

APPLICATIONS OF NUCLEAR MAGNETIC RESONANCE  
SPECTROSCOPY TO THE STUDY OF MEDIUM-SIZED RINGS

- I. CONFORMATIONAL PROPERTIES OF CYCLOHEPTANE
- II. CONFORMATIONAL PROPERTIES OF CYCLOOCTANE

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## ABSTRACT

Conformational equilibration in medium-sized rings has been investigated by the temperature variation of the fluorine-19 n. m. r. spectra of 1, 1-difluorocycloalkanes and various substituted derivatives of them. Inversion has been found to be fast on the n. m. r. time scale at  $-180^{\circ}$  for 1, 1-difluorocycloheptane, but slow for 1, 1-difluoro-4, 4-dimethylcycloheptane at  $-150^{\circ}$ . At low temperature, the latter compound affords a single AB pattern with a chemical-shift difference of 841 cps. which has been interpreted in terms of the twist-chair conformation with the methyl groups on the axis position and the fluorine atoms in the 4-position. At room temperature, the n. m. r. spectrum of 1, 1-difluoro-4-t-butylcycloheptane affords an AB pattern with a chemical-shift difference of 185 cps. The presence of distinct trans and gauche couplings from the adjacent hydrogens has been interpreted to suggest the existence of a single predominant form, the twist chair with the fluorine atoms on the axis position.

Investigation of 1, 1-difluorocyclooctane and 1, 1, 4, 4-tetrafluorocyclooctane has led to the detection of two kinetic processes both having activation energies of 8-10 kcal. /mole but quite different A values. In light of these results eleven different conformations of cyclooctane along with a detailed description of the ways in which they may be interconverted are discussed. An interpretation involving the twist-boat conformation rapidly equilibrating through the saddle and the parallel-boat forms at room temperature is compatible with the results.

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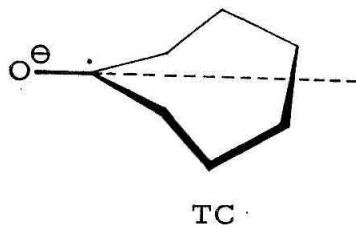
**PART I****CONFORMATIONAL PROPERTIES OF CYCLOHEPTANE**

## INTRODUCTION

Nuclear magnetic resonance has proven to be an excellent tool for the study of conformational problems; however, with systems such as cyclohexane and medium-sized rings in which complex spin-spin splittings occur, accurate results are usually difficult to obtain. The problem of complex coupling patterns in proton n. m. r. can be alleviated by massive deuteration and decoupling at the deuterium resonance frequency (1). However, the chemical-shift differences of protons in medium-sized rings are usually small (2) and thus are difficult to measure accurately. In addition, at very low temperature viscous broadening may obscure small chemical-shift differences.

In the present research on medium-sized rings two or more fluorine atoms have been substituted for hydrogen and the fluorine n.m.r. spectrum has been examined (3). Fluorine chemical shifts are much more sensitive to molecular environment and are usually 10-50 times larger than those for protons in similar environments. For example, the chemical-shift difference between the axial and equatorial fluorine atoms of 1, 1-difluorocyclohexane is 882 cps. (4), while the corresponding difference in the hydrogen atoms is 28 cps. (5). The study of the variation in the fluorine n. m. r. spectrum of 1, 1-difluorocyclohexane with temperature indicates an energy barrier to inversion of approximately 10 kcal. /mole (6). This result is in excellent agreement with barriers found with unfluorinated cyclohexanes (7, 8, 9), which indicates that fluorine substitution does not markedly affect the conformational properties of the ring.

Experimental studies of the conformational properties of cycloheptane are limited. Using spin-echo techniques, Meiboom (23) has observed a line-broadening process with an activation energy of less than 5 kcal./mole. Lown (27) has studied the e. p. r. spectrum of cycloheptyl ketyl at temperatures from  $-40^\circ$  to  $88^\circ$ . This radical ion affords a well resolved spectrum consisting of 1:2:1 triplets of 1:2:1 triplets which does not change with temperature. This spectrum indicates that cycloheptyl ketyl interconverts between two conformational forms which have plane of symmetry through the C—O bond axis at a rate much slower than that corresponding to the frequency difference of the two couplings ( $\sim 6 \times 10^7 \text{ s}^{-1}$ ). The preferred conformation is suggested to be the twist-chair form (TC). D. Roberts (28) has found that



both cis- and trans-4-t-butylcycloheptanol give nearly the same n. m. r. chemical-shift value for the  $\alpha$ -proton as cycloheptanol; furthermore, the rates of saponification of the acid phthalates of these three alcohols are nearly equivalent. A possible rationale for these results is afforded by a conformation such as the twist chair with the t-butyl group on the axis carbon atom. A careful examination of models shows that pseudorotation can flip an axial hydroxyl to an equatorial hydroxyl while keeping the t-butyl group in the axis position. The preferred

conformation in all three alcohols would be one with the hydroxyl group in an equatorial position.

## RESULTS

At room temperature, the fluorine n. m. r. spectrum of 1, 1-difluorocycloheptane is a quintet with  $J_{H-F} = 15.5$  cps. Under double irradiation at the proton resonance frequency a single sharp signal is observed. This sharp line shows no evidence of splitting as far down as  $-180^\circ$ ; moreover, in the undecoupled spectrum the H-F coupling remains constant at low temperature, although some line broadening occurs (Fig. 1).

At room temperature, the fluorine n. m. r. spectrum of 1, 1-difluoro-4, 4-dimethylcycloheptane is a quintet with  $J_{H-F} = 15.1$  cps. Under double irradiation at the proton resonance a single sharp signal is observed. This sharp line broadens and splits into an AB spectrum below  $-150^\circ$ . Using computer techniques (10, 11) (see Experimental), calculated spectra for various exchange rates were fitted to the experimental spectra between  $-150^\circ$  and  $-163^\circ$  (Fig. 2). Below  $-163^\circ$ , the chemical-shift difference remained constant at 841 cps. with  $J_{AB} = 237$  cps. From the Arrhenius plot of the results (Fig. 3), the activation energy for the rate process was calculated to be 5.2 kcal. /mole. Application of transition-state theory showed that at  $-150^\circ$ , the coalescence temperature, the free energy of activation was 5.0 kcal. /mole and the entropy of activation was  $-0.5$  e. u.

At room temperature, the fluorine n. m. r. spectrum of 1, 1-difluoro-4-methylcycloheptane is an AB pattern (under double irradiation) with a chemical-shift difference of 115 cps. with  $J_{AB} = 240$  cps. (Fig. 4). This chemical-shift difference decreases to 92 cps. at the

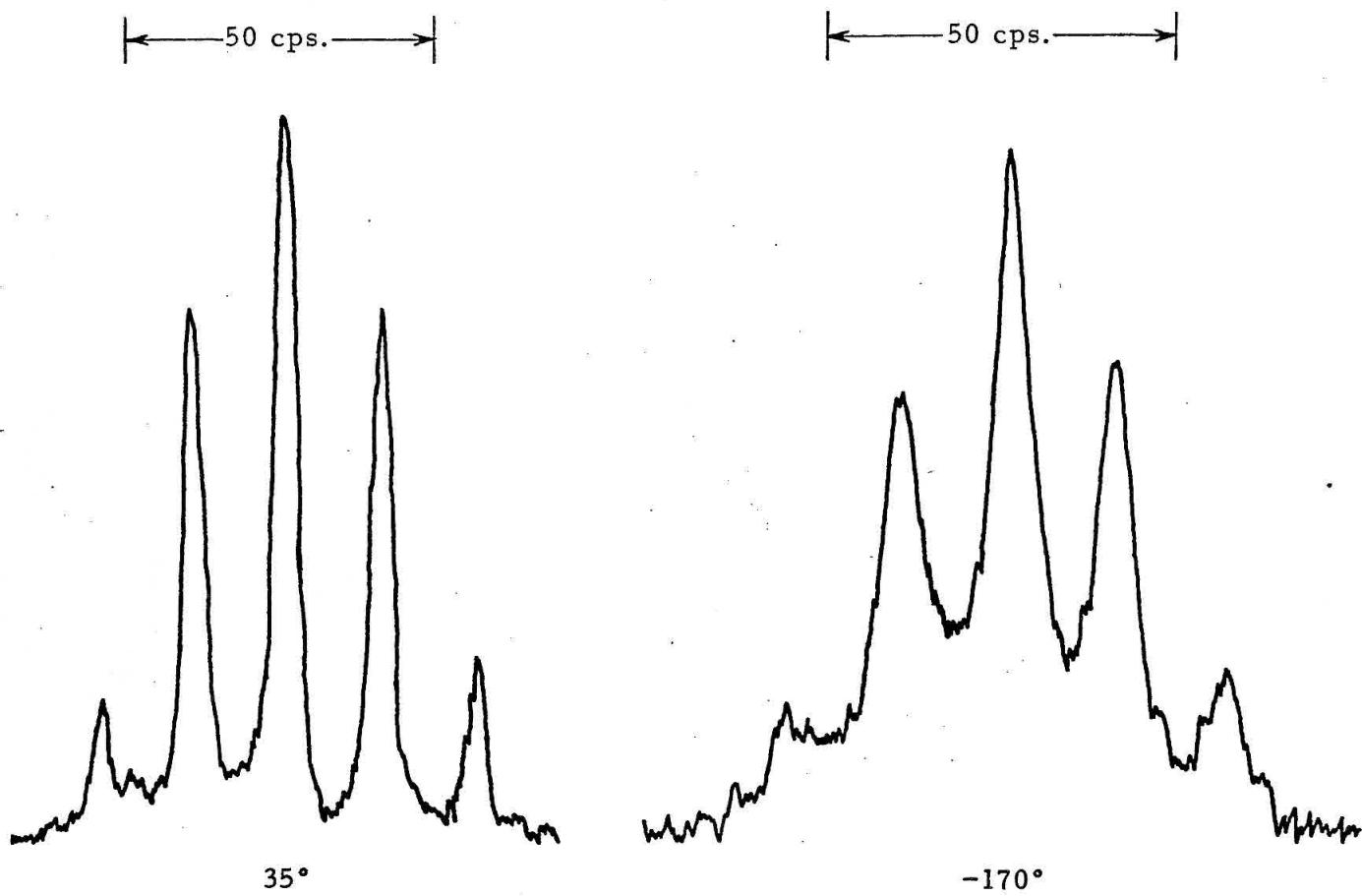


Figure 1. Room- and low-temperature spectra of 1,1-difluorocycloheptane.

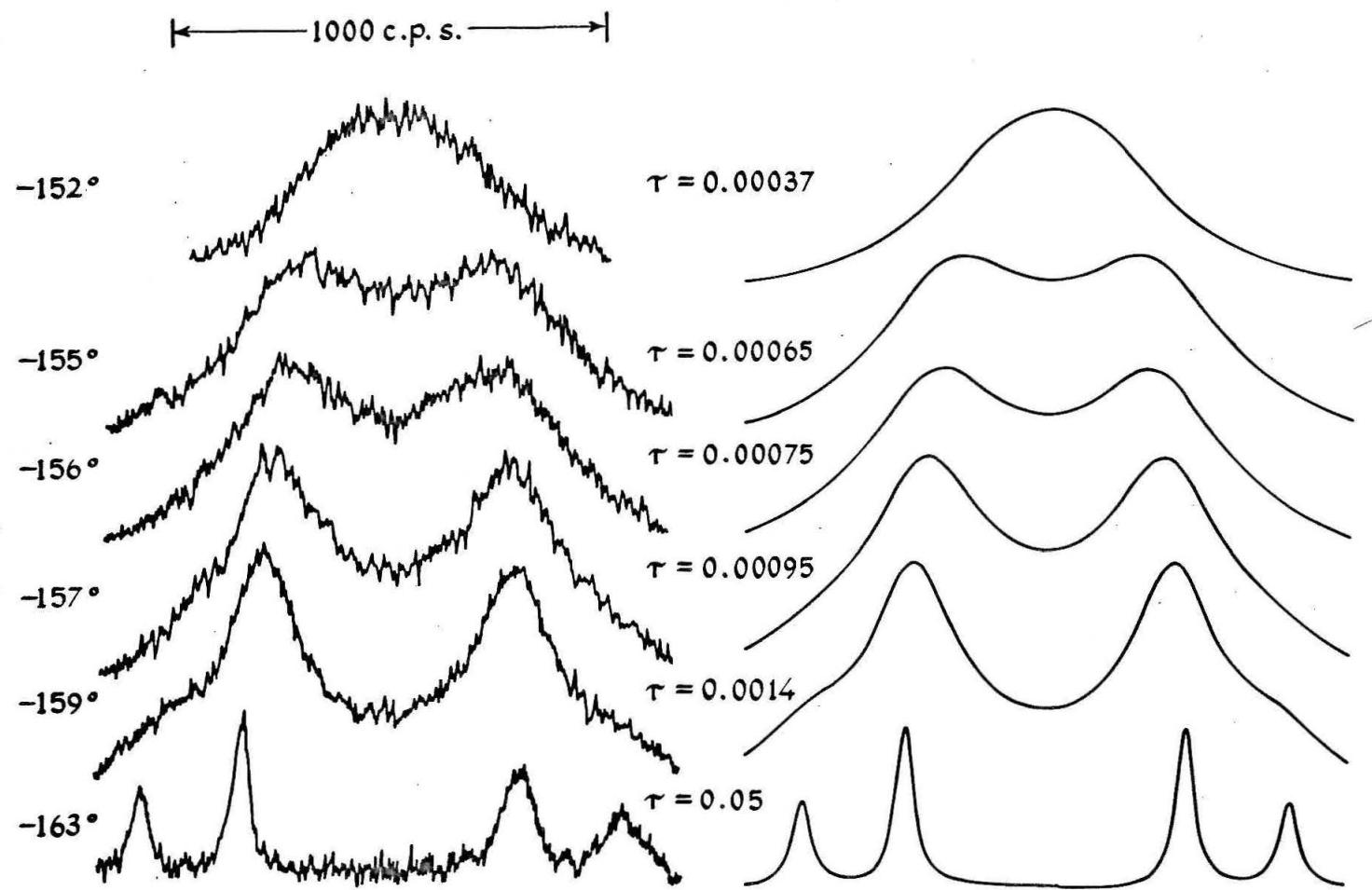


Figure 2. Experimental and calculated spectra of 1,1-difluoro-4,4-dimethylcycloheptane in propene.

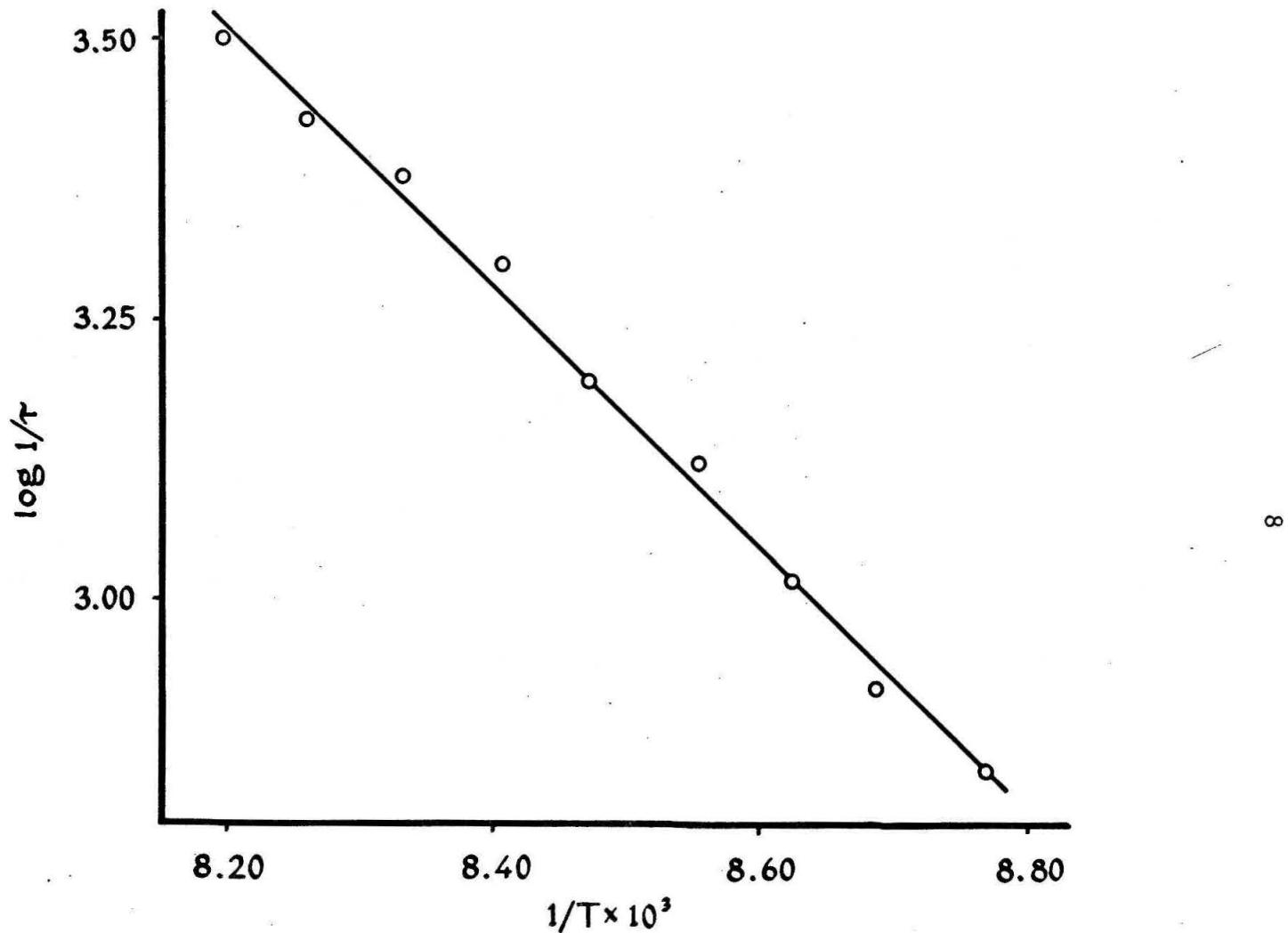


Figure 3. Arrhenius plot for 1,1-difluoro-4,4-dimethylcycloheptane (-150° to -163°).

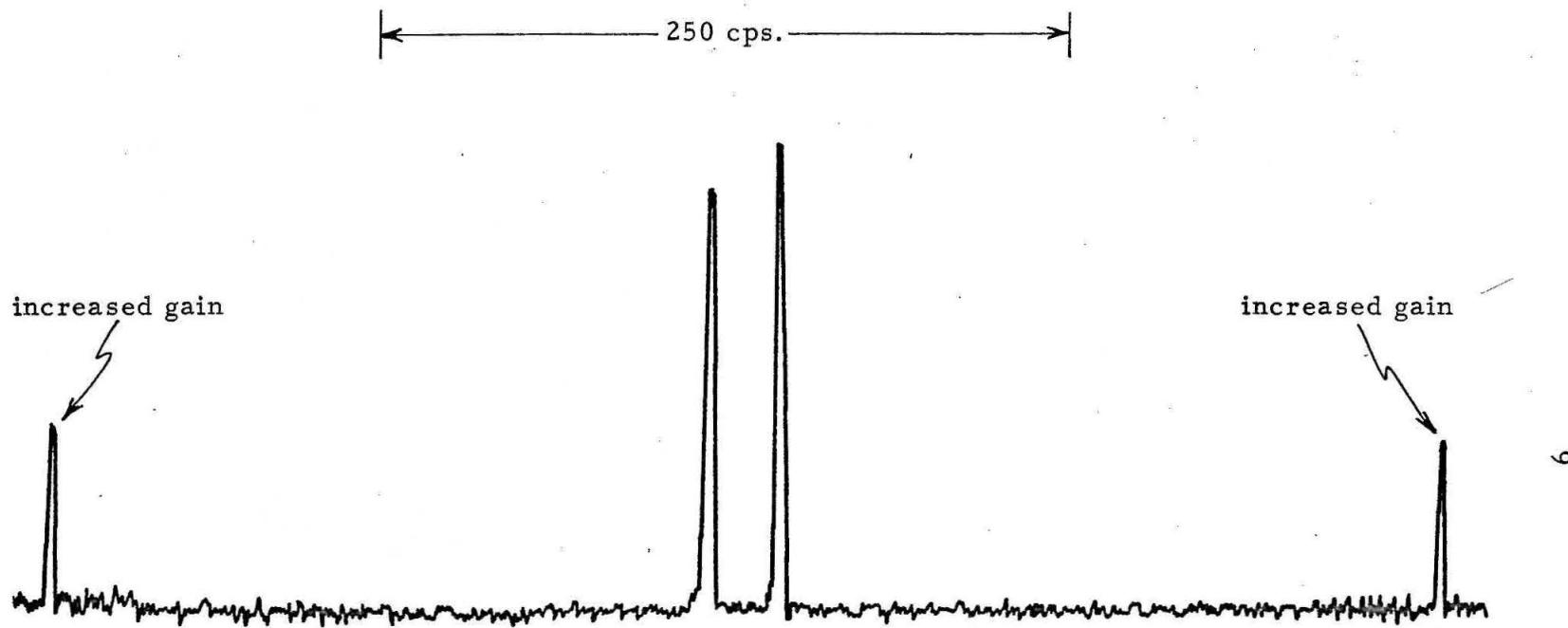


Figure 4. Experimental spectrum of 1,1-difluoro-4-methylcycloheptane at room temperature under double irradiation.

lowest temperature investigated (-125°).

At room temperature, the fluorine n. m. r. spectrum of 1,1-difluoro-4-t-butylcycloheptane is of the AB type with a chemical-shift difference of 185 cps. with  $J_{AB} = 240$  cps. (Fig. 5).

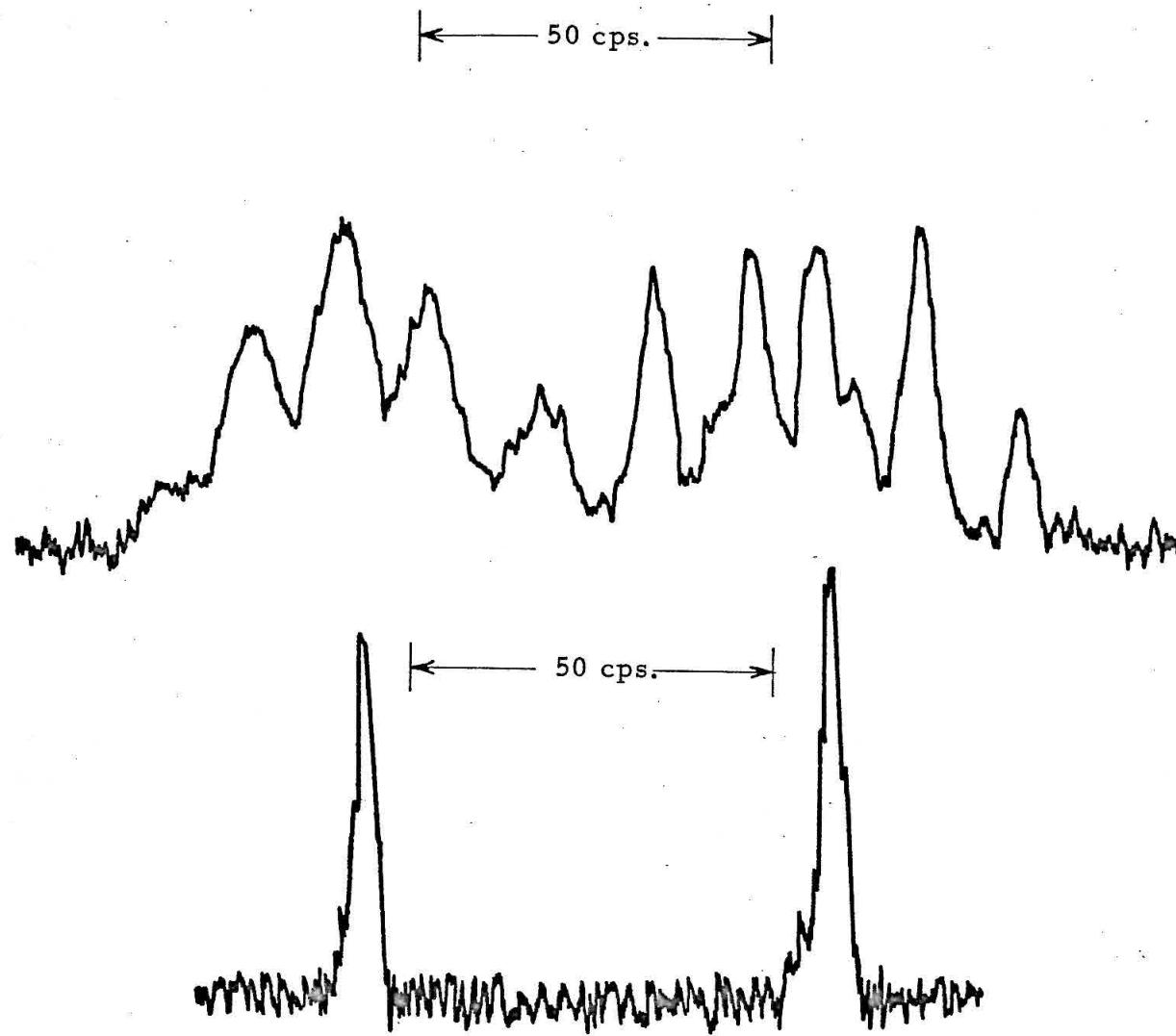


Figure 5. Experimental spectra of 1,1-difluoro-4-t-butylcycloheptane at room temperature (the wings of the  $A\bar{B}$  pattern are not shown; the lower spectrum was taken under double irradiation at the proton resonance frequency).

