

CONFORMATION AND REACTIVITY OF MEDIUM-SIZED RING COMPOUNDS

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Conformational analysis consists in the determination of the energy (or of the enthalpy) of a conformation by the application of certain rules based upon theoretical considerations and confirmed by experience. Since in general the determination of the absolute energy of a given conformation is not possible, such analysis is limited to comparisons of energy contents of various conformations of one chemical species (molecules, ions, radicals, transition states) or of the conformations of closely related species.

The most convenient parameters for the definition of the spatial arrangement of the atoms in a particle are bond distances (d), bond angles (ϑ) and torsion angles (τ), because they are independent of the coordinate system. A large body of experimental evidence shows that in stable particles (consequently not in transition states) the bond distances do not change appreciably upon modification of the conformation. For the purpose of conformational analysis one can, therefore, assume them to be constant and consider only the energy variations due to changes in the bond angles and in the torsion angles. The increase in energy content which arises from a deviation of the actual values of the parameters from their most favourable values is usually called strain (S). The energy increase directly brought about by a deviation of the bond angles from their optimum (*e.g.* tetrahedral) angle, is known as classical or Baeyer strain (S_B). The one which is directly due to a deviation of the torsion angles is often termed Pitzer strain (S_P). A third and very important component of the strain proceeds from the repulsive interactions between non-bonded atoms (S_N). These non-bonded interactions are determined by the same parameters d , ϑ and τ , on which the other two types of strain mentioned above also depend. However, the expression which defines this dependence in the case of non-bonded interactions between atoms which are separated from one another by several bonds is so complex, that it is more convenient to represent the strain S_N as a function of the interatomic distances r . Although the total strain can in principle be calculated on the basis of the three component strains which have been described above (*Figure 1*), quantitative conformational analysis is still quite unsatisfactory. For large molecules the deduction of strain from the variables ϑ and τ requires extensive calculations. Such is already the case for the medium-sized cycloalkanes: in cyclodecane, for instance, there occur 405 non-bonded interactions. This difficulty can, of course, be overcome with the help of electronic computers. The most serious trouble is that the functions f_1, f_2, f_3, f_4 *etc.* which connect the energy with the variables ϑ and τ are only imperfectly known. Consequently, the considerable computing effort

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is often hardly justified by the results. In spite of these difficulties, conformational analysis has assumed the greatest importance for organic chemistry, because several groups of compounds exhibit particularly stable conformations. The form of such conformations, which are associated with deep

$$\begin{aligned}\text{Total strain } S &= S_B + S_P + S_N \\ \text{Baeyer strain } S_B &= \sum f_1(\vartheta_i) \\ \vartheta_i &= \text{valence angles} \\ \text{Pitzer strain } S_P &= \sum f_2(\tau_j) \\ \tau_j &= \text{torsion angles} \\ \text{Non-bonded interactions} \\ S_N &= \sum f_3(\vartheta_i, \tau_j) = \sum f_4(r_n) \\ r_n &= \text{interatomic distances}\end{aligned}$$

Figure 1

energy minima, changes only little under further small strains. The classical example of a conformation of this type is the chair form of the cyclohexane skeleton. Here it is possible to disregard, in a first approximation, the changes of the Baeyer and of the Pitzer strain and to consider only the non-bonded interactions between atoms having a small interatomic distance r . When one chair form is prevented from switching into other chair forms by the presence of large substituents or by its enclosure in a polycyclic system this semi-quantitative treatment is particularly easy and yields valuable results. The abundance in nature of compounds containing cyclohexane ring systems and analogous six-membered heterocyclic structures has greatly contributed to the success of conformational analysis. A profusion of compounds is thus available on which conformational analysis in its simplified form can be verified, adapted for special applications, and its limitations explored¹.

In the group of cyclopentane and cycloheptane derivatives semiquantitative conformational analysis has not been as successful. These two ring systems do not possess a favoured conformation as stable as the chair form of cyclohexane and the energy barriers which separate the various stable conformations are not as high as in the cyclohexane series². The absence in cycloheptane of one of the important requisites for the successful application of a simplified semi-quantitative conformational analysis, *i.e.* the existence of one or at least of only a few stable conformations of the ring skeleton, gave rise to serious doubts on the possibilities of quantitative conformational analysis in the field of medium-sized ring compounds. On the other hand, it had been realized at a relatively early date that the special, and often very marked, physical and chemical peculiarities of medium-sized ring compounds, and in particular their comparatively high strain, were of a conformational origin, because models of such compounds in which the three components of strain are simultaneously minimal cannot be constructed³. Organic chemists could, however, only conjecture how the total strain is distributed over the various strain components, nor could they do more than speculate whether the medium-sized rings exist in one or more stable conformations, or whether they are to be regarded as relatively mobile particles with a large number of conformations almost equal in energy, but differing in form⁴. Some very important answers to these questions have been provided in the

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last few years by the X-ray analyst. A chemist faced with the problem of determining the form of chemical particles may, according to Dunitz, be compared to a person who has the task of drawing an exact picture of a room, which he can examine only in total darkness. Given enough time and freedom of movement, the person in question will be able to reach fairly exact conclusions if the structure of the room is stable. In the course of the process considerable damage to the less stable structures of the room and possibly to the investigator himself (and his reputation) is often hardly to be avoided. The X-ray analyst conversely turns on the light in the room and gets his picture in an easier and more exact way. He will, however, miss many interesting aspects of the state and nature of the room, which the chemist discovers in feeling his way about in darkness.

