

CONFORMATIONS OF MEDIUM RINGS

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ABSTRACT

The stable conformations of the medium-sized cycloalkanes and some cycloalkenes, as revealed mainly by x-ray analysis of suitable crystalline derivatives, are reviewed.

Most of the information on the equilibrium conformations of medium-ring compounds has been obtained by x-ray analysis of suitable crystalline derivatives. A multitude of conformations may be built for these rings but until recently it was virtually impossible to make reliable estimates of their relative energies. In the absence of criteria for estimating the energies there was no option but to make use of real or imaginary structural analogies, and it is not surprising that the earlier conformational models for medium rings were based on extrapolations from the established structures of cyclohexane derivatives. As far as I am aware the conformation that we now refer to as the stable cyclodecane conformation was not discussed at all in the organic chemical literature prior to its recognition in crystalline cyclodecane derivatives 10 years ago. Two other cyclodecane conformations that lie within a few kcal mole⁻¹ of the stable conformation were also completely overlooked until discovered in another crystalline derivative a few years later.

Unsubstituted cycloalkanes and cycloalkenes are, in general, not very suitable for x-ray studies since they are either liquids at room temperature or form disordered crystals. In solution, the methylene groups of cycloalkanes are all equivalent on the n.m.r. time scale, although they are distinguishable to some extent by vibrational spectroscopy¹. In crystals of cycloalkanes the atoms still undergo oscillatory motions of large amplitude about their mean positions. This leads to a smearing out of the electron density about the mean atomic positions and lowers the accuracy with which these positions can be defined. Under such circumstances the distinction between 'ordered' and 'disordered' crystals becomes rather arbitrary, and considerable caution is called for in the interpretation of the electron-density maps obtained by x-ray analysis.

One example where the electron-density distribution could not be unequivocally interpreted in terms of a definite atomic arrangement comes from the analysis of azacyclooctane hydrobromide, a crystal in which some of the apparent space-group symmetry operations may arise from randomness in the crystal structure. There was no problem about establishing the positions of the heavy bromine atoms, and the electron-density distribution phased on this arrangement was first thought to point to a crown-like conformation for the 8-membered ring; calculations based on this model gave excellent agreement with

the experimental data. An *R* factor of 6 to 7 per cent is good enough to satisfy most connoisseurs of crystal structure analyses but it was not good enough to satisfy one of my former students. Mrs Huber-Buser, who showed that it was possible to get just as good agreement with a variety of models, including some based on 7- or 9-membered rings! We had to conclude that, as a result of disorder in this crystal, no unequivocal interpretation of the x-ray data in terms of a unique molecular structure is possible.

With the development of automatic diffractometers for collecting x-ray data, of direct methods for solving crystal structures, and of computers for performing the lengthy calculations, there is a tendency to regard x-ray crystal structure analysis as a perfectly straightforward method for establishing the details of molecular architecture. To be sure, the method can often be applied in a straightforward, more or less routine fashion, but the above example shows that this is not always the case.

As soon as polar or highly polarizable substituents are introduced the tendency to give disordered crystals is greatly diminished. Most of our information on the conformations of medium-ring compounds comes from studies on such substituted derivatives so that the question arises: to what extent does the introduction of substituents affect the conformations of the rings? We can only answer this question when we have looked at some of the results.

Figure 1 shows the experimental values of the CCC bond angles and ring torsion angles in four ammonium-substituted cyclodecane derivatives: A and B are two crystalline forms of cyclodecane-1,6,-*trans*-diamine dihydrochloride and correspond to conformational isomers¹, C is the 1,6-*cis*-diamine dihydrochloride³ and D is cyclodecylamine hydrochloride⁴. The estimated standard deviations are somewhat less than 1° for the bond angles and somewhat greater than 1° for the torsion angles. In A and B the molecules lie on crystallographic inversion centres. Although small differences occur, one is struck by the essential similarity of the molecular parameters and can hardly escape the conclusion that all four derivatives have a common ring skeleton that is altered only slightly by considerable differences in its environment. We shall refer to this common skeleton as the stable conformation of cyclodecane. The sign of a torsion angle is unchanged by a rotation operation but reversed by a reflection or inversion operation; it follows that in all four cases the ring skeleton itself has approximate $C_{2h}(2/m)$ symmetry. From the results of all four analyses taken together molecular parameters for an 'averaged' ring with strict $C_{2h}(2/m)$ symmetry have been derived, and are shown in *Figure 2*. In this model the transannular H...H distances have been calculated assuming local $C_{2v}(mm2)$ symmetry of the methylene groups with $HCH = 107^\circ$ and $C-H = 1.10 \text{ \AA}$. These assumptions lead to transannular H...H separations as short as 1.85 Å, a distance that certainly corresponds to a strong repulsion between the non-bonded atoms. In the actual molecule the H atoms will be pushed farther apart from one another. Unfortunately, although the hydrogen atoms can be recognized in the electron-density distributions in all four cases, their positions cannot be measured by x-ray methods with the desired accuracy. A neutron diffraction study of a cyclodecane derivative would be of great value in this respect.

