol was quenched with dil. HCl, the solvent removed and the residue dissolved in chloroform. The chloroform solution was washed with water, dried over anhydrous Na_2SO_4 , and concentrated to give a solid which was purified by column chromatography or T.L.C. (ethyl acetate-hexane 80/20 v/v) depending on the amount of sulfoxide, and sublimation at $110^\circ\text{C}/0.05$ mm. The reaction mixture of benzyl methyl sulfoxide in 25 ml T.H.F. was poured into 150 ml of H_2O saturated with NaCl. The aqueous mixture was extracted with three 40 ml portions of CH_2Cl_2 . Exchange reaction in aqueous media was quenched with excess HCl and the sulfoxide was extracted with chloroform. In both cases the combined extract was dried and concentrated before being purified by column chromatography or T.L.C. (ethyl acetate-hexane 80/20 v v) and sublimation at $65^\circ\text{C}/.05$ mm.

A. Scintillation Counting

For benzyl methyl sulfoxide and for the biaryl sulfoxide 3, each sample for scintillation counting was prepared in the following

way: The purified aliquot (10-25 mg) weighed out accurately to 0.05 mg in a 20-ml polyethylene scintillation vial (Fisher) was dissolved in 10 ml toluene scintillation liquid and .1 ml scintanalyzed toluene. The amounts of the sulfoxide used in the later kinetic aliquots were increased in order to assure their counts close to that of the earlier aliquots. With each set of kinetic samples was included a set of standards for calibrating the counting efficiency of the machine, each sample was counted to 0.7% statistical error in a $^3\text{H} + ^{14}\text{C}$ window for about 3 minutes.

To accomplish the preparation of a calibration curve for each type of sulfoxide sample, 9 standard samples were made. Each sample was composed of 10 ml of toluene scintillation liquid, .1 ml of standard tritiated toluene with known activity (the activity was so chosen that the counts will be close to that of the kinetic sample) and an amount of the unlabelled sulfoxide (quenching agent) similar to that in the kinetic samples.

For benzyl methyl sulfoxide, since the kinetic sample usually weighed between 10-25 mg, the amounts of the quenching agent used for calibration were 9, 11, 13, 16, 19, 22, 25, 28 and 40 mg. For each standard counted, the machine registered an external standard ratio and a counting rate which is given as counts per minute (cpm). The external standard ratio is a parameter of the machine which measures the amount of sample quenching. The counting efficiency for each sample was determined by dividing the counting rate by the known dpm (disintegration per minute) of the sample. The calibration curve was obtained by

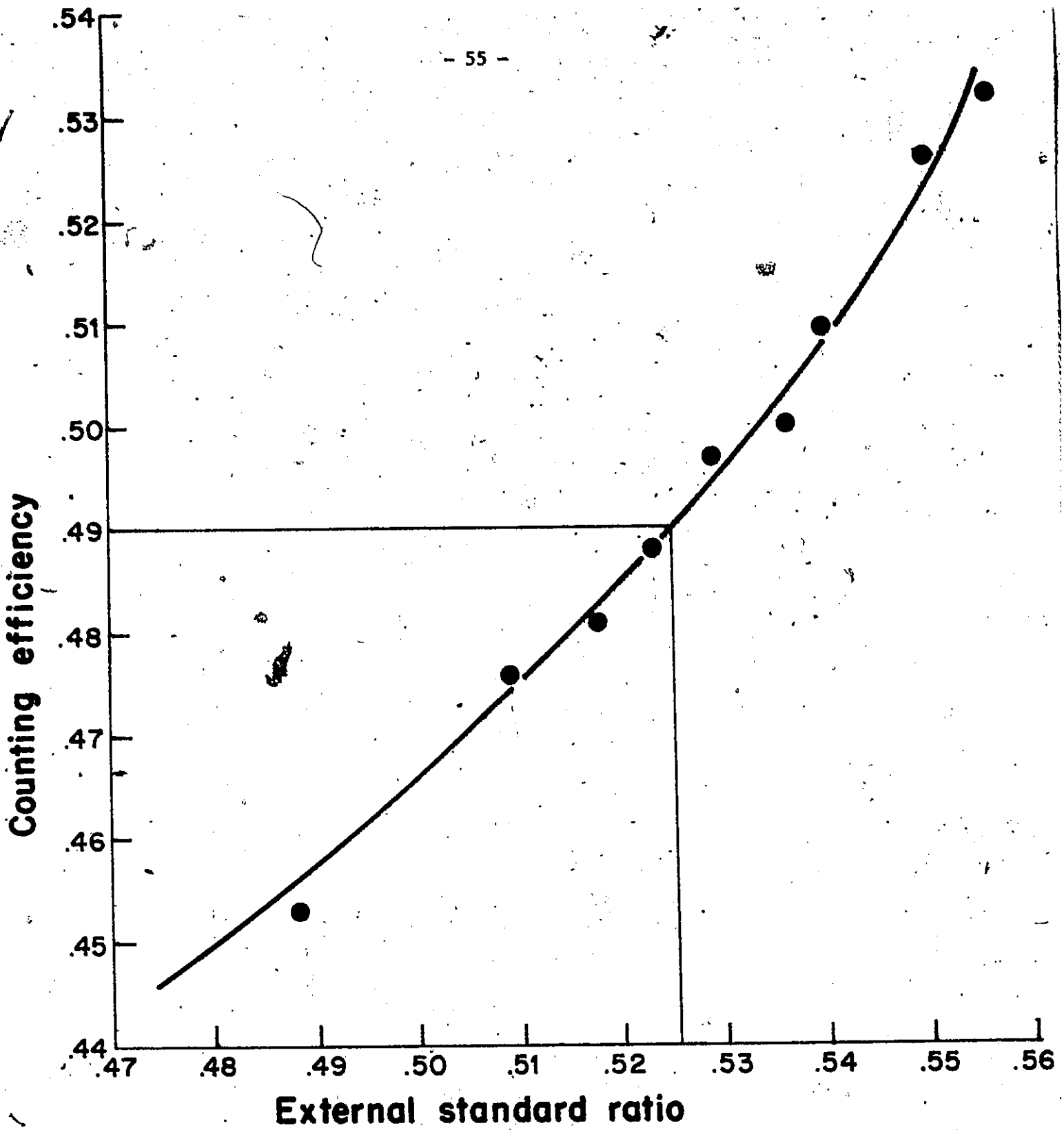


Figure 8. Calibration curve for counting ^3H in benzyl methyl sulfoxide.

plotting the counting efficiency against the external standard ratio. A sample curve for benzyl methyl sulfoxide was given in Figure 8. The counting efficiency is then obtained from this figure for each sample.

Calibration curve for water or *t*-butanol as a quenching agent was prepared in the same way as described for sulfoxide. Scintillation samples of tritiated water and tritiated *t*-butanol used for labelling were composed of 10 ml water-miscible liquid, .1 ml scintanalyzed toluene and .1 ml of the tritiated water or *t*-butanol diluted volumetrically to have a count of about 10^5 cpm.

B. Determination of $K^{T'}$ for Benzyl Methyl Sulfoxide

Benzyl methyl sulfoxide, 40 mg, was stirred in 4 ml of a solution of tritiated water containing sodium hydroxide (0.25 M) for 4 days at $29.8 \pm .1^\circ\text{C}$. At the end of the reaction, the sulfoxide was extracted with three 20-ml portions of chloroform. The tritiated water solution was distilled and prepared for scintillation counting. The sulfoxide after purification was also analyzed for tritium content. The equilibrium specific activity for tritiated water and sulfoxide were 2.8×10^6 dpm/meq OH and 4.39×10^6 dpm/mole respectively. In a separate experiment in which deuteration was carried out under the same conditions, the methylene protons were shown to be fully deuterated and the methyl protons had incorporated 55.2% of one deuterium (by n.m.r.). Assuming that the amount of deuterium incorporation is the same as that of tritium incorporation, $K^{T'}$, obtained as a ratio of the equilibrium tritium content in water to that in the methylene group (1 position) of the sulfoxide, is therefore 1.27.

C. Labelling Experiments

1. The Bridged Biaryl Sulfoxide 3

The following labelling experiments conducted in t-butanol or methanol generally gave 88% yield of the recovered sulfoxide.

a) Replacement of the α Protons by Deuterium (Sample 3-d₄)

When the biaryl sulfoxide (1 equiv.) was stirred in 6.4 ml of t-butanol-0-d containing potassium t-butoxide (.25M) at R.T. (room temperature) for 24 hours, H₂, H₃ and H₄ were found to be 90% deuterated and H₁ 80% deuterated (by n.m.r.).

b) Specific Deuteration in Place of Proton 3 (Sample 3-D₃)

When the sulfoxide (1 equiv.) was allowed to stir in 6.4 ml of methanol-0-d solution containing sodium methoxide (1.5 M) at R.T. for 24 hours, n.m.r. indicated 32% D₂ (i.e., 32% deuterium in place of H₂), 92% D₃ and 10.6% D₄ in the recovered sulfoxide.

c) Specific Tritiation in Place of Proton 1 (Sample 3-T₁)

Tritiation at position 1 consists of two consecutive steps, i.e., complete tritiation at all four α protons followed by detritiation at the three more labile protons.

When the biaryl sulfoxide (1 equiv.) was stirred at R.T. for 4 days in 12.8 ml of tritiated t-butanol solution containing potassium t-butoxide (0.4M) of specific activity 6.9×10^7 dpm/ml or 6.57×10^6 dpm/meq, the tritiated sulfoxide obtained after purification had a

specific activity of 2.2×10^7 dpm/mole or 5.5×10^6 dpm/meq of the exchangeable α proton. When the sulfoxide was deuterated under the same conditions, n.m.r. analysis of the recovered material showed that all four α -protons had reached the equilibrium isotopic distribution and no deuterium was incorporated into the methyl group on the aromatic ring. Thus all four α -protons should have been equally tritiated with a K^T value of approximately 1.2 under the reaction conditions employed. On treatment of this tetratritiated sulfoxide in a t-butanol solution of potassium t-butoxide (.11 M) for 25 hours at 30°C (the substrate concentration used was 10 mg/ml such that at equilibrium a negligible amount of isotope (1.5%) remained in place of the three more acidic protons), the sulfoxide had a final activity of 2.5×10^6 dpm/mole which is 45.5% of the original tritium content at H_1 .

