

Origin of the Chemical-Shift Isotope Effect. Stereochemical Evidence

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Abstract: The chemical shift of a fluorine-19 nucleus moves to higher field when deuterium is substituted for hydrogen either geminally (H-C-F → D-C-F) or vicinally (H-C-C-F → D-C-C-F). We have found that the vicinal chemical-shift isotope effect has a strong stereochemical dependence. When the H(D)-C-C-F dihedral angle is less than 90°, the isotope shift is about 0.15 ppm. When the nuclei are furthest apart, at 120 and 180°, the isotope shift increases to about 0.35 ppm. These results cannot be explained exclusively in terms of an electric-field model, which predicts an inverse dependence of the magnitude of the effect on the distance between the resonating and perturbing nuclei. Because the stereochemical dependence is similar to that observed for substituent inductive effects on the absolute magnitude of vicinal coupling constants and chemical shifts, we conclude that a major portion of the isotope shift results from vibrationally based inductive effects. Vicinal (σ) delocalization provides one mechanism for such a phenomenon.

Replacement of an atom by a heavier isotope generally causes surrounding magnetic nuclei to resonate at higher field.² The magnitude of the isotope shift depends on the identity of the perturbing and resonating nuclei and on their relative positions in the molecule (Table I). Deuterium causes relatively larger

generally decreases as the number of bonds between the perturbing and resonating nuclei increases.

Theoretical studies of the chemical-shift isotope effect have focused on the manner by which vibrational changes due to isotopic substitution affect the molecular shielding. Only the shift in the hydrogen molecule, however, is well understood.³ Changes in shielding on substitution of deuterium can arise because the lower zero-point energy of deuterium in an anharmonic potential well corresponds to a different interatomic separation. Even within an harmonic potential well, the change in the electronic distribution caused by the lower mean-square amplitude of the deuterium vibration can alter the shielding. Marshall³ showed that both effects could contribute to the observed result.

In complex systems, complete vibrational analyses are not possible, and the organic chemist has recourse to his usual assortment of electronic effects—inductive, field, steric, hyperconjugative, etc.—all of which are sensitive to zero-point vibrational changes.⁴ Gutowsky first suggested that the different vibrational amplitudes of C-H and C-D systems, even within the harmonic approximation, are the cause of the effect.⁵ Instead of a through-bond induction of electrons, he suggested that isotopic substitution alters the intramolecular electric field experienced by the resonating nucleus. This deshielding effect is inversely proportional to the distance from the source of the field. Since C-D has a smaller vibrational amplitude, it on the average is further removed from the resonating nucleus and hence conveys a smaller deshielding effect. Calculated values for geminal effects were found to be in close agreement with experiment.

Bernheim and Batiz-Hernandez offered an alternative explanation in terms of slight changes in molecular structure caused by isotopic substitution.^{2,6} In a study of geminal effects, they concluded that the differences in bond lengths and bond angles due to anharmonicity alter the local diamagnetic shielding sufficiently to cause the observed shifts. This explanation focuses on the wave function changes caused by this small alteration

Table I. Effect of Isotopic Substitution on Nuclear Shielding

Obsd nucleus	Isotopic change	No. of bonds	Typical isotopic shift, ppm ^a	Ref
¹ H	¹ H → ² H	1	0.04	<i>b</i>
		2	0.015	<i>c</i>
		3	0.01	<i>c</i>
¹⁹ F	¹ H → ² H	2	0.5	<i>d</i>
		3	0.2	<i>e</i>
	¹² C → ¹³ C	1	0.1	<i>f</i>
		2	0.03	<i>g</i>
		1	0.03	<i>h</i>
¹³ C	³² S → ³⁵ S	1	0.03	<i>h</i>
		2	0.01	<i>i</i>
	³⁵ Cl → ³⁷ Cl	1	0.3	<i>j</i>
2		0.1	<i>j</i>	
³¹ P	¹ H → ² H	1	0.5	<i>k</i>

^a Positive numbers indicate an upfield shift; the figures are only intended to indicate the general order of magnitude of the shift.

