

Nuclear Magnetic Resonance Spectroscopy. Conformational Properties of Substituted 1,1-Difluorocyclohexanes¹

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Abstract: Rates of ring inversion and conformational equilibria of *gem*-fluorocyclohexanes carrying various substituents were determined by fluorine magnetic resonance spectroscopy. For 1,1-difluorocyclohexane, 1,1,2,2-tetrafluorocyclohexane, 4-methyl-4-ethyl-1,1-difluorocyclohexane, 4,4-dimethyl-1,1-difluorocyclohexane, and 4-chloro-1,1-difluorocyclohexane, the activation energies (E_a) for ring inversion were found to fall between 8.0 and 11.2 kcal/mole. For 4-chloro-1,1-difluorocyclohexane, the difference in free energy for the conformation with chlorine equatorial and the conformation with chlorine axial was found to be -0.32 and -0.17 kcal/mole for solutions in propene and acetone, respectively, and practically independent of temperature. The corresponding free-energy difference for the conformations of 4-methyl-4-ethyl-1,1-difluorocyclohexane is -0.10 kcal/mole. With 3-methyl-, 4-methyl-, and 4-*t*-butyl-substituted 1,1-difluorocyclohexanes, the equilibria between the conformations is shifted so much in favor of one conformer that only qualitative conclusions could be drawn from the fluorine magnetic resonance spectra.

The utility of high-resolution nuclear magnetic resonance spectroscopy for investigation of conformational equilibria and rates of ring inversion in cyclohexane and substituted cyclohexanes is well known.³⁻⁷ Spin-echo techniques have also proved valuable for measuring inversion rates of cyclohexane derivatives.⁸ The changes in the nmr spectra which are used to measure the rates of ring inversion of cyclohexanes can usually be detected without much difficulty since the spectra usually cease undergoing change at or below about -80° , which often is not the case for larger and/or unsaturated rings. Nevertheless, it is frequently difficult to obtain accurate results from proton resonance studies because chemical-shift difference between the equatorial and axial protons is normally small (about 0.5 ppm for cyclohexane⁵) and the spectra are rendered complex by the spin-spin splitting possible for multiproton systems. This last difficulty can usually be alleviated by massive deuteration and decoupling of the deuterium.⁷

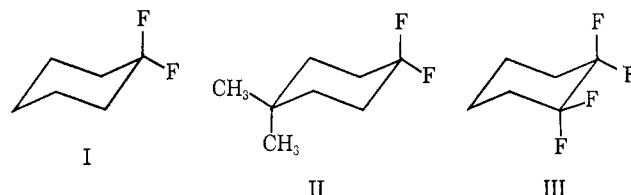
It is usually possible to work with much larger chemical shifts by replacing one or more of the hydro-

gens on a cyclic system by fluorine atoms and studying the fluorine magnetic resonance spectra. This "fluorine-labeling" technique has been already used for determination of the rate of ring inversion of 1,1-difluorocyclohexane^{9,10} and cyclohexyl fluoride,¹¹ as well as other types of cyclic compounds.¹²

In the present study, fluorine magnetic resonance spectroscopy was used for studying the position of rate of establishment of conformational equilibria of 1,1-difluorocyclohexane carrying various (mainly alkyl) substituents. Along with these, there was an additional point of interest regarding the dependence of the fluorine chemical shifts on the nature of the ring substituents.^{12c,d}

Results

Some Cyclohexanes for Which Inversion Rates Could Be Measured. At 35° , the fluorine resonances of 1,1-difluorocyclohexane¹³ (I), 4,4-dimethyl-1,1-difluorocyclohexane (II), and 1,1,2,2-tetrafluorocyclohexane



(9) K. Nagarajan and J. D. Roberts, unpublished; see *Angew. Chem.*, **75**, 20 (1963); *Angew. Chem. Intern. Ed. Engl.*, **2**, 53 (1963).

(10) J. Jonas, A. Allerhand, and H. S. Gutowsky, *J. Chem. Phys.*, **42**, 3396 (1965).

(11) F. A. Bovey, E. W. Anderson, F. P. Hood, and R. L. Kornegay, *ibid.*, **40**, 3099 (1964).

(12) (a) Cyclobutanes: J. B. Lambert and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 3884 (1965); (b) cycloheptanes and cyclooctanes: E. S. Glazer and J. D. Roberts, results presented at the 19th National Organic Symposium of the American Chemical Society, Tempe, Ariz., June 1965; E. S. Glazer, Ph.D. Thesis, California Institute of Technology, March 1966; (c) *cis*-decalins: J. T. C. Gerig and J. D. Roberts, *J. Am. Chem. Soc.*, **88**, 2791 (1966); (d) J. D. Roberts, *Chem. Brit.*, in press.

(13) 1,1-Difluorocyclohexane was reinvestigated so that its inversion rate could be compared under the same conditions (solvent and internal standard) as the other compounds studied and also because of the lack of consistency between results of earlier determinations of E_a for ring inversion.^{9,10}

(1) Supported in part by the National Science Foundation.

(2) On leave of absence from the Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia.

(3) For recent reviews, see H. Feltkamp and N. C. Franklin, *Angew. Chem.*, **77**, 798 (1965); *Angew. Chem. Intern. Ed., Engl.*, **4**, 774 (1965).

(4) E. L. Eliel, *Angew. Chem.*, **77**, 784 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965).