Before the back reaction was carried out, a trial detritiation kinetics was run under the same reaction conditions to determine the appropriate quenching time when the three faster protons had been completely detritiated. The tritium percentage vs time plot gave a curve which showed an abrupt drop at the beginning and was levelling off after 85% of the tritium had gone (see Figure 9).

d) Specific Tritiation in Place of Proton 2 (Sample $\underline{3}$ -T₂)

The biaryl sulfoxide $\underline{3}$ -T₁ (specific activity = 2.5×10^6 dpm/mole) was mixed with sample $\underline{3}$ -D₃ in a 1.8:1 proportion. The resultant sulfoxide, 980 mg, containing 100% H_1 , 89% H_2 , 67% H_3 and 97% H_4 (by n.m.r.) was treated with triethyloxonium fluoroborate to form the ethoxysulfonium salt and then hydrolyzed in sodium hydroxide

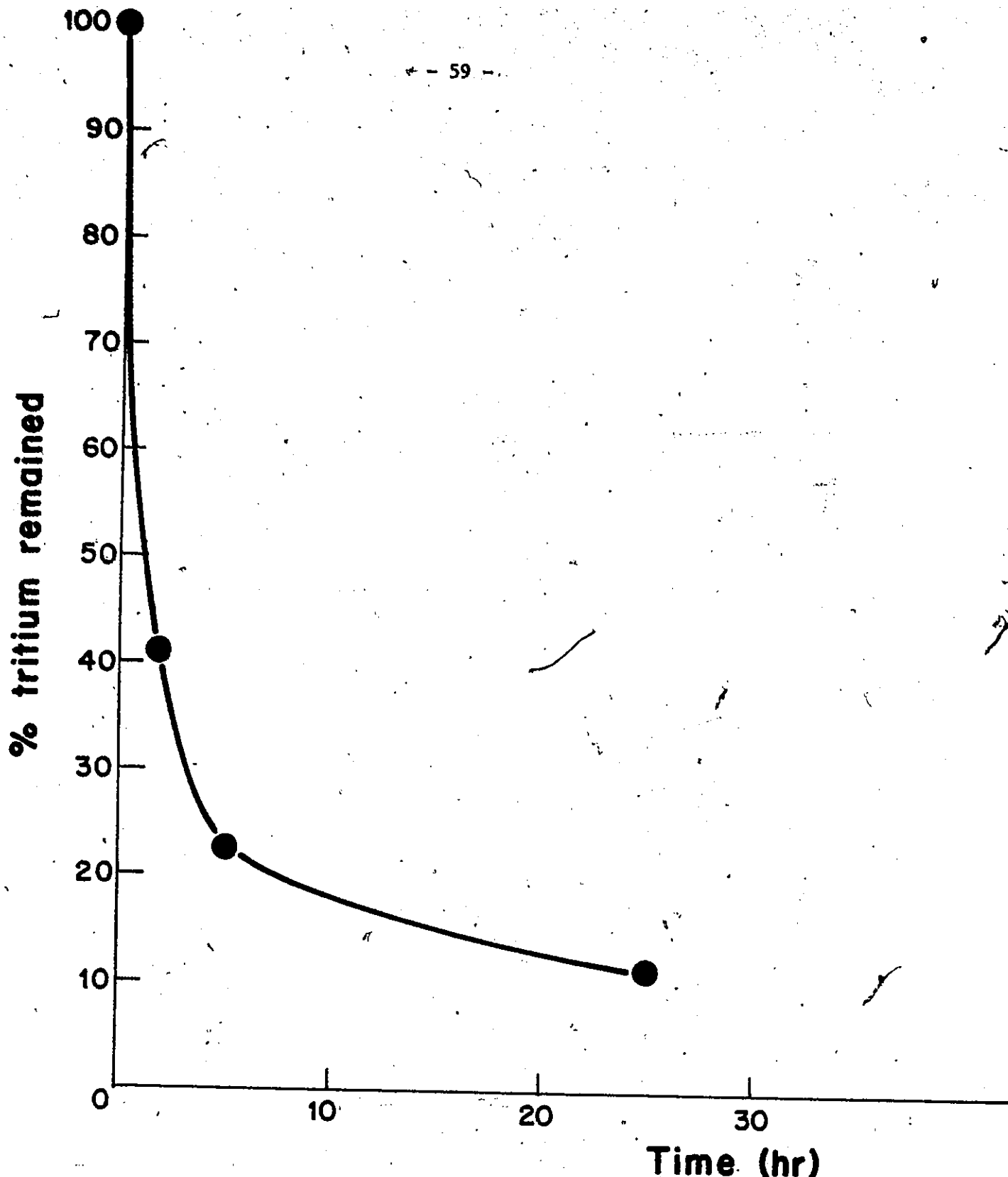


Figure 9. Back detritiation in place of H₂, H₃ and H₄ in the bridged biaryl sulfoxide 3/2

solution following the procedure of Johnson and McCants²⁴. The purified sulfoxide, 700 mg, (71% yield) contained 90% H₁, 98.8% H₂, 93.8% H₃ and 70.1% H₄ from which the percent inversion is calculated to be 89.5. This sample had a specific activity of 1.6×10^6 dpm/mole.

2. Benzyl Methyl Sulfoxide

a) Preparation of Sample 13a

To 25 ml of T.H.F. at room temperature in a 50 ml 2-neck flask equipped with a nitrogen inlet-outlet system and a rubber septum was added via the septum .15 ml (1.04 mmole) of diisopropylamine, then a solution of n-butyllithium in ether (.92 mequiv). After being stirred for 5 minutes at room temperature, the solution was cooled to -78°C and stirred for 10 minutes to allow temperature equilibration. Then a T.H.F. solution of benzyl methyl sulfoxide (1 mmole/ml) was injected and stirring was continued for 15 minutes at -78°C, then 15 minutes at -95°C. An excess of tritiated water (specific activity = 1.75×10^8 dpm/ml) was added with rapid stirring. Isolation and purification gave 110 mg (71% yield) of sample 13a of specific activity 1.44×10^6 dpm/mole. The kinetics of detritiation for this sample indicated 1.9% tritium had been incorporated into the methyl group (see Results of Kinetic Measurements).

b) Preparation of Sample 13b

Sample 13b was prepared in the same way as sample 13a except that the equilibration intervals at -78°C and -95°C before quenching

were both shortened to 10 minutes and the quenching was done with D_2O containing .3% tritiated water (specific activity = 2.1×10^8 dpm/ml). Isolation and purification gave 110 mg (71% yield) of sample 13b (specific activity = 1.74×10^6 dpm/mole) in which H_S was replaced with deuterium in preference to H_R in a ratio of 17:1 (by n.m.r.). The kinetics of detritiation for this sample indicated 4% tritium had been incorporated into the methyl group (see Results of Kinetic Measurements).

c) Preparation of Sample 13c

In a round-bottomed flask a solution of benzyl methyl sulfoxide (1 mmole) in 8 ml of tritiated water (specific activity = 2×10^9 dpm/ml) was stirred in a water bath at $29.8 \pm .1^\circ C$. A solution of 0.24 ml of NaOH in tritiated water (2.75M) was added. The solution was quenched after 11 minutes with excess HCl. Isolation and purification gave 120 mg (78%) of the labelled product. The compound has a specific activity of 5.98×10^5 dpm/mole (3.3% reaction).

Before labelling was carried out, a trial tritiation on a small scale (50 mg) was run under the same conditions to determine the time necessary for a 3% exchange to occur.

d) Preparation of Sample 13d

Sample 13d was prepared essentially in the same way as described for sample 13c except that the starting material used was

the dideuterated compound. The preparation of dideuterated compound was carried out in two steps to avoid any incorporation of deuterium into the methyl group; i.e., deuteration in place of H_S by quenching the lithiosulfoxide with D_2O followed by deuteration in place of H_R by base-catalyzed exchange.

Deuteration in place of H_S was carried out in the same way as described for the preparation of sample 13a except that the carbanion equilibration at $-78^\circ C$ was prolonged to 1 hour. The product obtained after isolation and purification by column chromatography only (72% yield) contained 87% D_S and 5% D_R (by n.m.r.).

Treatment of this sample with NaOD in D_2O (0.04M) for 5 hours at $29.8 \pm .1^\circ C$ gave mainly the dideuterated sulfoxide containing 90% D_S and 95% D_R with no deuterium in the methyl group as indicated by n.m.r. and m.s. which showed no trideuterated peak. Subsequent tritiation in tritiated water (specific activity = 2×10^9 dpm/ml) to 3% of the tritium pool gave the selectively labelled sample 13d, containing 90% D_S and 86% D_R (by n.m.r.) with a specific activity of 5.22×10^5 dpm/mole.

D. Kinetics

1. Potassium Alkoxide-Catalyzed Isotopic Exchange in 3

a) Runs 1-6 (Table 3)

All kinetic runs except 6 in Table 3 were performed on our Varian HA-100 n.m.r. spectrometer. Each kinetic run was carried out on 20 mg (0.078 mmole) of 3 dissolved in 0.35-0.4 ml t-butanol- $O-d$ or

methanol- d_4 in a thin-walled 5 mm n.m.r. tube. Upon the addition with vigorous shaking of 0.1-0.15 ml of t -butanol- $O-d$ or methanol- d_4 containing the desired concentration of base (final substrate concentration was 20 mg/.5 ml), the tube was placed in the spectrometer for continuing integral measurement with the timer started simultaneously.

All the n.m.r. tubes for the kinetic runs were cleaned and then dried at 100°C for at least 24 hours. The tubes were allowed to cool in a desiccator and flushed with dry nitrogen prior to use.

Rates of exchange for the α protons in 3 were determined by integration of the n.m.r. absorption of individual protons at given time intervals. In t -butanol- $O-d$, the rates of exchange for the four α protons were so different that under conditions where the concentrations of H_2 , H_3 and H_4 could be monitored readily, the slow proton, H_1 , exchanged too slowly for a convenient determination of its rate. The relative rates of H_1 and the next slowest proton H_3 were determined^{5b} at higher base concentration. The observed rate ratios were then adjusted to give the overall rates of exchange of H_2 , H_3 and H_4 relative to H_1 .

At the high concentration of crown ether 14 employed in run 3, the huge methylene peak of the crown ether 14 interfered with the H_2 absorption region and thus rendered the rate measurement for H_2 impossible. However, at lower crown ether concentration (i.e., run 4), intensity of the methylene absorption of crown ether was reduced, and H_2 exchange could be followed by integrating over the overlapping region, any increase in intensity was due to the exchange

of H_2 . The relative rates of the four α protons in t -butanol- O - d in the presence of crown ether was obtained from the rate ratios observed at two different base concentrations.

In run 6, again the high concentration of crown ether used did not allow the exchange of H_2 to be followed by n.m.r. integration, therefore the solution was quenched after H_4 had undergone 15% exchange, n.m.r. analysis of the recovered sample (purified on T.L.C. using ethyl acetate-chloroform 50:50 v/v as developing solvent) gave the one-point rate constants for the exchanges of H_2 , H_3 and H_4 .

