matography on neutral alumina (Woelm), distilled, and finally separated from traces of impurities by preparative vpc to give 5,5-difluoro-cis-hydrindan (4 and 5), bp 170–171°. The proton nmr spectrum of the products showed no low-field absorptions and the ^{19}F spectrum showed an AB quartet at 20° which was temperature dependent, appearing as two overlapping AB quartets at −130°.

Anal. Calcd for $C_9H_{14}F_2$: C, 67.5; H, 8.8. Found: C, 68.1; H, 8.8.

9-Methyl-5,5-difluoro-cis-hydrindan. Cupric acetate (500 mg) was added to a solution of methylmagnesium bromide prepared from 2 g of magnesium and 7 g of methyl bromide in tetrahydrofuran. The α,β-unsaturated ketone 8 (5 g) in tetrahydrofuran was added

over 30 min and the mixture heated under reflux for a further 5 hr. The resulting crude 9-methyl-cis-hydrindan-5-one (10) had a proton spectrum showing the 9-methyl group at δ 1.04 and no low-field protons. A 2-g sample of the crude ketone in 20 ml of methylene chloride and 0.24 ml of water was treated in a steel reaction vessel with 14.2 g of sulfur tetrafluoride for 16 hr at 20°. The usual isolation procedure gave a crude dark-brown product which was purified by chromatography on alumina prepared in pentane. Elution with pentane gave 0.9 g of 9-methyl-5,5-difluoro-cis-hydrindan whose ^{19}F spectrum showed a single AB quartet at 20°. Attempts to purify further the compound by preparative vpc were unsuccessful.

Nuclear Magnetic Resonance Spectroscopy. Conformational Equilibria and Equilibration of 4,4-Difluorocyclohexanone and 6,6-Difluoro-cis-decal-2-ones[1]

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Abstract: The rates of ring inversion and conformational equilibration of 6,6-difluoro-cis-decal-2-one and 10-methyl-6,6-difluoro-cis-decal-2-one have been determined using fluorine magnetic resonance spectroscopy. The activation energies were found to be 11.3 ± 0.3 and 9.5 ± 0.1 kcal/mol, respectively. 4,4-Difluorocyclohexanone, however, appears to exchange its fluorines between conformationally nonequivalent sites rapidly on the nmr time scale even at −180°.

Nuclear magnetic resonance spectroscopy has been employed very extensively for conformational analysis and determination of rates of conformational equilibration.[3] Recently, emphasis has been placed on the use of fluorine magnetic resonance spectroscopy as an aid to conformational analysis, because fluorine chemical shifts are much more sensitive to chemical environment[4] than those of protons. The advantages of fluorine magnetic resonance spectroscopy for studies of conformational equilibration have recently been reviewed.[5] Among the successful applications are those to cyclobutane,[6] cyclohexane,[7] cycloheptane,[5,8] cyclooctane,[8] and cis-decalin[9] derivatives.

The "fluorine-labeling" technique was used in the present study of cyclohexanone and of some cis-decal-2-

ones which have special interest as models of the A, B rings of the 3-keto steroids.

So far, no reports are available of the successful use of proton magnetic resonance to detect "freezing out" of the chair–chair interconversion of cyclohexanone at low temperatures.[10] Here, "fluorine labeling" might be expected to be helpful in studies of the interconversion of the cyclohexanone forms 1 and 2 because of the generally much larger chemical-shift differences between axial and equatorial fluorines than between axial and equatorial hydrogens.[7]

1   **2**
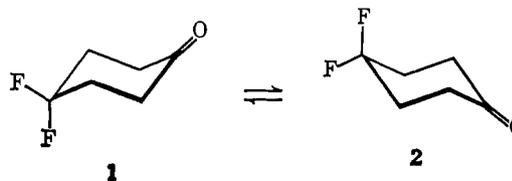
The inversion of cyclohexanone rings in other systems has not been studied. Molecular models show that cis-decal-2-one (3) like cis-decalin would be expected to interconvert between the two diasteromeric conformations 4 and 5.[11] Introduction of *gem*-fluorines at the 6 position of 3 provides two conformations, 6 and 7.

The equilibrium constant connecting 6 and 7 is not expected to be unity because the axial fluorine atom in

(1) Supported in part by the National Science Foundation.
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(3) For recent reviews, see H. Feltkamp and N. C. Franklin, *Angew. Chem.*, 77, 798 (1965); *Angew. Chem. Intern. Ed. Engl.*, 4, 774 (1965); and E. L. Eliel, *Angew. Chem.*, 77, 784 (1965); *Angew. Chem. Intern. Ed. Engl.*, 4, 761 (1965).
(4) A. Saika and C. P. Slichter, *J. Chem. Phys.*, 22, 26 (1954).
(5) J. D. Roberts, *Chem. Brit.*, 2, 529 (1966).
(6) J. B. Lambert and J. D. Roberts, *J. Am. Chem. Soc.*, 87, 3884 (1965).
(7) (a) F. A. Bovey, E. W. Anderson, F. P. Hood, and R. L. Kornegay, *J. Chem. Phys.*, 40, 3099 (1964); (b) S. Spassov, E. S. Glazer, D. L. Griffith, K. Nagarajan, and J. D. Roberts, *J. Amer. Chem. Soc.*, 89, 88 (1967). See also J. D. Roberts, *Angew. Chem.*, 75, 20 (1963); *Angew. Chem. Intern. Ed. Engl.*, 2, 53 (1963).
(8) (a) J. D. Roberts, Abstracts of 19th National Organic Chemistry Symposium of the American Chemical Society, Tempe, Ariz., June 1965, pp 77–85; (b) R. Knorr, C. Ganter, and J. D. Roberts, *Angew. Chem.*, 79, 577 (1968); (c) J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, and J. D. Roberts *J. Amer. Chem. Soc.*, in press.
(9) J. T. Gerig and J. D. Roberts, *ibid.*, 88, 2791 (1966).

