Nuclear Magnetic Resonance Spectroscopy. Conformational Equilibration of Cycloheptane and Cycloheptene Derivatives[1a,b]

Edward S. Glazer, Rudolf Knorr, Camille Ganter, and John D. Roberts*

Contribution No. 4359 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91109.

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Abstract: A study of the temperature dependence of the ^{19}F nuclear magnetic resonance (fmr) spectra of 4,4-difluoro-1,1-dimethylcycloheptane has shown that, at low temperatures, this substance exists predominantly in the twist-chair conformation with the methyl groups on the axis carbon atom. 1,1-Difluoro-4,5-*trans*-dibromocycloheptane, at low temperatures, exists predominantly in two different conformations with the fluorine atoms at the axis carbon atom. 5,5-Difluorocycloheptene, at low temperatures, exists in a single conformation best represented as the chair. Activation parameters have been obtained for the conformational equilibration of these derivatives. For 1,1-difluorocycloheptane, 1,1,3,3-tetrafluorocycloheptane, and 4,4-difluoro-1-*tert*-butylcycloheptane the conformational equilibria are still rapid on the nmr time scale at low temperatures and only qualitative conclusions can be drawn about their conformations.

Nuclear magnetic resonance (nmr) spectroscopy has proven to be a powerful tool for the study of fluctuating shapes of cyclic molecules.[2,3] In the present research, fluorine labeling[4] has been used to investigate conformational equilibration in cycloheptane and cycloheptene. As the experimental evidence regarding the conformations of these cyclic molecules is limited,[5] our present understanding of these molecules is largely derived from the strain-energy calculations and *a priori* predictions of Hendrickson.[6] Some of the more symmetrical possible conformations of cycloheptane and the energies calculated[6b] for each of them are shown in Figure 1. Some of the more symmetrical conformations of cycloheptene have been treated by Hendrickson's procedure and the energies so calculated[7] are shown in Figure 2.

Before presenting the spectroscopic results, we will consider some of the possible modes of interconversion that can occur among the various symmetrical conformations of cycloheptane and cycloheptene. In this analysis, we will pay particular attention to the movement of the ^{19}F atoms as the shape of the ring changes from one conformation to another. Our purpose will be to correlate the itinerary of the ^{19}F atoms through the various substituent sites with the spectral changes arising from exchange of the ^{19}F atoms among the different magnetic sites of the molecule. This analysis will greatly facilitate our understanding and interpretation of the nmr line-shape changes. It will be helpful to follow the ensuing discussion with molecular models of the Dreiding or Dreiding–Fieser type.

Modes of Interconversion. By analogy with cyclohexane, two families of cycloheptane conformations have been considered: the chair and the boat.[6a,8] Unlike cyclohexane where the chair represents a rigid conformation, both families of cycloheptane have a flexible character analogous to the family of boat conformations of cyclohexane. We will first consider the modes of interconversion within the boat and chair families and subsequently discuss the possible pathways for interconversion between the two families.

Out of the continuum of possible conformations in the chair family, Hendrickson[6a] has selected two symmetrical shapes: the chair (C, **2**), characterized by a plane of symmetry, and the twist chair (TC, **1**), having a twofold rotation axis. The latter conformation can be predicted to represent an energy minimum in this family by virtue of the fact that twisting C relieves torsional strain across the 4–4′ bond and nonbonded H···H interactions between the 3a–3′a positions. Analogous to the C_s (envelope) and C_2 (half-chair) conformations of cyclopentane,[9] the C and TC conformations of cycloheptane can undergo rapid equilibration *via* pseudorotation. During this process TC passes through C (representing the maximum in the energy profile), and then back into enantiomeric TC with the C_2 axis moved over one carbon atom. The complete pseudorotation cycle requires passing through 14 TC and 14 C forms. For our purposes it will be sufficient to examine the pseudorotation itinerary of a substituent in the TC forms, since these are expected to represent possible energy minima which can be detected spectroscopically. The pseudorotation itinerary is the sequence of positions that a substituent atom on the ring successively occupies during the pseudorotation process. The itinerary for 1,1-difluorocycloheptane is summarized in Figure 3 with both perspective drawings and shorthand notation.

By analogy to the chair family, Hendrickson[6a] has selected two symmetrical shapes in the higher energy boat family: the boat (B, **4**) and the twist boat (TB, **3**). The latter conformation occupies the energy minimum

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[1] (a) Work supported by the National Science Foundation. (b) Presented in part at the 19th National Organic Chemistry Symposium of the American Chemical Society, Tempe, Arizona, June 17, 1965.

[2] J. D. Roberts, *Chem. Brit.*, 529 (1966).

[3] G. Binsch, *Top. Stereochem.*, 3, 97 (1968).

[4] For an example of this method as applied to cyclooctane derivatives see J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, and J. D. Roberts, *J. Amer. Chem. Soc.*, 91, 1386 (1969).

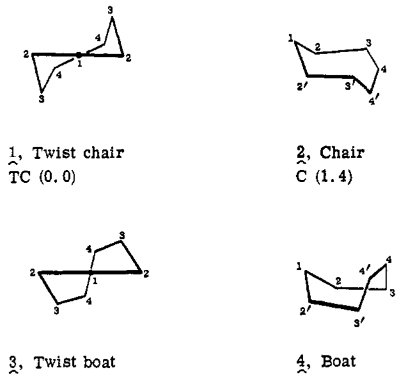
[5] (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 209; (b) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965; (c) R. Knorr, C. Ganter, and J. D. Roberts, *Angew. Chem., Int. Ed. Engl.*, 6, 557 (1967).

[6] (a) J. B. Hendrickson, *J. Amer. Chem. Soc.*, 83, 4537 (1961); (b) *ibid.*, 89, 7036 (1967); (c) *ibid.*, 89, 7043 (1967); (d) *ibid.*, 89, 7047 (1967).

