CONFORMATIONAL STUDY OF SOME FLUORINE-LABELED CYCLIC COMPOUNDS BY NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

I. 1, 1-DIFLUOROCYCLODECANE AND 3, 3-DIFLUORO-TRANS-CYCLODECENE

II. γ, γ-DIFLUORO-ϵ-CAPROLACTONE AND γ, γ-DIFLUORO-ϵ-CAPROLACTAM

Thesis by

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To my parents

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ABSTRACT

Low-temperature fluorine magnetic resonance spectroscopy has been used to investigate the conformational equilibration of four cyclic gem-fluorides. Ring inversion in 1, 1-difluorocyclodecane was stopped on the nmr time scale by -164°, and an activation energy of 7.0 kcal/mole was determined for this process. The spectra were interpreted in terms of the boat-chair-boat conformation. Changes in the spectra of 3, 3-difluoro-trans-cyclodecene occurred continuously over a wide range of temperature, from above ambient temperature to about -140°. The free energy of activation for the first process, which is nearly stopped on the nmr time scale by -30°, was 12.4 kcal/mole at 2.8°. Activation parameters were not calculated for the changes which took place at lower temperatures. At -148°, two conformations were present in a ratio of 85:15, and other conformations may be present in smaller amounts.

The activation energy for inversion of γ, γ-difluoro-ϵ-caprolactone was 12.4 kcal/mole, and the free energy of activation for this process was 10.0 kcal/mole at -53°. The spectra indicate that the compound exists in the chair conformation, and the activation parameters provide information about the barrier to cis-trans isomerization of esters. The free energy of activation for γ, γ-difluoro-ϵ-caprolactam was 10.4 kcal/mole at -53°. The lactam also prefers the chair conformation.

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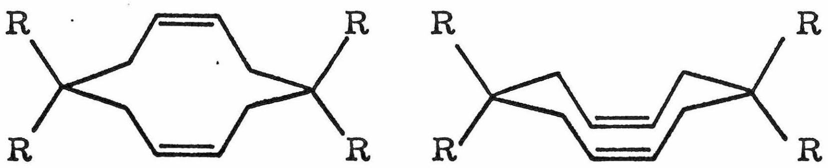
PART I

CONFORMATIONAL STUDY OF 1, 1-DIFLUOROCYCLODECANE AND 3, 3-DIFLUORO-TRANS-CYCLODECENE

INTRODUCTION and BACKGROUND

Although nmr spectroscopy is known to be well suited for conformational studies of cyclic compounds (1), this method has been used in relatively few cases for the investigation of ten-membered rings. *Trans*-cyclodecene-1, 2, 4, 4, 9, 9-d_6 has been studied by Binsch and Roberts (2), and the barrier to rotation of the double bond through the ring was found to be 10.7 kcal/mole. The spectrum broadened again below -143°, but the solution became too viscous for a detailed study of these changes. *Cis, cis*-1, 6-cyclodecadiene and several derivatives substituted at positions 4 and 9 have been examined (3, 4). Conformation A, but not B, was consistent with the observation of an AB quartet for the non-allylic methylene groups of **1** (R = $-CH_2OH$) (3). Barriers to ring inversion were also determined for several of the dienes. The nmr spectrum of the *t*-butyl protons of *t*-butyl cyclodecane was a 2:1 doublet at -145°, as a result of restricted rotation of the *t*-butyl group (5). The bands were broader than expected from viscosity broadening, and the authors suggested



A B

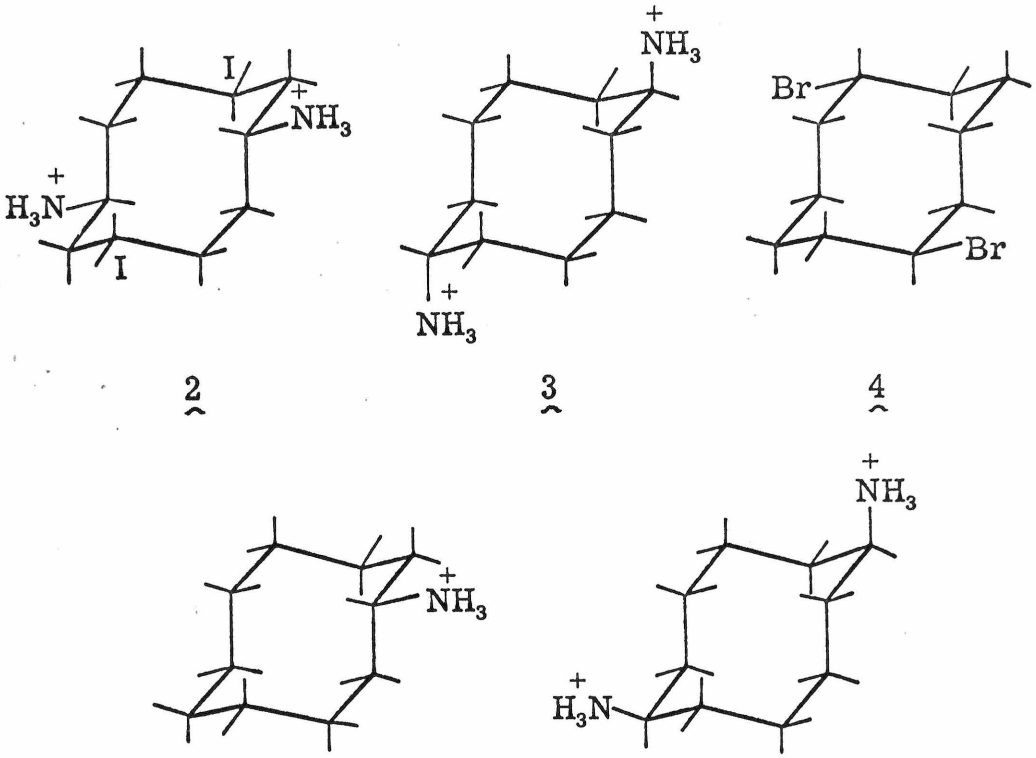
1

that this could be indicative of some kind of ring process. Cordes *et al.* have briefly reported (6) that the nmr spectrum of the methylene protons of 1, 1, 6, 6-tetramethylcyclodecane became more complicated when the compound was cooled to -50°.

The spectra of most medium-ring compounds under conditions of slow conformational equilibration are too complex for detailed analysis. Simplification of the pmr spectra can be achieved by replacement of part of the hydrogen atoms by deuterium atoms (7). An alternative approach involves substitution of one or more hydrogen atoms by fluorine and observation of the fluorine spectrum (8). The "fluorine-labeling" technique has been used in the present research to obtain information about the conformational equilibration of cyclodecane and *trans*-cyclodecene. Before considering the results from the nmr studies of the fluorinated compounds, it will be helpful to review what has been learned by other methods about the conformations of ten-membered rings.

Most of the experimental evidence for the preferred conformation of cyclodecane has come from X-ray investigations of crystalline derivatives (9-16). The conformations found in these studies are summarized below in Figure 1.

Trans-1, 6-diaminocyclodecane dihydrochloride, the first of the derivatives to be studied, was obtained in two crystal modifications (10, 11, 12). The ring conformation was the same in each case, but the substituents were found in different positions (**2** and **3**, Figure 1).



2 3 4

5 6

Figure 1. Conformations of crystalline cyclodecane derivatives. The ring conformation has a plane of symmetry (passing through the carbons labeled I in compound 2) and an axis of symmetry perpendicular to this plane.

The bromine atoms of trans-1, 6-dibromocyclodecane (4) (13) occupied still another set of positions. Cyclodecylamine hydrochloride sesquihydrate (5) (14, 15) and cis-1, 6-diaminocyclodecane dihydrochloride dihydrate (6) (16) were also found to have the boat-chair-boat conformation.

The three types of carbons have frequently been labeled I, II, and III, as shown in Figure 2.

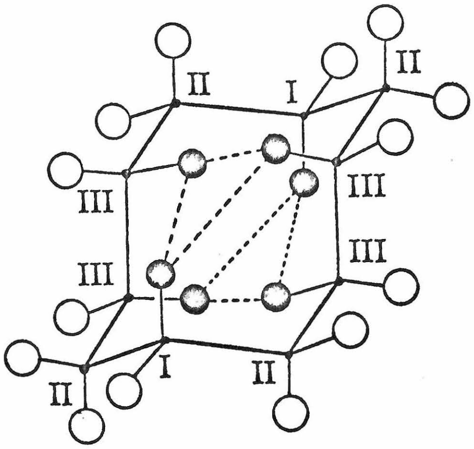


Figure 2. Intra-annular (●) and extra-annular (o) positions of cyclodecane.

Six substituent positions are associated with the three kinds of carbons. The positions denoted by an open circle have been referred to as "extra-annular"; the others, "intra-annular". The six intra-annular positions, which form two parallel planes above and below the ring, have severe non-bonded interactions and will be avoided, if possible, by substituents larger than hydrogen. For a *trans*-1, 6-disubstituted ring, there are four conformations which place the substituents in extra-annular positions, and examples of three of them have been mentioned. Only one favorable structure, the conformation found for **6**, exists for *cis*-1, 6-disubstituted derivatives.

Average values of the bond angles, bond lengths, and dihedral angles for compounds 2, 3, 5, and 6 were determined by Dunitz (9). The geometry of unsubstituted cyclodecane is probably closely approximated by these parameters, which are summarized in Figure 3.

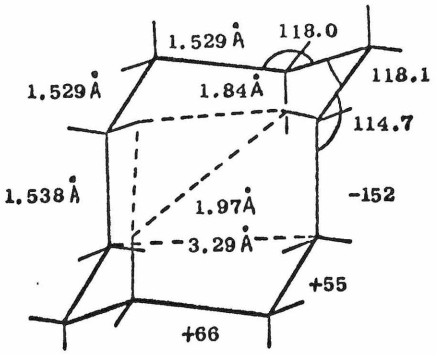


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Figure 3. Average parameters for substituted cyclodecanes: dihedral angles, bond angles, bond lengths, and transannular H···H and C···C distances.

The CCC bond angles are considerably larger than in normal alkanes, for which the angle is about 112.5° (17-19). Widening of the angles is most pronounced at carbons of types I and II and results in a larger and more favorable separation for intra-annular hydrogens on carbons of type III. The hydrogen-hydrogen distances shown in Figure 3 (1.84 and 1.97 Å) are, nevertheless, substantially smaller than the sum of the van der Waals radii. The hydrogen van der Waals radius has commonly been taken as 1.2 Å (20), but 1.5-1.6 Å is probably a more realistic value (21, 22).

Several ten-membered rings with trigonal carbons have been found to possess conformations resembling the stable cyclodecane conformation. The structure of cyclodecane-1, 6-dione has recently been described (23). The carbonyl groups occupy type III positions of the boat-chair-boat conformation, eliminating the strong hydrogen-hydrogen interactions at the III axial positions. The structural parameters are shown in Figure 4.

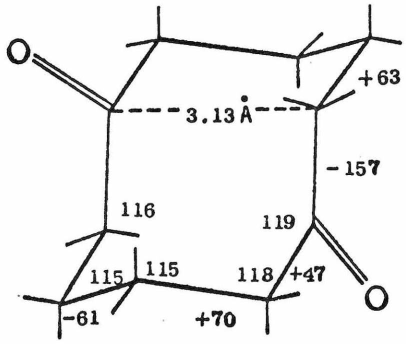

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Figure 4. Structure of cyclodecane-1, 6-dione: dihedral angles, bond angles, and one of the trans-annular C···C distances.

The transannular carbon-carbon distance in the diketone was 3.13 Å, slightly less than the corresponding distance of 3.29 Å in the average cyclodecane conformation. The closer approach of the carbons in the diketone was suggested to result from removal of the III axial H···H repulsions.

A similar conformation has been reported (24) for 2-oxacyclodecane-1, 6-dione (Figure 5).

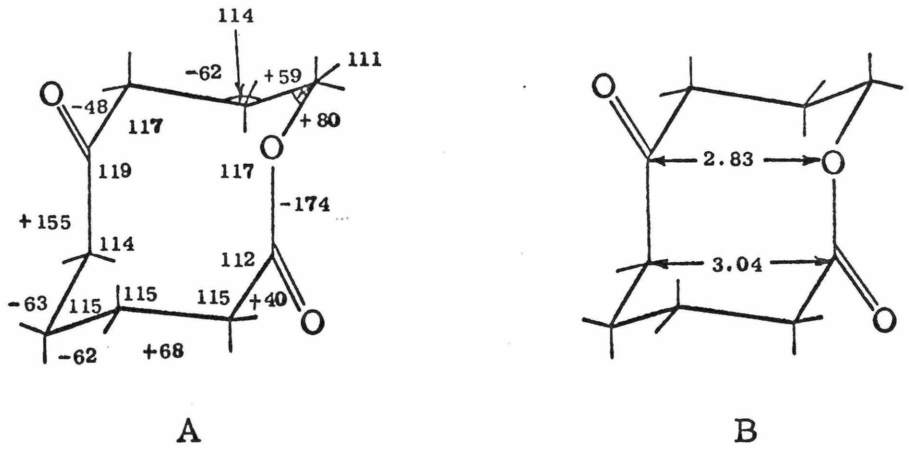

Figure 5. 2-Oxacyclodecane-1, 6-dione. A, bond angles and dihedral angles. B, selected transannular distances (in Å).

The most interesting feature of this ring is the short distance between the ether oxygen and the carbonyl carbon across the ring. The separation was less than the sum of the van der Waals radii (3.1 Å) and was thought to result from a weak attraction between the carbonyl carbon and a pair of non-bonded electrons of the ether oxygen.

The structure found (25) for a silver nitrate adduct of <u>cis</u>-cyclodecene also resembles the stable cyclodecane conformation, with the double bond between carbons of type II and III. The dihedral angles of the adduct are shown in Figure 6.

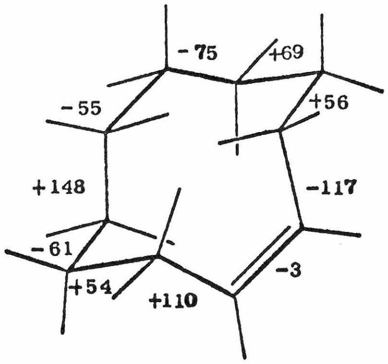

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Figure 6. Conformation and dihedral angles of a silver nitrate adduct of <u>cis</u>-cyclodecene.

A different conformation was found for a silver nitrate adduct of 5, 5, 8, 8-tetramethyl-<u>cis</u>-cyclodecene (26). Adopting the boat-chair-boat conformation would have necessarily placed two of the methyl groups in intra-annular positions. The high energy content and different conformation of the tetramethyl derivative, as compared to unsubstituted <u>cis</u>-cyclodecene, are reflected in the heat of hydrogenation and the anomalous reactions of the tetramethyl compound (27).

A final example of a ten-membered ring which has been shown by X-ray studies to have a structure resembling the boat-chair-boat conformation is 1, 6-dichlorocyclodeca-1, 3, 6, 8-tetraene (28). In this case, distortion of the cyclodecane conformation is quite severe to accommodate the four cis-double bonds.

Additional information about the conformations of cyclodecane has come from strain-energy calculations (22, 29-35). In these calculations, the total energy of a conformation is taken as the sum of several independent energy terms. The first detailed calculations of the medium rings were made by Hendrickson (29), who considered three contributions to the total energy: bond angle bending (Baeyer) strain, torsional (Pitzer) strain, and non-bonded hydrogen-hydrogen interactions. The potential functions used in calculating the strain from these sources were:

$$E_\theta = 0.020\,(\theta - 109.47°)^2$$

$$E_t = 1.40\,(1 + \cos 3\omega)$$

$$E_{HH} = 10^{4-2r} - 49.2/r^6$$

where

E_θ = bond angle bending strain in kcal/mole

E_t = torsional strain in kcal/mole

E_{HH} = non-bonded H–H interaction energy in kcal/mole

θ = C–C–C bond angle in degrees

ω = C–C–C–C torsion angle

r = H–H distance in Angstroms.

The total energy was taken as $E = \sum E_\theta + \sum E_t + \sum E_{HH}$, with the summations being over all the relevant angles and non-bonded H–H distances. H–H interactions between hydrogens bonded to the same carbon were assumed to be taken into account by E_θ. The minimum energy form of a given conformation was sought by calculation of the energy for a trial conformation, making changes in certain angles, and recalculation of the energy.

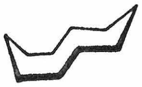
Some of the cyclodecane conformations which have been described by Hendrickson (31) are shown in Figure 7. Complete strain-energy calculations were carried out for only four of them in his first calculations (29) on the medium rings. The results are shown in Table 1, and the parameters for the "average" cyclodecane 7 are included for comparison. The crown conformation, which is not shown in Figure 7, has five rotation axes through bonds and five mirror planes through atoms and is analogous to chair cyclohexane (D_{3d}) and crown cyclooctane (D_{4d}).

The calculated dihedral angles for the BCB conformation are in fair agreement with the experimental value, but the bond angles are substantially too small. The error resulted from taking the bond angle of minimum strain as the tetrahedral angle; the C–C–C bond angle in n-alkanes, which presumably are relatively unstrained, is about 112.5° (17-19). The C–C–C angle in cyclohexane is also

10

Boat-chair-boat, BCB

0.0



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Boat-chair-chair, BCC

12

Chair-chair-boat, CCB

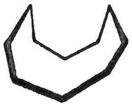
13

Chair-chair-chair, CCC

7.5 (22)

14

Chair-boat-chair, CBC



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Boat-boat, BB

Figure 7. Some conformations of cyclodecane. The nomenclature is that of Hendrickson (31). Calculated strain energies (in kcal/mole, relative to the BCB conformation) are given in several cases.

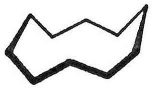
16

Boat-chair, BC

17

Long chair, LC

24.6 (31)



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Chair-chair, CC

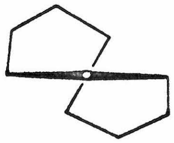
19

Twist-chair-chair, TCC

20

Twist-boat-chair, TBC

2.1 (38, 39)



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Twist-boat-boat, TBB

22

Twist-chair-boat-chair, TCBC

23

Twist-boat-chair-chair, TBCC

3.1 (38, 39)

Figure 7 (Continued). Some conformations of cyclodecane.

Table 1

Geometry and Energy of Cyclodecanes

Bond angles and dihedral angles,[a] degrees						
Description	θ_1	θ_2	θ_3	ω_1	ω_2	ω_3
Crown (D_{5d})	112.3	112.3	112.3	112.6	-112.6	112.6
CCC	112.4	112.4	112.4	81.0	-118.7	150.4
CCB	112.4	112.4	112.4	81.0		150.4
BCB	112.4	112.4	112.4	81.0	49.8	-150.4
BCB	116.0	116.0	116.0	71.0	52.4	-152.1
BCB (Exptl, 7)	118.0	118.1	114.7	66	55	-152

Energies[b]					
Description	E_θ	E_t	E_{HH}	ΣE	ΔE
Crown (D_{5d})	1.6	27.0	2.1	30.6	21.0
CCC	1.7	17.0	1.3	20.0	10.4
CCB	1.7	11.8	1.3	14.8	5.2
BCB	1.7	6.6	1.3	9.6	0.0
BCB	8.4	3.8	0.7	12.9	3.3

[a] Each of these conformations has a plane of symmetry passing through two carbons. The rings are numbered clockwise from one of these carbons (bond angle θ_1); ω_1 is the dihedral angle of the first bond adjacent to atom 1 in a clockwise direction.

[b] The energies are in kcal/mole. ΔE is the calculated energy of the conformation relative to that of the conformation calculated to have the lowest energy.

larger (111.9°) (32) than the tetrahedral angle. The boat-chair-boat conformation was calculated to have the lowest energy, but the estimates of the relative energies of the other conformations are probably inferior to the estimates obtained in later calculations using improved potential functions.

The next calculations on cyclodecane were carried out by Wiberg (33), who considered only the boat-chair-boat conformation. Two sets of potential functions were used:

Set I

$$\begin{aligned}
E_{\ell} &= 360\,(\ell-\ell_0)^2; \quad \ell_0(\mathrm{C-C}) = 1.54\,\text{Å}; \quad \ell_0(\mathrm{C-H}) = 1.09\,\text{Å} \\
E_{\theta} &= 0.11\,(\theta - 109.5°)^2 \\
E_{\omega} &= 0.33\,\cos^2(3\omega/2) \\
E_{HH} &= 0.35\{1 - \exp[-3.5(r-2.3)^2] - 1\} \\
E_{CC} &= -325/r^6 \\
E_{CH} &= -125/r^6
\end{aligned}$$

Set II

$$\begin{aligned}
E_{\ell} &= \text{Same as Set I} \\
E_{\theta} &= 0.007\,(\theta - 109.5°)^2 \qquad \mathrm{H-C-H} \\
&= 0.012\,(\theta - 109.5°)^2 \qquad \mathrm{H-C-C} \\
&= 0.018\,(\theta - 109.5°)^2 \qquad \mathrm{C-C-C} \\
E_{\omega} &= 0.165\,(1 + \cos 3\omega); \text{ identical to } E_{\omega} \text{ in Set I} \\
E_{HH} &= 10^4 \exp(-4.6\,r) - 49.2/r^6 \\
E_{CH} &= 1.29 \times 10^4 \exp(-4.12\,r) - 125/r^6 \\
E_{CC} &= 1.66 \times 10^4 \exp(-3.63\,r) - 325/r^6.
\end{aligned}$$

The calculations differed in several respects from the earlier calculations of Hendrickson. Strain due to bond length changes (E_ℓ) was included, as were nonbonded C–H and (in Set II) C–C interactions. The torsional energy was summed over all nine torsion angles about each C–C bond, so the torsional function was similar to the one used by Hendrickson. A computer minimization procedure using the method of "steepest descent" was used to find the geometry of the conformation of lowest energy.

