Carbowax 20M column at 110°) of the product mixture showed 65% IIIa-Cl and 35% IIIe-Cl. In a second experiment, the relative amounts of the two chlorides were 64% IIIa-Cl and 36% IIIe-Cl.

Hydrogen Chloride Addition to V.—Olefin V was prepared by the reaction of 4-*tert*-butylcyclohexanone with methylene iodide and magnesium turnings in ethyl ether solution.[39] Distillation of the product mixture through a spinning-band column gave >99% pure V,[39] bp 78° (18 mm), nmr (CCl_4) δ 4.52 (m, 2, $C{=}CH_2$). Hydrochlorination and product analysis were carried out in the same manner as for addition to IV. In two experiments, the IIIa-Cl:IIIe-Cl isomer ratios were 70:30 and 69:31.

Registry No.—*cis*-I (X = CO_2H), 943-28-2; *trans*-I (X = CO_2H), 943-29-3; *cis*-I (X = OSDNP), 37816-62-9; *trans*-I (X = OSDNP), 37816-63-0; *cis*-I (X = OCOCl), 15595-62-7; *trans*-I (X = OCOCl), 15595-61-6; *cis*-I (X = OH), 937-05-3; *trans*-I (X = OH), 937-06-4; *cis*-I (X = OAc), 10411-92-4; *trans*-I (X = OAc), 1900-69-2; *cis*-I (X = Cl), 13131-74-3; *trans*-I (X = Cl), 13145-48-7; *cis*-II (X = OAc), 20298-72-0; *trans*-II (X = OAc), 20298-71-9; *cis*-III (X = OAc), 15807-53-1; *trans*-III (X = OAc), 15807-52-0; *cis*-III (X = OH), 16980-55-5; *trans*-III (X = OH), 16980-56-6; *cis*-III (X = Cl), 25276-09-9; *trans*-III (X = Cl), 25276-10-2; IV, 3419-74-7; V, 13294-73-0; 4-*tert*-butylbenzoic acid, 98-73-7; 4-*tert*-butyl-1-cyclohexene, 2228-98-0; 2,4-dinitrobenzenesulfenyl chloride, 528-76-7; 4-*tert*-butylcyclohexanone, 98-53-3.

Acknowledgment.—We gratefully acknowledge the exchange of data and correspondence with Professor Harold Kwart and Mr. John Boghosian, University of Delaware, about the reactions of Ia-OSAr and Ie-OSAr before publication.

---

[39] G. Cainelli, F. Bertini, P. Gasselli, and G. Zubioni, *Tetrahedron Lett.*, 5153 (1967).

α-Fluoro-3,3,5,5-Tetrasubstituted Cyclohexanones. I. Synthesis and Conformational Analysis[1]

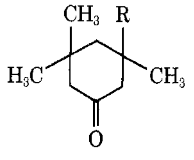
BERNARD L. SHAPIRO*[2] AND MICHAEL M. CHRYSAM III[3]

Department of Chemistry, Texas A & M University, College Station, Texas 77843

Received September 1, 1972

A series of new α-fluoro- and α,α-difluoro-3,3,5,5-tetrasubstituted cyclohexanones has been synthesized by the reaction of perchloryl fluoride with the α-hydroxymethylene derivatives of the following tetrasubstituted cyclohexanones: 3,3,5,5-tetramethylcyclohexanone (**1a**), 3-phenyl-3,5,5-trimethylcyclohexanone (**1b**), and 3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (**1c**). The monofluoro derivative of **1a**, the six possible mono- and difluoro derivatives of **1b**, and the three fluoroketones formed by substitution at C-6 of **1c** have been prepared and characterized. The axial or equatorial nature of the fluorine substituent has been studied as a function of solvent polarity by dipole moment measurements, infrared spectroscopy, and proton and fluorine nmr spectra. All of the results are consistent with the generalization that the fluorine of α-halocyclohexanones has a much greater preference to be equatorial in polar solvents than in nonpolar solvents. Anomalously high-field methyl resonances in the proton nmr spectra of the aryl-substituted fluoroketones furnish a sensitive indicator of the conformational equilibrium, and these lead to the conclusion that a 1,3-diaxial methyl–phenyl interaction is favored over a 1,3-diaxial dimethyl interaction by approximately 0.9 kcal/mol. The chemical shifts of the ring protons are consistent with chair conformations.

Recent work in this laboratory has been concerned with the nmr spectra and conformational analysis of highly substituted cyclohexanones and their derivatives. In these investigations[4–6] particular attention has been given to 3,3,5,5-tetrasubstituted cyclohexanones (*e.g.*, **1**), since, if these molecules are to exist in chair (or at least chairlike) conformations, a severe steric interaction between the axial substituents at C-3 and C-5 is inevitable.



1a, R = methyl
b, R = phenyl
c, R = 1–naphthyl

The proton nmr spectrum of 3,3,5,5-tetramethylcyclohexanone (**1a**) consists of three peaks which correspond to the methyl protons, the γ-methylene protons, and the α-methylene protons. This chemical equivalence is certainly due to a rapid interconversion between conformers. Although the magnitude of a 1,3-diaxial dimethyl interaction has been shown[7] to be approximately 3.7 kcal/mol, a calculation[8] of the conformational enthalpies of **1a** by the Westheimer method indicates that the chair conformer is favored over the most stable boat form by 3.8 kcal/mol. The 2-bromo and 2,6-dibromo derivatives of **1a** have been extensively studied.[9–14] Owing to the 1,3-diaxial interaction in these compounds, Ourisson, *et al.*,[9,10] have postulated the "reflex effect" by which the cis axial methyl groups are bent outward, causing the α carbons to be pushed together. In a study[11] of the crystal structures of 2-bromo- and *cis*-2,6-dibromo-3,3,5,5-tetramethylcyclo-

---

[1] Taken in part from the Ph.D. dissertation submitted by M. M. Chrysam III to the Department of Chemistry, Texas A & M University, 1970; this work was initiated at the Chemistry Department of the Illinois Institute of Technology, Chicago, Ill.

[2] To whom correspondence should be addressed.

[3] National Science Foundation Graduate Fellow, 1966–1970.

[4] B. L. Shapiro, M. J. Gattuso, N. F. Hepfinger, R. L. Shone, and W. L. White, *Tetrahedron Lett.*, 219 (1971).

[5] B. L. Shapiro, M. J. Gattuso, and G. R. Sullivan, *ibid.*, 223 (1971).

[6] M. J. Gattuso, Ph.D. Dissertation, Texas A & M University, 1970.

[7] N. L. Allinger and M. A. Miller, *J. Amer. Chem. Soc.*, **83**, 2145 (1961).

[8] N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *ibid.*, **91**, 337 (1969).

[9] C. Sandris and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1524 (1958).

[10] B. Waegell and G. Ourisson, *ibid.*, 496 (1963).

[11] L. C. G. Goaman and D. F. Grant, *Tetrahedron*, **19**, 1531 (1963).

[12] M. Anteunis, N. Shamp, and H. De Pooter, *Bull. Soc. Chim. Belg.*, **76**, 541 (1967).

[13] C. W. Jefford and B. Waegell, *ibid.*, **79**, 427 (1970).

[14] M. Anteunis and N. Shamp, *ibid.*, **79**, 437 (1970).

hexanone by X-ray analysis, the cis diaxial methyl carbon atoms were found to be separated by 3.4 Å (the distance between 3,5-diaxial substituents in an ideal cyclohexanone ring), and the ring angles were found to deviate markedly from the values in cyclohexanone itself, with the C_2–C_1–C_6 angle decreasing to 108° and the C_3–C_4–C_5 angle increasing to 121° for the monobromo derivative. The proton nmr spectra of 2-bromo- and 2-chloro-3,3,5,5-tetramethylcyclohexanone have been interpreted in terms of chairlike conformations.[12-14]

A detailed study[4,6] of 3-aryl-3,5,5-trimethylcyclohexanones (*e.g.*, **1b** and **1c**) by nmr spectroscopy demonstrated that these molecules exist in chairlike conformations and that the conformer having an axial aryl group is heavily favored, contrary to previous conclusions.[15,16] The most interesting and informative aspect of the proton nmr spectra of these compounds is the occurrence of a very high-field resonance for one of the methyl groups at C-5 (δ 0.15–0.4 ppm). These high-field shifts are considered to arise from the C-5 methyl group which is cis to an axial aryl substituent, since in this conformation the methyl protons spend a considerable portion of time in the shielding region of the aromatic ring. The equatorial C-5 methyl shift is quite normal (δ 1.0), while the C-3 methyl protons are deshielded (δ 1.3 to 1.8) because they lie near the edge of the aromatic substituent. The high-field methyl resonance appears only in the spectra of 1,1,3,3-tetrasubstituted cyclohexanoid systems having at least one aryl substituent, and it is not dependent on the presence of an sp^2-hybridized carbon in the ring.[4,6] Although this study established that one conformer is predominant, a reliable estimate of the amount by which a 1,3-diaxial aryl–methyl interaction is favored over the alternative 1,3-diaxial dimethyl interaction was not obtained.

We therefore felt that these systems could be made more amenable to study by the addition of a substituent which could provide a "handle" into the molecular conformation, *i.e.*, a means by which the conformational equilibrium could be altered in a known way. The conformations of mobile α-haloketones in solution have been shown to be dependent on the polarity of the solvent, since a solvent of high dielectric constant tends to stabilize the conformation having the higher dipole moment, *i.e.*, that with carbon–oxygen and carbon–halogen dipoles coplanar, relative to a solvent of low dielectric constant. For this reason α-haloketones have been the subject of considerable conformational study by numerous physical methods including dipole moments, optical rotatory dispersion, and nmr, infrared, and ultraviolet spectroscopy.[17]

The α-fluoro derivatives of ketones **1** are particularly appropriate choices for the present study. Since the size of the fluorine atom approximates that of the hydrogen atom more closely than that of the other halogens, the conformations of the fluoroketones are not expected to differ greatly from those of the parent ketones. Also, the presence of fluorine in the molecule increases the suitability for study by nmr spectroscopy, since measurement of fluorine chemical shifts which are very sensitive to stereochemical environment of the fluorine nucleus and the presence of ^{19}F–H and ^{13}C–^{19}F couplings in the proton and carbon-13 nmr spectra give useful aids in spectral interpretation and chemical shift assignments. In addition, these α-fluoro-3,3,5,5-tetrasubstituted cyclohexanones provide excellent substrates for the study of the geometric dependence of long-range H–H and H–F coupling constants, since the ring proton resonances are usually well separated and since there are no vicinal H–H couplings. Regrettably, in many previous nmr studies of cyclohexanoid systems such as 2-fluorocyclohexanone,[18] most of the long-range couplings and many of the ring proton chemical shifts were not reported, being obscured by the complexity of the spectra.

This paper, then, presents the details of the synthesis of the α-fluoro derivatives of **1**, their identification, the conformational conclusions which can be made in light of dipole moment measurements, and infrared and nmr spectra, all determined as a function of solvent polarity. Although the proton and fluorine nmr spectral parameters, directly related to stereochemical conclusions, are presented here, the complete tabulation of proton, fluorine, and carbon-13 parameters, together with a full discussion of the interpretation and significance of the spectral data, will be given elsewhere.[19]

Synthetic.—The α-fluoroketones were synthesized from the intermediate α-hydroxymethylene ketones by treating the sodium salt with perchloryl fluoride, using the method of Kende,[20] followed by alkaline hydrolysis to ensure cleavage of the α-formyl group.[21] Attempts to prepare 2-fluoro-3,3,5,5-tetramethylcyclohexanone from the corresponding 2-bromoketone by fluoride ion exchange failed,[22] and it was found that perchloryl fluoride does not react with the pyrrolidylenamine of **1a**.[23]

When 2-hydroxymethylene-3,3,5,5-tetramethylcyclohexanone was fluorinated, only 2-fluoro-3,3,5,5-tetramethylcyclohexanone (hereafter, TMF[24]) was obtained; however, in addition to the two isomeric monofluoroketones, a small amount of the corresponding α,α-difluoroketone forms upon fluorinating 2- and 6-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone and 6-hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone. Since the 2-hydroxymethylene derivative of **1c** was formed in very low yield (*ca.* 2%), this compound was not fluorinated.

The syntheses of the α-fluoro derivatives of **1b** are illustrated in Chart I. Isomers were separated by means of fractional crystallization and chromatography on silica gel. The isomers with the fluorine predom-

---

[15] M. Balasubramanian and A. D'Souza, *Tetrahedron*, **24**, 5399 (1968).

[16] M. Balasubramanian and A. D'Souza, *ibid.*, **25**, 2973 (1969).

[17] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, pp 460–469.

[18] Y. H. Pan and J. B. Stothers, *Can. J. Chem.*, **45**, 2943 (1967).

[19] B. L. Shapiro and M. M. Chrysam III, to be published.

[20] A. S. Kende, *Tetrahedron Lett.*, 13 (1959).

[21] J. Edwards and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 5262 (1959).

