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The Mechanism of the β-Elimination Reaction

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The latest studies on the mechanisms of the β-elimination reaction are considered and described systematically. The use of stereochemical and isotope effect data for the recognition of different types of reaction mechanisms is discussed. The bibliography includes 232 references.

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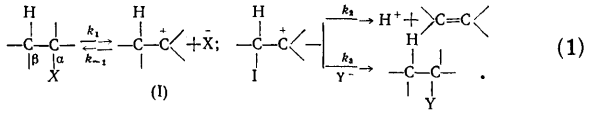
I. INTRODUCTION

Systematic research on the β-elimination mechanism began in 1927 when Ingold[1] attempted to investigate reactions of this type. Subsequently numerous studies devoted to the elucidation of the details of the mechanism were carried out[2-12]. All the mechanisms of the elimination reactions were divided into three classes[1-6]: *E*1, *E*2, and *E*1c*B*, in which the C–H bond is dissociated after, simultaneously with, or before the dissociation of the C–X bond respectively. There are also certain other less thoroughly investigated types of mechanisms.

II. THE *E*1 MECHANISM

1. General Characteristics of the β-Elimination Reaction via the *E*1 Mechanism

In 1935 Hughes[13] investigated a mechanism in which the slow stage is the ionisation of the initial reactant (substrate) preceding the rapid decomposition of the resulting carbonium ion. This unimolecular mechanism was called the *E*1 mechanism:



(1)

The carbonium ions (I) formed in the slow stage are subsequently consumed both in the elimination reaction and in nucleophilic substitution as a result of the interaction with the solvent molecules Y (or YH) or with other nucleophiles Y^- in the medium.

The occurrence of the reaction via the *E*1 mechanism is favoured by a molecular structure and media such that heterolysis of the C–X bond is faciliated[14]. In particular, the structural characteristics of the molecule, promoting the stabilisation of carbonium ions, play an important role[10,15]. For this reason, reactions via the *E*1 mechanism are more characteristic, for example, of tertiary, secondary, and α-aryl-substituted halides than of primary halides. Since the ability to carry a full positive charge is not characteristic of carbon atoms, stable carbonium ions have as a rule structures permitting extreme delocalisation of the positive charge[10,15]. The most important external factor, promoting a decrease of the positive ionic charge on carbon atoms, is solvation, because the vacant orbitals of the carbon atoms interact with the non-bonding electrons of the solvent molecules. Indeed, polar solvents promote the formation of carbonium ions and facilitate a reaction via the *E*1 mechanism, which competes in fairly strongly solvating but weakly nucleophilic media not only with the bimolecular *E*2 mechanism but also with the S_N1 mechanism. The elimination of toluene-*p*-sulphonic acid from *exo*-norbornyl toluene-*p*-sulphonate under the influence of a strong base in hydrocarbon solvents proceeds "purely" via the *E*2 mechanism. The same reaction in a tertiary alcohol involves predominantly the *E*1 mechanism[16]. The rates of the *E*1 reaction for menthyl and neomenthyl toluene-*p*-sulphonates in aprotic polar solvents vary in parallel with the dielectric constant of the solvent[17].

If the eliminated group X is an anion, its solvation by solvent molecules facilitates to a considerable degree the heterolysis of the C–X bond. In this case a smaller ion (for example Cl^-) will be solvated more effectively than a more diffuse ion (for example Br^-). When X is varied in the reactions of t-BuX in ethanol at 75°C, the ratio of the yield of the olefin to that of the substitution products increases in the sequence $\overset{+}{S}Me_2$ (0.18) < I (0.32) < Br (0.36) < Cl (0.44). When ethanol is replaced by acetic acid, the ratio changes in the same sequence, but to a more marked extent: from 0.12 for $\overset{+}{S}Me_2$ to 0.73 for Cl.[18] Since the solvation of anions is very important, weakly acid solvents (which interact with anions via hydrogen bonding) have a more ionising effect than basic solvents.

Since the carbonium ions formed as a result of the reversible heterolysis of the C–X bond can interact with the solvent, it is necessary that the β-hydrogen atoms should be split off rapidly. In the general case this last reaction stage has a low activation energy (~4 kcal $mole^{-1}$) and is highly exothermic; it is also favoured by the presence of substituents which are capable of being conjugated with the double bond formed.

If the rate of the carbonium ion formed in the slow stage of the reaction is decided in the subsequent rapid stages involving the elimination of a proton or interaction with the solvent, then the yield of the elimination product (as well as the ratio of the isomers if the latter are formed) should not depend on the nature of X for the given alkyl. Indeed this is approximately true for t-butyl, t-pentyl, s-octyl, and menthyl halides and the corresponding 'onium compounds in aqueous solvents[19]. In a series of t-butyl compounds whose ionisation potential varies by

a factor of 900 the same relative yield of the olefin are obtained throughout the series with a variation of ±15%. Under these conditions, the carbonium ion decomposes immediately, although the counterion (leaving ion) is still very close; it is actually possible that the two ions form an unseparated ion pair. In media with high dielectric constants, such as nitromethane and acetonitrile, the ions acquire considerable freedom and even the above slight difference (15%) in the yields of the olefin vanishes.

Thus the $E1$ mechanism is preferred, provided that all or some of the following conditions are fulfilled: the presence at the α-carbon atom of substituents which may delocalise the positive charge on this atom and can become involved in conjugation with the double bond formed between the α- and β-carbon atoms; an enhanced capacity of the leaving group for ionisation; the presence of a highly solvating medium; the absence of a strong base which alters the mechanism to $E2$. All these conditions promote the heterolysis of the α-C–X bond without the simultaneous cleavage of the β-C–H bond.

2. Stereochemistry of Elimination Via the $E1$ Mechanism

As early as 1940, Hückel [20] showed that the stereochemistry of β-elimination depends on the reaction mechanism. Subsequently Hughes and Ingold [21] developed on the basis of stereochemical rules a theory of $E1$ and $E2$ reactions on which all subsequent studies of the stereochemistry of the elimination reaction are based.

The $E1$ reaction proceeds via a carbonium ion, the formation of which requires only the solvation of one carbon atom attached to the substituent, which is split off and the solvation of the substituent itself. The neighbouring carbon atom is not affected in this process. The second stage of the reaction, involving the elimination of a proton from a neighbouring carbon atom, does not impose special steric requirements, since the carbonium ion has a planar structure. For this reason, both *cis*- and *trans*- hydrogen atoms can participate in the $E1$ reaction. The relative amounts of olefins formed then frequently correspond to the thermodynamic stabilities, i.e. Zaitsev's [Saytzett's] rule holds. However, this rule cannot always be applied to elimination via the $E1$ mechanism, since in reality the situation is much more complex. The main aim of the examples quoted beflow is to give a general idea of the trend in research in this field.

The solvolysis of cyclopentyl derivatives proceeds at an unusually high rate (compared with acyclic and cyclohexyl analogues) [22,23], but in the majority of the published studies the yield of elimination products is not quoted. The studies by Hückel and coworkers [24], devoted to the alcoholysis of cyclopentyl toluene-*p*-sulphonate, permit the following conclusions: the reaction involves mainly the formation of ethers with a slight admixture of cyclopentenes; *cis*- and *trans*-2-alkylcyclopentyl toluene-*p*-sulphonates give rise to a large amount of cyclopentenes in which the Δ^1-isomer predominates; the *cis*-isomers react faster than the *trans*-isomers and gives a greater amount of the olefin. The stage determining the structure of the final product in these reactions is apparently the formation of an ion pair.

Analysis of the relative rates of solvolysis of isomeric monosubstituted cyclohexyl arenesulphonates is outside the scope of the present review, but it is discussed in detail in other reviews [22,23]. It is sufficient to say that the ratio of the rates of acetolysis, formolysis, and alcoholysis of axial 3- and 4-alkylcyclohexyl toluene-*p*-sulphonates to the rates of reaction of their equatorial analogues is of the order of 3.2–3.9. [25] The ratio of the rates involving the 3-substituted compounds does not differ greatly from the ratio of the rates for the conformationally similar 4-substituted analogues. The fact that the solvolysis of the axial toluene-*p*-sulphonate is faster may be attributed to the removal of steric hindrance on ionisation. This explanation presupposes that the two transition states for the ionisation of the axial and equatorial leaving groups can have different free energies, but the difference should be smaller than the difference between the free energies of the ground states. This approach appears to be quite reasonable [26].

