

# Dynamics of Eight-Membered Rings in the Cyclooctane Class

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## I. Introduction

This review deals with conformational interconversions in eight-membered cyclic compounds in the "cyclooctane class". It is convenient to classify ring systems according to the degree of endocyclic unsaturation that is present. In this context, *endocyclic* unsaturation can be a full double bond as in cyclooctene, a partial double bond as in enantholactam, a fused three-membered ring, as in cyclooctene epoxide or a triple bond as in cyclooctyne. *Exocyclic* unsaturated compounds are placed in the same class as the corresponding saturated compounds, except in cases where the double bond is appreciably delocalized into an endocyclic position (*e.g.* lactones and lactams). Thus cyclooctane and cyclooctanone are grouped together, in what is called, for convenience, the cyclooctane class, which also includes heterocyclic compounds such as oxacyclooctane (oxocane). The desirability of this classification in a conformational discussion arises from the strong geometric constraint of endocyclic double bonds, which force certain ring torsional angles to be close to  $0^\circ$ . In the compounds grouped together in the cyclooctane class, the preferred *ring* torsional angle is close to  $60^\circ$  and the torsional barriers are only a few kcal/mole. There are, of course, borderline compounds, which fortunately are not common (*e.g.* *cis* fused four- and eight-membered rings). Bicyclic compounds such as [3.3.0]bicyclooctane or [3.3.1]bicyclononane, although containing saturated eight-membered rings, are so geometrically constrained that they will also be excluded from the present review.

In order to discuss conformational interconversions, a knowledge of ground conformational states is required, and this topic will form part of the review. The dynamics of eight-membered rings have been studied almost entirely by nmr methods, the sole exception being some mechanical relaxation measurements which will be discussed at the end of Section VII.A. Only a brief qualitative introduction of the dynamic nmr method will be given. Conformational interconversions are often discussed in terms of ring inversion and pseudorotation, and definitions of these terms, as used in this chapter, are presented and discussed in Section III. No special distinction is made in this review between the terms conformation, conformer, or form.

## II. Principles of Dynamic NMR

For details on the use of dynamic nmr to obtain kinetic parameters, the reader is referred to standard texts <sup>1)</sup> and other reviews.<sup>2-5)</sup> For the present purpose, it is useful to remember that the nmr spectrum of conformations which interconvert rapidly on the so-called nmr time scale will show averaged chemical shifts and coupling constants. When the interconversion

is slow, each conformation will give rise to its own characteristic spectrum. In the intermediate region, the spectrum is broadened, and suitable analysis <sup>4)</sup> can give rate constants (or life times) and free energies of activation ( $\Delta G^\ddagger$ ) for the interconversion.

Measurements of rate constants at more than one temperature enable calculations to be made of the Arrhenius activation energy, and of the enthalpy  $\Delta H^\ddagger$  and entropy  $\Delta S^\ddagger$  of activation. In most cases, the accuracy of the nmr data is not sufficient for meaningful values of these three parameters to be obtained <sup>5)</sup>, and in most of the experimental work to be presented in this chapter, only  $\Delta G^\ddagger$  will be given. However, strain energy calculations, with few exceptions, refer to  $\Delta H$  at absolute zero, and not to  $\Delta G$ . Since  $\Delta G = \Delta H - T\Delta S$ , and entropy effects appear to be only a minor perturbation in most cases, a comparison of  $\Delta G^\ddagger$  with  $(\Delta H^\ddagger)_{0^\circ\text{K}}$  can be justified, at least as a first approximation.

The nmr time scale, referred to earlier, corresponds to the inverse of the *difference* in resonance frequencies of interconverting systems. For protons, frequency differences are generally in the range of 1 to 100 Hz, while the differences for <sup>19</sup>F can be an order of magnitude larger. For  $\Delta G^\ddagger = 5$  kcal/mole, the interconversion rate constant will have a value appropriate for the intermediate spectral region at temperatures in the range of roughly  $-180^\circ$  to  $-150^\circ\text{C}$ , depending on the precise system being studied. Since high-resolution nmr spectra become very difficult to observe below these temperatures because of slow molecular tumbling, dynamic nmr studies cannot give information on free energy barriers much below 5 kcal/mole, even in the most favorable situation.

Only averaged spectra will be observed above about  $-130^\circ\text{C}$  when the energy barrier is 5 kcal/mole or less. For barriers of 10 kcal/mole, coalescence temperatures are typically in the range of  $-40^\circ$  to  $-80^\circ\text{C}$ , while a barrier of 15 kcal/mole will give rise to a broadened spectrum near room temperature.

### III. Definitions of Ring Inversion and Ring Pseudorotation

The term *ring inversion* has been widely employed in six-membered rings to describe the change from one chair to the alternate chair, a process which results in an exchange of axial and equatorial substituents.<sup>6)</sup> It has also been used extensively for analogous processes in other ring systems. Lambert <sup>7)</sup> has recently suggested that the word "inversion" be restricted to the atom (*e.g.* nitrogen) case and that the word *reversal* be used for rings. However, these words have such general meanings that they are nearly always qualified (*e.g.* ring reversal), and thus there seems to be little disadvantage to the use of the terms atom inversion and ring inversion even where both processes take place in the same molecule.

We offer two definitions of ring inversion, one strict, and one extended. For a process to be ring inversion, in the strict definition, all of the ring dihedral angles must change their *signs*, but not their absolute magnitudes. The definition given above is unambiguous, but it does not apply strictly to many situations, *e.g.* the axial methylcyclohexane — equatorial methylcyclohexane interconversion. To cover such systems we use an extended definition of ring inversion: ring inversion causes all the signs of the ring dihedral angles to change (except that dihedral angles which are close to  $0^\circ$  or  $180^\circ$  may or may not change signs) and the absolute magnitudes of these angles are either unaffected or only slightly changed. A further extension is possible and is useful in discussing nmr results: the dihedral angles can be averaged over one or more rapidly interconverting conformations.

The term *pseudorotation* was first applied to cyclopentane<sup>8)</sup>; like inversion, it has an atomic analogue in 5-coordinate compounds (*e.g.*  $\text{PF}_5$ ).<sup>9)</sup> The name means "false rotation", and it is therefore appropriate for any conformational process which results in a conformation superposable on the original, and which differs from the original in being *apparently* rotated about one or more axes. Pseudorotation, in analogy with real molecular and internal rotations, can be free, as in cyclopentane, or more or less hindered, as in cycloheptane and higher cycloalkanes. In moderately to severely hindered pseudorotation, it is appropriate to consider distinct stable conformations which are pseudorotation partners, and these cases are often amenable to study by dynamic nmr methods. When the barrier to pseudorotation is very low, or in the limit when pseudorotation is free, it is not really justified to talk about separate stable conformations (*e.g.* the  $\text{C}_2$  and  $\text{C}_8$  forms of cyclopentane), because strictly there is only one conformation, and the pseudorotation is simply a molecular vibration.

*Ring inversion* (when strictly defined) of achiral conformations is nothing more than a pseudorotation. Ring inversion in the cyclohexane chair, for example, leaves the molecule *apparently* rotated by  $60^\circ$  along the  $\text{C}_3$  axis. Nevertheless, in order to conform with common usage, we will exclude ring inversion from the definition of ring pseudorotation.

The above discussion deals with a strict definition of pseudorotation. As with ring inversion, it is desirable to have an extended definition of pseudorotation. Before we can do this, we need to introduce a suitable abstraction, which we will call the *ring skeleton* of a conformation. The ring skeleton is simply the geometrical figure corresponding to the conformation, with ring bonds considered as straight lines, and ring nuclei considered as the vertices of the figure. In the extended definition, pseudorotation (either free or hindered) is a process which results in the *apparent* rotation of the ring skeleton of the conformation (with minor changes in the ring skeleton being ignored) or (to extend the definition slightly to cover chiral conformations) which

converts the ring skeleton to its mirror image (again with minor changes in the ring skeleton being ignored). As before, it is useful to exclude from this definition those processes which can be called ring inversions (in the extended definition).

The extended definitions for ring inversion and (ring) pseudorotation will be used in the present chapter, unless stated to the contrary. These definitions are independent of mechanism, unlike Hendrickson's usage of these terms.<sup>10-13)</sup>

#### IV. Structural Data

Cyclooctane itself has been studied by numerous physical methods, but the usual methods of structural determinations have proven singularly unrewarding. The molecule contains too many atoms for a reliable structural analysis by infrared and Raman spectroscopy<sup>14)</sup>; all that can be safely said is that the molecule is not centrosymmetric. An X-ray diffraction study of crystalline cyclooctane (mp 14.4 °C) at 0 °C gave limited information because the crystals are disordered.<sup>15)</sup> Electron diffraction measurements on cyclooctane vapor at 40 °C could not be reconciled with any single rigid conformation, but seemed to indicate a mixture of forms (or at least a very flexible conformation) which could not be defined further.<sup>16)</sup> Nuclear magnetic resonance (nmr) studies at -130 °C exclude any conformation with a C<sub>2</sub> axis passing through carbon atoms, or a C<sub>s</sub> plane passing only through bonds.<sup>17)</sup> Interestingly, cyclooctane has been reported to have a small, but definite dipole moment in the gas phase.<sup>18)</sup>

Table 1. X-ray structures of some eight-membered rings

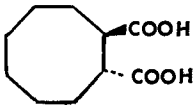
Compound	Structure	Conformation and positions of substituents <sup>1)</sup>	Dihedral angles for cyclooctane derivatives (in °) <sup>2)</sup>	Ref.
<i>trans</i> -1,2-Cyclooctane carboxylic acid		Boat-chair (BC-4 <i>e</i> ,5 <i>e</i> )	$\omega_1 = 62$ $\omega_2 = 47$ $\omega_3 = -106$ $\omega_4 = 71$ $\omega_5 = -70$ $\omega_6 = 101$ $\omega_7 = -43$ $\omega_8 = -63$	19)

Table 1 (continued)

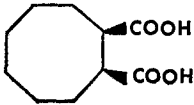
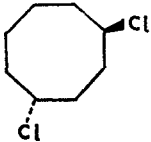
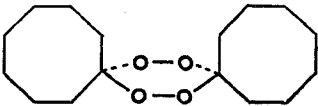
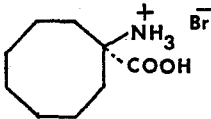
Compound	Structure	Conformation and positions of substituents <sup>1)</sup>	Dihedral angles Ref. for cyclooctane derivatives (in °) <sup>2)</sup>
<i>cis</i> -1,2-Cyclooctane carboxylic acid		Boat-chair (BC-2 <i>e'</i> ,3 <i>e</i> )	$\omega_1 = 60$ $\omega_2 = 48$ $\omega_3 = -105$ 20) $\omega_4 = 67$ $\omega_5 = -66$ $\omega_6 = 96$ $\omega_7 = -38$ $\omega_8 = -69$
<i>trans</i> -1,4-Dichloro cyclooctane		Boat-chair (BC-2 <i>e'</i> ,5 <i>a</i> )	$\omega_1 = 62$ $\omega_2 = 48$ $\omega_3 = -101$ 21) $\omega_4 = 60$ $\omega_5 = -63$ $\omega_6 = 100$ $\omega_7 = -41$ $\omega_8 = -68$
3,6-Spirooctylidene-1,2,4,5-tetraoxacyclohexane		Boat-chair (BC-2 <i>e'</i> ,2 <i>a'</i> )	$\omega_1 = 70$ 22) $\omega_2 = 37$ $\omega_3 = -98$ $\omega_4 = 66$ $\omega_5 = -64$ $\omega_6 = 101$ $\omega_7 = -49$ $\omega_8 = -61$
1-Aminocyclooctane carboxylic acid hydrobromide		Boat-chair (BC-2 <i>e'</i> ,2 <i>a'</i> )	$\omega_1 = 67$ 23) $\omega_2 = 41$ $\omega_3 = -98$ $\omega_4 = 67$ $\omega_5 = -65$ $\omega_6 = 98$ $\omega_7 = -46$ $\omega_8 = -63$

Table 1 (continued)

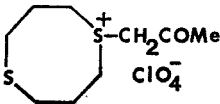
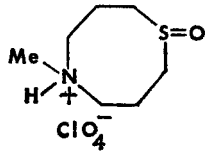
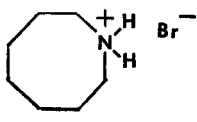
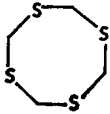
Compound	Structure	Conformation and positions of substituents <sup>1)</sup>	Dihedral angles for cyclooctane derivatives (in °) <sup>2)</sup>	Ref.
1-Acetyl-1-thionia-5-thia-cyclooctane perchlorate		Boat-chair (BC-3,7)		24)
5-Methyl-1-thia-5-azacyclooctane-1-oxide perchlorate		Boat-chair (BC-3,7)		25)
Azacyclooctane hydrobromide		(Boat-chair) <sup>3)</sup> (or crown)	—	26)
Tetrathiacane		Boat-chair (BC-2,4,6,8)		27)

Table 1 (continued)

Compound	Structure	Conformation and positions of substituents <sup>1)</sup>	Dihedral angles for cyclooctane derivatives (in °) <sup>2)</sup>	Ref.
<i>trans-syn-trans</i> -1,2,5,6-Tetrabromocyclooctane		Twist-chair-chair (TCC-1 <i>e</i> ,2 <i>e</i> ,5 <i>a</i> ,6 <i>a</i> )	$\omega_1 = 60$ $\omega_2 = -79$ $\omega_3 = 107$ $\omega_4 = -72$ $\omega_5 = 42$ $\omega_6 = -77$ $\omega_7 = 116$ $\omega_8 = -81$	28)
Metaldehyde or all- <i>cis</i> -tetramer of acetaldehyde		Crown 1 <i>e</i> ,3 <i>e</i> ,5 <i>e</i> ,7 <i>e</i>		29)
N-N'-Dimethyl-3,7-dithia-1,5-diazacyclooctane		Crown		30)
1,3,5,7-Tetranitro-1,3,5,7-tetraazacyclooctane		Crown		31)



Table 1 (continued)

Compound	Structure	Conformation and positions of substituents <sup>1)</sup>	Dihedral angles for cyclooctane derivatives (in °) <sup>2)</sup>	Ref.
3,7-Dimethyl-1,5-dioxo-3,7-diazacyclooctane-2,4,6,8-tetra-spirocyclopropane		Crown		32)
1,3,5,7-Tetrathia-2,4,6,8-tetraazacyclooctane		Crown		33)
Octasulfur		Crown		34)

<sup>1)</sup> Positions refer to the numbering of the carbon skeletons as shown in Fig. 1 and Fig. 2 (see also Table 3).