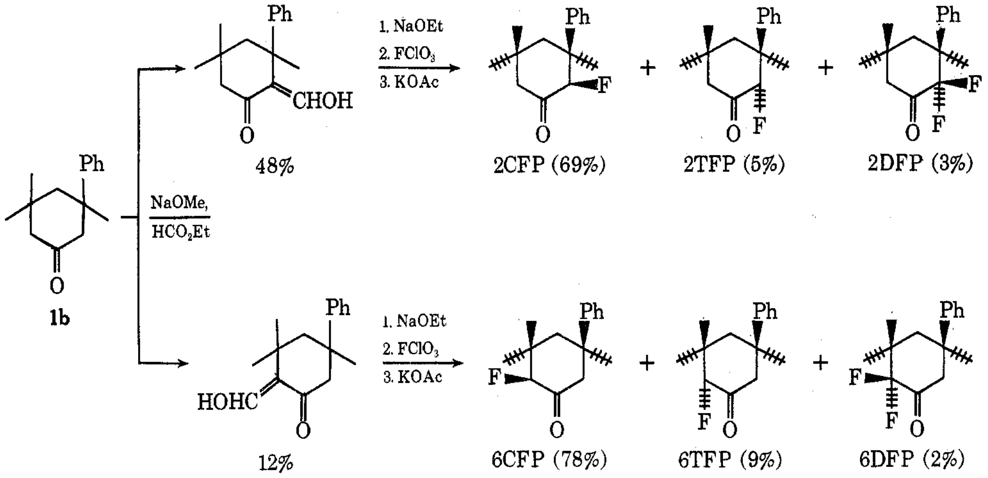
[22] This work; see Experimental Section.

[23] B. L. Shapiro and W. A. Thomas, unpublished results.

[24] The aryl-substituted fluoroketones are named according to whether the α fluorine is at C-2 or C-6 and cis or trans to the aryl group, always taken to be at C-3. In order to ensure clarity and brevity, and to avoid constant referrals to Roman numerals, the following abbreviations are used for the fluoroketones discussed in this work: 2-fluoro-3,3,5,5-tetramethylcyclohexanone, TMF; *cis*-6-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 6CFP; *trans*-6-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 6TFP; 6,6-difluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 6DFP; *cis*-2-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 2CFP; *trans*-2-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 2TFP; 2,2-difluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 2DFP; *cis*-6-fluoro-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone, 6CFN; *trans*-6-fluoro-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone, 6TFN; 6,6-difluoro-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone, 6CFN.

Chart I

Preparation and Yields of α-Fluoro-3-phenyl-3,5,5-trimethylcyclohexanones



inantly equatorial, *viz.*, 6CFP and 2CFP, are shown to be formed in much greater yield by dipole moment measurements (*vide infra*), in agreement with the results of earlier work.[21,25]

Several deuterated compounds were also prepared for use in spectroscopic studies. Base-catalyzed deuterium exchange was used to prepare 2,2,6,6-tetradeuterio-3,3,5,5-tetramethylcyclohexanone, 2-fluoro-2,6,6-trideuterio-3,3,5,5-tetramethylcyclohexanone, and 6-fluoro-2,2,6-trideuterio-3-phenyl-3,5,5-trimethylcyclohexanone. Finally, a mixture of four isomers of α-fluoro-4,4-dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone (2) was prepared by the sequence of reactions shown in Chart II.

Identification of Compounds.—Because of ambiguity in the proton nmr spectral data of the intermediate α-hydroxymethylene ketones,[19] identification of these compounds was accomplished by means of their fluorination products rather than vice versa. In the proton nmr spectra of the isomers designated 2CFP, 2TFP, and 2DFP, only the C-3 methyl (low field) is coupled to fluorine, indicating that these isomers are indeed derived from 2-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone. Similarly, the proton nmr spectra of 6CFP, 6TFP, 6DFP, 6CFN, 6TFN, and 6DFN reveal that fluorine is coupled only to one or both of the *C-5* methyl groups (the "normal" and the "high-field" methyl resonances), indicating that these fluoroketones are derived from the corresponding 6 hydroxymethylene ketones. Similarly, in the carbon-13 spectrum of the 2 isomers, the fluorine is coupled to C-3, the tertiary carbon bearing the aryl substituent, ($^2J_{^{13}\text{C}-^{19}\text{F}}$ = 18 Hz) but not to C-5, while in the 6 isomers the fluorine is coupled to C-5, but not to C-3.

The *cis*- and *trans*-monofluoroketones can be distinguished by means of their dipole moments and proton nmr spectra. As an example, the highest field methyl resonances of the compounds designated 6CFP and 6TFP in dilute solution in carbon tetrachloride occur at δ 0.29 and 0.43, respectively, which indicates that in nonpolar solvents the phenyl group is predominantly axial in both of these isomers. The dipole moments of 6CFP (4.09 D) and 6TFP (3.01 D) in cyclohexane are very similar to the observed dipole moments of *cis*- and *trans*-2-fluoro-4-*tert*-butylcyclohexanone (4.35 and 2.95 D).[25] Since the latter compounds exist exclusively in those conformations with equatorial and axial fluorine, respectively, the fluorine of 6CFP is predominantly equatorial and that of 6TFP is predominantly axial. Thus, if chair conformations are assumed, the isomer formed in greater yield, designated 6CFP, must be the cis isomer and 6TFP must be the trans isomer. From previous studies of 3,3,5,5-tetrasubstituted cyclohexanones and several α-bromo derivatives mentioned in the introduction, it should be expected that these fluoroketones exist in chair-like conformations, and there is evidence from the proton nmr spectra that this is indeed the case (*vide infra*).

Dipole Moments.—Dipole moments of the monofluoroketones, except for 2TFP, which was not obtained pure, were determined by the Guggenheim method in both cyclohexane and benzene. The results are given in Table I.

The greater dipole moments found in benzene than in cyclohexane indicate that these fluoroketones are conformationally mobile.[26] By comparing these dipole moments with those of *cis*- and *trans*-2-fluoro-4-*tert*-butylcyclohexanone (*vide supra*), is is obvious that, in cyclohexane solution, the fluorine is predominantly equatorial in 6CFP, 6CFN, and 2CFP and predominantly axial in 6TFP and 6TFN, while there appears to be a substantial amount of both conformers of TMF present at equilibrium.

The dependence of the observed dipole moments on the position of the conformational equilibria is given by the relation

$$\mu_{\text{obsd}}^2 = N_e\mu_e^2 + N_a\mu_a^2$$

---

[25] N. L. Allinger and H. M. Blatter, *J. Org. Chem.*, **27**, 1523 (1962).

[26] Although the dielectric constant of benzene (ϵ 2.28) is not appreciably greater than that of cyclohexane (ϵ 2.03), the effect of benzene on α-halocyclohexanones is greater than its bulk dielectric constant would suggest. For example, Allinger and Blatter[25] found that the dipole moments of 2-fluorocyclohexanone in heptane and benzene are 3.76 and 4.09 D, respectively, while the corresponding dipole moments of the rigid molecule, *cis*-2-fluoro-4-*tert*-butylcyclohexanone, are 4.37 and 4.35 D. The reason for this effect on mobile 2-halocyclohexanones is quite possibly the stability of the "collision complex"[27] between the considerably polarizable benzene and the equatorial conformer relative to that between benzene and the axial conformer.

[27] For an excellent discussion of benzene collision complexes, see J. Ronayne and D. H. Williams, "Annual Review of NMR Spectroscopy," Vol. 2, E. F. Mooney, Ed., Academic Press, New York, N. Y., 1969, pp 97–106.

CHART II
PREPARATION OF α-FLUORO-4,4-DIDEUTERIO-3-TRIDEUTERIOMETHYL-3,5,5-TRIMETHYLCYCLOHEXANONE

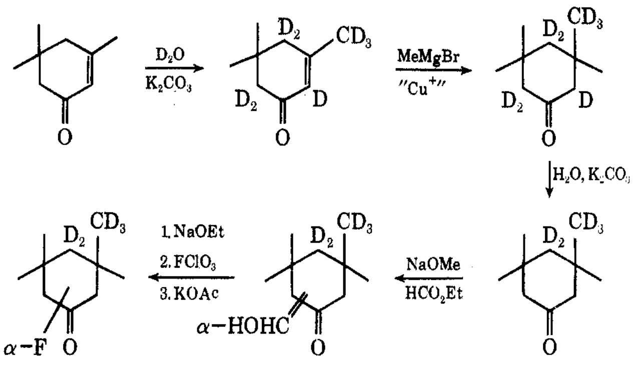


TABLE I
EXPERIMENTAL DIPOLE MOMENTS OF α-FLUORO-3,3,5,5-TETRASUBSTITUTED CYCLOHEXANONES

	Dipole moments[a]		
Compd	Cyclohexane	Benzene	$\Delta(\mu^2)$[b]
TMF	3.62 ± 0.01	3.93 ± 0.01	2.3
6CFP	4.09 ± 0.01	4.18 ± 0.01	0.8
6TFP	3.01 ± 0.01	3.31 ± 0.01	1.9
2CFP	3.94 ± 0.01	4.08 ± 0.01	1.2
6CFN	4.04 ± 0.02	4.12 ± 0.02	0.7
6TFN	3.04 ± 0.01	3.27 ± 0.02	1.5

[a] In Debye units, at 20°. [b] $\Delta(\mu^2)$ is the dipole moment in benzene squared minus the dipole moment in cyclohexane squared.

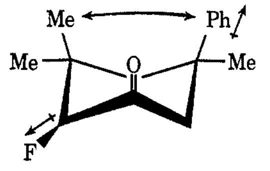
where N is the fraction, μ is the dipole moment, and e and a refer to the conformers having equatorial and axial fluorine, respectively. Of course, N_e and N_a could be calculated exactly if the dipole moments of the pure conformers were known, but no attempt was made to calculate these values because the molecular dipole moments are a sensitive function of inductive effects and geometry. So many assumptions regarding induced dipole effects and bond angles would be necessary as to make the results of any such calculation unreliable.

However, using the above equation, it can easily be shown that

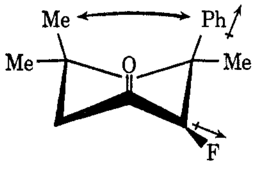
$$N_B - N_C = \Delta(\mu^2)/(\mu_e^2 - \mu_a^2)$$

where N_B and N_C are the fractions of the conformer with equatorial fluorine in benzene and cyclohexane, respectively, $\Delta(\mu^2)$ is the difference of the squares of the experimentally observed dipole moments in benzene and cyclohexane, and μ_e and μ_a are the dipole moments of the axial and equatorial conformers. If the quantity $(\mu_e^2 - \mu_a^2)$ can be considered constant throughout this series (probably only approximately true owing to the small dipole moment of the aryl substituents), the change in mole fraction of the equatorial conformer on going from cyclohexane to benzene solution is proportional to $\Delta(\mu^2)$. In short, the value of $\Delta(\mu^2)$ is indicative of the "conformational purity" of the compound: the lower the $\Delta(\mu^2)$ value, the greater the energy difference between the conformers [*cf. trans*-2-fluoro-4-*tert*-butylcyclohexanone,[26] for which the value of $\Delta(\mu^2)$ is 0.0 within experimental error]. Thus, from the values in Table I, it can be said that for a given solvent the equilibrium amount of the conformer with equatorial fluorine increases in the series TMF < 2CFP < 6CFP < 6CFN, and decreases in the series TMF > 6TFP > 6TFN.

The dipole moment of the conformer with fluorine equatorial is expected to be greater in the case of 6CFP than for 2CFP, since in the 6 isomer the C–F bond dipole is slightly opposed to that of the phenyl group (see **3**), while in the 2 isomer these dipoles are much more nearly coplanar (**4**), assuming that the 3,5-diaxial substituents are twisted outward (*vide supra*). However, since 2CFP has the lower dipole moment of the two isomers, it appears that the conformer having an axial fluorine is present to a greater extent than in 6CFP. The $\Delta(\mu^2)$ values support this conclusion.



3



4

Infrared Spectra.—It is well known that substitution of an α-halogen atom affects the carbonyl stretching frequency to an extent which depends on the relative orientation of the two dipoles.[17] For six-membered rings, axial and equatorial fluorine atoms have been reported[25,28-31] to cause C=O stretching frequency increases of 12–20 and 22–29 cm^{-1}, respectively.

Although the carbonyl bands of the parent ketones (**1**) are very broad, the C=O absorptions of the fluoroketones are sharp enough to show the presence of two conformations in many instances. As the dielectric constant of the solvent increases, the low-frequency band (axial F) is seen to disappear. The spectrum of TMF-d_3 also shows two absorptions of the same relative heights as TMF; therefore it is probable that Fermi resonance, shown[32] to cause doubling of the carbonyl resonance of some α-haloketones, is not involved in this case.

The carbonyl frequencies of the fluoroketones in CCl_4 solutions are listed in Table II. The high-frequency band (equatorial fluorine) is stronger for TMF, 6CFP, 2CFP, and 6CFN, whereas the low-frequency absorption is predominant for 6TFP and 6TFN with, finally, the two carbonyl resonances of 2TFP being comparable. The spectrum of 6CFN indicates that it is the most "conformationally pure" of the monofluoroketones, while 2CFP and 2TFP are more ambiguous in the sense that they are less "conformationally pure" than the corresponding 6 isomers. The $\Delta\nu$ values throughout the table are remarkably consistent and additive, the $\Delta\nu$ values of the difluoroketones being approximately equal to the sum of the values of the corresponding monofluoroketones. The use of the carbonyl absorption for anything more than a very crude quantitative estimate of conformational equilibrium is prohibited by the large amount of overlap, the fact that the extinction coefficients are unknown, and the possibility of hidden overtones of other resonances.