(5) (a) F. R. Jensen, D. S. Noyce, C. H. Sederholm, and A. J. Berlin, *J. Am. Chem. Soc.*, **82**, 1256 (1960); **84**, 386 (1961); (b) R. K. Harris and N. Sheppard, *Proc. Chem. Soc.*, 418 (1961); (c) W. B. Moniz and J. A. Dixon, *J. Am. Chem. Soc.*, **83**, 1671 (1961).

(6) (a) A. J. Berlin and F. R. Jensen, *Chem. Ind. (London)*, 998 (1960); (b) L. W. Reeves and K. O. Strømme, *Trans. Faraday Soc.*, **57**, 390 (1961); *Can. J. Chem.*, **38**, 1241 (1960); (c) S. Brownstein, *ibid.*, **40**, 870 (1962); (d) N. Muller and W. C. Tosch, *J. Chem. Phys.*, **37**, 1167 (1962); (e) N. O. Brace, *J. Am. Chem. Soc.*, **86**, 665 (1964).

(7) (a) F. A. L. Anet, M. Ahmad, and L. D. Hall, *Proc. Chem. Soc.*, 145 (1964); F. A. L. Anet and M. Z. Haq, *J. Am. Chem. Soc.*, **87**, 3147 (1965); (b) F. A. Bovey, F. P. Hood, E. W. Anderson, and R. L. Kornegay, *Proc. Chem. Soc.*, 146 (1964); *J. Chem. Phys.*, **41**, 2041 (1964).

(8) (a) S. Meiboom, results presented at the Symposium on High-Resolution Nuclear Magnetic Resonance, Boulder, Colorado, July 1962; (b) A. Allerhand, F.-M. Chen, and H. S. Gutowsky, *J. Chem. Phys.*, **42**, 3040 (1965); (c) A. Allerhand and H. S. Gutowsky, *ibid.*, **42**, 4203 (1965).

Table I. Fluorine Magnetic Resonance and Kinetic Parameters for Exchanging Cyclohexanes

Compound	Chemical shift, cps ^{a, b} Eq	Chemical shift, cps ^{a, b} Ax	J_{AB} , cps ^b	Coal. temp, °C	E_a , kcal ^c	$\log A$, sec ⁻¹	ΔF^* , kcal ^d	ΔH^* , kcal ^d	ΔS^* , eu ^d
1,1-Difluorocyclohexane (I) ^e	638	1522	237	-46	10.9 ± 0.4 ^f	13.8 ± 0.4 ^f	9.71	10.43	3.0 ± 2 ^f
4,4-Dimethyl-1,1-difluorocyclohexane (II) ^e	842	1496	235	-39	9.4 ± 0.5	12.0 ± 0.5	10.18	8.87	-5.4 ± 2
1,1,2,2-Tetrafluorocyclohexane (III) ^e	2562	2298	246	-29	8.0 ± 0.3	10.2 ± 0.3	10.87	7.51	-13.6 ± 2
4-Methyl-4-ethyl-1,1-difluorocyclohexane (IV) ^e									
Favored conformer	803	1509	235		8.4 ± 0.5	11.3 ± 0.5	9.84	7.92	-8.3 ± 2
Unfavored conformer	811	1453	235	-50	8.4 ± 0.5	11.3 ± 0.5	9.75	7.90	-8.0 ± 2
4-Chloro-1,1-difluorocyclohexane (V) ^h									
Favored conformer	767	1563	236		11.2 ± 0.3	13.7 ± 0.3	10.21	10.79	2.5 ± 1
Unfavored conformer	1025	1519	236	-38	10.7 ± 0.3	13.4 ± 0.2	9.90	10.21	1.4 ± 1

^a At 56.4 Mcps, upfield from trifluoroacetic acid (internal standard). ^b The uncertainty is 0.5%. ^c Eight to ten experimental points were used for each Arrhenius plot. ^d Average values for the temperature range investigated. ^e 1:3 v/v in propene. ^f Root-mean-square error. ^g 1:1 v/v in propene. ^h The same results were obtained (within the experimental error) for 1:1 v/v solutions in propene and acetone, except for the conformer ratio (see Table II).

(III) are binomial quintets (Figure 1a) which collapse to rather sharp singlets when the hydrogen couplings are eliminated by double irradiation. The failure to observe a chemical shift is of course consistent with fast ring inversion wherein the chemical shift difference of the equatorial and axial fluorines are averaged to zero by exchange of the fluorines between the two possible positions. The splitting in the quintets is the average of the couplings between the fluorines and the four adjacent protons and was found to be 12.0 cps for I,^{9,10} 13.2 cps for II, and 7.5 cps for III. The four fluorines in III are part of a potentially very complex $A_2A_2'X_2X_2'$ (or worse) system even under fast exchange conditions. We have not attempted to analyze this but have taken the observed splitting to be the mean value of the averaged vicinal H-F coupling (12-13 cps, as found for I and II) and the averaged CF_2-C-CH_2 coupling, which would then have to be about 3 cps. Many examples of such long-range, H-F coupling in saturated systems have been reported.¹⁴ It is both reasonable and likely that similar long-range couplings operate in I and II, especially for the fluorines when in the axial positions. However, the effect of these couplings on the averaged spectra is at most only large enough to broaden the component of the observed quintets

At lower temperatures, changes in the line shapes occur, an AB quartet finally resulting for the slow-inversion limit (Figure 1b and 2). As can be seen from the figures, the two halves of the quartet have different line shapes. This is the result of unequal couplings between the equatorial and axial fluorines and the neighboring protons. In accord with earlier studies of I^{9,10} and 2,2-difluoro-*cis*-decalins,^{12c} the doublet with sharper peaks was assigned to the equatorial fluorine and that with broader peaks to the axial fluorine. These assignments are made, assuming that a relationship similar to the Karplus relationship between dihedral angle and coupling constants for vicinal protons is also valid for vicinal proton-fluorine

couplings as suggested by studies on difluorocyclobutanes.¹⁵ The chemical shifts and geminal F-F couplings for the various compounds studied are summarized in Table I.