Because of the substrate concentration (0.16M) used in each kinetic run (except run 1^{5b}) at equilibrium a significant amount of hydrogen remained in the substrate. This equilibrium hydrogen content, C_e , was estimated from the isotopic content of the solvent at equilibrium. In t -butanol- O - d , since H_2 , H_3 and H_4 exchanged with comparable rates while H_1 remained unexchanged, C_e was taken as the solvent pool diluted by three protons for these three labile protons. C_e for H_1 was estimated from the isotopic content of solvent after complete exchange of all four α protons. In methanol, since H_3 exchanged at least 10 times faster than H_2 and H_4 , C_e 's were taken as solvent pool diluted by one and three protons for H_3 and the slower protons (H_2 and H_4) respectively. The pseudo-first-order plot for the hydrogen-deuterium exchange was obtained by plotting $\log (C_0 - C_e) / (C - C_e)$ vs time, where C_0 is the initial concentration. Each rate constant was obtained from the slope of the linear plot multiplied by 2.303.

b) Runs 7-10 (Table 4)

For all kinetic runs in which k^H/k^D and k^H/k^T for α proton exchanges in 3 were determined, each kinetic was performed in a 50 ml or a 100 ml round-bottomed serum-capped flask in a constant temperature bath (see Table 4 for the temperature used in each run). A known solution of specifically labelled sulfoxide was stirred continuously and allowed to equilibrate in the thermostat for at least 1 hour. An aliquot of a base solution of known concentration, similarly equilibrated, was syringed in. Aliquots were removed at intervals and quenched with HCl. Efforts were taken to keep the solution under nitrogen during exchange by filling a syringe with nitrogen and injecting prior to removing each kinetic aliquot. The sulfoxide was isolated and purified before being analyzed for tritium and deuterium content.

The deuterium content of each aliquot in runs 7 and 8 was determined by n.m.r. analysis. Data were obtained up to one half-life and were treated as simple pseudo-first-order. For run 9, the rate of deuterium uptake was determined by the increase in the intensity of the tetradeuterated peak d_4 in mass spectra. The equilibrium value C_e for the percentage of this peak was estimated to be $(.928)^4 \times 100$ where .928 is the equilibrium fraction of the deuterium content. Intensity of d_4 at the start, C_0 , was taken after the three faster protons had reached the equilibrium isotopic distribution. Since only two aliquots were available, the rate constant k_H , obtained from $\ln \frac{C_0 - C_e}{C - C_e} = k_H t$, was determined for each kinetic point and the average

is given in Table 4. The starting point of the detritiation kinetics was taken after 30% loss of the original tritium content, in order to be certain that the tritium label (1.5%) in place of the three more labile protons will have gone.

The rate of deuteration of H_2 in run 10 was determined by n.m.r. integration of H_2 absorption for each kinetic aliquot. Rate constant was determined in the same way as described in the preceding section (a). In the preparation of the sulfoxide specifically tritiated in place of H_2 , the inversion of sulfur configuration was found to be only 89.5%, this meant a residue of 10.5% tritium remained in place of H_1 . When each aliquot was corrected for a constant amount of this tritium, a linear first-order plot was obtained for the detritiation kinetics of H_2 .

2. Sodium Hydroxide-Catalyzed Isotopic Exchange in Benzyl Methyl Sulfoxide

The kinetic experiments in which k^H/k^T and k^D/k^T were determined were carried out in the same way as described in the preceding section for the determination of primary isotope effects involving α proton exchanges in sulfoxide 3. Base concentration was measured at the beginning and at the end of the kinetic run and was found to remain unchanged in all cases.

Rate constants k^H and k^D were determined by monitoring gain or loss of deuterium using mass spectrometry, the largest standard deviation is 1.5% of the rate constant. Rate constants obtained by m.s. analysis compare favorably with those obtained by n.m.r. integration

of the benzylic AB quartet as the exchange proceeded. Loss of tritium was measured by scintillation counting.

For each aliquot submitted for m.s. analysis, the background was assured clean in the region of interest, i.e., from $(M)^+$ to $(M+5)^+$, before eight spectra of the aliquots in the expanded region were taken. The average of the eight measurements were taken and the appropriate correction for the contribution of the natural isotopic abundance to each peak was made. The correction was empirical rather than calculated. This assured that the machine error will be minimized.

PART II

CONFORMATIONAL DEPENDENCES OF CARBANION STABILITY IN
N-NITROSO-6,7-DIHYDRO-1,11-DIMETHYL-5H-DIBENZ[c,e]AZEPINE

INTRODUCTION

The earliest evidence that a carbanion in the α position of a nitrosamine exhibits appreciable stability was provided by two independent studies^{48,49}. In each case base-catalyzed hydrogen-deuterium exchange was observed α to the nitrosamine function, demonstrating that the nitrosamine group exerts a potent stabilizing influence on the adjacent carbanion. Subsequently, Fraser and Wigfield⁵⁰ reported an interesting stereochemical behavior of these carbanions α to nitrogen in the bridged biaryl nitrosamine 17. The four benzylic protons in 17 underwent markedly different rates of base-catalyzed hydrogen-deuterium exchange in *t*-butanol-*O*-*d*. It was notable that each proton *syn* to the oxygen exchanged more rapidly than those *anti* and that the axial-like proton exchanged more rapidly than those in an equatorial-like environment.

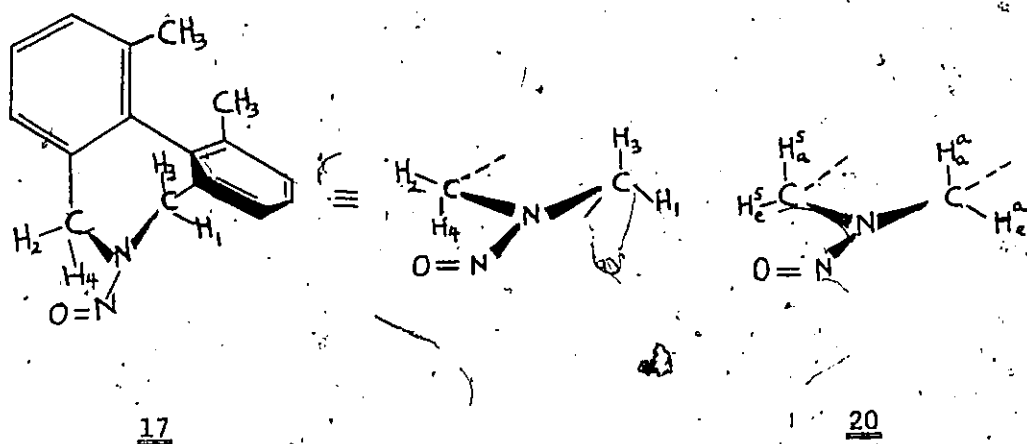
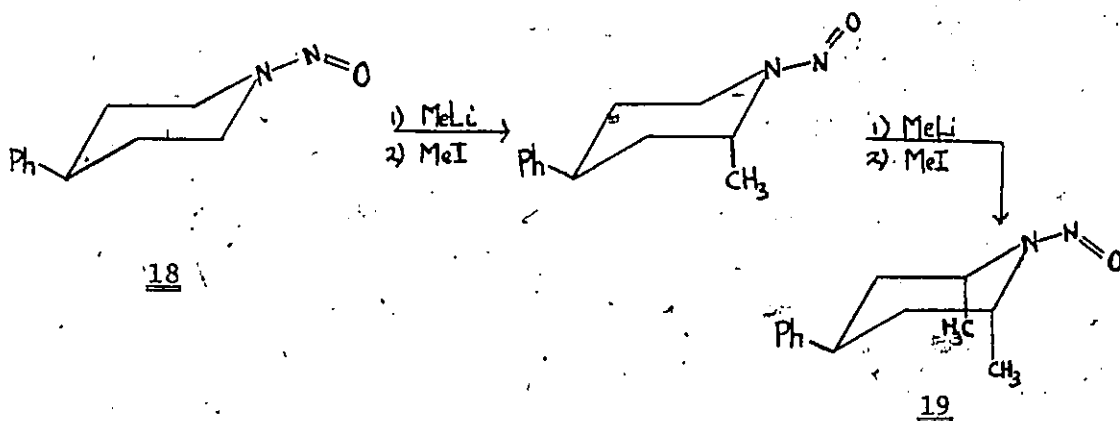


Figure 10. The three-dimensional formulas of the bridged biaryl nitrosamine 17 and N-nitroso-4-benzyl piperidine

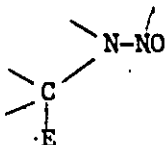
Subsequently, the use of the α -nitrosamino carbanion for synthetic transformations of secondary amines has been documented in a number of examples. In the reaction of anions of N-nitrosodimethylamine⁵¹ and many additional nitrosamine⁵² with a wide variety of electrophiles, yields of 70-95% were reported. Concurrent with these studies, similar results for the reactions of the anion of N-nitrosodibenzylamine⁵³ have been demonstrated. Table 8 summarizes the results. Subsequent study on N-nitroso-4-phenylpiperidine 18⁵⁴ showed that the α carbanions reacts in a highly stereoselective manner with methyl iodide, carbon dioxide and benzophenone to give solely the axial substitution product. Surprisingly a second methylation of the monomethyl derivative gave the 2,6-diaxial derivative in spite of the fact that the trans isomer is thermodynamically less stable.



In view of the synthetic potential of the reaction of nitrosamines which provides a new route to substitution in the α position of amines as demonstrated by Seebach's group and Fraser's group, it is of considerable practical as well as theoretical importance to ascertain

TABLE 8

Carbanion Reactions of Nitrosamines with a Wide Variety of Electrophiles to yield



Nitrosamine	Electrophile	E	% Yield
Methyl-ethyl-nitrosamine	Acetaldehyde	$\text{CH}_3\overset{ }{\text{C}}\text{HOH}$	5
Methyl-isopropyl nitrosamine	Benzylbromide	$\text{C}_6\text{H}_5\text{CH}_2-$	90
Methyl-benzyl-nitrosamine	Acetaldehyde	$\text{CH}_3\overset{ }{\text{C}}\text{HOH}$	100
N-nitroso-pyrrolidine	Benzylbromide	$\text{C}_6\text{H}_5\text{CH}_2-$	90
N-nitroso-piperidine	Acetaldehyde	$\text{CH}_3\overset{ }{\text{C}}\text{HOH}$	90
N-nitroso-perhydroazepin	Benzophenone	$\text{C}_6\text{H}_5\overset{ }{\text{C}}(\text{OH})\text{C}_6\text{H}_5$	90
N-nitroso-dibenzylamine ^a	Methyl iodide	$-\text{CH}_3$	91
N-nitroso-dibenzylamine ^a	Carbon dioxide	$-\text{COOH}$	99

^aThese two examples are taken from ref. 53. The remaining reactions are taken from ref. 52.

the reason behind the abnormally high stereoselectivity. Because of the limited accuracy of the original kinetic studies on the hydrogen-deuterium exchange of 17, it was decided to undertake a more thorough and extensive study of this isotopic exchange reaction.