(10) J. E. Anderson, D. D. McNicol, and B. D. Batts, unpublished results. See J. E. Anderson, *Quart. Rev.* (London), 19, 426 (1965).
(11) The existence of the enantiomeric forms of 4 and 5 and related substances to be discussed later is taken to be understood.
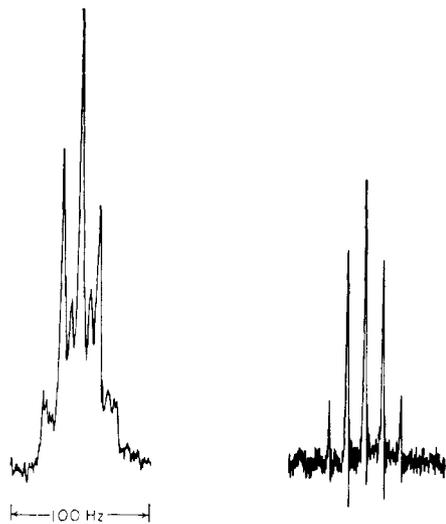
Figure 1. Fluorine magnetic resonance spectra at 56.4 MHz of 4,4-difluorocyclohexanone: left curve, at $-20°$ in admixture with 1,1-difluorocycloheptane (resonances not shown, to provide a standard for detection of line broadenings); right curve, deuterated by base-catalyzed exchange in the 2,2 and 6,6 positions, in dimethyl ether as solvent.

7 interacts with the hydrogen at the 4 position and no comparable interaction is expected for 6. Therefore, 6 is expected to predominate over 7.[9] An average AB spectrum of the *gem*-fluoro group is expected for rapid equilibration at high temperatures, while at low temperatures (and slow interconversion) two separate AB quartets are expected with that corresponding to conformer 6 being the more prominent. Introduction of a methyl group at position 10 should tend to destabilize both conformations 8 and 9 because of 1,3-diaxial interactions. These same interactions are also expected to affect the chemical shifts of the axial and equatorial fluorine atoms, particularly in 8.

3

4   5

6, R = H   7, R = H
8, R = CH₃   9, R = CH₃
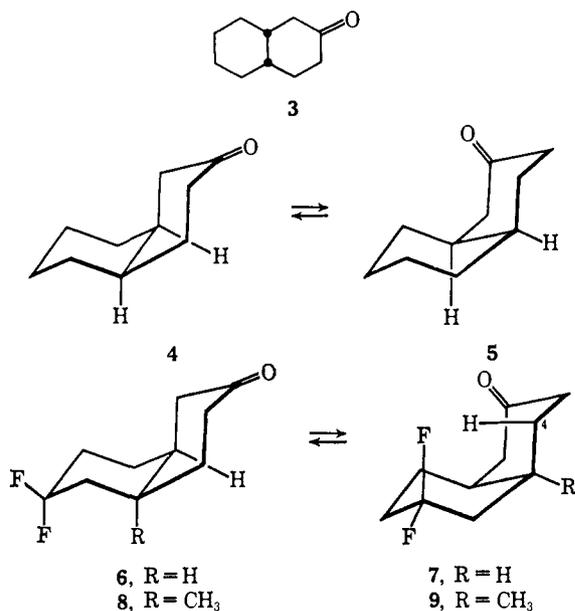
Synthetic Methods and Results

4,4-Difluorocyclohexanone was prepared from the commercially available 2-furanacrylic acid (10) which was converted first to diethyl 4-oxoheptanedioate

(11)[12-14] and then to diethyl 4,4-difluoroheptanedioate (12) with sulfur tetrafluoride.[15,16] The Dieckmann condensation with 12 afforded 2-carbethoxy-4,4-difluoro-cyclohexanone (13), which in chloroform solution appeared to be largely enolized as judged from its infrared spectrum. Hydrolysis of the ester group and decarboxylation gave 4,4-difluorocyclohexanone (14) as a volatile, low-melting solid.

10

11, R = O
12, R = F₂

13, R = CO₂C₂H₅
14, R = H
15, R = CH₃
16, R = Br
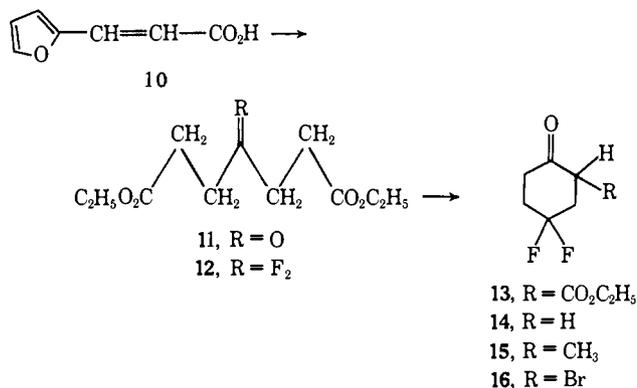
The fluorine spectrum of 4,4-difluorocyclohexanone (14) is a complex but symmetrical peak at room temperature, which turns into a symmetrical quintet on deuteration of the protons α to the carbonyl group (Figure 1). This shows that the fine structure arises from proton–proton and/or long-range proton–fluorine couplings. The quintet collapsed to a single peak with proton decoupling. Although the lines of the quintet ultimately broadened to give a singlet, no appreciable difference in line width of the fluorine resonance was observed down to $-183°$ in a mixture of propene, bromotrifluoromethane, and dimethyl ether as the solvent.