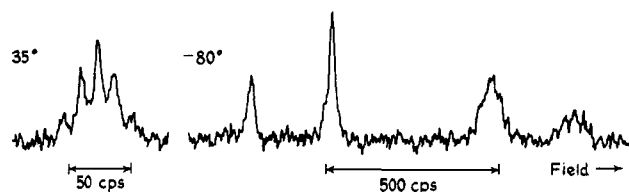


Figure 1. ¹⁹F nmr spectra of 4,4-dimethyl-1,1-difluorocyclohexane (1:3 v/v solution in propene) at 35 and -80°. The spectra were obtained at 56.4 Mc/sec, without H-F decoupling.

On the basis of peak broadness, the resonance peaks for the equatorial fluorine come at lower field and those for the axial fluorine at higher field (*cf.* Figure 1b) for all difluorocyclohexanes studied in the present work. The opposite is true, however, for III (Figure 2, bottom left) where, of course, there is also the possibility of vicinal $F_{eq}-F_{ax}$ coupling, which is expected to cause equal broadening in both the equatorial and axial parts of the spectrum. This is observed in the proton-decoupled spectrum of III, which is a symmetrical quartet with line widths of about 25 cps.¹⁶ Although no fine structure could be distinguished, this line width corresponds to the reported values of 10-20 cps for vicinal F-F coupling constants in substituted ethanes.¹⁷

The fluorine nmr spectra of 4-methyl-4-ethyl-1,1-difluorocyclohexane (IV) and 4-chloro-1,1-difluorocyclohexane (V) at 35° are basically AB quartets (Figure 3a and 4, top left) as expected for rapid interconversion of the two possible conformers with an equilibrium constant $\neq 1$ or $(\nu_{F_{ax}} - \nu_{F_{ax'}}) - (\nu_{F_{eq}} - \nu_{F_{eq'}}) \neq 0$. The spectra are complicated by H-F coupling. The

(15) J. B. Lambert and J. D. Roberts, *ibid.*, **87**, 3891 (1965).

(16) The line widths in the decoupled spectra of I and II were found to be 10 cps or less, depending on the resolution and effectiveness of decoupling.

(17) (a) H. S. Gutowsky, G. G. Belford, and P. E. McMahon, *J. Chem. Phys.*, **36**, 3353 (1962); (b) W. S. Brey, Jr., and K. C. Ramey, *ibid.*, **39**, 844 (1963).

(14) (a) R. E. Richards and T. Schaefer, *Trans. Faraday Soc.*, **54**, 1447 (1958); (b) J. Jonas and H. S. Gutowsky, *J. Chem. Phys.*, **42**, 140 (1965); (c) M. Takahashi, D. R. Davis, and J. D. Roberts, *J. Am. Chem. Soc.*, **84**, 2935 (1962); (d) A. D. Cross and P. W. Landis, *ibid.*, **84**, 1736 (1962), and later papers by Cross and co-workers.

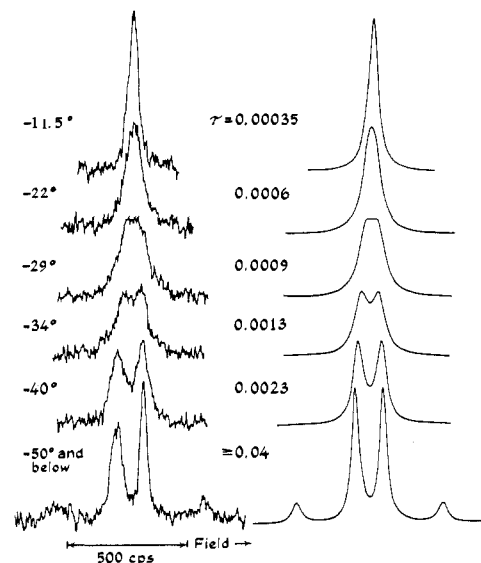
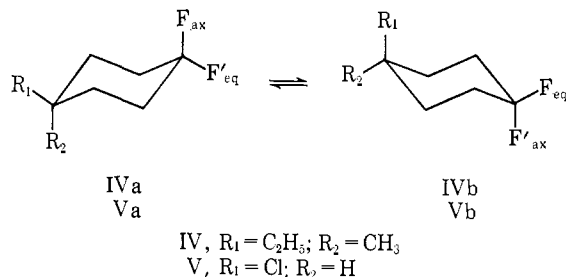


Figure 2. Experimental and calculated spectra of 1,1,2,2-tetrafluorocyclohexane (1:3 v/v solution in propene). The center of the spectra is 2430 cps upfield from trifluoroacetic acid (internal standard).

central peaks are clearly quintets, which partially overlap in the spectrum of IV (Figure 3a). The splitting observed in both spectra in the downfield quintets is about 11 cps, whereas in the upfield quintets it is about 13 cps. The outer peaks in the quartets also



have a complex structure, but these are not well resolved, the upfield ones being somewhat broader. With H-F decoupling the spectrum of IV changed to a symmetrical AB quartet.¹⁸ The origin of the complex spectra observed with IV at 35° is expected on the basis that the observed H-F couplings are average values and will be smaller, the more nearly equatorial the fluorines are on the average. The greater complexity of the outer peaks of the quartets compared to the inner peaks is a consequence of second-order effects when $J_{AB} \gtrsim \nu_{AB}$.

