Conformational Analysis. XIII. The Validity of the Nuclear Magnetic Resonance Method of Establishing Conformational Equilibria[1]

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Abstract: The basis for the nmr method of determining conformational equilibria in substituted cyclohexanes is examined. Comparison of conformationally analogous 3- and 4-*t*-butyl-substituted cyclohexyl derivatives indicates that the signals for the C_1 proton therein are not the same; conformational equilibria derived from the signal position in the 4-*t*-butyl compounds and the corresponding monosubstituted compound (Figure 1) are consistent with similar equilibria obtained by other methods, but those derived from 3-*t*-butyl compounds are out of line. However, in proton resonance of 2-*t*-butyl- and 5-*t*-butyl-substituted 1,3-dioxanes, the *t*-butyl group does affect the signals of certain ring and methyl substituent hydrogens in positions corresponding to the 4 position in cyclohexane. In the case of ^{19}F resonance it is found that in both 3-*t*-butyl- and 4-*t*-butyl-1,1-difluorocyclohexanes the position of the fluorine signals is affected by the alkyl substituent. Comparison of *cis*- and *trans*-4-*t*-butylcyclohexyl chlorides with cyclohexyl chloride at -81 to $-91°$ as a means of ascertaining the equatorial and axial C*H*Cl signals suggests that the 4-*t*-butyl compounds are better suited for this purpose inasmuch as the signal position changes with temperature and an extrapolation is required to utilize the measured low-temperature shifts. However, 4-*t*-butyl compounds are apparently not good models for ^{19}F shifts or for proton shifts in heterocyclic systems.

Nuclear magnetic resonance was used as a tool for assessing conformational equilibria in acyclic systems for the first time by Nair and Roberts in 1957.[2] A year later, Lemieux, *et al.*,[3] drew attention to the differences in chemical shifts and spin–spin coupling between equatorial and axial protons in cyclohexyl systems. The shift difference was utilized subsequently[4] by one of us to determine the position of the conformational equilibrium shown in Figure 1. In essence, the conformationally biased[5] 4-*t*-butyl systems III and IV (Figure 1) were used to obtain the chemical shifts of the axial and equatorial protons, respectively (ν_e and ν_a), and the conformational equilibrium constant K was[6]

$$K = (\nu_a - \nu)/(\nu - \nu_e) \qquad (1)$$

where ν is the observed chemical shift C*H*X in the rapidly equilibrating cyclohexyl system. Subsequently three other nmr methods for determining the position of conformational equilibrium in a substituted cyclohexane (Figure 1) were evolved. In one of these[7] ν_e and ν_a are measured in the monosubstituted cyclohexane itself, at a temperature so low that the two conformational isomers I and II (Figure 1) are not interconverted rapidly enough to lead to coalescence of the signals of the equatorial and axial protons. In another method,[7] the signal areas of these two protons are measured directly at the low temperature to give the population ratio; in yet another method[8] averaging of spin coupling rather than of chemical shift is employed. Reviews of these methods are available.[9]

In the method originally used by us (*cf.* Figure 1)[4,10] it must be assumed that the 4-*t*-butyl group does not in any way affect the chemical shift of the proton at C_1, for what is really needed is not the chemical shift of the C_1 proton in III and IV (Figure 1) but the corresponding shift in II and I. This assumption has subsequently been criticized;[11] the present work serves to explore this criticism and to establish the limitations of the nmr method based on chemical shifts.

^1H Spectra

At the onset of this work, the only comparison of chemical shifts in 3- and 4-*t*-butyl-substituted compounds was in the cyclohexanol system;[12] the data, shown in Table I, indicate that there is a definite effect of the *t*-butyl substituent in at least one of the two series if not both. Application of eq 1 to the 4-*t*-butylcyclohexanol data,[10a] taking the carbinol proton shift in cyclohexanol as -211 cps, gives $K = 2.8$, $-\Delta G°_{OH} = 0.6$ kcal/mol a value which is in good agreement with values for $-\Delta G°_{OH}$ in aprotic solvents found by other methods.[13] Using the data in the 3 series, one would obtain $K = 6.6$ $-\Delta G°_{OH} = 1.1$ kcal/mol, which is out of line with other values in the literature. We had earlier calculated[12] a parameter for the carbinol proton

(1) Paper XII: E. L. Eliel and F. J. Biros, *J. Amer. Chem. Soc.*, **88**, 3334 (1966).
(2) P. M. Nair and J. D. Roberts, *ibid.*, **79**, 4565 (1957).
(3) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958).
(4) E. L. Eliel, *Chem. Ind.* (London), 568 (1959).
(5) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1965, p 71.
(6) H. S. Gutowski and A. Saika, *J. Chem. Phys.*, **21**, 1688 (1953).
(7) (a) A. J. Berlin and F. R. Jensen, *Chem. Ind.* (London), 998 (1960); (b) L. W. Reeves and K. O. Strømme, *Can. J. Chem.*, **38**, 1241 (1960); (c) see also F. R. Jensen and C. H. Bushweller, *J. Amer. Chem. Soc.*, **88**, 4279 (1966).
(8) *E.g.*, F. A. L. Anet, *ibid.*, **84**, 1053 (1962); H. Feltkamp and N. C. Franklin, *ibid.*, **87**, 1616 (1965); H. Feltkamp, N. C. Franklin, K. D. Thomas, and W. Brügel, *Ann. Chem.*, **683**, 64 (1965).
(9) (a) H. Feltkamp and N. C. Franklin, *Angew. Chem.*, **77**, 798 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 774 (1965); (b) *Ann. Chem.*, **683**, 55 (1964); (c) E. L. Eliel, *Angew. Chem.*, **77**, 784 (1965); *Angew. Chem. Intern. Ed., Engl.*, **4**, 761 (1965); (d) ref 5, pp 152–156.
(10) See also: (a) E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962); (b) E. L. Eliel, E. W. Della, and T. H. Williams, *ibid.*, 831 (1963); (c) E. L. Eliel and B. P. Thill, *Chem. Ind.* (London), 88 (1963).
(11) F. R. Jensen and L. H. Gale, *J. Org. Chem.*, **25**, 2075 (1960).
(12) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 741 (1962).
(13) E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).

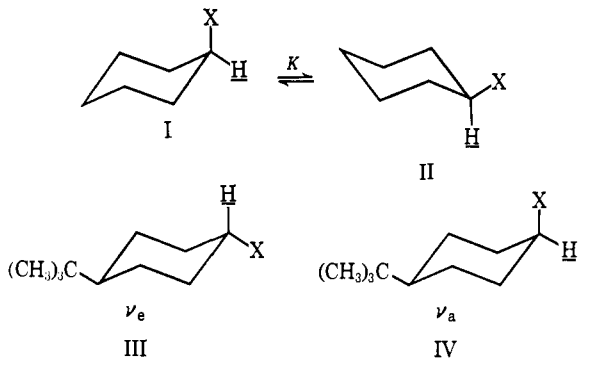


Figure 1.

