MECHANISMS OF BASE-CATALYSED ISOTOPIC EXCHANGE REACTIONS IN KETONES : STEREOELECTRONIC EFFECT

by

P.J. Champagne

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UNIVERSITY OF OTTAWA
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ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
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ABSTRACT

The stereoselectivity of isotopic exchange by the diastereotopic methylene protons was examined for two ketones: a) the conformationally rigid biarylcycloheptadienone, 16; b) the conformationally rigid tricycloketone, Twistan-4-one, 17.

a) The diastereotopic α-keto methylene protons in 16 were found to undergo H/D exchange with a rate ratio of 63:1 in methanol-0-d with sodium methoxide as base, the proton whose C-H bond is perpendicular to the direction of the C=0 bond exchanging fastest. The ratio decreased to 34:1 with sodium phenoxide base and 7:1 with sodium 2,6 - dimethylphenoxide as base (both in methanol-0-d), showing that the more labile proton is in the more sterically hindered position.

The effect of internal return was evaluated qualitatively by measuring the rate ratio for H/D exchange in the presence of crown ether. No change in stereoselectivity was observed. Also, the rate ratio for the back exchange (D/H) was measured as 12:1, a change consistent with the absence of internal return.

Attempts to quantitatively evaluate the effect of internal return by measurement of the primary isotope effects (k^H/k^T and k^D/k^T) gave unacceptable results, probably due to the large effect of experimental errors on the calculated internal return vales. The absence of internal return was therefore assumed. However, these primary isotope effects along with the D/H exchange ratio of 12:1 were used to estimate the k^H/k^D values and solvent isotope effects at the two diastereotopic positions. It was found that the two protons exhibit different primary isotope effects (k^H/k^D) and different solvent isotope effects.

For the fast position, $k^H/k^D = 3.8$, $k^{MeOD}/k^{MeOH} = 2.6$. For the slow positions, $k^H/k^D = 2.3$, $k^{MeOD} / k^{MeOH} = 1.2$. These results are consistent with the two protons having different exchange mechanisms and therefore with the stereoselectivity of H/D exchange being due to the stereoelectronic control effect.

The secondary isotope effect for the fast exchanging position was measured as $i = 1.18$.

b) The diasteriotopic α-keto methylene protons in 17 were found to undergo H/D exchange with a rate ratio of 300:1 in methanol-O-d with sodium methoxide as base and 340:1 with sodium phenoxide as base. It was therefore concluded that the diastereotopic protons were in sterically similar environments. Assuming no internal return and the same secondary and solvent isotope effects which had been measured directly for 16, the measured rate ratio for back exchange (D/H) for 17 of 52:1 was used to estimate $k^H/k^D = 5.8$ for the fast position and $k^H/k^D = 2.9$ for the slow position. These results are again consistent with differing mechanisms for exchange at the two diastereotopic positions and therfore with stereoelectronic control as the factor responsible for the high exchange ratio for these protons.

LIST OF CONTENTS

INTRODUCTION

STUDIES OF ISOTOPIC EXCHANGE IN THE BIARYL CYCLOHEPTADIENONE, 16.

Page

F. Determination of the Secondary Isotope Effect (i_f) for the Fast Methylene Position in 16.

I. Effect of Internal Return on Stereoselectivity in 16

3. Measurement of Primary Isotope Effects for 16

(a) Determination of k_f^H and k_f^T for 16 in Sodium Methoxide/Methanol-O-d

(b) Determination of k_s^H and k_s^T for 16 in Sodium Methoxide/Methanol-O-d

Page

O. Measurement of k_f^D, k_s^D, k_f^T and k_s^T for 16 in Sodium Methoxide/Methanol-O-d

Q. Alkylation of 16

U. Measurement of k_f^D and k_s^D for 17 in Sodium Methoxide/Methanol-O-H.

LIST OF TABLES

Page

INTRODUCTION

Table

RESULTS SECTION

Table

Page

EXPERIMENTAL SECTION

Table

LIST OF FIGURES

INTRODUCTION

A. Historical Development

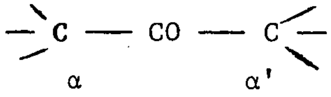
The importance of isotopic exchange of α-keto hydrogens in mechanistic studies has been realized since the first observation some 44 years ago(1) that acetone could exchange its hydrogen atoms for deuterium atoms in heavy water when catalyzed by an acid or base. The first measurement of the primary isotope effect for this reaction was achieved by Reitz(2), and the use of α-deuterated ketones in mechanistic studies has increased since that time.

Their are 15 different structural possibilities for the exchange of α-ketonic protons(3); they are given in Table 1 along with examples of compounds in which they are found. Kinetic expressions for isotopic exchanges in organic compounds(4) are able to give rigorous solutions for all but systems 1, 2, 6, 12, and 14 in Table 1, taking into account the primary and secondary isotope effects as well as the possibility of epimerization between partially exchanged species.

Until 1956 the experimental studies of α-ketone exchange were confined to the aliphatic ketones and to flexible cyclic ketones for which systems one can compare only the rates of exchange of the hydrogens on two different sides of the carbonyl, each of which may be influenced by different steric and electronic effects due to differing α and β substituents. The mechanistic aspects of the studies which are concerned with the enolization

TABLE 1

DIFFERENT SYSTEMS OF EXCHANGEABLE HYDROGENS

	Number of exchangeable hydrogens 		System number
	3 + 3	Acetone	1
	3 + 2	Me-CO-Et	2
	3 + 1	Me-CO-i-propyl	3
	3 + 0	Me-CO-t-butyl	4
4 Identical protons	2 + 2	Et-CO-Et	5
2 Identical α protons and 2 Identical α' protons	2 + 2	Et-CO-n-propyl	6
	2 + 1	Et-CO-i-propyl	7
	2 + 0	Et-CO-t-butyl	8
2 Identical protons	1 + 1	i-Propyl-CO-i-propyl	9
2 Different protons on 2 different carbons	1 + 1	i-Propyl-CO-i-butyl	10
	1 + 0	i-Propyl-CO-t-butyl	11
2 Different protons on each α and α' carbon	2 + 2	4-t-Butyl cyclohexanone	12
	1 + 1 + 1	trans-1-Decalone	13
	1 + 1 + 1 + 1	trans-2-Decalone	14
2 Different protons on the same carbon	1 + 1	Norcamphor	15

of ketones and the ketonization of enols are not necessarily the same as those for studies of more rigid cyclic ketones.

The base catalyzed exchange of α-keto protons proceeds via an enolate ion which then undergoes electrophilic attack by the solvent. Figure 1(3) shows the exchange diagram of the first proton in the case of a non-cyclic ketone; as the proton is removed from Cα or Cα' there is the formation of two enolates by two competitive reactions, with rate constants k_α and $k_{\alpha'}$ respectively. If the concentration of D atoms in the medium is high in comparison to the concentration of exchangeable H, the proton abstraction step is practically irreversible and the two enolates can only lead to the two mono-exchanged products 1α and 1α'. The ratio [1α]/[1α'] will be equal to the ratio of the rate constants for enolate formation kα/kα' and will depend only on the relative mobilities of the protons Hα and Hα'. The orientation of the exchange therefore is determined during the proton abstraction step.

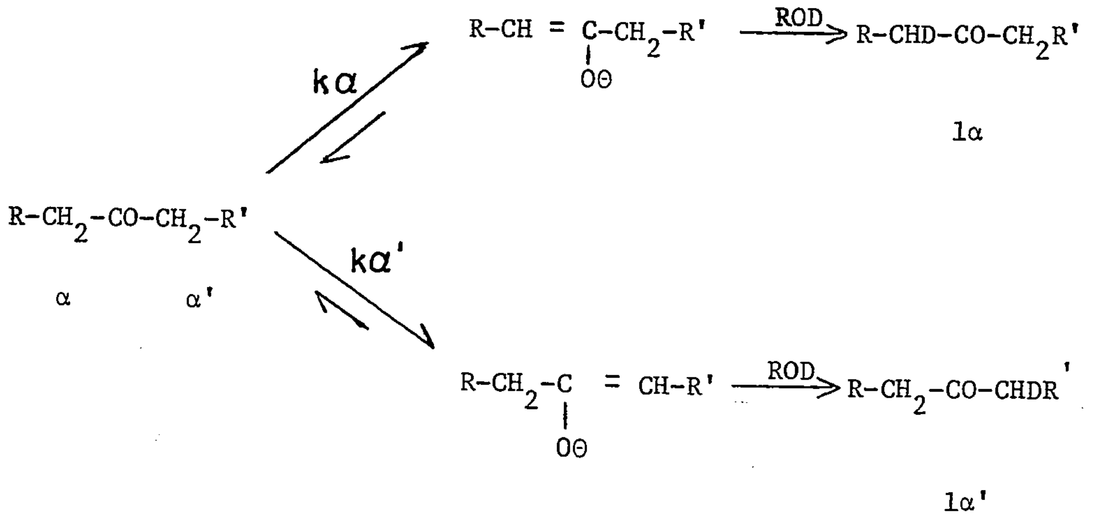


Fig. 1 Exchange diagram of the first proton of an acyclic ketone

The problem is somewhat different in the case of rigid cyclic ketones, where the two non-equivalent H atoms are located on the same C atom. The process is illustrated in figure 2(3) for 2-norbornenone but the process is the same for the decalones, steroid ketones, rigid cyclohexanones, etc.

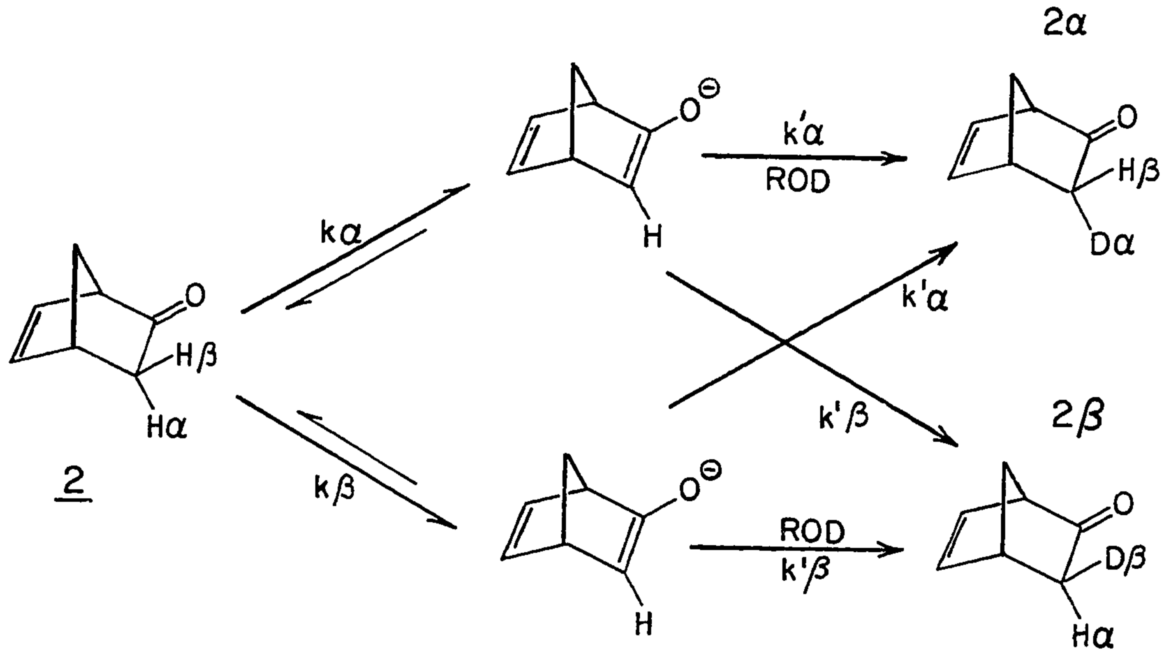
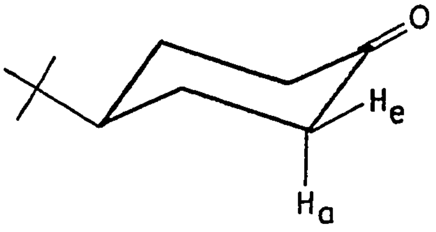


Fig. 2 Exchange diagram of the first proton of a rigid cyclic ketone

The removal of the two protons Hα and Hβ at different rates leads to the same enolate ion, (if solvent reorganization is fast and there is no sp^3 character in the carbanion), which is deuterated in the same manner whatever its origin. The ratio of the concentrations $[2\alpha]/[2\beta]$ depends only on the rate of the ROD attack upon each of the faces of the double bond and is equal to $k'\alpha/k'\beta$, i.e. the ratio of the two rate constants for ketonization of the enolate. The principle of microscopic reversibility enables us to say that the transition states are the same for enolate formation from the ketone and ketonization of the enolate and hence that $k'\alpha/k'\beta \simeq k\alpha/k\beta$. Therefore, D is incorporated into the α position in the same proportion as the H that was removed (provided that isotope effects are the same for the α and β positions).

The enolization of aliphatic ketones is a reaction subject to general acid and base catalysis, the slow step in the latter instance being the removal of an α-H by the base. The enolate ion is a high energy species, compared with the ketone ($\Delta G \simeq 8$ kcal/mole) and is therefore subject to rapid attack by electrophilic reagents present in the reaction medium. The large free energy difference between the ketone and the enolate ion indicates that the transition state for this step will be more similar to the enolate than to the original ketone. This is supported, for ordinary ketones, by the high value of the Brönsted coefficient $\beta \simeq 0.7$, the strong secondary isotope effects and the influence of substituents upon the rate of the reaction, all of which point to an activated complex which resembles the enolate. However the position of the transition state may vary with the nature of the substrate, the attacking base or the reaction medium.

The measurement of the ratio of rate constants, k_a/k_e, of the axial and equatorial protons located on the same carbon atoms of a rigid cyclohexanone, for example <u>3</u>, is one of the longstanding and important problems in conformational analysis. The difference in reactivity has been known for a long time, but the quantitative study of the problem was only undertaken by means of H/D exchange reactions less than 25 years ago. In 1956, Corey and Sneen(5) published their work on the enolization and ketonization of 3β-acetoxy-5α-androstan-7-one, <u>4</u>. In the presence of DBr in $CHCl_3$ the D isintroduced 1.5 times faster into the position 6β (ax.) than into the position 6α (eq.); in CH_3COOD the reactivity ratio is 9. Since the C10 axial methyl group is



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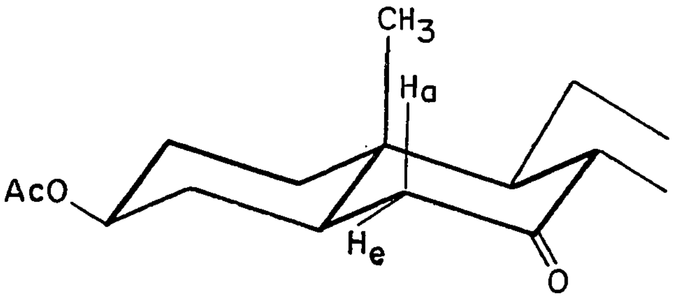

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known to hinder the reactivity of the β face and thus the axial attack by a factor of about 10 for DBr (strong acid) and about 5 for CH_3COOD (weak acid), these authors estimated the actual preferred axial introduction of D as 15 and 50 for DBR and CH_3COOD respectively. According to the theory of microscopic reversibility, the abstraction of the proton should occur with the same selectivity. The origin of this selectivity was attributed by Corey and Sneen(5) to the "stereoelectronic factor", which is "one which acts because of the restrictions placed on the geometry of the transition state and the location of the perturbed electrons by the energy lowering requirement of maximum bonding in the transition state, i.e., the requirement of that orientation of atoms and groups which provides the most effective electron delocalization". This theory has received support through the calculations of Tee(6) based on the "principle of least motion". In simpler form, the theory requires that the α-H removed must be perpendicular to the direction of the C=0 bond, in order to permit a stabilizing delocalization of the σ electrons of the C-αH bond towards the π orbitals of the carbonyl (a, Fig. 3).

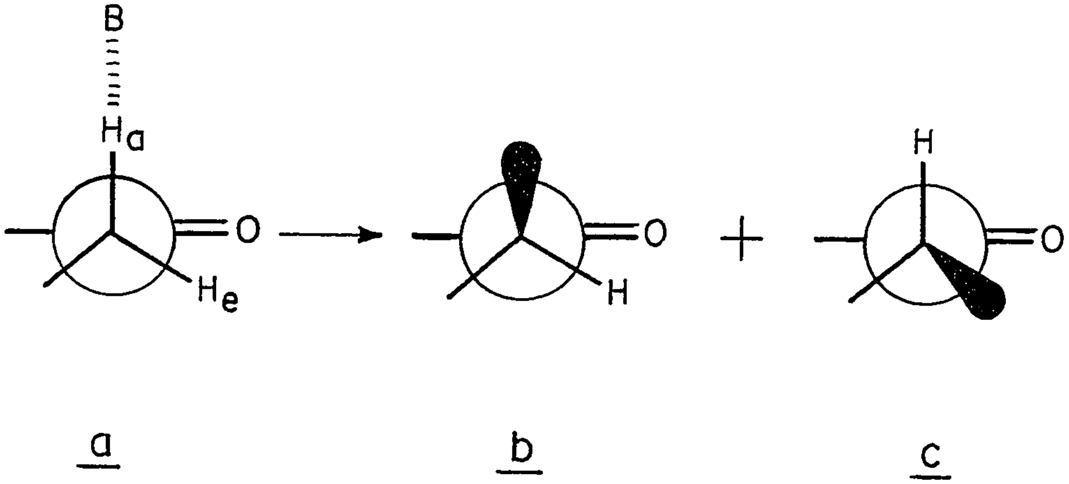
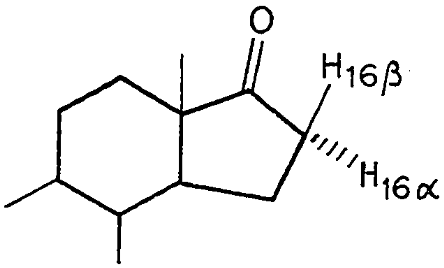


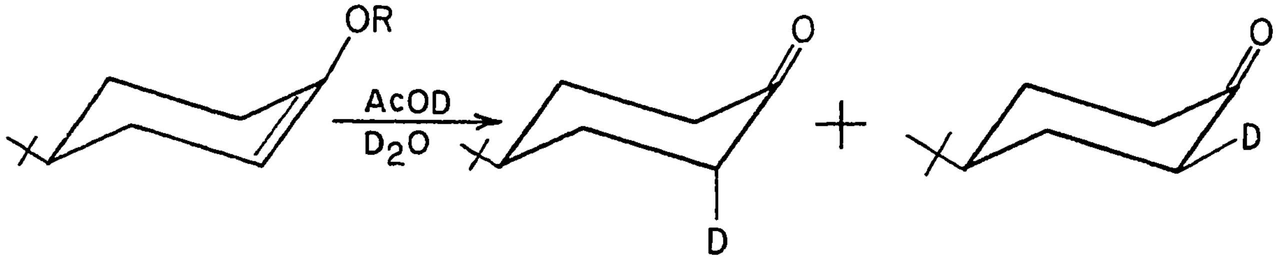
Fig. 3 Preferred conformation for α-proton removal with stereoelectronic control.

Recently, Wolfe et al(18) have calculated from _ab initio_ MO calculations that _b_ is more stable than _c_ by 18 kcal/mole. Djerassi et al(7) found that the 9α(ax.) and 12α(ax.) protons of 5α-androstan-11-one exchange much more rapidly than the 12β(eq.) proton. On the other hand, for 5α-androstan-7-one(8) in the presence of DBr and AcOD, the 6α (eq.) proton is exchanged twice as fast as the 6β(ax.) proton. In 1966, Fishman(9) confirmed the existence of the retarding effect of an axial methyl group; depending on the operating conditions, the 16α hydrogen of 5α-androstan-17-one, _5_, is exchanged 4-18 times faster than the 16β hydrogen. Also, in 1968, House et al(11) observed



_5_

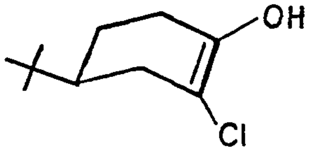
that the enol ether of 4-t-butylcyclohexanone, <u>6</u>, hydrolyses in AcOD/D_2O to give ca. 90% axial and 10% equatorial D, which corresponds to a ka/ke ratio of 9. However, the corresponding enolate anion showed lower preference for axial deuteration over equatorial deuteration (about 70:30 respectively). This result led House to conclude that while the enol or enol ether exhibits high selectivity in deuteration, the enolate anion itself shows little or none. The 70:30 ratio was explained by assuming that some of the enolate anion is deuterated at the oxygen and this portion accounts for the observed selectivity.



<u>6</u> 90 % 10 %

Casadevall et al$^{(12)}$ found that the enol, <u>7</u>, incorporates a proton 3 times faster in the axial than in the equatorial position.

The α-axial protons were shown to exchange about 2 times faster in acid (or 3.5 times faster in base) than the α-equatorial protons in trans-2-decalone, <u>8</u>, by Casadevall et al$^{(13)}$ and in trans-9-methyl-1-decalone, <u>9</u>, by Lamaty,$^{(14)}$ while for the base catalyzed H/D exchange of 4-t-butylcylohexanone, ka/ke ratios of 3.8 and 5.5 were measured by Lamaty$^{(14)}$ and Tsimitsis and van Dam$^{(15)}$ respectively.



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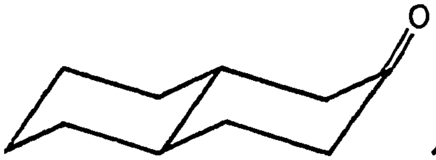

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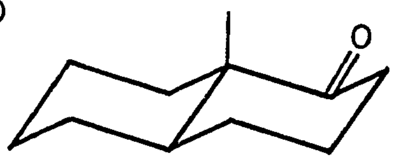

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House et al$^{(11)}$ and Valls and Toromanoff$^{(10)}$ have pointed out that the reaction of the cyclohexanone enolate can proceed by two transition states, both of which involve perpendicular attack of the electrophile, and their energy differences result from differences in strain in the chair and boat conformers produced therefrom, as shown in Figure 4.