Figures 1 and *2* show that the CCC angles in the cyclodecane ring are opened out to values of 115° to 118°, compared with the value of 112.5° in a

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polymethylene chain. Of the ten torsion angles, eight are close to 60° (synclinal) the remaining two being about 150° . All features of the experimental model are reproduced extremely well by strain-minimization calculations based on semi-empirical potential functions⁵.

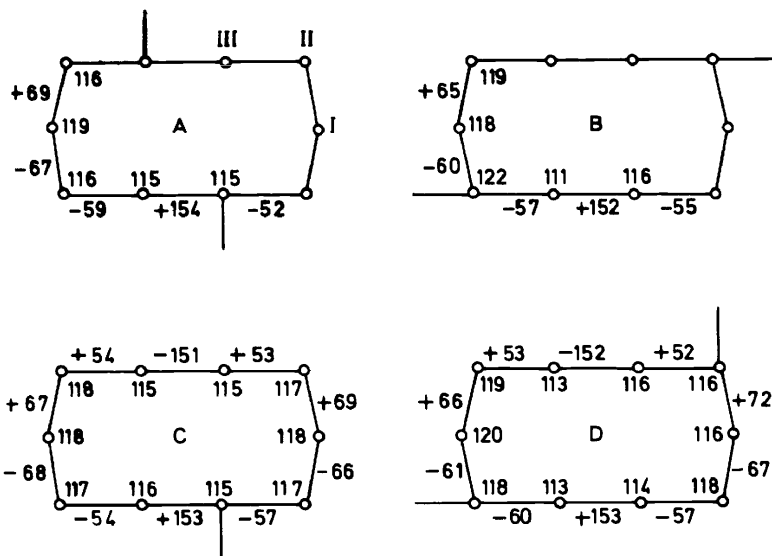


Figure 1. Experimental bond angles and torsion angles (in degrees) in four ammonium-substituted cyclodecane derivatives. A and B, cyclodecane-1,6-*trans*-diamine (dihydrochloride). (A) triclinic form. (B) monoclinic form; (C) cyclodecylamine (hydrochloride); (D) cyclodecane-1,6-*cis*-diamine (dihydrochloride). The positions of the $-\text{NH}_3^+$ substituents are indicated.

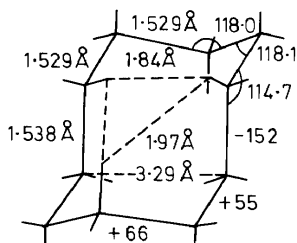


Figure 2. Cyclodecane: parameters derived for an 'averaged' ring of $C_{2h}(2/m)$ symmetry.

In contrast to the chair form of cyclohexane where all carbon atoms are equivalent, we can distinguish three types of carbon atom in the stable cyclodecane conformation, labelled I, II and III in Figure 3. There are six types of hydrogen atom, two intra-annular and four extra-annular, compared with the two types in chair cyclohexane. It is clear that conformational analysis of cyclodecane derivatives will be much more complicated than in the cyclohexane series but, nevertheless, some tentative rules can be drawn. Replacement of a hydrogen atom by a substituent should occur preferentially at the extra-annular positions. A monosubstituted derivative could then occur as one of seven isomers, three enantiomeric pairs of conformational isomers (IIa, IIe, III) and

one achiral conformational isomer (I), which must be rapidly interconvertible in solution, as indicated by n.m.r. evidence. There are four possible conformational isomers for a 1,6-*trans*-disubstituted derivative, all achiral, but only one pair of enantiomeric conformational isomers for a 1,6-*cis*-disubstituted derivative. As we have seen, the two crystalline forms of cyclodecane-1,6-*trans*-diamine dihydrochloride are not crystal modifications in the usual sense but

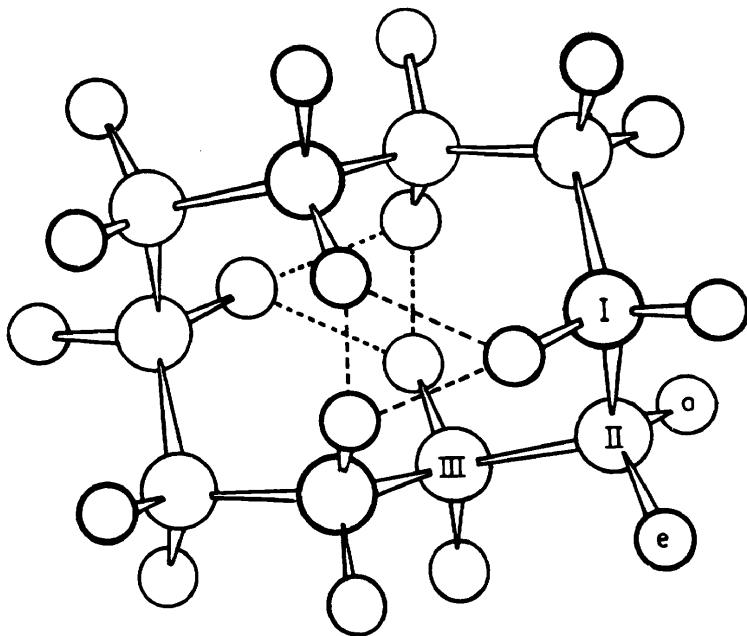


Figure 3. Cyclodecane: stable conformation.