The second factor responsible for the preferential ionisation of the axial leaving group compared with the equatorial group is that the positive charge formed is stabilised by the electronic interaction with the neighbouring β-C–H axial bond. This stabilisation can be regarded as a consequence of hyperconjugation or as a result of the involvement of the hydrogen atom in the stabilisation [27]. Whatever the nature of this stabilisation, it cannot be the decisive factor in the rate-limiting transition state in the formation of the cation as a result of the elimination of the equatorially oriented leaving group in the case of the chair conformation of the substrate, because the maximum effect requires the *trans*-orientation of the β-hydrogen and of the leaving group [26].

Examination of literature data [19,27-29] permits the conclusion that the E/S_N ratio in the $E1$ reaction involving *cis*-2-alkylcyclohexyl derivatives is greater than for the *trans*-isomers, while *anti*-elimination yields exclusively the Δ^1-cyclohexene. The last effect is a consequence of the particular geometry of the six-membered ring (compared with the acyclic compound) and the greater stabilisation of the carbonium ion owing to the formation of a hydrogen bridge or hyperconjugation with the axial hydrogen atom in the β-position. As regards the *trans*-isomers, it appears that both *trans*-cyclohexyl and *trans*-4-t-butylcyclohexyl arenesulphonates are solvolysed, passing through the "twist" conformation in the transition state. The study of secondary isotope effects in the acetolysis of β-deuterated *trans*-4-t-butylcyclohexyl brosylates [27] and cyclohexyl toluene-*p*-sulphonates [30,31] as well as certain other data [32-34] lead to the same conclusion.

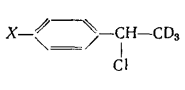
3. Isotope Effects in $E1$ Elimination

In principle, all three mechanisms of the β-elimination reaction can be distinguished by studying isotope effects [35]. More detailed differences within the limits of these broad classes can be effectively investigated by measuring the relative isotope effects for related compounds. Theoretical predictions and experimental findings obtained in the study of the isotope effects for the main types of mechanisms are given below. These predictions are qualitative and are based on the assumption that isotope substitution at the atom at which the type of bond is altered as a result of activation leads to an isotope effect (see, for example, Melander [36]). For more exact predictions, detailed calculations must be resorted to [37-40].

In the case of the $E1$ mechanism the primary isotope effect should be observed for a labelled group X and α-carbon [see scheme (1)], but not for labelled β-carbon and α- and β-hydrogens. Secondary isotope effects should be observed for α-hydrogens and for β-hydrogens

not involved in the reaction. The carbonium ion (I) is a reactive intermediate species and appreciable β-carbon and α- or β-hydrogen isotope effects should not be observed in its decomposition[41]. If the reaction of (I) with Y has a high activation energy, then an isotope effect (slight or possibly even negative, since a bond is formed) should be observed when a labelled Y is used. The few available literature data on the isotope effect for a labelled group X are in the main consistent with the above predictions[42-49]. Numerous examples of α-hydrogen isotope effects in solvolytic and other substitution reactions have been published[50,51]. It has been shown that $E1-S_N1$ reactions have higher α-hydrogen isotope effects ($k^H/k^D = 1.15$ at 25°C) compared with the expected value, which corresponds to an appreciable weakening of the α-C–H bond in the activation process. One may assume that the elimination (or substitution) reactions in which α-hydrogen isotope effects differing markedly from the limiting values of the k^H/k^D ratio (at 25°C ~1.22 for X = F, ~1.55 for X = Cl, ~1.125 for X = Br, ~1.09 for X = I, and ~1.22 for X = OTs)[53] are manifested involve at least partially a mechanism different from $E1$ or S_N1.

The occurrence of a β-hydrogen isotope effect in $E1$ reactions has been demonstrated[51-57]. This can be accounted for by hyperconjugation—the delocalisation of sp^3-s electrons of the β-C–H bond over the α-p orbitals being formed. One might expect that the stabilisation by hyperconjugation of the positive charge generated on the α-carbon atom plays a smaller role when the positive charge is conjugated with a benzene ring, particularly one containing an electron-donating group, which thus leads to a decrease of the β-hydrogen isotope effect. The results of studies confirming this conclusion in relation to the solvolysis of 1-aryl-1-chloroethanes are listed below[51]:



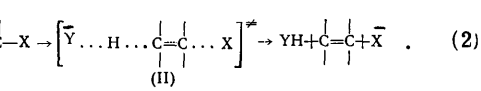
X	k^H/k^D
CH_3O	1.113
CH_3	1.200
H	1.224
NO_2	1.15
F	1.211

The standard value of the β-hydrogen isotope effect for the CH_3 group (data for t-butyl chloride[56]) is $k^H/k^D = 1.33$. All the values quoted above are significantly lower. The value for p-nitro-compounds is reduced compared with expectation owing to nucleophilic attack by the solvent on the α-carbon atom.

III. THE $E2$ MECHANISM

1. General Characteristics of β-Elimination Via the $E2$ Mechanism

The $E2$ mechanism is the commonest of all the elimination mechanisms and can be represented by the following scheme:



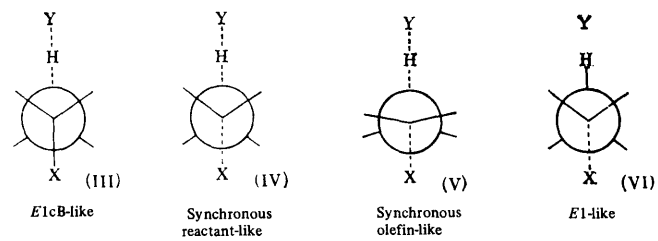
(2)

(II)

According to this scheme, the reactant Y, called the base, removes a proton from the β-carbon atom of the substrate and the electron-accepting leaving group X is synchronously separated from the α-carbon atom. This mechanism does not involve any intermediate stages and thus has only one transition state between the reactants and the products. The reaction is of second order overall—of first order with respect to each reactant.

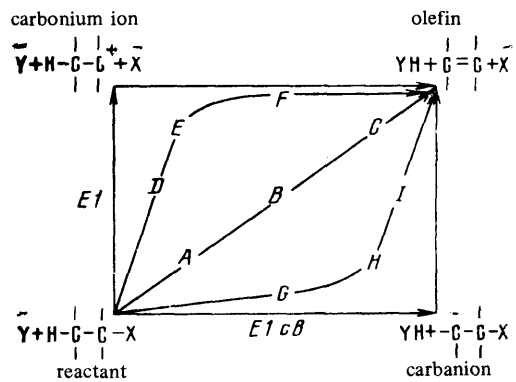
In his early studies Ingold[1] already pointed out that it is not obligatory that the dissociation and formation of bonds in an $E2$ reaction should occur absolutely synchronously; in 1956 Cram et al.[58] established that the structure of the transition state in $E2$ reactions may be different for different substrates under identical reaction conditions and may vary for the same substrate when the reaction conditions are altered. It has now been demonstrated that in reality there is a whole set of $E2$ mechanisms with different transition states[2,3,59,60] whose structure may vary smoothly with that of the substrate and the reaction conditions; these variations are limited on either side by extreme cases—$E1$-like and $E1cB$-like transition states—and do not extend beyond the region where true carbonium ions and carbanions exist. The mechanism is believed to be synchronous ($E2$) when a base is involved in the transition state, but there is no exchange of hydrogen atoms.

It is very important to emphasise that the type of the transition state is not a constant property of the substrate, but depends also on the nature of the solvent and the base. In such cases the predictions and interpretation of the experiments frequently become arbitrary and it is usually more correct to refer the reaction to a particular special case and to a specific type. Four main types of the transition states in $E2$ reactions are given below:



(III) (IV) (V) (VI)

*E*1cB-like | Synchronous reactant-like | Synchronous olefin-like | *E*1-like



Schematic illustration of the changes in the transition state in the elimination reaction (various types of the $E2$ mechanism).