<sup>2)</sup> The dihedral angles  $\omega_1$  and  $\omega_2$ , etc. refer to positions 8, 1,2,3; 1,2,3,4; etc. (*i.e.* they are the ring torsional angles about the 1,2 bond, the 2,3-bond, etc.).

<sup>3)</sup> The X-ray data, found to fit a crown structure in early work, were later found to fit the boat-chair equally well.

In contrast to the parent compound, several cyclooctane derivatives and related compounds have had their structures determined by X-ray diffraction (Table 1). Most of these compounds have boat-chair conformations, but *trans-syn-trans*-1,2,5,6-tetrabromocyclooctane is a twist chair-chair, and crown conformations are found in octasulfur, the *all-cis* tetramer of acetaldehyde, and related compounds.

## V. Strain Energy Calculations of Static Conformations

Semi-empirical strain energy calculations for cyclooctane have been carried out by four groups <sup>10-13,35-37</sup> (Table 2). The perspective drawings <sup>38</sup> in Fig. 1 were drawn by the computer program Ortep <sup>39</sup> with the parameters calculated by Hendrickson.<sup>11</sup>) Table 2 gives dihedral angles, the sets of

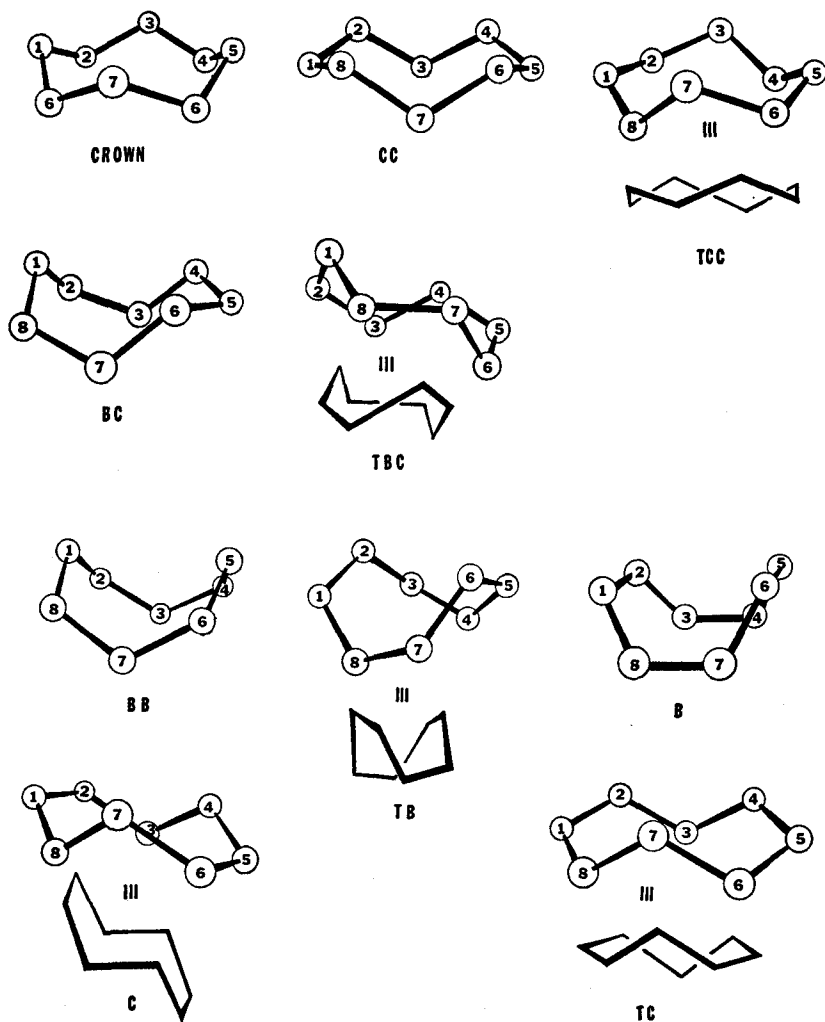


Fig. 1. Symmetrical conformations of cyclooctane <sup>38</sup>), according to the calculations of Hendrickson.<sup>11</sup>) Alternate views of some conformations are given

*isochronous carbons*<sup>a)</sup>, the symmetry groups, and the strain energies as calculated by the various workers. It should be noted that all the conformations in Table 2 have at least one symmetry element and that Wiberg<sup>35)</sup> and Hendrickson<sup>11)</sup> have presented data and arguments indicating that energy minima will occur in symmetrical conformations. The names given for the conformations are those proposed by Roberts in a recent paper.<sup>40)</sup> Hendrickson's  $S_4$  form is identical with the twist-boat of Roberts and this is the only difference between the nomenclature of the two investigators.<sup>b)</sup>

A particular conformational name will be applied also to related conformations. For example, the boat-chair name will be applied to conformations of  $C_8$  symmetry (or to forms with ring skeletons having only slightly distorted  $C_8$  geometry), provided that the dihedral angles have the same *sign sequence* (and in general the same magnitude) around the ring as shown for the BC form in Table 2.

Three factors contribute to the strain energies in the conformations of cyclooctane: (a) eclipsing strains; (b) internal angle strain; and (c) non-bonded repulsions (and attractions). No conformation of cyclooctane is strain-free. The "ideal" or diamond-lattice form is the boat-boat, but this suffers from large non-bonded repulsions, which would be even larger were these repulsions not partly relieved by an increase in the internal angle to  $118^\circ$  or  $119^\circ$ . The crown form on the other hand has mainly eclipsing strain, which can be partly relieved by introducing distortions which lead to the chair-chair and the twist-chair-chair forms. The boat-chair and twist-boat-chair both have intermediate amounts of torsional and non-bonded strains. The chair, twist-chair, and boat forms are all highly strained and are mainly of interest as potential transition states for the interconversion of other conformations.

The internal angles in all the conformations given in Table 2 are considerably greater than the  $111.5^\circ$  found in cyclohexane. In the crown, chair-chair, twist-chair-chair, boat-chair, and twist-boat-chair, the angles are in the range of  $115^\circ$  to  $117^\circ$ . The experimentally determined internal and dihedral angles for several boat-chair cyclooctane derivatives (Table 1) are very similar to those calculated by Hendrickson and by Bixon and Lifson.

<sup>a)</sup> Isochronous nuclei have the same nmr chemical shift by symmetry.

<sup>b)</sup> According to Hendrickson's nomenclature the twist-boat  $\equiv$  boat-boat, and the twist-boat-boat  $\equiv$  boat. Although this usage is perfectly logical, it leaves the important  $S_4$  form, which is intermediate between the boat-boat and the boat without a convenient name, and for this reason we prefer Roberts' nomenclature. Dunitz<sup>26)</sup> has deplored the use of names such as "boat-chair" and has emphasized the importance of dihedral angles in defining conformations. Our view is that names are highly convenient in written and verbal discussions, and that the *naming* and the *definition* of a conformation are different things.

Table 2. Symmetrical conformations of cyclooctane

Conformation	Symmetry group	Dihedral angles <sup>1)</sup> in °	Sets of isochronous carbons	Calculated relative strain energies in kcal/mole			
				H <sup>2)</sup>	BL <sup>3)</sup>	W <sup>4)</sup>	A <sup>5)</sup>
Crown	D <sub>4d</sub>	$\omega_1 = \omega_3 = \omega_5 = \omega_7$ = 87.5 $\omega_2 = \omega_4 = \omega_6 = \omega_8$ = -87.5	One set	2.8	3.62	0.26	2.09
Chair-chair (CC)	C <sub>2v</sub>	$\omega_1 = \omega_5 = -66.0$ $\omega_2 = \omega_6 = 105.2$ $\omega_3 = \omega_7 = -105.2$ $\omega_4 = \omega_8 = 66.0$	I: C <sub>1</sub> , C <sub>5</sub> II: C <sub>2</sub> , C <sub>4</sub> , C <sub>6</sub> , C <sub>8</sub> III: C <sub>3</sub> , C <sub>7</sub>	1.9	—	—	2.25
Twist-chair chair (TCC)	D <sub>2</sub>	$\omega_1 = \omega_5 = 56.2$ $\omega_2 = \omega_4 = \omega_6 = \omega_8$ = -82.4 $\omega_3 = \omega_7 = 114.6$	I: C <sub>1</sub> , C <sub>4</sub> , C <sub>5</sub> , C <sub>8</sub> II: C <sub>2</sub> , C <sub>3</sub> , C <sub>6</sub> , C <sub>7</sub>	1.7	1.89	-0.25	2.20
Boat-chair (BC)	C <sub>s</sub>	$\omega_1 = \omega_4 = 65.0$ $\omega_2 = 44.7$ $\omega_3 = -102.2$ $\omega_5 = \omega_8 = -65.0$ $\omega_6 = 102.2$ $\omega_7 = -44.7$	I: C <sub>1</sub> II: C <sub>5</sub> III: C <sub>2</sub> , C <sub>8</sub> IV: C <sub>3</sub> , C <sub>7</sub> V: C <sub>4</sub> , C <sub>6</sub>	0	0	0	0
Twist-boat chair (TBC)	C <sub>2</sub>	$\omega_1 = \omega_5 = 51.9$ $\omega_2 = \omega_4 = 44.8$ $\omega_3 = -115.6$ $\omega_6 = \omega_8 = -93.2$ $\omega_7 = 88.0$	I: C <sub>1</sub> , C <sub>6</sub> II: C <sub>2</sub> , C <sub>5</sub> III: C <sub>3</sub> , C <sub>4</sub> IV: C <sub>7</sub> , C <sub>8</sub>	2.0	—	—	—
Boat-boat (BB)	D <sub>2d</sub>	$\omega_1 = \omega_2 = \omega_5$ = $\omega_6 = 52.5$ $\omega_3 = \omega_4 = \omega_7 = \omega_8$ = -52.5	I: C <sub>1</sub> , C <sub>3</sub> , C <sub>5</sub> , C <sub>7</sub> II: C <sub>2</sub> , C <sub>4</sub> , C <sub>6</sub> , C <sub>8</sub>	1.4	—	4.44	—
Twist-boat (TB)	S <sub>4</sub>	$\omega_1 = \omega_5 = -37.6$ $\omega_2 = \omega_6 = 64.9$ $\omega_3 = \omega_7 = 37.6$ $\omega_4 = \omega_8 = -64.9$	I: C <sub>1</sub> , C <sub>3</sub> , C <sub>5</sub> , C <sub>7</sub> II: C <sub>2</sub> , C <sub>4</sub> , C <sub>6</sub> , C <sub>8</sub>	0.9	—	—	—

Table 2 (continued)

Conformation	Symmetry group	Dihedral angles <sup>1)</sup> in °	Sets of isochronous carbons	Calculated relative strain energies in kcal/mole			
				H <sup>2)</sup>	BL <sup>3)</sup>	W <sup>4)</sup>	A <sup>5)</sup>
Boat (B)	D <sub>2d</sub>	$\omega_1 = \omega_3 = \omega_5 = \omega_7$ = 0.0 $\omega_2 = \omega_6 =$ 73.5 $\omega_4 = \omega_8 =$ - 73.5	One set	10.3	—	8.96	—
Chair (C)	C <sub>2h</sub>	$\omega_1 = \omega_3 =$ - 76.2 $\omega_2 =$ 119.9 $\omega_4 = \omega_8 =$ 0.0 $\omega_5 = \omega_7 =$ 76.2 $\omega_6 =$ - 119.9	I: C <sub>1</sub> , C <sub>2</sub> , C <sub>5</sub> , C <sub>6</sub> II: C <sub>3</sub> , C <sub>4</sub> , C <sub>7</sub> , C <sub>8</sub>	8.3	—	6.09	—
Twist-chair (TC)	C <sub>2h</sub>	$\omega_1 = \omega_8 =$ 37.3 $\omega_2 = \omega_7 =$ - 109.3 $\omega_3 = \omega_6 =$ 109.3 $\omega_4 = \omega_5 =$ - 37.3	I: C <sub>1</sub> , C <sub>5</sub> II: C <sub>2</sub> , C <sub>4</sub> , C <sub>6</sub> , C <sub>8</sub> III: C <sub>3</sub> , C <sub>7</sub>	8.7	—	—	—

1) See Fig. 1 for conformational drawings.

2) From Ref. 11).

3) From Ref. 35).

4) From Ref. 36).

5) From Ref. 37).

Table 3 gives Hendrickson's labelling scheme for the external bonds and substituents and also gives the excess strain energy caused by a methyl group at various positions in the cyclooctane conformation. Carbon atoms which are flanked by identical dihedral angles lie on C<sub>2</sub> axes and have identical *isoclinal* external bonds. If these dihedral angles are not identical, but still have the same sign and similar magnitudes, the two external bonds become slightly different and are labelled quasi-axial (*a'*) and quasi-equatorial (*e'*). All other carbons have quite different external bonds, which are labelled axial (*a*) and equatorial (*e*). The terms axial and equatorial as used here do not necessarily imply the same features as are found in the cyclohexane chair form. Nevertheless, a single axial methyl group always results in a substantial excess strain energy (> 1.0 kcal/mole), while a single equatorial methyl group gives rise to a low strain energy (0.3 to 0.8 kcal/mole). Isoclinal, *a'* and *e'* methyl groups also have low strain energies.