correspond to two of the four conformational isomers that have separated in the crystallization process. The activation energy for interconversion is much greater in the crystal than in solution. The various possibilities for other substitution patterns can easily be worked out. A pair of geminal substituents can be placed only on a type II atom, from which it follows that for 1,1,3,3-, 1,1,4,4- and 1,1,6,6-tetrasubstitution all substituents can be extra-annular, whereas for 1,1,2,2- and 1,1,5,5-tetrasubstitution at least one substituent would have to occupy an intra-annular position in the normal cyclodecane conformation.

Just as introduction of a substituent into an intra-annular position is expected to increase the energy of a molecule, so removal of an intra-annular hydrogen can be expected to lower the energy. The model shown in *Figure 2* suggests that removal of a type III intra-annular hydrogen atom should be associated with a larger decrease in strain energy than removal of a type I intra-annular hydrogen atom. Hence we would expect that trigonal carbon atoms (carbonyl groups, carbonium ions) and hetero-atoms such as nitrogen or oxygen should occur preferentially at type III positions. As far as the evidence goes this seems to be the case. In crystalline cyclodecane-1,6-dione⁶ and 2-oxa-cyclodecane-1,6-

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dione⁷ the observed conformations (*Figure 4*) are obviously derived from, and closely related to, the stable cyclodecane conformation. The keto-carbon atoms and the ester-oxygen atoms are, as expected, in type III positions. One noticeable effect of the removal of transannular H...H interactions is the shortening

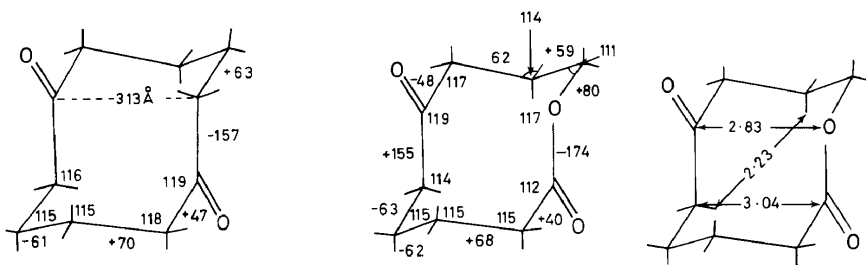


Figure 4. Molecular conformations of cyclodecane-1,6-dione and of 2-oxacyclodecane-1,6-dione (6-ketononanolide) showing bond angles and torsion angles (in degrees) and some transannular distances (in Å).

of the distance between opposite pairs of type III atoms. For $\text{CH}_2 \dots \text{CH}_2$ this distance is 3.29 Å, for $\text{CH}_2 \dots \text{CO}$ it is 3.04–3.13 Å and for $\text{O} \dots \text{CO}$ it is only 2.83 Å. This distance is considerably smaller than the sum of the van der Waals radii (3.1 Å) and it could easily be increased by slight alterations in the torsion angles. Probably it corresponds to weak transannular bonding associated with an $n : \pi^*$ interaction.

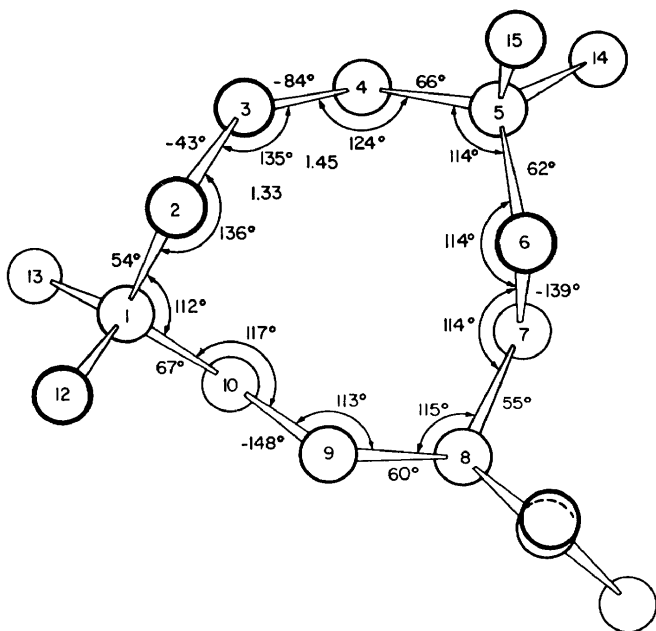


Figure 5. 1,1,5,5-Tetramethylcyclodecane-8-carboxylic acid. Conformation observed showing bond angles and torsion angles (in degrees). Except for the bonds 2—3 (1.33 Å) and 3—4 (1.45 Å) the C—C bond lengths lie in the range 1.50–1.55 Å.