A new method for the representation of a variety of transition states for $E2$ mechanisms, which proved to be the clearest and most convenient, was proposed recently[61]. The Figure represents schematically various $E2$ mechanisms on the basis of the potential energy surface diagram. Each section, denoted by a letter within the

limits of the diagram, corresponds to a definite type of activated complex with its own potential energy surface; the positions of these sections relative to the species designated in the corners of the diagram indicate the structural characteristics of the various activated complexes and their positions on the reaction coordinate.

For example, the activated complex *A* is reactant-like (with a slight weakening of the β-C–H and α-C–X bonds and a slight double-bond character of the α-C–β-C linkage). According to Hammond's postulate [62], this activated complex may be formed in reactions giving rise to a very stable olefin.

The activated complex *F* is "carbonium ion- and olefin-like" with a significant weakening of the α-C–X bond, an appreciable double-bond character of the α-C–β-C linkage, and considerable transfer of a hydrogen atom from β-C to the base. Section *B* describes the "central" synchronous transition state. Thus the transition state in an *E*2 reaction can occupy any point within the given diagram, without going outside its limits.

The relations between the factors influencing the structure of the transition state are very complex, but the predictions described below appear to be well-founded and agree with the experimental data which will be examined subsequently.

Type (III) (the *H* region in the Figure) is favourable for compounds in which the β-hydrogen atom is labile owing to the inductive *–I* effect of α- or β-substituents; the rate of reactions proceeding via such an activated complex will be appreciably influenced by factors determining the acidity of the β-hydrogen. Such reactions are particularly facilitated in the presence of substituents delocalising the negative charge owing to conjugation or of substituents with *cis*-steric effects (see above). The use of strong bases as well as solvents which do not favour the ionisation of groups eliminated from the α-position also favours the occurrence of reactions with an *E*1*cB*-like mechanism.

The "*E*1-like" type (VI) (the *E* region in the Figure) is favoured by factors such as the presence of electron-donating substituents, which increase the electron density at the α-carbon atom, steric effects, and solvents favouring the extension of the C–X bond. The strength of the bases and the polar and steric effects of β-substituents have little importance in this instance, but the α-substituent, which delocalises the positive charge owing to conjugation, should influence the reaction rate.

Evidently types (IV) and (V) (*E*2 synchronous types; *A* and *C* regions in the Figure) have the characteristics of types (III) and (VI), but exhibit a specific sensitivity to α- and β-substituents and a high β-hydrogen isotope effect. In such cases bulky α- and β-substituents give rise to a pronounced *cis*-effect, since the double bond in the activated complex is fairly well formed, but small substituents may favour this type of transition state as a result of conjugation.

The influence of various factors on the structure of the transition state and the rate of *E*2 reactions has been examined in a number of reviews [3–12], from which it follows that in general low concentrations of the base favour unimolecular reactions (*E*1, S_N1). On the other hand, at a high concentration of the base, bimolecular reactions predominate (*E*2, S_N2), the relative contributions of which depend both on the structure of the substrate and on the ratio of the basicity of the base employed (attack on H) to its nucleophilic strength (attack on C).

Another approach is based on the hypothesis that the rate of *E*2 reactions depends in this instance on the H_- function at a high concentration of the base if there is a vigorous transfer of the proton to the base in the transition state [63]. The ratios of the rates of the base-catalysed elimination for para-substituted β-chloroethyl phenyl sulphones in anhydrous acetonitrile when Et_3N, $Et_2NCH_2CH_2OH$, $EtN(CH_2CH_2OH)_2$, and $N(CH_2CH_2OH)_3$ are used as bases are 550 : 52 : 6.6 : 1 respectively [64]. This shows that the rate of reaction is correlated with the basicity of the bases. The Hammett reaction constants ρ for these reactions are respectively 1.81, 1.75, 1.72, and 1.64. Such variation of the reaction constant shows that the carbanionic character of the transition state becomes more pronounced with increasing base strength, moving into the *H* region (see Figure). Other investigators [65–67] arrived at the same result in studies of the influence of the base strength on the ratio of the yields of the products of *E*1, S_N1, *E*2, and S_N2 reactions and on the yield of isomeric olefins from various substrates. However, this type of correlation is not always observed [68–70]. The study of nine reactions in a concentrated NaOMe solution showed [71] that there is no direct correlation between the rates of reaction and the H_- acidity functions or the stoichiometric concentrations of the base.

The breakdown of the linearity in the relation between the rates of *E*2 elimination and base strength can be due to the smooth variation of the structure of the transition state [58] as the base strength is altered, which may lead to a change in mechanism. For this reason, in a study of the influence of the basicity of the medium both on the rate and the mechanism of the reaction, it is desirable not to confine the investigation to the measurement of the reaction rates alone and to determine also other characteristic reaction parameters (such as the reaction constant and the isotope effect) in order to be able to arrive at more clear-cut conclusions on comparing these parameters.

Such a combined study of the elimination of HBr from 2-arylethyl bromides in the t-BuOK–t-BuOH system has been carried out by Saunders and coworkers [72]. They investigated the influence of the addition of dimethyl sulphoxide (DMSO) on the rate, the isotope effect, the reaction constant, and the activation parameters of the above reaction. We observed that the addition of DMSO causes an unusually marked acceleration of the reaction (by a factor of 12 at 30°C for a 0.965 M DMSO solution and by a factor of 120 for the 2.23 M solution). Despite the fact that DMSO has a much higher dielectric constant than t-butyl alcohol, the value of *E* (and *Z*) for these solvents are almost identical [73]. Consequently there can be no great difference between their solvating capacities in relation to a neutral alkyl bromide and a transition state with a delocalised charge. Thus the acceleration could have been caused only by a change in the basicity of the t-butoxide. However, with increase of the DMSO concentration from 0.965 to 2.23 M, the rate of elimination for 2-phenylethyl bromide increases by a factor of 10, while the basicity changes only slightly (only by a factor of 1.5). The authors [74] believe that the usual basicities, determined experimentally, are unsuitable for the consideration of the influence of "basicity" on the structure of the transition state in the reaction. It was shown [74] that the base strength and the type of solvent are more important factors than the size of the base and the direction of its approach to the reagent. The association of the catalyst [75] as well as ion–dipole and ion–ion interactions between the base and the leaving group [76] play a particularly important role.

The idea that the hydrogen bonding and hence the "levelling effect" of protic solvents may influence the

basicity of oxygen-containing anions was tested experimentally 35 years ago [77]. Furthermore, the polarity of the transition state in an *E*2 reaction is usually lower than that of the initial state, since the ionic charge of the base is distributed over a larger area. For this reason, polar solvents should reduce the reaction rate. Since the charge in the transition state of the elimination reaction is more delocalised, the decrease of the rate is in this case manifested to a greater extent than in the corresponding substitution reaction (S_N2), which frequently accompanies bimolecular elimination reactions [78,79].

There is no need to consider in detail each individual investigation in the present instance, but one must note that studies in recent years have been largely devoted to an experimental test of the above considerations. They showed that both variation in base strength and solvent polarity [80-82] and changes in the structure of the substrate [83-86] influences the rate of elimination [87,88] and lead to a change in the structure of the transition state, as a result of which it may occupy an infinity of positions on the potential energy surface between the limiting "*E*1*cB*-like" and "*E*1-like" types [89].

2. Stereochemistry of the Elimination Reaction Via the *E*2 Mechanism

Until recently [90] the stereochemical characteristics of *E*2 reactions were thought to be determined by Ingold's four-centre rule, which states that bimolecular elimination proceeds smoothly only when the four centres involved in the reaction lie in the same plane, i.e. when the substituents being eliminated are in the transoid conformation (in the *anti*-position relative to one another) or in an eclipsed cisoid conformation. For rigid cyclic systems, an analogous rule was formulated by Barton, while the steric limitations in elimination reactions involving bridged rings are determined by Bredt's rule.

However, the current views on the stereochemistry of the *E*2 reaction have altered radically; it has been established that, for *cis*-coplanar leaving groups, the *E*2 reaction proceeds just as fast as in the case where the groups are *anti*-periplanar and that *cis*-*E*2 elimination cannot be ruled out either in acyclic or cyclic systems.