[7] G. Favini, G. Buemi, and M. Raimondi, *J. Mol. Struct.*, 2, 137 (1968).

[8] E. Mohr, *J. Prakt. Chem.*, [2] 103, 316 (1922).

[9] (a) K. S. Pitzer and W. E. Donath, *J. Amer. Chem. Soc.*, 81, 3213 (1959); (b) F. V. Brutcher, T. Roberts, S. J. Bair, and N. J. Pearson, *ibid.*, 81, 4915 (1959).



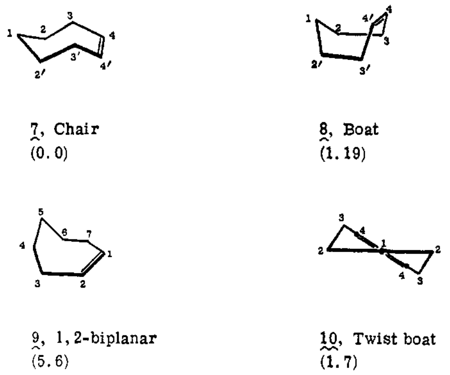
1, Twist chair
TC (0.0)

2, Chair
C (1.4)

3, Twist boat
TB (2.4)

4, Boat
B (2.7)

Figure 1. Conformations of cycloheptane. The numerical figures are for calculated energies in kcal/mol, relative to the TC conformation.



7, Chair
(0.0)

8, Boat
(1.19)

9, 1,2-biplanar
(5.6)

10, Twist boat
(1.7)

Figure 2. Conformations of cycloheptene. The numerical figures are for calculated energies in kcal/mol relative to the chair conformation.

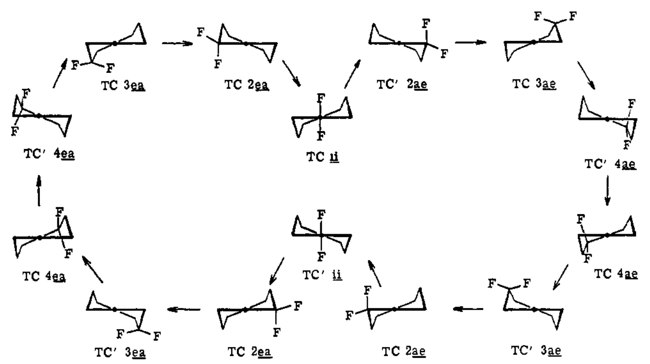


Figure 3. Pseudorotation itinerary for 1,1-difluorocycloheptane. The perspective drawings depict the clockwise movement of the C_2 axis around the ring. The shorthand notation represents the atom positions for the ^{19}F atoms on the TC conformations. Primes refer to mirror images. Substituent positions are labeled: i = isoclinal, e = equatorial, a = axial; the change from the designation ea to ae for the fluorines is inversion.

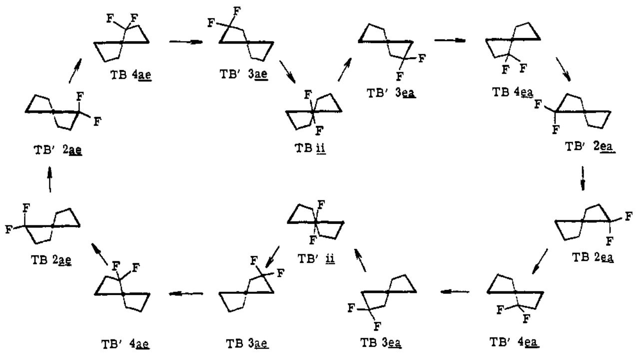
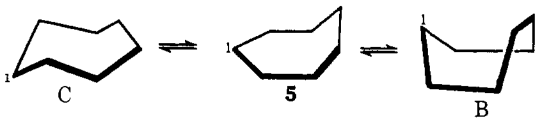


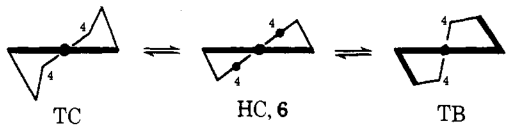
Figure 4. Pseudorotation itinerary for 1,1-difluorocycloheptane. The perspective drawings depict the clockwise movement of the C_2 axis around the ring. The shorthand notation represents the atom positions for the ^{19}F atoms on the TB conformations. Primes refer to mirror images.

in this family due to relief of torsional strain and improved nonbonded H···H interactions compared with B. As in the chair family, TB and B are capable of undergoing rapid pseudorotation with a low-energy barrier. During this process the C_2 axis in TB can be visualized as rotating, changing momentarily into a symmetry plane in B, and then reappearing in TB′, having moved over two carbon atoms. The complete pseudorotation cycle requires passing through 14 TB and 14 B forms. Since the TB conformations represent energy minima in this family, we will consider only the 14 TB forms in our consideration of the pseudorotation itinerary of 1,1-difluorocycloheptane shown in Figure 4.

In addition to the above pseudorotation processes within each family, there are several possibilities for interconversion between the chair and boat families. By analogy to ring inversion processes in cyclohexane, two pathways can be visualized. One model starting from C involves a methylene flip of C-1 through a form having five carbons in one plane (**5**). A better model



proceeds through an intermediate form having only four carbons in a plane. Starting from TC this pathway involves rotation of the 4–4 bond to the half-chair (HC, **6**). Further rotation maintaining the C_2 axis



throughout these changes leads directly into TB. Since the TC and TB represent energy minima and HC is a better model for transition between families than **5**, the latter interconversion would be expected to be a lower energy process (calcd, 8.1 kcal/mol[6a]). We are primarily concerned here with the sequence of atom changes during this inversion process (TC ⇌ TB) as shown below.

$$1\ \mathrm{ii} \rightleftharpoons 1\ \mathrm{ii}$$
$$2\ \mathrm{ea} \rightleftharpoons 2\ \mathrm{ea}$$
$$3\ \mathrm{ea} \rightleftharpoons 3\ \mathrm{ea}$$
$$4\ \mathrm{ea} \rightleftharpoons 4\ \mathrm{ae}$$
$$\mathrm{TC} \rightleftharpoons \mathrm{TB}$$

During this interconversion the atom sequence remains unchanged except for an exchange of equatorial–axial atoms in the 4-positions.

