THE PRINCIPLES OF CONFORMATIONAL ANALYSIS

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Introduction.—The word " conformation ", first used by W. N. Haworth,[1] can be defined in several ways. One of the most general definitions is as follows : the conformations of a molecule are those arrangements in space of the atoms of the molecule which are not superposable upon each other. Such a definition includes arrangements of atoms in which angle strain has been introduced, though this is not normally of great importance. Thus almost all molecules will have theoretically an infinite number of conformations. It is fortunate that the complexities which might arise from such considerations are minimised by the fact that, in general, only a few of the possible conformations are energetically preferred. In the German language the word " constellation ", of more recent origin,[2] is used in the same sense,[3] and in the literature of chemical physics the term "rotational isomer ".

For the vast majority of molecules the energy barriers between different conformations are too low to allow the separation of pure conformational isomers at normal temperatures in the liquid or vapour phase, but sufficient intramolecular congestion can raise the barrier enough to make such a separation possible experimentally. Familiar examples are provided by resolvable diphenyl derivatives.[4] Tri-*o*-thymotide has recently been shown to undergo spontaneous resolution into conformational enantiomorphs of low optical stability.[5]

The Preferred Conformations of Some Simple Hydrocarbons

In the last two decades many of the powerful methods of modern chemical physics, including electron and *X*-ray diffraction, infrared, Raman, and microwave spectroscopy, and statistical mechanics, have been used to demonstrate the existence and nature of preferred conformations in simple

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[1] W. N. Haworth, " The Constitution of Sugars ", E. Arnold and Co., London, 1929, p. 90.

[2] Ebel, " Stereochemie ", Ed. Freudenberg, Deuticke, 1932, p. 825.

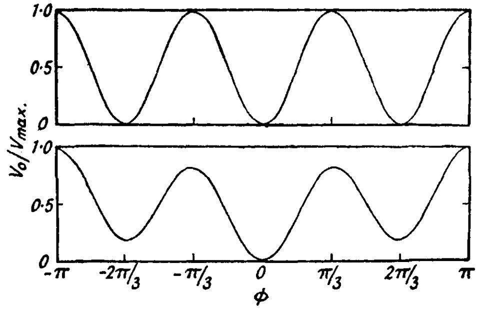
[3] Prelog, *J.*, 1950, 420.

[4] Turner and Harris, " Organic Chemistry ", Longmans, Green and Co., pp. 605 *et seq.* ; Shriner, Adams, and Marvel, " Organic Chemistry ", ed. Gilman, 2nd edn., Wiley, 1943, Vol. I, pp. 343 *et seq.*

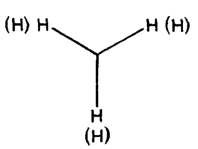
[5] Baker, Gilbert, and Ollis, *J.*, 1952, 1443 ; Powell, *Nature*, 1952, **170**, 155 ; Newman and Powell, *J.*, 1952, 3747. For examples of stable conformational isomers in other ring systems see, *inter al.*, Bentley and Robinson, *J.*, 1952, 947 ; Bell, *ibid.*, p. 1527 ; Wittig and Zimmermann, *Chem. Ber.*, 1953, **86**, 629 ; Hall and Turner, *J.*, 1955, 1242, and references given there.

molecules. For more detailed summaries of this background the reader is referred to the reviews by McCoubrey and Ubbelohde[6] and by Mizushima.[7]

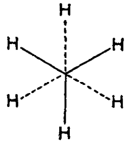
Ethane.—Fig. 1 illustrates[6] the energy of a molecule of ethane as a function of conformation, in this case depending only on the relative orientation of the two methyl groups. The molecule has the maximum energy when the set of three hydrogen atoms attached to the near carbon atom eclipse those attached to the far carbon atom when viewed down the C–C bond (1). The energy is at a minimum when each C–H bond bisects the angle formed by two C–H bonds of the other carbon atom (2). The barrier to rotation is estimated[8] as about 2·8 kcal. per mole.



FIGS. 1 and 2



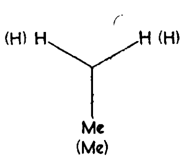
(1) 0°



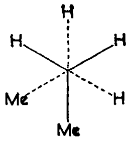
(2) 60°

Views down the C–C bond of ethane

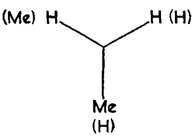
n-*Butane*.—The conformation of *n*-butane with lowest energy is the fully *transoid*, staggered conformation (3). The two other minima in the potential energy curve (Fig. 2)[6] correspond to the two enantiomorphous skew, or gauche, conformations (4). It has been calculated[9] that the energies of



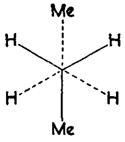
Fully eclipsed
(5)



Skew or gauche
(4)



Eclipsed
(6)



Staggered
(3)

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[6] McCoubrey and Ubbelohde, *Quart. Rev.*, 1951, **5**, 364.

[7] Mizushima, " The Structure of Molecules and Internal Rotation ", Academic Press, 1954.

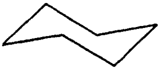
[8] *Inter al.*, Kistiakowsky, Lacher, and Stitt, *J. Chem. Phys.*, 1939, **7**, 289 ; Pitzer, *Chem. Rev.*, 1940, **27**, 39 ; McCoubrey and Ubbelohde, ref. 6.

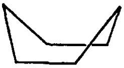
[9] Pitzer, *Discuss. Faraday Soc.*, 1951, **10**, 66, and references there cited.

the fully eclipsed (5), eclipsed (6), and skew (4) conformations are about 3·6, 2·9, and 0·8 kcal. per mole respectively greater than that of the staggered conformation (3). The last value is in excellent agreement with the temperature-dependence of the appropriate Raman lines.[10]

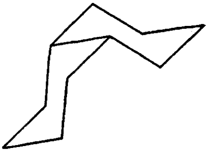
In aliphatic compounds the most stable conformation is usually that in which the substituents on adjacent tetrahedral carbon atoms adopt the fully staggered conformation [as (3)], the two largest groups (or, in qualification, the two most strongly repelling dipoles) taking up the 180° arrangement. Eclipsed conformations are always avoided wherever possible.

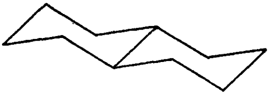
cyclo*Hexane*.—The conclusion by Sachse [11] and by Mohr [12] that *cyclo*hexane can exist in only two conformations free from angle-strain has long been accepted by chemists. That the chair conformation (7) is more stable than the boat (8) is attested by much physical evidence, including infrared [13] and Raman [14] spectroscopy, and electron diffraction,[15] and by thermodynamic considerations.[16, 17] Derivatives of *cyclo*hexane always tend to take up the chair conformation whenever this is stereochemically possible (see detailed discussion later).

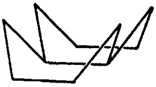

(7)


(8)

The Decalins.—If boat conformations are accepted as less stable than chair conformations then both *cis*- and *trans*-decalin have unique preferred conformations illustrated in (9) and (10) respectively. Hassel and his collaborators [15, 18, 19] have shown by electron diffraction that in the vapour phase molecules of *cis*-decalin do indeed exist in the two-chair conformation (9), rather than in the long unchallenged two-boat conforma-


(9)


(10)


(11)

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[10] Szasz, Sheppard, and Rank, *J. Chem. Phys.*, 1948, **16,** 704.

[11] Sachse, *Ber.*, 1890, **23,** 1363 ; *Z. phys. Chem.*, 1892, **10,** 203.

[12] Mohr, *J. prakt. Chem.*, 1918, **98,** 315.

[13] Rasmussen, *J. Chem. Phys.*, 1943, **11,** 249, and papers there cited.

[14] Kohlrausch and Wittek, *Z. phys. Chem.*, 1941, **48,** *B*, 177 ; Gerding, Smit, and Westrik, *Rec. Trav. chim.*, 1942, **61,** 561.

[15] Hassel and Viervoll, *Acta Chem. Scand.*, 1947, **1,** 149, and papers there cited.

[16] Aston, Schumann, Fink, and Doty, *J. Amer. Chem. Soc.*, 1941, **63,** 2029.

[17] Beckett, Pitzer, and Spitzer, *ibid.*, 1947, **69,** 2488.

[18] Hassel, *Tidsskr. Kjemi Bergvesen Met.*, 1943, **3,** 91.

[19] Bastiansen and Hassel, *ibid.*, 1946, **6,** 70 ; *Nature*, 1946, **157,** 765.

tion (11).[12] Much chemical evidence has also been adduced in favour of the conformation (9) for substituted *cis*-decalins.[20, 21, 22, 23]

Reasons for the Existence of Preferred Conformations

The interaction energy between two non-bonded atoms is weakly attractive up to distances of approximately the sum of the van der Waals radii of the atoms concerned. At distances less than this the interaction energy soon becomes repulsive and a high exponential function of interatomic distance.[24] In the fully staggered conformation of a straight-chain aliphatic compound the distances between non-bonded atoms approximate quite closely to the sum of the van der Waals radii. Any rotation about a C–C bond (see above) brings the atoms attached to the main chain closer together and calls into play destabilising (repulsive) forces. In general it can be said that the energy of a particular conformation of a molecule depends on the presence or, in specially formed cases (see above), the absence of repulsive interactions between non-bonded atoms. To a certain extent these repulsive interactions can be modified by bond-angle deformation. Modification by bond extension is not important because of the relatively large energy requirements for such a process. In the absence of direct physical evidence the most stable conformation of a molecule may then be selected by the principle of minimisation of (repulsive) non-bonded interactions. We would emphasise, however, that simple considerations of this kind are subject to qualification when other intramolecular forces due to hydrogen bonding or electrostatic effects (dipole or integral change interactions) come into play (see p. 81).

Consequences of the Existence of Preferred Conformations

In the last five years the importance of the existence of preferred conformations in organic molecules has become widely recognised under the title of " conformational analysis ". The present Review sets out to summarise, with the aid of the appropriate background, the more important aspects of the subject from the point of view of the organic chemist.[25]

The fundamental tenet of conformational analysis is that the physical and chemical properties of a molecule can be related to its preferred conformation. The more important applications of this concept may be classified as follows :

(i) Phenomena that are a direct consequence of a preferred conformation : (*a*) Physical properties such as specific absorption bands in the

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[20] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066.

[21] Barton, *Experientia*, 1950, **6**, 316 ; *J.*, 1953, 1027.

[22] Beyler and Sarett, *J. Amer. Chem. Soc.*, 1952, **74**, 1406.

[23] W. G. Dauben, Tweit, and Mannerskantz, *ibid.*, 1954, **76**, 4420.

[24] See, for example, C. K. Ingold, " Structure and Mechanism in Organic Chemistry ", Cornell Univ. Press, Ithaca, New York, 1953, Chapter II ; Hughes, *Quart. Rev.*, 1948, **2**, 107.

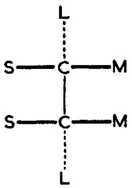
[25] For more fully documented accounts of certain phases of the problems see Orloff, *Chem. Rev.*, 1954, **54**, 347, and Klyne in " Progress in Stereochemistry ", Butterworths, London, 1954, Vol. I, Chapter II.

ultraviolet or infrared region. (*b*) Chemical effects dominated by steric compression, such as ester hydrolysis (reaction rates) and relative stabilities of epimers (equilibria).

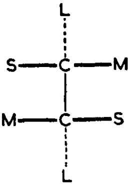
(ii) Phenomena due to the interplay of conformational preferences and the geometrical requirements of the transition states of reactions (usually collinearity or coplanarity of participating centres).

Some Illustrations from Aliphatic Chemistry

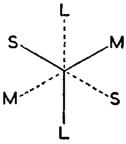
The Relative Stabilities of erythro- *and* threo-*Isomers*.—Let us consider the non-bonded interactions in an *erythro*-compound (12) as compared with those in its *threo*-diastereoisomer (13). In these and later formulæ S, M, and L denote substituents attached to the same carbon atom which are respectively smallest, medium and largest in effective size. Each substituent will repel the two adjacent substituents on the next carbon atom; the sum of these repulsive energies for the stable, staggered, conformation (14) of the *erythro*-compound and for the three more stable conformations, (15), (16), and (17), of the *threo*-isomer may be represented as follows:



(12)



(13)



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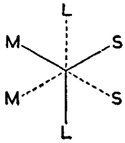
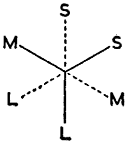
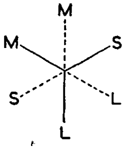


(15)



(16)



(17)

$$
\begin{aligned}
&(14) \quad 2(L:S) + 2(L:M) + 2(M:S)\\
&(15) \quad 2(L:M) + 2(L:S) + S:S + M:M\\
&(16) \quad 2(L:M) + 2(M:S) + L:L + S:S\\
&(17) \quad 2(L:S) + 2(M:S) + L:L + M:M
\end{aligned}
$$

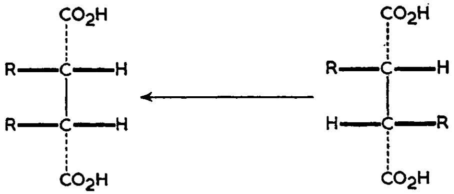
The differences in compression energy between the stable conformation of the *erythro*-compound and the three more stable conformations of the *threo*-compound are then:

$$
\begin{aligned}
(14) - (15) &= 2(M:S) - (M:M + S:S)\\
(14) - (16) &= 2(L:S) - (L:L + S:S)\\
(14) - (17) &= 2(L:M) - (L:L + M:M)
\end{aligned}
$$

Since repulsion is a high exponential function of interatomic distance $(M:M) \gg (M:S)$, $(L:L) \gg (L:S)$, and $(L:L) \gg (L:M)$, so that in each case (14) — (15), (14) — (16) and (14) — (17) should be a negative quantity.