^b E. Dayan, G. Widenlocher, and M. Chaigneau, *C. R. Acad. Sci.*, **257**, 2455 (1963). ^c R. A. Bernheim and H. Batiz-Hernandez, *J. Chem. Phys.*, **45**, 2261 (1966). ^d G. V. D. Tiers, *J. Amer. Chem. Soc.*, **79**, 5585 (1957). ^e Y. Kanazawa, J. D. Baldeschwieler, and N. C. Craig, *J. Mol. Spectrosc.*, **16**, 325 (1965). ^f S. G. Frankiss, *J. Phys. Chem.*, **67**, 752 (1963). ^g N. Muller and D. T. Carr, *ibid.*, **67**, 112 (1963). ^h R. J. Gillespie and J. W. Quail, *J. Chem. Phys.*, **39**, 2555 (1963). ⁱ W. S. Brey, Jr., K. H. Ladner, R. E. Block, and W. A. Tallon, *J. Magn. Resonance*, **8**, 406 (1972). ^j Y. K. Grishim, N. M. Sergeev, and Y. A. Ustynyuk, *Mol. Phys.*, **22**, 711 (1971). ^k A. A. Borisenko, N. M. Sergeev, and Y. A. Ustynyuk, *ibid.*, **22**, 715 (1971).

changes than heavy-atom isotopes because of the large change in the reduced mass of the system on deuterium substitution. Nuclei with normally large chemical-shift ranges exhibit the largest sensitivity to isotopic substitution elsewhere in the molecule. The isotope shift

(1) This work was supported by the National Science Foundation (Grants GP-34259X and GP-35868X).

(2) H. Batiz-Hernandez and R. A. Bernheim, *Progr. Nucl. Magn. Resonance Spectrosc.*, **3**, 63 (1967).

(3) T. W. Marshall, *Mol. Phys.*, **4**, 61 (1961).

(4) M. Wolfsberg, *Accounts Chem. Res.*, **5**, 225 (1972).

(5) H. S. Gutowsky, *J. Chem. Phys.*, **31**, 1683 (1959).

(6) Table I, footnote *c*.

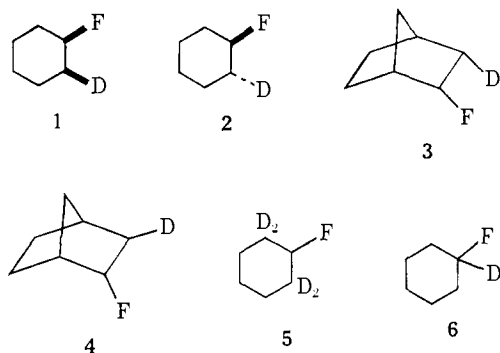
in structure rather than on intramolecular field effects. Therefore, the internuclear distance is not a direct factor in determining the magnitude of the effect. These authors presented calculations to support their theory.

Pendlebury and Phillips have offered a third explanation in studies of vicinal H(D)-C-C-F isotope effects.⁷ Stereochemically dependent inductive effects can arise from vicinal delocalization of σ electrons.⁸ An anti-periplanar arrangement of the H-C-C-F segment is characterized by a long-range positive bond order between H and F. The lower zero-point energy of deuterium reduces the covalent bond order and thereby produces a shielding of the vicinal fluorine. The well-defined stereochemical dependence of this mechanism is more complex than the r^{-2} dependence of the electric-field effect.

Support for the various mechanisms for the chemical-shift isotope effect has centered on calculations designed to demonstrate their feasibility rather than on experimental justification. In an effort to distinguish these mechanisms in the vicinal (three-bond) situation, we have examined the stereochemical dependence of the H(D)-C-C-F chemical-shift isotope effect.⁹ The electric-field model requires that the effect diminish as the H(D) and F nuclei become further removed from each other, whereas the vicinal delocalization model predicts a maximum effect when the nuclei are furthest removed (antiperiplanar). No straightforward distance dependence is predicted from the change-in-hybridization model.

Results

The well-known structures of cyclohexane and bicyclo[2.2.1]heptane were exploited to measure the stereochemical dependence of the chemical-shift isotope effect. Dihedral angles between D and F of about 60 and 180° are available from the former (1 and 2), and of 0 and 120° from the latter (3 and 4). Preparation of the