One important aspect of the stable cyclodecane conformation is that it provides the basis for the interpretation of many characteristic chemical properties of cyclodecane derivatives⁸. We do not have time to go into these matters in any detail, but mention two examples very briefly. One is the ready occurrence of 1,5-hydride shifts, rarely encountered elsewhere, and easily explained in terms of the stable conformation if it is assumed that the positively charged carbon atom of the cyclodecyl cation occurs preferentially at a type III position. The second example is the relatively high dissociation constant of cyclodecanone cyanhydrin, which is 2000 times greater than that of the corresponding cyclohexanone derivative. This can easily be accounted for in terms of the release of strain energy associated with the erasure of transannular H...H interactions in the 10-membered ring but not in the 6-membered ring.

We have already remarked that preservation of the normal cyclodecane conformation in a 1,1,2,2- or 1,1,5,5-tetrasubstituted cyclodecane derivative

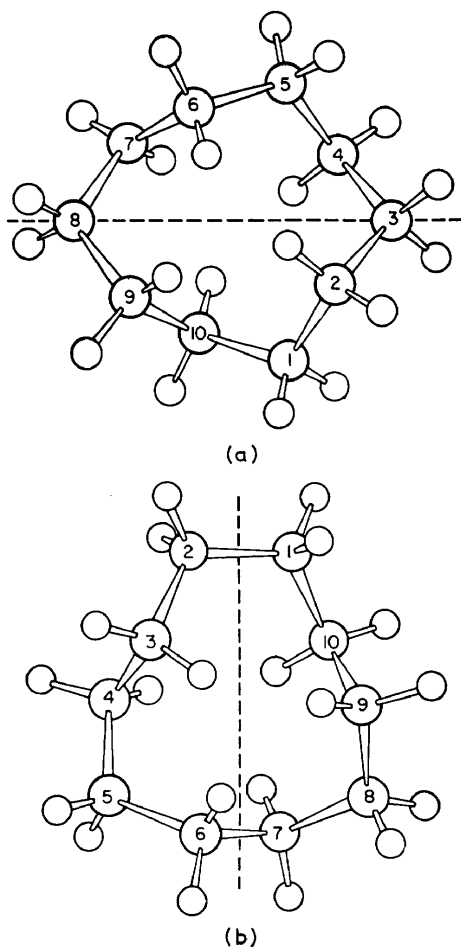


Figure 6. Two conformations of cyclodecane derived by strain-minimization calculations starting from 'observed' conformation of Figure 5.

would require at least one substituent to be placed in an intra-annular position. Either the normal conformation must distort to allow more room for the intra-annular substituent, or a change to another conformation must occur; both processes should be accompanied by an increase in strain energy. The investigation of an appropriately substituted cyclodecane derivative should then provide evidence on the alternative conformations available to the cyclodecane ring. A project along these lines has led to a rather interesting example of cooperation at the international level. The compounds were synthesized in Czechoslovakia, an x-ray analysis of the 1,1,5,5-tetramethylcyclodecane-8-carboxylic acid was carried out in Switzerland, the heats of combustion of 1,1,4,4- and 1,1,5,5-tetramethylcyclodecanes were measured in Holland, and strain-minimization calculations were carried out in Israel⁹. The final outcome, I am happy to report, was highly successful although we were quite worried for a time about the result of our x-ray analysis, shown in *Figure 5*. The ring conformation is distinctly different from the stable conformation but there are some rather disturbing features in the apparent molecular geometry: two of the C—C bond distances (1.33 Å and 1.45 Å) and three of the CCC angles (136°, 135°, 124°) lie so far outside the normal ranges as to indicate that something had gone wrong. Some of the atoms involved also appeared to undergo large amplitude oscillations, as indicated by the smearing out of the respective electron densities and by the large, highly anisotropic temperature factors. It seemed very likely that some kind of disorder was present. Although the 'observed' conformation with its too short bond lengths and too wide bond angles was obviously unsatisfactory as it stood it could at least serve as a starting point for a series of strain-minimization calculations. These calculations led not to *one* but *two* new conformations shown in *Figure 6*, and the 'observed' conformation could then be accounted for in terms of a disordered mixture of these new conformations in the proportion of approximately 4:1. The calculated excess strain energies of the two new conformations were 2.1 and 3.1 kcal mole⁻¹ relative to the stable cyclodecane conformation, and the heats of combustion of 1,1,4,4- and 1,1,5,5-tetramethylcyclodecanes gave an excess strain energy of 2.3 ± 0.3 kcal mole⁻¹ for the 1,1,5,5-isomer, in amazingly good agreement with the calculated values.