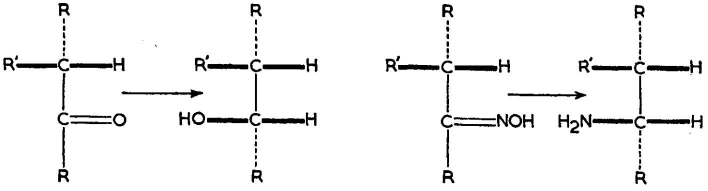
In general, then, for diastereoisomeric pairs of non-polar compounds in which differences in free energy are mainly due to differences in compression energy, the *erythro*-isomer should be more stable than the *threo*-isomer.

The relative stabilities have been established of many pairs of *meso*- and racemic and of *erythro*- and *threo*-isomers, either by direct equilibration or by introduction of the second asymmetric carbon centre in a reaction that is known to result (from its mechanism) in a mixture approximating to the equilibrium mixture. In many cases the expected stability order is found experimentally. For example, equilibration [26] of the racemic succinic acids (18 ; $R = R'$ = alkyl, aryl, halogen, or OH) gives the more stable *meso*-acids (19 ; $R = R'$). Similarly the *threo*-acids (18 ; $R \neq R'$ = alkyl, aryl, halogen, or OH) isomerise to the *erythro*-acids (19 ; $R \neq R'$). Racemic stilbene dichloride [27] and dibromide [28] isomerise to equilibrium mixtures composed chiefly of the *meso*-dihalides. In many examples of this kind, however, the situation is complicated by dipole interactions, which also favour the isomers which should be more stable from the conformational point of view.



(19) (18)

Cram and Abd Elhafez [29] have tabulated the products of reduction of ketones (20 ; R = aryl, R' = OH or NH_2) and of oximes (21 ; R = aryl, R' = OH or NH_2) with sodium and alcohol or with sodium amalgam, reagents that are accepted as producing the more stable epimer.[30] The *erythro*(or *meso*)-isomer (22 and 23) is always formed in greater amount.



(20) (22) (21) (23)

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[26] Fourteen examples are tabulated by Wagner-Jauregg (quoting Wolf) in " Stereochemie ", ed. Freudenberg, Deuticke, 1932, p. 873 ; see also Linstead and Whalley, *J.*, 1954, 3722.

[27] Zincke, *Annalen*, 1879, **198**, 135.

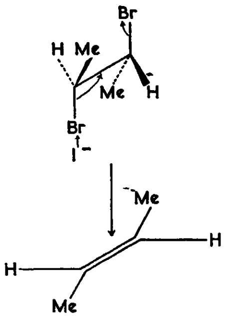
[28] Wislicenus and Seeler, *Ber.*, 1895, **28**, 2693 ; Buckles, Steinmetz, and Wheeler, *J. Amer. Chem. Soc.*, 1950, **72**, 2496 ; Abd Elhafez and Cram, *ibid.*, 1953, **75**, 339.

[29] *Idem*, *ibid.*, 1952, **74**, 5828.

[30] Barton and Robinson, *J.*, 1954, 3045.

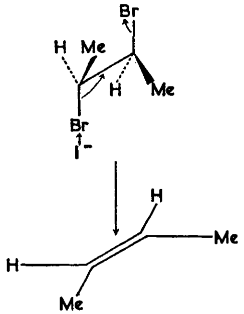
Rates of Elimination from erythro- *and* threo-*Compounds.*—In the debromination of 1 : 2-dibromides by iodide ion, symbolised below,[31] the *meso*-dibromide (24) always [32] reacts more rapidly than the DL-isomer (25). Since the transition state of an *E*2 reaction such as this requires that the four centres concerned in the reaction should be coplanar,[20, 33, 34] with the two C–Br bonds antiparallel, the conformation required for the *meso*-dibromide is (24), that for the DL-dibromide (25). In the transition state arising from (24) each methyl group is becoming eclipsed by a hydrogen atom, whereas in that arising from (25) the two methyl groups are becoming eclipsed. The transition state is therefore of higher energy with respect to the ground state for (25) than it is for (24). Correspondingly *meso*-stilbene dibromide is debrominated by iodide ion about one hundred times as fast as the racemic isomer.[32, 35]

(24)



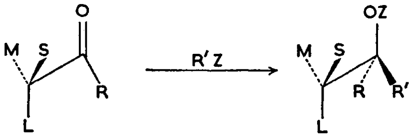
trans-But-2-ene

(25)



cis-But-2-ene

Cram's Rule of Asymmetric Induction.—From consideration of the products of proved configuration resulting from reactions involving addition to a carbonyl group adjacent to an asymmetric carbon atom, Cram and Abd Elhafez [29] were able to propose the following rule : " In reactions of the type (26) ⟶ (27) that diastereoisomer will predominate which would be formed by the approach of the entering group [R′] from the less hindered side of the double bond [of the carbonyl group] when the rotational conformation of the C–C bond is such that the double bond is flanked by the



(26) (27)

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[31] Winstein, Pressman, and Young, *J. Amer. Chem. Soc.*, 1939, **61,** 1645.

[32] Young, Pressman, and Coryell, *ibid.*, p. 1640.

[33] Young, Abs. Papers 8th Nat. Org. Chem. Symposium, Amer. Chem. Soc., St. Louis, Dec., 1939, p. 92.

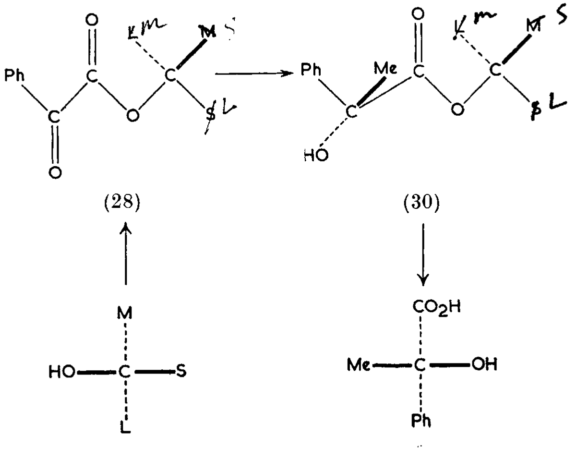
[34] Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2711.

[35] For a pertinent case involving dehydrochlorination see Cram and Abd Elhafez, *J. Amer. Chem. Soc.*, 1952, **74,** 5851.

two least bulky groups [S and M] attached to the adjacent asymmetric centre.'' Thus in the addition of Grignard reagents or reduction by lithium aluminium hydride the carbonyl-oxygen atom, being co-ordinated to the metal atom (MgX or AlH_3), becomes effectively the largest group and thus orients itself between S and M. The approach of the R′ group is then directed, as would be expected, from that side of the molecule to which S is attached rather than M.

Prelog's Approach to Asymmetric Synthesis.—Prelog and his collaborators [36] have submitted to conformational analysis the extensive experimental results of McKenzie and his school on the configurational course of the addition of Grignard reagents to phenylglyoxylic esters of asymmetric alcohols, and have been able to relate the sign of rotation of the atrolactic acid produced on hydrolysis with the configuration of the original asymmetric alcohol.

The most stable conformation of the phenylglyoxylic ester was considered to be (28) in which the two carbonyl groups are planar and *anti* to each other, with the two larger groups of the asymmetric alcohol (29) skew to the ester-carbonyl oxygen. Addition of methylmagnesium halide will be more rapid from the less hindered side of the carbonyl group leading to a preponderance of (30) over its diastereoisomer. Thus the formation of a partially racemic but lævorotatory atrolactic acid, showing an excess of the enantiomorph (31), indicates that the alcohol has the absolute configuration represented by (29). Conversely, a dextrorotatory atrolactic acid indicates that the parent alcohol has the opposite configuration to (29). This method has been applied [36] to the determination of the absolute configuration of several groups of natural products.



(28) (30)

(29) (31)

Relative Rates of Cyclisation.—The rate of any reaction proceeding

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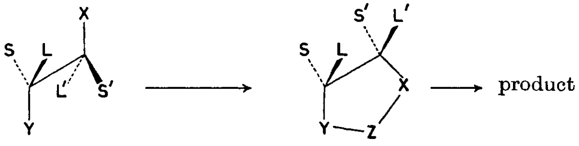
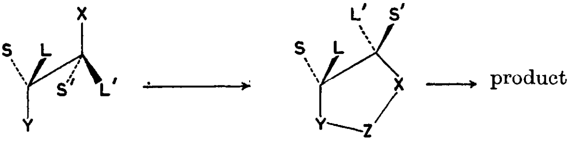
[36] Prelog, *Helv. Chim. Acta*, 1953, **36**, 308 ; Prelog and Meier, *ibid.*, p. 320 ; W. G. Dauben, Dickel, Jeger, and Prelog, *ibid.*, p. 325 ; and later years.

through an approximately planar transition state or intermediate, whatever the ring size and whether or not the final product is cyclic, will, in general, be smaller for the diastereoisomer reacting through the transition state or intermediate where large groups are eclipsed than for the isomer where smaller groups are eclipsed.

(*a*) 1 : 2-*cis*-Cyclisations. Thus the reaction of form (32) *via* (33) will be slower than the reaction of form (34) *via* (35).[37] Well-authenticated examples of this effect in a five-membered transition state are the rates of

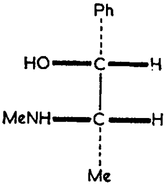


(32) (33)

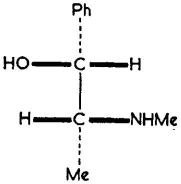


(34) (35)

acyl migration in 1 : 2-amino-alcohols, such as *erythro-* (36) (slow) and *threo-* (37) (fast) ephedrine, [38, 39] and the slower rate of condensation with acetone of *meso-* (38) than of racemic (39) dihydrobenzoin.[40] The readier



(36)



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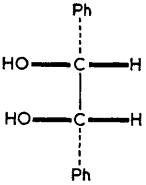

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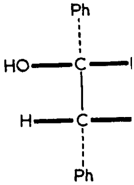

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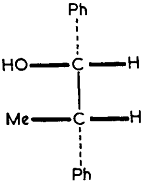

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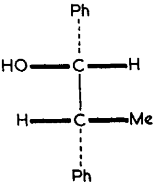

(41)

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[37] Some of the links in the ring may be partial bonds. Z may represent one or more ring atoms (or, conceivably, none), X and Y are atoms or groups of the type referred to in the cursive text.

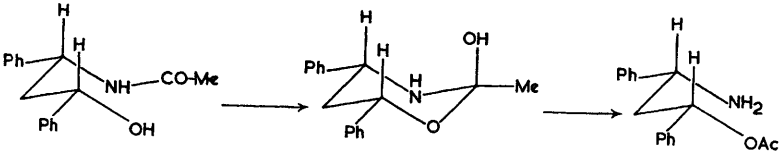
[38] Welsh, *J. Amer. Chem. Soc.*, 1947, **69**, 128 ; 1949, **71**, 3500.

[39] Fodor, Bruckner, Kiss, and Ohegyi, *J. Org. Chem.*, 1949, **14**, 337 ; see also Close, *J. Org. Chem.*, 1950, **15**, 1131.

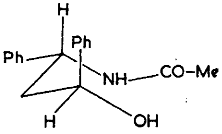
[40] Hermans, *Z. phys. Chem.*, 1924, **113**, 337.

pyrolysis [29] of the xanthate of *threo*- (40) than of *erythro*-1 : 2-diphenylpropan-1-ol (41) illustrates the operation of the effect in an approximately planar six-membered transition state.

(*b*) 1 : 3-*cis*-Cyclisations. The relative rates of cyclisation of *erythro*- and *threo*-isomers may be reversed when the transition state is *non-planar.* Wendler [41] has suggested that the diastereoisomer of 3-acetamido-1 : 3-diphenylpropan-1-ol which undergoes N → O acetyl migration in acid solution has the configuration (42), on the grounds that the intermediate (43) in the migration suffers from no serious non-bonded interactions. On the other hand the other diastereoisomer (44) does not undergo migration [42] because this would involve an intermediate (45) with a strong non-bonded repulsion between phenyl and hydroxyl (or methyl) groups.[43]



(42) (43)



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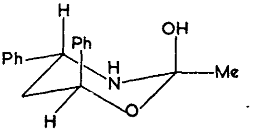
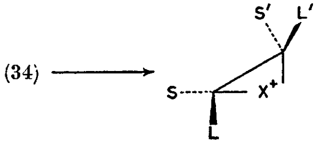


(45)

(*c*) 1 : 2-*trans*-Cyclisations. In a *trans*-cyclisation with displacement of an adjacent substituent through a planar cyclic transition state, symbolised in (34) → (46) as a general formulation of neighbouring-group participation,[44] the diastereoisomer (34) which reacted more rapidly in the *cis*-



(46)

cyclisation now passes into a product (46) where the large groups are eclipsed. It reacts therefore more slowly than its isomer (32), where the product has only eclipsing of the large and the small groups.

The reality of this effect for a three-membered transition state or inter-

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[41] Wendler, *Experientia,* 1953, **9**, 416.

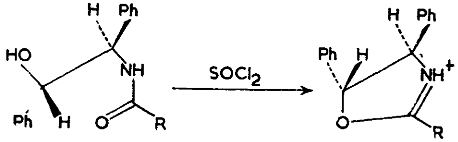
[42] Stühmer and Frey, *Arch. Pharm.*, 1953, **286**, 8.

[43] The hydroxyl group and one of the phenyl groups of the oxazine (45) are both axial (see p. 55).