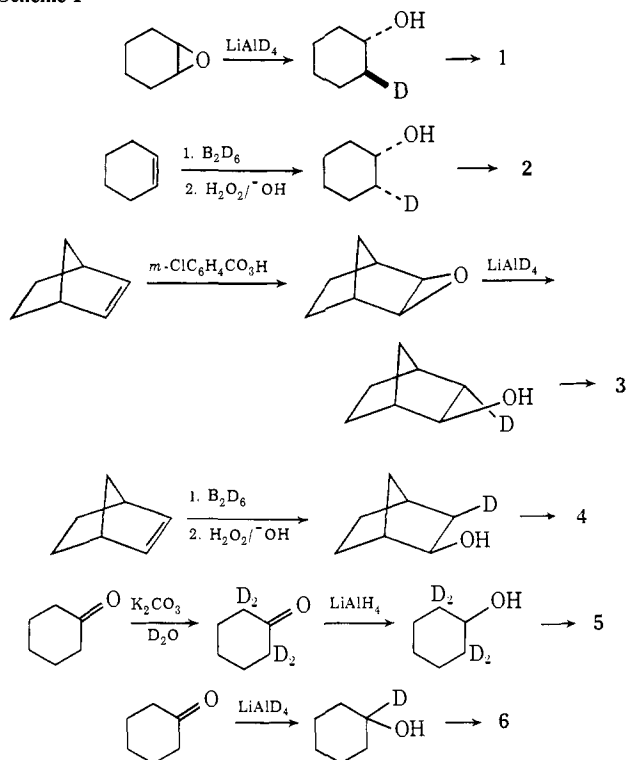
stereospecifically labeled alcohols is outlined in Scheme I. Treatment of these alcohols with 2-chloro-1,1,2-trifluoroethylamine, $(C_2H_5)_2NCF_2CFHCl$, afforded the desired fluorides with inversion of configuration. The fully deuterated cyclohexyl-2,2,6,6- d_4 fluoride (5) was also prepared to test the additivity of the isotope shift. To compare these three-bond effects with a two-bond effect, cyclohexyl-1- d fluoride (6) was prepared. The desired fluorides were isolated by preparative

(7) M. H. Pendlebury and L. Phillips, *Org. Magn. Resonance*, **4**, 529 (1972).

(8) J. A. Pople and D. A. Santry, *Mol. Phys.*, **7**, 269 (1963).

(9) J. B. Lambert and L. G. Greifenstein, *J. Amer. Chem. Soc.*, **95**, 6150 (1973).

Scheme I



vapor-phase chromatography. The stereochemistries of 1-4 suggested by the method of preparation were corroborated by the magnitude of the vicinal proton-fluorine couplings.

The chemical-shift isotope effects were determined by comparison of the ^{19}F chemical shifts of 1-6 with those in the corresponding undeuterated compounds. Each cyclohexyl system actually provides data for two molecules, the axial and the equatorial conformers. The shifts for the individual conformers were obtained by measuring the ^{19}F spectra under conditions of slow ring reversal at -85° . Thus compound 1 provided the isotope shift of an axial deuterium on an axial fluorine ($\sim 180^\circ$), and of an equatorial deuterium on an equatorial fluorine ($\sim 60^\circ$). Similarly, 2 provided the effect of an equatorial deuterium on an axial fluorine ($\sim 60^\circ$) and of an axial deuterium on an equatorial fluorine ($\sim 60^\circ$). All spectra were taken at identical concentrations with $CFCl_3$ as solvent and CF_3CCl_3 as lock signal and internal standard. The chemical shift of the solvent was too far removed from those of the substrates to serve as a useful standard. Trichlorotrifluoroethane was selected for the internal standard because it cannot exhibit hindered rotation at low temperature and because it should have no significant interactions with the substrates.

The isotope shifts (in parts per million) with respect to the corresponding undeuterated species are given in Scheme II. All the shifts are to higher field and are the average of four or five determinations. The relatively large uncertainty for 3 and 4 results from incomplete labeling. The observed isotope shifts are plotted as a function of the H(D)-C-C-F dihedral angle in Figure 1.

The temperature dependence of the chemical-shift isotope effect has not been thoroughly studied, although Brey and coworkers have observed slightly increased isotope shifts at low temperatures in several systems.¹⁰

(10) Table I, footnote i.