To determine what order of magnitude of fluorine chemical-shift difference is to be expected for a conformationally biased 4,4-difluorocyclohexanone, it was desirable to have an unsymmetrically substituted derivative. Several attempts to convert 14 to the corresponding α-methyl compound 15 by standard procedures were unsuccessful, but monobromination of 4,4-difluorocyclohexanone in the presence of hydrogen bromide did give the α-bromo ketone 16. Recently, several workers have shown that the ratio of axial and equatorial conformers of 2-bromocyclohexanone depends on concentration and on solvent polarity. For example, Allinger[17] has concluded from dipole-moment studies that there is a preference for the conformation with axial bromine in benzene, dioxane, and heptane, while Waegell and Ourisson[18] obtained similar results from infrared and ultraviolet spectroscopy and dipole-moment studies. Garbisch,[19] with the aid of both proton-spin coupling and chemical-shift data, showed the conformer with axial bromine to be preferred to the extent of 52 to 91 $\pm$ 4% in carbon tetrachloride solu-

(12) W. S. Emerson and R. I. Longley, Jr., *Org. Syn.*, 33, 25 (1953).
(13) W. Marckwald, *Ber.*, 20, 2811 (1887).
(14) W. Marckwald, *ibid.*, 21, 1398 (1888).
(15) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, 82, 543 (1960).
(16) D. G. Martin and F. Kagan, *J. Org. Chem.*, 27, 3164 (1962).
(17) N. L. Allinger, J. Allinger, and N. A. LeBel, *J. Amer. Chem. Soc.*, 82, 2926 (1960).
(18) B. Waegell and G. Ourisson, *Bull. Soc. Chim. Fr.*, 496 (1963).
(19) E. W. Garbisch, Jr., *J. Amer. Chem. Soc.*, 86, 1780 (1964).

tion, the higher extent of axial being found at the lowest concentrations in carbon tetrachloride.

The sample of 4,4-difluoro-2-bromocyclohexanone (16) contained some unchanged 4,4-difluorocyclohexanone which served as a useful standard for the low-temperature spectra. The room-temperature fluorine spectrum of neat liquid 16 showed an AB quartet with the upfield pair broader (corresponding to axial-like fluorines) than the downfield pair.[20] In order to obtain as nearly equal a distribution of conformers as possible, low-temperature spectra were taken of the bromo compound in an equimolar mixture with acetone (carbon tetrachloride was not suitable for low-temperature work). No evidence was obtained for "freezing out" of conformers down to $-109°$. The change in chemical shift and increase in the coupling constant (Table I) indicated an increase in the proportion of one

Table I. Temperature Dependence of the Chemical Shift of 2-Bromo-4,4-difluorocyclohexanone in Acetone

| Temp, °C	J_{F-F}, Hz	δ_A,[a] Hz	δ_B,[a] Hz	δ_{F-F}, Hz
-2	240	1084	1348	264
-33	240	1072	1375	303
-53	241	1070	1385	315
-69	242	1063	1406	343
-82	243	1061	1410	349
-88	244	1061	1415	354
-93	245	1060	1421	361
-99	246	1059	1424	366
-109	248	1056	1430	374

[a] Chemical shifts corresponding to observed AB quartet, upfield from trifluoroacetic acid.

of the conformers with decreasing temperature. On the assumption that ΔS for the interconversion of the conformations is zero, the change in fluorine chemical shift with temperature was analyzed by the procedure used successfully for determining conformational equilibrium constants for substituted 1,1-difluorocyclobutanes.[6] The results indicate that the difference in free energy between the conformers is about 1 kcal and that the dominant isomer is present to the extent of 87% at $-2°$ and has a chemical-shift difference between the fluorines of about 430 Hz. The small fluorine chemical-shift difference for this conformation suggests that it has the bromine axial (see later discussion). The minor isomer is calculated to have a chemical shift of about 900 Hz. These results are very important in helping to set a lower limit on the rate of the conformational equilibration 1 ⇌ 2. To barely achieve coalescence of two resonances separated by 400 Hz through exchange requires a mean lifetime before exchange on the order of 10^{-3} sec. It is clear from other studies[7b] that the observed line width for 14 at $-183°$ corresponds to a mean lifetime of at least a factor of 10, and more likely a factor of 100, less than 10^{-3} sec. A mean lifetime before exchange of 10^{-5} sec or less at $-180°$ requires that the free energy of activation for ring inversion of 14 has the small value of 2.3 kcal or less. Alternatively, the 4,4-difluorocyclohexanone ring may exist preferentially in a twist-boat form in which the fluorines

(20) The upfield position of the axial-like fluorines is unique among the gem-fluorocyclohexanes we have so far studied[7b,9] and may indicate an especially large effect arising from an axial bromine against axial fluorine interaction, an unanticipated influence of the carbonyl group, or appreciable nonchair character of the cyclohexanone ring.

are either equivalent because of the presence of a twofold symmetry axis, or else able to undergo very easy inversion by way of pseudorotation through a form with a twofold axis.

6,6-Difluoro-cis-decal-2-one (6 ⇌ 7) and the corresponding trans isomer were prepared from 4-benzoyloxycyclohexanone[21] (17) which was converted to 6-benzoyloxy-$\Delta^{1,9}$-decal-2-one (18) by the addition of methyl vinyl ketone to the morpholine enamine by the method of Stork and coworkers.[22] This cyclization is expected to lead to four possible isomers, 18a–18d.

17   18

19, R = H
21, R = CH₃

20, R = H
22, R = CH₃

6 ⇌ 7, R = H
8 ⇌ 9, R = CH₃
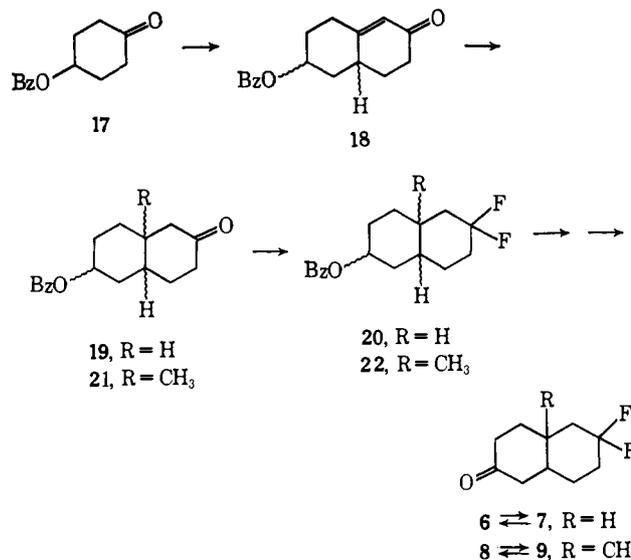
Addition of hydrogen to these substances, even if carried out under conditions known to favor formation of cis product for $\Delta^{1,9}$-decal-2-one,[23] could well be expected to give a substantial proportion of trans 19