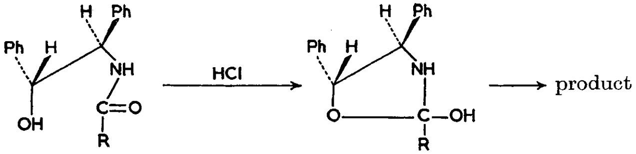
[44] Winstein, Morse, Grunwald, Schreiber, and Corse, *J. Amer. Chem. Soc.*, 1952, **74**, 1113.

mediate has been demonstrated in relative rates of phenyl-group migration (through phenonium-ion intermediates) for appropriate pairs of diastereoisomers.[44, 45] Curtin, in particular, has emphasised the role of such a " *cis*-effect " in controlling the relative rates of competing pinacolic aryl migrations of 1 : 2-diaryl systems.[46]

To emphasise the contrast between *cis*- and *trans*-1 : 2-cyclisations let us consider the reactions of the two diastereoisomeric 2-amino-1 : 2-diphenylethanols. Thionyl chloride cyclises the *N*-formate of the *erythro*-isomer (47 ; R = H), *via* the chlorosulphite and with inversion, to the oxazoline salt (48 ; R = H) under conditions that do not affect the formate (49) of



(47) (48)

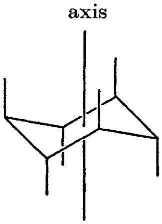


(49) (50)

the *threo*-isomer.[47] On the other hand the *threo*-*N*-acetate (49 ; R = Me) undergoes N → O acetyl migration through *cis*-cyclisation to the oxazolidine (50) on treatment with alcoholic hydrogen chloride, conditions which leave the *N*-acetate (47 ; R = Me) of the *erythro*-isomer unchanged.[39]

Some Illustrations from Alicyclic Chemistry

Examination of a model of the chair conformation of *cyclo*hexane shows that the C–H bonds are of two geometrically different types. Six of the



(51)

(52)

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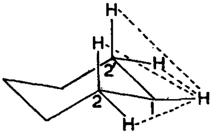
[45] Cram, *ibid.*, p. 2152.

[46] Curtin and Crew, *ibid.*, 1955, **77,** 354, and earlier papers ; for a review see Curtin, *Rec. Chem. Progr.*, 1954, **15,** 111.

[47] Weijlard, Pfister, Swanezy, Robinson, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73,** 1216. For related transformations see, *inter alia*, Elliott, *J.*, 1949, 589 ; 1950, 62 ; *Ann. Reports*, 1953, **50,** 277.

bonds lie parallel to the threefold symmetry axis of the ring as in (51) and have been designated " axial ".[48] The other six bonds radiate out from the ring as in (52) and have been named " equatorial ".[48]

In the chair conformation of *cyclo*hexane, each equatorial hydrogen atom is skew to the four hydrogen atoms on the two adjacent carbon atoms and about 2·5 Å distant from each of them [1 : 2-H : H interactions ; see (53)]. Each axial hydrogen atom is flanked by two equatorial hydrogen atoms attached to the adjacent carbon atoms in the same geometrical relation [1 : 2-H : H interactions ; see (54)]. Each axial hydrogen atom is also about 2·5 Å away from the other two axial hydrogen atoms on the same side of the ring [1 : 3-H : H interactions ; see (54)]. All other H : H or C : H interactions are relatively unimportant.



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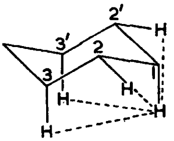
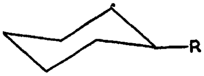


(54)

Preferred Conformations of Simple cyclo*Hexane Derivatives.*—A study of accurate scale models shows that any substituent larger than hydrogen in an axial conformation is closer to the two axial hydrogen atoms (1 : 3-interactions) on the same side of the ring than the same substituent in an equatorial conformation is to the adjacent equatorial and axial hydrogen atoms (1 : 2-interactions). In consequence the stronger (repulsive) 1 : 3-interactions dominate the energy relations and a substituent, in general, prefers to adopt an equatorial rather than an axial conformation.



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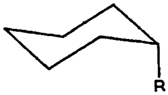

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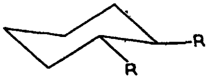

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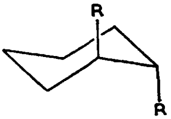

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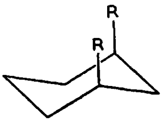

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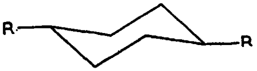

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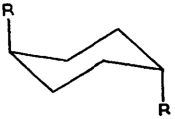

(62)

The extensive investigations of Hassel and his collaborators [49] on the

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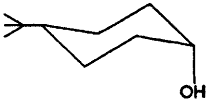
[48] Barton, Hassel, Pitzer, and Prelog, *Nature*, 1953, **172**, 1096. " Equatorial " and " axial " replace the earlier synonyms κ and ϵ (Hassel, *Tidsskr. Kjemi Bergvesen Met.*, 1943, **3**, 32) and " equatorial " and " polar " (Beckett, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488).

[49] Reviews : Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929 ; Hassel, *Research*, 1950, **3**, 504 ; *Quart. Rev.*, 1953, **7**, 221.

electron diffraction of *cyclo*hexane derivatives in the vapour phase—conditions where intermolecular interactions are at a minimum—have revealed that a *cyclo*hexane derivative normally exists predominantly in the chair conformation which has the maximum number of substituents equatorial. Thus monosubstituted *cyclo*hexanes are to be represented [50] as (55) rather than (56), *trans*-1 : 2-disubstituted *cyclo*hexanes as (57) rather than (58), *cis*-1 : 3-disubstituted derivates as (59) rather than (60) and *trans*-1 : 4-compounds as (61) rather than (62).

Such alternative chair conformations can be interconverted by merely passing the *cyclo*hexane ring through a planar or equivalent conformation. The interconversion of the two chair conformations through such an intermediate having angle-strain and higher non-bonded interactions generates an energy barrier between the two of only a few kcal./mole, too small to allow their separation in the liquid or vapour state by the classical methods of organic chemistry. Since rates of thermal equilibration of conformational isomers are therefore generally much greater than rates of chemical reactions, a reaction proceeding by a mechanism involving a transition state having geometrical requirements better satisfied by a less stable conformation may well follow a path mainly through that less stable conformation.[51] Monocyclic *cyclo*hexane derivatives [52] are therefore, from the point of view of reaction mechanism, always subject to conformational ambiguities. Condensed *cyclo*hexane systems discussed below, in which ring conversions are more difficult or geometrically impossible, do not suffer from the same objections. Winstein and Holness [53] have recently ensured conformational homogeneity in an ingenious manner by using *cis*- (63) and *trans*-*tert.*-butyl*cyclo*hexanol (64). The very bulky *tert.*-butyl grouping guarantees the absence of any significant proportion of conformations with this group axial.



(63)

(64)

Condensed cyclo*Hexane Ring Systems.*—The most stable conformation of a *cyclo*hexane ring system is that with the greatest number of chair rings (see above). In most cases this principle enables an unambiguous conformation to be deduced for such systems. Thus *trans-anti-trans*-perhydrophenanthrene is to be represented as (65), the *trans*-A/B steroids (66) as (67),[20, 21, 54] and oleanane (68), the most important parent hydrocarbon

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[50] These and similar formulæ in the present article are stylised representations of the true conformations. They are not intended to be accurate perspective or orthogonal projections.

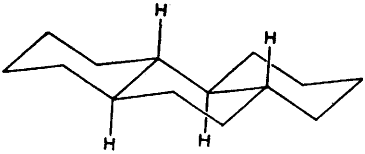
[51] Eliel, *Experientia*, 1953, **9**, 91.

[52] For an excellent review of monocyclic *cyclo*hexane derivatives, see Orloff, *Chem. Rev.*, 1954, **54**, 347.

[53] Winstein and Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562. We are most grateful to Professor Saul Winstein for informing us of his results before their publication.

[54] Barton and Rosenfelder, *J.*, 1951, 1048.

of the pentacyclic triterpenoids, as (69).[55] All these conformational assignments are quite unambiguous and are supported by a wealth of chemical evidence.[56]



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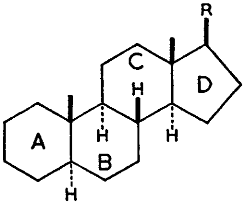

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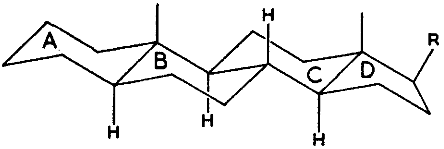

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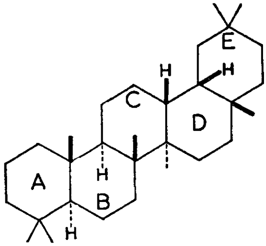

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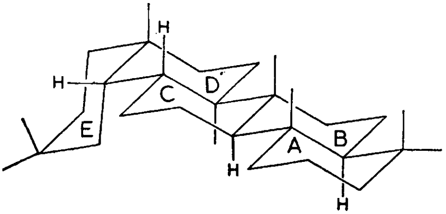

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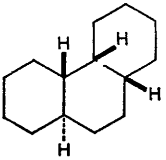

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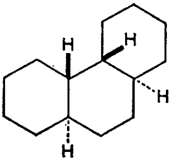

(71)

An interesting demonstration [57, 58] of the destabilising effect of boat conformations is provided by the fact that *trans-syn-cis*-perhydrophenanthrene, (70) where all rings can adopt chair conformations, is more stable than the *trans-syn-trans*-isomer (71), where one ring is forced to assume a boat conformation.

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[55] Barton and Holness, *J.*, 1952, 78 ; Barton, *J.*, 1953, 1027.

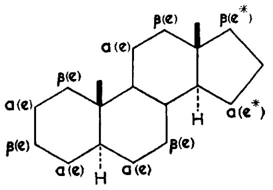
[56] Conformations deduced from minimisation of non-bonded interactions refer ideally only to isolated molecules, the conformations of which are entirely controlled by intramolecular forces. In the crystal lattice it is conceivable that intermolecular forces could become dominant and that different conformations might be favoured. Fortunately, in most cases, it appears that the ideal conformation of the isolated molecule is also preserved in the crystal. For impressive examples see : Carlisle and Crowfoot, *Proc. Roy. Soc.*, 1945, *A*, **184,** 64 (cholesteryl iodide) ; Fridricksons and Mathieson, *J.*, 1953, 2159 (lanostenyl iodoacetate) ; Carlisle and Abd El Rehim, *Chem. and Ind.*, 1954, 279 (methyl oleanolate iodoacetate).

[57] Linstead and Whetstone, *J.*, 1950, 1428.

[58] Johnson, *Experientia*, 1951, **7,** 315.

Calculation of Energy Differences between Geometrical Isomers.—The calculation of energy differences by semiempirical procedures [59] can be extended to provide the relative stabilities of conformational isomers.[60] The calculations led to the observed stability orders of chair- > boat-*cyclo*hexane, 2-chair *trans*-decalin > 2-chair *cis*-decalin, 2-chair *cis*-decalin > 2-boat *cis*-decalin. A more convenient method has been developed,[61] based upon Pitzer's treatment [62] of the methyl*cyclo*hexanes. This simple empirical approach assigns an interaction energy of 0·8 kcal./mole to each skew interaction as in *n*-butane (4). *cis*-Decalin, for example, has three skew interactions that do not occur in *trans*-decalin and is therefore *ca.* 2·4 kcal./mole less stable, in excellent agreement with experiment.[63] The calculations have been extended [61] to include perhydro-phenanthrenes and -anthracenes and the calculated relative stabilities of some of the isomers have been confirmed experimentally.[61, 64]

Reaction Rates and Equilibria controlled by Steric Compression.—(*a*) *Relative stabilities of epimers.* At a given secondary carbon atom in a *cyclo*hexane ring system a substituent, being necessarily larger than a hydrogen atom, is more stable in an equatorial than in the corresponding axial conformation. In a rigid fused ring system, in which conformational interconversion is impossible, the axial or equatorial conformation of a substituent depends directly on its configuration.[21] The most thoroughly explored ring system which tests this generalisation is the *trans*-A/B steroid nucleus (66), (67). In formula (72) the experimentally determined configuration (α or β) and the conformation (e or a) [65] of the more stable epimeric secondary alcohol is indicated at every relevant position of the nucleus; in every case the equatorial alcohol is more stable than its axial epimer.[21, 66] Similarly,



(72)

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[59] Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173; Westheimer and Mayer, *J. Chem. Phys.*, 1946, **14**, 733 and references there cited; Hill, *ibid.*, 1948, **16**, 938 and references there cited.

[60] Barton, *J.*, 1948, 340.

[61] Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 2118; Johnson, *ibid.*, 1953, **75**, 1498.

[62] Beckett, Pitzer, and Spitzer, *ibid.*, 1947, **69**, 2488.

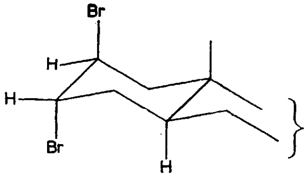
[63] The experimental value is 2·12 kcal./mole for the liquid phase at 25° (Davies and Gilbert, *J. Amer. Chem. Soc.*, 1941, **63**, 1585). An approximate correction [61] to convert the calculated value to the same state yields a figure of 2·07 kcal.

[64] Robins and Walker, *J.*, 1954, 3960; 1955, 1789; *Chem. and Ind.*, 1955, 772.

[65] e* represents an equatorial conformation with respect to ring C.

[66] See also Barton in Lettré, Inhoffen, and Tschesche, "Über Sterine, Gallensaüren, und verwandte Naturstoffe", Enke, Stuttgart, 1956.

compounds with enolisable substituents such as alkoxycarbonyl[67] on equilibration with base yield mainly the equatorial epimers.