The stable conformation and the two new conformations of somewhat higher energy appear at first sight to be quite different from one another. They have different symmetry properties, for example. The normal conformation has $C_{2h}(2/m)$ symmetry, the two others have only $C_2(2)$ symmetry, the dyad axis passing in one case through a pair of opposite atoms, in the other case through a pair of opposite bonds. However, since conformations (a) and (b) coexist in the same crystal structure they must be rather similar, and closer inspection reveals that the sequence of atoms 1,10,9,8,7,6,5,4, for example (*Figure 6*), is nearly superimposable in the two conformations. Both of the new conformations represent recognizable distortions of the stable one. In conformation (a) one can regard atom 5 as a type III atom that has been twisted out of its normal situation in such a way as to make it a type II with both its hydrogens extra-annular; and similarly for atom 1. In conformation (b), atoms 5 and 8 are type II and atoms 1 and 2 have been twisted out of their normal positions, preserving the dyad axis of the normal conformation but destroying its mirror plane.

Figure 7 shows that conformation (a) represents an intermediate in a pseudorotation pathway that converts an atom of any given type in the normal

conformation to an atom of another type. Thus atom 1, initially type II, is converted into type III and then into type I. At each pseudorotation step, a given atom is moved three places round the ring so that the complete pseudorotation

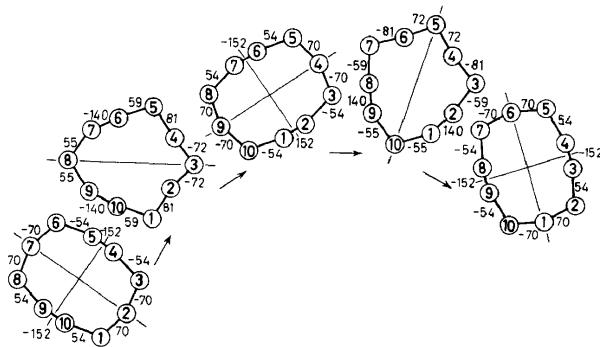


Figure 7. Possible pseudorotation pathway for stable cyclodecane conformation with conformation (a) as intermediate.

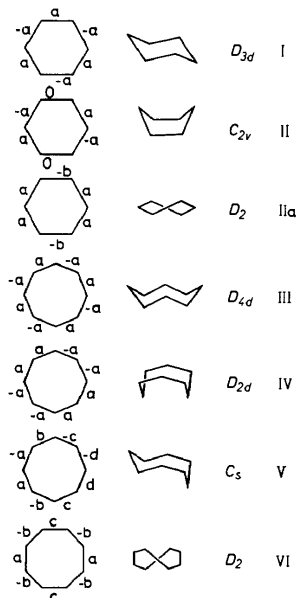


Figure 8. Torsion angle pattern and symmetry of some possible cyclohexane and cyclooctane conformations.

cycle requires ten steps. The activation energy for this particular pseudorotation path has not been calculated but is probably of the order of 5 to 10 kcal mole⁻¹.

For the cyclooctane ring the experimental evidence suggests that the most stable conformation is probably the one (Figure 8, V) to which the rather unfortunate description 'boat-chair' has been given. In my opinion it is a mistake to define ring conformations by descriptive names of this kind, espe-

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cially when, as is often the case, the names are further qualified by various adjectives. Expressions such as 'distorted saddle', 'spanned boat', 'twisted butterfly' may have significance for the person who uses them but they are often incomprehensible to the reader. The only unambiguous way of defining a ring conformation is to enumerate the sequence of torsion angles; a class of related ring conformations can be described by the general pattern of torsion angles, from which the symmetry elements or approximate symmetry can be inferred.

The conformation V (Figure 8) has been found in four crystalline cyclooctane derivatives¹⁰⁻¹³; it provides a satisfactory interpretation of the n.m.r. spectra of deuterated and substituted cyclooctane derivatives in solution¹⁴, and its position as most stable conformation seems to be also supported by strain-minimization calculations^{15, 16}. The approximate mirror symmetry of the ring is retained in spite of asymmetric perturbation from substituents, as indicated by the experimentally determined torsion angles in the four derivatives, shown in Figure 9. However, the conformation occurring in crystalline *trans-syn-trans*-1,2,5,6-tetrabromocyclooctane resembles VI (Figure 8) and spectral evidence

	a	b	c	d	
	71°	106°	47°	62°	
	70	101	43	63	
	67	105	48	60	
	66	96	38	69	
	64	101	49	61	
	66	98	37	70	
	60	101	48	62	
	63	100	41	68	
calculated	72	106	44	64	
	70	105	46	64	

Figure 9. Observed torsion angles in some crystalline cyclooctane derivatives.

suggests that a similar conformation occurs in solution¹⁷. The n.m.r. spectra of fluorinated cyclooctanes has been interpreted in favour of a low-symmetry version of IV (Figure 8)¹⁸. These findings would not be in conflict with the results of strain-minimization calculations, which suggest that other cyclooctane conformations differ so little in energy from V that perturbations arising from the ring environment might well alter the stability sequence.