18a   18c

18b   18d
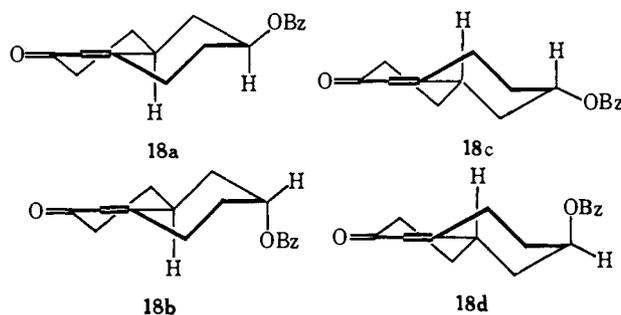
with either 18b or 18d because these substances have axial benzoate groups that could inhibit addition of hydrogen to the cis side. The proton nmr spectrum of 19 shows the 6 proton as a combination of a broad and a sharp signal with intensities expected for an almost equal mixture of axial and equatorial benzoate groups. The mixture of 19 isomers with sulfur tetrafluoride[14] at room temperature gave a 50% yield of 2,2-difluoro-6-benzoyloxydecalin (20). The shape and integral of the 6 proton remained the same as for the starting material, indicating that no inversion of the benzoate group occurred. Hydrolysis of 20 gave 2-hydroxy-6,6-difluorodecalin, which with Jones' re-

(21) E. R. H. Jones and F. Sondheimer, J. Chem. Soc., 615 (1949).
(22) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, J. Amer. Chem. Soc., 85, 207 (1963).
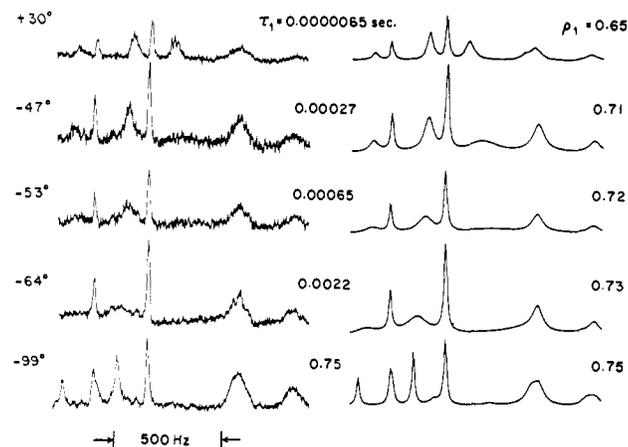(23) R. L. Augustine, J. Org. Chem., 28, 152 (1963).

Figure 2. Left side, fluorine spectra at 56.4 MHz of 6,6-difluoro-*cis*-decal-2-one (**6** ⇌ **7**) in diethyl ether as a function of temperature. Right side, theoretical spectra calculated as a function of τ_1 and p_1 (the subscripts referring to the dominant conformation **6**). The sharp peaks on the left side of the 30° spectrum arise from the equatorial fluorines of the *trans* isomer, present to the extent of about 48%. The computed spectra on the right are calculated on the basis of the presence of 48% of the *trans* isomer which is assumed to give a temperature-independent fmr spectrum.
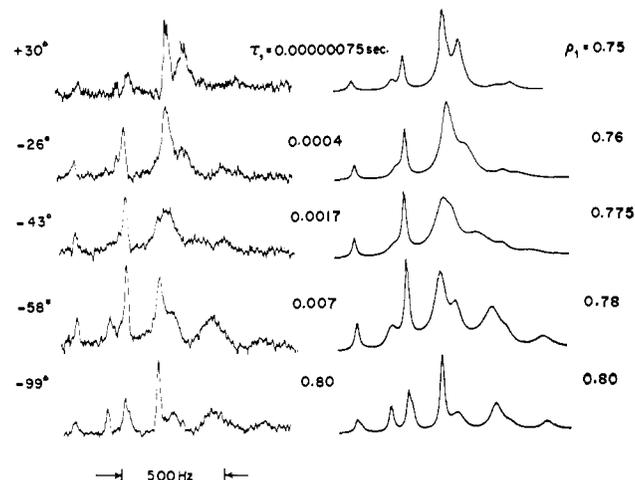

Figure 3. Left side, fluorine spectra at 56.4 MHz of 10-methyl-6,6-difluoro-*cis*-decal-2-one in acetone as a function of temperature. Right side, theoretical spectra calculated as a function of τ_1 and p_1 (the subscripts referring to the dominant conformation **9**). The sample contained 27% of the *trans* isomer which, in the calculation of the theoretical spectra, was assumed to give a temperature-independent fmr spectrum.

agent[24] afforded a mixture of *cis*- and *trans*-6,6-difluorodecal-2-one. The ^{19}F spectrum and vpc analysis showed the product to be an almost equal mixture of the *cis* (**6** and **7**) and *trans* isomers.

9-Methyl-6-benzoyloxydecal-2-one (**21**) was prepared by 1,4 addition of excess methylmagnesium bromide to the $\Delta^{1,9}$-ketone **18** in tetrahydrofuran in the presence of cupric acetate.[25] The proton spectrum of the crude product (**20**) showed the presence of the benzoate group and the absence of the vinyl protons, while the signals for the angular methyl group in the mixture of isomers appeared at δ 0.98 and 1.02. No apparent attack on the benzoate group occurred although a large excess of the reagent was used. Treatment of **21** with sulfur tetrafluoride followed by hydrolysis of the benzoate group of **22** and Jones oxidation[24] of the corresponding alcohol gave 10-methyl-6,6-difluorodecal-2-one whose ^{19}F spectrum showed it to be a 73:27 mixture of the *cis* (**8** and **9**) and *trans* isomers. Methylmagnesium bromide, in the presence of cupric acetate, normally adds to α,β-unsaturated fused-ring ketones to give products with *cis*-ring fusion,[25] and, in the similar addition of the same reagent to $\Delta^{1,9}$-decal-2-one, formation of 9-methyl-*cis*-decal-2-one appears to be quantitative.[9] However, as in the hydrogenation of **18**, addition to give the *cis* product is expected to be at least somewhat hindered by the axial benzoate groups in **18b** and **18d**.