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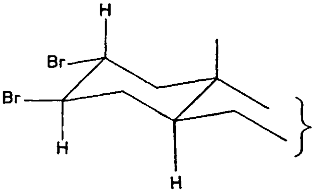
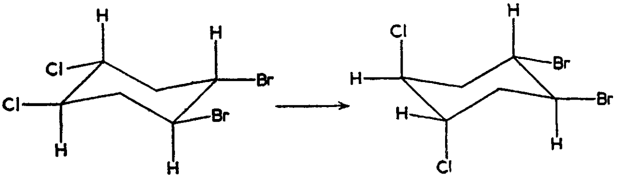


(74)

The relative stabilities of several steroidal 1 : 2-dihalides have been determined.[68] The diaxial cholestene 2β : 3α-dibromide (73), for example, rearranges to the diequatorial dibromide (74). This is a case where the forces of steric compression are opposed by those of dipole repulsion. No doubt form (73) is destabilised particularly by the large 2β-axial bromine ratio to axial 10-methyl interaction, for *cyclo*hexene *trans*-dibromide is rather more stable in the diaxial than in the diequatorial conformation.[69] It is interesting that the all-equatorial chloride bromide (75) rearranges, presumably by interchange of the bromine atoms and conformational inversion, to (76), the chlorine atoms taking up axial positions in preference to the larger bromine atoms.[70]



(75) (76)

Reduction of ketones or oximes with sodium and alcohol has long been known to give mixtures of epimeric alcohols or amines of approximately the same composition as direct equilibration. More recently it has been suggested that all reductions by alkali metals and proton donors proceeding through carbanions give predominantly the most stable product.[71] Included are reductions of conjugated dienes, $\alpha\beta$-unsaturated ketones, aromatic

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[67] Klyne, " Progress in Stereochemistry ", Butterworths, London, 1954, Vol. I, p. 37 *et seq.*

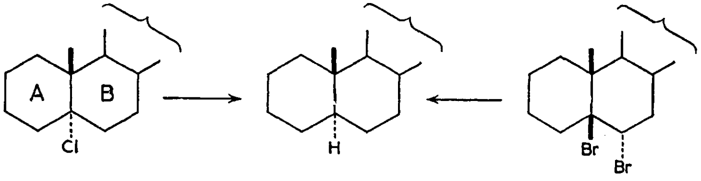
[68] Alt and Barton, *J.*, 1954, 4284.

[69] Bastiansen and Hassel, *Tidsskr. Kjemi Bergvesen Met.*, 1946, **6**, 96 ; Larnaudie, *Compt. rend.*, 1953, **236**, 909 ; Kwestroo, Meijer, and Havinga, *Rec. Trav. chim.*, 1954, **73**, 717 ; Kozima, Sakashita, and Maeda, *J. Amer. Chem. Soc.*, 1954, **76**, 1965 ; Bender, Flowers, and Goering, *ibid.*, 1955, **77**, 3463.

[70] Andersen, Hassel, and Lunde, *Acta Chem. Scand.*, 1952, **6**, 966.

[71] Barton and Robinson, *J.*, 1954, 3045 ; in view of the interesting results recently reported by Cram, Allinger, and Langemann (*Chem. and Ind.*, 1955, 919) the reservation must be made that the carbanions must be sufficiently long lived to exercise their stereochemical preference. See also : Johnson, Bannister, Bloom, Kemp, Pappo, Rogier, and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1953, **75**, 2275 ; Arth, Poos, Lukes, Robinson, Johns, Fleurer, and Sarett, *ibid.*, 1954, **76**, 1715.

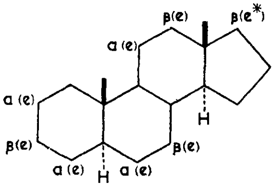
systems, and halides. For example,[71] 5α-chlorocholestane (77) and 5β : 6α-dibromocholestane (78) both afford cholestane (79), with the more stable *trans*-A/B fusion, on reduction with lithium and liquid ammonia.



(77) (79) (78)

The uniform production of products of more stable configuration is most simply explained by assigning to the carbanion a definite, but easily inverted, tetrahedral configuration and by assigning to the electron pair steric requirements somewhat larger than hydrogen but smaller than other substituents.

(*b*) *Relative rates of esterification and hydrolysis.* Since, at a given secondary carbon atom in a *cyclo*hexane system, the steric compression of an equatorial is less than that of an axial hydroxyl group, one would expect equatorial hydroxyl groups to be more easily esterified than their axial epimers and the same relation to hold for the hydrolysis of their esters. For the same reason an ester of an equatorial carboxylic acid should be hydrolysed more rapidly than its axial epimer. Using the *trans*-A/B steroid nucleus for illustration, formula (80) shows which epimeric ester is more rapidly hydrolysed.[21, 66] Agreement with expectation is complete. A closer correlation of hydrolysis rates with the relative magnitudes of non-bonded interactions can be secured without difficulty.[21, 66]



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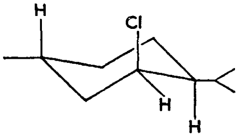

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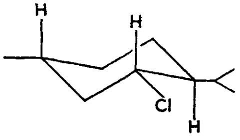
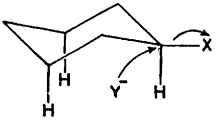


(82)

(*c*) *Relative rates of solvolysis.* It is difficult to compare the rates of pure $S_{\mathrm{N}}1$ replacement reactions of *cyclo*hexyl compounds owing to the ease with which competing reactions take place. It would be expected that the extra steric compression to which axial substituents are subjected would be at least one factor leading to faster solvolysis rates relative to those of the corresponding equatorial substituents. This is probably the case for the S_N1 solvolysis [72] of *neo*menthyl chloride (81) relative to menthyl chloride (82).

For S_N2 replacement processes, axially oriented substituents should be replaced more rapidly than equatorially oriented substituents. This is because the approach to the back of an equatorial substituent is hindered by the axial groups [see formula (83)]. For the epimer, approach of the reagent is hindered only by 2-substituents [see (84)]. Gallagher and Long [73] described an example of the expected difference when they showed that the axial 11β-bromine atom of methyl 3α-acetoxy-11β-bromo-12-oxocholanate (85) was replaced with inversion by OH^- more rapidly than was the equatorial 11α-bromine of its epimer.



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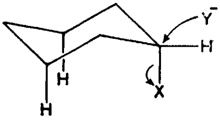

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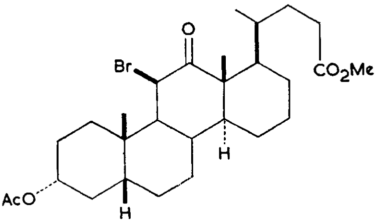

(85)

(*d*) *Rates of oxidation of secondary alcohols.* The relative rates of oxidation of epimeric pairs of secondary alcohols to the ketone by chromic acid or by hypobromous acid are just the reverse of the relative rates of hydrolysis of their carboxylic esters. The equatorial cholestan-3β-ol, for example, is oxidised to cholestanone more slowly than is the axial cholestan-3α-ol.[74] This is understandable if the rate-controlling step is not the formation of the corresponding chromate or hypobromite, but attack of some nucleophilic species on the hydrogen atom [21] after the ester has been formed. Westheimer *et al.*[75] have shown that this is indeed the case for certain chromic acid oxidations.

Chromic acid oxidation has recently been shown to be subject to steric acceleration ; [76] that is, the more hindered the alcohol, the greater is the

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[72] Hughes, Ingold, and Rose, *J.*, 1953, 3839 ; see also unpublished results cited in ref. 53.

[73] Gallagher and Long, *J. Biol. Chem.*, 1946, **162**, 521.

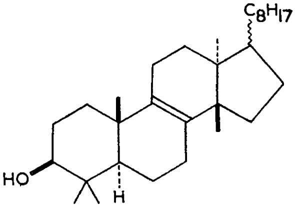
[74] Vavon and Jacubowicz, *Bull. Soc. chim. France*, 1933, **53,** 581.

[75] Westheimer *et al.*, *J. Amer. Chem. Soc.*, 1949, **71,** 25 ; 1951, **73,** 65 ; 1952, **74,** 4383, 4387.

[76] Schreiber and Eschenmoser, *Angew. Chem.*, 1955, **67**, 278 ; *Helv. Chim. Acta*, 1955, **38,** 1529.

release of compression energy in the transition state and the faster the reaction.

(*e*) *Conformational driving forces.* Steric acceleration of solvolysis is a well-known phenomenon [77] and one can envisage in similar terms the acceleration of carbonium-ion rearrangements through the release of compression energy accompanying the rearrangement. For example, the conversion of a high-energy boat conformation into a lower-energy chair conformation through some carbonium-ion rearrangement might be regarded as a reaction assisted by a conformational driving force. An interesting example [78] is possibly provided by the acid-catalysed rearrangement of euphenol (86) to *iso*euphenol (87). Analogous conformational driving forces no doubt play a part in the anomalous trans-annular reactions of medium-sized rings.[79]



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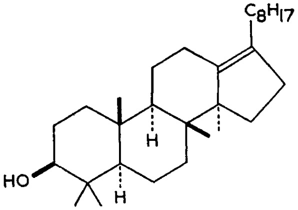

(87)

(*f*) *Dissociation constants.* Gane and Ingold [80] developed measurement of dissociation constants into a powerful method of investigating the conformations of symmetrical acyclic dicarboxylic acids in solution. In the *cyclo*hexane series [81, 82] the *cis*- and *trans*-1 : 2-dicarboxylic acids show a large difference in ΔpK_a, the difference in the pK_a's of the first and the second dissociation constants. The smaller ΔpK_a value for the *trans*-1 : 2-acid is due to the greater separation between the integral charges in the dianion, which adopts, because of electrostatic repulsion, the diaxial (88) rather than the diequatorial conformation (89). In the dianion from the *cis*-acid, for which only one chair conformation is possible (90), the charges are closer together,

	ΔpK_a	
	cis	*trans*
*cyclo*Hexane-1 : 2-dicarboxylic acid . . .	1·80	1·15
*cyclo*Hexane-1 : 3-dicarboxylic acid . . .	0·76	0·82

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[77] Hughes, *Quart. Rev.*, 1951, **5**, 245 ; F. Brown, Davies, Dostrovsky, Evans, and Hughes, *Nature*, 1951, **167**, 987 ; H. C. Brown and Fletcher, *J. Amer. Chem. Soc.*, 1949, **71**, 1845 ; Bartlett *et al.*, *ibid.*, 1955, **77**, 2801, 2804, 2806.

[78] Barton, McGhie, Pradhan, and Knight, *Chem. and Ind.*, 1954, 1325 ; *J.*, 1955, 876 ; see also Arigoni, Viterbo, Dünnenberger, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1954, **37**, 2306.

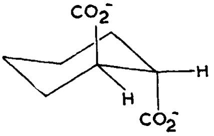
[79] Prelog, *J.*, 1950, 420 ; Cope, Fenton, and Spencer, *J. Amer. Chem. Soc.*, 1952, **74**, 5884 ; Prelog and Schenker, *Helv. Chim. Acta*, 1952, **35**, 2044 ; Prelog, Schenker, and Küng, *ibid.*, 1953, **36**, 471.

[80] Gane and Ingold, *J.*, 1931, 2153 ; Ingold, *ibid.*, p. 2179.

[81] Speakman, *J.*, 1941, 490, and references there cited.

[82] Barton and Schmeidler, *J.*, 1948, 1197.

in fact the same distance apart as in (89). In the 1 : 3-diacids the difference



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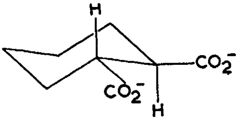

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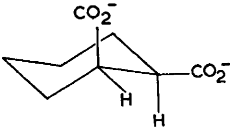
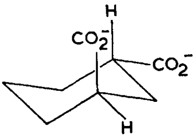


(90)

in ΔpK_a is smaller and, for similar reasons, the *trans*-acid has the larger value. This would be expected from the conformations (91) and (92), the negative charges being closer in the *trans*- than in the *cis*-acid. Analysis of dissociation-constant data [82] for the tricarboxylic acid (93) shows that here the balance of electrostatic factors makes (94) the preferred conformation for the trianion, rather than the alternative (95).



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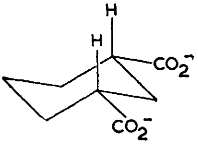

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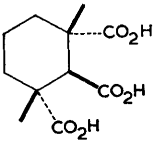

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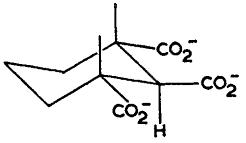

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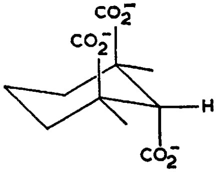

(95)

Similarly, for epimeric amino-acids, $\underbrace{\rangle\mathrm{NH}^+ \quad \mathrm{CO}_2^-}$, ΔpK is greater for the epimer in which the two poles are closer together in the preferred conformation.[83]

To the extent that ionisation of acids and bases is determined by the degree of solvation of the ions, in otherwise non-polar molecules, axial acids and amines would be expected to be weaker than their equatorial epimers, owing to greater hindrance to solvation in the axial ions. Amongst epimeric pairs of *cyclo*hexanecarboxylic acids, the stronger are those that can take up an equatorial conformation.[84] Even at position 3 of cholestane, the least hindered in the entire steroid nucleus, the equatorial 3β-dimethylamino-derivative is 0·20 pK unit stronger than the axial 3α-epimer in 50% aqueous *tert.*-butyl alcohol.[85]

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[83] See p. 80.

[84] Dippy, S. R. C. Hughes, and Laxton, *J.*, 1954, 4102.

[85] Bird and Cookson, *Chem. and Ind.*, 1955, 1479.