## DISCUSSION

The following discussion of the conformational analysis of cycloheptane is derived from the work of Hendrickson (12). In his calculations the total strain energy of a given conformation is taken as the sum of three independent energies: bond angle bending strain, torsional strain of the dihedral angles about single bonds, and nonbonded interactions of the hydrogens on the ring. The most formidable difficulty in these computations lies in the particular functions which relate energy to geometric parameters of the molecule. The exact form of these functions is not well understood and is generally derived indirectly from various empirical sources as spectroscopic or thermodynamic data. The energy functions used in Hendrickson's calculations are:

$$E_\theta = K_\theta (\tau - \theta)^2 : \text{bond angle strain}$$

$$E_t = K_t (1 - \cos 3\omega) : \text{torsional strain}$$

$$E_{HH} = 10^{4-2r} - 49.2/r^6 : \text{nonbonded interaction}$$

where

$$K_\theta = 0.0200 \text{ kcal. /mole/deg.}^2 \text{ for bending of C—C—C angle } (\theta) > r$$

$\theta$  = C—C—C bond angle

$\tau$  = tetrahedral angle =  $109.47^\circ$

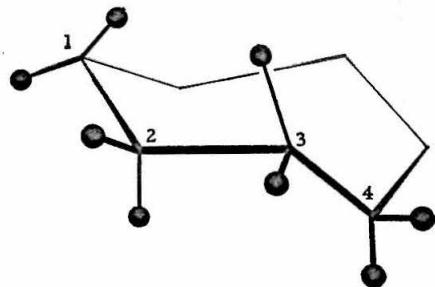
$K_t$  = 1.40 kcal. /mole

$\omega$  = C—C—C—C dihedral angle

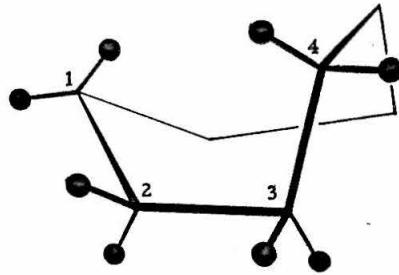
$r$  = internuclear distance of nonbonded hydrogens, in  $\text{\AA}$

In order to determine the most stable conformation of a given molecule it is necessary to calculate the total strain energy ( $\Sigma E = \Sigma E_\theta + \Sigma E_t + \Sigma E_{HH}$ ) summed over all the relevant angles and H-H distances in the molecule. Using this procedure this energy is then minimized with respect to independent variation of each of the parameters ( $r$ ,  $\theta$ ,  $\omega$ ) until a conformation of minimum energy is found.

Two families of cycloheptane have been treated by Hendrickson and will be considered in detail here. Both cycloheptane families contain flexible forms and can undergo pseudorotation similar to the cyclohexane boat forms. By analogy with the six-membered ring the two basic forms of cycloheptane are called the chair (C) and the boat (B).

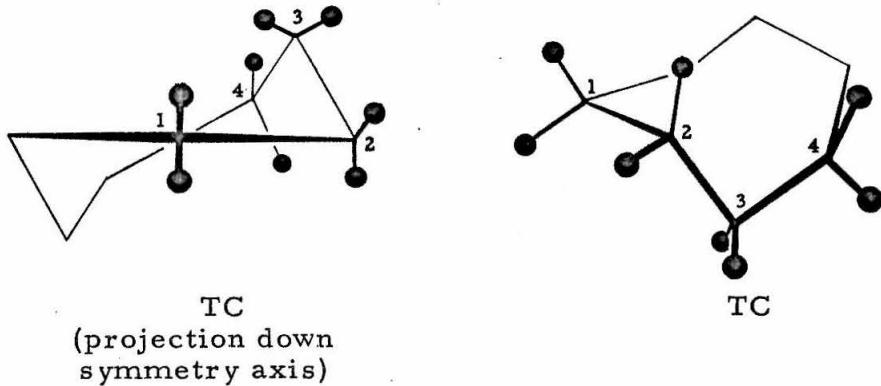


C



B

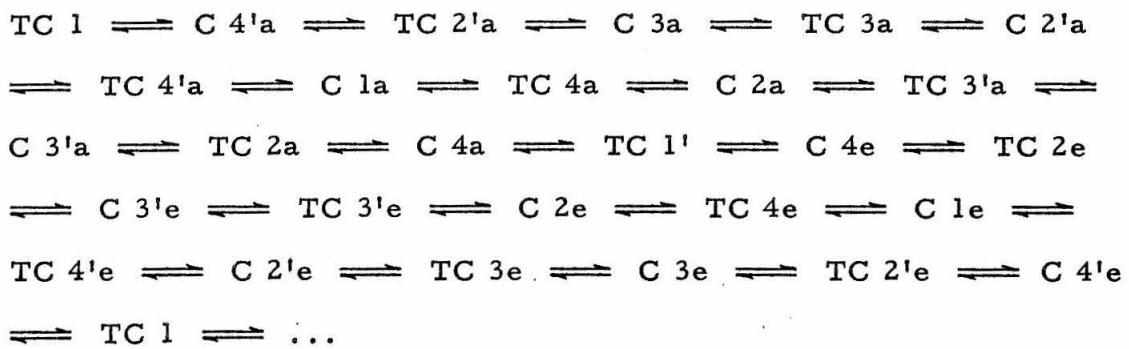
The chair has a serious H-H interaction across the axial  $C_3$ -position and also has some severe torsional strain around the ring, and particularly at the  $4, 4'$  positions. These interactions can be minimized to a certain extent by pseudorotation to a form with a two-fold symmetry axis, called the twist chair (TC). This conformation is preferred over the plane-symmetrical chair on grounds of torsional strain as well as



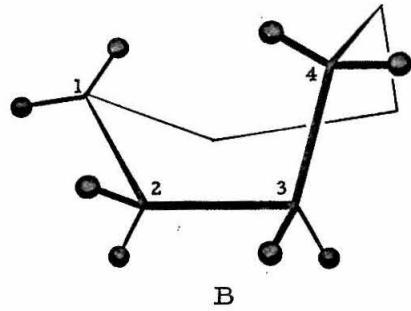
non-bonded interactions. However, even in the twist form the H-H interactions are serious across the axial  $C_3$ -positions. In order to minimize these interactions, an enlargement of the bond angles is necessary to produce the best balance of strains and repulsions. In the twist chair the lowest energy conformation has bond angles of  $112^\circ$ ; this form can pseudorotate to the chair at the cost of 2.2 kcal./mole. This pseudorotation process is accompanied by a regular flexing of bond angles:  $\theta = 112^\circ$  in the twist chair;  $\theta = 109.5^\circ, 112^\circ, 111^\circ, 116^\circ$  in the chair.

In the plane-symmetrical chair (C) there are four different kinds of methylene groups or eight different substituent positions on the ring; in the twist chair (TC) there are also four different kinds of methylene groups but only seven different substituent positions. Except for the axis positions on the twist chair, all the positions fall into equatorial (e) and axial (a) types, analogous to the cyclohexane chair. If a substituent is placed in one position in the chair family, it will

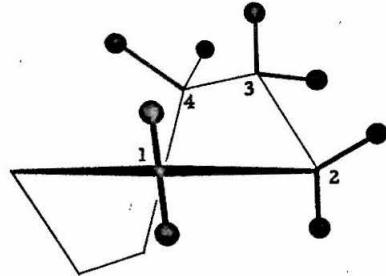
pass from that position through every position in the chair and twist-chair forms. If the substituents are no larger than hydrogen, the barrier to this pseudorotation will be 2.2 kcal. /mole. The detailed pseudorotation itinerary (TC  $\rightleftharpoons$  C) is indicated below (the prime numbers refer to the mirror-image configuration).



The second conformational family of cycloheptane contains the plane-symmetrical boat (B) and the twist boat (TB). The latter form



B

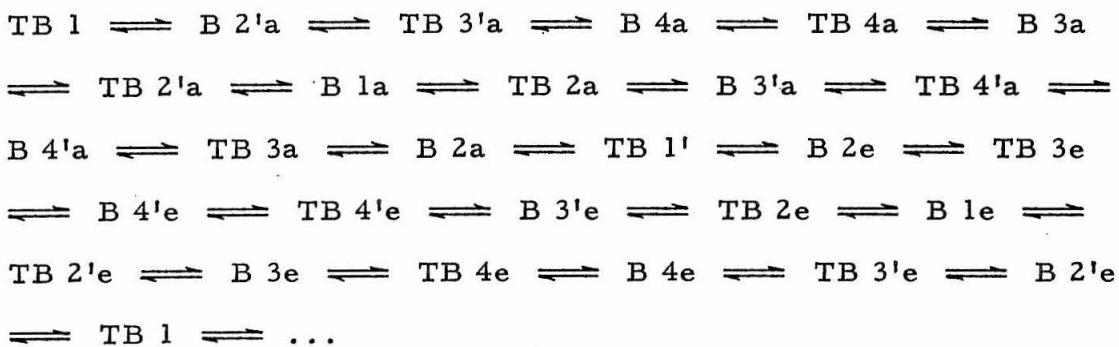


TB

(projection down  
symmetry axis)

has a two-fold symmetry axis and like the twist chair is preferred over the boat on grounds of torsional strain as well as non-bonded repulsions. The best twist-boat conformation energetically has enlarged bond angles

of  $113^\circ$ ; this form can pseudorotate to the boat ( $\theta = 114^\circ$ ) at the expense of only 0.5 kcal. /mole. In the boat and twist-boat conformations there are eight and seven different substituent positions, respectively. They fall into equatorial and axial types, except for the axis positions on the twist boat. If a substituent is placed in one position in the boat family, it will pass from that position through every position in the boat and twist-boat forms. If the substituents are no larger than hydrogen, the barrier to this pseudorotation process is 0.5 kcal. /mole. The detailed pseudorotation itinerary (TB  $\rightleftharpoons$  B) is indicated below.



In addition to the low-energy pseudorotatory processes that occur in both families, there is another process that involves a flip from one of the chair forms to one of the boat forms. This ring inversion process is analogous to the one in the cyclohexane series. The interconversion takes place by a rotation of the bond perpendicular to the symmetry axis in the twist chair to the half-chair transition state (HC) and then on to the twist boat. The barrier for chair-boat interconversion was calculated by Hendrickson to be 8.5 kcal. /mole (Fig. 6).

It can be seen from the calculated energies in Fig. 6 that the preferred twist-chair conformation is 2.5 kcal. /mole more stable than

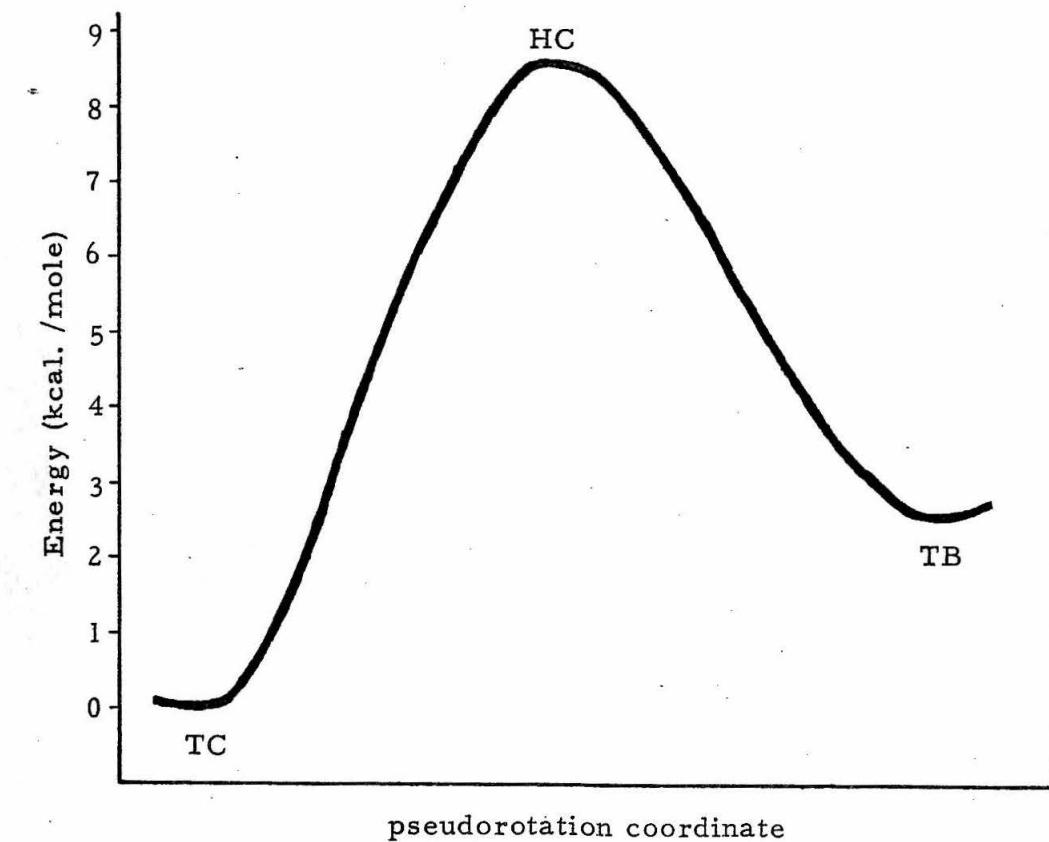


Figure 6. Chair-boat interconversion.

the preferred twist-boat conformation. Consequently one would expect the twist chair to be the predominant species at normal temperatures and to be rapidly pseudorotating to the chair and flipping to the twist-boat forms.

Despite the fact that cycloheptane is a conformationally complex system, it is possible to make certain semi-quantitative predictions about the effect of substituents on the interconversion among the different forms. Consider the case of methylcycloheptane: in the course of the pseudorotation of this molecule in the chair family, the methyl group passes through in a definite sequence fifteen distinguishable conformational positions on the chair and the twist chair. The pseudorotation itinerary consists of four axial and four equatorial positions in the chair and an axis carbon plus three axial and three equatorial positions on the twist chair. By applying the same energy minimization procedure used in cycloheptane itself, Hendrickson has calculated for each separate position the energy of the added methyl on the ring. The results of these calculations appear in Table I and in the energy contour of the pseudorotation shown in Fig. 7. The calculations indicate that all the equatorial positions on one ring conformation have the same energy; the equatorial positions of the twist chair have an energy 2.2 kcal./mole lower than those of the chair. The important fact to note in these calculations is that the energy of the axis positions of the twist chair is the same as that of the equatorial positions. Consequently, methylcycloheptane would be expected to exist predominantly in the twist-chair conformation with the methyl group in an equatorial or axis position. The energy of the axial positions in

Table I  
Energies of Methylcycloheptane Conformers (13)

Methyl position	"A" value (kcal. /mole)*
Twist chair	
1axis	0
2e	0
2a	4.3
3e	0
3a	4.9
4e	0
4a	1.4
Chair	
1e	2.2
1a	4.0
2e	2.2
2a	4.0
3e	2.2
3a	9.4
4e	2.2
4a	3.0

\*"A" value represents the difference from the average energy  
of the twist chair with a methyl in an equatorial position.

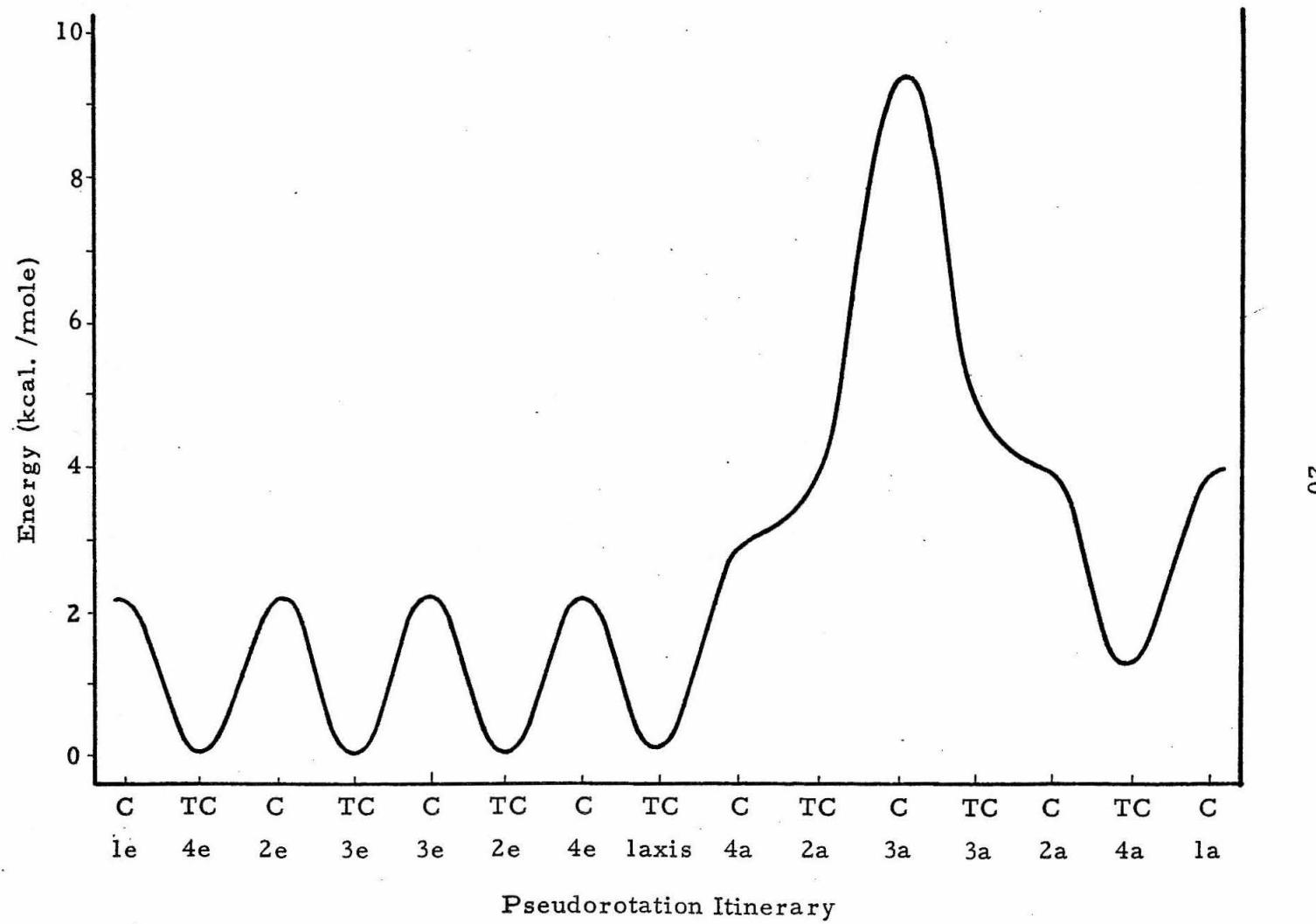


Figure 7. Pseudorotation of methylcycloheptane (13).

methylcycloheptane is much higher than in the corresponding cyclohexane molecule. The highest axial energy is that of the chair 3a-methyl (9.4 kcal./mole) where passage of the methyl group is particularly severe. This energy represents the height of the barrier to free pseudorotation among all the methylcycloheptane conformations. At room temperature, this barrier is sufficiently low to permit rapid pseudorotation among the fifteen conformations in the chair family with the predominant species being the twist-chair forms having equatorial and axis methyl groups.

The most important consequence of these calculations lies in the fact that the axis carbon atom has two equivalent substituent positions whose energy is the same as that of the equatorial positions. This means that any 1,1-disubstituted cycloheptane will prefer the conformation of the twist chair with the two substituents on the axis carbon atom. The preference for this form in 1,1-dimethylcycloheptane should be approximately 1.4 kcal./mole, this being the energy difference between the axial and equatorial methyls on the next-best position (TC 4e,4a). It is possible to derive from Hendrickson's calculations an energy contour for pseudorotation (Fig. 8) of 1,1-dimethylcycloheptane by using both the axial and equatorial energies of the methylcycloheptane conformations.

It can be seen from the energy contour that the chair 3e,3a-dimethyl is the highest energy conformation (11.6 kcal./mole) and represents the height of the barrier to free pseudorotation among all the dimethylcycloheptane conformations. At room temperature, this bar-

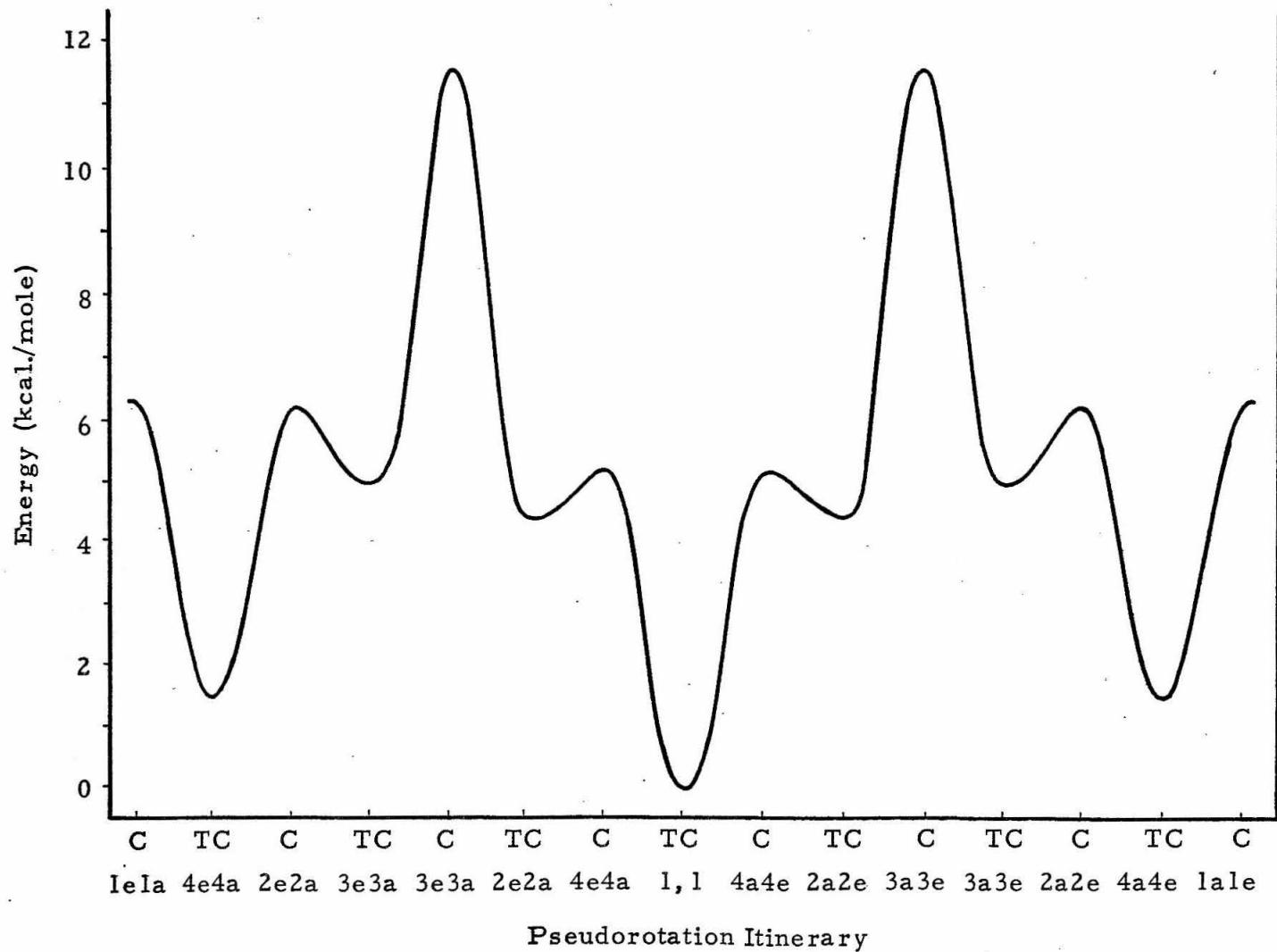


Figure 8. Pseudorotation of 1,1-dimethylcycloheptane.

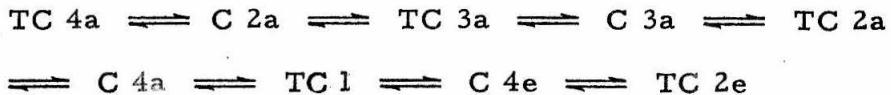
rier would be expected to be sufficiently low to permit interconversion among the eight distinguishable conformations in the chair family with the predominant species being the twist-chair form having axis methyl groups.