The labelling of hydrogens in the important boat-chair form of cyclooctane is shown in Fig. 2. Ignoring for the moment the distinction between

Table 3. Excess strain energy for methylcyclooctane

Conformation	Position of methyl group and stereochemical relationship <sup>1)</sup>	Excess strain energy in kcal/mole <sup>2)</sup>
Crown	1 <i>e</i>	≈ 0.5 <sup>3)</sup>
	1 <i>a</i>	≥ 1.5 <sup>3)</sup>
Chair-chair (CC)	1 <i>a</i> (α)	1.5
	1 <i>e</i> (β)	0.4
	2 <i>e</i> (α)	0.4
	2 <i>a</i> (β)	3.1
	3 <i>a</i> (α)	10.2
	3 <i>e</i> (β)	0.4
Twist-chair-chair (TCC)	1 <i>e</i> (α)	0.4
	1 <i>a</i> (β)	1.5
	3 <i>a</i> (α)	5.5
	3 <i>e</i> (β)	0.5
Boat-chair (BC)	1 <i>a</i> (α)	8.0
	1 <i>e</i> (β)	0.5
	2 <i>e</i> ' (α)	0.5
	2 <i>a</i> ' (β)	0.5
	3 <i>e</i> (α)	0.5
	3 <i>a</i> (β)	7.6
	4 <i>e</i> (α)	0.5
	4 <i>a</i> (β)	5.1
	5 <i>a</i> (α)	1.4
	5 <i>e</i> (β)	0.6
Twist-boat-chair (TBC)	1 <i>e</i> (α)	0.3
	1 <i>a</i> (β)	7.2
	2 <i>e</i> ' (α)	0.4
	2 <i>a</i> ' (β)	0.5
	3 <i>a</i> (α)	5.8
	3 <i>e</i> (β)	0.5
	4 <i>e</i> (α)	0.6
4 <i>a</i> (β)	3.0	

Table 3 (continued)

Conformation	Position of methyl group and stereochemical relationship <sup>1)</sup>	Excess strain energy in kcal/mole <sup>2)</sup>
Boat-boat (BB)	1a	8.1
	1e	0.6
	2 isoclinal	0.6
Twist-boat (TB)	1a' ( $\alpha$ )	0.6
	1e' ( $\beta$ )	0.5
	2a ( $\alpha$ )	7.4
	2e ( $\beta$ )	0.5
Boat (B)	1a	5.1
	1e	0.8
Chair (C)	1a ( $\alpha$ )	1.4
	1e ( $\beta$ )	0.7
	2e ( $\alpha$ )	7.4
	2a ( $\beta$ )	0.4
Twist-chair (TC)	1 isoclinal	0.4
	2a ( $\alpha$ )	4.6
	2e ( $\beta$ )	0.4
	3e ( $\alpha$ )	0.3
	3a ( $\beta$ )	8.8

1)  $\alpha$  and  $\beta$  are used here only to indicate *relative* stereochemistry within a conformation: a pair of  $\alpha$ , or a pair of  $\beta$  hydrogens are always *configurationally cis*, while an  $\alpha$  and  $\beta$  hydrogen are always *configurationally trans*.

2) From Ref. 12).

3) Calculations for the crown were not reported by Hendrickson; the values given are rough estimates based on non-bonded distances in the crown.

*a* and *a'* or *e* and *e'*, we can see from this figure and from Table 3 that vicinal *trans* substituents are either diaxial or diequatorial (as in the cyclohexane chair), *except* when the substituents are on C-2 and C-3 (or the equivalent C-7 and C-8), in which case one substituent is axial and the other equatorial. This particular feature has very important consequences for pseudorotation in the boat-chair, and will be discussed further in the next section.

Allinger and coworkers have carried out strain-energy calculations on cyclooctanone.<sup>41-43</sup> Their latest results<sup>43</sup>, which are given in Table 4,

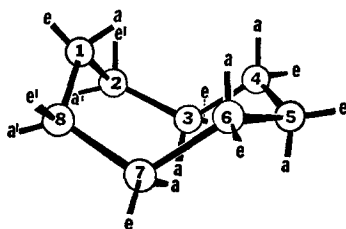


Fig. 2. Axial (*a*), equatorial (*e*), quasi-axial (*a'*) and quasi-equatorial (*e'*) positions in the boat-chair

show that the boat-chair with the carbonyl group at position 3 (*i.e.* BC-3) is the lowest energy conformation.

Strain energy calculations for other conformations in the cyclooctane class are unfortunately not available. In particular, there are no calculations for heterocyclic eight-membered rings. Finally, there is a need for more accurate and reliable calculations, which can give not only the equilibrium geometry and the strain energy, but also the vibrational frequencies. Only a very limited amount of work has been done along these lines.<sup>44,45)</sup>

Table 4. Relative strain energies in cyclooctanone Conformations

Conformation	Strain energy (kcal/mole <sup>1</sup> )
BC-1	2.9
BC-2	1.7
BC-3	0.0
BC-4	2.2
BC-5	3.9
TCC-2	1.5

1) Relative to BC-3.

## VI. Theoretical Interconversion Pathways

Hendrickson has investigated symmetrical interconversion pathways between cyclooctane conformations.<sup>13)</sup> In some cases at least, these paths are probably not as low-energy as unsymmetrical paths, which unfortunately are more difficult to calculate. In the crown family, which includes the chair-chair and twist-chair-chair forms, the situation is quite clear. The twist-chair-chair is of lowest energy and conversion to the chair-chair form involves only the energy difference between the two forms. Thus the chair-chair is a transition state for the degenerate interconversion of twist-chair-



chair forms, and the activation energy is calculated to be only 0.2 kcal/mole. The crown itself is an energy maximum on the energy surface for distortion to the chair-chair and twist-chair-chair forms, and lies only 1.1 kcal/mole above the latter conformation. Therefore, all the conformations of the crown family will interconvert extremely rapidly, certainly far too rapidly for the interconversions to be studied by nmr line shape methods, even at  $-200^{\circ}\text{C}$ . For cyclooctane itself, this means that for nmr purposes the effective (*i.e.* time-average) symmetry is that of the crown, which contains only one kind of carbon, and only two kinds of hydrogens. Furthermore, vicinal *trans* hydrogens are either diaxial or diequatorial, just as in the cyclohexane chair. Thus, interconversion of the twist-chair-chair through the chair-chair (and/or crown) results only in partial averaging, because all the hydrogens are not isochronous, but form two distinct sets, one set including all the axial protons and the other set all the equatorial protons.

For all the protons in the twist-chair-chair to be isochronous requires interconversion with forms not in the crown family. Any rapid interconversion of the twist-chair-chair with either the boat or chair or boat-boat or twist-chair automatically assures that all the protons become isochronous. Interconversion of the twist-chair-chair with the boat-chair (and/or twist-boat-chair) alone does not necessarily lead to a single set of protons.

Interconversions in *the boat family*, which includes the boat, twist-boat, and boat-boat forms, have been extensively discussed by Hendrickson<sup>13)</sup> and by Roberts and coworkers.<sup>40)</sup> The twist-boat is calculated to be of lowest energy in this family<sup>13)</sup>, and it also has the lowest symmetry, having four different sets of isochronous protons. Interconversion with the boat-boat, which has only three different sets of isochronous protons, reduces the four sets to three, and the time-average symmetry becomes the same as that of the boat-boat form. The boat-boat form has 8 isoclinal protons on alternate carbons, and 4 axial and 4 equatorial protons situated in pairs, also on alternate carbons. This form is calculated to be the transition state for the interconversion of two twist-boats, and the activation energy is therefore only 0.5 kcal/mole (Table 2). Thus, for cyclooctane itself, twist-boat forms will interconvert extremely rapidly with one another, such that for nmr purposes the symmetry will appear the same as that of the boat-boat form, even at  $-200^{\circ}\text{C}$ .

The twist-boat can also interconvert with the boat form itself. The effect is to make all the protons isochronous if the twist-boat is also in rapid equilibrium with the boat-boat form, as is extremely likely from the previous discussion. The boat is probably the transition state in this pathway (TB  $\rightarrow$  B  $\rightarrow$  TB) and thus the activation energy calculated is 9.4 kcal/mole. This pathway has a sufficient barrier for study by nmr line shape methods if cyclooctane actually exists in these forms. At high temperatures (*e.g.* room temperature) all the protons should be isochronous and should give

rise to a single line. At sufficiently low temperatures (*e.g.*  $< -130^{\circ}\text{C}$ ), the spectrum is expected to be very complex because of coupling between three different kinds of protons. If a deuterated cyclooctane with just two geminal protons is examined by proton nmr, with the deuterons decoupled, a particularly clear spectrum should be observed. In one half of the molecules (neglecting any small isotope effect) the protons will be isoclinal and will therefore give rise to an  $A_2$  spectrum, *i.e.* a single line of total intensity 2; in the remaining molecules the protons will be on carbons which bear axial and equatorial bonds, and will therefore give rise to an AB spectrum, *i.e.* four lines of total intensity 2. If the AB spectrum is accidentally degenerate, it will appear as a single line of intensity 2. It is impossible, however, for the spectrum to appear as a *single AB quartet* (experimental data on this point will be discussed later, but it may be mentioned here that a single AB quartet is in fact observed for the compound under discussion). If cyclooctane were to exist in a crown family form, this deuterated cyclooctane would be expected to give a single AB quartet at low temperatures. Thus, the observation of a single AB quartet in this case rigorously eliminates the boat-boat (and with very high probability the twist-boat also). The results, although compatible with a crown family form, do not require such a form. As we shall see later, a boat-chair conformation also fits the experimental data of a single AB quartet.

Interconversions which involve the *boat-chair* and *twist-boat-chair* (Table 5) are important because most simple cyclooctane derivatives have boat-chair conformations. Table 5 shows the effect of a rapid equilibrium between the boat-chair and other conformations, either singly or in various combinations. Some of these interconversions are unlikely to be important, but are given for completeness. For example, the interconversion of the boat-chair with the chair-chair form *alone* is improbable, since the activation energy for this process is undoubtedly very much larger than the barrier for the chair-chair to twist-chair-chair interconversion, which has already been discussed. A rocking motion of the boat-chair C-1 methylene group can lead to the chair-chair, a plane of symmetry being maintained during the change. Such a symmetrical path is calculated<sup>13)</sup> to have a very high energy (*ca.* 20 kcal/mole) but lower energy paths exist to the crown family. The path BC  $\rightarrow$  TBC  $\rightarrow$  TCC has a calculated activation energy of 11.4 kcal/mole, with the "transition state" being between the twist-boat-chair and the twist-chair-chair.<sup>13)</sup> This "transition state" has the same symmetry as the regular twist-chair-chair, but with  $\omega_{12} = \omega_{56} = 0^{\circ}$ , and can also lead to the boat conformation *via* Roberts' <sup>40)</sup> "parallel boat", a conformation not shown in Table 2.

One of the most important interconversion paths shown in Table 5 is the pseudorotation of the boat-chair *via* the twist-boat-chair as an intermediate. This pseudorotation was first recognized by Anet and St. Jacques<sup>17,46)</sup>,

and leads to the same averaging as the boat-chair to twist-chair-chair interconversion. Unfortunately, strain energy calculations are not available for the boat-chair pseudorotation, but qualitative considerations<sup>13,17,46)</sup> indicate that the barrier to pseudorotation should be quite low, perhaps a few kcal/mole.

Dreiding-Fieser models can be used to demonstrate the interconversion of the boat-chair to the twist-boat-chair, but some practice is required to hold the model correctly. The motions involved in the pseudorotation are shown in Fig. 3, which shows one half of a full pseudorotation, namely the conversion of the boat-chair to the twist-boat-chair. The second half of the pseudorotation is exactly the reverse of the first half, except that it is carried out after rotation of the twist-boat-chair by  $180^\circ$  about its  $C_2$  axis.

The twist-boat-chair is chiral and hence there are actually two mirror-image or enantiomeric conformations. Correspondingly, there are two mirror-image pseudorotation paths to the twist-boat-chairs from the boat-chair, which is achiral. These paths are conveniently labelled by the mirror-image letters *b* and *d*. If we arbitrarily assign the letter *b* to the process shown in Fig. 3, and if we use the proton in the 1-equatorial position as a label, we can write down the effect of pseudorotation as shown in Table 6.

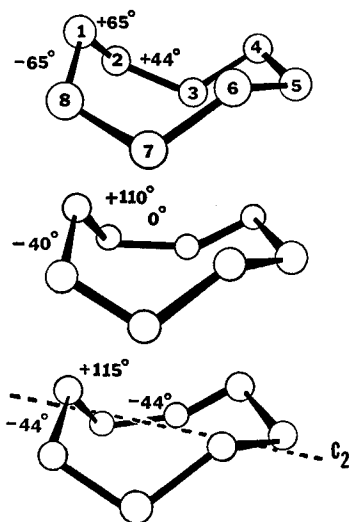


Fig. 3. Interconversion of the boat-chair (top) to the twist-boat-chair conformation (bottom)

Table 5. Nmr effects in the boat-chair

Conformations in rapid equilibrium with the boat-chair (BC)	Sets of isochronous nuclei		Time-average symmetry
	$^{13}\text{C}$	$^1\text{H}$	
Twist-boat-chair (TBC) } <sup>1)</sup> and/or crown and/or twist-chair-chair (TCC)		A: 1e, 2e', 3a, 4a, 5a, 6a, 7a, 8e'	$D_{4d}$
	One set	B: 1a, 2a', 3e, 4e, 5e, 6e, 7e, 8a'	
Chair-chair (CC)	I: 1,5	A: 1e, 5a B: 1a, 5e	$C_{2v}$
	II: 2,4,6,8	C: 2e', 4a, 6a, 8e' D: 2a', 4e, 6e, 8a'	
	III: 3,7	E: 3e, 7e F: 3a, 7a	
Twist-chair (TC)	I: 1,5	A: 1e, 5e B: 1a, 5a	$C_{2h}$
	II: 2,4,6,8	C: 2e', 4e, 6e, 8e' D: 2a', 4a, 6a, 8a'	
	III: 3,7	E: 3e, 3a, 7e, 7a	

Boat-boat (BB) and/or twist-boat (TB)	$\left. \begin{array}{l} \text{I: 1,3,5,7} \\ \text{II: 2,4,6,8} \end{array} \right\}^2)$	A: 1 <i>e</i> , 3 <i>e</i> , 5 <i>a</i> , 7 <i>e</i> B: 1 <i>a</i> , 3 <i>a</i> , 5 <i>e</i> , 7 <i>a</i> C: 2 <i>e'</i> , 2 <i>a'</i> , 4 <i>e</i> , 4 <i>a</i> , 6 <i>e</i> , 6 <i>a</i> , 8 <i>e'</i> , 8 <i>a'</i>	D <sub>2d</sub>
Boat (B) or chair (C)	$\left. \begin{array}{l} \left\{ \begin{array}{l} \text{twist-boat-chair} \\ \text{or} \\ \text{crown or} \\ \text{twist-chair-chair} \end{array} \right\} \text{and} \\ \left\{ \begin{array}{l} \text{boat-boat} \\ \text{or} \\ \text{twist-boat} \\ \text{or} \\ \text{twist-chair} \end{array} \right\} \end{array} \right\}^3)$	One set	D <sub>8h</sub>
Chair-chair (CC) and twist-chair (TC)	$\left. \begin{array}{l} \text{I: 1,5} \\ \text{II: 2,4,6,8} \\ \text{III: 3,7} \end{array} \right\}$	A: 1 <i>e</i> , 1 <i>a</i> , 5 <i>e</i> , 5 <i>a</i> B: 2 <i>a'</i> , 2 <i>e'</i> , 4 <i>a</i> , 4 <i>e</i> , 6 <i>e</i> , 6 <i>a</i> , 8 <i>e'</i> , 8 <i>a'</i> C: 3 <i>e</i> , 3 <i>a</i> , 7 <i>e</i> , 7 <i>a</i>	D <sub>2h</sub>

1) Additional averaging through CC has no further effect.