The calculated structure and experimental conformation 7 differed mainly in the bond angle at C_1; the values of θ_1 from the two calculations were 5 and 6° lower than for 7. Some distortion of the ring probably resulted from taking the tetrahedral angle as the angle of minimum energy.

Bixon and Lifson (34) have carried out calculations for BCB and BCC cyclodecane, using the potential functions below:

$$\begin{aligned} E_\ell &= 300\,(\ell - 1.533)^2 && \text{C–C only} \\ E_\theta &= 0.025\,(\theta - 112.5^\circ)^2 \\ E_\omega &= 1.70\,(1 + \cos 3\omega) \\ E_{HH} &= 10^4 \exp(-4.6\,r) - 49.2/r^6 \end{aligned}$$

The main departure from the two previous calculations was the use of 112.5° as the zero-strain angle. The torsional barrier was based on the barrier to rotation in propane, rather than the rotational barrier in ethane. A procedure rather similar to the one described by

Wiberg (33) was used to find the geometry of the conformation of minimum energy.

The calculated dihedral angles and bond angles for BCB cyclodecane are in good agreement with the average experimental values. The calculated conformation does not have exact C_{2h} symmetry; slight deviations from C_{2h} symmetry may help lower the H–H nonbonded repulsions. The energy of BCC cyclodecane was estimated at 4.52 kcal/mole greater than the BCB conformation.

Hendrickson (22) has recalculated the energies of BCB, CCC, and crown cyclodecane, using the potential functions below:

$$
\begin{aligned}
E_\theta &= 0.0230\,(\theta - 112°)^2 \\
E_t &= 1.325\,(1 + \cos 3\omega) \\
E_{HH} &= 2300 \exp(-3.6\,r) - 49.2/r^6 \\
E_{HC} &= 4012 \exp(-3.4\,r) - 125/r^6 \\
E_{CC} &= 7000 \exp(-3.2\,r) - 325/r^6.
\end{aligned}
$$

The results are summarized in Table 2. The torsion and bond angles of the BCB conformation are in excellent agreement with the average cyclodecane conformation $\underset{\sim}{7}$, and the calculated strain energy, relative to cyclohexane, agrees well with the experimental value. The calculated energy difference between the BCB ($\underset{\sim}{10}$) and CCC ($\underset{\sim}{13}$) conformations was 7.5 kcal/mole. The higher torsional energy of the CCC conformation accounts for most of the difference; according to the calculations, the bond angle strain and hydrogen-hydrogen

Table 2

Geometry and Energy of Cyclodecanes (22, 31)

Description	θ_1	θ_2	θ_3	ω_1	ω_2	ω_3
	Bond angles and dihedral angles[a], degrees					
Crown (D_{5d})	116	116	116	108.7	-108.7	108.7
CCC (13)	116	116	115	73.0	-115.0	150.3
BCB (10)	118	118	116	66.0	54.9	-152.0
BCB (Exptl, 7)	118	118	115	66	55	-152
LC (17)[b]	118	118	118	0	112.2	-72.7

Description	E_θ	E_t	E_{HH}	E_{CH}	E_{CC}	$\sum E$	E_0	E_{exp}	ΔE
				Energies[c]					
Crown (D_{5d})	3.68	24.23	6.70	0.61	-1.46	33.76	32.7		19.5
CCC (13)	3.04	14.21	5.91	0.14	-1.49	21.82	20.7		7.5
BCB (10)	6.44	2.82	7.66	-1.15	-1.44	14.32	13.2	13.5 ± 0.5[d]	0.0
LC (17)[b]	8.28	16.59	14.88	0.51	-1.33	38.93	37.8		24.6

Table 2 (cont'd)

[a] The rings are numbered as in Table 1 (footnote a).

[b] The bond angles, $\theta = 118°$, were not varied for the LC conformation.

[c] Energies are in kcal/mole. E_0 = calculated energy relative to cyclohexane chair = $\sum E - 1.08$; E_{exp} = experimental value relative to cyclohexane chair; ΔE = calculated energy relative to BCB cyclodecane.

[d] J. Coops, H. von Kamp, W. A. Lamregets, J. Visser, and H. Dekker, Rec. Tran. Chim., **79**, 1226 (1960).

nonbonded interactions are lower in **13** than in **10**. The torsional energy term also dominates in the calculations for crown cyclodecane, which is substantially higher in energy than the BCB conformation. Detailed calculations were carried out (31) for LC cyclodecane (**17**) for the first time. The effect of optimizing the bond angles was not investigated, but the conformation is clearly of high energy.

Allinger (35) has considered only the BCB conformation of cyclodecane. Although his calculations give good results for some systems, they do not work well for the medium rings, including cyclodecane. The calculated bond angles and energy are both too large.

Hendrickson (30) has calculated the strain energies of methylcyclodecane for each of the six substituent positions of the BCB conformation. The results are summarized in Table 3. The calculations provide a useful estimate of the relative energies for substitution at the various positions, but the energies in Table 3 should be considered quite approximate. An axial-equatorial methyl energy difference of only 0.7 kcal/mole was calculated for chair cyclohexane, in poor agreement with the experimental difference of 1.7 kcal/mole.

The equatorial methylcyclodecanes appear to have similar energies, with the 3e position slightly favored. The $-NH_3^+$ group of the monosubstituted cyclodecane **5** (Figure 1) occupies the 3e position, which tends to support a lower energy for substitution at this position. Conformations with the methyl group at positions 1a or 3a are of

Table 3

Energies of Methylcyclodecanes

Substituent position[a]	E[b]
1e	0.6
1a	8.6
2e	0.5
2a	0.6
3e	0.2
3a	13.4

[a] The carbon positions are defined in Figure 8.

[b] The energies are in excess of strain in the ring itself, in kcal/mole.

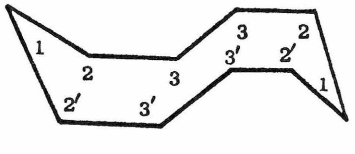


Figure 8. Numbering system for the carbons of cyclodecane.

quite high energy, as expected. The 2a position is nearly as strain free as the equatorial positions, according to the calculations. This result implies that *gem*-disubstituted cyclodecanes will prefer to have the substituents at position 2. Hendrickson found that the criterion for a carbon with *both* substituent sites essentially strain free is one of being bounded by dihedral angles of the same sign.

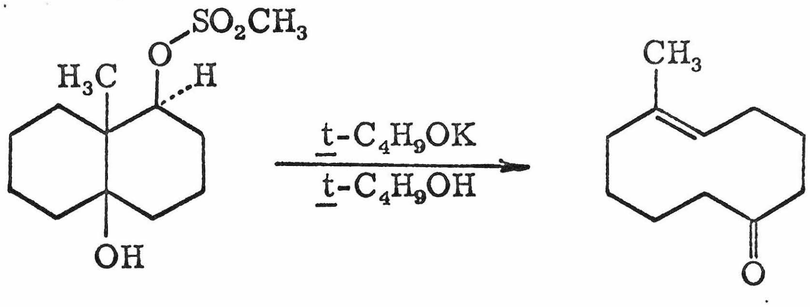
Although the results of the X-ray investigations and the strain-energy calculations leave little doubt that cyclodecane and a number of its derivatives exist largely in the BCB conformation, several ten-membered rings have been shown to prefer some of the other conformations in Figure 7. The high strain energy of 1a or 3a BCB methylcyclodecane was noted earlier. By appropriate substitution, the cyclodecane ring can be forced either to accept a methyl group in an intra-annular position of the BCB conformation or to adopt another conformation. 1, 1, 5, 5-Tetramethylcyclodecane-8-carboxylic acid was the subject of a careful study (36-39) to determine the consequences of intra-annular substitution. By a combination of X-ray analysis (36, 37) and strain-energy calculations (38, 39), the tetramethylcyclodecane was found to occupy a mixture of TBC (**20**) and TBCC (**23**) conformations (about 80% **20** and 20% **23**).

The calculated strain energies (38, 39) of TBC and TBCC cyclodecane, relative to the BCB conformation, were 2.1 and 3.1 kcal/mole, respectively. Experimental evidence for these energy differences came from combustion studies of 1, 1, 4, 4- and 1, 1, 5, 5-tetramethylcyclodecane. The former compound probably has the BCB conformation; the latter derivative can be expected to occupy the TBC and/or TBCC conformations, by analogy with 1, 1, 4, 4-tetramethylcyclodecane-8-carboxylic acid. The heat of combustion for the 1, 1, 5, 5-isomer was 2.3 ± 0.3 kcal/mole higher than for the 1, 1, 4, 4-isomer, in agreement with the calculated values.

Conformations analogous to LC (40), CBC (41), and BCB (42) cyclodecane have been considered for cis, cis-1, 6-cyclodecadiene and derivatives. A determination of the space group and unit cell of cis, cis-cyclodeca-3, 8-diene-1, 6-dione (43) led to the conclusion that the compound adopts the LC conformation in the solid state. As mentioned earlier, nmr studies (3, 4) of cis, cis-1, 6-cyclodecadiene and a number of derivatives substituted at positions 4 and 9 also support the long-chair conformation for this ring system. An X-ray analysis of tetraethyl cis, cis-3, 8-cyclodecadiene-1, 1, 6, 6-tetracarboxylate has been completed (44), but the results have not yet been published. Cis, cis-cyclodeca-1, 6-diene has recently been studied in the gaseous state by electron diffraction (45). The authors concluded that the diene exists largely in the LC conformation, although a reasonably good fit of the experimental radial distribution curve could also be obtained with a model based on the CBC conformation.

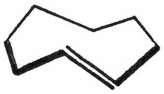
Trans-cyclodecene is another ten-membered ring for which conformations other than those analogous to BCB cyclodecane are important. The conformations of trans-cyclodecene are of particular interest because of the possibility of optical isomerism. Blomquist et al. (46) suggested that trans-cyclononene should exist in two separable enantiomorphic modifications. Interconversion of the enantiomers requires rotation of the double bond through the ring, and this motion is opposed by the interaction of the vinyl hydrogens with the hydrogens of the methylene groups on the opposite side of the ring. Cope and co-workers succeeded (47-51) in the separation of optical isomers of trans-cyclooctene and cis, trans-1, 5-cyclooctadiene. Resolution was best accomplished by releasing the cycloalkene from a diastereomeric platinum complex (47-49), although some degree of optical activity could be achieved by means of an asymmetric Hoffman elimination (50, 51). The (R)-configuration of the double bond was subsequently assigned (52, 53) to the levorotatory isomer of trans-cyclooctene.

An activation energy of 35.6 ± 0.9 kcal/mole was found (54) by a polarimetric technique for the racemization of trans-cyclooctene. Lengthening the methylene chain by one carbon substantially lowers the barrier to rotation of the olefinic double bond, and an activation energy of 20 ± 2 kcal/mole was determined (55) for the racemization of trans-cyclononene (35). The half life for the nine-membered ring was only about 6 sec at 30°. Optically active trans-cyclodecene could not be obtained (55) by the procedure which was successful for trans-cyclononene. The reaction shown below (56), starting with the optically active sulfonate, also failed to give an optically active product. The failure to resolve the ten-membered trans-cycloalkenes indicated that the barrier to racemization was low for these compounds.



Interconversion of the enantiomers of trans-cyclodecene-1, 2, 4, 4, 9, 9-d_6 was studied by Binsch and Roberts (57). At ambient temperature, the deuterium-decoupled pmr spectrum showed two sharp singlets at δ1.37 and δ2.04, in a ratio of 2:1. The signal from the allylic protons split into a close AB pattern on cooling to -74°, and the peak at higher field changed into a complex, unsymmetrical pattern. Further spectral changes, corresponding to slow interconversion of different conformations, resulted on cooling to -143°, at which temperature line broadening again occurred. At -164°, two featureless, partially overlapping peaks with line widths of about 30 Hz emerged, but further changes in the spectra could not be followed because of viscosity broadening. An activation energy of 10.7 ± 0.3 kcal/mole was determined for the interconversion of the enantiomers.

Binsch and Roberts proposed that two sets of diastereomers are possible for trans-cycloalkenes of medium ring size having an even number of carbons, while only one pair of enantiomers is possible for the odd-membered trans-cyclic olefins. The optical isomers considered for trans-cyclooctene are shown in Figure 10. Conformations corresponding to one of these sets (25 and 27) have been found (58) for a copper complex of the alkene. Conversion of a given conformation into its enantiomer requires rotation of both the C-1--C-2 and the C-5--C-6 bond segments through the ring. Either process alone converts the conformation into one of the diastereomers.



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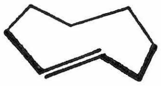

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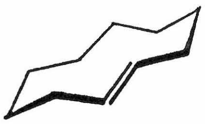
Figure 10. Trans-cyclooctene conformations.

The optical rotation of trans-cyclooctene may arise primarily from twisting of the double bond (59). If this is the case, the activation energy obtained by Cope and Pawson (54) could refer only to rotation of the double bond through the ring, rather than to racemization, which requires an additional process. For trans-cyclononene, only one element of dissymmetry is present, and this ambiguity does not exist.

Twelve conformations of trans-cyclodecene (six pairs of enantiomers) were considered in the interpretation of the nmr results for the deuterated compound. The conformations having the (R)-configuration of the double bond are shown in Figure 11. The C-6--C-7 bond segment in the ten-membered ring corresponds to the C-5--C-6 bond in trans-cyclooctene. Conversion of a given trans-cyclodecene conformation into its enantiomer can be accomplished by three processes: rotation of the double bond and the C-6--C-7 bond through the ring, and flipping of the methylene groups at positions 4 and 9.



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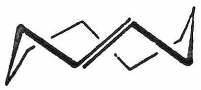

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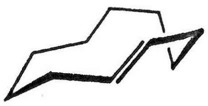

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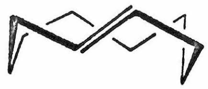

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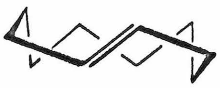

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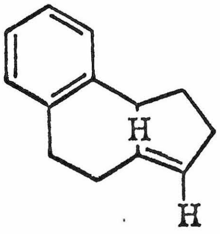
Figure 11. Conformations of trans-cyclodecene.

Examination of models suggested that flipping of the C-4 and C-9 methylene groups should be fast, relative to the other two processes, and it was assumed that restricted rotation of the C-6--C-7 segment would not have a significant effect on the spectrum of the allylic protons. The authors concluded that the changes above -74° in the low-field part of the pmr spectra were due to slow rotation of the double bond through the ring. The conformations in Figure 11 would give rise to an AB pattern for the allylic protons, and the average positions of these protons would be exchanged on conversion to the (S)-series by the double-bond rotation process. Broadening of the signal from the non-allylic protons at a slightly higher temperature than for the spectrum of the C-3 and C-10 protons was suggested to indicate that the barrier to rotation of the C-6--C-7 segment through the ring was a little higher than the barrier found for rotation of the C-1--C-2 bond (E_a = 10.7 kcal/mole).

Nmr spectroscopy was used subsequently (60, 61) to obtain information about the rates of double-bond rotation in the two compounds below, which could not be resolved (60, 62) through formation of the corresponding diastereomeric platinum complexes.



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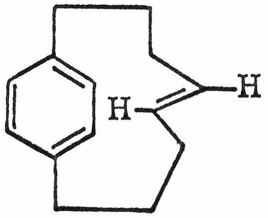

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The pmr spectra (60) of **34** showed no changes in the temperature range +107 to -87°; apparently the barrier to racemization is quite low. Conformational changes in a deuterated derivative of **35** and some related compounds (61) were suitable for study by the nmr method.

An X-ray determination of the structure of a *trans*-cyclodecene silver nitrate adduct has been reported (63). The conformation resembles TBCC cyclodecane. Dunitz has suggested (64) that the TBCC-type conformation (**29**, Figure 11) should be favored over the conformation corresponding to BCB cyclodecane (**32**) because the C=C–C–C dihedral angles in the former conformation are closer to the preferred angle (120°) (65-67) in open-chain alkenes. The nmr results show, however, that the conformation found for the silver nitrate adduct in the solid state is not the only conformation of *trans*-cyclodecene appreciably populated in solution. Only one process could have been observed in the pmr spectrum of *trans*-cyclodecene-1,2,4,4,9,9-d_6 if no conformations other than **29** (and its enantiomer) had been present. The observation of two well separated changes in the pmr spectra of the deuterated compound shows that at least one of the other diastereomers must have a significant population. The C–C=C–C dihedral angle in the silver nitrate adduct was only 138°, in contrast with the normal value of 180° for an unstrained *trans*-alkene. The possibility that the deviation from planarity of the double bond of *trans*-cyclodecene would be substantially less than found for the silver nitrate complex was considered unlikely.

The near-planarity of the double bonds in the silver nitrate adducts of cis-cyclodecene and 5, 5, 8, 8-tetramethyl-cis-cyclodecene was taken to indicate that there was no strong electronic effect of the silver ion on the geometry of the double bond. The Ag··· olefinic C distances of these complexes and the trans-cyclodecene adduct lay in the same range (2.4-2.5 Å), which supports the view that the bonding in the cis- and trans-adducts is similar. The possibility that the distortion of the trans-double bond resulted from steric repulsion between the silver ion and the α-CH_2 groups was rejected because shorter $Ag \cdots C_\alpha$ and $Ag \cdots H_\alpha$ distances have been observed in other compounds.

Dunitz calculated (63) that twisting the double bond by 42° would contribute approximately 30 kcal/mole to the total strain energy of trans-cyclodecene. This value was more than three times larger than an estimated upper limit of 8.6 kcal/mole, based on the strain energy of cyclodecane and the difference in the heats of hydrogenation of trans-cyclodecene and trans-2-butene. It was suggested (64) that the C–C=C–C dihedral angle depends on out-of-plane bending at the two sp^2 centers, as well as twisting of the double bond. A rough calculation, based on the force constants given by Arnott and Crawford (68) for ethylene, indicated that out-of-plane bending accounted for about 63% of the deviation of the C_{10}–C_1–C_2–C_3 dihedral angle from 180°, with the remainder of the distortion arising from pure twisting. The calculated strain energy was only 7 kcal/mole.

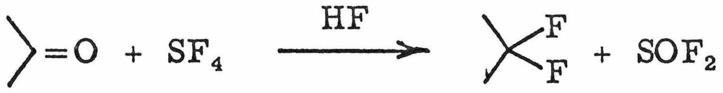
Dihedral angles of 150, 163, 165, and 167° were observed (69) for the silver-nitrate complexed endocyclic trans-double bonds of some ten-membered ring sesquiterpenes. These rather highly substituted rings existed in conformations corresponding to BCC or CCC cyclodecane.

Several of the conformations in Figure 7 are also important as possible intermediates in the interconversion of substituent positions in cyclodecane. A discussion of the modes of conformational interconversions in cyclodecane will be deferred until after the experimental results from the ^{19}F nmr studies have been described.

SYNTHESIS

A synthesis of 1, 1-difluorocyclodecane was required for determination of its barrier to ring inversion. Also, if possible, a derivative of trans-cyclodecene with a gem-fluoro group somewhere in the ring was desired for an extension of the study (57) of trans-cyclodecene-d_6.

Gem-fluorides can generally be obtained by treatment of the corresponding ketone with a mixture of sulfur tetrafluoride and a Lewis acid (frequently hydrofluoric acid) (70, 71).



Ketones with carbonyl groups that readily undergo addition reactions, such as cyclohexanone, are often fluorinated smoothly in excellent yield. Fluorination of the medium-ring ketones is considerably more difficult; 1, 1-difluorocyclooctane was obtained from cyclooctanone in only 9% yield (72) by treatment of the ketone with phenyl sulfur trifluoride. Attempts to prepare 1, 1-difluorocyclodecane by treatment of cyclodecanone with either sulfur tetrafluoride or phenyl sulfur trifluoride were unsuccessful (73).

The reactivity of the carbonyl group of cyclodecanone, as measured, for example, by the dissociation constant of the cyanohydrin (74) or the rate of reduction by sodium borohydride (75) is somewhat lower than for cyclooctanone, so the greater difficulty of fluorination of the ten-membered ketone is not surprising. The preferred conformation of cyclodecanone is probably as shown in Figure 12, by analogy with the structure of cyclodecane-1, 6-dione (Figure 4). Low reactivity of the carbonyl group towards reactions which result in replacement of the trigonal carbon with a tetrahedral carbon is to be expected as a consequence of the increase in transannular interactions.

A synthesis of 1, 1-difluorocyclodecane and 3, 3-difluoro-trans-cyclodecene was eventually accomplished by the route shown in Figure 13. The key step, which introduced the gem-fluoro group into the ten-membered ring, was the fluorination of sebacoin tosylate with a sulfur tetrafluoride--hydrogen fluoride mixture. The tosylate group in 38 appears to increase the reactivity of the carbonyl group toward the fluorinating agent. As indicated earlier, the ease with which a ketone undergoes the fluorination reaction seems to be qualitatively

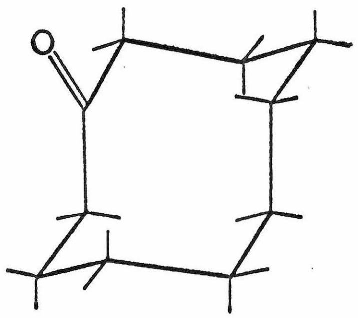


Figure 12. Possible conformation of cyclodecanone.

