STUDIES ON THE ELIMINATION REACTION
OF 2-ARYLETHYLANILINIUM SALTS

HYDROGEN ISOTOPE EFFECT STUDIES ON THE ELIMINATION REACTION OF 2-ARYLETHYLANILINIUM SALTS

by

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SCOPE AND CONTENTS:

The Hammett rho and the hydrogen isotope effects have been measured for the reaction of ethoxide ion in ethanol with a series of para-substituted 2-phenylethyldimethylanilinium bromides and the results have been compared with those previously obtained for the corresponding series of 2-arylethyltrimethylammonium bromides. The effect of change to a better leaving group on the magnitude of the isotope effects and on the way in which this structural change influences the sensitivity of reaction rates and isotope effects to structural changes at the β-carbon has been interpreted in terms of a model in which a less carbanionic transition state is associated with reactions involving the better leaving group.

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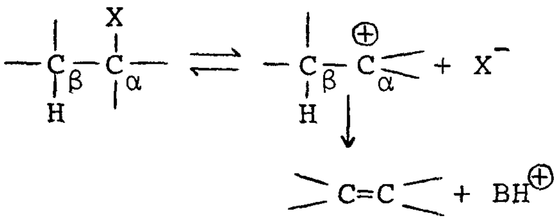
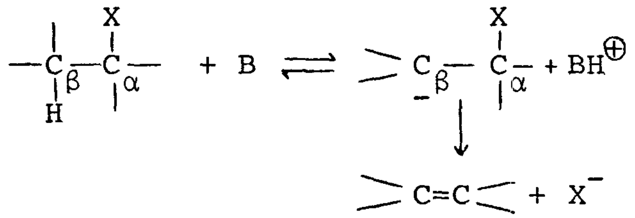
GENERAL INTRODUCTION

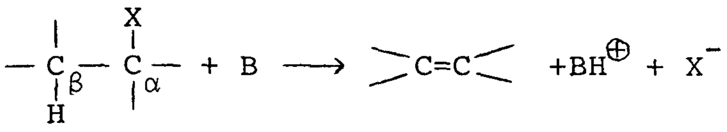
A β-elimination reaction involves the removal of two atoms or groups from adjacent carbon atoms to form a double bond between the carbon atoms. Usually, a hydrogen atom is removed from the β-carbon, and some "leaving group", X, such as trialkylammonium,dialkylsulfonium, or a halogen, is displaced from the α-carbon. The three most important possible reaction pathways followed by this type of reaction



$$-\underset{H}{\overset{|}{C_\beta}}-\overset{X}{\underset{|}{C_\alpha}}- \rightleftharpoons -\underset{H}{\overset{|}{C_\beta}}-\overset{\oplus}{C_\alpha}\!< + X^- \xrightarrow{} \;>C{=}C< + BH^\oplus \qquad (1)$$



$$-\underset{H}{\overset{|}{C_\beta}}-\overset{X}{\underset{|}{C_\alpha}}- + B \rightleftharpoons \;>\underset{-}{C_\beta}-\overset{X}{\underset{|}{C_\alpha}}- + BH^\oplus \xrightarrow{} \;>C{=}C< + X^- \qquad (2)$$



$$-\underset{H}{\overset{|}{C_\beta}}-\overset{X}{\underset{|}{C_\alpha}}- + B \longrightarrow \;>C{=}C< + BH^\oplus + X^- \qquad (3)$$

are presented by equations(1), (2) and (3), which represent the E1, E1cb, and E2 mechanisms, respectively.

The most commonly occuring mechanism for quaternary ammonium salts, of which the present study is concerned, is the E2 mechanism. This mechanism is characterized by a 'variable' transition state, a concept first proposed by Bunnett (1,2), where there is a continuum of possible E2 transition states, varying from a large amount of C_β-H bond rupture and a small amount of C_α-X bond rupture to a small amount of C_β-H bond rupture and a large amount of C_α-X bond rupture, obtainable by changes in substrate structure and reaction conditions.

An important diagnostic tool in the determination of transition state structure is the kinetic isotope effect. In elimination reactions, an isotope effect can be measured for C_β-H bond rupture, and another for C_α-X bond rupture. The leaving group isotope effect is readily interpretable since it increases the more the force constant of the C_α-X bond is weakened on progression from the initial to the transition state. There is difficulty, however, in interpreting the magnitude of the hydrogen isotope effect in terms of the amount of C_β-H bond rupture. It turns out that the hydrogen isotope effect is at maximum for reactions in which there is approximately half-transfer of the proton to base at the transition state. It follows that the interpretation in terms of transition state structure which can be given to changes in the hydrogen isotope effect in a reaction series depends upon whether the proton is more or less than half-transferred to base at the energy maximum for the reaction in this series. This has been established for the reactions of interest in this thesis, namely the E2 reactions of 2-arylethyltrimethylammonium salts, by Steffa and Thornton (3) who have measured the secondary isotope effect, $k^{^{-}OD}/k^{^{-}OH}$, associated with changing the base from ^{-}OH in H_2O to ^{-}OD in D_2O.

The first detailed investigation of the effect of structural changes in reactants on the magnitude of the β-hydrogen and leaving group isotope effects in β-elimination reactions was carried out by Smith (4) in these laboratories for the reaction of ethoxide ion in ethanol with a series of p-substituted 2-phenylethyltrimethylammonium ions. He showed quite convincingly that electron-withdrawing substituents, which strongly increase reactivity, cause a decrease in both the extent of C_β-H and C_α-X bond rupture at the transition state.

This result is contrary to the predictions of Bunnett (1,2) who has put forward the hypothesis that any structural change which makes one bond easier to break causes that bond to be broken more and the other reacting bond to be broken less at the transition state.

More recently, a detailed theoretical treatment of the effect of structural changes on bond distances in transition states has been made by Thornton (5) and has been applied to the β-elimination process. This approach, which has been based on a consideration of structural influences on the stretching modes of vibrational motion in the transition state, led him to the conclusion that a substituent which makes one reacting bond easier to break will lead to a transition state in which the rupture of both reacting bonds is less well developed than would be the case in the absence of this substituent; in other words, the transition state becomes more reactant-like.

Since an elelctron-withdrawing substituent on C_β in an elimination helps to disperse negative charge on the β-carbon thus making the C_β-H bond easier to break, then, according to Thornton, a change to a more electron-withdrawing substituent causes this bond to be broken less at the transition state, and the C_α-X bond also to be broken less. This is in complete agreement with Smith's results. On the other hand, some recent experimental studies by Bunnett on the relationship of leaving group tendency to transition state structure have given results which appear to support his own hypothesis.

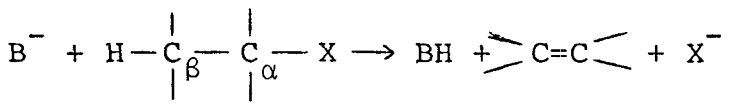
As a further step toward gaining an insight into the influence of reactant structure on transition state geometry, a study has been initiated in these laboratories on the effect of a change in the leaving group on the magnitude of the isotope effects in quaternary ammonium salt elimination reactions and on the way in which leaving group tendency influences the sensitivity of reaction rates and isotope effects to structural changes at the β-carbon. In the present study the Hammett rho and the hydrogen isotope effects have been measured for the reaction of ethoxide ion with a series of para-substituted 2-phenylethyldimethylanilinium salts, in which the leaving group is dimethylaniline, and have been compared with the results previously reported by Smith for the corresponding series of 2-arylethyltrimethylammonium salts in which the leaving group is trimethylamine.

HISTORICAL INTRODUCTION

A. β-Elimination Reactions

General

β-Eliminations are reactions in which two atoms or groups situated on adjacent atoms are lost to form an unsaturated product. The most important example of this type of reaction, both theoretically and synthetically, is the loss of hydrogen and some other atom or group from adjacent saturated carbon atoms to form an olefin. This is illustrated by equation (4)



$$B^- + H-C_\beta-C_\alpha-X \longrightarrow BH + {>}C{=}C{<} + X^- \qquad (4)$$

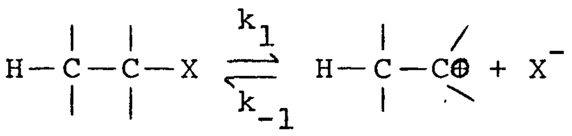
where B^- is a base, such as an alkoxide ion ($\bar{O}R$), and X is a "leaving group", such as a halogen atom, sulfonio (R_2S^+) or ammonio (R_3N^+) group.

Common Mechanisms of Elimination

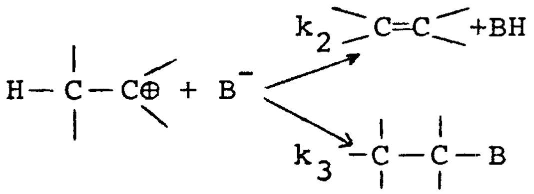
There are many possible reaction mechanisms for the elimination process, as has been outlined in several comprehensive reviews (1,2,6,7,8). The most common mechanisms, which will be considered here, differ in the timing of C_β-H and C_α-X bond rupture. They represent C_α-X breaking before (E1), during (E2), or after (E1cb) C_β-H bond breaking.

The E1 Mechanism

This mechanism is illustrated by equation (5) and (6) and was first proposed by Hughes (9). A carbonium ion intermediate is formed



$$H-C-C-X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H-C-C^{\oplus} + X^- \qquad (5)$$



(6)

first, which can either lose a β-hydrogen to give an olefin, recapture the leaving group or undergo subsitution with the base. The full kinetic expression for the formation of the olefin is presented in equation (7).

$$\text{Rate of elimination} = \frac{k_1k_2[\text{reactant}][B^-]}{k_{-1}[X^-]+(k_2+k_3)[B^-]} \qquad (7)$$

If $k_{-1}[X^-]$ is large with respect to $(k_2+k_3)[B^-]$, one finds that the reaction follows second-order kinetics, equation (8).

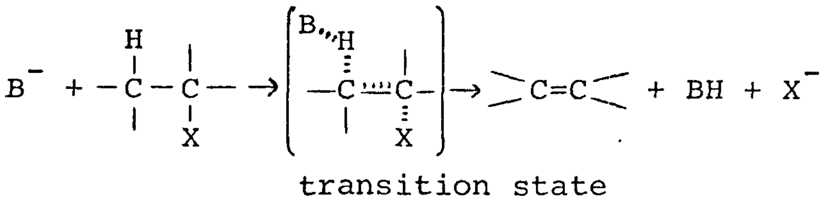
$$\text{Rate of elimination} = \frac{k_1k_2[\text{reactant}][B^-]}{k_{-1}[X^-]} \qquad (8)$$

If, on the other hand, $k_{-1}[X^-]$ is small with respect to $(k_2+k_3)[B^-]$, the reaction will exhibit first-order kinetics, equation (9). Most E1 elimination reactions follow this first-order kinetic expression.

$$\text{Rate of elimination} = \frac{k_1k_2[\text{reactant}]}{k_2+k_3} \qquad (9)$$

The E2 Mechanism

The concerted mechanism for β-elimination, equation (10), was first proposed by Hanhart and Ingold to account for the second-order kinetics observed in the decomposition of quaternary ammonium hydroxides (10). This



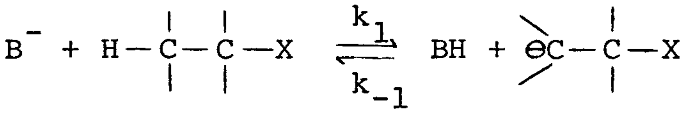
(10)

process is not stepwise, but passes through a transition state in which concerted C_β-H and C_α-X bond rupture is accompanied by double bond formation between the carbon atoms. It is evident that eliminations with the E2 mechanism will follow second-order kinetics, equation (11).

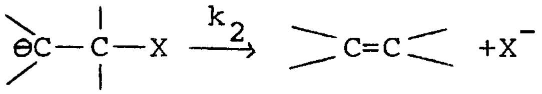
$$\text{Rate of Elimination} = k[\text{reactant}][B^-] \qquad (11)$$

<u>The Elcb Mechanism</u>

The mechanism is illustrated by equations (12) and (13). A carbanion intermediate is formed first, which can then either lose the leaving group



$$B^- + H-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BH + >\overset{\ominus}{C}-\overset{|}{\underset{|}{C}}-X \qquad (12)$$



$$>\overset{\ominus}{C}-\overset{|}{\underset{|}{C}}-X \xrightarrow{k_2} >C=C< + X^- \qquad (13)$$

to form an olefin, or recapture a proton and revert to reactant. The full kinetic expression for this elimination scheme is given by equation (14).

$$\text{Rate of elimination} = \frac{k_1k_2[\text{reactant}][B^-]}{k_2+k_{-1}[BH]} \qquad (14)$$

If $k_{-1}[BH]$ is large with respect to k_2, the rate expression becomes

$$\text{Rate of elimination} = \frac{k_1k_2[\text{reactant}][B^-]}{k_{-1}[BH]} \qquad (15)$$

equation (15), indicating that second-order kinetics will be followed, and, because the rate is proportional to $[B^-]/[BH]$, specific base catalysis will be observed. When $k_{-1}[BH]$ is very small with respect to k_2, the rate expression reduces to equation (16), now characterized by general base catalysis.

$$\text{Rate of elimination} = k_1[\text{reactant}][\text{B}^-] \qquad (16)$$

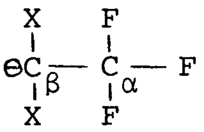
Determination of Mechanism

In most instances, the E1 elimination mechanism can be distinguished from the E2 and E1cb mechanisms on the basis of kinetic information alone—the reaction will follow a first-order rate law if it proceeds by an E1 mechanism.

Difficulty arises, however, in distinguishing between E2 and E1cb mechanisms, both of which give second-order kinetics. Among the methods which have been used to attempt experimental identification of the two mechanisms are tests for hydrogen-deuterium exchange between reactant and solvent, kinetic isotope effect measurements on the β-hydrogen and the leaving group, and studies on the relative rates of reaction with ethoxide and t-butyl thiolate as bases ($k_{t\text{-BuS}^-}/k_{\text{EtO}^-}$).

Since only the E1cb mechanism produces a carbanion intermediate, efforts have been made to prove or disprove its formation during the course of reaction. A common method, first applied by Skell and Hauser (11), of detecting a carbanion intermediate in a reaction is to carry out the elimination reaction in deuterated solvent, this solvent being the conjugate acid BH^+, of the basic reagent, B. If a carbanion is formed, deuterium may be incorporated into the reactant as the result of proton abstraction from the deuterated solvent in the reverse step of equation(12). The observation of deuterium in recovered reactant after the reaction has been carried out part way to completion has been considered as evidence for the E1cb mechanism. The limits of analysis are such, however, that deuterium incorporation will only be observed if the $k_2/k_{-1}[BH]$ ratio is less than about one hundred (12). As a consequence, the absence of evidence for exchange during an elimination reaction does not necessarily exclude an Elcb process since the reaction might be one in which the decomposition of the carbanion intermediate is very much faster than its return to reactant.

No deuterium exchange was found by Skell and Hauser in applying this test to the reaction of 2-phenylethyl bromide with ethoxide ion in ethanol. On the other hand, Hine (13) has observed that, in the reaction of 2-deuterio-2,2-dihalo-1,1,1-trifluoroethane with methoxide ion in methanol, the rate of deuterium exchange with the solvent is rapid compared to the rate of elimination giving $CF_2=CX_2$. It was suggested that only the presence of a carbanion intermediate, I, formed in a pre-equilibrium could account for these results. The stability of this carbanion was attributed to the fact



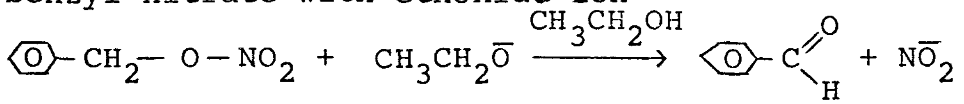
$$^{\ominus}CX_2{}_{\beta}-C_{\alpha}F_3$$

I

that fluorine is an extremely poor leaving group, especially when there are other fluorine atoms attached to the same carbon atom.

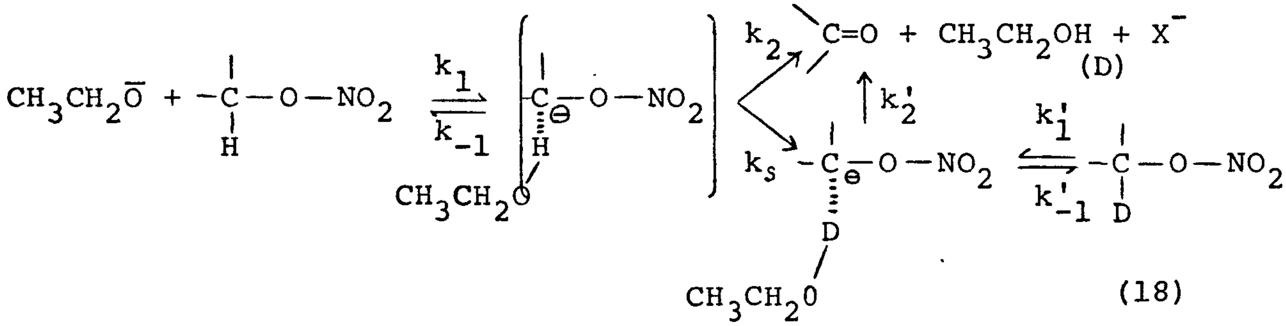
A similar observation of deuterium exchange accompanying elimination has been made in a number of other systems (14, 15, 16). To assume, however, that this necessarily is indicative of an Elcb mechanism is not justified, since the possibility exists that the actual elimination process proceeds by the concerted E2 mechanism, while a carbanion is produced in a parallel process which does not lead to elimination product. In summary then, the absence of deuterium pick-up in the reactant does not establish the E2 mechanism, nor does the evidence of deuterium incorporation prove the Elcb mechanism. Clearly, additional information is required before firmly establishing the mechanism of elimination processes which exhibit second-order kinetics.

Buncel and Bourns (17) combined the isotopic exchange test with kinetic isotope effect measurements to firmly establish the mechanism for the carbonyl-elimination reaction of benzyl nitrate with ethoxide ion



(17)

in ethanol, equation (17). In this reaction, they found only a slight amount of deuterium exchange. If the mechanism is Elcb, this result indicates that the carbanion formed reacts very quickly to give elimination product. Since this means that the removal of the leaving group would not be involved in a rate determining step, only a very small nitrogen effect should be observed. Buncel and Bourns observed an isotope effect of 2.0 per cent which is normal for a process in which the rupture of a bond associated with nitrogen is well advanced at the transition state. Although this eliminates the kind of Elcb process formulated in equations (12) and (13), the possibility still exists that reaction occurs with formation of a carbanion which is specifically hydrogen bonded to the molecule of ethanol formed by abstraction



(18)

of the β-hydrogen by base, equation (18). There would be an absence of deuterium exchange with solvent if $k_2 >> k_S$, and the C_α-X bond breaking step would be wholly or partially rate determining if $k_2 \leq k_{-1}$. Anything approaching a pre-equilibrium in the formation of the carbanion, however, would be expected to result in a very small hydrogen isotope effect associated with the abstracted hydrogen (18), whereas the observed effect, k_H/k_D, in the reaction of benzyl nitrate with ethoxide ion at 60°C was 5.0. A similar approach was used to establish that the reaction of 2-phenyltrimethylammonium ion with ethoxide ion in ethanol proceeds by a concerted mechanism (4).

Crosby and Stirling (19) studied the elimination of phenoxide from phenyl ethers in aqueous sodium hydroxide, equation (19), to determine the reaction mechanism. They

$$\begin{aligned} {}^{-}OH + Y\text{-}CH_2CH_2OPh &\xrightarrow{H_2O} Y\text{-}CH{=}CH_2 + {}^{-}OPh + H_2O \\ {}^{-}OD + Y\text{-}CD_2CH_2OPh &\xrightarrow{D_2O} Y\text{-}CD{=}CH_2 + {}^{-}OPh + D_2O \end{aligned} \qquad (19)$$

$Y = (CH_3)_2S^+$ or CH_3SO

found the isotope effects, k_H/k_D, for the sulfonium salt and the sulfoxide to be 0.66 and 0.78, respectively. The k_H/k_D ratios should be close to unity if the reaction mechanism involves a carbanion intermediate formed in a pre-equilibrium process. That the effects are actually less than unity was considered to result from the solvent effect which favors the intermediate carbanion formation in the deuterated solvent.

Further evidence supporting the Elcb mechanism for this reaction was provided by measuring the relative rates of reaction with *t*-butyl thiolate and ethoxide, $k\underline{t}\text{-BuS}^-/k\text{EtO}^-$, of a series of phenyl ethers covering a wide range of reactivity. The significance of the ratio, $k\underline{t}\text{-BuS}^-/k\text{EtO}^-$, proposed independently by Bunnett (20) and England (21), is that it depends on the degree of bond formation between base and hydrogen at the transition state. Thus, in the elimination reaction of a family of compounds of varying reactivity, this ratio should change if the mechanism of elimination is concerted. No significant change in the ratio was found for the compounds of the phenyl ether system. The Elcb mechanism, therefore, is strongly suggested as the mechanism of elimination.

When it has been established that a particular elimination reaction proceeds by the E2 mechanism, the next level of understanding of the process relates to the geometry of the transition state, that is, the extent to which the transfer of the β-hydrogen to base and the rupture of the bond between the departing atom and the α-carbon have proceeded at the energy maximum. A number of kinetic methods have been used for this purpose, including the determination of the $k\underline{t}\text{-BuS}^-/k\text{EtO}^-$ ratio to which reference was made in the preceding paragraph. Another method is based on the determination of the Bronsted β for the reaction of a series of structurally similar bases with a common substrate. This parameter, which measures the sensitivity of the reaction to changes in base strength, is considered to provide a measure of the degree of bonding between the base and the transferred hydrogen at the transition state (22). A related method involves the determination of the Hammett ρ for the reaction of a series of β-aryl-substituted substrates with a common base. This gives an indication of the extent to which negative charge has developed at the β-carbon in the transition state. Finally, the relative rates of elimination of tosylate and bromide ions, $k\bar{O}Ts$/ kBr^-, have been used as an indication of the extent of C-X bond rupture at the transition state (23), although several complications in the interpretation of this ratio have been pointed out (24).

In all of these methods for determining the character of the transition state in bimolecular eliminations, the kinetic response of the reaction to a structural or environmental change is considered to depend on the characater of that transition state. It must be realized, however, that the structural or environmental change may itself change the character of the transition state. Obviously, the best methods for analysing the nature of the transition state utilize structural or environmental changes that only affect the energy of the transition state, and not is character. In this light, it may well be considered that isotope effects associated with the β-hydrogen (a change from H^1 to H^2) and the leaving group (a change from N^{14} to N^{15} or S^{32} to S^{34}) provide the most direct approach to elucidating the character of the transition state in an elimination reaction.

B. Isotope Effects

General

The size of a kinetic isotope effect associated with an atom is determined by the extent to which the force constants associated with the atom change as the system progresses from the initial to the transition state. In an E2 process, the bond associated with the departing atom is normally broken without the formation of a new bond to the atom. As a consequence, the magnitude of the leaving group isotope effect can be expected to increase regularly with an increase in the extent of bond-weakening at the transition state. In contrast, rupture of the bond associated with the β-hydrogen is accompanied by the formation of a new bond of the proton to base. As a result, the β-hydrogen isotope effect is at a maximum for the transition state in which the stretching force constants associated with the partial bonds to hydrogen are equal. To understand the reason for these relationships, an outline will now be given of the general theory of kinetic isotope effects.

Isotope Effects in a Simple Bond Rupture Process

A reaction which involves the rupture of a single bond to an isotopic atom is represented by equation (20), where B and B' are the isotopes concerned, B representing the lighter isotope. The change in energy accompanying change in

$$\begin{aligned} &R_1—A—B—R_2 \xrightarrow{k} R_1—A + B—R_2 \\ &R_1—A—B'—R_2 \xrightarrow{k'} R_1—A + B'—R_2 \end{aligned} \qquad (20)$$

atomic position is illustrated by Figure (1). It is assumed

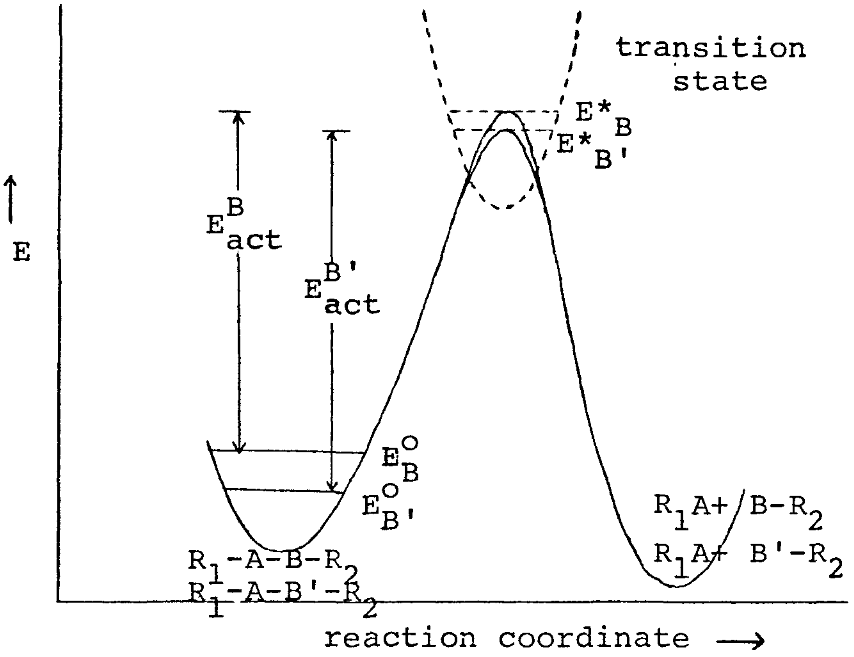


Figure 1

that the potential energy surfaces for a molecule and its isotopically labelled partner are the same. In its lowest vibrational state, a molecule has "zero-point" energy, according to equation (21), where ν is the frequency of

$$E^o = \Sigma \frac{1}{2} h\nu \qquad (21)$$

vibration for a particular mode of vibrational motion and the summation is taken over all of the vibrational modes of the molecule. Since a lower frequency of vibration will correspond to the heavier isotope, the zero point energy for it will be lower than for the lighter isotope.

In the transition state, the molecule has lost a vibration which has been replaced by an internal translation, allowing it to move along the reaction coordinate. That is, one of the vibrational modes associated with the isotope has disappeared in the transition state. Thus, the difference in zero point energies for the two isotopic transition states will be less than the difference in the reactant. The resulting larger energy of activation for the heavier isotope will make the rate ratio, k/k', greater than unity.

