QUARTERLY REVIEWS

STEREOCHEMISTRY OF *CYCLO*HEXANE

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Our knowledge of the spatial distribution of atoms in aromatic compounds is to-day considerably more detailed and precise than it is for organic compounds in which the chemical bonds between adjacent atoms are essentially of the " two-electron " type. Even in the case of *cyclo*hexane and other substances containing six-membered rings which are believed to be comparatively " rigid " much more work will have to be carried out before their stereochemical properties can be treated with a similar degree of confidence. Both from a purely theoretical point of view and because of the biological importance of many compounds belonging to this class it therefore appears worth while to gather new experimental evidence about their atomic arrangement.

During the last two decades efforts have in fact been made to establish fundamental facts, especially about the behaviour of the *cyclo*hexane ring, by using direct methods based on the diffraction of X-rays or electrons. The present Review gives a short survey of the principal experimental results so far obtained, but the complicated physical aspects are not discussed.

General Properties of the *cyclo*Hexane Ring.—The idea that the valency angles of the six carbon atoms of the *cyclo*hexane ring are tetrahedral, or nearly so, has been generally accepted by chemists, and the same may be said of the conclusions drawn from it by Sachse and by Mohr regarding the
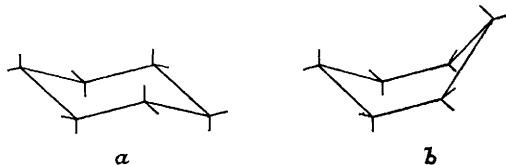

a b

Fig. 1

possible forms of the ring. Fig. 1*a* shows the rigid form (" staircase " or " chair " model) of the *cyclo*hexane molecule, Fig. 1*b* a special case of the alternative " movable " model, described as the " boat " or " tub " form. No objection can be raised against acceptance of the chair model of the *cyclo*hexane molecule from considerations regarding the nearest approach of hydrogen atoms (we can calculate the nearest approach with considerable confidence by assuming a C–C bond distance of 1·54 Å and a C–H bond

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distance of 1·10 Å). This model leads to a smallest hydrogen–hydrogen separation of about 2·5 Å, a distance which is not far from twice the van der Waals radius of hydrogen and should therefore be expected to be energetically favourable. This distance occurs 24 times within the molecule, a fact which no doubt contributes appreciably to stabilisation of the chair model. In the boat form, however, pairs of hydrogen atoms would be considerably closer if the carbon atoms retain their normal valency angles.[1] All the available experimental evidence actually indicates that practically all *cyclo*hexane molecules correspond to the chair form, both in the vapour and in the liquid phase.

One fact seems to have been given very little attention until 1943,[1] namely, that the hydrogen atoms of *cyclo*hexane in the symmetrical chair form may be divided into two geometrically different groups, each comprising six hydrogen atoms. The C–H bonds of the first group are parallel to the symmetry axis of the molecule which is usually placed vertically. Originally,[1] these bonds were designated as ε bonds ($\dot{\varepsilon}\sigma\bar{\iota}\eta\kappa\acute{\omega}\varsigma$ = upright). The bonds of the second group are not parallel, but all form an angle of $\pm$ 19·5° (109·5° − 90°) with the horizontal plane ; they were called κ bonds ($\kappa\acute{\varepsilon}\iota\mu\varepsilon\nu o\varsigma$ = prostrate). Some years later the designations " polar " (ε) and " equatorial " (κ) bonds were suggested [2] and have since been adopted by some authors. It may perhaps be objected to the original designations that they are less easily memorised, and to the latter that the expression " polar bond " may be misunderstood.* Throughout this Review the original designations will be used.

If we consider for a moment a *cyclo*hexane molecule of the symmetrical chair form to be " rigid " and replace one of its hydrogen atoms by another atom (*e.g.*, chlorine) it will easily be seen that the new molecule will be
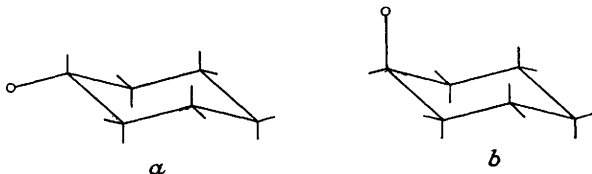

FIG. 2

represented by different models, depending on whether we replace a κ or an ε hydrogen atom of the original *cyclo*hexane molecule (Fig. 2a and b).