Physical Properties.—(*a*) *Infrared spectra.* The most far-reaching and valuable correlations between the conformations of molecules and their physical properties relate to light absorption.[86] The frequency of the C–O stretching vibration of secondary alcohols is always higher for the equatorial than for the axial epimer. Equatorial alcohols usually [87] show this band at about 1040 cm.$^{-1}$ and axial ones at about 1000 cm.$^{-1}$. Page [88] has recently found that for epimeric pairs of acetoxy- and methoxy-steroids the steroid C–O stretching frequency in the 1150—1000 cm.$^{-1}$ region is higher for the equatorial than for the axial epimer. The higher frequency of equatorial C–X stretching vibrations is probably quite general. These regularities are obviously of use for the assignment of configuration to alcohols derived from conformationally rigid system.[89] Even the C–D stretching frequency of appropriate deutero-compounds depends on whether the deuterium is axial or equatorial.[90] R. N. Jones and his collaborators [91] have shown that introduction of an equatorial α-halogen atom into a *cyclo*hexanone increases the carbonyl stretching frequency by about 20 cm.$^{-1}$, whereas an axial α-halogen atom scarcely affects the frequency.

(*b*) *Ultraviolet spectra.* Equatorial and axial α-halogeno-*cyclo*hexanones also differ characteristically in their ultraviolet absorption spectra. The effects are just the reverse of those in the infrared region. Thus an equatorial α-bromine atom shifts the weak absorption band, that occurs in all saturated ketones at about 280 mμ, to slightly shorter wavelengths, but an axial α-bromine atom produces a marked shift to longer wavelengths with a three- or four-fold increase in intensity.[92] Rather similar behaviour is shown by α-hydroxy- and α-acetoxy-ketones.[93] The approximate shift (Δλ) in wavelength of the weak band caused by α-substitution may be summarised as in the annexed Table.

α-Substituent	Δλ(mμ) e	Δλ(mμ) a
Cl	− 7	+ 22
Br	− 5	+ 28
OH	− 12	+ 17
OAc	− 5	+ 10

It should be noted that acetylation of an equatorial α-ketol shifts the maxi-

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[86] For a more detailed review see Braude and Waight, "Progress in Stereochemistry", ed. Klyne, Butterworths, 1954, p. 126; for the relation between conformation and ultraviolet absorption of cyclic conjugated dienes see Braude, *Chem. and Ind.*, 1954, 1557.

[87] Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1951, **73,** 3215; Cole, Jones, and Dobriner, *ibid.*, 1952, **74,** 5571; Fürst, Kuhn, Scotoni, and Günthard, *Helv. Chim. Acta*, 1952, **35,** 951.

[88] Page, *J.*, 1955, 2017.

[89] For example, see: Cole, *J.*, 1952, 4969; Aebi, Barton, Burgstahler, and Lindsey, *J.*, 1954, 4659. For correlation of infrared spectra and conformation of carbohydrates see: Barker, Bourne, Stacey, and Whiffen, *ibid.*, p. 171; Barker, Bourne, Stephens, and Whiffen, *ibid.*, pp. 3468, 4211.

[90] Corey, Sneen, Danaher, Young, and Rutledge, *Chem. and Ind.*, 1954, 1294.

[91] R. N. Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74,** 2828.

[92] Cookson, *J.*, 1954, 282.

[93] Cookson and Dandegaonker, *J.*, 1955, 352.

mum to longer wavelengths, whereas acetylation of the axial epimer shifts it to shorter wavelengths.[93, 94]

(*c*) *Adsorption and partition.* As one would expect from simple mechanical considerations, a compound with an equatorial polar group is, in general, more strongly adsorbed on a chromatographic column than its epimer with an axial substituent.[21] Examples where this order of elution from alumina is followed are the various 2 : 3-dihalogenocholestanes [95] and the dihydrolysergic acids.[96] However, exceptions have been noted,[97] perhaps because surface forces may compel adsorbed molecules to adopt conformations that are not preferred in solution. Least deviation from the rule would, therefore, be expected in partition chromatography and, indeed, Savard [98] observed that axial steroidal alcohols travel faster on paper than their equatorial epimers.

(*d*) *Refractive index and density.* The von Auwers–Skita rules,[99] according to which the *cis*-compound (of a pair of *cis–trans*-isomers) has the higher refractive index and density, break down when applied to 1 : 3-disubstituted *cyclo*hexanes, where the reverse order holds.[100] The rules are also frequently ambiguous when applied to polycyclic systems such as steroids. A modified rule is valid according to which for substituted *cyclo*hexanes the stereoisomer with the more axial substituents has a higher refractive index and density.[101] Kelly [102] has proposed a generalised version of the rule stating that for isomeric *cyclo*hexane and tetrahydropyran derivatives which are similarly substituted on corresponding ring carbon atoms the refractive indices and densities are inversely related to conformational stability.

Influence of Conformation on Reactions with Particular Stereoelectronic Requirements.—(*a*) *Diaxial bimolecular elimination.* The transition state of lowest energy for an ionic *E*2 reaction (elimination of X and Y) requires [21, 66, 103] the four centres concerned to be in one plane as in (96). In conformationally rigid ring systems based on *cyclo*hexane this geometrical

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[94] Baumgartner and Tamm, *Helv. Chim. Acta,* 1955, **38,** 441.

[95] Alt and Barton, *J.*, 1954, 4284.

[96] Stoll, Petrzilka, Rutschmann, Hofmann, and Günthard, *Helv. Chim. Acta,* 1954, **37,** 2039.

[97] Brooks, Klyne, and Miller, *Biochem. J.*, 1953, **54,** 212.

[98] Savard, *J. Biol. Chem.*, 1953, **202,** 457.

[99] Von Auwers, *Annalen,* 1920, **420,** 89 ; Skita, *Ber.*, 1920, **53,** 1792.

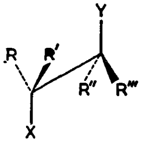
[100] Mousseron and Granger, *Bull. Soc. chim. France,* 1938, **5,** 1618 ; 1946, 218 ; Beckett, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69,** 2488 ; Goering and Serres, *ibid.*, 1952, **74,** 5908 ; Noyce and Denney, *ibid.*, p. 5912 ; Haggis and Owen, *J.*, 1953, 408 ; Darling, Macbeth, and Mills, *ibid.*, p. 1364.

[101] See Allinger, *Experientia,* 1954, **10,** 328.

[102] Kelly, personal communication.

[103] Young, Pressman, and Coryell, *J. Amer. Chem. Soc.*, 1939, **61,** 1640 ; Winstein, Pressman, and Young, *ibid.*, p. 1645 ; Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2117 ; Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72,** 1066 ; Barton and Rosenfelder, *J.*, 1951, 1048; for an interesting application in Wolff–Kishner reductions of α-ketols see Turner, Anliker, Helbling, Meier, and Heusser, *Helv. Chim. Acta,* 1955, **38,** 411.

requirement is satisfied by 1 : 2-*trans*-diaxial substituents, but not by 1 : 2-*trans*-diequatorial or, of course, by 1 : 2-*cis*-substituents. This rule, which replaces the less demanding rule of "*trans*-elimination", has been demonstrated especially in the debromination of 1 : 2-dibromides by iodide ion[104] as in (97).



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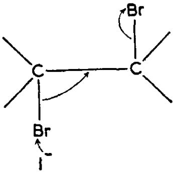

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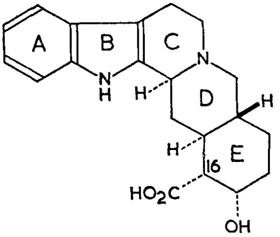
An example where the course of a reaction is controlled by preference for diaxial elimination concerns yohimbic acid (98) and its 16-epimer, corynanthic acid.[105] Base induces the elimination of sulphuric acid from the sulphuric acid ester of yohimbic acid [see (99)], but of carbon dioxide and sulphuric acid from the corresponding ester of corynanthic acid [see (100)]. In each case the reaction follows the course of diaxial elimination.



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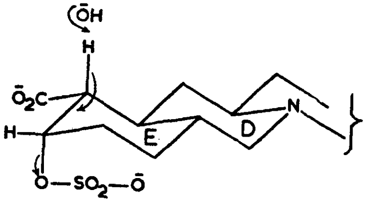

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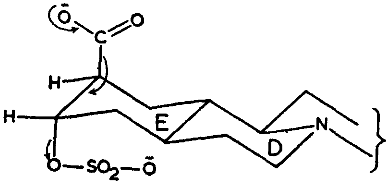

(100)

Many more examples of preferred diaxial elimination could be quoted. However, Bordwell and his colleagues[106] have recently shown that elimination of a *cis*-hydrogen atom, rather than of an alternative *trans*-one, may

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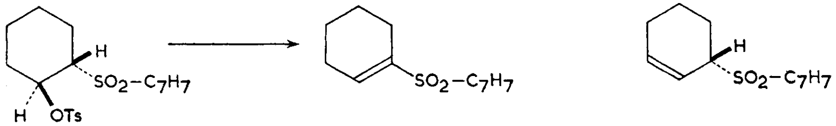
[104] In simple aliphatic compounds alternative mechanisms are possible: Hine and Brader, *J. Amer. Chem. Soc.*, 1955, **77**, 361.

[105] Cookson, *Chem. and Ind.*, 1953, 337; Janot, Goutarel, le Hir, Amin, and Prelog, *Bull. Soc. chim. France*, 1952, 1085.

[106] Weinstock, Pearson, and Bordwell, *J. Amer. Chem. Soc.*, 1954, **76**, 4748; Bordwell and Kern, *ibid.*, 1955, **77**, 1141; Bordwell and Peterson, *ibid.*, p. 1145.

take place when the former is made sufficiently acidic by a strongly electron-attracting group. Thus *trans*-2-toluene-*p*-sulphonyl*cyclo*hexyl toluene-*p*-sulphonate (101) undergoes second-order base-induced elimination of toluene-*p*-sulphonate ion, to give the *cyclo*hexene (102) rather than (103).

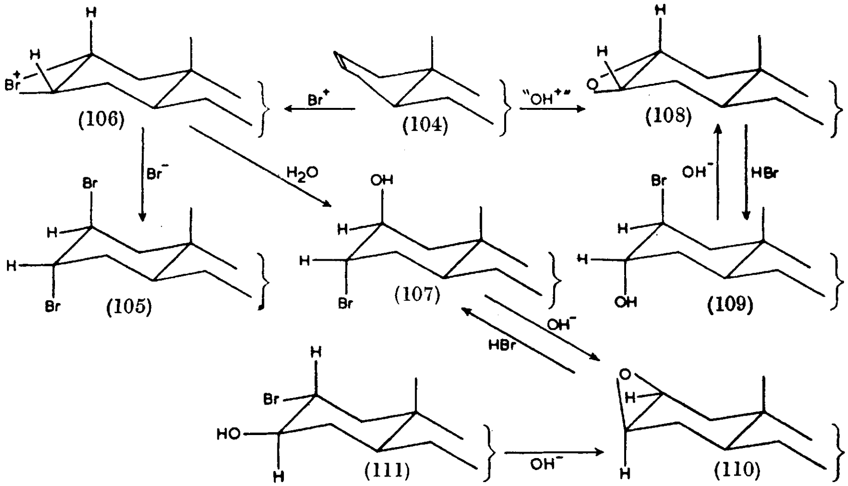


(101) (102) (103)

The *cis*-isomer, nevertheless, still reacts more rapidly (by *trans*-elimination and presumably through the diaxial conformation) than the *trans*-isomer, to give the same product.

(*b*) *Diaxial electrophilic addition.* The converse of the well-established rule (see above) of preferred diaxial elimination in ionic-type reactions would be preferred diaxial addition. It has recently been demonstrated [95] that electrophilic addition of halogen proceeds in this manner in systems where conformations are unambiguous. For example, bromine adds to cholest-2-ene (104) to give mainly the diaxial 2β : 3α-dibromocholestane (105), presumably through the 2α : 3α-bromonium ion (106). Similarly addition of hypobromous acid to cholest-2-ene affords mainly [107] the diaxial 3α-bromo-2β-hydroxycholestane (107).

(*c*) *Diaxial ring opening and closing in* cyclo*hexene oxides.* Either electrophilic or nucleophilic opening of epoxides affords mainly the diaxial product.[108] This is exemplified [95] for ring A of the steroids by the reaction



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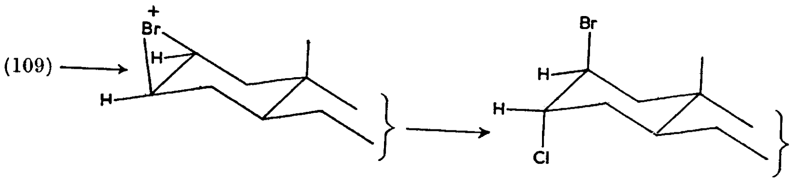
[107] Banerji, Barton, and Cookson, unpublished work ; preferred diaxial addition of hypohalous acid is a general rule.

[108] Fürst and Plattner, Abs. Papers 12th Int. Congr. Pure Appl. Chem., New York, 1951, p. 405 ; see also Barton *J.*, 1953, 1027.

of cholest-2-ene α-epoxide (108) with hydrogen bromide to give the diaxial 2β : 3α-bromohydrin (109) rather than the alternative *trans*-, but diequatorial, 3β : 2α-bromohydrin, and of the 2β : 3β-epoxide (110) to give the 3α : 2β-bromohydrin (107).

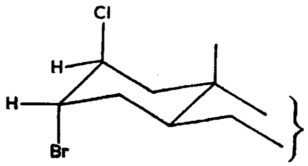
The expected faster ring closure of diaxial than of diequatorial halogenohydrins has also been observed.[107] Thus, under standard conditions, the times required for 90% reaction in the base-induced epoxide formation from the diaxial bromohydrins 3α-bromocholestan-2β-ol (107) and 2β-bromocholestan-3α-ol (109) are, respectively, 1·5 and 3·5 minutes. In contrast, 40 hours are required before the reaction of the diequatorial 2α-bromocholestan-3β-ol (111) has reached 90% of completion.

