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# THE STEREOCHEMISTRY AND MECHANISM OF DEHYDRATION OF CYCLOHEXANE DERIVATIVES

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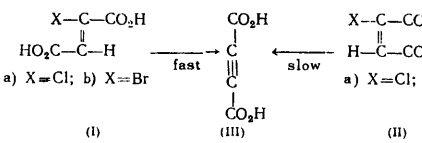
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## INTRODUCTION

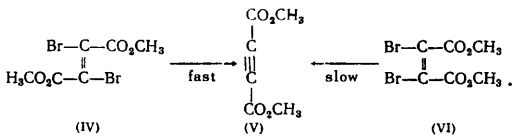
Since van't Hoff formulated the principles of the stereochemistry of tetravalent carbon, the attention of chemists has constantly been attracted to problems connected with the steric course of the fundamental chemical reactions, such as addition, elimination, and replacement, and with the differences in reactivity between geometric isomers. From a formal examination of the tetrahedral models of van't Hoff, it appeared natural that in substitution the entering atoms or group of atoms should occupy the same position as the leaving group, and that addition and elimination reactions should proceed most readily when the entering or leaving groups are as close as possible. This

concept was formulated by van't Hoff, and strongly supported by Wislicenus[1], as the *cis*-principle of steric elimination and addition. Wislicenus gave no experimental confirmation of his ideas, but he used them extensively as a general method for establishing the configuration of unsaturated compounds[1,2].

Michael[3,4] approached the study of steric behaviour in addition and elimination reactions in a different way. Taking as a basis his studies on the halogenofumaric and halogenomaleic acids, the configurations of which had been established independently, he showed that on being treated with alkali solutions the halogenofumaric acids (Ia, b) eliminate hydrogen halide to form acetylenedicarboxylic acid (III) (*trans*-elimination) more readily than the corresponding halogenomaleic acids (IIa, b) (*cis*-elimination).




Generalising Michael's observations, Pfeifer[5] suggested that the greater ease with which the elements of the hydrogen halide are eliminated when these are in the *trans*-position might be used to determine the configurations of unsaturated compounds (*trans*-principle of steric elimination). The validity of this principle was confirmed by Lossen[6], who found that when dimethyl dibromofumarate (IV) is debrominated with zinc, the reaction proceeds much more readily than the debromination of the diester of dibromomaleic acid (VI).




Shavanne[7], who held similar views, showed that *trans*-elimination can be much faster than *cis*-elimination, as exemplified by the isomeric *cis*- and *trans*-dichloroethylenes.

However, notwithstanding these and many similar reports, the idea that spatially adjacent groups are more readily eliminated was widely used to determine the configuration of compounds right up to the thirties. Thus, the configurations of the isomeric aldoximes and ketoximes, determined by Hantzschand Werner[8,9] on the basis of the *cis*-principle of the elimination of water with the formation of the corresponding nitrile, were not corrected until 1924–1925 (Meisenheimer[10]). The configurations of the amines of the terpene series established by Wallach[11] on the basis of the principle of preferential elimination of spatially adjacent groups was reexamined by Read *et al.*[12] as late as 1934. The configurations of the isomeric alicyclic alcohols, also adopted on the basis of this principle (Semmler[13], Wallach[14], and Zeitschel[15]) were corrected by Vavon and Barbier[16-18] in 1931.

Sufficient experimental evidence had accumulated in the early thirties to show that the *trans*-principle is valid for elimination reactions in solution (alkaline dehydrohalogenation, acid-catalysed dehydration of alcohols, conversion of oximes to nitriles, deamination of amines by nitrous acid, etc.). However, it was also known that the *cis*-elimination principle applies to pyrolytic reactions (the Chugaev reaction, pyrolysis of some esters, and cleavage of quaternary ammonium bases).

An understanding of the reasons for the differences in reaction stereochemistry became possible only with the development of the transition-state theory and of electronic theories in organic chemistry. A consideration of modern ideas on the steric principles of chemical reactions therefore presupposes elucidation of the relation between the stereochemistry and the reaction mechanism. This relationship appears, for example, because electron displacements in a system reacting in a definite way can only arise when the reaction groups are appropriately oriented (in the English literature this principle is formulated as "the steric requirements of the reaction"; for example, the *trans*-orientation of groups in bimolecular eliminations). The steric arrangement of the molecule can materially affect the reaction rate within the limits of a given mechanism (steric and synartetic acceleration); the change in reaction mechanism produced by structural factors is an extreme expression of such an effect.

The object of the present review is to examine the stereochemistry of direct and indirect dehydration† of alicyclic six-membered hydroxy-compounds. This limitation is made for two reasons: firstly, within the scope of a comparatively short review it is impossible to consider the literature on the dehydration of all organic compounds: secondly, it is in the case of six-membered alicyclic compounds that the steric principles of dehydration have been studied in greatest detail.

The overwhelming majority of the dehydration reactions of alicyclic alcohols that have been investigated may be divided into two main groups, reactions in solution and intramolecular pyrolysis reactions without a solvent or catalyst. The structure of the corresponding transition states forms the basis of the division of dehydration reactions into two groups. In the first group this structure is an open one and solvent molecules as well as ions in solution may take part in its formation. In the second group the transition state is closed (cyclic). The latter reactions are always unimolecular. We shall therefore examine the main stereochemical features of reactions of both types in turn.

## I. IONIC DEHYDRATION REACTIONS IN SOLUTION

The interpretation of the mechanism of these reactions as a special case of nucleophilic elimination was developed and experimentally confirmed by the Ingold–Hughes[19-22] school as early as the 1930's. The following are the main conclusions. Nucleophilic elimination reactions may proceed either by a unimolecular or by a bimolecular mechanism (E1 or E2)‡, according to the structure of the initial

† By "indirect dehydration" is understood elimination of the elements of the acid from the esters of the corresponding hydroxy-compounds.

‡ In recent years it has been shown that elimination reactions are not quite correctly represented by E1 and E2 mechanisms; because of solvent participation, these reactions are in fact polymolecular. However, since this solvent participation does not change the spatial direction of electron transfer, and therefore the stereochemical reaction requirements, we shall use the interpretations of Ingold on E1 and E2 elimination mechanisms.

molecule and the experimental conditions employed. The bimolecular E2 mechanism is characteristic of elimination reactions occurring in the presence of a strong base[19,22]. It may be represented by the following scheme:

$$Y^- + H-C_\beta R_2-C_\alpha R_2-X \longrightarrow Y\cdots H\cdots C_\beta R_2\cdots C_\alpha R_2\cdots X \longrightarrow YH + CR_2{=}CR_2 + X^-, \quad (1)$$

according to which a hydrogen atom is removed as a proton by means of the nucleophilic reagent (for example, the base $Y^-$), and simultaneously the $C_\beta - H$ bond electrons liberated are transferred to the octet of the $C_\alpha$ atom, and the electron-acceptor group X is eliminated as an anion. The E2 mechanism therefore implies that the formation of the new and the rupture of the old bonds are synchronous processes, the one facilitating the other. From the foregoing, it follows that a reaction proceeding by the E2 mechanism may be represented by a second-order kinetic equation: $V = K_2[Y^-][HCR_2-CR_2X]$.

The second possible elimination mechanism is the unimolecular E1 mechanism[20,22], which occurs in two steps:

$$\left.\begin{array}{l} HCR_2-CR_2X \xrightarrow[\text{slow}]{} HCR_2-C^+R_2+X^- \\ HCR_2-C^+R_2 \xrightarrow{\text{fast}} H^+ + CR_2{=}CR_2 \end{array}\right\}. \quad (2)$$

The first slow step is a unimolecular heterolysis (in which the nucleophilic reagent does not take part), as a result of which a carbonium ion is formed; this loses a proton by interaction with the solvent or with another nucleophilic reagent and is stabilised as an olefine. Since the reaction rate depends on the slowest step, the rate of an E1 reaction is independent of the concentration of the base and is represented by a first-order kinetic equation: $V = K_1[HCR_2CR_2X]$.

The kinetic method is therefore the main experimental procedure used to distinguish between E1 and E2 elimination mechanisms, and it has been developed in detail for this purpose by Ingold's school. In 1947 Cristol[23] suggested the use of kinetic results together with the analysis of the final mixture of products for the investigation of the steric course of elimination reactions, and a number of important general quantitative principles have been established by this means.

When the reaction mechanism cannot be decided unambiguously by the kinetic method, useful results may be obtained by the tracer method, developed for this purpose by Skell and Hauser[24]. With this method it is possible, for example, to distinguish between second-order bimolecular reactions and so-called elimination reactions of the conjugate base of the substrate (E1*cB*)[22]:

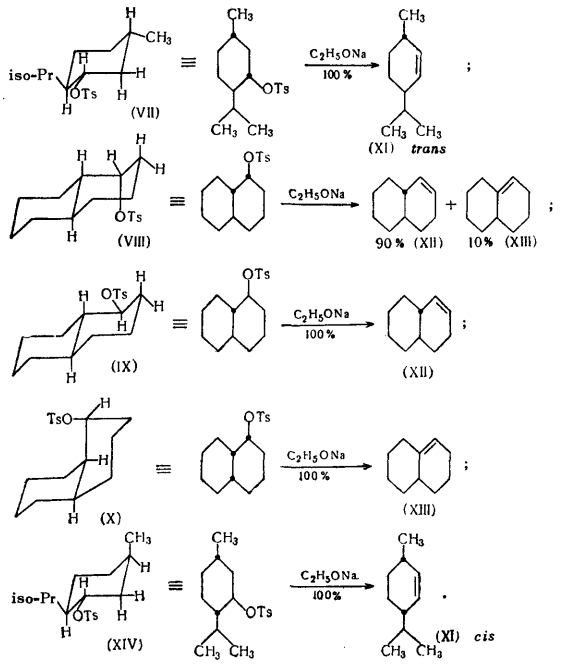
$$\left.\begin{array}{l} Y^- + HCR_2-CR_2X \rightleftarrows YH + C^-R_2-CR_2X \\ C^-R_2-CR_2X \rightarrow X^- + CR_2{=}CR_2 \end{array}\right\} \quad (3)$$

Such reactions are two-stage and include a reversible bimolecular step in which the conjugate base (carbanion) is formed; this then eliminates an electron-acceptor group as an anion and forms an olefine. The reversibility of the first stage of this reaction is utilised to verify it experimentally. If an E1*cB* mechanism operates in the presence of YH enriched with YD, the initial product $HCR_2CR_2X$ unreacted after a definite time must be enriched with $DCR_2CR_2X$. In contrast, with the synchronous E2 mechanism the unreacted compound should not contain deuterium.