The X-ray analyses of medium-sized ring compounds which will now be discussed were carried out for the greater part in our laboratory by Professor J. D. Dunitz and his research group⁵. Before turning to an examination of the results, it is necessary to define the concepts and symbols which will be used.

As has been mentioned before, a conformation is defined by the bond distances, the bond angles, and the torsion angles. Of these three parameters, the bond distances are practically constant and the bond angles change by only small amounts ($\pm 8^\circ$), which affect the spatial form to a relatively small degree, though they play a significant rôle in determining the strain. Thus the spatial form can be roughly described by specification of the torsion angles alone. It is sometimes convenient to assign special names to some typical groups of similar partial conformations. In the medium-sized ring compounds under consideration, we shall be mainly concerned with staggered conformations having torsion angles of $60^\circ \pm 30^\circ$ and $180^\circ \pm 30^\circ$, designated as syn-clinal (sc) and anti-periplanar (ap) respectively. The complete designation of a partial conformation requires also the sign of the torsion angle. The conventions which will be used in this lecture in determining the name and the sign of torsion angles are summarized⁶ in a Newman projection on *Figure 2*.

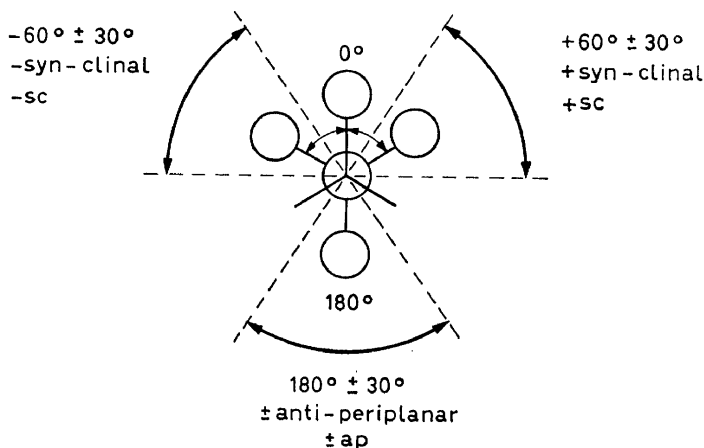


Figure 2. Designation of staggered partial conformations

There is also another convenient way of representing the conformation of a ring skeleton besides the one based on the indication of all torsion angles of the single bonds in the ring. The spatial environment of each member in a saturated carbon chain or ring is characterized by the two adjacent conformations. Taking into consideration only the staggered syn-clinal and anti-periplanar partial conformations, there result four conformational types of chain or ring members, which we designate as types I to IV, as shown in *Figure 3*.

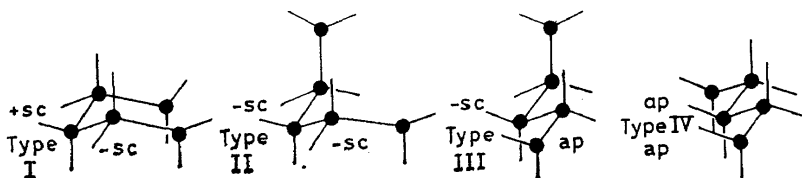


Figure 3

Chain or ring members of the conformational type I are flanked by two syn-clinal conformations of opposite sign. A member of type II is also flanked by two syn-clinal conformations, but in this case of the same sign. Members of type III are flanked by one syn-clinal and one anti-periplanar conformation. Members of type IV finally are flanked by two anti-periplanar conformations (as in the well-known zig-zag conformation).

The chair form of cyclohexane consists exclusively of the ring members of the conformational type I. In the conformation of cyclononane as determined by X-ray analysis (*Figure 4*) the conformational type I predominates and type II is encountered for the first time. In the conformation of cyclodecane (*Figure 5*, 1,6-*trans*-disubstituted) types I, II and III occur conjunctly, whereas one of cyclododecane (*Figure 6*) is composed of ring members of

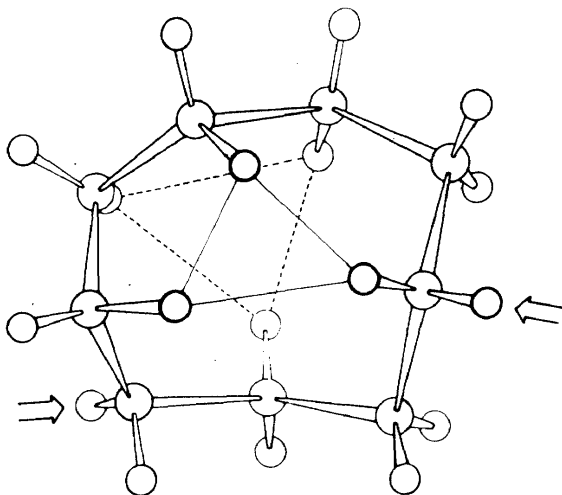


Figure 4

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types II and III exclusively. The striking divergence in the behaviour of medium-sized ring compounds of different size is explained by the marked differences in the conformational types of the individual ring members present in each (*cf.* Figure 7).