When the temperature is lowered, the AB pattern persists to about -30° (although the two central peaks in the spectrum of IV become coalesced into one quite broad peak). Below -30° the changes in line shape for IV very much resemble those found in the spectra of I-III. Somewhat different changes occur in the spectra of V, and those are shown in Figure 4.

The slow-exchange spectra of IV and V (below -75°) consist of two AB quartets, one for each conformer. This is not so readily observed in the uncoupled spectrum of IV, which looks like an AB quartet with

(18) No attempt was made to decouple the spectra of V.

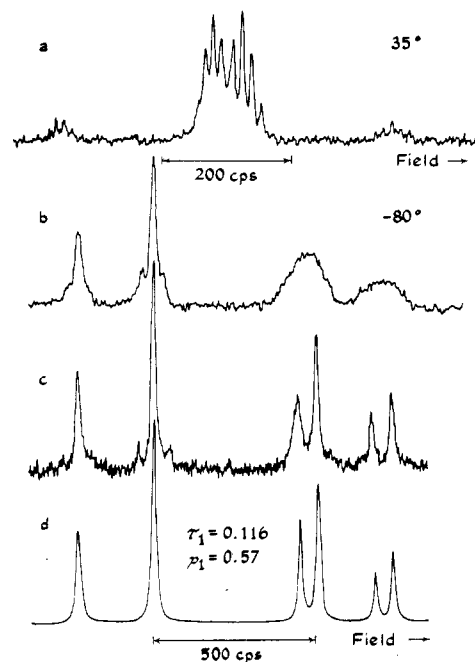


Figure 3. ¹⁹F nmr spectra of 4-methyl-4-ethyl-1,1-difluorocyclohexane (1:1 v/v solution in propene): (a) at 35° (no H-F decoupling, centered 1185 cps upfield from CF₃COOH); (b) at -80° (uncoupled); (c) at -80° (decoupled); (d) calculated. The last three are centered about 1140 cps upfield from CF₃COOH (internal standard).

very broad upfield part (Figure 3b). However, when the protons are irradiated, the broad peaks separate into two doublets (Figure 3c). The downfield peaks cannot be resolved in this way. There is also partial overlap of some of the peaks in the spectrum of V (Figure 4, bottom left), but the chemical shift and coupling parameters could still be easily obtained. The general correctness of the assignments was supported by the computed spectra.

Calculation of the theoretical spectra was performed by an IBM 7094 computer as a function of τ and/or the proportion of the possible conformers using FORTRAN IV coded programs based on the density-matrix equations of Alexander.¹⁹⁻²¹ The input for the programs included the chemical shifts and coupling constants for the equatorial and axial fluorines (as obtained from the slow-exchange spectra), the mole fractions p_i , and the mean life-times τ_i for each species, and also the "effective" relaxation time T_2 . The T_2 was adjusted so as to correspond to the experimental line width in the slow-exchange spectra, and the same value was used for calculations at intermediate temperatures.²²

The width and height of the computed curves could be adjusted along with the mole fractions and τ values

(19) S. Alexander, *J. Chem. Phys.*, **37**, 967, 974 (1962).

(20) G. M. Whitesides, Ph.D. Thesis, California Institute of Technology, 1964.

(21) The authors are indebted to Dr. J. T. C. Gerig and Mr. J. L. Beauchamp for making the computer programs available.

(22) The program for the intramolecular AB exchange, used for calculation of the spectra of compounds I-III, was written for only one T_2 , which was adjusted to the smaller line width of the equatorial fluorine (see Figure 2). This does not noticeably affect the accuracy of the results, since the computed spectra are relatively insensitive to small changes in T_2 in the intermediate range. With the second program, which applies to exchange between two AB systems (used for IV and V), different T_2 values for the equatorial and axial fluorines were used.