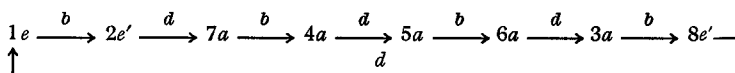
2) Additional averaging through CC and/or TC has no further effect.

3) These equilibria lead to complete averaging; combination of any one of these equilibria with any other given in this table, will of course also lead to complete averaging.

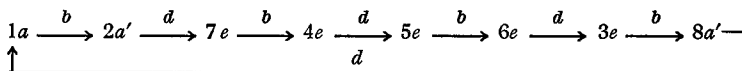
Table 6. Boat-chair pseudorotation (*via* TBC) in a monosubstituted cyclooctane

Pseudorotation step(s)	Effect on 1e substituent
<i>b</i>	1e $\longrightarrow$ 2e'
<i>d</i>	1e $\longrightarrow$ 8e'
<i>bb</i>	1e $\longrightarrow$ 2e' $\longrightarrow$ 1e
<i>dd</i>	1e $\longrightarrow$ 8e' $\longrightarrow$ 1e
<i>bd</i>	1e $\longrightarrow$ 2e' $\longrightarrow$ 7a
<i>db</i>	1e $\longrightarrow$ 8e' $\longrightarrow$ 3a

It can be seen that two pseudorotation steps of the same chirality have no net effect. A sequence of steps with alternating chiralities returns the conformation to its original state after eight steps as follows:



This sequence of steps is a  $(bd)_4$ -pseudorotation itinerary. The mirror-image itinerary gives rise to the same sequence but with all the arrows reversed in direction. Although the 1-equatorial proton passes through various axial and equatorial sites, only one half of the boat-chair positions (*i.e.* set A in Table 5) are visited during a cycle. If we follow the 1-axial proton, we find that it visits the other half of the available positions (*i.e.* set B in Table 5) as follows:



Replacement of a  $\text{CH}_2$  group in cyclooctane by a  $\text{CHX}$  or  $\text{CX}_2$  group, where X is achiral, or by a heteroatom such as O or S, leads to a *chemically* achiral molecule. If the conformational preference of the group or heteroatom is for the 1 or 5 positions in the boat-chair, the molecule is also conformationally achiral. However, if the preference is for any other positions, two enantiomeric conformers will result. In the latter case, dynamic nmr can be used to study the sequence of pseudorotations which leads to conformational racemization.

Experimental work, described in Section VII, shows that the barriers to pseudorotation are highly dependent on the nature of the  $\text{CX}_2$  group, but unfortunately, no strain energy calculations are available on this point.

Examination of models, however, shows that a bulky  $CX_2$  group, which can be accommodated at position 2 in the boat-chair, cannot be pseudorotated to the mirror-image position 8 without passing through very strained boat-chairs, *e.g.* the BC-1 conformation. Furthermore, the  $\omega_{23}=0$  conformation (Fig. 3) resulting from BC-1 is much more strained than is the corresponding form of cyclooctane itself.

At this point it becomes necessary to emphasize that *the number and letters* (*e.g.* 1 or 1*e*) used in the present discussion are part of a conformational labelling scheme, which must not be confused with any chemical labelling that may be required. In a monosubstituted cyclooctane, no chemical labelling is needed if the focus is on the substituent, just as in the description of pseudorotation presented above. If reference is made to a particular ring proton or carbon in a monosubstituted cyclooctane, however, a double labelling scheme becomes essential, and such a scheme is needed in general. In this chapter the capital letters A, B, C, . . . will always refer to chemical labelling. When numbers are used, the context will usually indicate whether a chemical or conformational label is being used. Numbers with added letters (*e.g.* 1*a*, 1*e*) are always conformational labels.

Table 5 shows that rapid interconversion of the boat-chair with either the boat or chair is sufficient to average all the protons in cyclooctane to one set. The chair is an energy maximum for the process  $BC \rightarrow TBC \rightarrow C \rightarrow TBC \rightarrow BC$ , and the activation energy from Table 2 is 8.3 kcal/mole. The boat path appears to be higher in energy than the chair path.<sup>13)</sup>

With cyclooctane and other eight-membered rings which have low barriers to pseudorotation, a complete averaging of the protons to one set can also be achieved by interconversion of the boat-chair with the twist-chair, boat-boat or twist-boat conformations. When pseudorotation is fast, the process which leads to complete averaging can be called ring inversion. Ring inversion through the twist-chair is calculated to have a higher activation energy (11.6 kcal/mole) than inversion through the chair. The boat-boat path has a very high activation energy (20 kcal/mole) if a plane of symmetry is maintained. However, an unsymmetrical path,  $BC \rightarrow TBC \rightarrow TB \rightarrow BB \rightarrow TB \rightarrow TBC \rightarrow BC$ , appears to be of much lower energy, but strain energy calculations are not available. From the experimental data on cyclooctane (Section VII. A) it is known that the process which leads to complete averaging must have an activation energy of about 8 kcal/mole, and therefore the boat-chair to boat-boat interconversion cannot have an activation energy lower than 8 kcal/mole (this assumes that cyclooctane exists in the boat-chair, as is highly probable). Thus all of the above paths appear to be reasonable mechanisms of ring inversion, at least in cyclooctane or simple derivatives. The presence of substituents can change the barriers for the various paths, so that all ring inversions may not necessarily have the same mechanism.

Recent experimental data on heterocyclic eight-membered rings (Section VII.C) show that the barrier to interconversion of the boat-chair with a crown family conformation is higher than the barrier for ring inversion in the boat-chair. The data also show that a crown family form does not undergo ring inversion without also interconverting with the boat-chair. The strain energy calculations <sup>13)</sup> do not reveal any path for ring inversion in the crown family of lower energy than the interconversion of this family with the boat-chair, in agreement with the experimental data.

It appears clear from the strain energy calculations and the experimental evidence (Section VII) that, at least for cyclooctane itself, the conformations of low energies can be grouped into three families which are separated by relatively high barriers (8 to 11 kcal/mole). The members of a given family, however, are separated from one another by much smaller barriers (0 to perhaps 4 kcal/mole). Table 7 contains a summary of these conclusions.

Table 7. Families of rapidly interconverting low-energy cyclooctane conformations

Name of family	Members	Sets of isochronous nuclei	
		carbon	hydrogen
Crown	Crown, chair-chair, twist-chair-chair	1	2
Boat-chair	Boat-chair, twist-boat-chair	1	2
Boat-boat	Boat-boat, twist-boat	1	3 <sup>1)</sup>

<sup>1)</sup> In the ratio of 2:1:1.

Certain 1,3-dioxocanes containing *gem*-dimethyl groups seem to exist in boat-chairs which have lower barriers for interconversion to the boat-boat than for interconversion to the twist-boat-chair, *i. e.* just the reverse of the normal situation. A discussion of these rather special systems will be deferred to Section VII.C, where the experimental data will be presented.

## VII. Experimental Data and Discussion

### A. Cyclooctane and Simple Derivatives

Proton nmr spectra of various deuterated cyclooctanes, and of cyclooctane itself, show a single chemical shift at room temperature, and two chemical shifts below about  $-120^{\circ}\text{C}$ . The free energy of activation,  $\Delta G^{\ddagger}$ , for this



process, *i.e.* for ring inversion, is 8.1 kcal/mole at  $-112^{\circ}\text{C}$ .<sup>47)</sup> The values given <sup>47)</sup> for  $\Delta H^{\ddagger}$  (7.4 kcal/mole) and  $\Delta S^{\ddagger}$  ( $-4$  eu) may have somewhat higher errors than those quoted ( $\pm 0.3$  kcal/mole and  $\pm 2$  eu respectively) because of systematic errors, as mentioned in Section II.

The spectra of the deuterated cyclooctanes show no further changes down to  $-175^{\circ}\text{C}$ , apart from some line broadening ascribable to slow molecular tumbling at low temperatures. The spectra at low temperatures (say  $-135^{\circ}\text{C}$ ) of the specifically deuterated cyclooctanes I, II and III (Fig. 4) exclude any systems which have the same time-average symmetry as the boat or boat-boat.<sup>17)</sup> For example, compound III, which has a single  $\text{CH}_2$  group gives rise to a single AB quartet and, as discussed in Section VI, this cannot be reconciled with a boat-boat or a twist-boat. The spectra are compatible with any conformation in the crown or boat-chair families, with the assumption that the crown to twist-chair-chair to chair-chair interconversion and the boat-chair to twist-boat-chair interconversion are very rapid even at low temperatures. This assumption is strongly supported by the strain energy calculations already presented. The crown and boat-chair family conformations require that the spectrum of I, which has two *cis* vicinal protons, be an AB quartet, as is indeed observed (Fig. 4). The spectrum of II, which has two *trans* vicinal protons should consist of two lines (*i.e.* two  $A_2$  spectra), again as observed.

Since strain energy calculations and experimental data strongly indicate that the barrier for interconversion from the crown family to the boat-chair family is of the order of 11 kcal/mole, it is not possible for cyclooctane to exist as a mixture of these two families, unless one family is present in such a small amount that its spectrum is lost in the noise. Thus, one family must be present to more than 95% in cyclooctane at  $-130^{\circ}\text{C}$ .<sup>6)</sup>

The nmr spectra of various rather *simple* cyclooctane derivatives discussed below are only consistent with the boat-chair conformation. Furthermore the structures in the crystalline state are boat-chairs (Table 1), with one exception which can be rationalized (see below). The conclusion that cyclooctane exists in solution as the boat-chair therefore appears inescapable.

One difficulty with the conformational picture presented above is that it does not immediately provide an explanation for certain pulse nmr measurements on cyclooctane carried out by Meiboom some ten years ago.<sup>48)</sup> A plot of  $\log(1/T_2 - 1/T_1)$  ( $T_1$  and  $T_2$  are the spin-lattice and transverse relaxation times respectively) against the reciprocal of the absolute temperature does not give a straight line in the temperature range  $-50^{\circ}$  to  $-105^{\circ}\text{C}$ , and indicates the presence of two processes. Ring inversion in the boat-chair can be one of these processes, but the second process cannot be the boat-chair pseudorotation, which is far too rapid in this temperature range to lead to any observable effect. The following explanation <sup>49)</sup> affords a pos-

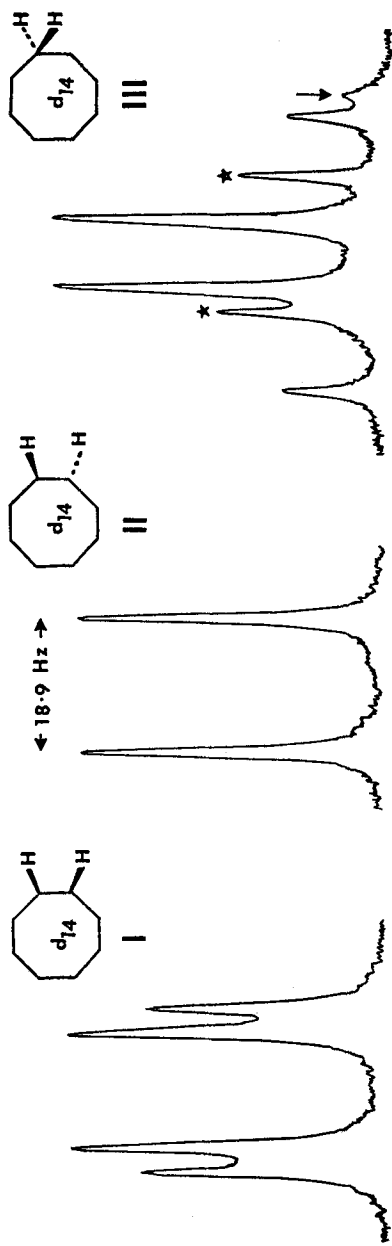


Fig. 4. 60 MHz Proton nmr spectra of three deuterated cyclooctanes at  $-140^{\circ}\text{C}$ .<sup>17</sup> The lines marked with stars arise from isotopic impurities having the partial structure  $-\text{CD}_2-\text{CHD}-\text{CD}_2-$ . The line marked with an arrow is a  $^{13}\text{C}$  satellite of internal tetramethylsilane

sible way out of this dilemma. The second process could be a boat-chair to crown family (*e.g.* TCC) interconversion, in which the population of the twist-chair-chair is quite low (<5%), as is required from the previously described nmr evidence. The situation would then be like that of methylcyclohexane<sup>50</sup>, where the interconversion of the axial form and the equatorial form is only observable under special conditions, because of the very unequal populations.<sup>6)</sup>

Methylcyclooctane and *t*-butylcyclooctane both give strongly temperature-dependent nmr spectra in a range close to that observed for cyclooctane itself.<sup>46,51</sup> Such a behaviour is not expected if these compounds have crown-family conformations, because the alkyl group will take up equatorial positions almost completely, and as discussed in Section VI, all equatorial positions in this family are expected to interconvert extremely rapidly even at low temperatures, leading to (virtually) temperature-independent nmr spectra, as in monoalkylcyclohexanes. In the boat-chair, by contrast, pseudorotation *via* the twist-boat-chair gives rise to two sets of positions, previously referred to as sets A and B (Table 3). Both sets have unhindered equatorial positions (set B also has relatively unhindered quasi-axial positions), and interconversion between set A and set B is the ring inversion process just discussed in cyclooctane itself. In an alkyl-cyclooctane, ring inversion by any of the mechanisms mentioned in Section VI merely interconverts conformations with equatorial alkyl groups in set A with conformations with equatorial groups in set B. The alkyl group, it should be noted, remains unhindered during the entire ring inversion process, and thus the activation energy should be very similar to that in cyclooctane itself.