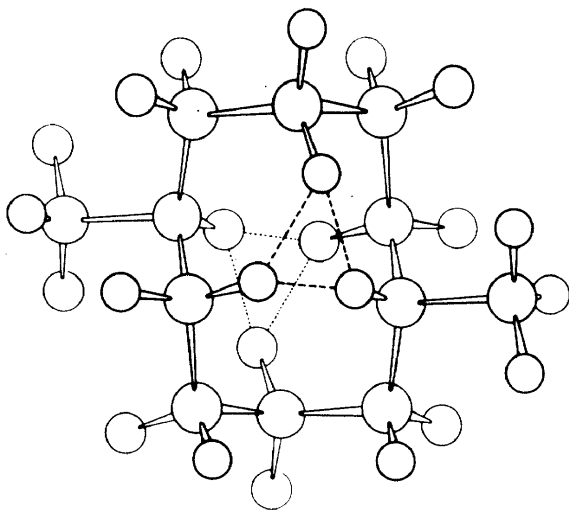


Figure 5

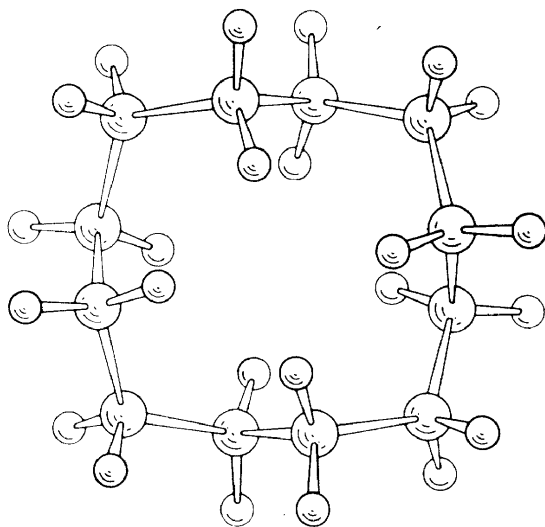


Figure 6

For the chemist, one of the most important results of the structure analysis of medium-sized rings is the derivation by X-ray methods of a particularly stable conformation of the ring skeleton in cyclodecane derivatives. This conformation had formerly never been taken into consideration. So far, three cyclodecane derivatives have been subjected to detailed X-ray analyses.

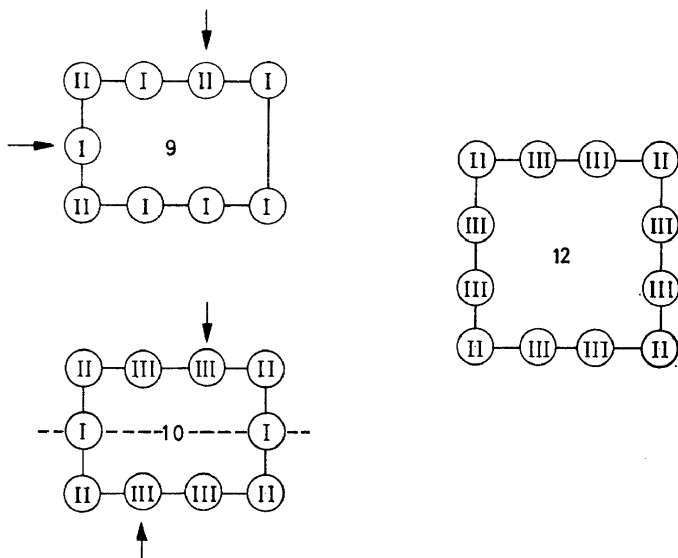


Figure 7

Dunitz and his research group have dealt with the structure of the dihydrochloride of *cis*-1,6-diaminocyclodecane⁷ as well as of the two crystalline modifications of the dihydrochloride of *trans*-1,6-diaminocyclodecane^{8, 9}, which correspond to two different conformers of this compound. Nowacki and Mladeck¹⁰ have determined by X-ray methods the conformation of the hydrochloride of aminocyclodecane. In all of these compounds the cyclodecane ring skeleton is subjected to strong ionic crystal forces differing greatly in their directions. In spite of this, the conformational details of the ring skeleton have turned out to be essentially identical¹¹ as shown in Figure 8. One may conclude, therefore, that the conformation of the cyclodecane ring skeleton deduced by X-ray analysis is not tied to the solid state but represents an intrinsic property of the ring. Such a conformation must be associated with a pronounced deep energy minimum and, consequently, fulfills one of the essential conditions required for a successful application of semi-quantitative conformational analysis. It is hence permissible to make the same simplifying assumptions as in the case of cyclohexane derivatives, *i.e.* to ascribe the differences in strain of the various conformations of a particle or of similar particles in first approximation to the non-bonded interactions.

