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THE PRIMARY HYDROGEN KINETIC ISOTOPE EFFECT IN THE
ELIMINATION FROM 2-PHENETHYL SYSTEMS.

A thesis presented in partial fulfilment of the
requirements for the degree of Master of
Science with Honours in Chemistry at
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ABSTRACT

The primary kinetic isotope effects for the base-catalysed E2 elimination from a series of substituted 2-phenethyl bromides and 2-phenethyldimethylsulphonium bromides in dimethyl sulphoxide-water as solvent at 20° have been measured. A broad maximum in the isotope effect was observed for the 2-phenethyl bromides. The Hammett ρ value for each reaction series at 20° has also been determined and both were large and positive. Arrhenius plots using the k_H/k_D ratios for each of the *p*-MeO substituted compounds at 20°, 30° and 40° were carried out to determine the importance of proton tunnelling in these reactions. The usefulness of the primary kinetic isotope effect as a measure of proton position in the E2 transition states for these reactions is discussed.

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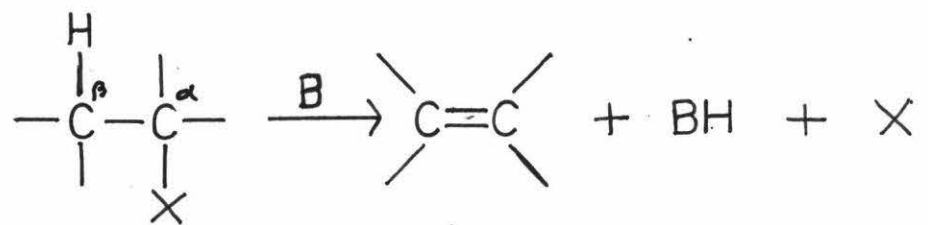
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1. INTRODUCTION

In recent years a considerable amount of data has been published concerning primary hydrogen kinetic isotope effects and their application to the elucidation of transition state symmetry in E2 elimination reactions. This has given rise to much theoretical speculation over the meaning attached to the observed trends. However, despite the quantity of data available, conflicting views have developed over the interpretation of the results. The work presented in this thesis is an attempt to resolve some of the uncertainty which surrounds this area of chemistry.

1.1 β-elimination reactions

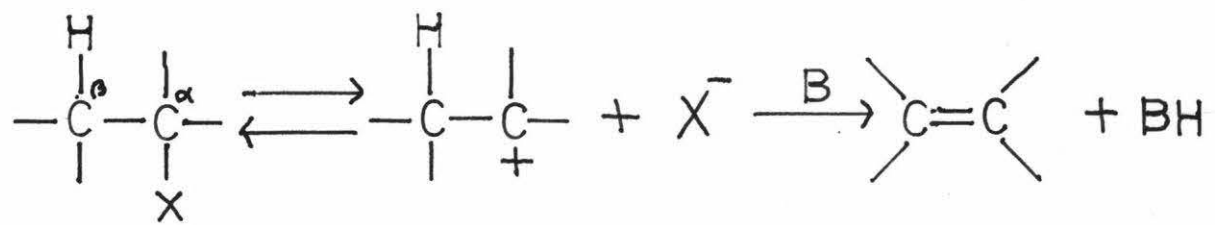
β-elimination reactions can be defined as those reactions in which two atoms or groups on adjacent carbon atoms are split off with consequent formation of a new carbon-carbon multiple bond. The overall reaction for the elimination of HX can be written as follows,



where B represents the base and X the leaving group. There are three basic types of mechanism for β-elimination reactions.