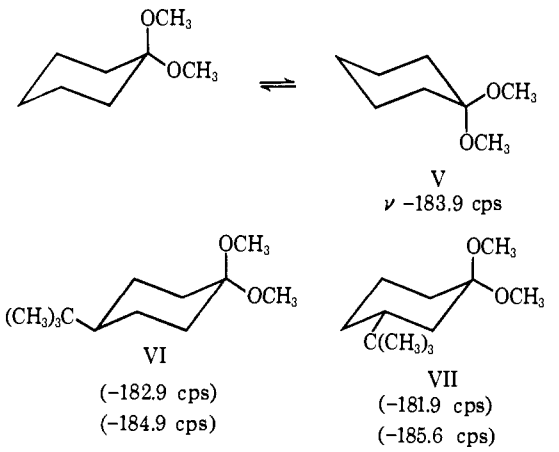


Figure 2.

shifts in (hypothetical) unsubstituted equatorial and axial cyclohexanol species on the basis of a statistical approach and arrived at values of −206 and −242 cps which would lead to $K = 6.2$, $-\Delta G°_{OH} = 1.1$ kcal/mol, but it must be stressed that the main virtue of this calculation (and the application of the resulting parameters) is in its *internal* consistency; the *absolute* values of the hypothetical shifts calculated are not very accurate and now appear to be less significant than the values experimentally observed in the 4 series.

Table I. C_1-Proton Signals in 3- and 4-*t*-Butyl-Substituted Cyclohexanes (*cf.* III and IV, Figure 1)

C_1 substituent, X	ν_{CHX}[a] Axial H *trans*-4	Axial H *cis*-3	Equatorial H *cis*-4	Equatorial H *trans*-3
OH[12]	202	206	236	244
F	281.1[b]	282.0[b]	304.6[b]	312.5[b]
Cl	221.5	225.5	262.5	269.8

[a] In cps downfield from tetramethylsilane in carbon tetrachloride solution at 60 Mcps. [b] Lower field signal of fluorine-split doublet. $J = 49.4 \pm 0.6$ cps in all cases.

Included in Table I are data for the *cis*- and *trans*-3- and -4-*t*-butylcyclohexyl fluorides and chlorides obtained in the present work.[14] Here again there is an obvious difference between the 3 and 4 series. Using the observed shift (lower field component of the C*H*F doublet) for cyclohexyl fluoride, $\nu = -291.6$ cps, the conformational equilibrium for fluorine, using the 4-*t*-butylcyclohexyl fluoride values for ν_e and ν_a, corresponds to $K = 1.25$, $-\Delta G°_F = 0.13$ kcal/mol. This value is in good agreement with values of 0.17 kcal/mol found by electron diffraction,[15] 0.15 and 0.24 kcal/mol by low-temperature nmr using chemical shifts,[7a,16] and 0.25 kcal/mol[7a] and 0.24–0.27 kcal/mol[16] by low-temperature nmr using area measurements. In contrast, use of the 3-*t*-butylcyclohexyl fluorides for ν_e and ν_a would give $K = 2.18$, $-\Delta G°_F = 0.46$ kcal/mol, which is incompatible not only with the values obtained by other methods but also with values for the larger halogens.[14] The situation with cyclohexyl chloride (ν −234.4 cps) is similar. Use of the shifts measured in the 4-*t*-butyl compounds gives $K = 2.18$, $-\Delta G°_{Cl} = 0.46$ kcal/mol, in good agreement with values ranging from 0.26 to 0.60 kcal/mol recorded in the literature and derived from electron diffraction,[17] infrared,[18] other nmr,[7,19] and Kerr constant[20] measurements. In contrast, use of the 3-*t*-butyl prototypes gives $K = 3.98$, $-\Delta G° = 0.82$ kcal/mol, an unreasonable value.

From the data so far presented it appears that a 4-*t*-butyl substituent does not affect the proton shifts at C_1 whereas a 3-*t*-butyl substituent does. In an alternative approach to this problem, we have measured the shifts of the methoxymethyl protons in cyclohexanone dimethyl ketal (V) and its 4- and 3-*t*-butyl homologs, VI and VII (Figure 2). In 4-*t*-butylcyclohexanone dimethyl ketal (VI) the axial and equatorial methoxy protons are clearly resolved in sharp signals occurring at −182.9 and −184.9 cps.[21] Cyclohexanone dimethyl ketal exists as an equilibrium mixture of equal parts of two indistinguishable conformational isomers (Figure 2) and will therefore show only a single average signal for its methoxy groups which signal must necessarily appear midway between the hypothetical signals for the purely equatorial and purely axial methoxyl. The observed signal is found as a sharp peak at −183.9 cps; it follows that the signals for the purely equatorial and purely axial methoxyls must occur at $-(183.9 + X)$ and $(183.9 - X)$ cps, respectively. Thus the observed signals for the methoxy groups in 4-*t*-butylcyclohexanone dimethyl ketal correspond to these signal positions (with $X = 1.0$) which, in turn, is consistent with the assumption that the 4-*t*-butyl group has no effect on the chemical shifts of the methoxyl groups of the ketal function.[22] The same is not true for a 3-*t*-butyl group;

(14) See also the accompanying paper: E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 689 (1968).
(15) P. Andersen, *Acta Chem. Scand.*, **16**, 2337 (1962).
(16) F. A. Bovey, E. W. Anderson, F. P. Hood, and R. L. Kornegay, *J. Chem. Phys.*, **40**, 3099 (1964).
(17) V. A. Atkinson, *Acta Chem. Scand.*, **15**, 599 (1961).
(18) (a) G. Chiurdoglu, L. Kleiner, W. Masschelein, and J. Reisse, *Bull. Soc. Chim. Belges*, **69**, 143 (1960); (b) K. Kozima and K. Sakashita, *Bull. Chem. Soc. Jap.*, **31**, 796 (1958).
(19) J. Reisse, J. C. Celotti, and G. Chiurdoglu, *Tetrahedron Letters*, 397 (1965).
(20) C. G. Le Fèvre, R. J. W. Le Fèvre, R. Roper, and R. K. Pierens, *Proc. Chem. Soc.*, 117 (1960).
(21) The assignment of the peaks is not of importance in the present work. However, in view of the signal position of the methoxy protons in the 4-*t*-butylcyclohexyl methyl ethers (*trans* (equatorial) isomer, −195.0 cps; *cis* (axial) isomer, −193.0 cps (E. L. Eliel, E. W. Dellaj and M. Rogić, *J. Org. Chem.*, **30**, 855 (1965))) it appears likely that the high-field signal should be assigned to the axial methoxy group.
(22) Although consistent with this assumption, the data do not demand it: if the 4-*t*-butyl group fortuitously shifts the signals for equatorial and axial methoxyl equally and in opposite directions, the same experimental observation would follow. It must also be pointed out that, even if true for methyl attached to oxygen attached to C_1, the assumption that a 4-*t*-butyl group has no effect on chemical shift may still not hold for hydrogen directly attached to C_1.

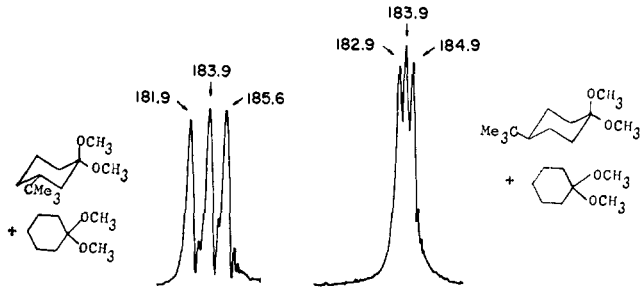


Figure 3. Nmr spectra of cyclohexanone dimethyl ketals.

the methoxy signals in 3-*t*-butylcyclohexanone dimethyl ketal at −181.9 and −185.6 cps do *not* correspond to the required signal positions for equatorial and axial methoxyl in cyclohexanone dimethyl ketal (*vide supra*), and it follows, therefore, that the 3-*t*-butyl group does affect the chemical shift of the C_1 methoxyls. In Figure 3 are shown the nmr spectra of mixtures of cyclohexanone dimethyl ketal and 3-*t*-butylcyclohexanone dimethyl ketal (A) as well as cyclohexanone dimethyl ketal and 4-*t*-butylcyclohexanone dimethyl ketal (B). It must be said that the spread of the shifts in both series is quite small and the significance of the observations is therefore somewhat limited.[23]