As the subject of this study, the bridged biaryl nitrosamine 17 possesses a number of interesting features. Rotation about the central biaryl bond is prevented by the methyl groups in positions 1 and 11, and rotation about the N-N bond is slow on the n.m.r. time scale. As a result, the four protons α to the nitrosamino function are magnetically nonequivalent. Since there is no vicinal coupling involving the α protons, a simple n.m.r. spectra of the compound is obtained. In the 100 MHz n.m.r. spectra of 17 in CDCl_3 , four doublets appear for the four α protons at τ 4.546(H_1), 4.588(H_2), 5.25(H_3) and 6.591(H_4). The inequality in geminal coupling constants, $J_{1,3} = 13.5$ Hz and $J_{2,4} = 14.9$ Hz identified the diastereotopic pairs. Stereochemical assignments for individual protons were made in analogy with those of Chow and Colon⁵⁵ for the α protons of N-nitroso-4-benzylpiperidine 20. It can be seen in Figure 10 depicting the three-dimensional formulas of 17 and 20 that the α protons in both compounds have identical dispositions with respect to the nitrosamino group. Because of these similarities in geometry, the chemical shifts for H_2 , H_3 and H_4 relative to H_1 are very close to those observed for the α protons of 20. Continuing with this analogy we will refer to H_3 and H_4 as ψ -axial, and to H_1 and H_2 as ψ -equatorial.

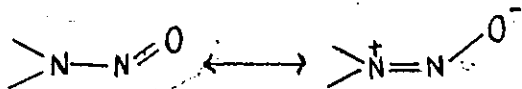
These assignments were confirmed in two ways. The downfield shifts induced by the addition of $\text{Eu}(\text{DPM})_3$ to 17 in CCl_4 were 0.56, 1.34, 0.53 and 0.93 ppm for H_1 to H_4 , respectively. The observed order of magnitudes $\text{H}_2 > \text{H}_4 > \text{H}_1 > \text{H}_3$ is consistent with the above assignments in view of their established distance dependence⁵⁶, i.e., the largest downfield shift is observed for the proton which is closest to the oxygen atom of the nitrosamino function. For further information, a sample selectively deuterated at H_4 was observed to undergo equilibration (via N-N rotation) with the label appearing at H_3 until equal intensities of H_3 and H_4 were attained. This demonstrates H_3 and H_4 to be in the same environment, with respect to the biaryl environment, as the above assignment demands.

RESULTS AND DISCUSSION

A. Barrier to Rotation about the N-N Bond in 17

Nitrosamines are known to possess a large barrier to rotation about the N-N bond because of the partial double bond character of the N-N bond resulting from the resonance interaction between the amine nitrogen and the nitroso group,

i.e.



The rotational barrier is usually in the range of 21-26 kcal/mole as estimated from n.m.r. studies of a variety of nitrosamines⁵⁷. Although an inversion process cannot be entirely ruled out, theoretical calculations by Rademacher and Stolevik⁵⁸ and by Battiste, Davis and Newman⁵⁹ provide strong support for the rotational pathway.

Since the 10 hour half-life reported⁵⁰ for the process of N-N rotation in t-butanol-O-d at 33°C was based on a single measurement and the rates of exchange of the α protons in a solution of potassium t-butoxide in t-butanol were based upon this figure, a more detailed examination of this rate process was undertaken. The original results⁵⁰ of the exchange rates measured at appropriate intervals using a T-60 n.m.r. spectrometer are summarized in Table 9. In contrast to the previous results, as Table 10 shows, we have found that H₃ exchanged with zero order in base concentration while rate of exchange of H₄ increased with base concentration (base order is approximately 1). In addition, H₂ remained essentially inert throughout the kinetic run, this is in serious inconsistency with the previously reported rates of 1:3 for the exchanges of H₃ and H₂ determined by the same method but at a different

TABLE 9
 Previous Study⁵⁰ on Proton Exchanges in 17
 in t-Butanol-0-d

[<u>t</u> -BuOK] (M)	H ₁	H ₂	H ₃	H ₄
0.006		1		>30
0.1		2.7	1	
0.2	1		3.5	
Relative rates	1	10	3.5	>300

base concentration. A possible explanation for the present results could be one in which H₃ was exchanging via rotation, and the rate of rotation is much faster than the exchange of H₂ at the base concentrations employed (0.002-0.01 M). If this were so, then the 10 hour half-life determined previously was in error. In order to clarify this, and since rotation about the N-N bond of 17 is finite and it interchanges the environments of H₁ and H₂ and of H₃ and H₄, it was important to measure the barrier as accurately as possible. Furthermore the possibility that the rate of rotation could be catalyzed by

TABLE 10
Preliminary Study on Proton Exchanges in 17
in t-Butanol-O-d ^a

Run #	[<u>t</u> -BuOK]M	Proton	10^5 k sec ⁻¹
1	0.002	H ₄	96
		H ₃	26
2	0.006	H ₄	235
		H ₃	25.3
3	0.01	H ₄	383
		H ₃	24.2

^aKinetic studies were made on a Varian T-60 n.m.r. spectrometer, probe temperature was 35 ± 1 degree. Rate constants were determined with an accuracy of $\pm 15\%$.

strong base had to be examined since rotation via the anion 17 might well be a low energy process⁶⁰. For this reason the barrier to rotation in 17 was determined in t-butanol-O-d and in 0.009 M and 0.2 M solutions of potassium t-butoxide in t-butanol-O-d. The results obtained by n.m.r. integration measurements at appropriate time intervals using an HA-100 n.m.r. spectrometer are all listed in Table 11. Since each rate constant was obtained by monitoring a different absorption peak, it is necessary to describe each measurement in some detail. For run 4, a sample selectively deuterated at H₄ was prepared by allowing exchange in 0.01 M t-butoxide-t-butanol-O-d to proceed for six minutes. Quenching with acid, followed by rapid isolation and redissolution gave a sample containing 67% deuterium at H₄ and 23% at H₃. The redistribution of this label to the equilibrium value was monitored by n.m.r. integral measurements.

For run 5, the concentration of base (0.009 M) was chosen so that although H₄ and some H₂ undergo base-catalyzed exchange, H₃ can be considered inert. Since H₃ exchanges about ten-fold slower than H₂ and H₂ exchanges very slowly ($t_{1/2} = 10$ hr) at still higher base strength (0.012 M), this inertness of H₃ is established. As a consequence, the rate of deuteration measured at H₃ after H₄ has completely exchanged (30 minutes) reflects the rate of rotation only. A correction for the proton content of the solvent pool was made as described in the Experimental section.

For run 6, it is assumed that at 0.2 M concentration of base, any deuteration at H₁ occurs via rotation only. The observation that

TABLE 11

Rate of Rotation about the N-N Bond in t-Butanol-0-d

Run #	[<u>t</u> -BuOK]M	Proton Monitored	10^5 k sec^{-1} ^a
4	0	H ₄	9.9±.3(0.999)
5	0.009	H ₃	9.6±.3(0.997)
6	0.2	H ₁	9.7±.2(0.999)

^aRate constants obtained by least squares analysis are quoted with the uncertainty in accuracy equal to the standard deviation of slope. Correlation coefficients in brackets, follow. All rate measurements were made at temperature of our HA-100 n.m.r. spectrometer, $27 \pm .5^\circ\text{C}$.

the half-life for exchange of H_1 is 16.5 hour in the presence of 0.6 M base validates this assumption. The rate measurements were conducted by monitoring the total integral of H_1 and residual H_2 . A correction for the proton content of the solvent pool was again made (see Experimental).

As Table 11 shows, the rates of rotation do not change appreciably with increasing concentration of potassium t-butoxide, but are equal within the limits of accuracy of measurement ($\pm 3\%$). The average value for the first-order rate constant is $9.7 \times 10^{-5} \text{ sec}^{-1}$ from which one can calculate a free energy barrier to rotation of 23 kcal/mole (at 27°C). This barrier equates to a half-life for rotation of 120 minutes. Thus the previously determined 10 hour half-life at 33°C was proven to be erroneous. Actually when we examined the data of the previous determination of the rate of rotation, it was found that by using a sample stereoselectively deuterated in place of H_4 , the rate of rotation was measured by the rate of increase in the intensity of the H_4 absorption, assuming the equilibrium concentration of H_4 was one proton. Since the deuterium label is equally distributed between the two axial-like positions 3 and 4 at equilibrium, the final concentration of H_4 should be half the total hydrogen content at these two positions instead of one proton. Therefore, it was the wrong treatment of data that led to the erroneous 10 hour half-life for the rate of rotation.

B. Determination of Base-Catalyzed Hydrogen-Deuterium Exchange Rates

The base-catalyzed hydrogen-deuterium exchange of each diastereotopic proton in 17 was monitored by integral measurement of each proton at periodic intervals using an HA-100 n.m.r. spectrometer. Since a finite amount of rotation occurs during the interval of study (except for H₄ whose half-life during exchange was three minutes), a correction factor must be included (see Experimental).

The rates of chemical exchange of the benzylic protons at several base concentrations are summarized in Table 12. The observed rates, when different from chemical rates, are given also. In run 7, the very large difference in the rates of exchange of H₄ versus H₂ restricts the accuracy of their measurement. Although measurement of the rate of exchange of H₄ would be more accurate at lower base concentration, there is a finite danger that at extremely low concentrations of base some quenching of base by small amounts of impurities can occur. The rates obtained in run 7 are estimated to be accurate to only ±20%, giving a value for the ratio k_4/k_2 of between 170 and 370 to 1. The remaining rate data is considerably more accurate. In fact the next poorest in accuracy involves the exchange rate of H₁ in run 9. The standard deviation in this rate constant derived from a least squares analysis is ±6%. All in all it would seem wise to deduce from all the data that protons H₁ to H₄ have rate constants of relative orders of magnitude 1:10³:10²:10⁵.

TABLE 12
 Rates of Exchange of α Protons in 17
 in t-Butanol-O-d

Run #	[<u>t</u> -BuOK]M	Proton	$10^5 k_{\text{obs}} \text{sec}^{-1}^{\text{a}}$	$10^5 k_{\text{chem}} \text{sec}^{-1}$	Relative Rates
7	0.012	H ₄	430±80 ^b	440	10 ⁵
		H ₂		1.8±.3(0.935)	10 ³
8	0.15	H ₃	33.4±1(0.995)	24.0	
		H ₂		264±3.5(0.998)	
9	0.6	H ₃	106.7±1.5(0.999)	97	10 ²
		H ₁	11.6±.7(0.980)	1.9	1

^aQuoted as in Table 11.

^bNo least squares analysis for this value because only two kinetic points were available for the exchange of this proton.