The effect of substituents on a cycloheptane ring is more complex than in cyclohexane where there are only

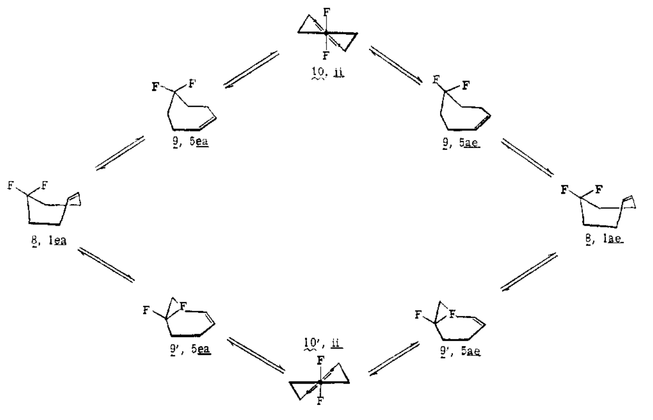
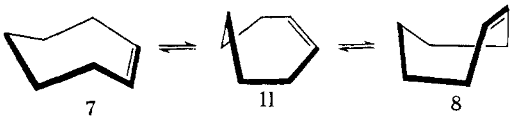


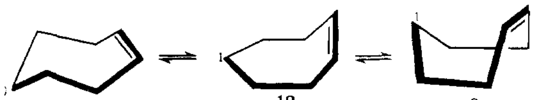
Figure 5. Pseudorotation itinerary of the boat family of 1,1-difluorocycloheptene. Primes refer to mirror images. The shorthand notation refers to the ^{19}F atom positions of each conformation as designated in Figure 2. The change from ea to ae for **8**, **9**, and **9'** involves inversion of the fluorine positions.

two kinds of distinguishable sites. In cycloheptane there are seven different substituent positions on both of the conformations of interest, TC and TB. These sites fall roughly into three classes: axial, equatorial, and isoclinal[10] (sites on the axis carbon atom). Calculations[6c] of the effects of methyl substitution indicate that, just as in cyclohexane, all equatorial positions are essentially free from strain; moreover, the isoclinal sites in TC and TB are nearly energetically equivalent to the equatorial positions. The fact that the isoclinal positions are free from strain leads to the important consequence that a *gem*-dimethylcycloheptane would be expected to prefer the twist-chair conformation with the methyls on the axis carbon atom. The axial positions are more crowded than those in cyclohexane except for the 3a position of TB (which is nearly strain free) and the 4a position of TC (which resembles an axial site in cyclohexane and is the least strained axial position on TC). Particularly severe interactions in the 3a positions of TC and C are expected to result in high strain energies for methyl substitution at these locations. Consequently, the pseudorotation barrier in methylcycloheptane would be determined by the energy of the C 3a-methyl conformation (calcd, 5.8 kcal/mol[6c]) which is much larger than the pseudorotation barrier of 1.4 kcal/mol for the unsubstituted molecule. Thus, for substituted cycloheptanes, pseudorotation should become more difficult as the substituent passes through the 3a position of C. However, as we will show later in more detail, the molecule can avoid getting stuck at this point in the itinerary by flipping over to the boat family (TC $\rightleftharpoons$ TB), pseudorotating among the boat forms (TB $\rightleftharpoons$ B $\rightleftharpoons$ TB'), and then flipping back into the chair family.

As for cycloheptane, there are two families of cycloheptene conformations: the chair and the boat. The chair family contains the plane symmetrical chair (**7**) which is relatively rigid and cannot undergo pseudorotation. In the boat family, three symmetrical shapes have been considered:[7] the plane symmetrical boat (**8**), the twist boat (**10**) having a C_2 axis and similar in shape to HC (**6**) cycloheptane, and the 1,2-biplanar form (**9**) in which carbon atoms 1, 2, 3, 6, and 7 are in the same plane (Figure 2). The forms **9** and **10** are intermediate in the pseudorotation itinerary from one boat (**8**) to another boat conformation. The 1,2-biplanar form (**9**) represents the height of the energy profile for pseudorotation (calcd, 4.41 kcal/mol[7]). The pseudorotation itinerary of 5,5-difluorocycloheptene is depicted in Figure 5.

The chair (**7**) is calculated to represent the minimum-energy conformation of cycloheptene.[7] In order for equilibration of substituent atoms to occur, the chair must undergo ring inversion to the boat family, pseudorotate among the boat forms, and then return to the chair. Two possible modes of interconversion can be envisioned. One mode involves wagging of the C=C through a form having six coplanar carbon atoms (**11**) into the boat form (**8**).[11] Another possibility involves wagging of C-1 through an intermediate having five carbon atoms in one plane (**12**) directly into the boat (**8**). This interconversion (analogous to C $\rightleftharpoons$ B cycloheptane) would be expected to be a lower energy process than the one proceeding through **11**.


7 11 8



7 12 8

Experimental Results

At ambient temperature, the fmr spectrum of 1,1-difluorocycloheptane (**13**) is a quintet in propene as solvent, with $^3J_{HF}$ = 15.5 Hz. On cooling the sample to −170°, no further spectral changes were observed other than general broadening due to increased viscosity and magnetic field inhomogeneity. $^3J_{HF}$ remained constant throughout the temperatures recorded.

