Intrinsic and Equilibrium NMR Isotope Shift Evidence for Negative Hyperconjugation

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Abstract: Intrinsic NMR isotope shifts are found at ^{19}F due to CD_3 substitution for CH_3 in *N*-methyl- and *N,N*-dimethyl-4-fluoroaniline and 4-fluoroanisole. These intrinsic shifts demonstrate isotopic perturbation of negative hyperconjugation, in which C–H(D) bonds act as electron acceptors. Comparison with carbocations and a carbanion through the use of a perturbational analysis based on MO calculations supports the hyperconjugative origin of intrinsic long-range isotope shifts. Equilibrium isotope effects on the protonation of anilines, measured through observation of equilibrium NMR isotope shifts, are also consistent with negative hyperconjugation.

The concept of negative hyperconjugation has had at least as controversial a history as positive hyperconjugation. However, negative hyperconjugation as an important source of the stabilizing influence of C–F bonds in fluoro anions is now well-established in theory.[1] Recent bond length measurements on a trifluoromethoxide salt provide experimental confirmation of the C–F expected bond lengthening.[2] Negative hyperconjugation by C–H bonds is also supported by theory,[3-10] but it is predicted to be much less important than C–F hyperconjugation,[1] and it is also less well-established experimentally. We now provide NMR isotope shift evidence for negative hyperconjugation by methyl groups in electron-rich systems.

In both positive and negative hyperconjugation by a methyl group, the interacting C–H bonds are predicted to be lengthened relative to those of noninteracting bonds. These bonding effects are shown below in 4-31G-geometry-optimized theoretical structures of the *tert*-butyl cation, ethyl anion, and methylamine.[8,10]
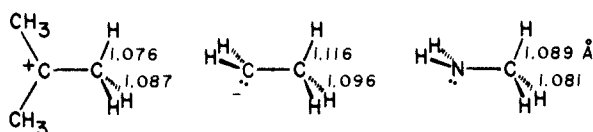
The lengthening in positive hyperconjugation arises from donation of bonding electron density out of a filled methyl group orbital of π symmetry into a vacant p orbital at an adjacent center. In negative hyperconjugation, the C–H bond is weakened by introduction of electron density into an antibonding methyl π^* orbital from an adjacent electron-rich orbital.

Positive hyperconjugation is widely accepted now, probably due primarily to two factors: first, the well-known stabilizing effect of methyl substitution on carbocations is consistent with an electron-releasing substituent effect, and second, kinetic isotope effect data are consistent with the predicted bonding changes associated with hyperconjugation. The electron-accepting substituent effect of negative hyperconjugation is not as conveniently

supported by analogous data. For example, solution basicities for amines ($NH_3 \approx Me_3N < MeNH_2 \approx Me_2NH$) differ in order from gas-phase proton affinities ($NH_3 < MeNH_2 < Me_2NH < Me_3N$).[11] The gas-phase proton affinities are in the opposite order of the sequence expected for an electron-accepting methyl effect, although this can be countered by noting that methanol is a stronger acid than water and methylamine is a stronger acid than ammonia in the gas phase. Such considerations led Hehre et al. to state that relative acidity is not an appropriate measure of the importance of anionic hyperconjugation.[3] However, these authors concluded from isotope effects on gas-phase equilibria and from molecular orbital calculations that the magnitudes and directions of secondary isotope effects do directly indicate the changes in bonding which occur as a result of negative hyperconjugation.
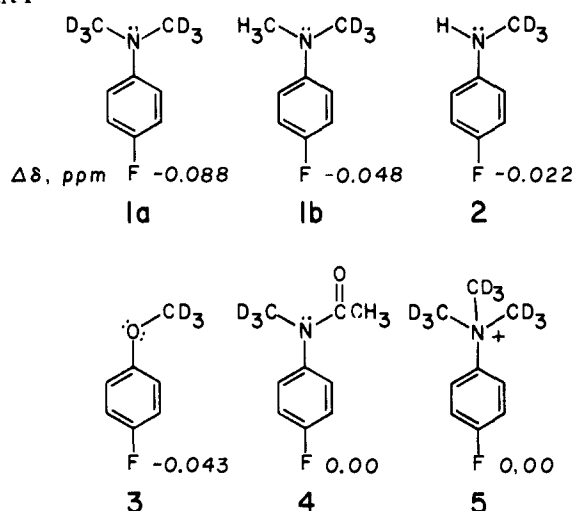
The positive hyperconjugative origin of secondary β-deuterium isotope effects on rates of solvolysis reactions proceeding through carbocationic transition structures has long been postulated, and there is extensive evidence regarding these isotope effects on energy content, including the conformational dependence of these effects.[12-15] The reduction in the C–H stretching force constants associated with hyperconjugation leads to the preferred formation of the light cations, as documented by observed k_H/k_D values greater than unity. Similarly, K_H/K_D values greater than unity are found for equilibria involving stable carbocations in solution and in the gas phase.[8,16] Many fewer data on β-deuterium isotope effects are available for reactions involving anionic transition structures or intermediates. However, both kinetic and thermodynamic measurements in solution and gas phase indicate a preference for formation of the light anion,[3,17-19] which is consistent with the theory of negative hyperconjugation. Isotope effects on acid–base equilibria of amines similarly show the thermodynamic preference for C–H over C–D interaction with the lone pair.[4,8,11,20,21]

