Nuclear Magnetic Resonance Spectroscopy. Conformational Properties of Cyclobutanes. Variation of Vicinal Hydrogen—Fluorine Coupling Constants with Temperature[1]
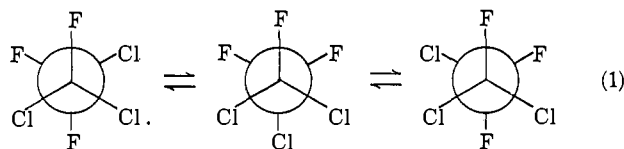
Joseph B. Lambert[2] and John D. Roberts

The observation of substantial temperature variations of the vicinal hydrogen–fluorine coupling constants in a series of cyclobutanes is consistent with the existence of an equilibrium between conformations. The temperature dependencies are discussed in terms of the models developed previously. The magnitude of these couplings as a function of the dihedral angle appears to follow a relationship similar to that described by Karplus for proton–proton couplings.

Introduction

The n.m.r. method discussed in the previous paper[3] provides a clear demonstration of the presence or absence of nonplanarity in difluorocyclobutanes, and the dipole moment method furnishes a reasonably accurate indication of the degree of puckering. The model of interconverting conformers was adopted by analogy with the properties of cyclohexane systems, but the size of the barrier is such that the model is more closely related to that of rapidly interconverting ethane rotamers. The model is valid provided that the conformers form ideal solutions with each other and have the same entropy and heat capacity over the observed temperature range. When this is the case, the observed molecular properties are weighted averages of the properties of the individual conformers. Changes in the populations with temperature will therefore bring about changes in observables such as the chemical-shift differences. Although the conformational properties of cyclobutanes were derived entirely from temperature-dependent fluorine–fluorine chemical-shift differences, there should be discernible changes in the vicinal hydrogen–fluorine coupling constants as well. Such behavior has been noted extensively in studies of the equilibria among rotamers of substituted ethanes (eq. 1)[4–7] for hydrogen–hydrogen, hydrogen–fluorine,

(1)

and fluorine–fluorine couplings, as well as in less general rotational equilibria (eq. 2–4).[8–10] Small temperature variations have, however, been observed for

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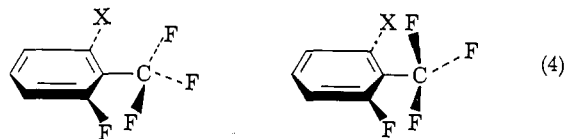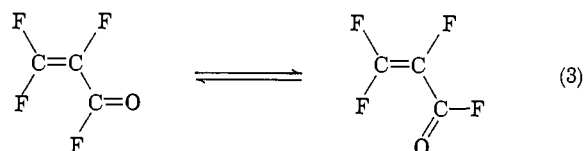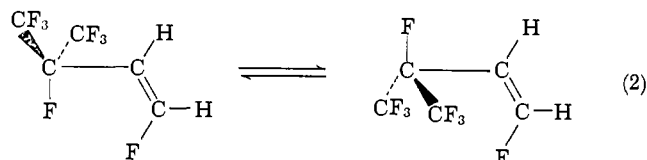
fluorine–fluorine couplings in systems, such as I and II, which are incapable of rotational isomerism. The

$$CF_3CFCl_2 \qquad\qquad CF_3CF_2CO_2H$$
$$\text{I} \qquad\qquad\qquad \text{II}$$
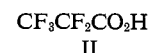
torsional oscillations which give rise to these changes appear to be less important for hydrogen–hydrogen and hydrogen–fluorine couplings.[11] Thus, in system 2, couplings between nuclei which are attached to the conformationally rigid double bond exhibit temperature variations which are negligibly small in comparison to the changes in the couplings between the vinyl protons and nuclei in the perfluoroisopropyl substituent.