C. Effects of Stereochemistry on the Relative Rates

In analyzing the effects of stereochemistry on the relative rates of the α proton exchanges in the nitrosamine 17, the orientation of the four benzylic protons with respect to the activating N-NO group will be categorized according to two criteria:

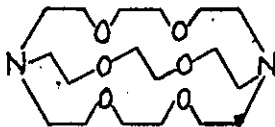
- a) orientation with respect to the π orbitals of the N-N=O function, i.e., H₄ and H₃ are said to be ψ -axial, H₂ and H₁, ψ -equatorial.
- b) orientation relative to the nitroso oxygen atom, i.e., H₄ and H₂ are syn to oxygen, while H₃ and H₁ are anti.

The data in Table 12 show that each ψ -axial proton exchanges much faster than its diastereotopic partner (roughly one hundred-fold with both the syn and anti pairs). For protons having the same disposition with respect to the π orbitals of the nitrosamino function, the syn vs anti factor can be seen to be even larger (roughly one thousand-fold).

In interpreting the hydrogen-deuterium exchange data in terms of carbanion stability, we must make sure that internal return¹² as well as isotope drowning⁶¹ which might invalidate the Brønsted correlation between kinetic and thermodynamic acidities are absent in the exchanges in question.

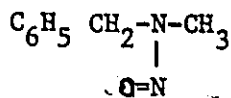
Two observations support the absence of these complicating factors. Treatment of 17 in T.H.F. at -78°C with 1.1 equivalent of methyl lithium, followed after 1 minute by excess methyl iodide gave solely the monomethyl derivative in which the methyl was ψ -axial and

syn⁵³ It would seem reasonable that the preference for an electrophilic substitution axial and syn in both T.H.F. and t-butanol-O-d reflects involvement of the same anion-stabilizing effects in both media. Since internal return cannot be involved in the methylation in T.H.F., it most probably is not of influence in the exchange reaction either. Secondly, the findings (to be given in detail below) that the rates of exchange of H₂ and H₃ and that of H₄ and H₃ were only slightly affected by the addition of the potassium ion complexing agents, dicyclohexyl-18-crown-6²⁶ and the macroheterocyclic diamine polyether (2.2.2) 21⁶² respectively support the contention as well. In the case of the bridged biaryl sulfoxide 3 (discussed in Part I of this thesis) known to involve internal return, the effect of added crown ether 14 on the absolute and relative rates have been appreciable. It then follows that the exchange rate of a ψ -axial versus ψ -equatorial proton is a measure of the difference in activation energies for the two proton abstractions.

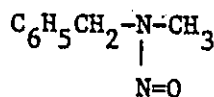


1. ψ -Axial versus ψ -Equatorial Selectivity

The high preference observed for the exchange of the axial-like protons over the equatorial-like proton cannot be explained by the steric influence of the biaryl system since it has been shown that, in the closely related thiepin dioxide system⁶³, the quasi-axial protons are more hindered. One other factor, preferred stabilization of the carbanion derived from H₄ and H₃ via overlap with the benzene rings also appear negligible. The preference is small and should amount to only 30% of the total accelerating influence of the benzene rings. Acceleration of a benzene ring relative to hydrogen was found to be 2.3 by measurement of the rates of exchange of the benzyl protons in the anti nitrosamine 22a relative to the methyl protons in the syn isomer 22s⁶⁴.

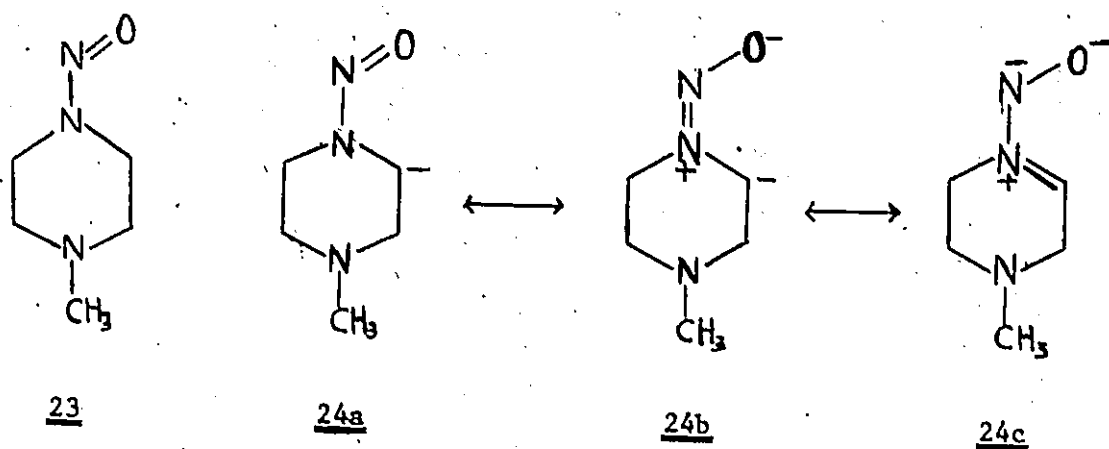


22a

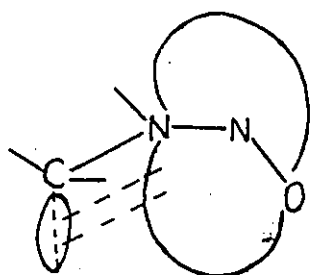


22s

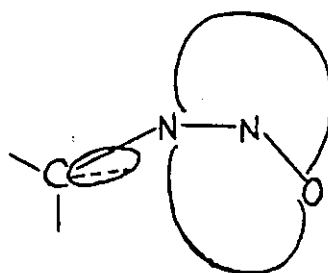
The lability of the α protons observed in the nitrosamine 23, i.e., N-nitroso-N'-methyl piperzaine, was suggested by Keefer and Fodor,⁴⁸ to be due to stabilization of the anion by the positive charge on the nitrogen as a result of resonance involving 24b. In the preliminary report of this work, it was pointed out that 24c might also be considered as contributing to the stability of the anion. This structure involves an allylic type delocalization which requires a proper orientation of the carbanion for an effective overlap to occur.



The relationship between stereochemical orientation and the extent of delocalization of the anion by an adjacent exocyclic π system is depicted in Figure 11.



ψ -axial interaction
(bonding)

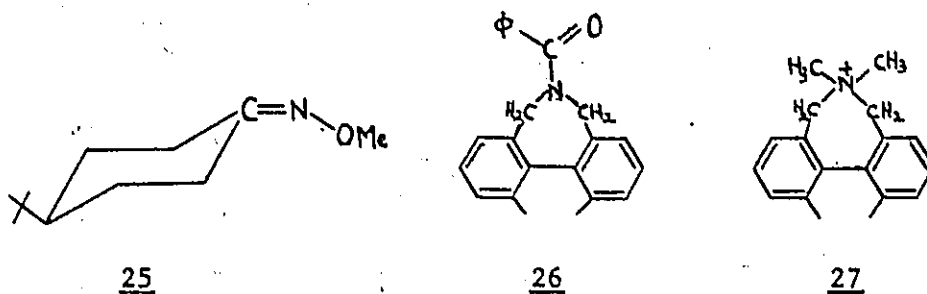


ψ -equatorial interaction
(non-bonding)

Figure 11

Thus, anions derived from the abstraction of the ψ -axial protons, H₃ and H₄, would be much more stable, since they possess proper alignment for overlap with the π system of the N-N=O function. Such overlap is geometrically restricted in anions resulting from abstraction of the ψ -equatorial protons, H₁ and H₂. The relative reactivities of the diastereotopic protons, however, is dependent on the structures of their transition states. As House pointed out⁶⁵, since the enolate is planar, the transition state for protonation or alkylation will not differ greatly from this configuration, in which the steric and the electronic effect is the same for either axial or equatorial attack. For example, a small degree of stereoselectivity was recently observed in the exchange of the α protons of 4-t-butylcyclohexanone ($k_{ax}/k_{eq} = 5:1$)⁶⁶. However, if the geometry of transition state structure approaches that of the ketone, the magnitude of the stabilization discrimination should increase in favor of the axial attack. Therefore, the higher selectivity observed in 17 for the preferential axial attack strongly infers that the nitrosamino carbanion retains some sp³ character. This seems reasonable since there would be an increase in steric repulsion between the remaining α hydrogen and the syn oxygen atom in a planar form. The large difference in the shieldings of the syn and anti α carbons of 19⁶⁷ is a strong indication that this interaction is appreciable even in the staggered chair conformation. With this structure of transition state, stereoelectronic control⁶⁸ or the differences in allylic stabilization will be greater. Thus strong evidence that resonance form 24c contributes

significantly to the anion stability is provided by the axial/equatorial rate ratio. Intuitive objections to its consideration on the basis of juxtaposition of partial negative charges should be tempered by consideration of the strong solvation present in the hydroxylic solvents used for the exchange.



If stereoelectronic control is responsible for the high axial-selectivity in the exchanges in nitrosamine 17, then other functional groups which consist of a properly aligned π system would also favor the axial attack. Indeed, recently in our laboratory⁶⁹ it has been found that in the potassium *t*-butoxide catalyzed hydrogen-deuterium exchange in *t*-butylcyclohexanone methoxime 25 in DMSO- d_6 , the rate ratio of the exchange of the *syn*-axial to the *syn*-equatorial proton was 40:1. This axial vs equatorial selectivity is comparable with that found in nitrosamine 17. In the benzamide 26, however, no information could be obtained as no exchange was detectable for the α protons in the potassium *t*-butoxide-*t*-butanol- $O-d^6$ medium (0.6 M) at room temperature for 24 hours.

Evidence against the importance of an 'ylide' type stabilization 24b is perhaps more conclusive. When quaternary iodide 27⁷⁰

was heated for 45 hours at 80°C then for another 24 hours at 100°C in t-butanol-O-d:CD₃OD (1:4.1 ratio) containing CD₃ONa, 0.30 M, no exchange was detectable. At 35°C in the same medium and at lower base concentration (0.22 M), the half-life for H₄ in 17 was twenty minutes⁵⁰.