In addition to its remarkable stability, the conformation of cyclodecane

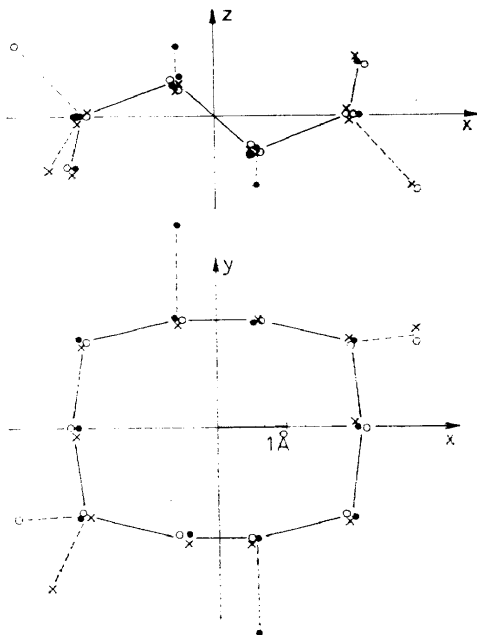


Figure 8. Representation of cyclodecane ring (with substituents) as found in *trans*-1,6-diaminocyclodecane dihydrochloride, triclinic (●) and monoclinic (○) forms and in the corresponding *cis*-compound (×). For certain of the atoms, the distinct points are hardly distinguishable from one another

(By courtesy J. D. Dunitz. *Proc. Chem. Soc.* **1961**, 463)

determined by X-rays has the following properties which must be taken into account in conformational analysis (Figure 9):

(i) The ring skeleton is composed of carbon atoms of the conformational types I (2 atoms), II (4 atoms) and III (4 atoms) and carries six different types of hydrogen atoms. The six hydrogen atoms situated on the inside of the ring and termed intra-annular hydrogens belong to two types, the 14 extra-annular hydrogens can be assigned to the four other types.

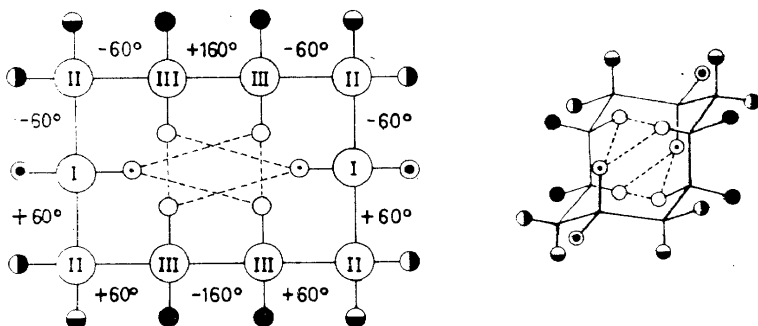


Figure 9. Schematic representations of the stable cyclodecane conformation

(By courtesy *Helv. Chem. Acta* **45**, 1356, 1962)

(ii) The bond angles have an average value of 117° , and so deviate considerably from the tetrahedral angle. Cyclodecane must, therefore, show significant Baeyer strain.

(iii) The torsion angles measure approximately 60° and 160° . Their values do not differ, or depart only by a small amount, from the optimum. Hence, cyclodecane should exhibit practically no Pitzer strain. Dale¹² has recently pointed out in a lecture that the only molecular model of cyclodecane which can be assembled with Stuart models that allow only torsion angles of $\pm 60^\circ$ and 180° , closely corresponds to the conformation found by X-ray analysis and displays only some slight deviation in the bond and torsion angles.

(iv) The interatomic distances of the six intra-annular hydrogens lie roughly in the range $1.8\text{--}2.2\text{\AA}$, and point to the existence of considerable non-bonded trans-annular interactions. These interactions can be expected to increase prohibitively upon replacement of the hydrogen atoms by larger atoms or atomic groups. We assume, therefore, that the intra-annular hydrogens cannot be substituted without a significant modification of the stable conformation of the ring skeleton to an energetically less favourable one.

The graphic representation of the chair form of cyclohexane—which has been used as the emblem of this Symposium—has certainly greatly contributed to the diffusion and understanding of conformational analysis. We have, therefore, attempted to find a similarly adequate representation for the stable conformation of cyclodecane. The one we have chosen (Figure 10) is derived from the well-known diamond lattice and is a fairly