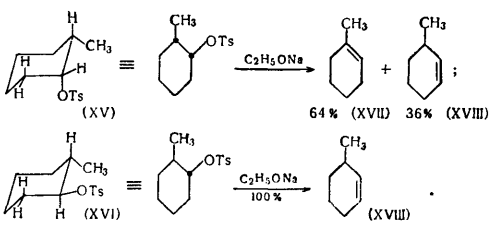
This method also found an interesting application in the elucidation of reaction mechanisms when the stereochemistry of the initial molecule does not allow the elimination mechanism expected from the experimental conditions (see below).

## 1. Stereochemistry of Bimolecular Dehydration Reactions

**Preferred orientation in bimolecular dehydrations.** In 1940 Hückel *et al.*[25] first clearly formulated the principle that the steric course of a reaction depends on its mechanism. Having analysed a large amount of experimental material, they showed that the *trans*--principle is rigidly followed in elimination reactions occurring in the presence of a strong base (they considered such reactions to be bimolecular). Of other reactions, they examined one of the types of indirect dehydration — the cleavage of the *p*-toluenesulphonates (tosylates) of *l*-menthol (VII) and the isomeric decalols (VIII)–(X)§ by sodium ethoxide. Since it was later rigorously proved[26,27] that the E2 mechanism applies to the cleavage of tosylates by strong bases, this reaction is a convenient example for examination of the stereochemistry of bimolecular indirect dehydration:

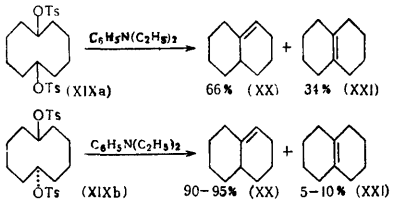



As the examples given show, the *p*-toluenesulphonic acid residue is eliminated together exclusively with the hydrogen situated *trans* to it. This was confirmed by Hückel *et al.*[28,29] with the isomenthyl tosylates (XIV) and also with those of the *cis*- and *trans*-2-methylcyclohexanols (XV) and (XVI):




§ Here and throughout the review hydrogen atoms in the *cis*-position are denoted by heavy dots.

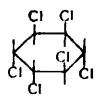
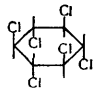
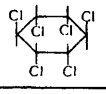
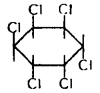
An interesting application of the concept of *trans*-orientation in the bimolecular cleavage of tosylates is the conversion of the tosylates of the isomeric cyclodecane-1,6-diols (XIXa, b) under the action of diethylaniline, which has been investigated by Cope and Holzman[30]:



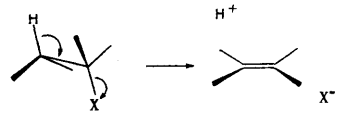

It was established that the *cis*-isomer (XIXa) thus forms a mixture of $\Delta^{1,9}$- and $\Delta^{9,10}$-octalins (XX) and (XXI) in the ratio 2:1, but the *trans*-isomer (XIXb) forms a mixture of the same products in the ratio (10–20):1. Since the authors showed that the isomeric octalins were not mutually interconvertible, they interpreted the reaction as stereospecific elimination: the first molecule of *p*-toluenesulphonic acid is eliminated more rapidly than the second, and the configuration of the isomeric tosylates of 9-decalol thus formed determines the structure of the final reaction products; *trans*-9-decalol tosylate yields a considerable quantity of $\Delta^{9,10}$-octalin (XXI), but the *cis*-isomer forms mainly $\Delta^{1,9}$-octalin (XX), in accordance with the elimination principle.

Cristol *et al.*[31] made a quantitative study of bimolecular indirect dehydration using dehydrochlorination of the isomeric hexachlorocyclohexanes. As the results in Table 1 show, the β-isomer, whose structure permits only *cis*-elimination of hydrogen chloride, is cleaved by bases at a rate about $10^4$ times slower than the isomeric compounds, and the energy of activation of the dehydration reaction is about 10 kcal mole$^{-1}$ higher.

TABLE 1. Dehydrochlorination of isomeric hexachlorocyclohexanes.

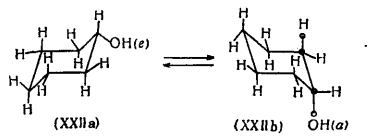
| Initial compound | $K$ at 30° | $E_{act}$, kcal mole$^{-1}$ |
|---|---|---|
| α  | 0.500 | 18.5 |
| β  | $2.11 \cdot 10^{-5}$ | 31.0 |
| γ  | 0.151 | 20.6 |
| ε  | 0.182 | 21.4 |

The reasons for preferential *trans*-orientation in bimolecular elimination have been discussed by Hughes, Ingold, and their coworkers[32]; they showed that "in the transition state for bimolecular elimination from the $HCR_2-CR_2X$ system, the energy of repulsion between the electron pairs can be reduced to a minimum, if the electrons of the $C_\beta-H$ bond enter the $C_\alpha$ atom octet on the side remote from X. The result of this steric course in the transfer of electrons is *anti*-elimination¶" (E2 rule).




The general applicability of the E2 rule to elimination reactions has been repeatedly confirmed on various examples[22,32,33], and it has been shown that the most favourable conformation of the molecule to undergo *anti*-elimination is that in which the four participating centres are coplanar.

Role of reaction conformations of cyclic alcohols in dehydration. The application of the E2 rule to the dehydration of alicyclic hydroxy-compounds requires primarily a detailed examination of their structures. According to the theory of conformational analysis[34], the hydroxy-compounds of the cyclohexane series consist of an equilibrium mixture of two chair conformations (XXIIa, b) with the hydroxy-groups arranged equatorially or axially:



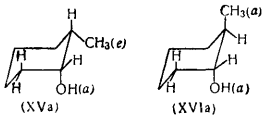

Under ordinary conditions, the preferred conformation is (XXIIa), its potential energy being about 2 kcal mole$^{-1}$ lower than that of conformation (XXIIb). However, this preferred conformation does not meet the steric requirements of bimolecular dehydration, whereas the second, energetically less suitable, conformation (XXIIb), with an axial hydroxy-group at $C_1$ and an axial hydrogen atom at $C_2$, has the coplanar arrangement of the four reaction centres (indicated by circles) and the antiparallel arrangement of the leaving groups† necessary for bimolecular dehydration.

Examination of the conformation of cyclohexane derivatives led Barton[33] to suggest that these compounds enter into chemical reactions in the conformation which more nearly meets the steric requirements of the given reaction; he termed these the reaction conformations for the particular reaction. If the reaction conformation is the less stable one, the corresponding reaction is preceded by the conversion from the preferred to the reaction conformation. Therefore, in bimolecular dehydration the reaction conformation is the one with *trans*-diaxial arrangement of the

¶ By "*anti*-elimination" is understood an arrangement of the leaving groups such that the angle between them is close to 180°. The term "*trans*-antiparallel elimination" is used in the same sense.

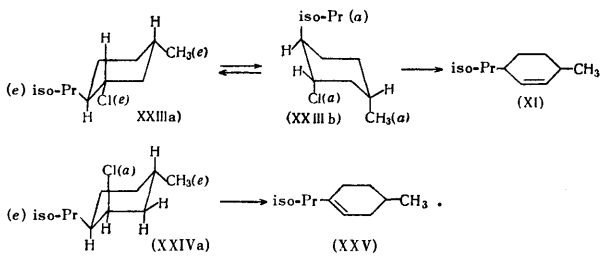
† It should be borne in mind that for some substituted cyclohexanols the conformation with an axial hydroxy-group may also be energetically preferred.

leaving groups[33,35], that is, conformation (XVa) for *cis*-2--methylcyclohexanol and (XVIa) for *trans*-2-methylcyclohexanol:



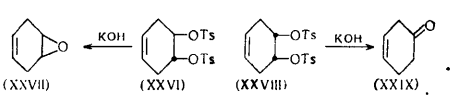
(XVa) (XVIa)

The idea that elimination in the cyclohexane derivative series is effected from the *trans*-diaxial conformation was confirmed by a study of bimolecular dehydrochlorination, one of the most interesting examples being the dehydrochlorination of menthyl- and neomenthyl chlorides (XXIII) and (XXIV) (Hughes, Ingold, and Rose[36]) with sodium ethoxide:



Having studied the kinetics of the conversion, these workers showed that menthyl chloride (XXIII) undergoes bimolecular dehydrochlorination forming $\Delta^2$-menthene at concentrations of $EtO^-$ greater than 1.0 *N* ($K_2^{124.9^\circ} = 0.68 \times \times 10^{-5}$), while neomenthyl chloride (XXIV) is converted by bimolecular dehydrochlorination to $\Delta^3$-menthene (XXV) at concentrations of $EtO^-$ about 0.1 *N* ($K_2^{124.9^\circ} = 131 \times 10^{-5}$). The marked difference between the rates was explained by comparing the reaction conformations of both epimers in the dehydrochlorination reaction. As the schemes presented show, only the energetically less suitable conformation (XXIIIb) can be the reaction conformation in bimolecular elimination from menthyl chloride, the product being the thermodynamically less stable $\Delta^2$-menthene (XXV). In contrast, for neomenthyl chloride the reaction conformation is the energetically‡ favoured conformation (XXIVa), which leads to the thermodynamically more stable $\Delta^3$-menthene (XXV) by *trans*-diaxial elimination.