Neither chloro*cyclo*hexane nor any other mono-derivative shows any sign of steric isomerism, so, if the two forms (ε and κ) of a mono-derivative both exist, one may easily change into the other. This is only possible if the activation energy of the process is much smaller than the energy known to be necessary for fission of a carbon–carbon bond. Obviously,

[1] O. Hassel, *Tidsskr. Kjemi*, 1943, **3**, 32.

[2] C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488.

* These terms, polar and equatorial, are used in most British papers and are often abbreviated to p and e. It is to be noted that p (and not e) corresponds to ϵ, that this use of polar should not be confused with the electrochemical use (cf. above), and that Roman font is used (to avoid confusion with $p = para$).—ED.

therefore, the process does not involve the breaking of such bonds : it will, however, probably be closely associated with normal thermal vibrations carried out by the carbon atoms of the six-membered ring.

Ring Conversion.—Now these six carbon atoms are arranged in two planes, three in each, with a mutual distance between the planes of approximately 0·5 Å. The oscillation of the two triangular groups may sometimes cause them to interchange positions without necessarily causing fission of chemical bonds. Such a process, although not causing any change of the total configuration of *cyclo*hexane molecule itself, necessitates that each hydrogen atom of the κ type shall be transformed into one of the ε type, and *vice versa*. In the case of a mono-derivative the conversion process transforms one of the two possible forms (Fig. 2a and b) into the other. If, on the other hand, we consider a derivative obtained by substituting equal numbers of κ and ε hydrogen atoms by atoms or groups of the same kind it may occur that the molecule is identical in form before and after a conversion of the type just described. This is so, for example, for the $1\varepsilon,2\varepsilon,4\kappa,5\kappa$-tetra-substituted *cyclo*-hexanes (Fig. 3). This molecule does not possess elements of symmetry other than a two-fold axis and in this special case a chemical separation of (+)- and (−)-forms will therefore be possible, at

FIG. 3

least in principle. A second example is afforded by any *trans*-1 : 3-disubstituted *cyclo*hexane if the two substituents are of the same kind. If the substituents are different, separation of (+)- and (−)-forms is still possible, but the picture of the molecule changes when a conversion of the ring takes place. Each of the two optical antipodes may therefore exist in two " conformations "[3] ($1\kappa : 3\varepsilon$ and $1\varepsilon : 3\kappa$) which will not necessarily have the
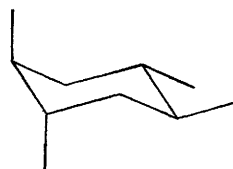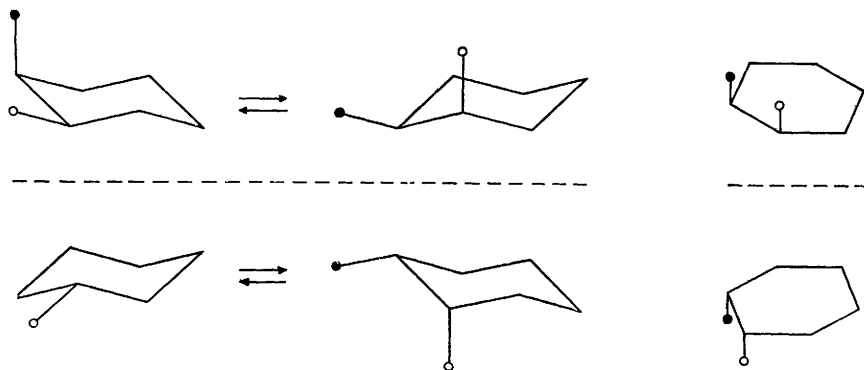

