Carbon Acidity. 53. Kinetic and Equilibrium Acidities of Fluorinated Bicycloalkanes[1a]

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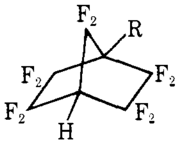
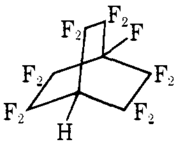
Abstract: Base-catalyzed tritium exchange kinetics in methanolic sodium methoxide are reported for 1*H*-4-Y-perfluorobicyclo[2.2.1]heptanes, Y = F (**1**), H (**2**), CH_3 (**3**), Br (**4**), I (**5**), CF_3 (**6**), 1*H*-perfluorobicyclo[2.2.2]octane (**7**), and 1*H*-perfluorobicyclo[2.2.1]hept-2-ene (**8**). The primary isotope effect for **2** is weak. Equilibrium cesium ion pair acidities are reported for compounds **1, 2, 3, 6, 7,** and **8** in cyclohexylamine relative to conjugated hydrocarbon indicators. A Brønsted plot of the kinetic and equilibrium acidities has a slope close to unity and is used to assign p*K* values to related halogenated carbon acids. The acidities of the fluorinated bicycloalkanes can be accommodated completely by a classical field effect as modeled by Kirkwood–Westheimer calculations.

The preparation and chemical study of highly fluorinated bicyclic compounds by Professor J. C. Tatlow and Dr. R. Stephens and their research group at the University of Birmingham form a most important contribution to modern fluorocarbon chemistry.[2] In addition, these compounds provide fascinating subjects for physical organic chemistry, especially as regards the nature and mechanism of fluorine substituent effects. Bridgehead hydrogens, for example, in these compounds are readily metallated and the corresponding carbanions are useful intermediates for further syntheses.[2b,c] In the present paper we present a study of the kinetic and equilibrium acidities of bridgehead hydrogens in the series of compounds **1–8** and evaluate the corresponding substituent effects.



1, R = F **4**, R = Br
2, R = H **5**, R = I
3, R = CH_3 **6**, R = CF_3



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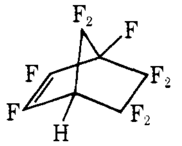

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Experimental Section

Compounds. Generous samples of compounds **1–8** were provided by Professor J. C. Tatlow and Dr. R. Stephens and have all been described previously.[2] All of the compounds gave single peaks on GLC analysis (Carbowax 20M or SE-30) and identity was confirmed by NMR and mass spectroscopy.[3] In some cases samples were resublimed immediately before use, especially in the equilibrium acidity studies. 1*H*,4*H*-Decafluorobicyclo[2.2.1]heptane-1,4-d_2 (**2**-d_2) was prepared by dissolving 198 mg (0.72 mmol) of **2** in 17 ml of 0.1 M sodium methoxide in methanol-*O*-*d*.[4] After 3 days the mixture was neutralized with D_2SO_4 and extracted with mesitylene. The washed and dried extract was separated by preparative GLC in 20% Carbowax 20M to give **2**-d_2, which was 93.6% d_2, 3.2% d_1. The mass spectrum shows no molecular ion and the analysis was calculated from peaks at *m/e* 258, 259, and 260.

Kinetics. Kinetic acidities were measured by tritium incorporation from sodium methoxide solutions in methanol-*O*-*t*. The high reactivity of some of the compounds required studies at low temperatures that were achieved by the use of slush baths[5] in large Dewar flasks. The following liquids were used as slushes with dry ice: ethylene glycol (−15 °C), CCl_4 (−22.9 °C), bromobenzene (−30.6 °C), chlorobenzene (−45 °C), cyclopentanone (−52.9 °C), chloroform (−63.5 °C), and 2-propanol (−74 °C). Temperatures were constant to ±0.2° except for ±0.3° at the lowest temperature. At temperatures of 0 °C and above, conventional baths and kinetic techniques were used. Kinetic aliquots were removed from a sealed flask, quenched with cold methanolic toluenesulfonic acid, and extracted with toluene. The washed and dried toluene extracts were counted by liquid scintillation techniques using a Nuclear-Chicago Mark I counter. Control experiments showed the extraction technique to give reproducible results. For the low-temperature runs each point was taken individually using a stock solution of substrate in methanolic sodium methoxide contained in a test tube sealed with a serum cap carrying a fragile bulb containing methanol-*t* (Figure 1). When temperature equilibration was reached, the fragile bulb was broken on a stainless steel spike. After the desired time interval the mixture was quenched with cold methanolic toluenesulfonic acid and extracted as before. Both methods gave excellent first-order kinetic behavior using infinity values determined from long reaction times. Rate constants were obtained with LSKINI[6] and converted to second-order rate constants by dividing by the sodium methoxide concentration as determined by titration at room temperature and correcting to reaction temperature using the known densities of methanol as a function of temperature.[7] Alternatively, sodium methoxide was contained in the bulb. This technique was especially important for runs with **4** and **5**, since long contact of these compounds with methanolic sodium methoxide liberated halogen, undoubtedly by nucleophilic attack by base at the bromine or iodine. During the course of a proton exchange run no significant liberation of halogen occurred and normal first-order kinetics was obtained. Compounds **1, 2, 3, 6,** and **7** were established not to have decomposed during the course of a kinetic run by GLC analysis of an aliquot of an infinity point. The effluent was bubbled into counting vials containing scintillation solution and counted. In each case, significant radioactivity was found only at the peak corresponding to the bicyclic substrate.