Examination of the role of reaction conformations in indirect bimolecular dehydrations also permits certain details of the stereochemical features of this reaction to be understood. Thus, for example, in a study of cleavage with potassium hydroxide of the isomeric *cis*- and *trans*--$\Delta^4$-cyclohexene-1,2-diols[37], it was found that the *trans*--isomer (XXVI) is converted to the corresponding epoxide (XXVII), but the *cis*-isomer (XXVIII) forms $\Delta^3$-cyclohexenone (XXIX) at a rate 6 to 7 times faster than that for the corresponding saturated diols:

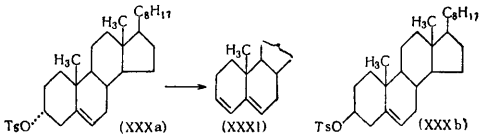


(XXVII) (XXVI) (XXVIII) (XXIX).

‡ From the point of view of conformational analysis the conformation with the maximum number of equatorial substituents is energetically more suitable.

The authors explain this in the following way. For compounds of the cyclohexene series, in the transition state the *meta*-diaxial interaction of the tosyl groups with hydrogen atoms is absent, and consequently the steric requirements of bimolecular dehydration are more easily met.

The necessity for *trans*-diaxial orientation of the leaving groups in bimolecular dehydration has been shown most clearly with polycyclic compounds; because of the rigid articulation in these, the transformation of rings, with all the axial groups becoming equatorial and *vice versa*, is excluded. The published experimental results deal mainly with the base-catalysed cleavage of the tosylates of steroid hydroxy-compounds. Thus, the tosylate of epicholesterol (XXXa) with an axial 3$\alpha$-hydroxy-group and a hydrogen atom at $C_4$ readily eliminates *p*-toluenesulphonic acid to give $\Delta^{3,5}$-cholestadiene[27] in 75–80% yield, when it is heated with sodium ethoxide in ethanol.

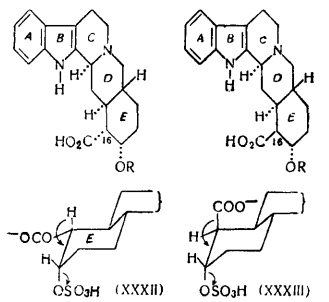


(XXXa) (XXXI) (XXXb)

The cholesteryl tosylate (XXXb), epimeric at $C_3$ and having an equatorial hydroxy-group, only undergoes a substitution reaction[38] under the conditions described.

The epimeric steroid compounds with the hydroxy-group at $C_{12}$ behave similarly; elimination of *p*-toluenesulphonic acid, which occurs even on shaking with alkaline aluminium oxide[39], is characteristic of the 12$\alpha$-isomers of these compounds (with an axial hydroxy-group).

The base-catalysed cleavage of the sulphuric esters of yohimbic (XXXII) and corynanthic (XXXIII) acids[40], which are epimeric at $C_{16}$, is an interesting example of bimolecular dehydration in the polycyclic alkaloid series.

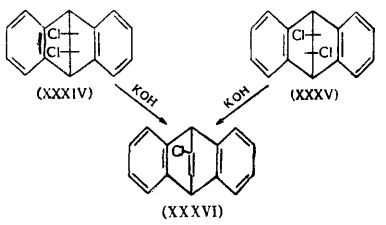


(XXXII) (XXXIII)

Here, as a result of *trans*-diaxial elimination, the ester (XXXII) eliminates only sulphuric acid, but the epimeric ester (XXXIII) undergoes simultaneous decarboxylation.

A striking confirmation of the necessity of a *trans*--coplanar arrangement of leaving groups for the normal course of bimolecular indirect dehydration was obtained by

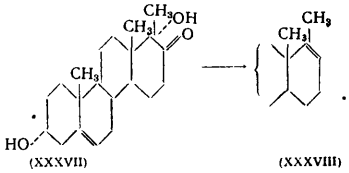
Cristol *et al.*[41] in studies on the alkaline dehydrochlorination of *cis*- and *trans*-11,12-dichloro-9,10-dihydro-9,10-ethyleneanthracene (XXXIV) and (XXXV).



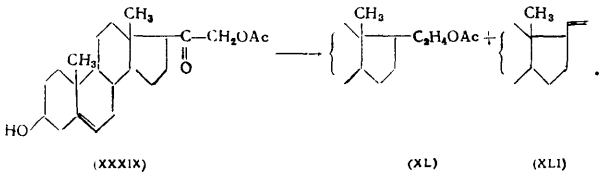

Because of the steric peculiarities of bridge systems of this type, the chlorine atoms at $C_{11}$ and the hydrogen at $C_{12}$ cannot be coplanar, that is, even the isomer (XXXIV) with the removable elements of hydrogen chloride *trans*-oriented does not satisfy the steric requirements of bimolecular dehydration. A consequence is the extraordinary low rate at which (XXXIV) is dehydrochlorinated ($K_2^{110°} = 6.39 \times 10^{-5}$), which is about the same as the rate of *cis*-dehydrochlorination of β-hexachlorocyclohexane (see p. 21) and $10^4$ times slower than the rate for the normal *trans*-diaxial dehydrochlorination (*cf.* Table 1).

A similar retardation of indirect dehydration due to the impossibility of a *trans*-diaxial orientation of the leaving groups was noted with *cis*-12-chloro-9,10-dihydro-9,10-ethanoanthracene 11-tosylate[42] and *endo-cis*-2,3-dichloronorbornane[43].

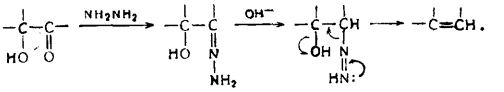
Bimolecular elimination under Kishner--reaction conditions. A special case of bimolecular dehydration arises when α-hydroxy-ketones are reduced under Kishner conditions. As early as 1940, Ruzicka and Meldahl[44] showed that the reduction of 17a-methyl-$\Delta^5$-D-homoandrostene-3α,17a-diol-17-one (XXXVII) is accompanied by the elimination of water and leads to the anomalous product (XXXVIII), without oxygen-containing functional groups at $C_{17}$.



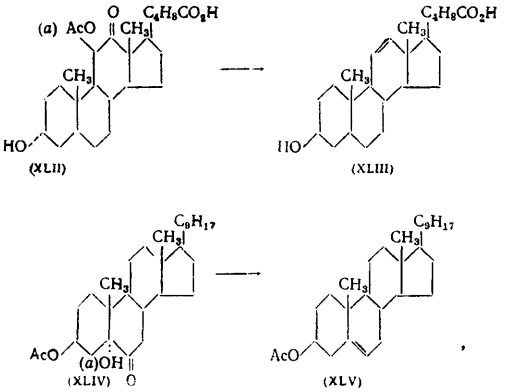

Barton *et al.*[45] found that the Kishner reaction proceeds similarly with the 21-acetate of $\Delta^5$-pregnene-3β,21-diol-20-one (XXXIX), forming $\Delta^{5,20}$-pregnadien-3β-ol (XLI) in addition to the normal reduction product (XL). To explain the



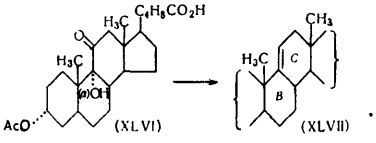

formation of the anomalous product (XLI), Barton suggested that bimolecular elimination occurs in addition to the main reaction:



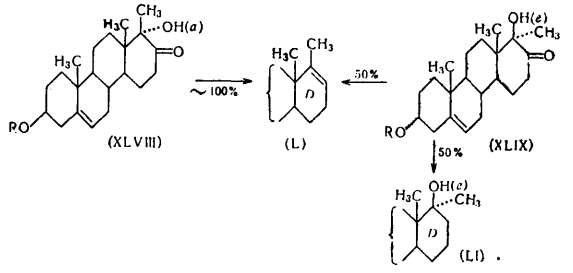
From the proposed mechanism, α-hydroxy-ketones with an axial hydroxy-group would be expected to undergo elimination under Kishner conditions with particular ease. This was confirmed by Long and Gallagher[46] with 3α-hydroxy-11β-acetoxy-12-oxocholanic acid (XLII) and by Barton and Robinson[47] with $\Delta^{22}$-ergostene-3β,5α-diol-6-one-3β-acetate (XLIV):




and also by Heymann and Fieser[48] with 3α-acetoxy-9α-hydroxy-11-oxocholanic acid (XLVI):

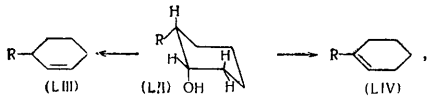



A characteristic difference in the behaviour of epimeric compounds, as exemplified by the hydroxy-ketones (XLVIII) and (XLIX), has been described by Turner[49]:




Kishner reduction of the 18α-hydroxy-ketone (XLVIII) with an axial hydroxy-group gives the elimination product (L) almost quantitatively, but the 18β-hydroxy-ketone (XLIX) with an equatorial hydroxy-group gives the normal reduction product (LI) (~50%) in addition to the $\Delta^{5,17}$-diene (L).

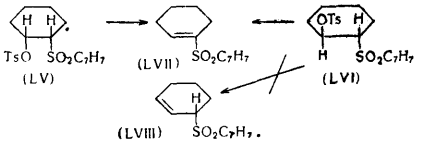
Structure of the initial molecule and the steric effect in bimolecular dehydration. The foregoing experimental results on the stereochemistry of bimolecular dehydration amply confirm Ingold's E2 rule, according to which the main factor determining the course of this reaction is the antiparallel orientation of the groups eliminated from the initial molecule. However, when the conformation of the initial molecule, for example (LII), permits elimination in two different ways:




other factors affecting the mode of elimination, and consequently the ratio of the isomeric products (LIII) and (LIV) formed in this reaction, must be considered. Of these Ingold[32,50] considers the polar factor to be the main one, that is, the possibility of stabilising the transition state leading to the corresponding olefine by hyperconjugation. According to Ingold, the main component in the mixture of isomers should therefore be the cycloolefine (LIV), the formation of which is in accordance with Zaitsev's extended rule[51].