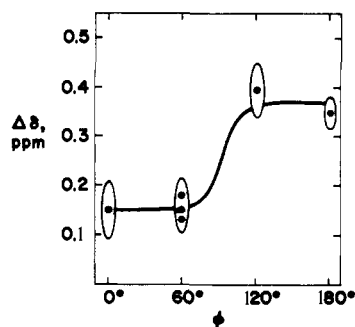
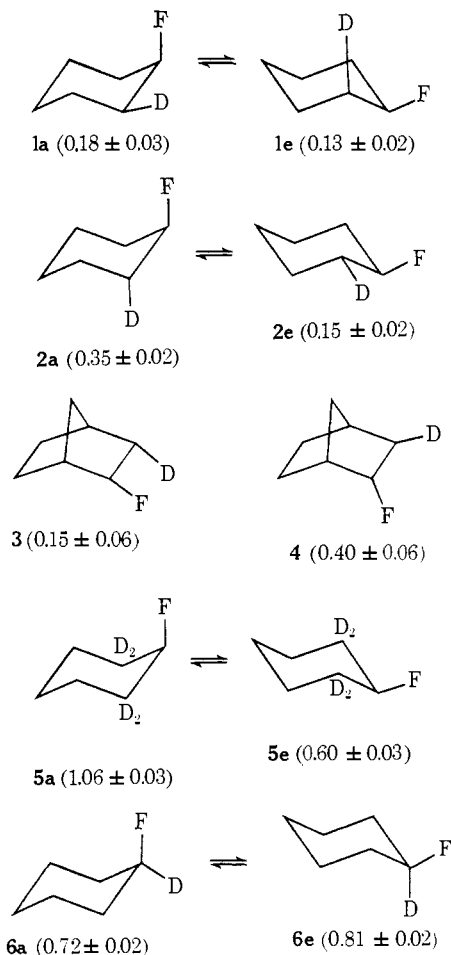


Figure 1. The H(D)-C-C-F chemical-shift isotope effect ($\Delta\delta$) as a function of dihedral angle (ϕ).

Scheme II



Because Brey's observed temperature effect was in the opposite direction from one proposed by Petrakis and Sederholm,¹¹ it was of interest to examine the isotope shift in our systems over a wide temperature range. Within the experimental accuracy of our measurements, no changes in the isotope shifts were observed between -85 and $+25^\circ$.

Infrared spectra for compounds **1**, **2**, **5**, **6**, and unlabeled cyclohexyl fluoride were obtained between 3200 and 700 cm^{-1} .¹² The spectra revealed marked changes resulting from the different stereochemical placement

of deuterium in the various isomers, but assignments of molecular vibrations were not attempted.

Discussion

The observed three-bond isotope shifts are quite large, the smallest, in **1e**, being 0.13 ppm (11 Hz). The geminal effects in **6** are consistently larger than the vicinal effects in **1-4**. The vicinal effect appears to be reasonably additive. Thus, the effect of four deuterium atoms on an axial fluorine atom in **5a** (1.06 ± 0.03 ppm) is essentially the same as the summed effect from **1a** and **2a** (0.98 ± 0.11). Similarly, the effect of four deuterium atoms on an equatorial fluorine atom in **5e** (0.60 ± 0.03 ppm) agrees with the summed effect from **1e** and **2e** (0.56 ± 0.08). The most significant observation, however, is the dependence of the vicinal isotope effect on the dihedral angle between the C-H(D) and C-F bonds. The largest isotope shifts are observed when the distance between the resonating (^{19}F) and perturbing (^2H) nuclei is greatest, 0.35 ppm for the axial-axial arrangement (180°) in **2a** and 0.40 ppm for the anticlinal arrangement (120°) in **4**. These results permit some definition of the mechanism of the isotope shift. The very large experimental error on the measurement of the isotope shift in **4** precludes our saying whether the 120 or the 180° relationship actually produces the larger shift.

Since the largest isotope shift is associated with the greatest internuclear separation, a distance-dependent electric-field effect cannot be the sole contributor to the isotope shift.⁵ In such a model, the largest shift is observed when the nuclei are at closest approach. Our observations do not rule out the possibility that the residual 0.13 - 0.15 -ppm shift observed in all cases results from such an effect. It is also unlikely that distant substituents such as we are examining could alter the molecular structure around the resonating nucleus enough to account for the observed isotope shifts.⁶ We cannot, however, logically exclude this possibility.

The remaining explanation, in terms of angular-dependent inductive effects, offers a viable possibility.⁷ Similar approaches have been used to explain the angular dependence of vicinal substituent (not isotope) effects on both chemical shifts and coupling constants. It has been observed that the largest inductive effect is exerted by a vicinal substituent on an H-C-C-H coupling constant when the bond to the substituent and one of the C-H bonds are antiperiplanar.¹³ Similarly, an antiperiplanar substituent exerts the largest effect on the shielding of a nucleus.¹⁴ Thus, upfield ^{19}F shifts have been observed when an antiperiplanar vicinal substituent (X-C-C-F) is replaced by a more electronegative group. Our present observations parallel these earlier effects. Deuterium may be considered to be more electronegative than hydrogen, in the sense that DCO_2H is more acidic than HCO_2H .⁴ The chemical-shift isotope effect can therefore be considered to be a simple inductive substituent phenomenon. The angular dependence derives from the favorable arrangement of orbitals for vicinal (σ) delocalization when the bonds are antiperiplanar.⁸ The maximum H-X bond order in an H-C-C-X fragment is observed in this arrangement. One prediction of the theory of σ -de-

(11) L. Petrakis and C. H. Sederholm, *J. Chem. Phys.*, **35**, 1174 (1961).