FIG. 4

[3] The word " conformation " is used by organic chemists to denote a particular arrangement of the atoms of a molecular species when more than one arrangement is possible. It should not, of course, be employed when molecular structures such as those of *cis*- and *trans*-decalin are being compared. In the German language, " constellation " is generally used in preference to " conformation " (cf. *J.*, 1952, 5061).

same energy.   The situation is the same for *cis*-1 : 2-disubstituted com-
pounds with two different substituents (see Fig. 4).   Measurement of the
relative amounts of the two configurations in the equilibrium mixture would
be ˙very interesting because it would probably throw some light on the
forces between the two kinds of substituents and their nearest (hydrogen)
neighbours (compare the case of 1ε : 2ε : 4κ : 5κ-tetrahalogeno*cyclo*hexanes
discussed below).

In other cases one of the two possible conformations of a *cyclo*hexane
derivative simply represents the mirror image of the other.   The equilibrium
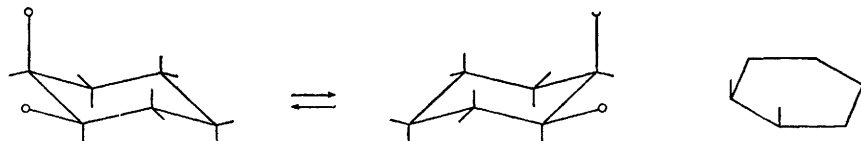mixture then necessarily contains equal amounts of the two configurations

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and a separation is not feasible, except possibly at extremely low tempera-
tures, or in the solid state if the substance happens to crystallise in enantio-
morphous crystals.   Usually, however, crystals containing equal amounts
of the two configurations (and thus corresponding to normal racemic com-
pounds) will represent the stable state, and not a mixture of enantiomorphous
crystals.   This normal behaviour is shown for instance by *cis-cyclo*hexane-
1 : 2-diol (Fig. 5).

It should be borne in mind that the usual representation of molecular
configurations of *cyclo*hexane derivatives and similar compounds showing a
planar six-membered ring and carbon valencies perpendicular to the plane
of the ring may be said to comprise the whole series of special shapes in
which a defined chemical individual can possibly appear.   Although such
a representation is not useful as a basis for detailed discussions regarding
the energy of the free molecule or its chemical reactions, it is well suited for
classification.   Thus, the symmetry of the picture directly indicates whether
a special representation comprises a pair of mirror image molecules or not.
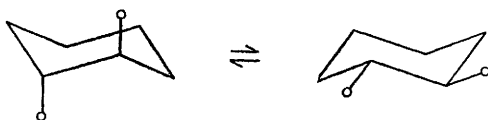It is therefore easy to find the number of steric isomers which correspond

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to a given structural formula by employing models of this kind.   The ex-
pressions *cis* and *trans* indicating the mutual positions of two substituents
linked to different carbon atom will probably continue to be used although
they do not generally (compare the case of *trans*-1 : 2-derivatives, Fig. 6)
give direct information concerning the real spatial arrangement of the
substituents.

Returning to the steric configurations based on the symmetrical chair form of the *cyclo*hexane ring, we may draw some general conclusions. Two substituents, each having a van der Waals radius larger than that of hydrogen (1·25 Å), will be expected to repel each other if they both occupy ε positions on the same side of the carbon ring. This may be of significance even to a single chlorine atom in an ε position because its distance from the two nearest hydrogen atoms (also in ε positions) would be smaller than the sum of the radii. A certain deformation of valency angles and a corresponding rise of the internal energy of the molecule might be the consequence of this repulsion.