To complete the picture of the conformational analysis of substituted cycloheptanes, we must consider the possibility of chair-boat interconversion. In cycloheptane itself the height of this barrier was calculated to be 8.5 kcal./mole, which is considerably higher than that for the pseudorotatory process between the chair and the twist chair. However, with substituents larger than hydrogen, the pseudorotation barrier becomes higher and especially bad for passage of the substituent through the chair 3a position; in fact, it might be expected that interconversion of substituted cycloheptanes would be slowed at lower temperatures through the 3a position, although partial pseudorotation through the equatorial positions would still remain rapid. This difficulty of passing through the 3a position can be averted if one of the chair family conformers flips into the boat family, pseudorotates among the boat forms, and then flips back to another chair conformer. This is possible because the order of position changes in the family itineraries is different, as seen on pages 15 and 16. When the twist chair flips to the twist boat, the following positional changes occur:

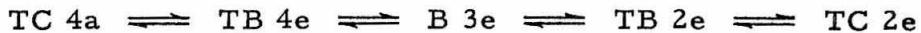
TB	1	2e	2a	3e	4a	4e
TC	1	2e	2a	3e	4e	4a

Consider the twist chair with a substituent in the 4a position.

This molecule can pseudorotate through the chair 3a position and on to the twist-chair 2e position in the following manner:

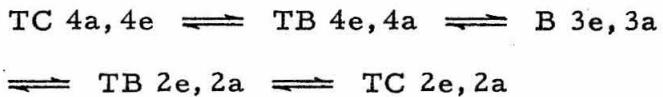


This molecule can accomplish this interconversion ( $\text{TC } 4\text{a} \rightleftharpoons \text{TC } 2\text{e}$ ) without passing through the high-energy 3a barrier in the following manner:



This process appears to be favored over pseudorotation because the substituent passes exclusively through equatorial positions in the course of the itinerary.

The possibility of flipping from one family to another also exists in 1,1-disubstituted cycloheptanes. The following route can be used for the interconversion:  $\text{TC } 4\text{a,4e} \rightleftharpoons \text{TC } 2\text{e,2a}$



In certain substituted cycloheptanes this process may be preferred over pseudorotation exclusively in the chair family.

Since Hendrickson has not considered the chair-boat flipping in his calculations on methylcycloheptane, it is not possible to make any quantitative predictions concerning the exact itinerary for the interconversion of substituted cycloheptanes. Qualitatively speaking, all

the conformations are interconvertible, via either pseudorotation within one family or flipping from one family to the other. When a bulky substituent is present, the latter process may become the best energetically, particularly as an escape route around the 3a position.

Using the above conformational principles derived from Hendrickson, we can consider the results obtained from the n. m. r. spectra of the geminal-substituted fluorocycloheptanes.

The case of 1, 1-difluorocycloheptane is somewhat ambiguous because no apparent change in the spectrum is observed as low as  $-180^{\circ}$ . The interpretation of this result is complicated by two problems which are important to the study of all exchange processes of this kind: 1) the populations of the various conformations, and 2) their rates of interconversion. A rapid rate of interconversion would permit the fluorine atoms to pass through all the positions on the ring, thereby affording a simple  $A_2$  spectrum. Indeed, Hendrickson has calculated a low activation energy for the pseudorotation process for cycloheptane itself. However, because fluorine atoms are slightly larger than hydrogen (van der Waals radii: H = 1.20 Å; F = 1.47 Å) (14), they would be expected to experience difficulty in passing through the chair 3a position, perhaps sufficient to slow the pseudorotation process at low temperature. In addition, the gem-difluoro group would be expected to have a small conformational preference, "A" value, which would affect the populations of the four distinguishable twist-chair forms.

It is possible, with some confidence, to make certain crude semi-quantitative predictions concerning these two conformational problems. The "A" value of a fluorine atom on a cyclohexane ring has

been determined by n. m. r. spectroscopy to be 0.25 kcal. /mole (15) or approximately 1/6 the "A" value of a methyl group (1.5 kcal. /mole). Using this factor of 1/6 the "A" value of a fluorine atom on a cycloheptane ring can be derived from the calculations of the energies of the methylcycloheptane conformations (see Table I).

The results appear in Table II and in the energy contour of the pseudorotation shown in Fig. 9. It can be seen from the energy contour for 1,1-difluorocycloheptane that the chair 3e, 3a is the highest energy conformation (4.2 kcal. /mole) and represents the height of the barrier to pseudorotation among all the difluorocycloheptane conformations. The predominant species can be predicted to be the twist chair 1,1 axis, which is favored over the next-best form, the twist chair 4e, 4a by approximately 0.2 kcal. /mole. At room temperature, neglecting entropy, this free-energy difference corresponds to an equilibrium constant of 1.40 with the more stable conformer (TC 1,1 axis) present in approximately 60%. At -180°, this free-energy difference corresponds to an equilibrium constant of 2.95 with the more stable conformer present in 75%. Therefore, if pseudorotation were slow at low temperature, an  $A_2$  spectrum for the TC 1,1 axis and an AB spectrum for the TC 4e, 4a in the ratio of 3:1 would be expected. It is possible that the latter conformer has a much higher energy than the calculations indicate and is not observed in the experimental spectrum. If the TC 1,1 axis conformer is the only species present, then the problem revolves around whether or not rapid or slow pseudorotation would be expected to produce different n. m. r. spectra for the

Table II  
Energies of Fluorocycloheptane Conformers

Fluorine position	"A" value (kcal. /mole)
Twist chair	
1axis	0
2e	0
2a	0.7
3e	0
3a	0.8
4e	0
4a	0.2
Chair	
1e	0.4
1a	0.7
2e	0.4
2a	0.7
3e	0.4
3a	1.6
4e	0.4
4a	0.5

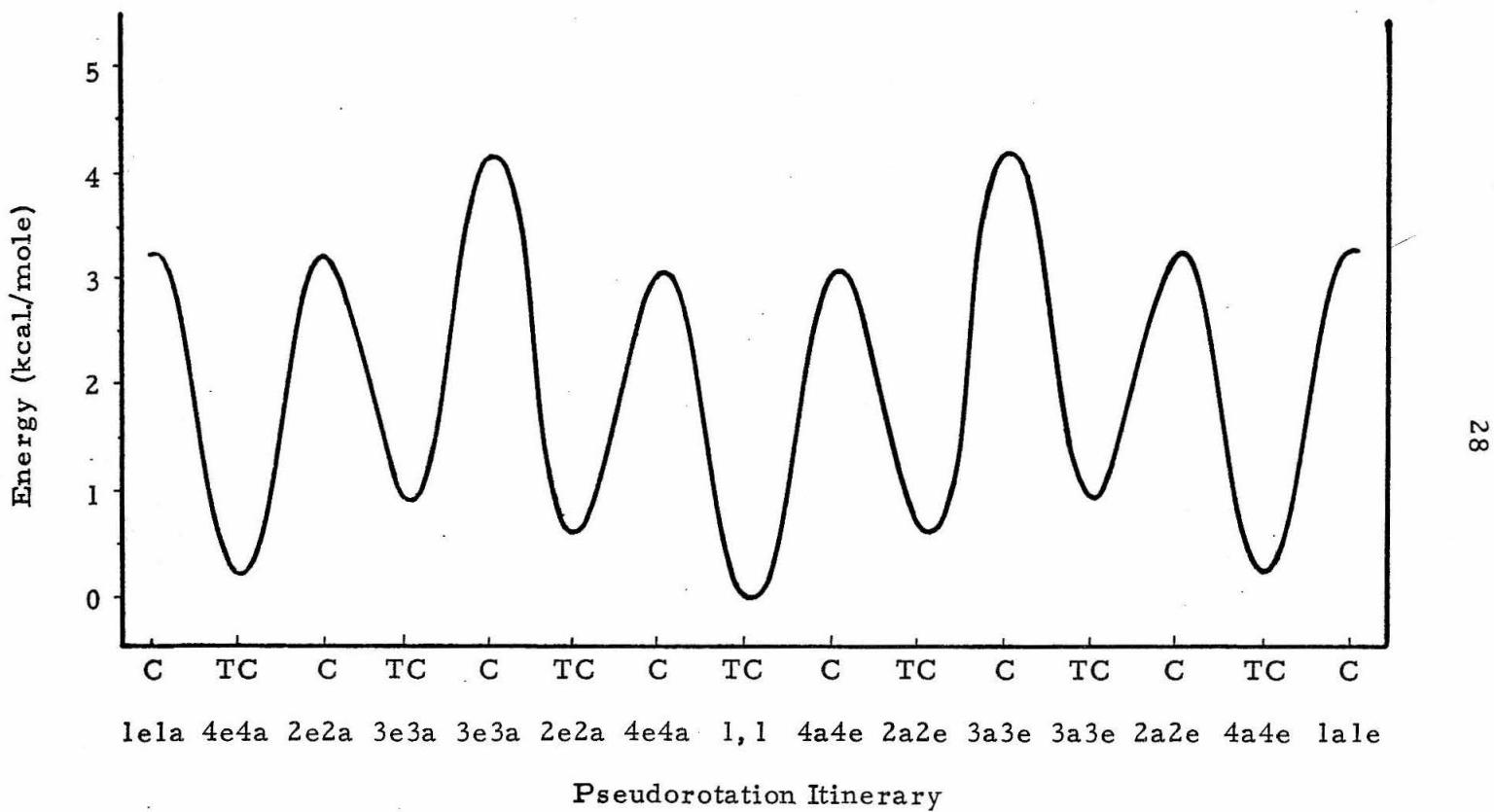
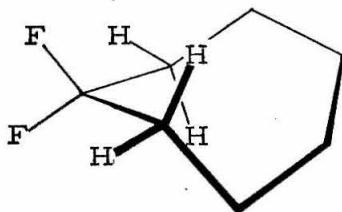


Figure 9. Pseudorotation of 1,1-difluorocycloheptane.

fluorine atoms. In the absence of decoupling an  $A_2X_4$  spectrum (a simple quintet) is observed for 1,1-difluorocycloheptane at  $-180^\circ$  (see Fig. 1). If pseudorotation were slow at  $-180^\circ$ , an  $A_2X_2Y_2$  spectrum would be expected because the adjacent hydrogens would have distinct axial and equatorial chemical shifts and would have distinct trans- and gauche- coupling constants with the axis fluorine atoms. Calculations



"frozen" TC 1, 1-axis conformer

of the fluorine n. m. r. spectrum for the "frozen" TC 1, 1-axis conformer appear in Fig. 10 using the following parameters (6):

$$\begin{aligned}
 \text{trans-}J_{\text{H-F}} &= 34.3 \text{ cps} \\
 \text{gauche-}J_{\text{H-F}} &= 11.5 \text{ cps} \\
 \text{gem-}J_{\text{F-F}} &= 245 \text{ cps} \\
 \text{gem-}J_{\text{H-H}} &= 15 \text{ cps}
 \end{aligned}$$

It can be seen that the coupling patterns in these spectra are more complicated than in the experimental spectrum. It seems most reasonable, therefore, that pseudorotation is rapid at low temperature, affording an averaged coupling pattern for the fluorine atoms on the

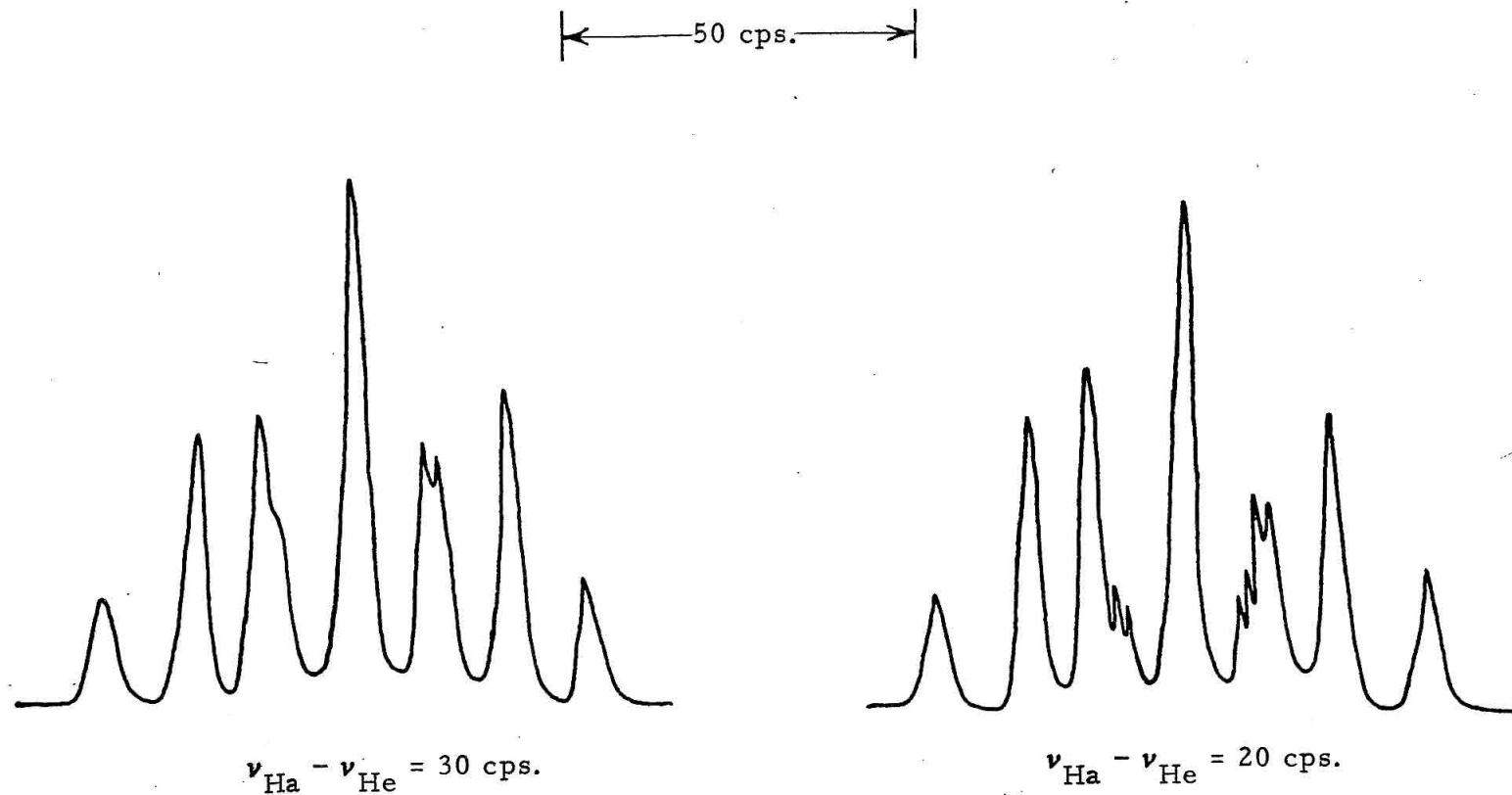
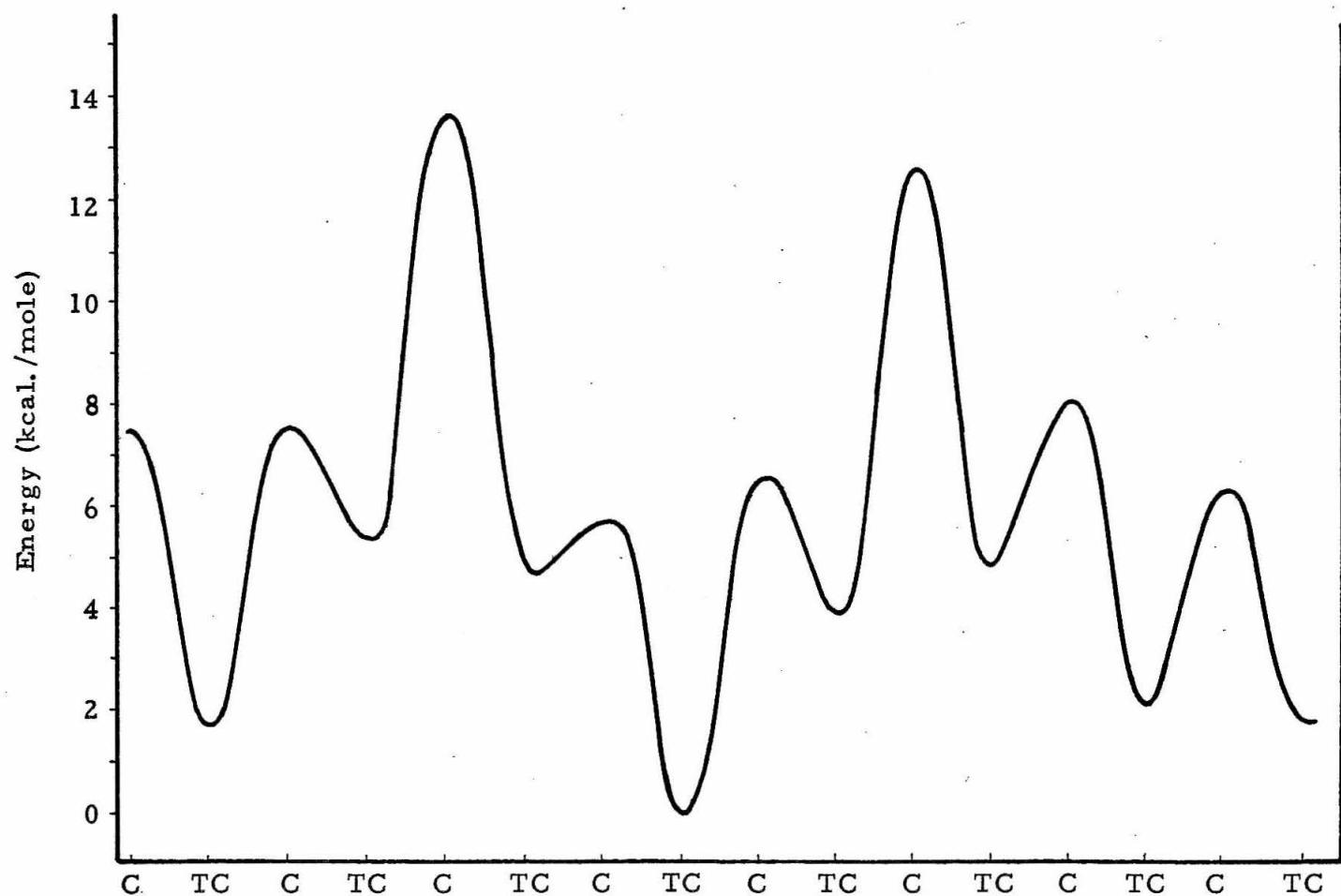


Figure 10. Calculated spectrum for 1,1-difluorocycloheptane (TC 1, 1-axis conformer)

axis carbon atom.

In contrast to the ambiguities encountered in difluorocycloheptane, the n. m. r. spectrum of 1, 1-difluoro-4, 4-dimethylcycloheptane shows clearly that inversion is slow below -150°. The single AB pattern that is observed is consistent with the previous discussion about preferred conformations of disubstituted cycloheptanes. It seems most reasonable that this spectrum corresponds to the twist-chair conformation with the methyl groups on the axis carbon atom and the fluorine atoms in the 4 position. There is some uncertainty as to the mode of inversion. It should be remembered that in substituted cycloheptanes, chair-boat flipping might become the preferred mode of inversion energetically, especially in order to avoid pseudorotation of the methyl group through the chair 3a position. To consider this question quantitatively, an energy contour for pseudorotation has been derived using the "A" values for methyl (Table I) and for fluorine (Table II). It can be seen from the energy contour (Fig. 11) that the chair 3a, 3e-difluoro-3e, 3a-dimethyl is the highest energy conformation (13.6 kcal. /mole) and represents the height of the barrier to free pseudorotation. Actually the energy of this conformation would be expected to be slightly higher than 13.6 kcal. /mole if the 3a-3'a F-CH<sub>3</sub> nonbonded interaction had been considered.

There is an alternate mode of inversion involving chair-boat flipping. This would allow the methyl group to avoid the chair 3a and boat 3a positions and also obviate its pushing past a fluorine atom in the 3'a position. The alternate mode of inversion would involve



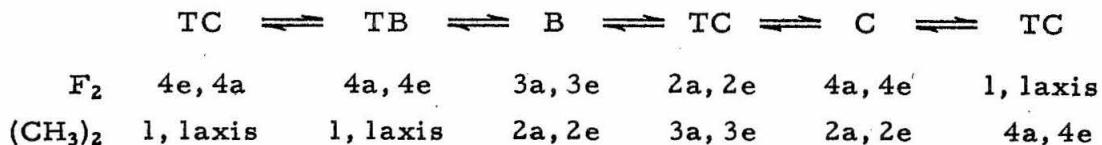
Pseudorotation Coordinate

Figure 11. Pseudorotation of 1,1-difluoro-4,4-dimethylcycloheptane.

several consecutive low-energy processes:

- 1) partial pseudorotation in the chair family,
- 2) chair-boat flipping to avoid the chair 3a conformation,
- 3) partial pseudorotation in the boat family,
- 4) boat-chair flipping.

A possible itinerary for inversion of the methyl groups and the fluorine atoms appears below.



In the fluorine n. m. r. spectra of monosubstituted cycloheptanes, 1, 1-difluoro-4-methylcycloheptane, and 1, 1-difluoro-4-t-butylcycloheptane, AB patterns with small chemical shifts are observed. From the previous discussion of methylcycloheptane these molecules would be expected to undergo rapid pseudorotation within the chair family with the predominant species being the twist-chair forms having equatorial and axis substituents. In order to consider the case of 1, 1-difluoro-4-methylcycloheptane, an energy contour for pseudorotation has been derived (Fig. 12).

The important consequence of this contour is that the fluorine atoms pass through all fifteen different conformational positions on the

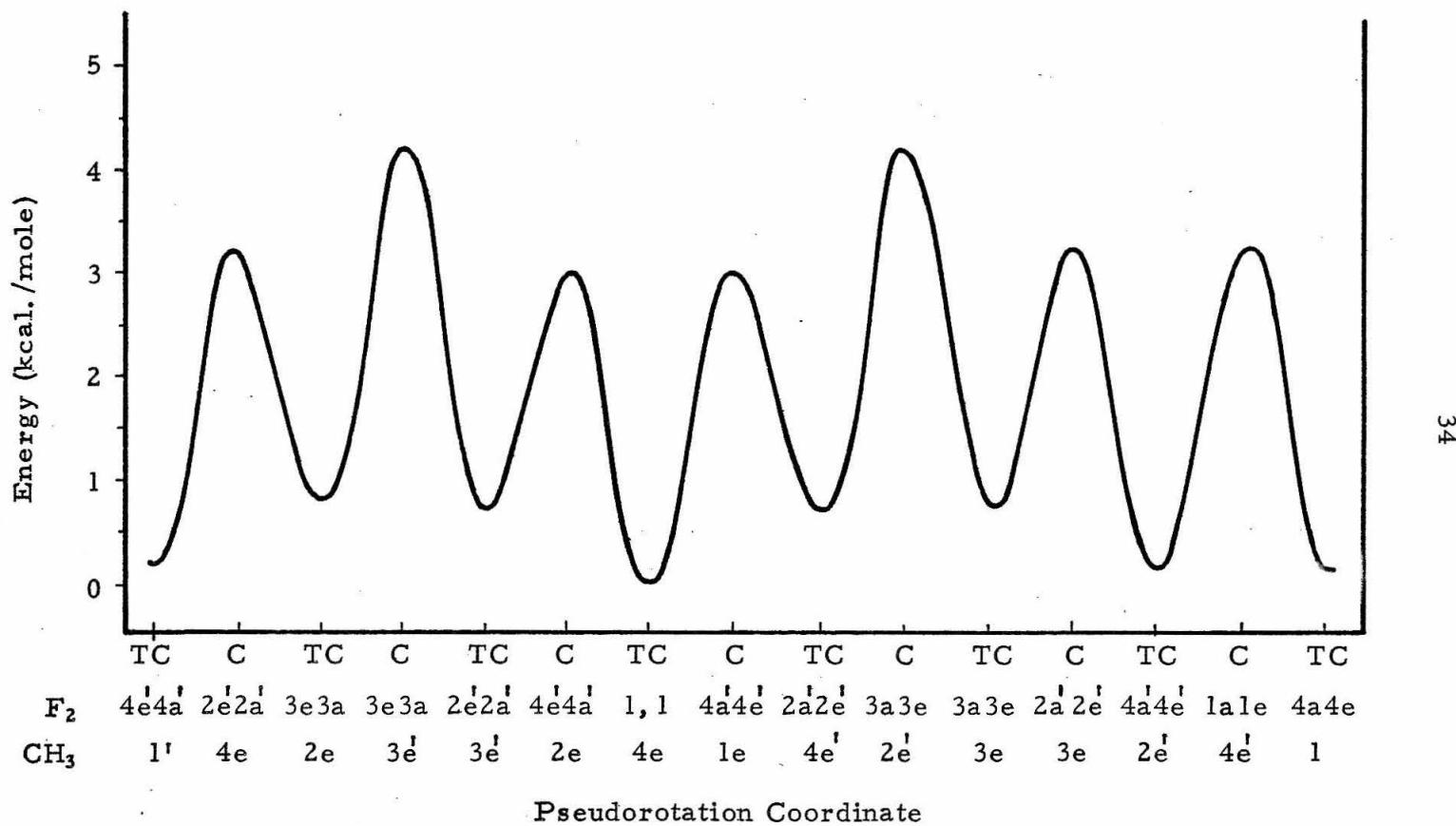


Figure 12. Pseudorotation of 1,1-difluoro-4-methylcycloheptane.