Brown[52,53] investigated another aspect of the problem: he showed conclusively that steric factors — size of substituent and of the attacking base — play a significant part in determining the ratio of isomers in addition to the polar factor.

The effect of the structure of the initial molecule is not limited merely to determining the preferred mode of elimination within the framework of the E2 rule. Recently, Bordwell[54], using the base-catalysed cleavage of the tosylates of the isomeric *cis*- and *trans*-2-*p*-toluenesulphonylcyclohexanols (LV) and (LVI), showed that when the molecule of the hydroxy-compound contains a strong electron-acceptor group, the polar factor (participation in the elimination of a hydrogen atom activated by this group) determines the mode of indirect dehydration, even when this mode is opposite to that expected from the principle of *trans*-diaxial elimination:

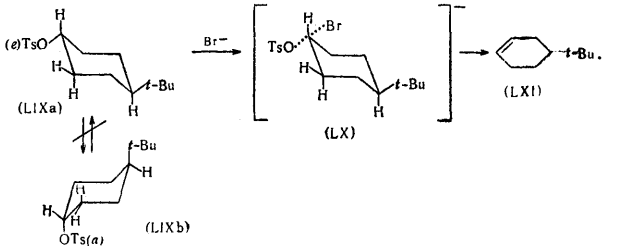



It was found that both isomeric tosylates are converted to the same primary cleavage product, the $\alpha\beta$-unsaturated sulphone (LVII), and the $\beta,\gamma$-unsaturated sulphone (LVII) is not formed in the reaction. This indicates that the elimination of the *trans*-tosylate (LVI) proceeds as a *cis*-elimination. A similar principle was found in the base-catalysed cleavage of *trans*-2-*p*-toluenesulphonylcyclopentyl tosylate, 1-*p*-toluenesulphonylprop-2-yl tosylate[55] and the barium salt of *trans*-2-sulphocyclopentyl hydrogen sulphate[56]. Here and in the cases described above (pp. 21 and 23) *cis*-elimination under conditions of bimolecular elimination is not in accord with the steric requirements of the E2 mechanism.

Since these reactions are much slower and require greater activation energies than *trans*-elimination under similar conditions, Ingold[57] suggested that the additional energy is used in "bending" the molecule and ensuring that its geometry is as close as possible to the geometrical requirements of the E2 mechanism. Ingold believes that the elimination itself proceeds according to the scheme proposed for the bimolecular reaction. Unfortunately, it has not yet been possible to verify Ingold's views experimentally.

The opposite view on the mechanism of *cis*-dehydration in the presence of a strong base has been put forward by Cristol, who suggested that reactions of this kind proceed not by an E2 but by an E1*cB* mechanism (see p. 20). As has been shown above, this mechanism can be verified experimentally by deuterium exchange. The application of this method to the dehydrochlorination of $\beta$-hexachlorocyclohexane[58] has shown that the transition state in this reaction is in fact a carbanion. However, this cannot be considered to be the general *cis*-elimination mechanism under conditions of bimolecular dehydration, since examination of the cleavage kinetics[59] and deuterium exchange[60] of the tosylate of *trans*-2-*p*-toluenesulphonylcyclohexanol (LVI) has shown that under the reaction conditions not even an unstable carbanion is formed.

A third possible mechanism has been suggested by Winstein[61] for the cleavage with bromide ions (second-order kinetics) of *trans*-diequatorial-4-*t*-butylcyclohexyl tosylate (LIXa), for which transition to the diaxial conformation (LIXb) is hindered (see p. 25):




This scheme includes attack of the $Br^-$ base ion at the $C_1$ atom with the formation of the transition state (LX), which can easily be converted to $\Delta^3$-*t*-butylcyclohexene (LXI) by simultaneous elimination of $H^+$, $Br^-$, and $OTs^-$.

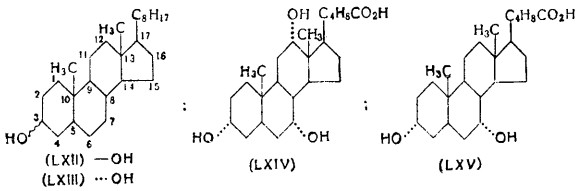
As none of these three mechanisms gives an entirely satisfactory explanation of the known experimental facts, the problem of the mechanism of *cis*-elimination under the conditions of bimolecular indirect dehydration cannot be regarded as solved.

## 2. Stereochemistry of Unimolecular Dehydration Reactions

From the general ideas on the mechanism of unimolecular elimination reactions (see p. 20) it follows that these reactions can occur in ionising solvents in the absence of a strong base. Such conditions exist in the acid-catalysed dehydration of alcohols, and also in the solvolysis of their tosylates in weak nucleophilic solvents (hydrolysis, acetolysis, alcoholysis, etc.). Since kinetic studies[32,62] have afforded rigorous proof that reactions of this type are unimolecular, they may be used as suitable examples in an examination of the stereochemical features of unimolecular dehydration.

Vavon and Barbier[16] showed that in the alkylcyclohexanol series the *cis*-isomers are dehydrated under milder thermal conditions and more rapidly than the *trans*-isomers. Their experimental results (Table 2) give a sufficiently clear idea of this difference in behaviour.

The dependence of dehydration rate on configuration has been repeatedly confirmed both in the monocylic-alcohol and in the hydroxy-steroid series[33]. As has been shown above, in the discussion on bimolecular reactions *trans*--dehydration proceeds most readily when the eliminated atomic groups occupy axial positions. This also holds for unimolecular dehydration[67,68]; a characteristic example is the dehydration of the epimeric cholestanol [3$\beta$(*e*)-OH group]§ (LXII) and epicholestanol [3$\alpha$(*a*)–OH group] (LXIII) on heating for 60 h with sulphuric acid[68,69]. Here the epimer (LXIII) with an axial hydroxy-group




forms a mixture of 2- and 3-cholestenes in 60% yield, but the epimer (LXII) reacts to the extent of only 28%.

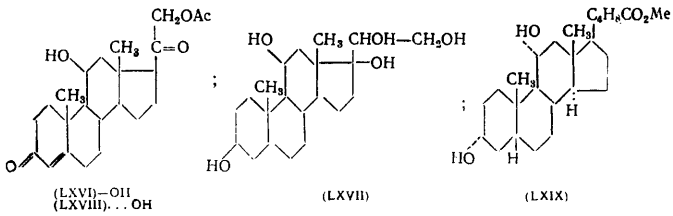
Acid catalysed dehydration in the steroid series also proceeds readily when the axial hydroxy-group at $C_7$ participates, as has been shown for cholic (LXIV) and chenodeoxycholic (LXV) acids[70-72]. Detailed studies have also been made on the dehydration of 11-hydroxy--steroids[73], which proceeds readily with natural

TABLE 2. Dehydration of isomeric alkylcyclohexanols.

| Alcohol | Time required for 25% dehydration, min | | | |
|---|---|---|---|---|
| | 77° | 120° | 140° | 160° |
| Cyclohexanol | | | 155 | |
| 2-Methylcyclohexanol, *cis* | | | 10 | |
| *trans* | | | | 78 |
| 2-Ethylcyclohexanol, *cis* | | | 9 | |
| *trans* | | | 43 | |
| 2-Propylcyclohexanol, *cis* | | | 11 | |
| *trans* | | | | 30 |
| 2-Isopropylcyclohexanol, *cis* | | | 9 | |
| *trans* | | | | 24 |
| 2-Butylcyclohexanol, *cis* | | | | 7 |
| *trans* | | | | 15 |
| 4-Isopropylcyclohexanol, *cis* | not examined | | | |
| *trans* | | | | 48 |
| 4-Butylcyclohexanol, *cis* | | | | 15 |
| *trans* | | | | |
| Neomenthol | | | 185 | 38 |
| Menthol | | | 10 | 30 |
| Isoborneol | 5 | | | |
| Borneol | | | | 37 |

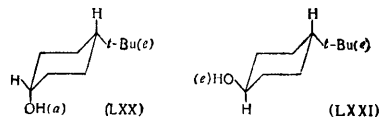
§ In accordance with the accepted nomenclature for steroid compounds, the substituent above the plane of the rings is termed the "$\beta$" -substituent and is denoted by a continuous line; the substituent below the plane is termed "$\alpha$" and is denoted by a dotted line.

compounds containing the 11$\beta$(*a*)–OH group. Thus, corticosterone acetate (LXVI)[74] and allopregnane-3$\beta$,11$\beta$,17,20,21--pentaol (LXVII)[75,76] are readily dehydrated by heating for 0.5 h with a mixture (1 : 9) of hydrochloric and acetic acids, but the 11$\alpha$(*e*)-hydroxy-compounds, 11$\alpha$-epicorticosterone acetate (LXVIII) and the methyl ester of 3$\alpha$,11$\alpha$-dihydroxycholanic acid (LXIX)[46] are not dehydrated under these conditions.




Preferential *trans*-elimination is also characteristic of the indirect dehydration that occurs in the solvolysis of the tosylates of cyclic alcohols; this has been observed in studies on the ethanolysis and acetolysis[77] of the tosylates of the isomeric menthols[78-80], decalols[79-82], cholestanols[83,84], and ergostanols[83].