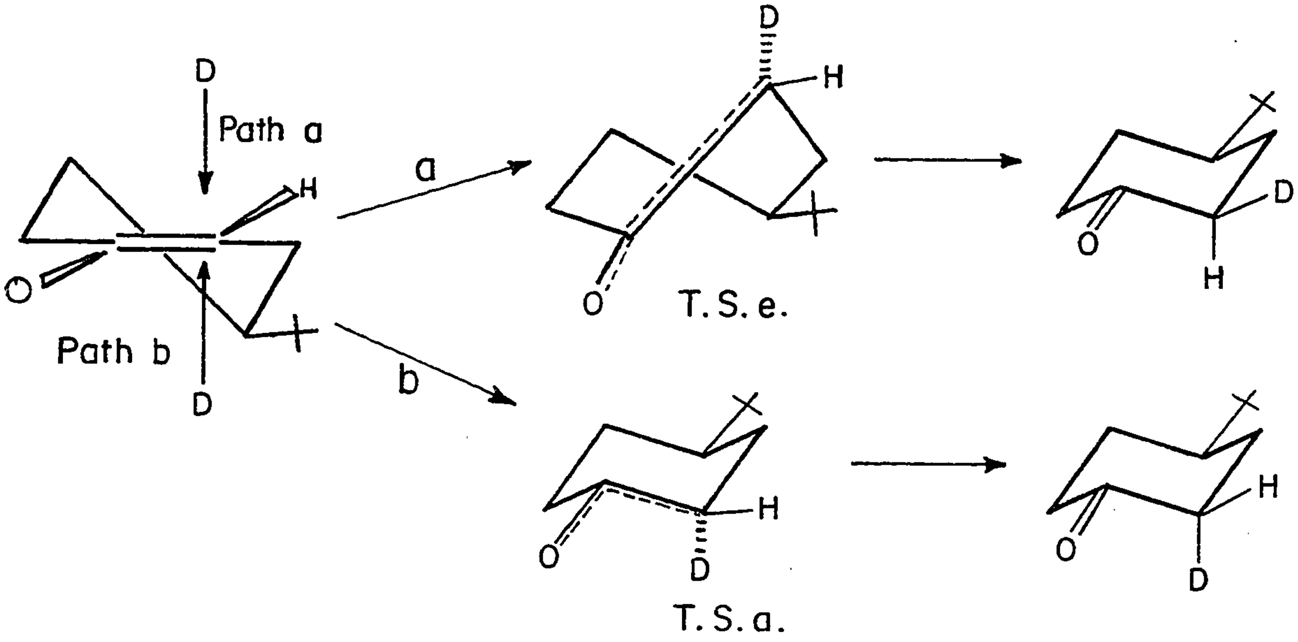
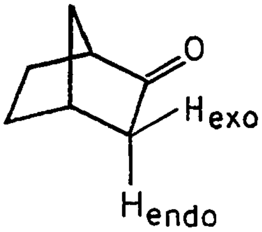


Figure 4. Ketonization of the enolate of 4-t-butylcyclohexanone

The transition state T.S.e. leading to introduction of an equatorial D has a "twisted boat" conformation, and the other, T.S.a., has a "chair-like" conformation. The free energy of T.S.a. should be lower than that of T.S.e and so the deuteron enters preferentially into the axial position. However, House's results(11) for alkylation of the enolate in Fig. 4 led him to conclude that the transition states for axial and equatorial attack are similar in energy and are enolate like in their geometry, i.e. that stereoelectronic factors are not important in this reaction.

Another field in which a great deal of research has been done in recent years is the α-exchange in rigid polycyclic ketones, mainly for derivatives of bicyclo [2.2.1] heptanone 10, and bicyclo [2.2.2] octanone 11.



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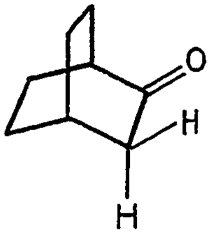

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The exo and endo α-protons, of course, have approximately the same orientation with respect to the carbonyl in 10 and 11 and both α-protons must exchange with the same rate (16) in 11. However, for 10, the exo proton exchanges 680 to 740 times faster than the endo proton in D_2O/dioxan with $OD^{\ominus}$ as catalyst.(14) (16) In some cases, endo substituents on the 6-position of 10 tend to increase this ratio of kexo/kendo while substituents on the one carbon bridge tend to decrease the ratio. However, this trend does not always hold true,(3) so the attractive explanation that the two carbon bridge is much more sterically hindering toward attack by the electrophile on the enolate than the one carbon bridge is somewhat tenuous at this time. The effect of endo-substituents at the more important 5-position in 10 have not yet been investigated.

The study of these bicyclic systems led Thomas et al(17) to the first demonstration of the non-equivalence of H/D and D/H exchange ratios in systems with non-equivalent protons on the α-carbon. It was demonstrated that the ratio kexo/kendo for deuteration is greater than that for dedeuteration by a factor of 2-8.(3) This surprising result becomes understandable if one considers the complete exchange diagram (Fig. 5.) which was recently given by Abad et al,(16a) and discussed in detail by Werstiuk(16b).

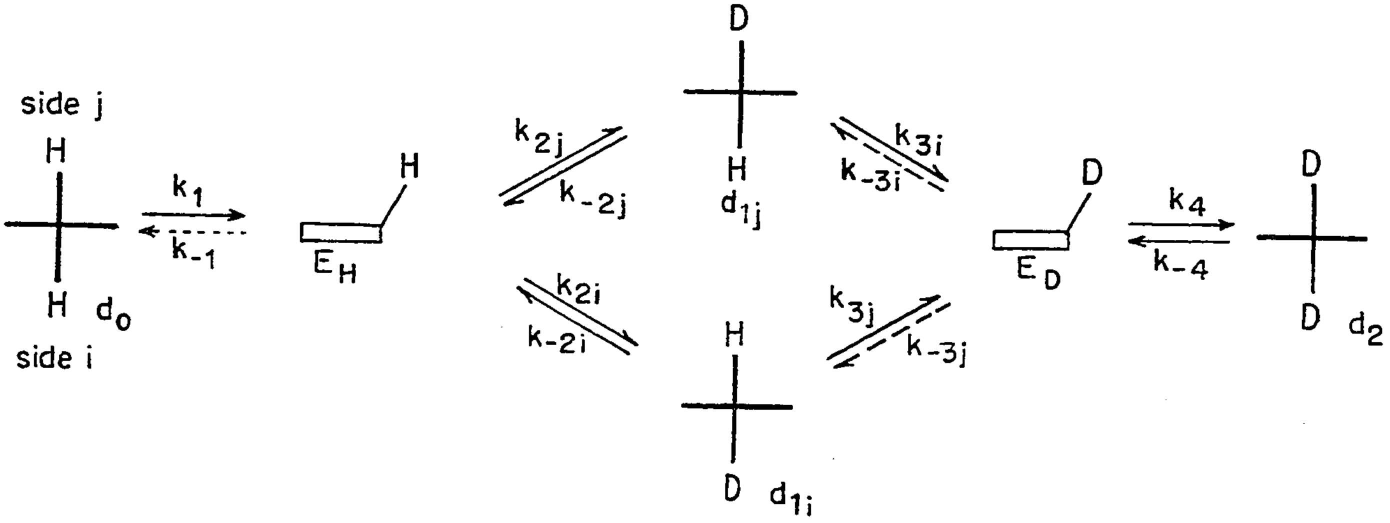


Fig. 5. Complete exchange diagram of two non-equivalent protons

In the presence of excess heavy water the formation of the enolate E_H is essentially irreversible, as is the passage from d_{1j} and d_{1i} to E_D. The general diagram of the dedeuteration reaction is almost identical, the difference being that the reactions k_4, k_{2i} and k_{2j} do not occur and are replaced by k_{-3j}, k_{-3i}, and k_{-1} (indicated with dotted lines). The important fact is the possibility of equilibrating the two mono-deuterated species, d_{1i} and d_{1j} through either the enolate E_H (direct reaction) or through the enolate E_D (reverse reaction). The risk of equilibration, however, is not great in the direct H/D exchange as may be shown by qualitative reasoning. Let us suppose that the proton on face j is more labile than the one on face i. Therefore, $k_{2j} > k_{2i}$ and the species d_{1j} will be more abundant than d_{1i}, i.e. $[d_{1j}]/[d_{1i}] = k_{2j}/k_{2i}$. From d_{1j} the equilibration, or the passage from d_{1j} to d_{1i}, supposes the rupture of a C-D bond, with rate constant k_{-2j}. The continuation of the exchange, or the passage from d_{1j} to E_D, supposes the breaking of a C-H bond for which the rate constant is k_{3i}. The competition between these two processes is dependent upon the ratio of the two constants k_{-2j}/k_{3i}. Since k_{-2j} is under the influence of an unfavourable primary isotope effect, ca. 6-8 depending on the particular case, the equilibration can only be important if k_j is much greater than k_i. The situation is quite different in the case of the reverse D/H exchange. Here d_{1i} is more abundant than d_{1j}, since $k_{-3j} > k_{-3i}$. The competition between the equilibration, $d_{1i} \rightarrow E_D \rightarrow d_{1j}$, and the continuation of the exchange, $d_{1i} \rightarrow E_H$, will depend on the ratio k_{3j}/k_{-2i}. But now, k_{-2i} is twice disadvantaged compared to k_{-3j}, firstly because of a considerable primary isotope effect and secondly because the D atom must be removed from the less reactive face of the molecule. The equilibration $d_{1i} \rightarrow d_{1j}$ will thus be the rule, the result being an apparent decrease in the selectivity of the exchange. According to Lamaty(3) and Werstiuk(16b) the system of differential equations derived from Fig. 5 can be solved for all rate constants and the observed changes in rate ratio explained quantitatively if the primary isotope effects are measured by independent means. In the case of norbornanone, 10, the normal k^H/k^D values of 6-8 give rise to the rate ratio diminution from 680 to 100, a factor of about 7.

B. Internal Return

1. Introduction

With reference again to Fig. 5, the initial proton abstraction, k_1 (or k_{-4} in the reverse direction), is considered to be irreversible. If there exist, however, constraints to the solvent reorganization required for the proton to be assimilated into the medium and to be replaced by a deuteron, the proton may return to the site from which it was removed. This process has been termed "internal return" and is important in this scheme because the amount of internal return can be different for the two positions and therefore affect the relative rates k_j and k_i.

Based on the Brönsted free-energy relationship between the kinetic and thermodynamic acidities, it is common practice to use the rates of hydrogen isotope exchange as a measure of carbanion stability. However, interpretation of the kinetic data can be made difficult by the existence of internal return. The presence of internal return in an isotopic exchange reaction involving carbanionic intermediates was first established by Cram and his co-workers(19 a) for exchange versus racemization studies in several phenyl substituted alkanes. A general treatment of internal return in such reactions follows from that work. In the exchange reaction formulated in Fig. 6 k_1^H and k_1^D are expected to be << k_{-1}^H, k_{-1}^D, k_2^H, k_2^D. The observed rate

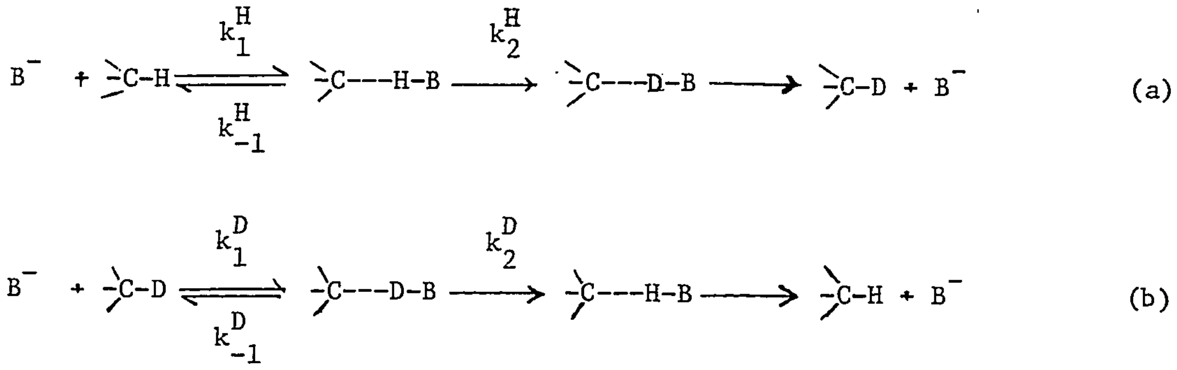


Fig. 6 Exchange reaction for (a) H→D and (b) D→H

constants are then given by equation (1) and (2), which combined give equation (3).

$$k^{H}\text{expt} = k_{1}^{H}\ k_{2}^{H}\ /\ (k_{-1}^{H} + k_{2}^{H}) \qquad (1)$$

$$k^{D}\text{expt} = k_{1}^{D}\ k_{2}^{D}\ /\ (k_{-1}^{D} + k_{2}^{D}) \qquad (2)$$

$$\frac{k^{H}\text{expt}}{k^{D}\text{expt}} = \frac{k_{1}^{H}\ k_{2}^{H}\ (k_{-1}^{D} + k_{2}^{D})}{k_{1}^{D}\ k_{2}^{D}\ (k_{-1}^{H} + k_{2}^{H})} \qquad (3)$$

If $k_{2}^{H} >> k_{-1}^{H}$ and $k_{2}^{D} >> k_{-1}^{D}$, then (3) becomes (4), and the ordinary

$$k^{H}\text{expt}/k^{D}\text{expt} = k_{1}^{H}/k_{1}^{D} \qquad (4)$$

kinetic isotope effect for dissociation of the carbon-hydrogen bond would be measured by exchange rates, that is, the observed rates reflect the ease of carbanion formation. However, if $k_{-1}^{H} >> k_{2}^{H}$ and $k_{-1}^{D} >> k_{2}^{D}$, then (3) becomes (5), and the observed isotope effect for exchange is the product of a

$$\frac{k^H_{expt}}{k^D_{expt}} = \frac{k^H_1}{k^H_{-1}} \times \frac{k^D_{-1}}{k^D_1} \times \frac{k^H_2}{k^D_2} = \frac{K^H}{K^D} \times \frac{k^H_2}{k^D_2} \qquad (5)$$

thermodynamic and a kinetic term. The value of K^H/K^D is expected to be close to unity since the isotope effects in k_1 and k_{-1} are essentially the same. Also, the term k^H_2/k^D_2 deals with a process in which no covalent bonds (only hydrogen bonds) are made or broken, and a value close to unity is again expected.

2. Qualitative Test For Internal Return

(a) Measurement of Primary Isotope Effects.

For a hydrogen isotopic exchange reaction, the difference in rates between the breaking of a C-H bond and a C-D bond is determined by the difference in activation energy $\Delta E^\ddagger$ 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 $\frac{1}{2}h\nu_H$. Since the frequency ν depends upon the isotopic mass, the difference in zero point energy of the two isotopic bonds is $\frac{1}{2}h(\nu_H-\nu_D)$. In the case of the transfer of the hydrogen isotope L from C-L to another atom B via a linear transition state $\overleftarrow{C}$ - - -L - - -$\overrightarrow{B}$, the symmetrical stretching vibration shown does not involve any movement of L. Consequently the symmetrical vibration frequency $\nu^\ddagger$ does not depend on the mass of L and $\frac{1}{2}h\nu^\ddagger_H - \frac{1}{2}h\nu^\ddagger_D = 0$. Only $\frac{1}{2}h(\nu_H-\nu_D)$, the net difference in activation energy $\Delta(\Delta E^\ddagger)$, is reflected in the isotope effect (Fig. 7a). The isotope effect k^H/k^D for a reaction involving cleavage of an aliphatic C-H bond was calculated by Bell(20) to be 6.2 at 298°K. Equation (5) in the introduction to this section shows that when $k_{-1} \gg k_2$, the measured isotope effect k^H_{expt}/k^D_{expt} will be approximately unity. Thus an observed

k^H/k^D value close to 1 indicates a substantial amount of internal return. If $k_{-1} << k_2$ (little or no internal return) then equation (4) shows that the measured isotope effect is equal to the true isotope effect of 6-8.

Some examples of low isotope effects are given in Table 2 and these were interpreted on the basis of $k_{-1} << k_2$.

(b) H/D versus D/H Exchange Rate Ratios

With reference to the exchange diagram for rigid ketones (Fig. 5) it was shown that the observed change in rate ratios for the forward (H/D) versus backward (D/H) reactions by a factor of 7 could be explained quantitatively by considering "normal" isotope effects of 6-8 which come into play for the D/H exchange reaction. Conversely, it can be said that if the exchange rate ratio for two different protons changes by a factor of about 7 in going from H/D to D/H exchange, then, provided that fairly "normal" primary isotope effects are operative, little or no internal return is indicated.

(c) Effect of Crown Ether on Exchange Rates

Since the cation in base catalyzed reactions in which anions are formed is known to participate in the carbanion forming hydrogen abstraction(19(a)(b)) it seems likely that the cation might be playing an important role in determining the stereoselectivity(22). In several cases where internal return is known to occur (23), the addition of crown ether was shown to alter the stereochemical course of the reaction 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 existance of internal return in the exchange.

3. Quantitative Test For 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,

Table 2

Low Primary Isotope Effects due to the Presence of Internal Return

Substrate	Base	Solvent	Primary Isotope Effect	Ref
toluene	<u>t</u>-BuOK	DMSO	0.6 (k^H/k^D)	21 (a)
thiophene	t-BuOK	DMSO	0.8 (k^D/k^T)	21 (b)
2-octyl phenyl sulfone	t-BuOK	t-BuOD	∿ 1 (k^H/k^D)	21 (c)
triphenylmethane	MeONa	MeOH	1.77 (k^H/k^T)	24

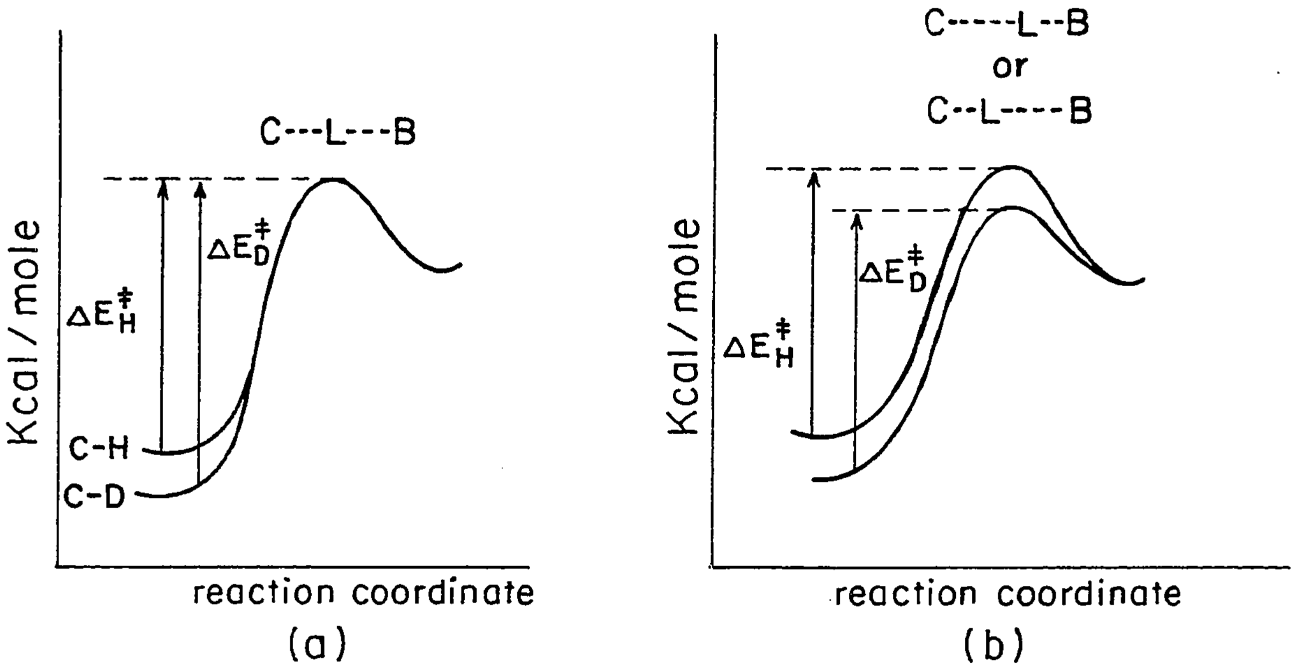


Figure 7. Zero-point energies and hydrogen isotope effect for a proton-transfer reaction (a) for a symmetrical transition state and (b) for an unsymmetrical transition state.

then the symmetric stretching vibration involves motion of the L atom and the stretching frequency will be dependant on the mass of L. This will give rise to a difference in the zero-point energies of the two transition states for the two isotopes, which may partly or completely balance that of the reactants (Fig. 7b). Consequently, the kinetic isotope effect will be lower than the calculated 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 involvement 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 (6) developed by Swain et al. The value of x is 2.26 by the Swain-Schaad treatment$^{(24(a))}$ and 2.344 by Streitwieser's treatment$^{(24(b))}$ 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.

$$\begin{aligned} k^H/k^D &= (k^D/k^T)^x \\ k^H/k^T &= (k^D/k^T)^{x+1} = (k^H/k^D)^{(x+1)/x} \end{aligned} \qquad (6)$$

When, by use of equation (6), 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 Streitwieser's group$^{(25)}$ for several base catalyzed reactions. Assuming the solvent isotope effect on the primary kinetic isotope effect is negligible, equation (7) expresses a^T, which is the ratio k^T_{-1}/k_2, in terms of the experimentally measured quantities A and B.

$$A + (A-B)a^T = \left[1-(B^{1/(x+1)}-1)a^T\right]^{x+1} \qquad (7)$$

where $$A = (k^D_{expt}/k^T_{expt})^{x+1} \; / \; (k^H_{expt}/k^T_{expt})$$

and $$B = (k^D_{expt}/k^T_{expt})^{x+1} \quad K^T/K^H$$

That k_2 is a diffusion step and therefore has no isotope effect implies that the carbanion (or enolate) is only hydrogen bonded to the solvent molecule BH (Fig. 6.), and thus the equilibrium $K^H = k^H_1/k^H_{-1}$ is determined by the relative energies of B-H and C-H. Therefore $K^T/K^H = K^{T'}$ for the equilibrium

$$RT + BH \overset{K^{T'}}{\rightleftharpoons} RH + BT$$

where $K^{T'}$ can be experimentally determined by measuring the relative tritium content in the solvent to that incorporated into 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 (8) which is derived from the experimental isotope effect given by

$$k^T_1/k^H_1 = k^T_{expt}/k^H_{expt} + a^T \;\; (k^T_{expt}/k^H_{expt} - K^{T'}) \qquad (8)$$

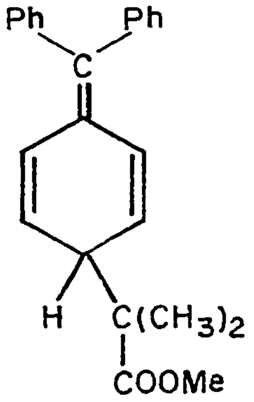
equation (3) rewritten for tritium in place of deuterium to give

$$k^T_{expt}/k^H_{expt} = \frac{k^T_1\,(k^H_{-1} + k_2)}{k^H_1\,(k^T_{-1} + k_2)}$$

Other isotope effects for the primary step, i.e., k^H_1/k^D_1 and k^D_1/k^T_1, are obtained from the determined k^T_1/k^H_1 by using equation (6).