(*d*) *Diaxial neighbouring-group participation.* By analogy with preferred diaxial ring closure to ethylene oxides (see above), neighbouring-group participation of the kind extensively studied in simpler systems by Winstein and his school [109] should proceed more readily when the *trans*-1 : 2-substituents concerned are both axial than when they are both equatorial. The replacement reactions of the various 2 : 3-halogenohydrins of cholestane vindicate this view.[95] For example, treatment of the 2β : 3α-bromohydrin (109) with thionyl chloride gave, *via* the bromonium ion (112), mainly the diaxial 2β : 3α-bromochloride (113) whilst the 3α : 2β-bromohydrin (107) afforded, *via* (106), mainly the diaxial 3α : 2β-chlorobromide (114). Under the same conditions the diequatorial bromohydrin (111) was recovered unchanged. The diaxial chlorohydrins, in which the less nucleophilic chlorine atom is known to provide a smaller driving force,[110] showed participation of chlorine in replacement of hydroxyl only in reaction with the strongest electrophilic reagent, phosphorus pentachloride.



(112) (113)

(107) ⟶ (106) ⟶



(114)

The phenomena referred to in this section, and also the relative ease of

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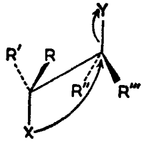
[109] Winstein and his collaborators, *J. Amer. Chem. Soc.*, many papers under the title " The Role of Neighbouring Groups in Replacement Reactions ", 1942 *et seq.*

[110] Winstein and Grunwald, *J. Amer. Chem. Soc.*, 1948, **70**, 828.

epoxide formation (see above), demonstrate again the important geometrical preference for four coplanar reaction centres.[111]

(*e*) *Diaxial rearrangements.* In *cyclo*hexane compounds rearrangements, in which the ring size is unchanged, take place most readily when the centres involved are coplanar [as in (115)], that is, when the group eliminated and the migrating carbon atom are both axial.[21, 66] The epimeric 17β-amino-17a-hydroxy-17a-methyl-D-homo-steroids provide an interesting and illustrative contrast in their modes of reaction with nitrous acid.[112] The 17a-α-hydroxy-group displaces nitrogen from the intermediate diazonium ion (116) to give the oxide (117) as expected from the discussion above. But the diazonium ion (118) from the 17aβ-hydroxy-compound, in which the antiparallel axial groups are N_2^+ and Me, undergoes methyl migration and ketonisation to give the oxide (119).



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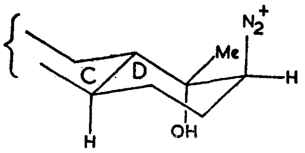

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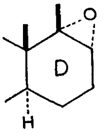

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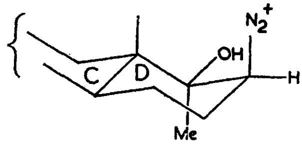

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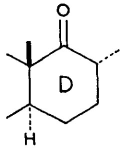

(119)

(*f*) *Ring contraction.* Under the compulsion of the same stereo-electronic force, which is the theme of much of this Review, rearrangements of *cyclo*hexane compounds involving ring contraction proceed most easily when the eliminated group is equatorial, for only then are the requisite 1 : 2-bonds coplanar and antiparallel. An instructive example [21, 66] is the dehydration of the epimeric triterpenoid 3β- and 3α-alcohols. The axial 3α-alcohols (120) are dehydrated simply to the Δ^2-compounds (121), whilst the equatorial 3β-alcohols (122) undergo, on treatment with phosphorus pentachloride, dehydration with ring contraction to give rearranged olefins (123).

(*g*) *Halogenation of ketones.* Use of infrared spectroscopy to determine

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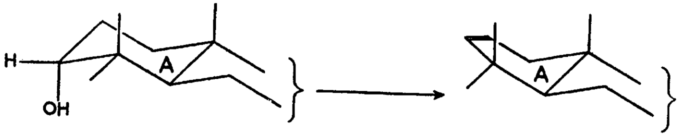
[111] This can also be discussed in terms of " orbital overlap " ; see Brutcher and Roberts, Abs. Papers, 126th Amer. Chem. Soc. Meeting, New York, 1954, p. 52-O. Change in ring size introduces a further factor ; see *idem*, Abs. Papers, 127th Amer. Chem. Soc. Meeting, Cincinnati, 1955, p. 39-N.

[112] Klyne and Shoppee, *Chem. and Ind.*, 1952, 470 ; Cremlyn, Garmaise, and Shoppee, *J.*, 1953, 1847 ; see also Ramirez and Stafiej, *J. Amer. Chem. Soc.*, 1955, **77**, 134.

configuration (see above) has established [113] that in the bromination of *cyclo*hexanones the axial α-bromo-ketone is always formed more rapidly than the equatorial epimer. This is attributed [113] to the favourable geometrical arrangement of the π-orbitals of the enol for overlap with the entering-bromine vacant orbital in the transition state for axial addition compared with equatorial addition [see (124)]. An alternative explanation, based on preferred diaxial electrophilic addition (see above) to the enolic ethylenic linkage followed by elimination of hydrogen bromide [see (125)], cannot yet be wholly excluded.



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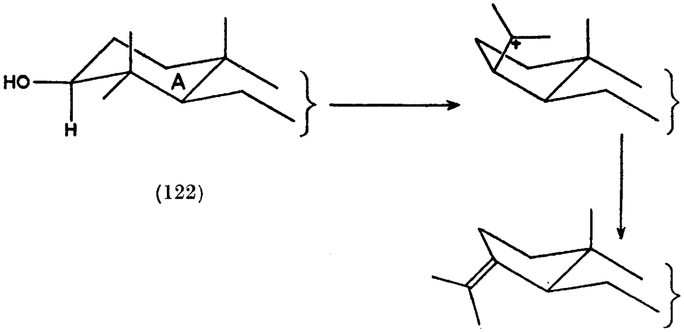

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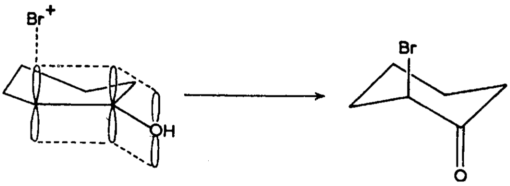

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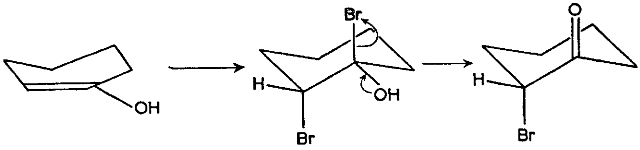

(125)

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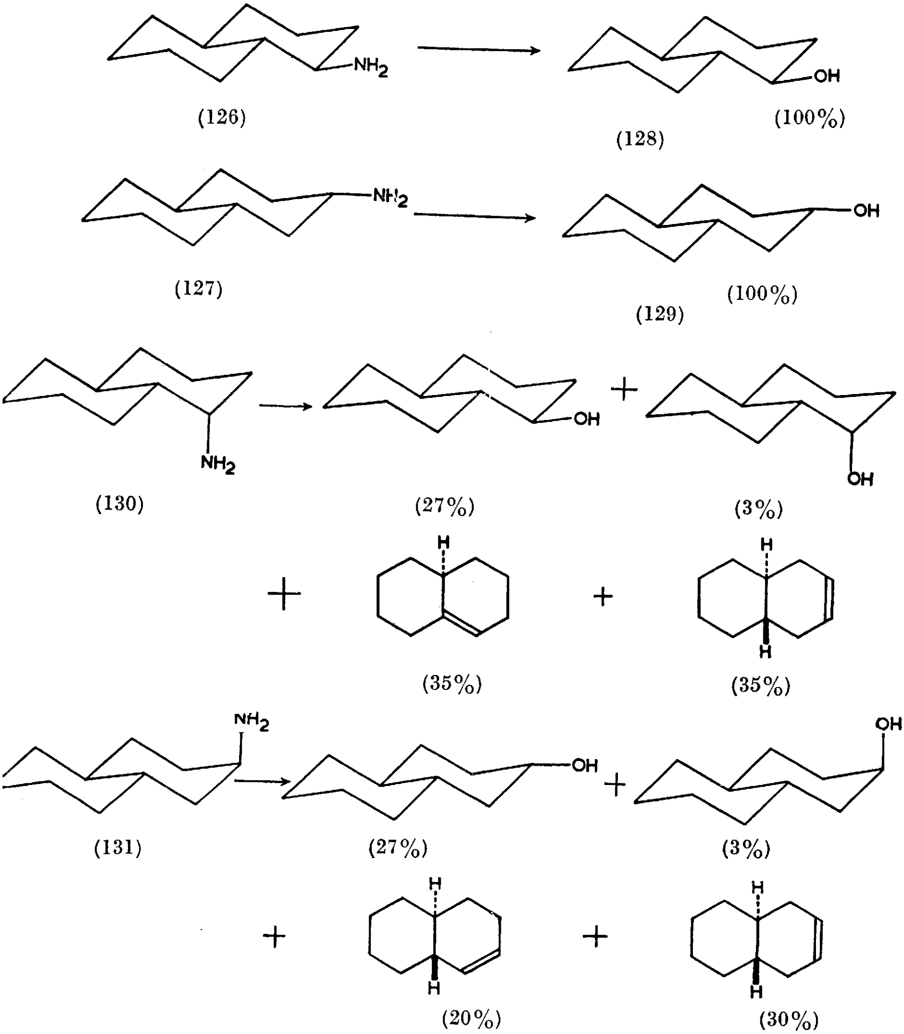
[113] Corey, *Experientia*, 1953, **9**, 329 ; *J. Amer. Chem. Soc.*, 1954, **76**, 175.

(*h*) *Reaction of amines with nitrous acid.* Another useful generalisation [114, 115] is that equatorial amines are converted by nitrous acid into alcohols of the same configuration but axial amines yield mostly olefin with some inverted alcohol. The course of the reaction differs somewhat, then, from that typical of acyclic amines where the intermediate diazonium ion decomposes by the S_N1 mechanism to form olefin and alcohol, mostly of



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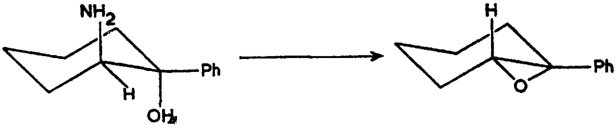
[114] Mills, *J.*, 1953, 260 ; Bose, *Experientia*, 1953, **9**, 256 ; cf. Barton and Rosenfelder, *J.*, 1951, 1048.

[115] W. G. Dauben, Tweit, and Mannerskantz, *J. Amer. Chem. Soc.*, 1954, **76**, 4420 ; W. G. Dauben and Jiu, *ibid.*, p. 4426 ; W. G. Dauben, Tweit, and MacLean, *ibid.*, 1955, **77**, 48, and references there cited.

inverted configuration.[116] Thus the products of deamination of the four *trans*-decalyl-amines are set out in the annexed chart. The two equatorial amines, (126) and (127), give equatorial alcohols only, (128) and (129) respectively. The two axial amines, (130) and (131), afford mostly olefin, accompanied by equatorial alcohol [115] as indicated.

Nitrous acid converts *trans*-2-amino-1-phenyl*cyclo*hexanol (132) into products derived from 1-phenyl*cyclo*hexene oxide (133). The *cis*-isomer (134), which by analogy with acyclic compounds would have been expected to undergo mainly phenyl migration to yield 2-phenyl*cyclo*hexanone, gives instead 99% of the ring-contracted *cyclo*pentyl phenyl ketone. The difference in behaviour may be attributed [117] to the fact that the conformation required for migration of the phenyl group is one of high energy relative to (134).



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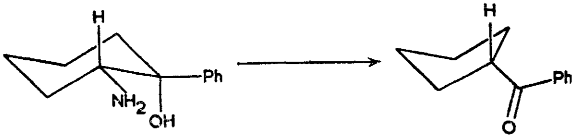

(134)

Some Illustrations from Heterocyclic Chemistry

Fortunately the substitution of hetero-atoms such as nitrogen and oxygen for one or more of the carbon atoms of a *cyclo*hexane ring causes, as will be clear from the data summarised in Table 1, only slight distortion of the ring. Consequently the generalisations that have emerged in the discussion of *cyclo*hexane chemistry can be carried over (with slight modification where necessary) to the heterocyclic analogues. Since the *p*-orbitals of nitrogen

TABLE 1 [118]

Bond lengths (Å)		Bond angles	
C–C	1·54	C–C–C	109°
C–N	1·47	C–N–C	109
C–O	1·44	C–O–C	111

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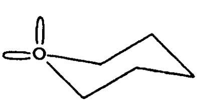
[116] Ingold, " Structure and Mechanism in Organic Chemistry ", G. Bell, London, 1953, p. 397.

[117] Curtin and Schumukler, *J. Amer. Chem. Soc.*, 1955, **77**, 1105.