2. Syn-Anti Selectivity

A comparison of the rates of exchange of H₂ vs H₁ or H₄ vs H₃ showed marked preference for syn exchange. Factors which might differ in their degree of stabilization of an anion as a function of this stereochemistry are a) steric, b) coulombic and c) cation effects. Since both steric and coulombic effects would be likely to stabilize the anion anti to the nitroso oxygen, some involvement of the cation seemed probable to account for the preferential syn stabilization. Indeed coordination of the cation with the carbanion and the ether oxygen has been used to explain the high degree of cis-stereospecificity of the rearrangement of allyl phenyl ether to the propenyl ether⁷¹ and also the preferential cis exchange in 1-methoxyacenaphthene³⁴. We therefore sought to examine the role of the potassium ion in the exchange reaction of 17. The fact that the crown ether 14²⁶ and the macroheterobicyclic diamine (2,2,2) 21⁶² form stable complexes with potassium ion suggested that the observation of a change in the rate of an hydrogen-deuterium exchange reaction on the addition of the complexing agent provides strong evidence for the involvement of potassium ion in the rate-determining step. Table 13 summarizes the

TABLE 13

Effects of Potassium Ion Complexing Agent (PCA) on Exchange Rates^a

Run	[t-BuOK]M	(PCA)M	Proton	10 ⁵ k _{obs} sec ⁻¹	10 ⁵ k _{chem} sec ⁻¹	Rate Ratio ^b	
						H ₂	H ₃
10	0.06	0.066 ^c	H ₃	12.2±2(0.873)	3.7		
			H ₂		35±2(0.988)	2.7	1.7
11	0.06	0.0	H ₃	14.9±.6(0.993)	6.3		
			H ₂		94±7(0.988)		
12	0.15	0.152 ^c	H ₃	25.3±1.5(0.983)	17		
			H ₂		54±6(0.940)	5	1.4
8	0.15	0.0	H ₃	33.4±1(0.99)	24		
			H ₂		264±6(0.999)		
13	0.065	0.069 ^d	H ₄		565		
			H ₃	25.6			
3	0.01	0.0	H ₄		383		
			H ₃	24.2			

^aQuoted as in Table 11.^bRatio of rates in absence and presence of potassium ion complexing agent.^cDicyclohexyl-18-crown-6 cyclic polyether was used.^dMacroheterobicyclic diamine 21 was used. This run was performed on T-60 with a probe temperature of 35±1°C.

data of the effect of the potassium complexing reagents 14 and 21 on the rates of exchange of H_2 , H_3 and H_4 . At 0.06 or 0.15 M concentration of base, the rate of exchange of H_3 is essentially unaffected by the addition of crown ether. The exchange of H_2 in the presence of excess crown ether does show a slight retardation, three-fold at 0.06M concentration of base and five-fold at .15 M concentration of base. Comparison of run 13 in Table 13 with run 3 in Table 10 assuming a base order of 1 shows that H_4 exchange was retarded by four-fold while H_3 exchange was essentially unaffected on the addition of the macroheterobicyclic diamine (2,2,2). If the role of potassium ion were to be of importance in preferential exchange of a syn proton, a retardation comparable to the 10^3 rate ratio would be anticipated. The observation of only slight retardation in the rate of exchange of the syn protons H_2 and H_4 is a strong indication that the potassium ion is not contributing to the syn selectivity. A further indication is furnished by examining the exchange rates in t-butanol-0-d using tetramethylammonium hydroxide as the base. These results are summarized in Table 14. Tetramethylammonium hydroxide is known to be well-dissociated in t-butanol³⁸ and therefore the cation is unlikely to participate in the proton abstraction step; we might expect the relative rates of H_4 vs H_3 and H_2 vs H_1 would be much reduced when tetramethylammonium hydroxide was used in place of potassium t-butoxide if potassium ion plays a role in favoring the syn-selectivity. These results showed that at the three base concentrations employed (0.005, 0.08 and 0.16 M), H_3 exchanged essentially via rotation (zero order

TABLE 14
Rates of Exchange of α Protons in 17 using
Tetramethylammonium Hydroxide as a Base

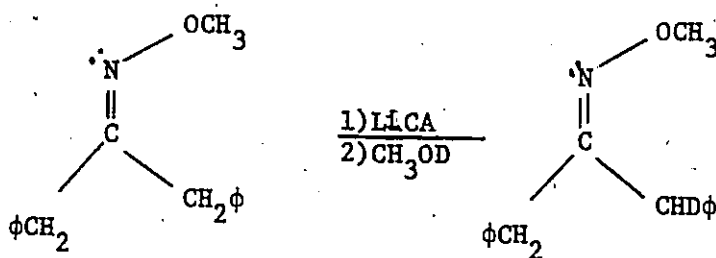
Run #	Base conc. M	Proton	$10^5 k \text{ sec}^{-1}$ ^a
14	0.005	H ₄	578
		H ₃	29.0
15	0.08	H ₃	30
		H ₂	10.2
16	0.16	H ₃	27.6
		H ₂	19.2

^aKinetic data were made on a Varian T-60 n.m.r. spectrometer, probe temperature was 35 ± 1 degree. Rate constants were determined with an uncertainty in accuracy of $\pm 15\%$.

as that theoretically derived by Epiotis⁷³ to account for, the greater stability of many cis over trans disubstituted ethylenes in which the substituents are fluorine, chlorine or alkoxy groups. Still earlier, a similar theoretical argument was expressed by Hoffmann and Olofson⁷⁴ to account for the reports by Bauld⁷⁵ of strong preferential formation of cis diacyloxy-olefins from the metal reductions of diketones.

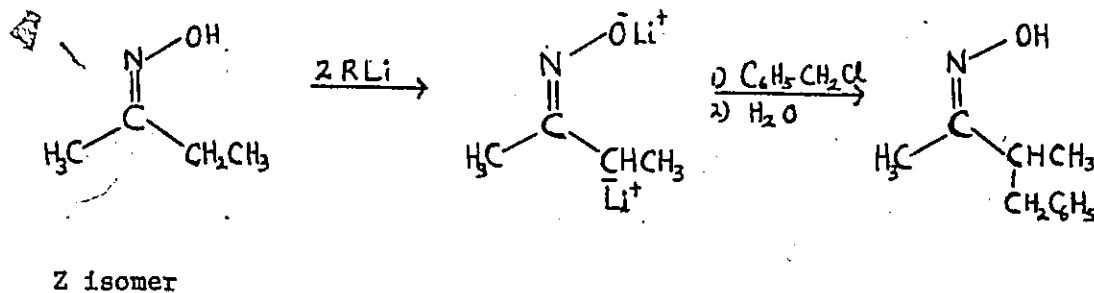
If one considers that formation of a cis olefin is energetically favored in spite of steric factors, it would not be unreasonable that the same influence of nonbonded attractive forces could lead to the greater syn selectivity in 17, since there will be no counter-balancing steric factors present.

If the above theoretical rationalization is valid, other stabilizing groups which will yield carbanion isoelectronic with butadiene dianion should similarly stabilize the syn carbanion. For example, the function $>C=N-OR$ would be an activating group of interest. Actually, a similar rationalization has been used to explain the syn-regioselectivity in the α deprotonation of dibenzyl ketone methoxime, 28⁷⁶.



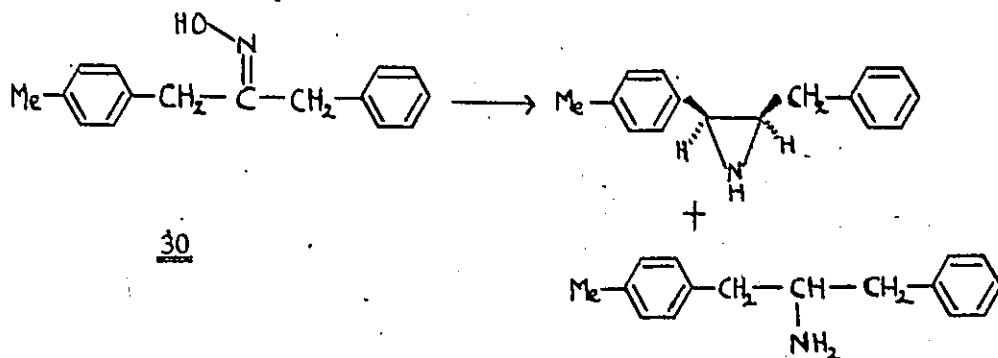
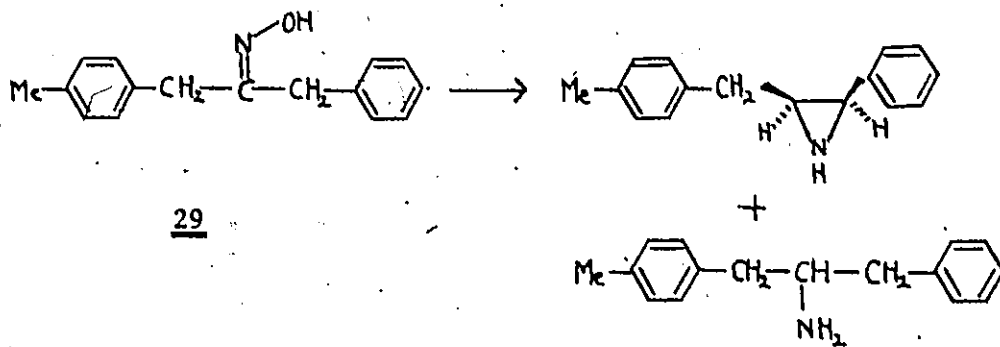
In the exchange of α protons in 25 catalyzed by potassium t-butoxide in DMSO- d_6 (<0.01 M)⁶⁹, it was found that under the reaction conditions where the syn-axial and the syn-equatorial protons exchanged with an half-life of 6 minutes and 4 hours respectively, the exchange of the anti protons was not detected after 5 hours. Furthermore, reaction of the anion of 25 with methyl iodide gave solely the syn-axial substituted product. This syn-selectivity is believed to be due to the stabilizing interaction between the carbanion site and the oxygen of the oxime function similar to that depicted in Figure 12.

Other examples of oxime which involve the same rationalization for the syn-selectivity are also available. The reaction of dilithium derivatives of ketoximes with alkyl halide and carbonyl compounds to give α -substituted oximes is regiospecific. The position of substitution being controlled by the stereochemistry of the oxime⁷⁷. For example, the *Z* isomer of 2-butanone oxime produced only the syn-substitution product.