Comparison of infinity radioactivities with independent determinations of the amount of tritium used gave a value of 0.75 ± 0.06 for the distribution of tritium between oxygen and carbon, the equilibrium constant for the reaction

$$R_F\text{-}H + CH_3OT \rightleftharpoons R_F\text{-}T + CH_3OH$$

Equilibrium Acidities. Equilibrium acidities towards indicator hydrocarbons and their cesium salts were determined in cyclohexylamine by the "single indicator" method published previously[8] with minor modifications. Solutions were prepared in a Vacuum Atmospheres glovebox under argon and the visible spectrum was recorded on a Perkin-Elmer Model 202 spectrometer. Except for compound **7** the spectra were stable for the duration of the measurements. Approximate p*K* values were obtained first by qualitative color tests with a series of hydrocarbon indicators. Addition of the test compound produced no change in solutions of cesium salts of more acidic hydrocarbons, whereas such addition quenched the colors of salts of less acidic hydrocarbons.

Results and Discussion

The kinetic results obtained for the sodium methoxide catalyzed tritium exchange of compounds **1–8** are summarized in Table I. Although the rate measurements were made by incorporation of tritium into each substrate from methanol-*O*-*t*, the derived second-order rate constants (k_2^T) are equiv-

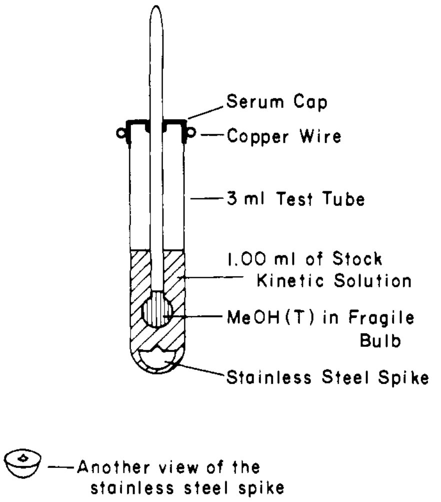


Figure 1. Kinetic technique at low temperature showing fragile bulb containing $CH_3OH(t)$ and stainless steel spike.

Table I. Tritium Exchange Rates in Methanolic Sodium Methoxide

Compd[a]	Temp, °C	10^2[NaOMe], M	$10^3k_2^T$, M^{-1} s^{-1}
1	-44.7	0.25	572
	-44.9	0.26	743
	-52.9	1.04	270
	-63.5	5.19	65, 79
	-74.1	5.19	14.8
2	10.1	1.05	24.4
	0.0	3.46	6.07
	-9.5	6.66	1.78
2-d_2	-14.7	0.93	0.89[b]
3	0.0	0.95	7.1
4	0.0	3.86	1180
	-10.4	3.86	365
	-22.9	3.86	78
	-63.8	3.86	0.072
5	0.0	3.78	1210
6	-31.0	4.58	2020
	-45.4	3.80	296
	-63.5	3.80	22.4
7	-71.8	1.11	7000
8	0.0	3.76	674
	-23.0	3.76	39.5
	-31.0	3.76	15.0

[a] Concentration of substrate was generally of the order of 10^{-2} M. [b] From initial rate; see text.