---

(28) J. Cantacuzene and D. Richard, *Bull. Soc. Chim. Fr.*, 2950 (1968).

(29) L. Mion, A. Casadevall, and E. Casadevall, *ibid.*, 2950 (1968).

(30) L. Mion, A. Casadevall, and E. Casadevall, *ibid.*, 3199 (1969).

(31) R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958).

(32) J. P. Bervelt, R. Ottinger, P. A. Peters, J. Reisse, and G. Chiurodoglu, *Can. J. Chem.*, **45**, 81 (1967).

TABLE II

CARBONYL ABSORPTION FREQUENCIES OF α-FLUORO-3,3,5,5-TETRASUBSTITUTED CYCLOHEXANONES IN CCl_4

Compd	$W_{1/2}$,[a] Hz	ν_{max}, cm^{-1}	$\Delta\nu_{max}$,[b] cm^{-1}	Shoulder,[c] cm^{-1}	$\Delta\nu_S$,[b] cm^{-1}
Ia	14	1718			
TMF	19	1743	25	1732 (s)	14
Ia-d_4[d]	15	1714			
TMF-d_3[e]	22	1740	26	1726 (s)	12
Ib	16	1721			
6CFP	12	1744	23	1734 (vw)	13
6TFP	17	1737	16	1745	24
6DFP	10	1757	36		
2CFP	13	1744	23	1734 (w)	13
2TFP	23	1738	17	1743 (vs)	22
2DFP	10	1757	36		
Ic	16	1720			
6CFN	13	1744	24	None	
6TFN	19	1735	15	1744	24
6DFN	10	1758	38		

[a] Approximate width at half-height; includes shoulder except where shoulder is weak. [b] $\Delta\nu = \nu_{C=O}$(fluoroketone) $- \nu_{C=O}$(ketone). [c] s = strong, w = weak, v = very. [d] 2,2,6,6-Tetradeuterio-3,3,5,5-tetramethylcyclohexanone. [e] 2-Fluoro-2,6,6-trideuterio-3,3,5,5-tetramethylcyclohexanone.

The C=O absorptions of the fluoroketones in acetonitrile (Table III) appear to indicate that only one conformer is present to any large extent; however, the bands are much broader for the trans fluoroketones than for the corresponding cis isomers, the width increasing in the order 2TFP < 6TFP < 6TFN. In particular, 6TFN exhibits a broad, fairly flat maximum possibly caused by a large percentage of the axial fluorine conformer. If this be the case, the shifts due to axial and equatorial fluorine are closer in magnitude in acetonitrile than they are in carbon tetrachloride.

TABLE III

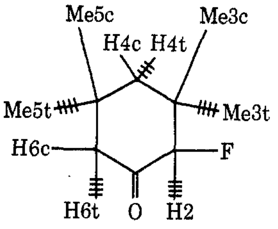
CARBONYL ABSORPTION FREQUENCIES OF α-FLUORO-3,3,5,5-TETRASUBSTITUTED CYCLOHEXANONES IN CH_3CN

Compd	$W_{1/2}$,[a] Hz	ν_{max}, cm^{-1}	$\Delta\nu_{max}$,[b] cm^{-1}
Ia	15	1712	
TMF	12	1736	24
Ia-d_4[c]	(26)[d]	(1705)[d]	
TMF-d_3[e]	12	1734	(29)
Ib	22	1715	
6CFP	10	1738	23
6TFP	15	1738	23
6DFP	9	1754	39
2CFP	11	1738	23
2TFP	13	1738	23
2DFP	8	1754	39
Ic	15	1715	
6CFN	10	1737	22
6TFN	16	1737	22
6DFN	9	1753	38

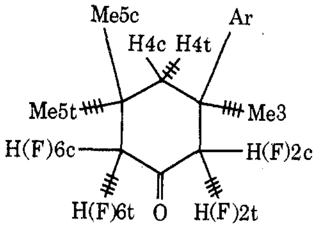
[a] Approximate width at half-height. [b] $\Delta\nu = \nu_{C=O}$(fluoroketone) $- \nu_{C=O}$(ketone). [c] 2,2,6,6-Tetradeuterio-3,3,5,5-tetramethylcyclohexanone. [d] Partially obscured by solvent. [e] 2-fluoro-2,6,6-trideuterio-3,3,5,5-tetramethylcyclohexanone.

The C–F stretching vibrations were not extensively studied in this work. However, in the spectrum of TMF in carbon tetrachloride the vibrations at 1034 and 1083 cm^{-1} are tentatively assigned to the axial and equatorial C–F bonds, respectively. The presence of a large number of bands in the 1000–1100-cm^{-1} region of the ir spectra of the α-fluoro derivatives of the aryl-substituted cyclohexanones precluded assignments of the C–F stretching vibrations.

Nmr Spectra.—The nomenclature used in discussing spectral data is shown in **5** and **6**. The protons of TMF are designated cis or trans with respect to the C-2 fluorine, while substituents in the other mono- and difluoroketones are labeled according to whether they are cis or trans to the aryl substituent at C-3.

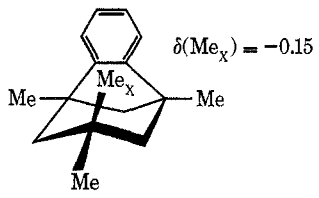


5



6

Methyl Proton Chemical Shifts.—The effect of an aryl substituent on methyl resonances has already been discussed (*vide supra*). Further support for the interpretation that an axial aryl substituent causes the anomalous high-field resonance is demonstrated by the observation[5] of the high-field methyl signal of the bicyclic hydrocarbon **7**, locked in the conformation shown. It may be noted that the high-field resonance of 6CFP, for which free rotation of the phenyl group occurs,[33] appears at δ 0.29, more than halfway between the resonance of **7** and that of a normal methyl resonance at $\delta \approx 1$.



7

The methyl chemical shifts of the aryl-substituted fluoroketones are given in Table IV. An examination of the chemical shifts in carbon tetrachloride reveals that all of these compounds exist predominantly in the conformation with an axial aryl substituent, since in each case Me5c appears at high field ($\delta \approx 0.5 \pm 0.1$). The more polar solvent acetonitrile-d_3 tends to minimize dipolar repulsion, stabilizing the conformation containing equatorial fluorine. Assuming an equilibrium between chairlike conformations, this stabilization should increase the population of the conformation with an axial aryl substituent in those compounds in which the fluorine is cis to the aromatic ring, leading to positive $\Delta\delta$(Me5c) values, and vice versa for those compounds with trans. These predicted trends are observed experimentally. Even the small $\Delta\delta$(Me5c) value of 6CFP being due to conformational change is fully supported by and consistent with the observed coupling constant variations discussed below.

It is necessary to evaluate the effect of fluorine on the chemical shift before the high-field methyl shifts can be

---

(33) This assumption is based on the observation that the aryl proton absorptions of 6CFP appear to be those of a not-uncommon type of tightly coupled AA'BB'C system,[34] rather than an ABCDE system which would be the case if free rotation were not possible.

(34) S. M. Castellano, private communication.

TABLE IV
THE METHYL CHEMICAL SHIFTS OF 3-ARYL-3,5,5-TRIMETHYLCYCLOHEXANONES (**1b** AND **1c**) AND THE DERIVED MONO- AND DIFLUOROCYCLOHEXANONES

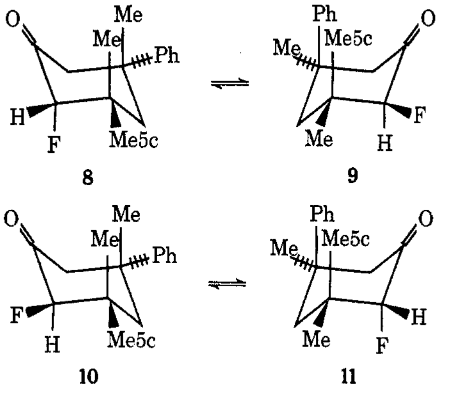
Compd	Solvent[a]	δ(Me3)	δ(Me5t)	δ(Me5c)	δΔ(Me5c)[b]
Ib[c]	CCl_4	1.333	1.011	0.353	0.04
Ib[c]	CD_3CN	1.316	1.005	0.317	
6CFP	CCl_4	1.342	1.099	0.291	0.11
6CFP	CD_3CN	1.306	1.088	0.177	
6TFP	CCl_4	1.360	1.051	0.434	−0.44
6TFP	CD_3CN	1.329	1.065	0.871	
2CFP	CCl_4	1.485	1.025	0.416	0.16
2CFP	CD_3CN	1.500	0.988	0.256	
2TFP	CCl_4	1.378	1.091	0.628	−0.33
2TFP	CD_3CN	1.379	1.106	0.961	
6DFP	CCl_4	1.372	1.090	0.394	0.05
6DFP	CD_3CN	1.348	1.093	0.342	
2DFP	CCl_4	1.474	1.057	0.427	−0.09
2DFP	CD_3CN	1.405	1.062	0.515	
Ic[c]	CCl_4	1.724	0.995	0.138	0.06
Ic[c]	CD_3CN	1.718	1.010	0.082	
6CFN	CCl_4	1.736	1.074	0.072	0.13
6CFN	CD_3CN	1.687	1.034	−0.064	
6TFN	CCl_4	1.757	1.044	0.256	−0.53
6TFN	CD_3CN	1.688	1.137	0.788	
6DFN	CCl_4	1.770	1.070	0.160	0.05
6DFN	CD_3CN	1.730	1.050	0.110	

[a] Concentrations of the fluoroketones are approximately 3 mol %; concentrations of **1b** and **1c** are 5% (w/w). [b] Δ(Me5c) is the chemical shift of Me5c in CCl_4 minus the chemical shift of Me5c in CD_3CN. [c] From ref 6.

employed to give a quantitative estimate of the percentage of each conformer present at equilibrium. In TMF, the chemical shift differences between Me3c and Me5c (δ 0.97 and 1.02) and Me3t and Me5t (δ 1.12 and 1.04) in acetonitrile should be indicative of the effect of an equatorial fluorine on the chemical shift of a vicinal methyl group, resulting in an upfield shift of 0.05 ppm for an axial methyl group and a downfield shift of 0.08 ppm for an equatorial methyl group. The effect of an equatorial fluorine on the chemical shift of a vicinal equatorial methyl group is demonstrated by a comparison of the Me5c resonance of 2CFP (δ 0.99) and 6CFP (δ 1.09), while the effect of the additional fluorine (axial) in 6DFP (δ 1.09) appears to be slight.[35] In a study of a series of 11 5α-fluoro steroids, Jacquesy and Levisalles[36] found that the presence of an axial fluorine at C-5 causes the vicinal axial C-19 methyl resonance to move downfield by 0.14 ± 0.03 ppm. Thus, although the effect of fluorine on methyl resonances is small in comparison with the effect of an aryl substituent, it is certainly not negligible.

In order to calculate the fractions of each conformation present in equilibrium, it is necessary to know the chemical shift of Me5c in each of the pure conformers. Although model compounds are not available, it is possible to make reasonable estimates of these chemical shifts in order to gain some insight into the conformational free energies, although values so calculated must be regarded as approximate, because of the dangers inherent in using estimated chemical shifts rather than observed limiting values (here, unavailable). For this calculation the conformational equilibria of 6CFP and 6TFP in both carbon tetrachloride and acetonitrile-d_3 are considered in Chart III. The following values were estimated for δ(Me5c) in the conformers indicated.

CHART III
CONFORMATIONAL EQUILIBRIA OF 6CFP AND 6TFP



Conformer	δ(Me5c)
8	1.10
9	0.14
10	1.19
11	0.24

The estimate for **9** is based on an extrapolation of the low-temperature chemical-shift data for Me5c in acetone (*vide infra*). The value of 1.10 for conformer **8** seems reasonable in view of the observed chemical shifts of 3-phenyl-5,5-dimethylcyclohexanone[6] and the 3,5-methyl-substituted cyclohexanones studied by Laszlo, *et al.*[37] In the latter case the effect of axial fluorine on the equatorial methyl resonance was assumed negligible. However, for 6TFP (**10** and **11**), these values were modified, since the equatorial–equatorial and axial–axial relationships of the fluorine and Me5c in conformers **10** and **11** were expected to result in downfield shifts of the order of 0.1 ppm (*vide supra*). By substituting these values into the equation $\delta_{obsd} = N_1\delta_1 + N_2\delta_2$, the equilibrium constants, K, and the difference in free energy between the conformers can be calculated and the results are given in Table V.

Two primary factors influence the overall conformational preferences: (1) a conformational energy difference (ΔG_x) between the 1,3-diaxial methyl–phenyl interaction and a 1,3-diaxial dimethyl interaction, assumed to be solvent independent; and (2) a conformational energy difference between equatorial and axial fluorine, which is solvent dependent and designated as

---

[35] The values for CD_3CN solutions are compared since the compounds are expected to be more conformationally pure in this solvent.