At room temperature, the fmr spectrum of 6,6-difluoro-*cis*-decal-2-one (**6**, **7**) appears as a broadened low-intensity pattern of the AB type with a chemical-shift difference of about 400 Hz (Figure 2). At about −90°, two AB quartets corresponding to **6** and **7** emerge. The sample contained 48% of the *trans* isomer which has a temperature-independent spectrum and serves as a useful standard although it partially overlaps the low-temperature spectrum of one of the *cis* conformers. Similarly, the room-temperature fmr spectrum of 10-methyl-6,6-difluoro-*cis*-decal-2-one (**8**, **9**) appears

(24) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).
(25) A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 356 (1962).

as a broadened AB-type spectrum overlapping the temperature-independent spectrum of the *trans* isomer (27%), while at −90°, two overlapping AB quartets corresponding separately to **8** and **9** emerge. Several illustrative spectra at different temperatures are shown in Figure 3. Trifluoroacetic acid was used as an internal standard and, in accord with earlier work with 1,1-difluorocyclohexane[7b] and with 2,2-difluorodecalins,[9] the sharper peaks were assigned to the equatorial fluorines and the broader peaks to the axial fluorines on the grounds that the dihedral angle–coupling constant relationship of Karplus applies, at least qualitatively, to hydrogen–fluorine couplings.[6,9] The average AB pattern for the room-temperature spectrum of 6,6-difluoro-*cis*-decal-2-one (**6**, **7**), like that of the 4-substituted 1,1-difluorocyclohexanes,[6] is complicated by H–F coupling, each peak appearing as a quintet. The splitting in the downfield quintets is about 12 Hz, whereas in the upfield quintets it is about 15 Hz. This difference is expected on the basis that the observed H–F couplings are average values and will be smaller the more nearly equatorial the fluorines are on the average.

Tentative identification of the fluorine resonances observed at low temperatures, where ring inversion is slow for 6,6-difluoro-*cis*-decal-2-one (**6** ⇌ **7**), can be made by comparing the chemical shift of the fluorine atoms with those of 2,2-difluoro-*cis*-decalin (**23** ⇌ **24**)[9] (see Table II). The equatorial fluorines of **6**, **7**,

23, R = H   **24**, R = H
25, R = CH₃   **26**, R = CH₃
27, R = C₂H₅   **28**, R = C₂H₅
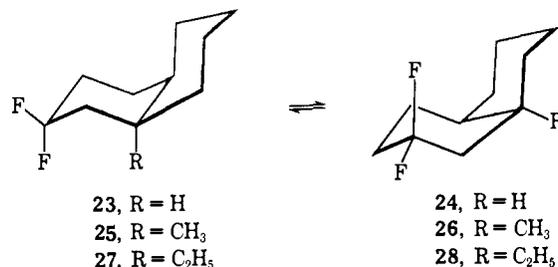
23, and **24** fall in the range 528–637 Hz upfield from trifluoroacetic acid; however, the axial fluorines in the

Table II. Nmr and Kinetic Parameters for 2,2-Difluoro-*cis*-decalin, 6,6-Difluoro-*cis*-decal-2-one, and Related Compounds

Compound	Solvent	Conformation	δ, Hz Equatorial[c]	Axial[c]	δF−F,[c] Hz	JF−F, Hz	% of conformation	Ea, kcal/mol	ΔG*, kcal/mol	ΔS*, eu
	Acetone[a]	23	593	1354	761	234	74	15.0 ± 0.9	12.3	8 ± 5
		24	528	875	347	236	26	14.5 ± 0.9	11.7	
	Propene[a]	23	597	1354	757	233	74	14.6 ± 0.7	12.2	6 ± 3
		24	541	875	334	239	26	13.9 ± 0.7	11.6	
	Propene[a]	25	302	699	397	242	48	9.2 ± 0.6	12.0	−12 ± 3
		26	451	995	544	239	52	9.1 ± 0.6	12.1	−13 ± 3
	Ether	6	637	1326	689	241	65	11.3 ± 0.3	9.5	6
		7	570	890	320	241	35	10.5 ± 0.3	9.1	4
	Acetone	8	371	704	333	237	25	9.2 ± 0.1	9.8	−5
		9	524	912	288	237	75	9.5 ± 0.1	10.4	−5
	Ether		786	1362	576[b]	241				
	Acetone	29	351	734	383	237				

[a] Data from ref 9. [b] M. J. S. Dewar and T. G. Squires [*J. Amer. Chem. Soc.*, **90**, 210 (1968)] have recently reported δF−F for this substance as 649 Hz in dimethylformamide and 646 Hz in acetone. The reason for the discrepancy and the difference between the δF−F reported by these workers of 707 Hz compared with the 657 Hz (both in acetone) which we reported earlier[9] for 2,2-difluoro-*trans*-decalin is not clear unless Dewar and Squires neglected to correct their line separations for (the large) JF−F, which correction brings the results into reasonable agreement. [c] CF₃COOH, external reference.

major conformers come at 1326 and 1354 Hz while, in the minor conformers they appear at 890 and 875 Hz, respectively, upfield from trifluoroacetic acid. The minor conformer of the decalone is therefore assigned the structure 7 for which, like 24, there is expected a substantial steric interaction between the axial fluorine at position 6 and the axial hydrogen at position 4.[9] This interaction should destabilize these conformers relative to 6 and 23 which have only 1,3-diaxial hydrogen–fluorine interactions and also produce a downfield chemical shift of the axial fluorines.