1.1.1 E1 mechanism

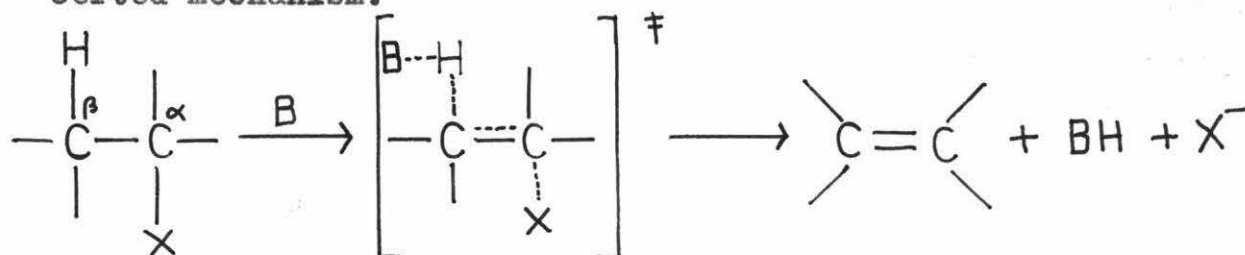
The C-H and C-X bonds are broken in separate steps. The first step involves reversible formation of a carbonium ion intermediate, while the second step involves irreversible loss of a β-proton to a base or solvent molecule.



The reaction kinetics are first order overall.

1.1.2

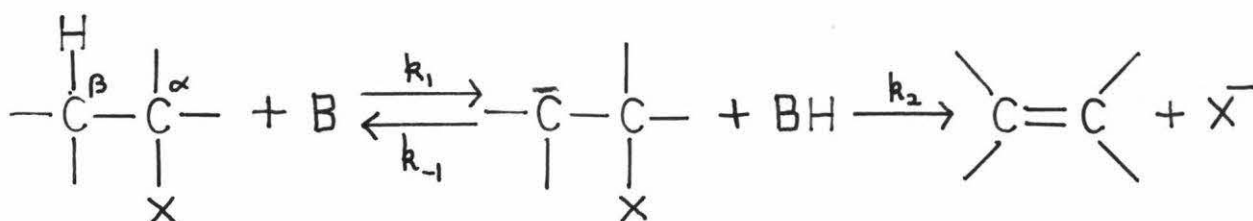
The C-H and C-X bonds are ruptured in the same step in a concerted mechanism.



In the transition state both the C-H and C-X bonds are partially broken, while the B-H and carbon-carbon double bonds are partially formed. The reaction kinetics are second order.

1.1.3 Elcb mechanism

This mechanism involves initial proton abstraction from the β -carbon to form a carbanion intermediate, followed by rupture of the C-X bond in a second step.



There are two possibilities within this mechanism. These are reversible carbanion formation ($k_1 \gg k_2$) and irreversible carbanion formation ($k_1 \ll k_2$).

1.2 Variable E2 transition state theories

In 1927 Ingold¹ raised the possibility that C-H and C-X bond breaking may not occur to equal extents in the E2 transition state. However, for many years afterwards the degree of rupture of these two bonds was treated as equal in the transition state, that is fully synchronous breaking was assumed to occur. In 1956 Cram² published evidence for varying E2 transition state geometry, which implied differences in the relative extents of C-H and C-X bond breaking and also in carbon-carbon double bond formation. Subsequently, there has been additional evidence to support the view that although the E2 mechanism is concerted it does not have to be entirely synchronous.

Bunnett (1962)³ developed a 'variable transition state' theory to account for experimental observations in E2 reactions. He proposed a whole spectrum of transition states which differ in the relative extents of C-X and C-H bond rupture.

1.2.1 E1-like transition state

This lies on one side of the transition state spectrum where C-X bond breaking is more advanced than C-H bond breaking. There is little double bond character in this transition state and the β -carbon has a partial positive charge. The transition state in this case approaches that for the first step of the E1 mechanism but differs from it in that the base is involved.

1.2.2 Elcb-like transition state

This transition state lies on the other side of the spectrum and involves a larger degree of C-H bond rupture than C-X bond rupture. The β -carbon therefore has a partial negative charge and again there is little double bond character. This transition state approaches that for the first step of the Elcb mechanism.

1.2.3 Central transition state

This transition state is intermediate between the two transition state extremes. The C-H and C-X bonds have equal degrees of rupture and considerable development of double bond character is proposed.

Thornton⁴ has proposed a theory which predicts the effects of substituent changes on the geometry of the E2 transition state. He also proposes a whole spectrum of transition states but these differ from the Bunnett theory in that they range from 'reactant-like' to 'product-like'. For a 'reactant-like' transition state there is little double bond character and little rupture of either the C-H and C-X bonds, whereas a 'product-like' transition state has much double bond character with extensive rupture of both the C-H and C-X bonds. However, there is disagreement between some of the predictions based on the Thornton theory and those of the Bunnett theory.