If it is true that the large variations in the fluorine–fluorine chemical-shift differences are due to conformational changes rather than torsional oscillations, then substantial variations should also be observable in the vicinal hydrogen–fluorine coupling constants, to which torsional oscillations appear to contribute negligibly. Observation of such variations would also comprise one of the first examples of temperature-dependent coupling constants other than in rotational equilibria.[12]

(1) Supported in part by the Office of Naval Research and the National Science Foundation.
(2) National Science Foundation Predoctoral Fellow, 1962–1965.
(3) J. B. Lambert and J. D. Roberts, J. Am. Chem. Soc., 87, 3884 (1965).
(4) R. W. Fessenden and J. S. Waugh, J. Chem. Phys., 37, 1466 (1962).
(5) R. J. Abraham and H. J. Bernstein, Can. J. Chem., 39, 39 (1961).
(6) H. S. Gutowsky, G. G. Belford, and P. E. McMahon, J. Chem. Phys., 36, 3353 (1962).
(7) H. S. Gutowsky, Pure Appl. Chem., 7, 93 (1963).
(8) N. Boden, J. W. Enelin, J. Feeney, and L. H. Sutcliff, Proc. Roy. Soc. (London), A282, 559 (1964).
(9) W. S. Brey and K. C. Ramey, J. Chem. Phys., 39, 844 (1963).
(10) J. Jonáš and H. S. Gutowsky, ibid., 42, 140 (1965).
(11) J. C. Schug, P. E. McMahon, and H. S. Gutowsky, ibid., 33, 843 (1960).
(12) Dudek and Dudek have, however, observed coupling constants with a temperature dependence derived from a totally different process; cf. G. O. Dudek and E. P. Dudek, J. Am. Chem. Soc., 86, 4283 (1964).
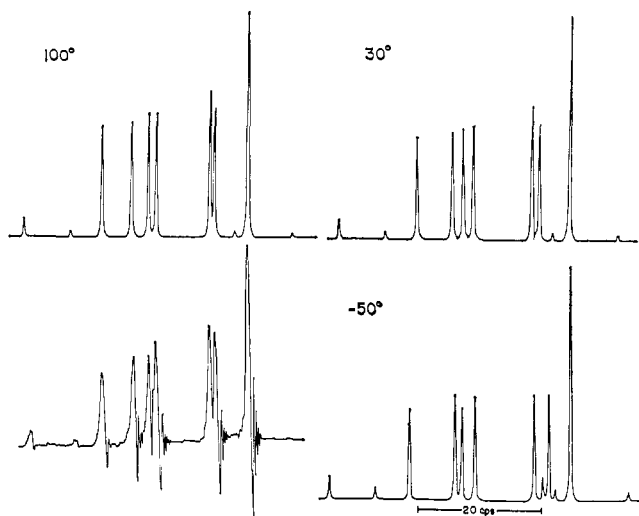
Figure 1. Calculated (−50, 30, 100°) and experimental (100°) 60-Mc.p.s. proton spectrum of 1,1-difluoro-2,2-dichloro-3-deuterio-3-phenylcyclobutane (III), with simultaneous irradiation at the deuterium frequency.

Results and Discussion

The complete analysis of the hydrogen–fluorine spectra of the ring nuclei of four of the cyclobutanes considered in the previous study[3] (III–VI) was carried out at −50, 30, and 100°. In no case was the spectrum
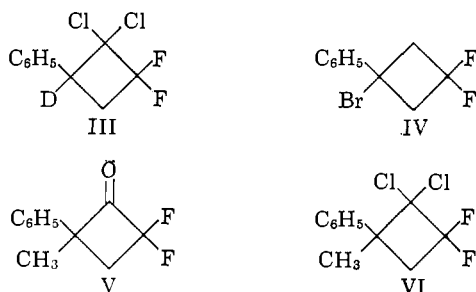
first order. The analysis of the ABXY systems in the spectra of V and VI was carried out in a straightforward manner by the method of Swalen and Reilly.[13] The ABCXY spectrum of III in which no deuterium was present proved to be intractable because the protons were very closely coupled. A deuterium atom was therefore placed in the 3-position by means of the following reaction sequence.
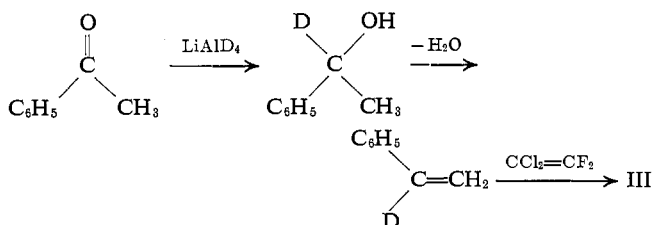
Irradiation of III at the deuterium frequency reduced the spectrum to an ABXY pattern which was amenable to analysis by the Swalen–Reilly procedure. The deceptively simple A_2B_2XY spectrum for IV could only be analyzed by trial and error with the Wiberg program.[14] Agreement between calculated and observed