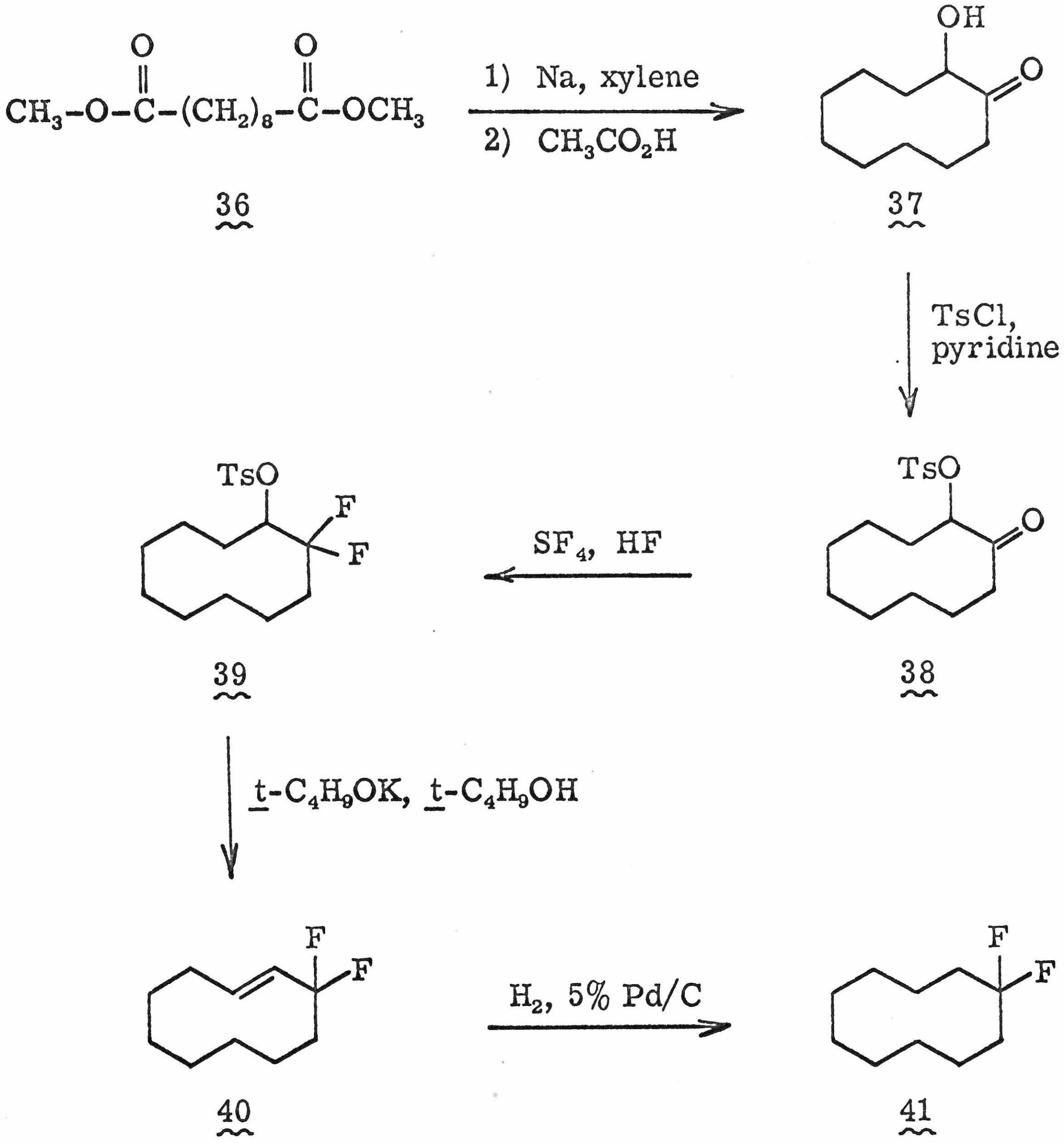
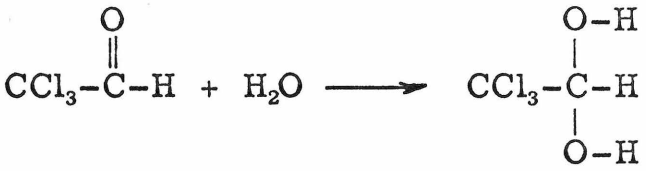


Figure 13. Synthesis of 3, 3-difluoro-trans-cyclodecene and 1, 1-difluorocyclodecane.

related to the tendency of the carbonyl group to undergo addition reactions, such as formation of the cyanohydrin or reduction by sodium borohydride. The presence of adjacent electron-withdrawing groups is known to affect the reactivity of a carbonyl compound, as shown, for example, by the formation of a stable hydrate from chloral on treatment with water.

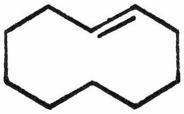


$$\mathrm{CCl_3-\overset{\displaystyle O}{\overset{\|}{C}}-H} + \mathrm{H_2O} \longrightarrow \mathrm{CCl_3-\underset{\underset{\displaystyle O-H}{|}}{\overset{\overset{\displaystyle O-H}{|}}{C}}-H}$$

The conditions for fluorination of sebacoin tosylate were rather critical, and the yield of difluoride was only 14%. Some *p*-toluenesulfonyl fluoride was formed in the reaction. The difluoro tosylate **39** was stable and did not decompose during the purification procedure. Treatment of the tosylate with potassium *t*-butoxide in dimethyl sulfoxide or lithium dicylohexylamide in benzene/hexane at room temperature gave immediately a deep red color, and none of the desired difluoride was isolated from these reactions. Refluxing a solution of the tosylate in potassium-*t*-butoxide/*t*-butyl alcohol for 19 hr gave the difluorocyclodecene in reasonable yield. With this base/solvent system, the mixture turned slightly yellow, but the red color did not appear.

The allylic difluoride was unstable and difficult to purify. Distillation under reduced pressure gave a cloudy distillate which soon turned brown and viscous, giving off bubbles of a gas which etched the container. Extensive decomposition resulted when purification by preparative vpc was attempted with an old, contaminated column. The small amount of difluoride which was obtained soon turned cloudy and decomposed. Purification was finally accomplished by preparative vapor phase chromatography with a nearly new column. Decomposition of the compound on the column was not observed until after about 1 gram had been collected in several portions.

The cycloalkene was assigned the *trans*-configuration on the basis of a strong band at 985 cm^{-1} in the ir spectrum. The C=C stretching frequency was 1675 cm^{-1}. Corresponding bands for the unsaturated ten-membered rings 42 - 45 below are given in Table 4.



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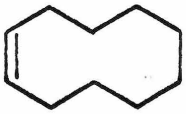

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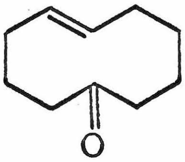

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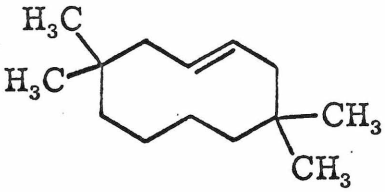

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The *trans*-configuration is also supported by the method of synthesis. *Trans*-cyclodecene was the major product from the reaction of cyclodecyl bromide with potassium *t*-butoxide in *t*-butyl alcohol (78). Evidence was presented for a *syn*-elimination mechanism in the formation of the *trans*-cyclodecene and an *anti*-elimination mechanism in the formation of the *cis*-cyclodecene. A reasonable transition state (46), based on the conclusions for the bromide, is

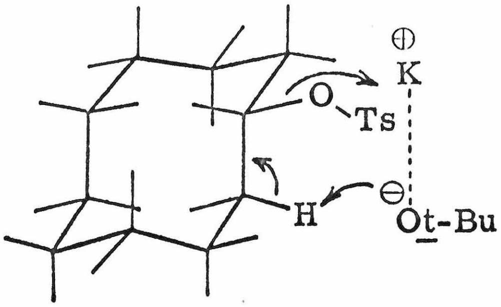
Table 4

IR Bands of Cyclodecenes

Compound	C=C stretch[a]		Out-of-plane $C{=}C{\diagup}^{H}$ deformation[a]		Reference
	cm^{-1}	μ	cm^{-1}	μ	
40 (Fig. 13)	1675	5.97	985	10.15	This work
42	1645	*6.08*	977.5- 980.5	*10.22-* *10.23*	76
43	1642	*6.09*	706	*14.17*	76
44			980	*10.2*	77
44			988	10.12	This work
45			*980* & *990*	10.20 & 10.10	6

[a] The values in the original units used are underlined.

shown below for the formation of *trans*-cyclodecene from cyclodecyl tosylate by treatment with potassium *t*-butoxide in *t*-butyl alcohol. A possible corresponding conformation (47) for the difluoro tosylate is also shown; formation of the *trans*-cycloalkene should clearly not be precluded by the *gem*-fluoro group.



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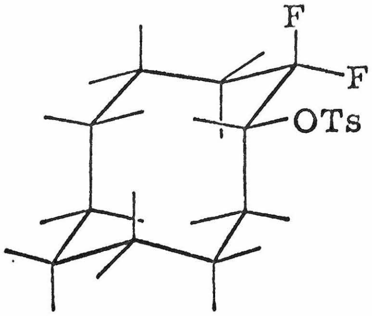

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Cis-cyclodecene probably has the BCB conformation, with the double bond between carbons of type II and III (Figure 6) (25). Formation of the cis-olefin from cyclodecyl tosylate may preferentially occur by elimination of the elements of p-toluenesulfonic acid from adjacent carbons of type II and III. In the case of the difluoro tosylate, the tendency of the fluorines to avoid the intra-annular positions would then help to block the formation of the cis-allylic difluoride.

The hydrogenation of 3, 3-difluoro-trans-cyclodecene proceeded quite smoothly; there was no evidence that the adjacent fluorines were disturbed during reduction of the double bond.

RESULTS

The ambient-temperature ^{19}F nmr spectrum of a vinyl chloride solution of 1, 1-difluorocyclodecane is a quintet 23.24 ppm upfield from internal ethyl chlorodifluoroacetate, with J_{HF} = 15.5 Hz. The spectrum broadens below -129° and splits into an AB quartet with a chemical-shift difference of 577 Hz and J_{FF} = 243 Hz at -164°. Exchange rates between -129 and -149° were determined by comparison of experimental spectra with theoretical spectra calculated as a function of τ, the pre-exchange lifetime (see Experimental section). The chemical-shift difference was assumed to decrease by 0.87 Hz per degree rise in temperature.

Representative spectra and an Arrhenius plot of the rate constants are shown in Figures 14 and 15, respectively. The activation energy and frequency factor were determined by the least-squares treatment to be $E_a = 7.0 \pm 0.2$ kcal/mole and log A = 14.45 ± 0.35. At -135°, the free energy of activation was 5.74 kcal/mole and the entropy of activation was 7.1 eu.

The ^{19}F nmr spectrum of 3, 3-difluoro-trans-cyclodecene in propene at 14° is an exchange-broadened singlet 30.0 ppm upfield from internal ethyl chlorodifluoroacetate. The effect of hydrogen-fluorine coupling can be seen by heating a carbon tetrachloride solution of the compound above ambient temperature; the spectrum changes into an unsymmetrical multiplet at these temperatures. On cooling to -30°, the spectrum splits into an AB pattern with

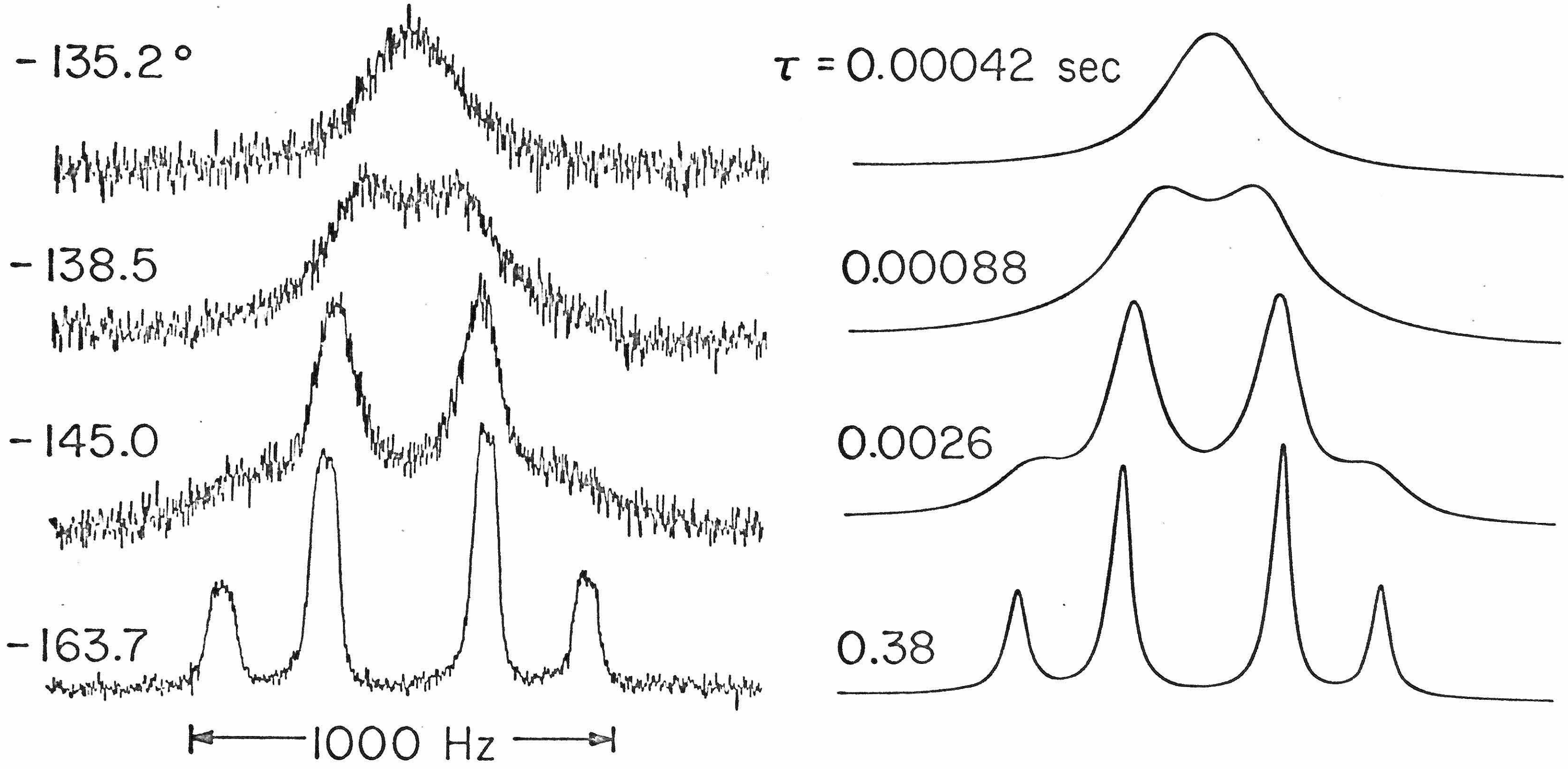


Figure 14. Experimental fluorine nmr spectra (left) of 1,1-difluorocyclodecane in vinyl chloride. On the right are spectra calculated as a function of τ, the mean lifetime before ring inversion.

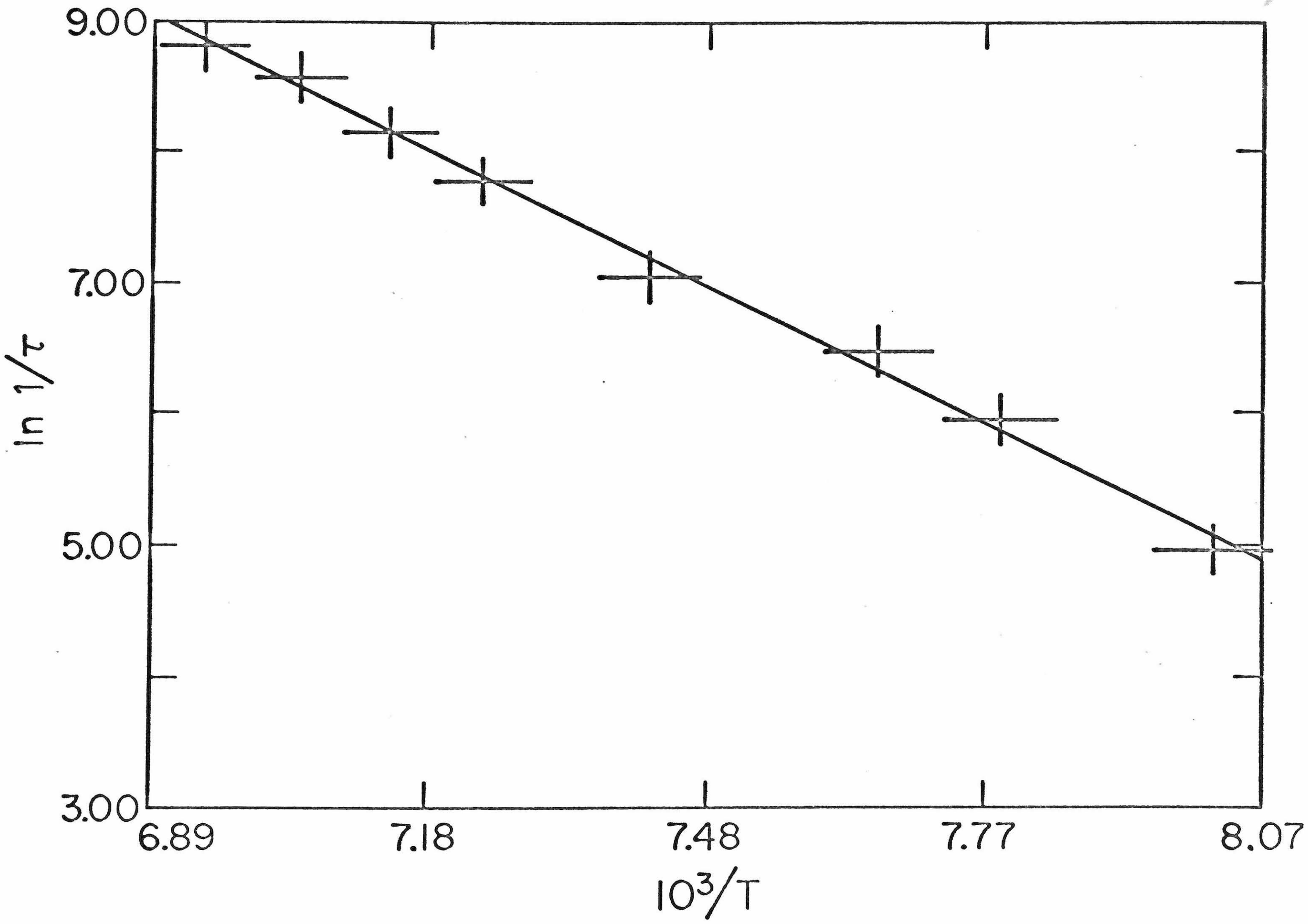


Figure 15. Arrhenius plot for 1, 1-difluorocyclodecane.

J_{FF} = 236 Hz and an apparent chemical-shift difference of 252 Hz. The separation of the two inner lines decreases by about 8 Hz as the temperature is lowered from -11 to -30°, apparently because the first process overlaps with changes that take place at lower temperatures. Rate constants were obtained for spectra taken between +17 and -11°; a chemical shift difference of 272 Hz was used for the calculations. Representative spectra and an Arrhenius plot of the rate constants are shown in Figures 16 and 17, respectively. The activation energy and frequency factor were $E_a = 14.9 \pm 0.4$ kcal/mole and $\log A = 14.68 \pm 0.28$. At 2.8°, $\Delta G^{\ddagger}$ was 12.4 kcal/mole and $\Delta S^{\ddagger}$ was 6.9 eu.

The spectrum broadens again below -30°, as shown in Figure 18. At -148°, two AB patterns with relative areas of 85:15 are present, and several smaller peaks arising from impurities and/or other conformations are also visible. The chemical shifts and coupling constants for the AB's are given below.

	ν_1(Hz)	ν_2(Hz)	$\Delta\nu$(Hz)	J_{FF}(Hz)
Major AB	1271	1610	339	237
Minor AB	1351	2181	830	227

These spectra are represented schematically in Figure 19. Exchange to produce an intermediate AB spectrum at higher temperatures could occur in two ways:

(I) $a_1 \rightleftharpoons b_2$ and $b_1 \rightleftharpoons a_2$ or

(II) $a_1 \rightleftharpoons a_2$ and $b_1 \rightleftharpoons b_2$.

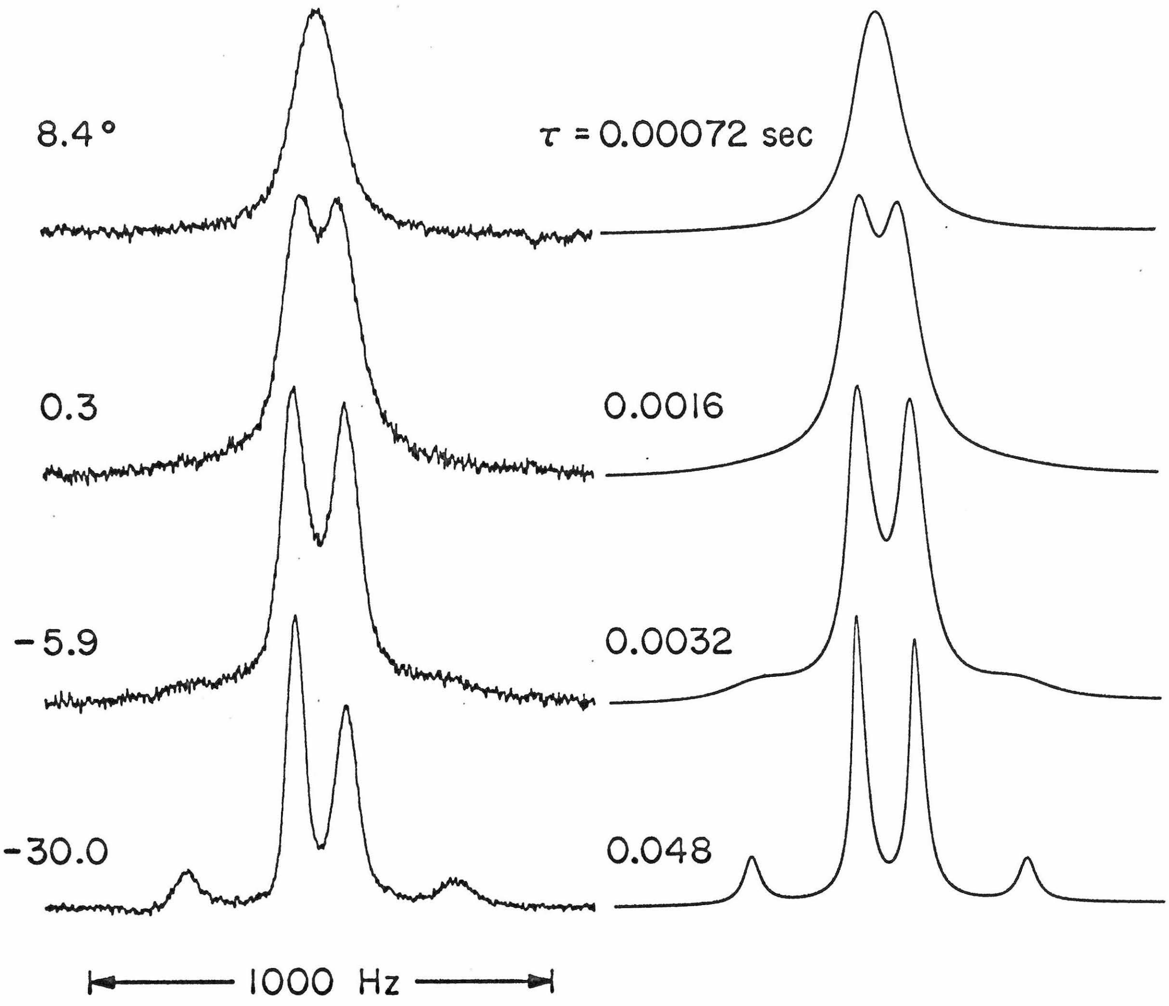


Figure 16. Experimental (left) and calculated (right) ^{19}F nmr spectra of 3, 3-difluoro-trans-cyclodecene in propene.