More O'Ferrall (1970)⁵ suggested that the progress of β -elimination reactions could be represented by a potential energy surface, with C-H distance along one axis and C-X distance along the other axis.

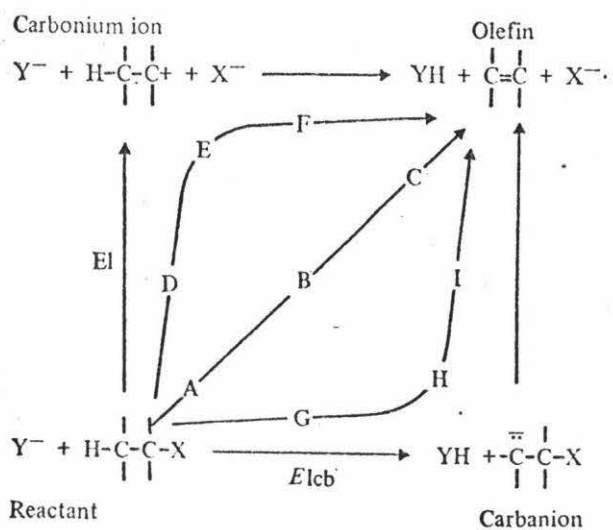
A schematic representation of the possible E2 mechanisms has been adapted from the potential surface diagrams of O'Ferrall by Fry⁶ (Figure 1). The E1cb mechanism is represented by movement along the horizontal C-H axis from the reactant origin to the carbanion, followed by vertical movement to the olefin. Vertical movement from the origin along the C-X axis to the carbonium ion followed by horizontal movement to the product represents the E1 mechanism. Diagonal movement corresponds to simultaneous breaking of the C-H and C-X bonds and represents the synchronous E2 mechanism. A whole spectrum of central transition states ranging from reactant-like to product-like can occur along the diagonal, one of which is represented by (B). An E1-like transition state can be represented by (E) and an E1cb-like transition state by (H). This approach can be used to predict the effect changes in leaving group, substituents, and reaction conditions will have on transition state structure.

1.3 Primary hydrogen kinetic isotope effect

For reactions in which a hydrogen bond is broken in the rate determining step different rates of reaction are observed if deuterium is substituted for hydrogen. This occurs because the mass difference between H and D atoms gives rise to a larger activation energy for the breaking of the deuterium bond compared to the hydrogen bond, hence giving a slower reaction rate for the deuterated compound. Proton transfer occurs in the rate determining step for all E2 reactions, hence a kinetic isotope effect should be observed in all cases. From theoretical considerations, based on the loss of stretching vibrational frequency for the C-H and C-D bonds in the transition state, the primary kinetic isotope effect expressed as a k_H/k_D rate ratio should be approximately 6.9⁷. However, there are many experimental observations which show considerable variation in the kinetic isotope effect with values both greater and less than the theoretical value. Westheimer⁸ proposed a theory

Figure 1.

Adapted More O'Ferrall potential surface diagram.



(From Fry, A., Chem.Soc.Rev., 1,
189 (1972.))

to explain low k_H/k_D ratios which was based on a simple linear three-centre model for the transition state. This theory predicts that the maximum isotope effect will only be observed for symmetrical transition states, with a progressive decrease in the k_H/k_D ratio as the transition state becomes more asymmetrical. Thus, for a reaction which involves the transfer of a proton to a base in the rate determining step, the k_H/k_D ratio should be a maximum when the proton is half-transferred in the transition state, and show lower values when the proton is either closer to the base or to the substrate. Theoretical predictions based on multi-centre models^{9,10} also suggest that a maximum will be observed when the proton is about half-transferred in the transition state but there is no general agreement over the size of this maximum.