A series of acetals and ketals in which somewhat more pronounced shifts are seen is found among 1,3-dioxanes. The data shown[25] in Figure 4 indicate that the chemical shift of the 2-protons in 5-*t*-butyl-1,3-dioxane (VIII), the shift of the 2-methyl protons in 2,2-dimethyl-5-*t*-butyl-1,3-dioxane (IX) and the chemical shift of the 5-methyl protons in 5,5-dimethyl-2-*t*-butyldioxane (X) are all affected in some way by the *t*-butyl substituent, inasmuch as the corresponding protons in the unsubstituted compounds XI, XII, and XIII, where true averaging of two equivalent conformations occurs, are not found at the calculated average position of the appropriate equatorial and axial signals in the prototypes VIII, IX, and X. In contrast, the calculated average position of the 2-protons in *cis*-4,6-dimethyl-1,3-dioxane (XIV) and of the 2-methyl protons in 2,2-*cis*-4,6-tetramethyl-1,3-dioxane (XV) coincide (within limits of experimental error) with the true average position in the corresponding mobile systems XI and XII, suggesting that the equatorial methyl groups at positions 4 and 6 do not disturb the hydrogen or methyl signals at position 2. The situation here is exactly the opposite to that in cyclohexane, possibly because of the subtly different shape of the 1,3-dioxane system (C–O distance of 1.42 Å in lieu of a C–C distance of 1.53 Å in cyclohexane) or possibly because of anisotropy effects caused by the ring oxygens when the system is slightly distorted by a *t*-butyl group.

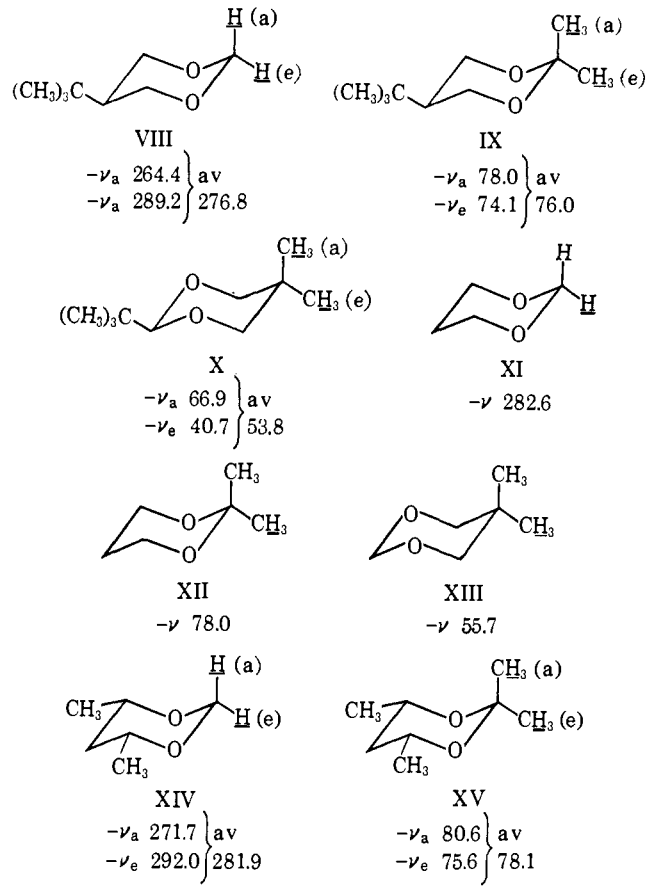


Figure 4. Chemical shifts in 1,3-dioxanes in cycles per second from tetramethylsilane in carbon tetrachloride solution measured at 60 Mcps.

^{19}F Spectra

In principle, ^{19}F spectra should lend themselves readily to conformational analysis; chemical shifts (*e.g.*, between equatorial and axial fluorines, *vide infra*) are about 20 times as large as in ^1H spectra and this fact, beside enhancing the accuracy of the calculated equilibrium constants, should also make it possible to observe mixtures of *cis*- and *trans*-4-*t*-butylcyclohexyl and unsubstituted cyclohexyl compounds, thus avoiding any possible solvent effects (which might affect individual observations of these compounds) and making unnecessary the often tedious separation of the 4-*t*-butyl-substituted epimers. To examine the effect of *t*-butyl groups on fluorine resonance at C_1, we prepared and examined 1,1-difluorocyclohexane (XVI, Scheme I) and its 4- and 3-*t*-butyl homologs (XVII and XVIII, Scheme I). The data shown in Scheme I clearly show that the averaged signal in XVI occurs far from midway between the signals for axial and equatorial fluorine in either the 4-*t*-butyl or the 3-*t*-butyl homolog.

The chemical shifts of the fluorine nuclei in the epimeric 3- and 4-*t*-butyl-1-chloro-1-fluorocyclohexanes (Figure 5) were also found not to average to the chemical shift of the ^{19}F nucleus in 1-chloro-1-fluorocyclohexane.

It is clear, in the light of these results, that ^{19}F resonance data from rigid prototypes cannot be used directly to calculate conformational equilibria in mobile analogs.[26] Similar observations have previously been

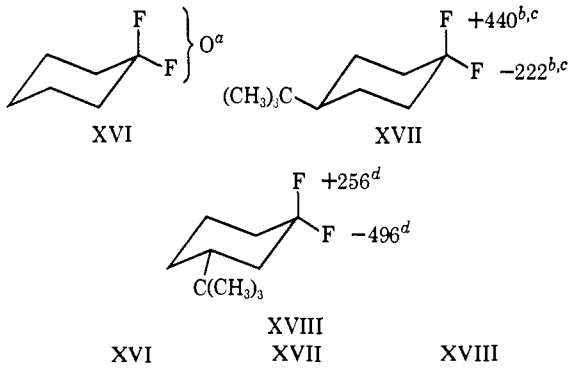
(23) The need for caution in drawing conclusions from small hift differences is underscored by a recent publication by M. Anteunis and D. Tavernier, *Bull. Soc. Chim. Belges*, 76, 475 (1967), in which the authors report exactly the opposite result from ours: averaging of signals in the 3-*t*-butyl series but not in the 4-*t*-butyl series. The only experimental differences is that their data were obtained in carbon disulfide, ours in carbon tetrachloride (added in proof). See also ref 24.

(24) M. Anteunis, *Bull. Soc. Chim. Belges*, 73, 731 (1964).

(25) From the Ph.D. Dissertation of M. Carmeline Knoeber, University of Notre Dame, Notre Dame, Ind., 1967.

(26) In the accompanying paper[14] an attempt is made to correct for the effect of the *t*-butyl group. The attempt succeeds reasonably well in the 4 series whereas in the 3 series it merely leads to agreement of the ^{19}F data with the ^1H data which, themselves, do not produce correct values, as explained above.

Scheme I. Chemical shifts of 1,1-Difluorocyclohexanes (neat mixtures) at 56.4 Mcps (referred to the parent compound as standards)



[a] Reference standard. [b] Axial signals at 343 (ν_1) and 579 (ν_2) cps; equatorial signals at −125 (ν_3) and −358 (ν_4) cps; shifts calculated by formula $\nu_a - \nu_e = \sqrt{(\nu_2 - \nu_4)(\nu_1 - \nu_3)}$. [c] Roberts[26,27] reports chemical shift differences of 662 cps and a coupling constant of 236 cps compared to the values of 661 and 235 cps reported here. [d] Axial signals at 156 and 392 cps; equatorial signals at −396 and −635 cps; shifts calculated as for 4 series.

made by Roberts and coworkers[27,28] who have also recorded the nmr spectra of 1,1-difluorocyclohexane and 4-*t*-butyl-1,1-difluorocyclohexane.[28] At the moment, it is an open question whether the large change caused by the distant alkyl group in the fluorine chemical shift is due to a long-range anisotropy effect of the alkyl group itself or whether it is the result of a subtle deformation of the cyclohexane framework.[29] In this regard it is interesting (but in no way decisive) that the pertinent signals in the 3-*t*-butyl compounds always occur at lower field than corresponding signals in the 4-*t*-butyl series, as seen in Tables I and II. The downfield shift is always more pronounced for the equatorial signal than for the axial one.