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 as $a^D = a^T\ (K^T/K^D)\ (k_1^D/k_1^T)$ where K^T/K^D is derived from K^T/K^H by equation (6).

The Streitwieser approach has been shown to be consistant with results obtained by other methods. For example a^H was found to have a value of 1.44(24) (i.e. 59% internal return for hydrogen exchange) in the exchange of triphenylmethane in methanolic sodium methoxide, compared with the 46-7% intramolecularity found in the rearrangement of <u>12</u> to <u>13</u>(26) in the same solvent/base system. In both cases the triarylmethyl anion is involved as an intermediate.



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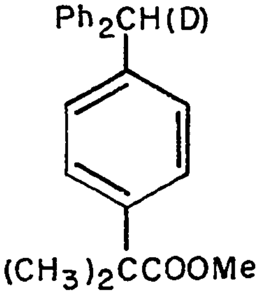
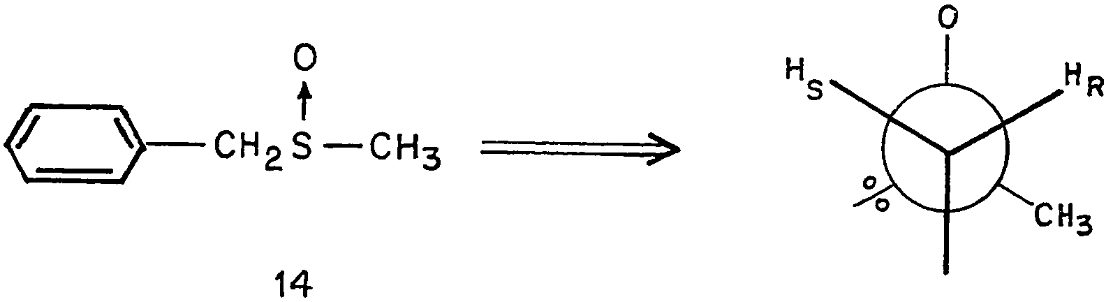


13

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 the value expected from a Swain-Schaad treatment. The x values were found to be 2.0 ± 0.2(25) for the fluorene at 25° and 9-methyl fluorene at 45°, indicating that internal return was of minor importance. When equation (7) derived by Streitwieser was applied to calculate a^T for those compounds, the isotope effects reported previously yielded a^T values of 0.016 ± 0.006 for fluorene at 25°C and 0.024 ± 0.022(24) for methylfluorene at 45°C. The results obtained from both treatments are virtually consistant with each other. Moreover, the k^H/k^D values of 6.3 obtained from k^D/k^T by equation (7) are in the normal high range for substantial proton transfer in the transition state, which will minimize internal return(20).

The Streitwieser method has been applied in the base catalyzed exchange of sulfoxides by Fraser and Ng(27). Internal return was found to be minimal in the exchange of benzylmethylsulfoxide 14 ($a^H = 0.03$ for H_R and $a^H = 0.14$ for H_S) but significant in the exchange of the biaryl sulfoxide 15 ($a^H \simeq 4$ for H_1 and $a^H \simeq 2.3$ for H_2).



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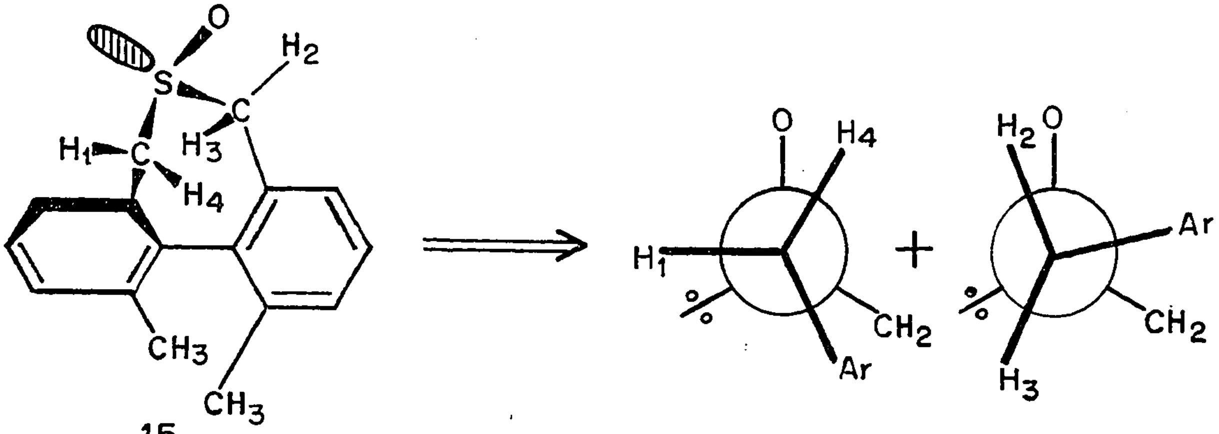


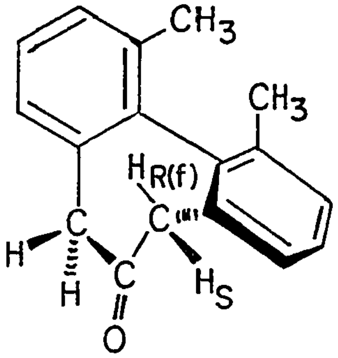
15

C. Aim Of This Research

Evidence that has been presented both for and against the theory of stereoelectronic control in the isotopic exchange of α-keto hydrogens in rigid cyclic ketones has suffered from the fact that the preference for exchange of one position over another has not been very pronounced and could be explained at least qualitatively by steric differences between the transition states. It was, therefore, our intention to study isotopic exchange rates in compounds for which the two α-keto protons had the required geometry (Fig. 3) for involvement of the stereoelectronic effect to favour exchange of one over the other and for which the system was more rigidly confined to this geometry. It was also necessary to choose systems for which it could be shown either that both types of protons were in the same steric environment or that any steric effect present would favour the exchange of that proton which is disfavoured by any stereoelectronic effect.

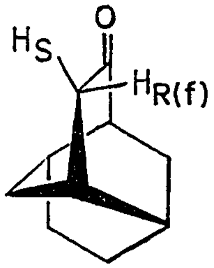
At the same time, such systems would provide the opportunity to test the application of Streitwieser's method for determination of the amount of internal return in the base catalyzed isotopic exchange of ketones in general and rigid cyclic ketones having different protons on the same α-carbon in particular, and to compare these quantitative results with the results from the qualitative tests for internal return.

It was with these objectives in mind that we chose to study the base catalyzed isotopic exchange rates of the α-keto protons first in the biaryl cycloheptadienone <u>16</u> which is prevented from racemization by the two methyl groups, and second in the more rigid twistan-4-one <u>17</u>.



4', 1"-dimethyl-1,2,3,4-dibenzcyclohepta-1,3-diene-6-one

16



tricyclo $[4.4.0.0^{3,8}]$ decan-4-one

17

Examination of a model of 16 shows that the proton labelled H_R (the pro R in R proton) is perpendicular to the direction of the C = 0 bond while the proton labelled H_S (pro S in R) is at an angle of about 30° from the C = 0 bond. The steric environment of H_R is such that any species approaching it should encounter serious interaction with the π system of the aromatic ring, while approach to the proton H_S appears to be relatively unhindered. Therefore any stereoelectronic preference for exchange of H_R will have to operate against the steric effects which favour exchange of H_S. Similar steric effects exist for protonation of the enol in this system.

Examination of the model of 17, on the other hand, shows that there should be very little steric resistance to approach of either α-keto proton and that any slight interactions should be the same for both protons.

Finally, it should be possible to measure the primary isotope effects and thus the amount of internal return for the two different protons on the same α-keto carbon.

STUDIES OF ISOTOPIC EXCHANGE IN THE BIARYL CYCLOHEPTADIENONE 16

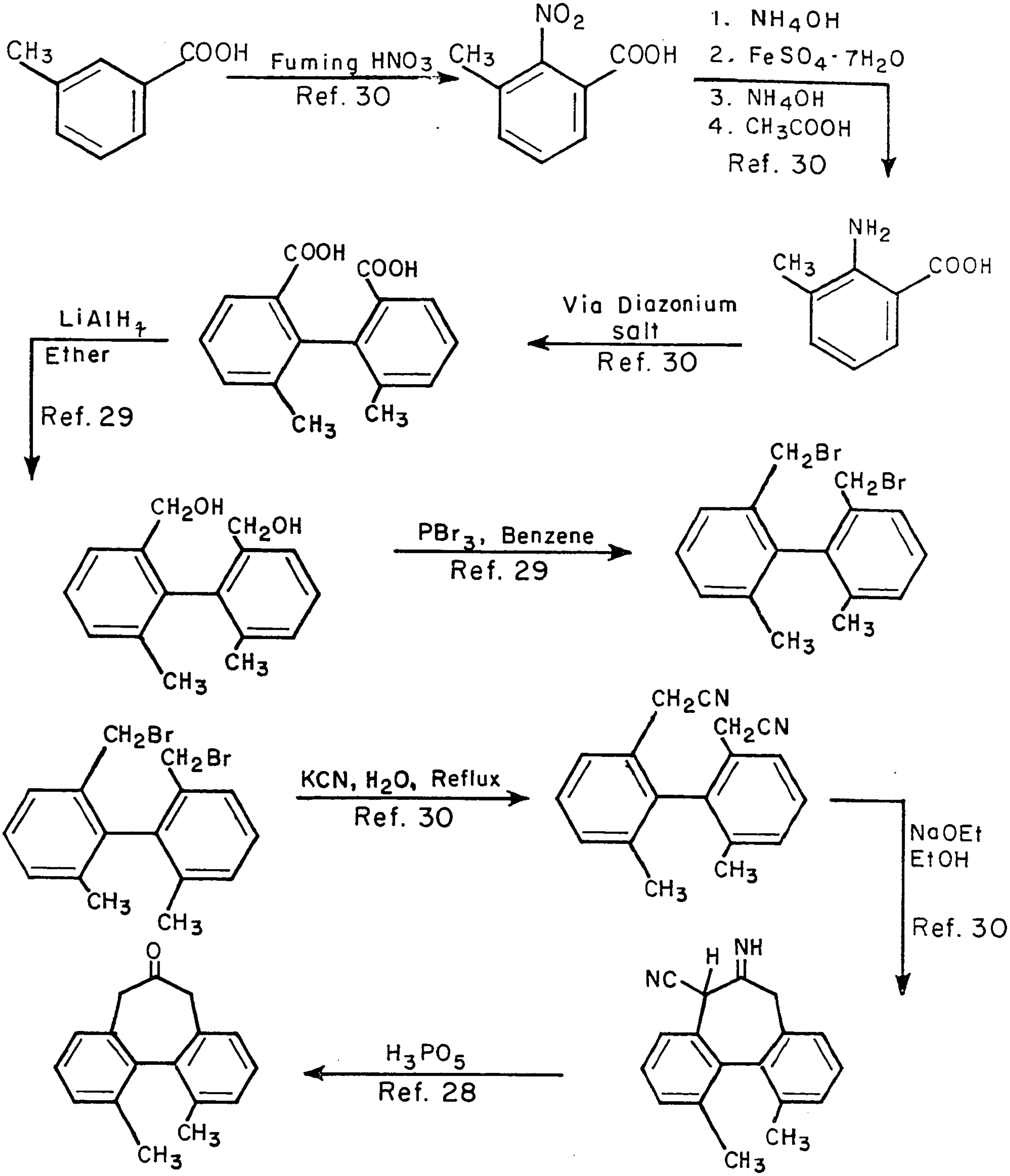
A. Introduction

The biaryl cycloheptadienone 16 was chosen as a model for this study for the following reasons: the protons on the α-keto methylene groups appeared to meet the geometrical and steric requirements outlined in the previous section; the synthesis of 16 had already been published;(28,29,30) the NMR spectrum of 16(31) had been shown to exhibit a clearly defined and well separated AB quartet for the α-keto methylene groups which would facilitate NMR studies on their exchange rates.

The immediate objectives were then to synthesize compound 16, to determine the proton assignments for the AB quartet, to find a base/solvent system in which the exchange rates of these protons could be measured accurately and measure the ratio of these exchange rates. These steps are described in the following sections.

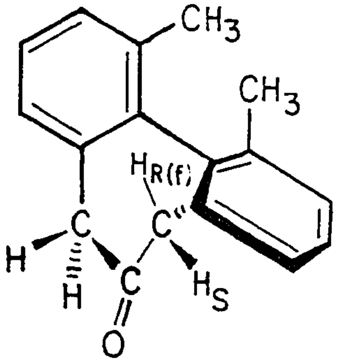
B. Synthesis Of The Biarylcycloheptadienone, 16

The synthesis of this ketone has been described by Mislow et al(28) with some of the steps having come from other references.(29,30) This synthesis is outlined below. Modification to some of the procedures (see EXPERIMENTAL for details) resulted in increased yields while for some other reactions, yields greater than the literature values were obtained as experience was gained by repeating these steps. As a result, the overall yield for this synthesis was increased from about 6 % to 20 %.


CH3
COOH
Fuming HNO3
Ref. 30
NO2
CH3
COOH
1. NH4OH
2. FeSO4·7H2O
3. NH4OH
4. CH3COOH
Ref. 30
NH2
CH3
COOH
Via Diazonium salt
Ref. 30
COOH
COOH
CH3
CH3
LiAlH4
Ether
Ref. 29
CH2OH
CH2OH
CH3
CH3
PBr3, Benzene
Ref. 29
CH2Br
CH2Br
CH3
CH3
CH2Br
CH2Br
CH3
CH3
KCN, H2O, Reflux
Ref. 30
CH2CN
CH2CN
CH3
CH3
NaOEt
EtOH
Ref. 30
H
NH
NC
CH3
CH3
H3PO5
Ref. 28
O
CH3
CH3

C. Stereochemical Assignments for Ketone 16

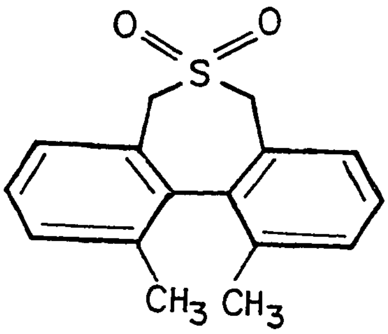
According to the rules(32a,b) for designation of the enantiomers of compounds such as 16 as R and S, the enantiomer shown previously and duplicated below is assigned as the R enantiomer. The quasi-axial proton (labelled H_R) is then the pro-R in R proton and the quasi-equatorial proton is pro-S in R.



16

The diastereotopic methylene protons in 16 cannot exchange environment since rotation about the biaryl bond is prevented by the o-methyl groups.(31) (The distribution of the isotopes was constant for several labelled samples of 16 whose NMR spectra were repeated after the samples had stood at room tempature for periods of several weeks.) These protons give rise to an AB quartet in the 100 MHz spectrum of 16 (in $CDCl_3$, $\delta_R = 3.497$; $\delta_S = 3.295$; $J_{RS} = 14.9$Hz). Assignment of these signals to the pro-R in R and pro-S in R positions respectively is based on two criteria. Firstly, the line widths of H_R and H_S differ appreciably, being 1.6 Hz for the low field portion of the AB quartet and 1.2Hz for the high field portion. Schaefer and co-workers(33) have clearly established that the magnitudes of long-range couplings between aromatic and benzylic protons are dependant upon the orientation of the benzylic C-H bond with respect to the plane of the benzene ring. The sum of the ortho, meta and para coupling constants to a benzylic proton is significantly greater when the C-H bond is perpendicular to the plane of the ring. We therefore assign the broader low field absorption to the proton having this orientation (i.e., H_R in 16).

Secondly, as will be shown later, the relative rates of exchange in 16 show that the low field protons exchange faster than the higher field protons and that the selectivity decreases with increasing bulk of the attacking base. Fraser and Schuber(34) have shown that the environment analogous to that of H_R is the more hindered in the structurally similar thiepin dioxide, 18. The measured steric influence on the relative exchange rates therefore support these proton assignments.



18

Since it is the H_R (Pro-R in R) proton that exchanges fastest in all cases, the quasi-axial (H_R) proton will be referred to as H_f (H_{fast}) and the quasi-equitorial proton as H_s (H_{slow}) throughout the remainder of this thesis.

D. Measurement of k_f^H and k_s^H For 16 in Sodium Deuteroxide/D_2O/ Dimethylsulfoxide-d_6

During the initial trials on this reaction it was noted that the small but unavoidable OH peak in the NMR spectrum with low concentration of D_2O was superimposed on the methylene AB quarter of 16 such that the change in the integral of the AB quartet could not be followed. However, this OH peak shifted downfield on addition of small amounts of D_2O and, under the conditions described in the EXPERIMENTAL, was well separated from the AB quartet. Larger concentrations of D_2O caused precipitation of the ketone.

Because of the high rate ratio ($k_f/k_s = 42$), the short time for exchange of the fast protons allowed for only five determinations of $[H_f]$ (only two of which were in the region of lowest error) while several integrals could be taken for $[H_s]$ (See Table R1).

The rate for H_s was calculated after H_f had exchanged to equilibrium and this rate (k_s^H) was used to calculate $[H_f]$ at the earlier times, from which k_f^H was calculated.

According to Sachs,(4C) for such a process, the lack of an exact rate expression results in a curvature for plots of ln (C_o/C_t) versus time and the amount of curvature increases as the exchange proceeds. For this reason, only those values of the rate obtained during the first half-life of the slow

Table R1

k_f^H and k_s^H in Sodium Deuteroxide/D_2O/ Dimethylsulfoxide-d_6 (1.52×10^{-3}M)

A_f^H	A_s^H	A_e^H	B^{**}	kt^*	Time,Sec	k_f^H,Sec^{-1}
2.000	2.000	-	-		0	
0.943	1.965	0.129	0.093	0.830	15	5.54×10^{-2}
0.638	1.930	0.142	0.121	1.317	30	4.39×10^{-2}
0.579	1.896	0.146	0.129	1.450	45	3.22×10^{-2}
0.365	1.863	0.156	0.150	2.170	60	3.62×10^{-2}
0.232	1.810	0.163	0.166	3.270	84	3.89×10^{-2}
						k_s^H,Sec^{-1}
0.176	1.557	0.176	0.075	0.278	230	1.21×10^{-3}
0.178	1.493	0.178	0.086	0.326	293	1.11×10^{-3}
0.182	1.396	0.182	0.103	0.403	336	1.20×10^{-3}
0.185	1.300	0.185	0.119	0.486	349	1.39×10^{-3}
0.189	1.203	0.189	0.136	0.578	458	1.26×10^{-3}
0.190	1.180	0.190	0.139	0.601	475	1.27×10^{-3}
0.191	1.165	0.191	0.142	0.617	505	1.22×10^{-3}
0.192	1.146	0.192	0.145	0.637	530	1.20×10^{-3}
0.192	1.126	0.192	0.149	0.658	582	1.13×10^{-3}
0.193	1.107	0.193	0.152	0.679	630	1.08×10^{-3}
0.196	1.043	0.196	0.163	0.753	713	1.06×10^{-3}
0.199	0.946	0.199	0.179	0.876	790	1.11×10^{-3}

$$^*kt = \frac{d_0 + h_0}{d_0 + h_0 + B} \ln\left(\frac{A_0 - A_e}{A_t - A_e}\right)$$

$^{**}B$ = concentration of isotope added to solvent by exchange from substrate.

$d_0 + h_0 = 42.88$ for this system.

See Figure 8 for plot of kt^* versus t.