The conformation of the cyclononane ring appears to be even more sensitive to the environment. In crystalline cyclononylamine hydrobromide¹⁹ the two independent molecules in the asymmetric unit are not identical although there are obvious similarities in the torsion angle patterns (Figure 10). The ring

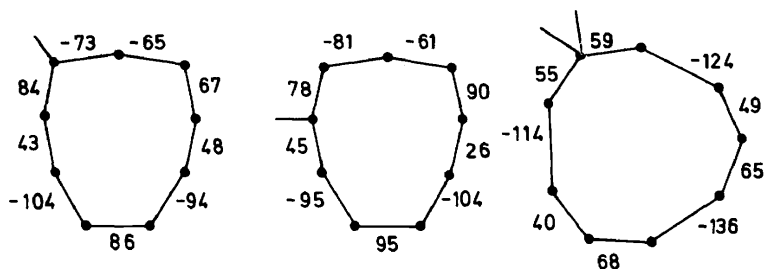


Figure 10. Observed torsion angles in cyclononylamine hydrochloride (two independent molecules) and in cyclononane-1-hydroxyl-1-dimethylphosphonate. The positions of substituents are indicated.

conformation has approximate C_2 symmetry in both molecules. In the crystalline 1-hydroxy-1-dimethylphosphonate of cyclononane²⁰ the 9-membered ring has quite another conformation with approximate D_3 symmetry. As far as strain-energy-minimization calculations are concerned, a conformation with nearly exact D_3 symmetry is predicted to be the most stable^{15, 16}. The large-amplitude oscillatory motions of the ring atoms observed in both crystalline derivatives studied might mean that the potential energy surface has several rather broad minima of roughly equal energy. In this case the concept of a well-defined stable conformation would tend to become somewhat blurred.

In this connection it would be very useful if strain-minimization calculations could provide us with information about the form of the potential energy surface in the neighbourhood of the minimum, in addition to the parameters of the minimum-energy conformation. A complete description of the many-dimensional surface might well require excessive computer time in complex cases but some useful information can often be obtained quite economically. If,

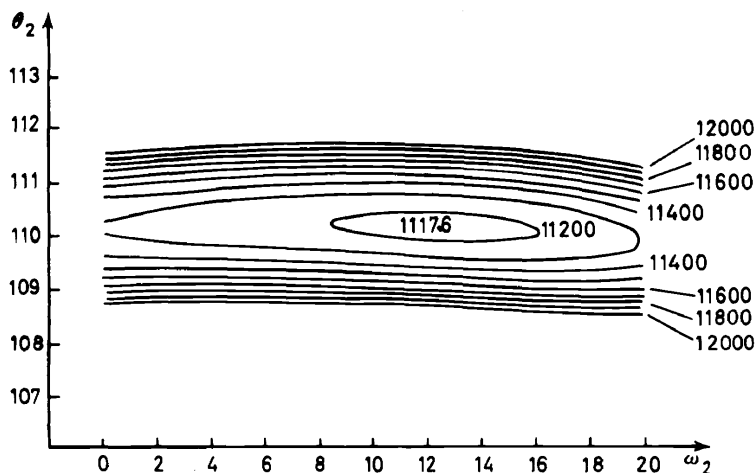


Figure 11. Potential energy surface calculated for bicyclo[2,2,2]octane assuming D_3 symmetry and constant, equal bond lengths. The independent parameters are ω_2 (torsion angle about the $-\text{CH}_2-\text{CH}_2-$ bond) and θ_2 (CCC bond angle at $-\text{CH}_2-$ group). Energies in cal mole^{-1} contour lines at intervals of $100 \text{ cal mole}^{-1}$.

as is often the case, the minimum energy conformation is found to be almost but not quite symmetrical, the energy profile in approaching the exactly symmetrical conformation must be fairly flat so that at least one low-energy torsional vibration is to be expected. We have recently made some calculations for the bicyclo[2.2.2]octane molecule²¹. On the assumption that the bond lengths remain effectively constant during a torsional vibration, the carbon skeleton can be described in terms of only 2 parameters for D_3 symmetry. The calculations were made for a range of semi-empirical potential functions, but the results are not very sensitive to the functions used. A typical result is shown in *Figure 11*. It shows the energy minimum displaced from D_{3h} symmetry with an 'equilibrium' torsion angle of about 12° . However, the energy barrier between the two symmetry-equivalent minima is only about $0.1 \text{ kcal mole}^{-1}$. Zero-point-energy is sufficient to confer effective D_{3h} symmetry on the system, but the energy profile is so flat that almost any perturbation of lower symmetry will lead to a twisted molecule of D_3 symmetry. Even a qualitative description of the potential energy surface can be very useful in estimating to what extent perturbations arising from substituents or from neighbouring molecules could affect the equilibrium parameters of the system being investigated.