(13) J. D. Swalen and C. A. Reilly, J. Chem. Phys., 37, 21 (1962).
(14) K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962.
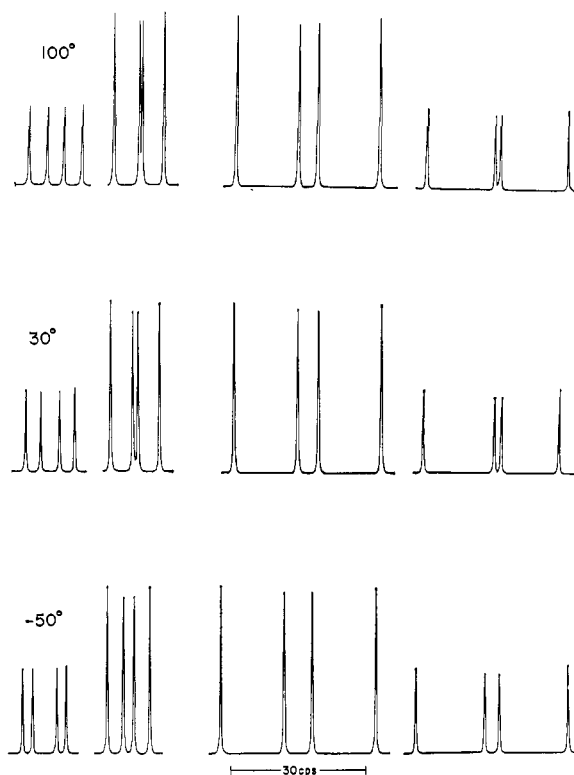

Figure 2. Calculated 56.4-Mc.p.s. fluorine spectrum of 1,1-difluoro-2,2-dichloro-3-deuterio-3-phenylcyclobutane (III).

spectra was as good as with the other systems, however. For all cases, observed line positions were obtained with an accuracy of ±0.05 c.p.s. from the average of at least four upfield and four downfield scans of both the proton and the fluorine spectra.

The ring-proton spectrum of III at 100° and the calculated spectra for all three temperatures are given in Figure 1.[15] The calculated fluorine spectra are presented in Figure 2. A quantitative comparison of the observed and calculated spectra of III at 100° is given in Table I. Since the observed spacings are not a direct measure of the couplings, the complete analysis is necessary in order to detect small changes in the coupling constants. Nevertheless, even qualitative examination of the spectra shows severe perturbations in peak positions with temperature. Particularly noticeable in the proton spectrum are the increase in the distance between the 8–14 and 2–8 transitions (the fifth and sixth from the left among the more intense peaks) and the exchange of relative positions of the 6–13 and 10–15 transitions (second and third peaks from the left) as the temperature is lowered. Similar changes occur in the fluorine spectra (Table I and Figure 2).

The spectra of the ring protons of IV (Figure 3) exhibit a temperature dependence which is most obvious in the tendency of the two central peaks to coalesce as the temperature is increased and in the development of additional fine structure in the second and fourth peaks as the temperature is decreased.

The analysis of the spectrum of VI has been discussed previously.[16] The spectral parameters, how-

(15) In these spectra, as well as all others, the field increases from the left to the right.
(16) M. Takahashi, D. R. Davis, and J. D. Roberts, J. Am. Chem. Soc., 84, 2935 (1962).