In this paper, we present *intrinsic* isotope effect evidence for negative hyperconjugation. While kinetic or equilibrium secondary isotope effects derive from a *change* in force constants between two structures, an intrinsic isotope effect is seen in a property

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Chart I

D_3C—N—CD_3 H_3C—N—CD_3 H—N—CD_3

Δδ, ppm   F −0.088   F −0.048   F −0.022

Ia   **Ib**   **2**

—O—CD_3 D_3C—N—CCH_3 D_3C—N$^+$—CD_3

F −0.043   F 0.00   F 0,00

3   **4**   **5**

associated with a single species and is thus potentially a more direct measure of bonding character. Recent NMR studies of stable carbocations have shown that deuteration produces changes in NMR chemical shifts that are apparently due to isotopic perturbation of positive hyperconjugation.[22-26] In an effect fundamentally arising from vibrational differences, the C–D bond behaves as a poorer electron donor than a C–H bond in positive hyperconjugation, as evident in long-range deshielding of nuclei in cations with the charge delocalized in a π system. We now demonstrate long-range upfield isotope shifts at ^{19}F in 4-fluoroanilines and 4-fluoroanisole that apparently arise from perturbation of negative hyperconjugation.
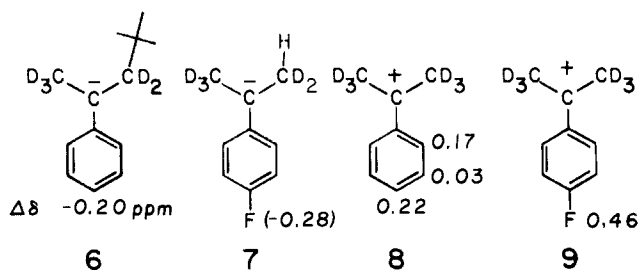
A perturbational analysis based on molecular orbital calculations is presented which supports the hyperconjugative origin of intrinsic long-range isotope shifts in both carbocations and electron-rich species. In addition, equilibrium isotope effects on the protonation of anilines are presented which also are consistent with negative hyperconjugation. These equilibrium isotope effects were determined through the observation of equilibrium NMR isotope shifts, which provide a new, convenient, and accurate method to obtain K_H/K_D data on amines.

Results and Discussion

Intrinsic Isotope Shifts. Intrinsic isotope shifts[27] due to replacement of CH_3 by CD_3 in N,N-dimethyl-4-fluoroaniline, **Ia** and **Ib**, N-methyl-4-fluoroaniline, **2**, and 4-fluoroanisole, **3**, are shown in Chart I. These were measured at 56.2 MHz and 27 °C from cyclohexane solutions of mixtures of the labeled and unlabeled compounds. The effects are additive: substitution of a single CD_3 group in **Ib** produces half the effect of substituting two CD_3 groups in **Ia**. Also shown in Chart I are isotope shifts for N-methyl-4-fluoroacetanilide, **4**, and (4-fluorophenyl)trimethylammonium iodide, **5**, measured in $CDCl_3$.