At ambient temperature, the fmr spectrum of 1,1,3,3-tetrafluorocycloheptane (**14**) is a quintet 3730 Hz upfield from $BrCF_3$ in 15% $BrCF_3$-propene (1:2), with $^3J_{HF}$ = 14.5 Hz. Under double irradiation at the proton resonance frequency, a single sharp signal is observed which shows no further spectral changes down to −150°.

At ambient temperature, the fmr of 4,4-difluoro-1,1-dimethylcycloheptane (**15**) is a quintet in propene as solvent with $^3J_{HF}$ = 15.1 Hz. With ^1H double irradiation, a single sharp signal is observed which broadens below −150° and splits into an AB spectrum. The rates of AB exchange as a function of temperature were determined by comparison of theoretical spectra calculated as a function of τ, the mean lifetime before exchange, in the usual way.[2,12] Below −163°, the chemical shift difference of the AB quartet remained constant at 841 Hz with J_{AB} = 237 Hz. The free energy of activation ($\Delta G^{\ddagger}$) for the exchange process is approximately 5.0 kcal/mol at −150°; the average entropy of activation is −0.5 eu; and E_a, the Arrhenius activation energy, is 5.2 kcal/mol. The upfield doublet

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(10) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **86**, 4854 (1964).

(11) E. A. Noe, Ph.D. Thesis, California Institute of Technology, 1970; see also, E. Noe and J. D. Roberts, *J. Amer. Chem. Soc.*, **94**, 2020 (1972).

(12) J. T. Gerig and J. D. Roberts, *ibid.*, **88**, 2791 (1966).

has a line width about twice as large as the downfield ones and is assigned to the axial fluorines.[13]

At ambient temperature, the fmr spectrum of 1,1-difluoro-*trans*-4,5-dibromocycloheptane (**16**) in dimethyl ether (15%) is a single line under double irradiation. This resonance broadens and splits below −114° into two single lines (in the intensity ratio 74:26) at 348 Hz (ν_a), 550 Hz (ν_b) upfield from internal trifluoroacetic anhydride. The equilibrium ratio (b/a = 0.35) was found to be temperature independent (the center of the signal remaining constant at 400 Hz) from +25 to −126° in the same way as has been reported for 1,2-*trans*-dibromocyclohexane.[14] The rates of exchange between −77 and −126° were calculated as above.[11] At the coalescence point, −114°, the free energies of activation are $\Delta G^{\ddagger}_{a \rightarrow b} = 7.5$ kcal/mol and $\Delta G^{\ddagger}_{b \rightarrow a} =$ 7.2 kcal/mol. The parameters of activation for the process a → b between −77 and −126° are: $E_a =$ 10.1 (±0.7) kcal/mol, $\Delta H^{\ddagger} = 9.8$ (±0.7) kcal/mol, $\Delta S^{\ddagger}$ = 14.1 (±4) eu. For the process b → a: $E_a = 10.1$ (±0.7) kcal/mol, $\Delta H^{\ddagger} = 9.8$ (±0.7) kcal/mol, $\Delta S^{\ddagger}$ = 16.3 (±4) eu.

At ambient temperature the fmr spectrum of 5,5-difluorocycloheptene (**17**) is a single line (under double irradiation) in a 10% solution of propene–$BrCF_3$, 4080 Hz from internal $BrCF_3$. The single line broadens and splits below −92° into an AB spectrum. The rates of exchange between −44 and −147° were calculated as above.[11] Below −115°, the chemical-shift difference of the AB quartet remained constant at 1602 Hz with J_{AB} = 248 Hz. The upfield doublet is more strongly coupled to the adjacent protons than the downfield ones and is, therefore, assigned to the axial fluorines.[13] The free energy of activation ($\Delta G^{\ddagger}$) for the exchange process is 7.45 kcal/mol at the coalescence temperature, −92°. Activation parameters are: E_a = 7.7 (±0.4) kcal/mol, $\Delta S^{\ddagger}$ = 0.2 (±2) eu.

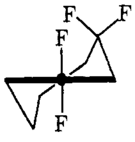
At ambient temperature, the fmr spectrum of 4,4-difluoro-1-*tert*-butylcycloheptane (**18**) is a complicated pattern in propene–Cl_2CF_2 (2:1). With proton double irradiation, an AB spectrum (ν_A = 4470 Hz, ν_B = 4650 Hz upfield from Cl_2CF_2, J_{AB} = 241 Hz) is observed with a chemical-shift difference of 180 Hz. At −125° the chemical-shift difference increases to 420 Hz (ν_A = 4330 Hz, ν_B = 4750 Hz). The upfield lines are about twice as broad as the downfield ones and are, therefore, assigned to the axial fluorine atoms.[12]

Discussion

We will consider the changes (or nonchanges) in the fmr spectrum for each substance described in the Experimental Section and attempt to correlate the spectral results with the conformational equilibrations discussed earlier.

That the spectrum of **13** exhibits no change with temperature down to −170° is consistent with a rapid process having an activation energy of less than 5 kcal/mol. Pseudorotation among the TC conformations is undoubtedly responsible for the rapid exchange process at low temperature, although ring inversion may also be occurring at intermediate temperature because both processes will average the ^{19}F chemical shifts exactly. The low activation energy is consistent with the strain-energy calculations[6] and also indicates that introduction of ^{19}F atoms does not significantly alter the energetics of conformational equilibrations in cyclic molecules.[13,15]

In order to convincingly rule out the possibility that pseudorotation and inversion have been slowed at low temperature and that the absence of change in the spectrum simply reflects the existence of a single conformation in which the ^{19}F atoms occupy the axis carbon atom,[16] the fmr spectrum of **14** was examined. This molecule would be expected to prefer conformation **19** in which one pair of ^{19}F atoms would necessarily be nonequivalent and exhibit a large chemical-shift difference and the second pair would reside on the axis carbon atom and exhibit a small chemical-shift difference. Rapid exchange of the ^{19}F atoms at low temperature is consistent with pseudorotation in the chair family, although inversion cannot be rigorously ruled out.