Table II. Fluorine Chemical Shifts[a]

	Axial fluorine	Equatorial fluorine
1,1-Difluoro-4-*t*-butylcyclohexane	+440[b]	−222[b]
1,1-Difluoro-3-*t*-butylcyclohexane	+256[b]	−496[b]
4-*t*-Butylcyclohexyl fluoride	+644[c]	−251[c]
3-*t*-Butylcyclohexyl fluoride	+503[c]	−433[c]
1-Chloro-1-fluoro-4-*t*-butylcyclohexane	+697[d]	−450[d]
1-Chloro-1-fluoro-3-*t*-butylcyclohexane	+496[d]	−721[d]

[a] In neat mixtures; cycles per second from standard indicated at 56.4 Mcps. [b] From 1,1-difluorocyclohexane. [c] From cyclohexyl fluoride.[14] [d] From 1-chloro-1-fluorocyclohexane.

Comparison of Methods

As already mentioned, in nmr determinations of conformational equilibria using chemical shifts, one may locate the reference signals of the pure conformers either at very low temperatures (by "freezing in" the equilibrium) or by using appropriate conformationally rigid or biased model compounds such as III and IV in Figure 1. The question arises as to which method gives better

(27) S. L. Spassov, D. L. Griffith, E. S. Glazer, K. Nagarajan, and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 88 (1967).
(28) J. D. Roberts, *Chem. Brit.* **2**, 529 (1966).
(29) This point has also been made in ref 27. Regarding a similar dilemma in proton resonance, see A. Segre and J. I. Musher, *J. Amer. Chem. Soc.*, **89**, 706 (1967).

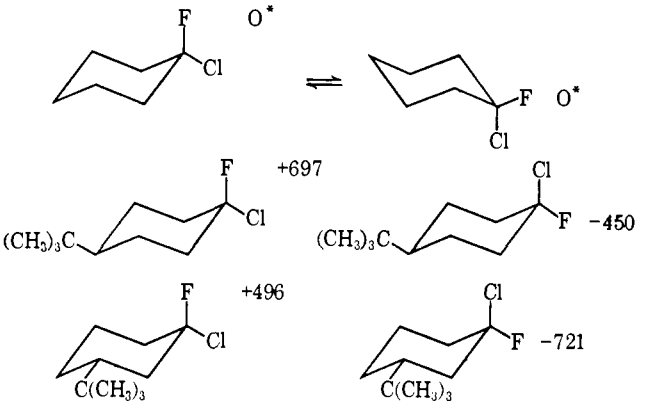


Figure 5. Chemical shifts of 1-chloro-1-fluorocyclohexanes (neat mixtures) at 56.4 Mcps (referred to the parent compound as standard). Asterisks indicate reference standard.

results, or (putting it in more specific terms) as to whether a change of temperature or the introduction of a holding group (such as 4-*t*-butyl) disturbs the salient signals less. It has already been shown above that a 4-*t*-butyl group shifts an ^{19}F signal at C_1 and that a 3-*t*-butyl group shifts either an ^{19}F or an ^{1}H signal at C_1. A comparison will therefore be made here only between the effect of a 4-*t*-butyl holding group and of lowering the temperature in the case of proton resonance. Pertinent data for cyclohexyl chloride, partly from the literature and partly from the present work, are shown in Table III.

Table III. *CH*Cl Shift for Cyclohexyl Chloride (equatorial, averaged and axial conformations) in Carbon Disulfide Downfield from Tetramethylsilane

Fixed conformation	$-\nu_e$, cps	$-\nu$,[a] cps	$-\nu_a$, cps	$-\Delta G°$, kcal/mol	Ref
4-*t*-Butylcyclohexyl chloride	218.2[b]	231.9	259.9[c]	0.42	This work, 14
Cyclohexyl chloride −91°	227.4[d]	236.1	266.4[d]	0.73[e]	7b
Cyclohexyl chloride −81°	224[d]	233.3	265.8[d]	0.74[e] 0.48[f]	7a 7a

[a] Value for cyclohexyl chloride at room temperature. [b] Value for III (Figure 1), X = Cl at room temperature. [c] Value for IV (Figure 1), X = Cl at room temperature. [d] Values for the two signals in cyclohexyl chloride at the low temperature indicated. [e] Raw value. [f] Extrapolated value, details of extrapolation process unavailable.

Although a variation in the observed shift for cyclohexyl chloride at room temperature (possibly due to inconsistencies in locating the center of the multiplet) makes comparison of the data from different investigations somewhat uncertain, there can be little doubt that the shifts for axial and equatorial *CH*Cl protons in *trans*- and *cis*-4-*t*-butylcyclohexyl chlorides are *not* the same as the corresponding shifts in the low-temperature spectra of cyclohexyl chloride itself. Perhaps even more significant is the observation that the value for $-\Delta G°_{Cl}$ derived from the 4-*t*-butyl standards agrees with the values found by other methods[7,14,17-20] mentioned earlier whereas the corresponding values derived from the raw low-temperature shifts are out of line. Apparently the discrepancy is due to a variation of the chemi-

cal shift in the purely axial and purely equatorial "frozen" cyclohexyl chloride with temperature.[30] The difficulty can be overcome by extrapolating the low-temperature shifts to room temperature,[7a] but, since details of the extrapolation procedure have not been published, the precision of the extrapolation cannot be assessed. A study of the nmr spectra (C*H*Cl signal) of *cis*- and *trans*-4-*t*-butylcyclohexyl chlorides as a function of temperature (Table IV) indicates that the signals are somewhat temperature dependent, but not so much so as to make possible a reconciliation of the 4-*t*-butylcyclohexyl chloride shifts at room temperature and the cyclohexyl chloride shifts at −81 and −91° shown in Table II.

Table IV. Proton (C_1) Shifts in the 4-*t*-Butylcyclohexyl Chlorides as a Function of Temperature

Temp, °C	$-\nu_e$[a] (III)[b]	$-\nu_a$[a] (IV)[b]	Temp, °C	$-\nu_e$[a] (III)[b]	$-\nu_a$[a] (IV)[b]
−57		263.4	−19	221.4	
−50		263.5	+29	221.5	262.5
−39		263.3	+55	220.3	261.8
−30	222.0		+98	220.5	
−21		262.7	+104		261.5

[a] In cycles per second from tetramethylsilane at 60 Mcps in carbon tetrachloride. [b] X = Cl.

Preparation of Fluoro Compounds

The *cis*- and *trans*-4-*t*-butylcyclohexyl fluorides, hitherto unknown, were prepared by treatment of 4-*t*-butylcyclohexanol with 2-chloro-1,1,2-trifluorotriethylamine, $(C_2H_5)_2NCF_2CHClF$, itself prepared from diethylamine and chlorotrifluoroethylene. This method, originally developed in Russia,[31] has been extensively applied to steroidal alcohols.[32,33] Since both epimeric fluorides were desired and since their separation by preparative gas chromatography proved to be relatively facile, we used the commercially available 4-*t*-butylcyclohexanol mixture (*ca.* 75% *trans* isomer) as starting material. Unfortunately, the combined yield of fluorides was not high and the major product of the reaction was olefin; even carrying out the reaction at low temperature[33b] did not improve the fluoride to olefin ratio greatly.