Bell (1966)¹¹ suggested that information about transition state symmetry could be obtained indirectly. For the transfer of a proton from an acidic substrate (SH) to a base (B) it was considered reasonable to assume that the transition state symmetry could be related to the expression,

$$\Delta pK = pK_{(SH)} - pK_{(BH)}$$

where $pK_{(SH)}$ refers to the acid strength of the substrate and $pK_{(BH)}$ refers to the acid strength of the conjugate acid of the base. When $\Delta pK = 0$ the proton should be half-transferred and so the transition state is symmetrical. For this case the k_H/k_D ratio should be at its maximum value. If ΔpK has a positive or negative value, the transition state should be asymmetrical with a consequent lower than maximum kinetic isotope effect. Therefore, in theory a plot of k_H/k_D versus ΔpK for such a system should produce a 'bell-shaped' curve with the k_H/k_D ratio passing through a maximum when $\Delta pK = 0$. An apparent maximum has experimentally been observed for proton removal from nitroalkanes¹², but this data has been criticised by Bordwell¹³ as being inconclusive. Bordwell maintains that either k_H/k_D is relatively insensitive to transition state symmetry or that the transition state symmetry does not appreciably change over wide ranges of ΔpK in systems studied so far.

1.3.1 Proton tunnelling

From the quantum mechanical viewpoint the wave nature of the proton suggests that there is a finite probability that some protons with less energy than the required activation energy can still react by tunnelling through the energy barrier. The probability for tunnelling by a deuteron is much less than for a proton, hence the k_H/k_D ratio can be larger than the theoretical maximum because of tunnelling effects. Bell (1970)¹⁴ has suggested that the kinetic isotope effect is in fact primarily determined by proton tunnelling, thus allowing changes in the k_H/k_D ratio to occur even though the proton position may remain unchanged over a wide ΔpK range.

The importance of proton tunnelling can be determined by considering the Arrhenius parameters for the reaction. From a plot of $\log(k_H/k_D)$ versus $(1/T)$ (where T is absolute temperature) the difference in activation energies for the proton and deuteron ($E_a^D - E_a^H$) can be calculated from the slope. The intercept gives the value of $\log(A_H/A_D)$. Proton tunnelling probably occurs if the value for $(E_a^D - E_a^H)$ is appreciably greater than the theoretical maximum value based on loss of stretching vibration of the C-H and C-D bonds in the transition state¹⁵. Proton tunnelling is also indicated if the A_D/A_H ratio is significantly greater than unity.

1.4 Hammett equation

The effect of meta or para substituents in a benzene ring on sidechain reactions has been correlated by the Hammett equation. The original form of the equation was,

$$\log \frac{k}{k_0} = \rho \sigma$$

where k is the rate constant for the sidechain reaction of a meta- or para-substituted benzene derivative, k_0 is the rate constant for the unsubstituted benzene derivative, σ is a substituent constant which is dependent on the substituent and its position in the benzene ring, and ρ is a reaction constant which is dependent on the nature of the substrate, on the reaction itself, and on the reaction conditions. A

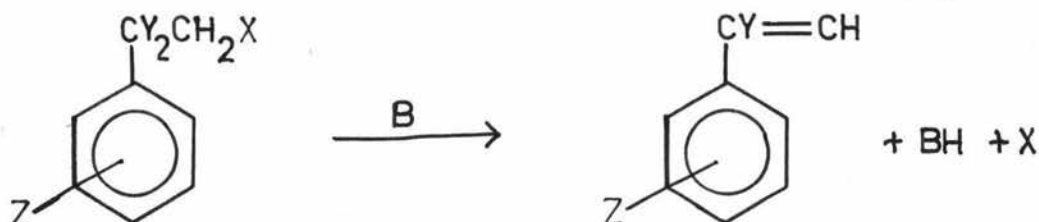
negative value for ρ indicates that the reaction involves the development positive charge in the transition state as it is assisted by electron releasing substituents. A positive ρ value indicates the development of negative charge in the transition state for the rate determining step.

Deviations from the Hammett correlation can occur when there is direct resonance interaction between the benzene ring para-substituents and the sidechain. Different standard reaction series can be used to allow for the effects of these interactions. When a sidechain can donate electrons by resonance interaction (+ M) to a benzene ring that contains a para (- M) substituent, then the reactivities can be better correlated by the σ^- parameters based on the ionization of anilines as the standard reaction series.