(12) L. G. Greifenstein, Ph.D. Dissertation, Northwestern University, 1973. The original infrared spectra are reproduced in this source.

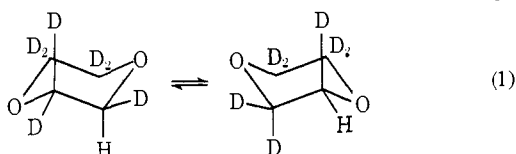
(13) D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, **86**, 2742 (1964); H. Booth, *Tetrahedron Lett.*, 411 (1965).

(14) L. Phillips and V. Wray, *J. Chem. Soc., Perkin Trans. 2*, 223 (1972).

localization that is not borne out by our data is that a synperiplanar arrangement (0° dihedral angle) brings about a change in the sign of the effect. System **3** was prepared to examine this possibility, but a normal upfield shift of 0.15 ppm was observed. A similar orientational prediction for substituent effects on vicinal coupling constants has been found not to be large.¹⁵

In summary, we have observed that there is a strong angular-dependent component to the H(D)-C-C-F chemical-shift isotope effect. The maximal effect is observed when the nuclei are farthest apart (antiperiplanar and antiperiplanar). These observations are contrary to the predictions from the distance-dependent electric-field effect. Because the largest σ bond order occurs when atoms are antiperiplanar, the observations are in accord with an angular-dependent inductive effect, analogous to those invoked to explain vicinal substituent effects on the absolute value of chemical shifts and coupling constants. Our data do not exclude the possibility that electric-field or other effects might be responsible for a large portion of the residual 0.15-ppm isotope shift that is present in all cases. In fact, the unusually large antiperiplanar isotope shift in **4** may result from a reinforcing of vicinal delocalization and electric-field effects, and the failure to observe a change in the sign of the effect in the synperiplanar **3** may result from a canceling of effects.

As a coda, it is interesting to note that the angular dependence of the chemical-shift isotope effect has been exploited, albeit unintentionally, in at least one study to lift the degeneracy of chemical shifts. The proton spectrum of 1,4-dioxane remains unchanged down to -150° . The failure to observe a change in the spectrum at low temperature could be interpreted as resulting from a particularly low barrier to ring reversal or from degenerate chemical shifts. Jensen and Neese¹⁶ observed that dioxane-*d*₇ gives separate resonances for the axial and equatorial protons at -107° (eq 1). Although



both protons are shifted upfield by the surrounding deuterium atoms, the axial proton is shifted to a greater extent (0.06 ppm) than the equatorial proton (0.03 ppm). We would attribute this result to the same type of angular dependence as observed in the H(D)-C-C-F case. The dioxane isotope shifts, which are the sum of one geminal and two vicinal effects, are smaller by an order of magnitude than those observed on ¹⁹F chemical shifts.

Experimental Section

Melting points were determined in a Hershberg apparatus and are uncorrected. Infrared spectra were measured on Beckman IR-5 and IR-10 spectrophotometers. Routine nmr spectra were recorded on a Varian T-60 spectrometer. Fluorine spectra were obtained using a Bruker HFX-10 spectrometer operating at 84.6 MHz. A Wilmad low-temperature thermometer was used to calibrate temperatures on the Bruker. Vapor-phase chromatography was

performed on a Hewlett-Packard Model 700 laboratory chromatograph, using 0.25 in. \times 6 ft and 0.5 in. \times 6 ft columns of SE-30 on Chromosorb W in copper tubing. Mass spectra were obtained by Dr. Leo Raphaelian on a Consolidated Electrodynamics Corp. Model 21-104 instrument.

Cyclohexanol-1-d was obtained by the reduction of cyclohexanone (10 g, 0.10 mol, Aldrich Chemical Co.) with lithium aluminum deuteride (3.5 g, 0.083 mol, Stohler Isotope Chemicals, Inc.) in anhydrous ethyl ether at 0° . Following work-up, distillation of the alcohol afforded 9.7 g (0.096 mol, 96% yield) of pure cyclohexanol-1-d: bp $75-77^\circ$ (20 mm); nmr (CCl_4) δ 1.2 (m, 6), 1.75 (m, 4), 3.63 (s, 1); ir (neat) 3420 (O-H), 2155 cm^{-1} (C-D).