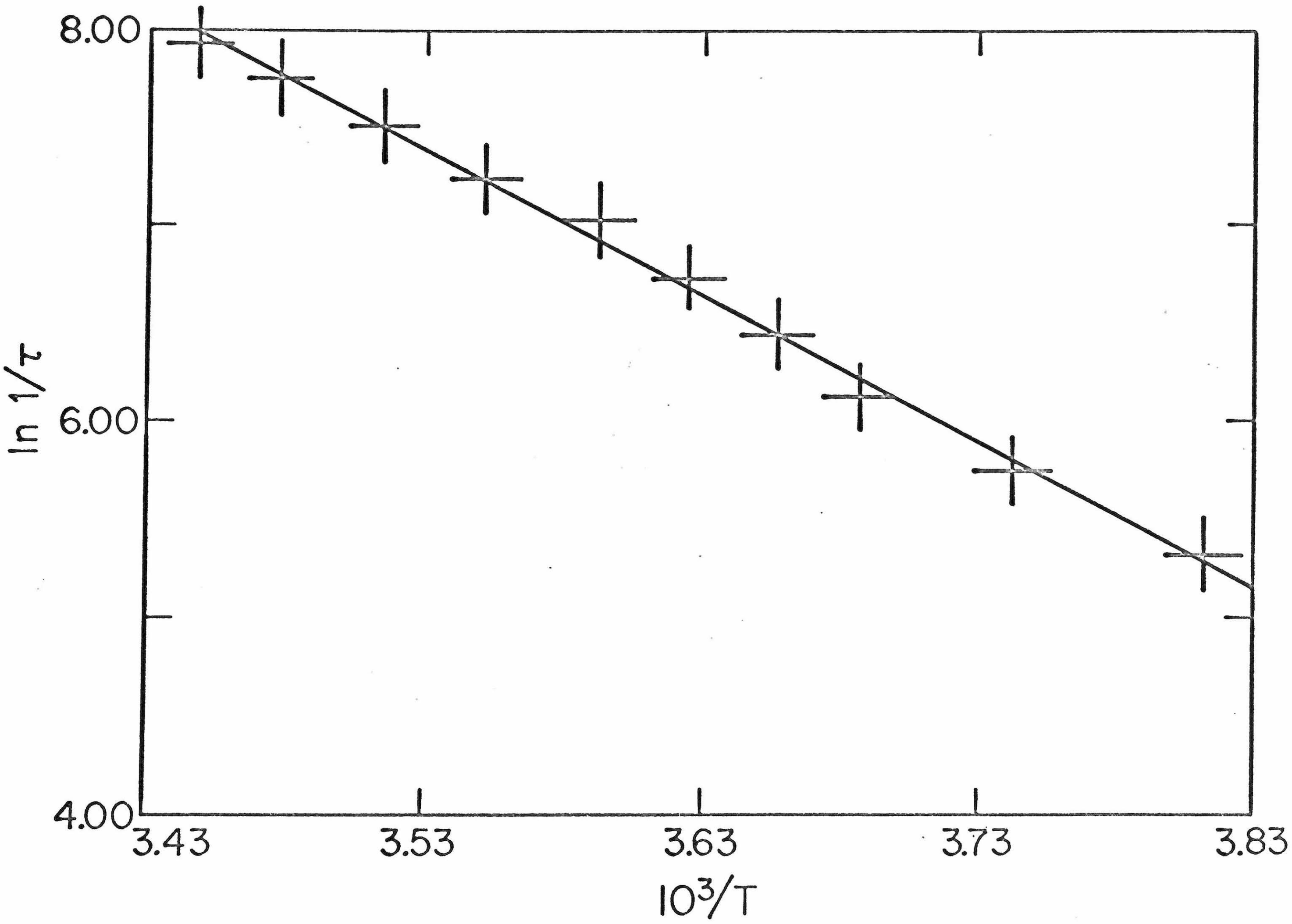


Figure 17. Arrhenius plot for 3, 3-difluoro-trans-cyclodecene.

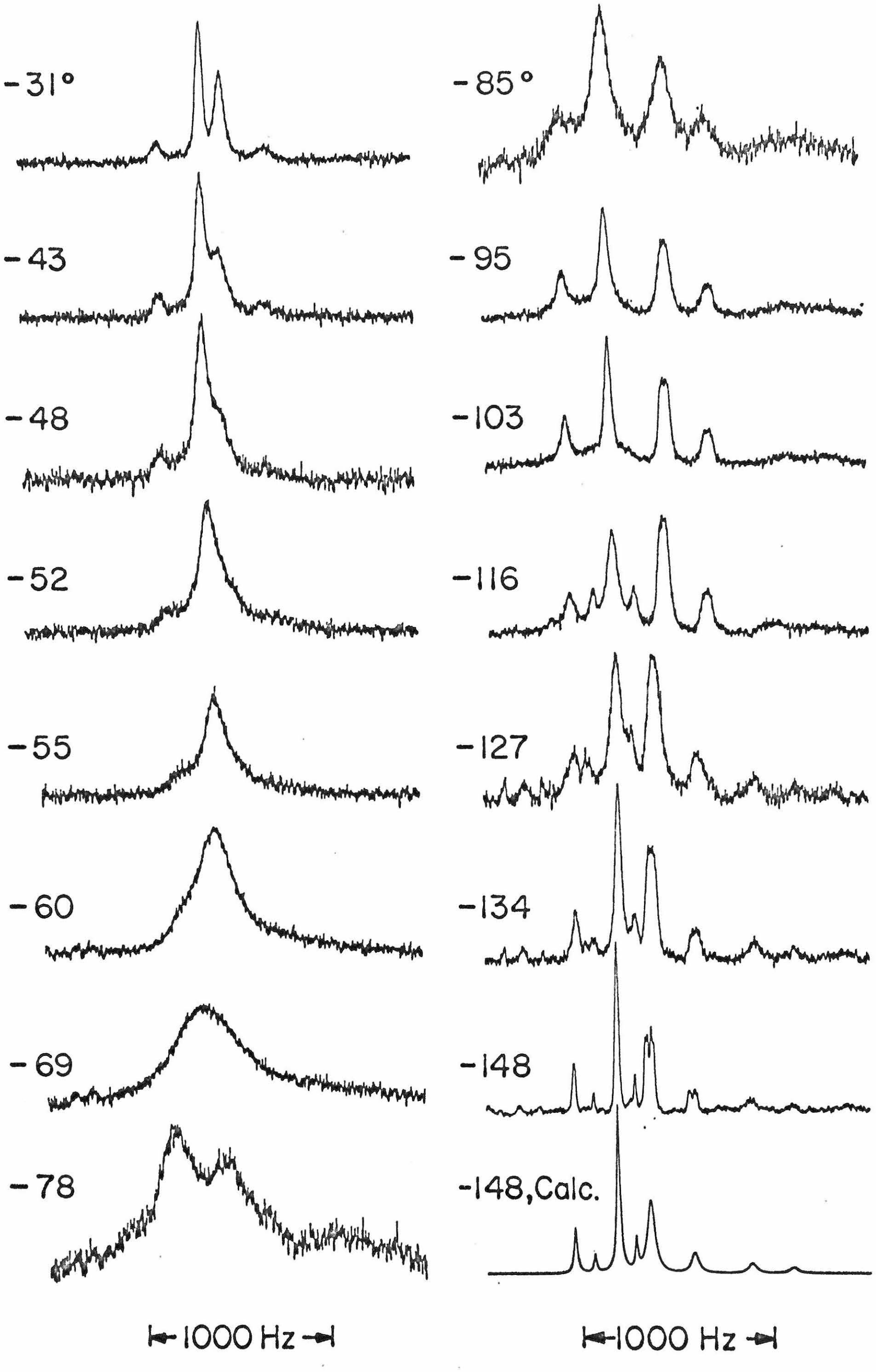


Figure 18. Low-temperature ^{19}F nmr spectra of 3,3-difluoro-trans-cyclodecene in propene.

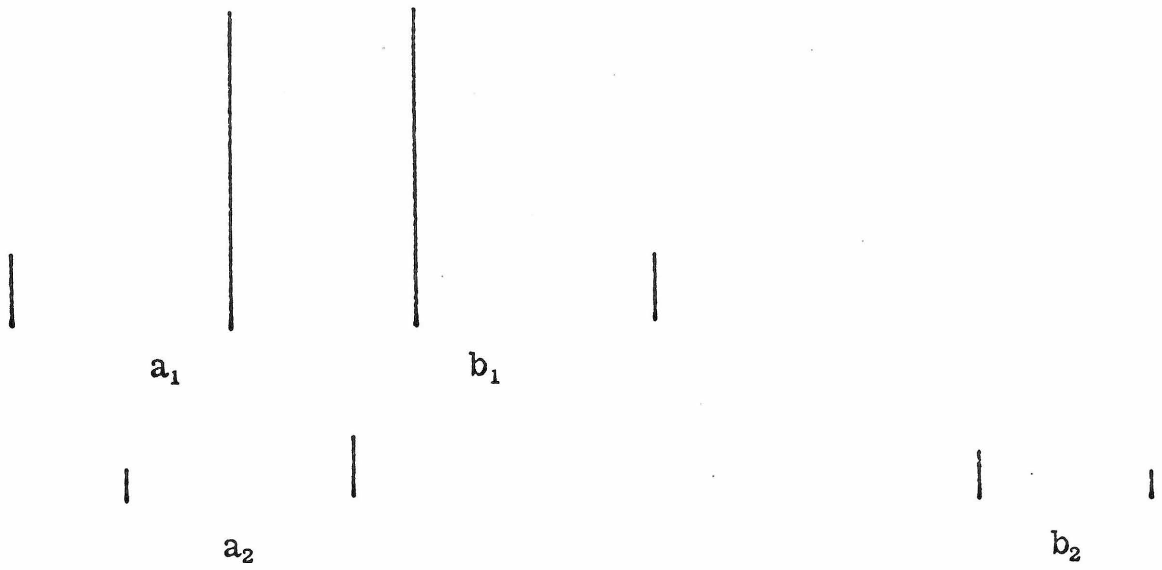


Figure 19. Schematic representation of the AB spectra of 3, 3-difluoro-trans-cyclodecene.

Chemical shifts were calculated (Table 5) for both types of exchange and for populations (p_1) of 0.85, 0.70, and 0.50. Unless a very large change in relative populations with temperature is assumed, the agreement between the calculated and experimental chemical shifts is poor. Significant amounts of other conformations may be present, and/or the chemical shifts may change with temperature.

Table 5

Fluorine Chemical Shifts of 3, 3-Difluoro-trans-cyclodecene[a]

Experimental[b]

		ν_1	ν_2	$\Delta\nu$
		1534	1786	252

Calculated

Mode of exchange	p_1	ν_1[c]	ν_2[d]	$\Delta\nu$
I	0.85	1408	1571	163
I	0.70	1544	1532	-12
I	0.50	1726	1481	-245
II	0.85	1283	1696	413
II	0.70	1295	1781	487
II	0.50	1311	1896	585

[a] The chemical shifts are in Hz, upfield from internal $CF_2ClCO_2C_2H_5$.

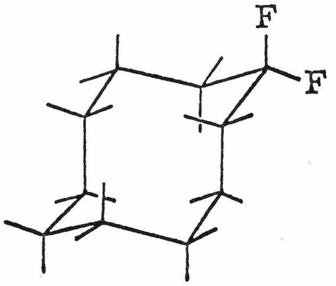
[b] The experimental chemical shifts here are the apparent values at -31°; as discussed in the text, the actual chemical shift difference appears to be larger by about 20 Hz.

[c] $\nu_1 = p_1\nu(a_1) + (1 - p_1)\nu(b_2)$ and $\nu_1 = p_1\nu(a_1) + (1 - p_1)\nu(a_2)$ for exchange modes I and II, respectively.

[d] $\nu_2 = p_1\nu(b_1) + (1 - p_1)\nu(a_2)$ and $\nu_2 = p_1\nu(b_1) + (1 - p_1)\nu(b_2)$ for exchange modes I and II, respectively.

DISCUSSION

The observation of a single AB pattern for the ^{19}F nmr spectrum of 1, 1-difluorocyclodecane at -164° is consistent with conformation 48 (and its mirror image). Conformations 49 and 50



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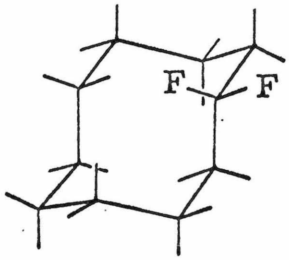

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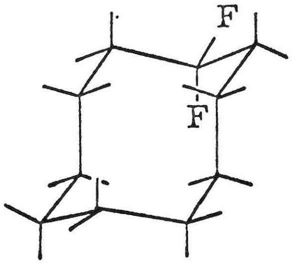

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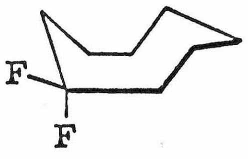
would place one of the fluorines in an intra-annular position, and should not be significantly populated at this temperature. A similar situation was observed (72) for 1, 1-difluorocyclooctane, except that here, two of five possible boat-chair conformations (51 and 52) were appreciably populated at -175°.



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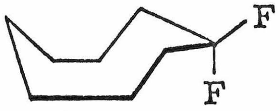

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The two peaks at higher field in the slow-exchange ^{19}F nmr spectra of difluorocycloalkanes generally arise from the axial fluorine (8, 79-81). Only in the case of 1,1,2,2-tetrafluorocyclohexane (81) have the signals at higher field been assigned to the equatorial fluorine. Assignment of the peaks to specific fluorines has been based on the relative line widths, which are usually determined by the extent of coupling to the adjacent protons. The Karplus relationship between dihedral angle and vicinal hydrogen-hydrogen coupling constant appears to be qualitatively applicable to hydrogen-fluorine couplings (82); as a consequence, in 1,1-difluorocyclohexane and other compounds having similar hydrogen-fluorine dihedral angles, the axial fluorine is more strongly coupled to the adjacent hydrogens and gives rise to considerably broader signals (8, 79-81).

In 1,1-difluorocyclodecane, the two low-field peaks are slightly broader than the high-field peaks. The fact that the peak widths are similar for the axial and equatorial fluorines appears reasonable on examination of a model. Large coupling constants are probably associated with the I-axial hydrogen and the axial fluorine, and with the III-axial hydrogen and the equatorial fluorine. Each of the fluorines will be coupled less strongly to the three remaining hydrogens. Because the line widths for the equatorial and axial fluorines do not differ greatly, there is at present no firm basis for assignment of peaks to specific fluorines.

Spectral parameters for several gem-fluorides are compared in Table 6. The H–F coupling constants are average values, taken from the ambient-temperature ^{19}F-nmr spectra. The values of J_{HF} for the seven, eight, and ten-membered rings are similar and are larger than for 1, 1-difluorocyclohexane. The fluorine-fluorine coupling constants are slightly larger in the medium-ring difluorides; this may be related to a smaller F–C–F angle in these compounds. A point of interest in connection with 48 is the more or less "normal" $\Delta\nu_{FF}$ for axial and equatorial gem-fluorines, despite the almost identical local environments of the fluorines; i. e., the atoms within three bonds of the fluorines are not only identical, but also are in similar, although not identical, steric relationships. Furthermore, each fluorine has a 1, 3 diaxial-type interaction with a hydrogen four bonds away. The nearest major point of difference between the environments of these fluorines is the planar W-configuration of the axial fluorine with a carbon four bonds away, while the equatorial fluorine lies in a planar W-configuration with a proton four bonds away. Because of the latter arrangement, there may be a moderate long-range H–F coupling, which could make the equatorial resonance somewhat broader than the axial resonance.

The ^{19}F-nmr spectrum of 1-(p-toluenesulfonyloxy)-2, 2-difluorocyclodecane (Figure 20) resembles the spectrum of 1, 1-difluorocyclodecane with respect to the relative line widths of the signals from axial and equatorial fluorines. The chemical-shift difference was 241 Hz; J_{FF} was 248 Hz. The spectrum can be interpreted in terms

Table 6

^{19}F NMR Parameters of Some Difluorocycloalkanes[a]

Compound	ν_1	ν_2	$\Delta\nu_{FF}$	J_{FF}	J_{HF}	Reference
1,1-Difluorocyclodecane	808[b]	1385[b]	577	243	15.5	This work
1,1-Difluorocyclooctane[c]			806	240	15.1	72
			940	245		
1,1-Difluorocycloheptane					15.5	83
1,1-Difluoro-4,4-dimethylcycloheptane			841	237	15.1	83
1,1-Difluorocyclohexane	1174[d]	2037[d]	863	231		This work
	638[e]	1522[e]	884	237	12.0	81

[a] All values are in Hz, at 56.4 MHz. [b] At -164°, relative to $CF_2ClCO_2C_2H_5$ (internal standard), for a 13% (v/v) solution in vinyl chloride. [c] Two AB's are present for 1,1-difluorocyclooctane at -175°. The smaller values of J_{FF} and $\Delta\nu$ are associated with the major conformation. [d] At -155°, relative to $CF_2ClCO_2C_2H_5$ (internal standard), for a 13% (v/v) solution in vinyl chloride. [e] Relative to CF_3CO_2H (internal standard), for a 1:3 (v/v) solution in propene.

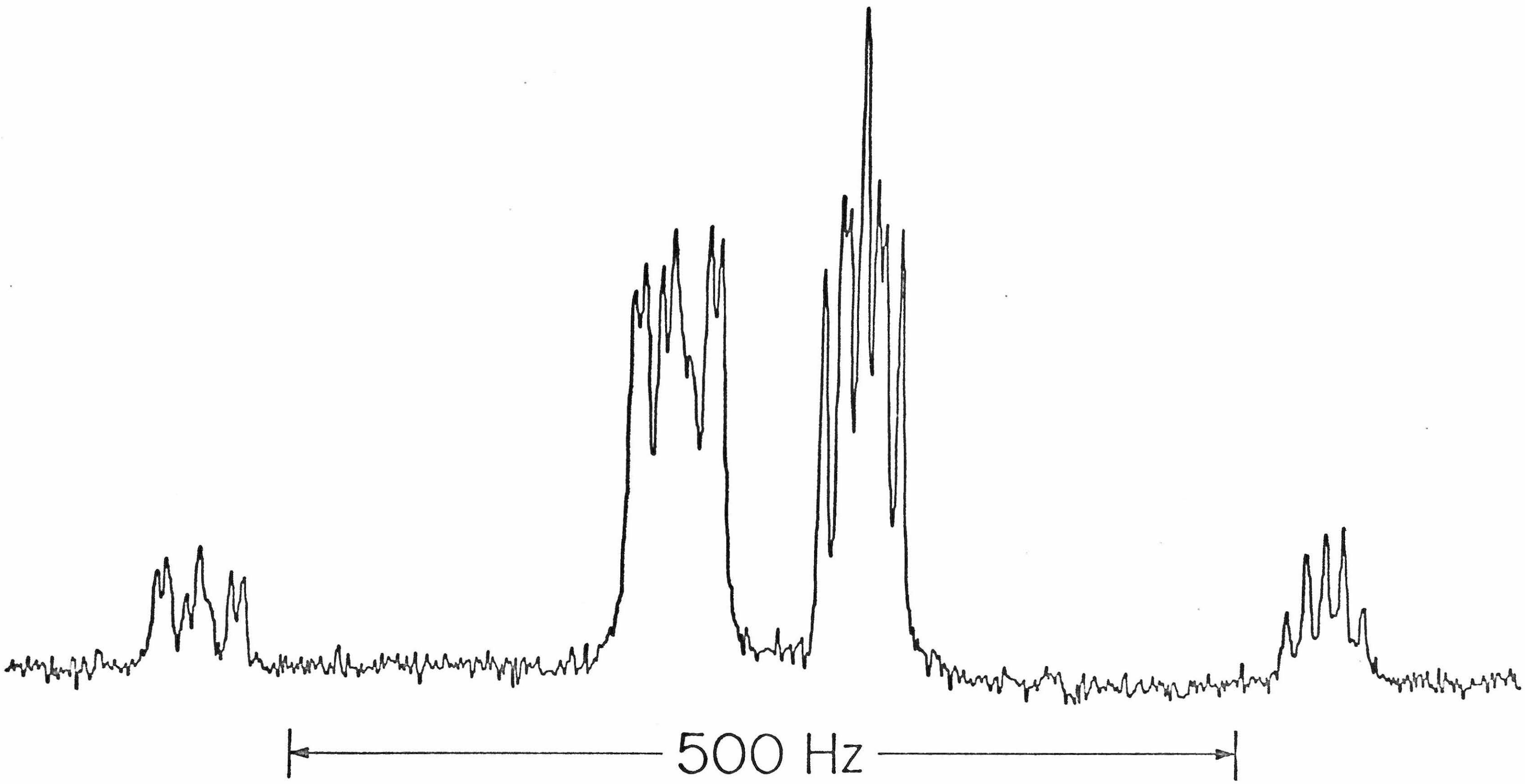
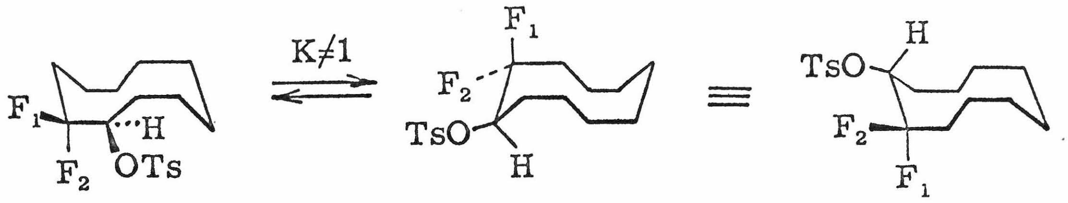


Figure 20. Ambient-temperature ^{19}F nmr spectrum of 1-(p-toluenesulfonyloxy)-2, 2-difluorocyclodecane. The spectrum was obtained by summing fourteen scans on the Varian C-1024 computer.

of a rapidly equilibrating mixture of the following two conformations, which are the only two structures that do not place a substituent in one of the intra-annular positions.