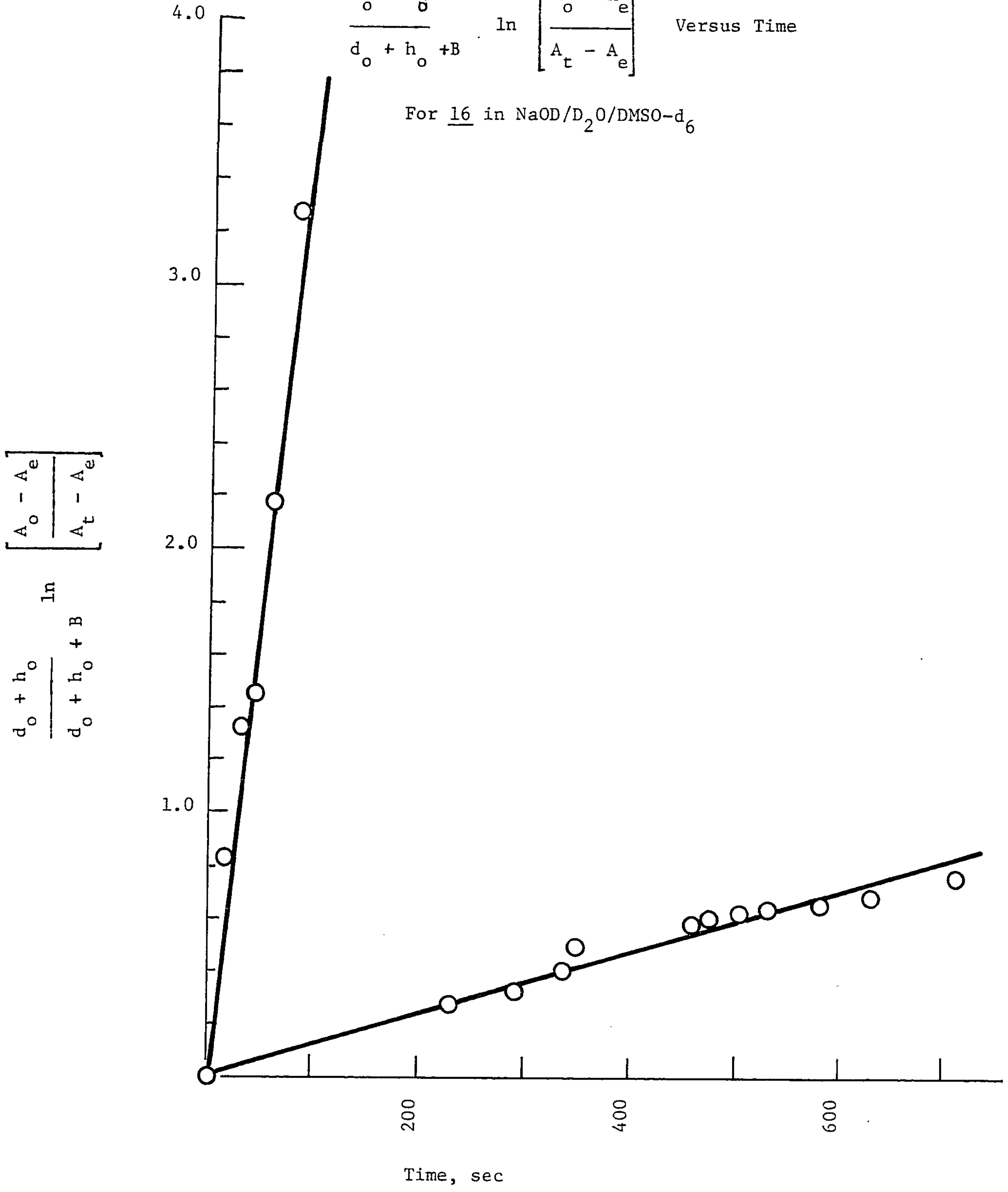
Note: 1) Superscripts always denote the type of bond being broken in the exchange.

2) The above expression for kt is the Sachs (4c) pseudo first order equation for equilibrating reactions and will be used for all rate constant calculation unless otherwise stated. This equation is described in full in the EXPERIMENTAL, page 71.

Figure 8

$$\frac{d_o + h_o}{d_o + h_o + B} \ln \left[\frac{A_o - A_e}{A_t - A_e}\right] \text{ Versus Time}$$

For 16 in NaOD/D_2O/DMSO-d_6



exchange (up to 800 sec) and those obtained during the first two half-lives of the fast exchange were included in the averaged value for k_f^H and k_s^H. These gave rise to the values $k_f^H = 4.95 \times 10^{-2}$ sec $^{-1}$ ±8% and $k_s^H = 1.19 \times 10^{-3}$ sec^{-1} ± 4% for a rate ratio of $k_f^H/k_s^H = 41.6$ by a best straight line fit. Because of the problems involved in having to add small amounts of water (D_2O) to this reaction and in determining the nature of the attacking base ($OD^{\ominus}$ or $CH_3SOCH_2^{\ominus}$) it was decided to investigate another base/solvent system for this reaction, that is, sodium methoxide in methanol-O-d.

E. Measurement of k_f^H and k_s^H For 16 in Sodium Methoxide/Methanol-O-d

After several preliminary measurements, the conditions for this reaction were adjusted to give quenched aliquots close to the half-life for the fast and slow protons (see EXPERIMENTAL for details). The proton concentrations were measured from the average of several NMR integrals over the region of methylene absorption for the recovered samples of partially exchanged 16. As for all the rate ratio determinations, the rate for the slow proton (k_s^H) was calculated first and then used to calculate the $[H_f]$ at the earlier time, from which k_f^H was obtained (see Table R2). It must be recognized that, because of the large rate difference, the majority of the slow protons exchange under the influence of the secondary isotope effect (i) since all the fast protons have exchanged for deuteriums. However, in the early stages, when H_f is just beginning to exchange, any H_s exchange is not under the influence of the secondary isotope effect and it is this early rate that must be used to calculate the small change in $[H_s]$ at the early times so that $[H_f]$ can be measured accurately. For this reason the value of i was measured (see next section for details) as $i = 1.18 \pm .02$ and was used to adjust k_s^H (expt) before using k_s to calculate $[H_f]$ for the early samples. This treatment gave rise to the following values: $k_f^H = 1.83 \times 10^{-2}$ sec $^{-1}$; $k_s^H = 2.90 \times 10^{-4}$ sec^{-1}; $\alpha = k_f^H/k_s^H = 63.1$ (see Table R2 for details). The ratio 63.1 corresponds to a difference in transition state free energies of 2.3 kcal/mole.

This value of k_f^H/k_s^H is an order of magnitude higher than any previous rate ratio measurements for such systems (see Historical section for examples). Before interpreting this high stereoselectivity in terms of stereoelectronic factors alone, it is necessary to consider the following factors which could also be contributing to the apparent rate difference between H_f and H_s: the π system of the benzene ring adjacent to each methylene group in <u>16</u> may have different stabilizing effects in the exchanges of H_f and H_s; the steric factors governing approach of the base to H_f and H_s might favour abstraction of H_f over H_s; the involvement of a substantial amount of internal return in the exchange of H_s could give rise to a stereoselectivity which does not accurately reflect the relative ease of anion formation. Each of these factors will be dealt with on an individual basis in the sections immediately following the determination of the secondary isotope effect.

F. Determination Of The Secondary Isotope Effect (i_f) For The Fast Methylene Position In 16.

1. Description of Method

The secondary isotope effect (i) is defined as the ratio of the rate of bond breaking between two atoms when one of those atoms is also bonded to a light isotope (e.g. breaking the C-H bond in HC-H) to the rate of bond breaking between the same two atoms when one of those atoms is also bonded to a heavier isotope (e.g. breaking the C-H bond in DC-H). In the case of proton abstraction, the presence of the heavier isotope will destabilize the

TABLE R2

Measurement of k_f^H and k_s^H for 16 in Sodium Methoxide/Methanol-0-d (2.9×10^{-3} M)

Time,Sec	A_f^H	A_s^H	A_e^H	B	$10^3 k^H$, Sec^{-1}	α
0	2.000	2.000				
40	0.978	1.972	0.041	0.179	$k_f^H = 18.3 \pm 5\%$	63 ± 10%
22780	0.072	0.928	0.072	0.170	$k_s^H = 0.290 \pm 5\%$	

TABLE R3

(a)

Measurement of S.I.E. (i_f) For 16 in Sodium Methoxide/Methanol-0-d (1.8×10^{-3}M)

Time,Sec.	${}_DA_f^H$	${}_HA_f^H$	A_e^H	B	${}_Dk_f^H$, Sec^{-1} x10^3	${}_Hk_f^H$, Sec^{-1} X10^3	i_f (b)	Avg. i_f
0	0.840	1.080						
60	0.556	0.654	.028	0.121	7.14	8.61	1.20	1.18 ± 5.3%
120	0.378	0.424	.034	0.190	7.04	8.16	1.16	

(a) Superscripts denote the bond being broken. Left hand subscripts denote the nature of the secondary atom.

(b) $i_f = {}_Hk_f^H \,/\, {}_Dk_f^H$

carbanion formation and the secondary isotope effect will usually have a value greater than unity.

In the case of the biarylcycloheptadienone 16, the high stereoselectivity between abstraction of H_f and H_s of 63:1 in the forward direction (H/D exchange) and 12:1 in the backward direction (D/H exchange) allows for the preparation of a derivative of 16 which is specifically labelled with deuterium in 50% of the H_s positions and has only hydrogen in the H_f positions. Figure 9 shows a spectrum of a partially deuterated sample of 16 which was run on the HA-100 NMR at 250 Hz sweep width with deuterium decoupling. The peaks A,C,D and F correspond to the four peaks in the AB quartet of 16 while peak B corresponds to the fast hydrogens on methylene carbons bearing a deuterium in the slow position and peak E corresponds to the slow hydrogens on methylene carbons bearing a deuterium in the fast position. The concentration of fast hydrogens on methylene carbons bearing a slow hydrogen is then given by the sum of peaks A and C.

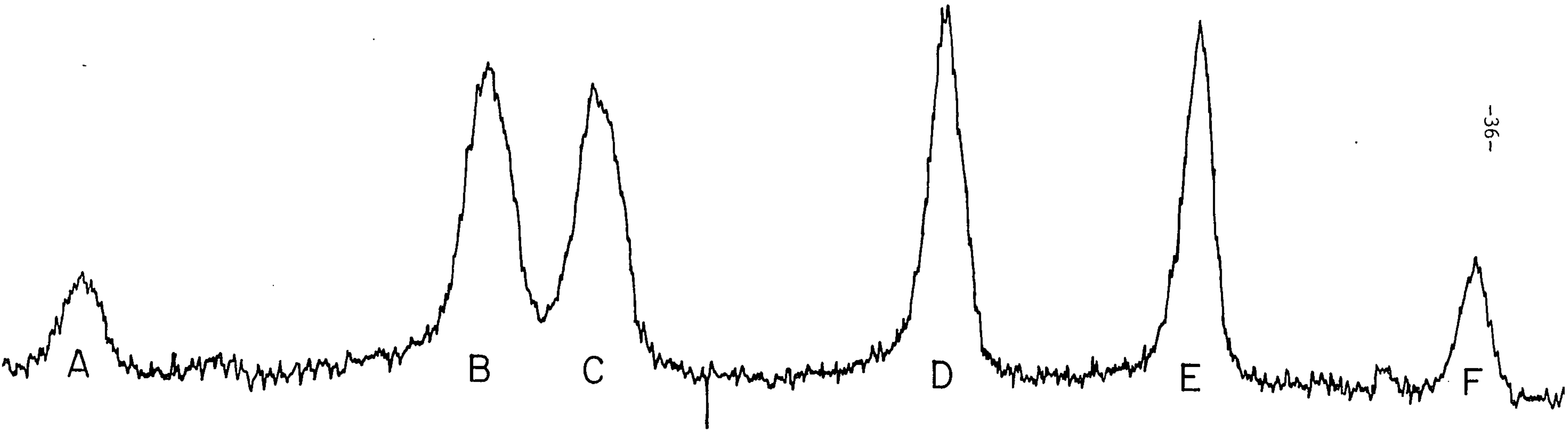
In a forward (H/D) exchange reaction one can now measure the rates of exchange of both types of fast protons (the extent of exchange of H_s or D_s is negligible over the short times involved) by measuring the rates of disappearance of peaks A + C and of peak B under identical reaction conditions. The ratio of these two rates gives directly the secondary isotope effect for exchange in the fast position, i_f. The secondary isotope effect for exchange in the slow position must be assumed to be the same since it cannot be measured directly due to the impossibility of maintaining a label in the fast position while the slow position is exchanging.

Since peaks B and C (Fig. 9) are not sufficiently separated to allow for separate integration of the two, it was decided to use peak height analysis for the rate determinations. It was therefore necessary to ensure

Figure 9

100 MHz, 250 Hz S.W. NMR Spectrum of Partially Deuterated <u>16</u> (in $CDCl_3$),

With Deuterium Decoupling



that the "monoproteo" peaks B and E were completely deuterium decoupled. Care was also taken to prevent saturation of the peaks. The decoupling frequency was adjusted until the peak heights of B and E were maximized and the line shapes were the same for B and C and for D and E. It was also necessary to measure the total proton content of the methylene groups for each sample. This was done by comparing the total methylene integral with that of the constant signal for the methyl groups of <u>16</u>. This method gave the same total proton concentration on both the HA-100 and the T-60 spectrometers. Relative peak heights could then be converted directly to relative proton concentrations.

Treatment of the results by Sachs equation (4C) for the two different quenched aliquots gave $i_f = 1.18 \pm 0.02$ (see Table R3 for details).

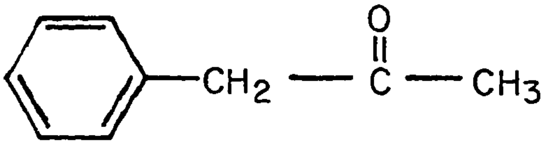
The maximum value of i has been calculated to be 1.88(38) which corresponds to complete proton transfer to the base at the transition state. The smaller i, the less is the extent of proton transfer, such that at half-transfer of the proton in the transition state the theoretically calculated value of i is the square root of the maximum value; i.e. $i = 1.37$. The correlation of secondary isotope effect with symmetry of the transition state has not been clearly established experimentally at this time. Values nearly as high as the theoretical maximum and as low as unity have been measured, for example, $i = 1.18$ for D/H isotope exchange in fluorene-9,9-d_2 (25) and in nitroethane (39a), and $i = 1.79$ for base catalyzed elimination of $(CH_3)_3N$ from $C_6H_5(CH_2)_2N(CH_3)_3^{+-}$ (39b). A better, but not ideal, model for comparison with our system is the base catalyzed exchange in bicyclo [2.2.2] octan-2-one (<u>10</u>) for which $i = 1.07$(16b). The above result shows that it is not valid to neglect the secondary isotope effect in discussions of isotope exchange rates in ketones.

2. Preparation of 16 Specifically Deuterated in 50% of the Slow (H_s) Positions, For Measurement of Secondary Isotope Effect.

This preparation was carried out after the rate ratio for loss of deuterium in 16 had been determined to be $k_f^D / k_s^D \simeq 10$. On this basis, the sample of 16 was deuterated to equilibrium in the fast position and to about 60% deuteration in the slow position and was then dedeuterated for approximately 0.5 half-lives of the slow deuteriums (see EXPERIMENTAL for details). This should provide about 5 half-lives of exchange for the fast position or about 95% exchange of the fast deuteriums.

G. Effect of the Aromatic π System on Stereoselectivity in 16

The effect of the aromatic π system on the stereoselectivity can be shown to be small. In a separate experiment, the benzylic protons of 1-phenylpropanone, 19, were shown to exchange 10 times faster than the methyl



19

protons. If one third of this 1.4 kcal/mole of stabilization is inductive(35) and the remaining 0.95 kcal is available through overlap as a function of cos θ (36) the difference in stabilization of $H_f(\phi=75^o)$ would be no more than 0.4 kcal/mole which corresponds to a factor of 2-3 times in the rate ratio k_f/k_s.

H. Effect of Steric Hindrance on Stereoselectivity in 16

In order to eliminate steric hindrance as the cause of the 63:1 stereoselectivity in the abstraction of protons from 16, it was decided to measure the stereoselectivity when bulkier bases than sodium methoxide were employed. If the enolate formation is the rate determining step and if the high stereoselectivity were due to steric hindrance to abstraction of H_s, then an increase in stereoselectivity would be expected when the bulk of the attacking base is increased. The two bases studied were sodium phenoxide and sodium 2,6 - dimethylphenoxide (see 1 and 2 below).

The measured selectivity of 34:1 with sodium phenoxide and 7.2:1 with sodium 2,6 - dimethylphenoxide shows that the stereoselectivity decreases with increasing bulk of the base, which indicates that H_f is in a more sterically crowded environment than H_s, a result predicted earlier from consideration of models of 16. Since methoxide may also suffer from steric suppression for abstraction of H_f, the 63:1 rate ratio represents a lower limit to the stereoselectivity in 16.

1. Measurement of k_f^H and k_s^H For 16 in Sodium Phenoxide/Methanol-O-d

Based on the estimates of these rate constants from pre-runs under the above conditions, times for this run were chosen such that the first and second aliquots would exhibit measureable (by NMR integration) amounts of exchange of the fast and slow protons respectively. The proton concentrations were determined from the average of several integrals over the region of methylene absorption (see EXPERIMENTAL for details). The measured rates (see Table R 4) were $k_f^H = 7.55 \times 10^{-3}$ sec.$^{-1}$ and $k_s^H = 2.23 \times 10^{-4}$ sec.$^{-1}$ which gives a rate ratio of $k_f^H/k_s^H = 33.8$

2. Measurement of $\alpha \doteq k_f^H/k_s^H$ for 16 in Sodium 2,6-Dimethylphenoxide/ Methanol-O-d

Since pre-trials for this run had indicated that the rate ratio was less than 10:1, it was decided to use the simplified expression $\alpha \doteq \log (Ao/At)_f / \log (Ao/At)_s$ which measures the ratio of rates directly from one sample (see details in EXPERIMENTAL) thereby eliminating systematic errors between samples.

Table R 4

Measurement of k_f^H and k_s^H in Sodium Phenoxide/Methanol-0-d (2.9×10^{-3}M)

Time,Sec	A_f^H	A_s^H	A_e^H	B	$10^3 k^H$, Sec^{-1} ±5%	$\alpha=k_f^H/k_s^H$ ±10%
0	2.000	2.000	-	-		
60	1.282	1.968	0.036	0.128	$k_f^H = 7.55$	33.8
700	0.059	1.719	0.059	0.378	$k_s^H = 0.223$	

Table R 5

Measurement of k_f^H and k_s^H in Sodium 2,6-Dimethylphenoxide/Methanol-0-d (0.98×10^{-3}M)

Time,Sec	A_f^H	A_s^H	$\alpha=k_f^H/k_s^H$ ±10%
0	2.000	2.000	7.2
610	0.820	1.765	

Table R 6

Measurement of k_f^H and k_s^H For <u>16</u> in Presence of Crown Ether in Sodium Methoxide/Methanol-0-d (1.6×10^{-3}M)

Time,Sec	A_{total}^H	A_f^H	A_s^H	A_e^H	B	$10^3 k^H$,Sec^{-1} ±5%	$\alpha=k_f^H/k_s^H$ ±10%
0	4.000	2.000	2.000	-	-		
99	2.725	0.764	1.961	0.044	0.218	$k_f^H= 10.0$	60
5825	0.865	0.074	0.791	0.074	0.193	$k_s^H= 0.168$	

This treatment gave a rate ratio $\alpha=7.2$ ($\alpha = k_f^H/k_s^H$) under the above conditions (see Table R 5).

I. Effect of Internal Return on Stereoselectivity in 16

1. Methods of Detecting Internal Return

As outlined earlier there are two qualitative methods and one quantitative method for detecting internal return in a base catalyzed reaction. The first of the qualitative methods assumes that the cation of the base is involved in the complex formation that accompanies abstraction of a proton. If the nature of this complex gives rise to internal return, then removal of the cation from involvement in the removal of the proton by complexing it with a crown ether should result in a change in the extent of internal return and thus a change in the rate of the exchange which could alter the rate ratio or stereoselectivity (23) if two different protons are exchanging as in 16.

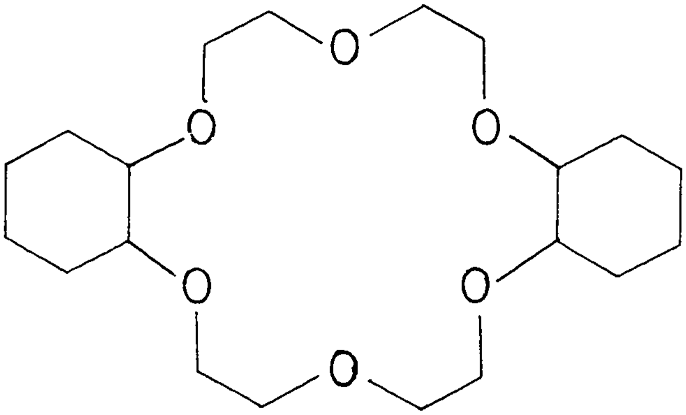
The second qualitative test for internal return is the measurement of the dimunition in the stereoselectivity in going from the forward (H/D) exchange to the reverse (D/H) exchange. As detailed earlier (P. 16) we would expect a decrease in the stereoselectivity by a factor of about 6-7 in the absence of internal return.

The quantitative measurement of internal return involves Streitwieser's equations which are given in detail in the INTRODUCTION. This method requires the measurement of k_f^H, k_f^T, k_s^H, and k_s^T in heavy solvent and of k_f^D, k_f^T, k_s^D and k_s^T in light solvent (where the superscripts denote the type of bond being broken) as well as the equilibrium constant $K^{T'}$ for tritiation of the substrate in light solvent.

The test with crown ether will be described first and the measurement of the reverse exchange and the measurement of primary isotope effects will be treated together since the isotope effect measurements include the measurement of the rate ratio for reverse exchange.

2. Measurement of k_f^H and k_s^H For 16 in the Presence of Crown Ether

Dicyclohexyl-18-crown-6, 20, was chosen as the crown ether for this study because of its availability and because it exhibits a stability constant (= log of equilibrium constant for complexing) of 4.08 when complexed with sodium ions in methanol(37). The crown ether was used in 10% molar excess of the base present.



20

Based on estimates from pre-trials for this reaction, the reaction conditions were chosen such that aliquots could be taken close to the half-life for the fast protons and for the slow protons (see EXPERIMENTAL for details).