Table II. Activation Parameters

Compd	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	k_2^T, 0 °C	σ_I
1	11.6	-8.0	42	0.52
2	19.2	2.0	6.1×10^{-3}	0.00
3			6.7×10^{-3}	-0.05
4	16.9	4.1	1.18	0.45
5			1.21	0.39
6	13.4	-1.1	62	0.41
7			$\sim 5 \times 10^3$	
8	15.9	-1.0	0.67	

alent to the values which would have been obtained had we followed loss of tritium from specially labeled compounds.[9] The reactivities vary over a large range and results at varying temperatures were required. Activation parameters and rates at 0 °C are summarized in Table II.

The primary isotope effect was measured by a study of **2**-d_2. The complete exchange kinetics of this compound with methanol-t is complex. The initial rate of incorporation of tritium compared to that of the protium compound gives k_D/k_H.[10-12] Any significant primary isotope effect results in preferential formation of the protium compound, whose tritiation rate then is k_T. The initial rate of tritiation of **2**-d_2 compared with that extrapolated from **2** at other temperatures (Table I) gives $k_H/k_D = 1.2$. A computer simulation[10] of the complete kinetic behavior of **2**-d_2 in this run confirmed an isotope effect close to unity.

The relatively small primary isotope effect is reminiscent of the similar behavior of polyfluorobenzenes in methanol[13] and chloroform in water.[11,14] In all of these cases the C–H bond is essentially completely broken at the rate-determining transition state; that is, these reactions are probably of the internal return type for which $k_{-I} \gg k_{II}$ in the following equation

$$RH + {}^-OCH_3 \underset{k_{-I}}{\overset{k_I}{\rightleftharpoons}} R^- \cdots \underset{\mathbf{9}}{HOCH_3} \xrightarrow{k_{II}} R^- + HOCH_3$$

$$k_{expl} = \frac{k_I k_{II}}{k_{-I} + k_{II}} \cong \frac{k_I}{k_{-I}} k_{II} \text{ for } k_{-I} \gg k_{II}$$

It has been pointed out previously[13] that for a related group of compounds for which all k_{II} are likely to be similar, relative k_{expl} values correspond to an equilibrium acidity in which the carbanion is hydrogen bonded to a solvent molecule.

$$\frac{k_{expl}'}{k_{expl}''} = \frac{\dfrac{k_I' k_{II}'}{k_{-I}'}}{\dfrac{k_I'' k_{II}''}{k_{-I}''}} \simeq \frac{k_I'/k_{-I}'}{k_I''/k_{-I}''} = \frac{K'}{K''}$$

For localized carbanions of the type considered here the equilibrium structure in a protic solvent such as methanol undoubtedly involves hydrogen bonding to solvent in a manner not dissimilar to the proton transfer intermediate **9.** Indeed, **9** may be the equilibrium carbanion and the step k_{II} may represent the rate-determining reaction for isotope exchange.

This analysis suggests that the relative kinetic acidities in Table II should provide a basis for evaluating substituent effects in fluorocarbon systems. Figure 2 shows a plot of log k_2 vs. σ_I for the compounds **1–6**, which differ only by substituent change at a bridgehead position. The results show a rough trend in the expected direction that electron-withdrawing substituents increase the acidity, but the points show more scatter than normally found for such straightforward $\rho\sigma_I$ plots. This effect suggests that the polar effect of C–X bonds is significantly modified by the presence of several fluorines. The magnitude of the approximate ρ (≈ 7) is relatively high and is undoubtedly associated with the proximity and direction of the C–X bond dipole to the localized carbanionic charge.

A more complete appraisal of these substituent effects would be assisted by a Bronsted plot in which the kinetic acidities are compared to equilibrium acidities, preferably in the same solvent. We were not able to measure pK's for these carbon acids in methanol, but an estimate can be made on the assumption that the equilibrium carbanion can be modeled by the product of step k_{II}. The model process is

$$RH + {}^-OMe \underset{k_{rev}}{\overset{k_{expl}}{\rightleftharpoons}} R^- + HOCH_3$$

$$K = \frac{k_{expl}}{k_{rev}} = \frac{K_{MeOH}(RH)}{K_{MeOH}(CH_3OH)}$$

where $K_{MeOH}(CH_3OH)$ is the ion product of methanol, $10^{-16.9}$ at 25 °C.[15] We take k_{rev} to be a diffusion-controlled process. In aqueous solution Eigen has shown that rate constants for such reactions have magnitudes of 10^9–10^{11} s^{-1}.[16] We use the value 10^9 for k_{rev} in methanol.[17] For **1**, k_{expl} is 2.6×10^2 M^{-1} s^{-1} at 25 °C; hence, K for **1** $\simeq 3 \times 10^{-7}$ M^{-1} or pK_{MeOH}(**1**)