To accurately assess the full effect of isotopic substitution on a multi-atom system in going from the initial to the transition state, one must consider all of the vibrational modes, both stretching and bending, of the initial and transition states. Using the methods of statistical mechanics to derive equations for the calculation of the ratio of the rate constants for the reaction of isotopic

$$\frac{k_1}{k_2} = \frac{S_1 S_2^*}{S_2 S_1^*} \frac{\nu_1^*}{\nu_2^*} [1 + \frac{G(u_i)}{2u_i} (\frac{hc}{kT})^2 \sum_j^{3n} (\frac{1}{m_{1j}} - \frac{1}{m_{2j}})(a_{ii} - a_{ii}^*)] \tag{22}$$

molecules from vibrational frequency data, Bigeleisen (25) has formulated equation (22), where ν_1^* is the imaginary frequency corresponding to translation of the molecule with the lighter isotope, m_{ij} the masses of the atoms in the molecule, u_i the reduced mass term, S_1 and S_1^* the symmetry numbers of the initial and transition states, and a_{ii} and a_{ii}^* the bond force constants. It can be seen that the ratio k_1/k_2, will increase as a_{ii}^* decreases. Thus, the leaving group isotope effect, which results from the rupture of a single bond, will increase regularly in a reaction series as the force constant of the C_α-X bond is progressively weakened at the transition state.

Hydrogen Isotope Effects

Unlike the isotope effect associated with a simple two bond rupture process, the hydrogen isotope effect is associated with a three-center process involving the abstracting base, equation (23).

$$AH + B \rightleftharpoons [A....H....B] \rightarrow A + HB \qquad (23)$$

The resulting linear transition state can be considered to be a linear molecule, having two stretching vibrations, symmetric and antisymmetric, along the x-axis (ignoring bending vibrations).

$$\leftarrow A \quad H \quad B \rightarrow \qquad\qquad \leftarrow A \quad H \rightarrow \leftarrow B$$

symmetric antisymmetric

These vibrations belong to the transition state alone, and are not associated with any residual reactant bond. The antisymmetric vibration is the translational mode that leads to product, whereas the symmetric vibration is a true vibration which contributes to the zero point energy of the transition state.

If the so-called symmetrical vibration is perfectly symmetrical, that is, if the force constants associated with the partial bonds of H to A and B are equal, the hydrogen atom will remain motionless and the vibrational frequency will be independent of the presence of the isotope in the transition state. Thus, there will be no change in the zero point energy of the transition state with isotopic substitution. A large isotope effect is to be expected in this instance, since the entire zero point energy difference of the ground state vibrational stretching mode (E_B^o - E_B^o, in Figure (1)) contributes to the activation energy difference for the reaction of the isotopic molecules. On the other hand, when the strengths of the partial bonds, A–H and B–H, at the transition state are not equal the isotope does not remain motionless and the frequency of the "symmetric" vibration will vary with substitution of the isotope. Accordingly, the zero point energy levels of the transition state will vary for the hydrogen and deuterium compounds, decreasing the difference in the energies of activation ($E^H_{act}-E^D_{act}$ in Figure (1)), and hence, decreasing the isotope effect.

The significant result of the influence of the symmetric vibration on the magnitude of the hydrogen isotope effect is that the isotope effect is lowered no matter which of the two bonds, AH or BH, in the transition state is the stronger, with the maximum hydrogen isotope effect being observed when the bonds are of equal strength. As illustrated by Figure (3), the maximum hydrogen isotope effect is observed when the proton is half-transferred from A to B at the transition state.

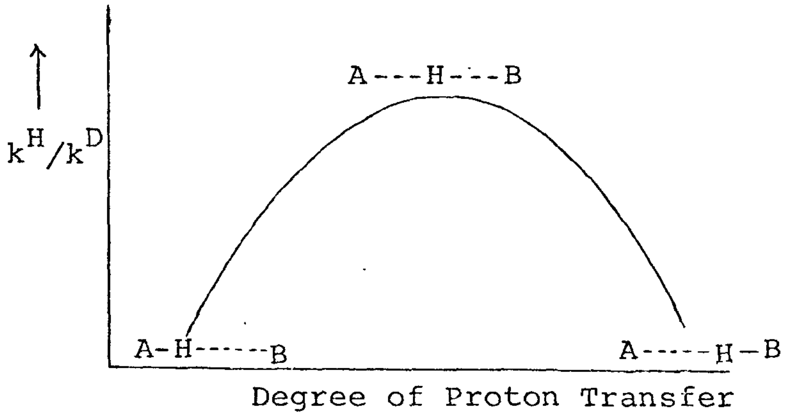
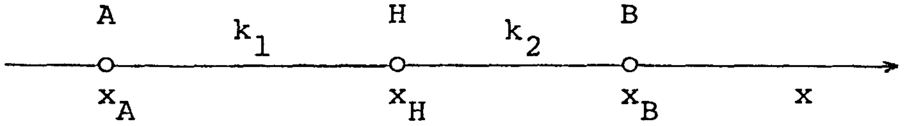


Figure 2

Attention was first drawn by Westheimer (26) in 1961 to the importance of considering the symmetric vibration in determining the zero point energy difference for the two isotopic transition states in a hydrogen transfer reaction. He presented a theoretical argument using a simplified version of the works of Johnston (27) and Bigeleisen (25).

His model is the linear transition state, II, where the atoms A,H and B are on the x-axis, x_A, x_H and x_B are



II

their displacements from equilibrium positions in the molecule, k_1 and k_2 are the force constants for the stretching of the bonds between A and H, and B and H, respectively, and β is the coupling constant associated with the stretching of these two bonds, a critical feature in this concept of the transition state molecule. Assuming that A,H, and B move in normal vibrations with harmonic motion, it can be shown that the displacements, x_A, x_H and x_B of the atoms can only be solved simultaneously when equation (24) is valid,

$$m_A m_H m_B \lambda^2 - (m_A m_H k_2 + m_A m_B k_1 + m_A m_B k_2 + m_H m_B k_1 - 2 m_A m_B \beta)\lambda + (m_A + m_H + m_B)(k_1 k_2 - \beta^2) = 0 \qquad (24)$$

where m_A, m_H and m_B are the masses of the atoms, and $\lambda = 4\pi^2\nu^2$. Since one frequency, the frequency that represents translational motion, must be either zero or imaginary, the equation must have λ equal to zero, or be negative, for one solution. This can happen when the last term, $k_1 k_2 - \beta^2$

of equation (24) is equal to zero (or negative, but this situation is not considered in the simplified mathematic treatment). Substitution of $\beta = \sqrt{k_1k_2}$ into equation (24) gives equation (25), which relates the frequency of the

$$\lambda = 4\pi^2\nu^{2*} = \frac{k_1}{m_A} + \frac{k_2}{m_B} + \frac{k_1+k_2-2\sqrt{k_1k_2}}{m_H} \qquad (25)$$

symmetric vibration to the masses of the atoms and the force constants of the bonds between them at the transition state.

Considering the situation where the two bonds are of equal strength and the isotopic atom is motionless, that is, $k_1=k_2=k$, equation (25) becomes equation (26). This

$$\lambda = 4\pi^2\nu^{2*} = k(\frac{1}{m_A} + \frac{1}{m_B}) \qquad (26)$$

expression shows that there is no influence of isotopic mass upon the frequency of the symmetric vibration at the transition state when the force constants of the two bonds to the isotope are equal. The entire difference in ground state zero point energies determines the size of the hydrogen isotope effect.

When the force constants are not equal, the extreme cases being either $k_1>>k_2$ or $k_1<<k_2$, giving equations (27) and (28), respectively, it can be seen that the mass of the

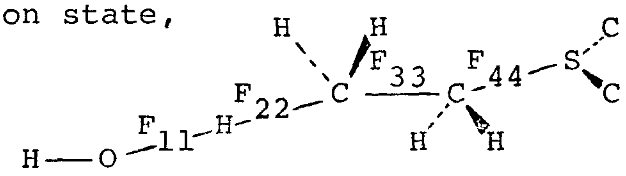
$$\lambda = 4\pi^2\nu^{2*} = k_1(\frac{1}{m_A} + \frac{1}{m_H}) \qquad (27)$$

$$\lambda = 4\pi^2\nu^{2*} = k_2(\frac{1}{m_B} + \frac{1}{m_H}) \qquad (28)$$

isotope effects the frequency. Thus, there will be a difference in the zero point energy for the two isotopic transition states, lowering the hydrogen isotope effect.

Quantitative Treatment of Isotope Effects in β-Elimination Reactions

Saunders (28) has carried out a detailed theoretical calculation of the hydrogen and sulfur isotope effects in the E2 reaction of ethyldimethylsulfonium ion with hydroxide ion using a computer program developed by Schachtschneider (29) and modified by Wolfsberg (30) for calculating vibrational frequencies. Using the following model for the transition state,



III

Saunders determined the influence of changes in the stretching and bending force constants of reacting bonds in the transition state on the magnitude of the two isotope effects. He gave special attention to the extent to which the stretching motions of the reacting bonds are coupled to each other in the transition state by considering the off-diagonal elements, defined in terms of the stretching force constants of the individual reacting bonds as follows:

$$F_{12} = A(F_{11}F_{22})^{1/2}$$

$$F_{23} = B(F_{22}F_{33})^{1/2} \qquad (29)$$

$$F_{34} = C(F_{33}F_{44})^{1/2}$$

In agreement with the predictions of the Westheimer three-center model, the hydrogen isotope effect was found to pass through a maximum. In addition, however, it was found to be quite dependent on the value of A, with larger values being associated with a large degree of coupling of the O-H and H-C motions. Since A must increase directly with the extent of proton transfer, there should be no complication in the qualitative interpretation of hydrogen isotope effects based on Westheimer's curve (Figure (2)) provided that the contribution of A to the isotope effect is not large compared with the contribution resulting from the extent of proton transfer. This may be illustrated by Figure (3), where the effect of A on the isotope effect for a hypothetical system is about 1/3 as important as the degree of proton transfer at half transfer of the proton.

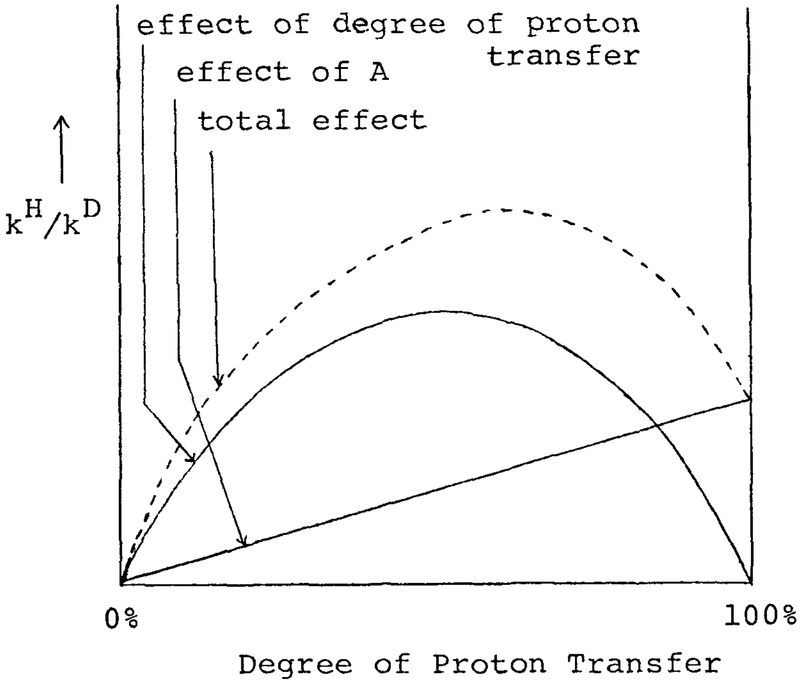


Figure 3

Neither the hydrogen nor sulfur isotope effects were found to be particularly sensitive to the ratio C/B, a measure of the relative extent to which the stretching motion of the C-S and C-H bonds is coupled with the C-C contraction in the transition state. As expected, however, the greater this ratio, that is, the greater the contribution of C-S stretch to the reaction coordinate, the greater the isotope effect associated with the S atom and the smaller that associated with hydrogen.

Of particular interest is the conclusion that, except when a bond is more than 90% broken at the transition state, neither is the magnitude of the hydrogen isotope effect appreciably dependent upon the degree of C-S bond weakening at the transition state nor is the sulfur isotope effect dependent on the extent of proton transfer. This is consistent with predictions of Wolfsberg and Stern (30) that force constant changes remote from the position of isotopic subsitution have a very small influence on the isotope effect.

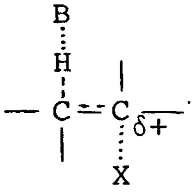
Particularly surprising was the relationship of the sulfur isotope effect to changes in C-S bond strength at the transition state. The isotope effect appears to become significant only when the bond is more than half broken. If this conclusion is valid, small isotope effects for the leaving group can be associated with reactions in which C-X bond rupture is quite far advanced at the transition state.

This study clearly demonstrates that a number of parameters can change an isotope effect. It is acknowledged by

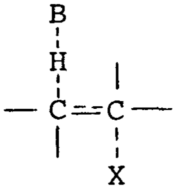
Saunders, however, that parameters able to be treated as independent variables in the calculations are probably inherently interdependent. Therefore, he concludes that a qualitative interpretation of isotope effects should be possible, but only when systematic changes in some structural or environmental feature of a reaction are made.

C. The Nature of the Transition State in E2 Processes

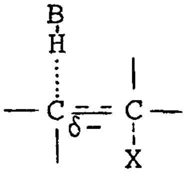
The familiar conception of the concerted elimination transition state, as depicted by IV, has the relative extent of C_β-H and C_α-X bond rupture approximately the same. The two bond rupture processes, however, depend on the structure of the reactant and reaction conditions, each of which may influence the two bonds differently. Accordingly, there is a continuum of possible E2 transition states, the extremes being "El-like" (V) and "Elcb-like" (VI).



V

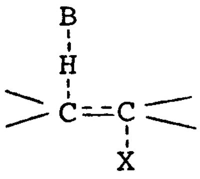


IV

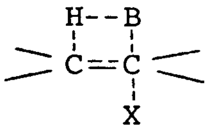


VI

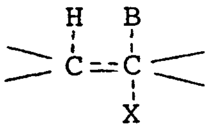
The intuitive presumption that the base must attack the β-hydrogen has been questioned in recent years (31,32) because of experimental findings which demonstrate that certain anions which are weak as bases toward hydrogen are effective in causing elimination. These anions are strong nucleophiles toward carbon and their ability to participate in the elimination process was attributed to partial covalent interaction of the base with C_α in the transition state. Thus, it was proposed that there is a continuum of possible E2 transition states that varied not only in the extent of reacting bond rupture but also with the position of the base relative to the β-hydrogen and the alpha-carbon. Strong hydrogen nucleophiles, which are weak carbon nucleophiles, such as alkoxides, utilize an "E2H" transition state, VII , or an E2H-like transition state, VIII, while those anions which are strong



VII



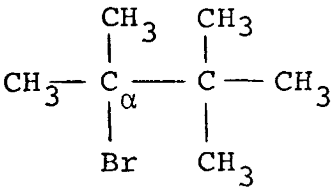
VIII



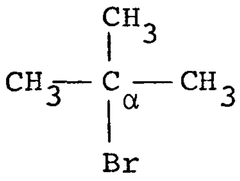
IX

carbon nucleophiles, such as halogens, presumably utilize an "E2C" transition state, IX, with solvent aiding in removal of the proton.

This proposal requires that the rate of elimination with weak hydrogen nucleophiles be strongly dependent on the accessibility of C_α to this reagent. Eck (33) measured the sensitivity of the elimination reaction to steric hindrance at C_α by measuring the relative rates of elimination of X and XI when chloride ion is the base. He found that the extent



X



XI

of steric retardation caused by changing from XI to X is approximately five-fold. Since steric retardation should have depressed the rate by several powers of ten if covalent interaction of chloride ion with C_α is necessary, he concludes that the notion of an "E2C" mechanism should be discarded.

Thus, the range of possible transition states in the concerted elimination reaction is best illustrated by V, IV and VI. The relative degrees of C_β-H and C_α-X bond-breaking are affected by many factors (2), including particularly the following: the ease or difficulty of detaching the leaving group from carbon; the strength of the base; substitutents on C_α ; substituents on C_β ; the leaving group inductive effect; and, the solvent. The character of the E2 transition state of a particular system is determined by the total effect of these factors, some of which may oppose others; that is, some tend to shift the character toward the E1-like extreme (V), while others cause a shift toward the E1cb-like extreme (VI).

Insight into the effect of structural and environmental factors on the extents of C_β-H and C_α-X bond weakening at the transition state for bimolecular elimination reactions can be obtained from kinetic isotope effects. As was shown in the previous section, the magnitude of the leaving group isotope effect is directly related to the extent of C_α-X bond rupture at the transition state. A structural change in an elimination reaction that results in an increase in the leaving group isotope effect for the reaction can readily be interpreted as indicating an increase in C_α-X bond weakening at the transition state. As was also shown, the magnitude of the hydrogen isotope effect can be expected to be at a maximum at approximately half-transfer of the proton at the transition state, and to be small for reactions whose transition state is either reactant or product-like. As a consequence, the interpretation of the relative magnitude of the hydrogen isotope effects in a reaction series is not straightforward. A structural change that results in a decrease in the hydrogen isotope effect for a reaction can mean that the C_β-H bond is strengthened at the transition state if the proton is more than half-transferred, or that the bond is weakened if the proton is less than half-transferred. The extent of proton transfer in a reaction series, therefore, must be known before one can use hydrogen isotope effects to determine the effect of structural or environmental changes on the transition state in elimination reactions.

The first detailed hydrogen isotope effect study on elimination reactions was made by Saunders (34) who measured the effect of changes in the leaving group on the β-hydrogen isotope effect in the reaction of a series of β-phenylethyl derivatives with ethoxide in ethanol, equation (30).

$$C_6H_5CD_2CH_2X + CH_3CH_2O^- \xrightarrow{CH_3CH_2OH} C_6H_5CD = CH_2 + CH_3CH_2OD + X^- \qquad (30)$$

His results, together with the Hammett <u>rho</u> values associated with a reaction series of ring-substituted compounds corresponding to each leaving group, as reported by a number of investigators, is presented in Table I.

The trend in <u>rho</u> values suggests that the poorer the leaving group ($-^+N(CH_3)_3$ poorer than -I), the greater the extent to which negative charge has developed at the transition state. This, in turn, suggests that the extent of proton transfer to base at the transition state increases with decreasing leaving group tendency. If this is so, then the

TABLE I

Kinetic Isotope Effects and Hammett Reaction Constants for the Reaction of 2-Phenylethyl Derivatives with Sodium Ethoxide in Ethanol at 30°C.

X	Hammett ρ	(ref.)	k^H/k^D
I	2.07	(35)	
Br	2.14	(35)	7.1
OT_s	2.27	(36)	5.7
Cl	2.61	(37)	
$^+S(CH_3)_2$	2.75	(38)	5.1
F	3.12	(37)	
$^+N(CH_3)_3$	3.77	(39)	3.0*

*at 50°C.

trend in the isotope effects in this reaction series indicates that the proton is more than half-transferred at the transition state, since the smaller isotope effects are associated with reactions in which the extent of proton transfer appears to be greatest.

There are weaknesses in this argument, however, since rho in this reaction series may be a measure of double bond character in the transition state rather than simply a measure of the amount of negative charge on the β-carbon. Furthermore, an increased development of negative charge, or of double bond character, may be more a consequence of a decrease in the extent of C_α-X bond rupture than of an increase in the extent of proton transfer. Clearly, less ambiguous evidence is required before placing an interpretation on the relationship between the magnitude of the β-hydrogen isotope effects and the extent of proton transfer.

The question of the extent of proton transfer to base in quaternary salt elimination reactions was finally resolved by Thornton (3) for 2-phenylethyl ammonium and sulfonium salts using the secondary isotope effect, $k^{^-OD}/k^{^-OH}$.

The relative basicity of the hydroxide and deuteroxide ion is determined by the equilibrium

$$2\,{}^-OD + H_2O \underset{}{\overset{K_B}{\rightleftharpoons}} 2\,{}^-OH + D_2O \qquad (31)$$

The related equilibrium for the conversion of one ^-OD bond of the solvated deuteroxide ion to one OD bond of heavy water is

$${}^-OD + \tfrac{1}{2}H_2O \overset{K}{\rightleftharpoons} {}^-OH + \tfrac{1}{2}D_2O \qquad (32)$$

K, therefore, must be the direct measure of the relative basicities of ^-OD and ^-OH. Since ^-OD is the stronger base, $K = K_B^{1/2} = k^{^-OD}/k^{^-OH} > 1$. The magnitude of this secondary isotope effect for complete proton transfer to the base can be calculated after consideration of the self-ionization constants of D_2O and H_2O , and L, defined by equation (35):

$$2H_2O \overset{K_H}{\rightleftharpoons} {}^-OH + H_3O^+ \qquad (33)$$

$$2D_2O \overset{K_D}{\rightleftharpoons} {}^-OD + D_3O^+ \qquad (34)$$

$$2D_3O^+ + 3H_2O \overset{L}{\rightleftharpoons} 2H_3O^+ + 3D_2O \qquad (35)$$

From equations (33) and (34) it is seen that

$$\frac{K_H}{K_D} = \frac{[{}^-OH][H_2O^+]}{[H_2O]^2} \cdot \frac{[D_2O]^2}{[D_3O^+][{}^-OD]} \qquad (36a)$$

Thus, K_H/K_D determines the equilibrium constant, K_{eq}, for the exchange reaction

$$2H_2O + {}^{-}OD + D_3O^+ \xrightleftharpoons{K_{eq}} 2D_2O + {}^{-}OH + H_3O^+ \qquad (36b)$$

where $K_H/K_D = K_{eq}$. From equations (36) (35) and (31), it is evident that

$$K_B = K_{eq}^{\ 2}/L$$

Since the equilibrium constant K_{eq} and L can be measured, $k^{-OD}/k^{-OH} = K_B^{1/2}$ can be calculated.

The maximum value for the secondary isotope effect, k^{-OD}/k^{-OH}, is 1.88 at 80°C, which corresponds to complete proton transfer to the base in the transition state. The smaller this ratio, the less is the extent of proton transfer. More specifically, at half-transfer of the proton, the ratio is the square root of the maximum value, or 1.37. The secondary isotope effects for the bimolecular elimination reactions of 2-phenylethyltrimethylammonium bromide, 2-(p-chlorophenylethyltrimethylammonium bromide, and 2-phenylethyldimethylsulfonium bromide are presented in Table II. The two 2-phenylethyltrimethylammonium salts appear to have a high degree of bond formation between proton and base, judging from the k^{-OD}/k^{-OH} values. Even after allowance for a substantial solvent isotope effect (say, 10%), the experimental isotope effect for the sulfonium ion indicates a transition state where the proton is half-transferred between substrate and base; the proton is therefore more than half-transferred

TABLE II

Isotope Effects for Reaction of 2-Phenylethyl Derivatives with Hydroxide Ion in Water

Substrate	k^{-OD}/k^{-OH} [a] at 80°C	k^{H}/k^{D} [b] at 50°C
$C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_2$	1.79	3.02*
p-$ClC_6H_4CH_2CH_2\overset{+}{N}(CH_3)_2$	1.73	3.48*
$C_6H_5CH_2CH_2\overset{+}{S}(CH_3)_2$	1.57	5.05

[a] Steffa and Thornton (3)

[b] Saunders (34)

* Measured in 50% ethanol-water

for the other compounds. A confirmation of this conclusion is provided by the primary hydrogen isotope effects, which decrease with increasing extent of proton transfer to base. It is only possible to have a trend toward lower primary isotope effects with increase in extent of proton transfer when the extent of proton transfer for the two trimethylammonium salts correspond to positions on the right hand side of the maximum of Figure (2).

It should be noted that, for the 2-arylethyltrimethylammonium system, the effect of the coupling between the C_β-H and O-H ($B={}^{-}OCH_2CH_3$) motions on the hydrogen isotope effect must be minor. In reference to the previous discussion concerning Saunder's calculations (p.21), if A made a more important contribution to the isotope effect than the extent of proton transfer at the transition state, the hydrogen isotope effects would increase regularly with the degree of proton transfer and there would be no maximum isotope effect in the region of half-transfer of the proton. It would be impossible to have a lowering of the isotope effect when a substituent change is made, such as the replacement of chlorine by hydrogen in the β-aryl group, whereby the proton is further transferred to base at the transition state.

Smith (4) in these laboratories has measured the leaving group isotope effects associated with the E2 reaction of ethyltrimethylammonium ion and 2-phenylethyltrimethylammonium ion with sodium ethoxide in ethanol. The results, taken in conjunction with the corresponding k^H/k^T ratios obtained by Simon (40), provide an insight into the effect of a β-aryl group on the relative timing of the two bond-rupture processes. The results, presented in Table III, indicate that there is less C_α-N bond weakening at the transition state when a β-hydrogen is replaced by the β-aryl group. Thornton's $^-$OD versus $^-$OH studies, which have established that the proton is more than half-transferred at the transition state for the trimethylammonium system, indicate that the change in the hydrogen isotope effect upon replacement of a β-hydrogen with the β-aryl group results from a decrease in C_β-H bond rupture. Thus, the effect of the β-aryl substituent on the two bond rupture processes is in the same direction.

TABLE III

Isotope Effects in the E2 Reaction of Quaternary Ammonium Salts at 60°C

Substrate	Reaction Conditions	$(k^{14}/k^{15}-1)100$	k^H/k^D
$CH_3CH_2\overset{+}{N}(CH_3)_3$	Ethoxide in ethanol	1.86[a]	
	basic hydrate (vacuum)		3.0[c]
	hydroxide in triethylene glycol		2.8[d]
$C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$	ethoxide in ethanol	1.42[b]	
	methoxide in methanol		4.2[c]

[a] Solvent: 95% ethanol

[b] Solvent: absolute ethanol at 40°C

[c] Simon (40)

[d] Calculated by Simon (40) from an experimental value of 1.23 at 130°C.

Smith also studied the effect of para-substituents on the β-aryl group on the transition state of β-elimination reactions by measuring the hydrogen and nitrogen isotope effects of 2-(p-substituted) phenylethyltrimethylammonium bromide in sodium ethoxide and ethanol. His results are shown in Table IV. As the substituent becomes more electron-withdrawing, the leaving group isotope effect indicates that there is less C_α-N bond rupture at the transition state, and the corresponding hydrogen isotope effect indicates less C_β-H bond rupture. Again it was found that a structural change which causes less C_β-H bond rupture at the transition state has the same effect on the C_α-X bond.

TABLE IV

Isotope Effects for the E2 Reaction of 2-Arylethyltrimethylammonium Ion with Sodium Ethoxide in Ethanol at 40°C.

para-Substituent	$(k^{14}/k^{15}-1)100$	k^H/k^D
OMe	1.37	2.64
H	1.42	3.23
Cl	1.14	3.48
CF_3	0.88	4.15

Further evidence supporting the conclusion that C_β-H and C_α-X bond rupture parallel each other at the transition state for E2 reactions has been provided by Smith (4) and Saunders (41) in their studies on the effect that a change in base strength has on the geometry of the transition state. Both workers used ethoxide ion in ethanol and t-butoxide ion in t-butyl alcohol, with Smith measuring the nitrogen isotope effects associated with the reactions of ethyltrimethylammonium ion, and Saunders measuring the hydrogen isotope effects and Hammett rho constants for the reactions of 2-phenylethyltrimethylammonium ion. The results are presented in Table V. The nitrogen isotope effects indicate that there is greater C_α-X bond rupture at the transition state for the reaction of ethyltrimethylammonium ion with the weaker base, ethoxide ion. Furthermore, the large difference in the two hydrogen isotope effects show that the C_β-H bond also is weakened more at the transition state for the reaction of 2-phenylethyltrimethylammonium ion with the weaker base. The rho values are also in accord with this interpretation of the hydrogen isotope effects since there is a more highly developed negative charge on the β-carbon at the transition state when the reaction is promoted by the weaker base.