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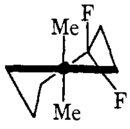
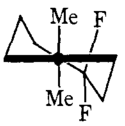
Examination of the low-temperature fmr spectrum of **15** afforded the first case of slow conformational equilibration in the cycloheptane series. A single AB pattern with a large chemical shift (ν_{AB} = 841 Hz) is consistent with conformations **20** and **21** with the methyl groups occupying the axis carbon atom as predicted by Hendrickson.[18] The AB pattern is similar in magnitude to 1,1-difluorocyclohexane (ν_{AB} = 884 Hz)[13] with the upfield doublet characteristic of an axial ^{19}F atom.



20, TC ii 4ea[17]



21, TC′ ii 4ae

The detailed itinerary of **15** depicting pseudorotation among the 14 TC forms and also indicating the possibilities for inversion to the boat family is shown in Scheme I. The maximum in the energy profile for pseudorotation in the chair family is expected to be represented by the [C3′ ae 3ae]‡ conformation. At this point along the itinerary, a serious 3a-methyl–3′a-fluorine interaction is experienced. Alternatively, the molecule can undergo inversion to TB, followed by partial pseudorotation in the boat family and subsequent reinversion to the TC forms at a different point along the itinerary. We are not able experimentally or otherwise to distinguish between these two possible

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(13) S. L. Spassov, D. L. Griffith, E. S. Glazer, K. Nagarajan, and J. D. Roberts, *ibid.*, **89**, 88 (1967).

(14) L. W. Reeves and K. O. Strømme, *Trans. Faraday Soc.*, **57**, 390 (1961).

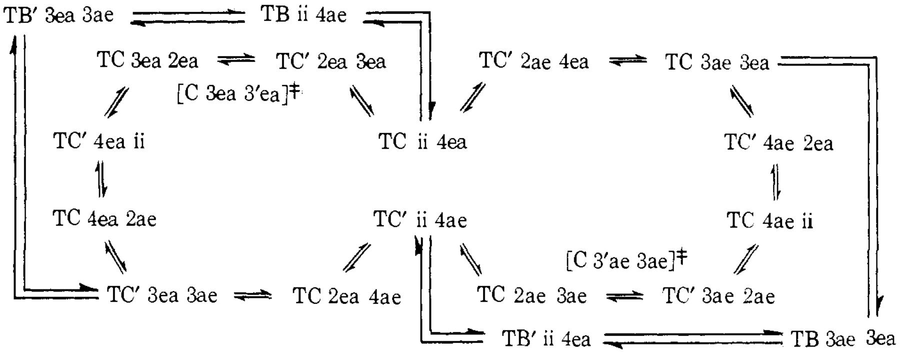
(15) However, this is not always the case in more highly substituted molecules, as in 3,3,5,5-tetramethyl-1,1-difluorocyclohexane; see D. Doddrell, C. Charrier, B. L. Hawkins, W. O. Crain, Jr., L. Harris, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, 67, 1588 (1970).

(16) An additional argument against this possibility is the fact that a change from the normal binomial quintet, $AA'(XX')_2$, which is characteristic of rapidly equilibrating *gem*-fluorocycloalkanes, to a more complicated pattern, $AA'X_2Y_2$, would be expected at slow exchange.

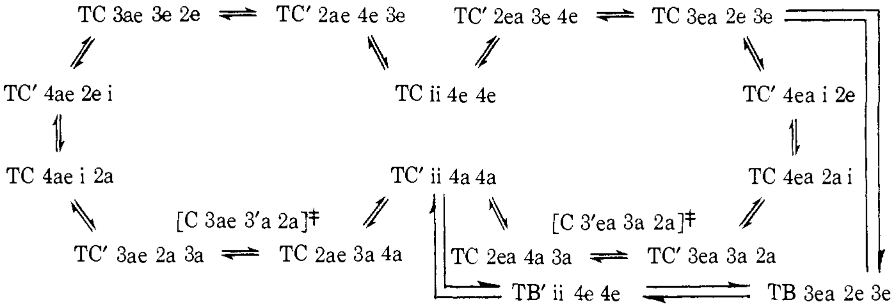
(17) This shorthand notation designates that the methyls are in the isoclinal positions (ii) and the fluorine atoms are in the 4 equatorial and 4 axial positions (4 ea) on the TC conformation.

(18) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **84**, 3358 (1962).

Scheme I

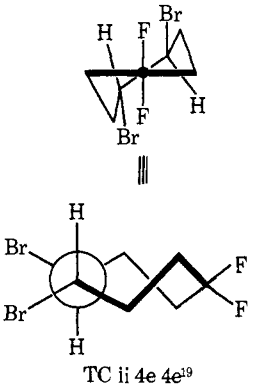


Scheme II

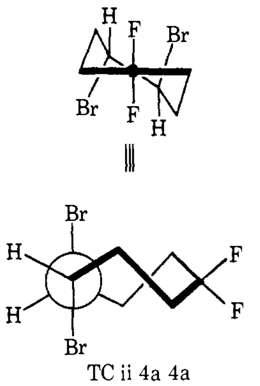


modes of equilibration. Examination of the conformational possibilities in the flow chart (Scheme I) indicates that in addition to the TC ii 4ea and TC′ ii 4ae forms, the other possible conformations which might represent energy minima in the chair family are the TC 4ae ii and TC′ 4ea ii forms. Although these conformations have an axial methyl group in the 4-position, the ^{19}F atoms occupy the favorable isoclinal position. Experimentally these conformations (an AB pattern with a small chemical shift would be expected) are not observed indicating the free energies of these forms is at least 1 kcal/mol (at −160°) higher than the free energies of the observed conformation.