The relative line widths for the difluoro tosylate and 1,1-difluorocyclodecane would be expected to be similar because in both conformations the –OTs group replaces a hydrogen gauche to each fluorine. However, that the splitting patterns on the right- and left-hand sides of Figure 20 are not the same suggests that the equilibrium constant connecting these two forms is not unity.

Two AB's in a ratio of about 60:40 were found (84) for the low-temperature ^{19}F-nmr spectrum of 1-(p-toluenesulfonyloxy)-2,2-difluorocyclohexane. The major AB quartet ($\Delta\nu_{FF}$ = 906 Hz) was tentatively assigned (84) to the conformation with the –OTs group equatorial. The minor AB had a chemical shift difference of 390 Hz. If the assignments are correct, then the conformation with the tosylate group gauche to each fluorine has a larger chemical shift difference than unsubstituted 1,1-difluorocyclohexane, and a similar situation might be expected for the ten-membered difluoro tosylate. The fact that the chemical shift difference for the AB pattern in Figure 20 is smaller than for 1,1-difluorocyclodecane can be rationalized in terms of an equilibrium mixture of the two conformations, because a fluorine which is axial in one conformation is equatorial in the other. An energy difference of only 0.4 kcal/mole (0.6 vs. 0.2) (Table 3) was calculated (30) for methyl substitution at the III and I equatorial positions of cyclodecane. Even if this difference is low by a factor of two or three (which is quite possible), there would still be an appreciable amount of the conformation with the tosylate group in the Ie position. Also, the equatorial-axial energy difference for cyclohexyl tosylate ($\Delta G = 0.515$ kcal/mole) (85) is smaller than for methylcyclohexane ($\Delta G \sim 1.7$ kcal/mole) (86).

The activation energy for ring inversion in 1,1-difluorocyclodecane provides an experimental barrier with which the calculated barriers for various ways of accomplishing ring inversion in cyclodecane can be compared.

Pseudo-rotation of the BCB conformation is the simplest way of interconverting substituent positions in cyclodecane. Hendrickson (29, 31) has found that, in general, a cycloalkane conformation with a plane of symmetry passing through an atom (P/A) can pseudo-rotate to a conformation with an axis of symmetry bisecting an adjacent bond (A/B), and conversely. Similarly, pseudo-rotation occurs between conformations possessing axes through atoms (A/A) and those with planes through bonds (P/B). Relatively few cycloalkane conformations are incapable of undergoing pseudo-rotation; chair cyclohexane and the crown forms of cyclooctane and cyclodecane are among the ring conformations for which, by Hendrickson's definitions (31), pseudo-rotation is not possible. In each of these cases, symmetry elements of opposite types (P/A and A/B) alternate throughout the ring.

The pseudo-rotation itinerary of BCB cyclodecane has been described (31) and is reproduced in Figure 21. Interconversion of axial and equatorial fluorine positions in 1, 1-difluorocyclodecane by this pathway is shown in Figure 22.

BCB LC

BCB 1e $\rightleftharpoons$ LC 2'e $\rightleftharpoons$ BCB 3'e $\rightleftharpoons$
LC 3'e $\rightleftharpoons$ BCB 2e $\rightleftharpoons$ LC 1 $\rightleftharpoons$
BCB 2a $\rightleftharpoons$ LC 3'a $\rightleftharpoons$ BCB 3'a $\rightleftharpoons$
LC 2'a $\rightleftharpoons$ BCB 1a $\rightleftharpoons$ LC 2a $\rightleftharpoons$
BCB 3a $\rightleftharpoons$ LC 3a $\rightleftharpoons$ BCB 2'a $\rightleftharpoons$
LC 1' $\rightleftharpoons$ BCB 2'e $\rightleftharpoons$ LC 3e $\rightleftharpoons$
BCB 3e $\rightleftharpoons$ LC 2e $\rightleftharpoons$ BCB 1e $\rightleftharpoons$ ...

Figure 21. Numbering system and pseudo-rotation itinerary for BCB and LC cyclodecane.

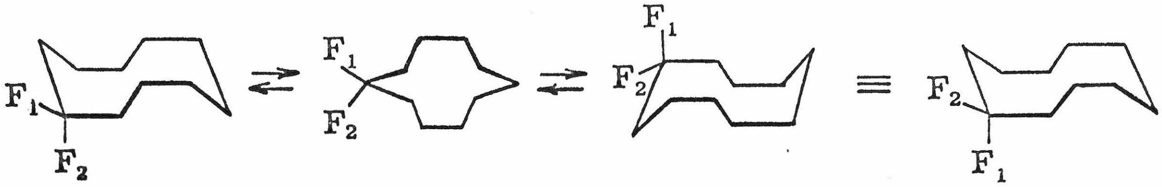


Figure 22. Interconversion of equatorial and axial fluorine positions in 1, 1-difluorocyclodecane.

Pseudo-rotation of BCB cyclodecane is anomalous in several respects, in part because of the presence of perpendicular symmetry elements of types P/A and A/B in this conformation. One of the unusual features of the pseudo-rotation itinerary is that the BCB form is its own pseudo-rotation partner. A substituent assumes in sequence the various possible positions on passing through alternate BCB conformations. Although the LC and BCB conformations alternate in the course of pseudo-rotation, they are not considered pseudo-rotation partners. As in the case of the BCB form, LC cyclodecane pseudo-rotates with itself.

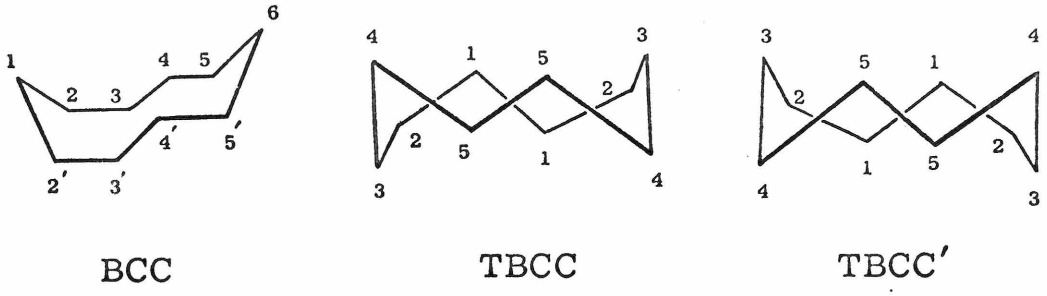
The calculated strain energy of the LC conformation (31) was 24.6 kcal/mole, relative to BCB cyclodecane. This value is considerbaly higher than the activation energy for ring inversion in 1,1-difluorocyclodecane (7.0 kcal/mole), which suggests that the LC form is not an intermediate in the interconversion of substituent positions in cyclodecane.

The barrier associated with pseudo-rotation is considerably lower for most cycloalkane conformations. For example, in B/TB cyclohexane and C/TC cycloheptane (31) the calculated barriers are 0.8 and 1.4 kcal/mole, respectively. For BC cyclooctane (31), the calculated barrier was 2.0 kcal/mole, but the procedure did not produce closed rings in the intermediate asymmetrical forms. The experimental barriers to pseudo-rotation in 1, 1-difluorocyclooctane (72) were $E_a = 8.0$ kcal/mole and $\Delta G^{\ddagger} = 4.9$ kcal/mole.

According to the strain-energy calculations (38), the TBC and TBCC conformations of cyclodecane (Figure 7) are closest in energy to the BCB form. It is of interest to examine whether these conformations can be used in a low-energy pathway for interconversion of substituent positions in cyclodecane.

Two separate pseudo-rotation itineraries are required for each of these conformations; the itineraries for BCC/TBCC cyclodecane are given in Figure 23. Equilibration of BCB and BCC conformations can be accomplished by flipping one of the methylene groups, maintaining the plane of symmetry which is present in both conformations. The BCB and TBCC conformations are interconverted by rotation of a carbon-carbon bond through the ring. The bonds which can be rotated to equilibrate these conformations are intersected by the symmetry axis, which is maintained during the process.

According to Hendrickson's condensed map of cyclodecane interconversions (31), a given BCB conformation should be able to



I BCC 1a ⇌ TBCC 1a ⇌ BCC 2a ⇌
TBCC′ 2e ⇌ BCC 3′e ⇌ TBCC 3e ⇌
BCC 4e ⇌ TBCC′ 4e ⇌ BCC 5′e ⇌
TBCC 5e ⇌ BCC 6e ⇌ TBCC′ 5e ⇌
BCC 5e ⇌ TBCC 4e ⇌ BCC 4′e ⇌
TBCC′ 3e ⇌ BCC 3e ⇌ TBCC 2e ⇌
BCC 2′a ⇌ TBCC′ 1a ⇌ BCC 1a ⇌ ...

II BCC 1e ⇌ TBCC 1e ⇌ BCC 2e ⇌
TBCC′ 2a ⇌ BCC 3′a ⇌ TBCC 3a ⇌
BCC 4a ⇌ TBCC′ 4a ⇌ BCC 5′a ⇌
TBCC 5a ⇌ BCC 6a ⇌ TBCC′ 5a ⇌
BCC 5a ⇌ TBCC 4a ⇌ BCC 4′a ⇌
TBCC′ 3a ⇌ BCC 3a ⇌ TBCC 2a ⇌
BCC 2′e ⇌ TBCC′ 1e ⇌ BCC 1e ⇌ ...

Figure 23. Pseudo-rotation of BCC cyclodecane. The TBCC and TBCC′ conformations are mirror images of one another.

enter either of the BCC/TBCC pseudo-rotation cycles by both the plane-symmetrical and axis-symmetrical processes, but this is not correct. Actually, a given BCB conformation can be directly equilibrated with two TBCC forms in one BCC/TBCC pseudo-rotation itinerary, or with two BCC conformations in the other BCC/TBCC cycle. These transformations are illustrated below, with the 2e BCB form as an example.

TBCC′ 2e ⇌ BCB 2e ⇌ TBCC 4e
BCC 5a ⇌ BCB 2e ⇌ BCC 2e

In this case, the two TBCC forms are in the first pseudo-rotation cycle of Figure 23; the BCC forms are in the second cycle. The TBCC conformations of the first itinerary can equilibrate with BCB conformations as follows:

TBCC 1a ⇌ BCB 3′a ⇌ TBCC′ 5e
TBCC′ 2e ⇌ BCB 2e ⇌ TBCC 4e
TBCC 3e ⇌ BCB 1e ⇌ TBCC′ 3e
TBCC′ 4e ⇌ BCB 2′e ⇌ TBCC 2e
TBCC 5e ⇌ BCB 3a ⇌ TBCC′ 1a

Examination of Figure 21 shows that transformations of types BCB ⇌ TBCC and TBCC ⇌ BCC will not interconvert BCB pseudo-rotation partners; in particular, ring inversion in 1,1-difluorocyclodecane cannot be accomplished in this way.

As in the case of the axis-symmetrical process, BCB pseudorotation partners cannot be equilibrated by transformations of types BCB $\rightleftharpoons$ BCC and BCC $\rightleftharpoons$ TBCC. Complete interconversion of cyclodecane positions is possible, however, if the BCB $\rightleftharpoons$ TBCC process is included. A pathway which is relevant for 1,1-difluorocyclodecane is shown below.

$$\mathrm{BCB\ 2e} \rightleftharpoons \mathrm{BCC\ 2e} \rightleftharpoons \mathrm{TBCC'\ 2a} \rightleftharpoons \mathrm{BCB\ 2a}$$

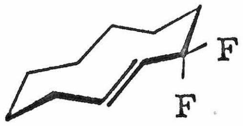
A barrier of at least 20 kcal/mole was estimated (31) for conversion of BCB cyclodecane to the BCC form, with the plane of symmetry maintained. Unless a lower-energy (unsymmetrical) process exists for the above conversion, or the estimate of the barrier is too high, then interconversions involving only BCB, BCC, and TBCC conformations are not important for complete equilibration of substituent positions in cyclodecane.

The TBC conformation of cyclodecane can be derived from the LC form by moving the two 3-carbons (or the 3′-carbons) of the latter conformation away from the center of the ring, with retention of the symmetry axis. Direct conversion of BCB cyclodecane to the TBC or BC conformations is not possible, and ring inversion cannot be accomplished by equilibria involving only these forms. It is of interest that, according to the calculations, deformation of the LC form to give the TBC conformation results in a decrease in strain energy from 24.6 to 2.1 kcal/mole (for the most stable TBC form). Hendrickson has suggested (31) that asymmetrical modes of conformational transformations may be important for rings larger than cycloheptane. Additional strain energy calculations will be required for a more complete understanding of the possible routes for interconversion of substituent positions in cyclodecane.

The spectral changes observed for 3,3-difluoro-trans-cyclodecene and trans-cyclodecene-d_6 are qualitatively similar. In each case, a single peak (neglecting H-F coupling in the difluoride) broadens and splits into a close AB pattern, and further changes take place at lower temperatures. The coalescence temperatures for the fluorinated compound are higher; in part, at least, this is a consequence of the larger fluorine chemical-shift differences.

It is seen from the spectrum at -148° (Figure 18) that the axial (upfield) fluorines are coupled more strongly to the adjacent hydrogens than the equatorial fluorines. There are eight conformations of the difluoride (Figure 24) corresponding to the cyclodecene conformations in Figure 11. In each of these conformations, the axial fluorine is expected to be strongly coupled to the 4-axial hydrogen and possibly also to one or both of the alkenic hydrogens. The III-axial hydrogen in 1,1-difluorocyclodecane is missing in the alkene, resulting in a narrower line width for the equatorial fluorines of 3,3-difluoro-trans-cyclodecene.

The changes occurring between -20 and -74° in the spectra for the allylic protons of the deuterated cyclodecene, and between +17 and -30° in the spectra of the fluorinated cyclodecene, are probably best interpreted as resulting from slow rotation of the double bond



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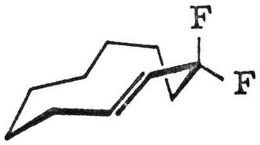

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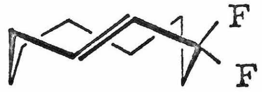

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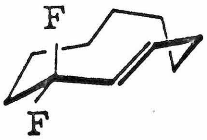

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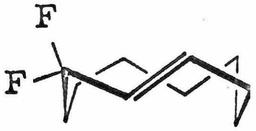

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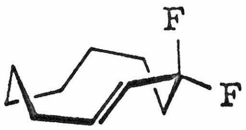

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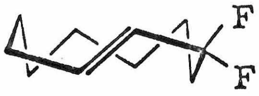

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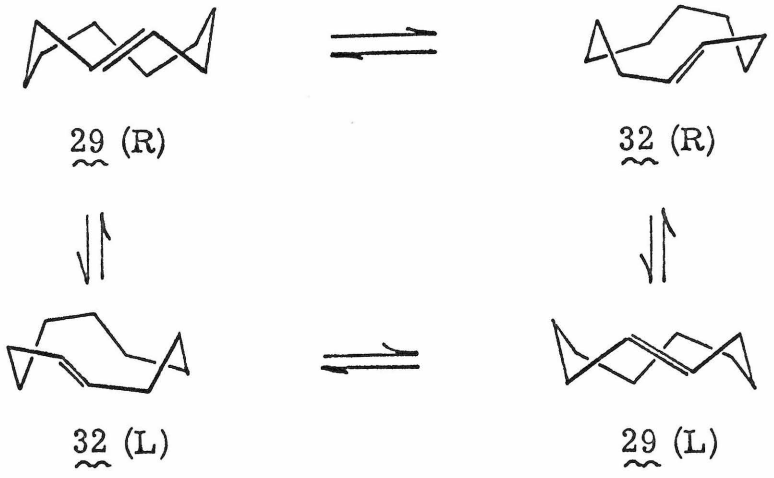
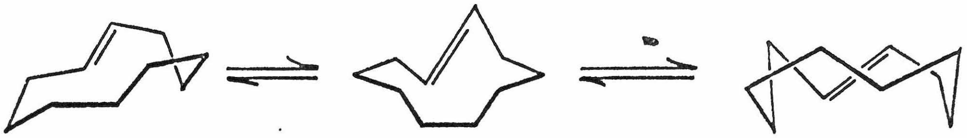
Figure 24. Conformations of 3, 3-Difluoro-trans-cyclodecene.

through the ring, although the possibility that these changes are a consequence of slow rotation of the C-6--C-7 segment through the ring or flipping of the C-4 and C-9 methylene groups is not rigorously excluded by the nmr spectra. As an example, if conformations 29 and 32 were the only conformations present, the following equilibria would be possible:



Transformations 29 (R) ⇌ 32 (L) and 32 (R) ⇌ 29 (L) are accomplished by rotation of the double bond through the ring. The remaining transformations can be accomplished by rotation of the C-6--C-7 bond segment through the ring, accompanied by flipping of the methylene groups at positions 4 and 9. Slowing of the process represented by either the vertical or the horizontal arrows would result in an AB pattern for the allylic protons, and two AB patterns would emerge after the remaining process became sufficiently slow.

Fanta (87) has suggested the following sequence as an alternative to rotation of the C-6--C-7 bond through the ring.



Models indicate that the barrier to this process should be low, which supports the assignment of the process with the higher coalescence temperature to rotation of the double bond through the ring.

Binsch has noted (88) that the changes above -74° in the signals from the non-allylic protons of trans-cyclodecene-d_6 could be interpreted by assuming rapid rotation of the C-6--C-7 segment, coupled with significant population differences of the diastereomers. The spectra of the fluorinated cyclodecene indicate that the condition of population differences is likely to be met and provide support for this interpretation.

$\Delta G^{\ddagger}$ and $\Delta S^{\ddagger}$ for trans-cyclodecene-d_6 at 2.8° were calculated from E_a and A in reference 57. The activation parameters for the two trans-cyclodecenes are compared in Table 7. The free energies of activation differ by only 0.4 kcal/mole, but the difference in activation energies (4.2 kcal/mole) is considerably larger. It is known (89, 90) that the values of $\Delta G^{\ddagger}$ obtained by the nmr method are

Table 7

Activation Parameters for trans-Cyclodecenes at 2.8°

Compound	$\Delta G^{\ddagger}$ (kcal/mole)	$\Delta S^{\ddagger}$ (eu)	E_a (kcal/mole)	Log A	Ref.
trans-Cyclodecene-d_6	12.0	-6.8	10.7±0.3	11.7±0.3	57
3,3-Difluoro-trans-cyclodecene	12.4	6.9	14.9±0.4	14.7±0.3	This work

generally more accurate and reproducible than the corresponding activation energies. The close agreement of the free energies of activation in Table 7 may be an indication that part of the difference in activation energies is due to systematic errors in the determination of the latter. A large part of the barrier to rotation of the double bond through the ring may arise from additional out-of-plane bending at the two sp^2 centers, reducing the interaction of the alkenic hydrogen with the CH_2 groups across the ring. Molecular models do not show any obvious reason for a large increase in activation energy on replacement of two of the α-hydrogens by fluorines.

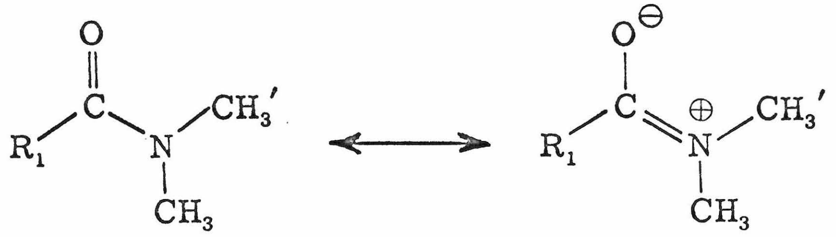
The spectra in Figure 18 show that two diastereomers are present at -148° in a ratio of 85:15, and smaller amounts of other conformations may be present. The free energy difference between the two major diasteromers is 0.43 kcal/mole. Models indicate that conformation 60 is unlikely to be appreciably populated. This conformation has nearly eclipsed ethane segments at bonds C_5-C_6 and C_7-C_8, and the C=C–C–C dihedral angles are about 60°, rather than the preferred value (64) of 120°. Conformation 54, which is analogous to the structure found (63) for the trans-cyclodecene-silver nitrate adduct, is likely to be one of the two major diastereomers present at -148°, although not necessarily the predominant conformation. At present, these is no basis for selection of the other diastereomer from among the six remaining conformations in Figure 24.