[36] R. Jacquesy and J. Levisalles, *Bull. Soc. Chim. Fr.*, 1884 (1966).

[37] M. Fetizon, J. Gore, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966).

TABLE V

CALCULATED CONFORMATIONAL FREE ENERGIES OF 6CFP AND 6TFP IN CARBON TETRACHLORIDE AND ACETONITRILE-d_3

Compd	Solvent	Equilibrium constant[a]	Conformational free energy difference, kcal/mol
6CFP	CCl_4	5.41	−1.03
6CFP	CD_3CN	26.0	−1.98
6TFP	CCl_4	3.96	−0.83
6TFP	CD_3CN	0.55	+0.36

[a] For the equilibria as written in Chart III.

ΔG_y in CCl_4 and ΔG_z in CD_3CN. Using the values in Table V, the following equations can be written.

$$\begin{aligned} -1.03 &= \Delta G_x + \Delta G_y \text{ (6CFP in } CCl_4) \\ -1.98 &= \Delta G_x + \Delta G_z \text{ (6CFP in } CD_3CN) \\ -0.83 &= \Delta G_x - \Delta G_y \text{ (6TFP in } CCl_4) \\ +0.36 &= \Delta G_x - \Delta G_z \text{ (6TFP in } CD_3CN) \end{aligned}$$

The three values which best fit[38] these four equations are $\Delta G_x = -0.87$, $\Delta G_y = -0.10$, and $\Delta G_z = -1.17$ kcal/mol. The fit is reasonably good considering the assumptions on which this calculation is based and is in good agreement with the values found by Stothers and Pan[18] for the conformational energies of 2-fluorocyclohexanone in these solvents (−0.35 and −1.17 kcal/mol, respectively). It has been observed that, for the ketone **1b**, δ(Me5c) = 0.30 in CS_2 at room temperature and δ(Me5c) = 0.08 at very low temperature.[6] Although this shift has been ascribed to a decrease in the rate of phenyl rotation at low temperature,[6] it is interesting to note that, if it is assumed that δ(Me5c) = 0.08 for the axial conformer, ΔG_x for **1b** is calculated to be −0.8 kcal/mol, in excellent agreement with the value found above.

The high-field methyl resonances of 2CFP and 2TFP are somewhat anomalous. Since the fluorine is across the ring from Me5c, there should be very little, if any, effect of fluorine on the methyl chemical shift. However, Me5c of 2CFP appears at lower field in CCl_4 than the corresponding resonance of 6CFP or even the parent ketone **1b**. Similarly, the Me5c resonance of 2TFP in CD_3CN is at lower field than that of 6TFP, even though in the latter compound an additional downfield effect due to the influence of vicinal equatorial fluorine on the equatorial methyl is expected (*vide supra*). If δ(Me5c) is assumed to be 0.08 and 1.10 in the pure conformers of 2CFP and 2TFP (*vide infra*), one obtains $\Delta G_x = -0.1$, $\Delta G_y = -0.4$, and $\Delta G_z = -0.9$. Thus it appears that the 1,3-diaxial methyl–phenyl interaction is barely favored over the 1,3-diaxial methyl–methyl interaction. The discrepancy between the free-energy values obtained for the 6 isomers and those calculated for the 2 isomers is possibly the result of an electrostatic interaction between the fluorine and the adjacent phenyl group.

Because of the difficulty in making accurate estimates for the limiting values of δ(Me5c) in the conformers 6CFN and 6TFN, the ΔG values were not calculated. However, inspection of the chemical shifts indicates that these values are probably not appreciably different from those calculated for the corresponding phenyl compounds.

The high-field methyl resonances of the two 6,6-difluoroketones are at slightly lower field (0.03 ppm) than the resonances of the parent ketones. Therefore, since these resonances are expected to be at lower field by at least 0.10 ppm from the influence of adjacent fluorine, these difluoroketones probably exist in the conformation in which the aromatic substituent is axial to a slightly greater extent than in the ketones from which they were derived. Coupling-constant variations in the spectrum of 6DFP on going from CCl_4 to CD_3CN (given below) indicate that the upfield shift of Me5c which accompanies the solvent change is conformational in origin. Again, the high-field methyl shift of 2DFP is anomalous in the sense that it appears downfield of the corresponding resonance of **1b** in CCl_4, and also because it moves *downfield* on going to CD_3CN as the solvent. The coupling constants of 2CFP were not thoroughly investigated.

Coupling Constants.—Although it is not the purpose of this paper to discuss all of the couplings observed in these compounds, the couplings on which the assignments of the methylene proton resonances are based are worthy of note here. Four-bond coupling between protons is expected to be largest for an all-trans or "W" arrangement of sp^3-hybridized bonds, which corresponds to equatorial–equatorial coupling in cyclohexanoid systems.[39] There is also evidence that a similar geometric dependence obtains for four-bond coupling between protons and fluorine.[40]

The four-bond couplings between the protons of the α-methylene protons and the fluorine nucleus with the C-4 methylene protons of some of the monofluoroketones are given in Table VI. Trans couplings (axial–equatorial) between these nuclei were not observed. The coupling assignments are based on the assumptions that the largest observed couplings are between equatorial nuclei and that the molecules exist in chairlike conformations. The corresponding couplings in the unlisted monofluoroketones are qualitatively consistent with those given in Table VI; however, the exact parameters were not determined.[41]

TABLE VI

FOUR-BOND COUPLINGS OF FLUORINE AND THE α-METHYLENE PROTONS WITH THE C-4 PROTONS

Compd	Solvent[a]	^4J, Hz $H\alpha c^b$–H4c	 $H\alpha t^b$–H4t	 F-H4c	 F-H4t
TMF	CCl_4	1.76	±0.3	4.59	0
TMF	CD_3CN	2.75	0	6.66	0
6CFP	CCl_4	3.22	0	6.50	0
6CFP	CD_3CN	3.54	0	7.23	0
6TFP	CCl_4	1.8	0	0	3.00
6TFP	CD_3CN	0	1.98	0	4.65
6TFN	CD_3CN	0	2.28	0	5.15

[a] Concentrations are 2–4 mol %. [b] $H\alpha$ = H6 of TMF, H2 of 6CFP, 6TFP and 6TFN.

The couplings of TMF and 6CFP are observed to increase as the dielectric constant of the solvent increases, since the conformer in which the coupled nuclei are

---

[38] Each of the four possible combinations of these equations was solved for ΔG_x, ΔG_y, and ΔG_z. The best values are considered to be the averages of the four solutions obtained.

[39] M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).

[40] A. B. Foster, R. Hems, L. D. Hall, and J. F. Manville, *Chem. Commun.*, 158 (1968).

[41] It was found that the observable splittings do not correspond exactly to the true coupling constants, which had to be determined by computer simulation of the spectra as *six*-spin systems.

equatorial becomes more predominant, with TMF undergoing the largest increase, as expected (*vide supra*). However the large coupling between H2c and H4c of 6TFP in carbon tetrachloride is found to diminish as the dielectric constant of the medium is gradually increased by adding acetonitrile. This decrease of ${}^4J_{H2c-H4c}$ is paralleled by an increase in ${}^4J_{H2t-H4t}$ and ${}^4J_{F-H4t}$ as these nuclei become equatorial. In 6DFP, the only difluoroketone whose nmr spectra were thoroughly analyzed, ${}^4J_{H2c-H4c}$ increases from 2.46 to 2.69 Hz and ${}^4J_{F6c-H4c}$ increases from 4.41 to 4.81 Hz on going from carbon tetrachloride to acetonitrile-d_3 solution.

These assignments based on coupling constants are strongly supported by the fact that the observed benzene-induced solvent shifts of the α-methylene and methine protons of the monofluoroketones are in excellent agreement with predicted[27] trends if the effect of the dielectric constant of the solvent on the conformational equilibrium is taken into account.[19]

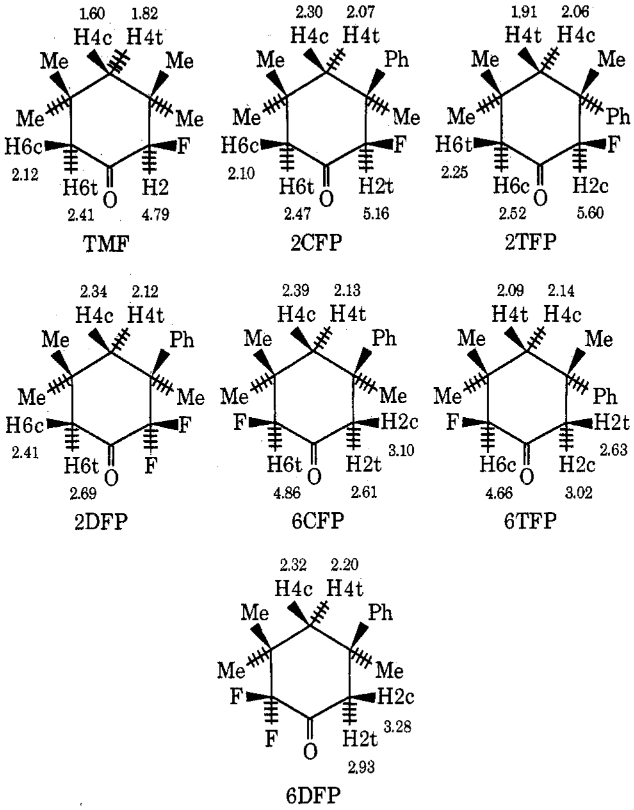
Chemical Shifts of the Ring Protons.—In order to demonstrate that these compounds exist in chair or chairlike conformations, it is necessary to show that the chemical shifts of the ring protons are consistent with the proposed geometry. In the following discussion, the chemical shifts in acetonitrile-d_3 are compared because most of the monofluoroketones exhibit a greater degree of conformational purity in this solvent than in the other solvents studied [however, 6TFP is expected to be the least "pure," with the conformer having equatorial fluorine favored by only slightly more than 2:1 (*vide supra*)]. Also, by comparing only solutions in the same solvent, solvent effects other than those which are conformational in origin can be minimized.

The chemical shifts of the ring protons of TMF and the α-fluoro-3-phenyl-3,5,5-trimethylcyclohexanones and the chair conformers which are expected, in light of the previous discussion, to predominate are illustrated in Chart IV. In this chart the fluorine of each of the monofluoroketones is equatorial, and the phenyl groups of 2DFP and 6DFP are axial. The axial methylene protons of TMF (H4t and H6t) resonate at lower field than their equatorial counterparts [as does the methine proton, which shifts to much higher field as the dielectric constant of the solvent decreases, δ(H2) 4.31 in CCl_4].

The chemical shifts of the α protons at C-6 should be little affected by the presence of an axial phenyl group and slightly deshielded by an equatorial phenyl group at C-3, since these protons are fairly remote but still in the ring plane of an equatorial C-3 aryl substituent. These trends are observed. The C-6 protons of 2CFP appear at approximately the same δ value as the corresponding protons of TMF, while the equatorial and axial protons of 2TFP are both deshielded to a small extent by the equatorial phenyl group. Also H6t of 6CFP is more axial and hence resonates slightly downfield of H2 of TMF. In the spectrum of 6TFP, H6c appears at higher field than H2 of TMF, even in the presence of the equatorial aryl substituent; however this is understandable in view of the large amount of the other conformer of 6TFP (*vide supra*). The fact that the C-6 protons of 2DFP resonate about 0.3 ppm to low field of the C-6 protons of TMF may be attributable to a combination of inductive and anisotropic effects of the additional fluorine.

Chart IV

Ring Proton Chemical Shifts of TMF and the α-Fluoro-3-phenyl-3,5,5-trimethylcyclohexanones in Acetonitrile-d_3 Solution

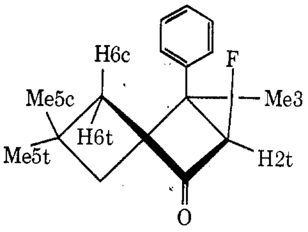


A *vicinal* phenyl group should have considerable influence on the ring-proton chemical shifts. Models indicate that, if the phenyl group is axial and facing the C-5 methyl, the equatorial C-2 proton is very close to the edge of the aromatic ring. This effect is particularly noticeable in the spectrum of 6CFP, where the H2c signal appears 1 ppm downfield of the corresponding resonance of TMF, and the axial proton is shifted downfield by 0.2 ppm. The C-2 protons of 6DFP exhibit the same trends but the shifts are slightly greater owing to the additional fluorine, as was observed for the C-6 protons of 2DFP (*vide supra*). The observation that the effect on the equatorial proton is diminished and more nearly equal to the effect on the axial proton in the trans isomers may be attributed to the fact that an equatorial aryl substituent is almost equidistant from the adjacent α protons and has greater rotational freedom, so that neither H2c nor H2t spends as much time near the edge of the aromatic ring as does the H2c proton when the phenyl group is axial.

The effect of a phenyl group on the resonances of γ protons is very similar to the effect on the adjacent α protons. In the spectra of 6DFP, 2CFP, 6DFP, and 2DFP, the axial phenyl group causes a downfield shift of *ca.* 0.7 ppm for the equatorial C-4 proton while the axial proton is deshielded by only 0.3 ppm relative to TMF. In the trans isomers the equatorial and the axial protons occur 0.3–0.5 ppm to lower field.