Since, because of the sluggishness of fluoride as a leaving group in nucleophilic displacement reactions, it did not seem attractive to prove the position of the fluorine in the presumed 4-*t*-butylcyclohexyl fluorides by replacing it by another, known group (such as thiophenoxide), we chose another approach. Starting from 4-*t*-butylcyclohexanol-1-*d*, if the fluorine replacement reaction proceeds normally, one should get *cis*- and *trans*-4-*t*-butylcyclohexyl-1-*d* fluorides in which the fluorine and deuterium are on the same carbon. If rearrangements (or elimination of HF followed by readdition in the reverse direction) occurred, on the other hand, the deuterium should not be geminal to the fluorine. The difference between the two possibilities can readily be established by nuclear magnetic resonance; in actual fact we found that the epimeric fluorides prepared from 4-*t*-butylcyclohexanol-1-*d* did not show appreciable nmr signals for the protons under fluorine (C*H*F) in ^1H resonance and the axial fluoride showed a major split[34] triplet in the ^{19}F resonance spectrum caused by the two *anti* protons (J = 44 cps) in contrast to the nondeuterated fluoride which showed an ^{19}F quartet due to simultaneous splitting by the geminal proton (J = 46 cps) and the vicinal *anti* protons. The equatorial deuterated fluoride shows a single sharp peak in ^{19}F resonance (the splitting due to *gauche* hydrogens was not observed at the scan rate used) whereas the undeuterated compound displays a sharp doublet (splitting by H_{gem}). The result unequivocally establishes the substantial absence[35] of rearrangement in the formation of the 4-*t*-butylcyclohexyl fluorides which therefore have the constitution assigned; their configuration may be assigned directly on the basis of their nmr spectra.[3]

1,1-Difluoro-4-*t*-butylcyclohexane and its 3 isomer were prepared from the corresponding ketones by a method described in the literature[36] for 1,1-difluorocyclohexane. Treatment of the ketones with phosphorus pentachloride gave a mixture of geminal dichloride and chloroolefins. The chloroolefins were separated by distillation and treated with liquid hydrogen fluoride to give mainly the geminal difluoro compounds, along with some geminal chlorofluoride. The latter became the major product when the reaction time was shortened, suggesting that it is probably an intermediate in the formation of the difluoride, the reaction course being chloroolefin (HF addition) → chlorofluoride (HCl elimination) → fluoroolefin (HF addition) → difluoride.

Experimental Section

The preparation of *cis*- and *trans*-3- and -4-*t*-butylcyclohexyl chlorides is described in the accompanying paper.[14] Cyclohexyl fluoride was prepared by reaction of cyclohexene with anhydrous hydrogen fluoride[37] and boiled at 41° (85 mm), $n^{20}D$ 1.4142 (lit.[38] bp 43.2 (100 mm), 42.5° (98 mm); $n^{20}D$ 1.4146, 1.4147).

4-*t*-Butylcyclohexyl Fluorides.[33a] **a. 2-Chloro-1,1,2-trifluorotriethylamine.** A 1-l., three-necked flask was equipped with a magnetic stirrer, inlet tube, thermometer and Dry Ice cooled reflux condenser, charged with 89 g (1.22 mol) of diethylamine, and placed in a Dry Ice–acetone bath, after having been weighed. A slow stream of chlorotrifluoroethylene was passed into the flask, maintaining the reaction temperature between −20 and +5°, until the haloethylene was no longer absorbed and began to reflux steadily in the condenser. At the same time, the weight of the flask was checked periodically. When addition was stopped, the weight had increased by 137 g or somewhat more (absorption of 1.18 mol of $CFClCF_2$). The reaction mixture was then let stand overnight.

b. 4-*t*-Butylcyclohexyl Fluoride. To the reaction mixture cooled to 0 to −5° was added 200 g (1.28 mol) of 4-*t*-butylcyclohexanol (commercial mixture, 70% *trans*, 30% *cis*) in 250 ml of dry ether with stirring. The reaction mixture was left in an ice bath overnight

(30) Similar difficulties for cyclohexyl fluoride (proton spectrum) have been indicated in ref 16. In this instance, however, low-temperature *fluorine* spectra gave a reasonable value of $-\Delta G°_F$.

(31) N. N. Yarovenko and M. A. Raksha, *Zh. Obshch. Khim.*, **29**, 2159 (1959).

(32) D. E. Ayer, *Tetrahedron Letters*, 1065 (1962).

(33) (a) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *Tetrahedron Letters*, 1249 (1962); *J. Org. Chem.*, **29**, 2187 (1964); (b) L. H. Knox, E. Velarde, S. Berger, I. Delfín, R. Grezemkovsky, and A. D. Cross, *ibid.*, 30, 4160 (1965).

(34) There is also a minor triplet splitting due to the two *gauche* protons in all cases; $J \cong 10$ cps.

(35) The ^{19}F spectrum of *trans*-4-*t*-butylcyclohexyl fluoride indicated that a *small* amount of rearrangement did occur, as evidenced by the (distinct) ^{19}F signal of the *cis*-3 isomer.

(36) H. Hopff and G. Valkanas, *Helv. Chim. Acta*, **46**, 1818 (1963); F. Cuthbertson and W. K. R. Musgrave, *J. Appl. Chem.*, 7, 99 (1957).

(37) W. Bockemüller "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p 233.

(38) F. Swarts, *Bull. Soc. Chim. Belges*, **45**, 624 (1936); A. V. Grosse and C. B. Linn, *J. Org. Chem.*, **3**, 26 (1938); J. H. Simons and A. C. Meunier, *J. Amer. Chem. Soc.*, **65**, 1269 (1943).

and was allowed to come to room temperature when the ice had melted. It was stirred for 6 hr at room temperature, poured into water, and separated, and the water layer twice extracted with ether. The ether layers were washed with water and sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The residue was concentrated and then fractionally distilled through a spinning-band column at 50 mm to give 112 g (68%) of 4-*t*-butylcyclohexane (bp 88°) and 15.5 g (9%) of mixed 4-*t*-butylcyclohexyl fluorides contaminated with some higher boiling material (bp 88–96°). The fluorides were separated by two successive passes through a Wilkens A-700 preparative gas chromatograph using a 20 ft × 3/8 in. column packed with 33% QF-1 on Chromosorb W at 128°. There was thus obtained 10 g of *cis*-4-*t*-butylcyclohexyl fluoride, $n^{20}D$ 1.4398, prominent infrared bands at 824, 913, 939, 1005, and 1030 cm^{-1}, and 1.5 g of *trans*-4-*t*-butylcyclohexyl fluoride, $n^{20}D$ 1.4377, infrared bands at 904, 975, 1008, 1026, and 1050 cm^{-1}.

Anal. Calcd for $C_{10}H_{19}F$: C, 75.89; H, 12.10. Found (*cis* isomer): C, 76.49; H, 12.14. Found (*trans* isomer): C, 76.39; H, 12.10.

A number of variations in conditions were studied, but in all cases the reaction product was mostly olefin and the fluoride consisted predominantly of the *cis* isomer. The results are summarized in Table V. The triethylamine was added in the hope that it would decrease olefin formation, but this expectation did not materialize. Its major effect turned out to be a considerable slowing down of the reaction.