On the lines of this argument an attempt was made ten years ago [4] to decide experimentally if the " free " chloro*cyclo*hexane molecules exist preferentially in the κ rather than the ε form. By means of the then new " sector method " of electron-diffraction, experimental distance–distribution curves were worked out both for chloro*cyclo*hexane and for *cyclo*hexane itself. The curve obtained by subtracting the latter curve from
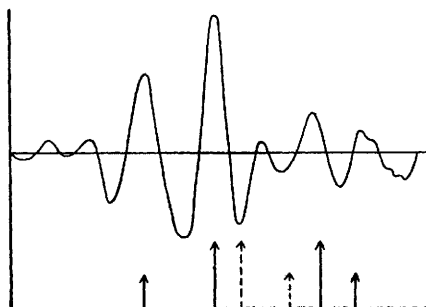

FIG. 7

the former should exhibit maxima for values of the abcissa (r values) corresponding to C–Cl distances occurring in the chloro-compound and not in the parent hydrocarbon. The result is shown in Fig. 7, where the arrows are proportional in length to the weight of the distances in question. The two unbroken arrows on the left correspond to C–Cl distances expected in both forms of chloro*cyclo*hexane and are therefore without interest in the present connection. The broken arrows represent C–Cl distances present only in the model in which the chlorine atom is in the ε position (Fig. 2b) ; the two unbroken arrows on the right indicate the corresponding C–Cl distances in the model having the κ chlorine atom (Fig. 2a). The conclusion cannot of course be drawn from this experiment that molecules with chlorine in the ε position are *not* present in the vapour phase, but their amount must obviously be considerably smaller than that of the κ form. Similar results were obtained a few years later for *cyclo*hexanethiol.[5]

The distance between two adjacent halogen atoms both in κ positions

[4] O. Hassel and H. Viervoll, *Tidsskr. Kjemi*, 1943, **3**, 35.

[5] O. Bastiansen and O. Hassel, *ibid.*, 1946, **6**, 96.

would, in an ideal model, probably be small enough to produce repulsive forces between them. Although sufficiently accurate measurements are still lacking the experimental evidence seems to indicate that the valency angles are in fact not strictly tetrahedral in such cases, a certain flattening of the carbon ring being the chief result. On the other hand it has been established beyond doubt that deformation is caused by repulsion between ε chlorine atoms and the nearest hydrogen atoms in the ε position ; it causes tilting of the C–Cl bond away from the chief axis of the carbon ring (by about 7°).[6] If the interaction energy due to the two carbon–halogen dipoles is also taken into account it becomes probable that the energy difference between the two forms of *trans*-1 : 2-dihalogeno*cyclo*hexanes ($\kappa\kappa$–$\varepsilon\varepsilon$; cf. Fig. 6) may be relatively small and that their concentrations in the equilibrium mixture therefore roughly equal.[5]

The number of simple derivatives of *cyclo*hexane available for molecular-structure determinations and likely to give more precise information about the forces acting between atoms or groups linked to the carbon atoms of the ring is limited, although new substances have been specially prepared for this purpose and investigated. Further work in this field seems to promise results of interest. If 1 : 2 : 3-trihalogeno*cyclo*hexanes, for example, capable of existing in the conformations $\kappa\kappa\varepsilon$ and $\varepsilon\varepsilon\kappa$, should prove to be present as " free " molecules predominantly in the $\kappa\kappa\varepsilon$ form, this would mean that the energy rise due to the 1κ–2κ interaction is smaller than that caused by the repulsion between an ε halogen atom and its nearest hydrogen neighbours.

The 1 : 2-dibromo-4 : 5-dichloro*cyclo*hexane in which both the chlorine atoms and the bromine atoms are *trans*, one pair occupying ε positions, and the other pair κ positions (Fig. 8), has been prepared in order to decide
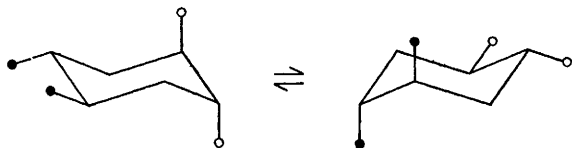

FIG. 8

which of the two pairs are in the ε position when the molecule takes the form having the smallest possible energy. The substance proved to be isomorphous with the corresponding tetrachloro- and tetrabromo-*cyclo*-hexanes, and the crystal structure showed that in the solid state the chlorine atoms occupy ε positions, the bromine atoms κ positions.[7] Electron-diffraction measurements of the " free " molecule of the vapour confirmed this result. No indications of the presence of molecules having the " con-verted " structure could indeed be detected.[8] This finding does not of course answer questions about the relative energy contributions of a pair of 1κ : 2κ halogen neighbours, and of an ε halogen atom. There are two ε

[6] O. Hassel and E. Wang Lund, *Acta Cryst.*, 1949, **2**, 309.