TABLE V

Hammett Correlations and Isotope Effects in the Reactions of Ethyltrimethylammonium Ion and 2-Phenylethyltrimethylammonium Ion with Ethoxide Ion and *t*-Butoxide Ion

Substrate	Base/Solvent	$(k^{14}/k^{15}-1)100^{c}$	k^{H}/k^{D}	rho^{a}
$CH_3CH_2\overset{+}{N}(CH_3)_3$	EtO^-/95% EtOH	1.86		
$C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$	EtO^-/EtOH		2.98^{b}	3.86
$CH_3CH_2\overset{+}{N}(CH_3)_3$	*t*-BuO^-/*t*-BuOH	1.41		
$C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$	*t*-BuO^-/*t*-BuOH		6.97^{a}	3.04

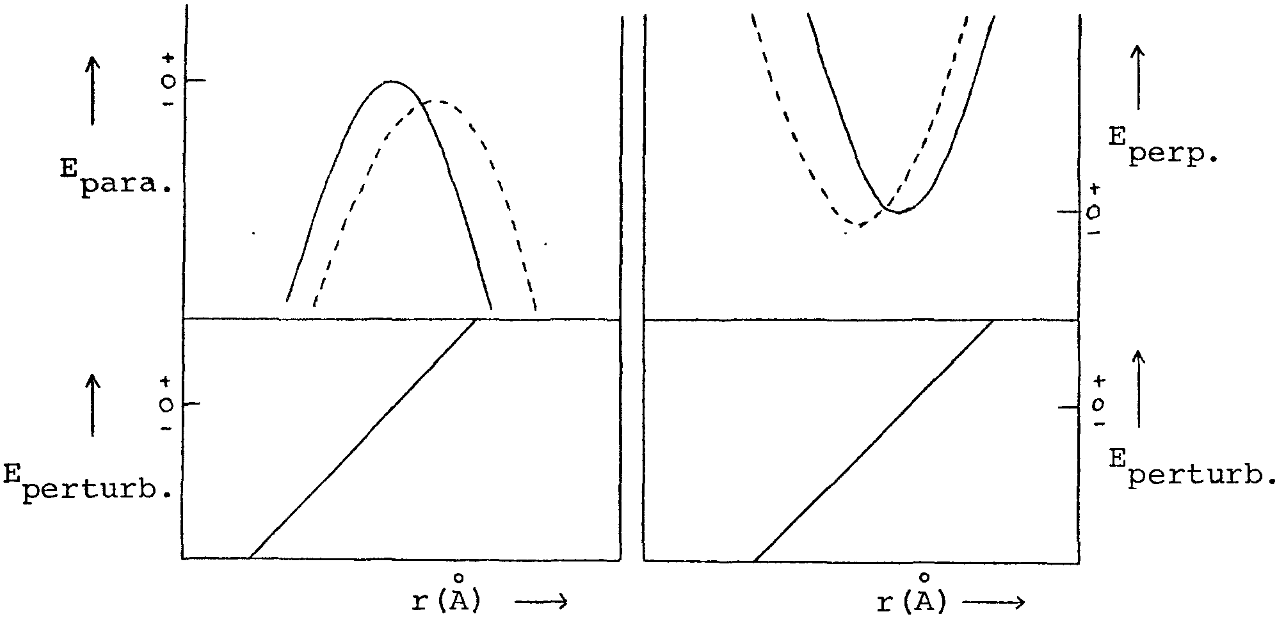
[a] Saunders (41) at 30°C

[b] Saunders (41) at 50°C

[c] Smith (4) at 60°C

A simple theory for predicting the effect of substituents on the geometry of a transition state has been proposed by Thornton (5) in which he considers the influence of substitutents on the motion along the reaction coordinate, designated as "parallel"motion (analogous to Westheimer's antisymmetric stretch), and on the normal modes of vibration, or "perpendicular" vibrations (Westheimer's symmetric stretch), of the transition state.

Thornton demonstrates that it is a valid approximation to describe the effect of a substituent on a bond by the addition of a linear perturbation to the parabolic potential energy function for that bond. For motion along the reaction coordinate, the potential energy as a function of distance can be approximated as an inverted parabola in the region of the potential energy maximum (Fig. (4a)). Because of this, the effect of a substituent on bond length which results from its effect on the motion along the reaction coordinate is exactly the opposite to its effect on the normal vibrational modes of the transition state (Figure (4b)). This leads Thornton to the following rule for predicting geometric



(a) Effect expected for parallel motion (dashed line)

(b) Effect expected for perpendicular motion (dashed line)

Figure 4

changes at the transition state: "Any substituent change which makes an increase (decrease) in the coordinate X of a transition state more difficult will lead to a perturbed equilibrium geometry in which X is decreased (increased) if the force constant for X motion is positive, but in which X is increased (decreased) if the force constant for X motion is negative".

The effect of substituents on both parallel and perpendicular motions must be considered for a complete description of the change in bond lengths at the transition state, but usually a consideration of the former is all that is necessary. This arises from the fact that the magnitude of the change in coordinate X is inversely proportional to the force constant, or the curvature of the potential energy surface in the region of energy maximum. Since in most systems this curvature is considerably smaller for parallel than for perpendicular motion, the change in bond length is determined largely by the substituent effect on the former. Thus, on examination of Thornton's rule, it is concluded that a substituent change which makes cleavage of a bond more difficult (or easier) results in that bond being more ruptured (or less ruptured) at the transition state, for most systems.

This theory is readily applicable to substituent effects in bimolecular elimination reactions where only the two reacting bonds closest to the substituent are considered, the others being assumed to "follow along". The parallel motion can be described as follows:

$$\begin{array}{ccccc} B & H & C_\beta & C_\alpha & X \\ \longrightarrow & \longleftarrow & \longrightarrow & \longleftarrow & \rightarrow \end{array}$$

An electron-withdrawing substituent of C_β will weaken the C_β-H bond and thus make the motion which extends this bond easier. It will also make compression fo the C_β-C_α bond more difficult. The latter effect on the parallel motion cannot be expected to be too important since the σ bond already present prohibits large changes in C_β-C_α bond length. Since, for parallel motion, a substituent change which makes cleavage of a bond easier results in that bond being more ruptured at the transition state, it follows that an electron-withdrawing substituent on C_β will shorten the C_β-H bond (while electron-releasing substituents will lengthen it). The B-H and C_α-X bonds will follow along in the direction of coordinate motion set by the C_β-H bond, the former being lengthened and the latter shortened to complete the change to a more reactant-like transition state. These predictions on the effects of substituents at C_β are borne out by the work of Smith (4) and Thornton (3) where electron-withdrawing substituents at C_β were found to cause a shortening of the C_β-H bond at the transition state, and a shortening of the C_α-X bond as well.

The theory predicts that increasing the base strength (making compression of the B-H bond easier) will increase the B-H bond length, and shorten both the C_β-H and C_α-X bonds, making the transition state more reactant-like. This prediction is in accord with the findings of Smith and Saunders (See pg. 36 Table V) who found that the transition state in the elimination of quaternary ammonium salts were more reactant-like for tert-butoxide ion than for ethoxide ion.

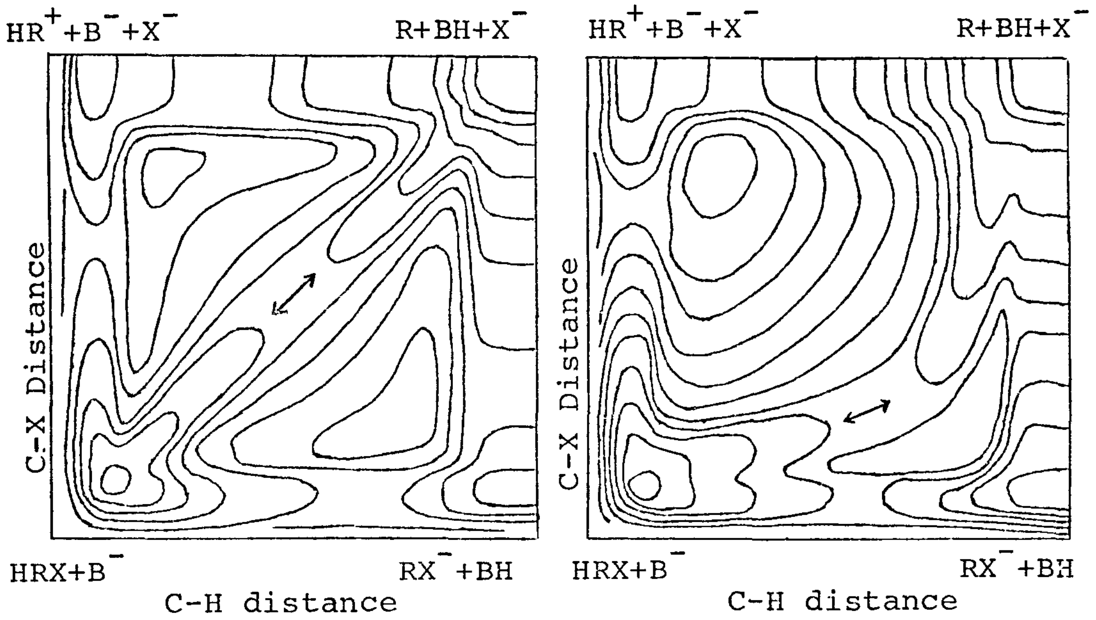
An interesting prediction of the Thornton theory is that the more product-like transition states have relatively more carbanion than carbonium ion character. The basis of this prediction is found through a consideration of the relative extents of motion along the reaction coordinate of atoms associated with reacting bonds. By making H move more relative to C_α , and C_β move more relative to X, it follows that making the transition state more product-like produces relatively more carbanion character at C_β than carbonium ion character at C_α ; that is, the transition state becomes more Elcb-like. This is supported by the relatively small hydrogen isotope effects observed by Smith (4) in the reaction of ethoxide ion with 2-arylethyltrimethylammonium ions ($k^H/k^D = 2.64$ to 4.15) which indicate that proton transfer is far advanced at the transition state. On the other hand, the nitrogen isotope effects of 0.9-1.4% would suggest that C_α-N bond rupture is also well developed, if the conclusions reached by Saunders (28) based on his theoretical calculations of sulfonium salt eliminations can be extended to ammonium systems. This, of course, would imply a concerted process with a quite fully developed double bond in the transition state, rather than the carbanion-like transition state predicted by Thornton. The relatively large rho value of 3.84 observed by Smith, however, supports the carbanion-like transition state and suggests that Saunder's conclusions, although possibly valid for the sulfonium system, cannot be carried over to the reaction of ammonium salts. This point will be discussed further later in the thesis.

A recent theory dealing with substituent effects on β-eliminations has been advanced by O'Ferrall (42). Its predictions agree, for the most part, with those of Thornton's theory eventhough the rationale of the two are quite different. Thornton considers the direct effect of substituents upon the lengths of bonds at the transition state of the β-elimination reaction, whereas O'Ferrall considers the effect of substituents on the energy of reactants, products and intermediates which, in turn, affect the energy and structure of the transition state. This latter approach was first introduced by Hammond (43) and applied to reactions involving the cleavage of a single bond. Now the same principles are applied to concerted elimination reactions with the additional consideration directed at the possible intermediate carbanion and carbonium ion structures that would be formed if the mechanism were not concerted, but stepwise.

O'Ferrall began with the basic premise that there need be no gradual transition from an E2 mechanism with an "Elcb-like" transition state to the Elcb mechanism as a result of small structural changes in the reactants. In other words, he proposes that at the point of mechanistic change reaction by the two mechanisms can proceed side by side through transition states which, although of the same energy, have quite different structures. Support for this view was derived from certain considerations arising from his study

(44,45) of the β-elimination reaction of 9-fluorenylmethanol. Similarly, he concludes that there can be mechanistic discontinuity in the border region between E1 and E2 pathways.

A schematic potential energy surface which allows for the possibility of reaction by both the concerted and stepwise mechanism is shown in Figure (5a), which forms the basis for O'Ferrall's model for predicting the influence on transition state structure of changes in the structure of reactants in an elimination process. In this model, the surface is considered to be of such flexibility as to transmit across its length and breadth the effect of energy changes



(a) P.E. surface for "normal" E2 transition state

(b) P.E. surface for "Elcb-like" E2 transition state

Figure 5

at any point. As a result, the structure of the transition state for a concerted elimination process is influenced, not only by the relative stabilities of reactants and products, but also by the stabilities of the reactive intermediates that would be formed if the mechanism were not concerted.

By reference to this representation of the potential energy surface, it can be seen that an increase in the stability of the elimination product, R, will correspond to a "downward pull" at the top right-hand corner of Figure (5a), with the result that the energy of the transition state is decreased and its structure moves toward the bottom left-hand corner, that is, becomes more reactant-like. On the other hand, an increase in the stability of the carbanion, R^-, means a downward pull at the bottom right-hand corner of the surface, again resulting in a lower transition state energy but a transition state structure which is closer to that of the carbanion. This is shown in Figure (5b), where it is seen that the transition state has a greater C_β-H and shorter C_α-X bond distance than in the transition state on the potential energy surface represented by Figure (5a).

It can be seen from this treatment that the effect of product stability on transition state structure is transmitted along the reaction coordinate while the effect of carbanion stability is transmitted from a direction which is normal to the reaction coordinate motion. These correspond, respectively, to the parallel and perpendicular motions in the Thornton treatment. What is significant, however, is that while Thornton assumes that, for most systems, structural changes can be expected to exert their major influence on the reaction coordinate motion, O'Ferrall proposes that, when structural changes primarily affect carbanion stability, their influence on transition state structure is necessarily exerted through perpendicular motion for a "normal" E2 transition state.

A substituent change may affect the stability of more than one species. For example, electron withdrawing substituents at the β-carbon may increase the stability of both the products and the carbanion intermediate, although intuitively the effect on the latter might be expected to outweigh that on the former. That this is so would seem to be indicated by the order of the substituent effects on the magnitude of k^H/k^D for the reaction of 2-arylethyltrimethylammonium salts with ethoxide (Table IV, page 35). Clearly, this order does not correspond to the order of product stability which, on the basis of λ_{max} values for the substituted styrenes (Table XII, page 96), would appear to be p-CH_3O >p-Cl>p-CF_3>H. On the other hand, the order of isotope effect values does, indeed, parallel the order of substituent effects on carbanion stability.

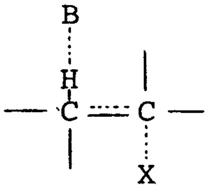
The direction of the effect of β-substitution on the hydrogen isotope effects in the 2-arylethyltrimethylammonium system appears rather convincingly to have established that electron-withdrawing substituents decrease the extent of proton transfer to base at the transition state rather than to increase it (See pg.35). This is in accord with Thornton's view that substituents will exert their influence on transition state structure primarily through their effect on the reaction coordinate motion and is contrary to the predictions of the O'Ferrall model which has substituents exerting their effect on perpendicular motion.

The isotope effect results and the conclusions drawn from them can be reconciled with the O'Ferrall model, however, if it is assumed that the potential energy surface for the β-elimination of 2-arylethyltrimethylammonium salts corresponds to the Elcb-like surface, Figure (5b). The E2 transition state on this surface has pronounced carbanionic character, and further changes in carbanion stability might be felt more strongly along the reaction coordinate than normal to it. This would, of course, lead to a decrease in C_β-H bond distance with increasing carbanion stability.

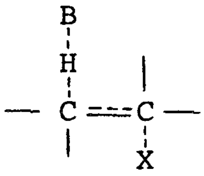
This rationalization of the hydrogen isotope effect results in terms of the O'Ferrall model leads to complications with respect to the interpretation of the nitrogen isotope effects observed in this system, Table IV, p. 35 . It will be recalled that Saunder's model calculations on the isotope effects in the elimination reactions of sulfonium salts (28) have led him to the conclusion that the sulfur isotope effect will be very small unless the C_α-S bond is considerably more than half-ruptured at the transition state. Yet, the carbanion-like transition state for the E2 process in Figure (5b) must have a C_α-X bond which is considerably less than half-ruptured. Such a transition state, therefore, would not seem to be in accord with the quite significant nitrogen isotope effects of 0.9 to 1.4 per cent observed in the β-arylethyltrimethylammonium system. It follows from this that if the conclusions reached by Saunders in his model calculations for the sulfur isotope effect in sulfonium salt eliminations are valid for nitrogen effects in the ammonium salt reactions, there is no way in which the O'Ferrall model can be reconciled with both the hydrogen and nitrogen isotope effects found in Smith's work. The approximate nature of Saunders' calculations and the possibility that the dependence of the leaving group isotope effect on the extent of C_α-X bond rupture may be quite different for the two classes of onium salts would suggest, however, that further studies are required before discarding the O'Ferrall approach.

Although Thornton and O'Ferrall have used quite different approaches to the problem of transition state structure in E2 processes, they have in common a recognition that structural changes in reactants will affect bond distances in the transition state through their effect on both parallel (reaction coordinate) and perpendicular motions involving reacting bonds. An entirely different 'theory' of transition state structure in bimolecular eliminations and one which has been based more on chemical intuition than on a consideration of the thermodynamic properties of the transition state species was proposed by Bunnett a number of years ago and has been supported by subsequent work in his laboratory.

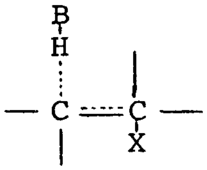
Bunnett (1,2) was the first to propose the concept of a'variable' E2 transition state where there is a continuum of possible transition states, represented by V, IV, and VI,



V



IV



VI

for a reaction series. The relative extents of C_β-H and C_α-X bond rupture are determined by substrate structure and reaction conditions.

The prediction of substituent influence on transition state structure in Bunnett's theory is different from that based on Thornton's rule. Thornton predicts that, for most systems, a substituent change which makes a bond easier to break will lead to relatively less rupture of that bond, and also of the other reacting bond, at the transition state. Bunnett, conversely, takes the position that a bond made more easy to break by a substituent change will result in relatively more rupture of that bond, and relatively less of the other reacting bond.

A consequence of this divergence in the theories in predicting the effect of a substituent change on the two bond rupture processes is a predicted difference in the trend toward double bond formation. Thornton's ideas lead to the prediction that a substituent change that increases the C_β-H bond rupture at the transition state will also cause the double bond to be strengthened, since a more product-like transition state results. The theory of Bunnett, on the other hand, requires that a maximum double bond development occur at the "central" transition state, IV, where the degrees of C_β-H and C_α-X bond rupture are equal, and that this development be weakened at transition states with character toward either the El-like* (V) or Elcb-like* (VI) extremes. Therefore, an increase in C_β-H bond rupture should result in less double bond formation when a system is central or somewhat toward to carbanionic side.

An evaluation of the theories can best be obtained in the light of experimental results relating to substituent changes at C_β , to changes in the leaving group at C_α, and to changes in base strength for β-elimination reactions.

As has been shown earlier (Table III p. 34; Table IV, p.35), Smith's work on ethyl and arylethyl quaternary ammonium salts indicate that a change to an electron withdrawing substituent at C_β causes both the C_β-H and C_α-X bonds to be ruptured less at the transition state. The secondary isotope effects, k^{-OD}/k^{-OH}, of the arylethyl quaternary ammonium system (see p. 32) measured by Steffa also indicate that electron withdrawing substituents decrease the extent of proton transfer to base. These results are in accord with Thornton's theory and disagree with Bunnett.

Support for Bunnett's theory is provided by his own work (46) in which an attempt was made to establish the effect of a change in leaving group on transition state structure

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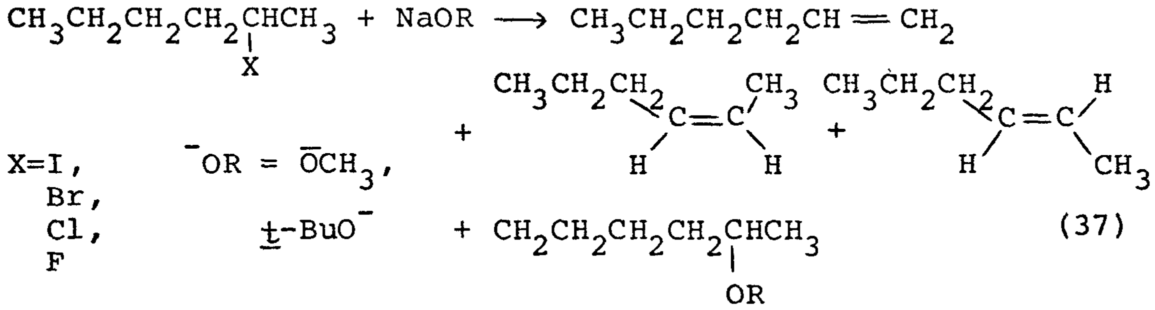
* Bunnett advocates the use of the terms "paenecarbonium" and "paenecarbanion" in place of "El-like" and "Elcb-like, respectively (2).

from the relative yields of products formed competitively in the elimination reaction of 2-hexyl halides, equation (37). A larger degree of double bond character at the transition state for this system can be expected to result in an increase in <u>trans</u> to <u>cis</u> product since the eclipsing of <u>cis</u>-destined alkyl groups, with resultant steric crowding, is greater. Also, a carbanionic transition would be expected to favor the formation of 1-alkene relative to 2-alkene because increasing negative charge on C_β causes an unfavourable inductive interaction with a β-alkyl substituent. Carbanionic or central transition states, on the other hand, should favor the formation of 2-alkene because of the favorable inductive and hyperconjugative interaction with the developing double bond. Bunnett's results are presented in Table VI. Since the lighter halogens are



(37)

TABLE VI

Elimination from 2-Hexyl Halides at 100°C

Halogen	Reagent: $\bar{O}CH_3/CH_3OH$[a] Ratio of 2-enes/1-ene	Reagent: $\bar{O}CH_3/CH_3OH$[a] Ratio of <u>trans</u>/<u>cis</u>	Reagent: $(CH_3)_3C\bar{O}/(CH_3)_3COH$[b] Ratio of 2-enes/1-ene	Reagent: $(CH_3)_3C\bar{O}/(CH_3)_3COH$[b] Ratio of <u>trans</u>/<u>cis</u>
I	4.2	3.6	0.45	1.8
Br	2.6	3.0	0.25	1.4
Cl	2.0	2.9	0.14	1.1
F	0.43	2.3	0.027	1.1

[a] Bartsch and Bunnett (46)

[b] Bartsch (47)

progressively poorer leaving groups, his theory predicts a consequent strengthening of the C_α-X bond, a weakening of the C_β-H bond with increasing negative charge on C_β, and a lessening of double bond character at the transition state. (He assumes a central transition state for reaction of 2-hexyl iodide). Thus, the favorable interaction of β-alkyl groups with the developing double bond and the eclipsing of *cis* destined substituents should diminish. The kinetic response to this change in character of the transition state would be a decrease in the 2-enes/1-ene and *trans*/*cis* ratios. Both of the responses are evident in Table VI.

The trend in the *trans*/*cis* ratios in Table VI is inconsistent with the theory of Thornton which predicts that an increase in β-carbanion character is necessarily coupled with an increase in double bond character, as is evident from a consideration of the reaction coordinate motion,

$$\underset{\longrightarrow}{B} \quad \underset{\longleftarrow\!\!\!-\!\!\!-}{H} \quad \underset{\rightarrow}{C_\beta} \quad \underset{\leftarrow}{C_\alpha} \quad \underset{\rightarrow}{X}$$

The poorer the leaving group the more product-like is the transition state, with the result that the *trans*/*cis* ratio should increase.

The base strength effect presented in Table VI also supports Bunnett's position. Since *t*-butyl alcohol has less tendency to solvate anions than methanol and *t*-butoxide ion is a stronger base than methoxide ion, his theory predicts that the transition state for elimination promoted by *t*-butoxide ion will be toward the carbanionic extreme with more C_β-H bond weakening, less C_α-X bond weakening, and less double bond character at the transition state than with methoxide ion. The use of the stronger base should result in an overall decrease in the 2-enes/1-ene and trans/cis ratios. This is what is observed. On the other hand, Thornton's rule predicts less carbanionic transition states with stronger bases since the C_β-H bond is more easily broken.

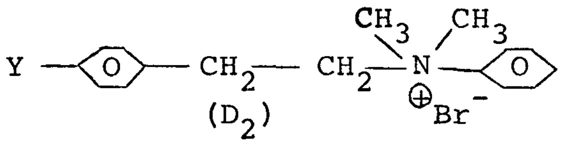
The decrease in the 2-enes/1-ene ratio might alternatively be rationalized, however, by considering the possibility of steric hindrance at the transition state for formation of the internal olefins with the bulky t-butoxide ion. Also, Bunnett obtained results for elimination with potassium t-butoxide in dimethyl sulfoxide that do not agree with his theory (48). Dimethyl sulfoxide has less capacity for solvation of the leaving group than t-butyl alcohol, and t-butoxide ion in dimethyl sulfoxide is a much stronger base than when in t-butyl alcohol. Both factors would seem to call for greater paenecarbanion character and, therefore, smaller 2-enes/1-ene ratios for elimination promoted by t-BuO$^-$/DMSO than t-BuO$^-$/t-BuOH. The observed ratios were actually higher, however, when t-BuO$^-$/DMSO is used. One cannot help but wonder about the reliability of this criterion of transition state structure.

Kinetic isotope effect measurements have been used to determine the effect of a change from $^-$OEt/EtOH to t-BuO$^-$/t-BuOH on transition state geometry in the elimination of quaternary ammonium salts. The results (Table V, p.36) agree with Thornton's prediction that a stronger base will lead to less bond rupture of the reacting bonds at the transition state. Also, the Hammett rho value is smaller for elimination with the stronger base, indicating less negative charge on C_β and less C_β-H bond rupture at the transition state with this base.

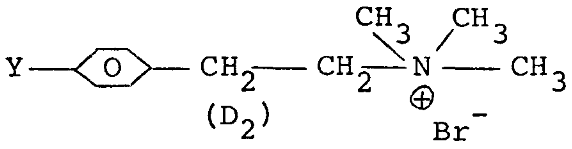
In conclusion, there appears to be sound experimental evidence to support both Thornton's and Bunnett's theories. Studies on the elmination reactions of quaternary salts have provided verification of Thornton's ideas, while work on neutral substrates has supported Bunnett's. It would seem, then, that if all the experimental techniques which have been used to probe transition state structure have validity, neutral and ionic compounds are affected differently by substituent changes. This could have something to do with the relative importance of parallel and perpendicular motion in determining the influence of substituents on transition state structure. Such a consideration is suggested by the O'Ferrall model. The reactions of onium salts are probably well to the carbanionic side of the transition state spectrum and their potential energy surface may be similar to that represented by Figure (5b), p42 . The transition states of the 2-hexyl halides, however, are not as carbanionic in nature and their potential energy surface for reaction may be closer to Figure (5a). It was pointed out earlier that a substituent change altering the stability of the intermediate carbanion of the model would be expected to affect the transition state structure of substrates with potential energy surfaces corresponding to Figures (5a) and (5b) differently, since the effect over the former surface is felt most strongly perpendicular to the coordinate motion of the transition state, while that over the latter is felt parallel to the coordinate motion. More data is obviously required, particularly that based on isotope effect measurements, before a full critical assessment of the theories is possible.