Table V. Yields of 4-*t*-Butylcyclohexyl Fluorides under Different Conditions

Solvent	Time, hr	Temp, °C	Yield, %: Olefin	Yield, %: Fluoride	% *cis* isomer (in fluoride)
Ether	14	20	52	12	87
	1.5	35	60	15	90
Ether–triethylamine	18	35	(31 combined)		45
	96	35	45	22	67
	132	35	39	24	82
Acetonitrile–triethylamine	5	82	(51 combined)		
	21	82	81	17	80

4-*t*-Butylcyclohexyl-d_1 Fluoride. This compound was prepared under conditions shown in Table V to give maximum yield of fluoride. 4-*t*-Butylcyclohexanol-1-*d* was prepared by reducing 4-*t*-butylcyclohexanone with lithium aluminum deuteride. The mixture of epimeric alcohols was used without purification. 2-Chloro-1,1,2-trifluorotriethylamine (23.3 g, 0.12 mol) previously prepared as described above was boiled under reflux with 14.2 g (0.11 mol) of the above alcohol in 80 ml of ether and 24 ml of triethylamine for 5 days. The solution was worked up as described above for the hydrogen analog and was then passed through a column of silica gel, 1 in. in diameter, 9 in. long, containing a bottom layer of potassium carbonate. The column was eluted with 100 ml of petroleum ether (bp 30–60°). Concentration of the eluate yielded 10.6 g which upon preparative gas–liquid partition chromatography on a 20-ft basic 33% QF-1 column on Chromosorb W at 140° yielded 5.6 g (37%) of olefin, 2.2 g (12.5%) of *cis*-4-*t*-butylcyclohexyl-1-*d* fluoride, and 0.2 g (1.1%) of the *trans* isomer. Prominent infrared peaks for the *cis* isomer occurred at 912, 930, and 1031 cm^{-1}; $n^{20}D$ 1.4388. Neither isomer contained carbonyl impurity.

Anal. Calcd for $C_{10}H_{18}DF$: C, 75.41; H, 12.01, D, 5.26 atom %. Found: C, 74.81; H, 12.10; D, 4.86 atom % (*cis* isomer).

1,1-Difluorocyclohexane and 1-Chloro-1-fluorocyclohexane.[36] These materials were prepared by the action of anhydrous hydrogen fluoride on 1-chlorocyclohexene.[36] Fractional distillation of the product (at 106 mm) separated 1,1-difluorocyclohexane, 1-chloro-1-fluorocyclohexane, and 1,1-dichlorocyclohexane. The difluoro compound was purified by preparative gas chromatography on a 12 ft × 3/8 in. column of 33% QF-1 on Chromosorb P at 92°. 1-Chloro-1-fluorocyclohexane decomposed on the same column at 128° and was purified by fractional distillation. 1,1-Difluorocyclohexane boiled at 45° (106 mm), $n^{20}D$ 1.3891 (lit.[36] 100–101° (760 mm), 100.5° (760 mm), $n^{20}D$ 1.3906); 1-chloro-1-fluorocyclohexane boiled at 73–76° (97–98 mm.), $n^{20}D$ 1.4361 (lit.[38] 141–142° (760 mm), 138.2° (760 mm), $n^{20}D$ 1.4382). The infrared spectrum of 1,1-difluorocyclohexane was identical with one of the same compound kindly supplied by Professor J. D. Roberts.[27]

1-Chloro-4-*t*-butylcyclohexene and 1,1-Dichloro-4-*t*-butylcyclohexane. Phosphorus pentachloride (218 g, 1.05 mol) was placed in a 500-ml, three-necked flask fitted with a calcium chloride tube, an electrically driven stirrer, and an inlet device for adding solid ketone. 4-*t*-Butylcyclohexanone (121 g, 0.785 mol) was added slowly as a solid at room temperature. The stirrer was operated by hand until enough ketone had been added to form a mush, after which it was driven mechanically. After the ketone had been added, the reaction mixture was allowed to stand overnight and was then poured onto ice and extracted with petroleum ether (bp 30–60°). The extract was cleared with sodium carbonate solution and water, dried over anhydrous magnesium sulfate, and concentrated. The residue was distilled through a spinning-band column to give 87.3 g (64%) of 1-chloro-4-*t*-butylcyclohexene, bp 113–117° (31–33 mm), 6.5 g of intermediate fraction, 19.6 g (12%) of 1,1-dichloro-4-*t*-butylcyclohexane (see below), and 11.5 g of a higher boiling fraction.

1-Chloro-4-*t*-butylcyclohexene was redistilled, bp 96.0–98.7° (12.3–14.0 mm), and its slightly yellow color removed by passage through an alumina column (13/4 × 1/3 in.). Prominent infrared peaks occur at 720, 810, 831, 913, 984, 1025, 1050, and 1655 cm^{-1}; $n^{20}D$ 1.4790.

Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.54; H, 9.92; Cl, 20.53. Found: C, 69.96; H, 10.23; Cl, 19.94.

The 1,1-dichloro-4-*t*-butylcyclohexane was redistilled, bp 99.2–100.0° (7.5–7.7 mm), and filtered through an alumina column as above; $n^{20}D$ 1.4782; prominent infrared peaks at 737, 787, 838, 900, 1005, 1020, and 1119 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}Cl_2$: C, 57.42; H, 8.67; Cl, 33.30. Found: C, 57.73; H, 8.54; Cl, 33.67.

1,1-Difluoro- and 1-Chloro-1-fluoro-4-*t*-butylcyclohexanes. Anhydrous hydrogen fluoride (120 g, 6 mol) was condensed in a polyethylene bottle and 67.3 g (0.39 mol) of 1-chloro-4-*t*-butylcyclohexene was added fairly rapidly at −10°. The reaction mixture was stirred at room temperature for 2.75 hr with a Teflon-covered magnetic stirring bar, during which time the hydrogen fluoride was allowed to evaporate slowly. The reaction product was poured onto ice and neutralized with sodium carbonate. Petroleum ether (bp 30–60°) was added, and the liquid phases were filtered from the solid fluoride which was washed with more petroleum ether. The water layer was separated and the petroleum ether layer washed with water and dried over anhydrous magnesium sulfate. The solution was concentrated and the residue distilled through a spinning-band column yielding 25.4 g (38%) of 1,1-difluoro-4-*t*-butylcyclohexane, bp 80–81° (26 mm), and 35.7 g of a mixture of 1-chloro-1-fluoro- and 1,1-dichloro-4-*t*-butylcyclohexanes, bp 81–126° (27 mm). The 1,1-difluoro-4-*t*-butylcyclohexane was purified by preparative gas chromatography using the earlier mentioned 12-ft QF-1 column at 160° and also by fractional distillation; bp 61° (9.5 mm); $n^{20}D$ 1.4210; prominent infrared peaks at 747, 769, 831, 933, 963, 990, 1106, 1130, 1199, and 1269 cm^{-1} (lit.[27] bp 83–84° (32 mm); $n^{20}D$ 1.4210; peaks at 1110, 1130, 1200, 1275, 1365, and 1380 cm^{-1}).

The second fraction (stereoisomers of fluorochloro compound) was purified by two successive distillations, bp 86.0–87.0° (11 mm); $n^{20}D$ 1.4501; prominent infrared peaks at 708, 808, 827, 872, 927, 956, 979, 1027, and 1072 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}ClF$: C, 62.33; H, 9.41; Cl, 18.40. Found: C, 62.56; H, 9.44; Cl, 18.46.

1-Chloro-3- (and -5-) *t*-butylcyclohexene and 1,1-Dichloro-3-*t*-butylcyclohexane. The above compounds were prepared analogously as their 4-*t*-butyl analogs from 94 g (0.43 mol) of phosphorus pentachloride and 45.3 g (0.29 mol) of 3-*t*-butylcyclohexanone. There was obtained 38.1 g (75%) of 1-chloro-3- (and -5-) *t*-butylcyclohexene, bp 86–104° (11 mm), and 7.1 g (11.5%) of 1,1-dichloro-3-*t*-butylcyclohexane, bp 104–120° (11 mm).