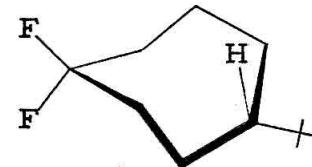
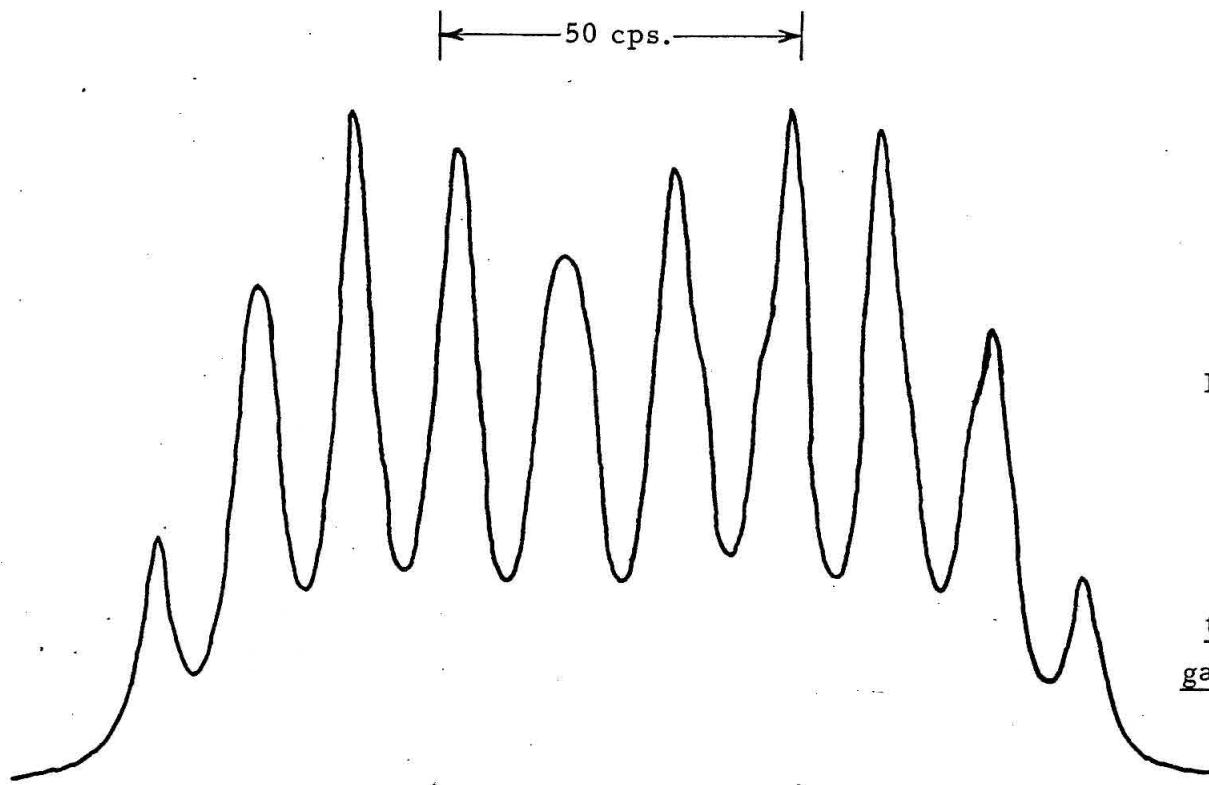
twist chair and the chair while the methyl group remains exclusively in equatorial or axis positions in the course of the itinerary. However, unlike unsubstituted difluorocycloheptane, the fluorine atoms pass only once through the axis position. The highest energy conformation is the chair 3e, 3a-difluoro-3e-methyl (4.2 kcal. /mole) and represents the height of the barrier to partial pseudorotation of the methyl group through only the equatorial and axis positions. Because this low-energy process permits the fluorine atoms to pass through every position on the ring, complete averaging of the fluorine chemical shifts of each ring position might be expected to afford a single line spectrum. However, exact averaging does not occur because the populations of the various twist-chair conformers is different; furthermore, the relationship of the methyl group to the fluorine atoms is different in each twist-chair form. The TC 1, 1-axis-difluoro-4e-methyl is predicted to be the most stable by approximately 0.2 kcal. /mole over the next-best form. In this conformation the chemical shifts of the fluorine atoms on the axis carbon atom would be expected to be slightly different because of the effect of the methyl group in the 4e position. The next-best conformations energetically would be predicted to be the TC 4e', 4a'-difluoro-1'-axis-methyl and the TC 4a, 4e-difluoro-1-axis-methyl. These conformations are very nearly equivalent and would be expected to almost exactly average the fluorine chemical shifts when pseudorotation is rapid. The other higher-energy twist-chair forms should be present in less than 10% and therefore have only small effects on the experimental spectrum. Consequently all the stable conformations of 1, 1-difluoro-4-methylcycloheptane would be predicted to afford aver-

aged AB patterns with small chemical-shift differences when pseudorotation is rapid. If the latter process were slowed, the following fluorine spectrum would be expected: an AB pattern with a small chemical-shift difference corresponding to the TC 1, 1-axis-difluoro-4-methyl present in 75%; and AB patterns with large chemical-shift differences corresponding to the next-best conformations present in 25%. However, the same ambiguity that exists with 1, 1-difluorocycloheptane occurs here because an explanation that assumes that the twist chair is "frozen" with the fluorine atoms on the axis carbon atom also fits the results. The major objections to this interpretation are that the calculations indicate that the barrier is low and that considerable amounts of other conformations should be present; moreover, the 25 cps. change in the AB chemical-shift difference from room temperature to  $-125^{\circ}$  suggests that some temperature-dependent averaging process is occurring.

Certain difficulties arise in attempting to derive an energy contour for pseudorotation of 1, 1-difluoro-4-t-butylcycloheptane. The "A" value of a t-butyl group will be substantially larger than that of a methyl group and may be different for each equatorial and axis position on the twist chair. Furthermore, the large size of the t-butyl group may drastically alter the conformational features of the ring in such a way as to place the bulky group as far away from the ring hydrogens as possible. Assuming the twist-chair conformation is retained, the order of stability of the twist-chair conformers with a t-butyl group can be qualitatively predicted from examination of models

to be:  $3e \sim 2e \sim 4e > 1$  axis. Unlike methylcycloheptane, the axis position cannot accommodate the bulky t-butyl group as well as the equatorial positions can. Consequently, the populations of the various twist-chair forms of 1, 1-difluoro-4-t-butylcycloheptane would be expected to be somewhat different from those of the corresponding methyl compound. The TC 1, 1-axis-difluoro-4e-t-butyl is predicted to be the most stable conformation. In the course of the pseudorotation itinerary the fluorine atoms can pass through all the different conformational positions on the ring while the t-butyl group remains exclusively in the equatorial or axis positions. However, in the course of this itinerary the fluorine atoms pass only once through the axis position as long as the t-butyl group cannot pass through the axial positions. Consequently, the fluorine atoms on the axis position will have distinct trans and gauche coupling constants with the adjacent hydrogen atoms. Crude calculations of the fluorine n. m. r. spectrum for the "frozen" TC 1, 1-axis conformer appear in Fig. 12.5.

The coupling patterns in this calculated spectrum are very similar to those observed in the experimental spectrum (see Fig. 5). This close similarity suggests that the predominant species is the TC 1, 1-axis-difluoro-4e-t-butyl conformer, although rapid pseudorotation among the other less stable twist-chair forms present in small amounts may still be occurring. Further low-temperature studies may clarify this point as it may be possible to slow the pseudorotation process and to obtain distinct fluorine signals for the other conformational positions on the twist chair.



TC 1,1-axis conformer

Parameters (see page 29):

$$\Delta\nu_{F-F} = 185 \text{ cps.}$$

$$J_{F-F} = 240 \text{ cps.}$$

$$\Delta\nu_{H-H} = 20 \text{ and } 30 \text{ cps.}$$

$$J_{H-H} = 15 \text{ cps.}$$

$$\underline{\text{trans-}}J_{H-F} = 34 \text{ cps.}$$

$$\underline{\text{gauche-}}J_{H-F} = 11.5 \text{ cps.}$$

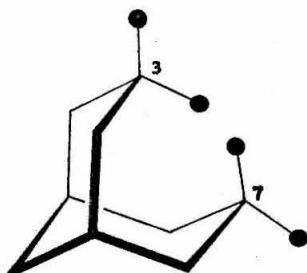
Figure 12.5. Calculated fluorine spectrum for 1,1-difluoro-4-t-butylcycloheptane (TC 1,1-axis conformer).

PART II

CONFORMATIONAL PROPERTIES OF CYCLOOCTANE

## INTRODUCTION

Although the conformations of cyclooctane have been extensively discussed in the literature, experimental evidence for the structure is limited and inconclusive. Bellis (16) has found that the infrared spectra of gaseous, liquid, and solid cyclooctane contain essentially the same bands. No unequal dependence of band intensities on temperature is observed in either the Raman or infrared spectrum of the liquid. This behavior implies that only one conformation or a mixture of rapidly interconverting conformations of equal energy exists under ordinary conditions. Detailed analysis of the vibrational spectrum of cyclooctane eliminates all point groups except  $D_{2d}$  to which the boat and saddle conformations belong (Table III). The infrared spectrum in the region of the methylene symmetrical deformation vibrational frequency shows three bands at 1450, 1470, and  $1477\text{ cm}^{-1}$ . On the basis of this evidence Churdoglu, Doehaerd, and Tursch (17) have excluded any conformation which does not have three different kinds of methylene groups. Dale, Laszlo, and Ruland (18) have studied bicyclo-[3, 3, 1]-nonane (A) and observed four methylene scissoring bands although

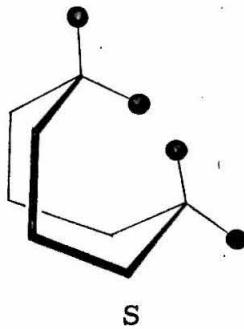


A

Table III  
Conformations of Cyclooctane

Conformation	Symmetry	Number of CH <sub>2</sub> groups
Crown	D <sub>4d</sub>	1
Stretched crown	C <sub>2v</sub>	3
Extended crown	D <sub>4</sub>	2
Boat	D <sub>2d</sub>	1
Saddle	D <sub>2d</sub>	2
Twist boat	C <sub>1</sub>	2
Parallel boat	D <sub>2</sub>	2
Chair	C <sub>2h</sub>	2
Boat chair	C <sub>2h</sub>	5
Bent chair	D <sub>2h</sub>	3

the known conformation contains only three different methylene groups (19). They have suggested that the two identical methylene groups in the 3- and 7- positions interact strongly to produce two bands. Exactly the same steric situation exists in the saddle conformation of cyclooctane (S), which could account for the two methylene bands in the  $1470\text{ cm}^{-1}$  region.



Sands and Day (20) have carried out an x-ray study of cyclooctane at  $0^\circ\text{C}$ . No detailed conclusions concerning the molecular conformation can be deduced from their limited data. O. Bastiansen, et al. (21), have studied the electron-diffraction spectrum of cyclooctane at  $40^\circ\text{C}$  and exclude the existence of a single "rigid" conformation. Their results suggest that a large number of interconvertible conformations occur with approximately the same probability.

Anet and Hartman (22) have reported that the n. m. r. spectrum of cyclooctane-d<sub>15</sub> underwent a change from a single sharp line at room temperature to two distinct lines separated by 18.8 cps. at  $-135^\circ$ . The activation energy for this inversion process was calculated to be 7.7 kcal./mole. The presence of only two lines (attributed to axial and equatorial protons) suggested that only one symmetrical conformation, in which all the methylene groups are equivalent, or a group of rapidly

interconverting conformations exists.

Using spin-echo techniques, Meiboom (23) has observed two different line-broadening processes in cyclooctane with activation energies of 8.1 and 8.2 kcal./mole, respectively.

## RESULTS

At room temperature, the fluorine n. m. r. spectrum of 1, 1-difluorocyclooctane is a quintet with  $J_{H-F} = 15.1$  cps. Under double irradiation at the proton resonance frequency a single sharp signal is observed. This sharp line broadens and splits into a closely packed AB spectrum below  $-100^\circ$ . Using computer techniques (see Experimental) calculated spectra for various exchange rates were fitted to the experimental spectra between  $-100^\circ$  and  $-121^\circ$  (Fig. 13). Below  $-121^\circ$ , the chemical shift remained constant at 165 cps. with  $J_{AB} = 245$  cps. From the Arrhenius plot of the results (Fig. 14), the activation energy for the rate process was calculated to be 8.4 kcal./mole. Application of transition-state theory showed that at  $-100^\circ$ , the coalescence temperature, the free energy of activation was 7.5 kcal./mole and the entropy of activation was 5.85 e. u.

Below  $-150^\circ$ , the closely packed AB spectrum broadens and subsequently splits into two AB spectra whose spectral parameters appear below.

Spectrum	Chemical shift (cps.)	$J_{AB}$ (cps.)	Population
$C_1$	806	240	63.5%
$C_2$	940	245	36.5%

These spectra are shown diagrammatically with labels  $a_1$  and  $a_2$  for the upfield resonances, which are superimposed, and  $b_1$  and  $b_2$  for the downfield resonances.

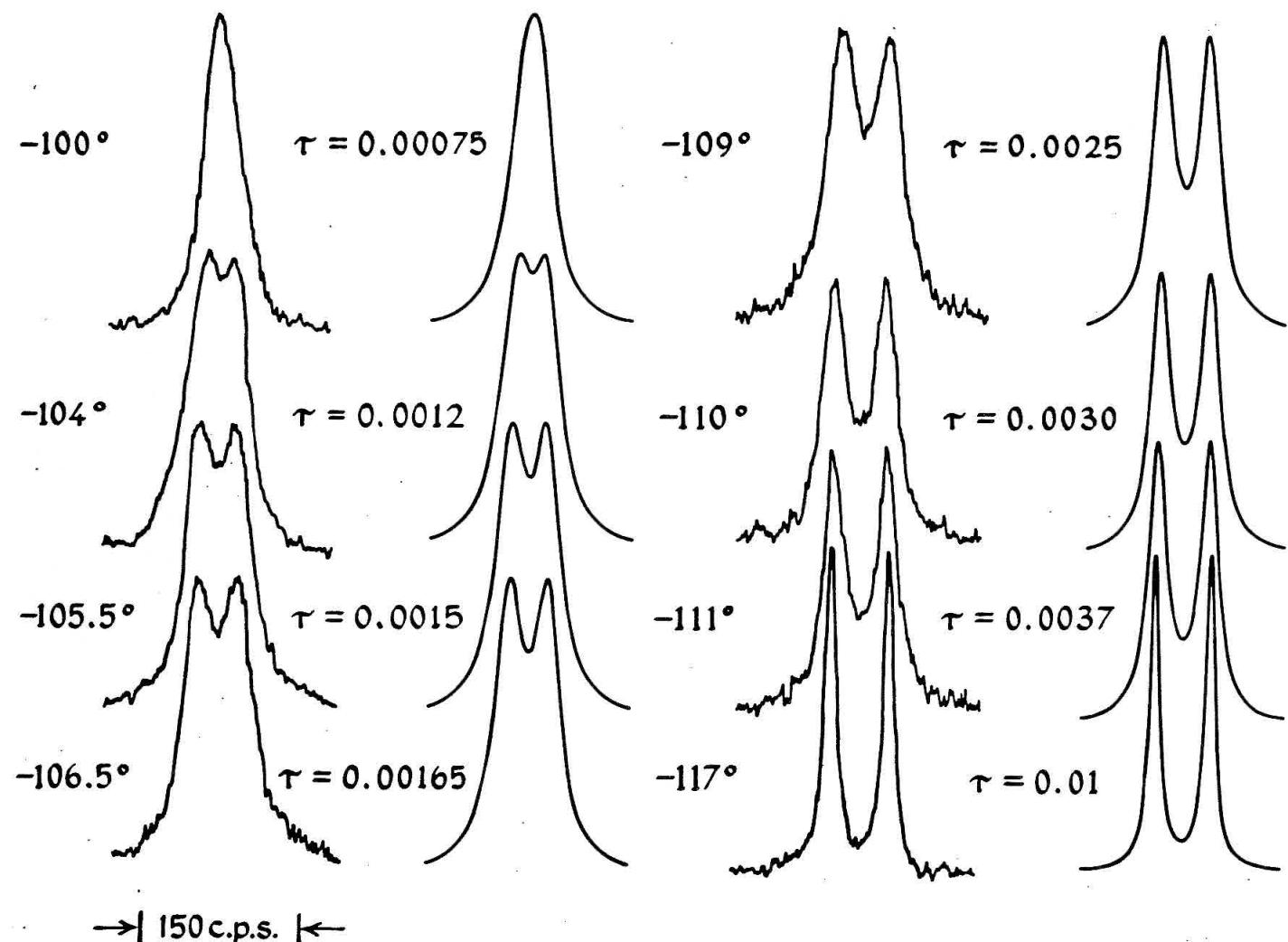


Figure 13. Experimental and calculated spectra of 1,1-difluorocyclooctane in propene ( $-100^\circ$  to  $-117^\circ$ ).

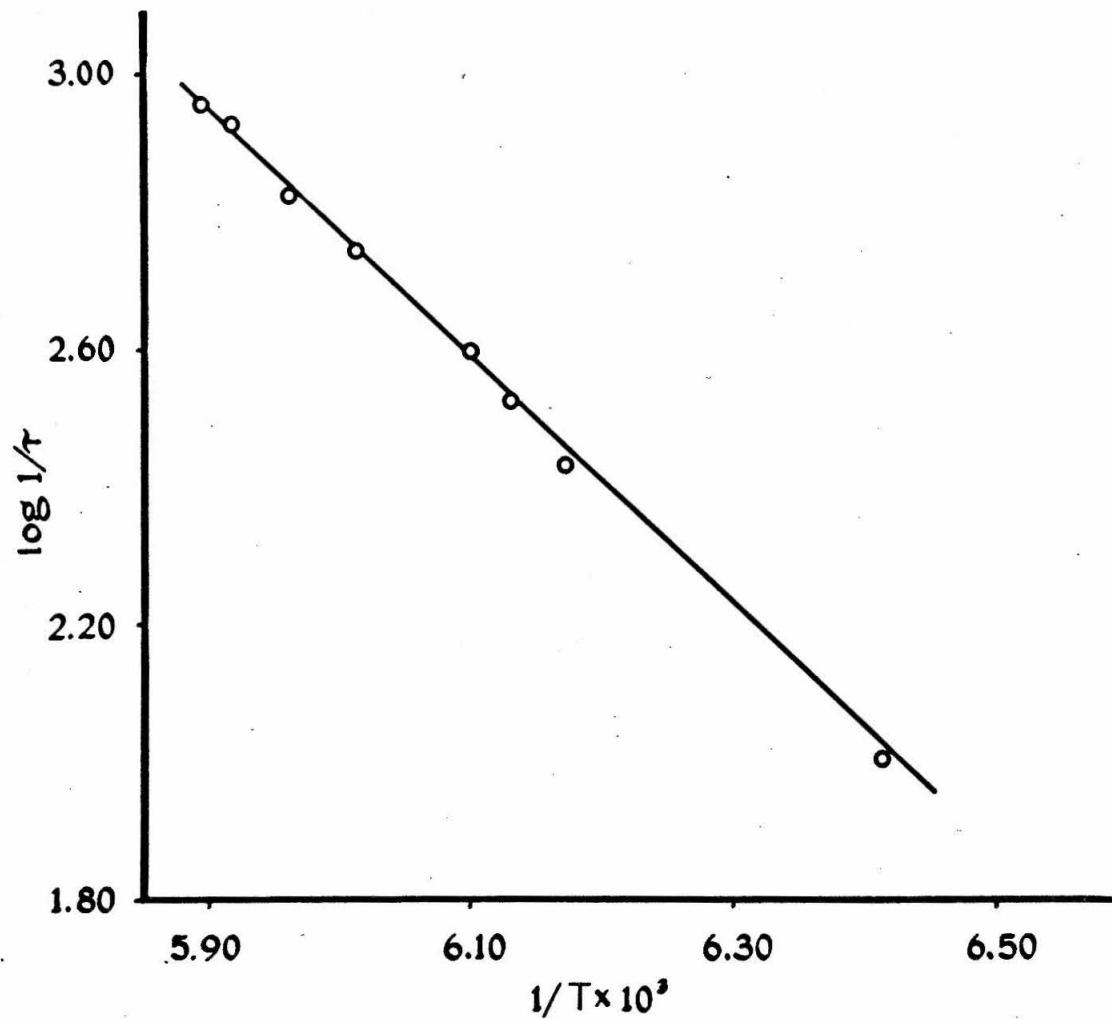
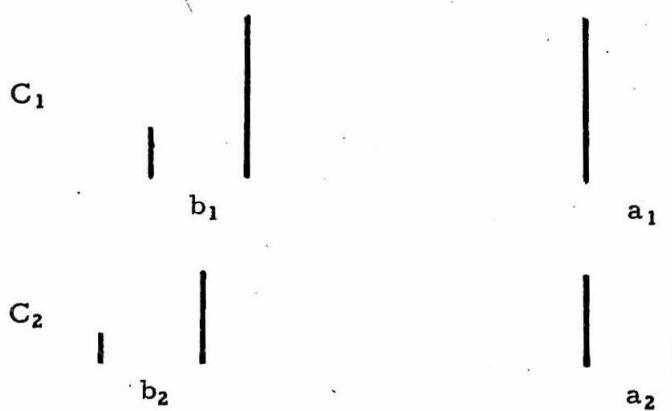


Figure 14. Arrhenius plot for 1,1-difluorocyclooctane ( $-100^\circ$  to  $-117^\circ$ ).



Averaging of these spectra at fast exchange can occur in three possible ways:

- (1)  $a_1$  with  $b_1$ ,  $a_2$  with  $b_2$ . This averaging process would produce two single lines of unequal intensity separated by 70 cps. at fast exchange.
- (2)  $a_1$  with  $a_2$ ,  $b_1$  with  $b_2$ . This averaging process would produce an AB spectrum with a chemical shift = 850 cps. at fast exchange.
- (3)  $a_1$  with  $b_2$ ,  $a_2$  with  $b_1$ . This averaging process will afford the correct fast-exchange spectrum, a closely packed AB, if the populations of the two spectra are 1.74:1.

Spectra were calculated for the latter exchanging sets of AB nuclei at various exchange rates and were fitted with the experimental spectra between  $-160^\circ$  and  $-170^\circ$  (Fig. 15). From the Arrhenius plot of the results (Fig. 16) the activation energy for the rate process was calculated to be 8.0 kcal./mole. Application of transition-state theory

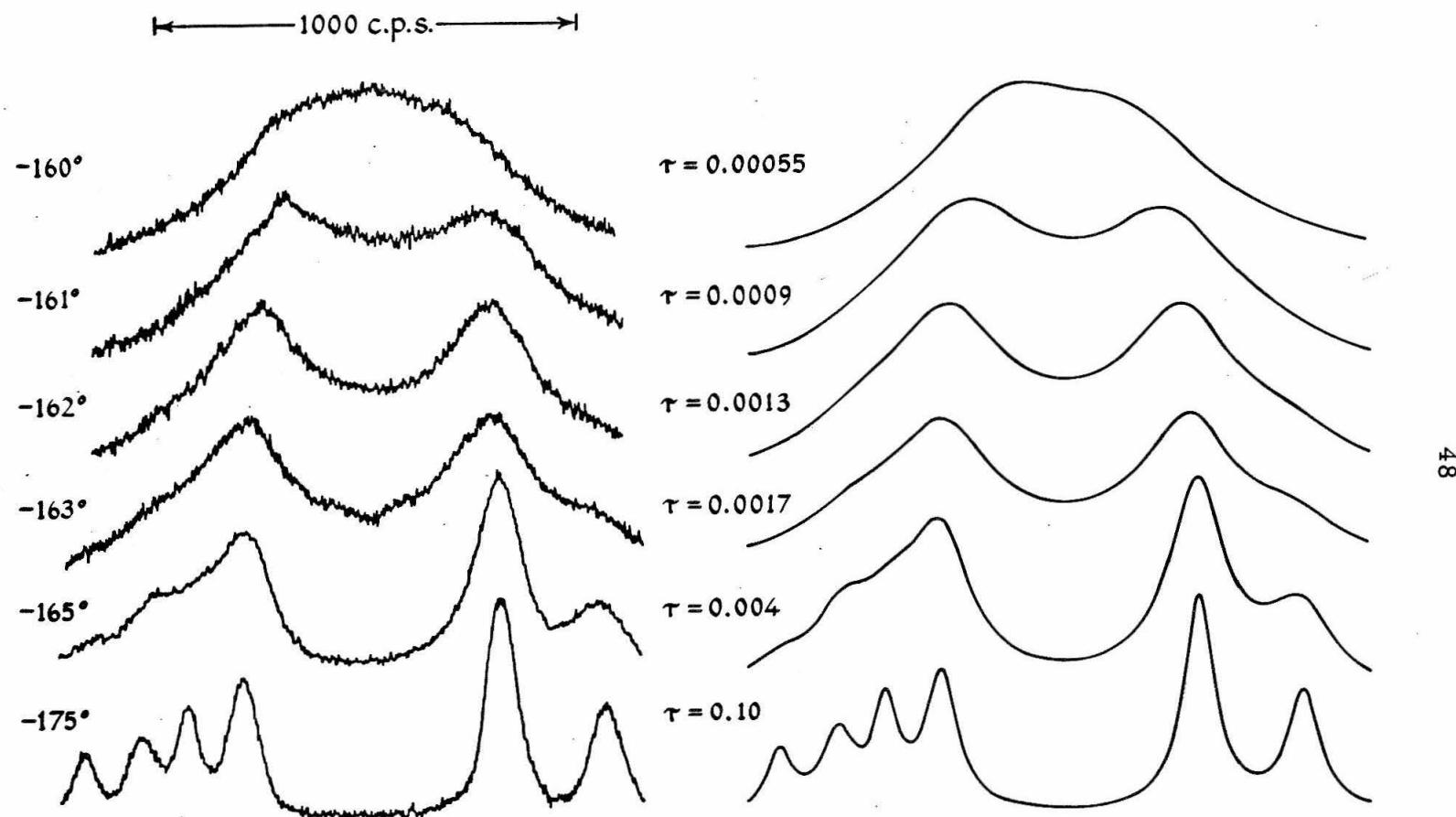


Figure 15. Experimental and calculated spectra  
of 1,1-difluorocyclooctane in propene (-160° to -175°).