A crown-family conformation also cannot explain the nmr spectrum of the acetonide of *trans*-1,2-cyclooctanediol, a compound which has a five-membered ring fused to the cyclooctane ring.<sup>46)</sup> A temperature-independent spectrum would be predicted, because a *trans*-fused five-membered ring can only be located at equatorial positions in crown-family conformations, and ring inversion is therefore prohibited. The nmr spectrum of this compound is actually strongly temperature-dependent at about  $-70^{\circ}\text{C}$ , thus excluding any conformation in the crown family, at least as the sole conformation.

In the boat-chair, both set A and set B have positions where a *trans*-fused five-membered ring can be located, and thus ring inversion is possible, and a temperature-dependent spectrum is allowed, in agreement with experiment. The ring inversion barrier is somewhat higher than in cyclooctane, but this could be due to the restraint caused by the five-membered ring. An explanation based on a mixture of twist-chair-chair and boat-chair conformations is also possible, but appears less likely.

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<sup>6)</sup> See section added in proof at end of text.

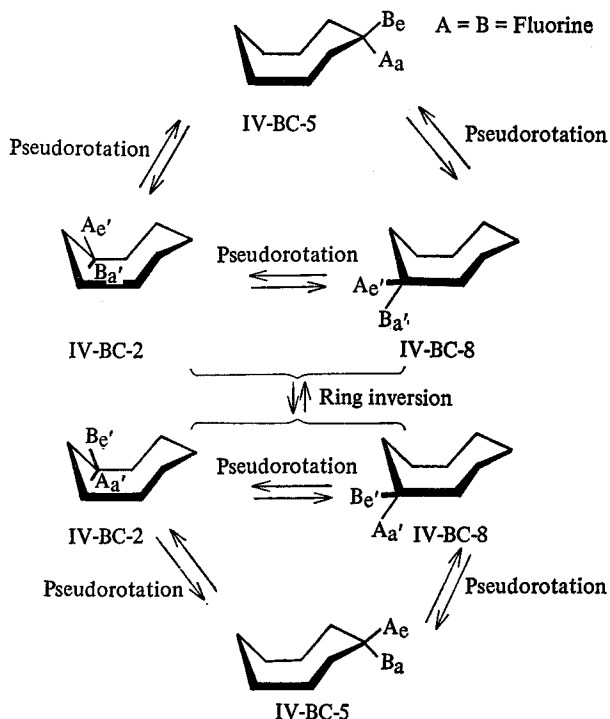
Symmetrical 1,1-disubstituted cyclooctanes provide very valuable conformational information. With fluorine as a substituent, in particular, it is possible to examine the  $^{19}\text{F}$  resonance spectrum and to take advantage of the large fluorine chemical shifts.<sup>40)</sup> Furthermore, although fluorine is appreciably larger than hydrogen, it is small enough to fit in not too hindered axial positions. Therefore, cyclooctane itself and 1,1-difluorocyclooctane (IV) should exist in the same conformation. The  $^{19}\text{F}$  spectrum of IV, taken with protons decoupled, changes from a single line at room temperature to an AB quartet ( $\delta_{\text{AB}} = 3.9$  ppm) at  $-120^\circ\text{C}$ , and to two AB quartets at  $-175^\circ\text{C}$  ( $\delta_{\text{AB}} = 14.3$  and  $16.7$  ppm, with intensities in the ratio of 2:1 respectively).<sup>40)</sup> The presence of two processes with free energies of activation of 7.5 and 4.9 kcal/mole is not compatible with crown-family conformations, which should show only a single process with an appreciable activation energy. An examination of the twist-chair-chair pseudorotation indicates that a  $\text{CF}_2$  group should not increase the barrier by any significant amount over the value (0.2 kcal/mole) calculated for cyclooctane. The crown-family conformations also cannot explain the small chemical shift difference between the fluorine nuclei at  $-120^\circ\text{C}$ .

Roberts<sup>52)</sup> originally considered a twist-boat conformation for IV, but the mounting evidence for a boat-chair conformation for cyclooctane and various derivatives, led Roberts and coworkers to suggest boat-chair conformations for IV also.<sup>40)</sup> Furthermore, the original explanation requires that pseudorotation of the twist-boat *via* the boat be of lower energy than the pseudorotation *via* the boat-boat and this is not supported by recent strain energy calculations.

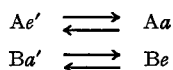
The  $^{19}\text{F}$  nmr spectra of IV can be nicely explained on the basis of the boat-chair conformation and the following reasonable assumptions:

- a) The  $\text{CF}_2$  group resides only at relatively unhindered boat-chair sites, *i.e.* only forms IV-BC-2, IV-BC-5, and IV-BC-8 are appreciably populated.
- b) The free energy barrier to pseudorotation *via* the twist-boat-chair is 4.9 kcal/mole, and is thus probably somewhat higher than in cyclooctane itself, for reasons given in Section VI, and discussed in greater details below.

Forms IV-BC-2 and IV-BC-8 are enantiomeric and must have the same populations. Since pseudorotation of IV-BC-2 into IV-BC-8 does not cause an exchange of the quasi-axial with the quasi-equatorial fluorine, it is an invisible process by  $^{19}\text{F}$  nmr, although this process can, in principle, be studied by  $^1\text{H}$  or  $^{13}\text{C}$  nmr. Pseudorotation of IV-BC-2 (or IV-BC-8) to



IV-BC-5 involves three pseudorotation steps and causes the following exchange of fluorines (shown only for the BC-2):



The exchange of quasi-equatorial with axial fluorines provides an explanation for the small chemical shift difference at intermediate temperatures, *i.e.* when pseudorotation is fast.

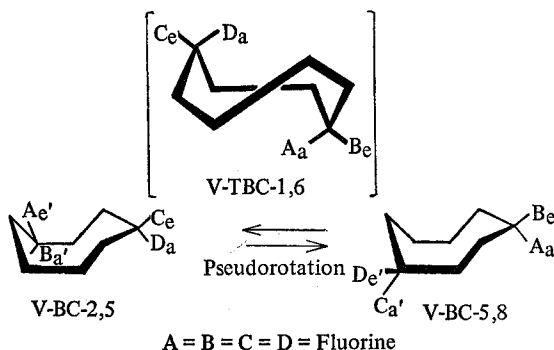
Roberts and coworkers were able to simulate the experimental spectra over the temperature range  $-160^{\circ}$  to  $-170^{\circ}\text{C}$ , using a computer program suitable for the exchange of two different AB systems. In this temperature range line widths in the absence of exchange are changing rapidly, so that relatively large errors could easily occur in calculations of kinetic parameters *other* than  $\Delta G^{\ddagger}$ , as pointed out by these authors. Thus no great significance can be attached to the calculated values of  $\Delta S^{\ddagger}$  and  $\Delta H^{\ddagger}$ .

The process with a  $\Delta G^{\ddagger}$  of 7.5 kcal/mole, results in the exchange of geminal fluorines and is a ring inversion of the kind already discussed. The intensity of 2:1 for the two AB systems in IV is not very well explained

by invoking only three boat-chair forms, as Roberts and coworkers have done. The BC-2 and BC-8 forms are equal in energy, and have no non-bonded fluorine-hydrogen repulsions. The BC-5 should have a little fluorine-hydrogen nonbonded strain (see Table 3) and should therefore contribute *less* than 33% to the total. A possible explanation is that there is some population of the BC-4 and BC-6 conformations. These forms should be only somewhat less stable than the BC-5 conformation, and should interconvert extremely rapidly to the BC-5 by a single-step pseudorotation (see discussion of 1,1,2,2-tetrafluorocyclooctane conformations below). Thus the sum of the BC-4 and BC-5 and BC-6 conformations might well amount to one third of the total.

The  $^{19}\text{F}$  nmr spectra of 1,1,4,4-tetrafluorocyclooctane (V) at low temperatures provides strong support for the interpretation of the spectrum of the 1,1-difluoro compound.<sup>40</sup> The spectrum of V changes upon lowering the temperature to a very strongly coupled AB system, which has not been investigated in detail. A further lowering of the temperature gives a second spectral change, as with IV, and at  $-160^\circ\text{C}$ , two nearly superposed AB quartets having the same intensity are observed. The  $\Delta G^\ddagger$  for this process is 6.1 kcal/mole at  $-130^\circ\text{C}$ . From the previous discussion, V-BC-2,5 and V-BC-5,8, are the only unstrained boat-chairs (note that 2,5, and 8 are conformational labels). These forms explain the presence in V of two AB systems with equal intensities at low temperatures.

A three-step pseudorotation itinerary (*dbd*) transforms V-BC-2,5 into V-BC-5,8 and results in an exchange of fluorines very similar to the exchange in 1,1-difluorocyclooctane. Models show that at one point in the itinerary,

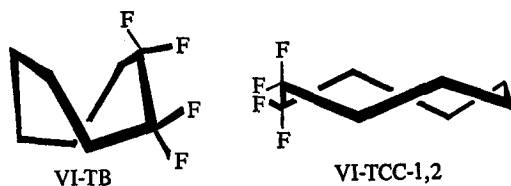


the system exists in the TBC-1,6 conformation, where *both*  $\text{CF}_2$  have bad non-bonded repulsions. The free energy of activation for pseudorotation in V is, in fact, 1.2 kcal/mole greater than the corresponding value in 1,1-difluorocyclooctane. These results allow a rough calculation of the  $\Delta G^\ddagger$

for pseudorotation in cyclooctane itself, which can be estimated to be  $(\Delta G^\ddagger)_{IV} - 1.2$ , *i. e.* 3.7 kcal/mole.

Another compound investigated by Roberts and coworkers is 1,1,2,2-tetrafluorocyclooctane (VI), an isomer of V. The  $^{19}\text{F}$  spectrum of VI changes upon lowering the temperature from a single line at room temperature to an AB quartet ( $\delta_{AB} = 8.85$  ppm) plus a rather broad singlet almost centered on the quartet at  $-65^\circ\text{C}$ . The AB system and the single line have approximately the same intensities. Below  $-80^\circ\text{C}$  the single line broadens and below  $-110^\circ\text{C}$  becomes a second AB system almost superposed on the original AB quartet, which is unchanged.

Roberts and coworkers<sup>40</sup> interpreted the spectra of VI in terms of twist-boats (without counting enantiomers, two different twist-boats are possible with the substitution pattern present in VI). Each twist-boat (*e.g.* VI-TB) has four different sites when all pseudorotations are slow, and under these conditions each form should give an  $^{19}\text{F}$  spectrum consisting of an ABCD system (approximately two separate AB quartets). The two different TB forms were assumed to have approximately equal populations and to have coincidences in chemical shifts so that the expected four AB quartets would be virtually coincident. With the appropriate chemical shift assignment, it can then be shown<sup>40</sup> that pseudorotation of the two different twist-boats *via* a boat-boat results approximately in an AB quartet and a single central line. Further pseudorotation through the boat form, *i.e.* ring inversion, results in a single chemical shift for all fluorines in VI.



The interpretation given above by Roberts and coworkers requires several coincidences, and is not free from objections. The difficulties with the twist-boat are as follows:

- despite the rather low strain energy calculated for this conformation, no cyclooctane derivative or related compound is known to exist unequivocally in that conformation;
- the strain energy for placing a  $\text{CF}_2$  group at the 2 position of the twist-boat must be quite considerable (see Table 3 for methyl strain energies) and since the twist-boat is already not the most stable cyclooctane conformation, this extra strain does not help;
- a rational alternative explanation in terms of the twist-chair-chair and the boat-chair can be formulated.

The boat-chair is clearly not a very good conformation for VI, because it is impossible to place the four fluorines in unhindered positions. In any case, as pointed out by Roberts and coworkers, a boat-chair conformation (alone) cannot explain the  $^{19}\text{F}$  nmr data. Roberts and coworkers have quite correctly emphasized the rather large dipolar energy which results from eclipsing two  $\text{CF}_2$  groups. The best conformation of VI should therefore be obtainable by minimizing (a) the fluorine non-bonded repulsions; (b) the dipolar repulsions; and (c) the inherent strain energy of the chosen cyclooctane conformation. The only conformations which fit the above restraints are the following: BC-4,5, TCC-1,2, CC-1,2 and TBC-7,8.

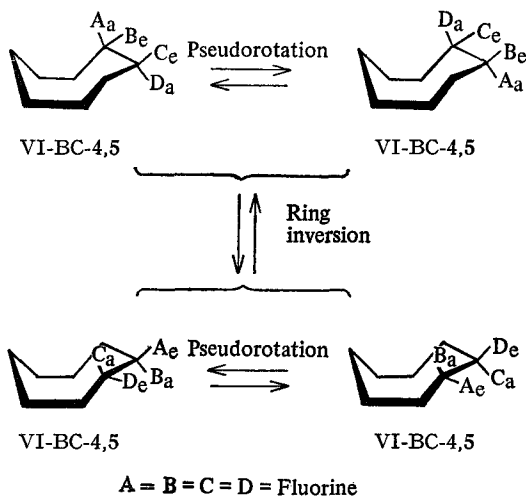
The BC-4,5 form has only one bad feature, namely, the strain of the  $4a$  fluorine. A  $4a$  methyl group on the boat-chair has a calculated strain energy of 5.1 kcal/mole (Table 3). The strain energy of a  $4a$  fluorine must be much less than that of a methyl group, and a value in the range of 1 to 2 kcal/mole would seem reasonable.<sup>53)</sup> The TCC-1,2 also has only one bad feature, namely, the higher strain energy of the TCC over the BC, and this amounts to 1.7 kcal/mole (see Table 3). The CC-1,2 should be rather similar in energy to the TCC-1,2; in any case these crown-family forms should interconvert very rapidly so as to give the effective symmetry of the TCC-1,2. It can now be seen that the BC-4,5 and the TCC-1,2 should be of about the same energies and might occur in about equal amounts.

The BC-4,5 can undergo pseudorotation to give back the same form, except that the  $\text{CF}_2$  groups have interchanged positions. However, axial and equatorial fluorines do not exchange, nor do the  $\text{CF}_2$  groups become eclipsed during the single-step pseudorotation. Such a pseudorotation should therefore have a  $\Delta G^\ddagger$  scarcely higher than that ( $\approx 4$  kcal/mole) in cyclooctane itself, and thus would be rapid at all temperatures at which the spectrum of VI was investigated. Ring inversion of the BC-4,5 conformation, which can take place by pseudorotation *via* a chair form, followed (or preceded) by several steps of comparatively low-energy pseudorotation *via* the twist-boat-chair, gives rise to the BC-5,6 conformation. The BC-5,6 is the mirror-image of the BC-4,5, and will therefore show the same kind of rapid pseudorotation described earlier for the BC-4,5. Therefore, the BC-4,5 and BC-5,6 conformers, will give rise to a single AB system at low temperatures, and to a single line at high temperatures. These changes can occur without any interconversion to the TCC-1,2.