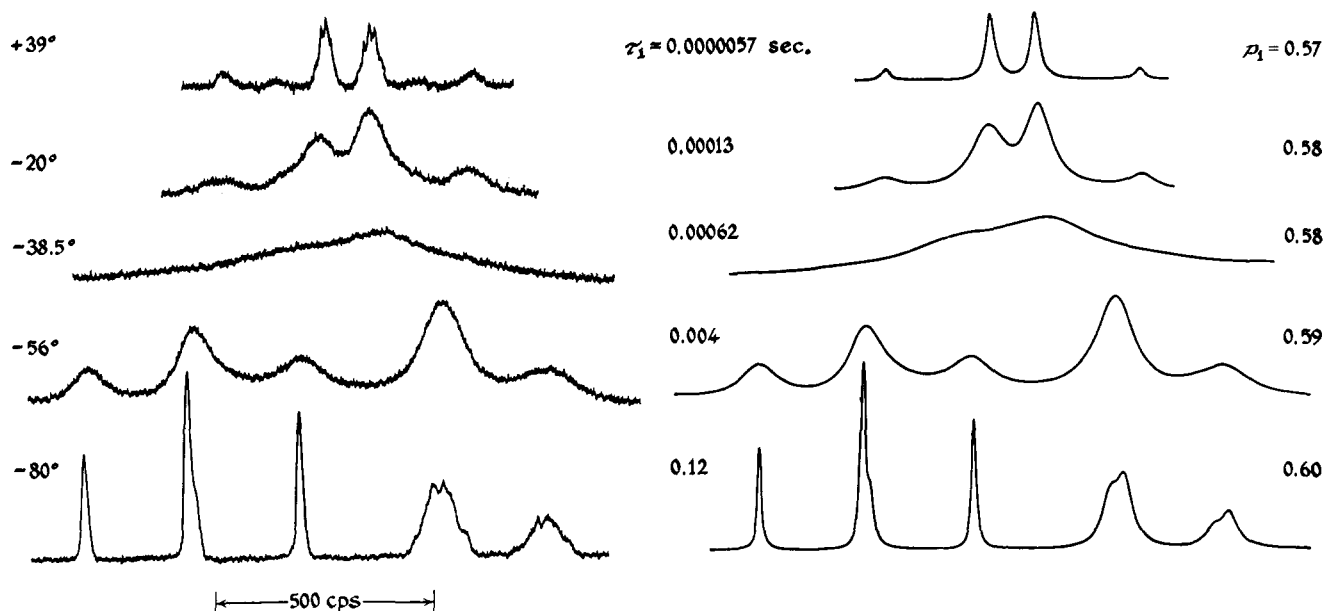


Figure 4. Experimental (left) and calculated (right) fluorine magnetic resonance spectra of 4-chloro-1,1-difluorocyclohexane. The experimental spectra are obtained at 56.4 Mc/sec in 1:1 v/v acetone solution and are centered about 1200 cps upfield from trifluoroacetic acid (internal standard).

until theoretical spectra superimposable with the experimental spectra were obtained. For IV and V, the mole fractions were initially estimated from the integrals of the corresponding peaks in the low-temperature spectrum and adjusted finally to conform to the computed spectra. The fast-exchange spectra are very sensitive to small changes in p_i and the relative proportions of the conformations at room temperature could be estimated quite accurately, assuming the chemical shifts of the separate conformers do not change appreciably with temperature (see below). In the intermediate range, the spectra are much less sensitive to small variations in p_i ; therefore interpolated values were used in this range. The proportions of the conformations and the corresponding free-energy differences for IV and V are summarized in Table II.

Table II. Conformational Equilibria for 4-Substituted 1,1-Difluorocyclohexanes

Compound	Solvent ^a	Temp, °C	% more stable conformer ^b	$-\Delta F^\circ$
4-Methyl-4-ethyl-1,1-difluorocyclohexane (IV)	Propene	25	54 ^c	0.10
		-75	57	0.11
4-Chloro-1,1-difluorocyclohexane (V)	Propene	25	63 ^d	0.32
		-75	70	0.33
	Acetone	25	57	0.17
		-75	60	0.16

^a 1:1 v/v. ^b Estimated accuracy $\pm 1\%$. ^c The same value was found for 1:1 v/v solutions in acetone and carbon tetrachloride and for neat liquid. ^d The same value was estimated for the neat liquid.

The Arrhenius parameters for ring inversion were obtained from least-squares fits to the variation of the logarithm of the rate constants $1/\tau$ with $1/T$. A typical plot is shown in Figure 5. The free energies, enthalpies,

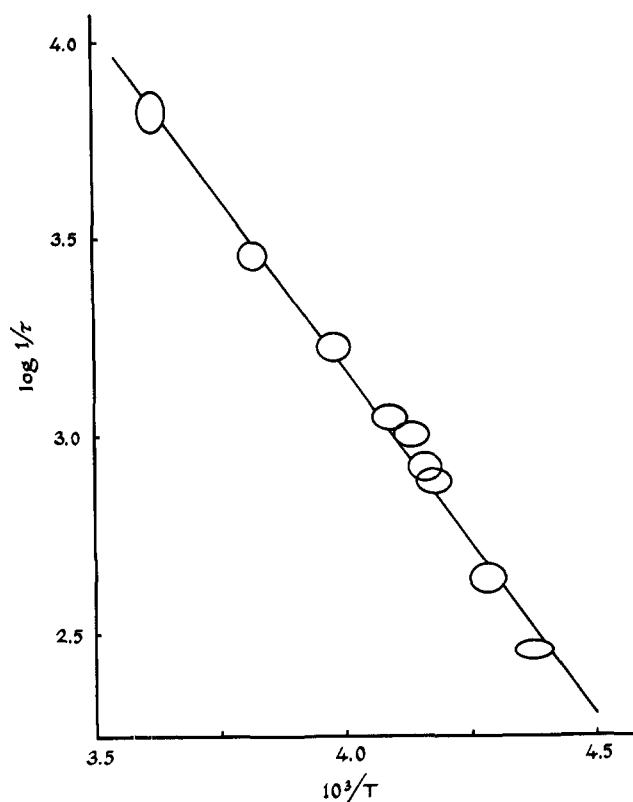


Figure 5. Arrhenius plot for 1,1,2,2-tetrafluorocyclohexane.

and entropies of activation were calculated in the usual way and the results, together with the nmr parameters, are presented in Table I.

Small but measurable changes of the positions of the fluorine resonances with the temperature were observed. Thus, for I and II, the average signal at room temperature was shifted upfield from the center of the low-temperature AB quartet 25 and 38 cps, respectively, which corresponds to a 2-3% increase in the

chemical shift (with respect to trifluoroacetic acid) for about a 100° increase in temperature. Similar upfield shifts of other fluorine resonances with increasing temperature have been reported for fluoroethanes.²³ No attempt was made to introduce corrections for these changes which may, in fact, be at least partly due to the standard and might well be similar for both the equatorial and axial fluorines. It is unlikely that the error in the equilibrium constants because of neglect of this factor is more than 2%.