The changes in the fmr spectrum of **16** from a single line to two single lines (under double irradiation) is best explained as arising from TC conformations **22** and **23**



TC ii 4e 4e[19]
22



TC ii 4a 4a
23

in which the ^{19}F atoms occupy the axis carbon atoms and the bromines are in the diequatorial or diaxial positions, respectively. The detailed itinerary of **16** depicting pseudorotation among the 14 TC forms and also indicating the possibilities for inversion to the boat family is shown in Scheme II.

The maximum in the energy profile for pseudorotation in the chair family is likely to best be represented by the [C3′ ea 3a 2a] conformation in which a serious 3a-bromine–3′a-fluorine interaction is present. Alternatively, the molecule can undergo inversion starting from the diaxial conformation to TB′ ii 4e 4e, pseudorotate to TB 3ea 2e 3e and undergo a reinversion to TC 3ea 2e 3e, thereby avoiding the high-energy conformations having axial bromines in the chair family. We are not able to distinguish between these two possible modes of equilibration experimentally or otherwise. Examination of the conformational possibilities in Scheme II indicates that the TC′ ii 4a 4a form is essentially rigid at low temperature because pseudorotation among the TC conformations would seriously aggravate the axial bromine interactions in the inside positions of the ring. However, the TC ii 4e 4e form is a flexible conformation and can pseudorotate among 6 TC conformations having equatorial bromines at little cost of energy. The conformations TC′ 4ea i 2e and TC′ 4ae 2e i are the best possibilities for energy minima among these forms. The fact that a fluorine atom is in the 4a-position in both forms should raise the free energies of these conformations by only a few tenths of a kcal/mol compared with TC ii 4e 4e where the fluorines are on the favorable isoclinal position. Thus, one of the observed singlets would be expected to correspond to an equilibrating mixture of several conformations with the predominant form being TC ii 4e 4e.

The room-temperature spectrum of **18** (AB pattern, ν_{AB} = 180 Hz) can be accounted for by two possibilities. (1) The molecule exists predominantly in the form TC ii 4e, the fluorines being nonequivalent by virtue of the presence of the *tert*-butyl group in the 4-equatorial position. (2) The molecule is a rapidly equilibrating mixture of the following conformations having the *tert*-butyl group in the equatorial or iso-

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[19] This shorthand notation labels the positions of the ^{19}F atoms first and proceeding clockwise around the ring labels the positions of the two bromine atoms.

clinal position (the encircled conformations represent energy minima in this itinerary)

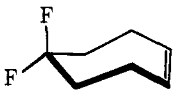
$$\boxed{\text{TC}'\text{ 4ea i}} \rightleftharpoons \text{TC 3ea 2e} \rightleftharpoons \text{TC}'\text{ 2ea 3e} \rightleftharpoons$$

$$\boxed{\text{TC ii 4e}} \rightleftharpoons \text{TC}'\text{ 2ae 4e} \rightleftharpoons \text{TC 3ae 3e} \rightleftharpoons$$

$$\text{TC}'\text{ 4ae 2e} \rightleftharpoons \boxed{\text{TC 4ae i}}$$

The latter possibility is supported by the increase in the AB chemical shift at low temperature to 420 Hz. This increase indicates the presence of the forms TC 4ae i and TC′ 4ea i, in which the fluorines are expected to exhibit AB pattern with a large chemical-shift difference as in **15**.[20] At low temperature, **18** can be regarded as a dynamically equilibrating mixture of several TC conformations with TC ii 4e being predominant because of the conformation preference of the *gem*-fluoro for the isoclinal position.

The single AB pattern observed at low temperatures for **17** is consistent with the chair conformation **24**. The chemical-shift difference (ν_{AB} = 1602 Hz) is



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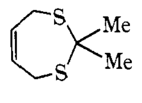
significantly larger in magnitude compared to **15** (ν_{AB} = 841 Hz); however, the upfield doublet has the broadened quality characteristic of axial ^{19}F atoms. Although we feel the single AB pattern is best interpreted in terms of **24**, we cannot rigorously rule out the boat form. A number of instances of the presence of both chair and boat conformations at low temperature have been reported for several benzocycloheptenes and for heterocyclic derivatives of cycloheptene and benzocycloheptene.[21] The two most noteworthy examples are **25**[22] and **26**;[23] however, these cases are not partic-



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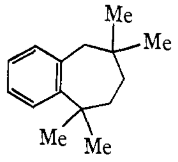

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ularly suitable for comparison with **24** because of the high degree of substitution.

The higher activation energy for **17** ($\Delta G^{\ddagger}$ = 7.45 kcal/mol) compared to the saturated molecule ($\Delta G^{\ddagger} <$ 5 kcal/mol) reflects the increased rigidity of the seven-membered ring by incorporation of a double bond. This behavior is the reverse of that observed in the six-membered ring in which the conformational mobility of cyclohexane ($\Delta G^{\ddagger} \cong$ 10 kcal/mol)[24] is less than that of cyclohexane ($\Delta G^{\ddagger}$ = 5.3 kcal/mol).[25] As no pseudorotation is possible in the chair, inversion to the boat, followed by pseudorotation among the boat forms and subsequent reinversion to the chair, are necessary for equilibration of the axial and equatorial ^{19}F atoms in **24**. These modes of interconversion are shown below with the substituent position representing the ^{19}F atoms.

$$\underset{\mathbf{7}}{\text{chair(1ea)}} \rightleftharpoons \underset{\mathbf{8}}{\text{boat(1ae)}} \rightleftharpoons \underset{\mathbf{9}}{\text{1,2-biplanar(5ae)}} \rightleftharpoons \underset{\mathbf{10}}{\text{twist boat(ii)}}$$

$$\rightleftharpoons \underset{\mathbf{9}}{\text{1,2-biplanar(5ea)}} \rightleftharpoons \underset{\mathbf{8}}{\text{boat(1ea)}} \rightleftharpoons \underset{\mathbf{7}}{\text{chair(1ae)}}$$

Pseudorotation among the boat forms is expected to be relatively facile (**9** is calculated to represent the height of energy profile for pseudorotation involving 4.41 kcal/mol[7]); consequently, chair–boat inversion is undoubtedly responsible for the higher activation energy observed.