Cyclohexanol-cis-2-d. To a stirred and cooled suspension of 4.3 g (0.10 mol) of lithium aluminum deuteride in 200 ml of anhydrous ethyl ether, under nitrogen, was added slowly 28 g (0.20 mol) of freshly distilled boron trifluoride etherate (Eastman Kodak Co.) in 25 ml of anhydrous ethyl ether. The boron trideuteride so generated was flushed in a nitrogen stream into a stirred solution of 10.5 g (0.13 mol) of cyclohexene (Aldrich Chemical Co.) in 200 ml of anhydrous tetrahydrofuran. The nitrogen stream was continued for 5 hr. The reaction mixture was then stirred under nitrogen at room temperature overnight. Sodium hydroxide (5%, 35 ml) and hydrogen peroxide (30%, 30 ml) were added slowly at 0° . The resulting mixture was refluxed for several hours. The mixture was then extracted with ethyl ether (3×150 ml). The combined extracts were washed with water and dried over MgSO_4 . Removal of the solvent and distillation of the alcohol afforded 12.5 g (0.12 mol, 92% yield) of pure cyclohexanol-cis-2-d: bp $75-77^\circ$ (20 mm); ir (neat) 3425 (O-H), 2180 cm^{-1} (C-D).

Cyclohexanol-trans-2-d. Cyclohexene oxide (8.9 g, 0.091 mol, Aldrich Chemical Co.) in 50 ml of anhydrous tetrahydrofuran was added slowly to a stirred suspension of 2.2 g (0.053 mol) of lithium aluminum deuteride in 200 ml of anhydrous tetrahydrofuran at 0° . The reaction mixture was refluxed overnight. After the slow addition of 5% NaOH (15 ml) at 0° , the mixture was refluxed for 3 hr. The solids were removed by filtration and extracted with boiling THF. The combined THF solutions were dried over MgSO_4 . Removal of the solvent and distillation of the alcohol gave 8.0 g (0.079 mol, 87% yield) of pure product: bp $75-77^\circ$ (20 mm); nmr (neat) δ 1.3 (m, 6), 1.8 (m, 3), 3.55 (br s, 1), 5.0 (s, 1); ir (neat) 3420 (O-H), 2200 cm^{-1} (C-D).

Cyclohexanone-2,2,6,6-d₄. Cyclohexanone was treated in five 20-g (0.2-mol) portions at 95° with successive solutions of 99.9% deuterium oxide (16 g, 0.8 mol, Bio-Rad Laboratories) containing NaCl (3 g) and K_2CO_3 (0.3 g) until the α -proton signal (δ 2.1) was no longer observable in the nmr spectrum. The organic layer was then taken up in ethyl ether. The aqueous layer was extracted with ether (3×100 ml), and the combined extracts were dried over MgSO_4 . Removal of the solvent and distillation of the product gave 85 g (0.83 mol, 83% yield) of pure, labeled ketone: bp $48-53^\circ$ (15-20 mm); nmr (neat) δ 1.78 (br s).

Cyclohexanol-2,2,6,6-d₄ was obtained from the reduction of cyclohexanone-2,2,6,6-d₄ (10 g, 0.096 mol) with LiAlH_4 (3.5 g, 0.092 mol) in anhydrous ethyl ether at 0° . Removal of the solvent and distillation of the alcohol afforded 9.3 g (0.09 mol, 94% yield) of pure product: bp $75-77^\circ$ (20 mm); nmr (CCl_4) δ 1.4 (m, 6), 3.45 (s, 1), 4.58 (s, 1); ir (neat) 3420 (O-H), 2225 cm^{-1} (C-D).

exo-2,3-Epoxynorbornane. A solution of *m*-chloroperbenzoic acid (28.4 g, 0.165 mol, Aldrich Chemical Co.) in 250 ml of anhydrous CH_2Cl_2 was added slowly to a stirred solution of 9.4 g (0.10 mol) of 2-norbornene (Aldrich Chemical Co.) in 300 ml of anhydrous CH_2Cl_2 at -10° . The reaction mixture was stirred at room temperature for 5 hr, and 150 ml of water was added. Sodium thiosulfite was added until the aqueous layer was negative to KI-starch paper. Sodium bicarbonate was then added until the aqueous layer was basic. The aqueous layer was extracted with CH_2Cl_2 (2×150 ml), and the combined extracts were dried over MgSO_4 . Removal of the solvent afforded 15.1 g (0.137 mol, 83% yield) of crude product: nmr (CCl_4) δ 0.6 (d, 1), 1.3 (m, 5), 2.38 (br s, 2), 2.86 (s, 2).