For β -elimination reactions a substituted benzene ring on either the α -carbon or β -carbon can be used to obtain a Hammett plot by varying the substituents. The ρ value so determined gives an indication of whether the transition state is positively or negatively charged, and hence gives some information on the relative extents of C-H and C-X bond breaking in the transition state.

1.5 Elimination from 2-phenethyl systems

The 1,2-elimination of HX from 2-phenethyl compounds under basic conditions can be written in the following general form,



where Z = meta- or para-substituent, Y = H or D, and X represents the leaving group. The elimination exhibits second order kinetics and reported ρ values are positive, thus it appears that the E2 transition state is carbanionic in character. It has been found¹⁶ that as the leaving group becomes progressively poorer along the series X = Br, OTs, SMe_2^+ and NMe_3^+ the ρ values for elimination in ethanol-ethoxide increase, being +2.14, +2.27, +2.75 and +3.77

respectively. This trend indicates that the transition state is becoming more carbanionic and thus would be expected to be accompanied by an increase in the ratio of C-H to C-X bond breaking. The kinetic isotope effect has been measured for this series and the k_H/k_D ratios observed were 7.11, 5.66, 5.07 (at 30°) and 2.98 (at 50°) respectively¹⁶. These figures have been commonly interpreted as indicating an increasing degree of proton transfer to the eliminating base as the transition state becomes more carbanionic in agreement with the variable transition state theory. However, there is disagreement about what these figures mean as regards to the extent of the proton transfer because of the inherent ambiguity in isotope effects which are smaller than the maximum.

It should also be possible to alter the character of the transition state by keeping the leaving group constant and varying the β -aryl substituent, as this would be expected to affect the acidity of the β -hydrogens. If the isotope effect is reflecting the extent of proton transfer it would be expected that it would either increase, decrease, or perhaps exhibit a maximum as the aryl substituent became progressively more electron-withdrawing. Blackwell et al¹⁷ have studied the effect of substituents on the k_H/k_D ratio for the elimination from a series of substituted 2-phenethyl bromides in tert-butyl alcohol with tert-butoxide base. The aryl substituents for the series were Z = p-MeO, H, p-Cl, m-Br, m-NO₂ and p-NO₂. However, no significant change in the magnitude of the isotope effect was observed.

A study of the change in the kinetic isotope effect caused by increasing the dimethyl sulphoxide (DMSO) concentration in the tert-butoxide catalysed elimination from 2-phenethyl bromide has been carried out by Cockerill et al¹⁸. Again, no change was observed in the isotope effect as the DMSO concentration was increased. Cockerill¹⁹ has studied the effect of varying DMSO concentrations on the hydroxide ion catalysed elimination from 2-phenethyldimethylsulphonium bromide in water. Significant changes in the isotope effect were observed when the DMSO concentration was varied from 0% to 84%. Over this

range the k_H/k_D ratio increased to a maximum then decreased again. The ρ value for this reaction was found to be positive with a value of 2.11 in water at 50°, but this value increased rapidly as DMSO was added until a solvent composition of 20% DMSO was reached. The ρ value showed little further change as more DMSO was added after this point.

1.6 Present work

It was decided to study substituent effects on the k_H/k_D ratio for hydroxide ion catalysed elimination from substituted 2-phenethyldimethylsulphonium bromides in DMSO-water in the hope of observing a maximum in the isotope effect. A maximum in the isotope effect for the unsubstituted compound had previously been observed by Cockerill, as noted on page 9, but he did not carry out any substituent effect studies. The effect of substituent changes on the 2-phenethyl bromides in this system was also studied in order to determine whether substituent effects on the k_H/k_D ratio depend on the base-solvent system and/or the leaving group. The solvent composition used was 50.2 mole % DMSO because, according to the work of Cockerill, this appears to be where the k_H/k_D ratio is at a maximum for 2-phenethyldimethylsulphonium bromide. It was expected that any changes in k_H/k_D caused by changes in the β -aryl substituent would be more apparent if the size of the isotope effects themselves were large rather than small.