PART II

γ, γ-DIFLUORO-ϵ-CAPROLACTONE AND γ, γ-DIFLUORO-ϵ-CAPROLACTAM

INTRODUCTION AND BACKGROUND

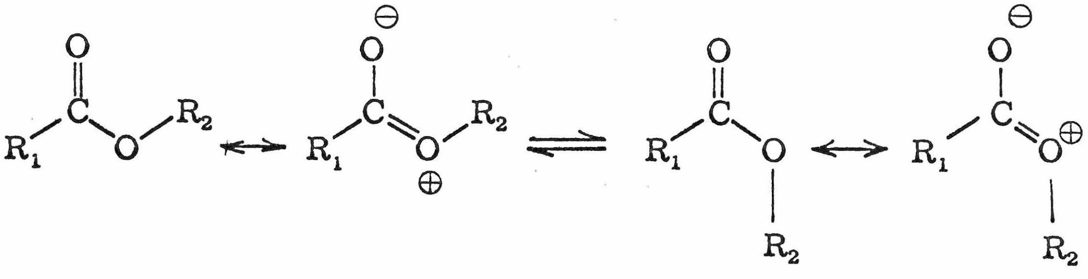
Nmr evidence for π character in the C–N bonds of amides was first obtained by Phillips (91) in 1955. The methyl groups cis and trans to R_1 in dimethylformamide and dimethylacetamide gave rise to separate signals at ambient temperature, showing that rotation of the $-N(CH_3)_2$ group about the bond to the carbonyl carbon was restricted by resonance interaction of the nitrogen lone-pair electrons with the carbonyl group. A number of quantitative studies of this process have subsequently been made, beginning with Gutowsky's determination (92) of the barriers to rotation in DMF and DMA. The activation parameters found by different workers have varied widely. Estimates of the activation energy for DMF (93) have ranged from 6.3 to 28.2 kcal/mole, with values of log A between 4.6 and 17.2. Many different sources of error, including the use of inadequate procedures for obtaining the rate constants from the experimental spectra, probably contributed to the inaccuracy of these earlier results. Recently, the following activation parameters were obtained from total line-shape analyses of the spectra for DMA-d_6 (94) and DMF (95).



DMA-d_6	DMF
E_a = 19.6 kcal/mole	E_a = 20.5 ± 0.2 kcal/mole
log A = 13.8	log A = 12.7
$\Delta G^{\ddagger}$ = 18.2 kcal/mole	$\Delta G^{\ddagger}$ = 21.0 kcal/mole
$\Delta H^{\ddagger}$ = 19.0 kcal/mole	$\Delta H^{\ddagger}$ = 20.3 ± 0.2 kcal/mole
$\Delta S^{\ddagger}$ = +2.7 eu	$\Delta S^{\ddagger}$ = -1.7 eu

The values of $\Delta S^{\ddagger}$ obtained by these authors are reasonably close to zero. Another recent determination of the barrier in DMF (96), also using the total line-shape method for obtaining the rate constants, gave $E_a = 20.8 \pm 0.6$ kcal/mole and $\Delta S^{\ddagger} = 0 \pm 1$ eu, in excellent agreement with the above results.

The C–O bond in esters is also expected to have π character. If the charged resonance structures below are sufficiently important, there will be an appreciable barrier to rotation about this bond.



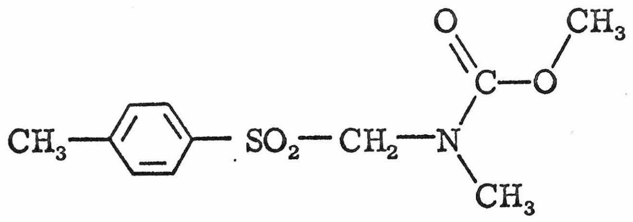
61

trans

62

cis

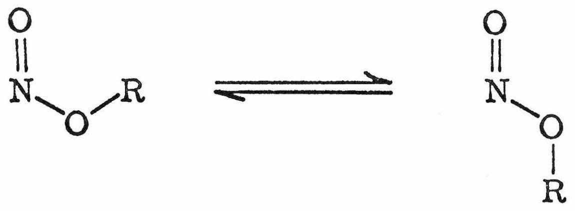
Nmr evidence for this interaction has been lacking. A barrier (E_a) of 16 kcal/mole was reported (97) for 63 and was attributed



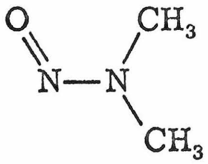
63

at first to hindered rotation in the ester function, but the authors later reinterpreted their results in terms of slow rotation about the C–N bond (98).

Hindered rotation in alkyl nitrites has been detected by the nmr method (99, 100) and provides indirect evidence for an appreciable barrier to *cis*-*trans* isomerization in esters. A recent



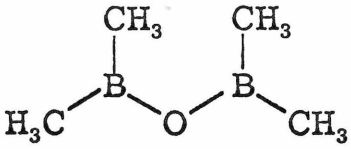
determination (96) of the barrier to rotation about the N–O bond in methyl nitrite, using the total line-shape method, gave E_a = 11.4 kcal/mole and $\Delta S^{\ddagger}$ = -2 eu. The barrier for the corresponding N–N rotation in dimethylnitrosamine (64) ($\Delta G^{\ddagger}$ ~23 kcal/mole (101))



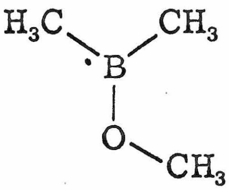
64

is nearly the same as for DMF ($\Delta G^{\ddagger}$ = 21.0 kcal/mole (95)). If the same difference also applies to *cis*-*trans* isomerism of alkyl nitrites and esters, then the barrier for the latter process is expected to be on the order of 10-11 kcal/mole.

Nmr evidence for boron-oxygen π-bonding is also known. Activation energies of 8.6 and 8.5 kcal/mole were reported (102) for rotation about the B–O bonds of dimethylboric anhydride (65) and dimethylmethoxyboron (66).



65



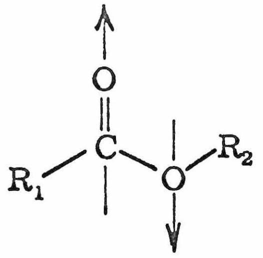
66

Dipole-moment studies have shown (103) that esters generally have a strong preference for the *trans*-configuration (61), which accounts for the failure to detect *cis*-*trans* isomerism by nmr spectroscopy. The calculated dipole moments for 61 and 62 are

1.64 and 3.50 D, respectively (104). The experimental values (e.g., 1.7 D for methyl acetate (103)) are closer to the calculated value for the trans-configuration. Lactones with eight or fewer ring members have predominantly the cis-configuration and are characterized by substantially higher dipole-moments (e.g., 4.45 D for ϵ-caprolactone) (105, 106). If the cis form of open-chain esters were appreciably populated at higher temperatures, the dipole moment would be expected to increase with temperature. Experimentally, it was found (107) that they are nearly independent of temperature, which is evidence for a large energy difference between the cis- and trans-isomers. From an IR study of monomeric formic acid in the vapor phase, Pitzer and Miyazawa (108) concluded that the energy difference between the two forms was 2.0 kcal/mole. For esters, the corresponding difference is probably higher. Huisgen and Ott (105) found that the free energies of activation for the alkaline hydrolysis of the seven and fourteen-membered lactones differed by 3.8 kcal/mole, and suggested that this value could be an approximate measure of the energy difference for the cis- and trans-configurations of esters. Attempts to evaluate this difference by accoustical measurements have also been made (104, 109-113), but the method does not give consistent results. As an example, the cis form of ethyl formate has been reported as 0.5 (109), 2.3 (111), 2.5 (113), and 5.85-6.1 (110) kcal/mole less stable than the trans form.

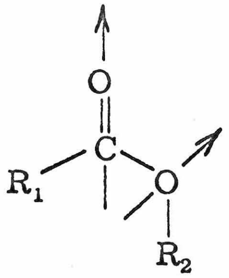
Detailed structural determinations for methyl formate (114) and formic acid (115) by microwave spectroscopy have confirmed the trans-configuration for these compounds. The carbon-oxygen skeleton of methyl formate was said to be planar. (The question of planarity was not discussed for formic acid.) Other workers (116) have suggested that the alkyl group attached to oxygen is about 20-30° out of the plane of the O–C=O triangle. Dewar and Rona (117) have discussed the conditions for which planarity can be expected in related systems, and have carried out a rough calculation for amides. Possible small deviations from planarity will not be important to the present discussion.

The reasons for the greater stability of the trans-configuration are not fully understood. The interaction of the C–O (methoxyl) bond dipoles with the carbonyl bond dipole probably contributes to the energy difference. Piercy and Subrahmanyam (104) have calculated



61

trans



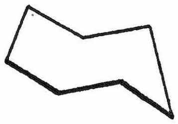
62

cis

an energy difference of approximately 1.2 kcal/mole from this contribution. The cis form is probably also disfavored by the small (or zero) dihedral angle between the R_1–C and R_2–O bonds, as in eclipsed ethane (118, 119).

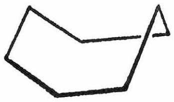
Most of the estimates of the barrier to rotation about the C–O bonds of carboxylic acids and esters have come from IR (108, 120) or accoustical (104, 109-113) studies. Pitzer and Miyazawa (108, 121) concluded from their IR investigation of formic acid that the potential maximum for this compound was at 98° from the favored (trans) configuration and was $10._9$ kcal/mole above the trans minimum. A later IR study (120) of methyl formate and methyl acetate gave "two-fold potential barriers" of $13._1$ and $15._9$ kcal/mole, respectively. However, the same method gave potential barriers of 14 kcal/mole for C–N rotation in N-methylacetamide and N-methylformamide (120). These values are not in good agreement with the barriers obtained recently for dimethylformamide and dimethylacetamide by the nmr method (94-96), which suggests that the ester C–O rotational barriers obtained by IR measurements may not be very accurate. The acoustical method gives values which are unreasonably low. The activation energy for conversion of the trans form of ethyl formate to the cis form was 5.88 kcal/mole, according to Tabuchi (113), who carried out the first of the quantitative studies. The later estimates are also low. In 1968, for example, Bailey and North (109) reported $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in methyl formate (for the cis → trans conversion) as 7.8 kcal/mole and -1.8 eu. For ethyl propionate, the corresponding values were 1.2 kcal/mole and -18.5 eu.

In the work to be described here, activation parameters were determined for ring inversion in γ,γ-difluoro-ϵ-caprolactone and γ, γ-difluoro-ϵ-caprolactam. The two most likely conformations for these compounds are the chair (67) and boat (68) forms.



67

Chair



68

Boat

ORD data (122) for substituted caprolactones have been interpreted in terms of the chair conformation. The boat conformation was assigned to δ-valerolactone in the basis of ORD measurements (123), but the preferred conformation of this compound may actually be the half-chair (124). Because of the possible error in the determination of the δ-valerolactone conformation by the ORD method, independent evidence for the conformation of the seven-membered lactone appeared desirable. Evidence for hindered rotation about the C–O bond of the ester group was also expected from the ^{19}F nmr study of the difluorolactone. The chair form of ϵ-caprolactone can undergo ring inversion (exchange of equatorial and axial positions) by pseudorotation, as in cycloheptane, with loss of the resonance interaction of the ether-oxygen lone pair electrons with the carbonyl groups, or with retention of the resonance interaction by procedures analogous to the inversion pathways which obtain with cycloheptene.

The experimental barrier to ring inversion will be a lower limit for each of the possible pathways, which will be discussed in detail in a later section.

γ, γ-Difluoro-ϵ-caprolactam was prepared for comparison of its barrier to ring inversion with the barriers in the lactone and in 5,5-difluorocycloheptene (125), and for determination of the ring conformation. The resonance energy of amides is sufficiently high that ring inversion could be assumed to occur with retention of the C–N π character, unless the barrier was in the vicinity of 20 kcal/mole or higher. Very little evidence is available on the conformation of the seven-membered lactam. Results from an ESR study of a radical obtained by irradiation of crystalline ϵ-caprolactam (126) were interpreted in terms of a boat conformation.

RESULTS

The ^{19}F-nmr spectra of an acetone solution of γ,γ-difluro-ϵ-caprolactone at ambient temperature is a quintet (J_{HF} = 14.5 Hz) centered 1734 Hz upfield from internal ethyl chlorodifluoroacetate. On cooling to -30°, the spectrum broadens and splits into an AB pattern, with spectral parameters as given in Table 8. Representative spectra and an Arrhenius plot of the rate constants are shown in Figures 25 and 26. The activation parameters for ring inversion were $E_a = 12.4 \pm 0.3$ kcal/mole, $\log A = 15.0 \pm 0.3$, $\Delta G^{\ddagger} = 10.0$ kcal/mole at -53°, and $\Delta S^{\ddagger} = +8.6$ eu at -53°.

The ^{19}F-nmr spectrum of γ,γ-difluoro-ϵ-caprolactam in acetone at 64° is a quintet (J_{HF} = 14.1 Hz) centered 1653 Hz upfield from ethyl chlorodifluoroacetate, the internal standard. The spectrum shows exchange broadening already on cooling to ambient temperature (39°), and on further cooling to -81° an AB pattern emerges, with spectral parameters as given in Table 8. Because of solubility problems, the exchange lifetime was obtained at only one temperature (-53°, $\tau = 0.0047$ sec) . $\Delta G^{\ddagger}$ was calculated to be 10.4 kcal/mole at this temperature. The spectra at -53 and -81° are shown in Figure 27.

Table 8

^{19}F-NMR Parameters[a]

Compound	ν_1	ν_2	$\Delta\nu_{FF}$	J_{FF}	Reference
γ,γ-Difluoro-ϵ-caprolactone	1267[b]	2018[b]	751	240	This work
γ,γ-Difluoro-ϵ-caprolactam	1026[c]	2062[c]	1035	241	This work
5, 5-Difluoro-cycloheptene	3280[d]	4882[d]	1602	248	125

[a] All values are in Hz, at 56. 4 MHz.

[b] At -85°, relative to $CF_2ClCO_2C_2H_5$ (internal standard), for a 21% (by weight) solution in acetone.

[c] At -81°, relative to $CF_2ClCO_2C_2H_5$ as internal standard, for a 9% (by weight) solution in acetone.

[d] Relative to bromotrifluoromethane as internal standard, for a 10% solution in propene.

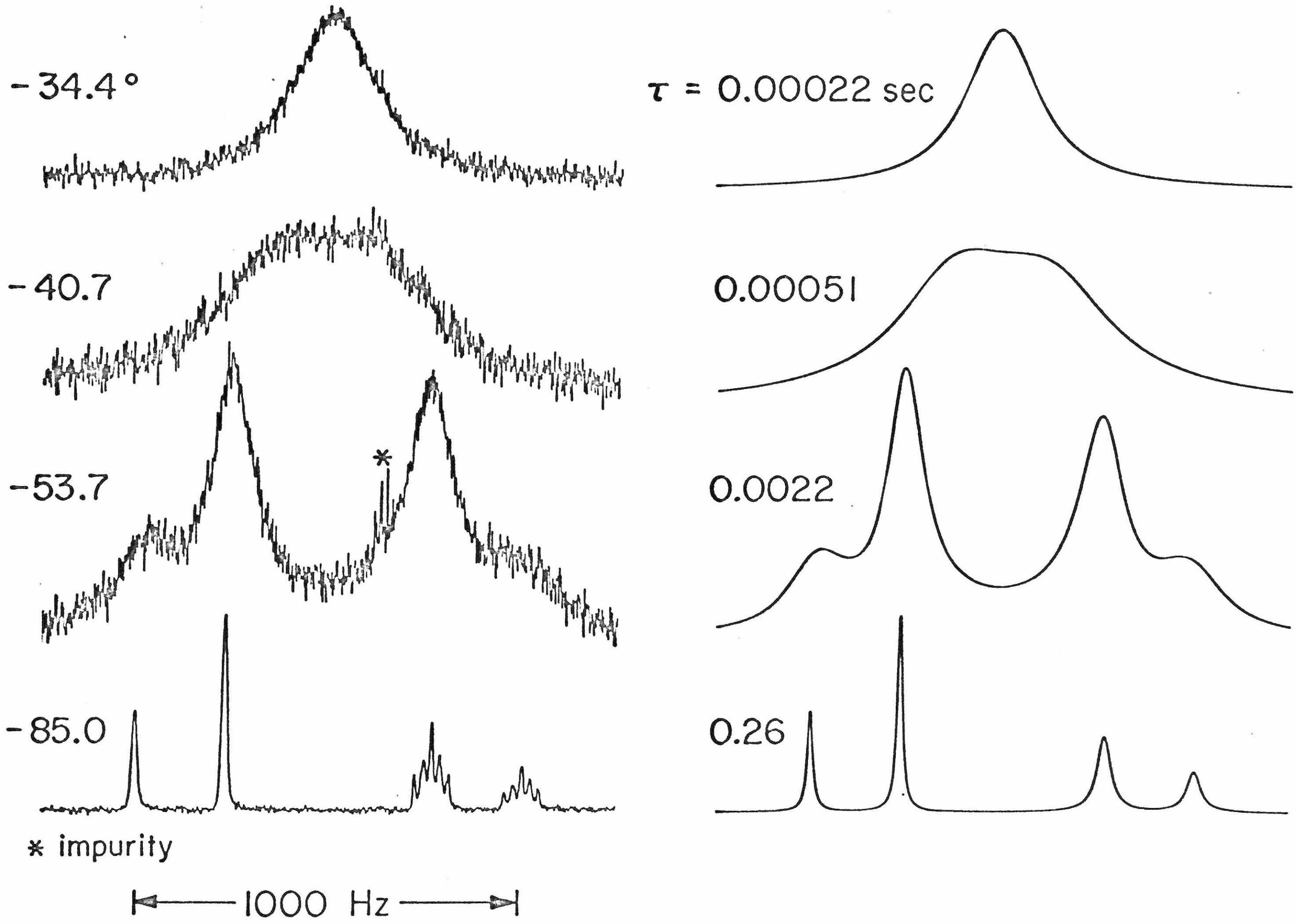


Figure 25. Experimental (left) and calculated (right) ^{19}F nmr spectra of γ, γ-difluoro-ϵ-caprolactone in acetone.

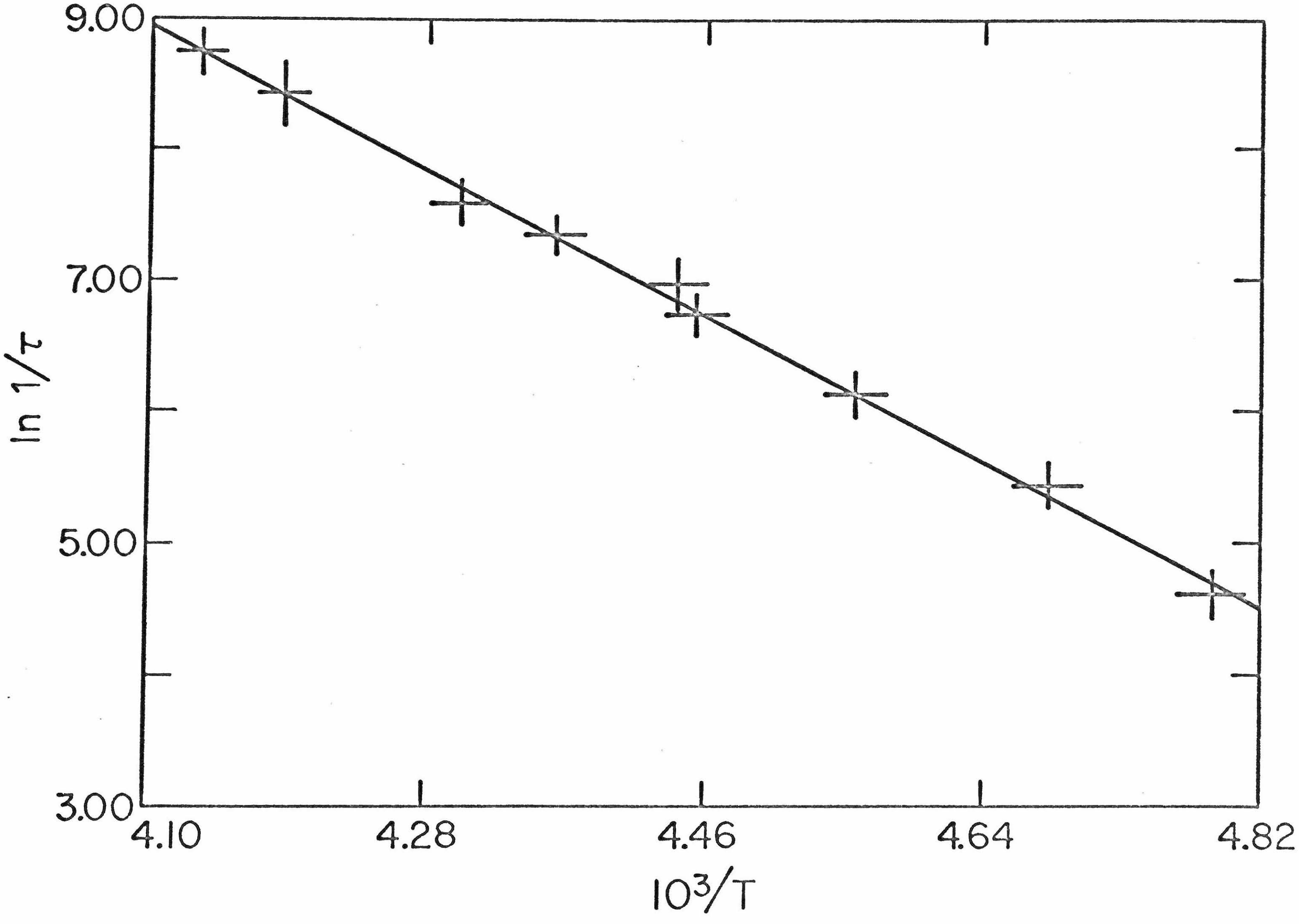


Figure 26. Arrhenius plot for γ, γ-difluoro-ϵ-caprolactone.