[7] *Idem*, *Acta Chem. Scand.*, 1952, **6**, 238.

[8] O. Bastiansen and O. Hassel, *ibid.*, 1951, **5**, 1404.

halogen atoms in the molecule but only *one* pair of κκ neighbours, and the halogen atoms are chlorine and bromine respectively. The conclusion seems justified, however, that the 1ε–3ε repulsion between an ε halogen atom and its two nearest (ε) hydrogen neighbours raises the energy of the molecule more in the case of bromine than in that of chlorine. The angle of deflexion of the ε C–Cl bond away from the ring axis appears to be nearly the same in the dibromodichloro- as in the tetrachloro-compound.

The finding that mono-derivatives have their lowest energy in the form in which the substituent occupies the κ position is substantiated by many other experimental results. All the *trans*-1 : 4-dihalogeno-compounds so far investigated have been observed only in the κκ-configuration (dichloro-, dibromo-, di-iodo-, and bromochloro-*cyclo*hexane).

Although the piperazine ring is certainly not identical in shape with that of *cyclo*hexane their similarity should probably be great enough to make it probable that the 1 : 4-dihalogenopiperazines will also be most stable in the configuration which corresponds to the κκ form of the *trans*-1 : 4-dihalogeno*cyclo*hexanes. This has been found to be the case for the dichloro-compound, both in the crystalline and in the gaseous state.[9] It should be remembered that here the κε conformation (corresponding to the *cis*-forms of 1 : 4-dihalogeno*cyclo*hexanes) might be present in the equilibrium mixture.

One is, of course, not justified in drawing direct conclusions from the results obtained for other halogen derivatives when considering the stability of the configurations of fluorinated *cyclo*hexanes. It has been observed that dodecafluoro*cyclo*hexane has a structure which does not deviate very much from an ideal structure with a carbon ring of the chair form. This seems to indicate that the repulsion between two ε fluorine atoms in the 1 : 3-position is much smaller than between two other halogen atoms in similar positions (see below). Taking this and the strong electronegativity of the fluorine atom into consideration it may perhaps be justified to expect that mono-fluoro*cyclo*hexane will be more stable in the ε than in the κ conformation, contrary to the finding in the case of other halogeno*cyclo*hexanes. An electron-diffraction investigation of this compound, and also of *trans*-1 : 4-difluoro*cyclo*hexane in the vapour state, would thus be of considerable interest.
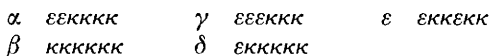
The " Benzene Hexachlorides " and the Cyclitols.—The molecular structure of a number of derivatives of *cyclo*hexane has been investigated during recent years, mostly for halogen derivatives. In some cases the positions of the substituents in the molecule were unknown, or at least uncertain, when the structure analysis was started. So far, it appears, the molecular structure actually observed for a given chemical individual always represents the configuration which we would expect to possess the lowest internal energy on simple steric considerations and accepted values of van der Waals radii.

It seems appropriate to pay special attention to the series of benzene hexachlorides (1 : 2 : 3 : 4 : 5 : 6-hexachloro*cyclo*hexanes). Theoretically eight

[9] P. Andersen and O. Hassel, *Acta Chem. Scand.*, 1949, **3**, 1180.

steric isomers are possible, of which one should be separable into mirror-image (+ and −) forms.   The idea expressed several years before determination of the structure was finished, namely, that this compound is the α-isomer, the chief product of the reaction between benzene and chlorine, has been found to be correct, and separation of one active form in a pure state has been accomplished.[10]