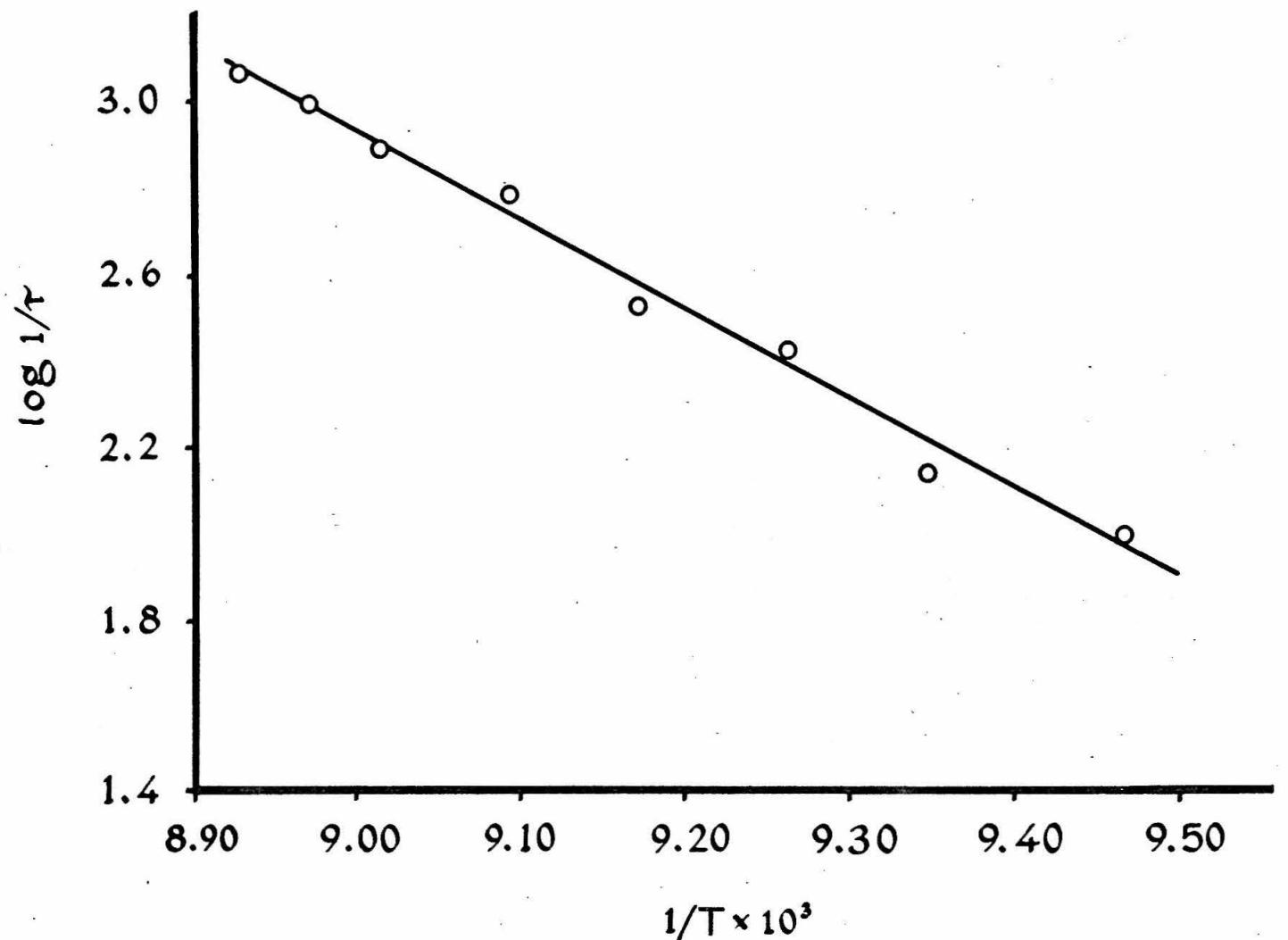


Figure 16. Arrhenius plot for 1,1-difluorocyclooctane (-160° to -175°).

showed that at  $-160^{\circ}$ , the coalescence temperature, the free energy of activation was 4.9 kcal./mole and the average entropy of activation was 28.1 e.u.

At room temperature, the fluorine n.m.r. spectrum of 1,1,4,4-tetrafluorocyclooctane is a quintet with  $J_{H-F} = 13.7$  cps. Under double irradiation at the proton resonance frequency a single sharp line, 734 cps. upfield from trifluoroacetic acid, is observed. Below  $-85^{\circ}$  this sharp line broadens and splits into a closely packed AB spectrum, 693 cps. upfield from the internal standard, and an AB spectrum with a large chemical-shift difference, present in less than 10% and 1455 cps. upfield from the internal standard (Fig. 17). Assuming that the change in the chemical shift of 41 cps. of the main signal between room temperature and  $-85^{\circ}$  arises exclusively from averaging with the upfield AB spectrum having the large chemical-shift difference, the latter was calculated to be present in 5.4%. The spectral parameters of the two AB spectra at  $-85^{\circ}$  appear below.

Spectrum	Chemical shift (cps.)	$J_{AB}$ (cps.)	Population
$C_1$	*	*	94.5%
$C_2$	779	245	5.4%

\*The chemical-shift difference and the coupling constant have not been as yet determined. Decoupling of the adjacent protons (as in 1,1-difluorocyclooctane at  $-100^{\circ}$ ) is necessary in order to observe the fluorine chemical-shift difference which is expected to be approximately 100 cps.

Below  $-130^{\circ}$ , the closely packed AB spectrum broadens and splits into two large AB spectra whose spectral parameters appear

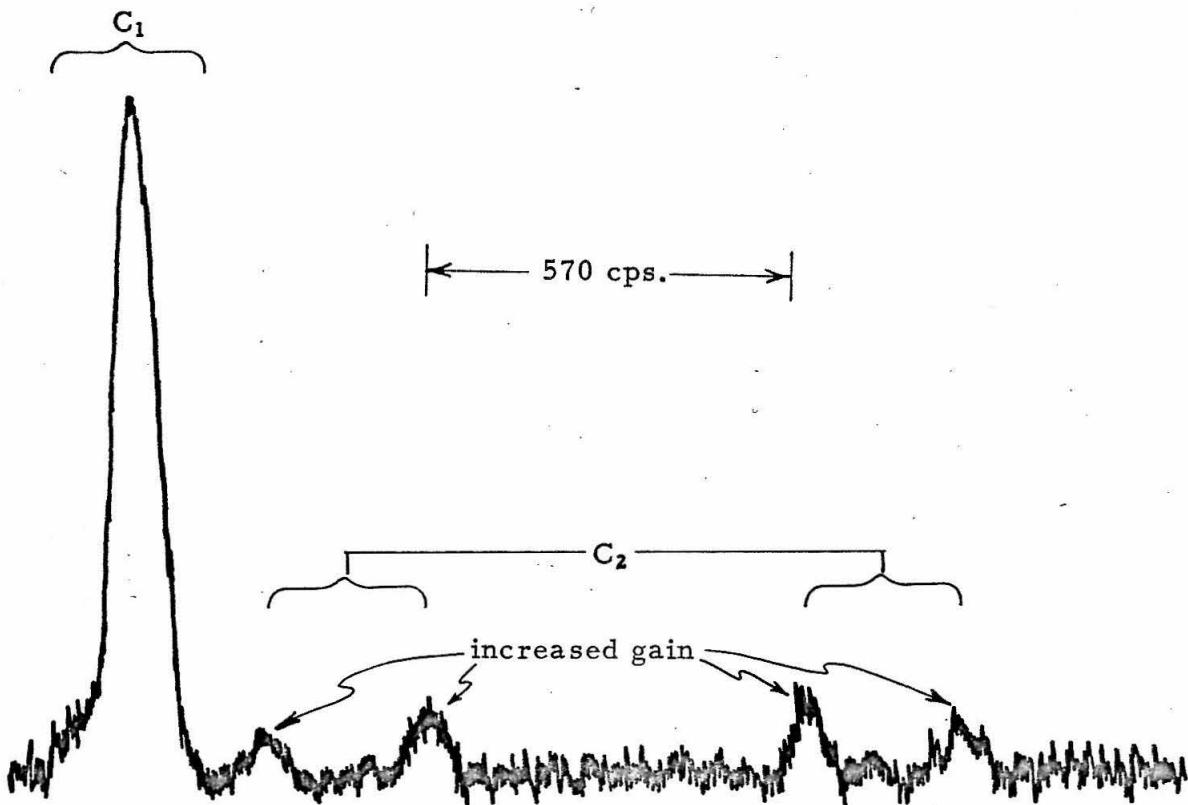


Figure 17. Experimental spectrum of 1,1,4,4-tetrafluorocyclooctane at  $-85^\circ$  in propene.

below. The large AB spectrum present in small amounts undergoes no change in this temperature range.

Spectrum	Chemical shift (cps.)	$J_{AB}$ (cps.)	Population
$C_3$	920	253	50%
$C_4$	837	253	50%

The same averaging procedure used for 1,1-difluorocyclooctane was applied in this case. Spectra were calculated for the correct sets of exchanging AB nuclei and were fitted to the experimental spectra between  $-130^\circ$  and  $-143^\circ$  (Fig. 18). From the Arrhenius plot of the results (Fig. 19), the activation energy for the rate process was calculated to be 9.4 kcal./mole. At  $-136^\circ$ , the coalescence point, the free energy of activation was 6.2 kcal./mole and the entropy of activation was 23.2 e.u.

At room temperature, the fluorine n.m.r. spectrum of 1,1,2,2-tetrafluorocyclooctane is a broad multiplet which collapses to a single sharp line under double irradiation at the proton resonance frequency. This sharp line broadens and splits at  $-55^\circ$  into two patterns: an AB with a large chemical-shift difference and an AB with a small chemical-shift difference (Fig. 20). The spectral parameters of these spectra appear below.

Spectrum	Chemical shift (cps.)	$J_{AB}$ (cps.)	Population
$C_1$	587	261	50%
$C_2$	*	*	50%

\* See page 50.

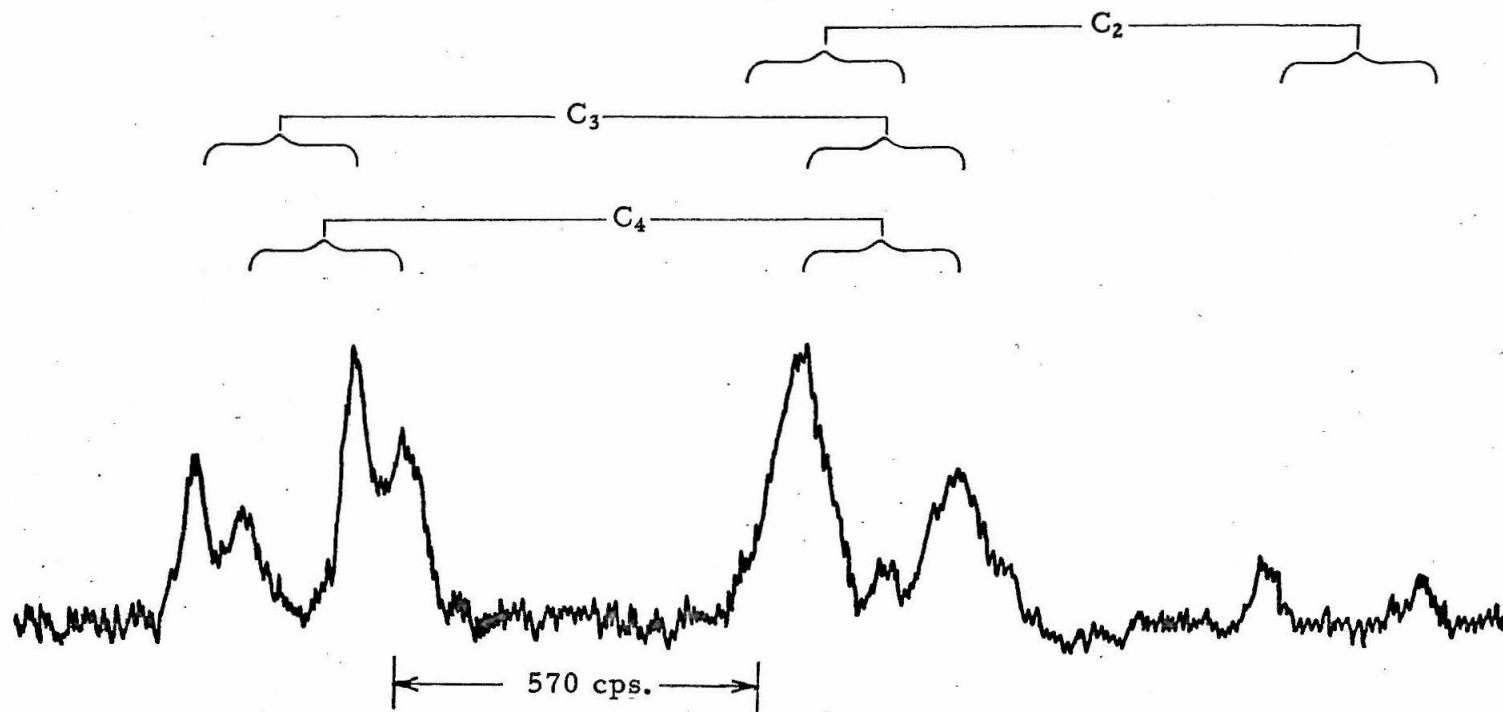


Figure 18. Experimental spectrum of 1,1,4,4-tetrafluorocyclooctane in propene (-150°).

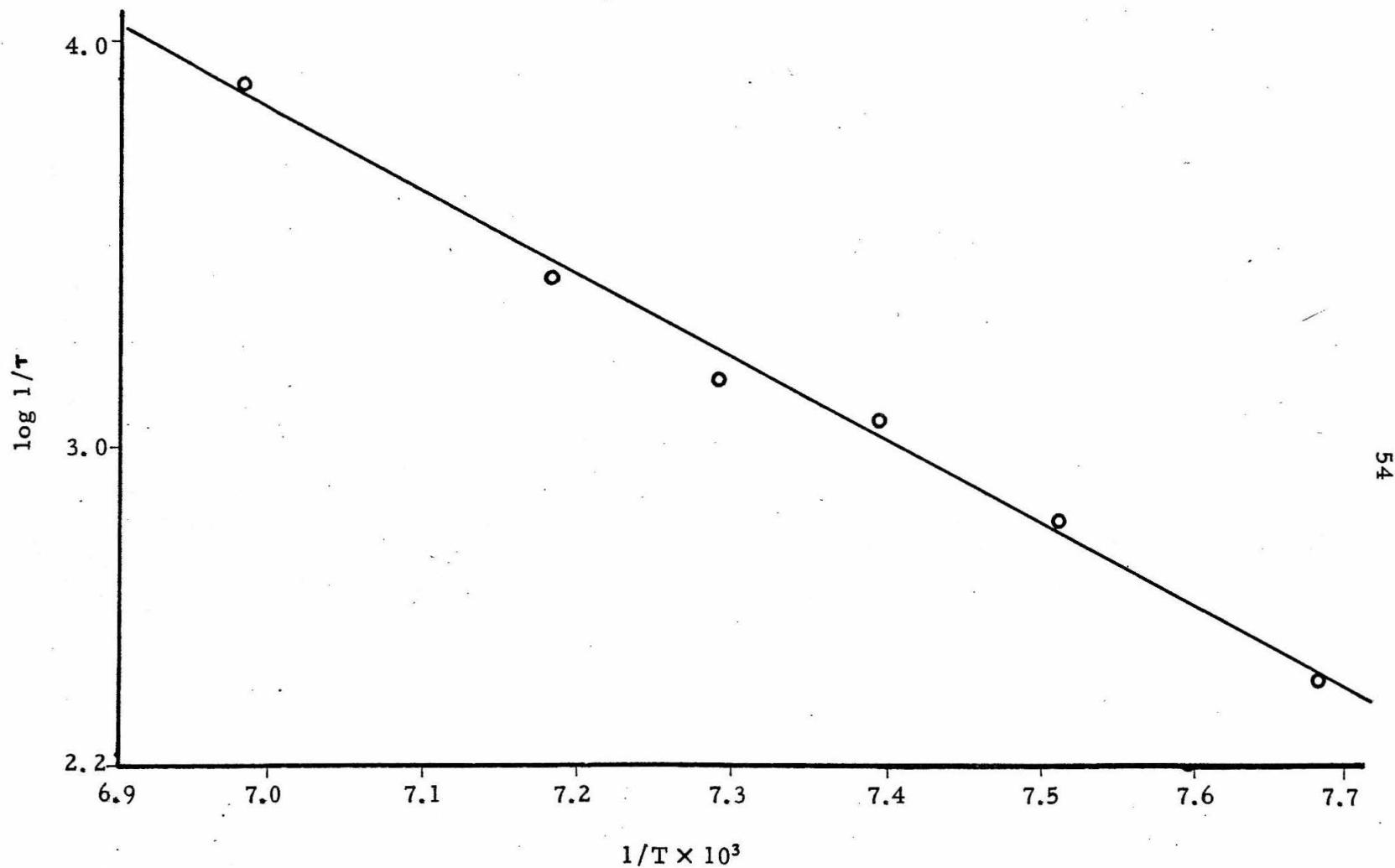


Figure 19. Arrhenius plot for 1,1,4,4-tetrafluorocyclooctane (-130° to -143°).

At  $-85^{\circ}$ , the single AB spectrum with the small chemical-shift difference broadens and splits into an AB pattern with a large chemical-shift difference (Fig. 20). No line shape changes are observed at these temperatures for the AB spectrum which already had a large chemical-shift difference at  $-55^{\circ}$ . Analysis of the kinetic parameters for the two rate processes occurring in this molecule appears to be complicated at the present time. A qualitative estimate of approximately 10 kcal. / mole for the activation energy of both processes can be considered to be reasonable.

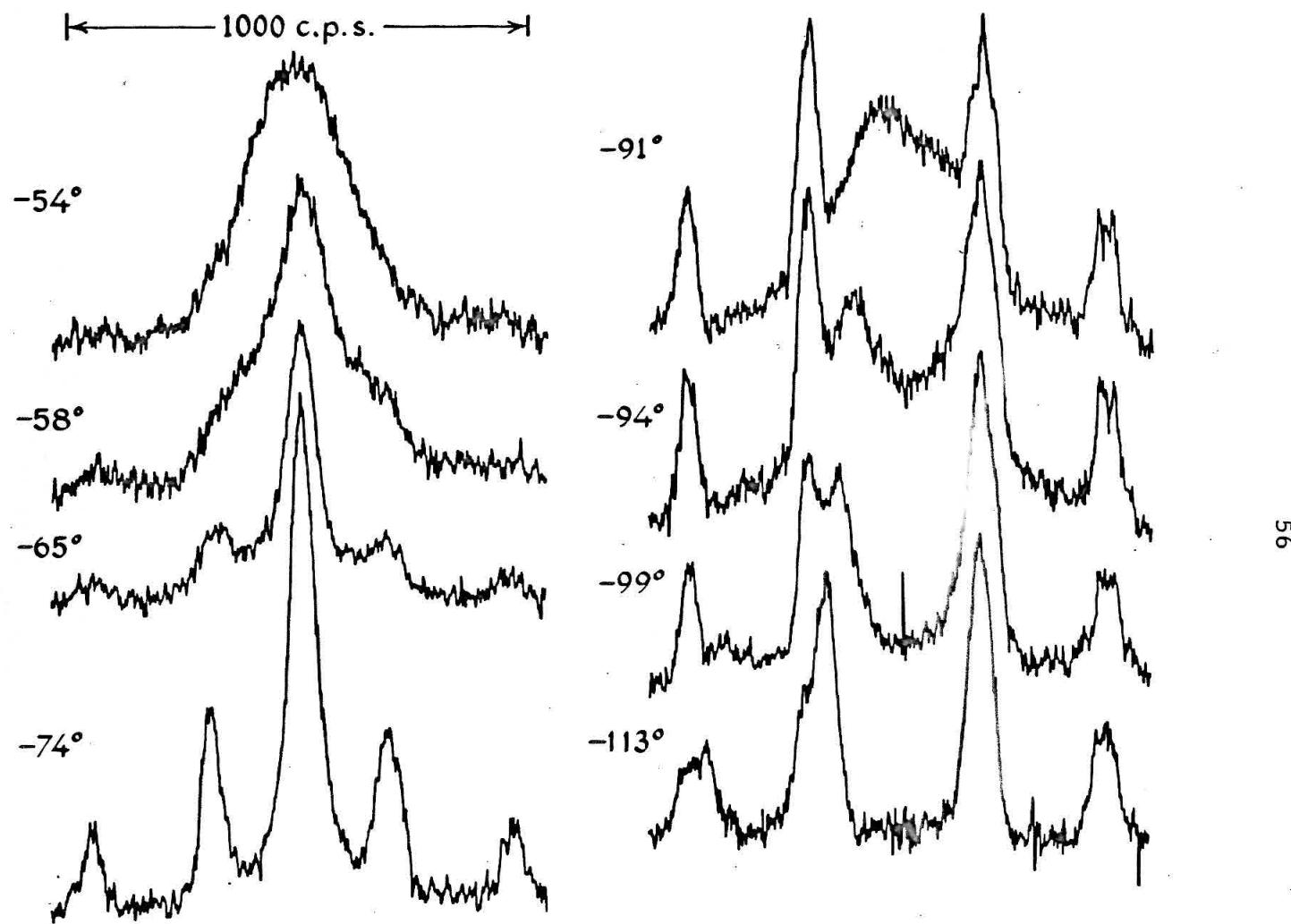
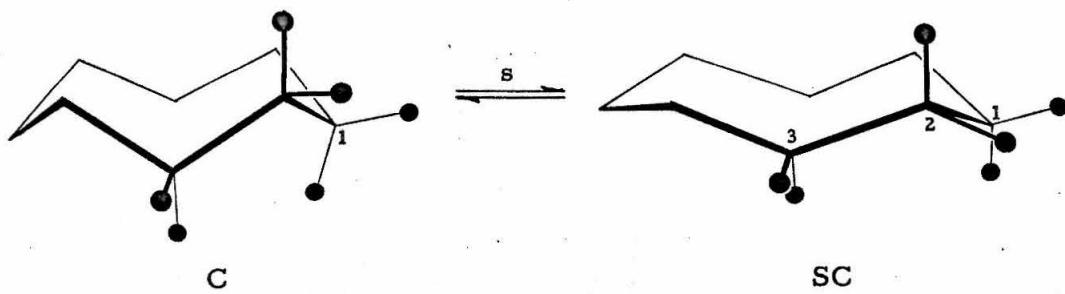


Figure 20. Experimental spectra of 1,1,2,2-tetrafluorocyclooctane in propene ( $-54^\circ$  to  $-113^\circ$ ).

## DISCUSSION

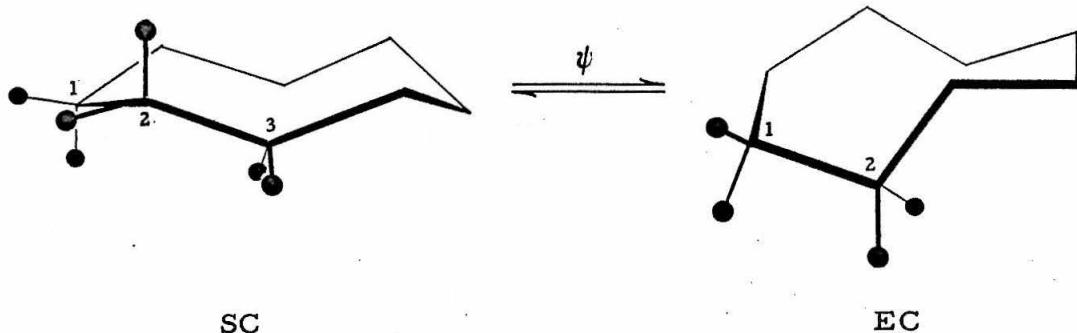
Because of the overwhelming number of possible conformations, conformational analysis of cyclooctane is more complex than that of cycloheptane and cyclohexane. In the following discussion, we will consider eleven different conformations along with a detailed description of the ways in which they may be interconverted (24).