Cyclohexanes for Which Inversion Rates Could Not Be Measured. Unlike compounds I–V discussed above, 3-methyl-1,1-difluorocyclohexane (VI), 4-methyl-1,1-difluorocyclohexane (VII), and 4-*t*-butyl-1,1-difluorocyclohexane (VIII) exhibit fluorine nmr spectra which do not change much from room to low temperature. The reason is the large conformational preference of the alkyl groups which makes the spectra correspond almost wholly to the conformer with equatorial alkyl group. The spectra are very similar in appearance to the slow-exchange spectra of I and II (*cf.* Figure 1b). When the temperature is decreased, only a small increase in the chemical-shift difference between the equatorial and axial fluorine occurs. The proton-decoupled spectra are symmetrical AB quartets with line widths equal to that of the internal standard (trifluoroacetic acid). Data for these compounds are summarized in Table III.

Table III. Fluorine Magnetic Resonance Parameters for Nonexchanging Cyclohexanes

Compound	Chemical shift, cps ^{a,b}		J_{AB} , cps ^b	Increase in the chemical shift difference, ^c %
	Eq	Ax		
3-Methyl-1,1-difluorocyclohexane (VI) ^d	709	1423	239	2 (–30°)
4-Methyl-1,1-difluorocyclohexane (VII) ^d	899	1509	238	8 (–50°)
4- <i>t</i> -Butyl-1,1-difluorocyclohexane (VIII) ^d	854	1526	236	1.5 (+10°)

^a At 56.4 Mc/sec, upfield from trifluoroacetic acid (internal standard). ^b The uncertainty is believed to be 0.5%. ^c From +35° down to the indicated temperature; below this temperature the chemical shift did not change appreciably. ^d 1:3 v/v in propene.

Discussion

The activation energy for ring inversion of I, found in the present work, has an intermediate value between those already reported for the same compound by high-resolution nmr (12 and 9.1–9.5 kcal/mole^{9,10}) and spin-echo studies (9.8–9.9 kcal/mole^{7b}). Our value is in good agreement with most of the results obtained for cyclohexane itself^{5,8} and particularly with a recent study on cyclohexane- d_{11} ($E_a = 10.85$ kcal/mole and $\Delta H^* = 10.9$ kcal/mole.²⁴ That the energy barriers appear to be lower for II and IV might be the result

(23) R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, **43**, 602 (1965).

(24) F. A. L. Anet, private communication.

of strain in the ground state,^{5c} owing to the 1,3-interactions between the *syn*-axial hydrogens and alkyl group. Similar effects associated with the introduction of alkyl groups have been reported for 2,2-difluoro-*cis*-decalins.^{12c}

It has been reported earlier^{5b} that for 4,4-dimethylcyclohexane no change occurs in the proton spectrum from room temperature down to –120°. The present results with II indicate that this must be the result of a small proton chemical-shift difference below the coalescence temperature.

The activation energy of 11.2 kcal/mole for inversion of the stable conformer of V corresponds well to the value of 10.85 kcal/mole reported for chloro- and bromocyclohexane.^{6c} The activation parameters for III are generally smaller than for most cyclohexane derivatives although reasonably comparable to what has been reported²³ for perfluorocyclohexane ($\Delta F^* = 9.9$ kcal/mole, $\Delta H^* = 7.5$ kcal/mole, and $\Delta S^* = -10.7$ eu). Interestingly, in both III and perfluorocyclohexane²³ the fluorines are much more shielded than those in the difluorocyclohexanes, and the resonance assigned to the equatorial fluorine is at higher field than that of the axial fluorine. It therefore appears that vicinal fluorines have a greater effect on fluorine chemical shifts than vicinal hydrogens, which conclusion is possibly important in other connections.^{12b}

The conformational free-energy difference determined for IV (Table II) agrees reasonably well with the difference between the separate values for ethyl (1.65–2.25 kcal/mole) and methyl (1.5–2.1 kcal/mole) groups obtained by other methods.²⁶ There seemed to be no change in this value between solutions in propene, carbon tetrachloride, acetone, or in the neat liquid.

For V the situation was different in that a solvent effect was observed on the conformational ratio, but not on the fluorine chemical shifts in the slow exchange limit, which are the same within the experimental error. This is perhaps surprising because for chlorocyclohexane itself, $-\Delta F^\circ$ is reported to fall in the range 0.4–0.5 kcal/mole as judged by proton nmr studies^{6b,c,27,28} and to be independent of the solvent.²³

The nearly equal values for $-\Delta F^\circ$ at 25 and –75° for IV and V suggest no net change in conformational entropy with temperature. This is to be expected for cyclohexanes bearing only spherically symmetrical substituents²⁶ (as V), but seems less likely for IV which carries an ethyl group.

With regard to the nonexchanging cyclohexanes for which one conformer predominates, it is possible the very small change in chemical shift observed with VIII as a function of temperature means that this substance is not completely “frozen” as the conformer with the *t*-butyl group equatorial at room temperature. However, since it is unlikely that the *t*-butyl group would assume an axial position in the chair form in preference to a flexible form,²⁶ the change in chemical shift, if it in fact results from equilibration with another form, is probably associated with a flexible form.

If we assume that the equatorial and axial fluorine

(25) G. V. D. Tiers, *Proc. Chem. Soc.*, 389 (1960).

(26) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, “Conformational Analysis,” Interscience Publishers, Inc., New York, N. Y., 1965, pp 44 and 439–440.

(27) J. Reisse, J. C. Celotti, and G. Chioroglu, *Tetrahedron Letters*, 397 (1965).