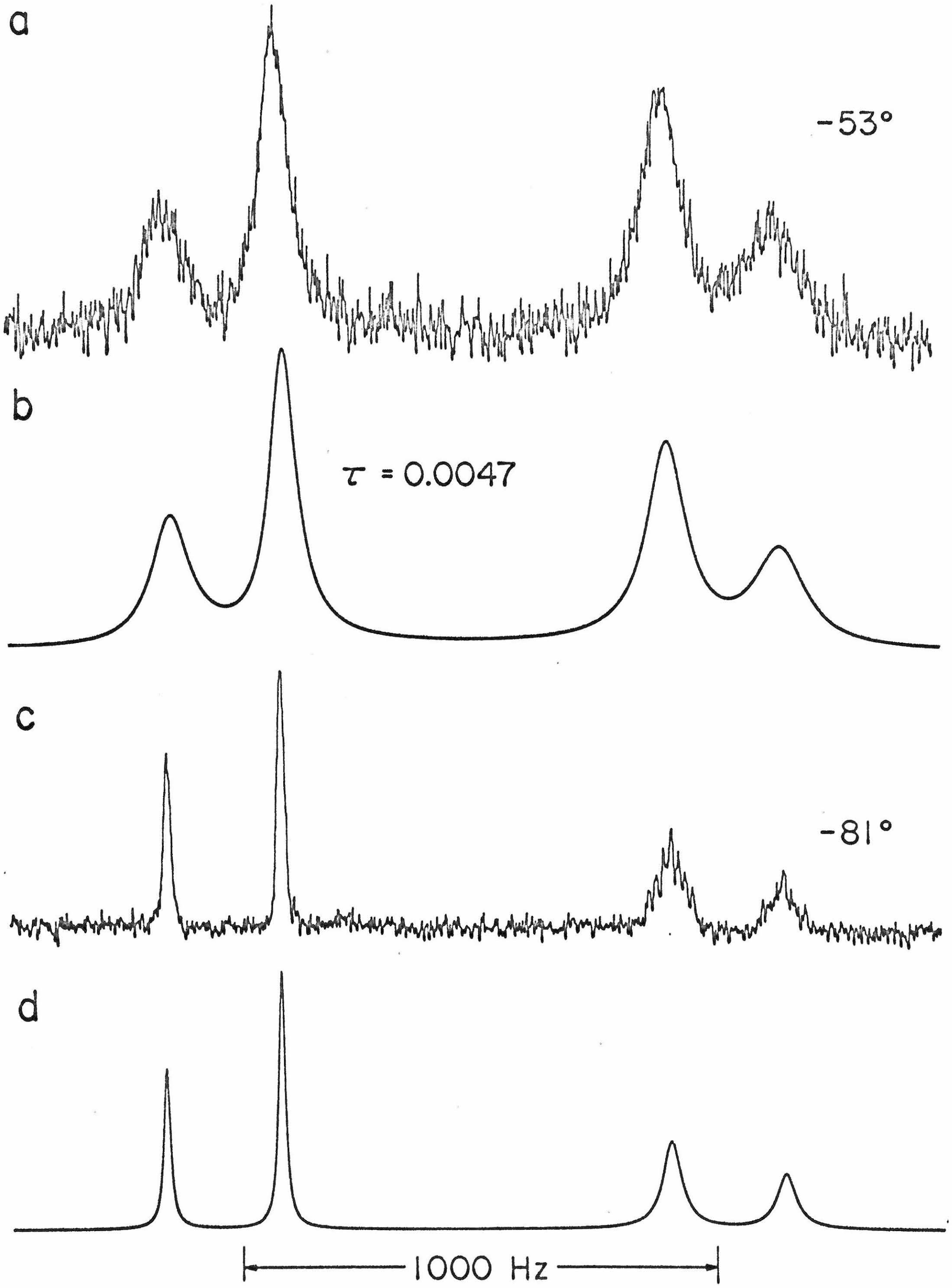
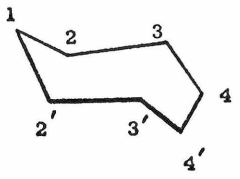


Figure 27. Experimental (a and c) and calculated (b and d) ^{19}F nmr spectra of γ,γ-difluoro-ϵ-caprolactam.

DISCUSSION

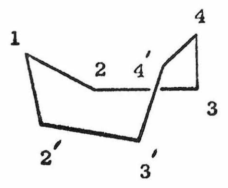
The coupling constants J_{HF} and J_{FF} for the difluoro lactone and lactam are normal. The chemical-shift differences are substantially smaller than in 5, 5-difluorocycloheptene and are closer to the value for 1, 1-difluorocyclohexane (884 Hz). The relative line widths are comparable to those in 1, 1-difluorocyclohexane, as would be expected for either the chair or boat forms of the lactone and lactam.

A description of the possible conformational changes in cycloheptane and cycloheptene will be useful for a later discussion of the conformations of ϵ-caprolactone and ϵ-caprolactam. As in cyclohexane, there are two plane-symmetrical forms of cycloheptane, the chair and boat conformations (69 and 70, Figure 28). The corresponding pseudo-rotation partners are the twist-chair and twist-boat forms 71 and 72. Pseudo-rotation of chair cycloheptane accomplishes complete equilibration of substituent positions in the C and TC forms, as shown in the itinerary of Figure 29. According to Hendrickson (31), the energy profile for the pseudo-rotation cycle is a simple sine function, with the twist-chair conformation at the point of minimum energy and the chair conformation at the point of highest energy. The calculated barrier for this process, which also represents the energy difference for the two forms, is only 1. 4 kcal/mole. The geometry and energy for each of the conformations in Figure 28 are given in Table 9. Bixon and Lifson (34) have also calculated a low energy difference (0. 67 kcal/mole) for the C and TC conformations.



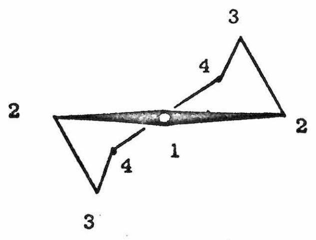
69

Chair, C



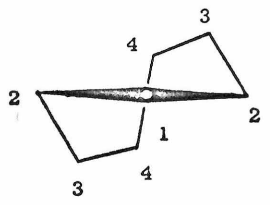
70

Boat, B



71

Twist-chair, TC



72

Twist-boat, TB

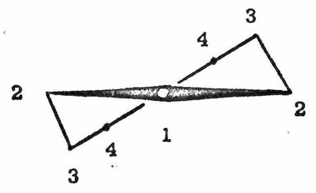


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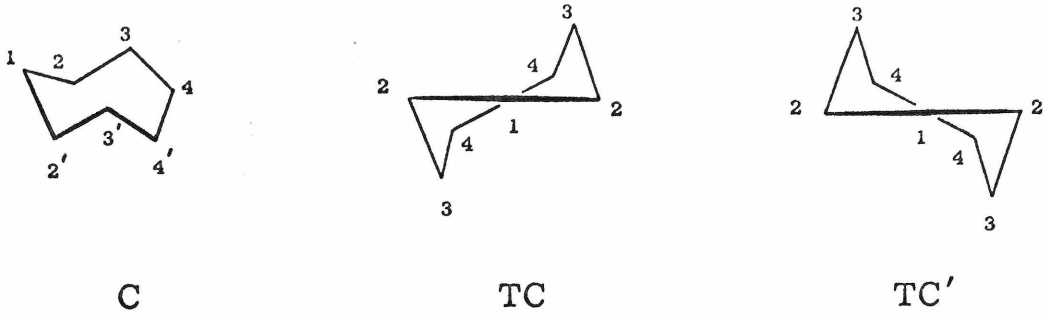
Figure 28. Conformation of cycloheptane.



C 1e ⇌ TC 4e ⇌ C 2e ⇌
TC′ 3e ⇌ C 3′e ⇌ TC 2e ⇌
C 4e ⇌ TC′ 1 ⇌ C 4a ⇌
TC 2a ⇌ C 3′a ⇌ TC′ 3a ⇌
C 2a ⇌ TC 4a ⇌ C 1a ⇌
TC′ 4a ⇌ C 2′a ⇌ TC 3a ⇌
C 3a ⇌ TC′ 2a ⇌ C 4′a ⇌
TC 1 ⇌ C 4′e ⇌ TC′ 2e ⇌
C 3e ⇌ TC 3e ⇌ C 2′e ⇌
TC′ 4e ⇌ C 1e ⇌ . . .

Figure 29. Pseudo-rotation of chair cycloheptane.

For cycloheptane, pseudo-rotation of the chair form will be the process of greatest interest for the present discussion. Several other conformational changes will be briefly mentioned here, two of which will be considered in greater detail for cycloheptene.

Table 9

Geometry and Energy of Cycloheptanes (22, 31)

Bond angles and dihedral angles,[a] degrees

Description	θ_1	θ_2	θ_3	θ_4	ω_1	ω_2	ω_3	ω_4
TC (71)	116	115	113	115	39.1	-88.1	72.3	-54.3
C (69)	115	114	115	118	-63.8	83.5	-66.1	0
TB (72)	115	115	115	115	45.4	-64.4	-17.9	74.6
B (70)	115	115	115	116	-57.5	-30.9	69.9	0
73	112	112	116.6	121	45.1	-89.0	36.9	0
TC/TB‡[b]	112	112	117.4	121	45.6	-86.2	26.8	14.0

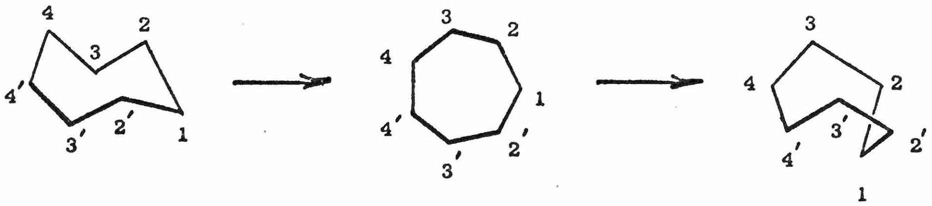
Energies, in kcal/mole

Description	E_θ	E_t	E_{HH}	E_{CH}	E_{CC}	E_{NB}	ΣE	ΔE
TC (71)	1.24	4.41	2.12	-0.51	-0.16	1.45	7.10	0.0
C (69)	2.46	4.60	2.21	-0.60	-0.15	1.46	8.52	1.4
TB (72)	1.45	5.39	3.15	-0.70	0.22	2.66	9.50	2.4
B (70)	1.77	5.55	2.88	-0.73	0.27	2.42	9.74	2.7
73	4.70	7.64	2.73	-0.70	-0.05	1.98	14.32	7.2
TC/TB‡[b]	5.07	8.25	2.72	-0.80	-0.04	1.88	15.20	8.1

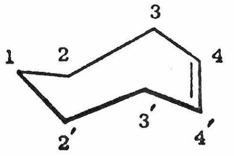
[a] The carbons are numbered as in Figure 28; ω_1 is the dihedral angle of the first bond adjacent to carbon 1 in a clockwise direction.

[b] This conformation is the highest energy form in the axis-symmetrical interconversion of TC and TB conformations.

(The changes possible for cycloheptene are also possible for cycloheptane.) The TC and TB forms of cycloheptane can be interconverted by an axis-symmetrical process; the calculated barrier is 8.1 kcal/mole (31), and the conformation of highest energy was said to be intermediate between the form with $\omega_4 = 0$ (73) and a subsequent form with $\omega_3 = 0$. Boat and chair conformations can be interconverted by two plane-symmetrical processes. Wagging of C-1 to accomplish this interconversion has been described by Hendrickson (31), but neither the barrier for this transformation nor the geometry of the intermediate conformation of highest energy was calculated. The other plane-symmetrical process, which does not appear to have been considered previously for cycloheptane or cycloheptene, involves moving the two 3-carbons upward and outward and the two 4-carbons downward, with the ring passing through a conformation having six coplanar carbon atoms.

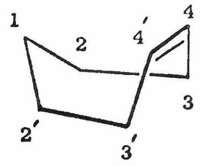


As in cycloheptane, there are chair and boat conformations of cycloheptene (74 and 75, Figure 30). The chair conformation of cycloheptene, unlike chair cycloheptane, is relatively rigid and



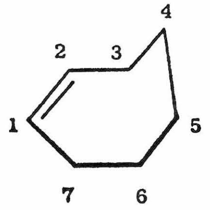
74

Chair, C



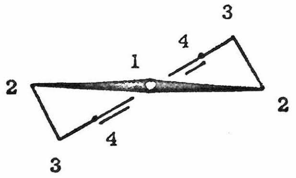
75

Boat, B



76

Twist, T



77

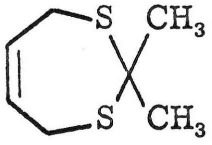
A

Figure 30. Conformations of cycloheptene.

cannot be converted into other conformations or undergo ring inversion without substantial changes in the bond angles. The boat form is more flexible, and ring inversion in this conformation can be accomplished without major deformation of bond angles. Conformations 76 and 77 are intermediates in the pathway for interconversion of equatorial and axial positions in boat cycloheptene. The first of these forms (76) is characterized by dihedral angles of 0° for ω_{12}, ω_{45}, and ω_{17}; carbons 1, 2, 3, 6, and 7 lie in the same plane. The symbol A will be used here for this conformation. The second conformation has a two-fold rotation axis and is comparable to 73, an intermediate form in the axis-symmetrical interconversion of TC and TB conformations of cycloheptane. This conformation has been called the twist-form and will be designated by the sumbol T. It should be noted that ring inversion in boat cycloheptene via forms 76 and 77 is not the same as pseudo-rotation of boat cycloheptane. The process just described for cycloheptene will be denoted here by the symbol ϕ.

The other conformational changes of importance to the present discussion are the plane-symmetrical interconversions of chair and boat forms of cycloheptene. These transformations are exactly analogous to the previously described interconversions of C and B cycloheptane conformations. Wagging of C-1 in cycloheptene will be denoted in this thesis by S(1), and the other plane-symmetrical process will be designated by S(3).

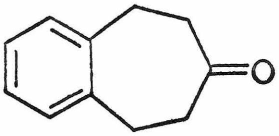
Relative energies of 0, 1.19, 5.60, and 1.71 kcal/mole have been calculated (127) for the C, B, A, and T conformations of cycloheptene, respectively. The calculated CCC bond angles of the $-CH_2-CH_2-CH_2-$ units are too small, as a consequence of having taken the optimum bond angle for these ring segments as the tetrahedral angle, rather than a value closer to 112.5°. The calculated energies may still be of some use for a qualitative comparison of the relative energies of the conformations. The A form was said to be the conformation of maximum energy on the path for ring inversion in boat cycloheptene. The calculated barrier for this process is low (4.41 kcal/mole), as expected from examination of models. The activation parameters for ring inversion in 5,5-difluorocycloheptene (125) were $\Delta H^{\ddagger} = 7.4 \pm 0.1$ kcal/mole and $\Delta S^{\ddagger} = -0.2 \pm 2$ eu, and the results were interpreted in terms of the chair conformation. Several heterocyclic cycloheptenes, including 78 (128), exist as a mixture of boat and chair forms. The methyl protons of 78 at -119° gave rise to three lines, as expected for chair and boat conformations in a ratio of about 2:1, with ring inversion of the chair form stopped, but with inversion of the boat form still rapid on the nmr time scale.



78

Barriers have been reported for several benzocycloheptenes (129-131) and for heterocyclic derivatives of cycloheptene and benzocycloheptene (128, 132). Strain energies were calculated (131) for three conformations of benzocycloheptene and derivatives, and the chair conformation of the unsubstituted compound was estimated to be more stable than the boat form by 2.4 kcal/mole. Allinger

(133) calculated that the boat conformation of cycloheptene was more stable than the chair form by 0.94 kcal/mole; this conclusion is in disagreement with most of the evidence presently available, including Allinger's dipole-moment study of 79 (134).



79

The barriers for ring inversion in the difluoro lactone and lactam are substantially higher than for 5,5-difluorocycloheptene and, as in the case of the cycloheptene derivative, are best interpreted in terms of the chair conformation. The assignment of the chair form to the 7-membered lactone is in agreement with the conclusions based on ORD measurements (122). The results from an ESR study of a radical derived from irradiation of crystalline ϵ-caprolactam (126) were interpreted in terms of the boat conformation. This conclusion is not in agreement with the results for γ,γ-difluoro-ϵ-caprolactam in solution.

Several pathways for accomplishing inversion in chair cycloheptene are shown in Figure 31. Axial and equatorial positions can be interchanged by plane-symmetrical processes (S(1) and S(3)) alone, as in steps 1 and 2 or 8 and 9. However, because the barrier to

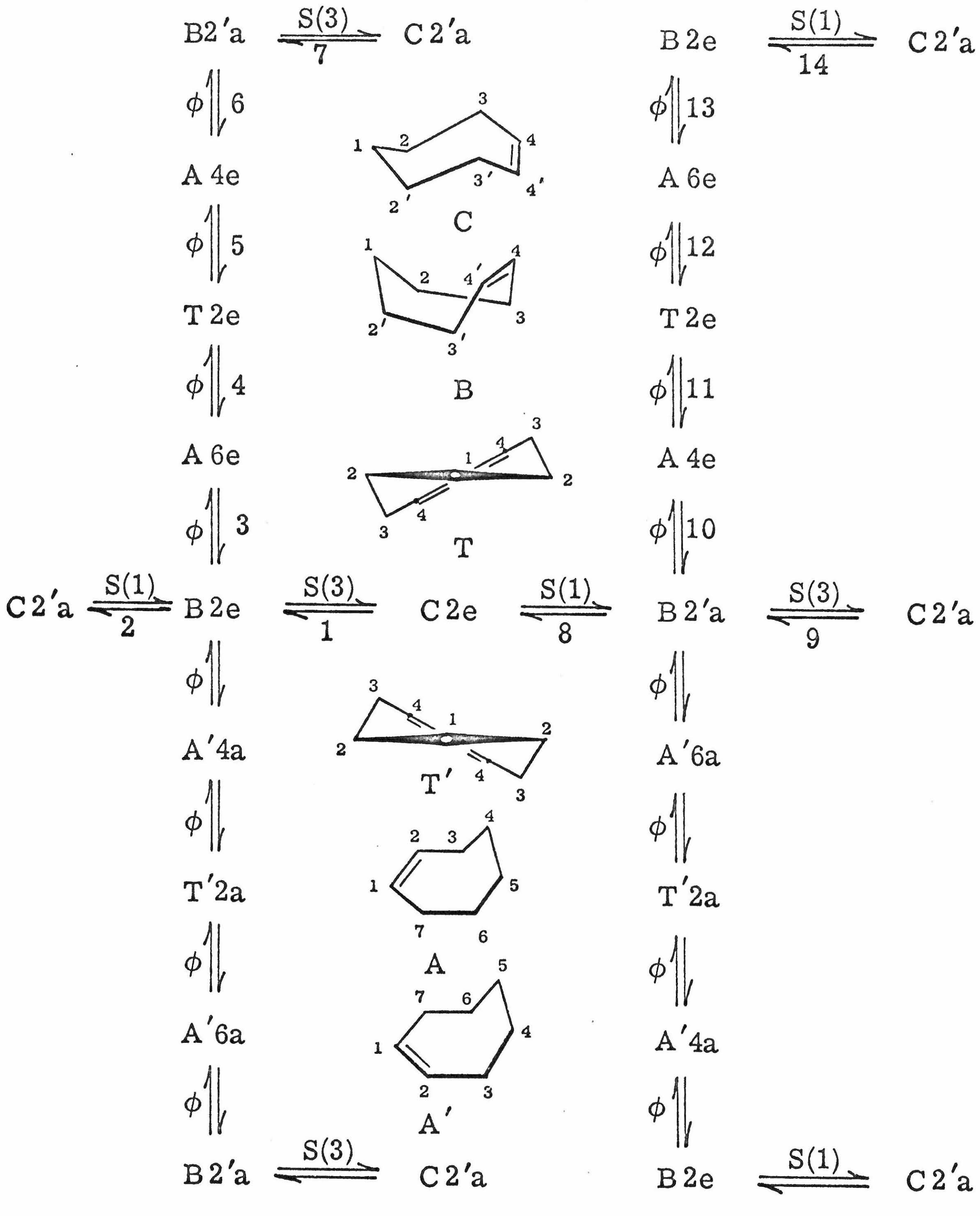
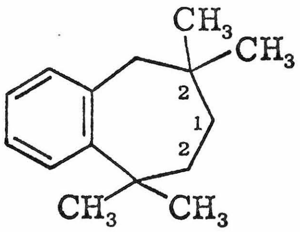


Figure 31. Some conformational changes in cycloheptene.

inversion in the boat conformation is probably low, the pathways which combine this process (ϕ) with one of the plane-symmetrical processes are expected to be favored. Steps 1, 3, 4, 5, 6, and 7, for example, use only ϕ and S(3), and the sequence 8, 10, 11, 12, 13, and 14 uses only ϕ and S(1).

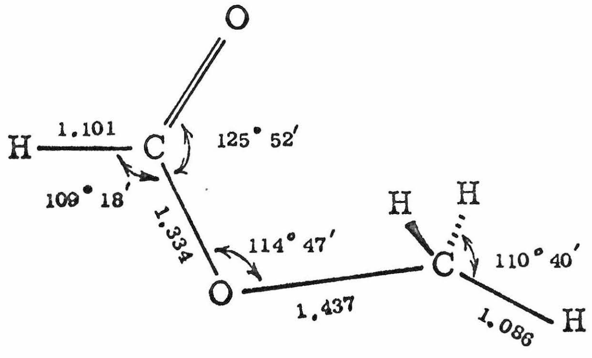
Grunwald and Price (129) interpreted the spectra of 80, which exists as a mixture of C and B forms, in terms of flipping of the 1- and 2-carbons. Inversion of this compound by the ϕ process is expected (135) to be effectively blocked by interactions between the methyl groups. Pathways alternative to the one described by Grunwald and Price for chair-chair inversion would be the steps 1 and 2 or 8 and 9 of Figure 31. Flipping of the 2-carbons in chair cycloheptene will not be considered further in this thesis, except to note here that the process connects the chair form with a conformation somewhat resembling the A form.