[118] Maccoll in " Progress in Stereochemistry ", ed. Klyne, Butterworths, 1954, p. 361.

and oxygen appear to maintain an approximately tetrahedral distribution,[119] the analogy becomes even more complete. Tetrahydropyran, for example,



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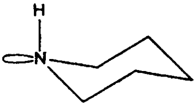

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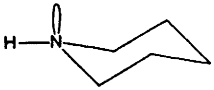
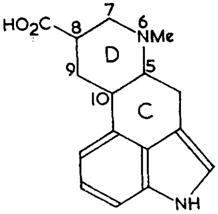


(137)

is represented by (135) and piperidine by (136) and (137), in which, by analogy with the stereochemistry of carbanions (see p. 78), the former may be expected to predominate.[120]

Alkaloid Chemistry.—(*a*) *The lysergic acids.* The four stereoisomeric dihydrolysergic acids (138) probably represent the piperidine compounds that have been most thoroughly investigated from the conformational point of view.[121] Reduction of lysergic acid (139) with sodium and butanol gives



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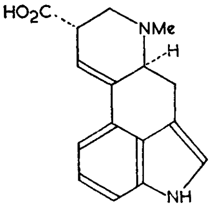

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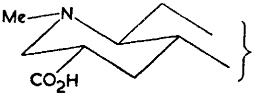
mainly dihydrolysergic acid-I. This is, therefore, the most stable of the four stereoisomers of (138) and may be assigned the conformation and stereo-



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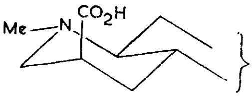

(141)

chemistry depicted in partial formula (140), with all substituents on the piperidine ring equatorial. The expression (141) must then represent the 8-epimer, dihydro*iso*-lysergic acid-I, for vigorous alkaline hydrolysis of derivatives of the latter acid affords the equatorial epimer (140). The methyl ester of the equatorial dihydrolysergic acid-I (140) is hydrolysed more rapidly than that of the axial acid (141). Nitrous acid deamination

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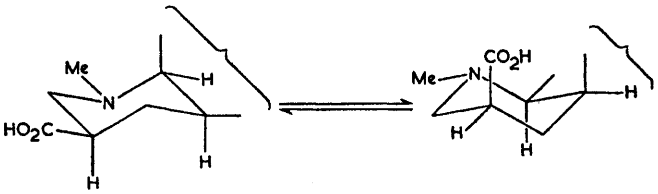
[119] C. A. Coulson, " Valence ", Oxford Univ. Press, 1952, p. 209.

[120] For illustrations of piperidine ring conformations see Leonard, Thomas, and Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 1552, and references there cited ; Przybylska and Barnes, *Acta Cryst.*, 1953, **6**, 377 ; Lindsey and Barnes, *ibid.*, 1955, **8**, 227 ; Visser, Manassen, and de Vries, *ibid.*, 1954, **7**, 288.

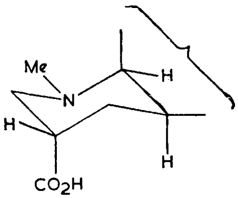
[121] Stoll, Petrzilka, Rutschmann, Hofmann, and Günthard, *Helv. Chim. Acta*, 1954, **37**, 2039, and references there cited ; see also Stenlake, *J.*, 1955, 1626.

of the primary amine produced by Curtius degradation of the equatorial acid (140) proceeds to give the corresponding alcohol with retention of configuration. In contrast, the epimeric axial amine, obtained in the same way from the axial acid (141), suffers elimination on deamination.

The two remaining isomeric dihydrolysergic acids, dihydro- and dihydro-*iso*-lysergic acid-II, must have rings C and D *cis*-fused. Of the two alternative conformations possible for this ring system, that having the large aromatic group equatorial [as in (142)] is preferred to that where it is axial [as in (143)]. Dihydro*iso*lysergic acid-II is the more stable epimer and thus



(142) (143)



(144)

has the equatorial carboxyl group (142). In confirmation the methyl ester of this acid is more rapidly hydrolysed than is that of dihydrolysergic acid-II (144).

Table 2 shows that the difference between the first and the second dissociation constants of the two pairs of amino-acids is less for the equatorial epimers than for the axial epimers, where the dissociable groups are closer together.

TABLE 2

Dihydro-acid	Δp*K*
-lysergic acid-I (e) (140)	3·00
-*iso*lysergic acid-I (a) (141)	4·80
-lysergic acid-II (a) (144)	4·61
-*iso*lysergic acid-II (e) (142)	3·41

(*b*) *The tropane alkaloids.* These alkaloids comprise another thoroughly investigated group,[122] though the bridged piperidine ring system (145) intro-

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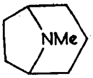
[122] For excellent and comprehensive reviews see Stoll and Jucker, *Angew. Chem.*, 1954, **66,** 376, and especially Fodor, *Acta Chim. Acad. Sci. Hung.*, 1955, **5,** 380 ; *Experientia*, 1955, **11,** 129.

duces some atypical features in conformational behaviour. Esters of tropine (146) are hydrolysed more slowly [123] than those of ψ-tropine (147). The axial hydroxyl group of tropine (146) can be isomerised to the equatorial configuration in ψ-tropine [124] (147), and the axial carboxyl group of ecgonine (148) to the equatorial one of ψ-ecgonine [125] (149).



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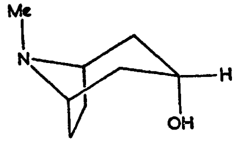

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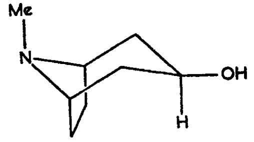

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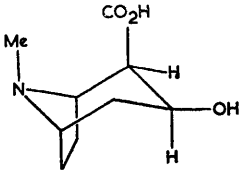

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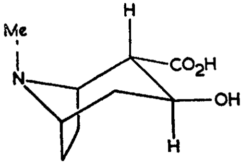

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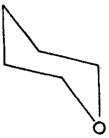

(150)

Carbohydrate Chemistry.—Much of the chemistry of the pyranose sugars has been placed on a rational basis by the admirable work of Reeves,[126] who has investigated the conformations of sugars by examining their capacity for complex formation with " cuprammonium " solutions and their rates of reaction with lead tetra-acetate. In all cases where it is geometrically possible the pyranose ring adopts the chair conformation (150), which is also preferred in the crystal lattice.[127]

The complexes formed by 1 : 2-glycols in cuprammonium solution contain the copper atom linked to the two oxygen atoms in a five-membered ring. The geometrical requirements are therefore similar to those of the cleavage of 1 : 2-glycols with lead tetra-acetate, in which a cyclic complex of Pb^{IV} is an intermediate, at least for glycols that react relatively rapidly.[128] Although the data for lead tetra-acetate concern relative rates and those

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[123] Sixma, Siegmann, and Beyerman, *Proc. k. ned. Akad. Wetenschap.*, 1951, **54** *B*, 452 ; Siegmann and Wibaut, *Rec. Trav. chim.*, 1954, **73**, 203 ; Hromatka, Csoklich, and Hofbauer, *Monatsh.*, 1952, **83**, 1323. For a discussion see Fodor, ref. 122 ; Nickon and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5566. For a discussion of the occurrence of the boat piperidine conformation in tropanes see, *inter al.* : Zenitz, Martini, Priznar, and Nachod, *ibid.*, p. 5564 ; Sparke, *Chem. and Ind.*, 1953, 749 ; Archer and Lewis, *ibid.*, 1954, 853.

[124] Willstätter, *Ber.*, 1896, **29**, 936.

[125] Findlay, *J. Amer. Chem. Soc.*, 1953, **75**, 4624 ; 1954, **76**, 2855.

[126] Reeves, *ibid.*, 1949, **71**, 215, 2116 ; 1950, **72**, 1499 ; 19574, **6**, 4595 ; *Adv. Carbohydrate Chem.*, 1951, **6**, 107.

[127] *Inter al.*, Cox, Goodwin, and Wagstaff, *J.*, 1935, 1495 ; Cox and Jeffrey, *Nature*, 1939, **143**, 894 ; Astbury and Davies, *ibid.*, 1944, **154**, 84 ; Beevers and Cochran, *Proc. Roy. Soc.*, 1947, *A*, **190**, 257 ; McDonald and Beevers, *Acta Cryst.*, 1950, **3**, 394.

[128] Criegee and Büchner, *Ber.*, 1940, **73**, 563.

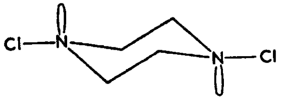
for cuprammonium complexing concern equilibria, the close parallel between the two reactions, summarised in Table 3, is thus not unexpected. For both reactions the most favourable arrangement of the glycol is when the two alcohol groups are in one plane. This is satisfied by a *cis*-1 : 2-glycol on a five-membered ring or on the " sides " of a boat six-membered ring.[129] For both reactions a *cis*(e,a)-glycol is more favourable than a *trans*(e,e)-glycol, because it allows a closer approach to coplanarity (see below). In almost every case the conformation indicated by the behaviour of the pyranoses and their derivatives with cuprammonium agreed with that required for a minimisation of non-bonded interactions (maximum number of equatorial substituents).

TABLE 3

Ring form	1 : 2-Glycol group	Rate of reaction with lead tetra-acetate	Extent of reaction with cuprammonium solution
Furanose	*cis* *trans*	Instantaneous Slow	Large None
Pyranose (chair)	*cis* (e,a) *trans* (e,e) *trans* (a,a)	Rapid Slow Very slow	Medium Small None
Pyranose (boat)	*cis* (side of boat)	Instantaneous	Large

The formation of acetals by carbohydrate molecules and related polyhydric alcohols can also be rationalised in a satisfactory manner by conformational considerations.[130] The chemistry of the inositols also lends itself to conformational analysis.[131]

Other Six-membered Heterocyclic Rings.—Several other heterocyclic analogues of *cyclo*hexane have been shown by physical methods to exist in



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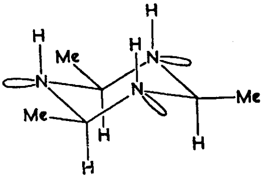

(152)

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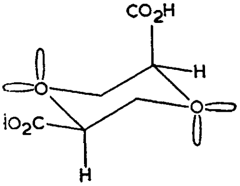
[129] The point could also be illustrated by the complex-formation of glycols with boric acid, so extensively studied by Böeseken and his colleagues (Böeseken, *Adv. Carbohydrate Chem.*, 1949, **4**, 189).

[130] Barker and Bourne, *J.*, 1952, 905 ; Barker, Bourne, and Whiffen, *ibid.*, p. 3865 ; Mills, *Chem. and Ind.*, 1954, 633.

[131] Chargaff and Magasanik, *J. Biol. Chem.*, 1948, **175**, 939, and references there cited ; Magasanik, Franzl, and Chargaff, *J. Amer. Chem. Soc.*, 1952, **74**, 2618 ; Angyal and MacDonald, *J.*, 1952, 686 ; Posternak and Reymond, *Helv. Chim. Acta*, 1953, **36**, 260.

the chair conformation. Thus the preferred conformations of 1 : 4-dichloropiperazine [132] and of 2 : 4 : 6-trimethyl-1 : 3 : 5-triaza*cyclo*hexane (" aldehyde ammonia ") [133] are (151) and (152) respectively. As in the *cyclo*hexane series, *cis*-1 : 4-dioxan-2 : 5-dicarboxylic acid (153) is less stable than the *trans*-acid (154), and the *cis*-2 : 6-diacid (155) is more stable than the *trans*-analogue [134] (156). α-Tristhioacetaldehyde (157) is, as expected, less stable than the β-isomer [135] (158).



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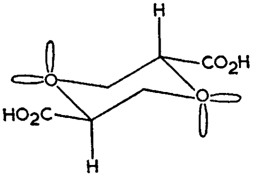

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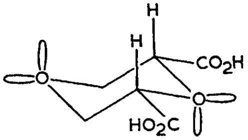

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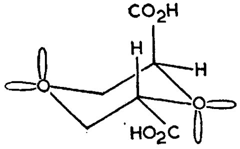

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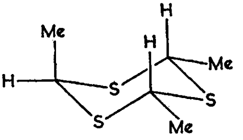

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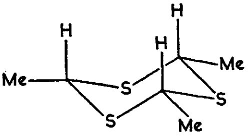

(158)

Conformations of Six-membered Rings containing Trigonal Atoms.—The successive substitution of trigonal for tetrahedral carbon atoms in a six-membered ring results, in general, in an increasing approach of the ring to planarity. All possible combinations of tetrahedral and trigonal ring atoms cannot be considered here ; each system requires separate evaluation, and generalisations about the properties of equatorial and axial bonds in saturated rings can be applied only with reserve.

(*a*) cyclo*Hexanones.* In *cyclo*hexanone (159) the single trigonal carbon atom introduces only slight distortion relative to *cyclo*hexane itself, though it obviously modifies some of the non-bonded interactions : for example, an α-equatorial substituent is almost eclipsed by the carbonyl group. In *cyclo*hexane-1 : 4-dione (160) the interactions are still further modified and the dipole moment is compatible with the presence of about 10% of the boat conformation.[136]

(*b*) cyclo*Hexenes.* The two conformations of *cyclo*hexene not involving

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[132] Andersen and Hassel, *Acta Chem. Scand.*, 1949, **3**, 1180.

[133] Lund, *ibid.*, 1951, **5**, 678.

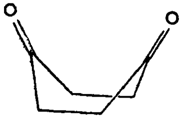
[134] Summerbell and Stephens, *J. Amer. Chem. Soc.*, 1954, **76**, 731, 6401.

[135] Baumann and Fromm, *Ber.*, 1891, **24**, 1428 ; Chattaway and Kellett, *J.*, 1930, 1352 ; Hassel and Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149.