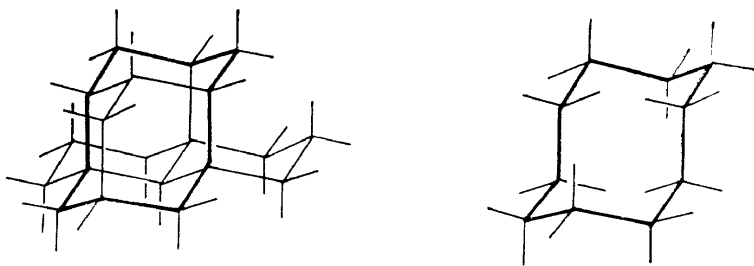


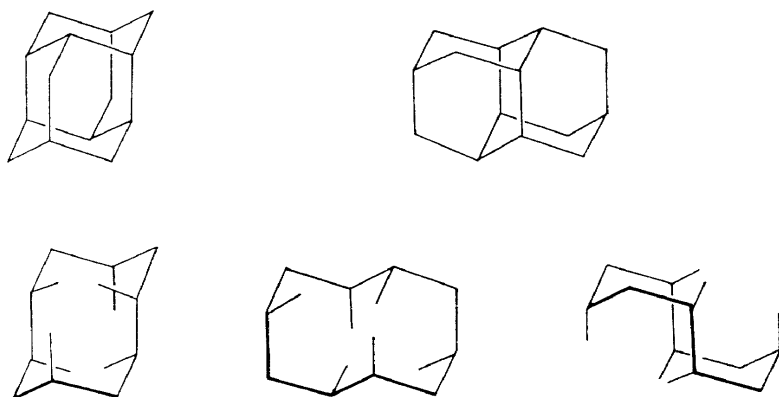
Figure 10. Derivation of the stable cyclodecane conformation from diamond lattice

faithful picture of the actual conformation, if one disregards the slight differences in the bond and torsion angles. As demonstrated in Figure 11 one can deduce the same representation by replacing four carbon atoms in pentacyclotetradecane by six intra-annular hydrogen atoms. The hitherto unknown pentacyclotetradecane appears as the emblem of the I.U.P.A.C. Congress to be held in London in 1963, and we have given it the provisional trivial name of "congressane 63". Figure 11 also contains two further representations of the stable conformation of cyclodecane, derived from "congressane 63" of which both are useful to emphasize some special aspects. In Figure 9, the preferred new graphic representation is also compared with the former schematic one.

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In contrast to the chair conformation of cyclohexane, which can accommodate a substituent only in two energetically different positions—axial and equatorial, a substituent at a tetrahedral ring member of the stable conformation of cyclodecane can be placed in four different extra-annular positions (Figure 12). There is at present no reason to give any one of the four preference over the others. Several facts, among others N.M.R.-spectra,

Congressane 63



Cyclodecane

Figure 11. Derivation of the stable cyclodecane conformation from "congressane 63"

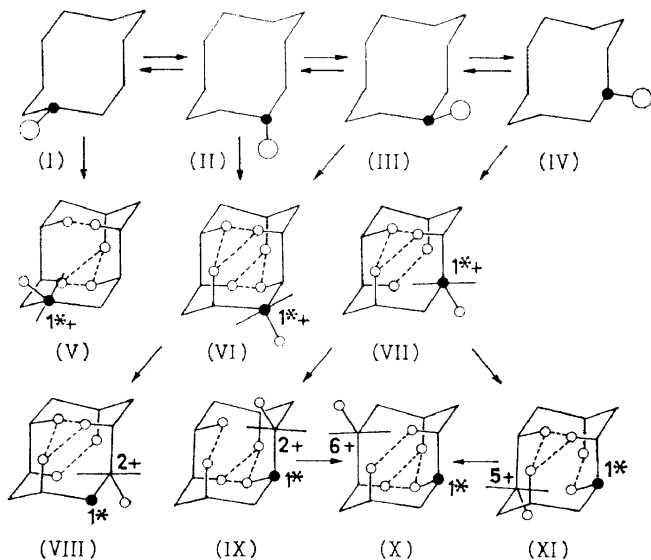


Figure 12
(By courtesy *Helv. Chim. Acta*, **45**, 1357, 1962)

appear to indicate that in stable particles a substituent can swing from one position into another, and that the four positions are, therefore, in equilibrium. The situation changes substantially if the substituent is attached to a trigonal ring member, as in cyclodecanone, or if a trigonal ring member carries a positive charge, as in the cyclodecyl cation. Three conformations are possible for such particles, since tetrahedral ring members of three different conformational types (I, II, III) can be replaced by a trigonal one. Upon consideration of the non-bonded interactions it is clear that if a trigonal ring member replaces a tetrahedral one of type I or III, the resulting conformation will be less strained than that of cyclodecane, because the substitution in this case removes one intra-annular hydrogen and, consequently, two of the total of six transannular interactions. The relaxation might be expected to be greater at a ring member of type III than at one of type I, since one of the interactions removed in the former case corresponds to a particularly small interatomic distance. On the other hand, no significant release of strain should occur in the replacement of a tetrahedral ring member of type II by a trigonal one. We, therefore, expect that the conformation with a trigonal ring member in the place of a tetrahedral one of type III will be energetically favoured and hence predominate. Many chemical peculiarities of monosubstituted cyclodecanes can be explained qualitatively and sometimes even interpreted semi-quantitatively on the basis of these simple assumptions.