Treatment of the results as outlined earlier gave the following values (see Table R 6 for details): $k_f^H = 10.0 \times 10^{-3}$ sec^{-1}; $k_s^H = 1.68 \times 10^{-4}$ sec^{-1}; $k_f^H/k_s^H = 60$. The stereoselectivity for the exchange of H_f and H_s in 16 is therefore the same (within experimental error) in the presence and absence of crown ether. The crown ether did cause a slight increase in the absolute rates for both fast and slow protons as would be expected if the cation were being complexed and therefore removed from the base ion pair (41).

Since crown ethers have been shown to cause a large change in rates or rate ratios (23) in the cases where internal return is known to be important, the present result can be taken as an indication that internal return is not important in the exchange of H_f and H_s in 16.

3. Measurement of Primary Isotope Effects for 16

a) Determination of k_f^H and k_f^T for 16 in Sodium Methoxide/Methanol-O-d

(i) Preparation of 16 Specifically Tritiated in the Fast Position

In order to measure the primary isotope effect k^H/k^T for the fast position, it was necessary to measure k_f^H and k_f^T under identical conditions, i.e., in the same reaction. This required preparation of a sample of 16 which was specifically labelled with tritium in the fast position. Based on the previously measured value of k_f^H for 16 in MeOD, and allowing for a solvent isotope effect of about 2-3, it was estimated that a reaction time of about 7 seconds in tritiated MeOH under the same conditions as those used for measurement of k_f^H would provide substrate 16 tritiated to about 5% of the equilibrium value in the fast position and to 1/63 of this value in the slow position. A small correction (1.6% of the initial specific activity) must then be applied to each specific activity to account for the tritium in the slow position. The above conditions actually gave incorporation of 4.3% of available tritium in the fast position (see EXPERIMENTAL for details).

(ii) Measurement of k_f^H and k_f^T for 16 in Sodium Methoxide/Methanol-0-d.

The times at which aliquots would be taken for this measurement were based on the previously measured rate for exchange of H_f in this solvent/base system and an estimated k_f^H/k_f^T value of about 10 based on preliminary trials (see EXPERIMENTAL for details). The early samples were analyzed by mass spectrometry for proton content and the later samples were analyzed by scintillation counting for total tritium content (refer to EXPERIMENTAL for a detailed description of each of these methods). The results of these measurements are reported in Table R 7 and give rise to the following values: $k_f^H = 9.22 \times 10^{-3}$ sec $^{-1}$ ± 3.6% (average of first two samples); $k_f^T = 6.76 \times 10^{-4}$ sec $^{-1}$ ± 2.4% (average of first two samples). Therefore the calculated primary isotope effect is $k_f^H/k_f^T = 13.6$ ± 6%.

The detailed discussion of the primary isotope effects will be done at the end of this section, but it can be mentioned here that in the absence of internal return, application of equation 6 (from the INTRODUCTION, P. 18) to this measured value of k_f^H/k_f^T gives $k_f^H/k_f^D = 6.2$, a "normal" primary isotope effect.

b) Determination of k_s^H and k_s^T For 16 in Sodium Methoxide/Methanol-0-d

(i) Preparation of 16 Tritiated in the Slow Position.

In order to measure the rate of removal of slow tritiums, it was necessary only to prepare a sample which was fully tritiated in both fast and slow positions. Samples for tritium counting could then be taken after it was certain that the fast position had exchanged to its equilibrium tritium concentration (see EXPERIMENTAL for details).

Table R7

Measurement of k_f^H and k_f^T For <u>16</u> in Sodium Methoxide/Methanol-0-d $(1.27\times10^{-3}M)$

Time, Sec	A_f^H (a)	A_e^H	B	k_f^H, Sec^{-1}	A_f^T, dpm/mg (b)	A_e^T	B (c)	k_f^T, Sec^{-1}	k_f^H/k_f^T ±6%
0	2.000				199.3				
32	1.480	0.032	0.090	9.55×10^{-3}					
100	0.842	0.043	0.201	8.89×10^{-3}					13.6
220	0.332	0.051	0.289	8.70×10^{-3}					
276	0.192	0.054	0.313	9.47×10^{-3}	164.8	0.92	0.058	6.91×10^{-4}	
650					130.2	1.82	0.112	6.60×10^{-4}	
810					121.2	2.04	0.129	6.20×10^{-4}	

(a) Calculated From a_{total}^H assuming $k_f^H = 63.1\ k_s^H / i$

(b) Calculated From A_{total}^T assuming $[T_s] = 1.6\%\ [T_{total}]$

(c) For all tritium measurements, B = effective concentration of tritium in solvent due to exchange of protons being studied.

(ii) Measurement of k_s^H and k_s^T for 16

Since no measurement of the fast exchange was taken in this run, the exchange was done at higher base concentration to minimize any possible base quenching effects and shorten the times between aliquots. Sample times for the proton exchange were based on the previously measured value of k_s^H assuming the reaction to have a first order dependence on base concentration. Preliminary trials had indicated $k_s^H/k_s^T < 10:1$ so the reaction times for the aliquots for tritium counting were adjusted accordingly. Proton concentrations were determined by mass spectral analysis as described earlier. The results of these measurements are given in Table R 8. Only those samples for which the slow protons were less than 75% exchanged were included to give the value of $k_s^H = 8.96\text{x}10^{-4}\ \text{sec}^{-1} \pm 1.4\%$ (average of first two samples). Similarly, for the detritiation measurements, only those values of specific activity obtained after it was certain that the fast tritium concentration had been reduced to its equilibrium value and before 75% exchange of the slow tritium were used to calculate the value of $k_s^T = 1.97\text{x}10^{-4}\ \text{sec}^{-1} \pm 4.6\%$ (average of two samples). The calculated value of the primary isotope effect was therefore $k_s^H/k_s^T = 4.55 \pm 6\%$. This would indicate a k_s^H/k_s^D value of 2.9 in the absence of internal return, a low primary isotope effect.

c) Determination of k_f^D, k_s^D, k_f^T and k_s^T For 16 in Sodium Methoxide/Methanol-O-H

(i) Preparation of 16 Deuterated and Tritiated to Equilibrium in Both Fast and Slow Positions.

In order that the rate ratio for reverse exchange (k_f^D/k_s^D) could be measured along with the primary isotope effects (k_f^D/k_f^T and k_s^D/k_s^T) in the

Table R 8

Measurement of k_s^H and k_s^T For <u>16</u> in Sodium Methoxide/Methanol-0-d (6.03×10^{-3}M)

Time, Sec	A_s^H	A_e^H	B	10^4 k_s^H, Sec^{-1}	A_{total}^T, dpm/mg	A_e^T	B	$10^4 k_s^T$, Sec^{-1}	k_s^H/k_s^T
0					1978.3				
25					1709.2				
620	1.182	0.068	0.128	8.84	1128.6				
1205	0.714	0.076	0.206	9.09	958.5	25.8	0.010		
2400	0.308	0.082	0.274	8.81	774.0	31.2	0.074		4.55±6%
3610	0.176	0.085	0.296	8.33	654.4	34.2	0.115		
7200					333.2	42.6	0.226	2.07	
10,000					225.8	45.4	0.262	1.88	
13.000					148.5	47.6	0.289	1.89	
					79.4	49.5	0.313	1.81	

same reaction, it was necessary to prepare a sample of 16 which was fully deuterated and tritiated in both fast and slow positions. The reaction conditions for this preparation (see EXPERIMENTAL for details) were based on the previously measured values for k_f^H and k_s^H in methanol-O-d.

(ii) Measurement of k_f^D, k_f^T, k_s^D and k_s^T

The reaction conditions and sample times for measurement of these constants were based on pre-trials which estimated the reverse rate ratio (k_f^D/k_s^D) to be ≃ 10. Estimates of k_f^T and k_s^T could be obtained by applying equation 6 (P. 18) to the measured k^H/k^T values from the previous section (see EXPERIMENTAL for details).

Deuterium contents were determined by mass spectral analysis and tritium contents were determined by scintillation counting (both methods are described in the EXPERIMENTAL). Rate constants were calculated as described earlier and the results are given in Table R9.

In the case of deuterium exchange, the aliquots taken at intermediate times could not be used for calculation of k_s^D since it was not certain that all of D_f had exchanged and also since most of the D_s exchange at these points had taken place under the influence of the secondary isotope effect cause by deuterium in the fast positions. The last three aliquots, however, gave the value of $k_s^D = 0.328 \times 10^{-3} \text{sec}^{-1}$ with good agreement between samples (standard deviation = ± 2%). For the fast exchange, the first five samples were used in the calculation of $k_f^D = 3.97 \times 10^{-3} \text{sec}^{-1}$, (the sixth sample had exchanged more than 90%) but the agreement between the rate constants calculated from these samples was not as good (standard deviation ≃ ± 6.8%). These two results give rise to a stereoselectivity of $k_f^D/k_s^D \simeq 12.1 \pm 8.8\%$ which has decreased by a factor of 5.2 from the forward exchange stereoselectivity of 63 ± 10%.

Table R 9

k_f^D, k_s^D, k_f^T and k_s^T For 16 in Sodium Methoxide/Methanol-O-H (6.11×10^{-3}M)

Time,Sec	A^D_{total}	A^D_f	A^D_s	A^D_e	B	10^3 k^D,Sec^{-1}	10^3 k^D_{avg},Sec^{-1}
0	3.827	1.914	1.914				
110	3.068	1.212	1.856	0.011	0.134	k_f^D = 4.16	
180	2.720	0.903	1.817	0.015	0.187	k_f^D = 4.19	
295	2.404	0.639	1.765	0.019	0.231	k_f^D = 3.75	k_f^D = 3.97±6.8%
400	2.176	0.461	1.715	0.022	0.262	k_f^D = 3.61	
500	1.927	0.258	1.669	0.025	0.296	k_f^D = 4.13	
775	1.687	0.138	1.549	0.028	0.317	(k_f^D = 3.61)	
1425	1.335	0.039*	1.299*	0.032			
1945	1.151	0.034		0.034	0.150	(k_s^D = 0.282)	
2720	0.886	0.037		0.037	0.196	(k_s^D = 0.305)	
3580	0.697	0.039		0.039	0.228	(k_s^D = 0.307)	
4600	0.489	0.042	0.447	0.042	0.264	k_s^D = 0.329	
5780	0.362	0.043	0.319	0.043	0.286	k_s^D = 0.327	k_s^D = 0.328±2%
7000	0.273	0.044	0.229	0.044	0.301	k_s^D = 0.327	

Time,Sec	A^T_{total} dpm/mg	A^T_f	A^T_s	A^T_e	B	10^3 k^T,Sec^{-1}	10^3 k^T_{avg},Sec^{-1}
0	11,430	5,715	5,715				
295	9,621	4,184	5,437	47	0.060	k_s^T = 1.065	
400	9,136	3,794	5,342	61	0.116	k_f^T = 1.033	k_f^T = 1.051±2%
775	7,587	2,566	5,021	103	0.190	k_f^T = 1.054	
2720	4,082			197			
3580	3,164	250	2,914	250	0.170	k_f^T = 0.199	
4600	2,741	265	2,476	265	0.190	k_s^T = 0.195	k_s^T = 0.201±4%
5785	2,155	280	1.875	280	0.230	k_s^T = 0.210	

*Calculated using experimental values of k_f^D and k_s^D

In the case of the tritium exchanges, treatment of the results (Table R9) as described earlier gave the following rate constants with good agreement between samples: $k_f^T = 1.05\text{x}10^{-3}\text{sec}^{-1}$ ± 2% (average of 3 samples); $k_s^T = 0.201\text{x}10^{-3}\ \text{sec}^{-1}$ ± 4% (average of 3 samples); stereoselectivity $= k_f^T/k_s^T =$ 5.23 ± 6%. The primary isotope effects are then $k_f^D/k_f^T = 3.78 \pm 8.8\%$ and $k_s^D/k_s^T = 1.63 \pm 6\%$.

d) <u>Measurement of $K^{T'}$ For 16</u>

As mentioned in the INTRODUCTION, in order to apply the equations of Streitwieser to the calculation of the amount of internal return, it is necessary to measure the equilibrium constant, $K^{T'}$, for the reaction below:

$$\underline{16} - \text{T} \quad + \quad \text{ROH} \quad \overset{K^{T'}}{\rightleftharpoons} \quad \underline{16} - \text{H} \quad + \quad \text{ROT}$$

$$\text{where } K^{T'} = \frac{[\underline{16}\text{-H}]\ [\text{ROT}]}{[\underline{16}\text{-T}]\ [\text{ROH}]} \equiv [\text{ROT}]\ /\ [\text{ROH}]\ /\ [\underline{16}\text{-T}]\ /\ [\underline{16}\text{-H}]$$

$$= \Big[\text{Specific Activity of Solvent (dpm/meq) / Specific Activity of Substrate (dpm/meq)}\Big]_{\text{Equilibrium}}.$$

A sample of 16 was therefore equilibrated in tritiated methanol-O-H under the same conditions used for measurement of rate constants. Once equilibrium had been established, it was necessary only to recover the ketone and determine the specific activity of both solvent and ketone at equilibrium (see EXPERIMENTAL for details). The ratio of these specific activities gave $K^{T'} = 1.23$ ± 3%. This result compares with the value of $K^{T'} = 1.32$ for 9-phenylfluorene measured by Streitwieser et al(25) and $K^{T'} = 1.27$ for 14 measured by Ng(40).

Application of equation (6) allows the calculation of the corresponding values for the equilibria established in the reactions studied here. That is,

$1/k^{T'} = (K^H/K^T) = (K^D/K^T)^{3.344} = (K^H/K^D)^{3.344/2.344}$, giving $K^T/K^D = 1.064$ and $K^D/K^H = 1.156$. The value of (K^T/K^D) is required for application of Streitwieser's equations while all of these ratios are required for calculation of the equilibrium concentrations to be used for application of the Sachs' pseudo first order rate equation (4c).

4. Quantitative Estimate of Internal Return

The above measured values of isotope exchange rates allows the calculation of the following primary isotope effects (experimental values):

$(k_f^H/k_f^T) = 13.6 \pm 6\%$; $(k_s^H/k_s^T) = 4.55 \pm 6\%$;

$(k_f^D/k_f^T) = 3.78 \pm 8.8\%$; $(k_s^D/k_s^T) = 1.63 \pm 6\%$; $K^{T'} = K^T/K^H = 1.23 \pm 3\%$.

Application of Streitwieser's equations (equations (7) and (8), P. 19) gives rise to the following values for internal return (recall that internal return is defined as $a = k_{-1}/k_2$ from Figure 6, P. 14):

$a_f^T = 0.058$; $a_f^H = 11.7$ (92% internal return for H/D exchange);

$a_s^T = 0.045$; $a_s^H = 0.32$ (24% internal return for H/D exchange).

If one accepts these results as valid, then the fast position on 16 undergoes five times more internal return than the slow position, which in turn means that the measured stereoselectivity of 63:1 for the H/D exchange is a minimum value and is due mainly to the stereoelectronic control effect.

J. Discussion of Exchange Rate Measurements for 16.

It now becomes necessary to compare the results of the qualitative and quantitative estimates of internal return in 16. The crown ether test indicates little or no internal return (no difference in k_f^H/k_s^H with and without crown ether).

The change in stereoselectivity in going from H/D to D/H exchange (63 to 12.1) by a factor of 5.2 is consistent with the expected factor of about 6-7 and thus indicates internal return to be of little importance in this reaction. On the other hand, the quantitative test indicates internal return to be important in both positions, much more so in the fast than in the slow position.

The qualitative tests are in agreement with the prediction of Hunter(42) that internal return should not be important in polar solvents such as methanol. These are supported by the fact that the measured values of $k_f^H/k_f^T = 13.6$ converts (by equation (6)) to $k_f^H/k_f^D = 6.3$ which is in the range calculated by Bell(30). On the other hand the measured value of $k_s^H/k_s^T = 4.55$ results in $k_s^H/k_s^D = 2.9$, a low primary isotope effect which, as mentioned earlier, can arise either from internal return at this position or from an unsymmetrical transition state for the exchange, or from both effects. A change of 3.4 in the primary isotope effects between the fast and slow positions seems a bit large if caused only by differences in transition state symmetry (extent of proton removal at the transition state). There is no good model available for comparison with <u>16</u> for which primary isotope effects have been measured for two such diastereotopic protons where the two protons probably exhibit different pK_a's, but we can choose for comparison the study of the dehydrochlorination of DDT(43) with various bases. Significant changes in k^H/k^D were measured as the pK_a of the base was varied. For example, the value of k^H/k^D increased from 3.1 with $PhS^\ominus$ as base to 6.2 with $PhO^\ominus$ as base (a change of about + 5 pK units) then decreased again to about 3.5 with $EtO^\ominus$ as base (a further change of + 5 pK units).

The quantitative treatment for this system suffers also from some internal inconsistancies. The "normal" value of $k_f^H/k_f^D = 6.3$, when corrected for the amount of internal return calculated, becomes 35.6, an intuitively unacceptable value. Also, because of the repeated exponential effect of the primary isotope effects in the calculation of internal return (refer to equation 7, P. 19), the standard deviations of these isotope effects give rise to a large uncertainty in the amounts of internal return. For the fast system, the range obtained by varying k_f^H/k_f^T and k_f^D/k_f^T by ± 6% and ± 8.8% respectively is 75% to 93% internal return. The same treatment for the slow system gives a range of 20% to 54% internal return, so that within experimental error, the amount of internal return could be nearly the same in the two positions.

It can be seen from the above that for the quantitative treatment to be reliable, the isotope effects should be measured to an accuracy of ± 2-3%, which means that the individual rate constants would have to be measured to ± 1-1.5%. This accuracy is difficult to achieve with the most ideal systems and is probably impossible with the system under study for the following reasons: the relatively high reactivity of the methylene protons in <u>16</u> requires the use of very dilute base solutions (of the order of 10^{-3} M NaOMe/MeOH) such that any base quenching which occurs might affect the fast and slow exchanges differently; for the same reason as above, rate constants measured from different runs are not directly comparable since the base concentration might vary as much as 10-15% between runs; partially deuterated samples of <u>16</u> cannot be purified by standard techniques without risk of back exchange or of scrambling the label (this is especially important in preparation of samples for scintillation counting); mass spectral analysis was complicated by back exchange if the instrument contained traces of impurities with exchangeable protons; the fact that the compound contains four exchangeable protons, two fast and two slow decreases the accuracy of the mass spectrometric deuterium analyses by increasing the number of deuterated species and therefore the number of isotope corrections that must be made (refer to Table E1 in the EXPERIMENTAL for an example of the calculation of the proton content for a representative sample);

the low stereoselectivity $k_f^T/k_s^T = 5$ in MeOD creates problems in determining the individual concentrations of T_f and T_s for each sample. All of these factors were controlled as rigorously as possible and the standard deviations given for each measurement are probably close to the best accuracy attainable with this system. In view of the above difficulties, the kinetic measurements should be re-examined on the basis of assuming no internal return.

The fact that the primary isotope effect is larger in the fast position than the slow position (6.3 and 2.9 respectively as calculated from the measured k_f^H/k_f^T and k_s^H/k_s^T values assuming no internal return) can be verified by estimating the values of k_f^H/k_f^D and k_s^H/k_s^D from the measured rates for forward and backward exchange, assuming a constant solvent isotope effect of 2 and assuming the reactions to be first order in base (which appears qualitatively to be true). The rate constants $k_f^H = 18.3 \times 10^{-3} \text{sec}^{-1}$ in MeOD ($2.9\text{x}10^{-3}$ M base) and $k_f^D = 3.9\text{x}10^{-3}$ in MeOH ($6.13\text{x}10^{-3}$ M base) give $k_f^H/k_f^D = 4.96$, while $k_s^H = 2.9\text{x}10^{-4}\text{sec}^{-1}$ in MeOD (2.9×10^{-3}M base) and $k_s^D = 3.28\text{x}10^{-4}$ sec $^{-1}$ in MeOH ($6.13\text{x}10^{-3}$ M base) give $k_s^H/k_s^D = 0.93$. From the isotope effect measurements, $k_f^H = 9.22 \times 10^{-3}\text{sec}^{-1}$ in MeOD ($1.27\text{x}10^{-3}$ M base) and $k_s^H = 8.97\text{x}10^{-4}$ sec^{-1} in MeOD ($1.27\text{x}10^{-3}$M base) combined with the above rate constants for reverse exchange in MeOH (k_f^D and k_s^D at $6.13\text{x}10^{-3}$M base), we find $k_f^H/k_f^D = 5.71$ and $k_s^H/k_s^D = 1.4$. These independant methods show that $k_f^H/k_f^D > k_s^H/k_s^D$ by about a factor of 2.

Having accepted the fact that $k_f^H/k_f^D > k_s^H/k_s^D$ with at least some (and probably most) of the difference arising from differences in transition state symmetry, it then becomes necessary to take into account the findings of Hibbert et al$^{(44)}$ and Jones et al$^{(45)}$ that when the primary isotope effects vary for the above stated reason, the solvent isotope effects may also vary. A reasonable estimate of the solvent isotope effects for the two different exchangeable positions in 16 can be made by considering the rates of detritiation in light and heavy solvents, since internal return, if present at all, is always very small for breaking of a C-T bond. Assuming these exchange reactions to be first order in base, the following second order rate constants can be calculated from their measured first order counterparts: k_f^T (MeOD) = 0.529 l/mole sec; k_f^T (MeOH) = 0.172 l/mole sec; k_s^T (MeOD) = 0.0327 l/mole sec; k_s^T (MeOH) = 0.0328 l/mole sec. These rate constants must be adjusted in recognition of the fact that in heavy solvent (protonated starting material) T_f exchanges with no secondary isotope effect and T_s exchanges under the influence of the secondary isotope effect (i=1.18) while in light solvent (deuterated starting material) T_f exchanges under the influence of a secondary isotope effect while T_s does not. The corrected second order rate constants are therefore: k_f^T (MeOD) = 0.529 l/mole sec; k_f^T (MeOH) = 0.203 l/mole sec; k_s^T (MeOD) = 0.0386 l/mole sec; k_s^T (MeOH) = 0.0328 l/mole sec; from which k_f(MeOD)/k_f(MeOH) = 2.6 and k_s (MeOD)/k_s (MeOH) = 1.2.