Chemical conformational analysis according to Winstein. In 1940 Hückel[85] suggested that the known difference in the rates of solvolysis of the tosylates of isomeric alcohols could be used to determine their configurations, and in 1955 Winstein and Holness examined the possibility of quantitatively evaluating the conformational composition of these compounds on the basis of differences in their rates of solvolysis[86]. Their method is based on the following principle. The observed unimolecular solvolysis rate is related to the mole fractions of the conformations in the initial compound containing axial or equatorial hydroxy-groups by the equation $K = K(e)N(e) + K(a)N(a)$, where $K$ is the constant of the observed first-order reaction rate, $K(e)$ and $K(a)$ are the respective rate constants for the solvolysis of compounds containing only one conformation with either an (*e*)- or an (*a*)-hydroxy-group, these being the same in different compounds; $N(e)$ and $N(a)$ are the mole fractions of the (*e*)- and (*a*)-conformations. This equation can only be applied successfully if the conformationally homogeneous compounds, for which $N(e)$ or $N(a)$ is zero can be obtained. As examples of such compounds the authors examined *cis*- and *trans*-4-t-butylcyclohexanols (LXX) and (LXXI), for which the conformations with an equatorial arrangement of the *t*-butyl group are more favoured by 5.4–5.8 kcal mole$^{-1}$ than the corresponding rotational isomers. It is highly probable that this value ensures conformational homogeneity, so that for (LXX) $N(e) = 0$, and for (LXXI) $N(a) = 0$.

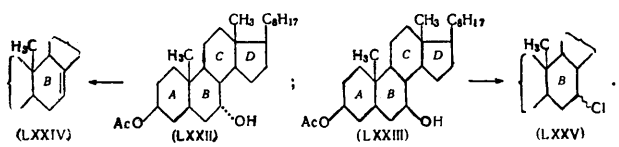



Winstein determined the values of $K(e)$ and $K(a)$ from an examination of the solvolysis of the tosylates of the alcohols (LXX) and (LXXI); these were then used to evaluate the conformational composition of cyclohexanol [$N(a)$ = = 19 ± 7%] and some of its homologues. This approach to

the quantitative evaluation of the conformational composition of compounds was critically examined by Hückel and his coworkers [87-89], who showed conclusively that the solvolysis rate depends substantially on the experimental conditions (solvent, reaction time, presence of additives, temperature). Even when solvolysis is effected under standard conditions, quantitative conformational analysis on the basis of Winstein's equation leads to considerable errors [89], firstly, because solvolysis is not always a rigorously unimolecular reaction, and, secondly, because the structure of the initial molecule significantly affects the rate of solvolysis. Therefore $K(e)$ and $K(a)$ are not constant for different compounds. These limitations do not change the qualitative hypotheses on the relation between mechanism and steric orientation in the elimination reaction, but they exclude the possibility of a quantitative approach to these phenomena.

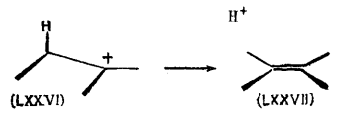
Limitation of steric specificity in unimolecular dehydration. Although *trans*-elimination markedly predominates over *cis*-elimination in unimolecular dehydration, this reaction is not so rigorously stereospecific as bimolecular dehydration, in which the rate of *cis*-elimination is many times less than the rate of *trans*-elimination, and the difference in the activation energies of the two processes exceeds 10 kcal mole$^{-1}$. [31] Moreover, as has been shown above (see p.24), dehydration by the bimolecular mechanism does not occur if the configuration of the initial molecule does not allow *trans*--antiparallel elimination. In contrast, as can easily be seen from the examples above, the rate of *trans*-elimination in unimolecular dehydrations is only a few times the rate of *cis*-elimination, which proceeds by the same mechanism.

A striking example of the absence of well defined steric selectivity under unimolecular reaction conditions is the dehydration of hydroxy-compounds with phosphorus oxychloride and pyridine [90] or thionyl chloride and pyridine [91]. Notwithstanding the comprehensive experimental data on this question, a sufficiently clear preponderance of *trans*--diaxial elimination has been observed in only a few cases. Thus, Fieser [92] showed that *trans*-diaxial elimination is preferred for the monoacetates of Wintersteiner's epimeric diols (LXXII) and (LXXIII); the 7$\alpha$-epimer[$(a)$-OH] (LXXII) is readily converted to $\Delta^7$-cholestenol (LXXIV), but the 7$\beta$-epimer (LXXIII) [$(e)$-OH] undergoes substitution only.




Similar reactions have been observed by Barton [93] with lanostane-3$\beta$,7$\alpha$-diol acetate, and by Davis and Petrow [94,95] with the isomeric cholestane-3,5,6-triols. However, in other reported cases the results obtained cannot be explained by preferential *trans*-elimination. Thus, the dehydration of 11$\alpha$- and 11$\beta$-hydroxy-compounds of the steroid series with $POCl_3$ in pyridine proceeds equally smoothly with both isomers, permitting a double bond to be introduced into the $\Delta^{9,11}$-position [96-99].

The lack of rigorous stereospecificity in the unimolecular dehydration reaction is easy to understand if its mechanism is considered. Reactions of this type are known to start with ionisation, the transition state being a planar carbonium ion (LXXVI). If this ion is capable of prolonged existence, it assumes a planar form and in this limiting case elimination is independent of the initial spatial configuration.




If the elimination is completed before the leaving group $X^-$ is removed a sufficient distance from the planar ion, *anti*(*trans*)-elimination will occur preferentially. If, however, nucleophilic groups, suitably arranged to maintain the configuration of the carbonium ion until the elimination is completed, are present, *syn*(*cis*)-elimination (E1 rule) [22] will occur.

Unimolecular dehydration reactions can therefore only be used to determine the configuration of the initial compounds with great caution, and the explicit claim frequently encountered in the literature (Barton [33], Barton and Rosenfelder [67]) that *trans*-elimination is the rule in ionic elimination reactions is justified only when the structural details of the initial compound and the mechanism of the given ionic reaction have been fully considered.

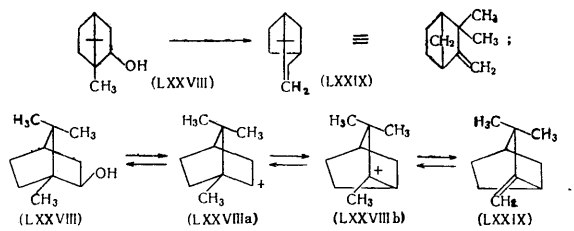
Apart from the lack of stereospecificity in this reaction, the use of multistage unimolecular reactions to obtain information about the configuration of the relevant compounds is complicated by the further consideration that the intermediate carbonium ion may undergo a variety of rearrangements. Thus, in nearly all the acid-induced dehydrations mentioned above the cycloolefines¶ formed isomerise with respect to the double bond, and in some cases the carbon framework of an initial molecule with a given structure and configuration may undergo extensive rearrangement. A particularly interesting example of a conversion of this type is the Wagner–Meerwein rearrangement, which frequently accompanies dehydration.

Stereochemistry of the Wagner-Meerwein rearrangement. A detailed examination of the extensive published work on this rearrangement, which has played such a large part in the development of modern ideas in theoretical organic chemistry, is outside the scope of this review. Here we shall only consider those stereochemical features that are directly related to the mechanism and the stereochemistry of unimolecular dehydration.

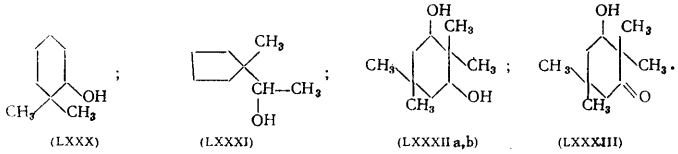
In his classical work Meerwein [100] showed that the rearrangement of the cyclic framework that occurs, for example, in the dehydration of isoborneol (LXXVIII) to camphene (LXXIX), and which had been studied by Wagner [101] using terpene alcohols, is quite general and can be

¶ Isomerisation with respect to the double bonds also occurs in solvolysis of the tosylates, because *p*-toluenesulphonic acid accumulates in the reaction mixture. To avoid this, Hückel [85] suggested that the solvolysis of tosylates should be carried out in the presence of sodium bicarbonate or calcium carbonate.

effected in monocyclic systems having a *gem*-dimethyl substituent adjacent to the carbon atom carrying the hydroxy-group:

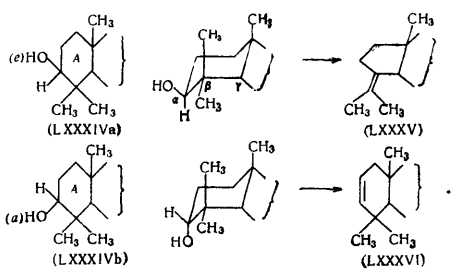


Examples of such compounds are 2,2-dimethylcyclohexanol (LXXX), 1-methyl-1-(α-hydroxyethyl)cyclopentane (LXXXI)[100], the isomeric *cis*- and *trans*-2,2,5,5-tetramethylcyclohexane-1,3-diols (LXXXIIa,b)[102], and 2,2,5,5-tetramethylcyclohexan-1-ol-3-one (LXXXIII)[103], dehydration of which is accompanied by the Wagner–Meerwein rearrangement.



Somewhat later Ruzicka and coworkers showed that a similar rearrangement occurs in the dehydration of triterpenoid compounds containing the 2,2-dimethylcyclohexanol fragment, for example, oleanolic acid[104], lupanol[105], α-amyrin[106,107], and α-amyrenonol[107,108]. Similar examples are known in the steroid series[109–112].