The remarkable behaviour of the acetolysis of cyclodecyl toluene-*p*-sulphonate¹³ may serve as a first example. At 50° this reaction proceeds 536 times faster than the acetolysis of the corresponding cyclohexyl derivative and 174 times faster than the one of cyclododecyl toluene-*p*-sulphonate. About 80 per cent of the reaction product is the less stable *trans*-cyclodecene, the rest being the more stable *cis* isomer. The equilibrium mixture of the two isomers under the same conditions contains only about 3 per cent of *trans*-cyclodecene. The acetolysis of cyclodecyl toluene-*p*-sulphonate is accompanied by 1,2- and by transannular 1,5-hydride shifts, as has been shown by comprehensive experiments with compounds labelled with ¹⁴C and with deuterium. All of these striking findings can be explained by assuming that in the rate-determining step the cyclodecyl cation with the stable conformation of the ring skeleton (*Figure 12*) is the primary unstable intermediate. The conformational stabilization of this cyclodecyl cation must be responsible for the acceleration of the acetolysis, as it is to be expected that the transition state of the endothermic reaction is spatially and energetically closely related to this unstable intermediate. The thermochemical strain of cyclodecane in relation to cyclohexane amounts¹⁴ to about 12 kcal mol⁻¹; the difference in reaction rates between cyclohexyl and cyclodecyl toluene-*p*-sulphonate corresponds to a difference in activation energy of about 4 kcal mol⁻¹. In removing one hydrogen from its intra-annular position in cyclodecane approximately one third of the strain is released, in semi-quantitative agreement with the experiment.

The stereospecific and kinetically controlled formation of the cyclodecenes apparently takes place in a second product-determining step from the stable cyclodecyl cation. The lesser the difference in spatial arrangement between this cation and the transition state of the elimination, the greater is the rate

of this reaction step. The value of the torsion angle between the empty p -orbital of the cation and the C—H bond of the leaving hydrogen can be taken as a rough measure of this difference: the smaller this torsion angle, the faster the elimination. An easy calculation shows that in the stable cyclodecyl cation this torsion angle is 5° in the elimination yielding *trans*-cyclodecene, and 30° in the one leading to *cis*-cyclodecene. The smallness of these conformational changes and their quantitative difference explain the preponderance of the elimination over the substitution reaction as well as the stereospecific formation of the less stable *trans*-cyclodecene. The stable conformation of the cyclodecyl cation also accounts for the non-classical course of the acetolysis established by examination of the distribution of the label in products obtained from labelled cyclodecyl toluene- p -sulphonate. Without discussing in detail the rather complicated experimental results, the following discussion will illustrate the application of the stable conformation of the cyclodecyl cation. The alternatives to the elimination reaction are, on the one hand, the 1,2-hydride shifts, and on the other hand the rarely encountered 1,5-hydride shifts. That these exceptional shifts occur is due to the small distance between the empty p -orbital and the intra-annular hydrogen in position 5 of the stable conformation of the cyclodecyl cation. Thus, the cyclodecyl cation originally formed can rearrange easily by hydride shifts to three differently labelled cyclodecyl cations without much change in the conformation of the ring skeleton. Proton elimination from the original cyclodecyl cation and from three rearranged ones leads to a mixture of differently labelled cyclodecenes. The experimentally found distribution of label agrees fairly well with the predicted one. To reach a complete agreement it is necessary to assume one additional rearrangement shown in Figure 12.

The dissociation constant of cyclodecanone cyanohydrin¹⁵ will be the second example of conformational analysis in the cyclodecane series. The value of this dissociation constant is over 2,000 times larger than the one of cyclohexanone cyanohydrin. At the time the measurements were made, this dramatic difference was interpreted on the basis of hypothetical conformations of cyclanones designated as "O-outside" and "O-inside"³. These designations, which have found use in the chemical literature, are to be considered as obsolete. A more pertinent interpretation of the observed values can now be provided in terms of the stable conformation of the cyclodecane skeleton. In analogy to the cyclodecyl cation, cyclodecanone can assume three conformations. Of these, again, the one in which the trigonal carbon atom replaces a tetrahedral carbon of type III will be energetically favoured because of the larger release of strain it involves (Figure 13). Such a stable conformation has all the essential characteristics of the old "O-inside" one, whereas the two others are equivalent to the "O-outside" conformation. The release of strain which accompanies the dissociation of cyclodecanone cyanohydrin to cyclodecanone is similar to the one observed in the acetolysis of cyclodecyl toluene- p -sulphonate to the cyclodecyl-cation and accounts semi-quantitatively for the observed large difference of the free enthalpy of reaction in the cyclohexane and the cyclodecane series.