RESULTS AND DISCUSSION

The present study involved a determination of reaction rates and β-hydrogen isotope effects for a series of 2-arylethyldimethylanilinium bromides, XIII. A comparison of the results with those obtained by Smith (4) for the reactions of a corresponding series of 2-arylethyltrimethylammonium bromides, XIV, provides an insight into the effect of a change in the leaving group on transition state geometry. In particular, the relative values of the Hammett rho in the two series gives a measure of the extent to which negative charge is developed at the transition state while the hydrogen isotope effects show the extent to which the β-hydrogen is transferred to base. The sensitivity of the hydrogen isotope effects to substitution obtained from plots of k^H/k^D vs σ^- is interpreted in terms of the relative carbanionic character of the transition state in the two systems using the O'Ferrall model.



XIII



XIV

Y = OCH_3,
H,
Cl,
CF_3

The kinetic experiments for the undeuterated and 2-arylethyldimethylanilinium-2,2-$\underline{d}_2$ ions were carried out using ethoxide ion in ethanol as base at 40°C. The reaction of the p-CF_3-substituted compound was too fast at 40°C to enable kinetic measurement. For this salt, rate constants for the deuterated and undeuterated compounds at 40°C, and hence the isotope effect, were determined from extrapolation of rate constants measured at 10°C and 20°C, with the same concentration of base as was used for the other salts. In this way, it was possible to compare isotope effects for all compounds under the same conditions of ionic strength.

The results of the kinetic runs for the anilinium salts are presented in Table VII. A sample kinetic run for each compound with a plot of the data can be found in the Appendix. Hammett plots of log k/k_o vs σ^- are shown in Figures (6) and (7) for the undeuterated and deuterated series, respectively. The slope, rho, for the former is +2.69, with a correlation coefficient r of 0.998. The slope of the plot for the deuterated series is +2.56, with a correlation coefficient of 0.992.

Dimethylaniline is a better leaving group than trimethylamine since the former is a much weaker base. The rate constants in Table VIII reflect this difference in leaving tendency between the two amines. The relative rates of reaction of similarly substituted compounds in the two systems, however, cannot be taken as an accurate measure of the difference in reactivity since kinetic measurements were done at different ionic strengths. The trimethylammonium salts were reacted in solutions at a combined salt and base concentration of 0.12 molar, whereas the dimethylanilinium salts were reacted in 0.02

TABLE VII

Rate Constants for the Reaction of 2-Arylethyldimethylanilinium Ions with Sodium Ethoxide in Ethanol

([Q.A.S.] = 0.00648 - 0.00652 m./l.; [$\bar{\text{O}}$Et] = 0.01268 - 0.01272 m./l.)

Para Subst.	Temp. ±0.03°C	k^H a	k^D a	k^H/k^D b
		x10^2 l mole^{-1} sec^{-1}		
OCH_3	40.05	0.246±0.003	0.0619±0.0006	
		0.242±0.001	0.0622±0.0007	
		0.246±0.002	0.0616±0.0005	
		0.242±0.003	0.0606±0.0004	
		0.244±0.003	0.0601±0.0008	
			0.0609±0.0008	
			0.0602±0.0006	
		0.244±0.002	0.0611±0.0008	3.99±0.06
Cl	40.05	8.04 ±0.05	1.64 ±0.01	
		8.03 ±0.03	1.62 ±0.01	
		8.06 ±0.04	1.63 ±0.01	
			1.61 ±0.02	
		8.04 ±0.02	1.63 ±0.01	4.93±0.03
H	40.05	1.50 ±0.01	0.289 ±0.002	
		1.48 ±0.01	0.290 ±0.003	
		1.51 ±0.02	0.290 ±0.003	
		1.50 ±0.02	0.302 ±0.003	
		1.47 ±0.02	0.287 ±0.003	
		1.50 ±0.02	0.289 ±0.003	
		1.46 ±0.01	0.286 ±0.003	
		1.45 ±0.02	0.289 ±0.003	

Table VII cont'd

Para Subst.	Temp ±0.03°C	k^{H} [a]	k^{D} [a]	k^{H}/k^{D} [b]
		x 10^{2}	l $mole^{-1}$ sec^{-1}	
H	40.05	1.45 ±0.01	0.298 ±0.002	
		1.45 ±0.01	0.289 ±0.002	
		1.46 ±0.02	0.287 ±0.003	
		1.46 ±0.02	0.293 ±0.003	
			0.294 ±0.002	
			0.291 ±0.002	
		1.47 ±0.02	0.291 ±0.004	5.05±0.09
CF_3	10.05	1.98 ±0.01	0.347 ±0.003	
		2.03 ±0.02	0.351 ±0.004	
		2.05 ±0.02	0.350 ±0.003	
		2.04 ±0.02	0.351 ±0.003	
		2.03 ±0.03	0.350 ±0.002	5.80±0.09
	20.05	8.88 ±0.08	1.53 ±0.01	
		8.87 ±0.08	1.53 ±0.01	
		8.80 ±0.07	1.57 ±0.01	
		8.81 ±0.05	1.54 ±0.01	
		8.82 ±0.09	1.58 ±0.01	
		8.82 ±0.06		
		8.83 ±0.03	1.55 ±0.02	5.70±0.08
	40.05	127[c] ±7	23[c] ±1	5.5 ±0.4

---

[a] The rate error limits for each kinetic run is based on a least squares analysis, and that for the mean of a series of runs is the standard deviation.

[b] Deviation = $\pm(k^{H}/k^{D})[(r^{H}/k^{H})^{2}+(r^{D}/k^{D})^{2}]^{1/2}$, where r is the standard deviation of k.

[c] Extrapolated from the rates obtained at 10.05°C and 20.05°C.

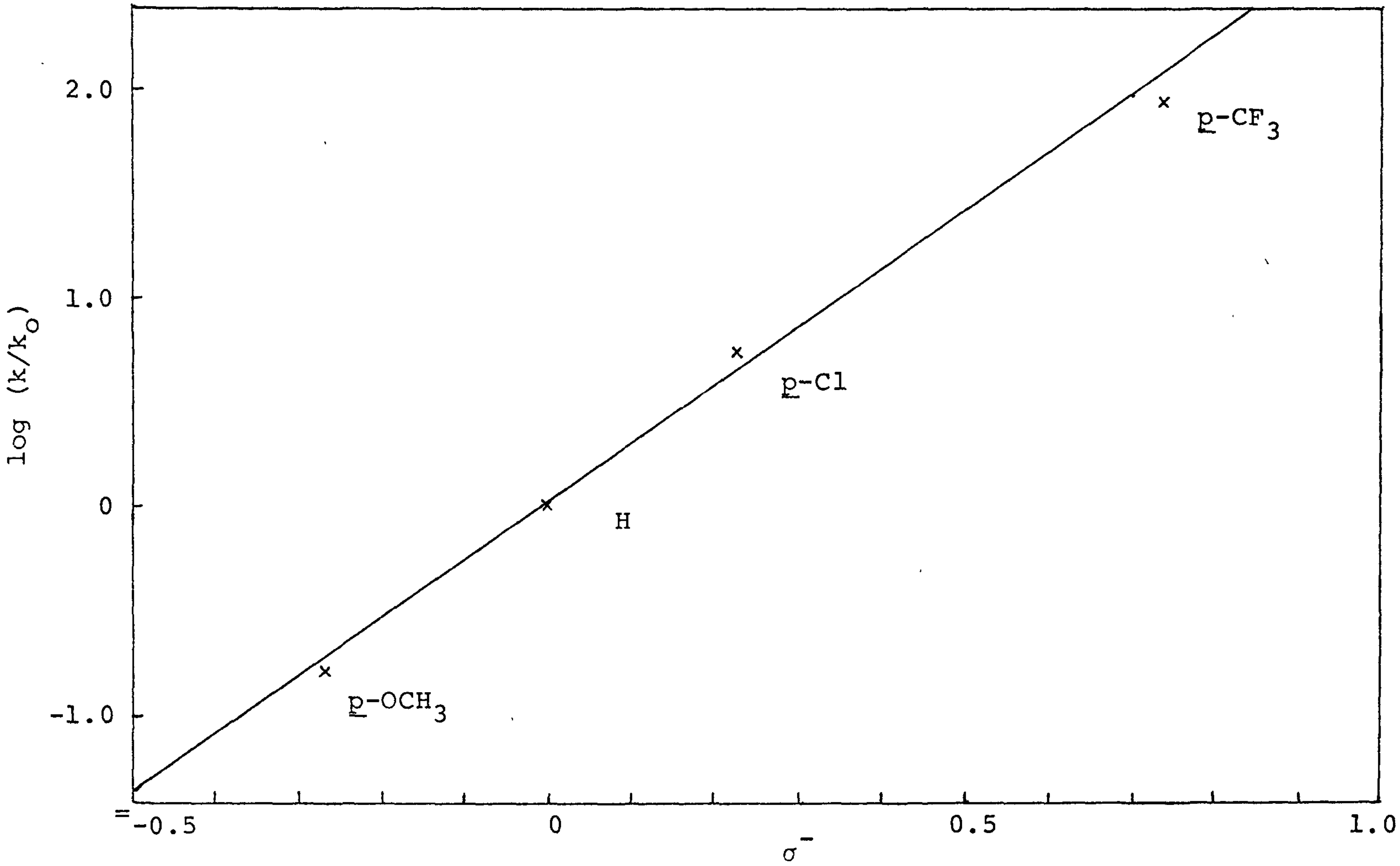


Figure 6

Plot of Log (k/k$_o$) versus σ^- for the Reaction of 2-Arylethyldimethylanilinium Ions with Sodium Ethoxide in Ethanol at 40°C.

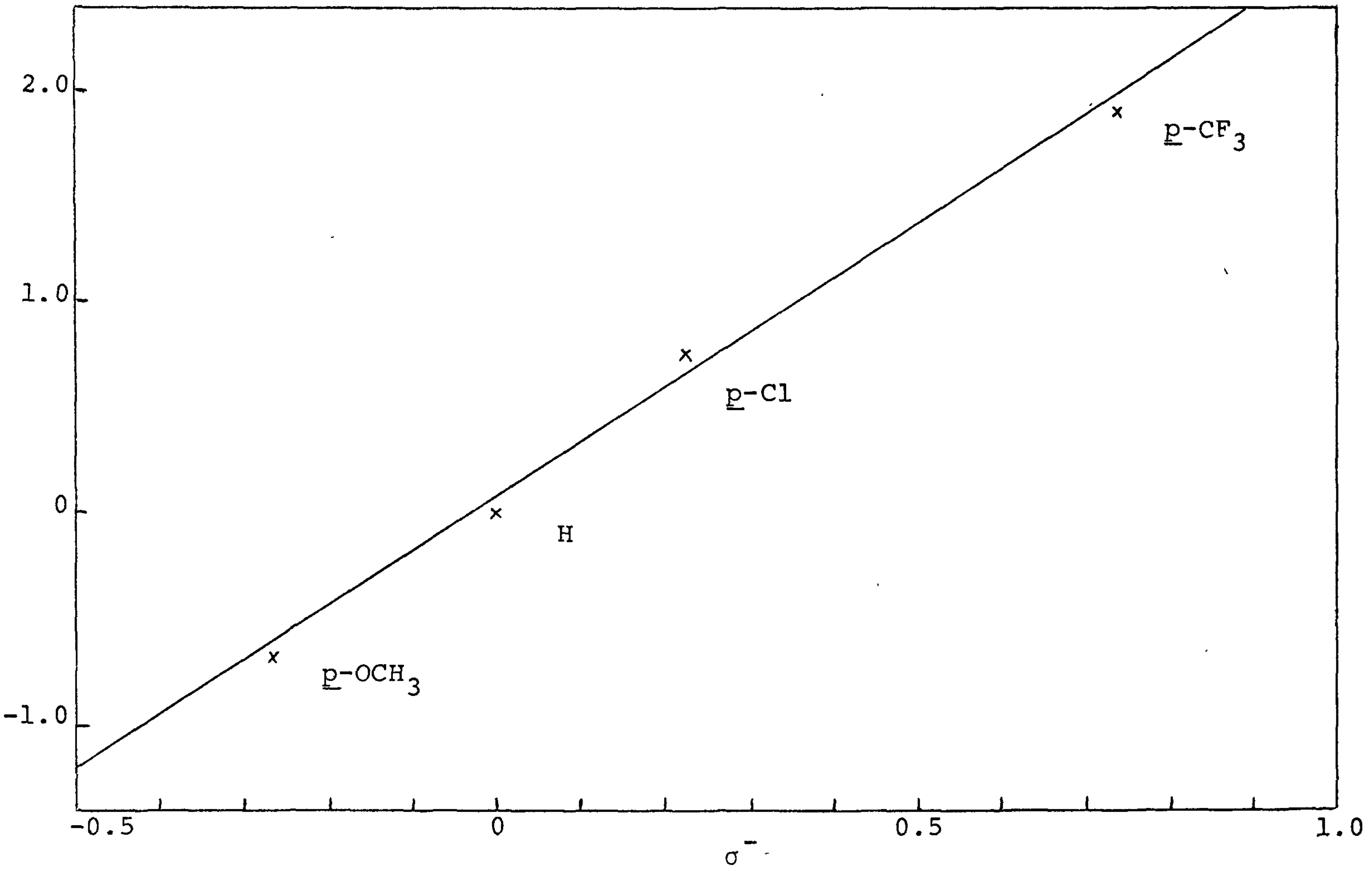


Figure 7

Plot of Log (k/k_o) versus σ^- for the Reaction of 2-Arylethyldimethylanilinium-2,2-$\underline{d}_2$ Ions with Sodium Ethoxide in Ethanol at 40°C.

TABLE VIII

Rate Constants for the Reaction of 2-Arylethyltrimethylammonium and 2-Arylethyldimethylanilinium Ions with Sodium Ethoxide in Ethanol at 40°C.

Leaving Group	Trimethylamine*		Dimethylaniline	
Para Subst.	k^H $\times 10^3$ l mole^{-1}sec^{-1}	rel.rate**	k^H $\times 10^3$ l mole^{-1}sec^{-1}	rel.rate**
OCH_3	0.0418	1	2.44	58.4 (1)
H	0.432	10.3	14.7	352 (6.00)
Cl	3.00	71.9	80.4	1920 (32.9)
CF_3	194	4,640	1,270	30,400 (522)

* Smith (4)

**All relative rates, except those shown in parenthesis, are based on a value of unity for the reaction of 2-p-methoxyphenyltrimethylammonium ion. Figures in parentheses show the relative rates for the anilinium series.

molar solution. Since a medium with a greater ionic strength will retard the formation of neutral olefins from ionic starting materials the differences in rates are somewhat enhanced.

Of particular interest is the sensitivity of the rate constants to substitution at the β-phenyl group. A measure of the sensitivity in rates is the Hammett rho constant; the larger the rho value the greater the sensitivity to substitution. Since the rho constants are +3.66 and +3.47 (4) for the undeuterated and deuterated 2-arylethyltrimethylammonium ions, respectively, and +2.69 and +2.56 for the undeuterated and deuterated 2-arylethyldimethylanilinium salts, there is a smaller sensitivity of rates with the series of compounds in which the leaving group is dimethylaniline. Accordingly, there is less development of negative charge at C_β in the transition state for reaction with the better leaving group. The fact that the transition state is less carbanionic suggests that the extent of proton transfer to base is smaller with the better leaving group. It does not establish this, however, since lesser carbanionic character would also result if there were a greater relative increase in C_α-X bond rupture (see p. 29)

A comparison of the hydrogen isotope effects for the two systems, presented in Table IX, reinforces the conclusions reached on the basis of the rho values and provides an answer to the question as to the relative extent of proton transfer in the two systems. The hydrogen isotope effects are

TABLE IX

Hydrogen Isotope Effects Found for the E2 Reaction of 2-Arylethyltrimethylammonium and 2-Arylethyldimethylanilinium Ions with Sodium Ethoxide in Ethanol at 40°C.

Leaving Group	Trimethylamine*	Dimethylaniline
Para Subst.	k^H/k^D	k^H/k^D
OCH_3	2.64	3.99
H	3.23	5.05
Cl	3.48	4.93
CF_3	4.15	5.5

* Smith (4).

substantially larger for compounds with the better leaving group than those for the corresponding compounds of the trimethylammonium series. A combination of Steffa's $k^{\bar{O}D}/k^{\bar{O}H}$ studies and Smith's hydrogen isotope effect measurements (see p.33) have established that the proton is more than half-transferred from carbon to base at the transition state for the reaction of 2-arylethyltrimethylammonium ions with sodium ethoxide in ethanol. Since the hydrogen isotope effects of the dimethylanilinium system are greater, the proton must be less transferred with the better leaving group. Steffa's secondary isotope effect studies on the two systems are in agreement with this analysis. The $k^{\bar{O}D}/k^{\bar{O}H}$ ratio for 2-phenylethyldimethylanilinium ion was found to be 1.62, whereas that for 2-phenylethyltrimethylammonium ion was 1.79, indicating that the former has less bond formation between base and proton in the transition state(3).

The three 'theories' relating to the effect of changes in reactant structure on transition state geometry which were presented in the Historical Introduction all predict that a better leaving group results in less C_β-H bond rupture at the transition state. They disagree, however, in the effect of such a structural change on the extent of C_α-X bond rupture. Bunnett considers that making the C_α-X bond easier to break will result in that bond being broken to a greater extent at the transition state. This shift toward the E1-like extreme is characterized by less C_β-H bond rupture. Thornton, on the other hand, predicts that since the C_α-X bond is more readily broken with a better leaving group it will be less broken at the transition state. As a consequence, the transition state is more reactant-like, with less C_β-H bond rupture as well. Finally, when considering O'Ferrall's model for substituent effects, the effect of a better leaving group is represented by a lowering of the entire top side of Figure (5a), p.42 , since this substituent change reduces the energy for formation of both the olefin and the intermediate 'carbonium ions'. The overall effect on the two bond rupture processes can be broken down into one component operating along the reaction coordinate and another which is normal to it. The two act in the same direction in so far as C_β-H bond rupture is concerned, an increased stability of X decreasing the extent of proton transfer to base at the transition state. They are opposing, however, in their influence on C_α-X bond rupture, with the result that the net effect is small and may be in either direction.

An increase in electron-withdrawing power of the <u>para</u>-substituent on the β-aryl group results in an increase in the hydrogen isotope effect for the 2-arylethyldimethylanilinium ion, as can be seen in Table IX. Eventhough the unsubstituted and chloro-substituted compounds give isotope effects that are inconsistent with this trend, the effects are close enough in absolute value to keep the overall trend intact. With the knowledge that the dimethylanilinium system is on the right hand side of the Westheimer curve (Figure (2), p.18), based on the secondary isotope effect for the unsubstituted compound (3), it is concluded that an increase in the electron withdrawing ability of the β-substituent causes a decrease in the extent of proton transfer at the transition state. (It had been hoped that, if the CF_3-substituted salt has its proton less than half-transferred, it would be readily interpretable by having the hydrogen isotope effect less than that corresponding to the Cl-substituted compound. As it turns out, since the isotope effect of the former is greater, only $k^{\bar{O}D}/k^{\bar{O}H}$ studies will provide this particular information on the extent of proton transfer at the transition state).

Thornton's theory predicts that an increase in the electron withdrawing ability of the β-aryl group results in the C_β-H bond being less broken at the transition state since this structural change makes the bond easier to break. Consequently, there is an increase in the hydrogen isotope effect if the system is on the right-hand side of the Westheimer curve. This is observed in both the trimethylammonium and dimethylanilinium systems. Bunnett, on the other hand, predicts that such a substituent change at C_β results in a shift toward the carbanionic extreme with more C_β-H bond rupture. If this were so, however, the two salt systems should show a decrease in effect as one proceeds down Table IX. The fact that they do not provides cogent proof of the invalidity of Bunnett's ideas on substituent effects with these ionic substrates.

O'Ferrall's model can lead to predictions agreeing with Thornton, and the experimental results, if, as discussed in the Historical Introduction, the potential energy surfaces for the two salt systems are characterized by Elcb-like transitions states for the E2 elimination process. In this way, stabilization of the carbanion by an electron-withdrawing substituent causes the effect on the transition states to be felt more strongly along the reaction coordinate than normal to it, resulting in less C_{β}-H bond rupture. This is precisely the assumption made by Thornton when he considers that structural changes in reactants in β-elimination processes affect transition state geometry mainly through their influence on "parallel" (reaction coordinate) motion.

The relationship between the hydrogen isotope effects and the electron-withdrawing power of the substituents at C_{β} for the two systems is illustrated by Figure (8) where log k^{H}/k^{D} is plotted against σ^{-}. Although the scatter is very large for the dimethylanilinium system (a correlation coefficient of 0.836 compared with 0.956 for the trimethylammonium system) there is a good indication that the sensitivity of the ammonium ions to substitution is greater. The slope corresponding to the latter system is 1.84 while it is 1.23 for the former. O'Ferrall's model can give an insight into the reason for this difference in sensitivity. One simply has to consider that the E2 transition state is less carbanionic for the 2-arylethyldimethylanilinium ions, as has been established by the rho values and the hydrogen isotope effects. The less carbanionic the E2 transition state on the potential energy surface of the model the less is the effect of a increase in 'carbanion' stability felt along the reaction coordinate and the more it is felt in a

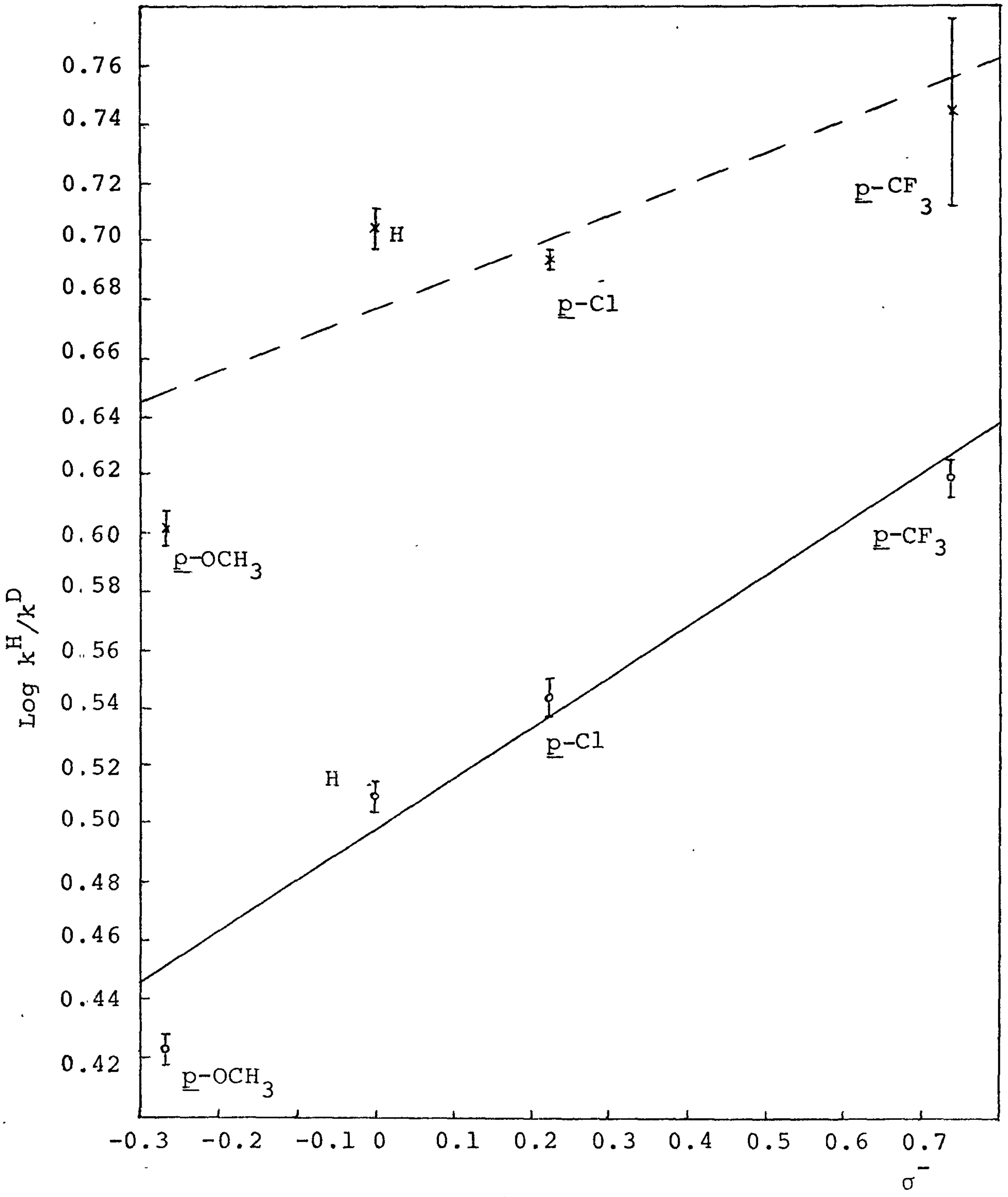


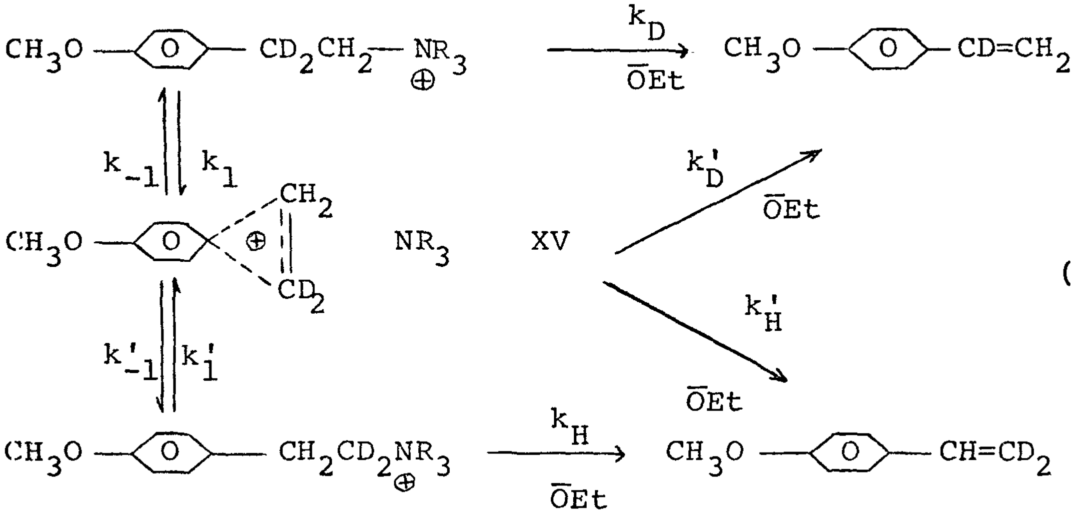
Figure 8

Plot of Log k^H/k^D versus σ^- for the Reaction of 2-Arylethyltrimethylammonium Ions (—ǫ—ǫ—) and 2-Arylethyldimethylanilinium Ions (– ✕ – ✕ –) with Sodium Ethoxide in Ethanol at 40°C.

direction normal to it (Fig. (5b), p.42). Since the effect along the former direction will decrease the extent of C_β-H bond rupture while that along the latter will increase the length of this bond, a transition state with less carbanionic character experiences a less dramatic change in C_β-H bond length at the transition state with a change to a more electron-withdrawing substituent.