As long as we are not interested in absolute configurations of optically active molecules a satisfactory description of the molecular structure of a *cyclo*hexane derivative may be given simply by indicating for every substituent whether it is of the ε or the κ type.   The five structurally known benzene hexachlorides may, for example, be listed as follows (cf. Fig. 9) :

$$\begin{array}{llllll} \alpha & \varepsilon\varepsilon\kappa\kappa\kappa\kappa & \gamma & \varepsilon\varepsilon\varepsilon\kappa\kappa\kappa & \varepsilon & \varepsilon\kappa\kappa\varepsilon\kappa\kappa \\ \beta & \kappa\kappa\kappa\kappa\kappa\kappa & \delta & \varepsilon\kappa\kappa\kappa\kappa\kappa \end{array}$$

By comparing the observed configurations with those of the conversion forms obtained by simply changing each ε into κ and *vice versa*, it is seen that the γ-isomer is the only one which would retain its configuration.   It
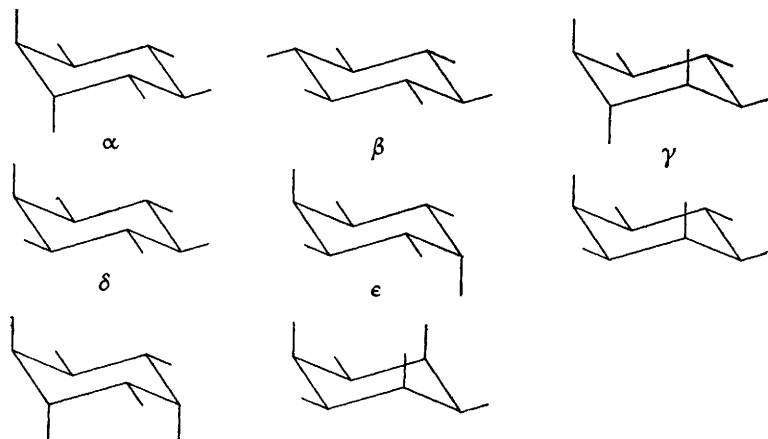

Fig. 9

is significant that the conformations listed above and actually observed for the other four isomers do not contain a single pair of ε-chlorine atoms in the 1 : 3-position whereas the configuration obtained by " conversion " of the carbon ring would contain at least two such pairs.   It strengthens the argument mentioned above that the presence of a pair of ε-halogen atoms in 1 : 3-position will raise the energy of a *cyclo*hexane derivative markedly. The expected deviation from an ideal structure caused by the presence in the γ-isomer of the 1ε : 3ε chlorine pair is clearly brought out by the X-ray analysis.[11, 12]

[10] S. J. Cristol, *J. Amer. Chem. Soc.*, 1949, **71**, 1894.

[11] W. van Vloten, C. A. Kruissink, B. Strijk, and J. M. Bijvoet, *Acta Cryst.*, 1950, **3**, 139.

[12] Many more examples of halogenated *cyclo*hexanes might be quoted ; cf. O. Hassel, *Research*, 1950, **3**, 504.

Molecular structures of the corresponding hydroxy-compounds (*cyclo*-hexanehexols) have so far not been extensively studied. The elucidation of these structures would, however, be of special interest both because these substances are biologically important and because very little is known about the forces acting between hydroxy-groups in compounds of this kind. It would, for example, be most interesting to know whether intramolecular hydrogen bonds are formed, and if so to discuss their significance for the molecular conformation. Recently [13] a paper dealing with the reaction between cyclitols and acetone has been published which is of considerable interest in connection with problems discussed in the present Review.

Experimental evidence seems to indicate that the replacement of methylene groups in *cyclo*hexane by oxygen atoms does not cause very marked changes in the shape of the six-membered ring. X-Ray work on carbohydrates containing pyranose rings substantiate this view. The stereochemistry of sugars therefore has to follow, within certain limits, the same lines as that of *cyclo*hexane derivatives.[14]