The primary isotope effect (k^H/k^D) can now be recalculated from the H/D and D/H measurements using these solvent isotope effects, giving $k_f^H/k_f^D = 3.8$ and $k_s^H/k_s^D = 2.3$

These primary isotope effects are consistant with both the fast and slow exchange passing through unsymmetrical transition states with the slow transition state being more product like than the fast, which would be expected for this compound since formation of an enolate by extraction of H_s requires a much larger change in the geometry of the cycloheptadienone ring. It must be pointed out, however, that the conclusion of Hibbert(44) and Jones(45) that the solvent isotope effect is low when the primary isotope effect is low due to a reactant-like transition state and high when the primary isotope effect is low due to a product-like transition state is clearly incompatible with the fast protons of 16 being more acidic than the slow protons (i.e. less transferred in the transition state). Due to the small number of examples available at this time, their correlation may or may not be applicable in the present case. Thus the overall picture, if internal return is absent, would indicate that the diastereotopic protons in 16 exchange with different primary isotope effects and different solvent isotope effects.

In relation to the complete exchange diagram for such systems (P.11), Werstiuk(16b) and Lamaty(3) have been able to explain the difference in stereoselectivity for the H/D and D/H exchange by assuming no internal return, negligible secondary isotope effects and equal primary and solvent isotope effects for the two exchanging positions. The change in stereoselectivity can also be explained using the above measured values for these effects. The secondary isotope effect exhibits its influence twice since it retards k_s^H in the forward direction and it retards k_f^D in the backward direction. The difference in primary isotope effects has a retarding effect of 2.3/3.8 while the difference in solvent isotope effects has a retarding effect of 1.2/2.6. These factors would reduce the measured value of 63 for the H/D exchange selectivity to a predicted value of 11.9 for the D/H exchange selectivity, which is in very good agreement with the measured value of 12.1.

The mechanism shown (P. 11) by Werstiuk and Lamaty requires exchange with inversion through a common, symmetrically solvated enolate while the above explanation requires no reversibility and is therefore consistant with the involvement of two different enolate anions for the fast and slow exchanges. This difference may lie only in the symmetry of solvation or may extend to a difference in the extent of s character in the two enolates.

In summary, the isotope effect measurements on 16 have not provided a clear assessment of the exchange processes. We have shown that they can be interpreted as evidence that there is no internal return and can be used to explain the H/D versus D/H exchange selectivities. As a corollary to this interpretation the Streitwieser approach must be considered invalid in this case.

Alternatively, acceptance of the Streitwieser treatment suggests that internal return is greater in the fast than the slow position with the requisite related acceptance of a primary isotope effect of $k_f^H/k_f^D = 35$.

A third alternative explanation of the observed stereoselectivities, that by Werstiuk and Lamaty as outlined above cannot be ruled out by our rate studies. Our studies do show, however, an alternative to the back reaction (exchange with inversion) and, indeed, that both the secondary isotope effects and differing solvent isotope effects seen to be important factors whose acceptance is not influenced by the problem of internal return.

It is our feeling that the first of these alternate explanations (i.e. no internal return, differing primary and solvent isotope effects) is most consistant with the observed data. However, none of these interpretations goes against the involvement of stereoelectronic control as the effect causing the large stereoselectivity for the H/D exchange in 16. Only a much greater amount of internal return in the slow position than in the fast position would argue against stereoelectronic control as an important factor in these exchanges and this condition has not been indicated by any of the tests carried out. One further test which might indicate whether internal return is giving a false picture of the transition state stabilities for the exchange of H_f and H_s is the alkylation of 16 in strong base. Results of the methylation of 16 are reported in the following section.

K. Alkylation of 16

In order to test whether the measured stereoselectivity of H/D exchange in 16 could be correlated with the stereoselectivity of alkylation, it was decided to determine the stereochemistry of the products of methylation of this compound. Examination of Dreiding models of 16 indicates that the quasi-axial (fast) position should be more sterically hindered than the quasi-equatorial (slow) position (a fact which was verified by the decrease in selectivity of the exchange with bulkier bases) making the latter the thermodynamically preferred position. For this reason the alkylation and subsequent recovery of product were carried out at or below room temperature. As outlined in the EXPERIMENTAL, both monoalkylated and dialkylated products, along with starting material, were recovered. Only one type of methyl doublet was seen in both these products and that appeared at high field. Models of 16 indicate that a methyl group in the quasi-axial position would be strongly shielded by the π orbitals of the aromatic rings while those in the quasi-equatorial position would be slightly deshielded. Treatment of these products with base in CD_3OH resulted in the growth of a new methyl doublet at lower field (δ1.42, 1.35) with a concurrent decrease in the high field methyl doublet (δ0.89, 0.77). The monalkylated material equilibrated with 85% of the methyl absorption at lower field while the dialkylated material equilibrated with 75% of the methyl absorption at lower field. Examination of the NMR spectrum of the crude product mixture showed no trace of a doublet at or near δ 1.42, 1.35, indicating less than 3% alkylation in the quasi-equatorial position. This result can be compared with the alkylation of the structurally similar thiepin dioxide, 18, for which Viau (47) obtained only one high field doublet on methylation. In base, this doublet was completely replaced by a new methyl doublet at lower field. The stereoselectivity of methylation of 16 is then at least as high and in the same direction as that of the H/D exchange.

L. SUMMARY:

The preceding measurements of steric effects, primary, secondary and solvent isotope effects, selectivities in the H/D and D/H exchanges and selectivity of methylation for 16 are consistant with a mechanism for base catalyzed exchange which involves different transition states for the diastereotopic protons H_f and H_s and probably different anions as well, as illustrated in the extreme of pure sp^3 character by b and c of Figure 3 (P. 7). This mechanism, in turn, is consistant with a process of stereoelectronic control as the reason for the high selectivity for exchange and for alkylation. As mentioned earlier, this interpretation requires only that internal return not be greater for the slow position than for the fast position. While there is disagreement between the qualitative and quantitative estimates of the extent of internal return, none of these tests indicates in any way that internal return is greater in the slow position than in the fast position.

There should be no reluctance to accept the fact that two protons on the same carbon can exhibit different isotope effects. The fact that these protons give rise to an AB quartet in the NMR spectrum is due solely to their different environments and they could be thought of as two different compounds undergoing isotopic exchange.

Since 16 is not a prefectly rigid system, it can be expected that even less flexible systems might exhibit a greater amount of stereoelectronic control. For this reason, it was decided to study the stereoselectivity of exchange of the diastereotopic methylene protons in twistan-4-one, 17, as described in the second section following.

M. Possible Future Experiments on 16

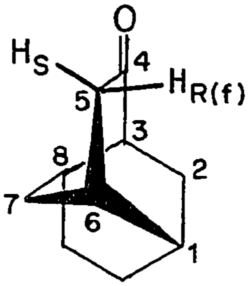
It is not clear at this point whether internal return can be reliably and quantitatively measured for this system due to the sensitivity of the Streitwieser treatment to the propagation of experimental error. Perhaps the best test available is to measure by as direct a route as possible the primary isotope effects and solvent isotope effects for both systems and then test whether these can explain all of the observed exchange selectivities. For example the values of k^H/k^D for the two different positions in 16 might be measured directly by measuring the rates of tritiation of the protonated and deuterated substrate under the same conditions in light solvent. The k^T values in light and heavy solvent could then be used to calculate the solvent isotope effects for the two positions. These isotope effects combined with the secondary isotope effect as measured for 16 could then be applied to the above test.

At first sight it would seem that a measurement of the Brönsted β's for this system might clarify the nature of the transition state symmetries, but the different steric environments of the fast and slow protons creates a problem in the choice of bases, restricting it perhaps to a series of *para* substituted phenolate ions. Also the abstraction of a proton from the slow position in 16 which requires so much change in geometry to attain a planar enolate might be considered comparable to the abstraction of a proton in the nitroalkane series, for which Bordwell(46) has shown that the Brönsted coefficients exhibit unusual behaviour.

STUDIES OF H/D AND D/H EXCHANGE
FOR TWISTAN-4-ONE, 17

A. Assignment of Stereochemistry for 17

The tricyclic ketone, twistan-4-one (17) is asymmetric and therefore exists as two enantiomers. According to the IUPAC rules for assignment of stereochemistry,(32 a,b) the enantiomer of 17 given earlier and reproduced below is named (1S, 3S, 6R, 8S) - twistan-4-one or, more briefly, 1S-twistan-4-one, since the configurations at carbons 3, 6 and 8 are defined by that at C-1



17

(the other enantiomer having the R configuration at C-1). In the enantiomer shown above, the C-H bond which is perpendicular to the direction of the C=0 bond is the pro-R in 1S-17 proton and is labelled H_R. The proton labelled H_S is the pro-S in 1S-17 proton and its C-H bond is at an angle of about 30° from the direction of the C=0 bond. Since the assignment of pro-R and pro-S to these two protons is reversed for the other (1R) enantiomer, which could lead to confusion, and since it is always the proton labelled H_R in the enantiomer shown that exchanges fastest, from this point on the proton at 90° to the C=O bond will be referred to as H_f (H_{fast}) and the other as H_s (H_{slow}).

The assignment of the more rapidly exchanging proton to that labelled H_f (H_{fast}) in 17 was made by ^1H NMR. A Dreiding model indicates a dihedral angle of 80° between H_f and the bridgehead proton at C6 (Fig. 8). According to the Karplus equation (48) a coupling constant of less than 1 Hz would be expected between these protons. For its diastereotopic partner (H_s), a coupling of at least 4Hz would be anticipated. The 100 MHz spectrum of 17 (0.2M in furan) shows a doublet, δ 2.35, J=15 Hz and a quartet, δ 1.95, J=15 and 4Hz for the protons at C-5. It is the doublet at δ 2.35 with no observable vicinal coupling, which first disappears on deuteration and is thus assigned to H_f as in Fig. 8.

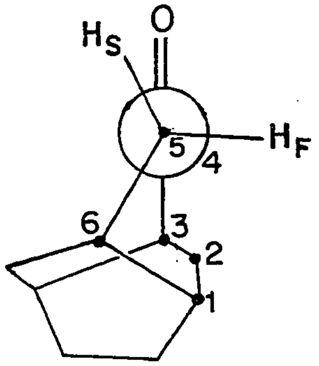


Fig. 10 View of 17 with Neuman projection of CH_2-C=O group

B. Measurement of k_f^H and k_s^H for 17 in Sodium Methoxide/Methanol-O-d

The times for the aliquots in this run were based on estimates of the fast and slow rates from previous trial runs. The samples were analyzed by mass spectrometry (see EXPERIMENTAL for details) and the proton contents were calculated as the number of available protons remaining out of 2 originally. Treatment of the mass spectral data was as described for compound 16, as was the method used to calculate the rate constants. This data gave the following results for 17 (see Table R 10 for details): $k_f^H = 2.10\ hr^{-1}$; $k_s^H = 7.00 \times 10^{-3}\ hr^{-1}$. The calculated stereoselectivity was therefore k_f^H/k_s^H = 300 ± 6.7%.

This high stereoselectivity is greater by a factor of 5 than that measured for 16 and does not suffer from the ambiguity caused by the adjacent phenyl rings in 16. It could, therefore, result from any or all of the following: steric effects; preferential internal return; stereoelectronic control. The following sections will deal with steric effects and internal return in that order.

C. Steric Effect on Stereoselectivity of Exchange in 17

1. Measurement of k_f^H and k_s^H for 17 in Sodium Phenoxide/Methanol-0-d

In order to test whether one of H_f or H_s was more hindered than the other towards attack by base, the bulk of the attacking base was increased by changing to sodium phenoxide in methanol-0-d. It can be seen from Table R 11 that there was no change in the stereoselectivity (within experimental error) as a result of increasing the bulk of the attacking base. This result indicates that H_f and H_s are in very similar steric environments in 17, as was predicted earlier from a study of models of this compound.

The approximately ten-fold decrease in the second order rate constants is consistent with a general base-catalyzed mechanism for the exchange, which requires formation of the anion in the rate determining step.

Table R 10

k^H_f and k^H_s for 17 in Sodium Methoxide/Methanol-0-d (0.093 M)

Time, Hr	A^H_{total}	A^H_f	A^H_s	A^H_e	B	k^H, hr^{-1}	k^H_f/k^H_s
0	2.000	1.000	1.0	-	-		
1	1.150	0.1584	0.9916	0.044	0.227	$k^H_f = 2.10$	300±6.7%
65.7	0.705	0.0545	0.6505	0.055	0.080	$k^H_s = 0.007$	

Table R 11

k^H_f and k^H_s for 17 in Sodium Phenoxide/Methanol-0-d (0.38M)

Time, Hr	A^H_{total}	A^H_f	A^H_s	A^H_e	B	k^H, hr^{-1}	k^H_f/k^H_s
0	2.00	1.000	1.000	-	-		
0.5	1.655	0.6565	0.9985	0.032	0.092	$k^H_f=0.873$	340±6.7%
169	0.720	0.0542	0.6658	0.054	0.076	$k^H_s=0.00257$	

Table R 12

k^D_f and k^D_s for 17 in Sodium Methoxide/Methanol-0-H (0.10M)

Time, Hr	A^D_{total}	A^D_f	A^D_s	A^D_e	B	k^D, hr^{-1}	k^D_{avg}, hr^{-1}	k^D_f/k^D_s
0	1.952	0.976	0.976					
0.85	1.869	0.895	0.974	0.026	0.022	$0.134=k^D_f$	$k^D_f=0.129$±4%	51 ±6%
2.0	1.759	0.787	0.972	0.029	0.051	$0.124=k^D_f$		
168	0.724	0.054	0.670	0.054	0.075	$2.55\text{x}10^{-3}=k^D_s$	$k^D_s=2.52\text{x}10^{-3}$±2%	
336	0.526	0.059	0.467	0.059	0.128	$2.48\text{x}10^{-3}=k^D_s$		

D. Effect of Internal Return on Stereoselectivity of Exchange in 17

1. Measurement of k_f^D and k_s^D for 17 in Sodium Methoxide/Methanol-0-H

Since the fast and slow positions in 17 might be expected to experience secondary and solvent isotope effects similar to those for the fast and slow positions in 16, it was decided to measure the stereoselectivity for the D/H exchange in 17 and test whether the combination of secondary and solvent isotope effects could account for any non-equivalence of stereoselectivity for the H/D and D/H exchange.

Deuterium contents were determined by mass spectrometry as for 16 and the data (Table R 12) were treated as previously described. The measured stereoselectivity for the D/H exchange process was $k_f^D/k_s^D = 51.2$, a decrease by a factor of 6 from the rate ratio for the H/D exchange.

Assuming the solvent isotope effects to be 2.6 for the fast position and 1.2 for the slow position as for 16, the second order rate constants for 17, (after correcting for secondary isotope effects) of $k_f^H =$ 22.58 l/mole hr, $k_f^D = 1.52$ l/mole hr, $k_s^H = 0.0889$ l/mole hr and $k_s^D =$ 0.0252 l/mole hr can be used to calculate $k_f^H/k_f^D = 5.72$ and $k_s^H/k_s^D = 2.94$. Applying these primary, secondary and solvent isotope effects to the measured k_f^H/k_s^H value of 300 would then account for all of the observed difference in stereoselectivity between the H/D and D/H exchange in 17, indicating that both internal return and reversibility of exchange are small.

2. Discussion

These results are again consistent with a greater amount of proton transfer in the transition state for the exchange of H_s than for the exchange of H_f.

The reasonable conclusion is that the stereoselectivity of isotopic exchange in compound 17 clearly demonstrates the "stereoelectronic effect" proposed by Corey and Sneen(5) and supported by the theoretical calculations of Tee(6) and Wolfe(18).

As would be expected from Corey and Sneen's definition of the stereoelectronic factor (P. 6), the stereoselectivity of H/D exchange increases as the rigidity of the ring system increases from 4-t-butylcyclohexanone through 16 to the twistanone 17. The differences in stereoselectivities of exchange for these three compounds arise from the differing energy barriers to attainment of that orientation of atoms and groups which allows for maximum orbital overlap in the transition states.

The distance of the anchoring group from the reaction site in 4-t-butylcyclohexanone allows the formation of the boat and chair form transition states (see P. 9 for mechanism) for which the free energy difference is about 2-3 kcal/mole (the barrier to ring inversion in cyclohexanone has been measured by Anet et al(49) as 4.0 kcal/mole). The energy differences between these transition states, therefore reflect only the differences in strain between the chair and boat conformers which must be less than 4 kcal/mole. The small ratio for H/D exchange of $kax/keq = 3.5 - 5.0$ for 4-t-butylcyclohexanone indicates that this molecule is not sufficiently constrained at the reaction site to demonstrate the stereoelectronic effect to its fullest extent.

Compound 16, on the other hand, possesses greater rigidity at the reaction site in that the transition state for formation of a planar enolate (or protonation of the enolate) by abstraction of H_s requires a more highly strained conformation for maximum orbital overlap than that required for abstraction of an equatorial α-hydrogen in 4-t-butylcyclohexanone. This conformation, from examination of Dreiding models appears to possess considerable bond angle strain as it lies on the pathway to inversion of the biaryl chirality. Removal of H_f, however, occurs readily, since very little change in geometry is required to maintain maximum orbital overlap in the transition state. This large difference in transition state energies is then reflected in the increased stereoselectivity for H/D exchange of $k_f/k_s = 63$.

In the H/D exchange of twistan-4-one, 17, the enolate involved is constrained in a twist-boat conformation, and this, in all probability, requires that the transition states contain some of the sp^3 character shown for the two carbanions b and c in Figure 3 (P. 7). Maximum overlap of the carbanion with the π system of the carbonyl occurs for b (removal of H_f), while in c (removal of H_s) overlap will be greatly reduced by the near orthogonality of the sp^3 and π orbitals. This preferential overlap is, in fact, the stereoelectronic effect, and gives rise to the observed stereoselectivity for 17 of $k_f/k_s = 300$.

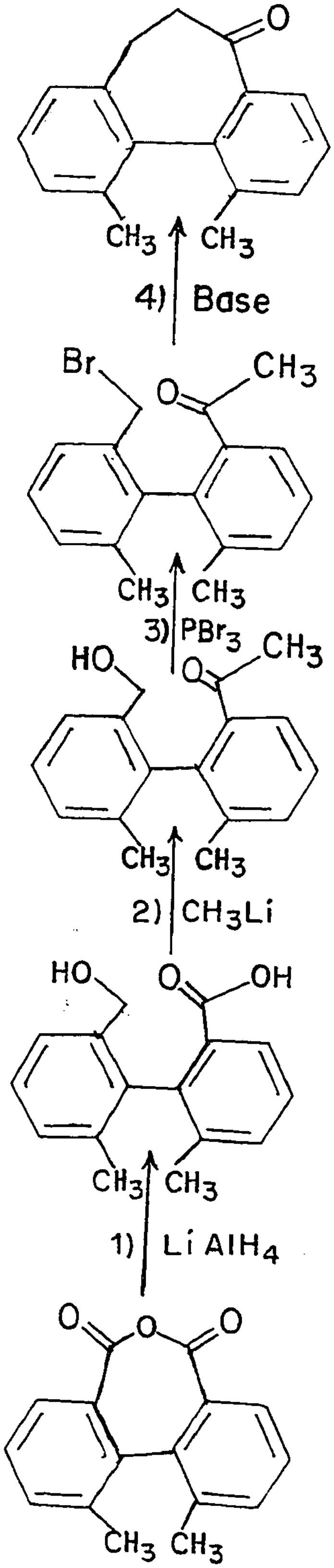
From the preceding discussion it is expected that even greater exchange selectivities (and hence more stereoelectronic control) might be demonstrated by systems which are more constrained to their ground state geometries than 17. One such compound is suggested in the following section.

E. Other Rigid Ketones of Interest

In order to evaluate the effect of the aromatic π system in 16 on the stereoselectivity of isotope exchange and to investigate the stereoselectivity in systems more rigid than 17, attempts were made to synthesize compounds 21 and 22 by the proposed routes shown below.