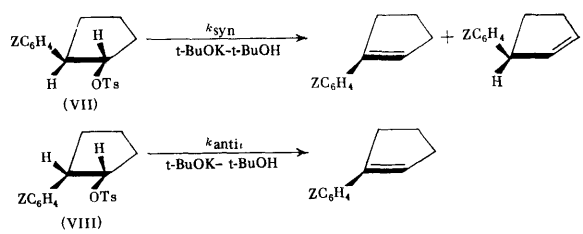
Furthermore, β-elimination reactions have been achieved with bridge compounds despite being "forbidden" by Bredt's rule. These problems are discussed in special reviews [25,91-96]. It is important to note that both the bulk of the base and of the leaving group and the degree of branching of the substrate molecule play a role in the alteration of the relative contributions of *cis*- and *trans*-elimination reactions [94,97-99]. Analysis of the proportions of the products of elimination from PhCHDCHDX (X = *p*-$MeC_6H_4SO_3$ or Cl) using t-BuOK in t-BuOH, DMSO, or benzene showed [100] that *syn*-elimination takes place only in benzene and that *syn*- and *anti*-elimination reactions lead to different primary hydrogen isotope effects. The above study gives an idea of the important role in *syn*-elimination of the ion pair formed by the base.

The latest studies on the general aspects of the stereochemistry of this reaction [101] as well as *syn*-elimination [102-104] again confirmed the influence of the formation of the ion pair on the stereochemistry of the process [105] and also the important role of the base and the solvent [106]. After it was discovered that macrocyclic ethers (crown ethers) [107] are able to be coordinated to alkali metal cations and to separate the complex ion pair formed by the base [108,109], investigators of the elimination mechanism acquired a valuable instrument for the elucidation of the role of ion pairs in *syn*- or *anti*-elimination. Such information can be obtained by comparing the steric results of the reaction of a given compound with a base in the presence and absence of the crown ether.

Data have been published [110] for the reaction involving elimination from *trans*-2-phenylcyclopentyl toluene-*p*-sulphonate in the t-BuOK–t-BuOH system at 50°C. In the absence of the crown ether, the ratio of 1-phenylcyclopentene (the *syn*-elimination product) and 3-phenylcyclopentene (the *anti*-elimination product) was 9.8–11.8 (depending on the reaction time). After the addition of the macrocyclic ether (dicyclohexyl-18-crown-6) in an amount equal to that of the base, the ratio became 0.43, i.e. the steric course of the reaction was altered sharply. An analogous result was achieved [111] also in the reactions of other alicyclic toluene-*p*-sulphonates with t-BuOK. The addition of the crown ether in this instance also drove the reaction along the *anti*-elimination pathway.

An interesting result was likewise obtained [112] in a study of the linear 5-decyl toluene-*p*-sulphonate with t-BuOK in t-butyl alcohol, benzene, and dimethylformamide (DMF). It was found that the base in the form of an ion pair and the ions separated by the crown ether are involved only in *anti*-elimination but in quite different ways: in the former case the product is mainly a *cis*-olefin and in the latter a *trans*-olefin. The influence of the crown ether is then manifested only in t-butyl alcohol and in benzene, while in DMF the ratio of the reaction products does not change when the crown ether is added. This finding evidently shows that in DMF the base exists in a fully dissociated state also in the absence of the crown ether. Thus the use of crown ethers established that weakly polar and protic solvents promote the reaction via the *syn*-elimination pathway, while in polar aprotic solvents *anti*-elimination predominates. Furthermore, it follows from these experiments that in the bimolecular reaction *syn*-elimination is caused by the base in the form of a close ion pair, while *anti*-elimination proceeds under the influence of the separated ions. The use of crown ethers for the investigation of the *E*1*cB* mechanism is described by Hunter et al. [113]

Numerous studies in recent years were devoted to the stereochemistry of *E*2 reactions in alicyclic systems. The discovery that the *syn*-elimination accelerated by bases in the series of *trans*-2-arylcyclopentyl toluene-*p*-sulphonates (VII) is faster than the *anti*-elimination for the *cis*-isomers (VIII) leads not only to the conclusion that *syn*-elimination is a concerted reaction [93] but also indicates the dependence of the relative rates of synchronous elimination on the dihedral angle [100].



$k_{syn}/k_{anti} = 9.1$ (Z = H);
$\rho_{syn} = 2.8$; $\rho_{anti} = 1.5$;
$k^H/k^D = 5.6$ (50°C) . (3)

The large *syn*/*anti* ratio, the more positive value of ρ for the *syn*-process, and an isotope effect which is close to a maximum, together with the undoubted second-order

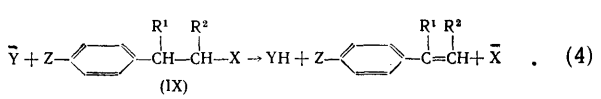
kinetics constitute rigorous proof of a *syn*-coplanar *E*2 mechanism with an appreciable carbanionic character (*H* transition state, see Figure). Owing to conformational limitations, *anti*-elimination from the *cis*-toluene-*p*-sulphonates (VIII) proceeds via an "*E*1-like" mechanism.

Preferential *syn*-elimination has also been demonstrated in a series of cyclo-octyl [25] and cyclodecyl [94,114-116] derivatives. Mainly *exo*-*cis*-bimolecular elimination predominates in the series of norbornyl derivatives [117-123]. In addition, it has been shown that the rate of reaction is strongly influenced by the steric strain in the ring. Thus the relative rates of β-elimination in the series of cyclopentyl, cyclohexyl, cycloheptyl, and cyclo-octyl toluene-*p*-sulphonates are 16.25, 1.0, 12.62, and 152.0 respectively [124].

The report of the synthesis of bridged olefins [125-129] initiated a new stage in the chemistry of bridged compounds. These olefins were obtained by the Hofmann cleavage of quaternary ammonium compounds and dehydrochlorination in the presence of collidine [129]. Bicyclo[3,3,1]non-1-ene is also synthesised from a salt of *endo*-2-methanesulphonoxybicyclo[3,3,1]nonane-2-carboxylic acid [126]. The synthesis of these compounds constitute an evident infringement of Bredt's rule.

3. Isotope Effects in *E*2 Elimination

The primary isotope effects in the *E*2 mechanism should be observed when a labelled base, labelled α-carbon and β-carbon atoms, labelled group X to be eliminated, and labelled α-hydrogen are used. Secondary isotope effects can occur for α-hydrogen atoms and the non-eliminated β-hydrogen atoms. The isotope effect may then serve as a criterion for the elucidation of the structure of the transition state [130,131]. The isotope effect of the solvent (the replacement of water by D_2O) is studied for this purpose [132]. Saunders and Edison [133] found that the isotope effects k^H/k^D for compounds (IX, $Z = R^1 = R^2 = H$) with different leaving groups (X = Br, OTs, $\overset{+}{S}Me_2$, and $\overset{+}{N}Me_3$) are respectively 7.11, 5.66, 5.07, and 2.08. This series agrees with the increase of the carbanionic character of the activated complex and may be identified with the gradual transition from the *B* region to the *H* region (see Figure). Such changes should be accompanied by an increased shift of the β-hydrogen from the carbon atom to Y and thus by a decrease of the isotope effect, which is in fact observed. A similar result was obtained in another study [126].