Assignments of the resonance lines to the isomers 8 and 9 is more difficult. In the work[9] on the methyl-decalin conformations 25 and 26, the populations were found to be nearly equal, the 1,3-diaxial interactions of the ring methylenes and the angular methyl group with the fluorines being rather evenly balanced. The general trends of the chemical shifts noted at the time the work was done led to assignment of conformation 25 to the species with the farthest downfield axial resonance. It now appears that this assignment was incorrect, because there seems to be a pattern of downfield shifts of both axial and equatorial fluorine resonances produced by 1,3-diaxial interaction of the *gem*-fluoro group with an angular methyl group. The best example of this is 10-methyl-6,6-difluoro-*trans*-decal-2-one (29) where the equatorial and axial resonances are
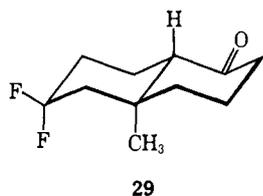
at 371 and 734 Hz, respectively, which represent downfield shifts of 435 and 628 Hz, relative to the corresponding fluoro derivative of *trans*-decal-2-one without

the methyl group. With this lead to work with, the relation between a number of chemical shifts and conformations becomes more clear. Examples include the angular methyl- and ethyldecalins 25 and 27 (the latter of which was assigned the correct conformation earlier),[9] the 10-methyl-*cis*-decal-2-one 8 and the 6,9-dimethyl-*cis*-decalin 30[9] (provided that 30 is the correct structure, not 31).
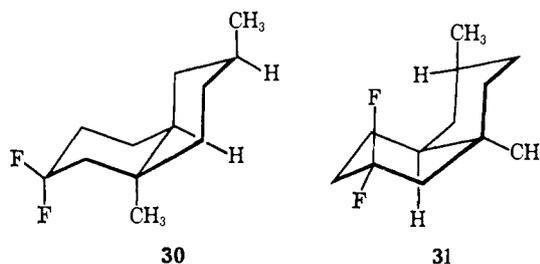
That 9 is a rather more stable conformation than 8 is wholly reasonable, the general shape and flexibility of the cyclohexanone ring being such that 1,3-diaxial interactions of the methyl group with the ketone ring in 9 should be smaller than the corresponding interaction of the methyl with the fluorine-substituted ring in 8.

A more or less consistent pattern of fluorine shifts in saturated six-membered rings now seems to be emerging which, if it holds up, may well have far-reaching application to stereochemical problems. Upfield shifts result from *gauche* interactions and are more pronounced on axial than on equatorial fluorines (compare 23 with both 1-methyl-2,2-difluoro-*cis*-decalin[9] and 3-methyl-2,2-difluoro-*cis*-decalin[9]). Downfield shifts result from 1,3-diaxial interactions, with axial fluorines being more affected than equatorial fluorines (see discussion above). Finally, groups in the 4 position seem to cause upfield shifts and, with these, the effects are apparently much greater on equatorial fluorines than on axial fluorines.[7b,26]

Theoretical spectra as a function of τ, the mean lifetimes of the conformers before inversion, were generated by an IBM 7094 computer using Gerig's[9] modification of Alexander's[27] equations. The computed spectra reasonably reproduce the line positions, shapes, and relative intensities for 6,6-difluoro-*cis*-decal-2-one (Figure 2) and 10-methyl-6,6-difluoro-*cis*-decal-2-one (Figure 3) as a function of temperature. The experimental spectra could only be matched by assuming that averaging occurs between the axial fluorine in one conformation and the equatorial fluorine in the other,[9] with an allowance for an upfield temperature-dependent shift of the axial fluorines of about 30 Hz per 100° rise in temperature. Similar chemical shift changes with temperature have been observed for 1,1-difluorocyclohexanes[7] and 1,1-difluoroethanes.[28] The variation of the rates of inversion with temperature were fitted to the Arrhenius equation by the method of least squares[29] and the enthalpies, entropies, and free energies of activation were calculated by standard equations.[30]

The activation energy (E_a) for ring inversion of 6,6-difluoro-*cis*-decal-2-one (6 $\rightleftarrows$ 7) was found to be 11.3 ± 0.3 kcal/mol for the major conformer, which is considerably less than the activation energy found for 2,2-difluoro-*cis*-decalin[9] (14.0 ± 0.8 kcal/mol) (Table II) and other decalin derivatives[9] and, in fact, very nearly the same as that of 1,1-difluorocyclohexane (E_a = 10.9 ± 0.4 kcal/mol).[7b] The results corroborate the expectation of a very low barrier for 4,4-difluorocyclohexanone because clearly there is very little resistance supplied by the cyclohexanone ring in 6 to attainment of the boat–boat configuration.[9] The angular methyl group in 10-methyl-6,6-difluoro-*cis*-decal-2-one is expected to destabilize the ground-state configuration 8 in the same way as has already been postulated for 9-methyl-2,2-difluoro-*cis*-decalin,[9] through 1,3-diaxial interactions. However, the effect certainly should be less for 9 because of distortion of the ring arising from the carbonyl group. It is therefore not surprising that the activation energies for interconversion of 8 $\rightleftarrows$ 9 and 6 $\rightleftarrows$ 7 are closer together than those for 23 $\rightleftarrows$ 24 and 25 $\rightleftarrows$ 26.

Experimental Section

Melting and boiling points are uncorrected. Vapor phase chromatographic separations were carried out with an Aerograph Model 700 "Autoprep" gas chromatograph, using SE 30 columns. Elemental analyses were supplied by Elek Microanalytical Laboratories, Torrance, Calif.

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

Fluorine magnetic resonance spectra were recorded at 56.4 MHz with the Varian Model A-56/60A spectrometer (6,6-difluoro-*cis*-decal-2-one and the corresponding 10-methyl derivative) or with a Varian Model V-4300 D spectrometer. Fluorine chemical shifts are reported in hertz upfield from trifluoroacetic acid as internal standard.

At low temperatures, the samples were thermostated with precooled nitrogen passing through a dewar-jacketed probe. The gas

temperature was monitored by a copper–constantan thermocouple and the sample temperatures were calibrated by comparison with a copper–constantan thermocouple inserted in the sample. For the spectra taken with the A-56/60A spectrometer, the Varian V-6057 variable temperature accessory was used. The control temperatures were again calibrated by inserting a copper–constantan thermocouple directly into the sample and by determining the freezing points (loss of high-resolution signal) of pure pyridine and chloroform. These freezing points were also checked with a thermocouple inserted into the sample tube. The spectra of both 6,6-difluoro-*cis*-decal-2-one and 10-methyl-6,6-difluoro-*trans*-decal-2-one required a sweep width of 1500 Hz and were compiled from several scans on a Varian C-1024 time-averaging computer. The theoretical spectra and the Arrhenius plots were computed by an IBM 7094 computer coupled to a Calcomp plotter.