The TCC-1,2 is axially symmetric and will therefore give an AB system when ring inversion is slow, and a single line when ring inversion is fast. Furthermore, the barrier to ring inversion is expected to be higher in the twist-chair-chair than in the boat-chair conformation, both from strain energy calculations and by analogy with other compounds known to contain crown-family conformations.



Dynamics of Eight-Membered Rings in the Cyclooctane Class



Thus, the AB quartet in VI at  $-65^\circ\text{C}$  can be assigned to the TCC-1,2, which, at that temperature, is undergoing slow ring inversion; the single broad line in VI at  $-65^\circ\text{C}$  can be assigned to the BC-4,5 which is inverting moderately rapidly to the BC-5,6, with both boat-chairs undergoing very rapid single-step pseudorotations. At  $-109^\circ\text{C}$ , ring inversion has become slow in the boat-chair, but pseudorotation is still fast.

The two alternate explanations for the low-temperature nmr spectra of VI are potentially distinguishable. Even the  $^{19}\text{F}$  spectra are not quite the same: the twist-boats should give two ABCD systems (with suitable coincidences in chemical shifts), while the 1:1 mixture of the boat-chair and twist-chair-chair should give two different AA'BB' systems. Unfortunately, vicinal fluorine-fluorine coupling constants are extremely small, so that two apparent AB systems are expected from both explanations.

Roberts and coworkers<sup>40</sup> have also discussed the  $^{19}\text{F}$  spectrum of perfluorocyclooctane (VII), a compound which was first investigated by Thomas.<sup>54</sup> The  $^{19}\text{F}$  spectrum of VII changes from a single line at room temperature to an approximate AB system and a single line at about  $-90^\circ\text{C}$ . No further change takes place down to  $-170^\circ\text{C}$ . At intermediate temperatures (about  $-65^\circ\text{C}$ ), the central components of the AB system merge into one broad line, but the single line is still separate, although somewhat broadened also.

A boat-boat (or a twist-boat pseudorotating rapidly through the boat-boat) has been suggested as the conformation of VII.<sup>40</sup> The spectrum at low temperatures expected from the boat-boat is the sum of an AB and  $A_2$  system of equal intensity, in agreement with experiment. However, attempts to calculate the line shape at intermediate temperatures, with the assump-

tion of a boat transition state were not successful.<sup>40</sup> It was suggested that the interconversion mechanism is interconversion to a boat-chair, which pseudorotates rapidly. Line shape calculations<sup>55</sup>, however, do not fit this model either, nor a model where the boat-chair both pseudorotates and inverts rapidly.

The spectrum actually requires that exchange within the AB quartet be much faster than exchange with the A<sub>2</sub> system and this can only be done by having two separate processes. In one of these processes, the only exchange is within the AB quartet as in the following pseudorotation sequence: BB → BC → TC → BC → BB. In this model the boat-chair must not pseudorotate rapidly, nor must the twist-chair interconvert rapidly with the chair. The process, which is a pure ring inversion of the boat-boat, does not appear very probable because of the restrictions stated, but the presence of many CF<sub>2</sub> groups could conceivably cause unusual effects. To complete the explanation of the spectral features at intermediate temperatures requires a second process, *e.g.* pseudorotation through the boat, or some leakage of the twist-chair to the chair. The system now has enough freedom with two arbitrarily different rate constants that *any* exchange scheme of an AB plus A<sub>2</sub> system can be simulated.

Since the <sup>19</sup>F spectra of 1,1,2,2-tetrafluorocyclooctane can be explained satisfactorily on the basis of two different conformations, one in the crown, and the other in the boat-chair family, the question arises as to whether the spectra of perfluorocyclooctane can be explained on a similar model. The answer is that such an explanation is possible, but only if some unusual effects are accepted. The AB quartet at -65 °C can be assigned to a crown family conformation which is inverting slowly but pseudorotating rapidly. The single line would then have to be a rapidly inverting and pseudorotating boat-chair. The problem with this picture is that the single line remains unchanged to -170 °C, and this requires the boat-chair to invert rapidly at this temperature. A very low barrier to ring inversion in the boat-chair does not occur in the previously discussed compounds. Because perfluorocyclooctane must be a very strained molecule, however, analogies with simple cyclooctane derivatives may not be valid. It seems clear that more evidence is needed in order to resolve the conformational picture in perfluorocyclooctane.

In the discussion on 1,1,4,4-tetrafluorocyclooctane the argument was made that substitution of a methylene group in cyclooctane by a difluoromethylene group increases the barrier to pseudorotation by about 1.2 kcal/mole, owing to the presence of additional non-bonded repulsions in the transition state for the boat-chair to twist-boat-chair interconversion. Supporting evidence for this view comes from proton nmr studies on 1,1-dimethylcyclooctane (VIII) and on the ethylene ketal (IX) and the ethylene dithioketal (X) of specifically deuterated cyclooctanone.

## Dynamics of Eight-Membered Rings in the Cyclooctane Class

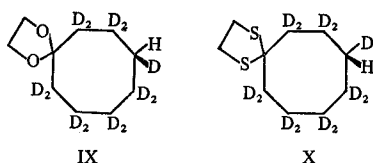


Table 8. Barriers in cyclooctane and some derivatives

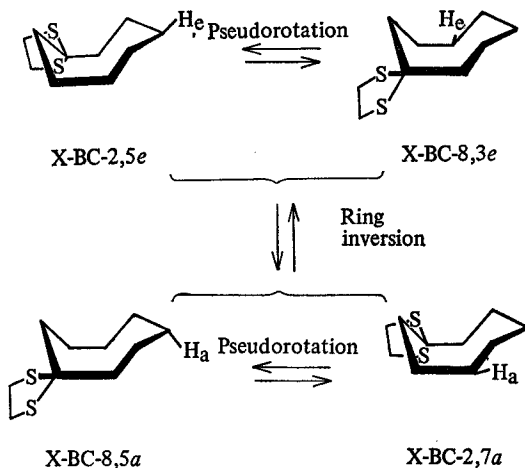
Substituents on cyclooctane	$\Delta G^\ddagger$ (kcal/mole)		Ref.
	Ring inversion	Pseudo- rotation	
None	8.1	<5	47)
Methyl	<i>ca.</i> 8	<5	46)
1,1-Difluoro	7.5	4.9	40)
1,1-Ethylenedioxy	7.6	5.3	56,57,58)
1,1,4,4-Tetrafluoro	1)	6.1	40)
1,1-Ethylenedithioxy	8.5	6.6	38,57)
1,1-Dimethyl	8.0	8.0	38,59)
1,2,5,6-Tetrabromo	11.1	—	28)

1) The ring inversion barrier is difficult to obtain because of a nearly degenerate spectrum.

The dithioketal (X) gives particularly clean-cut results and will be discussed first. The  $\gamma$ -proton label in X gives rise to a single line at room temperature, and to two equal-intensity lines with a chemical shift difference of 0.42 ppm below  $-110^\circ\text{C}$ . Below about  $-140^\circ\text{C}$  the high-field component of the doublet splits into two lines separated by 0.22 ppm, while the low field component also gives two lines but separated by only 0.06 ppm. Thus, there are two processes which affect the spectra of X, and free energies of activation are given in Table 8.

Compound X is actually a racemic mixture because of the  $\gamma$ -proton label, but in the following discussion we will refer only to one of the two enantiomers. The nmr results can be interpreted in terms of the following four conformations.

The interconversion of the BC-2,5*e* with the BC-8,3*e* (or the BC-8,5*a* and BC-2,7*a*) can be accomplished by two different pseudorotation itineraries, namely, by passage through the BC-1 or BC-5 conformations. Irrespective of the path, this interconversion has the interesting effect of shifting the  $\gamma$ -proton from one axial site to another axial site (or one equatorial site to another equatorial site). This is consistent with the large chemical shift



splitting (0.42 ppm) observed at intermediate temperatures, and the much smaller additional splitting found at very low temperatures. In contrast to 1,1-difluorocyclooctane, there is no evidence for a BC-5 conformation being appreciably populated in the dithioketal X.

The ethylene ketal, IX, also shows two distinct nmr processes, but the  $\Delta G^\ddagger$  for pseudorotation is distinctly lower than in X (see Table 8). Rather broad spectra were obtained at the temperatures (*ca*  $-173^\circ\text{C}$ ) required to slow down pseudorotation in IX, and nothing can be said about the possible presence of the BC-5 form. Apart from this, the spectra of IX are quite analogous to those of X.

1,1-Dimethylcyclooctane (VIII) shows only a single observable change at 100 MHz in its proton spectrum. The methyl band, which is a single line at room temperature becomes a doublet below  $-120^\circ\text{C}$ . There are also changes in the ring proton bands at about the same temperature. The spectrum does not show any further changes below  $-130^\circ\text{C}$ . Because of the complexity of the ring proton bands, it is not possible to determine whether pseudorotation is slow or rapid at  $-130^\circ\text{C}$ . In contrast,  $^{13}\text{C}$  Fourier transform spectra, obtained with protons noise decoupled, (Fig. 5), are strikingly simple and informative. The methyl  $^{13}\text{C}$  band splits in two below  $-120^\circ\text{C}$ , and so do all the ring carbons, with the exception of C-1 and C-5. The spectrum at  $-130^\circ\text{C}$  corresponds exactly to a conformation which lacks any element of symmetry, *e.g.* BC-2 and its mirror-image, BC-8. Therefore, pseudorotation and ring inversion must both be slow and from the line shapes at intermediate temperatures, it is apparent that  $\Delta G^\ddagger$  for both processes is about 8.0 kcal/mole at  $-120^\circ\text{C}$ .

The pseudorotation barriers given in Table 8 are strongly dependent on the size of the  $\text{CX}_2$  group, whereas the barrier to ring inversion remains

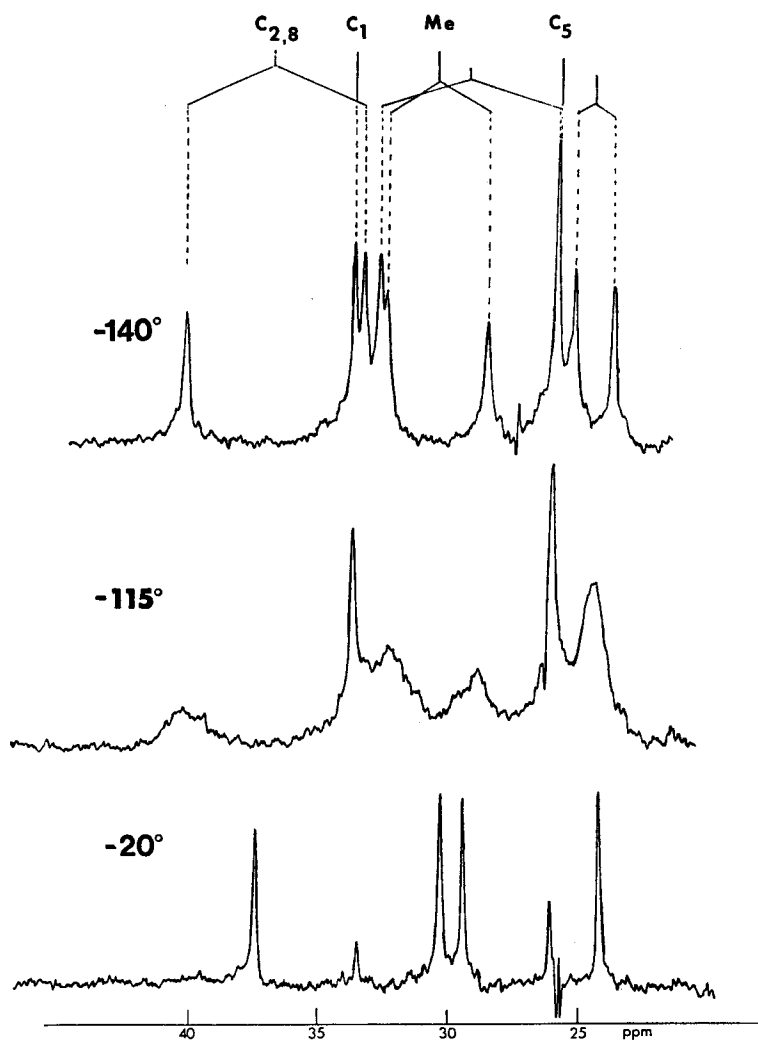
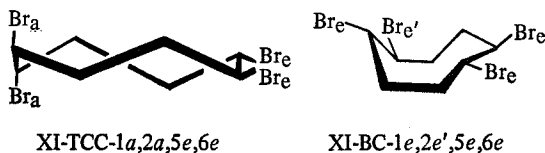


Fig. 5. Fourier transform  $^{13}\text{C}$  spectra of 1,1-dimethylcyclooctane at various temperatures.<sup>59)</sup> Protons are noise decoupled. Only a partial assignment of carbon resonances has been made

more or less constant at  $8.0 \pm 0.5$  kcal/mole. For the 1,1-dimethyl compound (VIII), the BC-1 or the BC-3 and BC-7 conformations must be intermediates in the pseudorotation itinerary. Hendrickson's calculations (Table 3) for the excess strain energy of a methyl group show that these intermediates must be about 7 to 8 kcal/mole higher in energy than the BC-2 or BC-8 conformation, and this is consistent with a barrier to pseudorotation of 8 kcal/mole in VIII.

Ring inversion through the chair form can take place with the methyl groups in VIII remaining in relatively unhindered positions during the entire process, and thus the barrier to ring inversion is not expected to be greatly affected by the presence of two geminal substituents, in agreement with the data in Table 8.

The final compound to be considered in this section is *trans-syn-trans*-1,2,5,6-tetrabromocyclooctane<sup>28)</sup> (XI), which exists in the crystalline state as the twist-chair-chair (TCC-1*a*,2*a*,5*e*,6*e*). Nmr data are in agreement with this conformation in solution, and the barrier to ring inversion is 11.1 kcal/mole at  $-66^\circ\text{C}$ . This is a much higher barrier than is found in the cyclooctane boat-chairs, and agrees with similar barriers found in crown family conformations of heterocyclic eight-membered rings. The nmr spectra apparently indicate the presence of 10% of another conformation, which is probably the boat-chair, BC-1*e*,2*e*,5*e*,6*e*. The boat-chair has all the bromines equatorial, whereas the twist-chair-chair has one pair of bromines di-axial and the other pair di-equatorial. Di-equatorial bromines, especially if the external torsion angle (Br-C-C-Br) is smaller than  $60^\circ$ , are unfavorable because of repulsions between the bromine atoms. This could be the reason for the tetrabromo compound existing predominantly in the twist-chair-chair. The results clearly show that the twist-chair-chair cannot be very much higher in energy than the boat-chair for cyclooctane itself, otherwise the substituent effects would not be able to make the twist-chair-chair the major conformation in XI.