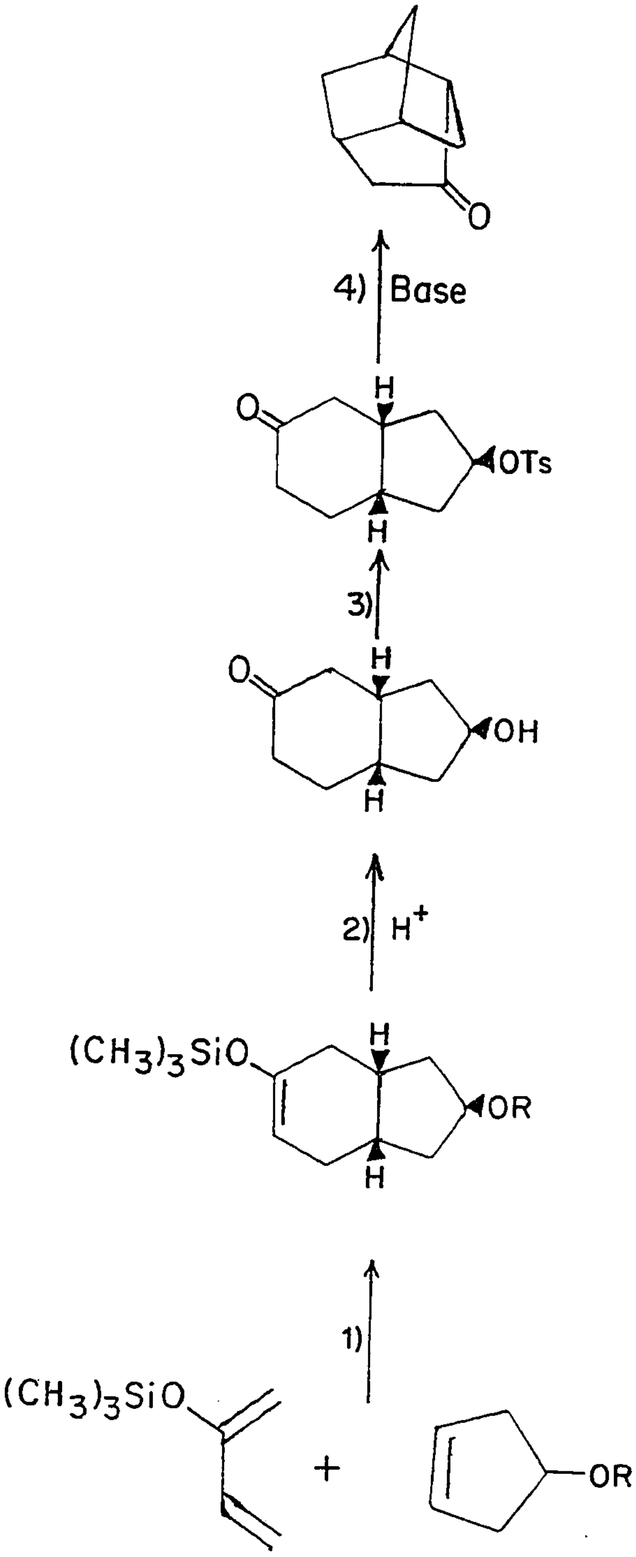
Scheme A

21

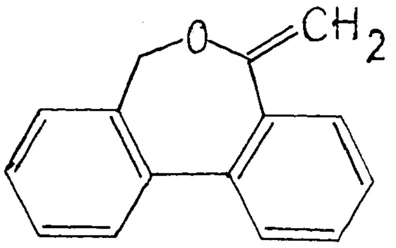


Scheme B

22



Scheme A for the model compound diphenic anhydride resulted in O-alkylation for the final ring closure (step 4) under conditions of phase transfer catalysis to give 23.



23

Compound 21 might also have been made through transposition of the carbonyl group of 16, but this route was not pursued because compound 22 seemed to offer the possibility of much higher stereoselectivity.

The starting materials for scheme B were synthesized successfully (with R=H and R=$Si(CH_3)_3$) but the Diels-Alder reaction (step 1) did not go in refluxing benzene and gave intractable tars in two separate trials when the reactants, neat, were treated in a sealed tube at 150°C.

EXPERIMENTAL

A. Heavy water (99.9 atom % D), methanol-O-d (99 atom % D), methyl alcohol-d_3 (CD_3OH 99 atom % D) and dimethylsulfoxide-d_6 (99.5 atom % D) were obtained from Merck, Sharp and Dohme Canada Ltd. Tritiated water (25mC/ml) and standard tritiated toluene (4.5×10^6 dpm/ml) were obtained from New England Nuclear Corporation. Solutions of lower specific activity were prepared by volumetric dilution. Tritiated methanol and methanol-O-d were prepared by dilution of tritiated water with the respective solvents. Dicyclohexyl-18-crown-6 cyclic polyether obtained from Aldrich was used without further purification.

Diphenyloxazole (PPO) and 2,2'-p-phenylene-bis (5-phenyloxazole) (POPOP), liquid scintillation counter grade, were obtained from Baker Co. Scintanalyzed toluene was obtained from Fisher Scientific.

Diisopropyl amine was distilled from calcium hydride before use. Dry tetrahydrofuran (THF) was distilled from lithium aluminum hydride just prior to its use. n-Butyllithium (2.1M in hexane) was purchased from Ventron Corporation.

All weighings for scintillation counting were done on an E. Mettler Zurich Type H-16 balance to 0.05 mg. NMR spectra were taken in deuterochloroform solution (unless otherwise stated) on a Varian T-60 spectrometer or a Varian HA-100 spectrometer equipped with an SD-100 deuterium spin decoupler. Control tests showed the T-60 integration to be as accurate as the HA-100 integration so the T-60 NMR was used for analysis unless otherwise stated. Tritium counting was carried out in a Beckman LS-150 scintillation counter equipped with an external standard channels ratio function. Kinetic samples which involved Mass Spectrometric analysis were run on an AEI MS-903 mass spectrometer. The experimental conditions reported are those found to give the most accurate and reliable results after a minimum of two pre-trials for each rate determination.

Unless otherwise stated, the experimental data were treated by the Sachs equation$^{(4c)}$ for equilibrating pseudo-first order reactions as given below.

$$\frac{d_o + h_o}{d_o + h_o + B} \quad \ln \left[\frac{A_o - A_e}{A_t - A_e}\right] = kt$$

where d_o = initial concentration of exchangeable deuterium in solvent.

h_o = initial concentration of exchangeable hydrogen in solvent.

B = concentration of hydrogen (or deuterium or tritium) in solvent due to exchange with substrate.

A = Concentration of hydrogen (or deuterium or tritium) in substrate.

A_e = Equilibrium concentration of hydrogen (or deuterium or tritium) in substrate.

B. Preparation Of Solutions For Kinetic Measurements

1) Sodium Deuteroxide solutions in D_2O were prepared by adding D_2O volumetrically by syringe to the required amount of clean, dry sodium in a cooled serum capped flask which had been flushed with nitrogen. The deuterium gas formed was allowed to escape through a second syringe needle. The base was then titrated with standard hydrochloric acid solution.

2) Sodium methoxide in methanol and methanol-O-d solutions were prepared both as stated above for the D_2O solutions, and by dissolving a weighed amount of fresh, dry sodium methoxide in the respective solvent. Both methods gave base solutions which remained clear and colourless and maintained their base strength for periods up to three months when stored in

the refrigerator under nitrogen and with the serum caps taped and wrapped with parafilm.

3) Solutions of sodium phenoxide in methanol-O-d were prepared by dissolving weighed amounts of sodium methoxide in the required amount of methanol-O-d containing an equimolar quantity of phenol. Because of the low base concentrations used, the increase in the proton pool generated by this method was negligible.

4) Solutions of sodium 2,6-dimethylphenoxide in methanol-O-d were prepared as stated above for the sodium phenoxide solutions.

5) Toluene scintillation liquid was prepared by dissolving 4 gm of PPO and 1 gm of POPOP in 1 liter of scintanalyzed toluene.

C. Standard Isolation Procedures

1) Extraction Procedure For NMR Samples

When extraction was to be used for recovery of the partially exchanged ketone, the reaction mixture was quenched with 0.1 NHCl and the resulting suspension was extracted three times with spectral grade methylene chloride. The organic phase was dried over anhydrous magnesium sulphate, filtered and the solvent removed on the rotary evaporator. Traces of solvent were removed by drying under a vacuum of about 0.2 millimeters of mercury for at least one hour. Control tests using deuterated acid indicated no isotope exchange due to this work-up procedure.

Since the partially exchanged ketone samples were unstable in their isotope content towards chromatographic purification and recrystallization resulted in large losses, samples for NMR analysis were prepared as above unless otherwise specified. Ketone 16 was not sublimeable below its melting temperature with the available vacuum.

2) Preparation Of Samples For Scintillation Counting And For Mass Spectrometry.

Each sample for scintillation counting and for mass spectrometry was prepared in the following way: the aliquot to be quenched was withdrawn from the reaction by syringe and added to three times its volume of distilled water containing hydrochloric acid 10% in excess of the base present. The resulting suspension was covered and stored in the refrigerator overnight, after which time the pure, white ketone had precipitated out. This precipitate was filtered, washed with distilled water, and dried under vacuum to constant weight.

D. Scintillation Counting

The purified aliquot (5-25 mg) was weighed out accurately in a 20 ml. polyethylene scintillation vial (Fisher) and was dissolved in 10 ml of the toluene scintillation liquid. With each set of quenched samples was included a set of standards for calibrating the counting efficiency of the machine. Samples were counted with an ^3H window for varying times depending on the sample size and specific activity to give maximum 1.0% statistical error except in a few cases where, due to small sample size, the error rose to 1.5%.

Due to a shortage of available ketone 16, the standard samples used to calibrate the counting efficiency of the scintillation counter were made up by adding increasing amounts (0 to 0.2 ml) of chloroform to solutions of 0.01 ml of standard tritiated toluene in 10 ml of toluene scintillation liquid, such that the range of standard sample quenching was greater than the range involved in tritium counting of quenched samples.

For each standard sample 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 which measures the amount by which the sample quenches an external standard source in two counting channels, one for higher energy (b) and one for lower energy (a) counts. The effect of quenching is to decrease the net count rate in channel b (cpm_b) and to increase the net count rate in channel a(cpm_a). The channels ratio (cpm_b/cpm_a) is thus a measure of the quenching Q, and since it depends only on the shape of the beta spectrum, it is independant of the sample activity.

The counting efficiency for each sample was determined by dividing the measured counting rate by the known dpm (disintegrations per minute) of the standard samples. The calibration curve was obtained by plotting the calculated counting efficiency against the external standard ratio. The counting efficiency for each kinetic sample was then obtained from this curve using the external standard ratio for that sample. In this way, counts per minute could be converted to specific activity or dpm per milligram. A sample calibration curve is shown here as figure 10.

E. Method of Treatment of Mass Spectral Data

Proton (or deuterium) concentrations for all measurements of primary isotope effects were determined by mass spectrometric analysis. Each sample was analyzed several times over a range of six m/e units above and below the parent molecular ion (M^+). Each set of peak heights was normalized to a total of 100, then averages were taken for each m/e value. This analysis on the parent compound (16) showed a large PMI (M^+), and $(M+1)^+$ and $(M+2)^+$ peaks which were 20.27% and 2.54% respectively of the M^+ peak. Therefore, each peak height was corrected by subtracting from it 20.27% of its $(M-1)^+$ peak and 2.54% of its ($M-2^+$) peak. The concentrations of the d_0, d_1, d_2, d_3 and d_4 species could then be calculated from these corrected peak heights. (See Table E1 for a detailed

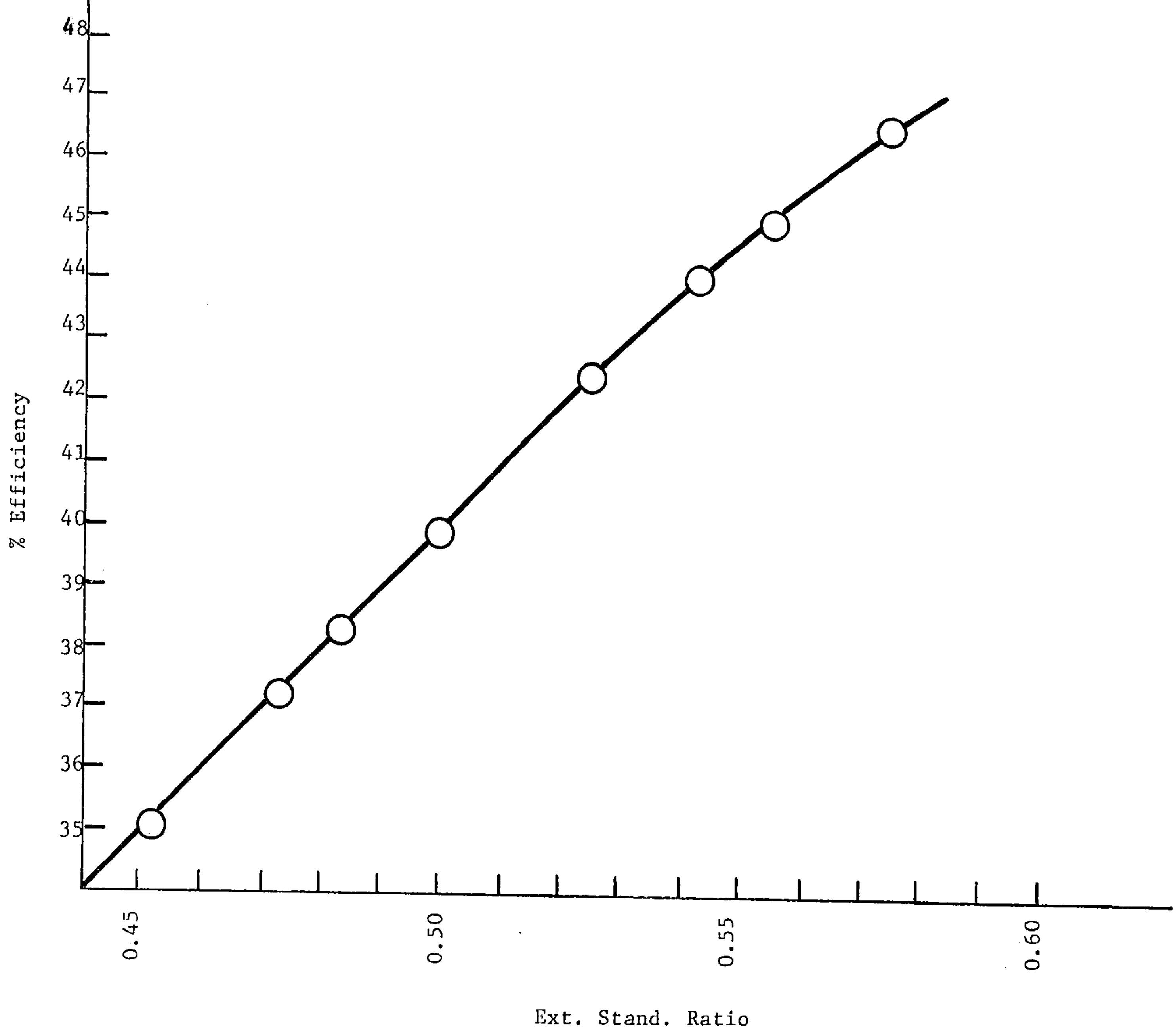


Figure 11. Sample Calibration Curve For Scintillation Counting

Specific Activity For Each Standard Sample = 3.4×10^4 dpm

Table E1

Mass Spectral Data for k_f^H/k_f^T Measurement for 16. (220 Sec Sample)

Normalized Peak Heights ($d_0+d_1+d_2+d_3+d_4$ = 100)

Run	m/e --	236(d_0)	237(d_1)	238(d_2)	239(d_3)	240(d_4)
1		2.58	22.42	58.42	14.67	1.[illegible]
2		2.64	22.77	58.12	14.53	1.94
3		2.67	22.27	58.36	14.62	1.78
4		2.72	22.73	58.35	14.38	1.82
5		2.76	22.91	58.02	14.35	1.96
6		2.89	22.78	57.57	14.60	2.17
7		2.68	22.79	58.18	14.39	1.97
8		2.86	23.36	57.54	14.27	1.97
9		2.70	22.83	58.09	14.57	1.83
10		2.73	23.15	57.67	14.49	1.96
11		2.66	22.92	57.88	14.60	1.95
	Average	2.72	22.81	58.02	14.50	1.93
Correct for (M+1) and (M+2)of d_0			-0.55	-0.07		
		2.72	22.26	57.95	14.50	1.93
Correct for (M+1) and (M+2)of d_1				-4.51	-0.57	
		2.72	22.26	53.44	13.93	1.93
Correct for (M+1) and (M+2)of d_2					-10.83	-1.36
		2.72	22.26	53.44	3.10	0.57
Correct for (M+1) and (M+2)of d_3						- .63
		2.72	22.26	53.44	3.10	0
Normalize to total 100		3.30	27.30	55.60	3.80	0

Total [H] (expressed as # of protons remaining out of 4 available for exchange)

$$= \frac{4d_0 + 3d_1 + 2d_2 + d_3}{d_0 + d_1 + d_2 + d_3 + d_4} = 2.30$$

example). All proton concentrations (or deuterium for the reverse exchange) are given as the number of protons (or deuterons) remaining out of the 4 originally available for exchange.

The same treatment was used for mass spectral data for twistan-4-one (17) except that the $(M-1)^+$, $(M+1)^+$ and $(M+2)^+$ corrections for each M^+ peak were 1.16%, 13.0% and 1.45% respectively.

This treatment gives individual rate constants accurate to ± 4% - 6%. Still better precision is obtained when rate constants are obtained from several quenched aliquots.

F. Synthesis Of 4', 1"-Dimethyl-1,2,3,4-Dibenzcyclohepta-1,3-dien-6-one, 16

The synthesis of this ketone which has been described by Mislow et al (28) and others (29,30) is outlined below. Modification to some of the procedures which resulted in higher yields are shown. Since the sequence is a stepwise conversion, only the product name is given for all but the first reaction.

1) 2-Nitro-3-methylbenzoic acid from m-toluic acid. (30)

Lit. yield:	52%
Expt. yield:	74%
Modification:	None

2) 2-Amino-3-methylbenzoic acid. (30)

Lit. yield:	74%
Expt. yield:	70%
Modification:	None

3) 6,6'-Dimethyl-2,2'-diphenic acid(30)

Lit. yield: 66%

Expt. yield: 79%

Modification: All reagents except amino acid increased by 25% over literature.

4) 6,6'-Dimethyl-2,2'-bis-(hydroxymethyl)-biphenyl(29)

Lit. yield: 85%

Expt. yield: 85%

Modification: None

5) 6,6'-Dimethyl-2,2'-bis-(bromomethyl)-biphenyl(29)

Lit. yield: 90%

Expt. yield: 90 - 99%

Modification: None

6) 6,6'-Dimethyl-2,2'-bis-(cyanomethyl)-biphenyl(30)

Lit. yield: Not Reported

Expt. yield: 95%

Modification: None

7) 4',1"-Dimethyl-5-cyano-1,2,3,4-dibenz-1,3-cycloheptadiene-6-imine (30)

Lit. yield: 66%

Expt. yield: 85%

Modification: After filtration of product, dilution of filtrate with water yields a further amount of solid product.

8) 4',1"-Dimethyl-1,2,3,4-dibenz cyclohepta-1,3-diene-6-one(28)

Lit. yield: 48%

Expt. yield: 85 - 90%

Modification: None

G. Measurement of k_f^H and k_s^H For 16 in Sodium Deuteroxide/D_2O/Dimethylsulfoxide-d_6

To 20 mg (0.0848 mmole) of 16 in 0.5 ml of dimethysulfoxide-d_6 in an NMR tube flushed with nitrogen, was added 0.03 ml of D_2O and 0.01 ml of sodium deuteroxide/D_2O solution (0.082M) for a final base strength of 1.52×10^{-3}M. The methylene AB quartet region was integrated at appropriate time intervals using a T-60 NMR Spectrometer. These integrals were converted to number of available protons remaining by comparison with the integral of the constant methyl singlet. The data (Table E2) were treated by the Sachs equation(4C) as described earlier. This treatment gave rise to slightly curved plots of the ln terms versus time (Fig. 8)

H. Measurement of k_f^H and k_s^H For 16 In Sodium Methoxide/Methanol-0-d

To 40 mg (0.17 mmole) of 16 and 1.0 ml of methanol-0-d under nitrogen in a serum-capped flask was added, with stirring at 29.0 ± 0.1°C, 0.016 ml of sodium methoxide/methanol-0-d solution (0.186M) for a final base concentration of 0.0029M. A 0.5 ml aliquot was withdrawn by syringe after 40 seconds and quenched by transfer to 1.5 ml of hydrochloric acid solution (0.1N). The remainder was similarly quenched after 2,780 seconds. The ketone samples were recovered by extraction, taken up in deuterochloroform and the spectra with several integrals were run on the T-60 NMR spectrometer. These integrals were converted to number of available protons remaining by comparison with the constant integrals for the methyl signal. The results are given in Table E3.

Table E2

k_f^H and k_s^H For <u>16</u> in Sodium Deuteroxide/D_2O/Dimethylsulfoxide-d_6

Time, Sec	A_{total}^H	Time, Sec	A_{total}^H
0	4.000	349	1.485
15	2.908	458	1.392
30	2.568	475	1.374
45	2.475	505	1.355
60	2.228	530	1.337
84	2.042	582	1.318
230	1.733	630	1.300
293	1.671	713	1.238
336	1.578	790	1.145

Table E3

k_f^H and k_s^H For <u>16</u> in Sodium Methoxide/Methanol-O-d

Time, Sec	A_{total}^H
0	4.00
40	2.95
2780	1.00

I. Determination of the Secondary Isotope Effect (i) for the Fast Methylene Position in 16

1. Preparation of 16 Specifically Deuterated in 50% of the Slow(s) Methylene Positions

Reaction conditions were based on previous pre-trial estimates of deuteration and dedeuteration rates.

a) Added 0.01 ml of sodium methoxide/methanol-O-d (0.18 M) under nitrogen with stirring to 100 mg (0.424 mmole) of 16 in 2.46 ml of methanol-O-d. The reaction was stirred at 29.4 ± 0.1°C for 2,780 seconds, after which time the reaction was quenched and the ketone (76 mg) extracted. The NMR of this ketone showed approximately 0.8 protons remaining in the high field (slow) position.

b) The ketone 16 (d_3) (76 mg, 0.322 mmole) from above was dissolved in 1.83 ml of methanol under nitrogen and 0.065 ml of sodium methoxide/methanol solution (0.045 M) was added with stirring at 29.0 ± 0.1°C. This reaction was quenched after 6,980 seconds and the ketone extracted as described previously. The NMR of this product showed a total of 3.08 hydrogens in the two methylene positions. The 100 MH_z spectrum on 250 Hz sweep width with deuterium decoupling gave the following breakdown for this 3.08 hydrogens: CD_fH_s = 0.08H; CH_fD_s = 0.84H; CH_fH_s = 2.16H; (See Table E4).

2. Measurement of Secondary Isotope Effect, i_f

To 40 mg (0.17 mmole) of the monodeutero 16 from above in 0.99 ml of methanol-O-d under nitrogen was added, with stirring, 0.01 ml of sodium methoxide/methanol-O-d solution (0.18M) at 29.0 ± 0.1°. After 60 seconds, 0.5 ml was withdrawn by syringe and quenched as previously described. The remainder was quenched after 120 seconds. The ketone samples were recovered by extraction and examined by 100 MHz NMR as above. Peak height analysis on these samples and on the starting mono-deutero sample as described earlier gave relative rates for exchange of the fast hydrogens with and without the secondary isotope effect. The 60 second and 120 second samples gave $i_f = 1.16$ and $i_f = 1.20$ respectively, for an average value of $i_f = 1.18 \pm 0.02$. (See table E4 for data).