The same conformational conclusions are apparent from the ring proton shifts when the aryl substituent is a 1-naphthyl group. However, when the naphthyl group is axial (6CFN and 6DFN), the H4c and H2c resonances are shifted downfield by *ca.* 1.5 and 1.1 ppm, respectively, relative to the corresponding resonances of TMF.[19] The H2c shift is close to that experienced by H2c of 6CFP, but the H4c difference is much larger, which probably indicates that the B ring of the 1-naphthyl group spends considerably more time near C-4 than C-2.

In summary, it is found that the chemical shifts of the ring protons of the aryl-substituted fluoroketones are consistent with the corresponding values of TMF if the effects of the aryl substituent are considered. These results strongly support the assumption that these compounds exist as an equilibrium mixture of chair conformations. Indeed, models indicate that, if these molecules existed in a twist-boat (flexible) conformation (*e.g.*, **12**), the aryl substituent would have a significant shielding influence on the chemical shift of a cis proton at C-6, which was not observed.



12

Effect of Temperature on Chemical Shifts.—There are at least four temperature-dependent factors which can alter the conformational equilibrium of the fluoroketones: (a) the equilibrium constant increases if ΔG is negative, and decreases if ΔG is positive, as the temperature is lowered; (b) the dielectric constant of the solvent increases as the temperature decreases, thereby stabilizing dipolar interactions in the more polar conformer; (c) solute–solute association may increase with decreasing temperature, causing an increase in the effective dielectric constant in the vicinity of the solute; and (d) increased solute–solvent association may also increase the apparent dielectric constant.

Several preliminary low-temperature proton nmr spectra were obtained in the course of this work. In acetone-d_6 6CFP, TMF, and 6TFP are all expected to exist predominantly in that conformation with fluorine equatorial. Therefore each of the factors mentioned above has the same effect on the equilibrium, *i.e.*, to increase the percentage of the conformer in which the C=O and C–F dipoles are aligned. The data in Table VII show that, as the temperature is lowered, the axial methine protons of TMF, 6CFP, and 6TFP move to lower field while the equatorial methylene protons of TMF are shifted upfield. In addition, the Me5c resonances of 6CFP and 6TFP move to higher and lower fields, respectively. All of these observations indicate that the fluorine is becoming more equatorial. The magnitudes of the shift changes of the methine proton resonances (these resonances should be directly comparable, since in each case this proton is remote from the aryl substituent) show that the conformational change of 6TFP is greater than that of TMF, which in turn is greater than that of 6CFP, as expected if the aryl substituent prefers to be axial.

TABLE VII

VARIATION OF SELECTED PROTON CHEMICAL SHIFTS WITH TEMPERATURE

Compd	Solvent[a]	Temp, °C	δ(CHF)	δ(Me5c)
TMF	$(CD_3)_2CO$	31	4.83	*b*
TMF	$(CD_3)_2CO$	−43	5.02	
TMF	$(CD_3)_2CO$	−95	5.14	
6CFP	$(CD_3)_2CO$	31	4.94	0.22
6CFP	$(CD_3)_2CO$	−43	5.08	0.15
6CFP	$(CD_3)_2CO$	−95	5.15	0.14
6TFP	$(CD_3)_2CO$	31	4.64	0.82
6TFP	$(CD_3)_2CO$	−43	4.87	0.89
6TFP	$(CD_3)_2CO$	−95	5.08	1.00
TMF	CS_2	31	4.27	
TMF	CS_2	−43	4.40	
TMF	CS_2	−60	4.45	
6TFP	CS_2	31	4.03	0.434
6TFP	CS_2	−43	4.03	0.372
6TFP	CS_2	−60	4.04	0.377

[a] Concentrations are *ca.* 2% by weight. [b] Assignment uncertain.

The methine proton chemical shift of TMF in carbon disulfide indicates that the relative amount of the most stable conformer (equatorial fluorine) becomes greater as the temperature is decreased. The Me5c resonance of 6TFP in carbon disulfide indicates that at room temperature the aryl substituent is predominantly axial, and therefore that the fluorine is also predominantly axial. As the temperature is lowered, the equilibrium constant should change in favor of the more stable conformer, and consequently both the Me5c and H6c resonances should move upfield. However, when the temperature is lowered from 31° to −43°, δ(H6c) is constant, while Me5c absorbs only 0.06 ppm to higher field. Lowering the temperature to −60° leads to a very small (0.01 ppm) downfield shift of both of these resonances. These shifts indicate that the effect of temperature on the equilibrium is opposed and approximately equal to the effect of increasing effective dielectric constant at low temperature.

Experimental Section

General Synthetic Remarks.—All solvents and common reagents used for synthesis were reagent grade. The 2-bromo-3,3,5,5-tetramethylcyclohexanone, mp 48.5–49.5° (lit.[9] mp 50–51°), was prepared and purified by W. A. Thomas. Ethyl formate and isophorone (practical grades, Eastman) were dried and distilled before use. Commercial *n*-pentane and *n*-hexane were washed with concentrated sulfuric acid, aqueous potassium carbonate, and water, dried with sodium and magnesium sulfate, and distilled, discarding the first and final 10% of the distillate. The 3,3,5,5-tetramethylcyclohexanone, bp 101° (30 Torr), was prepared and purified by B. C. Mikuska. Tetramethylene sulfone (Aldrich) was stored over molecular sieves. The following materials were used as received: aluminum oxide, neutral, and silica gel (Woelm, activity grade I, Alupharm Chemicals); cuprous chloride (reagent, Fisher Scientific); deuterium oxide (99.7%, Merck Sharp and Dohme of Canada); methyl bromide (gas, Matheson Co.); molecular sieves, Linde type 3A (Matheson Coleman and Bell); perchloryl fluoride (gas, Pennsalt Chemicals); and sodium methoxide (Olin Chemicals).

Boiling points are uncorrected. Capillary melting points are corrected and were determined using a Mel-Temp melting point apparatus (Laboratory Devices, Cambridge, Mass.). Refractive indices were measured on a Bausch and Lomb Abbe-3L refractometer, temperature controlled at 20.0°. Infrared spectra were measured on a Beckman IR-12 spectrophotometer using internal calibration, or a Beckman IR-8 spectrophotometer calibrated by means of the 1603-cm^{-1} absorption of a polystyrene film. Nuclear magnetic resonance spectra were recorded on Varian A-60 or HA-100 spectrometers. Mass spectral data were obtained by Professor Ronald D. Grigsby of the Department of Biochemistry and Biophysics of Texas A & M University, using a Consolidated Electrodynamics Model 21-110B mass spectrometer. Microcombustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or Micro-Tech Laboratories, Skokie, Ill.

2,4,4,6,6-Pentadeuterio-3-trideuteriomethyl-5,5-dimethyl-2-cyclohexen-1-one (Isophorone-d_8).—This is an adaptation of the procedure of Anet.[42] A mixture of 55.2 g (0.40 mol) of isophorone, 5.4 g (0.039 mol) of potassium carbonate, and 160 g (8.0 mol) of deuterium oxide was refluxed with stirring for 48 hr. At this time, the lower layer (D_2O) was drawn off and another 5.4 g of potassium carbonate and 160 g of fresh D_2O were added. After refluxing for 48 hr, the process was repeated once more. The final mixture was extracted twice with ether and the ether solutions were combined, washed twice with water, and dried over magnesium sulfate. The ether was evaporated and the remaining brown liquid was distilled on a spinning band column to yield 47.5 g (0.326 mol, 81%) of colorless product: bp 88.5–89.5° (15 Torr); ir (CCl_4) 1660 cm^{-1} (C=O); nmr (neat) δ (methyls) 0.97; n^{20}_D 1.4757; mass spectrum molecular ion *m/e* 146, abundant fragment peaks *m/e* 131, 103, 88, 60, 42. *Anal.* Calcd for $C_9H_6D_8O$: mol wt, 146.1547. Found: mol wt, 146.1557 (mass spectrum). The nmr spectrum indicated that, overall except for the *gem*-dimethyl protons, the isophorone was greater than 98% deuterated.

2,4,4,6,6-Pentadeuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone.—This reaction was run using the cuprous iodide–tri-*n*-butylphosphine complex which is described by House, *et al.*,[43] and which was prepared according to the method of Kaufman and Teter.[44] Into a 1000-ml flask equipped with a stirrer, an addition funnel, and a gas inlet was placed 11.0 g (0.455 mol of magnesium turnings and 500 ml of anhydrous ether. The system was flushed with dry nitrogen, and methyl bromide was bubbled into the solution at a moderate rate with stirring until all of the magnesium was dissolved. Then the excess methyl bromide was displaced with dry nitrogen as the flask was cooled with a Dry Ice–carbon tetrachloride mixture. A solution of 1.8 g (0.0045 mol) of tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] and 36.5 g (0.25 mol) of isophorone-d_8 in 100 ml of anhydrous ether was added over a period of 0.5 hr. After the addition, the mixture was stirred with cooling for 10 min. The reaction mixture was then added to 500 ml of 1 *M* ammonium chloride solution. The ether layer was separated and the aqueous layer was washed with ether. The ether extracts were combined, washed once with water, and dried over magnesium sulfate. The ether was evaporated and the resulting pale yellow liquid was distilled on a spinning band column to yield 31.8 g (0.197 mol, 78%) of colorless product: bp 106–108° (50 Torr); ir (neat) 1712 cm^{-1} (C=O); nmr (neat) δ (methyls) 1.01.

4,4-Dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone.—The procedure used for the deuteration of isophorone (*vide supra*) was employed, starting with 31.0 g (0.191 mol) of 2,4,4,6,6-pentadeuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone, 1.34 g of potassium carbonate, and 40 ml of H_2O. The ketone was refluxed for three 48-hr periods. Extraction yielded a colorless liquid (27.1 g, 89%) which was not purified: nmr (neat) δ (methyls) 1.02; n^{20}_D 1.4524; mass spectrum molecular ion *m/e* 159, abundant fragment peaks *m/e* 144, 128, 101, 86, 83, 72, 57. *Anal.* Calcd for $C_{10}H_{13}D_5O$: mol wt, 159.1668. Found: mol wt, 159.1678.

2,2,6,6-Tetradeuterio-3,3,5,5-tetramethylcyclohexanone.—A procedure similar to that employed above was used starting with 14.3 g (0.093 mol) of 3,3,5,5-tetramethylcyclohexanone, 20 g (1.0 mol) of deuterium oxide, and 0.67 g of anhydrous potassium carbonate. The ketone was refluxed for two 20-hr periods. An nmr spectrum of the crude product indicated that it was very pure and that the ketone was more than 97% deuterated in the α positions. This reaction afforded 11.55 g (0.073 mol, 79%) of colorless product which was not subjected to further purification: ir (CCl_4) 1715 cm^{-1} (C=O); nmr δ (methyls) 1.04; n^{20}_D 1.4519; mass spectrum molecular ion *m/e* 158, abundant fragment peaks *m/e* 143, 128, 97, 85, 84, 72, 57. *Anal.* Calcd for $C_{10}H_{14}D_4O$: mol wt, 158.1605. Found: mol wt, 158.1604.

3-Phenyl-3,5,5-trimethylcyclohexanone (1b).—This compound was prepared according to established procedures[6,15,45] starting with 317.9 g (2.3 mol) of isophorone, 313 g (2.0 mol) of bromobenzene, 48.5 g (2.0 g-atoms) of magnesium, and 6.0 g (0.061 mol) of cuprous chloride. The isophorone was added to the Grignard reagent with ice-bath cooling, over a period of 2 hr. The mixture was then allowed to return to room temperature and was stirred for an additional 8 hr. Then, using the procedure of Skattebøl, *et al.*,[46] just enough of a saturated ammonium chloride solution was added to the reaction mixture to cause the inorganic salts to precipitate (about 250 ml). The resultant clear solution was filtered, and the precipitate was washed twice with 100-ml portions of anhydrous ether. The ether solutions were combined and the ether was evaporated. The crude product was distilled through a vertical condenser from a trace of *p*-toluenesulfonic acid in order to remove some of the dienes and unreacted isophorone. The fractions boiling at 90–104° (0.5 Torr) were redistilled on a spinning band column to afford 186 g (0.86 mol, 43%) of the colorless ketone: bp 100–101° (1 Torr); ir (CCl_4) 1721 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 0.35, 1.01, 1.34; n^{20}_D 1.5291.

3-(1-Naphthyl)-3,5,5-trimethylcyclohexanone (1c).—This compound was prepared by an established procedure,[6] starting with 38.9 g (1.60 g-atoms) of magnesium, 331.2 g (1.6 mol) of 1-bromonaphthalene, 221 g (1.6 mol) of isophorone, and 5 g (0.051 mol) of cuprous chloride. A short-path distillation afforded the ketone **1c**, bp 148–158° (0.5 Torr), which was recrystallized twice from hexane: yield 162 g (0.61 mol, 38%); mp 64–66°; nmr (CCl_4) δ (methyls) 0.15, 1.01, and 1.73.