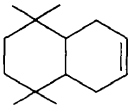
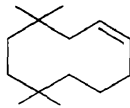
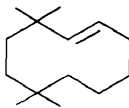
At first sight one might expect that the introduction of a $\text{C}=\text{C}$ double bond with its high rotation barrier of about $65 \text{ kcal mole}^{-1}$ into a ring would increase the torsional rigidity of the molecule by effectively removing one degree of torsional freedom. An additional factor to be considered is that the preferred torsion angle about a sp^2-sp^3 single bond is not 60° or 180° , but close to 120° , corresponding to eclipsing of the double bond with one of the $\text{C}-\text{H}$ bonds of the α -methylene group. These constraints are rather severe. Dale has pointed out²² that 'the introduction of one double bond into a macrocyclic ring immobilizes four successive carbon atoms, but the direction thereby imposed on each of the continuing chains is such that no absolutely strain-free conformation of the saturated chain can be found'. The fact that almost all known cycloalkanes have low melting points is interpreted as evidence of their conformational instability.

At Zürich we have tried to establish a basis for understanding the behaviour of the cyclodecenes. We chose the 10-membered ring because of the characteristic stereospecific transannular addition reactions to cyclodecenes, but also because of the interesting results obtained by Sicher and co-workers on the relative stabilities of the six possible 1,1,4,4-tetramethylcyclodecene isomers (*Table 1*)²³. Here were some clear-cut results that ought to be explainable in conformational terms, we thought. Besides, we hoped that the well-defined conformations of the cyclodecane ring might serve as a guide in deriving possible conformations for the unsaturated compounds.

Our initial results, obtained from crystal structure studies of olefin- AgNO_3 complexes, seemed quite encouraging. *Figure 12* shows the conformations observed in the complexes of *cis*-cyclodecene²⁴, *trans*-cyclodecene²⁵, and 1,1,4,4-tetramethyl-*cis*-cyclodecene⁷²⁶. The *cis*-olefin conformation is obviously very closely related to the stable cyclodecane conformation, in which incorporation of the *cis* double bond between atoms of type II and III requires a minimal change in torsion angles. Of the six 1,1,4,4-tetramethylcyclodecene isomers prepared by Sicher and co-workers the *cis*-6-ene is the only one that can adopt the same conformation as *cis*-cyclodecene with all methyl substituents

extra-annular and it is not surprising that this isomer is easily the most stable, occurring as more than 90 per cent in the equilibrium mixture. The least stable of the six isomers is the *cis*-7-ene; its conformation, shown in *Figure 12*, is

Table 1. Thermodynamical data for 1,1,4,4-tetramethylcyclodecenes²³

	% at equilibrium	ΔG^* kcal mole ⁻¹	Heat of hydrogenation $-\Delta H$, kcal mole ⁻¹
			
7-ene			
			
6-ene			
			
5-ene			

* With respect to the most stable olefin.

recognizable as a rather extreme distortion of the stable cyclodecane conformation in which a pair of type III atoms has been forced outwards to accommodate the *cis* double bond in a position that is normally transoid.

The conformation observed in the *trans*-cyclodecene- AgNO_3 complex is

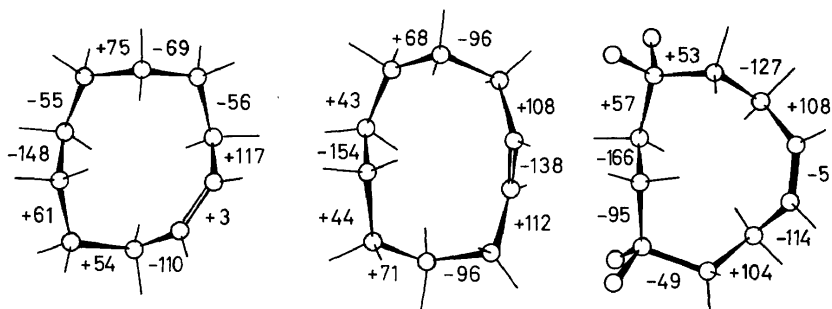


Figure 12. Observed conformations with torsion angles (in degrees) in AgNO_3 adducts of *cis*-cyclodecene, *trans*-cyclodecene and 1,1,4,4-tetramethyl-*trans*-cyclodecene-7.

also related to the stable cyclodecane conformation. The *trans* double bond occupies the transoid position between a pair of type III atoms and the $\text{C}=\text{C}-\text{C}-\text{C}$ chain is rotated about its own axis to produce torsion angles of about 120° around the bonds adjacent to the double bond. In contrast to the two *cis* double bonds, which are very nearly planar, the *trans* double bond in the AgNO_3 complex appears to be twisted by about 40° out of planarity!