6-Benzoyloxy-$\Delta^{1,9}$-decal-2-one (18). 4-Benzoyloxycyclohexanone[21] (88 g, mp 57–60°) was treated with morpholine (44 g) and benzene (200 ml) in a Dean–Stark apparatus according to the method of Stork, *et al.*,[22] and afforded the corresponding morpholine enamine (83 g), mp 143–146° after crystallization from acetone. This enamine (75 g) in 200 ml of dry dioxane was heated under reflux with 20 g of redistilled methyl vinyl ketone. The orange solution was mixed with 100 ml of water and again heated under reflux for 14 hr. The mixture was extracted with ether and washed with water, 20% hydrochloric acid, and sodium bicarbonate. Distillation gave 39 g of 4-benzoyloxycyclohexanone, mp and mmp 55–60°. Chromatography of the still residue (12.5 g) on 200 g of acid-washed alumina in hexane and elution with 1:1 benzene–hexane gave an additional 2.2 g of impure 4-benzoyloxycyclohexanone. Further elution with the same solvent afforded 6.9 g of 6-benzoyloxy-$\Delta^{1,9}$-decal-2-one (18), mp 131–132°, after crystallization from ether–acetone. The pmr spectrum of 18 showed, besides aromatic protons, signals for one proton at δ 5.8 (H at C-1) and one proton at 5.42 (H at C-6).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.5; H, 6.7. Found: C, 75.3; H, 6.7.

6-Benzoyloxydecal-2-one (19). 6-Benzoyloxy-$\Delta^{1,9}$-decal-2-one (3.5 g) in 100 ml of ethanol containing 5 ml of 3 *N* hydrochloric acid was treated with hydrogen over 0.35 g of 10% palladium-on-charcoal catalyst. The theoretical amount of hydrogen was adsorbed in 30 min, sodium bicarbonate added, and the catalyst removed by filtration. Evaporation of the solvent left 3.7 g of oily 6-benzoyloxydecal-2-one. This substance, although appearing to be homogeneous by thin layer chromatography (tlc), showed in the pmr spectrum, in addition to the aromatic protons, a signal at δ 5.32 of width 8 Hz and a signal at 5.0 of width 14 Hz which together equalled one proton and indicated that configurations with the 6-benzoyloxy group equatorial and axial were both present.

2,2-Difluoro-6-benzoyloxydecalin (20). The crude 6-benzoyloxyoctal-2-one (2 g) was mixed with 15 ml of methylene chloride and 0.13 g of water, then treated with 7.9 g of sulfur tetrafluoride in a 200-ml steel pressure vessel by the procedure of Gerig and Roberts.[9] After 16 hr, the dark product was poured into water, washed with sodium bicarbonate solution, and extracted with methylene chloride and the extract dried over Na_2SO_4. The solvent was removed on a steam bath and the residue taken up in benzene and ccromatographed on a column of 20 g of neutral alumina (Woelm) which had been washed with hexane. Elution with benzene–hexane and benzene gave 1.1 g of 2,2-difluoro-6-benzoyloxydecalin as a colorless oil, homogeneous by tlc and less polar than the starting ketone. The ^{19}F spectrum was complex and not temperature dependent.

6-Hydroxy-2,2-difluorodecalin. Crude 6-benzoyloxy-2,2-difluorodecalin (1 g) was heated under reflux with 0.5 g of sodium hydroxide in a mixture of 5 ml of methanol and 1 ml of water for 30 min. Water was added, the methanol removed by evaporation, and the product extracted with ether. Acidification of the aqueous layer gave 0.33 g of benzoic acid (mp and mmp 121°). Evaporation of the ether layer gave 0.48 g (73%) of 6-hydroxy-2,2-difluorodecalin. The nmr spectrum showed the absence of aromatic protons and the 6 protons appeared at δ 4.17 (width $\sim$8 Hz) and 3.6 (width $\sim$16 Hz).

6,6-Difluorodecal-2-one. 6-Hydroxy-2,2-difluorodecalin (0.4 g) in acetone at 0° was treated with Jones reagent[24] under nitrogen for 30 min. Water was added and the product extracted with ether. The yield of a mixture of *cis*- and *trans*-6,6-difluorodecal-2-one was 0.38 g.

Anal. Calcd for $C_{10}H_{14}OF_2$: C, 63.8; H, 7.5. Found: C, 64.1; H, 7.6.

(26) G. A. Yousif and J. D. Roberts, *J. Amer. Chem. Soc.*, **90**, 6428 (1968); see also R. D. Stolow, T. W. Giants, and J. D. Roberts, *Tetrahedron Lett.*, in press.

(27) S. Alexander, *J. Chem. Phys.*, **37**, 967 (1963).

(28) R. A. Newmark and C. H. Sederholm, *ibid.*, **43**, 602 (1965).

(29) H. Margeneau and G. M. Murphy, "The Mathematics of Physics and Chemistry," Vol. II, D. Van Nostrand and Co., Inc., Princeton, N. J., 1964, p 517.

(30) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, p 71.

Although tlc indicated the product to be homogeneous, vpc on an SE 30 column at 200° showed it to be an approximately equal mixture of *cis* and *trans* isomers and this composition was confirmed by the fmr spectrum, to which the contribution of the *trans* isomer was temperature independent, while that of the *cis* isomer was highly temperature dependent.

9-Methyl-6-benzoyloxydecal-2-one (21). Methyl bromide (7 g) in tetrahydrofuran was added to 2 g of magnesium in 100 ml of tetrahydrofuran. After completion of the reaction, 0.5 g of cupric acetate monohydrate was added and this was followed by addition over 30 min of a solution of 5 g of 6-benzoyloxy-$\Delta^{1,9}$-octal-2-one (18) (mp 131–132°) in 50 ml of tetrahydrofuran. The mixture was heated under reflux for 5 hr and the Grignard complexes decomposed with saturated ammonium chloride solution. After acidification, the product was extracted with ether and adsorbed on a hexane-washed column of 90 g of alumina (Woelm, neutral). Elution with two 50-ml portions of 1:1 ether–hexane gave 2.9 g of a mixture of isomeric 9-methyl-6-benzoyloxydecal-2-ones. The nmr spectrum showed the benzoate group but no vinyl protons, while signals for the angular methyl group came at δ 0.95 and 1.05. Futher elution with the same solvent gave 1.7 g of less pure material, possibly containing some of the 1,2-addition product.