2- and 6-Hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone (*Caution!*).[47]—The following procedure is adapted from the method of Johnson and Posvic.[48] To a dry, nitrogen-filled, 3-l. flask provided with a mechanical stirrer, a nitrogen inlet, and a dropping funnel was added 1250 ml of benzene (dried over molecular sieves) and 109.0 g (2.02 mol) of sodium methoxide. A very slow stream of nitrogen was passed over the stirred suspension, which was cooled with an ice bath while a mixture of 150 g (2.03 mol) of ethyl formate and 218.0 g (1.01 mol) of 3-phenyl-3,5,5-trimethylcyclohexanone (**1b**) was added dropwise over a period of 2 hr. After the addition, the mixture was allowed to return slowly to room temperature and stirred vigorously for 18 hr. The resulting brown mixture was then extracted with 750 ml of water followed by three 200-ml portions of 1 *M* sodium hydroxide solution. The aqueous extracts were combined, washed once with ether (the wash ether was added to the benzene layer above), and acidified with concentrated hydrochloric acid. The milky suspension was then saturated with sodium chloride and extracted thoroughly with ether. The ether solution was washed with three 150-ml portions of saturated sodium chloride solution and dried with anhydrous sodium sulfate. After the ether was evaporated, 141.2 g (58%) of an oily solid remained. Since the crude yield was less than what was expected on the basis of the results of previous experiments, the benzene–ether solution was evaporated to give 75 g (35%) of almost pure 3-phenyl-3,5,5-trimethylcyclohexanone. This recovered starting material (0.35 mole) was condensed with 51.9 g (0.7 mol) of ethyl formate and 37.8 g (0.7 mol) of sodium methoxide as above. This reaction yielded an additional 54.1 g (72%) of crude product, and 20 g of starting material was recovered. The nmr spectrum of the combined crude products (195.3 g total, 79%) showed that the two isomers were formed in an approximate ratio of 4:1 (6 isomer predominant), and that the mixture was free of substantial impurities.

The crude product was dissolved in 400 ml of boiling hexane, and the solution was allowed to deposit crystals at room temperature. After 10 hr, 111 g (A) of 6 isomer, mp 87–92°, was collected. The filtrate was evaporated to two-thirds of its volume and an additional 8.0 g (B) was collected, mp 89–92°. The process was repeated to give 0.9 g (C), mp 89–91°. The remaining solution was put in a refrigerator overnight. A large crystalline mass formed in which two types of crystals were apparent, one small and white and the other large and yellow. The crystals

---

[42] F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).

[43] H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

[44] G. B. Kaufman and L. A. Teter, *Inorg. Syn.*, **7**, 9 (1963).

[45] M. S. Kharasch and P. O. Tawney, *J. Amer. Chem. Soc.*, **63**, 2308 (1941).

[46] L. Skattebøl, E. R. H. Jones, and M. C. Whiting, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 792.

[47] *Note:* Care should be taken not to allow 2-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone to come into contact with the skin, since it may cause a severe rash, followed by blistering and cracking of the skin. These symptoms disappear approximately one week after last contact, leaving no scars.

[48] W. S. Johnson and H. Posvic, *J. Amer. Chem. Soc.*, **69**, 1361 (1947).

were decanted from the liquid (D) and were dissolved in 100 ml of hexane and seeded with the 6 isomer. After 8 hr, 2.1 g (E) of 6 isomer, mp 85–89°, was removed from the solution (F).

Filtrate D was evaporated to two-thirds of its volume, seeded with a small chip of one of the large yellow crystals formed above, and placed in the refrigerator. After 8 hr, 5.2 g (G) of yellow crystals was collected, mp 56–75° (*ca.* 90% 2 isomer by nmr). When the filtrate was evaporated, 8.1 g (H) of a red oil remained (*ca.* 60% 2 isomer many impurities present.) Filtrate F was evaporated to three-fourths of its volume and seeded with G to yield 45.5 g (I) of crystals, mp 56–60°, *ca.* 70% 2 isomer. The filtrate was evaporated, leaving 5.6 g (J) of a yellow oil which was combined with H. After several hours an additional 2 g (K) of impure 2 isomer was collected and washed with hexane. The remaining oil was chromatographed on a 2.5 × 40 cm silica gel column in order to remove the impurities which prevent crystallization. The chromatogram was developed with 350 ml of hexane, 200 ml of 4% (v/v) ether–hexane, and 200 ml of 7% ether–hexane. Nothing was eluted in these fractions. This was followed by five 150-ml portions of 8% ether–hexane. The first four of these fractions contained both isomers with the 2 isomer predominant and decreasing [11.0 g (L), combined total]. The last fraction (0.3 g) contained mostly 6 isomer and impurities, and was discarded. The isomeric mixtures G, I, K, and L were combined and chromatographed on a 500-g silica gel column. The column was developed with 1200 ml of hexane and 800 ml of 4% ether–hexane. Nothing was eluted in these fractions. This was followed by six 300-ml portions of 5% ether–hexane. The first three of these fractions deposited crystals which were recrystallized from hexane to give 20.0 g (M) of pure 2 isomer, mp 66–67°. The second three fractions deposited 9.1 g of crystals which were recrystallized twice from hexane to give 8.2 g (N) of pure 6 isomer, mp 89–91°. The filtrates from all of the fractions were combined (25.1 g) and again chromatographed on silica gel to yield an additional 9.5 g (P) of pure 2 isomer, mp 66–67°.

The fractions A, B, C, E, and N were combined and recrystallized twice from 250 ml of hexane. This afforded 119.0 g (48%) of pure 6 isomer, mp 89.5–91.0°. Two grams of these white crystals was sublimed [(bath temperature 80° (0.5 Torr)] for analysis and spectroscopic measurements: mp 89.5–91.0°; ir (CCl_4) 1639, 1598 cm^{-1} (C=C–C=O); nmr (CCl_4) δ (methyls) 0.58, 1.20, 1.33.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.73, 78.52; H, 8.26, 8.27.

The fractions M and P were combined as pure 2 isomer, 29.5 g (12%), mp 66–67°. Two grams of this white crystalline solid was recrystallized from hexane with cooling and sublimed [bath temperature 60° (0.5 Torr)]; mp 66–67°; ir (CCl_4) 1640, 1590 cm^{-1} (C=C–C=O); nmr (CCl_4) δ (methyls) 0.71, 1.02, 1.62.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.53, 78.37; H, 8.13, 8.07.

2-Hydroxymethylene-3,3,5,5-tetramethylcyclohexanone.—The same procedure that was used to prepare the hydroxymethylene derivatives of the phenyltrimethyl ketone was followed, starting with 30.8 g (0.200 mol) of 3,3,5,5-tetramethylcyclohexanone, 29.6 g (0.40 mol) of ethyl formate, and 23.0 g (0.43 mol) of sodium methoxide in 200 ml of dry benzene. After evaporation of the final ether solution, there remained 31.4 g of a colorless liquid (pure by nmr) which turned an intense violet on addition to alcoholic ferric chloride solution. Distillation on a spinning band column afforded 27.8 g (76%) of product: bp 55.0 ± 0.5° (0.45 Torr); ir (CCl_4) 1637, 1593 cm^{-1} (C=C–C=O); nmr (neat) δ (methyls) 0.99, 1.24; $n^{20}{}_D$ 1.4926.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.50, 72.47; H, 10.02, 9.97.

2- and 6-Hydroxymethylene-4,4-dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone.—The same procedure as above was employed using 22.3 g (0.140 mol) of 4,4-dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone, 20.7 g (0.28 mol) of ethyl formate, and 16.1 g (0.30 mol) of sodium methoxide. The crude product, 21.2 g (81%) of a pale yellow liquid, was shown by nmr to be a pure mixture of equal quantities of the two isomers, and this was used without further purification, nmr (CCl_4) δ (methyls) 0.97, 1.21.

2- and 6-Hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone.—The same procedure (above) was employed using 71.0 g (0.265 mol) of 3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (1c), 42.9 g (0.58 mol) of ethyl formate, and 29.0 g (0.53 mol) of sodium methoxide. The methoxide was suspended in 250 ml of dry benzene, and the formate and the ketone were added as a solution in 200 ml of dry benzene. The product was isolated as usual except that after the aqueous solution of the sodium salts of the products was acidified, the solution was saturated with sodium chloride and the crude hydroxymethylenes were removed by filtration. The solid was recrystallized twice from hot carbon tetrachloride. This product, the 6 isomer, was obtained as colorless cubic crystals, 58 g (74%), mp 164–166°. A small amount of this substance was sublimed [bath temperature 50° (0.5 Torr)] for analysis and spectroscopic measurements: mp 164–166°; ir (CCl_4) 1639, 1596 cm^{-1} (C=C–C=O); nmr (CCl_4) δ (methyls) 0.28, 1.21, 1.70; mass spectrum molecular ion *m/e* 294, abundant fragment peaks *m/e* 279, 261, 233, 223, 220, 193. *Anal.* Calcd for $C_{20}H_{22}O_2$: mol wt, 294.1614. Found: mol wt, 294.1634.

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found C, 81.69, 81.54; H, 7.43, 7.25.

The filtrates from the above recrystallizations were evaporated to a brown oil. This oil was dissolved in ether and placed in a refrigerator for 2 days. A small quantity of 6 isomer precipitated, leaving a red gum. The gum was kneaded in a small amount of hexane, giving a yellow solid which was recrystallized twice from hexane. The 2 isomer was obtained as 1.5 g (1.9%) of an impure yellow powder: mp 89–114°; nmr (CCl_4) δ (methyls) 0.87, 1.16, 1.87; ir (CCl_4) 1635, 1592 cm^{-1} (C=C–C=O); mass spectrum molecular ion *m/e* 294, abundant fragment peaks *m/e* 279, 261, 247, 223, 195. *Anal.* Calcd. for $C_{20}H_{22}O_2$: mol wt, 294.1614. Found: mol wt, 294.1617.

***cis*- and *trans*-6-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone (6CFP and 6TFP), and 6,6-Difluoro-3-phenyl-3,5,5-trimethylcyclohexanone (6DFP).**—This reaction was carried out in a 3-l. flask equipped with a magnetic stirrer, a nitrogen inlet above the reaction mixture, an inlet for perchloryl fluoride (HOOD!)[49] which extended almost to the bottom of the flask, and a gas outlet which was connected (Tygon tubing) to a 50-ml bubbler filled with absolute ethanol. The system was connected to the perchloryl fluoride cylinder through an empty 500-ml gas-washing bottle in order to eliminate the possibility that the reaction mixture might be drawn suddenly into the cylinder. To an ice bath cooled solution of 12.5 g (0.5 g-atom) of sodium in 1100 ml of absolute ethanol was added (in one portion) 108 g (0.44 mol) of powdered 6-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone. The solution turned bright yellow. A slow stream of nitrogen was passed through the system as gaseous perchloryl fluoride was bubbled vigorously into the stirred solution for 1 hr. Nitrogen was bubbled through the solution for 1 hr, after which 30 g of potassium acetate was added and the solution was heated just to boiling. Then 1600 ml of water was added and the solution was stirred until it cooled to room temperature. The mixture was extracted with eight 100-ml portions of ether. The ether layers were combined and washed with three 100-ml portions of 1 *M* sodium hydroxide solution, three 100-ml portions of water, and 100 ml of a saturated sodium chloride solution. The ether solution was dried with anhydrous sodium sulfate and evaporated. The remaining mass (100.5 g) was dissolved in 120 ml of boiling hexane and left to stand overnight. The next day 79.2 g of crystals were collected and these were recrystallized to give 75.3 g (A) of 6CFP, mp 85.7–86.5°. The filtrate was evaporated to give 20.5 g (B) of a viscous, pale yellow liquid which nmr showed to contain 6TFP and 6CFP in a 3:2 ratio. Five grams of mixture B was chromatographed on a 2.8 × 58 cm column of silica gel. The chromatogram was developed with 400 ml of hexane, 300 ml of a 1.5% (v/v) ether–hexane solution, and 850 ml of 2% ether–hexane.[50] The column was then eluted with 3% ether–hexane. The first 300 ml contained 160 mg (C) of 6DFP and a small amount of impurity. The next 200 ml of eluent contained 730 mg (D) of a mixture of 6TFP and 6DFP. The following six fractions (*ca.* 200 ml each) afforded a total of 2.1 g (E) of slightly impure (by nmr) 6TFP. The column was

---

(49) *Caution:* Perchloryl fluoride is moderately toxic and a powerful oxidizing agent. All perchloryl fluoride reactions should be run, using safety shields, in a hood.

(50) Elution with benzene–hexane was subsequently shown to be much more effective in separating 6DFP and 6TFP. However, using this eluent, 6TFP and 6CFP are not well separated and a second chromatography using ether–hexane is necessary. It was found that, when 6.5 g of a 6TFP–6CFP mixture (6:1) was allowed to stand on a silica gel column for several weeks, the ratio of isomers in the 5.8 g of material collected was 48:1, with 6CFP favored. Therefore the chromatography of mixtures of the fluoro isomers should be carried out as rapidly as possible without sacrificing separation.

then washed with ether to obtain 1.6 g of yellow solid, which was recrystallized to yield 1.3 g (F) of 6CFP, mp 83–84°. Fraction E was rechromatographed on silica gel, using 3% ether–hexane. The first 400 ml contained nothing, and the next 300 ml afforded 1.9 g (G) of pure colorless 6TFP. The last 100 ml contained *ca.* 0.2 g of impure 6TFP which was added to the remainder of mixture B, as was fraction D from the first chromatography. The combined mixture was chromatographed three times as above yielding an additional 3.9 g (H) of 6CFP, 7.1 g (I) of 6TFP, and 1.9 g (J + K) of 6DFP.