Table I. 1,1-Difluoro-2,2-dichloro-3-deuterio-3-phenylcyclobutane at 100°

Tran-sition	Obsd. frequency, c.p.s.	Calcd. frequency, c.p.s.	O–C
15–16	0.00[a,b]	−0.05	0.05
9–12	4.16	4.05	0.11
10–13	7.70	7.66	0.04
3–6	11.73	11.75	−0.02
11–14	183.00	183.00	0.00
4–7	188.66	188.60	0.06
5–8	189.03	189.21	−0.18
1–2	194.73	194.80	−0.07
14–16	553.70	553.71	−0.01
7–12	567.47	567.46	0.01
8–13	571.44	571.63	−0.19
2–6	585.40	585.40	0.00
11–15	736.70	736.76	−0.06
4–9	752.04	752.01	0.03
5–10	753.44	753.19	0.25
1–3	768.40	768.45	−0.05
6–12	8986.87	8987.03	−0.16
3–9	8994.94	8994.73	0.21
13–16	9000.00[a]	9000.05	−0.05
6–13	9005.04	9004.96	0.08
10–15	9007.77	9007.75	0.02
3–10	9009.03	9009.06	−0.03
8–14	9017.95	9017.97	−0.02
2–8	9018.76	9018.73	0.03
5–11	9024.24	9024.18	0.06
1–5	9024.24	9024.32	−0.08
			Av. 0.07

[a] The first fluorine transition is arbitrarily set at 0.00 c.p.s.; the first strong proton transition is arbitrarily set at 9000.00 c.p.s. [b] Increasing numbers represent increasing field.

Table II. 1,1-Difluoro-3-methyl-3-phenylcyclobutanone-2 at 100°

| Tran-sition	Obsd. frequency, c.p.s.	Calcd. frequency, c.p.s.	O–C
15–16	0.00	−0.05	0.05
10–13	12.31	12.23	0.08
9–12	13.45	13.51	−0.06
3–6	25.75	25.82	−0.07
11–14	249.00	248.95	0.05
5–8	261.31	261.27	0.04
4–7	262.45	262.47	−0.02
1–2	274.75	274.82	−0.07
14–16	284.03	284.10	−0.07
7–12	295.93	295.94	−0.01
8–13	298.55	298.56	−0.01
2–6	310.46	310.37	0.09
11–15	533.03	533.10	−0.07
4–9	544.93	544.91	0.02
5–10	547.55	547.59	−0.04
1–3	559.46	559.37	0.09
6–12	9000.00	8999.94	0.06
3–9	9012.19	9012.26	−0.07
13–16	9014.33	9014.20	0.13
6–13	9025.34	9025.29	0.05
10–15	9026.48	9026.48	0.00
8–14	9028.45	9028.66	−0.21
2–8	9036.91	9037.11	−0.20
3–10	9038.92	9038.88	0.04
12–16	9039.51	9039.55	−0.04
5–11	9041.04	9040.98	0.06
1–5	9050.75	9050.66	0.09
7–14	9051.37	9051.40	−0.03
9–15	9053.25	9053.11	0.14
4–11	9064.87	9064.92	−0.05
			Av. 0.07
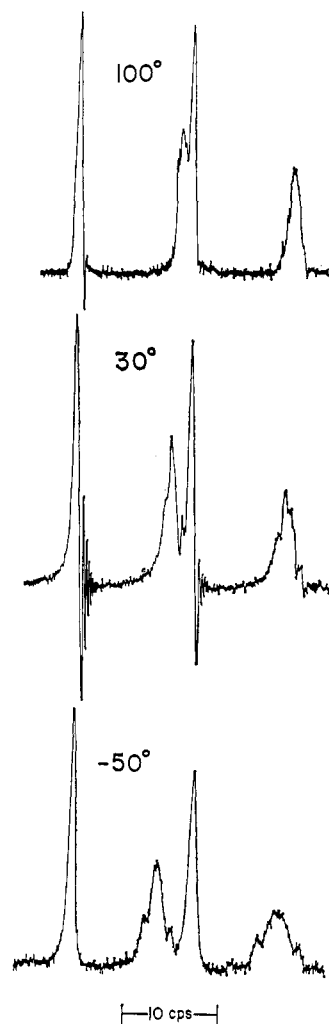
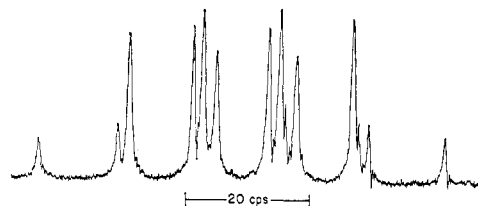Figure 3. Proton spectrum of 1,1-difluoro-3-bromo-3-phenylcyclobutane (IV) at 60 Mc.p.s.