J. Measurement of k_f^H and k_s^H for 16 in Sodium Phenoxide/Methanol-0-d

To 40 mg (0.17 mmoles) of 16 and 1.0 ml of methanol-0-d under nitrogen in a serum capped flask at 29.0°C was added, with stirring 0.016 ml of sodium phenoxide/methanol-0-d solution (0.182 M). A 0.5 ml aliquot was withdrawn and quenched as before after 60 seconds, and the remainder was quenched after 700 seconds.

The ketone samples were recovered by extraction as described earlier, and examined on the 60 MHz and 100 MHz spectrometers (see Table E5). The 100 MHz spectra indicated that the ratio ($\alpha = k_f/k_s$) was sufficiently high that the late sample showed only the equilibrium concentration of H_f. The integrals from the T-60 NMR were used to calculate k_f^H and k_s^H using the method outlined earlier in this thesis.

K. Measurement of $\alpha = k_f^H/k_s^H$ For 16 in Sodium 2,6-Dimethylphenoxide/Methanol-0-d

To 20 mg (0.0848 mmoles) of 16 and 0.5 ml of methanol-0-d in a serum capped flask, under nitrogen at 29.0±0.1°C, was added, with stirring, 0.01 ml of sodium 2,6-dimethylphenoxide/methanol-0-d solution (0.05M) for a final base concentration of 0.00098M. The reaction was quenched after 610 seconds by the addition of 1.5 ml of hydrochloric acid solution (0.1M) and the ketone was recovered by extraction as described earlier.

The 100 MHz spectrum at 250 Hz sweep width with deuterium decoupling was used to calculate $\alpha = k_f^H/k_s^H$ where $\alpha = \log (A_0/A_t)_f / \log (A_0/A_t)_s$. The

Table E 4

Determination of Secondary Isotope Effect (i_f) For <u>16</u>

Time, Sec	# CH_fD_s*	# CH_fH_s*
0	0.840	1.08
60	0.556	0.654
120	0.378	0.424

* Peak heights have been converted to number of available hydrogens of each type remaining.

Table E 5

k_f^H and k_s^H For <u>16</u> in Sodium Phenoxide/Methanol-O-d

Time,Sec	A^H_{total}
0	4.00
60	3.250
700	1.778

relative concentrations of H_f and H_s were obtained by measuring the integrals of the left and right hand sides respectively of the AB quartet and the related monoproteo peaks and comparing these integrals to the constant integral for the methyl singlet (See Table E6).

The above method for calculation of $\alpha = k_f^H/k_s^H$ from one quenched sample is valid only when α is sufficiently small that the slow proton exchanges measureably before the fast proton has exchanged to equilibrium. This was the case for the present measurement only.

L. Measurement of k_f^H and k_s^H For 16 in Sodium Methoxide/Methanol-0-d in the Presence of Crown Ether

To 40 mg (0.17 mmoles) of 16 in 0.96 ml of methanol-0-d under nitrogen in a serum-capped flask was added, with stirring at room temperature, 0.01 ml of a solution containing 84 mg of dicyclohexyl-18-crown-6 polyether in 1.0 ml methanol-0-d and then 0.034 ml of sodium methoxide/methanol-0-d solution (0.047 M). This gave a solution that was 1.6×10^{-3}M in base and 2.0×10^{-3}M in crown ether.

A 0.5 ml aliquot was quenched after 99 seconds as previously described and the remainder was quenched after 5,825 seconds. The ketone samples were recovered by the standard extraction and analyzed on the T-60 NMR spectrometer. The results (Table E7) were treated as described previously.

M. Measurement of k_f^H and k_f^T For 16 in Sodium Methoxide/Methanol-0-d

1) Preparation of 16 Tritiated in the Fast (R) Position.

To 400 mg (1.696 mmole) of 16 in 9.7 ml of tritiated methanol under nitrogen in a serum-capped flask was added, with stirring, 0.3 ml of sodium

Table E 6

k_f^H/k_s^H For <u>16</u> in Sodium 2,6-Dimethylphenoxide/Methanol-O-d

Time, Sec	A_{total}^H	A_f^H	A_s^H
0	4.000	2.000	2.000
610	2.585	0.820	1.765

Table E 7

k_f^H and k_s^H For <u>16</u> in Presence of Crown Ether in Sodium Methoxide/Methanol-O-d

Time, Sec	A_{total}^H
0	4.00
99	2.725
5825	0.865

methoxide/methanol (0.1M) for a final base strength of 3.0×10^{-3}M. The reaction was quenched after 7 seconds by adding 30 ml of distilled water containing 0.3 ml of hydrochloric acid solution (0.1 M). After standing overnight in the refrigerator, the precipitated ketone was filtered off, washed with water and dried under vacuum to a constant weight of 324 mg of ketone 16, tritiated to about 5% reaction in the fast position (16-T_f). The specific activity was 202.5 dpm/mg (Table E8).

2) Measurement of k_f^H and k_f^T

To 296 mg (1.255 mmoles) of ketone 16-T_f and 7.37 ml of methanol-0-d under nitrogen in a serum-capped flask was added, with stirring, 0.133 ml of sodium methoxide/methanol-0-d solution (0.0715M) for a final base concentration of 1.27×10^{-3}M. The following aliquots were withdrawn and quenched as described earlier: 0.1 ml after 32 seconds; 0.1 ml after 100 seconds; 0.1 ml after 220 seconds; 2.4 ml after 276 seconds; 2.4 ml after 650 seconds; 2.4 ml after 810 seconds.

After sitting covered in the refrigerator overnight, the samples were filtered, washed with water and dried under vacuum to constant weight. The first four samples were analyzed by mass spectrometry for deuterium uptake and the last three samples, along with the starting material, were analyzed as described previously for tritium content.

The data for measurement of k_f^H and k_f^T were treated by the Sachs equation as described previously (see Table E8 for details).

Table E 8

k_f^H and k_f^T For 16 in Sodium Methoxide/Methanol-0-d

Time,Sec	d_0	d_1	d_2	d_3	d_4	A^H_{total}	A^T_{total}(dpm/mg)	A_f^{T*}(dpm/mg)
0	100.0	-	-	-	-	4.00	202.5	199.3
32	53.7	39.1	7.2	-	-			
100	17.3	47.5	34.5	0.65	-	2.82		
220	3.3	27.3	65.6	3.80	-	2.30		
276	2.7	22.4	67.0	7.30	0.60	2.16	168.0	164.8
650						1.92	133.4	130.2
810						1.88	124.4	121.2

*Corrected for 1.6% T_s

Table E 9

k_s^H and k_s^T For 16 in Sodium Methoxide/Methanol-0-d

Time,Sec	d_0	d_1	d_2	d_3	d_4	A^H_{total}	A^T_{total}(dpm/mg)
0	100	-	-	-	-	4.00	1978.3
25	11.1	42.5	44.6	1.8		2.63	1709.2
620	0.2	3.5	33.7	45.9	16.7	1.25	1128.6
1205	0.1	1.4	15.1	44.3	39.1	0.79	958.5
2400	-	0.3	4.9	28.7	66.2	0.39	774.0
3610	-	0.1	2.5	21.3	76.2	0.26	654.4
7200	-		1.6	17.2	81.2	0.20	333.2
10000							225.8
13000							148.5
20000							79.4

N. Measurement of k_s^H and k_s^T For 16 in Sodium Methoxide/Methanol-0-d

1) Preparation of Ketone 16 Equally Tritiated in the Fast (R) and Slow (S) Positions.

To 630 mg (2.76 mmoles) of 16 and 20 mg (0.37 mmole) of sodium methoxide under nitrogen in a serum-capped flask were added, with stirring 12.0 ml of methanol and 3.0 ml of tritiated methanol. The reaction was stirred at room temperature for 90 hours to ensure that both positions were labelled to the equilibrium concentration of tritium. The reaction was then quenched and standard isolation gave 530 mg of the labelled product. The specific activity was 1,978 dpm/mg (Table E9).

2) Measurement of k_s^H and k_s^T

To 450 mg (1.91 mmoles) of the above labelled ketone 16 and 10.3 ml of methanol-0-d under nitrogen in a serum capped flask was added, with stirring at 29.0 ± 0.1°C, 0.95 ml of sodium methoxide/methanol-0-d (0.0715 M) for a final base concentration of 6.03×10^{-3}M. The following aliquots were withdrawn by syringe, quenched and the ketone recovered as previously described: 0.25 ml after 620 seconds; 0.25 ml after 1,205 seconds; 0.25 ml after 240 seconds; 2.0 ml after 3,610 seconds; 2.0 ml after 7,200 seconds; 2.0 ml after 10,000 seconds; 2.0 ml after 13,000 seconds; 2.0 ml after 20,000 seconds. The first four samples were submitted for mass spectrometric determination of deuterium content and the last five samples were analyzed as previously described for tritium content. The data for determination of k_s^H and k_s^T were treated as previously described. Only those data for which it was clear that all of the fast tritium and about half of the slow-tritium had already exchanged were used to calculate k_s^T (see Table E9).

O. Measurement of k_f^D, k_s^D, k_f^T and k_s^T for 16 in Sodium Methoxide/Methanol-O-d

1) Preparation of 16 Equilibrated with Deuterium and Tritium in the Fast and Slow Positions

To 570 mg (2.42 mmoles) of 16 in 14.4 ml of tritiated methanol-O-d in a serum capped flask under nitrogen added 78 mg of sodium methoxide for a base concentration of 0.1 M. The reaction was stirred at 29.0 ± 0.1°C for 4 days to ensure complete equilibration, then quenched by adding 45 ml of 0.4 N HCl solution. The ketone was recovered as previously described. The specific activity of the sample was 11,429.5 dpm/mg and the concentration of deuterium was 3.827 available D out of a possible 4 (i.e. 95.7% deuteration) (see Table E 10).

2) Measurement of k_f^D, k_s^D, k_f^T, k_s^T

To 380 mg (1.61 mmole) of 16 labelled as above in 8.92 ml of methanol-O-H in a serum capped flask under nitrogen was added, with stirring at 29.0 ± 0.1°C, 0.58 ml of sodium methoxide/methanol-O-H (0.10 M) for a final base concentration of 0.00611 M. The following aliquots were withdrawn by syringe, quenched and the ketone recovered as described previously: 0.25 ml after 110 seconds; 0.8 ml after 180 seconds; 0.8 ml after 295 seconds; 0.8 mls after 400 seconds; 0.8 ml after 500 seconds; 0.8 ml after 775 seconds; 0.25 ml after 1425 seconds; 0.25 ml after 1945 seconds; 0.8 ml after 2720 seconds; 0.8 ml after 3580 seconds; 0.8 ml after 4600 seconds; 0.8 ml after 5785 seconds; the remainder after 7000 seconds.

Tritium and deuterium analyses were carried out on the applicable aliquots and the results (Table E 10) were treated as previously described.

Table E 10

k_f^D, k_s^D, k_f^T and k_s^T for 16 in Sodium Methoxide/Methanol-0-H

Time, Sec	d_0	d_1	d_2	d_3	d_4	A^D_{total}	A^T_{total} (dpm/mg)
0			1.36	14.57	84.07	3.827	11,429.5
110	1.64	4.13	16.24	41.79	36.20	3.068	
180	3.08	9.13	38.99	60.31	27.48	2.720	
295	2.87	9.47	41.44	36.77	9.44	2.404	9,621.2
400	3.22	12.93	50.88	28.91	4.05	2.176	9,136.3
500	6.35	19.48	52.15	19.21	2.81	1.927	
775	6.55	28.53	54.70	10.10	0.12	1.687	7,587.1
1425	13.03	41.75	43.94	1.28	-	1.335	
1945	19.86	46.51	32.31	1.32	-	1.151	
2720	32.38	47.33	19.64	0.66	-	0.886	4,081.7
3580	43.92	42.99	12.42	0.67	-	0.697	3,164.2
4600	58.41	34.73	6.43	0.44	-	0.489	2,740.7
5785	62.74	27.09	3.31	-	-	0.362	2,154.6
7000	75.05	22.65	2.30	-	-	0.273	

P. Determination of $K^{T'}$ for 16

Tritiated methanol (1.0 ml , 124.7 meq) was added with stirring to a sealed flask under nitrogen containing 40 mg (0.68 meq) of 16 and 2.7 mg of fresh, dry sodium methoxide, for a base strength of 0.05 M. The reaction mixture was stirred at 29.0 ± 0.1°C for four days, after which time the reaction was quenched and the ketone recovered as outlined previously. The purified ketone as well as a 10 μl. sample of the original tritiated methanol were analyzed for tritium content, along with a set of standards using methanol as the quenching agent. The measured specific activities for original tritiated methanol and final tritiated ketone were 6.93×10^5 dpm/meq. and 5.47×10^5 dpm/meq. respectively. The original tritium content of the methanol will have been diluted by 2.87% by the exchange with the ketone, so the final specific activity of the tritiated methanol is 6.73×10^5 dpm/meq.

The value of $K^{T'}$, obtained as the ratio of the equilibrium tritium content in methanol to that in one position of the ketone is therefore 1.23.

Q. Alkylation of 16

1. Mono and Dimethylation of 16

To 25 ml of dry THF under nitrogen at room temperature and containing 0.10 ml of diisopropylamine and about 0.5 mg of 2,2'-dipyrydyl as indicator was added 0.35 ml of n-butyl lithium (2.1 M). The deep red solution was stirred for 15 minutes, then cooled to 0° C for 15 minutes, after which a solution containing ketone 16 in dry THF was added slowly until the red colour had disappeared. This titration required 115 mg (0.635 mmoles) of ketone 16. After stirring for 5 minutes, 0.2 ml (a seven-fold excess) of methyl iodide was added and the reaction progress was followed by TLC. After 5 minutes, a new spot was formed with an R_f value slightly greater than the starting material.

This spot had increased in proportion after 20 minutes and after one hour the spots were about equal in intensity under ultraviolet light. These proportions had not changed after 2 hours and 40 minutes, so the reaction was allowed to warm up to room temperature. The TLC of the reaction mixture after 4 hours again showed no change from one hour at $0^{o}C$. The reaction was quenched with 3 drops of 0.05 M hydrochloric acid solution and the T.H.F was removed at room temperature on the rotary evaporator. The residual suspension was extracted with ether, dried over magnesium sulphate, filtered and the ether removed at room temperature on the rotary evaporator and then under 0.1 millimeter of mercury pressure. This process yielded 99 mg of crude material whose T-60 NMR spectrum showed a new doublet at δ 0.89 and δ 0.77 and a complex methylene absorption centered around δ 3.4.

Preparative TLC separation of the two major fractions with R_f values of 0.61 and 0.71 yielded 30 mg each of two different products. The T-60 NMR spectrum of the faster moving fraction showed it to be mostly dimethylated material while that of the slower moving fraction showed it to be mostly monomethylated product. These assignments were verified by the mass spectra which showed parent ions at m/e = 264 and m/e = 250 in the ratio 5.8:1 for the $R_f = 0.71$ fraction and at m/e = 264, 250 and 236 in the ratio 4.5:24:1 for the $R_f = 0.61$ fraction. The expected fragment peaks showing stepwise loss of CO, CH_3, and CH_3 were present for each parent molecular ion.

2. Epimerization of the Mono and Dimethylated 16

Each of the above fractions, when dissolved in d_3-methanol-O-H and catalyzed by a trace of sodium methoxide, showed a decrease in the magnitude of the high field methyl doublet with concurrent growth of a new lower field methyl doublet which, in both cases, became the major of the two doublets. For the dimethylated fraction the low field methyl doublet constituted 73% of the total at equilibrium, while for the monomethylated fraction, the low field methyl doublet equilibrated at 85% of the total methyl doublet absorption. The new lower field methyl doublet appeared at δ 1.42 and δ 1.35 for both fractions.

3. NMR Analysis of Alkylation Products of 16

The NMR spectrum of the original crude product mixture showed no reaction product containing methyl groups in the pseudo-equatorial(s) position, even after work-up, although concentrations of 3% or greater should be detectable in this system.

Further evidence for the structure of the two products comes from the 100 MHz NMR spectra at 250 Hz sweep width. The dimethylated product showed one major six proton singlet at δ 2.21 for the aromatic methyl groups and a two proton quartet at δ 3.53 with J = 6.75 Hz for the methine proton. The monomethylated product showed two singlets at δ 2.298 and δ 2.196 for the aromatic methyl groups and a one proton quartet at δ 3.65 with J = 6.8Hz and a two proton AB quartet at δ 3.395 with J = 2.75 Hz.

R. Purification of Twistan-4-one, 17

The sample of 17 used in this work was graciously donated by Professor Deslongchamps(50) and was purified by sublimation at 0.1 mm. mercury and room temperature. Its NMR spectrum, mass spectrum and melting point were consistent with the structure of authentic 17(50).

S. Measurement of k_f^H and k_s^H for 17 in Sodium Methoxide/Methanol-O-d

To 40 mg. (0.266 mmoles) of 17 in 0.5 ml of methanol-O-d under nitrogen in a serum-capped flask was added, with stirring at 29.0 ± 0.1°, 0.5 ml of sodium methoxide/methanol-O-d (0.186M) for a final base concentration of

0.093 M. The following aliquots were quenched and extracted as described previously and the recovered ketone samples sublimed at room temperature and 0.1 millimeters of mercury: 0.5 ml after 1 hour; 0.5 ml after 66 hours. The samples were analyzed by mass spectrometry for deuterium content and the data (Table E11) were treated as described for compound 16.

T. Measurement of k_f^H and k_s^H For 17 in Sodium Phenoxide/Methanol-0-d

To 40 mg (0.266 mmoles) of 17 under N_2 in a serum-capped flask was added, with stirring at 29.0 ± 0.1°C, 1.0 ml of sodium phenoxide solution (0.38M). The following samples were quenched and extracted as described previously, then sublimed and submitted for mass spectrometric deuterium analysis: 0.5 ml after 0.5 hours; 0.5 ml after 169 hours. The data (Table E 12) were treated as previously described.

U. Measurement of k_f^D and k_s^D For 17 in Sodium Methoxide/Methanol-0-H

1. Preparation of Twistan-4-one-5,5-d_2

To 100 mg (0.665 mmoles) of Twistan-4-one under nitrogen in a serum-capped flask was added, with stirring at room temperature, 10 ml of methanol-0-d containing 800 mg (14.8 mmoles) of sodium methoxide for a base concentration of 1.48M. The reaction was quenched after 4 days, extracted and the product sublimed as previously described, yielding 90 mg of material 97.6% deuterated in each of the fast and slow positions (Table E 13).

2. Measurement of k_f^D and k_s^D

To 80 mg (0.534 mmoles) of the above labelled Twistan-4-one under nitrogen in a serum capped flask was added, with stirring at 29.0 ± 0.1° C, 2.0 ml of sodium methoxide/methanol solution (0.1M). The following samples were quenched and extracted and the products sublimed as described earlier: 0.5 ml after 51 minutes; 0.5 ml after 2.0 hours; 0.5 ml after 168 hours; 0.5 ml after 336 hours. These samples were analyzed by mass spectrometry for deuterium content and the data (Table E 13) were treated as described earlier for equilibrating first order reactions.

Table E 11

k_f^H and k_s^H For <u>17</u> in Sodium Methoxide/Methanol-O-d

Time, hrs	d_0	d_1	d_2	A^H_{total}
0	100.00	-	-	2.000
1.0	15.16	84.60	0.24	1.150
65.7	5.57	59.03	35.40	0.705

Table E 12

k_f^H and k_s^H For <u>17</u> in Sodium Phenoxide/Methanol-O-d

Time, hrs	d_0	d_1	d_2	A^H_{total}
0	100.00	-	-	2.000
0.5	65.85	33.71	0.44	1.655
169	6.83	56.25	36.92	0.720

Table E 13

k_f^D and k_s^D For <u>17</u> in Sodium Methoxide/Methanol-O-H

Time, hrs	d_0	d_1	d_2	A^D_{total}
0	0.23	4.32	95.45	1.952
0.85	-	13.14	86.86	1.869
2.00	0.19	23.79	76.02	1.759
168	27.63	72.37	-	0.724
336	47.43	52.57	-	0.526

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CLAIMS TO ORIGINAL RESEARCH

1. Measurements of the rates of H/D and D/H exchange in methanol have been made for the diastereotopic α-keto methylene protons in 4',1"-dimethyl-1,2,3,4-dibenzcyclohepta-1,3-dien-6-one, 16 and in tricyclo $[4.4.0.0^{3,8}]$ decan-4-one, 17.

2. The primary isotope effects, k^H/k^T and k^D/k^T have been measured for the fast and slow protons in 16, as has the secondary isotope effect for one of the two diastereotopic protons.

3. A comparison has been made between the quantitative and qualitative tests for internal return. The qualitative tests agree with the predictions of no internal return in protic solvents. The quantitative test indicates internal return in both positions but yields unreasonable values for the k^H/k^D values.

4. The measured exchange rates for hydrogen, deuterium and tritium give rise to estimates for the k^H/k^D values which indicate that the diastereotopic protons are subject to differing primary and solvent isotope effects. No such measurement has been reported previously for two hydrogens on the same carbon.

5. A mechanism involving some sp^3 character for the anion involved in the exchange of the slow proton in 17 (and possibly in 16) or an unsymmetrically solvated anion has been proposed.

6. The high ratio of the rates of isotope exchange for the diastereotopic protons in 16 (63:1) and 17 (300:1) is given as evidence for the importance of stereoelectronic control in the isotopic exchange of ketones. This is the first strong evidence to support this previously proposed theory.

7. The primary, secondary and solvent isotope effects measured for <u>16</u> offer an alternate explanation for the difference in stereoselectivity between H/D and D/H exchange to that which requires reversibility with inversion.