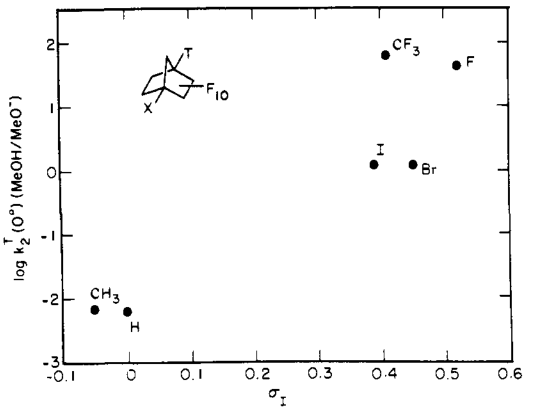


Figure 2. Kinetic acidities of decafluorobicyclo[2.2.1]heptanes compared to σ_I of 4 substituent.

Table III. Equilibrium Cesium Ion Pair Acidities in Cyclohexylamine

Compd	Indicator[a]	No. of runs	pK_{CsCHA} per H	Av pK_{CsCHA} per H
1	1,2-BF	4	20.4 ± 0.2	20.5 ± 0.3
	3,4-BF	4	20.5 ± 0.2	
2	2,3-BF	3	22.4 ± 0.1	22.3 ± 0.2
	4,5-MP	4	22.2 ± 0.2	
3	2,3-BF	2	23.3 ± 0.1	23.4 ± 0.1
	4,5-MP	2	23.4 ± 0.1	
6	1,2-BF	6	20.7 ± 0.1	20.7 ± 0.2
	3,4-BF	4	20.8 ± 0.2	
7	9-PF	3	18.2 ± 0.2	18.3 ± 0.3[c]
	3,4-BF	3	18.5 ± 0.3	
8[b]	1,2-BF	2	20.8 ± 0.4	21.6 ± 0.7
	4,5-MP	2	22.3 ± 0.1	

[a] Indicators and pK_{CsCHA} (per H) are 1,2-BF, 1,2-benzfluorene, 20.35; 2,3-BF, 2,3-benzfluorene, 23.47; 3,4-BF, 3,4-benzfluorene, 19.75; 4,5-MP, 4,5-methylenephenanthrene, 22.93; 9-PF, 9-phenylfluorene, 18.49; taken as standard (ref 19). [b] This compound is unstable in CHA and the derived pK value has greater uncertainty. [c] Approximate pK in Me_2SO is 23.

$\simeq pK_{MeOH}(CH_3OH) + 6.5 \simeq 23$ in methanol. This value has an estimated uncertainty of a few pK units. On this basis the compounds **1**–**8** have a pK_{MeOH} range of about 20–26 in methanol.

We were able to measure equilibrium cesium ion pair acidities for several of the bicyclic compounds in cyclohexylamine. The change in absorbance of a known mixture of an indicator hydrocarbon (HIn) and its cesium salt (Cs^+In^-) on addition of a known amount of the test compound allows the determination of the equilibrium constant that corresponds to an acidity difference.[8]

$$RH + Cs^+In^- \xrightleftharpoons{K_{eq}} R^-Cs^+ + HIn$$

$$pK_{CsCHA}(RH) = pK_{CsCHA}(HIn) + \log K_{eq}$$

The resulting pK_{CsCHA} values summarized in Table III provide relative equilibrium cesium ion pair acidities for these compounds in cyclohexylamine and to this extent are not ambiguous. The values are scaled, however, to the pK_{CsCHA} values of the indicator hydrocarbons whose carbanions are extensively delocalized. For sufficiently related delocalized systems, the relative pK values are much the same for ion pairs in cyclohexylamine as for the essentially free ions in Me_2SO.[18-20] Furthermore, the absolute pK_{CsCHA} numbers for such delocalized systems are quite similar to pK values that refer approximately to an aqueous solution standard state as established both by H_- methods for some of the indicators[21,22] and by relationship with cyclopentadiene, whose pK_a has been measured in aqueous sodium hydroxide.[23]