9-Methyl-2,2-difluoro-6-benzoyloxydecalin (22). 9-Methyl-6-benzoyloxydecal-2-one (2.4 g), 0.14 g of water, and 20 ml of methylene chloride were shaken in a steel vessel with an excess (9 g) of sulfur tetrafluoride for 16 hr. The crude product was taken up in methylene chloride, washed with sodium bicarbonate, and purified by filtration through a pad of neutral alumina (Woelm). The pad was washed with benzene and, after evaporation of the solvent, there was obtained 1.7 g of crude liquid 9-methyl-2,2-difluoro-6-benzoyloxydecalin.

9-Methyl-6-hydroxy-2,2-difluorodecalin. Crude 9-methyl-6-benzoyloxy-2,2-difluorodecalin (1.3 g) prepared as above was heated under reflux with 0.5 g of sodium hydroxide in a mixture of 5 ml of methanol and 1 ml of water for 30 min. The mixture was diluted with water and extracted with ether. Acidification of the aqueous layer gave 0.34 g of benzoic acid while evaporation of the ether layer gave 0.56 g of crude 9-methyl-6-hydroxy-2,2-difluorodecalin.

10-Methyl-6,6-difluorodecal-2-one. The crude 9-methyl-6-hydroxy-2,2-difluorodecalin (0.56 g) was dissolved in 15 ml of acetone at 0°, treated with Jones reagent[24] under nitrogen, and allowed to stand for 30 min. Water was added and the product extracted with ether to give 0.4 g of 10-methyl-6,6-difluorodecal-2-one as a colorless oil which, from its ^{19}F spectrum, was shown to be a mixture of 73% of the *cis* and 27% of the *trans* isomers. The product was purified by preparative vpc and characterized by its fmr, pmr, and mass spectra.

Diethyl 4-Oxoheptanedioate (11). 2-Furanacrylic acid (69.0 g, 0.5 mol) was heated under reflux with 230 g of ethanol and saturated with gaseous hydrogen chloride (90 min). The solvent was evaporated and the residue neutralized with sodium bicarbonate solution and extracted with benzene and ether to give, after distillation, 81

g of diethyl 4-oxoheptanedioate, bp 115–119° (0.4 mm) (lit.[12-14] bp 286°, 116–121° (0.3 mm)).

Diethyl 4,4-Difluoroheptanedioate (12). Diethyl 4-oxoheptanedioate (8.0 g) was mixed with 30 ml of methylene chloride (30 ml) and 1.5 ml of water and treated in a steel reaction vessel with 60 g of sulfur tetrafluoride at 65° for 9 hr. After 12 hr at room temperature, the bomb was opened and the crude product taken up in methylene chloride, washed with water until neutral, and distilled. After a forerun of 1.2 g of diethyl 4-oxoheptanedioate, there was obtained 5.8 g (66%) of diethyl 4,4-difluoroheptanedioate as a pale yellow liquid, bp 95–98° (0.15 mm). The product was found to be homogeneous by vpc and, as expected, the fmr spectrum showed only a simple quintet.

Shorter reaction times and/or lower temperatures gave less complete formation of 12, whereas higher temperatures converted the ester groups into trifluoromethyl groups.

2-Carbethoxy-4,4-difluorocyclohexanone (13). Diethyl 4,4-difluoroheptanedioate (6.18 g, 0.0245 mol) was added dropwise to a refluxing ethanolic solution of sodium ethoxide prepared by dissolving 1.13 g (0.04 g-atom) of sodium in 30 ml of ethanol. The mixture was heated under reflux for 3 hr, the ethanol removed under reduced pressure, and the residue heated to 100–125° at a pressure of 0.5 mm for 1 hr. The mixture was cooled, acidified with 60 ml of 10% acetic acid, and extracted with ether. The extract afforded 4.5 g (89%) of crude 2-carbethoxy-4,4-difluorocyclohexanone which showed infrared absorptions in chloroform at 1740 (w), 1715 (w), and 1650 cm⁻¹ (s). The material gave an intense violet color with ferric chloride solution. It was not further purified but used directly in the next step.

4,4-Difluorocyclohexanone (14). Crude 2-carbethoxy-4,4-difluorocyclohexanone (4.5 g) was mixed with a solution of 2.4 g of potassium hydroxide in 65 ml of water and allowed to stand at 20° for 9 hr. After acidification with 6 N hydrochloric acid, the mixture was heated under reflux for 4.5 hr, cooled, and extracted with ether. The extract afforded a semicrystalline product which was purified by sublimation at 20° and 0.3 mm. The resulting 4,4-difluorocyclohexanone (1.2 g) had mp 35–36° and showed an infrared maximum at 1724 cm⁻¹. The fmr spectrum in CCl_2F_2 showed a complex multiplet 1395 Hz upfield from trifluoroacetic acid.

Anal. Calcd for $C_6H_8OF_2$: C, 53.7; H, 6.0. Found: C, 53.6; H, 6.2.

2-Bromo-4,4-difluorocyclohexanone (16) was prepared from 60 mg of 4,4-difluorocyclohexanone in 10 ml of chloroform with the aid of 12 ml of a 2% v/v solution (1 equiv) of bromine in chloroform and 1 drop of concentrated hydrobromic acid to act as catalyst. The bromine was rapidly decolorized, the solution was washed with sodium bicarbonate solution and dried, and the solvent was removed. The resulting 2-bromo-4,4-difluorocyclohexanone was contaminated with some unchanged starting ketone which acted as convenient internal reference. The chemical shifts of the fluorines of 16 were somewhat temperature dependent as might be expected for a mixture of conformers with composition changing with temperature. The experimental data are given in Table 1.