[136] Le Fèvre and Le Fèvre, *J.*, 1935, 1696. For an investigation of the importance of boat conformations in androstane- and ætiocholane-3 : 17-dione, as determined by dipole-moment measurements, see Nace and Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 4063.

appreciable angle strain are shown schematically in (161) and (162).[137] The conclusion by Beckett, Freeman, and Pitzer [138] from thermodynamic data that the "half-chair" conformation (161) is more stable than the "half-boat" (162) by 2·7 kcal. per mole is supported [139] (with the usual reservations: see above) by the *X*-ray analysis of several crystalline substances, all of which have the half-chair conformation (161). In this conformation the ethylenic linkage keeps the two trigonal and allylic carbon atoms approximately in one plane. The two non-allylic methylene groups are completely staggered with respect to each other, so that their C–H bonds resemble normal axial and equatorial bonds in *cyclo*hexane. The bonds attached to the two allylic carbon atoms approximate only to axial and equatorial bonds and may be described as quasi-axial (a′) and quasi-equatorial (e′) [see (161)]. The few examples available [137] suggest that substituents are usually more stable in equatorial and quasi-equatorial than in axial and quasi-axial conformations.[140]

(159)



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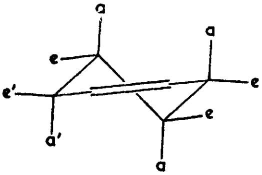
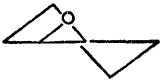


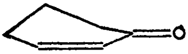
(161)

(*c*) cyclo*Hexene oxides.* Electron diffraction [141] shows that the six-membered ring of *cyclo*hexene oxide adopts a conformation (163) similar to the half-chair conformation of *cyclo*hexene itself.

(162)



(163)



(164)

(*d*) cyclo*Hexenone and* cyclo*hexenyl cations, anions, and radicals.* In *cyclo*hex-2-enone the introduction of a third trigonal carbon atom destroys

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[137] Barton, Cookson, Klyne, and Shoppee, *Chem. and Ind.*, 1954, 21. See also: Raphael and Stenlake, *ibid.*, 1953, 1286; Orloff, *Chem. Rev.*, 1954, **54**, 409; Corey and Sneen, *J. Amer. Chem. Soc.*, 1955, **77**, 2505.

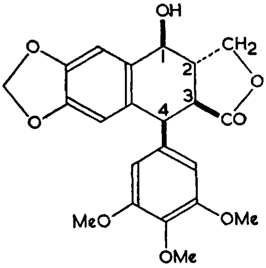
[138] Beckett, Freeman, and Pitzer, *ibid.*, 1948, **70**, 4227.

[139] *Inter al.*, Carlisle and Crowfoot, *Proc. Roy. Soc.*, 1945, *A*, **184**, 64; Pasternak, *Acta Cryst.*, 1951, **4**, 316; Lasheen, *ibid.*, 1952, **5**, 593; Bastiansen and Markali, *Acta Chem. Scand.*, 1952, **6**, 442, 587; cf. Lindsey and Barnes, *Acta Cryst.*, 1955, **8**, 227. This conformation seems to have been first suggested for tetralin by Mills and Nixon (*J.*, 1930, 2510) and for *cyclo*hexene by Böeseken and Stuurman (*Proc. k. ned. Akad. Wetenschap.*, 1936, **39**, 2).

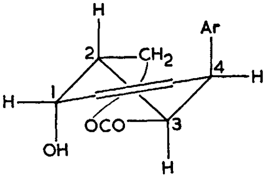
[140] But see Goering, Blanchard, and Silversmith, *J. Amer. Chem. Soc.*, 1954, **76**, 5409.

[141] Ottar, *Acta Chem. Scand.*, 1947, **1**, 283. For a discussion of the reactions of *cyclo*hexene oxides and anhydro-sugars in terms of this conformation see, *inter al.*, Cookson, *Chem. and Ind.*, 1954, 223, 1512; Angyal, *ibid.*, p. 1230.

any resemblance to boat or chair conformations. If all the ring carbon atoms except $C_{(5)}$ are approximately coplanar, the ring can adopt only one conformation (164) which is free from angle strain. *cyclo*Hexenyl cations, anions, and radicals may be expected to have similar conformations. Owing to the greater overlap possible between (say) the *p*-orbital of a nucleophilic species and the partially vacant orbital of a *cyclo*hexenyl cation in the transition state for quasi-axial addition than for quasi-equatorial addition, one might expect that addition to a *cyclo*hexenyl cation would give usually, as the kinetically controlled product, the quasi-axial isomer. Thus in the geometrically equivalent tetralin series, S_N1 hydrolysis of the bromide from podophyllotoxin [142, 143] (165) gives the quasi-axial *epi*-podophyllotoxin [144] (166) although it is the less stable epimer.



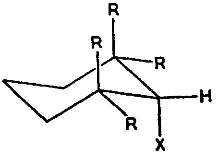
(165)



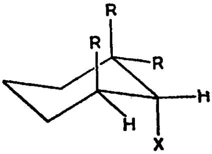
(166)

Conformational Anomalies.—Whilst the principles of conformational analysis, as outlined in this Review, serve to correlate a great many experimental facts in a satisfactory manner, there are certain cases where anomalies of behaviour have been observed. In the sequel some of the more important of these are discussed.

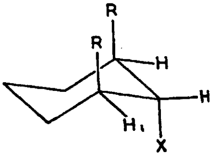
(*a*) *Polysubstituted* cyclo*hexanes.* Attention has been directed [145] to certain 2 : 2 : 6 : 6-tetrasubstituted *cyclo*hexyl compounds in which the usual stability order of epimers is reversed. A simple consideration of non-bonded interactions shows that if a 2 : 2 : 6 : 6-tetrasubstituted *cyclo*hexyl compound



(167)



(168)



(169)

is more stable in the axial (167) than in the equatorial form, then the same reversed stability order must, on the assumption of fixed conformations,

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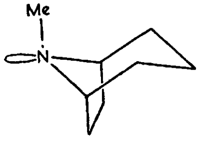
[142] Hartwell and Schrecker, *J. Amer. Chem. Soc.*, 1951, **73**, 2909.
[143] Schrecker and Hartwell, *ibid.*, 1952, **74**, 5676.
[144] *Idem, ibid.*, 1953, **75**, 5916.
[145] Barton, *Chem. and Ind.*, 1953, 664.

hold for (168) and (169). All other R-substituted *cyclo*hexyl compounds should, however, follow the usual stability order. An interesting example in compounds of the class (169) has been discussed by Fodor and his collaborators,[122] whose evidence suggests [146] that in tropane derivatives the methyl group is axial, as in (170).



(170)

(*b*) *Dipoles and integral charges.* All the discussion in this Review on the relative stabilities of epimers and of alternative conformations refers, strictly, only to non-polar molecules in which the forces between atoms close together, but not directly linked, are repulsive and inversely proportional to a high power of interatomic distance. In addition to such repulsive forces, induced by the approach of the outer electronic orbitals of different atoms, account must be taken of normal (attractive or repulsive) electrostatic forces between integral charges or dipoles which vary inversely with a much lower power of distance.[147] An example where conformation appears to be determined more by integral charge interaction than by non-bonded repulsions has already been cited on p. 63 [see (88)].

Physical evidence shows that the *trans*-1 : 2-dihalogeno-*cyclo*hexanes consist of comparable concentrations of the diequatorial and diaxial conformations,[148] an anomaly usually attributed to dipole repulsion in the diequatorial conformations. The Raman spectra of the *trans*-1 : 4-dihalogeno*cyclo*hexanes have been interpreted [149] as showing the presence, in solvents such as ether, of a preponderating concentration of the diaxial conformation, although only the expected diequatorial conformation exists in the crystal. Conformational equilibria are, of course, a function of temperature and, especially for polar substances, of the polarity of the medium. In spite of reservations with regard to 1 : 2-dihalogeno*cyclo*hexanes, the preferred conformations of most polyhalogeno*cyclo*hexanes of the benzene hexachloride type appear to be those with the maximum number of equatorial substituents.[150, 151]

[146] This argument accepts, of course, that the bulk of a methyl group should be greater than that of an electron pair. One must note, however, that *X*-ray diffraction (Visser, Manassen, and de Vries, *Acta Cryst.*, 1954, **7**, 288) of tropine hydrobromide reveals that the methyl group is equatorial, not the hydrogen atom. As always in the crystalline state, the conformation may be influenced by intermolecular forces.

[147] Ingold, " Structure and Mechanism in Organic Chemistry ", G. Bell, London, 1953, Chap. III.

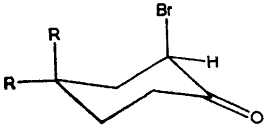
[148] *Inter al.*, Bastiansen and Hassel, *Tidsskr. Kjemi Bergvesen Met.*, 1946, **6**, 96 ; Larnaudie, *Compt. rend.*, 1953, **236**, 909 ; Tulinskie, Di Giacomo, and Smyth, *J. Amer. Chem. Soc.*, 1953, **75**, 3552 ; Kozima, Sakashita, and Maeda, *ibid.*, 1954, **76**, 1965 ; Bender, Flowers, and Goering, *ibid.*, 1955, **77**, 3463 ; Kwestroo, Meijer, and Havinga, *Rec. Trav. chim.*, 1954, **73**, 717.

[149] Kozima and Yoshino, *J. Amer. Chem. Soc.*, 1953, **75**, 166.

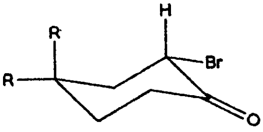
[150] Bastiansen, Ellefsen, and Hassel, *Acta Chem. Scand.*, 1949, **3**, 918 ; Norman, *ibid.*, 1950, **4**, 251 ; van Vloten, Kruissink, Strijk, and Bijvoet, *Acta Cryst.*, 1950, **3**, 139.

[151] The reactions of these substances illustrate well the stereospecificity of addition and elimination. See, *inter al.* : Cristol, Hause, and Meek, *J. Amer. Chem. Soc.*, 1951, **73**, 674 ; Hughes, Ingold, and Pasternak, *J.*, 1953, 3832 ; Kolka, Orloff, and Griffing,

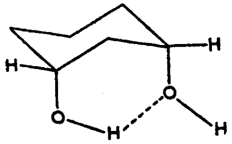
The delicate balance between dipolar and steric repulsions is nicely illustrated by the following example.[152] 2-Bromo*cyclo*hexanone exists in solution in the axial (171 ; R = H) rather than in the equatorial conformation (172 ; R = H) in which repulsion between the $C\overset{\longrightarrow}{=}O$ and $C\overset{\longrightarrow}{-}Br$ dipoles would be greater. The 4 : 4-dimethyl derivative, however, exists in the conformation with the bromine equatorial (172 ; R = Me), since the methyl group introduces a large repulsive 1 : 3-interaction into the axial conformation (171).



(171)



(172)



(173)

(*c*) *Hydrogen bonds.* It is possible for intramolecular hydrogen bonds to introduce sufficiently powerful attractive forces to modify or reverse normal conformational preferences. Thus in the O–H stretching region of the infrared spectrum *cis-cyclo*hexane-1 : 3-diol in dilute solution in carbon tetrachloride shows evidence [153] of strong internal hydrogen bonding due to the diaxial conformation (173).

(*d*) *Differential reactivity of* cyclo*hexane*-1 : 2-*diols*. *cis*-Substituents on a *cyclo*hexane ring, one of which must be equatorial and one axial, are separated by the same distance as *trans*-substituents when both of these are equatorial. So, at first sight, cyclisation reactions involving either *cis*- or diequatorial *trans*-substituents might be expected to take place equally easily. However, for all reactions requiring an approximately coplanar transition state and not involving replacement of the *cyclo*hexane substituents, *cis*(e,a)-compounds react more rapidly than *trans*-(e,e)-compounds. Familiar examples are the reactions of 1 : 2-diols with lead tetra-acetate [154] and with periodic acid,[155] and of 1 : 2-amino-alcohols with lead tetra-acetate,[156] and acyl migration in 1 : 2-amino-alcohols.[157]

Hassel and Ottar,[158] in a slightly different context, first drew attention to the different response of a chair ring to the two different types of distortion imposed on it by bringing *cis*(e,a)- or *trans*(e,e)-substituents into more nearly coplanar positions. The distortion induced by forcing adjacent equatorial

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J. Amer. Chem. Soc., 1954, **76,** 3940 ; Riemschneider, *Monatsh.*, 1955, **86,** 101 ; Cornubert and Rio, *Bull. Soc. chim. France*, 1955, 60, and previous papers by the several authors.

[152] Corey, *J. Amer. Chem. Soc.*, 1953, **75,** 2301, 3297 ; 1954, **76,** 175.

[153] Kuhn, *ibid.*, 1952, **74,** 2492 ; 1954, **76,** 4323.

[154] Criegee, Kraft, and Rank, *Annalen*, 1933, **507,** 184 ; Prelog, Schenker, and Günthard, *Helv. Chim. Acta*, 1952, **35,** 1598.

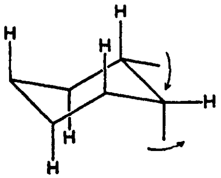
[155] Price and Knell, *J. Amer. Chem. Soc.*, 1942, **64,** 552.

[156] McCasland and Smith, *ibid.*, 1951, **73,** 5164 ; Posternak, *Helv. Chim. Acta*, 1950, **33,** 1597.

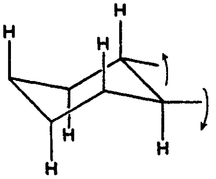
[157] Fodor and Kiss, *Nature*, 1949, **164,** 917 ; *J. Amer. Chem. Soc.*, 1950, **72,** 3495.

[158] Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1,** 929.

and axial substituents more nearly into the same plane (174) leads to a flattening of the ring and an increase in endocyclic valency angles: the axial atoms or groups move further away from one another. The whole movement resembles an incipient conformational inversion and requires



(174)



(175)

little energy. On the other hand, forcing two equatorial bonds more nearly into the same plane (175) entails a reduction in the separation of the axial atoms or groups, and therefore much more energy is required.

In agreement with this approach normally only *cis*(e,a)-*cyclo*hexane-1 : 2-diols condense with acetone to form *iso*propylidene derivatives.[159]

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[159] For an interesting exception, see Angyal and Macdonald, *J.*, 1952, 686.