Condensed Ring Systems.—Molecules in which bridges are formed between two carbon atoms of a *cyclo*hexane ring may of course be treated in the same way as ordinary disubstituted *cyclo*hexanes, at least if the bridge contains a sufficient number of atoms to allow the valencies of the *cyclo*hexane carbon atoms to retain their normal angles. The special case in which the bridge is formed between adjacent carbon atoms of the *cyclo*hexane ring and contains four methylene groups is of special interest. It was early suggested that the so-called *trans*-decalin consists of two ordinary *cyclo*hexane rings having two carbon atoms in common as indicated in Fig. 10*b* ; the two
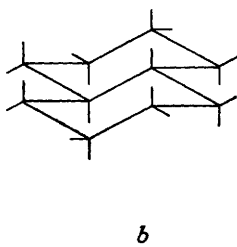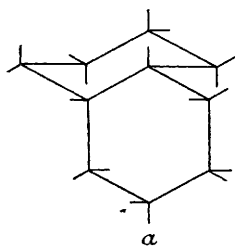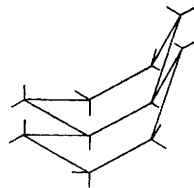

FIG. 10   FIG. 11

rings are joined by the use of κ bonds only. It would have seemed natural to assume that the *cis*-form of decalin is also based on normal *cyclo*hexane rings of the chair form joined by one κ and one ε bond of each ring (Fig. 10*a*). Mohr,[15] however, suggested a structure (Fig. 11) built up of two *cyclo*hexane rings of the boat form, a view still to be found in textbooks although it is certainly not in agreement with experimental results [16] and its very

[13] S. J. Angyal and C. G. Macdonald, *J.*, 1952, 686.

[14] O. Hassel and B. Ottar, *Acta Chem. Scand.*, 1947, **1**, 929 ; R. E. Reeves, *J. Amer. Chem. Soc.*, 1950, **72**, 1499.

[15] E. Mohr, *J. pr. Chem.*, 1918, **98**, 315.

[16] O. Bastiansen and O. Hassel, *Nature*, 1946, **157**, 765 ; *Tidsskr. Kjemi*, 1946, **6**, 70.

unfavourable H–H distances were pointed out ten years ago.[17]   The designations *cis* and *trans* for the two stereoisomeric decalins orginally indicated the mutual positions of the two hydrogen atoms linked to the carbon atoms which the two *cyclo*hexane rings have in common.   As the molecular structures of the two compounds are now known it seems appropriate to associate the two designations with the positions of the bonds starting and terminating the bridges rather than with the hydrogen atoms of the two CH-groups.

The extension of the work carried out on the decalins to fully hydrogenated aromatic hydrocarbons originally containing more than two benzene rings (now in progress) will no doubt be of interest especially if small deviations from " ideal " structures can be detected.   Such deviations, indications of which were observed in *cis*-decalin, are to be expected also in other compounds containing two *cyclo*hexane rings in the *cis*-position because some hydrogen–hydrogen distances would be a little smaller than 1·9 Å if all valency angles remain strictly " tetrahedral ".

The establishment of the molecular structure of *cis*-decalin has already had interesting consequences in the chemistry of compounds containing a greater number of condensed six-membered rings of the *cyclo*hexane type.

Before closing this short survey we think it necessary to draw attention to one special point :   So far not a single case has been found in which the *cyclo*hexane ring appears in the boat form (except, of course, when a bridge is formed between 1 : 4-carbon atoms).   It seems likely, however, that rings may be stabilised in this form in certain special cases.   If one or more methylene groups are replaced by carbonyl groups, for example, or by single bivalent atoms, some of the arguments against the boat form are weakened.   The finding[19] that *cyclo*hexane-1 : 4-dione shows a considerable dipole moment in solution is probably not a result of partial enolisation, but indicates rather the presence of a considerable proportion of molecules with a carbon ring of lower symmetry than that of the chair form.   Here X-ray analysis of the crystal would be of great interest but it has not so far been carried out.[18]

[17] O. Hassel, *Tidsskr. Kjemi*, 1943, **3**, 91.

[18] The crystals probably belong to the space group $P2_1$ with 2 molecules in the unit cell.

[19] C. G. LeFèvre and R. J. W. LeFèvre, **3.**, 1935, 1696.