The isotope shifts at ^{19}F in the electron-rich aniline and anisole species are in the upfield direction, indicative of shielding due to a higher electron density at fluorine in the deuterated species. We have previously observed a similar upfield shift at the para carbon of a benzylic carbanion, **6**,[24] Chart II. Our attempts to make analogous 4-fluorophenyl carbanions failed, as did attempts to make the N-methyl-4-fluoroanilide ion by removing a proton from **2**. However, we can estimate an isotope shift at ^{19}F in **7** to be −0.28 ppm, based on the isotope shift for **6** and the linear relation[28]

Chart II

D_3C—C—CD_2 D_3C—C—CD_2 D_3C—C$^+$—CD_3 D_3C—C$^+$—CD_3

Δδ −0.20 ppm   F (−0.28)   0.22   F 0,46

                                0.17
                                0.03

6   **7**   **8**   **9**

between para carbon ^{13}C shifts of monosubstituted benzenes and ^{19}F chemical shifts for para-substituted fluorobenzenes.[29] In the related carbocations **8** and **9**, the analogous estimate of Δδ$_F$ = 0.463 for **9** from the Δδ$_C$ = 0.222[30] for **8** is matched by the observed Δδ$_F$ = 0.461 ppm for **9**.

Deuterium substitution appears to perturb the hyperconjugative interactions so that a C–D bond acts as a poorer electron donor than a C–H bond under conditions of high electron demand and as a poorer electron acceptor under conditions of excess electron supply. Negative hyperconjugation in carbanions is of importance comparable to positive hyperconjugation in carbocations, if judged by the magnitude of isotope shifts in **6–9**. Isotope shifts are smaller in the less-electron-rich species **1-3**, which is consistent with reduced hyperconjugative effects.

That the isotope shifts originate from hyperconjugative interactions rather than inductive effects is also indicated by the negligible Δδ$_F$ in **4**, where the lone pair is strongly delocalized by the carbonyl, and in **5**, which has no lone pair available for hyperconjugation. Taft el al. previously noted that the magnitude of the downfield isotope shifts at fluorine in methyl(4-fluorophenyl)carbenium ions was related to the electron demand on the methyl group.[22] The possibility that the isotope effects for **1**, **2**, and **3** arise from conformational or geometry changes has not been completely eliminated, but such changes arising from steric interactions with the ortho hydrogens were ruled out in a carbenium ion by interposing an alkyne link between the side chain and the ring,[22] and no such effect is seen in **4**. The continuum of isotope effects as the alkyl interactions vary from positive to negative hyperconjugation is clearly demonstrated by the present results and is further indicated in the discussion below on a perturbational model for isotope shifts.

Ideally, intrinsic isotope shifts would be measured in the gas phase on isolated molecules. We have used cyclohexane as the standard solvent as a reasonable alternative. With the basic anilines, there are potentially complicating isotope effects on equilibria of self-association and solvation. For instance, self-association could be important for **2**, where H bonding is a possibility, and solvation could be important if a polar solvent is used. Variation in isotope shifts for **Ia** and **2** with conditions was found, but the variations are comparable to the experimental uncertainty (±0.005 ppm) in several cases, and in all cases the upfield direction of the isotope shifts is not changed. For **Ia**, the Δδ$_F$ is −0.088 ppm in cyclohexane, −0.084 in $CDCl_3$, −0.078 upon 4-fold dilution in $CDCl_3$, and −0.054 in 50% aqueous dioxane (pH > 8). A similar change is seen for **Ib**, from Δδ$_F$ = −0.048 in cyclohexane to −0.035 for a dilute solution in $CDCl_3$. For **Ia** in $CDCl_3$, the Δδ$_F$ of −0.078 at 25 °C changes to −0.065 at −53 °C. These variations are consistent with an isotope effect on H bonding from the solvent to the aniline which would result in a downfield

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(27) Negative values indicate upfield isotope shifts, defined by Δδ$_F$ = δ$_F$(unlabeled) − δ$_F$(labeled).

(28) Different slopes are found for π-acceptor and π-donor substituents: Hehre, W. J.; Taft, R. W.; Topsom, R. D. *Progr. Phys. Org. Chem.* **1976**, *12*, 183.