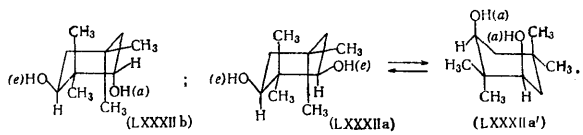
Barton[33] has examined the stereochemistry of systems that undergo the Wagner–Meerwein rearrangement, and from an analysis of a large amount of experimental work he showed that this rearrangement proceeds more readily if an equatorial hydroxy-group takes part in the reaction. To illustrate this conclusion, we shall examine the conformation of ring *A* in α-amyrin (LXXXIVa), which is common to the triterpenoids studied by Ruzicka and contains an equatorial hydroxy-group, and ring *A* in epiamyrin (LXXXIVb), containing an axial hydroxy-group:



From these molecular models it is clear that the presence of an (*a*)-OH group (epiamyrin) ensures the conditions necessary for normal *trans*-diaxial dehydration with the formation of product (LXXXVI), but dehydration in which an (*e*)-OH group participates (α-amyrin) is accompanied by rearrangement of the carbon framework.

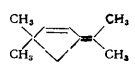
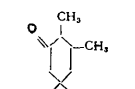
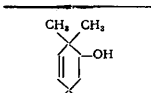
From the steric principles established in the polycyclic series for the Wagner–Meerwein rearrangement, the conformation with the (*e*)-OH group is the one expected to favour this rearrangement in monocyclic compounds. This is confirmed by the conversions of the isomeric *cis*- and *trans*-2,2,5,5-tetramethylcyclohexanediols (LXXXIIa,b) (Allan *et al.*[102]). When subjected to acid-catalysed dehydration, both isomers form a mixture of cyclic products containing 1,1-dimethyl-4-isopropenyl-$\Delta^2$-cyclopentene (LXXXVII), 2,3,5,5-tetramethylcyclohexanone (LXXXVIII), and 2,2,5,5-tetramethyl-$\Delta^3$-cyclohexenol (LXXXIX), the proportions depending on the configuration of the initial alcohols (Table 3).

The results may be explained by examining the conformations of the isomeric diols. The *trans*-diol exists in only one possible conformation (LXXXIIb) with one axial and one equatorial hydroxy-group.



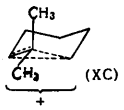
Accordingly, on dehydration 50% of it undergoes a Wagner–Meerwein rearrangement with participation of the equatorial hydroxy-group and 50% reacts with participation of the axial hydroxy-group [normal dehydration to (LXXXIX) and Nametkin† rearrangement followed by dehydration leading to the ketone (LXXXVIII)]. The *cis*-diol (LXXXIIa), which can participate in the last two reactions only in its energetically less suitable diaxial conformation (LXXXIIa′), must be more prone to Wagner–Meerwein rearrangement, for which the reaction conformation is the energetically favoured one (LXXXIIa). This conclusion agrees well with the experimental results.

TABLE 3.

| | | % of *trans*-diol (LXXXIIb) | % of *cis*-diol (LXXXIIa) |
|---|---|---|---|
|  | (LXXXVII) | 53 | 88 |
|  | (LXXXVIII) | 30 | 12 |
|  | (LXXXIX) | 17 | |

† Barton[33] showed that the Nametkin rearrangement[113–115] proceeds more easily if the hydroxy-group participating in it occupies an axial position.

The stereospecificity of the Wagner–Meerwein rearrangement accompanying unimolecular dehydration cannot be explained if it is assumed that the transition state for this reaction is the classical carbonium ion (LXXVIIIa)[116], which then rearranges to the ion (LXXVIIIb) (see p. 27). With such a mechanism both epimeric alcohols should form the same carbonium ion, and the reaction should be independent of the configuration of the initial compound. In order to explain the stereospecificity of the Wagner–Meerwein rearrangement, it has therefore been suggested that it is effected through a non-classical ion in which the positive charge is distributed over the possible reaction centres[117].


(XC)

Delocalisation of charge is known to lower the potential energy of a system. Therefore, if the non-classical ion interpretation is correct, reactions in which rearrangement occurs would be expected to have lower activation energies, that is, greater velocities, than reactions that proceed without rearrangement.

The acceleration effect on the rate of direct and indirect dehydration reactions in which rearrangement occurs can be observed experimentally‡. This is illustrated by the following figures:

Solvolysis at 80° in 80% aqueous ethanol:

bornyl chloride (no rearrangement) $K_1 = 1.5 \times 10^{-7}$

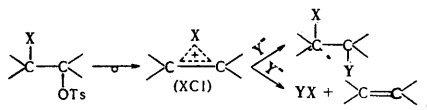
isobornyl chloride (rearrangement) $K_2 = 1.4 \times 10^{-2}$

As has been pointed out in the discussion on bimolecular dehydrations, the synchronous primary reaction step — here ionisation and rearrangement of bonds — is most easily achieved when four coplanar reaction centres participate in it. Since $C_{\alpha,\beta,\gamma}$ atoms and the hydroxy-group at $C_\alpha$ participate in the Wagner–Meerwein rearrangement, the steric requirements are best met when an equatorial hydroxy-group takes part in the reaction.

The physical reality of the non-classical carbonium ion as a transition state in dehydration reactions has been demonstrated experimentally on several examples by deuterium exchange; these are outside the scope of this review[119–122].

Winstein and coworkers have published a series of papers devoted to a systematic study of substitution and elimination reactions, including the non-classical carbonium ion; with them may be included the investigations of other workers on the participation of adjacent groups in solvolysis of 2-substituted cyclohexyl tosylates[123].

This participation is reflected in changes in the solvolysis rate, in configuration, and even in the structure of the reaction products; essentially, the electron pair of the $C_2$–X bond participates in the ionisation at $C_1$, which determines the rate of solvolysis; the non-classical intermediate ion (XCI) is then solvated by the nucleophilic solvent, or it interacts with the anion:

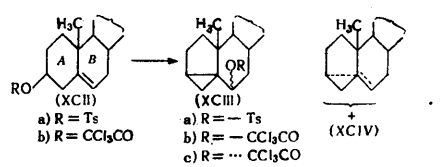

(XCI)

Reactions in which adjacent groups participate show rigorous stereospecificity, as would be expected from the hypothesis that the formation of the carbonium ion and the reaction of the nucleophilic substituent X with the cationic centre are synchronous; these reactions are characteristic only of *trans*-substituted cyclohexyl tosylates.

Alt and Barton[124] examined the conformations of compounds in which adjacent groups participate and showed that here the *trans*-diaxial positions of the "leaving" and "participating" groups were the most favourable; they suggested that this should be used to establish the configurations of isomeric bromohydrins and oxides.

We are unable to review all the experimental work on the participation of adjacent groups, but one particular aspect, *i*-steroid rearrangement, should be considerdd here.

Stereochemistry of *i*-steroid rearrangement. In 1932 Stoll[83] found that boiling with alcohol or with acetic acid and potassium acetate converts the tosylates of steroid hydroxy-compounds containing a $\Delta^{5,6}$ double bond and a 3β-hydroxy-group (cholesterol, ergosterol, stigmasterol) (XCII) to derivatives of the isomeric hydroxy-compounds, which differ from the corresponding derivatives of the epi-series. Wallis *et al.*[125,126] showed that the compounds formed have the "*i*-steroid structure" (XCIIIa).


(XCII) a) R = Ts b) R = $CCl_3CO$

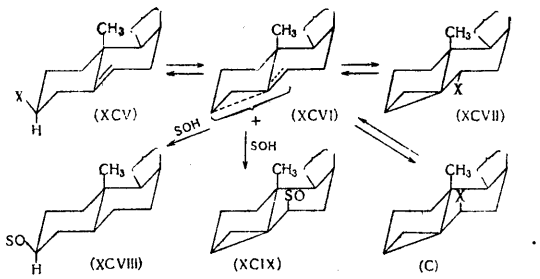
(XCIII) a) R = — Ts b) R = — $CCl_3CO$ c) R = ··· $CCl_3CO$

(XCIV)

From a comparison of the kinetics of the process (unimolecular reaction $K_1^{50°} = 7.9 \times 10^{-3}$) with the kinetics of solvolysis of cyclohexyl tosylate ($K_1^{50°} = 0.111 \times 10^{-3}$), Winstein[127] suggested that the $\Delta^{5,6}$ double bond participates in the solvolysis as an adjacent group, and he concluded that the ion (XCIV) is the transition state[128–130] in this reaction. In further studies on the mechanism of this reaction Kosower and Winstein[131] examined the methanolysis and hydrolysis of cholesteryl trichloroacetate (XCIIb), the epimeric (at $C_6$) *i*-cholesteryl trichloroacetate (XCIIIb) and epi-*i*-cholesteryl trichloroacetate (XCIIIc), and they showed that all these compounds yield the same reaction mixture

‡ In the English literature this effect is called "synartetic acceleration", in the American "anchimeric acceleration".

containing 88–89% of *i*-cholesterol. The results unambiguously indicate that the same cation (XCVI) is formed as an intermediate in all three reactions:




The elimination of the anion $X^-$ synchronously with the interaction of the $\Delta^{5,6}$ double-bond electrons and the $C_3$ cationic centre, necessary for the formation of the ion (XCVI), is in accord with the rigorous stereospecificity of the *i*-steroid rearrangement. Since entry of the $\Delta^{5,6}$ double-bond electrons into the octet of the $C_3$ atom is energetically most favoured from the side opposite to that of the leaving group, the *i*-steroid rearrangement proceeds readily when the OH group is equatorial; under similar conditions compounds with the axial 3α-hydroxy-group undergo normal dehydration to cholesta-3,5-diene[132–134].

Rearrangement with participation of the $\Delta^{5,6}$ double bond, exemplified by studies on cholesterol, has now been investigated in detail on a number of steroid[135–138] and terpenoid[139–144] compounds, and is known as homoallyl interaction[145–146].

## II. INTRAMOLECULAR PYROLYTIC DEHYDRATION

Since Smith[147], and later Kraft[148], showed that olefines could be prepared by pyrolysing esters of the corresponding alcohols, this method has been widely used in organic chemistry. However, it was not until much later that a detailed investigation of the stereochemical features of the reaction was made. The pyrolytic cleavage of xanthates (the Chugaev reaction) has been examined in greatest detail, and we shall primarily be concerned with this.