In the crown family three forms of cyclooctane have been considered: crown (C), stretched crown (SC), and extended crown (EC). The crown, the most symmetrical form, has only one kind of methylene group or two nonequivalent positions on the ring. Although the crown is relatively free of cross-ring interactions, the ring has serious semi-eclipsing of the hydrogen atoms. This torsional strain can be relieved to a certain extent by pulling apart the two carbon atoms on opposite sides of the ring, i. e., stretching the crown. The conformational change from the crown to the stretched crown occurs without loss of the basic axis of symmetry of either form and is denoted as the symmetrical mode (s) of interconversion. The stretched crown has



three kinds of methylene groups or six nonequivalent positions on the ring. The symmetrical mode of interconversion to the crown will average all the methylene groups; however, an "axial" substituent will pass only through the "axial" positions on the ring, and an "equatorial" substituent only through the "equatorial" positions. In other words, this mode of interconversion does not allow inversion of substituents.

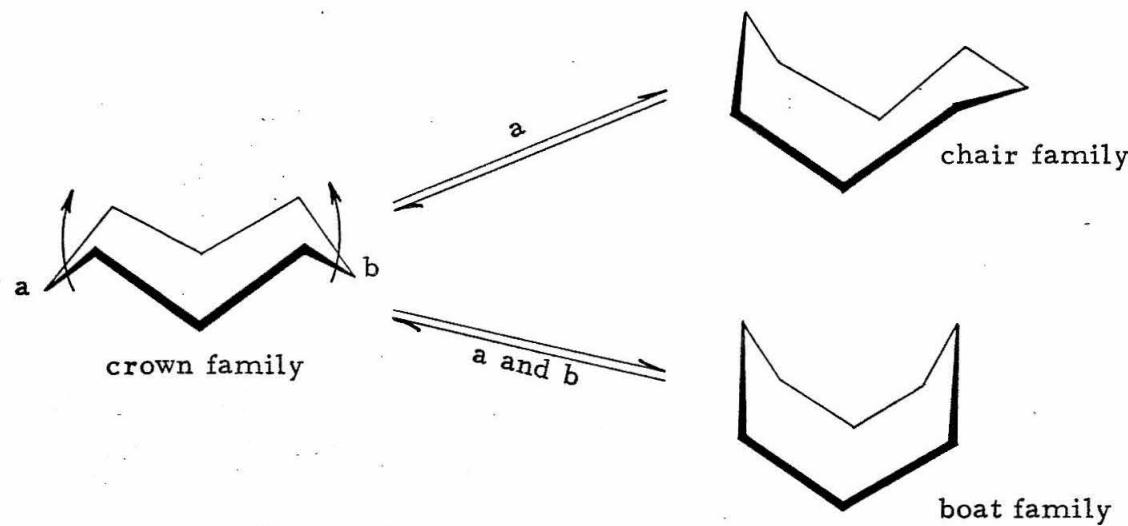
The stretched crown has reduced torsional strain, but the ring has a serious interaction of hydrogens directly across the ring from one another. This inside interaction can be relieved to a certain extent by twisting the 1,2 and 1,5 bonds such that they lie in the plane of the molecule. This extended form of the crown has two methylene groups or four nonequivalent positions on the ring. The conformational change proceeding from the stretched to the extended crown involves a continuous change of dihedral angles such that the molecule passes through a continuum of asymmetric forms to a symmetrical form and then ultimately back to the initial symmetry in which each atom now occupies the next ring position in the itinerary. This mode of interconversion is denoted as pseudorotation ( $\psi$ ). In this particular instance  $\psi$  proceeds from the stretched crown ( $C_{2v}$ ) through a continuum of asymmetric to the extended crown ( $D_2$ ) and subsequently back to the stretched form in which atom 1 has become atom 2. In the course of the pseudorotation itinerary, a methylene group can pass through every position on the ring; however, an "axial" substituent can pass only through the "axial" positions on the ring and an "equatorial" sub-



stituent only through the "equatorial" positions. Thus, pseudorotation does not allow inversion of substituents.

Although inversion cannot occur within the crown family, this process can be envisioned proceeding through the boat and chair families (Fig. 21). These forms can undergo pseudorotation which will exchange the "axial" and "equatorial" atoms. Subsequent interconversion back to the crown family affords an inverted form with the substituents exchanged. The conformational changes within the crown family and with the boat and chair families are summarized in Fig. 22.

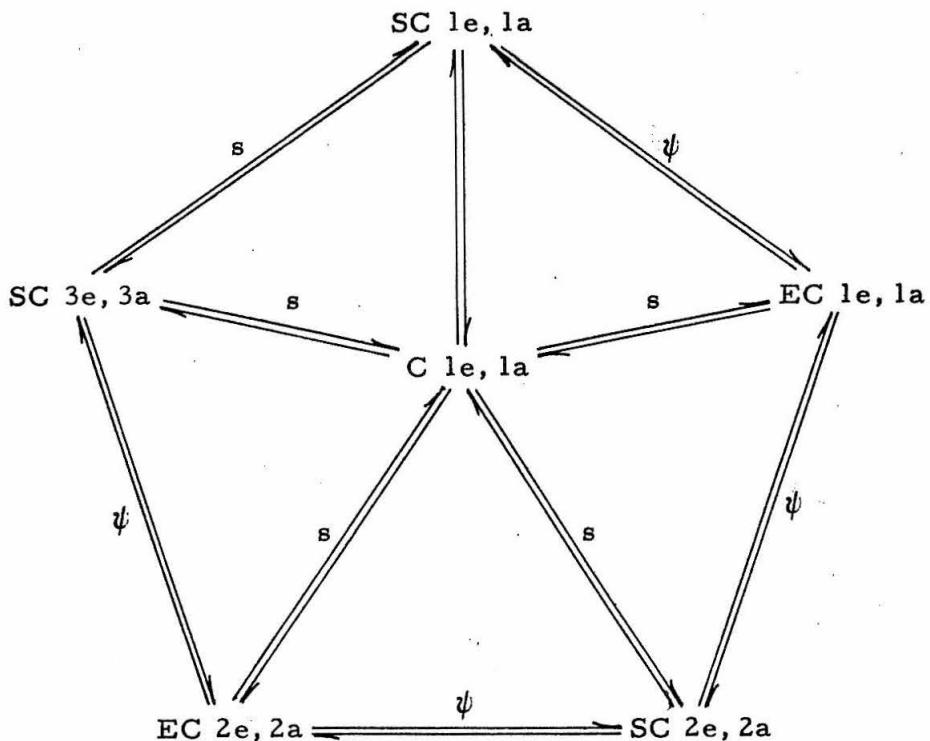
When all the interconversions (inversion,  $\psi$ , and  $s$ ) are rapid, substituents will pass through every position on the ring. In the case of geminal-substituted fluorocyclooctanes these rapid conformational changes will average the environments of the different kinds of fluorine atoms. At room temperature, the n. m. r. spectra indicate that inversion is occurring rapidly since only one averaged fluorine signal is observed. At intermediate temperatures (below  $-100^\circ$  for 1,1-difluoro-



60

Figure 21. Interconversion from crown family to chair and boat families.

s and  $\psi$  interconversions:



Inversion:

(C, SC, or EC) 1e, 1a  $\rightleftharpoons$  chair or boat  $\rightleftharpoons$  (C, SC, or EC) 1a, 1e

1e: atom in the 1 position "equatorial"

1a: atom in the 1 position "axial"

Figure 22. Conformational interconversions of the crown family.

cyclooctane and 1,1,4,4-tetrafluorocyclooctane; below -55° for 1,1,2,2-tetrafluorocyclooctane) the inversion process is slowed; however, interconversions within the crown family should still be rapid. The fluorine n. m. r. spectra at intermediate temperatures would be expected to be an averaged, large AB pattern since the fluorine atoms in the course of their itinerary around the ring never change their "axial-equatorial" nature. It is possible that interconversion among the crown forms could afford an averaged small AB pattern; however, the crown forms cannot account for the large AB patterns present in the tetrafluorides. The vicinal tetrafluoride affords two AB patterns in approximately equal amounts, one with a very small and one with a large chemical shift. The 1,4-tetrafluoride also affords two AB patterns, but the one having a large chemical shift is present in very small amounts. In both cases, interconversion within the crown family should average all the forms and produce a single AB spectrum with either a large or small chemical shift but not both.

The major objection to the crown family is that no one form or mixture of forms is consistent with the slow-exchange spectra of the three compounds. Table IV gives a summary of the expected slow-exchange spectra of the three crown forms assuming them to be "frozen" conformations. Clearly none of these forms fits all three compounds; in fact, only the extended crown is consistent with any single one. The crown is particularly bad since it would give only one AB spectrum at low temperature. On the other hand, the stretched crown has too many different positions. Even if one assumes that the inside position is too crowded to accommodate fluorine atoms, there are

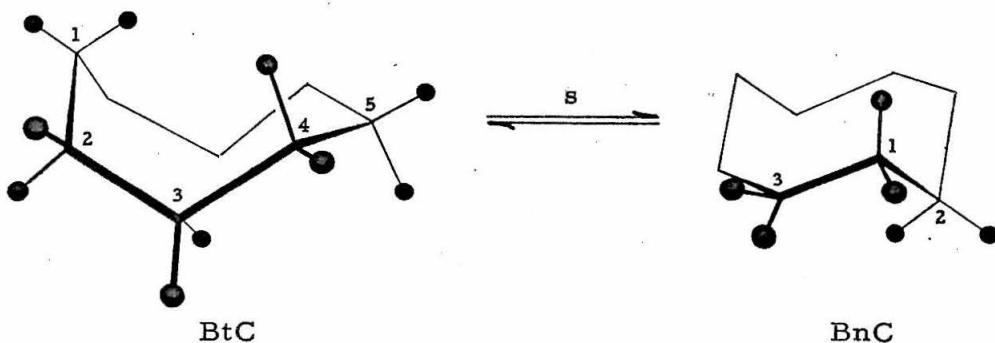
	1, 1-Difluoro- cyclooctane	1, 1, 2, 2-Tetrafluoro- cyclooctane	1, 1, 4, 4-Tetrafluoro- cyclooctane			
Conformation	Number of AB spectra	Amount	Number of AB spectra	Amount	Number of AB spectra	Amount
Crown	1	100%	1	100%	1	100%
Stretched crown	3	1>2>>3	4	1, 2>>2, 3	4	1, 2>>2, 3
Extended crown	2	1>2	4	1, 1>>1, 2>>2, 2	4	1, 1>>1, 2>>2, 2
Experimental results	2	63%:37%	at least 2	50%:50%	2	50%:50%
					1	5.4%

63

Table IV. Slow-exchange n. m. r. spectra expected for the crown family.

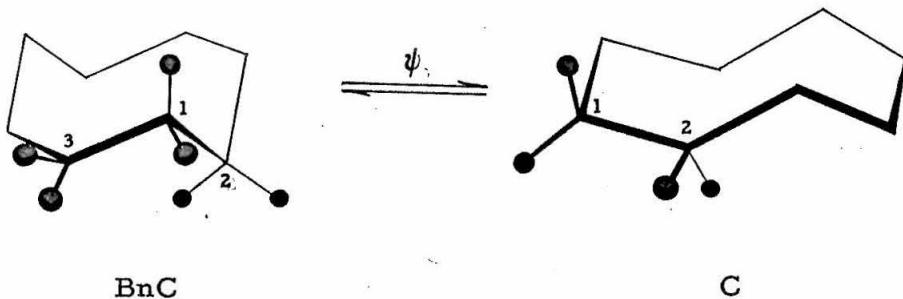
complications in the interpretation. For example, the spectrum of the vicinal tetrafluoride indicated at least two different forms at low temperature, but neglecting the inside position, this compound has only one possible form in the stretched crown. Finally, although the extended crown fits the slow-exchange spectrum of the difluoride excellently, it has too many possible tetrafluorides.

In the chair family, four forms of cyclooctane have been considered: boat chair (BtC), bent chair (BnC), chair (C), and twist chair (TC). The boat-chair form is the starting point for interconversions in the chair family. This form is closely related to the crown family, one atom in the crown having been moved up through the plane of the molecule keeping the rest of the atoms more or less fixed. The boat chair has five different kinds of methylene groups or ten nonequivalent positions on the ring. In the symmetrical mode, this form can stretch to the bent chair and further transform back into another boat-chair form. In the course of this process, positions 1 and 5, 2 and 4 are

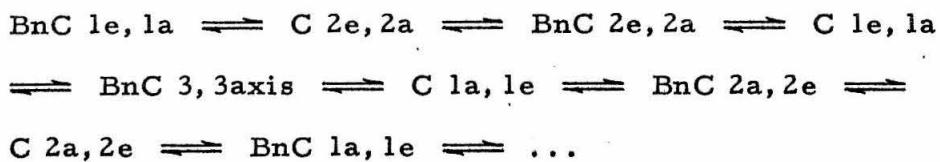


exchanged, but the "axial-equatorial" nature of the atoms is not disturbed. However, since position 3 proceeds through a form having an

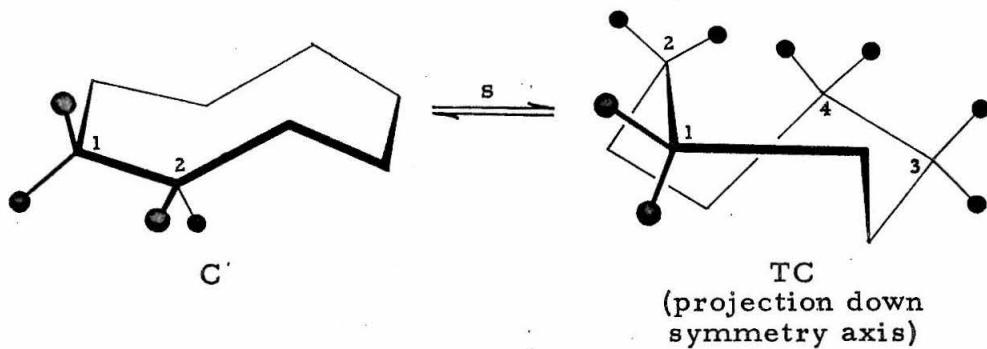
axis of symmetry passing through that carbon atom, the atoms are inverted at that position. The bent chair has three different methylene groups, but only five nonequivalent positions on the ring because the axis carbon atom 3 has two equivalent positions. This form can undergo pseudorotation by passing into the chair form. The latter has two kinds of methylene groups or four nonequivalent positions on the ring. In the course of the pseudorotation itinerary, an atom can pass through every position on the ring in both the BnC and the C. This inversion process is shown below, along with the pseudorotation itinerary for one set of atoms.



### Pseudorotation itinerary:



When both  $\psi(BnC \rightleftharpoons C)$  and  $s(BtC \rightleftharpoons BnC)$  are rapid, a substituent can pass through every position of the ring in all three forms. Therefore, unlike the crown family, inversion can be accomplished within the chair family. Another possible mode of interconversion involves the chair and the twist chair. The latter form has four kinds of methylene groups and eight nonequivalent positions on the ring. Interconversion between  $C \rightleftharpoons TC$  in the symmetrical mode also accomplishes inversion as shown below in the detailed itinerary of one set of atoms.



**Itinerary:**

$$\begin{aligned}
 & C \text{ 1e, 1a} \rightleftharpoons TC \text{ 2e, 2a} \rightleftharpoons C \text{ 1a, 1e} \rightleftharpoons TC \text{ 2a, 2e} \\
 & \rightleftharpoons C \text{ 2a, 2e} \rightleftharpoons TC \text{ 4a, 4e} \rightleftharpoons C \text{ 2a, 2e} \rightleftharpoons \\
 & TC \text{ 1a, 1e} \rightleftharpoons C \text{ 1a, 1e} \rightleftharpoons TC \text{ 3a, 3e} \rightleftharpoons C \text{ 1e, 1a} \\
 & \rightleftharpoons TC \text{ 3e, 3a} \rightleftharpoons C \text{ 2e, 2a} \rightleftharpoons TC \text{ 1e, 1a} \rightleftharpoons \\
 & C \text{ 2e, 2a} \rightleftharpoons TC \text{ 4e, 4a} \rightleftharpoons \dots
 \end{aligned}$$

Conformation	1, 1-Difluoro- cyclooctane	1, 1, 2, 2-Tetrafluoro- cyclooctane	1, 1, 4, 4-Tetrafluoro- cyclooctane
Boat chair (BtC)			
if BtC $\rightleftharpoons$ BnC is fast	2 AB and A <sub>2</sub>	2 AB and ABC <sub>2</sub>	2 AB and ABC <sub>2</sub>
if BtC $\rightleftharpoons$ BnC $\rightleftharpoons$ C is fast	A <sub>2</sub>	A <sub>2</sub>	A <sub>2</sub>
Bent chair (BnC)			
if BtC $\rightleftharpoons$ BnC is fast	2 AB and A <sub>2</sub>	2 AB and ABC <sub>2</sub>	2 AB and ABC <sub>2</sub>
if BnC $\rightleftharpoons$ C is fast	A <sub>2</sub>	A <sub>2</sub>	A <sub>2</sub>
Chair (C)			
if BnC $\rightleftharpoons$ C } is fast or C $\rightleftharpoons$ TC	A <sub>2</sub>	A <sub>2</sub>	A <sub>2</sub>
Twist chair (TC)			
if C $\rightleftharpoons$ TC is fast	A <sub>2</sub>	A <sub>2</sub>	A <sub>2</sub>
Experimental results	small AB	at least 2 large AB and 1 small AB	small AB and large AB (in small amounts)

L9

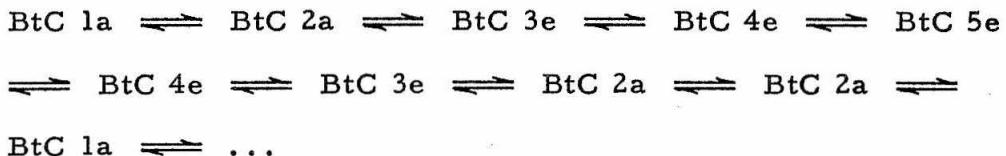
Table V. Fluorine n. m. r. spectra expected for the chair forms at intermediate temperature.

At room temperature, interconversions within the chair family are expected to be rapid, and the environments of the atoms on the ring will be averaged. The fluorine n. m. r. spectra of the three geminal-substituted cyclo $\delta$ ctanes will afford a single averaged signal which is consistent with the experimental results. At intermediate temperatures there are three possibilities open to the chair forms: if inversion is still rapid ( $BnC \rightleftharpoons C \rightleftharpoons TC$ ), the n. m. r. spectra would remain a single averaged signal; if inversion is slow, the spectra would split into several large AB patterns, the number depending on which chair form predominates. Neither of these possibilities is consistent with the results of 1, 1-difluorocyclo $\delta$ ctane. The third alternative route is interconversion between the boat and bent chair which will not invert the entire molecule. In this process positions 1 and 5, 2 and 4 in the BtC are exchanged while the set of atoms on carbon 3 are rapidly inverting. The n. m. r. spectrum of the difluoride would consist of two averaged AB patterns (with either large or small chemical shifts) and a single line or  $A_2$  pattern. In Table V are summarized the expected fluorine n. m. r. spectra for the four chair forms at intermediate temperatures. No single conformation or mixture of these conformations is consistent with the experimental results at intermediate temperatures.

At low temperature when all the interconversions among the chair forms are slowed, the n. m. r. of the fluorine-labelled compounds would become complex. Only the familiar chair conformation will afford a simple spectrum: two AB patterns for the difluoride. However,

the number and intensities of the AB spectra of the tetrafluoride do not fit the experimental results. In Table VI are summarized the expected n. m. r. spectra for the four chair forms assuming them to be "frozen" molecules.

Another mode of interconversion exists for the boat chair which has not been considered by Hendrickson. By synchronously moving atom 2 up and atom 2' down, pseudorotation ( $\psi$ ) to another boat-chair form can be accomplished. The itinerary for this interconversion appears below.



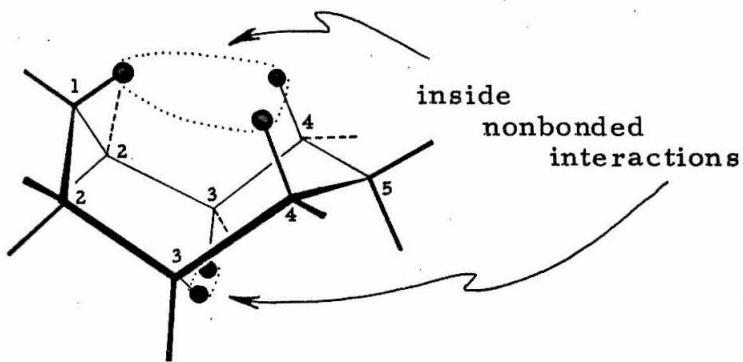
It can be seen that in the course of the pseudorotation itinerary an atom passes through five "equatorial" and three "axial" positions. Therefore, inversion cannot be accomplished by this process. However, when interconversion with the BnC (s) occurs in conjunction with pseudorotation of the BtC, inversion can be accomplished.

At room temperature when both  $\psi$  and s are rapid, a single averaged fluorine signal would be expected. At intermediate temperatures, if s is slow but  $\psi$  is still rapid, an averaged AB spectrum would be expected for 1,1-difluorocyclooctane. At low temperature when both  $\psi$  and s are slow, five distinct AB patterns should be observed for the "frozen" boat chair. It is possible to explain this inconsistency with the experimental results by assuming that the "inside" positions in the BtC cannot accommodate the fluorine atoms because of the seri-

	1, 1-Difluoro- cyclooctane	1, 1, 2, 2-Tetrafluoro- cyclooctane	1, 1, 4, 4-Tetrafluoro- cyclooctane
Conformation	Number of AB spectra	Number of AB spectra	Number of AB spectra
Boat chair	5	8	8
Bent chair	3	4	4
Chair	2	4	4
Twist chair	8	6	8

Table VI. Fluorine n. m. r. spectra expected for the chair forms at low temperature.

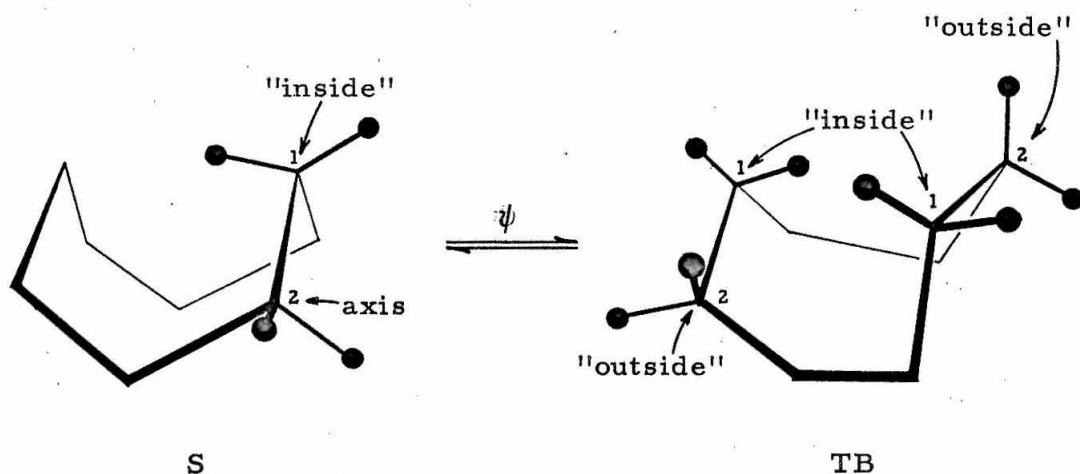
ous nonbonded interactions.



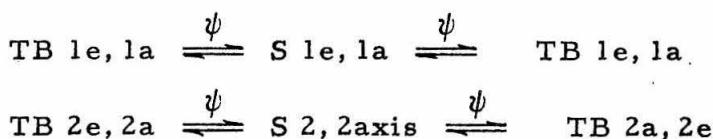
If this is a valid assumption, the "frozen" BtC forms would be expected to have the gem-difluoro group in the 2 and 5 positions, which would afford two AB patterns with large chemical shifts. It can be seen from the pseudorotation itinerary (see page 69) of the BtC that atoms in these positions are interchanged; when  $\psi$  is rapid, an AB with a small chemical shift would be expected.

The third family of cyclooctane conformations, containing the boat and saddle forms, has not been considered in detail by previous workers (25,26). The saddle (S) is a highly symmetrical form having two different kinds of methylene groups (referred to as "inside" and "axis") but only three nonequivalent positions on the ring. The molecule has an axis of symmetry passing through C-2, which possesses two equivalent positions. Although the saddle has the least torsional strain of any of the cyclooctane conformations, it possesses two serious cross-ring H-H interactions. Twisting the saddle so that these 1,4 hydrogen atoms are between two sets of hydrogen atoms in the middle of the opposite C-C bond relieves the serious cross-ring inter-

actions. This interconversion ( $\psi$ ) takes the saddle into the twist-boat conformation (TB). The latter form has two different kinds of methylene groups (referred to as "inside" and "outside") and four nonequivalent positions on the ring. The pseudorotation process (S  $\rightleftharpoons$  TB) along with the itinerary of two sets of atoms is shown below.