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Table I. Intrinsic NMR Isotope Shifts and MNDO[a] Simulation for 4-Fluorophenyl Systems

1-substituent	$\Delta\delta_F$, ppm	q_π	$10^5\Delta q_\pi$
$C(CHD_2)CD_3^-$	−0.28[b]	1.970 336	11.4
$NHCD_3$	−0.022	1.948 412	2.8
$N(CD_3)_2$	−0.088	1.947 667	5.0
$N(CH_3)CD_3$	−0.048	1.947 667	2.5
$N(CD_3)COCH_3$	0.00	1.946 825	1.9
OCD_3	−0.043	1.945 109	2.1
$COCD_3$	0.00	1.935 934	0.3
$N(CD_3)_3^+$	0.00	1.919 446	6.4
$C(OH)CD_3^+$	0.087	1.894 268	−7.0
$C(CD_2CH_3)CH_3^+$	0.180	1.883 428	−5.8
$C(CH_2CH_3)CD_3^+$	0.228	1.883 428	−8.2
$C(CD_2CH_3)CD_3^+$	0.402	1.883 428	−14.0
$C(CH_3)CD_3^+$	0.230[c]	1.881 871	−7.9
$C(CD_3)_2^+$	0.461[c]	1.881 871	−15.9
$CHCD_3^+$	0.324[c]	1.877 128	−9.4

[a] MNDO method: Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. Stewart, J. J. P. *QCPE* **1977**, Program No. 455. Electron densities q_π, are for undeuterated compound. Changes in electron densities, Δq_π, are produced by 0.02-Å bond shortening to simulate C–D bonds. [b] Estimated value, as described in text. [c] Reference 24.

isotope shift if it were the dominant effect (see discussion of protonation equilibria). A $\Delta\delta_F$ of −0.02 at low pH for **1a** probably indicates H bonding from the anilinium ion to the solvent, since **5** shows no isotope effect in $CDCl_3$.

For **2**, changing the solvent to $CDCl_3$, diluting, and lowering the temperature caused no variations that gave values of $\Delta\delta_F$ outside experimental error of the value of −0.022 ppm in cyclohexane. Here, minor isotope effects on solvation may be counterbalanced by changes in self-association. However, a 50% aqueous dioxane solution (pH 7.03) shows no isotope shift, which indicates H bonding from the solvent, as seen for **1a**. Use of a H-bond-accepting solvent, THF, resulted in a $\Delta\delta_F$ of −0.035 ppm for **2**. For **3**, the $\Delta\delta_F$ of −0.043 in cyclohexane, −0.045 in THF, and −0.039 in $CDCl_3$ are all within experimental error of each other.

Perturbational Model for Intrinsic Isotope Effects. The intrinsic NMR isotope shift is fundamentally vibrational in origin, since the electronic potential energy surface for a molecule depends on nuclear charges, not nuclear masses (Born–Oppenheimer approximation). NMR shielding differs for isotopomers because the observed shielding is a vibrationally averaged property rather than the shielding for a fixed nuclear configuration. Bonds to deuterium have lower zero-point vibrational energies and smaller vibrational amplitudes than bonds to hydrogen. Theoretically, isotope effects on NMR shifts may arise from these differences even in harmonic vibration, but recent theoretical studies suggest that the chief contribution to isotope shifts comes from the anharmonic part of the expression for NMR chemical shielding.[31,32] A C–D bond should be slightly shorter than a C–H bond if stretching vibrations are anharmonic, and experimental studies confirm the difference in bond lengths.[33-35] Isotopic substitution results in an effective change in average molecular geometry and thus different wave functions are needed to describe isotopomers.