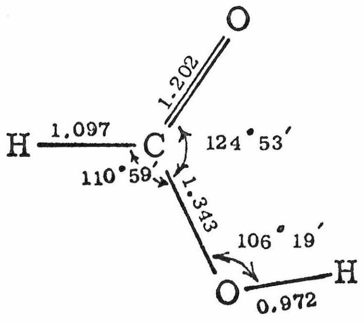


80

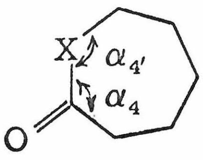
Molecular models clearly indicate that, as the preferred CCC angles at carbons 4 and 4′ increase (e. g., as on going from C cycloheptane to C cycloheptene), the barrier to C ⇌ B interconversion by S(3) will decrease. The effect on S(1) of increasing these angles is not as obvious, but models suggest that the barrier will increase; if θ_4 and $\theta_{4'}$ of cycloheptene are enlarged to the point that carbons, 2, 2′, 3, 3′, 4, and 4′ are coplanar, then flipping of C-1 becomes nearly impossible.

Unfortunately, the bond angles for the compounds of interest (cycloheptene, ϵ-caprolactone, and ϵ-caprolactam) are not available for comparison. The bond angles in cyclohexene that correspond to θ_4 and $\theta_{4'}$ in cycloheptene were determined (136) to be 124 ± 2°, and the CCC angle in propene (137) was 124.3 ± 0.3°. With these two compounds as models, bond angles on the order of 124° might be expected for cycloheptene. Estimates from closely related compounds are difficult to obtain for the lactone. The structures of methyl formate (114) and formic acid (115) are given below.





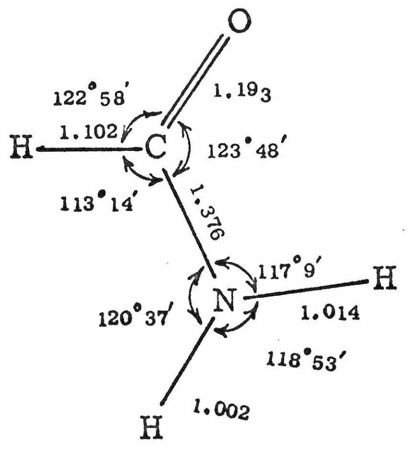
These values suggest that the angles α_4 and $\alpha_{4'}$ in the lactone (81) may be smaller than in cycloheptene. The greater barrier to ring inversion in the difluoro lactone, as compared to 5, 5-difluorocycloheptene, might be rationalized by assuming that the chair ⇌ boat interconversion in cycloheptene normally occurs by the S(3) process. The increased barrier in the lactone would then result from a higher barrier for S(3), or from changing over to S(1) for the inversion process. The bond angles corresponding to α_4 in 81 were reported (138, 139) as 121 and 120° for two 6-membered lactones. The angles corresponding to $\alpha_{4'}$ were also large (124°). These lactone rings were part of fused-ring systems in complex natural products, so the compounds may not be better models for the bond angles in 81. The difference in angles between the 7-membered lactone and cycloheptene may, however, be less than suggested by the geometries of methyl formate and formic acid. For large deformations, even a relatively small difference in the preferred bond angles could make a significant change in the barrier to inversion.

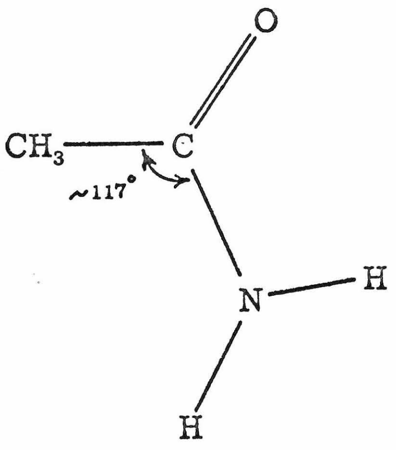


81, X = O

82, X = NH

An explanation similar to the one offered for the lactone could also be applied to the lactam. Angles are given below for formamide (140) and acetamide (141). The data for formamide are from a microwave study. The bond angle shown for acetamide is an average of two values and was determined by X-ray analysis of the crystalline compound.





In cycloheptene, each of the alkenic hydrogens appears to be nearly eclipsed with an adjacent methylene hydrogen. This could lead to a destabilization of the ground state, which would be partially relieved in the transition state for inversion by S(3). In the lactone and the lactam, on the other hand, the dihedral angles in this part of the ring should not be so much more favorable in the transition state for S(3) than in the ground state. This effect would also lead to a smaller barrier for inversion in cycloheptene than in the two heterocyclic compounds.

Further speculation on the causes for the relatively high barrier in the difluoro lactam and lactone does not appear to be warranted at the present time. Detailed structural parameters for the three rings would be of interest. Strain-energy calculations for the S(1) and S(3) processes could also be helpful. In the calculations, the effects of varying θ_4 and $\theta_{4'}$ should be determined, and the possibility of different force constants for angle bending in the heterocyclic compounds should be taken into consideration, as well as the different barriers for rotation about bonds, where these bonds are not the same.

Interconversion of equatorial and axial fluorine positions in γ,γ-difluoro-ϵ-caprolactone via pseudo-rotation of the chair conformation requires twisting about the bond between the carbonyl carbon and the methoxyl oxygen, and will result in loss of the resonance energy. Several points should be considered in employing the barrier in the lactone as a measure of the barrier to cis-trans isomerization in esters: (1) The potential barrier for conversion of the stable (trans) form of an open-chain ester to the cis form will be higher than the barrier for the reverse process (represented by the lactone) by an amount equal to the ground-state energy difference, which appears to be on the order of 4 kcal/mole (105). (2) Even in the absence of the resonance interaction, the chair form and twist-chair forms of the lactone would not have identical energies. However, the eclipsed ethane segment in chair cycloheptane is absent in the lactone, and the

nonbonded interactions of the 3a hydrogens in chair cycloheptane may be smaller in the lactone. It seems unlikely that the barrier to pseudo-rotation in ϵ-caprolactone is greatly affected by this factor.
(3) If pseudo-rotation did not require sufficient rotation about the C–O bond, the loss of resonance energy would be less than maximum. Molecular models indicate, however, that the relevant dihedral angle changes by over 90° during the process (105° has been suggested (106) for one of the chair forms of ϵ-caprolactone). The largest of the calculated dihedral angles for C or TC cycloheptane (See Table 9) is 88.1° for one of the TC angles. The point of maximum energy in conversion of a cis-ester to the trans-isomer probably comes at a dihedral angle somewhat less than 90°, so this factor is unlikely to substantially lower the pseudo-rotation barrier in ϵ-caprolactone.
(4) Ring inversion could actually take place through chair $\rightleftharpoons$ boat interconversions, as discussed previously for cycloheptene. The barrier for pseudo-rotation of the chair form will be at least as high as the experimental barrier, and the values of $\Delta G^{\ddagger}$ and E_a for the lactone are probably best regarded as approximate lower limits for the barriers to conversion of the cis-isomer of an open-chain ester to the trans-isomer.

The potential barrier for conversion of trans-formic acid to the cis-isomer in the vapor phase was reported (108) as $10._9$ kcal/mole. If the cis-trans energy difference (2 kcal/mole) is subtracted, and 10% is added as a rough correction (142) for the liquid phase, then the resulting value (10 kcal/mole) is quite similar to the barriers in the lactone.

It is not completely clear to this author whether the "two-fold potential barriers" determined (120) for methyl formate and methyl acetate (13.$_1$ and 15.$_9$ kcal/mole) should be regarded as barriers for conversion of the *cis* form to the *trans* form. or the reverse, or some kind of average. If the first of these possibilities is correct, then subtracting 4 kcal/mole for the energy difference of *cis*- and *trans*-isomers, and adding 10% for correction to the liquid phase (it is not clear whether the barrier for methyl acetate was for the liquid or vapor phase) would bring the values into reasonable agreement with the barriers in the lactone.

EXPERIMENTAL

Melting points were taken on a Büchi melting-point apparatus and are uncorrected. Preparative vapor-phase chromatographic separations were carried out with a Varian Aerograph Autoprep Model 700 gas chromatograph, using 3/8-in × 20-ft columns. Analytical vapor-phase chromatograms were obtained with either a Perkin-Elmer Model 154C or a Hewlett Packard Model 5750 gas chromatograph. One of two columns was used: a 1/8-in × 8-ft column of 20% carbowax on 45/60 Chromosorb P or a 1/8-in × 6-ft column of 20% FFAP on 45/60 Chromosorb P. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Infrared spectra were taken on a Beckman Model IR-7 spectrometer. Proton nmr spectra were obtained with either a Varian A-60A or A-56/60A spectrometer. Chemical shifts are reported in ppm downfield from internal tetramethylsilane. Fluorine nmr spectra were measured on the Varian A-56/60 A spectrometer. The spectra were calibrated by the sideband technique using a Lenkurt Model 6200 DS audio oscillator and a Hewlett-Packard Model 5216A counter. The signal-to-noise ratio of the low-temperature fluorine spectra was improved as necessary with a time-averaging computer, Varian Model C-1024; the number of scans required varied between 1 and 14. The Varian Model V-6040 variable-temperature accessory was used to control the temperature.

The methanol chemical shift difference was used to determine the temperatures for γ,γ-difluoro-ϵ-caprolactone above -65°. The other temperatures were measured by replacement of the sample tube with an open tube containing a suitable solvent and a copper-constantan thermocouple.

Theoretical spectra were generated by an IBM 360/75 computer using the Gerig program (143), which is based on the equations of Alexander (144). The parameters used in calculation of the spectra included a chemical shift, a mean lifetime, τ, and an "effective" relaxation time, T_2, for each nucleus in the system. The relaxation times were selected to reproduce, as far as possible, the line shapes in the spectra taken at the slow-exchange limit. The values of τ were determined by comparison of the calculated and experimental spectra.

Ethyl chlorodifluoroacetate was used as an internal standard for the low temperature ^{19}F nmr spectra. The concentrations of the various solutions were: 1, 1-difluorocyclodecane, 13% by volume in vinyl chloride; 3, 3-difluoro-trans-cyclodecene (above -30°), 43% by volume in propene; 3, 3-difluoro-trans-cyclodecene (below -30°), 23% by volume in propene; γ,γ-difluoro-ϵ-caprolactone, 21% by weight in acetone; γ,γ-difluoro-ϵ-caprolactam, 9% by weight in acetone.

Sebacoin. -- The acyloin condensation of dimethyl sebacate was carried out on a one-mole scale according to the procedure of Allinger (145). The yield of recrystallized product was 102.7 g (60%), mp 39.2-40.8° (lit. mp 38-39°) (145); ir (CCl_4) 1705 (C=O) and

3500 cm^{-1} (O–H).

Sebacoin Tosylate. -- A solution of 102.3 g (0.601 mole) of sebacoin in 310 ml pyridine was cooled to 5°, and 154 g (0.807 mole) of p-toluenesulfonyl chloride was added with stirring and cooling. After 12 hr at 5° under a nitrogen atmosphere, the mixture was poured into 650 ml of iced 2 N hydrochloric acid. The solid product was extracted into methylene chloride. The organic phase was separated and washed five times with 2 N hydrochloric acid, twice with saturated sodium bicarbonate solution, and twice with water. The solution was dried over magnesium sulfate, and the solvent was removed with the aid of a rotary evaporator. Recrystallization of the residue from ether gave a first crop of 147.8 g (76%) of white crystals, mp 89-90° (lit. mp 86-87°) (146); ir (CCl_4) 1160, 1182, 1380, and 1599 cm^{-1} (tosylate); 1718 cm^{-1} (C=O). Concentration of the filtrate gave a second crop of 16.9 g, mp 88.8-89.8°.

1-(p-Toluenesulfonyloxy)-2,2-difluorocyclodecane. -- In a 200-ml pressure reaction vessel constructed of Hastelloy C alloy was placed 31 g (95.7 mmole) of sebacoin tosylate, 69 ml of methylene chloride, and 2.95 g (164 mmole) of water. The bomb was sealed, cooled to dry ice-acetone temperature and evacuated. Sulfur tetrafluoride (113.5 g, 1.05 mole) was condensed into the bomb, and the vessel was rocked for 10.3 hours at ambient temperature (19-23°) (70, 71). The reaction mixture was shaken vigorously with a saturated sodium bicarbonate solution and filtered through a pad of Celite. The solution was shaken twice more with saturated sodium bicarbonate solution and dried over magnesium sulfate.

Most of the methylene chloride was removed at the rotary evaporator to give a black, viscous residue. The combined residues from 213 g of sebacoin tosylate were chromatographed in two portions over 7.17 kg of neutral alumina. The column was eluted with petroleum ether (30-60°) containing increasingly large amounts of benzene until the product began to elute from the column, and the chromatography was finished with 100% benzene. The brown solid (38.5 g) was dissolved in ether and filtered from a small amount of insoluble material. Three crystallizations (charcoal) from ether gave 28.0 g of white crystals, mp 106.8-108°, and 4.2 g of a second crop of white solid, mp 106.5-107.5°; combined yield, 32.2 g (14.1%); ir (CCl_4), 1177, 1188, 1360, and 1601 cm^{-1} (tosylate). The pmr spectrum of a Silanor C solution showed absorption at δ 1.1-2.5 (19 H), with a sharp peak at δ 2.43 and a rather sharp peak centered at δ 1.54, a multiplet at δ 4.7-5.4 (1 H), and an AA′BB′ pattern at δ 7.2-8.0 (4 H). The ambient-temperature ^{19}F nmr spectrum was an AB pattern centered 28.0 ppm upfield from internal ethyl trifluoroacetate, with J_{FF} = 248 Hz and $\Delta\nu$ = 241 Hz. A thin layer chromatogram (Eastman sheet, developed with petroleum ether:ether :: 5:2) showed a single spot with an R_f value of 0.6.

Anal. Calc'd. for $C_{17}H_{24}F_2O_3S$: C, 58.94; H, 6.98; F, 10.97; S, 9.26. Found: C, 59.17; H, 7.13; F, 11.17; S, 9.14.

3,3-Difluoro-*trans*-Cyclodecene. -- A solution of 11.9 g (34.4 mmole) of difluorotosylate and 7.68 g (68.5 mmole) of potassium t-butoxide in t-butyl alcohol (183 ml) was refluxed for 19 hr. The mixture was cooled to room temperature, poured into 600 ml of ice water, and extracted with ether. The ether solution was washed six times with water and dried over magnesium sulfate. Most of the ether was removed by distillation under reduced pressure, and the residue was diluted to a volume of 35 ml with petroleum ether. A white solid (0.6 g, starting material) separated from solution after storing at -15°, and was collected by filtration. The filtrate was dried (Drierite) and concentrated by distillation under vacuum.

Two fifths of the product was purified by preparative vpc on a column of 30% FFAP on 45/60 Chromosorb P. The temperatures of the injection port, column, detector, and collector tip were 180, 150, 195, and 152°, respectively. The yield of clear, colorless liquid was 1.01 g (42%); ir (thin film), 985 (trans-disubstituted olefin); 1675 (C=C); and 3050 cm^{-1} (olefinic C–H). The pmr spectrum of a dichlorodifluoromethane solution showed absorption at δ 1.20-2.53 (14 H) with a rather sharp peak at δ 1.48, and a complex multiplet at δ 5.30-6.47 (2 H). The ^{19}F nmr spectrum at 14° is an exchange-broadened singlet centered 30.0 ppm upfield from internal ethyl chlorodifluoroacetate. A mass spectrum showed the parent ion at m/e 174. An analytical vapor-phase chromatogram indicated a purity of 99% or greater. The low-temperature ^{19}F nmr spectra showed the possible presence of traces of one or more impurities.

Anal. Calc'd. for $C_{10}H_{16}F_2$: C, 68.93; H, 9.26; F, 21.81. Found: C, 68.89; H, 9.24; F, 21.87.

1,1-Difluorocyclodecane. -- Most of the petroleum ether was distilled under reduced pressure from half of the crude 3,3-difluoro-trans-cyclodecene, and the residue was dissolved in 42 ml of 100% ethanol. Five-percent palladium on charcoal (0.221 g) was added, and the mixture was stirred under hydrogen for 28 hr at room temperature. The hydrogen was supplied by means of a balloon attached to the flask.

The solution was filtered through a Büchner funnel, and most of the solvent was removed by distillation with the aid of the water aspirator. The crude product was purified by preparative vpc using a column of 30% Carbowax on 45/60 Chromosorb P. The temperatures of the injection port, column, detector, and collector were 168, 152, 178, and 143°, respectively. One gram of a clear, colorless liquid was obtained (33% yield from the tosylate). The pmr spectrum of a dichlorodifluoromethane solution showed absorption at δ 1.40-2.50, with a sharp peak centered at δ 1.60. The ^{19}F nmr spectrum of a vinyl chloride solution at ambient temperature was a quintet (J_{H-F} = 15.5 Hz) centered 23.24 ppm upfield from internal ethyl chlorodifluoroacetate.

Anal. Calc'd. for $C_{10}H_{18}F_2$: C, 68.15; H, 10.29; F, 21.56. Found: C, 68.22, 68.30; H, 10.21, 10.17; F, 21.52, 21.65.

γ,γ-Difluoro-ϵ-caprolactone. -- The oxidation was carried out by a procedure similar to the one described by Duckworth and

Sager (146) for the preparation of ϵ-caprolactone from cyclohexanone. Ninety-percent hydrogen peroxide (0.818 g) was added dropwise with stirring at 5-10° to 5.97 g of trifluoroacetic anhydride. 4,4-Difluorocyclohexanone (2.76 g, 20.6 mmole) (147) was melted and added dropwise with stirring at a temperature of 10-15°. After the addition was complete, the mixture was stirred at 10-15° for 10 min and at 8° for 15 min. Chloroform (40 ml) was added, and the cold solution was added with stirring and cooling to 3.87 g potassium carbonate in 10 ml water. Isolation of the product according to the literature (146) directions gave crude material, which was purified by sublimation at a pressure of 0.2 mm and a bath temperature of about 70°. The yield after 5 sublimations was 1.61 g, collected in two fractions. The first fraction of 1.28 g, had mp 71.3-72.4°; ir (CCl_4) 1757 and 1164 cm^{-1}. The pmr spectrum showed multiplets at δ 1.9-3.0 (6 H) and δ 4.25-4.5 (2 H). The ^{19}F nmr spectrum at ambient temperature was a quintet ($J_{H-F} = 14.5$ Hz), centered 30.74 ppm upfield from internal ethyl chlorodifluoroacetate. The mass spectrum showed the parent ion at m/e 150.

Anal. Calc'd. for $C_6H_8F_2O_2$: C, 48.00; H, 5.37; F, 25.31. Found: C, 47.96; H, 5.32; F, 25.41.

4,4-Difluorocyclohexanone. -- A solution of 1.98 g of 4,4-difluorocyclohexanol (147) in 45 ml of acetone was cooled in an ice bath to 5°, and Jones reagent (148) added dropwise with stirring. The solution was stirred at room temperature for 45 min, poured into ice water, and extracted five times with 90 ml portions of ether.

The combined ether portions were washed with saturated sodium bicarbonate solution, and most of the ether was removed by distillation through a Vigreux column at atmospheric pressure. The flask was evacuated briefly at the rotary evaporator, giving a residue of 1.3 g. A vapor-phase chromatogram showed the presence of unreacted alcohol in addition to the ketone. The ir spectrum (CCl_4) showed carbonyl absorption at 1724 cm^{-1} [lit. ($CHCl_3$), 1724 cm^{-1} (149)]. The crude product was used in the next step without further purification.

γ,γ-Difluoro-ϵ-caprolactam. -- Polyphosphoric acid (25 ml) (150) was placed in a flask containing the 1.3 g of crude ketone, and 0.77 g of sodium azide was added in small portions over a period of 5 minutes (151). The temperature was raised to 50° after 20 minutes and was increased to 70° after 23 hours. Seventy-one hours after the reaction was started, the mixture was cooled to room temperature and poured with stirring into 175 ml of ice water. Cold 50% sodium hydroxide was added with cooling and stirring until a pH of about 8 was reached, and the lactam was extracted with six 100-ml portions of chloroform. The solution was dried ($MgSO_4$), and the solvent was removed by distillation, giving an orange-brown solid. Sublimation (5 times) at 0.2 mm and 70-80° gave a total of 0.449 g, collected in three fractions: a first fraction of impure light-yellow solid (94 mg); a second fraction of white solid (114 mg; mp 105-106°); and a third fraction of white solid (241 mg, mp 105.5-106.5°), the latter of which was used for the spectral and elemental analyses. The ir spectrum

(CCl_4) showed absorption at 725 (weak, broad), 1677 (strong), 3095, 3220, 3305, and 3422 cm^{-1}. The pmr spectrum of a hexadeuteroacetone solution showed a broad peak centered at δ 7.35 (N–H), a multiplet centered at δ 3.25 ($N-CH_2-$), and a series of peaks between δ 3.0 and 1.7 arising from the remainder of the hydrogens. The ^{19}F nmr spectrum of an acetone solution at 64° was a quintet resonance (J_{H-F} = 14.1 Hz) centered 29.31 ppm upfield from internal ethyl chlorodifluoroacetate. The mass spectrum showed the parent ion at *m/e* = 149.

Anal. Calc'd. for $C_6H_9F_2NO$: C, 48.32; H, 6.08; F, 25.48. Found: C, 48.26; H, 6.10; F, 25.44.

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