Certain deviations from the expected linear relationship between log k^H/k^D and σ^- exhibited by the two salt systems in Figure (8) should be examined. The wide scatter of points in the anilinium plot is well beyond the precision limits of experimental technique, which are indicated for each point by error bars. The largest error is in the isotope effect value corresponding to the p-CF_3-substituted compound which arises from the need to extrapolate rates obtained at 10°C and 20°C to determine the rates of the deuterated and undeuterated compounds at 40°C. It is partricularly difficult to understand why the hydrogen isotope effect of the unsubstituted compound is higher than that of the p-chloro-substituted ion (at best, within the error limits, they are equal). The isotope effects of the 2-arylethyltrimethylammonium system show no similar deviation. This would suggest that there has been some systematic error, source unknown, in the measurement of the isotope effect of either the p-chloro- or unsubstituted compound in the anilinium series.

Careful inspection of both curves suggests that the isotope effects are abnormally low for the p-methoxy-substituted compounds. A possible explanation for this is that there is a scrambling of the beta and alpha carbon atoms through the intermediacy of the phenonium ion XV , a species which has been shown to be an intermediate in solvolytic processes (49,50,51). A reaction scheme with this intermediate for the deuterated species is given by equation (28). Olefin could be formed solely by the E2 process, the kinetics of



(28)

the reaction determined by a combination of the rate constants, k_D and k_H, or in part or in total directly from the phenonium ion intermediate itself (rate constants k'_D and k'_H). The latter mechanism is similar to that proposed by Sneen (52) who considers that elimination reactions proceed through an ion-pair intermediate. If the elimination were to proceed mainly through this intermediate, however, one might expect a considerable amount of substitution whereas the experimental infinity points taken of the kinetic runs for the undeuterated p-methoxy compound were only about 4%* below the

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* This difference was attributed to polymerization, since the compound was so slow reacting that the infinity points had to be determined by heating the reaction vessel for six hours at 60°C. For this reason, it was deemed pointless to determine experimental infinity points for the corresponding deuterated species, which is even slower reacting.

theoretical value for 100% formation of styrene. Furthermore, the hydrogen isotope effects for such a process might be expected to be much smaller than that observed since bimolecular elimination for the high energy intermediate should be through a transition state in which transfer of hydrogen to base is not far advanced, in other words, a very reactant-like transition state.

A way of testing the hypothesis that the apparent deviation in hydrogen isotope effects for reaction of the p-methoxy-substituted compounds is a result of carbon scarmbling is to determine the positions of deuterium incorporation in the styrene product, since it can be seen in equation (28) that such scrambling results in the formation of both $CH_3OC_6H_4CH{=}CD_2$ and $CH_3OC_6H_4CD{=}CH_2$. An n.m.r. analysis of the deuterated methoxy styrene formed from 2-(p-methoxyphenyl)ethyldimethylanilinium-2,2-$\underline{d}_2$ bromide after 66% reaction indicated 15±2% deuterium incorporation at the terminal carbon. On the other hand, no carbon scrambling was observed in the n.m.r. spectra of the styrenes formed from 2-(p-methoxyphenyl)ethyltrimethylammonium-2,2-$\underline{d}_2$ bromide and 2-phenylethyldimethylanilinium-2,2-$\underline{d}_2$ bromide to a resolution of ±5%.

It is tempting to conclude from these results that part of the elimination product from the deuterated and undeuterated p-methoxy anilinium compounds is formed through the intermediacy of XV . There is an alternative explanation, however, which is not related to the elimination reaction mechanism. This is that the reactant is not isotopically pure but contains some salt in which deuterium is attached to the alpha-carbon as a result of partial scrambling during synthesis.

This receives support when one considers the different reaction conditions used in the synthesis of 2-(p-anisyl)ethylaniline and 2-(p-anisyl)ethylamine. The formation of the latter was performed by reaction of the tosylate with dimethylamine in ether at room temperature for nine days (there was a four hour reflux before isolation of the product), while 2-(p-anisyl)ethylaniline was synthesized by reacting the tosylate with N-methylaniline in nitromethane at 100°C for six hours. The critical difference in the two procedures is that 2-(p-anisyl)ethylaniline was prepared in a much more highly ionizing solvent.

Unfortunately all of the synthesized 2-(p-anisyl)ethyldimethylanilinium-2,2-d_2 bromide had been used in the kinetic studies and in the preparation of olefin to test for carbon scrambling in product, so it was not possible to test for scrambling in starting material. This matter certainly requires further investigation since it is important to know if scrambling can occur in the actual elimination process of quaternary salts.

EXPERIMENTAL

The Synthesis of a Series of Unlabelled 2- Arylethyldimethylanilinium Salts

General

In the preparation of unlabelled 2- arylethyldimethylanilinium bromides, the three final synthetic steps were the same for all four compounds. The 2- arylethylalcohol was treated with tosyl chloride to form the 2- arylethyl tosylate. This was followed by displacement of tosylate ion by N-methylaniline and quaternization of the resultant N,N-methyl-2-arylethylaniline by reaction with methyl bromide.

The initial synthetic steps were determined by the commercially available starting material. Preparation of unsubstituted salt began with 2- phenylethyl alcohol (Eastman Organic Chemicals). Preparation of the methoxy-substituted salt began with 2- (p-anisyl) acetic acid (J.T. Baker Chemical Co.). The carboxylic acid was converted to ethyl 2- (p-anisyl) acetate, and the ester then reduced with lithium aluminum hydride to 2- (p-anisyl) ethanol. The synthesis of the chloro-substituted salt began with p-chlorobenzyl cyanide (Matheson Coleman and Bell). The nitrile was converted to ethyl 2- (p-chlorophenyl) acetate and the ester was reduced to 2- (p-chlorophenyl) ethanol. Synthesis of the trifluoromethyl-substituted salt began with p-trifluoromethylbenzoic acid (Pierce Chemical Co.). The benzoic acid was converted to p-trifluoromethylbenzoyl chloride by reaction with thionyl chloride. Alcoholysis of the acid chloride gave ethyl p-trifluoromethylbenzoate. The ethyl benzoate was reduced with lithium aluminum hydride to give p-trifluoromethylbenzyl alcohol which was converted to p-trifluoromethylbenzyl bromide by treatment with hydrobromic acid. Displacement of the bromide ion with cyanide gave p-trifluoromethylbenzyl cyanide and the nitrile was esterified to ethyl 2- (p-trifluoromethylphenyl) acetate. The ester was then reduced with lithium aluminum hydride to give 2- (p-trifluoromethylphenyl) ethanol.

All melting points in the following procedures have been corrected.

2- Phenylethyldimethylanilinium Bromide

Preparation of 2- Phenyl p-Toluenesulfonate

This compound was prepared by the method of Tipson (53). 2- Phenylethyl alcohol, distilled before use, b.p. 122°C/20 mm, 30.0 g (0.245 mole), was dissolved in dry pyridine (300 ml.) which had been purified by refluxing for 8 hours over barium oxide and then distilling. The solution was cooled to -5°C in an ice-salt bath and p-toluenesulfonyl chloride*, 60g (0.33 mole), was added with shaking to effect solution. After two hours, water was added in portions (5 ml., 10 ml., and 20 ml.) at 5 minute intervals with swirling while the temperature was kept below 5°C. The reaction mixture was then diluted with water (300 ml.) and was extracted with chloroform (3 x 250ml.).

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* The p-toluenesulfonyl chloride was purified immediately before use. Thirty-five grams of p-toluenesulfonyl chloride was dissolved in 70 ml. of chloroform and the solution diluted to 400 ml. with 30-60° petroleum ether. The resulting solution was treated with Norit A Decolorizing Carbon and filtered. The volume of the filtrate was reduced to 65 ml. on a rotary evaporator and the p-toluenesulfonyl chloride was allowed to crystallize from the concentrated solution.

The combined chloroform extracts were washed with ice-cold 10% sulfuric acid (5 x 200ml.) followed by 10% sodium bicarbonate (3 x 200ml.) and finally with water (3 x 250ml.) The chloroform layer was dried over anhydrous sodium sulfate and then taken to dryness under reduced pressure to yield 2- phenylethyl p-toluenesulfonate, 58.0 g (85.5%), m.p. 36.5-38.0°C (Saunders (34), m.p. 37.4-38.0°C).

Preparation of N,N- Methyl-2-Phenylethylaniline

A solution of 2- phenylethyl p-toluenesulfonate, 20.0 g (0.072 mole), and N- methylaniline, 9.0 g (0.084 mole), in nitromethane (20 ml.) was swept with dry nitorgen for 15 min. The flask was then stoppered securely and the reaction mixture was heated on the steam bath for 9 hours. The nitromethane was removed under reduced pressure, water (20 ml.) was added, and the resulting solution was treated with sodium carbonate until reaction ceased. The aqueous layer was then extracted with ether (5 x 20 ml.). The combined ether layers were dried over sodium sulfate and distilled to yield N,N-methyl-2- phenylethylaniline, 7.1 g (59%), b.p. 133°C/1mm (Kharasch(54), b.p. 124-128°C/0.3mm).

Preparation of 2- Phenylethyldimethylanilinium Bromide

N,N- Methyl-2-phenylethylaniline, 6.6 g (0.032 mole), in nitromethane (40 ml.) was cooled and treated with ice-cold methyl bromide, 6.0 g (0.063 mole), and allowed to stand at room temperature for one day. Ether (100 ml.) was then added to precipitate the salt, which was collected and recrystallized four times from ethanol-ether to yield 8.5 g (87%), m.p.

168.5-169°C (Steffa (3), m.p. 169-170°C). Anal.* Calcd. for $C_{17}H_{22}NBr$: C, 62.75; H, 6.58; N, 4.58. Found: C, 62.72; H, 6.59; N, 4.63.

2- (p- Anisyl) ethyldimethylanilinium Bromide

Preparation of Ethyl 2- (p- Anisyl) acetate

A solution of 2- (p- anisyl) acetic acid, 36.2 g (0.218 mole), in absolute ethanol (113 ml.) containing concentrated sulfuric acid (4.5 ml.) was refluxed for 7 hours. At the end of this period, the solution was cooled and then poured into water (50 ml.). The upper layer was separated and washed with 10% sodium carbonate with sodium chloride being added to facilitate the separation of the layers. Distillation of the product gave 37.7 g (89%), b.p. 160°C/21 mm (Livshits (55), b.p. 136-137°C/10mm).

Preparation of 2- (p- Anisyl) ethanol

Ethyl 2- (p- anisyl) acetate was reduced with lithium aluminum hydride in ether to 2- (p- anisyl) ethanol by the method of Amundsen and Nelson (56). Ethyl 2- (p- anisyl) acetate, 37.7 g (0.19 mole), in anhydrous ether (57 ml.), was added dropwise with stirring to an ice-cold slurry of lithium aluminum hydride, 7.8 g (0.21 mole), in anhydrous ether (340 ml.), and the mixture gently refluxed for one hour. The reaction mixture was allowed to cool, and water was then slowly added to decompose the excess hydride. The precipitated salts were removed by filtration and the ether

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* Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

layer was dried over anhydrous sodium sulfate. Removal of the ether under reduced pressure followed by distillation gave 2- (p-anisyl) ethanol, 25.8 g (87%), b.p. 158°C/21 mm (DePuy (35), b.p. 110-113°C/1 mm).

Preparation of 2- (p- Anisyl) ethyl p- Toluenesulfonate

p- Toluenesulfonyl chloride, 36.0 g (0.19 mole), purified by the procedure described on Page 72 of this thesis, was added in three portions to an ice-cold solution of 2- (p- anisyl) ethanol, 25.8 g (0.17 mole), in purified anhydrous pyridine (72 ml.). The solution was swirled occasionally and kept at 0°C for two days. The reaction mixture was added slowly to ice-cold 15% sulfuric acid (250 ml.) and then chloroform (100 ml.) was added to achieve solution of the while precipitate. The organic layer was separated and the aqueous layer extracted with chloroform (5 x 100 ml.). The combined organic layers were washed successively with 15% sulfuric acid, saturated sodium chloride, 10% sodium bicarbonate, and finally with saturated sodium chloride solution. The chloroform solution was then dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to give 2- (p- anisyl) ethyl p- toluenesulfonate, 38.6 g (75%), m.p. 57.5-58.0°C (Winstein (57), m.p. 57-58°C).

Preparation of N,N- methyl-2- (p- Anisyl) ethylaniline

This compound was prepared by the same method as was used for N,N- methyl-2-phenylethylaniline. 2- (p- Anisyl) ethyl p- toluenesulfonate, 38.6 g (0.126 mole), was heated with N- methylaniline, 15.0 g (0.14 mole), for six hours to give, after recrystallization from ethanol, 14.3 g (47%), m.p. 44°C.

Preparation of 2- (p- Anisyl) ethyldimethylanilinium Bromide

Quaternization was carred out in the usual manner. N,N- Methyl-2- (p- Anisyl) ethylaniline, 14.3 g (0.061 mole), was treated with methyl bromide, 12 g (0.13 mole), to produce 2- (p- anisyl) ethyldimethylanilinium bromide, 19.0 g (92%), m.p. 128.5-129.0°C. Anal. Calcd. for $C_{17}H_{22}NOBr$: C, 60.75; H, 6.55; N, 4.17. Found: C, 60.70; H, 6.53; N, 4.20.

2- (p- Chlorophenyl) ethyldimethylanilinium Bromide

Preparation of Ethyl 2- (p- Chlorophenyl) acetate

A solution of p-chlorobenzyl cyanide, 76 g (0.50 mole), 95% ethanol (102 ml.) and conc. sulfuric acid (53 ml.) was refluxed for 8 hours. At the end of this period, the solution was cooled and the product isolated by the same procedure for ethyl 2- (p- anisyl) acetate. Distillation of the product gave 81 g (81%), b.p. 137°C/12 mm (Smith (4), b.p. 96-98°C/1mm).

Preparation of 2- (p- Chlorophenyl) ethanol

This compound was prepared by the method of Amundsen and Nelson (56) by the reduction of 2- (p- chlorophenyl) ethyl acetate with lithium aluminum hydride was described in the synthesis of 2- (p- anisyl) ethanol. Ethyl 2- (p-chlorophenyl) acetate, 62.7 g (0.314 mole), was reduced with lithium aluminum hydride, 12.0 g (0.314 mole), to produce 2- (p- chlorophenyl) ethanol, 40.4 g (83%), b.p. 93°C/0.3 mm (DePuy (35), b.p. 98-100°/1mm).

Preparation of 2- (p- Chlorophenyl) ethyl p- Toluenesulfonate

This compound was prepared by the same method as was used for 2- (p- anisyl) ethyl p- toluenesulfonate. 2- (p- Chlorophenyl) ethanol, 34.0 g (0.22 mole), was treated with p- toluenesulfonyl chloride, 46.0 g (0.24 mole), to produce 2- (p- chlorophenyl) ethyl p- toluenesulfonate, which was recrystallized twice from n-hexane-30-60° petroleum ether-chloroform, 54.0 g (80%), m.p. 78.5-79.0°C (Bushman (39), m.p. 79.5-80.1°C).

Preparation of N,N- Methyl-2- (p- Chlorophenyl) ethylaniline

This compound was prepared by the same method was was used for N,N- methyl-2- phenylethylaniline except that this tertiary anine was isolated using column chromatography instead of distilling. 2- (p- Chlorophenyl) ethyl p-toluenefulfonate, 12.0 g (0.038 mole), was heated with N-methylaniline, 5.0 g (0.047 mole), for 14 hours. A 1/2" by 20" column of silica gel and an elutent of 4:1 petroleum-ether-benzene was used to obtain pure N,N- Methyl-2- (p- chlorophenyl) ethylaniline, 5.6 g (59%), m.p. 44.5-45.0°C.

Preparation of 2- (p- Chlorophenyl) ethyldimethylanilinium Bromide

Quaternization was carried out in the usual manner. N,N- Methy-2- (p- chlorophenyl) ethylaniline, 6.0 g (0.025 mole), was treated with methyl bromide, 4.8 g (0.050 mole), to produce 2- (p- chlorophenyl) ethyldimethylanilinium bromide, 4.5 g (54%), m.p. 130.5-131.0°C. Anal. Calcd. for $C_{16}H_{15}NClBr$: C, 56.30; H, 5.59; N, 4.11. Found: C,56.31, H, 5.68; N, 4.06.

2-(p-Trifluoromethylphenyl)ethyldimethylanilinium Bromide

Preparation of p- Trifluoromethylbenzoyl Chloride

To p- trifluorobenzoic acid, 50.0 g (0.26 mole), was added thionyl chloride (62.5 ml.), purified by the method described in Fieser and Fieser (58), and the mixture was refluxed on the steam bath for 24 hours. After removal of the excess thionyl chloride under reduced pressure, distillation gave p- trifluoromethylbenzoyl chloride, 51.1 g (93%) b.p. 113°C/72 mm (Jones (59), b.p. 199-200°C (750 mm).

Preparation of Ethyl p- Trifluoromethylbenzoate

Absolute (super-dry) ethanol, 35 g (0.77 mole), was added dropwise to a solution of p- trifluoromethylbenzoyl chloride, 48.0 g (0.23 mole), and pyridine, 18.2 g (0.23 mole), at 10°C and the reaction mixture was refluxed for three hours. After cooling, the reaction mixture was poured into water (100 ml.) and extracted with benzene (3 x 50 ml.). The combined benzene extracts were then washed successively with 10% sulfuric acid, 10% sodium bicarbonate, and water. After removal of the solvent under reduced pressure, distillation gave ethyl p- trifluoromethylbenzoate, 46.8 g (93%), b.p. 107-109°C/25 mm (Haas (60), b.p. 80.0-80.5°C/5.5 mm).

Preparation of p- Trifluoromethylbenzyl Alcohol

Ethyl p- trifluoromethylbenzoate, 46.8 g (0.21 mole), in dry ether (210 ml.) was added dropwise over a period of three hours to a slurry of lithium aluminum hydride, 6.1 g (0.16 mole), in dry ether (106 ml.). This mixture was refluxed for two hours and, after cooling, water was added dropwise to destroy the excess lithium aluminum hydride.

After the slow addition of 10% sulfuric acid (200 ml.), the ether layer was separated, washed successively with 10% sodium bicarbonate and water, then dried over anhydrous sodium sulfate. After removal of the ether under reduced pressure, distillation gave p- trifluoromethylbenzyl alcohol, 34.9 g (93%), b.p. 120°C/50 mm (Haas (60), b.p. 78.5-80.0°C/4mm).

Preparation of p- Trifluoromethylbenzyl Bromide

p- Trifluoromethylbenzyl alcohol, 34.9 g (0.20 mole), was added to 48% hydrobromic acid, 105 g (0.65 mole), and the resulting solution was refluxed for three hours. The reaction mixture separated into two layers on cooling. The aqueous layer was extracted with ether (3 x 100 ml.) and the combined organic layers were washed successively with water, 10% sodium bicarbonate, and water. The ether solution was dried over anhydrous sodium sulfate and removal of the solvent under reduced pressure followed by distillation gave p- trifluoromethylbenzyl bromide, 44.1 g (93%), b.p. 110°C/34 mm (Haas (60), b.p. 65-66°C/5 mm).

Preparation of p- Trifluoromethylbenzyl Cyanide

This compound was prepared by cyanide displacement on p- trifluoromethylbenzyl bromide by the method described in Vogel (61). Sodium cyanide, 11.8 g (0.24 mole), and water (12 ml.) were placed in a 100 ml. flask fitted with a reflux condensor. The mixture was warmed on the steam bath to dissolve the cyanide and then a solution of p- trifluoromethylbenzyl bromide, 44.1 g (0.185 mole), in 95% ethanol (54 ml.) was added dropwise over a period of thirty minutes. The mixture was heated on the steam bath for four hours, then cooled and the precipitated sodium bromide removed by suction filtration. The filtrate was concentrated under reduced pressure and, after the addition of water (130 ml.), was extracted with ether (3 x 130 ml.). The combined ether extracts were dried over anhydrous sodium sulfate and the ether was removed under reduced pressure. The product was distilled to give p- trifluoromethylbenzyl cyanide, 28.7 g (84%), b.p. 141°C/29 mm (Smith (4), b.p. 131-132°C/20 mm).

Preparation of Ethyl 2- (p- Trifluoromethylbenzyl) acetate

This compound was prepared by the same method as was used for ethyl 2- (p- chlorophenyl) acetate. p- Trifluoromethylbenzyl cyanide, 28.7 g (0.155 mole), was refluxed with ethanol (50 ml.) to give ethyl 2- (p- trifluoromethylphenyl) acetate, 31.2g (87%), b.p. 130°C/29 mm.

Preparation of 2- (p- Trifluoromethylphenyl) ethanol

This compound was prepared by the same method as was used for 2- (p- anisyl) ethanol. Ethyl 2- (p- trifluoromethylphenyl) acetate, 27.2 g (0.117 mole), was treated with lithium aluminum hydride, 5.65 g (0.149 mole), to produce 2- (p- trifluoromethylphenyl) ethanol, 16.5 g (75%), b.p. 124°C/20 mm.

Preparation of 2- (p- Trifluoromethylphenyl) ethyl p-Toluenesulfonate

This compound was prepared by the same method as was used for 2- (p- anisyl) ethyl p- toluenesulfonate. 2- (p- Trifluoromethylphenyl) ethanol, 16.5 g (0.087 mole), was treated with p- toluenesulfonyl chloride, 20.0 g (0.104 mole), to produce after recrystalliztion from ethanol (p- trifluoromethylphenyl) ethyl p- toluenesulfonate, 26.2 g (88%), m.p. 89-90°.

Preparation of N,N- Methyl-2- (p- Trifluoromethylphenyl) ethylaniline

This compound was prepared by the same method as was used for N,N- Methyl-2- (p- chlorophenyl) ethylaniline. 2- (p- Trifluoromethylphenyl) ethyl p- toluenesulfonate, 13.0 g (0.037 mole), was heated with N-methyl aniline, 6.0 g (0.056 mole), for 17 hours to produce N,N- methyl-2- (p- trifluoromethylphenyl) ethylaniline, 6.2 g (59%), b.p. 127°C/0.25mm*.

Preparation of 2- (p- Trifluoromethylphenyl) ethyldimethylanilinium Bromide

This compound was prepared by the same method as was used for 2- phenylethyldimethyanilinium bromide. N,N- methyl -2- (p-trifluoromethylphenyl)ethylaniline, 6.2 g (0.023mole), was treated with methyl bromide, 4.5 g (0.047 mole), to give 2- (p- trifluoromethylphenyl) ethyldimethylanilinium bromide, 5.8 g (69%), m.p. 155.5-157.0°C. Anal. Calcd. for $C_{17}H_{19}NF_3Br$: C, 54.58; H, 5.08; N, 3.75. Found: C, 54.62; H, 5.16; N, 3.74.

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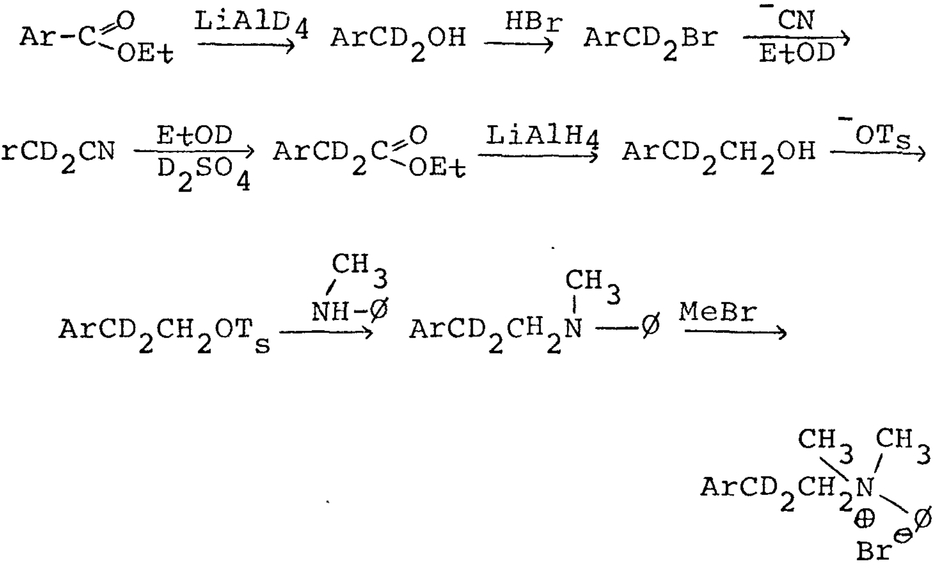
* It was found that distilling this amine, instead of using a chromatographic means of separation, decreased the yield to 44%. The yield of chloro-substituted amine changed only slightly with the variation in method of isolation.

The Synthesis of Deuterated 2- Arylethyldimethylanilinium Bromides

General

2- Phenylethyldimethylanilinium-2, 2- $\underline{d}_2$ bromide and 2- (p̲- anisyl) ethyldimethylanilinium-2, 2- $\underline{d}_2$ bromide were prepared by the same synthetic route. The synthesis began with the preparation of ethyl phenylacetate-α,α- $\underline{d}_2$ and ethyl p̲- anisylacetate-α,α- $\underline{d}_2$ by the treatment of the sodium salt of the corresponding arylmalonate with deuterium oxide. The deuterated ethyl arylacetates were converted to the quaternary anilinium salts by the following steps: reduction of the esters to the corresponding alcohols, conversion of alcohols to tosylates and thence to tertiary amines, and, finally, quaternization of the amines to form the quaternary anilinium salts.