Figure 4. Proton spectrum of 1,1-difluoro-3-methyl-3-phenylcyclobutanone-2 (V) at 60 Mc.p.s.

ever, were improved considerably by the use of the iterative method.[13] Only small changes in the appearance of the spectrum occurred with temperature variations. Analysis of the spectrum of the cyclobutanone V was not possible at low temperatures because of viscosity broadening which obscured the fine structure. The spectrum of the ring protons at 100° was completely identical with that at room temperature (Figure 4).[17] Table II presents a quantitative comparison of the observed and calculated spectra.

Table III presents the results of these analyses. In each case, the subscripts 1 and 2 refer to fluorine nuclei and 3 and 4 to hydrogen nuclei; the lower number in each pair refers to the nucleus resonating at lower field.

(17) Spurious peaks which arise from ring-out of sharp resonances should not be confused for actual transitions.

Compd.	Temp., °C	δ_{34}, c.p.s.	J_{13}, c.p.s.	J_{14}, c.p.s.	J_{23}, c.p.s.	J_{24}, c.p.s.
III	−50	8.88	8.18	0.73	21.89	12.77
	30	6.07	8.57	1.75	20.52	12.59
	100	5.23	8.76	2.46	20.08	12.18
IV	−50	1.10	7.80	9.95	13.10	13.05
	30	0.75	8.90	10.60	12.52	12.45
	100	0.55	9.55	10.85	11.90	11.85
V	30	19.87	10.97	15.09	16.17	10.28
	100	20.10	10.79	14.87	16.15	10.34
VI	−50	29.50	8.69	0.64	21.22	13.65
	30	32.92	8.79	0.91	21.02	13.93
	100	35.35	8.89	1.34	20.40	13.63

The geminal fluorine–fluorine chemical-shift difference, δ_{12}, and coupling constant, J_{12}, are discussed in ref. 3. The calculations were fairly insensitive to the geminal proton–proton coupling, J_{34}, and to the cross-ring couplings in IV. The former was typically about −13 c.p.s., and the latter were effectively zero. The accuracy of the spectral parameters was ±0.1 c.p.s. for IV and V, and slightly better than this value for III and VI.

The largest temperature variation of the fluorine–fluorine chemical-shift difference, δ_{12}, was observed in the case of IV,[3] followed in magnitude by III, with VI showing only a small dependence,[18] and V almost none at all. These phenomena are paralleled by the effects on vicinal coupling constants and proton–proton chemical-shift differences recorded in Table III. The data are adequately interpreted in terms of a classical equilibrium between conformations. The magnitude of the variations are as large as those observed in equilibria among rotamers of substituted ethanes. Since data are lacking to substantiate any contributions to the temperature variation of hydrogen–fluorine coupling constants from torsional oscillations, it is reasonable to neglect the phenomenon in this study.