exo-2-Norbornanol. *exo*-2,3-Epoxynorbornane (5.5 g, 0.05 mol) in 50 ml of anhydrous dimethoxyethane (DME) was added slowly to a stirred suspension of 1.9 g (0.05 mol) of LiAlH_4 in 200 ml of anhydrous DME. The reaction mixture was allowed to reflux for 36 hr. After the slow addition of 5% NaOH (15 ml) at 0° , the reaction mixture was further refluxed for 3 hr. The solids were removed by filtration and the filtrate was dried over MgSO_4 . Removal of the solvent gave 5 g (0.045 mol, 90% yield) of crude alcohol: nmr (CCl_4) δ 1.35 (m, 8), 2.08 (m, 2), 3.58 (d, 1), 3.80 (s, 1).

(15) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 284.

(16) F. R. Jensen and R. A. Neese, *J. Amer. Chem. Soc.*, **93**, 6329 (1971).

exo-2-Norbornanol-endo-3-d. Analogous treatment of 2,3-epoxy-norbornane with lithium aluminum deuteride afforded the labeled alcohol: nmr (CCl₄) δ 1.25 (m, 7), 2.1 (m, 2), 2.78 (s, 1), 3.58 (s, 1); ir (neat) 3410 (O-H), 2225 cm⁻¹ (C-D).

exo-2-Norbornanol-exo-3-d. Treatment of 2-norbornene in an analogous fashion to that described for cyclohexanol-*cis-2-d* afforded this labeled compound in 85% yield: nmr (CCl₄) δ 1.2 (m, 7), 2.1 (d, 2), 2.85 (s, 1), 3.57 (d, 1); ir (neat) 3450 (O-H), 2230 cm⁻¹ (C-D).

2-Chloro-1,1,2-trifluorotriethylamine.¹⁷ A three-necked flask fitted with a Dry Ice condenser, thermometer, and gas inlet was charged with diethylamine (25 g, 0.35 mol, Aldrich Chemical Co.). Chlorotrifluoroethylene (Matheson) was added until the reaction mixture reached -15°. This mixture was stirred at -10° for 36 hr and then allowed to come to room temperature. The product was used at once, without purification: nmr (CCl₄) δ 1.1 (t, 6), 2.97 (q of t, 4), 5.61 (d of d, 1/2), 6.54 (d of d, 1/2).

Fluorocyclohexane.¹⁷ Cyclohexanol (7.0 g, 0.07 mol, Aldrich Chemical Co.) in 50 ml of anhydrous ethyl ether was added slowly to a stirred solution of 2-chloro-1,1,2-trifluorotriethylamine (ca. 0.10 mol) at -10°. The resulting mixture was stirred overnight at room temperature. Water (50 ml) was then added slowly. The aqueous layer was removed and extracted with ethyl ether (3 × 100 ml). The combined ether extracts were washed with dilute HCl, saturated NaHCO₃, water, and brine. The solution was dried over MgSO₄. Removal of the solvent and distillation of volatile products afforded a mixture of cyclohexene and fluorocyclohexane. The desired compound was isolated by preparative vapor-phase

chromatography (SE-30, 80°, 35 ml/min): nmr (CFCl₃) δ 1.27 (m, 10), 4.13 (br d, 1, *J* = 48 Hz).¹²

Fluorocyclohexane-*cis-2-d* (1). Similar treatment of cyclohexanol-*trans-2-d* afforded this compound: nmr (CFCl₃) δ 1.45 (m, 9), 4.34 (br d, 1, *J* = 48 Hz).¹²

Fluorocyclohexane-*trans-2-d* (2). Analogous treatment of cyclohexanol-*cis-2-d* gave this fluoride: nmr (CFCl₃) δ 1.4 (m, 9), 4.3 (br d, 1, *J* = 48 Hz).¹²

endo-2-Fluorobicyclo[2.2.1]heptane (*endo-2-Fluoronorbornane*). Similar treatment of *exo-2-norbornanol* afforded a mixture of 2-norbornene and the desired product. The fluoride was isolated by preparative vapor-phase chromatography (SE-30, 150°, 35 ml/min): mp 77-79° (lit.¹⁸ 79-81°); nmr (CFCl₃) δ 1.23 (m, 8), 2.20 (m, 2), 4.34 (br d, 1, *J* = 55 Hz).