The third example is concerned with the rate of the oxidation of the stereoisomeric cyclodecane-1,2-diols with lead tetra-acetate¹⁶. Whereas in

the cyclopentane and in the cyclohexane series the *cis*-diols react faster than the *trans*-stereoisomers, the two stereoisomeric cyclodecane-1,2-diols show opposite behaviour. It was early recognized that a conformational effect must be responsible for these results, because on stereoelectronic grounds a fast fragmentation requires a transition state in which both C—O bonds are co-planar⁴. The conformational effects which favour such a transition state will therefore accelerate the reaction. Conversely, those which obstruct

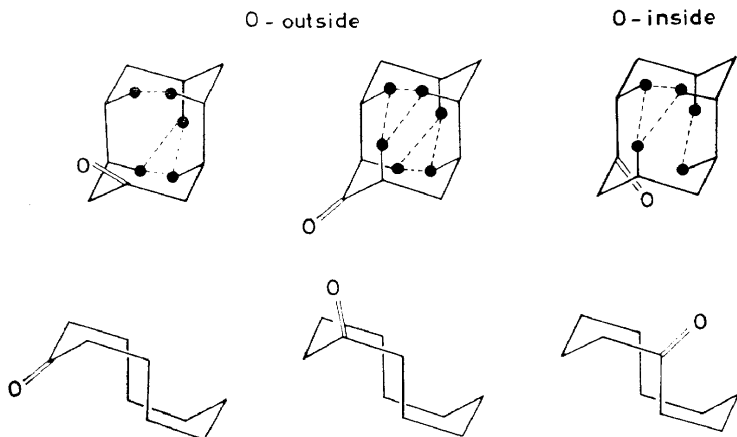


Figure 13

co-planarity of the two C—O bonds will retard the reaction. The relative position of the extra-annular substituents in the stable conformation of the cyclodecane skeleton is depicted in Figure 14. The positions that bear the same mark (a full or empty circle) are *cis* to one another, those that bear different marks are *trans*. Disregarding chirality, it is evident from the figure that a *cis*-1,2-disubstituted cyclodecane derivative, for instance *cis*-cyclodecane-1,2-diol, can occur in two conformations, whereas the *trans* isomer can occur in three. The mutual spatial arrangement of the two hydroxyl groups of both stereoisomers in the cyclohexane and in the cyclodecane series is very much the same, as may also be deduced from the i.r. spectra¹⁷. As mentioned above, the stereoisomers differ greatly in their rate of oxidation with lead tetra-acetate. For the *cis* diols the rates are of the same order of magnitude. In the *trans* isomers, however, *trans*-cyclohexane-1,2-diol reacts approximately 25 times slower than the *cis* diol, whereas for *trans*-cyclodecane-1,2-diol the oxidation takes place about 38 times faster than for the corresponding *cis* isomer. An examination of the transannular strain in the ideal transition state where the two C—O bonds are co-planar offers an explanation of these results. In both conformations of *cis*-cyclodecane-1,2-diol co-planarity is accompanied by a release of transannular strain. For two of the three possible conformations of *trans*-cyclodecane-1,2-diol the opposite is the case, in analogy to the cyclohexane-1,2-diols. However, in the third possible conformation of *trans*-cyclodecane-1,2-diol, co-planarity of the two C—O bonds is coupled with an even greater release of transannular

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strain than in the *cis* stereoisomer. An impressive experimental proof that this conformation is responsible for the high rate of oxidation of the *trans* diol can be provided by studying derivatives which cannot assume it: the rate of oxidation of 1-phenyl-*trans*-cyclodecane-1,2-diol is indeed 57 times smaller than the one of the *cis* isomer¹⁸ as predicted by conformational analysis.

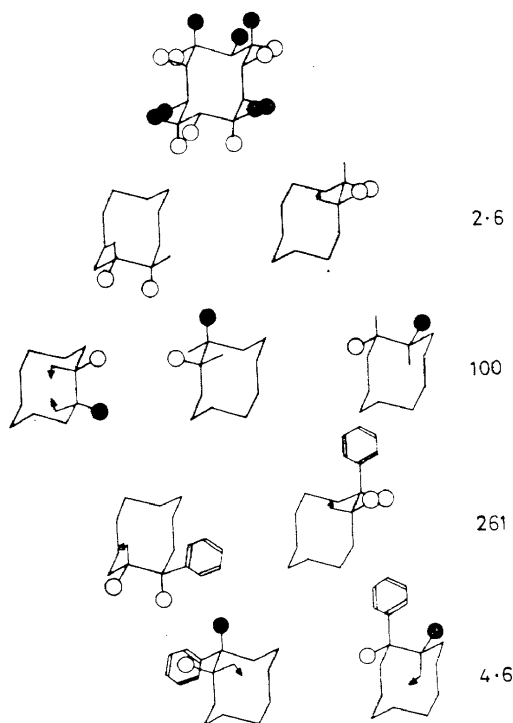


Figure 14. The numbers refer to relative rates of oxidation

A discussion of the 1,6-disubstituted cyclodecane derivatives which have formed the object of the X-ray analyses will close the consideration of this series. Examination of *Figures 14* and *15* shows that only one stable conformation is possible for the *cis*-1,6-disubstituted cyclodecane derivatives, and that is the one actually found by X-ray analysis of the dihydrochloride of *cis*-1,6-diaminocyclodecane⁷. The stable conformation of the cyclodecane skeleton allows four conformations to be deduced for a *trans*-1,6-disubstituted cyclodecane derivative. Two of these have been observed in the two crystalline modifications of the dihydrochloride of *trans*-1,6-diaminocyclodecane^{8, 9}. The fact that these two modifications are mutually interconvertible by modification of the conditions of crystallization, indicates that the energy barrier between them cannot be very high.