A different synthetic route was followed for the preparation of the p̲- chloro- and p̲- trifluoromethyl-substituted compounds. This is outlined by the following equations:



$$\mathrm{Ar{-}C}{\genfrac{}{}{0pt}{}{\nearrow \mathrm{O}}{\searrow \mathrm{OEt}}} \xrightarrow{\mathrm{LiAlD_4}} \mathrm{ArCD_2OH} \xrightarrow{\mathrm{HBr}} \mathrm{ArCD_2Br} \xrightarrow[\mathrm{EtOD}]{{}^{-}\mathrm{CN}}$$

$$\mathrm{ArCD_2CN} \xrightarrow[\mathrm{D_2SO_4}]{\mathrm{EtOD}} \mathrm{ArCD_2C}{\genfrac{}{}{0pt}{}{\nearrow \mathrm{O}}{\searrow \mathrm{OEt}}} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{ArCD_2CH_2OH} \xrightarrow{{}^{-}\mathrm{OTs}}$$

$$\mathrm{ArCD_2CH_2OTs} \xrightarrow{\overset{\mathrm{CH_3}}{\mathrm{NH{-}}\emptyset}} \mathrm{ArCD_2CH_2}\overset{\mathrm{CH_3}}{\underset{}{\mathrm{N}}}{-}\emptyset \xrightarrow{\mathrm{MeBr}}$$

$$\mathrm{ArCD_2CH_2}\overset{\oplus}{\mathrm{N}}(\mathrm{CH_3})(\mathrm{CH_3})\emptyset\ \mathrm{Br}^{\ominus}$$

The appropriate p- substituted ethyl benzoate was first reduced with lithium aluminum deuteride to give the p-substituted benzyl-α,α- d_2 alcohol which was converted to the corresponding bromide by treatment with hydrobromic acid. Because the next step, which involves the displacement of bromide ion with cyanide ion, was found to give the nitrile with a significant loss of deuterium when carried out in hydroxylic solvents (Smith (4)), this reaction was carried out in a mixture of EtOD and D_2O. Similarly, when the nitrile was converted to the acetate ester, a mixture of EtOD and D_2SO_4 was used. The remaining steps were identical to those followed in the synthesis of the unlabelled compounds.

The n.m.r. analyses of the acetate esters for the unsubstituted, the p- chloro-substituted, and the p- trifluoromethyl-substituted quaternary ammonium salts indicated only about 92- 95% deuterium incorporation at C_α. In order to increase the deuterium content at this position, these esters were dissolved in deuterated ethanol-O-d and treated with sodium to effect change.

The deuterium analyses* of the acetate esters and the quaternary anilinium salts, shown in Tables X, XI, indicated that the compounds were 96-99.5% deuterated at C_α and C_β respectively.

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* Deuterium analyses on the acetate esters and the quaternary anilinium salts were performed by Mr. J. Nemeth, 303 W. Washington St., Urbana, Ill., using the falling-drop method.

Table X

Results of Deuterium Analyses on the Ethyl 2- Arylacetates

Acetate Ester	Atoms D/Molecule
Ethyl 2- (*p*- Anisyl) acetate-α,α- $\underline{d}_2$	1.94
Ethyl 2- Phenylacetate-α,α- $\underline{d}_2$	1.98
Ethyl 2- (*p*- Chlorophenyl) acetate-α,α- $\underline{d}_2$	1.98
Ethyl 2- (*p*- Trifluoromethylphenyl) acetate-α,α- $\underline{d}_2$	1.97

Table XI

Results of Deuterium Analyses on the 2- Arylethyldimethylanilinium Bromides

Quaternary Anilinium Ion	Atoms D/Molecule
2- (*p*- Anisyl) ethyldimethylanilinium-2,2- $\underline{d}_2$	1.99
2- Phenylethyldimethylanilinium-2,2- $\underline{d}_2$	1.98
2- (*p*- Chlorophenyl) ethyldimethylanilinium-2,2- $\underline{d}_2$	1.96
2- (*p*- Trifluoromethylphenyl) ethyldimethylanilinium-2,2- $\underline{d}_2$	1.92

2- Phenylethyldimethylanilinium-2,2- $\underline{d}_2$ Bromide

Preparation of Ethyl 2- Phenylacetate-α,α- $\underline{d}_2$

A solution of diethyl phenylmalonate (Eastman Organic Chemicals), 93g (0.39 mole), in sodium-dried 30-60° petroleum ether (390 ml.) was first filtered through a 1/2" by 10" column of absorption alumina and then added over a period of six hours to a well-stirred mixture of petroleum ether (170 ml.) and a 50% dispersion of sodium hydride in mineral oil (18.6 g). After two hours of stirring, the resulting white solid was removed by filtration, washed repeatedly with petroleum ether, and dried by pumping overnight in a vacuum desiccator. The resultant dry sodium salt was added to deuterium oxide (67 g) and the mixture was refluxed for eight hours under a purified nitrogen atmosphere. The organic layer was separated and the aqueous layer was extracted with ether (3 x 50 ml.). The combined organic layers were dried over anhydrous magnesium sulphate and, after removal of the solvent under reduced pressure, distilled through a short Vigreux column to give ethyl phenylacetate-α,α- $\underline{d}_2$, 7.7 g (12%), b.p. 118.5°C/21 mm (Saunders (41), b.p. 73-74°C/0.5 mm).

The n.m.r. analysis of the ester indicated only about 95% deuterium incorporation at C_α. Further deuterium incorporation was effected by dissolving ethyl phenylacetate-α,α- $\underline{d}_2$, 8.9 g (0.054 mole), in ethanol-O-$\underline{d}$ (30 ml.) and treating the solution with sodium, 0.18 g (0.008 mole), in a sealed flask at room temperature for two hours. Then, approximately 25 ml. of the ethanol-O-$\underline{d}$ were removed on a vacuum line at room temperature and a fresh 25 ml. aliquot of ethanol-O-$\underline{d}$ was added to the mixture. After another two hours, deuterium oxide (30 ml.) was added to the reaction mixture which was then extracted with 30-60° petroleum ether (5 x 25 ml.). The petroleum ether extracts were dried over magnesium sulfate and evaporated under reduced pressure. The residue was distilled to give ethyl phenylacetate-α,α- $\underline{d}_2$, 6.6 g (74%). Deuterium analysis indicated 1.98 atoms D/molecule.

Preparation of 2- Phenylethanol-2,2- $\underline{d}_2$

This compound was prepared by a lithium aluminum hydride reduction of ethyl phenylacetate-α,α- $\underline{d}_2$ using the procedure previously described for the synthesis of 2- (p-anisyl) ethanol. Ethyl phenylacetate-α,α- $\underline{d}_2$, 6.6 g (0.040 mole), was reduced with lithium aluminum hydride, 1.4 g (0.037 mole), to yield 2- phenylethanol-2,2- $\underline{d}_2$, 4.0 g (81%), b.p. 105-106°C/13 mm (Undeuterated compound, b.p. 122°C/20 mm).

Preparation of 2- Phenylethyl-2,2- $\underline{d}_2$ p- Toluenesulfonate

This compound was prepared from 2- phenylethanol-2,2- $\underline{d}_2$ by the procedure described for the synthesis of the undeuterated compound. 2- Phenylethanol-2,2- $\underline{d}_2$, 4.0 g (0.032 mole), was treated with p- toluenesulfonyl chloride, 7.0 g (0.037 mole), in dry pyridine (40 ml.) to produce 2- phenylethyl-2,2- $\underline{d}_2$ p- toluenesulfonate, 3.0 g (44%), m.p. 36°C (Undeuterated compound, m.p. 36.5-38.0°C).

Preparation of N,N- Methyl-2-phenylethylaniline-2,2- $\underline{d}_2$

This compound was prepared by the same method as was used for the corresponding undeuterated compound. 2- Phenylethyl-2,2- $\underline{d}_2$ p- toluenesulfonate, 3.0 g (0.011 mole), was treated with N- methylaniline, 2.0 g (0.019 mole), to give N,N- methyl-2-phenylethylaniline-2,2- $\underline{d}_2$, 1.1 g (48%), b.p. 105-107°C/0.08mm (Undeuterated compound, b.p. 133°C/1mm).

Preparation of 2- Phenylethyldimethylanilinium-2,2- $\underline{d}_2$ Bromide

Quaternization was carried out by treating N,N- methyl-2- phenylethylaniline-2,2- $\underline{d}_2$, 1.1 g (0.0053 mole), with methyl bromide, 1.0 g (0.011 mole), to give 2- phenylethyldimethylanilinium-2,2- $\underline{d}_2$ bromide, 0.88 g (54%), m.p. 169-170°C (Undeuterated compound, m.p. 168.5-169°C). Deuterium analysis indicated 1.98 atoms D/molecule. Anal. Calcd. for $C_{16}H_{18}D_{2}NBr$: C, 62.34; H, 7.18; N, 4.54. Found: C, 62.68; H, 6.69; N, 4.50.

2- (p- Anisyl) ethyldimethylanilinium-2,2- $\underline{d}_2$ Bromide

Preparation of Diethyl p- Anisylmalonate

This compound was prepared by condensing ethyl oxalate with ethyl 2- (p- anisyl) acetate in the presence of base by the method described in Organic Synthesis (62). Cleanly-cut sodium, 11.2 g (0.49 mole), was added in small portions to absolute ethanol (263 ml.) in a 1 litre three-necked flask, fitted with a mercury-sealed stirrer, reflux condensor and dropping funnel, and the mixture was warmed until the sodium had completely dissolved. After cooling the solution to 60°C, ethyl oxalate, 71 g (0.486 mole), was added rapidly with vigorous stirring, followed immediately by the addition of ethyl 2- (p- anisyl) acetate, 100 g (0.486 mole). Stirring was continued for one-half hour at 60°C and the solution then allowed to stand at room temperature for twelve hours during which the product separated as a nearly solid paste. Following the addition of dry ether (400 ml.), the solid was filtered, repeatedly washed with dry ether, then pumped dry in a vacuum desiccator for twelve hours. The resulting solid was then treated with dilute surlfuric acid (16 ml. of conc. sulfuric acid in 260 ml. of water) in order to liberate the p- anisyloxaloacetic ester. The yellow oil which separated was combined with ether extracts (3 x 60 ml.) of the aqueous phase and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure the residual oil was placed in a modified Claisen flask with a fractionating side-arm and heated under reduced pressure of approximately 10 mm in an oil bath. The temperature of the bath was gradually increased to, then maintained at 160°C until the evolution of carbon monoxide had ceased. Distillation of the product gave 80.4 g (62%) of diethyl p- anisylmalonate, b.p. 138°/0.4 mm (Smith (4), b.p. 171-172°/3 mm).

Preparation of Ethyl 2- (p- Anisyl) acetate-α,α- d_2

This compound was prepared from diethyl p- anisylmalonate by the procedure described for the preparation of ethyl phenylacetate-α,α- d_2 from diethyl phenylmalonate. Unfortunately, the anisyl ester was not sufficiently soluble in petroleum ether. However, a 1:1 mixture of petroleum ether-ether was found to achieve solution.

A solution of diethyl p- anisylmalonate, 40.0 g (0.15 mole), was treated with a 50% dispersion of sodium hydride in mineral oil (7.1 g) to produce the sodium salt which was heated with deuterium oxide (33 ml.) to form ethyl 2- (p- anisyl) acetate-α,α- d_2, 5.3 g (18%), b.p. 91°C/0.5 mm (Undeuterated compound, b.p. 160°C/21 mm). Deuterium analysis indicated 1.94 atoms D/molecule.

Preparation of 2- (p- Anisyl) ethanol-2,2- d_2

This compound was prepared by the lithium aluminum hydride reduction of ethyl 2- (p- anisyl) acetate-α,α- d_2 using the procedure described for the corresponding undeuterated compound. Ethyl 2- (p- anisyl) acetate-α,α- d_2, 7.0 g (0.036 mole), was treated with lithium aluminum hydride, 1.43 g (0.038 mole), to produce 2- (p- anisyl) ethanol-2,2- d_2 4.0 g (73%), b.p. 77-78°C/0.06 mm (Undeuterated compound, b.p. 158°C/21 mm).

Preparation of 2- (p- Anisyl) ethyl-2,2- d_2 p- Toluenesulfonate

This compound was prepared from the corresponding alcohol by the same procedure used for the synthesis of the undeuterated compound. p- Toluenesulfonyl chloride, 7.0 g (0.037 mole), was added to 2- (p- anisyl) ethanol-2,2- d_2, 4.0 g (0.027 mole), to produce the deuterated tosylate, 6.4 g (79%),m.p. 57-58°C (Undeuterated compound, m.p. 57.5-58.0°C).

Preparation of N,N- Methyl-2- (p- Anisyl) ethylaniline-2,2- d_2

This compound was prepared by the same method as was used for N,N- methyl-2-phenylethylaniline 2- (p- Anisyl) ethyl-2, 2- d_2 p- toluenesulfonate, 6.4 g (0.021 mole), was treated with N- methylaniline, 6.0 g (0.056 mole), to give N,N- methyl-2- (p- anisyl) ethylaniline-2,2- d_2, 2.0 g (40%), m.p. 45°C (Undeuterated compound, m.p. 44°C).

Preparation of 2- (p- Anisyl) ethyldimethylanilinium-2,2- d_2 Bromide

Quaternization was carried out by treating N,N- methyl-2- (p- anisyl) ethylaniline-2,2- d_2, 2.0 g (0.0084 mole), with methyl bromide, 1.5 g (0.016 mole), to give 2- (p-anisyl) ethyldimethylanilinium-2,2- d_2 bromide, 1.5 g (53%), m.p. 130-131°C (Undeuterated compound, m.p. 128.5-129.0°C). Deuterium analysis indicated 1.99 atoms D/molecule. Anal. Calcd. for $C_{17}H_{20}D_2NOBr$: C, 60.36; H, 7.14; N, 4.14. Found: C, 60.50; H, 6.93; N, 4.15.

2- (p- Chlorophenyl) ethyldimethylanilinium-2,2- $\underline{d}_2$ Bromide

Preparation of p- Chlorobenzyl-α,α- $\underline{d}_2$ Alcohol

This compound was prepared by the lithium aluminum deuteride reduction of ethyl p- chlorobenzoate (Fairfield Chemical Co.) using the procedure described for the reduction of unlabelled ethyl p- trifluoromethylbenzoate. Ethyl p-chlorobenzoate, 23.5 g (0.125 mole), was reduced with lithium aluminum deuteride, 3.0 g (0.079 mole), to produce, after recrystallization from n-hexane, p- chlorobenzyl-α,α- $\underline{d}_2$ alcohol, 15.0 g (82%), m.p. 69-71°C (Smith (4), 72-73°C).

Preparation of p- Chlorobenzyl-α,α- $\underline{d}_2$ Bromide

This compound was prepared by the procedure described for p- trifluoromethylbenzyl bromide. p- Chlorobenzyl-α,α- $\underline{d}_2$ alcohol, 15.0 g (0.104 mole), was refluxed for three hours with 48% hydrobromic acid, 45 g (0.28 mole) to give, after recrystallization from water-ethanol, p- chlorobenzyl-α,α- $\underline{d}_2$ bromide, 13.9 g (76%), m.p. 49-50°C (Smith (4), 50.5-51.0°C).

Preparation of p- Chlorobenzyl-α,α- $\underline{d}_2$ Cyanide

This compound was prepared by the same procedure was used for p- trifluoromethylbenzyl cyanide only using deuterated solvent. p- Chlorobenzyl-α,α- $\underline{d}_2$ bromide, 12.6 g (0.061 mole), in ethanol-O-$\underline{d}$ (19 ml.) was treated with anhydrous sodium cyanide, 3.0 g (0.061 mole), dissolved in deuterium oxide (5.2 ml.) to give, after recrystallization from ethanol-O-$\underline{d}$, p- chlorobenzyl-α,α- $\underline{d}_2$ cyanide, 5.5 g (60%), m.p. 27-28°C (Smith (4), 28-30°C).

Preparation of Ethyl 2- (p- Chlorophenyl) acetate-α,α- $\underline{d}_2$

This compound was prepared by the same procedure as was used for the ethyl 2- (p- chlorophenyl) acetate only using deuterated solvent. p- Chlorobenzyl-α,α- $\underline{d}_2$ cyanide, 9.0 g (0.058 mole) was refluxed in ethanol-O-d (14.2 ml.) with sulfuric acid-$\underline{d}_2$ (6.3 ml.) to give ethyl 2- (p- chlorophenyl) acetate-α,α- $\underline{d}_2$, 8.4 g (70%), b.p. 140°C/20 mm (Undeuterated compound, b.p. 137°C/12 mm).

The n.m.r. analysis indicated only about 92% deuterium incorporation at C_α. Utilizing the same procedure of deuterium exchange as was used for ethyl phenylacetate-α,α- $\underline{d}_2$, ethyl 2- (p- chlorophenyl) acetate-α,α- $\underline{d}_2$, 8.4 g (0.045 mole), was treated with ethanol-O-d and sodium to produce ethy 2- (p- chlorophenyl) acetate-α,α- $\underline{d}_2$, 6.0 g (71%). Deuterium analysis indicated 1.98 atoms D/molecule.

Preparation of 2- (p- Chlorophenyl) ethanol-2,2- $\underline{d}_2$

This compound was prepared by the same procedure as was 2- (p- anisyl) ethanol. 2- (p- Chlorophenyl) acetate-α,α-$\underline{d}_2$, 6.0 g (0.032 mole), was treated with lithium aluminum hydride, 1.4 g (0.037 mole), to give 2- (p- chlorophenyl) ethanol-2,2- $\underline{d}_2$, 3.0 g (64%), b.p. 133-134°C/13 mm (Undeuterated compound, b.p. 93°C/0.3 mm).

Preparation of 2- (p- Chlorophenyl) ethyl-2,2- $\underline{d}_2$ p- Toluensulfonate

This compound was prepared by the same method as was used for 2- (p- anisyl) ethyl p- toluenesulfonate. 2- (p-Chlorophenyl) ethanol-2,2- $\underline{d}_2$, 3.0 g (0.021 mole), was treated with p- toluenesulfonyl chloride, 6.0 g (0.031 mole), to produce 2- (p- chlorophenyl) ethyl-2,2-$\underline{d}_2$ p- toluenesulfonate, 5.0 g (95%), m.p. 78-79°C (Undeuterated compound, m.p. 78.5-79°C).

Preparation of N,N- Methyl-2- (p- Chlorophenyl) ethylaniline-2,2- d_2

This compound was prepared by the same method as was used for N,N- methyl-2- phenylethylaniline. 2- (p- Chlorophenyl) ethyl-2,2- d_2 p- toluenesulfonate, 5.0 g (0.016 mole), was treated with N-methylaniline, 3.0 g (0.028 mole), to produce N,N- methyl-2 (p- chlorophenyl) ethylaniline-2,2- d_2, 2.2 g (56%), b.p. 118°C/0.04 mm (Undeuterated compound, b.p. 172-173°/2 mm).

Preparation of 2- (p- Chlorophenyl) ethyldimethylanilinium-2,2- d_2 Bromide

Quaternization was achieved by treating N,N- methyl-2- (p- chlorophenyl) ethylaniline-2,2- d_2, 2.2 g (0.0091 mole), with methyl bromide, 2.0 g (0.021 mole), to produce 2- (p- chlorophenyl) ethyldimethylanilinium-2,2- d_2 bromide, 1.6 g (52%), m.p. 130.0-130.5°C (Undeuterated compound, m.p. 130.5-131.0°C), Deuterium analysis indicated 1.96 atoms D/molecule. Anal. Calcd. for $C_{16}H_{17}D_2NClBr$: C, 56.07; H, 6.17; N, 4.09. Found: C, 55.98; H, 5.97; N, 3.93.

2- (p- Trifluoromethylphenyl) ethyldimethylanilinium-2,2- d_2 Bromide

Preparation of p- Trifluoromethylbenzyl-α,α- d_2 Alcohol

This compound was prepared by the same method as the corresponding undeuterated compound. Ethyl p- trifluoromethylbenzoate, 30.0 g (0.133 mole), was added to lithium aluminum deuteride, 3.0 g (0.079 mole), to give p- trifluoromethylbenzyl-α,α- d_2 alcohol, 20.0 g (84%), b.p. 122°C/35 mm

(Undeuterated compound, b.p. 120°C/50 mm).

Preparation of *p*- Trifluoromethylbenzyl-α,α- $\underline{d}_2$ Bromide

This compound was prepared by the same procedure as was the corresponding undeuterated compound. *p*- Trifluoromethylbenzyl-α,α- $\underline{d}_2$ alcohol, 20.0 g (0.116 mole), was added to 48% hydrobromic acid, 60 g (0.37 mole), to give *p*- trifluoromethylbenzyl-α,α- $\underline{d}_2$ bromide, 19.5 g (73%), b.p. 107-108°C/36 mm (Undeuterated compound, b.p. 110°C/34 mm).

Preparation of *p*- Trifluoromethylbenzyl-α,α- $\underline{d}_2$ Cyanide

This compound was prepared from *p*- trifluoromethylbenzyl-α,α- $\underline{d}_2$ bromide by the method described for the corresponding undeuterated compound only using deuterated solvent in the cyanide displacement reaction. *p*- Trifluoromethylbenzyl-α,α- $\underline{d}_2$ bromide, 19.0 g (0.079 mole), in 95% ethanol-O-*d* (23 ml.) was treated with anhydrous sodium cyanide, 5.1 g (0.104 mole), dissolved in deuterium oxide (5.2 ml.) to give *p*- trifluoromethylbenzyl-α,α- $\underline{d}_2$ cyanide, 8.5 g (57%), b.p. 122-123°C/16 mm (Undeuterated compound, b.p. 141°/29 mm).

Preparation of Ethyl 2- (*p*- Trifluoromethylphenyl) acetate-α,α- $\underline{d}_2$

This compound was prepared by the same procedure as was ethyl 2- (*p*- chlorophenyl) acetate only using deuterated solvent. *p*- Trifluoromethylbenzyl-α,α- $\underline{d}_2$ cyanide, 6.2 g (0.033 mole), was refluxed in ethanol-O-*d* (10 ml.) with sulfuric acid- $\underline{d}_2$ (4 ml.) to give ethyl 2- (*p*- trifluoromethylphenyl) acetate-α,α- $\underline{d}_2$, 4.0 g (67%), b.p. 118°C/15 mm (Undeuterated compound, b.p. 130°C/29 mm).

The n.m.r. indicated only about 93% deuterium incorporation at C_α . Utilizing the same procedure of deuterium exchange as was used for ethyl phenylacetate-α,α- $\underline{d}_2$, ethyl 2- (p- trifluoromethylphenyl) acetate-α,α- $\underline{d}_2$, 8.0 g (0.037 mole), was treated with ethanol-O-d and sodium to produce ethyl 2- (p- trifluoromethylphenyl) acetate-α,α- $\underline{d}_2$, 4.8 g (60%) Deuterium analysis indicated 1.97 atoms D/molecule.

Preparation of 2- (p- Trifluoromethylphenyl) ethanol-2,2- $\underline{d}_2$

This compound was prepared by the same procedure as was 2- (p- anisyl) ethanol. 2- (p- Trifluoromethylphenyl) acetate-α,α- $\underline{d}_2$, 4.8 g (0.022 mole), was treated with lithium aluminum hydride, 1.0 g (0.026 mole), to produce 2- (p- trifluoromethylphenyl) ethanol-2,2- $\underline{d}_2$, 3.4 g (78%), b.p. 116°C/16 mm (Undeuterated compound, b.p. 124°C/20 mm).

Preparation of 2- (p- Trifluoromethylphenyl) ethyl-2,2- $\underline{d}_2$ p- Toluenesulfonate

This compound was prepared by the same method as was used for 2- (p- anisyl) ethyl p- toluenesulfonate. 2- (p- Trifluoromethylphenyl) ethanol-2,2- $\underline{d}_2$, 3.4 g (0.019 mole),was treated with p- toluenesulfonyl chloride, 6.0 g (0.031 mole), to produce 2- (p- trifluoromethylphenyl) ethyl p- toluensulfonate, 4.5 g (78%), m.p. 88°C (Undeuterated compound, m.p. 89-90°C).

Preparation of N,N- Methyl-2- (p- Trifluoromethylphenyl) ethylaniline-2,2- $\underline{d}_2$

This compound was prepared by the same method as was used for N,N- methyl-2- (p- chlorophenyl) ethylaniline.

2- (*p*- Trifluoromethylphenyl) ethyl-2,2 -*d*$_2$ *p*- toluenesulfonate, 4.5 g (0.013 mole), was treated with N- methylaniline, 2.5 g (0.023 mole), to give N,N- methyl-2- (*p*- trifluoromethylphenyl) ethylaniline-2,2- *d*$_2$, 1.8 g (68%).

Preparation of 2- (p- Trifluoromethylphenyl) ethyldimethylanilinium -2,2- *d*$_2$ Bromide

Quaternization was carried out by treating N,N- methyl-2- (*p*- trifluoromethylphenyl) ethylaniline-2,2- *d*$_2$, 1.8 g (0.0065 mole), with methyl bromide, 1.3 g (0.014 mole), to give 2- (*p*- trifluoromethylphenyl) ethyldimethylanilinium-2,2-*d*$_2$ bromide, 1.45 g (59%), m.p. 155.5-157.0°C (Undeuterated compound, m.p. 155.5-157.0°C). Deuterium analysis indicated 1.92 atoms D/molecule. Anal. Calcd. for $C_{17}H_{17}D_2NF_3Br$: C, 54.29; H, 5.58; N, 3.72. Found: C, 54.56; H, 5.56; N, 3.67.

Kinetic Studies

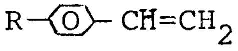
General

A spectroscopic method, described by Saunders and Williams (38) and used previously in these laboratories by Smith (4) and Frosst (63), was used to follow the rate of reaction of the deuterated and undeuterated 2-arylethyldimethylanilinium ions with sodium ethoxide in ethanol. The products, para-substituted styrenes, exhibit strong absorption in the ultra-violet region. An additional product, dimethylaniline, also absorbs in this region. While its formation did not complicate the kinetic calculations, its presence had to be taken into account when determining the theoretical infinity points of each run.

Both λ_{max} and the molar extinction coefficient at λ_{max} for styrene, p-methoxystyrene, and p-chlorostyrene had previously been reported by Bushman (39) and his values for these constants were used in the work of this thesis. The values for p-trifluoromethylstyrene were determined by Smith (4). The optical properties of all four styrenes, together with dimethylaniline, are given in Table XII

Table XII

U.V. Absorption of p-Substituted Styrenes and Dimethylaniline in 95% Ethanol



R	λ_{max} mμ	Molar Extinction Coefficient (x 10^{-4})	
		R-Styrene	Dimethylaniline
H	248	1.38	1.36
OCH_3	258	1.92	1.40
Cl	253	1.97	1.38
CF_3	250	1.62	1.17

Procedures

Preparation of Sodium Ethoxide Solutions For Kinetic Measurements

Anhydrous ethanol (500 ml.), purified by the method of Lund and Bjerrum (64), was placed in the vessel shown in Fig. 9 and cooled in an ice-water bath. Purified nitrogen gas (65) was bubbled through the vessel for one hour. Sodium metal, 7.5 g (0.33 mole), was then added in small portions and the mixture was allowed to stand at 0°C until all of the sodium had dissolved (6 hours). The resultant stock solution (0.66 N) was stored in the refrigerator and aliquots were used to prepare solutions for kinetic measurements.