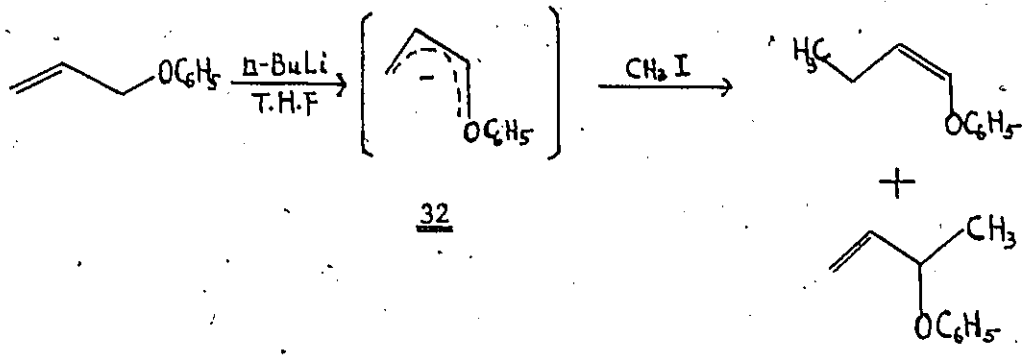
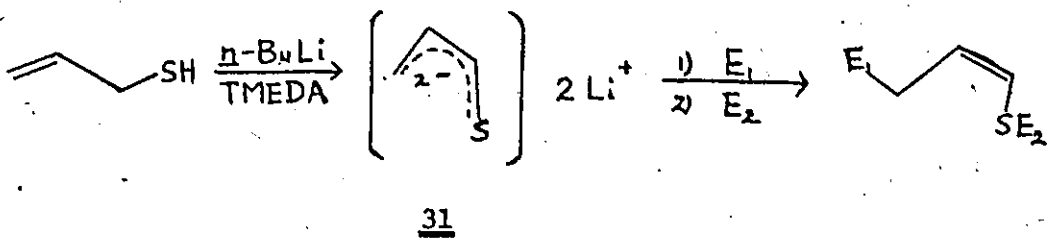
Also the lithium aluminum hydride reduction of an oxime to the related aziridine is found to proceed with considerable syn

stereoselectivity⁷⁸. For example, a single different aziridine was obtained from each isomer 29 and 30



The anions of allyl thiol⁷⁹ and allyl ether⁸⁰ react with electrophiles to give a mixture of α and γ adducts, in which the γ adducts were formed almost exclusively (>95%) in the cis configuration. Therefore, the intermediate anions, the doubly metallated 2-propenethiol 31 and the allyloxy carbanion 32, were believed to assume the cis configuration.

In the above examples in which alkyl lithium was used as the proton-abstraction base, although internal chelation of lithium ion with the carbanion and the oxygen or sulfur can account for the syn-selectivity, it is probable that the observed regioselectivity



could be rationalized on the basis of the electronic structures of the derived atoms. These anions possess the six π electrons system with an attractive nonbonded interaction between the α carbon and the oxygen or sulfur as depicted in Figure 12.

EXPERIMENTAL

The macroheterobicyclic diamine 21 used was a generous gift from Professor Lehn of the University of Strasbourg, France. Dicyclohexyl-18-crown-6 obtained from Aldrich was used without further purification. Preparation of t-butanol- O - d and base solutions of potassium t-butoxide in t-butanol- O - d with and without dicyclohexyl-18-crown-6 cyclic polyether 14 or macroheterobicyclic diamine 21 were prepared as described in the experimental of Part I of this thesis. Base concentration was then checked by titrating the solution with standard aqueous hydrochloric acid to the phenolphthalein end-point before each run. J.T. Baker grade 10% aqueous solution of tetramethylammonium hydroxide was evaporated under reduced pressure. Solutions involving the quaternary ammonium hydroxide were made by dissolving the required amount of base into the solvent.

All kinetic runs were performed either on a Varian T-60 or a Varian HA-100 n.m.r. spectrometer. Each kinetic run except 4 was carried out on 17 mg (0.067 mmole) of 17 dissolved in 0.3-0.4 ml of t-butanol- O - d in a thin-walled 5 mm n.m.r. tube. Upon the addition with vigorous shaking of 0.1-0.3 ml of t-butanol- O - d containing the desired concentration of base (final substrate concentration is 17 mg/.5 ml or 17 mg/.6 ml), the tube was placed in the spectrometer for continuing integral measurement with the timer started simultaneously. All the n.m.r. tubes for kinetic runs were cleaned and dried at 100°C for at least 24 hours. The tubes were allowed to cool in a desiccator and flushed with dry nitrogen prior to use.

Kinetic data were treated with a least squares program²⁷ on an IBM 360. In general, data were obtained over one-half-life (unless otherwise noted) and at least four points were taken for each plot.

Compound 17 was prepared as described previously⁵³.

A. Preparation of the Nitrosamine 17 Selectively Deuterated at H₄

N-nitroso-6,7-dihydro-1, 11-dimethyl-5H-dibenz[c,e]azepine, 25 mg, was weighed out into an n.m.r. tube and dissolved in 5 ml of t-butanol-0-d. After locating the overlapping absorption of protons 1 and 2 on a Varian T-60 n.m.r. spectrometer, a solution of 0.2 ml of potassium t-butoxide in t-butanol-0-d (0.035 M) was added to the nitrosamine solution. H₄ was shown to be almost completely deuterated after 6 minutes by the change of the doublet representing H₂ to a singlet. The solution was quickly poured into a round-bottomed flask and immediately quenched with .17 ml of 0.05 M hydrochloric acid in t-butanol-0-d. The solvent was removed using a rotary evaporator for 7 minutes without any heating. The solid residue was dissolved in .25 ml of pre-cooled chloroform (4°C) and the solution was separated from the undissolved inorganic salt by pipetting into another flask. Chloroform was immediately removed and the residue dried in vacuum (<1 mm) for 5 minutes. Redissolution of the dry residue (16.8 mg) in .5 ml t-butanol-0-d gave a sample containing 67% deuterium at H₄ and 23% at H₃ as determined from integration of the proton absorptions.

B. Preparation of the Bridged Biaryl Benzamide 26

The bridged biaryl benzamide 26 was prepared by benzylation of the corresponding amine, 6,7-dihydro-1,11-dimethyl-5H-dibenz[c,e]azepine⁵³, using the pyridine method⁸¹. The product after recrystallization from cyclohexane-hexane mixture was obtained in 56% yield and had m.p. 136-137°C. n.m.r.: 2.19 (s, 6H), 3.58 (d, J=14 Hz, 1H),

3.76 (d, J=13 Hz, 1H), 4.36 (d, J=14 Hz, 1H), 5.20 (d, J=13 Hz, 1H), and 6.68-7.5 (m. 6H)

C. Kinetics

1. Runs 1-3 (Preliminary Studies)

The three kinetic runs in Table 10 were carried out on a Varian T-60 n.m.r. spectrometer whose probe temperature was 35 ± 1 degrees. The spectrum of 17 on the spectrometer has the H_4 absorption interfered by the side bands of the huge absorption of the nearby t-butyl hydrogens and the OH peak happens to appear close to the H_3 absorption region, thus making the direct integration of these two protons unfavorable. The method chosen for measuring the rate of disappearance of these protons was integration of the overlapping absorption region of H_1 and H_2 . As H_4 is exchanging, the doublet of its diastereotopic partner H_2 merges into a singlet and overlaps over the inner peak of the H_1 doublet. The increase in the intensity of this overlapping peak was followed to give the exchange rate of H_4 . Since the rate of exchange of H_4 is much faster than that of H_3 and the rate of rotation, kinetic measurement for H_4 was complete before H_3 showed any deuteration, therefore the H_1 doublet remained unchanged during the kinetic measurements for the exchange of H_4 , any increase in the intensity of the overlapping peak was due to the deuteration of H_4 . Deuteration of H_3 was determined by following the disappearance of the low field half of the H_1 doublet. Rate of deuteration of H_2 was determined by following the decrease of the total integral of H_1

and H₂ absorptions, assuming H₁ exchange was negligible during the kinetic run. (This assumption was valid as we can see in the latter determination of the relative rates, H₂ exchanging 10³ fold faster than H₁). All the kinetic runs in Table 10 were treated as pseudo-first order reactions, i.e., rate = k[H] where k = k'[Base].

2. Runs 4-6 (Determination of the Rate of Rotation)

The kinetic runs 4-12 in Tables 11, 12 and 13 were performed on a Varian HA-100 n.m.r. spectrometer, equipped with a SD-100 deuterium decoupler. The probe temperature was maintained at 27 ± 0.5°C degrees throughout all kinetic runs. Rate measurements for H₃ and H₄ were made by integrating over the individual proton while that for H₁ and H₂ were carried out by following the decrease in the total integral of H₁ and H₂.

From run 4 in which the rate of rotation about N-N bond was determined in the absence of base, a sample containing 67% deuterium at H₄ and 23% at H₃ was dissolved in t-butanol-0-d and the increase in the intensity of H₄ absorption to the equilibrium value (45.0% deuterium or 55% hydrogen at H₃ and H₄) was followed by integral measurement. A first-order plot of $\ln \frac{[H_4]_0 - [H_4]_e}{[H_4]_t - [H_4]_e}$ versus time, where [H₄]_e is the concentration of H₄ at equilibrium, gave a slope which is the first-order rate constant for rotation.

Rate of rotation in the presence of base was determined by base concentrations which assure no chemical exchange of the proton monitored. As a consequence, for run 5, the rate of deuteration

measured at H_3 after H_4 has completely exchanged (30 minutes) reflects the rate of rotation only. For the rotation process, i.e., $H_3 + D_4 \xrightarrow{\text{rot}} D_3 + H_4$, rate = $k''_{\text{rot}} [H_3][D_4]$. At the concentration of base employed (0.009 M), H_4 has an half-life for exchange of 4 minutes which is much smaller than that of rotation (120 minutes), therefore any H_4 formed by rotation will be quickly deuterated and equilibrated with the solvent pool and the rate can be expressed as $k'_{\text{rot}} [H_3][\text{ROD}]$. This second-order expression should not be reduced to first-order because the deuterium pool of the solvent does not remain constant throughout the kinetic run but is being diluted by hydrogen and thus retards the rate of exchange. By treating the kinetic as a second-order reaction, this dilution effect is corrected.

At the substrate concentration (0.135M or 17 mg/.5 ml) used, each proton deuterated will dilute the deuterium concentration of the solvent by 1.3%; moreover, the stock t-butanol-0-d contains only 97.5% deuterium, therefore at equilibrium a significant amount of hydrogen isotope remains at H_3 . In other words, the deuteration goes from 0% to only 95% deuterium instead of 100%. Because of this solvent pool effect, the latter points of a kinetic will thus be significantly affected. A corresponding correction to the second-order rate expression was made by subtracting the equilibrium value, $[H_3]_e$, from each measured concentration of H_3 . The complete rate expression is then

$$\log\left(\frac{[\text{ROD}]_t}{[\text{ROD}]_0} \cdot \frac{[H_3]_0 - [H_3]_e}{[H_3]_t - [H_3]_e}\right) = \frac{[\text{ROD}]_0 - ([H_3]_0 - [H_3]_e)}{2.303} k'_{\text{rot}} t \quad (4)$$

The equilibrium value $[H_3]_e$ was taken as the deuterium content of the solvent as diluted by two substrate protons, assuming that H_1 and H_2 were inert during the deuteration of H_3 via rotation at this base concentration. The second-order rate constant, k'_{rot} , was obtained from the slope of the linear log plot versus time and was converted to the first-order rate constant, k_{rot} , on multiplication by the initial concentration of *t*-butanol-*O*-d, $[ROD]_0$. Since deuteration of H_3 was followed after H_4 is completely deuterated, the initial concentration of the solvent $[ROD]_0$ was taken as the solvent pool diluted by one substrate proton. Proton content of the solvent at time t was estimated from the decrease in the total integral of the four benzylic protons at the corresponding time plus the original proton content in the solvent (2.5%).