Stereochemistry of the Chugaev reaction. In 1899 Chugaev[149] proposed a method for preparing olefines by pyrolysis of the corresponding xanthic esters:

$$RCH_2CH_2OH \xrightarrow{Na} RCH_2CH_2ONa \xrightarrow{CH_3I+CS_2} RCH_2CH_2O{-}\overset{\overset{S}{\|}}{C}{-}SCH_3 \xrightarrow[150°-200°]{} RCH{=}CH_2 + COS + CH_3SH.$$

The direct dehydration under Chugaev[150] conditions proceeds at a comparatively low temperature (150°–200°) in the absence of acidic reagents; this minimises isomerisation of the olefines formed and permits alcohols that are sensitive even to traces of acid (pinacol[151], dimethylcyclobutylcarbinol[152]) to be smoothly dehydrated and also enables the reaction to be used for determining the structures of the initial and final compounds.

Extensive rearrangement of the carbon framework with an appreciable yield occurs under Chugaev conditions only in the pyrolysis of the xanthates of isoborneol, leading to camphene[153]. In the other cases examined (fenchol, camphanol), the products of this kind of isomerisation form less than 5% of the total yield. Epimerisation of the initial xanthate ester before pyrolysis[154], or conversion to more stable compounds[155,156], has been observed only in isolated cases.

Table 4 gives the most characteristic examples of the Chugaev reaction with alicyclic hydroxy-compounds, and clearly shows the stereospecificity of this reaction, which proceeds mainly with *cis*-elimination (in which the hydrogen atom at $C_\beta$ participates, or if this is absent, as in fenchol, the hydrogen atom at $C_\gamma$) accompanied by the formation of a three-membered ring. Other conditions being similar, *cis*-elimination by the Chugaev reaction leads mainly to the most highly substituted olefine, in agreement with Zaitsev's rule[51].

To explain the rigid stereospecificity of the Chugaev reaction, Hückel[25] suggested that it proceeds through a

TABLE 4. Dehydration of cyclic alcohols under Chugaev conditions.

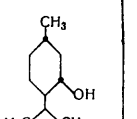
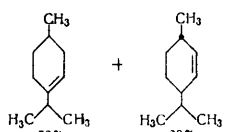
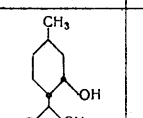
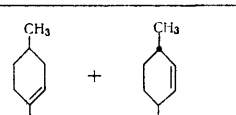
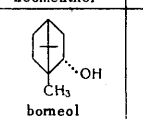
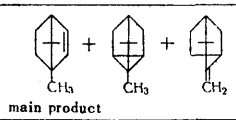
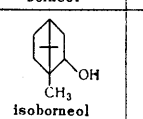
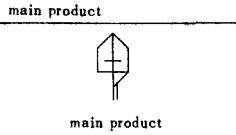
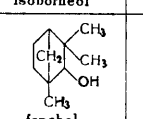
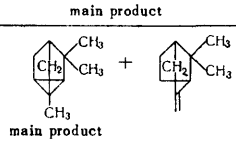
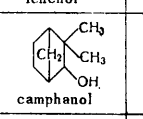
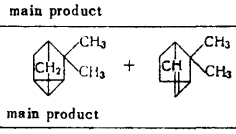
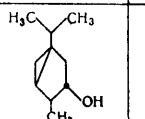
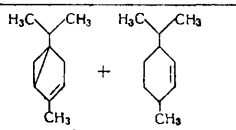
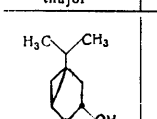
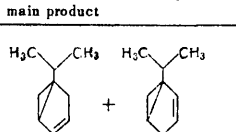
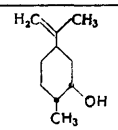
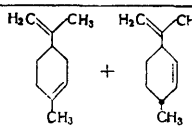
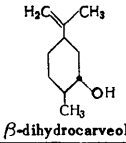
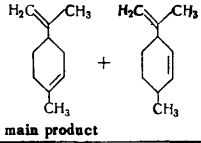
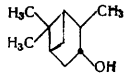
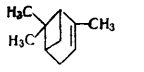
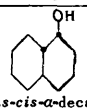
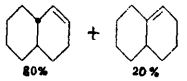
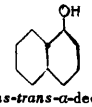
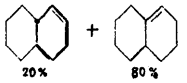
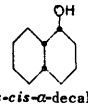
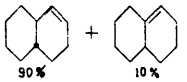
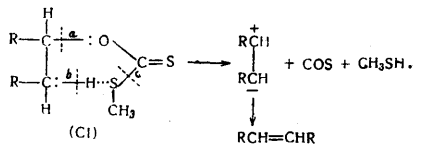
| Initial alcohol | Reaction products and proportions | References |
|---|---|---|
|  menthol |  70% 30% | 25, 157–159 |
|  neomenthol |  20% 80% | 25 |
|  borneol |  main product | 160–163 |
|  isoborneol |  main product | 153, 154 |
|  fenchol |  main product | 164–166 |
|  camphanol |  main product | 167 |
|  thujol |  main product | 168–172 |
|  neothujol |  main product | 173 |

TABLE 4. (contd.)

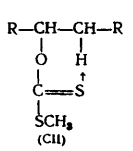
| Initial alcohol | Reaction products and proportions | References |
|---|---|---|
|  α-dihydrocarveol |  main product | 174–177 |
|  β-dihydrocarveol |  main product | 174–177 |
|  pinocampheol |  main product | 178 |
|  *trans-cis*-α-decalol |  80% 20% | 25, 179 |
|  *trans-trans*-α-decalol |  20% 80% | 25, 179 |
|  *cis-cis*-α-decalol |  90% 10% | 25, 179 |

quasi-cyclic intermediate complex (CI), the C–O bond (*a*), the C–H bond (*b*) and the C–S bond (*c*) being ruptured simultaneously with the formation of the S–H bond.




This mechanism enabled Hückel to explain the possibility of elimination with participation of the hydrogen atom at $C_\gamma$: the xanthic acid residue is sufficiently long to form a seven-membered quasi-cyclic transition complex.

Later Stevens and Rechmond[180] ascribed a somewhat different structure (CII) to the intermediate complex in the Chugaev reaction:



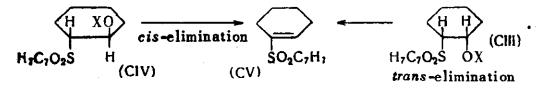

Unlike Hückel, who assumed that the complex (CI) is formed because of the electron-donating properties of the thiol sulphur atom, these workers assumed that the thione sulphur atom acts as an electron donor. Both these mechanisms, with slight modifications, have also been accepted by other workers[181–184], but a mechanism has also been considered in which the xanthates are first isomerised to dithiocarbonates[185].

An experimental test of the mechanism of the Chugaev reaction was made by O'Connor and Nace[184,186]; using cholesteryl xanthates having different substituents on the thiol S atom, they showed that pyrolysis of the xanthates is a homogeneous first-order reaction, unaffected by inhibitors of radical reactions. Moreover, the rate of decomposition of the xanthates increases with the electronegativity of the substituent on the S atom. It was also shown that the entropy of activation of the Chugaev reaction is negative, which indicates a highly ordered transition state.

The results are in good agreement with the idea of a quasi-cyclic transition state arising from a donor-acceptor bond. However, it was not clear whether a thiol or a thione sulphur atom acted as proton acceptor. This problem was solved by Salomaa[187], who compared the reactivities of the methyl carbonates, methyl thiolcarbonates, methyl thionecarbonates, and xanthates of menthol and fenchol; he showed conclusively that the thione sulphur atom acts as proton acceptor. Salomaa's results also show that the cleavage of xanthates does not include a stage in which dithiocarbonates are formed, since the esters containing an oxygen atom in the carbonyl group are much more resistant to pyrolytic cleavage than the corresponding thione esters.

Polar effect of the substituent and possibility of *trans*-elimination in the Chugaev reaction. The mechanism described satisfactorily explains preferential *cis*-elimination in the Chugaev reaction§. However, as was pointed out by Alexander and Mudrak[190,191], in some cases, in addition to the main *cis*-reaction in the pyrolysis of xanthates, there is also a *trans*-oriented side reaction. Examples include the formation of 20% of $\Delta^3$-menthene from neomenthol[25], the mild cleavage of *cis*-2-methyltetralol to give 2-methyl-3,4-dihydronaphthalene, and the mild cleavage of *cis*-2-methylindanol to give 2-methylindene[190].

Since it is conceivable that the anomalous course of the Chugaev reaction is related to the activation of the hydrogen atom participating in it, Bordwell and Landis[192] studied the pyrolysis of the xanthates of *cis*- and *trans*-2-*p*-toluenesulphonylcyclohexanols (CIII) and (CIV) and showed that both isomeric products are converted to the αβ-unsaturated sulphone (CV) only:




Therefore, when the molecule contains a strong electron-acceptor group that increases the mobility of the adjacent hydrogen atom, the consequent participation of the activated hydrogen atom in the reaction controls the mode of hydrolysis, and the spatial arrangement of the eliminated groups plays a subordinate role; this also happens in some bimolecular dehydrations (see p. 24).

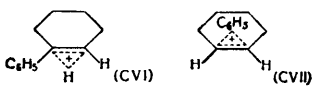
§ The composition of the pyrolysis product of other derivatives of xanthic acid is practically identical with the composition of the products of pyrolysis of its methyl esters[188,189].

Because *trans*-elimination in the Chugaev reaction is not in accord with the mechanism described above, Bordwell and Landis[193] suggested an alternative mechanism, according to which a bipolar ion is formed[193]. They have not, however, confirmed this mechanism experimentally.