### Pseudorotation itinerary:



la: "inside" position; "interior" atom

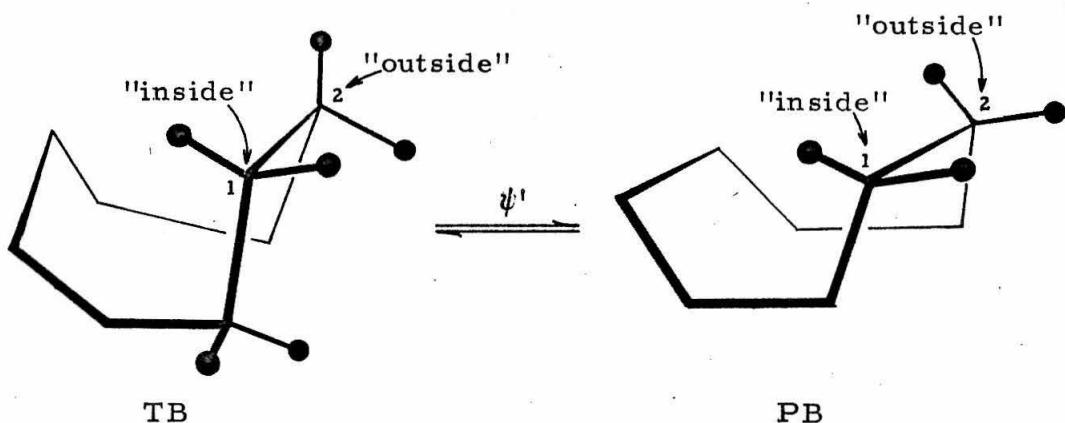
le: "inside" position; "exterior" atom

2a: "outside" position; "interior" atom

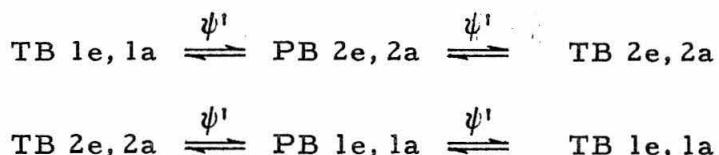
2e: "outside" position; "exterior" atom

When atoms start out on an "inside" carbon atom in the TB, they pass through the "inside" position in the S and ultimately return to the "inside" carbon atom in the TB, which is the enantiomer of the starting form. In the course of this process the substituents never exchange "interior" and "exterior" positions and always return to their original positions. When atoms start out on an "outside" carbon atom in the TB, they pass through the axis carbon atom in the S and ultimately return to an "outside" carbon atom in the TB, which is an enantiomer of the starting form. However, in the course of this process, the substituents are inverted by virtue of the fact that they pass through a position containing a symmetry axis. It is important to note that  $\psi$  never interconverts the "inside" and "outside" or the "inside" and "axis" positions of the TB and S, respectively. In addition,  $\psi$  allows inversion to occur only when a substituent can pass through the "axis" position of the S.

The second interconversion in this family involves the TB and the parallel boat (PB). This process involves a twisting of the 1,2-, 3,4-, 5,6-, 7,8- C-C bonds such that they are aligned parallel. Actually it is not possible to make all four bonds parallel with normal tetrahedral models. This parallel form appears to have improved cross-ring interactions, but there is more severe eclipsing of hydrogen atoms than in the TB. The PB has two different kinds of methylene groups ("inside" and "outside") and four nonequivalent positions on the ring. The pseudorotation process,  $\psi'$ , between the TB and PB, along with the itinerary for two sets of atoms, is shown at the top of page 74.

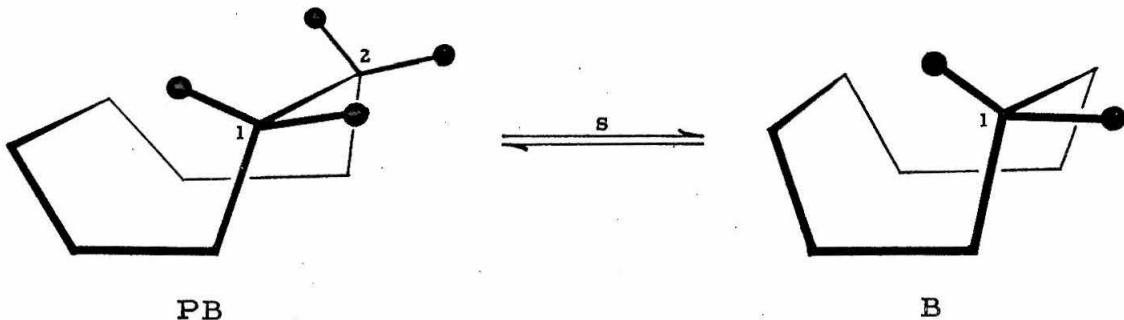


**Pseudorotation itinerary:**

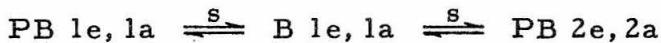


$\psi$  interchanges the "inside" and "outside" positions of the TB and PB; however, this process does not allow inversion of the "interior" and "exterior" atoms to occur.

The third interconversion in this family between the PB and the boat (B) involves a rotatory motion of the two halves of the molecule. The boat appears to have the worst eclipsing situation of any of the conformations and, in addition, has several serious H-H interactions across the ring. The boat has one kind of methylene group and two nonequivalent positions. The interconversion process (in the symmetrical mode) along with the itinerary of the atoms is shown at the top of page 75.



**Itinerary:**



The *s* interconversion also exchanges the "inside" and "outside" positions of the PB, but does not allow inversion of substituents to occur.

It is possible to envision other interconversion processes occurring among the boat forms. For example, the TB can pass directly into the B and back to the TB without proceeding through the PB. This direct process can also be accomplished by successive  $\psi'$  and *s* interconversions. In addition, the S can proceed through the B to another S via the TB without passing through the PB. This scheme,  $S \xrightleftharpoons{\psi} \text{TB} \xrightleftharpoons{\psi''} \text{B} \xrightleftharpoons{s} \text{PB} \xrightleftharpoons{\psi'} \text{TB}$ , accomplishes the same end as the scheme  $S \xrightleftharpoons{\psi} \text{TB} \xrightleftharpoons{\psi'} \text{PB} \xrightleftharpoons{s} \text{B}$ ; however, the latter has the advantage of having one fewer interconversions: the process between the TB and the B. The itinerary of a substituent starting out in the S and proceeding through all the positions on the ring in the four boat forms is shown in Fig. 23. It can be seen that when  $\psi$ ,  $\psi'$ , and *s* are rapid, inversion can occur

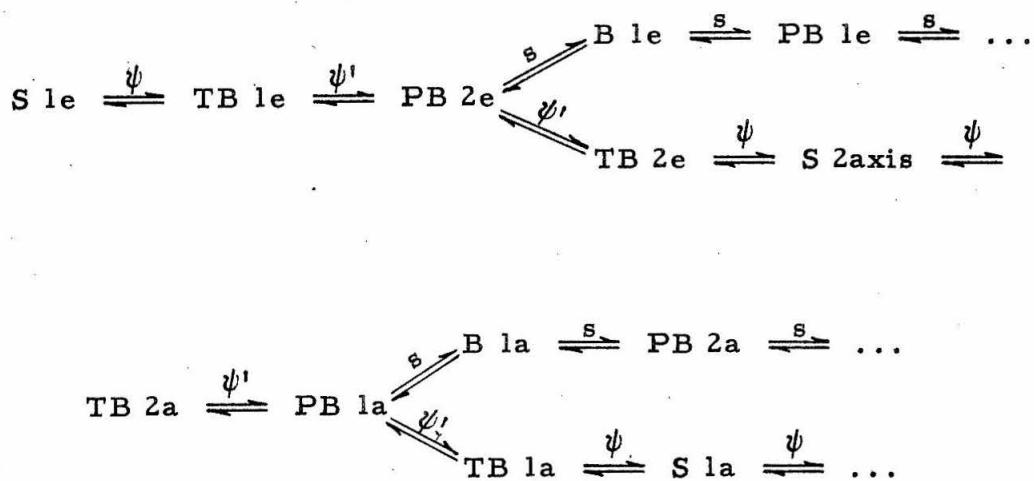


Figure 23. Conformational interconversions of the boat and saddle forms.

among the four boat forms; furthermore, if  $s$  is slow but  $\psi$  and  $\psi'$  are still rapid, inversion can still occur among the S, TB, and PB forms.

At room temperature, interconversions among the boat forms are expected to be rapid, resulting in a single averaged signal for the fluorine n. m. r. spectra of the three geminal-substituted cyclooctanes. At intermediate temperatures inversion must be slowed. If  $\psi$  is slow and  $\psi'$  and  $s$  are fast, the S will be "frozen", but interconversion between the TB, PB, and B forms would still be rapid. Also if  $\psi$  is fast and  $\psi'$  and  $s$  are slow, interconversion between the S and TB will be rapid, but slow among the TB, PB, and B. The fluorine n. m. r. spectra of 1,1-difluorocyclooctane expected for the boat forms with inversion slowed as a result of the above two possibilities are summarized in Table VII.

Irrespective of which of the two possibilities is operating at intermediate temperatures, the saddle form, which gives both an AB and an  $A_2$  pattern for 1,1-difluorocyclooctane, is inconsistent with the experimental results. It should also be noted that in order to fit the results at intermediate temperatures for the other forms inversion must be slowed by stopping  $\psi$  while  $\psi'$  and/or  $s$  is fast. Thus, interconversions among the TB, PB, and the B are occurring rapidly at these temperatures. Interconversion with the S is slow at these temperatures.

At lowest temperatures, interconversions among the boat forms would be expected to be slow. The slow exchange spectra of 1,1-difluorocyclooctane expected for the three boat forms are:

Table VII  
 Fluorine N. m. r. Spectra Expected  
 for the Boat Forms at Intermediate Temperature

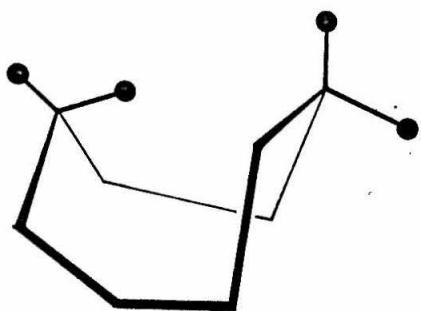
Conformation	Spectrum of 1, 1-difluorocyclooctane
S	
$\psi$ slow; $\psi'$ and s fast	AB and A <sub>2</sub>
$\psi$ fast; $\psi'$ and s slow	AB and A <sub>2</sub>
TB	
$\psi$ slow; $\psi'$ and s fast	averaged AB
$\psi$ fast; $\psi'$ and s slow	AB and A <sub>2</sub>
PB	
$\psi$ slow; $\psi'$ and s fast	averaged AB
$\psi$ fast; $\psi'$ and s slow	2AB
B	
$\psi$ slow; $\psi'$ and s fast	averaged AB
$\psi$ fast; $\psi'$ and s slow	AB

## Conformation Fluorine n. m. r. of 1, 1-difluorocyclooctane

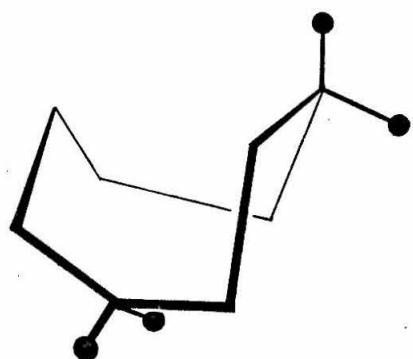
TB	two AB (unequal intensities)
PB	two AB (unequal intensities)
B	AB

Clearly the B cannot account for the low-temperature experimental results. In order to decide between the TB and the PB, both of which would give the observed two AB patterns of unequal intensities, it will be necessary to consider 1, 1, 4, 4-tetrafluorocyclooctane. This molecule can exist in two possible boat forms: symmetrical boat having a plane of symmetry; unsymmetrical boat having no plane of symmetry. These two forms can be interconverted at room temperature when pseudorotation through S is rapid. At intermediate temperatures four kinds of conformations will appear. Two are based on the unsymmetrical boat: twist-unsymmetrical boat (TUB) and parallel-unsymmetrical boat (PUB). The other two are based on the symmetrical boat: twist-symmetrical boat (TSB) and parallel-symmetrical boat (PSB) (see next page).

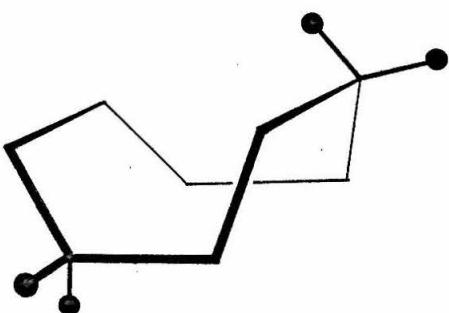
Considering the unsymmetrical boat forms, first one can clearly see that the two possible TUB forms are enantiomers, each having an "inside" and an "outside" set of fluorine atoms. On the other hand, the two possible PUB are different molecules, one having both sets of fluorine atoms "inside" and one having them "outside". These two different conformations would be expected to be of different energies with the "outside-outside" form the predominant species. At intermediate temperatures the TUB and PUB forms are interconverted assuming that  $\psi'$  is rapid. The fluorine n. m. r. spectrum would be



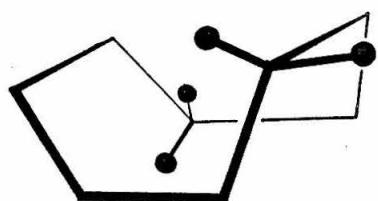
TSB



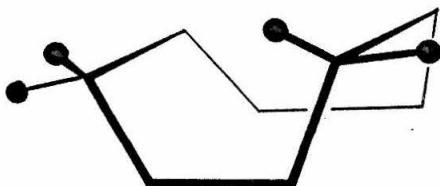
TUB



"outside-outside" PUB



"inside-inside" PUB



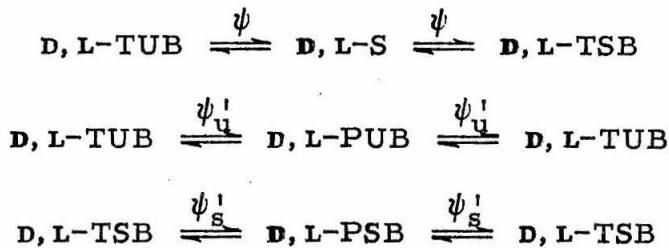
PSB

expected to be an averaged AB pattern similar to the spectrum of the difluoride. At low temperature, interconversion among the four forms would be expected to be slow and the conformations would be "frozen". The TUB would give two AB patterns similar to those found in the difluoride with one exception: the intensities of the AB patterns would be equal since the two identical forms have one set of fluorine atoms "inside" and one set "outside". The PUB would also be expected to give two AB patterns, one for each different conformation; however, since the "outside-outside" form should be overwhelmingly favored at low temperature, the AB patterns should not be of equal intensity.

The unsymmetrical and symmetrical forms are interconverted rapidly when  $\psi$  is fast. At intermediate temperatures when this process is slowed, one might expect to observe the symmetrical forms also. These forms would be expected to be unfavorable due to a serious cross-ring interaction between the "interior" fluorine atoms. In addition, interconversion of the TSB and the PSB would be expected to be more difficult since these fluorine atoms must pass one another in the PB. Therefore, the symmetrical forms would be present in small amounts and would be "frozen out" at higher temperatures than the unsymmetrical forms. The AB pattern which was observed upfield from the main signal may represent one of these forms. The chemical shifts for the fluorine atoms of this conformer are vastly different from those observed for the unsymmetrical forms and might be attributed to the close spatial interaction of the "inside" fluorine atoms.

The conformational interconversions of 1,1,4,4-tetrafluorocyc-

cloöctane are summarized below.

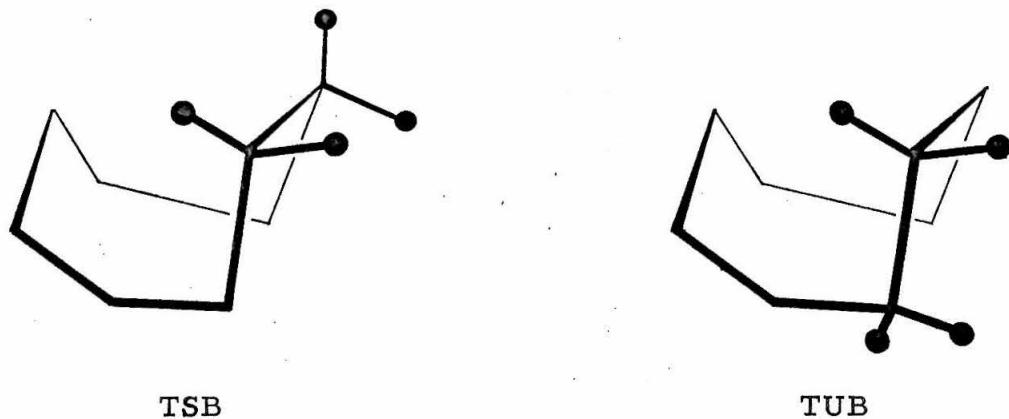


at room temperature:  $\psi$ ,  $\psi'_u$ , and  $\psi'_s$  fast

at intermediate temperature:  $\psi$  and  $\psi_s'$  slow;  $\psi_u'$  fast

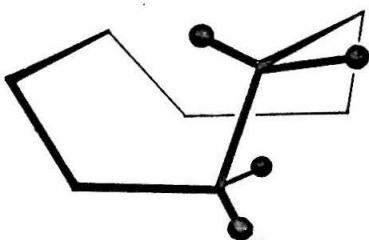
at low temperature:  $\psi$ ,  $\psi_u'$ , and  $\psi_s'$  slow

The vicinal tetrafluoride can also exist in two possible twist-boat conformations based on the symmetrical and unsymmetrical boat forms.

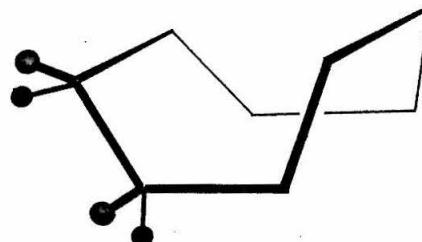


These two forms and their enantiomers have one set of fluorine atoms on an "inside" carbon atom and one set on an "outside" carbon atom. Except for slight differences in the staggering of the vicinal fluorine atoms the TUB and TSB should have similar energies and be present in

approximately equal amounts. These forms are interconverted rapidly at room temperature by pseudorotation through the saddle. At intermediate temperatures when  $\psi$  is slow, the TUB and TSB forms can no longer interconvert; however, the "inside" and "outside" positions in the separate forms can still be exchanged by pseudorotation through the PUB and the PSB. The TSB can pass into a PSB form which has one set of fluorine atoms "inside" and one set "outside". On the other hand the TUB can pass into two possible PUB forms depending on which enantiomer of the TUB is used. One form has both sets of fluorine atoms "inside" and the other has both sets "outside".



"inside-inside" PUB



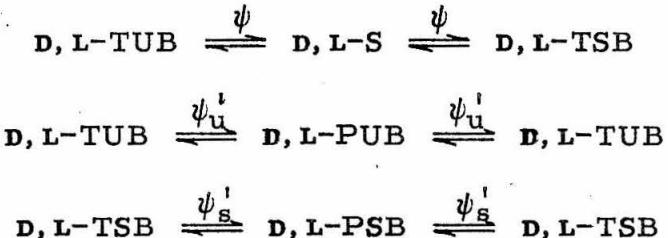
"outside-outside" PUB

The TUB, therefore, has two modes of interconversion: one involving the high energy "inside-inside" PUB and the other involving the lower energy "outside-outside" PUB. The TSB has only one mode of interconversion that is through the intermediate energy "inside-outside" PSB. The transition state for the  $\text{TSB} \rightleftharpoons \text{PSB} (\psi_s')$  involves severe eclipsing of the vicinal fluorine atoms as they move from "inside" to "outside" positions; moreover, the "interior" fluorine atoms

are forced to push past the hydrogen atoms across the ring. On the other hand, the transition state for TUB  $\rightleftharpoons$  "outside-outside" PUB ( $\psi_u'$ ) does not eclipse the vicinal fluorine atoms and pushes only one "interior" fluorine atom past the cross-ring hydrogen.

On the grounds of torsional strain as well as nonbonded interactions,  $\psi_u'$  would be expected to be a lower energy process than  $\psi_s'$  by several kcal. /mole. The spectrum of the vicinal tetrafluoride indicates that the difference in the energies of these interconversions may be important. At intermediate temperatures ( $-55^\circ$  to  $-85^\circ$ ), the spectrum of this molecule showed two AB patterns: one with a large chemical shift and the other with a small chemical shift. The former pattern is attributed to the TSB which can no longer interconvert to its enantiomer. The latter pattern results from averaging of the TUB forms. At lower temperatures when  $\psi_u'$  is slowed, an AB pattern with a large chemical shift corresponding to the "frozen" TUB is observed.

The conformational interconversions of 1,1,2,2-tetrafluorocyclooctane are summarized below.



at room temperature:  $\psi$ ,  $\psi_s'$ , and  $\psi_u'$  fast

at intermediate temperature:  $\psi$  and  $\psi_s'$  slow;  $\psi_u'$  fast

at low temperature:  $\psi$ ,  $\psi_s'$ , and  $\psi_u'$  slow

## CONCLUSIONS

The available evidence presented in this thesis is compatible with the twist-boat form rapidly equilibrating through the saddle and parallel-boat forms at room temperature. The presence of two rate processes for 1, 1-difluorocyclooctane and for 1, 1, 4, 4-tetrafluorocyclooctane is consistent with the spin-echo studies of Meiboom (23) for cyclooctane and suggests that fluorine substitution does not markedly affect the conformational properties of the ring.

The calculations of Hendrickson (25), Wiberg (26), and Griffith (29) of the total strain energies of various cyclooctane conformations (Table VIII) indicate that the twist-boat form, despite being a somewhat crowded conformation, is of comparable energy with the two lowest energy forms, the extended crown and the boat chair.

At the present time, the conformational features of cyclooctane are so subtle and complicated by virtue of the overwhelming number of forms and interconversions that any interpretation must be regarded as tentative.

Table VIII  
Minimum Energies of Cyclooctane Conformations\*

	Wiberg (kcal.)	Hendrickson (kcal.)
Crown	3.6	14.3
Stretched crown	----	13.5
Extended crown	2.6	12.2
Boat	12.2	21.6
Saddle	5.1	15.7
Twist boat	3.2 (29)	----
Chair	9.4	20.0
Boat chair	4.0	11.9

\*In both sets of calculations the parameters were those used by Hendrickson (see page 12). The calculations of Wiberg and Griffith include all C—H and C—C nonbonded interactions (attractive) and therefore are lower in energy than those of Hendrickson.

**EXPERIMENTAL**

## EXPERIMENTAL

Melting points and boiling points are uncorrected. Infrared spectra were measured on the Beckman Infrared Spectrometer, Model IR-7. Vapor-phase chromatography experiments were performed on the Perkin-Elmer Model 154C chromatograph.

Elementary analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Proton magnetic resonance spectra were measured at room temperature on the Varian Associates Model A-60 spectrometer operated at 60.0 Mcps. and 14,100 gauss. Fluorine magnetic resonance spectra were measured on the Model V-4300 B spectrometer operated at 56.4 Mcps. Heteronuclear double-resonance experiments were accomplished with the Nuclear Magnetic Resonance Specialties Model SD-60 spin decoupler. Calibrations were effected by the sideband technique with the use of the Hewlett-Packard Model 200 AB audio oscillator and Model 521-C frequency counter. Low-temperature spectra were measured on the Model V-4300 B spectrometer by passing a stream of pre-cooled nitrogen through a dewar system into the sample insert (30). Rather large flows of nitrogen were necessary at very low temperature. Temperatures were recorded by a copper-constantan thermocouple placed above the receiver coil.

Chemical shifts, coupling constants and relaxation times were determined from the slow-exchange spectra. Theoretical spectra were generated by an IBM 7094 II computer (coupled to a Moseley X-Y plotter) using a Fortran IV coded program based on the equations of

Alexander (10, 11, 31). Input to the program included a relaxation time,  $T_2$ , for each nucleus in the system and the mean lifetimes,  $\tau_1$  and  $\tau_2$ , for each AB set of nuclei. The values of  $\tau$  were determined by direct comparison of the observed and calculated spectra and are believed to be accurate to 10% or better.

1, 1-Difluorocycloheptane. - Into a 100-ml. three-necked round-bottomed flask equipped with a dropping funnel, reflux condenser and magnetic stirrer was placed 16.6 g. (0.1 mole) of phenylsulfur trifluoride (32). The reaction flask was heated to 60° on a steam bath and 11.2 g. (0.1 mole) of cycloheptanone was added dropwise in small portions over 30 minutes. An exothermic reaction occurred and the reaction flask was cooled in an ice bath when the temperature rose above 100°. After the addition of the ketone was completed, the solution was heated on an oil bath at 100° for 30 minutes. The dark thick reaction mixture was poured into ice water and extracted with pentane. The pentane extracts were washed with dilute sodium bicarbonate and dried over magnesium sulfate. After removal of the solvent, distillation of the residue at reduced pressure afforded 2.2 g. of 1, 1-difluorocycloheptane, b. p. 44°-46° (55 mm.). Vapor phase chromatography indicated the material was greater than 99% pure. The infrared spectrum showed absorption bands in the 1000-1400  $\text{cm}^{-1}$  region indicative of carbon-fluorine bonds. The proton magnetic resonance spectrum afforded three broad bands at 1.0-2.0 p. p. m. The fluorine-19 magnetic resonance spectrum showed a quintet characteristic of a gem-difluoro group with  $J_{\text{H-F}} = 15.5$  cps.