The same treatment was applied to run 6 in which H_1 undergoes deuteration via rotation only. The first kinetic point was taken after H_2 was completely exchanged. Since the rate measurement of H_1 deuteration was conducted by integrating over the overlapping absorption regions of H_1 and H_2 , each spectral integral of H_1 was corrected for H_2 residue which is equal to the proton content of the solvent pool at any time.

3. Runs 7-9 (Determinations of Base-Catalyzed Exchanges of H_1 to H_4)

In the rate determinations of the base-catalyzed exchanges of the four benzylic protons, the observed rates were corrected for the effect of rotation which interchanges the environments of H_1 and H_2 and of H_3 and H_4 .

The exchange of H_4 (run 7) which has an half-life of three minutes was followed up to 70% completion, the retardation of rate by rotation was considered negligible during the interval of kinetic study (3.5% rotation only). Since the exchange went so fast that only two kinetic points were available, the kinetic was treated as a pseudo-first order reaction as described in Section (1).

For H_3 , contribution of deuteration via rotation to the observed deuteration was appreciable. At the concentrations of base employed in runs 8 and 9 (0.15 and 0.6 M, respectively), any H_4 formed by the rotation process, i.e., $H_3 + D_4 \rightarrow D_3 + H_4$, is instantaneously replaced by deuterium and equilibrated with the solvent pool, therefore the rate component of deuteration due to rotation is the same, i.e., rate = $k'_{rot} [H_3][ROD]$. Simultaneous base-catalyzed exchange has a rate = $k'_{chem} [H_3][ROD]$. Thus the observed rate = $k'_{rot} [H_3][ROD] + k'_{chem} [H_3][ROD]$, i.e., $k'_{obs} = k'_{rot} + k'_{chem}$. The k'_{obs} was then determined using equation 4, taking $[H_3]_e$ as the isotopic content of the solvent pool as diluted by three substrate protons. The second-order rate constant k'_{obs} was converted to the first-order rate constant k_{obs} as described in the preceding section (2), thus $k_{obs} = k_{rot} + k_{chem}$. The first order rate constant for the chemical exchange was obtained by $k_{chem} = k_{obs} - k_{rot}$ where k_{rot} was the average value determined in section (2).

The same treatment was applied to the measurement of the exchange of H_1 since H_2 remained deuterated to the isotopic distribution of the solvent pool during the measurements of $[H_1]_t$. The equilibrium

value $[H_1]_e$ is the isotopic content of the solvent pool after complete exchange of all four α protons.

Deuteration of H_2 was followed by integral measurement of the overlapping absorption regions of H_1 and H_2 . As a result, the total deuterium uptake via H_2 exchange is not altered by the rotation. For run 8, in which H_2 has an half-life of 5 minutes, the last kinetic point was taken at 9 minutes, the effect of rotation was considered negligible (7.5% rotation). However, when $k_{rot} \gg k_2 \gg k_1$ and H_1 is considered inert, rotation is faster than the deuteration of H_2 , therefore any deuterium uptake via H_2 exchange will be quickly equilibrated between the two quasi-equatorial protons H_1 and H_2 , as a result, the effect of rotation effectively doubles the quantity of H_2 available for exchange. For run 7 in which the relative rate k_{rot}/k_{chem} for H_2 is 5, the exchange of H_2 was only followed to 20% completion (4 hours) and in this range the effect of rotation does not change the derived value of k .

A sample determination of the rate of base-catalyzed exchange is given below. The experimental data for the exchange of H_1 in run 9 are summarized in Table 15.

The plot of the log term in the last column vs time is shown in Figure 13. Least squares treatment of the data gives a slope of 0.00299 min^{-1} or 0.00005 sec^{-1} which is equal to $\frac{[ROD]_0 - [H_1]_0}{2.303} k'_{obs}$. The k'_{obs} obtained from the least squares treatment is $1.17 \times 10^{-5} \text{ M}^{-1} \text{ sec}^{-1}$, which on multiplication by $[ROD]_0$ gives $k_{obs} = 11.6 \times 10^{-5} \text{ sec}^{-1}$, k_{chem} obtained by $k_{obs} - k_{rot}$ is $1.9 \times 10^{-5} \text{ sec}^{-1}$.

TABLE 15

Deuteration Kinetics of H₁ in Run 9

Time (min)	[H ₁] _t M ^a	[ROD] _t M	$\log\left(\frac{[H_1]_0 [ROD]_t}{[H_1]_t [ROD]_0}\right)$
0	.104	9.900	0
16.9	.0902	9.869	0.060
25.3	.0861	9.855	0.088
40.0	.0733	9.830	0.149
48.4	.0651	9.820	0.180
60.0	.0643	9.817	0.205
77.7	.0626	9.815	0.217
85.0	.0558	9.815	0.274
94.5	.0545	9.810	0.277
116	.0505	9.803	0.309
161.5	.0298	9.784	0.538

^aEach [H₁]_t has been corrected for residual [H₂] and the equilibrium value [H₁]_e.

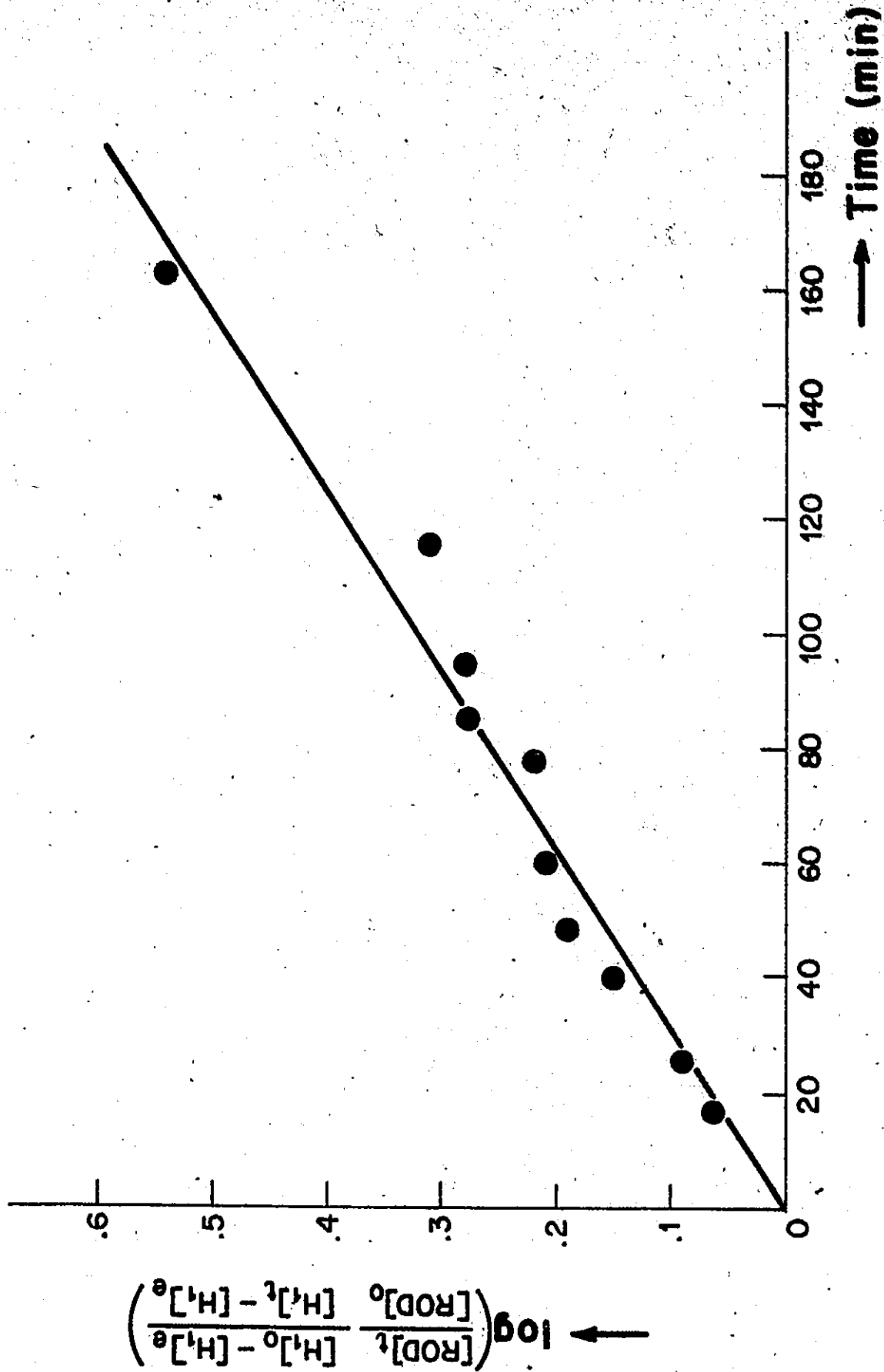


Figure 13. Hydrogen-deuterium exchange of H₁ in the Nitrosamine 17 (run 9)

4. Runs 10-13 (Effects of Potassium Ion Complexing Agent on Rates of Exchange)

Runs 10-13 were treated as simple first-order reactions since qualitative results were obtained. Rate constants for chemical exchange were obtained by $k_{obs} - k_{rot}$ where k_{rot} was $9.7 \times 10^{-5} \text{ sec}^{-1}$ as determined in runs 4-6.

5. Runs 14-15

The kinetic experiments and determination of rate constants were carried out as described in Section (1) for runs 1-3.

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CLAIMS TO ORIGINAL RESEARCH

1. The presence of internal return in the potassium alkoxide-catalyzed exchange of the α protons in the conformationally rigid biaryl sulfoxide 3, 1,11-dimethyl-5,7-dihydrodibenz[c,e]thiepin S-oxide, in t-butanol and methanol has been established.
2. A mechanism for the exchange reaction between the α protons in 3 and t-butanol or methanol has been proposed to interrelate the low isotope effects involving the exchanges and the effects of potassium ion complexing agent on the stereoselectivity of the exchanges.
3. A quantitative assessment of the amount of internal return has been made for the exchanges of the methylene protons in benzyl methyl sulfoxide.
4. The rotational barrier for the N-N bond in the conformationally rigid biaryl nitrosamine 17, N-nitroso-6,7-dihydro-1,11-dimethyl-5H-dibenz[c,e]azepine, has been determined.
5. Accurate measurements of the rates of exchange of the four benzylic protons in 17 have been made in t-butanol-O-d containing potassium t-butoxide. Since experiments established no counterion involvement, preferential axial exchange and syn exchange have been rationalized on the basis of the symmetry properties of the anionic intermediates.