To simulate the isotope effect on the vibrationally averaged geometry, we use a bond-shortening perturbation in conjunction with MO calculations.[36] MNDO calculations were performed on **1–5**, **7**, **9**, and a few additional *p*-fluorophenyl carbenium ions. The only constraint put on the otherwise complete geometry optimization was the assumption of a coplanar heavy atom
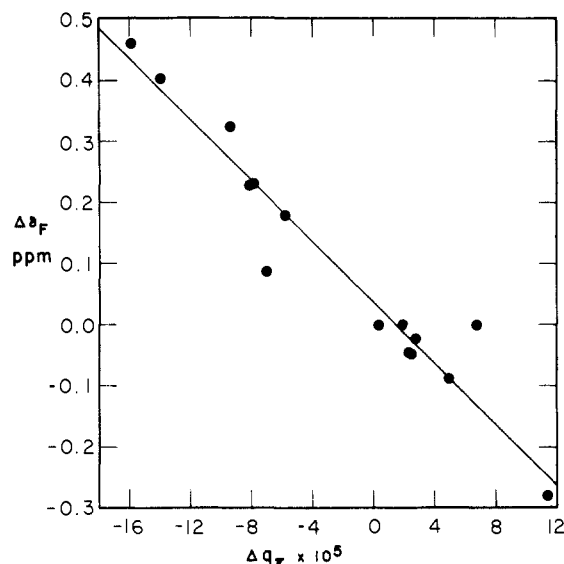

Figure 1. Plot of NMR isotope shift at ^{19}F in 4-fluorophenyl species vs. the change in π-electron density at fluorine induced by C–H bond shortening in MNDO calculations. The linear relation is $\Delta\delta_F = -2500\Delta q_\pi + 0.036$, with correlation coefficient = 0.964.

framework for all systems except **5**. For deuterium substitution, the appropriate C–H bonds were then shortened by an arbitrary 0.02 Å in a subsequent single SCF calculation with no further geometry optimization.[37] The difference in π charge at the fluorine atom between the optimized structure and the perturbed structure was calculated for comparison with NMR isotope shifts. The results are listed in Table I, along with observed isotope shifts.

Qualitatively, the calculations show that deuterium bond-shortening decreases electron density at fluorine in the cations and increases electron density at fluorine in the electron-rich species. This perturbational approach thus simulates the isotope effects on charge distribution which are assumed to be the origin of the NMR isotope shifts. The change in π electron density at fluorine reflects the change in electron supply in the entire π system, not just a change in π polarization. For instance, the Δq_π of 11.4 × 10⁻⁵ at fluorine for **7** is only 3.9% of the total Δq_π, which appears primarily at the ortho, para, and ipso ring carbons. We have previously shown that this perturbational model is at least partly successful in also simulating the angular dependence of positive hyperconjugation.[36]

Quantitatively, the correlation between the observed NMR isotope shifts and the calculated perturbation in electron density is good, as shown in Figure 1 for the data in Table I.[37] The correlation demonstrates a continuous range of hyperconjugative effects, from positive hyperconjugation in cations, to weak negative hyperconjugative effects in electron-rich species, to negative hyperconjugation in carbanions.

Equilibrium Isotope Shifts. Bond weakening associated with negative hyperconjugation in electron-rich species should be a source of β-deuterium kinetic or equilibrium isotope effects, in analogy to the effects of positive hyperconjugation in cation-forming reactions. Substitution of CD_3 for CH_3 in electron-rich systems should increase the basicity because of the well-known preference of deuterium for the more tightly bound site. This phenomenon has been observed previously,[3,17-21] although the cause has not always been ascribed to hyperconjugative effects.

We have measured K_H/K_D values for protonation equilibria in aqueous dioxane of anilines **1a** and **2** from chemical shift differences at ^{19}F between the labeled and unlabeled species. At a pH where the anilines are partially protonated, the ^{19}F signal

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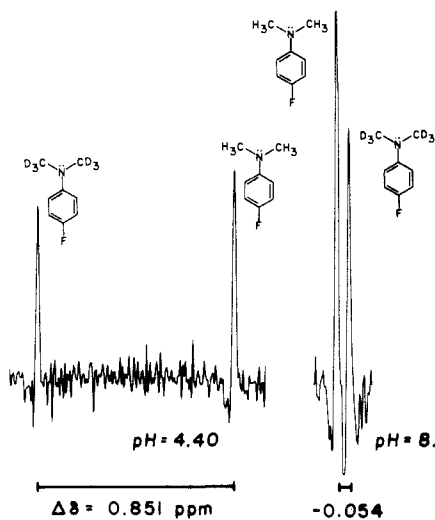(34) Richardson, E. H.; Brodersen, S.; Krause, L.; Welsh, H. L. *J. Mol. Spectrosc.* **1962**, *8*, 406.