Fractions A, F, and H were combined as pure 6CFP, giving a total yield of 80.5 g (0.343 mol, 78%) of white crystals. Some of this material was sublimed [bath temperature 45° (0.5 Torr)] for nmr and dipole moment studies: mp 85.7–86.5°; ir (CCl_4) 1744 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.34, 1.10, 0.29.

Anal. Calcd for $C_{15}H_{19}OF$: C, 76.89; H, 8.17; F, 8.11. Found: C, 76.78, 77.04; H, 8.19, 8.16; F, 7.41, 7.48.

Fractions G and I were combined as pure (by nmr) 6TFP for a total yield of 9.0 g (0.0385 mol, 8.7%) of this colorless liquid: ir (CCl_4) 1737 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.37, 1.05, 0.43; mass spectrum molecular ion *m/e* 234, abundant fragment peaks, *m/e* 219, 214, 199, 171, 159, 145. *Anal.* Calcd for $C_{15}H_{19}OF$: mol wt, 234.1415. Found: mol wt, 234.1436.

Fraction J (1.0 g) was combined with C (0.16 g) since, in addition to 6DFP, both of these contained significant impurities (*ca.* 5–10% by nmr). This mixture was used for obtaining carbon-13 nmr spectra. Fraction K, a colorless liquid (0.9 g), was pure 6DFP by nmr and this was used for proton spectra and ir studies. Therefore the yield was approximately 2.0 g (0.008 mol, 1.8%): ir (CCl_4) 1757 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.37, 1.09, 0.39; mass spectrum molecular ion *m/e* 252, abundant fragment peaks *m/e* 237, 189, 175, 159, 145. *Anal.* Calcd. for $C_{15}H_{18}OF_2$: mol wt, 252.1323. Found: mol wt, 252.1335.

Summary.—6-Hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone (108 g, 0.44 mol) gives 80.5 g (0.343 mol, 78%) of 6CFP, mp 85.7–86.5°; 9.0 g (0.038 mol, 8.7%) of 6TFP, a colorless liquid; and approximately 2 g (0.008 mol, 1.8%) of 6DFP, also a colorless liquid.

2,2,6-Trideuterio-6-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone.—Approximately 1 g of 6CFP was placed in a bottle with 30 ml of D_2O and 1 g of anhydrous potassium carbonate. The bottle was capped and heated on a steam bath, with stirring for 24 hr. After this time, an nmr spectrum of the crude product indicated that sufficient deuterium incorporation had taken place, and that the reaction had been accompanied by considerable decomposition. The product was extracted with ether. The ether solution was washed with water and a saturated salt solution, and dried with sodium sulfate. Evaporation of the ether left an oil which was dissolved in a few milliliters of pentane and seeded with 6CFP. The resultant oily crystals were almost completely deuterated at C-6 and greater than 60% deuterated at C-2. This impure product was used to differentiate between C-2 and C-4 in the carbon-13 nmr spectrum[19] without further purification, nmr (CCl_4) δ (methyls) 1.33, 1.10, 0.29.

***cis*- and *trans*-2-Fluoro-3-phenyl-3,5,5-trimethylcyclohexanone (2CFP and 2TFP), and 2,2-Difluoro-3-phenyl-3,5,5-trimethylcyclohexanone (2DFP).**—The fluorination of 2-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone was carried out in the same manner as the fluorination of the 6 isomer starting with 3.0 g (0.13 g-atom) of sodium and 27.6 g (0.113 mol) of the 2-hydroxymethylene ketone in 250 ml of absolute ethanol. Perchloryl fluoride was bubbled into the solution for 30 min. The crude product was isolated as 25.0 g of a viscous yellow liquid, which was dissolved in 50 ml of hexane and refrigerated overnight. The next day 19.8 g of oily white crystals were collected. The crystals were recrystallized from 45 ml of hexane to give 17.8 g (B) of large white crystals, mp 79–80°. The filtrate was evaporated leaving 6.0 g (A) of a yellow oil. An examination of the methyl resonances in the nmr spectrum of liquid A indicated that the relative proportions of 2TFP/2CFP/2DFP/starting material were approximately 1.9:1.0:1.0:1.0.

This mixture was chromatographed on a 3 × 60 cm silica gel column,[51] eluting first with a benzene–hexane mixture (gradually increasing from 20 to 60% benzene). Nothing was eluted in the first 800 ml. The next 350 ml contained 1.09 g (C) of impure 2DFP, while the following fraction contained nothing. At this point the eluent was changed to ether–hexane, gradually increasing from 0 to 2.5% (v/v). Nothing was eluted in the next 2200 ml. Then, using 3% ether–hexane, 0.96 g of starting material was collected. This was closely followed by a number of impurities and then impure 2TFP and 2CFP with the proportion of 2CFP increasing on elution.[52] All of the last fractions were combined, dissolved in a small amount of hexane, seeded with 2CFP, and refrigerated. In this way, an additional 0.5 g (D) of 2CFP was collected, mp 76–77°. The filtrate was evaporated to 2.5 g of liquid (E) which an nmr spectrum showed to be *ca.* 70% 2TFP.

The total yield of isolated 2CFP (B and D) was 18.3 g (0.078 mol, 69%): mp 79–80°; ir (CCl_4) 1744 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.49, 1.03, 0.42; mass spectrum molecular ion *m/e* 234, abundant fragment peaks, *m/e* 219, 188, 159, 136, 83.

Anal. Calcd for $C_{15}H_{19}OF$: C, 76.89; H, 8.17; F, 8.11; mol wt, 234.1415. Found: C, 76.84, 77.05; H, 8.35, 8.52; F, 7.70, 7.68; mol wt, 234.1422.

The impure 2DFP (C) was recrystallized from pentane, yielding 0.85 g (0.0034 mol, 3%): mp 50–52°; ir (CCl_4), 1757 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.49, 1.07, 0.44; mass spectrum molecular ion *m/e* 252, abundant fragment peaks *m/e* 237, 196, 159, 154, 133.

Anal. Calcd for $C_{15}H_{18}OF_2$: C, 71.41; H, 7.19; F, 15.06; mol wt, 252.1323. Found: C, 70.40, 70.56; H, 7.38, 7.40; F, 15.53, 15.42; mol wt, 252.1325.

The mixture E was again chromatographed on silica gel using ether–hexane as the eluent. The resulting fractions were combined into three mixtures: (1) slightly impure 2TFP (0.33 g, does not contain 2CFP) (this colorless liquid was used for proton nmr studies and mass spectral analysis); (2) a mixture of 2TFP and 2CFP (0.93 g, 4:1 ratio); and (3) a mixture of 2TFP and 2CFP (0.53 g, 1:1 ratio). The total yield of 2TFP in the above mixtures is approximately 1.4 g (0.006 mol, 5.3%): ir (CCl_4) 1738 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.38, 1.10, 0.64; mass spectrum molecular ion *m/e* 234, abundant fragment peaks *m/e* 219, 188, 159, 136, 83. *Anal.* Calcd for $C_{15}H_{19}OF$: mol wt, 234.1415. Found: mol wt, 234.1420.

Summary.—2-Hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone (27.6 g, 0.113 mol) gives 18.3 g (0.078 mol, 69%) of 2CFP, mp 79–80°; approximately 1.4 g (0.006 mol, 5.3%) of 2TFP (impure liquid); and 0.85 g (0.0034 mol, 3%) of 2DFP, mp 50–52°.

***cis*- and *trans*-6-Fluoro-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (6CFN and 6TFN), and 6,6-Difluoro-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (6DFN).**—This fluorination was accomplished by the same procedure (*vide supra*) starting with 4.0 g (0.17 g-atom) of sodium and 50.0 g (0.170 mol) of 6-hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone in 350 ml of absolute ethanol. Perchloryl fluoride was bubbled into the solution for 30 min. The crude reaction product, a yellow solid, was recrystallized from 200 ml of absolute ethanol, yielding 36.0 g of 6CFN (A), mp 123°. The filtrate was evaporated, leaving 6 g of a yellow liquid which was chromatographed on a column of 100 g of silica gel. The chromatogram was developed with 500 ml of ether–hexane (0–8%). The next five 100-ml fractions (10% ether–hexane) contained mixtures of all three compounds and were combined (B).

The following four fractions contained a total of 1.4 g of almost pure 6CFN which was combined with A and recrystallized from 75 ml of boiling hexane by adding just enough acetone to dissolve the materials, yield 34.9 g (0.123 mol, 72.5%), mp 126–128°. A few grams of these white crystals (6CFN) was sublimed [bath temperature 100° (0.5 Torr)] for spectroscopic and dipole moment studies: mp 126.5–128°; ir (CCl_4) 1743 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.73, 1.08, 0.07.

Anal. Calcd for $C_{19}H_{21}OF$: C, 80.25; H, 7.44; F, 6.68. Found: C, 80.11, 80.30; H, 7.30, 7.48; F, 6.66, 6.75.

Mixture B was again chromatographed on silica gel. The chromatogram was developed with 200 ml of hexane and 100 ml of 3% ether–hexane and then eluted with 100-ml portions of 5% ether–hexane. The first two fractions afforded 0.93 g of a colorless, viscous liquid (C) and the next four fractions yielded 2.6 g of a white, crystalline solid (D). The liquid C was identified by nmr as impure (80%) 6DFN: yield *ca.* 0.9 g (0.003 mol, 1.8%); ir (CCl_4) 1757 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.77, 1.07,

---

(51) An attempt to chromatograph a mixture of 2TFP and 2CFP on alumina resulted in total decomposition of both compounds. The decomposition products were not identified.

(52) It was found that, if benzene–hexane is used to elute these monofluoroketones, 2CFP is eluted first; however, the separation is still very poor.

0.16; mass spectrum molecular ion *m/e* 302, abundant fragment peaks *m/e* 287, 209, 195, 167, 165, 153. *Anal.* Calcd for $C_{19}H_{20}OF_2$: mol wt, 302.1477. Found: mol wt, 302.1464.

The crystals D were recrystallized from 50 ml of hexane, affording 2.16 g (0.0076 mol, 4.5%) of 6TFN: mp 122.5–123.5°; ir (CCl_4) 1735 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.77, 1.05, 0.26.

Anal. Calcd for $C_{19}H_{21}OF$: C, 80.25; H, 7.44; F, 6.68. Found: C, 79.79, 79.98; H, 7.41, 7.27; F, 6.69.

Summary.—6-Hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (50 g, 0.17 mol) gives 34.9 g (0.123 mol, 72.5%) of 6CFN, mp 126–128°; 2.16 g (0.0076 mol, 4.5%) of 6TFN, mp 122.5–123.5°; and approximately 0.9 g (0.003 mol, 1.8%) of 6DFN (an impure, colorless liquid).

2-Fluoro-3,3,5,5-tetramethylcyclohexanone (TMF).—The usual procedure (*vide supra*) was used employing 4.83 g (0.21 g-atom) of sodium and 37.4 g (0.21 mol) of 2-hydroxymethylene-3,3,5,5-tetramethylcyclohexanone. The crude product was recrystallized three times from pentane (with cooling), yielding 21.0 g (0.122 mol, 58%) of crystalline TMF, mp 34–36°. This compound was then sublimed [25° (0.5 Torr)]: mp 36.0–36.5°; bp 37° (0.15 Torr); ir (CCl_4) 1743 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{17}OF$: C, 69.73; H, 9.95; F, 11.03. Found: C, 69.98, 69.88; H, 9.82, 9.69; F, 11.40, 11.68.

α-Fluoro-4,4-dideuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone.—The same procedure (*vide supra*) was used to fluorinate α-hydroxymethylene-4,4-dideuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone. The product consists of four isomers which were not separated and the yield was only 30% owing to accidental losses, mp 33.5–34°.

2-Fluoro-2,6,6-trideuterio-3,3,5,5-tetramethylcyclohexanone.—A mixture of 4.62 g (0.0268 mol) of 2-fluoro-3,3,5,5-tetramethylcyclohexanone, 30 g (1.5 mol) of deuterium oxide, 1.05 g of anhydrous potassium carbonate, and a trace of sodium methoxide was vigorously stirred in an air bath at 55°. After 7 days, the reaction mixture was extracted with methylene chloride. Since the deuteration was incomplete, the process was repeated. The product was then extracted with methylene chloride and recrystallized three times from pentane. This reaction afforded 2.1 g (0.012 mol, 45%) of the deuterated fluoroketone, mp 34–35°, ir (CCl_4) 1740 cm^{-1} (C=O).

Attempted Preparations of 2-Fluoro-3,3,5,5-tetramethylcyclohexanone from the Corresponding 2-Bromoketone. A.—Approximately 0.8 g of 2-bromo-3,3,5,5-tetramethylcyclohexanone, 6 ml of acetonitrile, and 2 g of potassium fluoride (dried at 150° for 12 hr) were refluxed for 24 hr. An nmr spectrum of the crude product indicated that no reaction had taken place.