Anal. Calcd. for  $C_7 H_{12}F_2$ : C, 62.65; H, 9.03; F, 28.32.

Found: C, 62.41; H, 9.27; F, 28.27.

4, 4-Dimethylcycloheptanone. - A 10.0-g. sample (0.07 mole) of 4, 4-dimethylcyclohexanone prepared by the method of Bordwell and Wellman (33) was treated with 4.2 g. (0.1 mole) of diazomethane in 400 ml. of ether and 75 ml. of ether (34). The reaction mixture was cooled in an ice bath for several hours and allowed to sit for 1 week at room temperature. The solution was then filtered free of any polyethylene, dried over magnesium sulfate and the solvent removed by distillation. The residue was distilled through a 20-cm. spiral column to yield 4.5 g. of product, b.p. 80°-83° (13 mm.). The proton magnetic resonance spectrum showed: 2.1-2.5 (multiplet), 1.3-1.7 (multiplet), 0.9 (singlet) p.p.m. with the integrated areas 2:3:3.

1, 1-Difluoro-4, 4-dimethylcycloheptane. - A mixture of 10.0 g. (0.07 mole) of 4, 4-dimethylcycloheptanone, 25 ml. of methylene chloride and 1 ml. of water was placed in a 200-ml. pressure reaction vessel constructed of Hastelloy C alloy. The bomb was sealed, cooled to Dry Ice-acetone temperature and evacuated before 59 g. (0.5 mole) of sulfur tetrafluoride was condensed into the bomb (35, 36). The vessel was placed in a Parr rocking apparatus for 15 hrs. at room temperature. The bomb was then vented and the contents were taken up in 100 ml. of methylene chloride and poured into ice water. The methylene chloride layer was washed several times with 10% sodium bicarbonate and dried over sodium sulfate. After distillation of the solvent, the dark residue was chromatographed on alumina, affording a color-

less liquid. Distillation at reduced pressure afforded 3.2 g., b.p. 90°-92° (30 mm). Vapor phase chromatography indicated the purity was greater than 99%. The infrared spectrum possessed characteristic carbon-fluorine absorption in the 1000-1400  $\text{cm}^{-1}$  region. The proton magnetic resonance spectrum showed: 1.2-2.3 (multiplet), 0.85 (singlet) p.p.m. with the integrated areas 5:3. The fluorine-19 spectrum afforded a quintet with  $J_{\text{H}-\text{F}} = 15.1$  cps.

Anal. Calcd. for  $\text{C}_9\text{H}_{16}\text{F}_2$ : C, 68.56; H, 9.37; F, 22.06.

Found: C, 68.36; H, 9.54; F, 22.01.

4-Methylcycloheptanone. - Ring enlargement of 11.2 g. (0.1 mole) of 4-methylcyclohexanone (Aldrich Chemical Co.) was carried out according to the procedure described for preparation of 4,4-dimethylcycloheptanone. Distillation of the product afforded 5.0 g. of a colorless liquid, b.p. 78°-81° (20 mm.), (lit. 99° (40 mm.)) (34).

1,1-Difluoro-4-methylcycloheptane. - A 5.0-g. sample (0.04 mole) of 4-methylcycloheptanone was reacted with 30 g. (0.25 mole) of sulfur tetrafluoride according to the procedure described. Elution chromatography of the crude material afforded 0.5 g. of desired product. Infrared spectrum showed characteristic carbon-fluorine absorption bands in the 1000-1400  $\text{cm}^{-1}$  region. The proton magnetic resonance spectrum showed: 1.0-2.5 (multiplet), 0.9 (doublet). The fluorine-19 magnetic resonance spectrum afforded an AB pattern with  $J_{\text{F}-\text{F}} = 240$  cps. characteristic of a gem-difluoro group.

4-t-Butylcycloheptanone. - Ring enlargement of 10.0 g. (0.065 mole) of 4-t-butylcyclohexanone (Aldrich Chemical Co.) was carried

out according to procedure described. Distillation of the product afforded 4.2 g., b.p. 75°-80° (2 mm.), (lit. 68° (0.2 mm.)) (28).

1, 1-Difluoro-4-t-butylcycloheptane. - A 4.2-g. (0.024 mole) sample of 4-t-butylcycloheptanone was reacted with 30 g. (0.25 mole) of sulfur tetrafluoride according to the procedure described. Elution chromatography of the crude material afforded 0.4 g. of desired product. The infrared spectrum showed characteristic carbon-fluorine bands in the 1000-1400  $\text{cm}^{-1}$  region. The fluorine-19 magnetic resonance spectrum afforded an AB pattern with  $J_{\text{F-F}} = 240$  cps. characteristic of a gem-difluoro group.

1, 1-Difluorocyclooctane. - Cyclooctanone (10 g., 0.08 mole) was treated with 16.6 g. (0.1 mole) of phenylsulfur trifluoride according to the procedure described for the synthesis of 1, 1-difluorocycloheptane. Distillation afforded 1 g. of product, b.p. 40°-42° (33 mm.). Vapor phase chromatography indicated the material was greater than 99% pure. The infrared spectrum showed characteristic carbon-fluorine bands in the 1000-1400  $\text{cm}^{-1}$  region. The proton magnetic resonance spectrum afforded three broad bands at 1.0-2.0 p.p.m. The fluorine-19 magnetic resonance spectrum showed a quintet with  $J_{\text{H-F}} = 15.1$  cps.

Anal. Calcd. for  $\text{C}_8\text{H}_{14}\text{F}_2$ : C, 64.83; H, 9.53; F, 25.63.

Found: C, 64.99; H, 9.66; F, 25.55.

1, 4-Cyclooctanediol. - According to the procedure of Cope et al. (37), 100 g. (0.795 mole) cyclooctene oxide was solvolyzed in formic acid (38). Distillation of the reaction mixture afforded two fractions,

the higher boiling fraction, b. p. 85°-98° (0.2 mm.) containing 27.8 g. of 1,2- and 1,4- cyclooctanediols. The diol mixture was treated with 25 g. anhydrous cupric sulfate in 300 ml. of acetone. After filtration the acetone was removed and the ketal distilled. The residue was crystallized from ethyl acetate to yield 11.0 g. of 1,4-cyclooctanediol, m. p. 83°-86° (lit. 84.6°-86°) (37).

1, 4-Cyclooctanedione. - Oxidation of 11.0 g. (0.0715 mole) of 1, 4-cyclooctanediol with chromium trioxide in pyridine according to the procedure of Sarett (38) was carried out. Distillation afforded 4.80 g. of a low melting point solid, b. p. 63°-67° (0.2 mm.), (lit. 73°-76° (1 mm.)) (37).

1, 1, 4, 4-Tetrafluorocyclooctane. - 1, 4-Cyclooctanedione (4.8 g, 0.032 mole) was reacted with 50 g. (0.42 mole) of sulfur tetrafluoride according to the procedure described. Distillation afforded 2.25 g. of product, b. p. 65°-70° (22 mm.). The infrared spectrum showed characteristic carbon-fluorine absorption in the  $1000-1400\text{ cm}^{-1}$  region. The fluorine-19 magnetic resonance spectrum afforded a quintet with  $J_{\text{F-F}} = 13.7$  cps.

2-Hydroxycyclooctanone. - According to the procedure of Allinger (40), an acyloin condensation of 113.8 g. (0.495 mole) of diethyl suberate was carried out. Distillation afforded 14.3 g. of suberoin, b. p. 70° (2.8 mm.), (lit. 75° (1.5 mm.)) (41).

1, 2-Cyclooctanedione. - Oxidation of 16.69 g. (0.1175 mole) of suberoin with 20.0 g. (0.043 mole) of bismuth trioxide according to the procedure of Blomquist and Liu (41) afforded 4.0 g. 1,2-cyclo-

Octanedione, b. p. 65°-74° (3.4 mm.) (lit. 68.8°-69.5° (3mm.)). The quinoxaline derivative of this diketone was prepared, m. p. 120°-122° (lit. 120.2°-120.7°) (41).

1, 1, 2, 2-Tetrafluorocyclooctane. - 1, 2-Cyclooctanedione (4.0 g., 0.0285 mole) was treated with 59.0 g. (0.5 mole) of sulfur tetrafluoride according to the procedure described. After elution chromatography, distillation afforded 1.0 g. of colorless product, b. p. 150°. Vapor phase chromatography indicated that the material was 95% pure. The infrared spectrum showed strong absorption in the 1050-1200  $\text{cm}^{-1}$  region. The proton magnetic resonance spectrum showed broad bands at 1.5-2.5 p. p. m. The fluorine magnetic resonance spectrum showed a broad unresolved multiplet, and a single sharp line under double irradiation at the proton resonance frequency (42).

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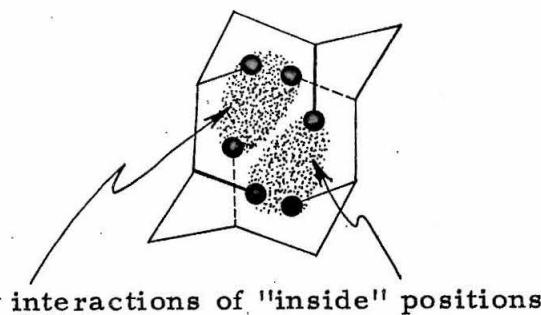
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**PROPOSITIONS**

## Proposition I

It is proposed to examine the low-temperature  $C^{13}$  n. m. r. spectrum of cyclodecane.

The n. m. r. studies of the conformational problems of medium-sized rings have involved the use of  $H^1$  and  $F^{19}$  nuclei. Proton n. m. r. has the disadvantage of affording complex coupling patterns and small chemical-shift differences. Substitution of a gem-difluoro group introduces the problem of conformational preference, which may become very serious in higher-membered rings. Cyclodecane has been predicted by x-ray studies (1, 2) and theoretical calculations (3) to exist in a single stable conformation. The "inside" positions on the cyclo-



decane ring have extremely severe nonbonded interactions and cannot accommodate groups larger than hydrogen. Consequently, in the slow-exchange spectrum the "inside" fluorine resonances would be missing or of low intensity; in addition, the activation energy for inversion might be raised considerably as a result of passage of the gem-difluoro

group through the "inside" positions.

The use of  $C^{13}$  n. m. r. spectroscopy would be an excellent technique for studying the conformational problems of cyclodecane. To date kinetic studies have been unexplored in this field due to poor resolution and to difficulties with working with dilute solutions. Recently Paul and Grant (4) have obtained improved  $C^{13}$  n. m. r. spectra in natural abundance by the use of proton decoupling and nuclear Overhauser techniques. Their studies of the  $C^{13}$  n. m. r. spectra of alkanes indicate that  $C^{13}$  chemical shifts are extremely sensitive to molecular environment (5). Lauterbur and Burke have measured the  $C^{13}$  n. m. r. spectra of cycloalkanes at room temperature and have found that the  $C^{13}$  chemical-shift difference between cyclohexane and cyclodecane is 1.6 p. p. m. (24.2 cps.) or 5 times larger than the corresponding  $H^1$  chemical shift difference (6).

It is proposed to investigate the temperature variation of the  $C^{13}$  n. m. r. spectrum of cyclodecane. If the molecule can be "frozen" into a single stable conformation at low temperature, each different carbon atom would be expected to afford a distinct  $C^{13}$  resonance; the relative areas of these peaks will correspond to the number of times each carbon atom recurs in the conformation.

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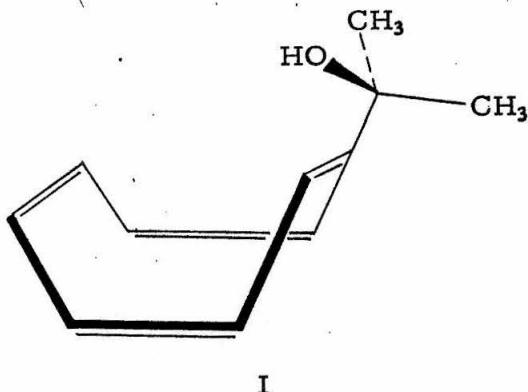
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## Proposition II

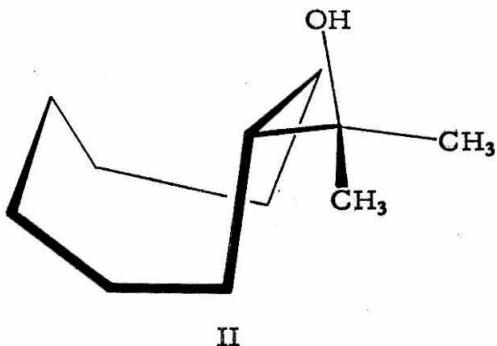
In a monosubstituted cyclooctane, the twist-boat conformations exist in enantiomeric forms. It is proposed to examine the n. m. r. spectra of such compounds at low temperature.

The twist-boat (TB) conformation of cyclooctane appears to provide the most satisfactory explanation for the experimental results obtained in this thesis (1). The TB is a dissymmetric molecule and possesses two possible enantiomeric forms, but at room temperature pseudorotation through the symmetrical saddle conformation rapidly interconverts these enantiomers. Below  $-100^{\circ}$  this process is believed to be slowed on the n. m. r. time scale and the two enantiomers can no longer interconvert.

The magnetic nonequivalence of a methylene group close to an asymmetric center has been used to investigate conformational equilibria (3, 4). N. m. r. spectroscopy can provide the same type of information that optical rotation measurements would, without the necessity of resolving the sample. Anet, Bourn, and Lin (5) have used this technique to investigate the ring inversion and the bond shift of cyclooctatetraene. At low temperature the n. m. r. spectrum of cyclooctatetraenyl-2, 3, 4, 5, 6, 7-d<sub>6</sub>-dimethylcarbinol showed two bands for the methyl resonances as expected from a structure such as I in which the two methyl groups are chemically nonequivalent.



It is proposed to examine the n. m. r. spectrum of cyclooctyl-dimethylcarbinol at low temperature. Below  $-100^{\circ}$  the methyl groups would be expected to split into a doublet expected from the twist-boat conformation (II) which can no longer interconvert to its enantiomeric



form. Interconversion via the parallel-boat (PB) conformation would still be expected to be rapid at  $-100^{\circ}$  (1), but this process will only exchange the dimethylcarbinol group between the two "equatorial" positions on the ring. Below  $-160^{\circ}$  when the  $TB \rightleftharpoons PB$  process is slowed,

the methyl resonances would consist of two doublets corresponding to the two possible "equatorial" positions of the dimethylcarbinol group.

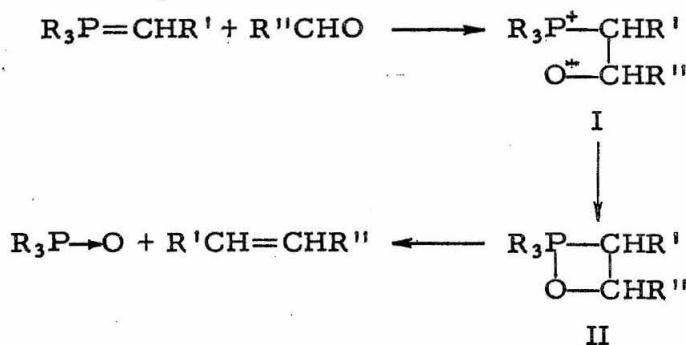
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## Proposition III

In the Wittig reaction equilibration of the two stereoisomeric betaines through an intermediate ylid has been suggested to account for the formation of both cis and trans olefins. It is proposed that the intermediate ylid be isolated and subjected to decomposition.

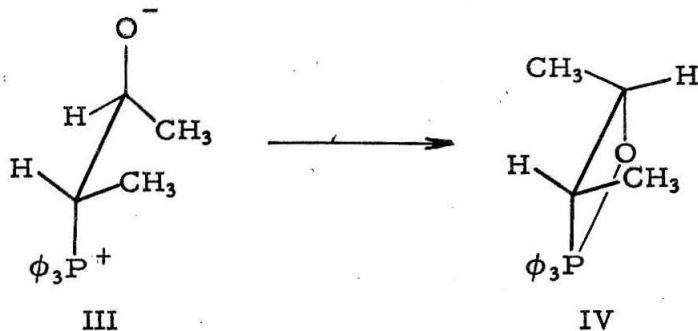
Although the synthetic applications of the Wittig reaction are well known (1), the mechanism is still not well substantiated (2, 3).



The importance of I and/or II has not been definitely established. With certain unstable ylids (those ylids which do not contain an electron delocalizing group on the carbon atom), the intermediate betaine (I) has been isolated by reaction with hydrogen iodide (4).

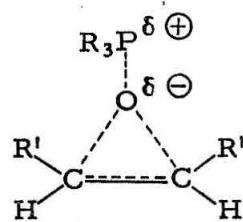
The reaction of phosphines with epoxides proceeds through a betaine intermediate and has been studied to elucidate the reversibility or irreversibility of betaine formation (5). Denney and Boskin (6) have shown that trans but-2-ene epoxide yielded a mixture of 72% cis but-2-ene and 28% trans but-2-ene; the cis but-2-ene epoxide yielded 81% trans but-2-ene and 19% cis but-2-ene. The mechanism proposed dis-

placement on carbon by the phosphine to give III followed by rotation and bond formation to give IV. This mechanism predicts that trans



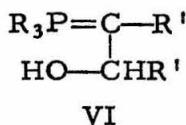
epoxide will afford cis olefin, and cis epoxide will afford trans epoxide. Bissing and Speziale (5) also have observed small amounts of cis olefin from cis epoxide, and trans olefin from trans epoxide in the reaction of stilbene epoxides and 4-octene epoxides with phosphines.

There are two reasonable explanations for the formation of cis olefin from cis epoxide and trans olefin from trans epoxide. The first involves nucleophilic attack of the phosphine at oxygen leading to V.



V

A second plausible explanation entails partial equilibration of the stereoisomeric betaines via an intermediate ylid (VI). This mechan-



ism would require abstraction of a relatively nonacidic hydrogen by oxygen and would have to be fast enough to compete with betaine decomposition. Attempts to detect this intermediate ylid by competition experiments with a reactive aldehyde were unsuccessful (5). However, this ylid would be expected to react slowly, if at all, with an aldehyde due to steric hindrance. Because proton abstraction necessary for equilibration may be rapid, slow reaction of the ylid with an aldehyde may not occur.

It is proposed to quench the reaction of triphenyl phosphine with cis or trans but-2-ene epoxides with hydrogen iodide, isolate the intermediate betaine (4), and subject it to decomposition. Formation of both cis and trans olefins from this betaine would suggest the intervention of an intermediate ylid through which the two stereoisomeric betaines are equilibrated; moreover, an explanation involving nucleophilic attack of the phosphine at oxygen would be eliminated as a reasonable mechanism for the formation of both cis and trans olefins.

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## Proposition IV

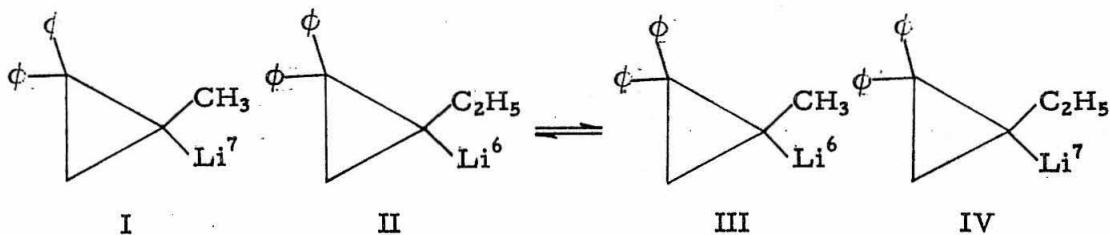
It is proposed to study the  $\text{Li}^7$  n. m. r. spectrum of cyclopropyl organolithium compounds in order to investigate the question of intermolecular exchange.

Proton n. m. r. spectroscopy, as well as chemical studies, have demonstrated considerable configurational stability of the lithium-bearing carbon atom in cyclopropyl systems (1). In such molecules intermolecular exchange can only occur via a path which does not result in loss of configuration. It is of considerable interest to determine the kinetic parameters of this intermolecular exchange process in organolithium compounds.

Rapid intermolecular exchange of methyl groups in solutions of trimethylaluminum and dimethylcadmium and in solutions of dimethylzinc and dimethylcadmium has been reported by McCoy and Allred (2). Brown and Ladd (3) have studied the  $\text{Li}^7$  n. m. r. spectrum of  $\text{LiC}_2\text{H}_5$ ,  $\text{LiC}_2\text{D}_5$ , and  $\text{LiC}(\text{CH}_3)_3$  as a function of temperature and concluded that slow intermolecular exchange of alkyl groups occurs in the temperature range examined. The exchange mechanism of these investigations of relatively simple organometallic compounds is unknown. Recently Brown and Seitz (4) have examined the  $\text{Li}^7$  n. m. r. spectra of ether solution of methyl lithium and ethyllithium from  $30^\circ$  to  $-80^\circ$ . At room temperature, a single line is observed with a chemical-shift value approximately the weighted average of the methyl lithium ( $-1.32$  p. p. m. relative to aqueous  $\text{LiBr}$ ) and the ethyllithium ( $-0.72$  p. p. m. relative

to aqueous LiBr) values. The line broadens at lower temperatures and appears as a distinct multiplet at about  $-50^\circ$ . The activation energy for this intermolecular exchange process was estimated to be about 5.5 kcal./mole.

It is proposed to examine the  $\text{Li}^7$  n. m. r. spectrum of the following molecules (I and II) in ether solution:



Because these cyclopropyl systems are expected to be configurationally stable at the lithium carbon atom, any intermolecular exchange that occurs must involve a retention mechanism. If exchange is slow at room temperature, a single  $\text{Li}^7$  resonance signal having the chemical-shift value observed for I will be observed; on the other hand, if exchange is rapid at room temperature, a single  $\text{Li}^7$  resonance signal with an averaged chemical-shift of the I and IV values will be observed. At low temperature if exchange can be slowed, distinct  $\text{Li}^7$  resonances from I and IV would appear.

## References

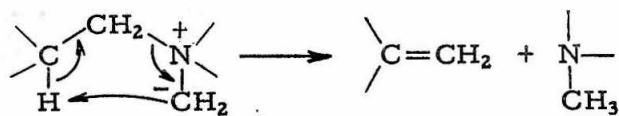
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## Proposition V

It is proposed to investigate the mechanism of the Hofmann decomposition of quaternary ammonium hydroxides of cyclooctane, cyclononane, and cyclodecane.

The Hofmann elimination has generally been described as an E2 reaction involving the concerted elimination of a  $\beta$ -proton by hydroxide ion and the removal of a tertiary amine (1). One of the requirements of the E2 mechanism is that the  $\beta$ -proton and the leaving nitrogen moiety be coplanar and in the trans conformation. However, Hofmann eliminations for compounds having only a cis- $\beta$ -hydrogen atom are also known. For example, trans-2-phenylcyclohexyltrimethylammonium hydroxide has been shown to proceed through direct cis elimination (2, 3). The experimental evidence (4) supports an Elcb route (two-step  $\beta$ -carbanion mechanism). This example represents a special case due to the presence of the phenyl group which increases the acidity of the  $\beta$ -hydrogen atom.

The Hofmann decomposition of N, N, N-trimethyl-2-t-butyl-3, 3-dimethylbutylammonium hydroxide has been shown to proceed principally by an ylide mechanism (5).



This compound represents a case where steric factors favor a cis over a trans elimination and where the  $\beta$ -hydrogen is activated only by the

quaternary nitrogen atom.

The Hofmann decomposition of cyclooctyltrimethylammonium hydroxide leads to a mixture of cis- and trans-cyclooctene in an approximate ratio of 2:3. With the corresponding quaternary bases of cyclononane and cyclodecane, the trans olefins were obtained by the Hofmann elimination in yields of approximately 90% (6). However, in all these compounds the cis isomer is the more stable (7). Formation of these trans-cycloalkenes via the normal E2 mechanism would necessitate placing the bulky trimethylammonium group in the axial position. Examination of molecular models of these compounds suggests that such a molecule would be severely strained. A more reasonable explanation is that these rings can assume conformations in the transition states in which a trans- $\beta$ -hydrogen is in the same plane as the trimethylammonium group and that an intramolecular cyclic mechanism (analogous to the cis-ylid mechanism) occurs in which a tertiary amine group and a trans- $\beta$ -hydrogen are eliminated.

In order to investigate the possibility of an ylide mechanism occurring in these compounds, the decomposition of N, N, N-trimethyl-cycloalkylammonium hydroxide- $\alpha$ ,  $\alpha'$ -d<sub>4</sub> should be examined. The presence of substantial amounts of deuterium in the trimethylamine formed would support an ylid-type mechanism.

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