(28) E. L. Eliel, to be published.

chemical shifts are approximately equal in both conformations of VII, a simple calculation shows that the observed 8% change in the chemical-shift difference corresponds to 96% of the more stable conformer at 35°, which compares favorably with the value of 95% calculated for methylcyclohexane on the basis of the ΔF° value of the methyl group. The same calculation for VI suggests 99% of the conformer with the equatorial methyl group at 35°. There seems to be a real difference between the 3- and 4-methyl-substituted compounds which is in the direction expected if the equilibrium in the case of VI is shifted more toward the form with equatorial methyl because of 1,3 interaction between the *syn*-axial fluorine and methyl group in the conformer with axial methyl.

The results so far obtained do not provide any very good correlation between the fluorine chemical shifts and nature of the ring substituents. In marked difference with what was observed with decalins,^{12c} the chemical shifts of the equatorial fluorine seem to be more sensitive to the molecular environment (the observed changes range over about 7 ppm) than the chemical shifts of the axial fluorines (observed changes over 2 ppm). In general, the observed effects seem to be too large to permit widespread use of the chemical shifts of "fixed" 1,1-difluorocyclohexanes as standards for chemical shifts in inverting systems with even reasonably similar structures.^{4,28} Further progress in this area will depend critically on some independent means of determining the sensitivity of fluorine chemical shifts in ring compounds to changes in molecular geometry and/or electrical effects of remote substituent groups.^{12d}

The energy barriers for ring inversion and the positions of conformational equilibria determined in the present work are in general in very excellent agreement with results obtained with nonfluorinated analogs. This provides strong evidence for the utility of the fluorine-labeling technique¹² for obtaining results of general significance in studies of conformational equilibria and equilibration.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were recorded on the Perkin-Elmer Model 237 spectrometer employing 1% solutions in carbon tetrachloride. Analytical vapor-phase chromatographic analyses were performed on the Loenco Model 15B gas chromatograph using Carbowax or Ucon-Polar columns. For preparative separations, the Wilkens Model A-700 Autoprep chromatograph equipped with a 9-ft 20% Ucon-Polar on Chromosorb W column was used. Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Proton magnetic resonance spectra were taken at room temperature with the Varian Model A-60 spectrometer operating at 60 Mc/sec, using tetramethylsilane as internal standard.

Fluorine magnetic resonance spectra were recorded at 56.4 Mc/sec, with the Varian Model V-4300D spectrometer or with the Varian Model A-56/60A spectrometer (for 4-chloro-1,1-difluorocyclohexane). Chemical shifts reported are in cps upfield from trifluoroacetic acid as internal standard. The spectra were calibrated with audio side bands of the reference signal using a Hewlett-Packard Model 200 AB audio oscillator and Model 521-C frequency counter. The hydrogen-fluorine decoupling was achieved with the NMR Specialties Model SD-60 spin decoupler. The fluorine chemical shifts and F-F coupling constants were obtained with greater accuracy from the decoupled spectra and are in each case the average of six or more spectra swept in both directions.

Table IV. Preparation and Physical Properties of *gem*-Fluorocyclohexanes and 1,1,2,2-Tetrafluorocyclohexane

	Mole, ketone	Mole, SF ₄	Temp, °C	Temp, °C	Time, hr	Yield, %	Bp, °C (mm)	<i>n</i> _D ²⁰	Infrared bands, cm ⁻¹	Calcd, %			Found, %		
										C	H	F	C	H	F
3-Methyl-1,1-difluorocyclohexane (VI)	0.07	0.8	60	10 ^b	35	112-113(742)	1.3913	1030, 1055, 1120, 1160, 1270, 1320, 1360	62.66	9.02	28.32	62.54	9.18	28.19	
4-Methyl-1,1-difluorocyclohexane (VII)	0.05	0.8	70	6 ^b	25	117-118(745)	1.3924	1070, 1110, 1160, 1260, 1350, 1365	62.66	9.02	28.32	61.72	9.16	28.84	
4- <i>t</i> -Butyl-1,1-difluorocyclohexane (VIII)	0.05	0.5	<i>e</i>	20	19	83-84(32)	1.4210	1110, 1130, 1200, 1275, 1365, 1380	68.13	10.29	21.57	68.16	10.24	21.65	
4,4-Dimethyl-1,1-difluorocyclohexane (II)	0.03	0.6	65	8 ^b	35	123-124(745)	1.4010	1040, 1100, 1170, 1185, 1270, 1360	64.84	9.52	25.64	65.02	9.46	25.61	
4-Methyl-4-ethyl-1,1-difluorocyclohexane (IV)	0.07	0.5	<i>e</i>	21	57	56-58(18)	1.4130	1100, 1275, 1340, 1360	66.64	9.94	23.42	66.79	9.89	23.40	
4-Chloro-1,1-difluorocyclohexane (V)	0.04	0.4	<i>e</i>	38	25	122-123(742)	1.4260	1110, 1260, 1280, 1350, 1370	46.61	5.87	24.58	47.24	5.94		
1,1,2,2-Tetrafluorocyclohexane (III)	0.09	0.7	50	24 ^b	14	109-110(745) ^f	1.3580 ^d	1030, 1120, 1140, 1180, 1265, 1340, 1370	46.16	5.16	48.68	46.11	5.03	48.70	

^a Positions are given of some of the strong absorptions in the region 1000-1400 cm⁻¹, where carbon-fluorine stretching absorptions usually appear: L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1962, p 329. ^b Allowed to cool to room temperature over 10-12 hr. ^c Mp 32°. ^d At 35°. ^e Room temperature.