The lower boiling fraction was passed through an alumina column in petroleum ether solution and was analyzed gas chromatographically (10-ft column, 20% QF-1 on Chromosorb P at 127°). The fraction contained 4% of dichloro impurity and the ratio of 3-*t*-butyl to 5-*t*-butyl compound (see below) was 1:4. The fraction was redistilled to give 32.8 g, bp 87–92° (11 mm), of material suitable for the preparation of the difluoro compound (see below). For isolation of the individual chloroolefins, the material was subjected to preparative gas chromatography on a 12-ft QF-1 column at 160°. The first eluate was identified as 1-chloro-3-*t*-butylcyclohexene be-

cause it had a relatively narrow vinyl proton (at 345.7 cps), half-width 4.5 cps, and three allylic protons centered at 130 cps; $n^{20}D$ 1.4818.

Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.54; H, 9.92. Found: C, 69.72; H, 9.93.

The second eluate proved to be 1-chloro-5-*t*-butylcyclohexene, wide vinyl proton at 342.0 cps (half-width 8.0 cps) and four allylic protons centered at 127 cps; $n^{20}D$ 1.4802.

Anal. Calcd for $C_{10}H_{17}Cl$; C, 69.54; H, 9.92; Cl, 20.53. Found: C, 69.67; H, 9.84; Cl, 20.64.

The higher boiling fraction was redistilled to give 5.5 g of 1,1-dichloro-3-*t*-butylcyclohexane, bp 104.8–105.8° (10.7–11.0 mm); $n^{20}D$ 1.4820; prominent infrared peaks at 736, 762, 815, 866, and 932 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}Cl_2$: C, 57.42; H, 8.67; Cl, 33.90. Found: C, 57.59; H, 8.70; Cl, 33.74.

1,1-Difluoro-3-*t*-butylcyclohexane and 1-Chloro-1-fluoro-3-*t*-butylcyclohexanes. A mixture of 1-chloro-3- and 1-chloro-5-*t*-butylcyclohexenes (32.8 g, 0.19 mol) was added rapidly to cold anhydrous hydrogen fluoride (77 g) in a polyethylene bottle, and the reaction mixture was let stand at room temperature for 2.2 hr. It was worked up as described above for the 4 isomer. Fractional distillation yielded 22.9 g (69%) of 1,1-difluoro-3-*t*-butylcyclohexane, bp 60–79.5° (11 mm), and 4.9 g of 1-chloro-1-fluoro- and 1,1-dichloro-3-*t*-butylcyclohexanes, bp 79.5–100° (11 mm). Redistillation gave 16.1 g of 1,1-difluoro-3-*t*-butylcyclohexane purified by percolation through alumina. The material had prominent infrared bands at 938, 962, 1017, and 1090 cm^{-1}; $n^{20}D$ 1.4211.

Anal. Calcd for $C_{10}H_{18}F_2$: C, 68.15; H, 10.29. Found: C, 67.84; H, 10.13.

The second fraction was redistilled to give 1.8 g of 1-chloro-1-fluoro-3-*t*-butylcyclohexane, bp 84–88° (11 mm). Percolated through an alumina column it had $n^{20}D$ 1.4562; prominent infrared peaks at 728, 838, 874, 880, 890, 986, and 1072 cm^{-1}. The compound was obtained in higher yield by rapidly adding a mixture of 38 g (0.22 mol) of the chloroolefins to 12.7 g (0.63 mol) of liquid hydrogen fluoride in a polyethylene bottle at −30°, stirring (without external cooling) for 25 min, and then immediately pouring the mixture onto crushed ice and potassium hydroxide (40 g). The organic layer was separated, the aqueous layer was extracted with petroleum ether, and the combined extracts were dried over calcium chloride. Concentration and fractional distillation yielded 22 g (52%) of the chlorofluoride, bp 81–83° (9 mm), $n^{20}D$ 1.4552, in addition to 10.5 g of somewhat higher boiling material. Analysis showed this material to be slightly impure.

Anal. Calcd for $C_{10}H_{18}FCl$: C, 62.33; H, 9.41; Cl, 18.40. Found: C, 63.53; H, 9.72; Cl, 18.88.

3-*t*-Butylcyclohexyl Fluorides. 2-Chloro-1,1,2-trifluoroethylamine (78.5 g, 0.41 mol, redistilled, bp 48–50° (17 mm)) prepared as described earlier was added to 35.4 g (0.23 mole) of mixed 3-*t*-butylcyclohexanol in 500 ml of methylene chloride cooled to −70° in a Dry Ice–acetone bath. The mixture was placed in an ice–salt bath and kept there for 49 hr. One-half of the cold mixture was passed through an alumina column (500 g) which resulted in an exothermic reaction at the top of the column. The olefin and fluoride were eluted with petroleum ether (bp 30–60°).

Since this procedure seemed less than optimal, the other half of the mixture was treated with 40 g of sodium hydroxide in 200 ml of water while still in the ice–salt bath. The organic layer was removed and the aqueous layer extracted with petroleum ether. The combined extracts were dried over potassium carbonate and concentrated, and the product was passed through an alumina column with the aid of petroleum ether. Here again an exothermic reaction occurred on the column.

The eluates from the two batches were therefore combined and separated by preparative gas chromatography on a 20-ft basic QF-1 column at 137° yielding 14.3 of olefin, 3.7 g of crude *trans*-fluoride, and 0.9 g of crude *cis*-fluoride. The fluorides were purified by a second passage through the column and redistilled; configurations are assigned on the basis of the nmr spectra (see below).

The *trans*-fluoride had $n^{20}D$ 1.4392; prominent infrared bands at 899, 1045, and 1228 cm^{-1}. The *cis*-fluoride (longer retention time), $n^{20}D$ 1.4382, had prominent infrared bands at 952, 962, 991, 1029, and 1186 cm^{-1}.

Anal. Calcd for $C_{10}H_{19}F$: C, 75.89; H, 12.10. Found (*trans* isomer): C, 75.76; H, 12.17. Found (*cis* isomer): C, 75.93; H, 12.09.

3-*t*-Butylcyclohexanone Dimethyl Ketal.[39] A solution of 10.0 g (0.065 mole) of 3-*t*-butylcyclohexanone, 8.8 g (0.85 mol) of 2,2-dimethoxypropane, 6.2 g of methanol, and 0.009 g of *p*-toluenesulfonic acid was heated in a round-bottomed flask equipped with a spinning-band column. Acetone was distilled off overhead. When the temperature of the distillate reached 63°, the reaction was stopped, and 1 ml of a solution of methanolic sodium methoxide (0.3 g of sodium in 30 ml of methanol) was added to the cooled flask. The reaction mixture was then fractionally distilled and yielded two fractions of 3-*t*-butylcyclohexanone dimethyl ketal, bp 101.0–102.0° (10.6 mm) (2.9 g) and bp 102.0° (10.6 mm), $n^{20}D$ 1.4518 (7.6 g); total yield 10.5 g (81%). The material has a strong smell of rhubarb and its nmr spectrum (in carbon tetrachloride) showed peaks at 181.9 and 185.6 cps downfield from tetramethylsilane (at 60 Mcps). Prominent infrared bands were found at 815, 850, 900, 929, 953, 1013, 1068, 1092, 1114, and 1146 cm^{-1}.

Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.24; H, 12.06.