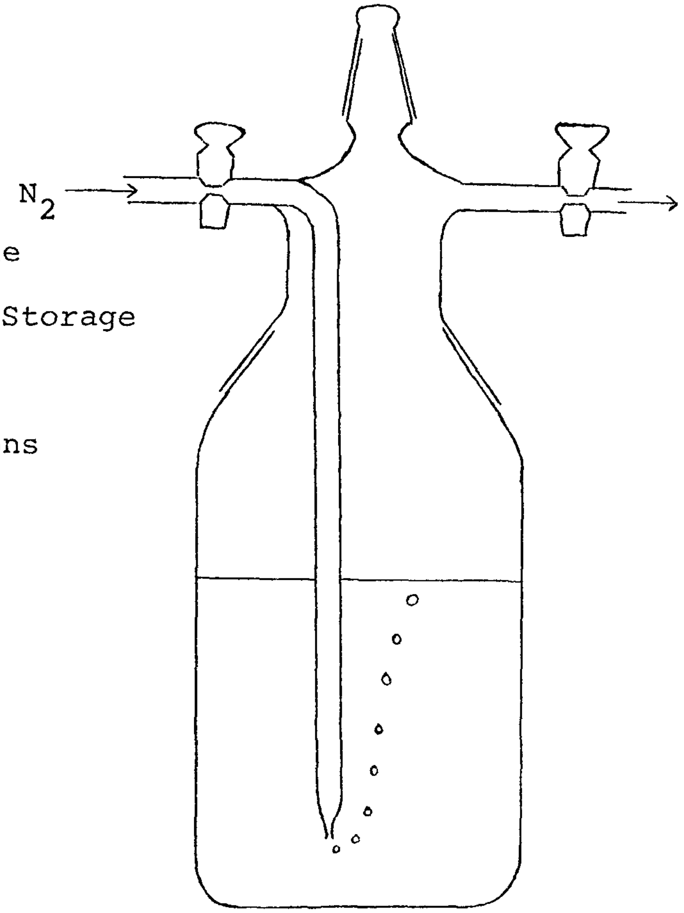


Fig. 9 Apparatus for the Preparation and Storage of Stock Sodium Ethoxide Solutions

Kinetic Measurements

An accurately weighed amount (ca. 0.2m.mole) of the desired quaternary anilinium salt was placed into the reaction vessel, which was simply a 50 ml. volumetric flask with a ground-glass stopper. Care was taken to assure that the salt concentration did not vary by more than 1% in all of the kinetic experiments. Anhydrous ethanol (20 ml.) was delivered into the flask by a calibrated pipette, the salt was dissolved, and the flask was placed in the constant-temperature bath maintained at the desired temperature.

A standard sodium ethoxide solution was prepared by taking a 10 ml. aliquot of the stock sodium ethoxide solution and diluting it with anhydrous ethanol (90 ml.). This basic solution was standardized by removing 5 ml. aliquots and titrating with standard sulfuric acid (0.01 N) and backtitrating with standard sodium hydroxide (0.01 N), using bromocresol green as the indicator. As with the salt, care was taken to assure that the base concentration did not vary by more than 1% in the experiments. The flask containing the standard sodium ethoxide solution was then placed in the bath.

After the solutions had reached equilibrium (ca. one hour at 40°C) a five ml. aliquot of the standardized base was transferred to the reaction flask using a calibrated quick-delivery pipette. Time zero was taken when one-half of the sodium ethoxide solution had been added.

At regular intervals, a calibrated one millilitre hypodermic syringe with a six inch needle was inserted into the reaction vessel after removing the stopper, a sample withdrawn,and the stopper replaced. Each sample was quenched* by dilution with 95% ethanol and then further diluted to a standard volume. The solution was mixed thoroughly and the optical density determined using a Perkin-Elmer Hitachi Spectrophotometer set at the appropriate wavelength for the particular olefin formed.

The rate constants for all of the deuterated and undeuterated 2-arylethyldimethylanilinium salts were determined using second-order conditions in which the ethoxide component was in approximately two-fold excess. The reactions were found to follow a second-order rate law, equation (29), where a and b are the initial concentrations of ethoxide and

$$k = \frac{2.303}{t(a-b)} \log \frac{b}{a} \frac{(a-x)}{(b-x)} \qquad (29)$$

quaternary salt respectively, and x is the concentration of the styrene at time t, obtained by multiplying the mole fraction reacted, $O.D._t/O.D._\infty$, by the initial salt concentration. The second-order rate constant, k, was evaluated from the slope of the line obtained by the least squares treatment using an I.B.M. 7040 computer, and multiplying this slope by

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*Separate experiments showed that there was a measureable increase in optical density over a period of one hour for the diluted reaction mixture containing the fastest reacting compound, 2-(*p*-trifluoromethylphenyl)ethyldimethylanilinium bromide. This situation was corrected by adding a few drops of acetic acid (0.12 N) to the dilution flasks before quenching.

the ratio 2.303/(a-b). Each kinetic experiment was carried out to 60 per cent reaction, except those of the deuterated p-methoxy-substituted salt which were only carried to 30 per cent reaction, and good linear plots were obtained for all reactions.

Data for a representative kinetic experiment for each compound and the appropriate plot of this data are given in the Appendix.

Tests for Carbon Scrambling in Olefin

2-(p-Anisyl)ethyldimethylanilinium-2,2-d_2 Bromide

The reaction of quaternary salt, 0.77 g (0.0023 mole) with sodium ethoxide (0.09 M) in ethanol (50 ml.) at 40°C was allowed to proceed to 66% completion. To the reaction mixture was added water (75 ml.) and the solution was extracted with four portions (25 ml.) of petroleum-ether 30°-60°. The petroleum layers were combined, washed with two aliquots (20 ml.) of water and dried over sodium sulfate. Most of the solvent was removed by distillation through a fractionating column of glass helices. The p-methoxystyrene, contaminated with some petroleum-ether, was analyzed by n.m.r. for deuterium at the terminal carbon. The analysis indicated 15 ± 2% deuterium incorporation at C_α.

2-Phenylethyldimethylanilinium-2,2-d_2 Bromide

The procedure described in the previous paragraph was applied to this salt. The salt, 0.48 g (0.0016 mole) was reacted with sodium ethoxide (0.06 M) to 99% completion of reaction. The n.m.r. analysis indicated no deuterium incorporation at C_α to ±5%.

2-(p-Anisyl)ethyltrimethylammonium-2,2-d_2 Bromide

The procedure applied for the anilinium salts was to this compound. The salt, 1.25 g (0.0045 mole) was reacted in a 100 ml. flask with sodium ethoxide (0.13M) to 82% completion of reaction. n-Pentane was used for extraction. The n.m.r. analysis indicated no deuterium incorporation at C_α to ±5%.

APPENDIX

Table XIII

Data for a Typical Kinetic Experiment in the Reaction of 2-Phenylethyldimethylanilinium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C

(Initial concs.: b=0.00650 m./1.; a=0.01272 m./.1)

Time min.	Optical Density	Dilution Factor	(x) m./1.	$\log \frac{a-x}{b-x}$
9.0	.350	50	.0064	.314
17.9	.321	100	.00116	.337
27.7	.458	100	.00166	.360
36.4	.548	100	.00198	.377
44.3	.637	100	.00231	.396
53.7	.295	250	.00267	.419
63.0	.331	250	.00300	.444
72.6	.358	250	.00325	.464
82.1	.387	250	.00351	.489

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.00237196\ \text{min}^{-1}$$

$$k = \frac{2.303 \times 0.00237196}{60 \times 0.00622}$$

$$= 1.46 \times 10^{-2}\ \text{l. mole}^{-1}\ \text{sec}^{-1}$$

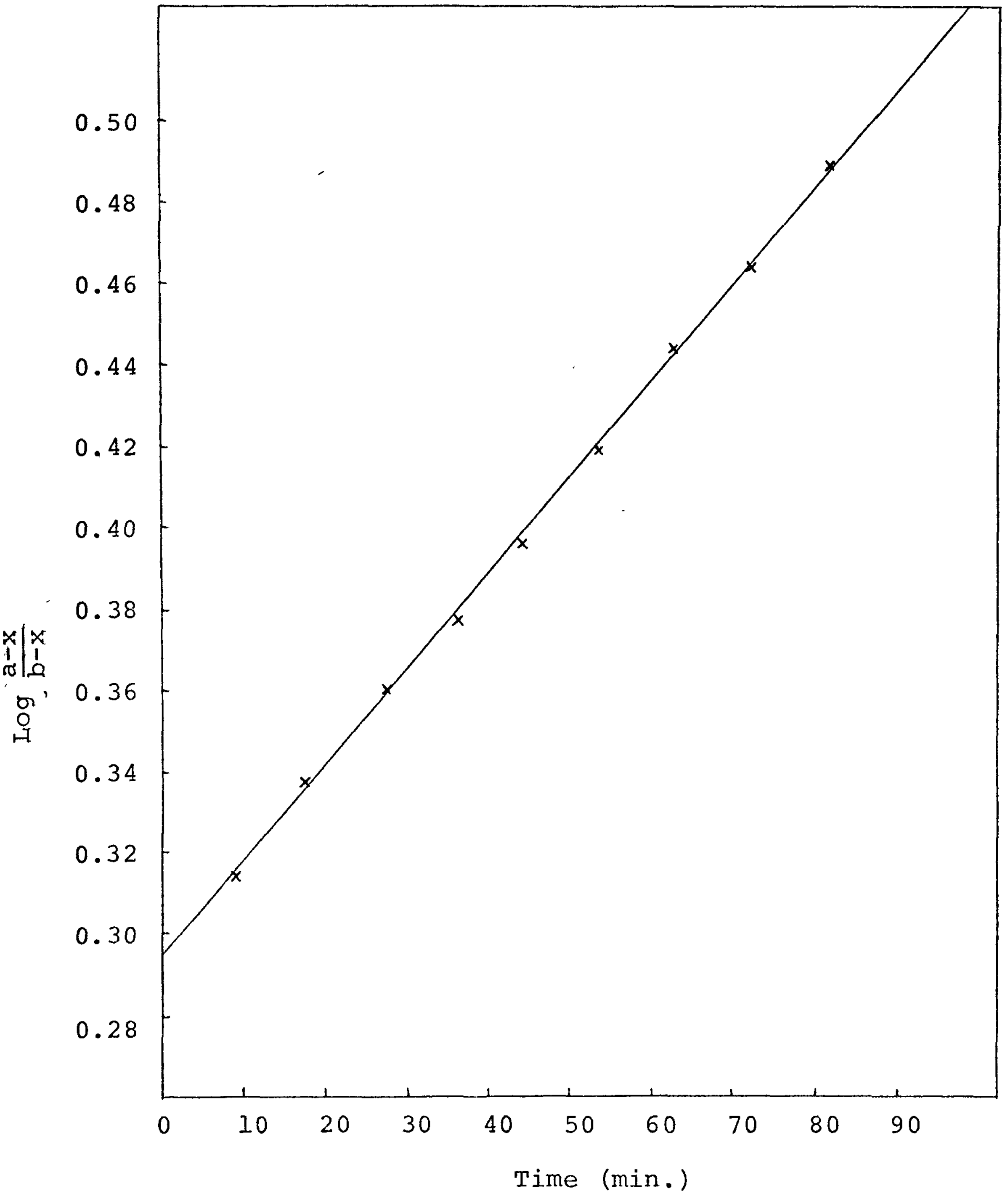

Fig.10 Plot of the kinetic data given in Table XIII for a typical kinetic experiment for the reaction of 2-phenylethyldimethylanilinium bromide and sodium ethoxide in anhydrous ethanol at 40°C.

TABLE XIV

Data for a Typical Kinetic Experiment in the Reaction of 2-Phenylethyldimethylanilinium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C.

(Initial concs.: b=0.00651 m./l.; a=0.01268 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
70.3	.261	100	.00094	.324
99.4	.347	100	.00126	.339
125.1	.420	100	.00152	.350
153.5	.487	100	.00177	.364
181.5	.558	100	.00202	.377
208.9	.610	100	.00222	.386
240.6	.270	250	.00245	.401
271.2	.296	250	.00269	.418
311.8	.325	250	.00295	.436

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.00457911\ \text{min}^{-1}$$

$$k = \frac{2.303 \times 0.000457911}{60 \times 0.00617}$$

$$= 2.86 \times 10^{-3}\ \text{l. mole}^{-1}\ \text{sec}^{-1}$$

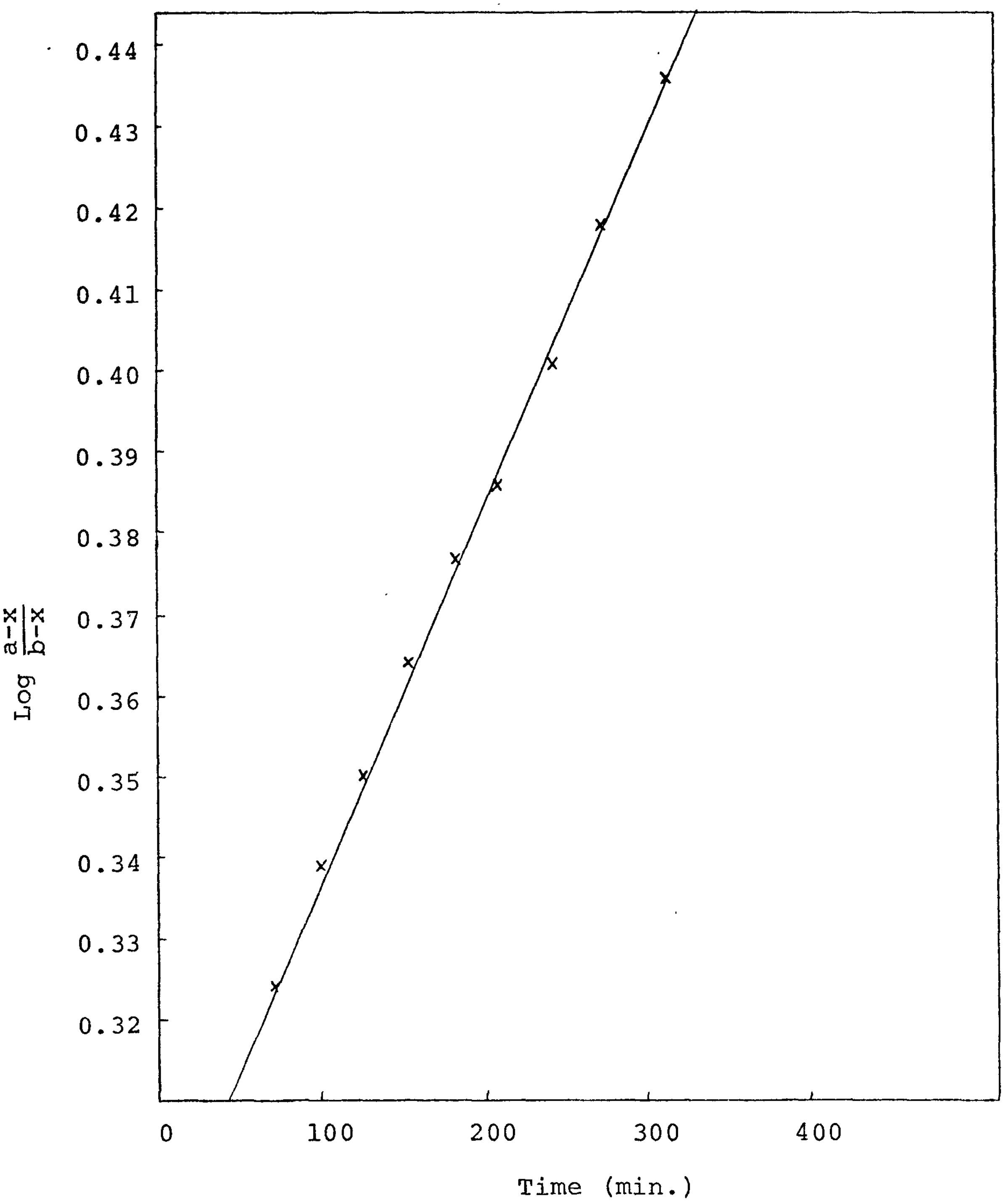

Fig.11 Plot of the kinetic data given in Table XIV for a typical kinetic experiment for the reaction of 2-phenylethyldimethylanilinium-2,2-$\underline{d}_2$ bromide and sodium ethoxide in anhydrous ethanol at 40°C

TABLE XV

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Chlorophenyl)ethyldimethylanilinium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C.

(Initial concs.: b=0.00648 m./l.; a=0.01271 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
3.24	.364	100	.00107	.332
4.02	.448	100	.00132	.342
4.90	.520	100	.00154	.354
5.67	.590	100	.00174	.365
6.58	.265	250	.00196	.377
7.57	.294	250	.00217	.387
9.66	.352	250	.00260	.417
11.63	.399	250	.00295	.442
13.60	.441	250	.00326	.468

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.0131132\ \text{min}^{-1}$$

$$k = \frac{2.303 \times 0.0131132}{60 \times 0.00623}$$

$$= 8.06 \times 10^{-2}\ \text{l. mole}^{-1}\ \text{sec}^{-1}$$

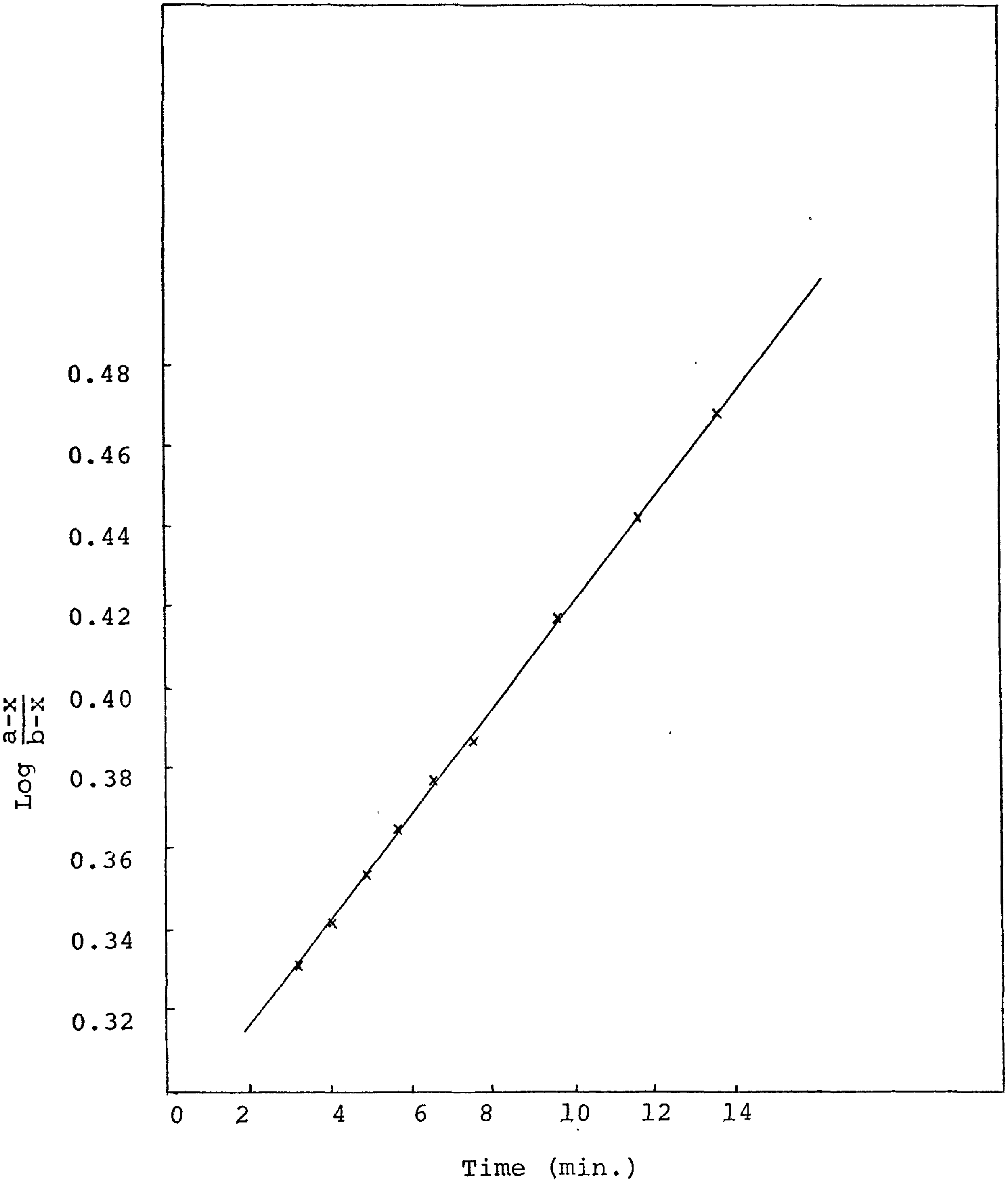

Fig. 12 Plot of the kinetic data given in Table XV for a typical kinetic experiment for the reaction of 2-(p-chlorophenyl)ethyldimethylanilinium bromide and sodium ethoxide in anhydrous ethanol at 40°C.

TABLE XVI

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Chlorophenyl)ethyldimethylanilinium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C.

(Initial concs.: b=0.00648 m./l.; a=0.01271 m./l.)

Time min.	Optical Density	Dilution Facto-	(x) m./l.	$\log \frac{a-x}{b-x}$
5.97	.340	50	.00050	.310
12.10	.313	100	.00092	.324
16.33	.402	100	.00119	.337
21.13	.492	100	.00146	.348
25.31	.570	100	.00169	.360
30.33	.648	100	.00192	.371
34.71	.291	250	.00215	.385
39.49	.320	250	.00237	.400
44.58	.342	250	.00253	.408
50.40	.372	250	.00275	.425
54.88	.391	250	.00289	.435
59.83	.416	250	.00308	.450

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.00259956 \text{ min}^{-1}$$

$$k = \frac{2.303 \times 0.00259956}{60 \times 0.00623}$$

$$= 1.61 \times 10^{-2} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

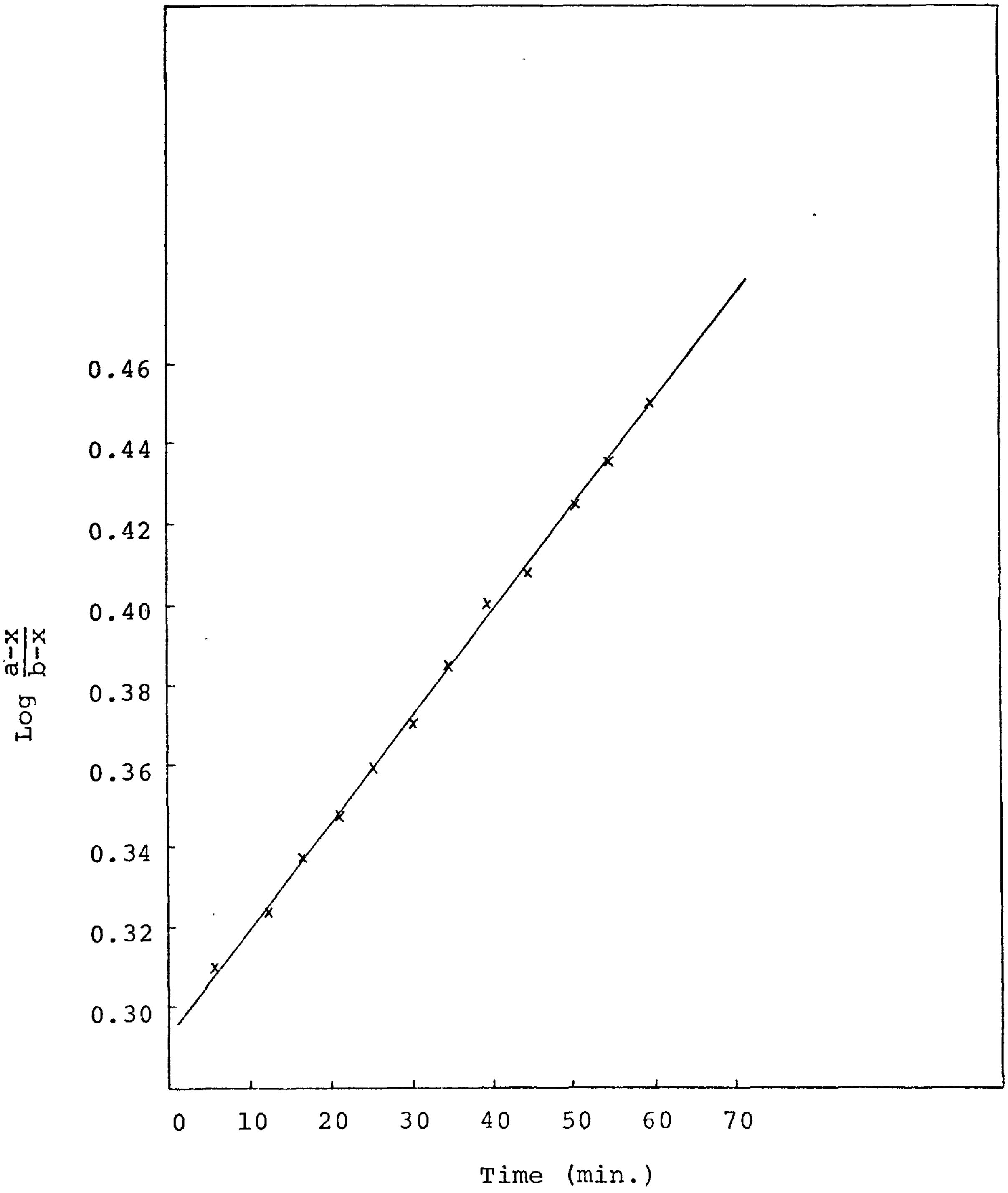

Fig. 13 Plot of the kinetic data given in Table XVI for a typical kinetic experiment for the reaction of 2-(p-chlorophenyl)ethyldimethylanilinium-2,2-d_2 bromide and sodium ethoxide in anhydrous ethanol at 40°C.

TABLE XVII

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Anisyl)ethyldimethylanilinium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C.