(IX) (4)

The influence of the reaction medium on the isotope effect has been observed in reactions of dimethyl-(β-phenylethyl)sulphonium salts (IX, $Z = R^1 = R^2 = H$, $X = \overset{+}{S}Me_2$). [134,135] The rate of the reaction of the HO^- ion with sulphonium bromide in a water–DMSO mixture increases sharply with increased DMSO content and the isotope effect of the medium k^{32}/k^{34} diminishes from 1.0074 in pure water to 1.0011 in ~20% DMSO. The β-hydrogen isotope effect in this range of solvent compositions does not vary appreciably, but, when the DMSO content increases still further, the ratio k^H/k^D passes through a maximum and then decreases again. The influence of the added DMSO was interpreted by the authors as a result of the increase of the effective base strength owing to a change in the degree of solvation, which displaces the activated complex in the direction of the carbanion-like transition state (from the *B* region to the *H* or *G* region). This should lead to a decrease of the polarisation of the α-C–S bond in the transition state, which entails a decrease of the sulphur isotope effect. On further increase of the DMSO content, the stability of the carbanion increases and the activated complex now becomes more reactant-like (i.e. shifts from the *C* region in the direction of the *A* region) in conformity with Hammond's postulate [62]. If it is supposed that in 20% DMSO the β-hydrogen in the transition state is transferred to the base Y to an extent greater than 50%, the addition of DMSO should initially lead to a transition state with a symmetrically linked β-hydrogen atom (to which corresponds the maximum value of k^H/k^D) and then to a state in which the β-hydrogen atom is displaced towards Y to an extent less than 50% (decrease of k^H/k^D) and this was in fact observed in the study quoted above [135]. Thus, when the DMSO content is increased, the position of the saddle point on the potential energy surface illustrated in the Figure will be displaced from the *B* region in the direction between the *G* and *H* regions and then back again towards the *A* region.

Willi [85] determined the primary isotope effects for the reactions of 2-deutero-2,2-diphenylethyl-*p*-Z-benzenesulphonates with sodium methoxide in methylcellosolve for Z = OMe, H, and NO_2 and obtained 5.27, 5.42, and 6.70 respectively. It appears that, when Z = OMe, the activated complex is in the *H* region and has a more pronounced carbanionic character. On passing to *Z* = H and NO_2, the degree of transfer of the β-hydrogen to the base diminishes, which brings it closer to the symmetrical position. β-Hydrogen isotope effects in *E*2 reactions have also been investigated in other studies [64,136-143].

In recent years data concerning the presence or absence of the β-hydrogen isotope effect have been widely used to solve the problem whether the *E*2 reaction proceeds via the *syn*- or *anti*-elimination mechanism in various systems [94,97,114,144-150]. It was shown [119,151,152] that *syn*-elimination predominates in norbornyl and bicyclo[2,2,2]-octyl derivatives. In these compounds $(k^H/k^D)_{anti} > (k^H/k^D)_{syn}$.

Finley and Saunders [153] carried out an extensive study of the primary β- and secondary α- and β-hydrogen isotope effects in the *E*2 reactions of cyclohexyl toluene-*p*-sulphonates in the presence of EtONa–EtOH and t-BuOK–t-BuOH. Both secondary isotope effects (α- and β-) are large (k^H/k^D = 1.14–1.15 and 1.36–1.51), while the primary β-effect is higher in t-butyl alcohol (k^H/k^D = 7.53) than in ethanol (k^H/k^D = 4.47). The structure of the activated complex in this reaction apparently corresponds to the "central" complex (*B* region, see Figure). The large secondary isotope effects are due to the appreciable sp^2 character of the α- and β-carbon atoms in the transition state. If this is so, then the primary β-hydrogen isotope effect in ethanol will correspond to the transition state in which the hydrogen atom is transferred from the β-carbon atom to the base Y to an extent less than 50%. The activated complex in t-butyl alcohol should then move in the direction of the symmetrical state acquiring at the same time carbanionic character and leading to an increase of the isotope effect, which has in fact been observed [153].

IV. THE *E*1*cB* MECHANISM

1. General Characteristics of β-Elimination Via the *E*1*cB* Mechanism

The *E*1*cB* mechanism is the third β-elimination mechanism proposed by Ingold[154]. It differs from the usual *E*2 mechanism by the fact that it corresponds to a two-stage process involving the formation of an intermediate discrete carbanion, while *E*2 elimination is a synchronous process proceeding via a single transition state from the substrate to the product[2,154]. Two main types of this mechanism are distinguished:

(1) Type *A*, in which the first rate-limiting stage is the bimolecular formation of a carbanion and the second stage is the relatively rapid removal of the leaving group from the α-carbon atom:

$$Y+H-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-X \xrightarrow{\text{slow}} YH+\underset{|}{\overset{|}{\overset{-}{C}}}-\underset{|}{\overset{|}{C}}-X \xrightarrow{\text{fast}} \underset{|}{\overset{|}{C}}=\underset{|}{\overset{|}{C}}+\overset{-}{X} \quad . \qquad (5)$$

(X)

(2) Type *B*, in which the first stage is the rapid reversible formation of a carbanion, while the second, rate-limiting stage involves the unimolecular decomposition of the carbanion; if the base is not in this case the lyate ion derived from the solvent, whose conjugate acid YH may be present in excess, second-order kinetics are observed:

$$\overset{-}{Y}+H-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-X \underset{k_{-1}}{\overset{\text{fast } k_1}{\rightleftharpoons}} YH+\underset{|}{\overset{|}{\overset{-}{C}}}-\underset{|}{\overset{|}{C}}-X \xrightarrow[k_2]{\text{slow}} \underset{|}{\overset{|}{C}}=\underset{|}{\overset{|}{C}}+\overset{-}{X} \quad . \qquad (6)$$

(XI)

Second-order kinetics are usually observed for both types of the *E*1*cB* mechanism, as for the bimolecular *E*2 mechanism, since there is no kinetic criterion for distinguishing these mechanisms. If the pre-equilibrium carbanionic elimination (type *B*) takes place in protic solvents, then the β-hydrogen atoms of the substrate can exchange for the solvent protons at a rate exceeding the rate of elimination. Such exchange may be observed either by using a labelled substrate in an unlabelled solvent or conversely by using an unlabelled substrate in a labelled solvent. The occurrence of deuterium exchange is evidence for a pre-equilibrium *E*1*cB* mechanism; on the other hand, the absence of exchange indicates an irreversible *E*1*cB* mechanism (type *A*) or an *E*2 mechanism.

Breslow[155] suggested that, depending on the relative energetics, rapid hydrogen exchange may be an unrelated side reaction in *E*2 elimination. However, this hypothesis has been criticised[6,156,157]. In particular, Hine et al.[156], who investigated the elimination of HF from 2,2-dihalogeno-1,1,1-trifluoroethanes, established that in a methanol solution of methoxide the compounds exchange hydrogen at a significantly higher rate than that of their elimination reaction. The activating influence of the α-fluorine atoms and β-halogen atoms together with the well known difficulty of eliminating fluorine in the form of an anion from a saturated carbon atom (even more so from a carbon atom linked to other halogen atoms[158,159]) make it very likely that a carbanion is formed in this elimination reaction. Hine et al.[160] believe that, if the carbanion is formed, then in all probability it is an intermediate in the elimination reaction, since the transfer of its free electron pair should accelerate the formation of the olefin more effectively than the partial transfer of the same electron pair in the *E*2 transition states. In his study of the k_{OTs}/k_{Br} ratio as a criterion of the degree of dissociation of the C–X bond Hoffmann[161] also concluded that all the experimental examples known hitherto confirm this hypothesis. Thus the conditions and structures which ensure the formation and stabilisation of the carbanion favour the *E*1*cB* mechanism. The formation of a carbanion requires the abstraction of a proton from the CH acid. In elimination reactions bases are always used for this purpose. However, the presence of activating substituents, similar to the nitro- and carbonyl-groups, as well as other substituents with strong $-I$ and $-M$ effects may increase the acidity of the β-hydrogen to such an extent that the compound may give rise to a carbanion without the addition of an external base—the alkalinity of glass, for example, may be sufficient for this purpose. All the factors responsible for both the formation and stabilisation of carbanions are widely discussed in Cram's book[162]. These problems have been considered in a number of reviews[11,12,163–167] in relation to the elimination reaction. The influence of solvents on the reactions of carbanions is discussed in Ritchie's review[168].