The absence of a measurable effect in V again suggests that the cyclobutanone must be nearly planar. Although VI shows only small temperature variations,


III, VI

IV
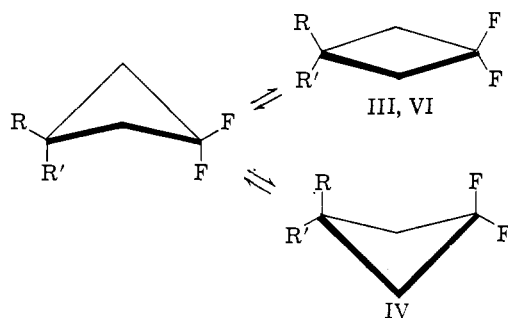
the values of the coupling constants are strikingly similar to those of III. The geometry of the species which comprises the equilibrium for VI must resemble the geometry of III more closely than that of IV. This may reflect a greater difference in "size" between phenyl and methyl than between phenyl and bromine.[19] If

(18) The small range of variation of δ_{12} with temperature prevented the derivation of the conformational properties of VI according to the method in ref. 3.

(19) D. R. Davis, R. P. Lutz, and J. D. Roberts, *J. Am. Chem. Soc.,* 83, 246 (1961).

the methyl group is significantly "smaller" than bromine, it may well act like hydrogen in having an axial conformation which is almost planar.[3]

Takahashi and co-workers[16] have synthesized VI with deuterium placed on the C-4 atom. Provided the cycloaddition reaction is stereospecific, they were able to show that the low-field proton (3) is *cis* to the phenyl group. If the *trans* hydrogen–fluorine coupling is larger than the *cis* coupling, as is the case with vicinal hydrogen–hydrogen couplings, then J_{23} is the coupling constant between *trans*-oriented nuclei, and fluorine atom 2 must be *trans* to the phenyl group. The same assignment will be used for III on the basis of the similarity of the coupling parameters.


III, R = D
VI, R = CH₃
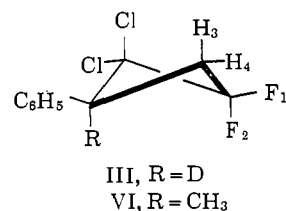
To clarify this point, Newman projections may be drawn for the planar axial[3] and the nonplanar equatorial conformations of III (and probably VI). If

VIIa   VIIb
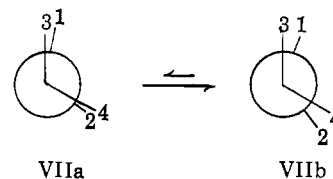
the relationship between hydrogen–fluorine couplings and dihedral angles is similar to that described by Karplus[20,21] for hydrogen–hydrogen couplings, then one would expect that J_{23} (axial–axial) would be large, J_{14} (equatorial–equatorial) would be small, and J_{13} and J_{24} would be intermediate in magnitude, since the equatorial conformer VIIb predominates. This is precisely the behavior which is recorded in Table III for both III and VI. For the planar geometry VIIa, however, nucleus 1 bears the same relationship to nucleus 4 as 2 does to 3. As the population of this conformer increases with temperature, J_{23} should therefore decrease and J_{14} should increase, as a result of the appropriate changes in the dihedral angles. The smaller changes in J_{13} and J_{24} are expected from consideration of the range of dihedral angles involved.

Compound IV was described[3] as existing in two distinct nonplanar conformations of similar energies (VIIIa and VIIIb). J_{24} and J_{13} in this representation

VIIIa   VIIIb
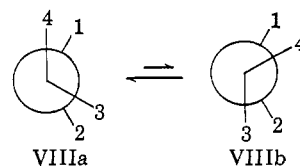
are averages of large axial–axial and small equatorial–equatorial couplings. Therefore, they are intermediate in magnitude with respect to the analogous couplings (J_{14} and J_{23}) in III and VI. Since J_{24} decreases with

(20) M. Karplus, *J. Chem. Phys.,* 30, 11 (1959).

(21) M. Karplus, *J. Am. Chem. Soc.,* 85, 2870 (1963).

temperature, it must represent the axial–axial coupling in the preferred conformer VIIIa. The remaining two coupling constants, J_{14} and J_{23}, correspond to the less sensitive axial–equatorial couplings in III and VI (J_{13} and J_{24}), and are therefore intermediate in value. An unambiguous assignment of steric relationships cannot be made on the evidence at hand, since interchanging nuclei 3 and 4 would not alter the interpretation. J_{13} was taken as the equatorial–equatorial coupling, rather than J_{14}, because it is smaller and displays a slightly more pronounced temperature variation.