Cyclohexanone dimethyl ketal[40] and 4-*t*-butylcyclohexanone dimethyl ketal[40] were prepared as previously described. The parent compound boiled at 83.3–84.4° (51 mm), $n^{20}D$ 1.4389, and had an nmr signal at −183.9 cps; the signals of the 4-*t*-butyl homolog were found at −182.9 and −184.9 cps.

Nmr Spectra. Proton Spectra. The nmr spectra were recorded on a Varian HR-60 instrument at 60 Mcps. The temperature within the probe was 29°. The concentration of solutions was 17–25%. Chemical shifts were measured by the side-band technique using a Hewlett-Packard audio oscillator and counter. Multiple up and down scans were made in all cases. Tetramethylsilane was the internal standard.

The axial proton of *cis*-3- and *trans*-4-*t*-butylcyclohexyl halides displayed a distinct nonet whose center peak was sharply defined and easily located, even in dilute solutions. The equatorial proton of the *trans*-4- and *cis*-3-*t*-butylcyclohexyl halides usually appeared either as a poorly defined triplet or as a doublet with slight indication of a third peak, depending on whether the field was increasing or decreasing. In a few spectra, five peaks could be distinguished, as would be expected from the coupling with four *gauche* hydrogens. In the usual case of the doublet, the shift was measured to the downfield peak which appeared to correspond to the center of the multiplet. The C_1-proton of the unsubstituted cyclohexyl halides appears as a septet with a well-defined central peak at increasing field and as a symmetrical sextet with a decreasing field. Close examination suggests that the peak is really a septet and when the two central peaks were equivalent, the shift was therefore measured to the downfield one of the two.

In the case of the fluorides, all the peaks were duplicated, due to a fluorine coupling constant of 49.0–49.5 cps. The upfield peak, in accordance with previous observations,[16] was not very clearly defined in its proton splitting pattern whereas the downfield peak was well resolved. All shifts were therefore measured to the downfield peak rather than to the midpoint between the two peaks. Since the fluorine coupling constant is virtually the same in all cases, this procedure causes no error in the computation of the conformational equilibria. In representative cases, calculations based on the midpoint of the doublet gave the same result as those based on the downfield peak.

cis-4-*t*-Butylcyclohexyl-1-*d* fluoride showed virtually no peak in the C*H*F region of the spectrum except for a very small signal ascribed to an impurity of 4-*t*-butylcyclohexene (about 1%). This peak was not due to a fluoride since it was not split. In control experiments, the C*H*F proton of *cis*-4-*t*-butylcyclohexyl fluoride could readily be detected in a 1.3% solution in $CFCl_3$. *trans*-4-*t*-Butylcyclohexyl-1-*d* fluoride showed no C*H*F peak; however, the level at which this rather broad peak can be detected is higher than in the case of the *cis* isomer.

Fluorine Spectra. The fluorine spectra were recorded at 56.4 Mcps. Since difficulties were encountered in obtaining a suitable frequency standard, mixtures of *cis*- and *trans*-4-*t*-butylcyclohexyl fluorides and cyclohexyl fluoride, of *cis*- and *trans*-3-*t*-butylcyclohexyl fluoride and cyclohexyl fluoride, of 3-*t*-butyl-1,1-difluorocyclohexane and 1,1-difluorocyclohexane, of 4-*t*-butyl-1,1-difluorocyclohexane and 1,1-difluorocyclohexane, of 3-*t*-butyl-1-chloro-1-fluorocyclohexane (mixed isomers) and 1-chloro-1-fluorocyclohexane, and of 4-*t*-butyl-1-chloro-1-fluorocyclohexane (mixed isomers) and 1-chloro-1-fluorocyclohexane were prepared and their spectra recorded. Side bands were obtained to allow each spectrum to be calibrated internally. The spectrum of the unsubstituted mono- or

(39) N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521, 525, 1814 (1960).

(40) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, **84**, 2371 (1962).

dihalide was used as the (arbitrary) standard of reference in each case. Fluorine coupling constants (in cycles per second) for the geminal difluorides and proton coupling both geminal and vicinal are listed below. Since $J_{gem} \approx J_{anti} > J_{gauche}$ it follows that axial

F–F (*gem*) 236 ± 3	H–F (*anti*) 44
H–F (*gem*) 46	H–F (*gauche*) 10

fluorine in the monofluorides appears as a quartet (large split) of triplets (small split) whereas the equatorial fluorine in the monofluorides appears as a doublet of two sharp peaks.

The ^{19}F resonance of *cis*-4-*t*-butylcyclohexyl-1-*d* fluoride showed a triplet of triplets, J_{anti} = 40 cps. *trans*-4-Butylcyclohexyl-1-*d* fluoride analogously shows a *single*, somewhat sharp peak. However, it also showed some contamination due to the *cis* isomer and a third component whose signals coincided with that of *cis*-3-*t*-butylcyclohexyl fluoride. Thus a minor amount of rearrangement may have taken place in the displacement of hydroxyl by fluorine.

Conclusion

It is clear from the data here presented that either a 3- or a 4-*t*-butyl group has a strong effect on fluorine resonance at C_1. On the other hand, whereas a 3-*t*-butyl group does somewhat affect proton shift at C_1, a 4-*t*-butyl group in a carbocyclic system apparently does not and it therefore appears that the nmr method as originally proposed[4] is suitable for determining conformational equilibria in cyclohexanes. The reason why a 4-*t*-butyl group has no adverse effect while a 3-*t*-butyl group does has its parallel both in the kinetic[1] and in the equilibrium[41,42] method of conformational analysis and the phenomena may all have a common cause in that the 4-*t*-butyl-substituted compounds (III, IV) and the monosubstituted compound (I ⇌ II) suffer deformations of a similar kind, whereas the 3-*t*-butyl-substituted compound suffers either no deformation at all or a lesser deformation.[41,43,44] However, these considerations do not seem to apply to a heterocyclic systems such as 1,3-dioxane.[45]

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Conformational Analysis. XIV. Conformational Equilibria of Cyclohexyl Halides[1]

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Abstract: The conformational equilibria of cyclohexyl fluoride, chloride, and bromide have been determined by nuclear magnetic resonance (^1H) as a function of solvent, using the 4-*t*-butylcyclohexyl halides as conformationally rigid models. The $-\Delta G°$ values are: 0.15 kcal/mol for fluorine, 0.43 kcal/mol for chlorine, and 0.37 kcal/mol for bromine, and are remarkably independent of solvent. The value for chlorine was confirmed by an infrared method. 3-*t*-Butylcyclohexyl fluorides and chlorides are not suitable models for conformational equilibrium determinations. ^{19}F nmr spectra can be used for such determination in the 4-*t*-butylcyclohexyl fluoride series only with use of a correction factor computed from the nmr spectra of 1,1-difluorocyclohexanes. A convenient method for the synthesis of *cis*- and *trans*-4-*t*-butylcyclohexyl chlorides and their 3 isomers from the corresponding alcohols *via* the chloroformates is described.

It is well known[2] that conformational equilibrium in a substituted cyclohexane favors the equatorial position of the substituent (Figure 1). Conformational equilibrium in a 1,2-disubstituted ethane (Figure 2) often favors the *anti* conformation over the *gauche*, despite the fact that the latter has a twofold statistical advantage. It would appear that similar steric factors are operative in the two cases and it has often been stated[2c] that the axial interaction in a substituted cyclohexane corresponds to two *gauche* interactions in a 1-substituted propane (Figure 2, X = CH_3). The heavy lines in Figure 1 show these interactions as incorporated in the cyclohexane with axial substituent. In fact, the enthalpy difference[3] between axial and equatorial methylcyclo-

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