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(37) The shortening of 0.02 Å is more than twice the expected actual effect,[31-35] but this value was chosen so that round-off errors in calculating charge densities would be relatively small. A better model would also consider alteration of the bond angles.[36b] The slope of the correlation is 2500 ppm per electron which, although fortuitous because of the crudeness of the model, is similar to the 2100 ppm/e slope previously found for fluorine chemical shifts.[28]

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Table II. ^{19}F NMR Chemical Shifts for
N,N-Dimethyl-4-fluoroaniline and Isotope Shifts for **1a** as a Function
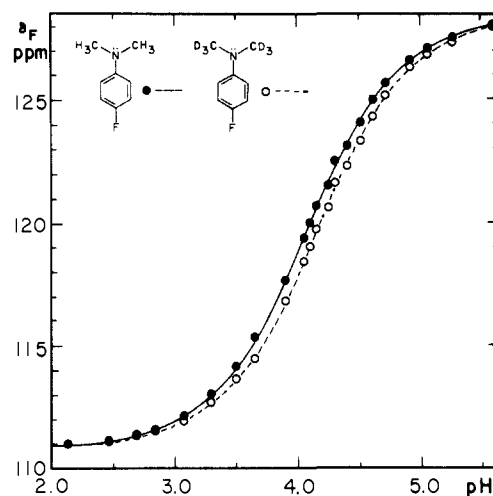of pH and the Derived K_H/K_D Values for Anilinium Ion Dissociation

pH	δ_F	$\Delta\delta_F$	K_H/K_D
0.50	110.62	−0.021	
0.93	110.85	−0.027	
1.70	110.94	−0.016	
2.15	111.00	0.000	
2.48	111.16	0.032	1.275
2.70	111.44	0.086	1.279
2.85	111.60	0.113	1.242
3.08	112.20	0.222	1.246
3.30	113.08	0.368	1.248
3.50	114.20	0.531	1.245
3.65	115.41	0.683	1.245
3.90	117.75	0.878	1.245
4.05	119.47	0.949	1.246
4.10	120.09	0.954	1.244
4.15	120.79	0.960	1.248
4.25	121.62	0.938	1.249
4.30	122.61	0.905	1.252
4.40	123.28	0.851	1.252
4.50	124.20	0.764	1.252
4.60	125.10	0.645	1.250
4.70	125.85	0.542	1.256
4.90	126.78	0.379	1.262
5.05	127.28	0.281	1.267
5.25	127.72	0.162	1.240
5.58	128.30	0.037	
5.70	128.26	0.032	
5.98	128.49	−0.011	
6.10	128.51	−0.021	
6.25	128.55	−0.032	
6.60	128.59	−0.048	
8.20	128.71	−0.054	
9.55	128.69	−0.048	
11.20	128.67	−0.054	
12.70	128.68	−0.054	

Table III. ^{19}F NMR Chemical Shifts for *N*-Methyl-4-fluoroaniline
and Isotope Shifts for **2** as a Function of pH and the Derived K_H/K_D
Values for Anilinium Ion Dissociation

pH	δ_F	$\Delta\delta_F$	K_H/K_D
1.65	112.03	0.000	
2.25	112.14	0.000	
3.00	112.77	0.081	1.125
3.15	113.07	0.110	1.125
3.28	113.40	0.130	1.113
3.50	114.26	0.222	1.125
3.65	115.17	0.277	1.120
3.85	117.19	0.401	1.120
3.90	117.28	0.417	1.125
3.95	120.69	0.488	1.122
4.00	118.30	0.450	1.122
4.05	121.84	0.471	1.118
4.13	122.73	0.450	1.117
4.33	124.84	0.363	1.115
4.43	125.86	0.292	1.112
4.78	128.61	0.054	1.101
5.23	128.88	0.021	1.085
5.43	128.96	0.016	1.126
5.68	128.97	0.011	
5.95	129.08	0.000	
7.03	129.15	0.000	
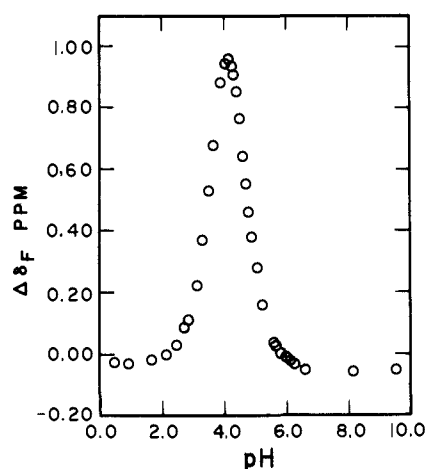
Figure 3. pH dependence of the isotope shift between *N,N*-dimethyl-4-fluoroaniline and **1a** in 50% aqueous dioxane.