There remains to be discussed briefly the conformational analysis in the cyclononane series. In the crystal of cyclononylamine hydrobromide two

conformations were found differing in the orientation of the ammonium group, but having nearly identical ring skeletons¹⁹. This points to the existence of a pronounced energy minimum for the observed conformation of the ring skeleton, a rather remarkable result considering that this conformation is a quite asymmetrical one. The assumption that the conformational analysis may be successfully applied to the study of cyclononane derivatives, therefore, seems justified.

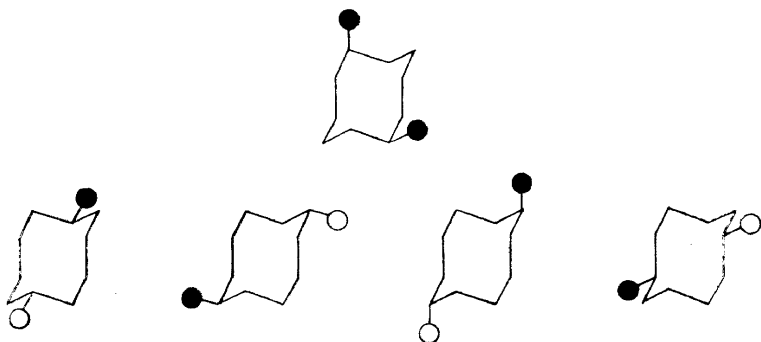


Figure 15

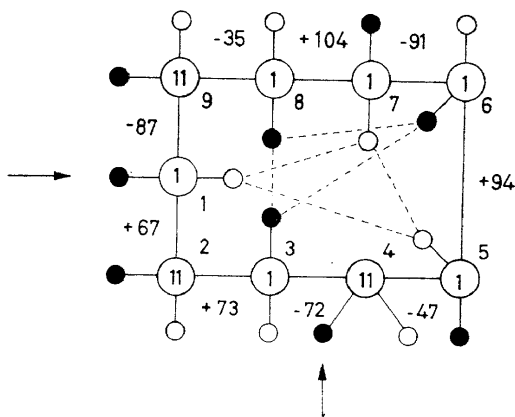


Figure 16

(By courtesy *Helv. Chim. Acta*, **45**, 1664, 1962)

The main properties of the stable conformation of cyclononane, represented in Figure 16, can be summarized as follows:

(i) The conformation consists of nine conformationally different carbon atoms, six of which belong to type I and three to type II. All of the eighteen hydrogen atoms are conformationally different, but can be divided in two groups, intra-annular (six hydrogens) and extra-annular (twelve hydrogens).

(ii) The bond angles in the cyclononane skeleton have an average value of 117° , which leads to significant Baeyer strain.

(iii) The deviations from the optimal torsion angles are in many cases quite large, and Pitzer strain should, therefore, be also significant.

(iv) The distances between the intra-annular hydrogens are small, and one must expect relatively high non-bonded interactions.

In spite of the differences, the stable cyclononane conformation with its intra-annular hydrogens is strongly reminiscent of the stable cyclodecane conformation. This similarity explains many of the analogies in the chemical behaviour of compounds of the two series. Considerations such as those made in the case of cyclodecane derivatives in regard to the increase or the release of transannular strain provide interpretations of the acetolysis of cyclononyl toluene-*p*-sulphonate²⁰, of the value of the dissociation constant of cyclononane cyanohydrin¹⁵ and of the anomalous oxidation rates of the stereoisomeric cyclononane-1,2-diols²¹. The results differ here quantitatively but run along the same lines as those obtained with the corresponding cyclodecane derivatives.

Experience so far with conformational analysis of medium-sized ring compounds, though of a fragmentary nature, encourages predictions and experiments, in order to confirm or invalidate the views expressed above. It should be possible to "freeze-out" certain conformations of medium-sized rings by substitution or enclosure in polycyclic systems and thus to bring about interesting changes in their properties. The systematic attempts to prepare compounds which cannot occur in the conformations encountered so far, and the examination of their conformations and behaviour, seems to be a particularly attractive field of research.

In recent times numerous representatives of medium-sized ring compounds have been found in nature and have been thoroughly investigated, especially in the Laboratory of Czechoslovak Academy of Sciences²². As far as we are aware, conformational analysis has not yet been applied in the study of such natural products. If my lecture will stimulate work in this direction its presentation before a Symposium on natural compounds will have been justified.

Before closing my lecture, I have the pleasant duty of expressing my gratitude to all the co-workers who have been engaged in obtaining the results I have presented. I am particularly indebted to Professor J. D. Dunitz for many fruitful and stimulating discussions, and to Dr B. G. Engel for translating the German manuscript.

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