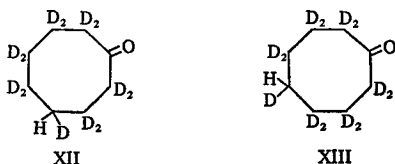
Conformational energy barriers have been studied in various cyclooctane derivatives by mechanical relaxation methods.<sup>60,61)</sup> The frequency and temperature range of such measurements are very large, but the identities of the processes observed are not as clear as in nmr measurements. With poly(cyclooctyl methacrylate) a process with an activation energy of 10.6 kcal/mole is found, and has been interpreted in terms of a boat-chair

ring inversion.<sup>60</sup> However, nmr results on various cyclooctane derivatives, including cyclooctyl formate and cyclooctyl acetate<sup>56</sup>, show that 10.6 kcal/mole is too high a value for ring inversion. A more likely process, in our view, is a boat-chair to twist-chair-chair interconversion, which is expected to have a slightly higher barrier than the boat-chair ring inversion.

In summary, the experimental nmr data presented in this Section strongly support the boat-chair as the lowest energy conformation for simple cyclooctane derivatives. The twist-chair-chair is of next lowest energy and the presence of certain substituents can make this conformation be the dominant one. Boat-boat family conformations are only (if ever) found in very special compounds.

## B. Cyclooctanone and Related Compounds

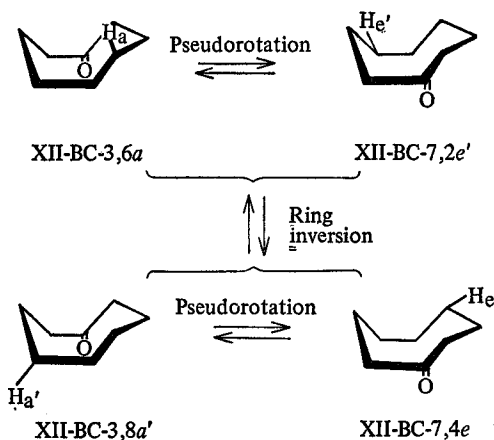
The 60 MHz spectra of the cyclooctanone- $d_{13}$  isomers, XII and XIII are extremely informative.<sup>38,56,57,58</sup> The isomer XII which has a single proton in the  $\gamma$  position, gives a single line at room temperature, two lines below  $-122^\circ\text{C}$ , and four lines of equal intensity below  $-147^\circ\text{C}$ . Isomer XIII, which has the proton label in the  $\delta$  position gives a single line at room temperature, and two lines below  $-112^\circ\text{C}$ , with no further change at lower



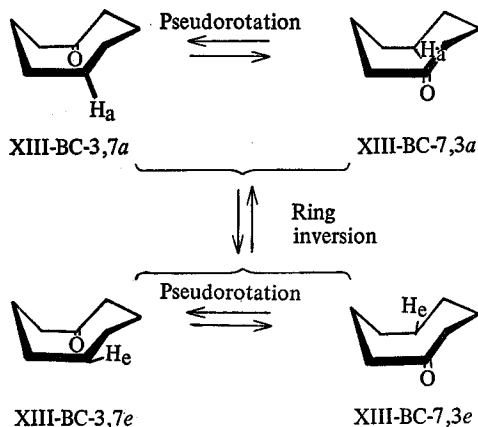
temperature. The high-field line in the doublet of XIII is only 0.63 ppm downfield from internal tetramethylsilane, some 0.5 ppm more shielded than expected for a methylene proton.

The  $\gamma$  labelled isomer XII is actually a racemate, but it is sufficient to consider one of the enantiomers as was done with the ethylene dithioacetal of XII, which was discussed in Section VII. A. There are then four conformations: BC-3,6*a*, BC-7,2*e'*, BC-3,8*a'*, and BC-7,4*e*, as shown below.

The interconversion of BC-3,6*a* with BC-7,2*e'* on the one hand and BC-3,8*a'* with BC-7,4*e* on the other hand can occur by two different pseudorotation itineraries, and evidence will be presented later that the itinerary in which the BC-1 form is an intermediate is of lower energy than the alternative itinerary, in which the BC-5 form is an intermediate. The pseudorotation just described accounts for the two lines at intermediate temperatures



in the  $\gamma$  isomer. In the  $\delta$  isomer this process has no effect on the  $\delta$  proton chemical shifts as it results in an interconversion of the type  $\text{BC-3,7a} \rightleftharpoons \text{BC-7,3a}$ . These results show that the boat to twist-boat-chair interconversion is indeed the process with the lower barrier in XII. The higher temperature process in XII and the only process observed in XIII are then ring inversion.



The high-field chemical shift observed in XIII at low temperatures is well explained by the boat-chair conformation, since the  $\delta$  proton in the axial position is directly above the  $\pi$  bond of the carbonyl group and should thus be strongly shielded.<sup>5)</sup>

Table 9 gives the free energy barriers for conformational interconversions in cyclooctanone. This table also gives the barrier to pseudorotation in



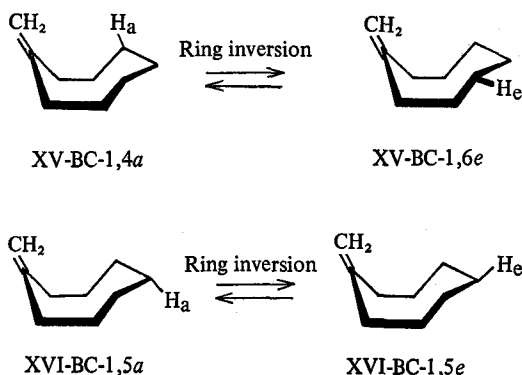
Table 9. Barriers in cyclooctanone and related compounds

Compound	$\Delta G^\ddagger$ (kcal/mole)		Ref.
	Ring inversion	Pseudo-rotation	
Cyclooctanone	7.5	6.3	38,56,57,58)
5- <i>t</i> -Butylcyclooctanone	—	8.0	56,58)
Methylenecyclooctane	8.1	—	38,57)

5-*t*-butylcyclooctanone (XIV). No ring inversion is to be expected in XIV since the large *t*-butyl group must take up the equatorial position exclusively, and thus the one nmr process observed in the ring proton bands must be pseudorotation. The abnormally large barrier to pseudorotation in XIV finds a ready rationalization in the fact that the pseudorotation itinerary in XIV, unlike that of cyclooctanone, must proceed through the BC-5 conformation (where 5 indicates the carbonyl position) in order for the *t*-butyl group to remain equatorial during the entire itinerary. This also indicates that cyclooctanone itself does not pseudorotate most easily *via* the BC-5 conformation, as otherwise there should be little difference in the pseudorotation barriers in the two compounds.

The BC-3 conformation for cyclooctanone is supported by recent strain energy calculations, which have already been mentioned (Section V). Qualitatively, the BC-3 conformation is also very reasonable, since the non-bonded repulsions between the 3 and 7 methylene groups in the cyclooctane boat-chair conformation are largely removed in the BC-3 form. The 1 position in the boat-chair also has the same kind of advantage that the 3 position has. However, the 3 position is also favored because of the relief of eclipsing strain which occurs in that position, but not in the 1 position (see Table 2 for dihedral angles in the boat-chair). This point will be amplified in the following discussion on methylenecyclooctane.

The nmr spectra of the methylenecyclooctanes XV and XVI corresponding to ketones XII and XIII show the following features: <sup>38,56,57</sup>) only a single process is observed, and the  $\delta$  proton in XVI does not have an unusually shielded chemical shift. The barrier for this process (Table 9) corresponds to a ring inversion. The evidence strongly suggests the symmetrical BC-1 conformation for methylenecyclooctane. The BC-1 form immediately explains the absence of a pseudorotation process, since such a process is invisible (although by no means non-existent) in that conformation. The normal chemical shifts of the axial  $\delta$  proton is also consistent with the BC-1 conformation, since that proton is not near the face of the vinylidene group, as it is in the BC-3 form.



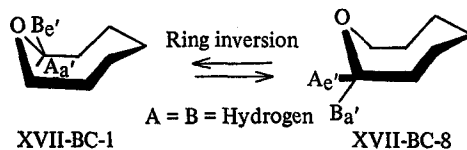
It is perhaps surprising that methylenecyclooctane does not have an analogous conformation to that of cyclooctanone. A possible explanation is based on the fact that the carbonyl and vinylidene groups are quite different from one another where eclipsing effects are concerned. For example, the barriers to methyl rotation in acetone and isobutylene are 0.8 and 2.2 kcal/mole, respectively.<sup>62,63</sup> This means that, other things being equal (*e.g.* non-bonded repulsions), the carbonyl group should prefer a position which, in the corresponding hydrocarbon, is as much eclipsed as possible. The vinylidene group, on the other hand should not show a strong preference for eclipsed positions. The energy difference from this effect is of the order of 1.4 kcal/mole, which is quite sufficient to explain the nmr results, especially since the significant data refers to temperatures below  $-100^\circ\text{C}$ . At room temperature, the BC-3 conformation should still be dominant for cyclooctanone, but a small percentage of the BC-1 conformation may well occur. Conversely, methylenecyclooctane should be mainly in the BC-1 conformation at room temperature, with a minor amount of the BC-3 form also being present. Unfortunately, nmr becomes a very uncertain tool when applied to systems which are undergoing rapid averaging, even though, in principle, information could be obtained from the temperature dependence of chemical shifts. A safer approach is to look for minor conformations at low temperatures, and the best method is probably Fourier transform  $^{13}\text{C}$  nmr.<sup>50,64</sup>

### C. Heterocyclic Eight-Membered Rings

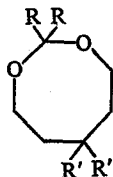
The conformational picture in heterocyclic eight-membered rings is quite varied, even though only a few classes of compounds have been investigated. We will begin with heterocycles containing up to four oxygen atoms in the ring.

Oxocyclooctane, or oxocane (XVII), has been studied by Anet and De-gen.<sup>65)</sup> Although the 60 MHz proton spectrum of XVII shows little change at low temperatures, a single process is easily observed at 251 MHz. The  $\alpha$  protons, for example, give one broad line at room temperature and two broad lines below  $-122^\circ\text{C}$ , with the rather small chemical shift difference of 0.18 ppm. No further change takes place at lower temperatures, and the  $^{13}\text{C}$  nmr spectrum of XVII is temperature independent to  $-170^\circ\text{C}$ .

Since oxygen is much smaller than a methylene group, the same kind of situation occurs in XVII as was discussed in the previous section. The barrier to methyl rotation in dimethyl ether is 2.7 kcal/mole<sup>66)</sup>, only slightly lower than in propane, where the barrier is 3.4 kcal/mole. Oxocane should therefore have the BC-1 conformation, as in methylenecyclooctane rather than the BC-3 and BC-7 conformations. The presence of only a single process in the proton spectrum of XVII is immediately consistent with the BC-1 conformation, but requires rapid pseudorotation between the BC-3 and BC-7 forms at  $-170^\circ\text{C}$  if the latter two forms are the correct conformations. The pseudorotation barrier in XVII should be higher than in cyclooctane, and probably comparable to that in cyclooctanone (6.3 kcal/mole). Thus, pseudorotation of the BC-3 form should not be rapid at  $-170^\circ\text{C}$ , and further support for this hypothesis is provided by 1,3-dioxocane (see below). It is therefore probable that oxocane has the BC-1 conformation.



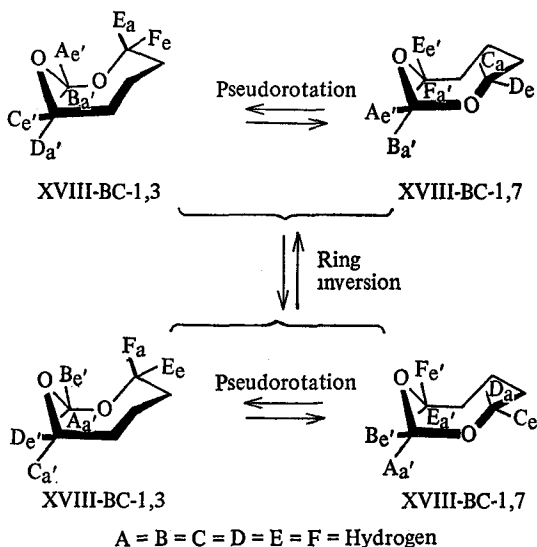
1,3-Oxocane (XVIII) and several of its *gem*-dimethyl derivatives have been studied by nmr.<sup>65,67)</sup>



- XVIII:  $R = R' = \text{H}$   
 XIX:  $R = \text{Me}, R' = \text{H}$   
 XX:  $R = \text{H}, R' = \text{Me}$   
 XXI:  $R = R' = \text{Me}$

The methylenedioxy proton band in XVIII changes from a single line at room temperature to an AB quartet ( $\delta_{\text{AB}} = 0.13$  ppm) below  $-125^\circ\text{C}$ . No further change takes place in these bands down to  $-170^\circ\text{C}$ , but the other methylene protons give complex bands which show two clear nmr processes, one at about  $-125^\circ\text{C}$ , and the other at  $-155^\circ\text{C}$ .