The coupling constants in the cyclobutanone V, like those of IV, have intermediate values which fall within a 6-c.p.s. range. The molecules, however, are fundamentally different, since V is probably statically planar, but IV is in dynamic equilibrium between nonplanar conformations ("dynamic planarity"). Conia and co-workers[22] have analyzed the first-order spectra of several substituted cyclobutanones. They find that 21 vicinal hydrogen–hydrogen couplings fall in the range 6.4 to 9.7 c.p.s. The similarity of these couplings is in contrast to the wide range of hydrogen–fluorine couplings for cyclobutanes known to be nonplanar, e.g., III. Without a temperature study, it is impossible to differentiate between static (V) and dynamic (IV) planarity from the magnitudes of the couplings alone. The deviations from a planar configuration, by analogy with the behavior of V, are probably small for these systems also.

Analysis of both the magnitude and the temperature dependence of the vicinal coupling constants substantiates the conformational model described previously.[3] Cyclobutanones and cyclobutenes are statically planar unless there are severe perturbations from substituents in the former case. Cyclobutanes substituted at one position with two groups of equivalent size exist as two distinct nonplanar conformers. When there is only one substituent, or if the second substituent is small, the second conformer is probably planar. The dependence of the hydrogen–fluorine coupling constants on the dihedral angle appears to be similar to the behavior described by Karplus for hydrogen–hydrogen couplings.

(22) B. Braillon, J. Salaün, J. Goré, and J.-M. Conia, Bull. soc. chim. France, 1981 (1964).

Experimental

The preparation of all the compounds utilized in this study with the exception of III has been described previously.[3]

α-Methylbenzyl-α-d Alcohol. To a solution of 0.5 g. (0.0119 mole) of lithium aluminum deuteride in 95 ml. of diethyl ether contained in a 200-ml., three-necked, round-bottomed flask equipped with a reflux condenser and a dropping funnel was added 5 g. (0.0416 mole) of acetophenone in 20 ml. of anhydrous ether in a dropwise manner. After the solution had been stirred for 1 hr., the complex was destroyed with 4 ml. of distilled water. The mixture was poured into 75 ml. of 1 N hydrochloric acid and stirred until no solid remained. The layers were separated, the aqueous portion was extracted four times with ether, and the combined organic portions were dried over magnesium sulfate. After the drying agent was removed by filtration and the ether by distillation, the product was distilled to give 4.66 g. (0.0378 mole, 90.9%) of α-methylbenzyl-α-d alcohol, b.p. 65° (2 mm.). The n.m.r. spectrum showed the label to be located specifically in the α-position.

Styrene-α-d. α-Methylbenzyl-α-d alcohol (4.65 g., 0.0378 mole), containing about 10 mg. of p-toluenesulfonic acid as catalyst and 10 mg. of picric acid as polymerization inhibitor, was heated in a 50-ml., round-bottomed flask at a temperature of 160° and a pressure of 100 mm. Styrene-α-d codistilled with water over the range 40 to 80° into a flask which contained about 10 mg. of picric acid. When the distillation was nearly complete, the distillate was taken up in diethyl ether, the layers were separated, and the organic portion was dried over magnesium sulfate. The solution was filtered to remove the drying agent, and the ether was removed from the filtrate by distillation. The residue was distilled to give 3.31 g. (0.0315 mole, 83.3%) of styrene-α-d, b.p. 64° (60 mm.). The specificity of the label was assured by the n.m.r. spectrum, which lacked a resonance for the α-proton.

1,1-Difluoro-2,2-dichloro-3-deuterio-3-phenylcyclobutane. The synthesis was achieved in the same manner as that of the unlabeled material,[3] with stereospecific placement of the deuterium from styrene-α-d in the 3-position of the adduct.