Stereochemistry of pyrolysis of other esters. The development of organic synthesis in the field of polycyclic compounds has given rise to a demand for new convenient and reliable methods of introducing a double bond into a given position in the six-membered ring. For this purpose, detailed studies[194-199] have been undertaken on the pyrolysis of cyclic alcohols[194-199] and their esters, including acetates[183,185,195,200-217], benzoates[193,195,213-223], carbonates[187,193], sulphites[193,224-227], as well as other esters[228-231]. The results show that the thermal stability of esters is inversely proportional to the p$K$ value of the corresponding acid[232]. This enabled convenient preparative methods to be developed for the elimination of one hydroxy-group in the presence of others. Thus, for example, the esters of anthraquinonecarboxylic acid are cleaved in pyrolysis more readily than the benzoates, and the benzoates more readily than the acetates[204,222,223].

Studies of ester hydrolysis kinetics with acetates[233,234], formates[233], and propionates[235] have shown that this is a homogeneous first-order reaction, which is not affected by the addition of radical-reaction accelerators[236]. Because the reaction rates and energies and entropies of activation are similar, O'Connor and Nace[184] suggested that the pyrolysis of cholesteryl acetate, cholesteryl ethyl carbonate, and cholesteryl xanthate proceed through the same mechanism, involving the quasi-cyclic transition complex (CII) (see p.30); this has been demonstrated experimentally by De Puy and King[217] using a tracer method. The stereochemistry of pyrolytic reactions undergone by both mono- and poly-cyclic compounds is in good agreement with this mechanism. Table 5 gives the relevant data illustrating the preference for *cis*-elimination in pyrolysis.

However, it cannot be concluded from the similarity in mechanism and stereochemistry that the pyrolysis of xanthates is identical with that of other esters. The pyrolysis of esters of organic acids proceeds at high temperatures (acetates, for example, pyrolyse above 400°), and the accumulation of considerable quantities of organic acid in the reaction facilitates the isomerisation of the olefine produced; this applies even more to the pyrolysis of esters of inorganic acids. This is exemplified by Berti's[225] comparison of the results of the pyrolysis of the methylsulphites and xanthates of the isomeric *cis*- and *trans*-2-phenylcyclohexanols (Table 6). The results obtained clearly showed the great steric selectivity of the Chugaev reaction, but Berti interpreted them as indicating that the mechanism for the sulphites differs fundamentally from the Chugaev mechanism; for the *cis*-isomer, the sulphite mechanism includes the non-classical ion (CVI), formed with participation of a hydrogen atom, as a transition state; for the *trans*-isomer the transition state is the "phenonium" ion (CVII):




However, a critical examination of these conclusions in their application to the pyrolysis of *cis*-2-*t*-butylcyclohexyl methylsulphate[193] showed that Berti's mechanism

TABLE 5. Stereochemistry of pyrolysis of hydroxy-compounds and their esters.

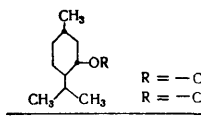
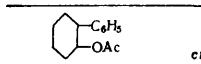
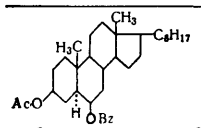
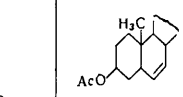
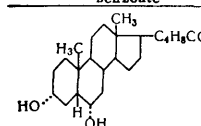
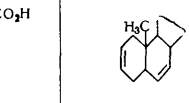
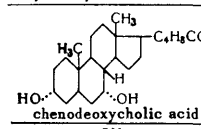
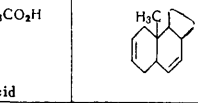
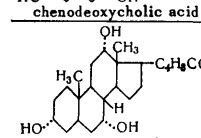
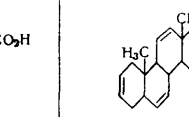
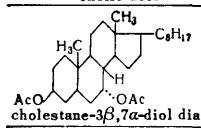
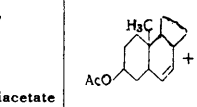
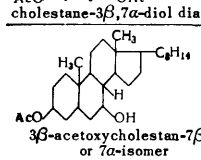
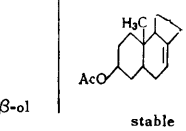
| Initial compound | Olefines obtained and their proportions | References |
|---|---|---|
|  R = —COCH3 / R = —COC6H5 | Δ²-menthene + Δ³-menthene: 33% 66% / 33% 66% | 206, 207 / 236 |
|  cis / trans | 3-phenylcyclohexene + 1-phenylcyclohexene: 92.8% 7.2% / 13.5% 86.5% | 183 |
|  3β-acetoxycholestan-6β-ol-benzoate |  | 237 |
|  hyodeoxycholic acid |  | 181 |
|  chenodeoxycholic acid |  | 181, 198 |
|  cholic acid |  | 181, 195 |
|  cholestane-3β,7α-diol diacetate |  | 223, 237 |
|  3β-acetoxycholestan-7β-ol or 7α-isomer |  stable | 198 |

TABLE 6.

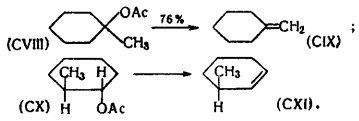
| Compound | Temp. of pyrolysis, °C | Yield of olefine | 1-Phenylcyclohexene, % from sulphite | 1-Phenylcyclohexene, % from xanthate |
|---|---|---|---|---|
|  C6H5, cis | 200 | 93 | 22 | 96 |
| OR trans | 200 | 88 | 35 | 12 |

was not in accord with the experimental results. Actually, an ion of the type (CVI) should here lead to 1-phenylcyclohexene by *trans*-elimination, but in fact, 3-phenylcyclohexene was isolated from the pyrolysis products in 95% yield.

A parallel study of the pyrolysis of the xanthates and sulphites of cyclic alcohols by Bordwell and Landis showed

that in a large number of examples the primary products of these reactions are similar, clearly indicating a common mechanism. The actual difference in the final results of pyrolysis is due to isomerisation under conditions of sulphite cleavage.

The problem of the relative effects of polar and steric factors on the stereochemistry of pyrolysis of acetates is dealt with in the literature. Bailey *et al.*[210,216,238,239] conclude that pyrolysis of acetates is a specific method for the synthesis of thermodynamically less stable olefines (corresponding to Hofmann's rule). Thus, for example, pyrolysis of 1-methylcyclohexyl acetate (CVIII) gives methylenecyclohexane (CIX) in 76% yield, but pyrolysis of *trans*-2-methylcyclohexyl acetate (CX)[240] gives 3-methylcyclohexene (CXI) as the main product:




Thus, according to Bailey *et al.*, the mode of pyrolysis of acetates is determined not by the spatial orientation of the leaving groups but by the preferential elimination of hydrogen from the methylene group. Similar results have been published by Traynham and Pascual[241], and also by Siegel and Dunkel[211].

The obvious disagreement of these results with those obtained for the Chugaev reaction (see p. 29) compelled Royals[212], Benkeser and Hazdra[213], and also De Puy *et al.*[214,217] to reinvestigate the pyrolysis of acetates. From an analysis of the pyrolysis products by gas chromatography, these workers showed on a large number of examples that the experimental results of Bailey's school were erroneous¶. It was found that the pyrolysis of acetates leads to a complex mixture of reaction products, in which the compounds isolated by Bailey were not always the predominant ones. The results obtained were interpreted by De Puy *et al.*[214,217] as a proof of the lack of selectivity in the pyrolysis of acetates within the limits permitted by the *cis*-elimination principle. The mode of this reaction is therefore determined by the orientation of the leaving groups in the initial molecule. If several elimination routes are possible, the proportions of the reaction products will be determined entirely by statistical considerations. These views of De Puy[217] are in good agreement with the experimental findings.

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Two conclusions can be drawn from the published work on the stereochemistry of direct and indirect dehydration of six-membered alicyclic hydroxy-compounds. First, this reaction is stereospecific only when rupture of the old and formation of the new bonds are synchronous (bimolecular dehydration, rearrangements involving a non-classical transition ion in unimolecular dehydration, pyrolytic reactions); in reactions that proceed by a stepwise mechanism (monomolecular dehydration) steric selectivity is more weakly expressed and sometimes it is entirely lacking. Second, for stereospecific reactions the dehydration route is determined in the general case by the "reaction requirements", which are concerned with the orientation of the leaving groups corresponding to the given reaction mechanism (*trans*-orientation of the leaving groups in bimolecular dehydration and *cis*-orientation in pyrolysis). Compounds containing an activated hydrogen atom at $C_\beta$ are exceptions; with these the preferred dehydration route is that which ensures participation of the mobile hydrogen atom; if this route does not correspond to the mechanism of the given reaction, then, as a rule, the mechanism undergoes substantial changes.

¶ In 1959, Bailey *et al.*[215] also reexamined their previous results, and their new results, obtained with the aid of gas chromatography, agree well with those of Royals, Benkeser and Hazdra, and De Puy.


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# THE ANALYSIS OF COMPLEX ORGANIC MIXTURES BY GAS CHROMATOGRAPHY

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## INTRODUCTION

Gas chromatography is now one of the most effective methods of analysing organic substances. The following represents a far from complete list of mixtures which can be studied by gas chromatography: petroleum and petroleum products boiling at up to 600°, organic fluorine- and chlorine-containing compounds, the combustion products from internal combustion engines, essential oils, resins, solvents for plastics and lacquers, fruit and vegetable components, tobacco smoke, the products of the Fischer–Tropsch synthesis, air, paraffin waxes, etc.

The present review is devoted to the problems of the analysis of complex mixtures by gas chromatography, with particular reference to methods for the analysis of the liquid hydrocarbons present in various natural products.

## 1. THE IDENTIFICATION OF CHROMATOGRAPHIC PEAKS

In the analysis of different mixtures by gas chromatography, an extremely important problem is the identification of the resulting chromatographic peaks. This is often made much more difficult by lack of the pure individual substances thought to be present in the mixtures being analysed. In this case it is necessary to use the various relationships between the elution characteristics of the components and their other properties.