This unexpected distortion is obviously of interest in connection with the

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derivation of potential energy functions for the out-of-plane deformations of the double bond. In order to investigate the possible effect of the Ag^+ coordination on the deformation of the *trans* double bond, the conformation of an uncomplexed *trans*-cyclodecene derivative had to be established. The search for a suitable crystalline derivative was rather long and the compound chosen for study, *trans*-cyclodecen-5-yl-p-nitrobenzoate, kindly provided by Professor Goering, has finally turned out to have a disordered structure, just in the part of the ring that is of special interest to us²⁴. At least two, and possible three, conformations must be present to account for the observed electron-density distribution. Parameter values, not very accurate, can be derived only for the major component, present to perhaps 70 to 80 per cent, which has a conformation quite unrelated to that of the complexed olefin or to the stable cyclodecane

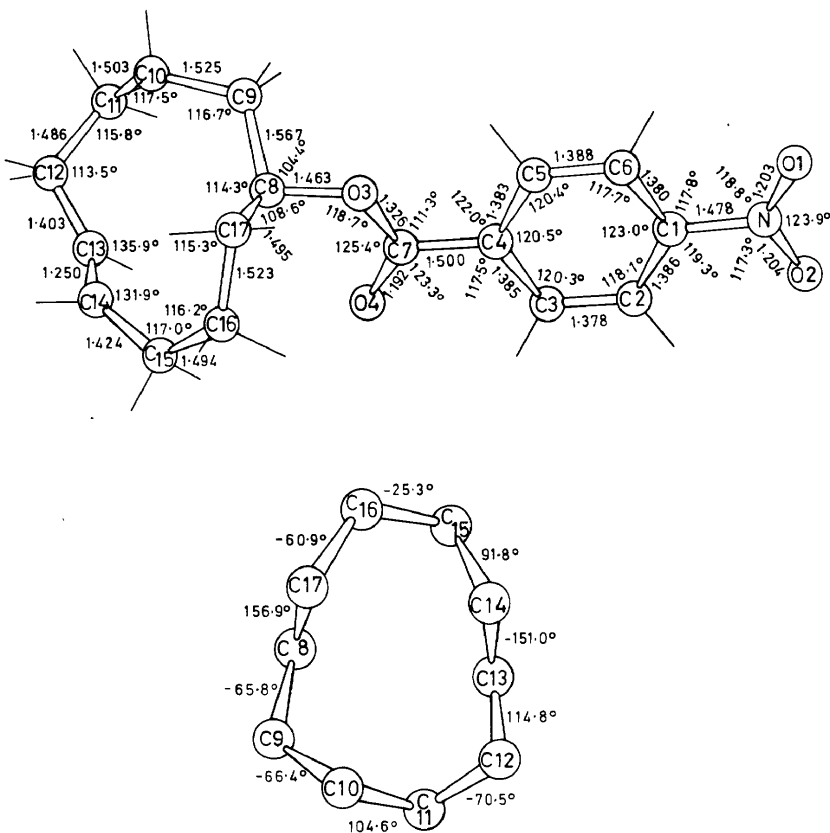


Figure 13. Experimental molecular parameters for major conformer in crystalline *trans*-cyclodecen-5-yl-p-nitrobenzoate.

conformation (Figure 13). Thus our idea that the conformations of the olefins could be derived from the stable cyclodecane conformation has not turned out to be as useful as we had hoped. The conformation of the *trans*-olefin does bear some resemblance to the less stable conformation B of cyclodecane but there is

no obvious reason why it should be more stable than several equally plausible-looking alternatives. At any rate, the torsion angle about the *trans* double bond deviates by about 30° from 180° so that reasonable potential functions for double-bond twisting and bending must be available before strain-minimization calculations can be applied to the conformations of cyclo-olefins containing *trans* double bonds.

We can summarize our results as follows: *cis*-cyclodecene has a well-defined conformation, related to the stable cyclodecane conformation, with a planar double bond system. For *trans*-cyclodecene the x-ray evidence points to a number of rather ill-defined conformations of roughly equal energy, all destabilized by the presence of twisted double-bond systems. This seems quite in line with the enthalpy and entropy changes ($\Delta H = -3.6$ kcal mole⁻¹, $\Delta S = -4.7$ e.u.) reported for the isomerization of *trans*- to *cis*-cyclodecene²⁷, and with the small free energy differences between the three 1,1,4,4-tetramethyl-*trans*-cyclodecene isomers which are unlikely to have the same ring conformation.

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