Crosby and Sterling[169–171] investigated the influence of 17 activating groups on the rate and mechanism of the reaction

$$\overset{-}{Y}+Z-CH_2CH_2-X \rightarrow Z-CH=CH_2+\overset{-}{X}+YH \quad , \qquad (7)$$

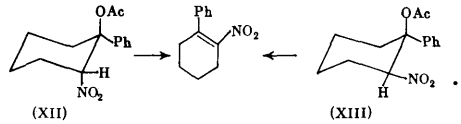
where X is the leaving phenoxy-group and Z represents activating substituents, which are listed below in order of decreasing activating influence:

$$NO_2,\ \overset{+}{P}Ph_3,\ \overset{+}{S}Me_2,\ COMe,\ CHO,\ SO_2OEt,\ SO_2Ph,\ SO_2Me,$$
$$CN,\ COOEt,\ SO_2N(CH_2Ph)_2,\ SOPh,\ CONH_2,\ SOMe,$$
$$CONEt_2,\ \overset{+}{N}Me_3,\ COO^-.$$

On passing from NO_2 to SOMe in this series, the reaction rate constant diminishes by a factor of 10^6. The rate constants are correlated with σ_R^-, but not with σ and σ*. This shows that the resonance stabilisation of the carbanion is an important factor in the activation of such systems. Furthermore, a satisfactory correlation is observed between the reaction rate constant and pK_a and the ionisation rate constant of the $Z-CH_3$ acid (a CH acid) as well as the rate constants for the nucleophilic addition of alkoxides to a series of vinyl compounds of the type $Z-CH=CH_2$.[172] Bearing in mind together with these findings the low values of the isotope effect and the reaction constant ρ as well as its insensitivity to changes in the substituents attached to the leaving phenoxy-group, the authors[169–171] concluded that elimination from these phenoxyethyl compounds proceeds via a pre-equilibrium *E*1*cB* mechanism at least for sulphoxides (Z = SOMe) and for compounds more reactive than the latter.

Rappoport and coworkers[173] compared the results obtained by Crosby and Stirling with data for the addition of various nucleophiles[172,174–180] and for nucleophilic vinyl substitution (which proceeds via addition and elimination)[181] with the approximate ionisation rate constants k_i and the dissociation constants K_a of the CH acids $Z-CH_3$[182] (for all the Z investigated by Crosby and Stirling). He concluded that all the data rigorously confirm the hypothesis of the *E*1*cB* mechanism of reaction (7).

The methoxide-catalysed *anti*- and *syn*-elimination of HOAc from the nitroacetates (XII) and (XIII) and the elimination of HOMe from the corresponding methoxy-compounds have been compared[183].



(XII) (XIII) (8)

It was established that the elimination of HOMe involves the reversible formation of a carbanion on treatment with MeOH–MeONa ($E1cB$ mechanism, type B). Having considered the relative reaction rates, the effect of substituents, the deuterium isotope effects, and the activation parameters for the reactions of the acetoxy- and methoxy-compounds, the authors[183] concluded that elimination from both (XII) and (XIII) proceeds via an intermediate carbanion and that elimination with participation of mobile protons activated by the NO_2, MeCO, and CN substituents in general usually proceeds via the carbanionic mechanism.

This conclusion[183] is in full agreement with the conclusions reached by Crosby and Stirling, because the above substituents include the series of activating groups for which the $E1cB$ mechanism has been demonstrated. It has been established[184] that the reactions of these compounds as well as their 4,4-dimethyl analogues in the presence of pyridine in $CHCl_3$–EtOH also proceed via the $E1cB$ mechanism. For this reaction, the activation energy $E_a = 6.9$ kcal mole^{-1}, the activation entropy $\Delta S^{\neq} = -50$ e.u., the isotope effect $k^H/k^D = 4.5$, and the reaction constant $\rho = 1.45$, which is in full agreement with the proposed mechanism. A study[185] of the elimination of methyl alcohol from the isomeric *cis*- and *trans*-1-methoxy-2-nitro-1-phenylcyclopentanes also demonstrated the operation of a carbanionic mechanism for both isomers. Carbanionic mechanisms have been shown to occur in the elimination of substituted benzoic acids from 4-aroyloxy-2-butanones with formation of vinyl ketones[186], in the elimination of water from 2-cyano-1-hydroxy-2-(*p*-nitrophenyl)ethane[187], and in the elimination of AcOH from 9-acetoxy-10-methyl-*cis*-2-decalone[188]. Evidently, in all the examples β-hydrogen is activated by one of the groups which Crosby and Stirling investigated. Particular mention should be made of studies[189–191] which established convincingly by detailed kinetic investigations and the investigation of isotope effects that the β-elimination of water from 9-fluorenylmethanol in aqueous alkaline media and in alcohol proceeds via an $E1cB$ mechanism with a slight contribution by the $E2$ mechanism.

The scope of this review does not allow a detailed consideration of the studies devoted to β-elimination from carbamates, various sulphones, etc.[192–196], for which the $E1cB$ mechanism has been demonstrated.

There can now be no doubt about the possibility of β-elimination in activated systems by a carbanionic mechanism. Extensive studies have been carried out in this field on the influence of activating groups on the mobility of β-hydrogen and on the stabilisation of the carbanion formed. Furthermore, intensive research into the influence of the medium and bases on the kinetics and mechanism of this reaction is being prosecuted.

2. Stereochemistry of β-Elimination via the $E1cB$ Mechanism

The hypothesis of complete *trans*(*anti*)-stereospecificity of $E2$ reactions was adopted at an earlier stage. It was confirmed for almost all the examples investigated and the manifestation of *trans*-specificity in the reaction was therefore regarded as sufficient evidence to assume the $E2$ mechanism. Any breakdown of this stereospecificity was therefore regarded as evidence for the operation of another mechanism. In particular *syn*-stereospecificity was frequently accounted for by the $E1cB$ mechanism. However, now that it is known that an $E2$ reaction can be both *anti*- and *syn*-stereospecific, the occurrence of *syn*-elimination should not apparently be regarded as evidence for elimination via the $E1cB$ mechanism. Nevertheless, Ingold[197] emphasised that the $E1cB$ mechanism should be either *syn*-stereospecific or non-stereospecific. We shall now consider to what extent this postulate actually holds in relation to the available experimental facts.

Jones et al.[198] synthesised diastereoisomeric 5-butyl-2-hydroxycyclohexyl-*p*-tolyl sulphones and measured the rates of piperidine-catalysed bimolecular elimination DMSO for the corresponding *trans*,*trans*-, *cis*,*trans*-, and *trans*,*cis*-isomeric sulphonate esters. Since a conjugated sulphone is the only product of these reactions, the implication is that two of these sulphonates undergo *syn*-elimination, while the *cis*,*trans*-isomer undergoes *anti*-elimination (formally diequatorial elimination). The relative rates change at most by a factor of 1.4 and are insensitive to the nature of the leaving group (either OTs or OMe). The *trans*,*cis*-compound (axial OSO_2R), axial SO_2Ar) reacted faster. The addition of piperidine hydrochloride causes a slight but nevertheless appreciable decrease of the rate. However, when the reaction is carried out in a deuterated solvent, the takeup of deuterium is insignificant. These data were explained by a mechanism with irreversible formation of a carbanion ($E1cB$, type A). Preliminary investigation of analogous isomeric 4-t-butyl-2-chlorocyclohexyl phenyl sulphones yielded additional facts confirming the above conclusions (see also Refs. 199 and 200).

The base-catalysed elimination of acetic acid from 2-nitro-1-phenylcyclohexyl acetates (XII) and (XIII) proceeds via a carbanionic mechanism, since the *syn*-elimination from (XII) is faster than the *anti*-elimination from (XIII). An appreciable deuterium isotope effect was observed; both processes show similar sensitivities to changes in temperature, medium, and substituents[184, 201]. The inclusion of *gem*-dimethyl groups in the 4-position increases the rate of elimination from (XII) and decreases the rate of elimination from (XIII). Furthermore, the corresponding nitronate ion was detected spectrophotometrically during the reaction in a study[184,185] of methoxy-analogues of (XII) and (XIII). Comparison of kinetic data, isotope effects, and the influence of substituents for the acetoxy- and methoxy-derivatives established the occurrence in these reactions of carbanionic processes of three types[183]: with an irreversible second-order carbanionic mechanism for (XII) and (XIII), with a reversible second-order carbanionic mechanism for the methoxycyclohexyl compounds, and with an irreversible first-order carbanionic mechanism (see below) for the methoxycyclopentyl compounds {k_1 is the rate constant for the rate-limiting stage and $k_2 \gg k_{-1}[BH]$}. The study of Bordwell et al.[183] yielded convincing evidence for a carbanionic mechanism of the *syn*- and *anti*-elimination from these compounds. Ring deformation apparently plays an important role in these processes. Special mention was made of the fact that the synchronous *anti*-$E2$ mechanisms for compound (XII) and its methoxy-analogues did not compete with the carbanionic process. Thus both *syn*- and *anti*-elimination proceed in this instance via an intermediate carbanion.