Figure 2. Proton-decoupled 56.2-MHz ^{19}F NMR spectra of *N,N*-dimethyl-4-fluoroaniline and **1a** in 50% aqueous dioxane. the spectrum at pH 8.2 shows the small, upfield, intrinsic NMR isotope shift, and the spectrum at pH 4.40 illustrates the large, downfield, equilibrium isotope shift. A resolution-enhancing weighting function was applied to the FID before Fourier transformation in generating these spectra.

of the labeled anilines is found *downfield* of the unlabeled species, as shown in Figure 2 and Tables II and III. The downfield equilibrium isotope shift indicates that the labeled aniline is more basic and hence more fully protonated. In the 4-fluoroanilines, full protonation results in a downfield shift of the ^{19}F resonance on the order of 10 ppm. The downfield isotope shift reaches a maximum approximately at the pH where the pH is equal to the pK_a of the anilinium ion (Figure 3). These isotope shifts reflect the displacement between titration curves, shown in Figure 4, for the deuterated and undeuterated species.

Figure 4. Titration curves obtained by plotting ^{19}F chemical shifts of *N,N*-dimethylaniline and **1a** vs. pH.

Equilibrium constants, K_H and K_D, for the deprotonation of anilinium ions can be determined at any pH from the position of the ^{19}F signals relative to the ^{19}F signals of the neutral aniline at high pH and anilinium ion at low pH. The most accurate determination of K_H/K_D values will be from the measurements

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in the pH range near where the maximum isotope shifts are found because errors in the limiting values for the ^{19}F chemical shifts are least significant at that point. The K_H/K_D ratios for anilinium ion dissociation should be nearly constant at all pH's, as shown in Tables II and III. The K_H/K_D values are more accurate than could be found from separate determinations of K_a's; the ratios do not depend on accurate determinations of pH.[38]

The K_H/K_D values are 1.117 (standard deviation (SD) 0.011) for 2 and 1.252 (SD 0.011), or 1.119 per CD_3, for 1a. These effects are similar per CD_3 to the literature K_H/K_D values of 1.61 (1.17 per CD_3) for trimethylamine-d_9,[20] 1.14 for 2,4-dinitro-N-methyl-d_3-aniline,[21] and 1.11 for 2,4,6-trinitro-N-methyl-d_3-aniline.[21] The K_H/K_D values for protonation equilibria of N-methylanilines are consistent with negative hyperconjugation. It is interesting that the values per methyl group are virtually identical for 1 and 2, while the intrinsic isotope shift is smaller for 2. One possible explanation is that 2 may be nonplanar,[39] so that the influence of isotopic perturbation of hyperconjugation may not be transmitted well via the π system as is necessary for the observation of long-range intrinsic NMR isotope shifts at ^{19}F.

The isotope shift method used to determine the K_H/K_D values is very convenient and sensitive and should prove useful in future studies aimed at establishing the conformational dependence of the equilibrium isotope effects. Knowledge of the conformational dependence of both intrinsic and equilibrium isotope effects is needed to verify the relation to negative hyperconjugation in the same manner that the conformational dependence of kinetic isotope effects in solvolysis provided convincing evidence of positive hyperconjugation. However, the fact that long-range *intrinsic* shifts for electron-rich species are in the *opposite* direction of intrinsic shifts for electron-deficient species is already a powerful argument for a primarily hyperconjugative rather than inductive origin of such shifts.