The low-temperature measurements were accomplished by passing precooled nitrogen through a dewar-jacketed probe with monitoring of the temperature by a copper-constantan thermocouple. For the spectra taken with the A-56/60A spectrometer, the Varian V-6057 variable temperature accessory was used. The temperatures were calibrated by replacing the sample tube with a similar one containing another thermocouple, and also by the temperature dependence of the chemical shift of the methanol hydroxyl group. The temperatures are believed to be accurate to $\pm 2^\circ$.

The theoretical spectra and the Arrhenius plots were computed by an IBM 7094 II computer coupled to a Moseley X-Y plotter.

All of the *gem*-fluorocyclohexanes used in this study (except 1,1-difluorocyclohexane) and 1,1,2,2-tetrafluorocyclohexane were synthesized by the reaction of sulfur tetrafluoride with the corresponding ketones.²⁹ The ketones were synthesized as below or obtained commercially.

1,1-Difluorocyclohexane was obtained from K & K Laboratories, Plainview, N. Y.; bp 97–98° (745 mm), n_D^{25} 1.3914 (lit.³⁰ bp 100.5°, n_D^{25} 1.3906).

4,4-Dimethylcyclohexanone was prepared starting from isobutyraldehyde and methyl vinyl ketone, according to the procedure described by Bordwell and Wellman;³¹ mp 38–39° (lit.³¹ 39–40°).

4-Methyl-4-ethylcyclohexanone. 4-Acetyl-4-methylpimelonitrile was prepared from methyl ethyl ketone and acrylonitrile,³² and converted *via* several intermediates into 4-methyl-4-ethylcyclohexane;³³ bp 92–95° (13 mm); carbonyl absorption, 1710 cm^{-1} (lit.³³ bp 95–98° (15 mm)).

4-Chlorocyclohexanone was prepared starting from 1,4-cyclohexanedione, by way of 4-chlorocyclohexanol obtained from the

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(33) R. N. Burnell and W. I. Taylor, *J. Chem. Soc.*, 3307 (1957).

mono-*p*-toluenesulfonate ester.³⁴ Oxidation³⁵ with sodium dichromate-sulfuric acid in ether at 0° gave the expected ketone (carbonyl absorption, 1715 cm^{-1}) which was used without purification.

The difluorocyclohexanes²⁹ were purified by distillation, except for the 4-*n*-butyl and 4-chloro compounds, which required preparative vpc at 90–100°. The purity of the products was checked by analytical vpc, infrared spectra (absence of carbonyl absorption), and elemental analyses. The proton nmr spectra were in agreement with the assigned structures, but not very characteristic, there being sharp signals for the alkyl substituents and broad peaks for the ring protons in the aliphatic region. The best evidence for the structure of the compounds was usually the fluorine resonance spectra.

The conditions used for synthesis²⁹ and physical properties of the hitherto unknown six *gem*-fluorocyclohexanes and 1,1,2,2-tetrafluorocyclohexane are summarized in Table IV.

In attempting to synthesize 2-methyl-1,1-difluorocyclohexane in a similar way from the corresponding ketone, a liquid with bp 111–112° (744 mm) was isolated, which seems to be **2-methyl-1,1,2-trifluorocyclohexane** (10% yield). This substance had in its proton resonance spectrum a doublet centered at 1.5 ppm for the methyl group ($J_{\text{HF}} = 22$ cps) and broad multiplet (1.4–2.5 ppm) for the ring protons. The fluorine spectrum showed a closely packed multiplet at about 2030 cps upfield from trifluoroacetic acid. Practically no change in the spectrum was observed at low temperature. Significant infrared absorptions were observed at 900, 980, 1045, 1120, 1175, 1350, and 1440 cm^{-1} .

Anal. Calcd for $\text{C}_7\text{H}_{11}\text{F}_3$: C, 55.25; H, 7.28. Found: C, 54.68; H, 7.09.

Several attempts to prepare 1,1,4,4-tetrafluorocyclohexane through the reaction of 1,4-cyclohexanedione with sulfur tetrafluoride at various conditions were unsuccessful, only starting material being isolated from the reaction mixture.

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Preferred Conformations of the Cycloheptane Rings of A-Homosteroids¹

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Abstract: The conformational analytical procedure developed by Hendrickson for cycloheptanes has been applied to ring A of the A-homosteroids I–IV. Dipole moment, nuclear magnetic resonance, and optical rotatory dispersion data were used to assist in the selection of the preferred conformations, and, of these physical methods, the latter proved the most informative. The data in each case were consistent with a room-temperature equilibrium mixture of three “twist-chair” conformations. The reported conformations of the seven-membered rings of several other A-homosteroids, and of (+)-3- and (–)-4-methylcycloheptanones, for which ORD or CD data were available, have been reexamined and the previous assignments shown to be incorrect. Twist-chair conformations appear to be favored exclusively for the examples studied and, in the absence of overriding control of the conformations by bulky substituents, the carbonyl group prefers to be situated at the axis or adjacent carbon of the twist chair.

During the course of our studies on the specificities of certain steroidases and on the factors controlling the activity of steroid hormones, a series of steroids possessing a seven-membered ring A was synthesized. The structural and configurational range of A-homosteroids prepared to date^{2,3} is summarized by structures

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I–IV. Since the steroidases of interest to us exhibit marked stereospecificity⁴ in their combination with substrates and inhibitors, it was necessary to establish the preferred conformations of the cycloheptane rings of the above steroids in order that meaningful specificity studies could be carried out.

The procedures reported in the literature for the

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