B.—Three grams of the bromoketone was refluxed with 5 g of potassium bifluoride in 50 ml of ethylene glycol for 5 hr. Again, none of the desired product was apparent in the nmr spectrum of the product.

C.—Into a flask equipped with a Dean–Stark trap was placed 5.8 g of 2-bromo-3,5,5-tetramethylcyclohexanone, 15 g of potassium fluoride, 50 ml of tetramethylene sulfone, and 10 ml of benzene. The flask was heated and 10 ml of benzene and 2 ml of water were collected in the trap. The mixture was then stirred at 200° for 36 hr. The contents were allowed to cool, mixed with an equal quantity of water, and extracted with pentane. An nmr spectrum showed considerable decomposition and none of the desired product.

Dipole Moments.—A WTW Dipolemeter, type DM01 (Kahl Scientific Instrument Corp., El Cajon, Calif.), was used for all of the dielectric constant measurements. The following materials were used to calibrate the measuring scale of the Dipolemeter. Gaseous nitrogen, prepurified, was dried with concentrated sulfuric acid and then with Drierite (ϵ 1.0005[53]). Reagent cyclohexane (J. T. Baker Chemical Co.) was washed with concentrated sulfuric acid and then water, dried with magnesium sulfate, and distilled, discarding the first and final 15%, bp 81–82° (ϵ 2.0228[54]). Benzene (spectroquality, Matheson Coleman and Bell) (ϵ 2.2825[54]) and carbon tetrachloride (Spectrograde, Eastman) (ϵ 2.2363[54]) were used without further purification. Each of the liquids was stored overnight with one-half of its volume of molecular sieves (Linde type 4A, Allied Chemical) which had been washed five times with cyclohexane and dried *in vacuo* at 100°. The number of scale divisions per dielectric constant unit is given by the least squares slope of a plot of dielectric constant *vs.* scale reading. The four points were found to give an excellent linear relationship. Before each determination the calibration was checked using nitrogen and the solvent being used for that particular determination.

A Bausch and Lomb Model 33-45-03-01 precision refractometer was used to measure refractive indices. An adjustment of the absolute accuracy of the instrument was made only coarsely using water; however, this does not affect the relative accuracy to any appreciable extent. The precision attainable assuming a sharp dividing line is approximately ±0.00003. Sodium light was used for all measurements.

The dielectric cell and this refractometer were connected in series to a Haake Model F constant-temperature circulator. The temperature of the circulating water was maintained at 20.0 ± 0.02°.

The samples of 6TFP and 6TFN were placed in a vacuum (0.5 Torr) for 2 hr, and all of the other fluoroketones were sublimed prior to measurement. Cyclohexane, purified as above, and benzene were stored over molecular sieves. Solutions were prepared in a cool, dry room, and care was taken to ensure that all solutions were unstoppered for the same short length of time. The sample of pure solvent was treated in the same manner as the solutions. The measurements were made in the following manner. The cell was flushed with dry nitrogen and the scale reading corresponding to nitrogen was determined. Approximately 20 ml of the first solution was then transferred to the cell by pipette and the solution was covered and allowed to come to thermal equilibrium for 15 min, during which time the refractive index of the solution was measured three times. After the dielectric constant was determined, the cell was rinsed thoroughly with the solvent and dried with nitrogen until the previously determined reading for nitrogen was obtained. The remaining solutions were treated similarly. As a trial measurement, the dipole moment of *m*-nitroaniline was determined to be 4.85 ± 0.02 D (lit.[55] 4.89 D).

Dipole moments, which were determined using the method developed by Guggenheim[56] and subsequently modified by Smith,[57] were calculated for the relation

$$\mu^2 = \frac{27kTM_2(\alpha_\epsilon - \alpha_n)}{4\pi N_L d_1(\epsilon_1 + 2)^2}$$

where μ is the molecular dipole moment, k is the Boltzmann constant, T is the absolute temperature, N is Avogadro's number, M_2 is the molecular weight of the solute, and d_1 and ϵ_1 are density and the dielectric constant of the solvent, respectively. The quantities α_ϵ and α_n are the slopes of the dielectric constant, ϵ_{12}, and refractive index, n_{12}, of the solution as a function of the weight fraction of solute, W_2, respectively. The values of the dipole moments and the experimental data from which they were calculated are given in Table VIII.

Infrared Spectra.—The concentration of samples was 0.5 to 1.5% by weight in spectroquality carbon tetrachloride, acetonitrile, or benzene (Matheson Coleman and Bell). The spectra were recorded on a Beckman IR-12 infrared spectrophotometer employing prism-grating optics. The carbonyl absorptions of the fluoroketones were measured on an expanded scale of 10 cm^{-1}/in. at a scan rate of 3.2 cm^{-1}/min, and all spectra were recorded in double-beam operation using 0.2-mm KBr cells. The slit width was sufficiently narrow to allow a resolution of 1.5 cm^{-1} to be attained. The positions of the shoulders were estimated visually.

Nmr Spectra.—Proton nmr spectra were recorded several times on the 50-Hz scale of a Varian HA-100 spectrometer at a sweep rate of 1000 sec. The chemical shifts of the methyl protons and some of the ring protons were determined directly from the measured peak frequencies. Most of the ring proton chemical shifts and all H-H and H-F coupling constants were determined by spectrum simulation and iterative fitting using LAOCN3, a computer program developed by Castellano and Bothner-By.[58] A detailed description of instrumental techniques and spectral interpretation will be published later.[19]

---

[53] H. E. Watson, G. G. Rao, and K. L. Ramaswamy, *Proc. Roy. Soc., Ser. A*, **143**, 558 (1934).

[54] R. Mecke and K. Rosswog, *Z. Electrochem.*, **60**, 47 (1956).

[55] J. W. Smith and S. M. Walshaw, *J. Chem. Soc.*, 3217 (1957).

[56] E. A. Guggenheim, *Trans. Faraday Soc.*, **45**, 714 (1949).

[57] (a) J. W. Smith, *ibid.*, **46**, 394 (1950). (b) J. W. Smith, "Electric Dipole Moments," Butterworths, London, 1955.

[58] S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).

TABLE VIII

DIPOLE MOMENT DATA (20°)

W_2	ϵ_{12}	n_{12}	W_2	ϵ_{12}	n_{12}	W_2	ϵ_{12}	n_{12}
TMF in Cyclohexane			TMF in Benzene			6CFP in Cyclohexane		
0.000000	2.0234	1.42532	0.000000	2.2829	1.50065	0.000000	2.0228	1.42532
0.001116	2.0310	1.42532	0.001328	2.2959	1.50057	0.001598	2.0326	1.42543
0.001899	2.0359	1.42526	0.002357	2.3062	1.50053	0.003197	2.0432	1.42552
0.003043	2.0431	1.42523	0.003247	2.3146	1.50045	0.004596	2.0519	1.42564
0.004368	2.0522	1.42520	0.004063	2.3230	1.50041	0.006693	2.0658	1.42578
0.004987	2.0563	1.42520	0.005037	2.3325	1.50036	0.007647	2.0713	1.42584
0.007241	2.0710	1.42520	0.006234	2.3441	1.50031	0.009176	2.0816	1.42593
0.010387	2.0917		0.007703	2.3591	1.50026	0.010818	2.0923	1.42599
M_2 = 172.24, d_1 = 0.7791, α_ϵ = 6.57, α_n = −0.06, μ = 3.62 ± 0.01 D			M_2 = 172.24, d_1 = 0.879, α_ϵ = 9.87, α_n = −0.16, μ = 3.93 ± 0.01 D			M_2 = 234.32, d_1 = 0.7791, α_ϵ = 6.42, α_n = 0.18, μ = 4.09 ± 0.01 D		
6CFP in Benzene			6TFP in Cyclohexane			6TFP in Benzene		
0.000000	2.2831	1.50069	0.000000	2.0228	1.42572	0.000000	2.2825	1.50045
0.001450	2.2950	1.50072	0.001701	2.0289	1.42580	0.002113	2.2935	1.50053
0.002788	2.3056	1.50074	0.003655	2.0356	1.42596	0.003299	2.2995	1.50055
0.004047	2.3163	1.50076	0.005345	2.0418	1.42607	0.004584	2.3062	1.50057
0.005518	2.3292	1.50079	0.007506	2.0496	1.42618	0.007011	2.3195	1.50065
0.006978	2.3417	1.50081	0.009393	2.0562	1.42629	0.007647	2.3231	1.50065
0.008132	2.3513	1.50084	0.011344	2.0632	1.42641	0.009095	2.3304	1.50069
0.009616	2.3629	1.50089						
M_2 = 234.32, d_1 = 0.879, α_ϵ = 8.38, α_n = 0.06, μ = 4.18 ± 0.02 D			M_2 = 234.32, d_1 = 0.7791, α_ϵ = 3.56, α_n = 0.17, μ = 3.01 ± 0.01 D			M_2 = 234.32, d_1 = 0.879, α_ϵ = 5.29, α_n = 0.08, μ = 3.31 ± 0.01 D		
2CFP in Cyclohexane			2CFP in Benzene			6CFN in Cyclohexane		
0.000000	2.0242	1.42578	0.000000	2.2825	1.50065	0.000000	2.0254	1.42575
0.001707	2.0341	1.42590	0.001605	2.2953	1.50069	0.001752	2.0341	1.42595
0.003678	2.0459	1.42601	0.003311	2.3088	1.50072	0.003240	2.0425	1.42612
0.005540	2.0564	1.42612	0.004389	2.3174	1.50074	0.004466	2.0489	1.42623
0.007136	2.0667	1.42620	0.004642	2.3196	1.50074	0.006337	2.0586	1.42643
0.008672	2.0758	1.42629	0.005863	2.3295	1.50077	0.007857	2.0672	1.42663
0.010219	2.0849	1.42641	0.007288	2.3408	1.50079	0.009365	2.0749	1.42679
						0.010996	2.0842	1.42698
M_2 = 234.32, d_1 = 0.7791, α_ϵ = 5.96, α_n = 0.17, μ = 3.94 ± 0.01 D			M_2 = 234.32, d_1 = 0.879, α_ϵ = 8.01, α_n = 0.06, μ = 4.08 ± 0.01 D			M_2 = 284.38, d_1 = 0.7791, α_ϵ = 5.35, α_n = 0.32, μ = 4.04 ± 0.02 D		
6CFN in Benzene			6TFN in Cyclohexane			6TFN in Benzene		
0.000000	2.2825	1.50069	0.000000	2.0252	1.42572	0.000000	2.2825	1.50069
0.001514	2.2926	1.50079	0.001813	2.0309	1.42593	0.002003	2.2911	1.50081
0.002624	2.2999	1.50089	0.003829	2.0378	1.42612	0.003207	2.2964	1.50089
0.004147	2.3100	1.50098	0.005250	2.0417	1.42629	0.004693	2.3023	1.50098
0.005462	2.3197	1.50108	0.006689	2.0461	1.42644	0.005901	2.3085	1.50108
0.007128	2.3312	1.50120	0.008225	2.0512	1.42661	0.007125	2.3137	1.50115
0.009002	2.3436	1.50133	0.009729	2.0557	1.42676	0.009283	2.3232	1.50133
0.010176	2.3529	1.50142						
M_2 = 284.38, d_1 = 0.879, α_ϵ = 6.89, α_n = 0.21, μ = 4.12 ± 0.02 D			M_2 = 284.38, d_1 = 0.7791, α_ϵ = 3.15, α_n = 0.30, μ = 3.04 ± 0.01 D			M_2 = 284.38, d_1 = 0.879, α_ϵ = 4.40, α_n = 0.21, μ = 3.27 ± 0.02 D		

Registry No.—**1a,** 14376-79-5; **1b,** 25109-54-0; **1c,** 33044-58-5; 6CFP, 37781-16-1; 6TFP, 37781-17-2; 6DFP, 37781-18-3; 2CFP, 37781-19-4; 2TFP, 37781-20-7; 2DFP, 37781-12-7; 6CFN, 37781-13-8; 6TFN, 37781-14-9; 6DFN, 37781-15-0; TMF, 37783-39-4; isophorone-d_8, 14397-59-2; isophorone, 78-59-1; 2,4,4,-6,6-pentadeuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone, 37783-42-9; 4,4-dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone, 37783-43-0; 6-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone, 37783-44-1; 2-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone, 37786-75-7; 2-hydroxymethylene-3,3,5,5-tetramethylcyclohexanone, 37786-76-8; 6-hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone, 37786-77-9; 2-hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone, 37818-68-1; α-fluoro-4,4-dideuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone, 37786-78-0; α-hydroxymethylene-4,4-dideuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone, 37786-79-1; 2-fluoro-2,-6,6-trideuterio-3,3,5,5-tetramethylcyclohexanone, 37786-80-4.

Acknowledgments.—We wish to acknowledge general financial support for this research by The Robert A. Welch Foundation of Houston, Texas; the Fund for Organized Research of Texas A & M University; the National Institutes of Health (Research Grants GM-09143 and GM-12415); and the Upjohn Company of Kalamazoo, Mich.