Experimental Section

NMR Spectroscopy. Proton-decoupled ^{19}F NMR spectra at 56.2 MHz were obtained on a JEOL FX-60Q NMR equipped with a 5-mm ^{19}F probe. The isotope shifts were determined with a 500-Hz spectral width and 4–10 pulses. A resolution enhancing weighting function was applied to the FID before Fourier transformation in some cases. The chemical shifts were recorded in parts per million (ppm) upfield from internal 1-bromo-4-fluorobenzene and converted to ppm upfield from $CFCl_3$. The chemical shift of 1-bromo-4-fluorobenzene is 115.6 ppm upfield from $CFCl_3$.[41]

pH Dependence of Isotope Shifts. A mixture of 0.7 mL of N-methyl-4-fluoroaniline and 1.4 mL of 2 was dissolved in 25 mL of dioxane and 25 mL of deionized water. (In the case of N,N-dimethyl-4-fluoroaniline, 0.69 g of undeuterated compound and 0.37 g of 1a were dissolved in 15 mL of dioxane and 15 mL of deionized water.) The pH values of the aliquots of the stock solution were adjusted by 5%, 10%, or 20% concentrated hydrochloric acid and/or 5%, 10%, or 20% aqueous sodium hydroxide. The aqueous solutions with different concentrations were used so as to minimize volume differences after pH adjustments. The effect of slight variation in solute concentration is negligible since the isotope shifts showed little dependence upon concentration. ^{19}F NMR measurements with 2500-Hz spectral width and 20–40 pulses were taken after each adjustment. The chemical shifts were determined in reference to external (capillary) benzotrifluoride (δ_F 63.72)[41] in spectra of 10 000-Hz width and then were converted to ppm upfield from $CFCl_3$. The pH was measured before and after each NMR measurement, and the average is reported. A Fisher Model 107 digital pH meter with glass electrode was used to measure the pH.

Preparation of Materials. N,N-Dimethyl-4-fluoroaniline and 1a were prepared by Hofmann methylation[42] of 4-fluoroaniline with iodomethane (CH_3I) or iodomethane-d_3 (CD_3I). Separation of the product mixtures using flash chromatography[43] with a solution of 30% (v/v) ether in hexanes as the eluant gave the pure compounds. In similar fashion, N-methyl-4-fluoroaniline and CD_3I gave 1b. N-Methyl-4-fluoroaniline and 2 were prepared by acetylating 4-fluoroaniline with acetic anhydride to give 4-fluoroacetanilide, followed by methylation[44] with CH_3I or CD_3I to give N-methyl-4-fluoroacetanilide or 4 and hydrolysis[45] to give N-methyl-4-fluoroaniline or 2. 5 was prepared by reaction of 4-fluoroaniline with an excess of CD_3I in methanol. 4-Fluoroanisole and 3 were prepared by methylation of 4-fluorophenol with CH_3I or CD_3I in acetone, catalyzed by K_2CO_3.[46]

4-Fluoroactophenone-α,α,α-d_3 was prepared by exchange of the ketone in D_2O with NaOD as the catalyst. The protonated ketone was formed by dissolving 4-fluoroacetophenone in 1:1 SbF_5/FSO_3H in SO_2ClF at −78 °C.[29b] The 2-(4-fluorophenyl)-2-butyl cations were formed from the appropriately labeled 2-(4-fluorophenyl)-2-butanols by ionization in 1:1 SbF_5/SO_2ClF and SO_2ClF at −78 °C.[29b] The labeled alcohols were synthesized by Grignard reactions of previously D_2O-exchanged 2-butanone, 4-fluoroacetophenone, or 4-fluoropropiophenone with 4-fluorophenylmagnesium bromide, ethylmagnesium bromide, or methylmagnesium iodide.

(38) The observed δ is the weighted average of the chemical shift for the aniline, δ_1, and the anilinium ion, δ_2, i.e., $\delta = x\delta_1 + (1 - x)\delta_2$, where x is the fraction of dissociation. Since $K = (x)(H^+)/(1 - x)$, it can be shown that $K_H/K_D = (\delta_H - \delta_2)(\delta_D - \delta_1)/(\delta_H - \delta_1)(\delta_D - \delta_2)$. See also: Ellison, S. L. R.; Robinson, M. J. T. *J. Chem. Soc., Chem. Commun.* **1983**, 745.

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