In the base-catalysed dehydrochlorination of the diastereoisomeric 1-chloro-1,2-diphenyl-2-toluene-*p*-sulphonylethanes[202], the *erythro*- and *threo*-isomers underwent full *trans*- and *cis*-elimination respectively. Thus both diastereoisomers yielded 2-toluene-*p*-sulphonyl-*cis*-stilbene. The authors suggest a synchronous mechanism for the *erythro*-isomer and a carbanionic mechanism for the *threo*-isomer. The same system was studied in another investigation[203].

The amine-accelerated elimination of HF from fluoroethanes activated by the sulphonyl group is *syn*-stereospecific[204]. The study of the isotope effect in this reaction indicates an *E*1*cB* mechanism involving the formation of an ion pair (see also Hunter and Shearing[205]).

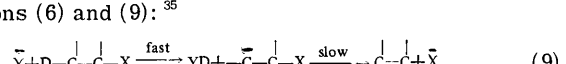
There have been very few studies on the stereochemistry of the *E*1*cB* mechanism. However, the available examples have shown that the mechanism is more likely to be *syn*-stereospecific than *anti*-stereospecific: this is in its turn consistent with Ingold's hypothesis[197].

3. Isotope Effects in the *E*1*cB* Elimination

We considered above two generally accepted types of the *E*1*cB* mechanism. If the formation of the carbanion is the rate-limiting stage (type *A*), then the primary kinetic isotope effects should occur for the labelled base Y the β-carbon atom, and the eliminated β-hydrogen atom. Whether or not secondary isotope effects are observed under these conditions for the α-hydrogen atoms or the non-eliminated β-hydrogen atoms should probably depend on the change in the hybridisation of the β-carbon orbitals on formation of the carbanion. Since the carbanion decomposes solely into the reaction products, the observed rate should not be sensitive to isotope substitution at the α-carbon atom or in the leaving group X. On the other hand, if the formation of the carbanion (XI) is a fast and reversible stage and its conversion into the reaction products is rate-limiting (type *B*), primary kinetic isotope effects should be observed for the labelled group X, α-carbon, and β-carbon, while in the case of a labelled group Y and labelled β-hydrogen atoms, equilibrium isotope effects may be observed. Secondary isotope effects may occur also for α-hydrogen atoms.

There are few literature data for isotope effects in *E*1*cB* reactions involving labelled Y, α-carbon, or X. Almost all the isotopic studies have been carried out with labelled β-hydrogen. The β-hydrogen isotope effects are characteristic of both *E*2 reactions and *E*1*cB* (type *A*) reactions. The latter can therefore be distinguished only by comparing the magnitudes of these effects[130,131].

The situation is much more complex for the *E*1*cB* (type *B*) mechanism. *E*2 and *E*1*cB* (type *A*) reactions can proceed with a normal isotope effect, characterising these mechanisms, while the *E*1*cB* (type *B*) mechanism will exhibit only a small equilibrium isotope effect reflecting the different equilibrium concentrations of carbanions in reactions (6) and (9):[35]



$$\bar{Y} + D-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-X \underset{}{\overset{\text{fast}}{\rightleftharpoons}} YD + -\underset{|}{\overset{|}{\bar{C}}}-\underset{|}{\overset{|}{C}}-X \xrightarrow{\text{slow}} \underset{|}{\overset{|}{C}}=\underset{|}{\overset{|}{C}} + \bar{X} \quad . \qquad (9)$$

In this case definite conclusions can be reached only by comparing the rates of elimination of the unlabelled substrate in the unlabelled solvent with the rate of elimination of the labelled substrate in the labelled solvent. A normal isotope effect will be observed if the reaction proceeds via the *E*2 or *E*1*cB* (type *A*) mechanism, while the equilibrium isotope effect (the isotope effect of the solvent) will obtain for the *E*1*cB* (type *B*) mechanism. If, as frequently happens, YH and YD are solvents, the effective concentrations are constant and equal and the ratio of the observed rates is then equal to the ratio of the isotopic equilibrium constants[35]. Depending on the bond energy in RH relative to YH, the above ratio can vary from a value less than unity (the usual case) to one slightly greater than unity.

In the elimination of methanol from 4-methoxy-2-butanone and 4-methoxy-2-pentanone with formation of 3-but-2-enone and 3-pent-2-enone via the *E*1*cB* mechanism the exchange of β-hydrogen atoms (in the α-position relative to the carbonyl group) with D_2O-OD^- is rapid and the overall isotope effect $k^H_{obs}/k^D_{obs} = 0.87$ and 0.77 respectively[206]. In full conformity with the *E*1*cB* (type *B*) mechanism, Crosby and Stirling[171] also observed a rapid exchange in the elimination of phenol from dimethyl-(2-phenoxyethyl)sulphonium iodide and methyl-2-phenoxyethyl sulphone ($k^H_{obs}/k^D_{obs} = 0.66$ and 0.78 respectively).

When acetic acid was eliminated from 2-acetoxy-1-nitro-2-phenylcyclohexanes and the corresponding cyclopentanes and in the elimination of methanol from *trans*-2-methoxy-1-nitro-phenylcyclopentane[183,184], large β-hydrogen isotope effects ($k^H_{obs}/k^D_{obs} = 4.9-8.1$) were observed in all the reactions, as expected for the *E*1*cB* (type *A*) mechanism with a more or less symmetrical transfer of β-hydrogen from β-carbon to Y.

Yet another version of the *E*1*cB* mechanism was investigated by Rappoport[207-213] and Bordwell et al.[185] (see also Refs. 190, 195, 197, 198). If the entire substrate is converted into a carbanion under the influence of the base in the rapid stage of the reaction, further addition of the base no longer has any effect on the concentration of the carbanion and the elimination proceeds subsequently as a pseudo-first-order reaction. There is no isotope effect in such reactions, since the molecule no longer contains the isotopic atom in the rate-limiting stage. When HCN was eliminated from 2,6-dimethyl-4-(1,1,2,2-tetracyanoethyl)aniline in the presence of triethyl- or tri-n-butylamine, $k^H/k^D = 0.93$ was found[214]. Bordwell et al.[185] obtained $k^H/k^D = 1.7$ for the elimination of methanol from *trans*-2-methoxy-1-nitro-2-phenylcyclopentane using NaOMe–MeOH; k^H/k^D for the first stage (the formation of a carbanion) was normal and equal to 7.5. The same value was obtained for the formation of a carbanion from 2-nitro-1-phenylpropane using sodium t-butoxide in t-butyl alcohol[183].

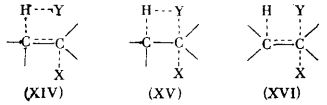
When water is eliminated from 9-fluoroenylmethanol, different β-hydrogen isotope effects are observed in water and methanol, the exchange being faster than elimination in both water and methanol[191,215]. In agreement with the results of the majority of the above studies, the isotope effects in the exchange processes are large ($k^H/k^D \simeq 7$). For water, the overall isotope effect (the isotope effect of the solvent) is $k^H/k^D = 0.92$ (the rate of reaction of the unlabelled substrate in unlabelled water was compared with the rate of reaction of the labelled substrate in labelled water[215]). The corresponding value for methanol is 0.36. Such an isotope effect of the solvent should in fact be expected for the reversible substrate–carbanion stage when the *E*1*cB* (type *B*) mechanism operates. It is unlikely that a combination of the primary isotope effect and the isotope effect of the solvent would give rise to such a low overall value of k^H/k^D for the *E*2 mechanism. However, More O'Ferrall and Slae[215] concluded on the basis of a detailed analysis of the initial rates of reaction of a labelled substrate in a labelled solvent and of an unlabelled

substrate in an unlabelled solvent that the competing $E2$ mechanism nevertheless makes a slight contribution to the reaction.