(Initial concs.: b=0.00650 m./l.; a=0.01274 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
40.2	.369	50	.00060	.314
79.8	.315	100	.00102	.330
120.9	.428	100	.00138	.346
159.8	.522	100	.00169	.360
189.3	.590	100	.00191	.375
239.9	.283	250	.00228	.395
280.1	.312	250	.00252	.410
319.9	.339	250	.00274	.425
360.0	.362	250	.00292	.438
400.0	.391	250	.00316	.458
459.8	.426	250	.00344	.483

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.000399014 \text{ min}^{-1}$$

$$k = \frac{2.303 \times 0.000399014}{60 \times 0.00624}$$

$$= 2.46 \times 10^{-3} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

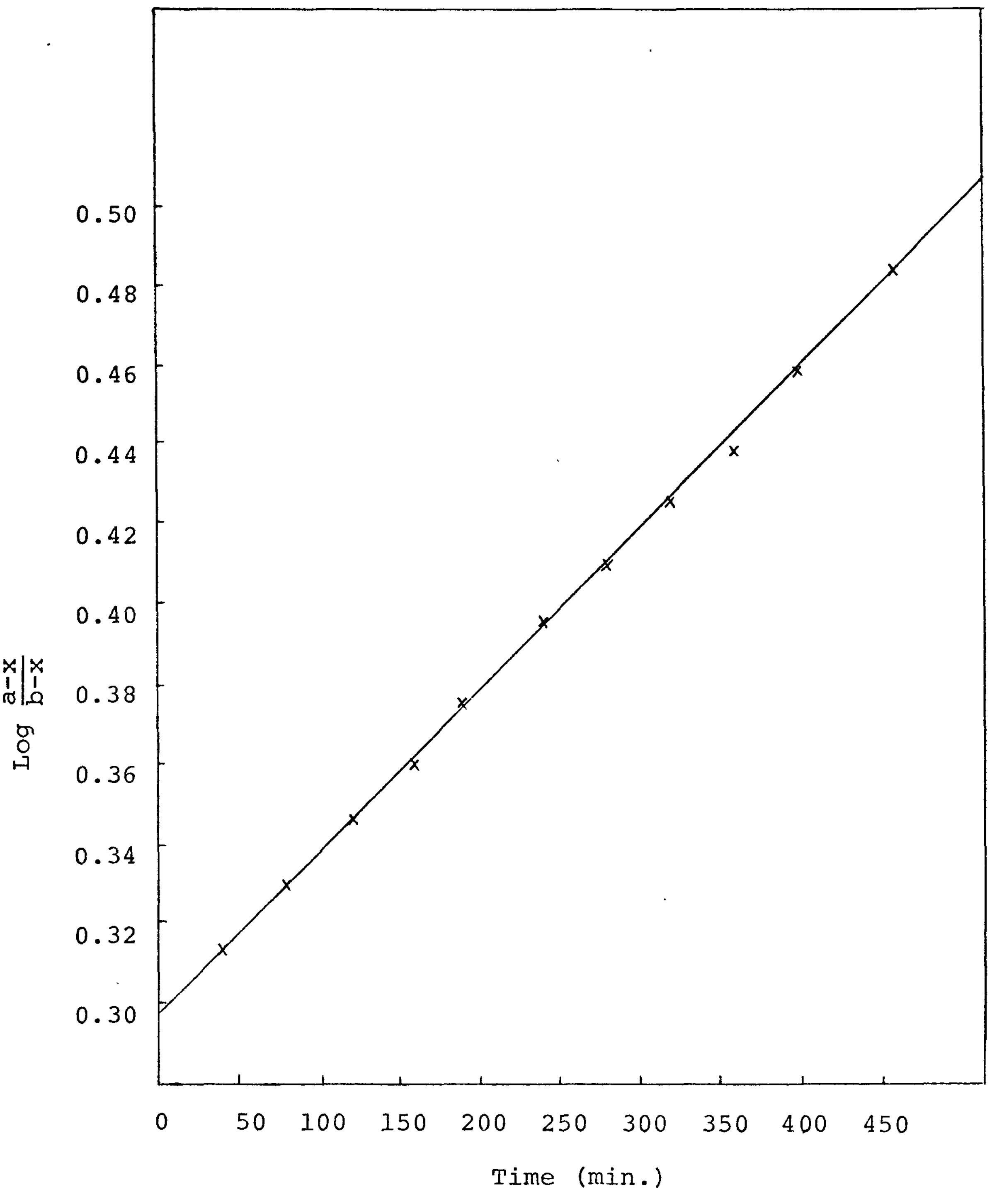

Fig. 14 Plot of the kinetic data given in Table XVII for a typical kinetic experiment for the reaction of 2-(p-anisyl)ethyldimethylanilinium bromide and sodium ethoxide in anhydrous ethanol at 40°C.

TABLE XVIII

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Anisyl)ethyldimethylanilinium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C.

(Initial concs.: b=0.00650 m./l.; a=0.01274 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
110	.305	50	.00051	.309
150	.381	50	.00063	.314
182	.449	50	.00075	.318
220	.491	50	.00081	.320
269	.578	50	.00096	.326
310	.323	100	.00107	.330
371	.360	100	.00119	.337
428	.399	100	.00133	.341
505	.455	100	.00151	.350
591	.509	100	.00169	.359
652	.541	100	.00180	.364
710	.580	100	.00192	.371
771	.607	100	.00202	.376

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.000100329 \text{ min}^{-1}$$

$$k = \frac{2.303 \times 0.000100329}{60 \times 0.00624}$$

$$= 6.16 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

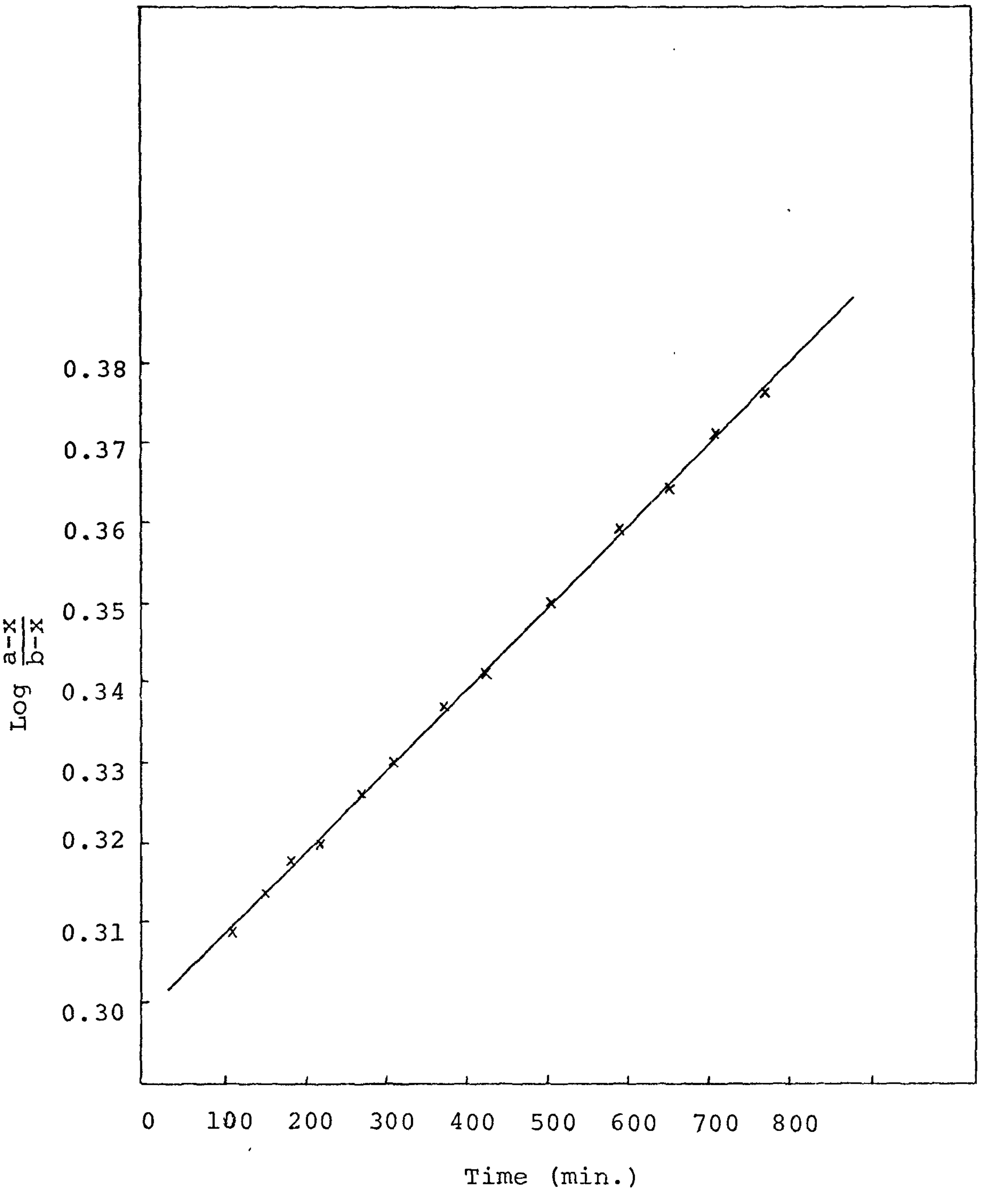

Fig.15 Plot of the kinetic data given in Table XVIII for a typical kinetic experiment for the reaction of 2-(p-anisyl)ethyldimethylanilinium-2,2-d_2 bromide and sodium ethoxide in anhydrous ethanol at 40°C.

TABLE XIX

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Trifluoromethylphenyl)ethyldimethylanilinium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 20°C.

(Initial concs.: b=0.00652 m./l.; a=0.01272 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
1.24	.392	50	.00065	.312
2.05	.292	100	.00096	.324
2.95	.383	100	.00126	.338
4.43	.510	100	.00168	.359
5.22	.585	100	.00192	.371
6.05	.649	100	.00213	.382
7.14	.292	250	.00240	.400
8.01	.315	250	.00259	.412
9.05	.343	250	.00282	.428
10.12	.361	250	.00297	.439
12.09	.401	250	.00330	.466
13.84	.434	250	.00356	.491

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.0142086 \text{ min}^{-1}$$

$$k = \frac{2.303 \times 0.0142086}{60 \times 0.00620}$$

$$= 8.80 \times 10^{-2} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

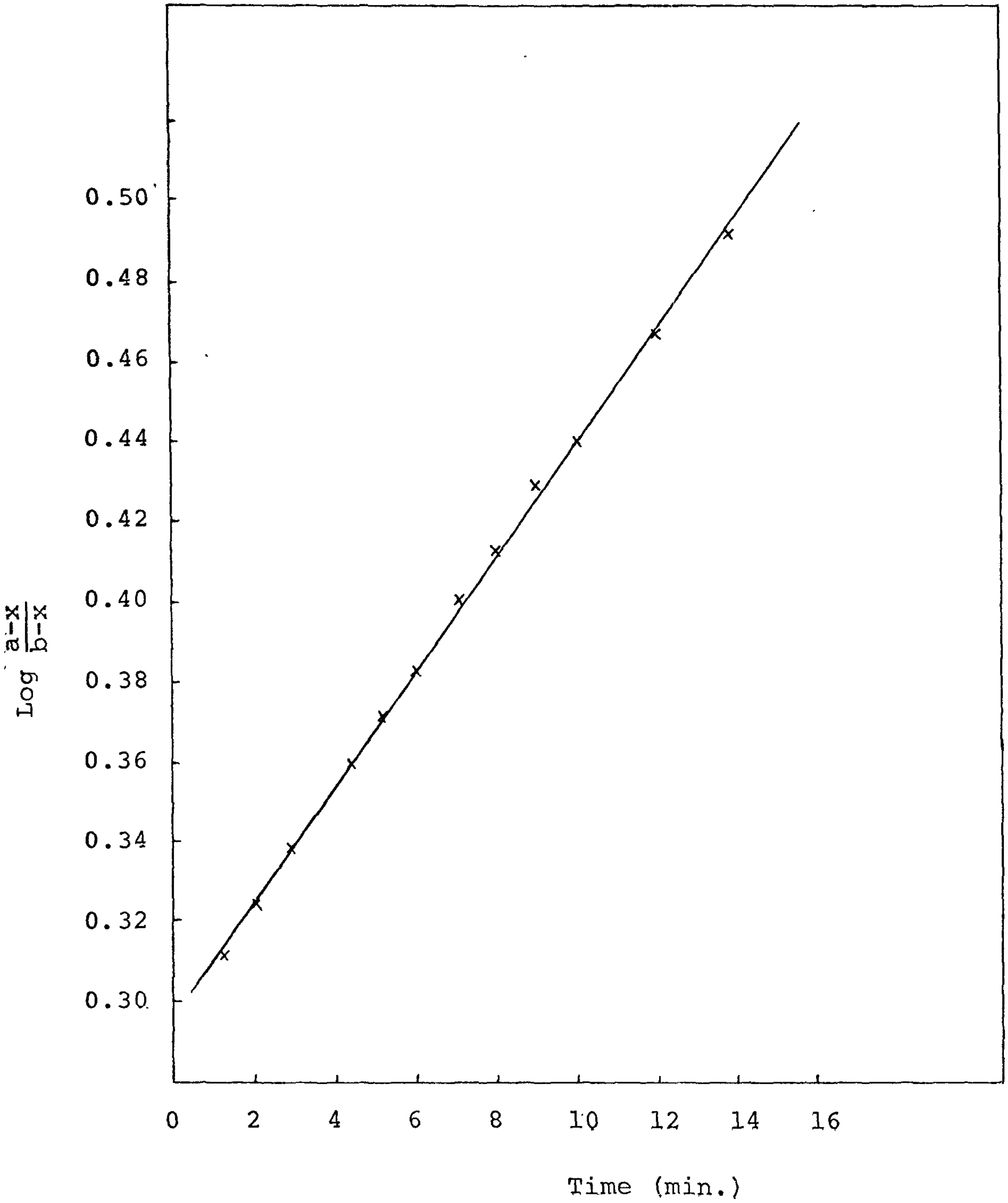

Fig.16 Plot of the kinetic data given in Table XIX for a typical kinetic experiment for the reaction of 2-(p-trifluoromethylphenyl)-dimethylanilinium bromide and sodium ethoxide in anhydrous ethanol at 20°C.

TABLE XX

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Trifluoromethylphenyl)ethyldimethylanilinium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at 20°C.

(Initial concs.: b=0.00650 m/l.; a=0.01272 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\text{Log}\ \frac{a-x}{b-x}$
4.88	.269	100	.00044	.305
12.10	.281	100	.00092	.325
17.14	.367	100	.00121	.339
21.38	.440	100	.00144	.347
26.59	.518	100	.00170	.362
32.09	.592	100	.00194	.373
38.26	.269	250	.00221	.390
43.35	.296	250	.00243	.401
49.52	.324	250	.00266	.418
55.74	.344	250	.00282	.430
66.08	.389	250	.00319	.459

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.00245912\ \text{min}^{-1}$$

$$k = \frac{2.303 \times 0.00245912}{60 \times 0.00622}$$

$$= 1.53 \times 10^{-2}\ \text{l. mole}^{-1}\ \text{min}^{-1}$$

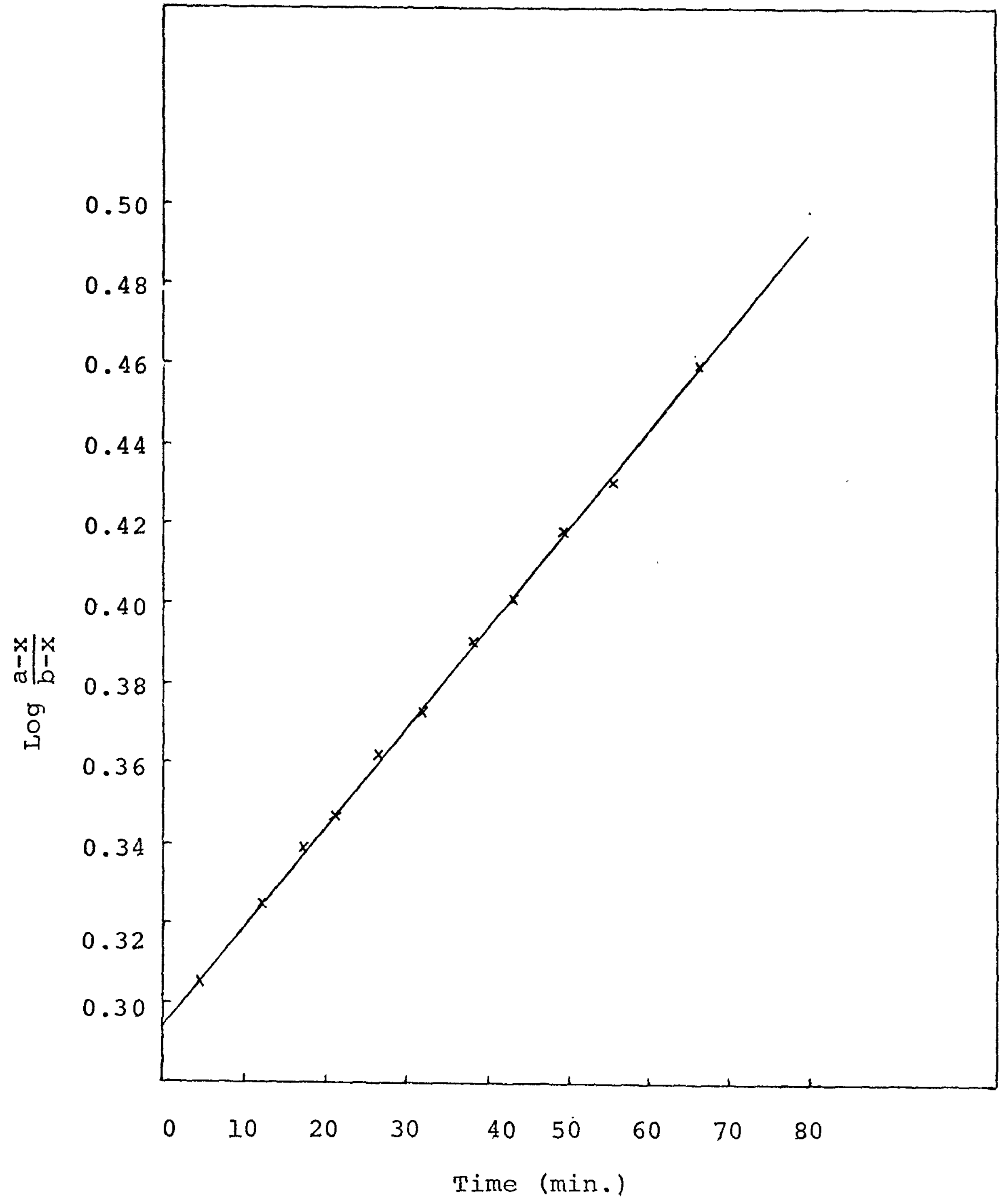

Fig.17 Plot of the kinetic data given in Table XX for a typical kinetic experiment for the reaction of 2-(p-trifluoromethylphenyl)-dimethylanilinium-2,2-d_2 bromide and sodium ethoxide in anhydrous ethanol at 20°C.

TABLE XXI

Data for a Typical Kinetic Experiment in the Reaction of 2-p-Trifluoromethylphenyl)ethyldimethylanilinium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 10°C

(Initial concs.: b=0.00650 m./l.; a=0.01273 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
5.09	.400	50	.00066	.316
9.26	.309	100	.00101	.330
13.18	.391	100	.00128	.340
17.64	.489	100	.00160	.356
21.40	.561	100	.00184	.367
25.58	.640	100	.00210	.384
30.33	.290	250	.00238	.400
36.15	.325	250	.00266	.419
41.66	.355	250	.00291	.438
48.13	.381	250	.00313	.455
55.57	.420	250	.00344	.481
60.84	.438	250	.00359	.497

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.00327735 \text{ min}^{-1}$$

$$k = \frac{2.303 \times 0.00327735}{60 \times 0.00623}$$

$$= 2.03 \times 10^{-2} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

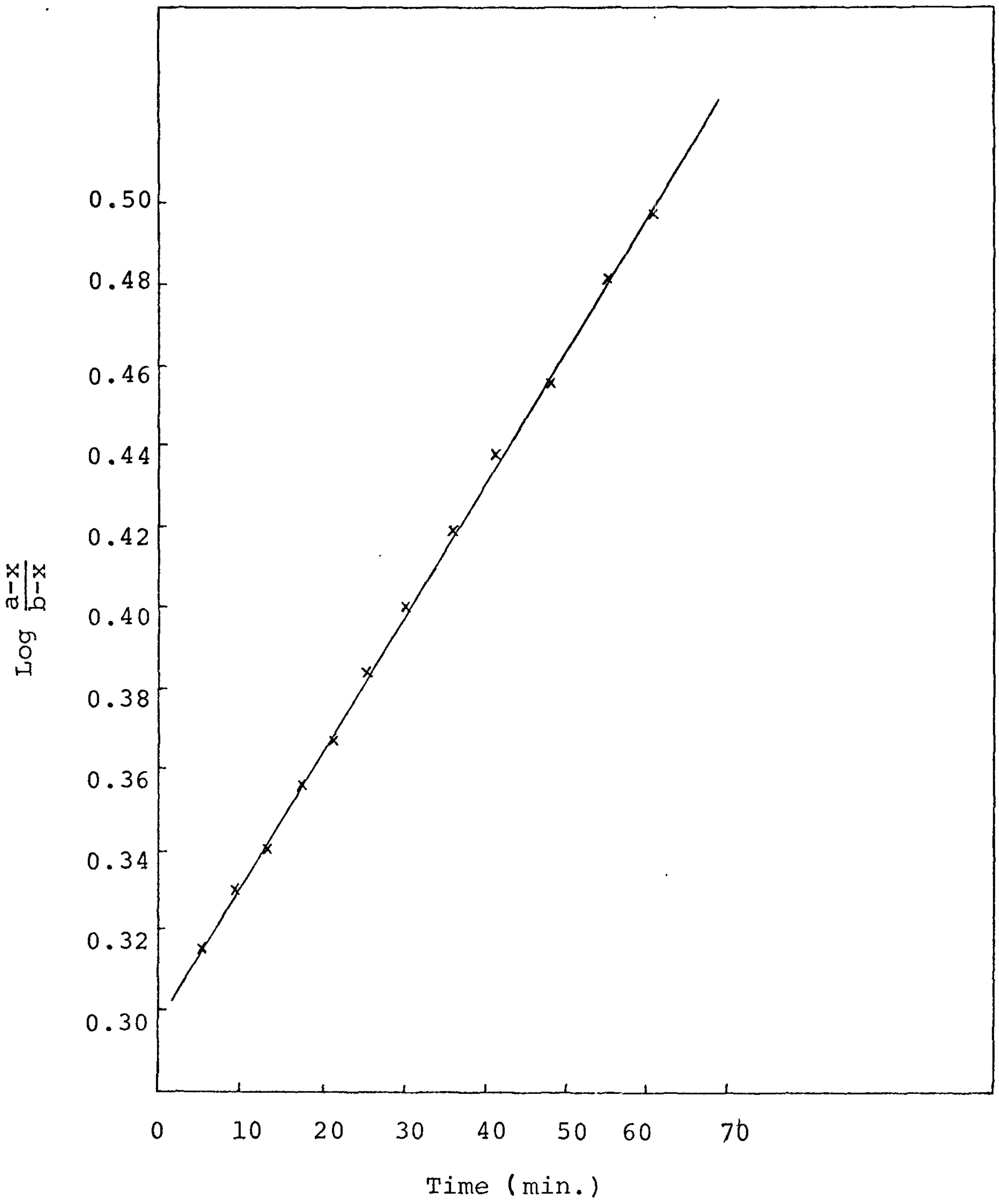

Fig.18 Plot of the kinetic data given in Table XXI for a typical kinetic experiment for the reaction of 2-(p-trifluoromethylphenyl)-dimethylanilinium bromide and sodium ethoxide in anhydrous ethanol at 10°C.

TABLE XXII

Data for a typcial Kinetic Experiment in the Reaction of 2-(p-Trifluoromethylphenyl)ethyldimethylanilinium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at $^{-2}$10°C

(Initial concs.: b=0.00649 m./l.; a=0.01273 m./l.)

time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
33.2	.385	50	.00063	.314
50.9	.272	100	.00089	.325
69.9	.349	100	.00115	.337
90.1	.430	100	.00141	.348
110.1	.499	100	.00163	.358
130.5	.571	100	.00187	.371
160.1	.260	250	.00213	.386
180.6	.285	250	.00233	.398
200.5	.311	250	.00255	.412
223.6	.331	250	.00271	.424

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.000572655 \text{ min}^{-1}$$

$$k = \frac{2.303 \times 0.000572655}{60 \times 0.00624}$$

$$= 3.51 \times 10^{-3}$$

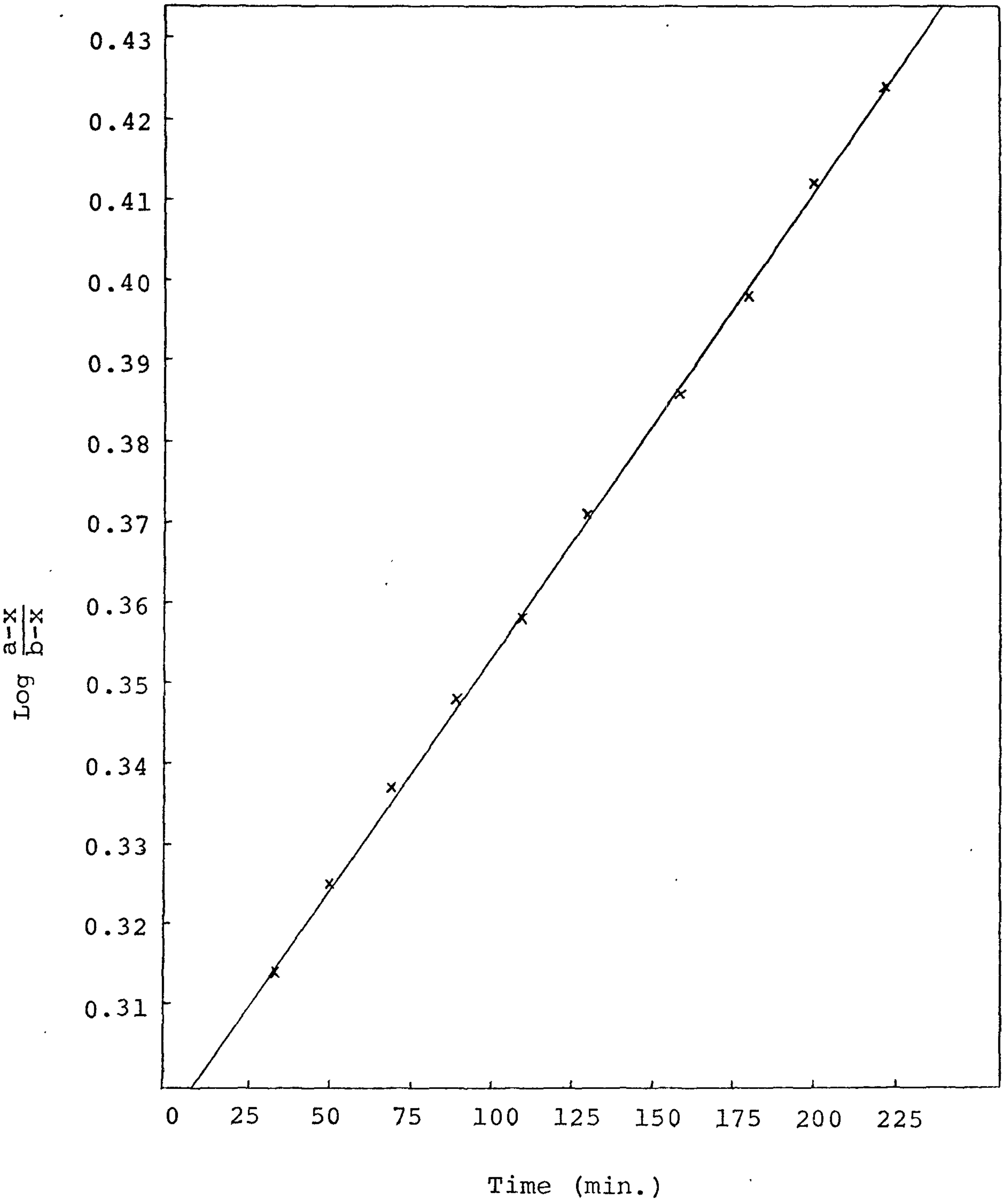

Fig. 19 Plot of the kinetic data given in Table XXII for a typical kinetic experiment for the reaction of 2-(p-trifluoromethylphenyl)-dimethylanilinium-2,2-d_2 bromide and sodium ethoxide in anhydrous ethanol at 10°C.

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