endo-2-Fluorobicyclo[2.2.1]heptane-endo-3-d (*endo-2-Fluoronorbornane-endo-3-d*, 3). Analogous treatment of *exo-2-norbornanol-endo-3-d* led to this fluoride: nmr (CCl₄) δ 1.31 (m, 7), 2.30 (m, 2), 4.43 (br d, 1, *J* = 55 Hz).

endo-2-Fluorobicyclo[2.2.1]heptane-*exo-3-d* (*endo-2-Fluoronorbornane-*exo-3-d**, 4). Similar treatment of *exo-2-norbornanol-*exo-3-d** afforded this compound: nmr (CFCl₃) δ 1.22 (m, 7), 2.2 (m, 2), 4.40 (br d, 1, *J* = 55 Hz).

Fluorocyclohexane-2,2,6,6-*d*₄ (5). The same procedure applied to cyclohexanol-2,2,6,6-*d*₆ gave this product: nmr (CHCl₃) δ 1.40 (m, 6), 4.45 (d, 1, *J* = 48 Hz).¹²

Fluorocyclohexane-1-*d* (6). Analogous treatment of cyclohexanol-1-*d* gave this product: nmr (CFCl₃) δ 1.41 (m, 10).¹²

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Effects of Substituents on Combination and Disproportionation of Diarylketyl Radicals and Radical Anions

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Abstract: Photoreduction of benzophenone and of benzophenones containing a para substituent, CO₂⁻, SO₃⁻, and N(CH₃)₂⁺, has been studied in aqueous 2-propanol over the pH range 6.5-12.4. Benzophenone yields the pinacol to pH 11.5, and at pH 12.1 some benzhydrol, which may arise largely from decomposition of the pinacol. The substituted ketones are photoreduced normally to pinacols in acid medium. They are photoreduced in part to hydrols at intermediate pH, 8-9, at which the pinacols are stable, by disproportionation reactions of the ketyl radical ions with ketyl radicals, which compete with the combination reactions. The substituents also render the pinacols more readily decomposed by base. Factors affecting photoreduction to pinacols and to hydrols—acidity of the ketyl radical, pH, polarity of medium, and strength of the central C-C bond of the pinacol—are considered.

Some aromatic carbonyl compounds are photoreduced by primary and secondary alcohols,¹ while many others, with electron-donating substituents and with low-lying π,π* excited states, do not undergo this reaction or do so with low efficiency.^{2,3} Where the reaction proceeds, it generally leads in neutral and acidic medium to pinacols, with maximum theoretical quantum yield of 2 for reduction of the carbonyl compound,^{4,5} and, in basic medium, generally to hydrols,⁶

(1) G. Ciamician and P. Silber, *Ber.*, **33**, 2911 (1900); **34**, 1541 (1901).

(2) J. N. Pitts, Jr., H. W. Johnson, Jr., and T. Kutawa, *J. Phys. Chem.*, **66**, 2456 (1962).

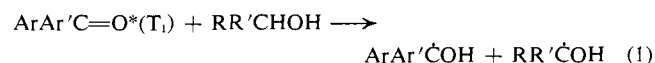
(3) G. Porter and P. Suppan, *Trans. Faraday Soc.*, **61**, 1664 (1965).

(4) J. N. Pitts, R. L. Letsinger, R. P. Taylor, J. M. Patterson, G. Recktenwald, and R. B. Martin, *J. Amer. Chem. Soc.*, **81**, 1068 (1959).

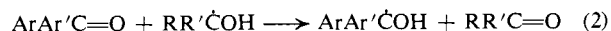
(5) A. Beckett and G. Porter, *Trans. Faraday Soc.*, **59**, 2038 (1963).

(6) (a) W. E. Bachmann, *J. Amer. Chem. Soc.*, **55**, 391 (1933); (b) *ibid.*, **55**, 355 (1933).

with maximum quantum yield of 1. The reactions begin by abstraction of H by the excited triplet carbonyl compound⁷ from the α-C of the alcohol, leading to ketyl radicals (eq 1). An aliphatic alcohol derived rad-



ical may reduce a ground-state ketone molecule (eq 2).⁴ When the alcohol reducing agent is itself the re-



duction product of the ketone, *i.e.*, as in the benzophenone-benzhydrol system, reduction of a second, ground-state, ketone may not occur so as to increase

(7) W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Amer. Chem. Soc.*, **83**, 2789 (1961).