It is worthwhile to compare our $\Delta G^{\ddagger}$ values obtained for difluorocycloheptane with the values observed for other difluorocycloalkanes (Table I). It is evident from this summary that the odd-membered cycloalkanes have significantly lower $\Delta G^{\ddagger}$ values than the even-membered ones, consistent with the more flexible character of the odd-membered rings; moreover, the latter become more mobile as the chain increases from cyclohexane to cyclodecane.

Table I. Conformational Equilibration for Difluorocycloalkanes

Compound	$\Delta G^{\ddagger}$, kcal/mol	^{19}F spectrum at low temperatures
1,1-Difluorocyclopentane	<5[a]	Unchanged at −155°
1,1-Difluorocyclohexane	9.7[b]	884 Hz at −80°
1,1-Difluorocycloheptane	<5	Unchanged at −170°
1,1-Difluorocyclooctane	7.5[c]	165 Hz at −120°
	4.9[c]	806 and 940 Hz at −170°
1,1-Difluorocyclononane	<5[d]	Unchanged at −150°
1,1-Difluorocyclodecane	5.7[e]	577 Hz at −160°

[a] R. Knorr, unpublished results. [b] Reference 13. [c] Reference 4. [d] E. S. Glazer, unpublished results. [e] Reference 11.

Our nmr results compare well with the strain-energy calculations of Hendrickson[6b] and confirm the TC conformation as the predominant form of cycloheptane in solution. This conclusion agrees with the conformation found in the crystalline state by X-ray crystallographic studies of dimeric cycloheptanone peroxide.[26]

A word of caution is necessary relative to applying results for substituted difluorocycloheptanes to their hydrogen analogs. The presence of a *gem*-fluoro group in **16** and **18** greatly simplifies the conformational picture as the ^{19}F atoms prefer the isoclinal positions. Consequently, the equilibrating mixture of conformations having the bulky group equatorial is predominantly composed of the conformation with the ^{19}F atoms residing on the axis carbon atom. This, of course, would not apply to the hydrogen analogs of **16** and **18**.

Experimental Section

The nmr spectra were recorded with a Varian A56/60A and a HA-60 spectrometer operating at 56.4 MHz for fluorine and 60.0

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[20] It is interesting that the opposite behavior has been observed for 4,4-difluoro-1-methylcycloheptane in which the chemical-shift difference changes from 125 to 92 Hz at −125°; see E. S. Glazer, Ph.D. Thesis, California Institute of Technology, 1966.

[21] For a thorough summary, see G. Binsch, *Top. Stereochem.*, **3**, 165 (1968).

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[23] E. Grunwald and E. Price, *J. Amer. Chem. Soc.*, 87, 3139 (1965).

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[25] F. A. L. Anet and M. Z. Haq, *J. Amer. Chem. Soc.*, 87, 3147 (1965).

[26] P. Groth, *Acta Chem. Scand.*, 18, 1801 (1964).

MHz for proton, both instruments being equipped with probes suitable for low-temperature work. Decoupling was accomplished with a Nuclear Magnetic Resonance Specialties Model SD-60 spin decoupler, monitored with a Hewlett-Packard Model 524L counter. The sample temperatures were measured with a calibrated copper–constantan thermocouple which was inserted inside the quartz dewar near the sample.

1,1-Difluorocycloheptane. Cycloheptanone (11.2 g, 0.1 mol) was treated with phenylsulfur trifluoride (16.6 g. 0.1 mol) in the manner used for the preparation of cyclooctanone[4] and yielded 2.2 g (16%) of the desired product with bp 44–46° (55 mm). The ir spectrum ($CHCl_3$) showed characteristic carbon–fluorine bands in the 1000–1400-cm^{-1} region. The pmr spectrum showed three broad bands at δ 1.0–2.0.

Anal. Calcd for $C_7H_{12}F_2$: C, 62.65; H, 9.03; F, 28.32. Found: C, 62.41; H, 9.27; F, 28.27.

1,1,3,3-Tetrafluorocycloheptane. Cycloheptane-1,3-dione was prepared by ring enlargement[27] of the monoketal of cyclohexane-1,3-dione in an overall yield of 9%; ir (CCl_4) 1727, 1702 cm^{-1}; pmr 105–130 (multiplet, 4.5 H), 135–165 (multiplet, 4 H), 207 Hz (singlet, 1.6 H).

Cycloheptane-1,3-dione (5.05 g, 4.0 mmol) was treated with sulfur tetrafluoride (31 g, 0.285 mol) in the manner used for the preparation of 2,2-difluoro-*cis*-decalin[12] and yielded 1.82 g (27%) of crude product with bp 130–131°. Separation of the pure tetrafluoride from three side products by glc was successful on a SE-30 column (3 m) followed by a Ucon-Polar column (3 m, on Chromosorb) at 80°: mp 6–9°, n^{24}D 1.3818; ir (CCl_4) 2945, 2873, 1456 cm^{-1}; pmr 105 (multiplet, 4.4 H), 130 (multiplet, 4 H), 161 Hz (quintet, $J = 14.5$ Hz, 1.6 H).