Thus it is seen from the data described above that the study of the isotope effects using substrates labelled in various positions makes it possible to distinguish both different mechanisms and different types of the same mechanism. The $E2$ and $E1cB$ (type A) mechanisms can be distinguished by studying the isotope effects for substrates with labelled α-carbon or X.

V. THE $E2H-E2C$ MECHANISMS

As early as 1956, de la Mare and Vernon [216] demonstrated the greater effectiveness of a weak base (the thiophenoxide ion) compared with a strong base (the ethoxide ion) in the elimination reaction which they catalysed (see the review of Saunders and Cockerill [163]). After this, it was frequently shown that very easy elimination is induced also by other weak bases, particularly halide ions in dipolar aprotic solvents [3,6,217-222]. Some workers [3,6,221-222] claimed that these reactions are more or less normal $E2$ reactions, but Winstein and coworkers [223] suggested that they be put in a separate $E2H-E2C$ group, which was also supported by other workers [224,225]. It is suggested that, in the $E2H-E2C$ range of mechanisms, the removal of β-hydrogen in the elimination reaction is accompanied to a greater or lesser extent and activated by attack by the Y base on the α-carbon atom ("from the rear" in relation to the C–X bond), as shown in models of activated complexes:



(XIV) (XV) (XVI)

E2H *E2C*

It is seen from the models that (XIV) does not differ in any way from the central synchronous $E2$ mechanism; (XV) and (XVI) differ primarily by the fact that the base Y attacks α-carbon and not β-hydrogen as in the $E2$ mechanism. This in fact makes them similar to the transition state in the S_N2 substitution reaction, and for this reason all $E2H-E2C$ mechanisms are combined under the general name "concurrent mechanisms". A characteristic feature of these reactions is that they are more effectively accelerated by weak bases provided that the latter are strong nucleophiles; the ratio of the products and certain characteristics of the reaction are altered somewhat under these conditions.

For example, treatment of secondary butyl and pentyl bromides as well as the corresponding toluene-*p*-sulphonates with strong nucleophiles and very weak bases in dipolar solvents (NBu_4Br in DMSO containing 2,6-lutidine) yields mainly the *trans*-olefin, in agreement with Zaitsev, while the reaction with a strong base and a weak nucleophile (t-BuOK–t-BuOH) yields mainly the *cis*-olefin, in agreement with Hoffmann [224]. Another communication [225] reported the influence of the alkyl, aryl, benzyl, bromo-, and methoxycarbonyl substituents on the rate of bimolecular elimination; according to the authors, the spectra of transition states ranging from $E2H$ to $E2C$ are obtained and the sensitivities of various transition states to changes in substituents are very different. The $E2C$ transition state, which is olefin-like, gives a high yield of the most stable isomer (the *trans*-olefin according to Zaitsev), provided that the requirement that the hydrogen atom and the leaving group are in the *anti*-positions is not too rigorous. Similar results are quoted in other papers by Parker and coworkers [223,226-229].

McLennan and Wong [230] determined $\rho = 2.11$ for the dehydrochlorination of $(p\text{-}RC_6H_4)_2CHCCl_3$ (R = OMe, Me, H, F, Cl, Br, or NO_2) in ethanol at 65°C, which is accelerated by sodium thiophenoxide. For the S_N2 reaction involving the substitution of chlorine by thiophenoxide in $(p\text{-}RC_6H_4)_2CHCHCl_2$ (R = OMe, Me, H, Cl, Br), which leads to $(p\text{-}RC_6H_4)_2C{=}CHSPh$, $\rho = 0.41$. Comparison of these values with that obtained for an $E2$ reaction in the presence of EtO^-–EtOH ($\rho = 2.34$) led the author to the conclusion that in the latter case dehydrochlorination proceeds via an $E2H$ transition state. The transition state in dehydrochlorination by a thiolate ion is $E2C$-like according to the author.

However, there have been very few studies on this problem; conclusions are frequently reached on the basis of secondary factors and those arrived at by one investigator are frequently disproved by others. Thus Parker, Winstein, and coworkers [223,224,231] proposed an $E2C$ mechanism for the reactions of secondary and tertiary butyl halides in acetone under the influence of weak bases (halide ions), while the results of Eck and Bunnett [232] conflict with this finding. It has been shown that, in the β-elimination of HBr from 2-bromo-2,3,3-trimethylbutane and from t-butyl bromide in acetone or dioxan, induced by chloride ions, the more "hindered" substrate reacts faster than the less "hindered" one [232]. This finding shows that the ion of the base does not approach the α-carbon atom in the transition state as required by the $E2C$ mechanism. Bunnett pointed out in his argument against the validity of the $E2C$ mechanism (and the necessity for it) [6,223] that elimination in such systems proceeds via the normal $E2$ mechanism ($E2H$ in terms of the new terminology of Winstein and Parker), but the relative nucleophilic reactivity of RS^-, RO^-, and tentatively Cl^- in relation to β-H depends on the degree of binding of the given base to the hydrogen in the transition state. When the base is strongly bound to the hydrogen, the alkoxide ion is more reactive, but, when the base interacts with β-hydrogen only slightly, the thiolate ion is a more effective base for the acceleration of an $E2$ reaction.

At any rate, as long as our understanding of the way in which the change in the solvating capacity of the solvent influences carbonium ions and carbanions in $E2$ reactions for different substrates with different bases is inadequate, one must be very cautious in adopting a particular view on this problem.

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Examination of the data in this review and the studies which have not been described here owing to lack of space permits certain generalisations concerning the β-elimination mechanism. If the substrate does not contain activating groups at the β-carbon atom but does have a leaving group with an enhanced tendency towards ionisation and an electron-donating substituent at the α-carbon atom, then in a strongly solvating weakly acid medium (in the absence of a base) unimolecular elimination via an $E1$ mechanism takes place for this type of substrate.

On the other hand, if the substrate contains an electron-donating substituent, which increases the electron density at the α-carbon atom, and an electron-accepting substituent, which induces a positive charge on the β-carbon atom, then, when the medium consists of a strong base in an aprotic polar solvent, bimolecular

elimination via an $E2$ mechanism takes place. Accordingly, any group which may neutralise the induced positive charge on the β-carbon atom by giving up electrons inhibits the reaction via an $E2$ mechanism.

If the electron-accepting group at the β-carbon atom and the base employed are moderately strong, then elimination proceeds via an "$E1$-like" $E2$ mechanism at a moderate rate. As the electron-accepting capacity of the substituent at the β-carbon atom becomes more pronounced and the strength of the base increases, there is also an increase in the rate of elimination. The elimination mechanism over a certain range of changes of this kind is then gradually altered from the "$E1$-like" type to the central synchronous type and further to the "$E1cB$-like" type, while remaining within the framework of the $E2$ mechanism. On further increase of the electronegativity of the group at the β-carbon atom and of the strength of the base employed, the bond between the β-hydrogen and carbon is weakened to such an extent that the substrate gives up this hydrogen in the form of a proton and forms a carbanion, the $E2$ mechanism being thus converted into an $E1cB$ (type A) mechanism. On the other hand, if the substrate contains a fairly strong electron-accepting group capable of stabilising the conjugate base of the substrate (such as C=O, C=N, NO_2 etc.), then the bond linking the β-hydrogen atom becomes so labile that there is no necessity for a very strong base and even in the presence of weak bases the substrate splits off this hydrogen in the form of a proton during the rapid reversible stage, forming the conjugate base—a carbanion, which loses the leaving group in the subsequent slow stage by a unimolecular process, being converted into an olefin, i.e. an $E1cB$ (type B) mechanism operates.

Thus one may conclude that each of the above specific types of the β-elimination mechanism is, strictly speaking, possible only for a specific compound under fixed conditions and that any changes in the structure of the substrate and in the reaction conditions lead to a shift of the mechanism towards the type which is preferred under the new conditions. Since the transition from one mechanism to another takes place gradually, the simultaneous occurrence of the reaction via two adjacent mechanisms is possible under borderline conditions.

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