The nmr data can be simply explained on the basis of the BC-1,3 and its mirror image BC-1,7. Below  $-155^{\circ}\text{C}$  both pseudorotation and ring inversion are slow; above  $-155^{\circ}\text{C}$ , pseudorotation becomes fast and above  $-125^{\circ}\text{C}$  ring inversion is also fast. The BC-1,3 and BC-1,7 conformations have oxygens at the favorable 1,3 and 7 positions, and furthermore these forms have the ether dipoles in a low-energy arrangement, exactly as found in dimethoxymethane.<sup>68)</sup> The measured dipole moment of 1,3-dioxocane is 0.7D, in agreement with the BC-1,3 form.<sup>67)</sup> Free energy barriers for 1,3-dioxocane are given in Table 10.<sup>65)</sup>



The isomeric dimethyl-1,3-dioxocanes, XIX and XX, have coalescence temperatures of  $-80^{\circ}\text{C}$  and  $-120^{\circ}\text{C}$  respectively, while the 2,2,6,6-tetramethyl compound XXI has a coalescence temperature of  $-70^{\circ}\text{C}$ .<sup>67)</sup> Boat-chair conformations (BC-1,3 and BC-1,7) have been assigned to the 2,2-dimethyl derivative XIX. For the 6,6-dimethyl and the 2,2,6,6-tetramethyl derivatives, boat-boat conformations were suggested, since the boat-chair with an axial methyl group in the 4 or 6 position was considered to be impossibly strained on the basis of Hendrickson's calculations (Table 3). However, the situation here is not nearly as bad as in the corresponding cyclooctane system. In the BC-1,3 conformation the axial methyl group at the 6 position should have a much smaller repulsive interaction with the 1-oxygen than with a methylene group in the corresponding dimethyl-cyclooctane. Further nmr work on these compounds, carried out at 251 MHz,

Table 10. Barriers in oxocanes

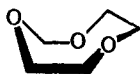
Compound	$\Delta G^\ddagger$ (kcal/mole) <sup>1)</sup>	
	Ring inversion	Pseudo-rotation
Oxocane	7.4	
1,3-Dioxocane	7.3	5.7
1,3,6-Trioxocane	8.7	
	6.8	
1,3,5,7-Tetroxocane	12.9	—

<sup>1)</sup> Data from Ref. <sup>65)</sup>.

has revealed a second nmr process in each case.<sup>69)</sup> The conformations of XX and XXI therefore cannot have any symmetry and the boat-boats, which have  $C_2$  symmetry in the above compounds, can be excluded. Twist-boats do not appear likely because the barrier to pseudorotation through the boat-boat should be even less than in cyclooctane, where calculations give a barrier of only 0.5 kcal/mole. Thus the twist-boats and boat-boats should give the same kind of spectra, and both can be excluded. It appears that boat-chairs offer satisfactory explanations of the nmr spectra of XX and XXI <sup>69)</sup>, although some unusual features are found. In XIX and XXI, the time-average symmetry at intermediate temperatures is  $C_2$ , rather than the normal  $C_8$  symmetry, as is found in XX or 1,3-dioxocane itself. This must mean that the boat-chair to twist-boat-chair interconversion is the process with the higher energy barrier, just the reverse of the usual situation. To be consistent, we have to define the high-energy process as ring inversion. The low-energy process, which is responsible for the  $C_2$  time-average symmetry at intermediate temperatures, is probably a pseudorotation *via* the twist-boat-chair, the twist-boat and the boat-boat forms. In Section VI this interconversion was suggested as a mechanism for ring inversion but if the boat-chair to twist-boat-chair interconversion is slow, this interconversion is no longer a ring inversion, but is then simply a pseudorotation. Further experiments are needed to clarify the conformational picture in these methylated dioxocanes. It is clear, however, that *gem*-dimethyl groups drastically increase the barrier to the boat-chair to twist-boat-chair interconversion, just as in 1,1-dimethylcyclooctane (Section VII.A).

The cyclic formal of diethylene glycol, *i.e.* 1,3,6-trioxocane, shows a very interesting temperature-dependent nmr spectrum, especially at 251 MHz.<sup>65,67)</sup> The C-2 proton band changes from a single line at room temper-

ature to a widely-spaced AB quartet ( $\delta_{AB} = 0.8$  ppm) and a single line below  $-80^\circ\text{C}$ . The intensities of the AB quartet and the single line are approximately the same. At still lower temperatures, only the single line changes, giving rise to a narrowly-spaced AB quartet ( $\delta_{AB} = 0.07$  ppm) below  $-135^\circ\text{C}$ .<sup>65</sup> The widely-spaced AB quartet has been assigned to a crown family conformation and the narrowly-spaced quartet to a boat-chair. The chemical shift difference between the protons on C-2 in 1,3-dioxocane, which exists as a boat-chair, is also quite small, namely 0.13 ppm, and this should be a general feature of methylene protons at the 2 and 8 positions in the boat-chair, because these carbon atoms lie on local and approximately  $C_2$  axes. The most likely boat-chair for trioxocane is the BC-1,3,6 conformation.



BC-1,3,6

The final compound in the oxygen series of heterocycles which has been studied by nmr is the cyclic tetramer of formaldehyde or 1,3,5,7-tetroxocane.<sup>65,67</sup> The proton spectrum is a single line at room temperature and changes to a widely-spaced AB quartet ( $\delta_{AB} = 0.64$  ppm) and a single line below  $-15^\circ\text{C}$ . No further splittings take place down to  $-170^\circ\text{C}$ , although the single line is quite broad at  $-160^\circ\text{C}$ , and might actually be an unresolved AB quartet with a very small chemical shift.<sup>65</sup>

The nmr spectra of tetroxocane bear a striking resemblance to those of trioxocane, and similar conclusions can be drawn. Thus, the widely-spaced AB quartet can be assigned to a crown family conformation. Because the cyclic tetramer of acetaldehyde has been found to have a crown conformation by X-ray diffraction<sup>29</sup>, it is quite likely that tetroxocane exists in solution at least in part as a crown. The single line can then be assigned to a boat-chair family conformation, which is pseudorotating rapidly, and may or may not also be inverting rapidly depending on whether the "single line" really represents a single chemical shift or an unresolved AB quartet. An interesting feature of the nmr spectra of tetroxocane is the dramatic temperature-dependence in the relative population of the AB quartet and the single line.

Thermodynamic calculations, based on integrated intensity measurements, show that the crown form has the lower enthalpy, and also the lower entropy ( $\Delta S = 8.5$ <sup>67</sup> or  $6 \pm 2$  eu<sup>65</sup>). The low entropy of the crown finds an explanation in the high symmetry of this conformation, compared to the low symmetry of the boat-chair. The best boat-chair for tetroxocane appears to be the BC-1,3,5,7 conformation. However, the ether functions at positions 3 and 7 have their dipoles close together in an unfavorable orientation but

a slight distortion of the boat-chair in the direction of the twist-boat-chair should relieve this repulsion.

The appearance of crown forms in tetroxocane and other compounds with heteroatoms in the 1,3,5 and 7 positions probably results from two stabilizing effects: (a) a slightly lower eclipsing barrier for the  $-\text{O}-\text{CH}_2-$  versus the  $-\text{CH}_2-\text{CH}_2$  fragment; in the crown there are eight partially eclipsed bonds which would benefit from relief of torsional strain; (b) distorted crowns, *i.e.* the chair-chair and twist-chair-chair may suffer from higher dipolar repulsions than does the crown. Unfortunately, there are no conformational energy calculations available on any of the heterocyclic systems.

The sulfur analogue of tetroxocane, namely 1,3,5,7-tetrathiocane, gives rise to a single line in the proton spectrum from room temperature down to  $-170^\circ\text{C}$ .<sup>27)</sup> Since crown family conformations have invariably been found to have relatively high barriers to inversion and large chemical shift differences between geminal protons, a crown conformation seems to be excluded for tetrathiocane. The structure of tetrathiocane in the crystalline state is in fact the boat-chair, BC-2,4,6,8.<sup>27)</sup> This conformation has somewhat different dihedral angles from the regular cyclooctane boat-chair, and the relatively long carbon-sulfur bonds allow the methylene groups to take up positions which would normally have larger non-bonded repulsions. In contrast, the BC-2,4,6,8 conformation of tetroxocane appears from molecular models to have a large amount of non-bonded repulsions as a result of the comparatively short carbon-oxygen bonds.

The data on barriers to ring inversion in heterocyclic boat-chairs (Table 10) show a trend to lower barriers when the number of hetero-atoms is increased, and in the absence of *gem*-dimethyl substitution, pseudorotation barriers are also quite low. It is therefore reasonable to expect that the barriers to pseudorotation and inversion in the tetrathiocane boat-chair might be too low for nmr detection, and this would, of course, explain the temperature-independent spectrum.

A series of eight-membered rings with various heteroatoms at the 1,3,5 and 7 positions has been studied by Lehn and Riddell.<sup>70)</sup> Compound XXII ( $\text{R} = \text{Me}$ ;  $\text{X} = \text{S}$ ) (Table 1) is known to be a crown in the crystalline state<sup>30)</sup>, and the dynamic nmr spectra are also consistent with this conformation. The free energy barrier to ring inversion (14.8 kcal/mole) and the chemical shift difference between geminal protons (0.32 ppm) are both much larger than would be expected for a boat-chair, but are of the order of magnitude found in other crowns. Barriers to ring inversion in related compounds, where the nitrogen substituent is different from methyl, or where selenium replaces sulfur, are given in Table 11. Since all the barriers are relatively high, it appears very likely that these compounds also exist in crown conformations.

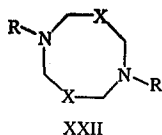
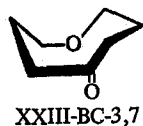


Table 11. Barriers in diazadithio and diazadiselenia cyclooctanes

Groups in XXII		$\Delta G^\ddagger$ (kcal/mole)
R	X	
Me	S	14.8
Et	S	14.6
<i>i</i> Pr	S	14.6
Ph	S	13.4
Me	Se	14.4

The final compound to be discussed in this section is 5-oxocanone, (XXIII), a molecule which has a potential transannular interaction of the ether oxygen with the carbonyl group.<sup>71)</sup> The proton nmr spectrum shows two processes with free energies of activation of 9.0 and 7.8 kcal/mole. The <sup>13</sup>C nmr spectrum shows only a single process, which corresponds to the lower-energy process observed in the proton spectrum. The spectra are quite analogous to those of cyclooctanone (Section VII.B), and strongly support a conformation without any symmetry. The BC-3,7 conformation shown below represents one of two possible mirror-image conformations. This conformation fits the nmr data and is also expected to be the most stable boat-chair form of XXIII. As with cyclooctanone, the lower energy process has been ascribed to pseudorotation of the boat-chair *via* the twist-boat-chair.<sup>72)</sup>



Since the interconversions of the conformations of XXIII are very similar to those described in detail for cyclooctanone, no further discussion will be given here.

## VIII. Conclusions

Most "simple" cyclooctane compounds, including ketones and heterocyclic analogues, exist predominantly in boat-chair conformations. Compounds



with special substitution patterns, or with hetero-atoms, often exist partially or mainly in crown family conformations (crowns or twist-chair-chairs). Boat-chairs generally have medium barriers (*ca.* 8 kcal/mole) to ring inversion, and, except in monosubstituted cyclooctanes and cyclooctane itself, have barriers to pseudorotation (*via* the twist-boat-chair) which depend a great deal on substituents, but which are large enough ( $>4.5$  kcal/mole) for measurements by dynamic nmr methods. Cyclooctane itself has an unobservably low barrier to pseudorotation.

Ring inversion of crown family conformations generally proceeds by interconversion, over a relatively high barrier (10 to 12 kcal/mole), to boat-chairs, which invert relatively easily. Pseudorotation barriers in crown family conformations such as the twist-chair-chair are extremely low and not detectable by direct line-shape measurements.

The least known conformational family is the boat-boat. It seems that a very special substitution pattern is required to make conformations in this family more stable than those of the crown and boat-chair. Highly fluorinated cyclooctanes possibly exist in the twist-boat or boat-boat conformations; however, additional evidence is badly needed to support the conformational assignments which have been made. A boat-boat conformation (in the cyclooctane nomenclature) does occur in [3.3.1]bicyclononane, which contains a 1,5-bridged cyclooctane ring.<sup>73)</sup>

While only further experiments will show whether the conformational picture outlined in this chapter has real validity, the author believes that the main conclusions drawn will stand the test of time.

*Added in proof.* The conclusions reached in Section VII. A concerning the probable presence of a small amount of a crown-family conformation in cyclooctane has now been directly verified by both  $^{13}\text{C}$  and  $^1\text{H}$  nmr spectroscopy.<sup>74)</sup> The crown-family conformation occurs at concentrations of 6, 2 and 0.3% at room temperature,  $-45^\circ$  and  $-125^\circ\text{C}$   $125^\circ\text{C}$  respectively. The  $\Delta H^\circ$  and  $\Delta S^\circ$  for the boat-chair to crown conformation are  $1.9 \pm 0.2$  kcal/mole and  $1 \pm 1$  eu respectively and the  $\Delta G^\ddagger$  for this process is  $11.2 \pm 0.4$  kcal/mole at  $-45^\circ$ .

The presence of about 10% boat-chair conformation in *trans-syn-trans* 1,2,5,6-tetrabromocyclooctane (XI) (see Section VII.C) has been confirmed by 251 MHz  $^1\text{H}$  nmr.<sup>75)</sup> The *trans-anti-trans* isomer of this compound has been found by 251 MHz  $^1\text{H}$  nmr to be an approximately 1:1 mixture of a crown-family and a boat-chair conformation.<sup>75)</sup>

Boat-chairs have been assigned to *cis*- and *trans*-1,5-diacetoxycyclooctanes and the former shown to undergo pseudorotation with a barrier ( $\Delta G^\ddagger$ ) of 6.5 kcal/mole (the ring inverted form is present in too small a concentration to be detected).<sup>76)</sup> The *trans* isomer has a barrier to pseudorotation which is too low for nmr measurement, but the barrier to ring inversion (8.0 kcal/mole) can now be obtained because the conformations which are related by inversion are equally populated. The barriers are similar to those in compound IX, and the interconversion scheme given <sup>76)</sup> is in complete agreement with the principles given in this chapter.

1,5-Cyclooctadione and 1,5-dimethylenecyclooctane both appear to exist in BC-3,7 conformations.<sup>77)</sup> 1,2-Dithiacyclooctane exists in the BC-3,4 form with a barrier to ring inversion of 9.1 kcal/mole, and an unobservably low barrier to pseudorotation.<sup>78)</sup> This latter process (BC-3,4  $\rightleftharpoons$  BC-6,7) does *not* require passage through a 0° torsional angle for the disulfide group. The barrier for the boat-chair pseudorotation in cyclooctane has been calculated to be 3.3 kcal/mole<sup>79)</sup>.

*Acknowledgements.* I wish to thank the National Science Foundation for financial support of our work on the conformations of eight-membered rings, and I am most grateful to my collaborators, Drs. S. Hartman, M. St. Jacques, G. N. Chmurny, P. M. Henrichs, W. D. Larson, J. J. Wagner, P. J. Degen and J. E. Krane.

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