Anal. Calcd for $C_7H_{10}F_4$: C, 49.41; H, 5.92; F, 44.67. Found: C, 49.38; H, 5.84; F, 44.67.

4,4-Difluoro-1,1-dimethylcycloheptane. Ring enlargement of 4,4-dimethylcyclohexanone[28] afforded 4,4-dimethylcycloheptanone in a yield of 45%; pmr δ 2.1–2.5 (multiplet), 1.3–1.7 (multiplet), 0.9 (singlet).

4,4-Dimethylcycloheptanone (10.0 g, 0.07 mol) was treated with 31 g of sulfur tetrafluoride (0.285 mol) by the same procedure as above and afforded 3.2 g (29%) of difluoride, bp 90–92° (30 mm). The ir spectrum ($CHCl_3$) showed characteristic carbon–fluorine bands in the 1000–4000 cm^{-1} region; pmr δ 1.2–2.3 (multiplet), 0.85 (singlet).

Anal. Calcd for $C_9H_{16}F_2$: C, 66.64; H, 9.93; F, 23.43. Found: C, 66.63; H, 9.93; F, 23.41.

4,4-Difluoro-1-*tert*-butylcycloheptane. Ring enlargement of 4-*tert*-butylcyclohexanone[29] afforded 4-*tert*-butylcycloheptanone in 85% yield; ir (CCl_4) 1705 cm^{-1}; pmr 54 (singlet, 8.6 H), 60–150 Hz (multiplet, 11.4 H).

4-*tert*-Butylcycloheptanone (1.78 g, 0.011 mol) was treated with 11.5 g of sulfur tetrafluoride (0.011 mol) by the same procedure as above and afforded 1.2 g (60%) of difluoride: ir (CCl_4) 2968, 2975 cm^{-1}: pmr 52 (singlet, 8.9 H), 65–150 Hz (multiplet, 11.1 H).

4-Cycloheptenone. To 4-cyclohepten-1-ol[30] (7.4 g, 0.066 mol) in 61 ml of pyridine was added in small portions a mixture of 13.5 g (0.135 mol) of chromium trioxide with 135 ml of pyridine. After the mixture was stirred for 4.5 days at room temperature, the reaction mixture was poured into ice water and extracted with chloroform. The resulting emulsion was then filtered through Celite and the chloroform layer was washed twice with water, six times with 2 *N* aqueous hydrochloric acid, once with water, once with saturated aqueous sodium bicarbonate solution, and three times with water. After removal of the solvent the brown oil was chromatographed on neutral alumina of activity II and the desired product was eluted with pentane in about 40% yield.

***trans*-4,5-Dibromocycloheptanone.** 4-Cycloheptenone (2.405 g, 0.0219 mol) and 0.50 g of calcium carbonate in 6 ml of carbon tetrachloride were cooled to −5°. Within 20 min, 25 ml (0.025 mol) of a 1 *N* solution of bromine in carbon tetrachloride was added to the stirred mixture. After immediate addition of 10 ml of 2 *N* sodium hydroxide, the carbon tetrachloride layer was separated, washed, and dried over sodium sulfate. Evaporation of the solvent yielded 5.69 g of partially crystalline material. Crystallization from cyclohexane with alumina afforded 1.62 g of product, mp 78–81°. The mother liquor after filtration through 5 g of Florisil gave an additional crop of 2.79 g. Total yield of product was 75%. Upon further recrystallization from cyclohexane, the melting point was 79–82°; ir (CCl_4) 2955, 2920, 2850, 1711 cm^{-1}; pmr 110–200 (multiplet, 8 H), 292 Hz (multiplet, 2 H).

Anal. Calcd for $C_7H_{10}Br_2O$: C, 31.14; H, 3.73. Found: C, 31.04; H, 3.92.

1,1-Difluoro-*trans*-4,5-dibromocycloheptane. *trans*-4,5-Dibromocycloheptanone (1.6 g, 0.006 mol) was treated with 6.5 g of sulfur tetrafluoride (0.06 mol) by the same procedure as above and afforded 1.74 g (99%) of difluoride, mp 52–54°; ir (CCl_4) 2955, 2920, 2855 cm^{-1}; pmr 100–180 Hz (multiplet, 7.9 H), ~280 Hz (multiplet, 2.1 H).

Anal. Calcd for $C_7H_{10}Br_2F_2$: C, 28.80; H, 3.45; F, 13.01. Found: C, 28.88; H, 3.42; F, 13.08.

5,5-Difluorocycloheptene. To a stirred mixture of 887 mg (3.04 mmol) of 1,1-difluoro-*trans*-4,5-dibromocycloheptane, 15 ml of anhydrous ether, and 4.5 ml of glacial acetic acid was added 0.5 g (7.6 mg-atoms) of zinc dust. After 15 min, the solution was filtered, washed with 2 *N* sodium hydroxide and water, dried over calcium chloride, and separated by vpc. The yield was 230 mg (57%) of pure 5,5-difluorocycloheptene (by glc).

Anal. Calcd for $C_7H_{10}F_2$: C, 63.62; H, 7.63; F, 28.76. Found: C, 63.66; H, 7.62; F, 28.84.

Calculations. Theoretical spectra were computed with the aid of programs devised by Drs. J. L. Beauchamp, G. M. Whitesides, J. T. Gerig, and F. J. Weigert based on the equations of Gutowsky and Holm[31] and the equations of Alexander.[32] The parameters used in the calculation include a chemical shift, a coupling constant a mean lifetime (τ), an "effective" relaxation (T_2), and the population for each nucleus in the system. The Arrhenius and Eyring parameters were obtained by the least-squares plot of $-\log \tau$ *vs.* $1/T$.

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