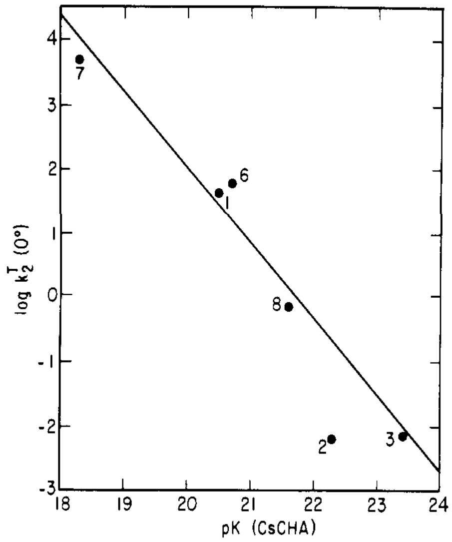


Figure 3. Brønsted plot of kinetic acidities of fluorinated bicyclic compounds in CH_3OH/CH_3ONa vs. pK's in CsCHA/CHA. The least-squares line shown is: $\log k_2 = 25.785 - 1.1881 pK_{CsCHA}$.

The fluorinated bicyclic carbon acids, however, form carbanions whose anionic charges are expected to be essentially localized. As a result, ion-pair and solvation effects will generally differ from those of the delocalized indicators and the assigned pK_{CsCHA} values may no longer correspond to those appropriate to protic solvents. Electrostatic interaction with the gegenion is undoubtedly greater for the bicyclic ions than for the delocalized indicators. Relative to such indicators, therefore, **1**–**8** are expected to be several pK units more acidic in the CsCHA system than in Me_2SO, in complete analogy to the corresponding differences established for acetylenes.[24] In protic solvents, hydrogen bonding of the localized carbanions is undoubtedly more important than for delocalized carbanions. This additional solvation effect is in the same direction as the above ion-pair effect, such that pK's relative to delocalized carbanions are expected to be lower in protic solvents than in Me_2SO and other polar aprotic solvents. If the two pK-lowering effects of cesium ion pairing and hydrogen bonding are of comparable magnitudes, the pK_{CsCHA} values assigned to the present structures may actually be reasonably close to the actual aqueous pK_a values.

The foregoing analysis suggests that the cesium ion pair pK values in CHA (pK_{CsCHA}) should be acceptable substitutes for methanol pK's (pK_{MeOH}) for a Brønsted correlation with the kinetic acidities. Indeed, the pK_{CsCHA} values in Table III are of the same magnitude as the approximate pK_{MeOH} values of 20–26 deduced above entirely from the kinetic data. In particular, comparison of the pK of **1** in methanol (~23) derived from kinetic data is only slightly higher than that in cyclohexylamine (20.5). The difference is substantially less than that for hydrocarbons with delocalized carbanions, which appear to have pK values about six units higher in methanol than the assigned ion-pair values in CHA.[25] That is, the effects of hydrogen-bonding solvation of the localized carbanions in methanol appear to be somewhat more stabilizing than the greater ion-pair association in CHA. Nevertheless, the difference is not great and the agreement between the derived pK_{MeOH} of **1** in methanol and the pK_{CsCHA} found in CHA is conveniently close considering that they refer to different standard states.

The Brønsted plot comparing log k_2^T from Table II with the pK_{CsCHA} values in Table III is shown in Figure 3. Five of the points define a satisfactory linear relationship, but the point for **2** deviates seriously. This deviation derives from the observations that H and CH_3 substituents have comparable kinetic acidities toward CH_3O^-/CH_3OH, but differ by about 1 pK unit toward CsCHA in cyclohexylamine. The latter result is undoubtedly real, since both compounds were measured with the same hydrocarbon indicators and reproducible results were obtained. Among the compounds studied in this work, **2** is unique in that it has two hydrogens per molecule instead of one. Both hydrogens probably hydrogen bond to solvent in both methanol and cyclohexylamine and such hydrogen bonding is expected to be less in the corresponding carbanion. The observed behavior is then in the direction that such hydrogen bonding and loss of additional solvation energy is greater in methanol than in cyclohexylamine, perhaps because of steric or solvent polarity considerations. This interpretation carries the corollary that the methyl substituent in these fluorocarbon substituents is substantially more electron donating relative to hydrogen than in typical hydrocarbon systems.

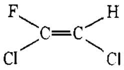
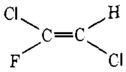
The least-squares correlation in Figure 3 (excluding **2**) has a slope of −1.19. A correction should be applied for a temperature effect. Figure 3 compares rate data at 0 °C with pK values at the spectrometer temperature of 34 °C. The corresponding Brønsted slope at 34° would be about 1.05, a value that does not differ from unity by more than the probable experimental error. The extrapolation assumes that the relative rates differ only in enthalpy of activation and that the slope, correspondingly, is inversely proportional to the absolute temperature. The small difference of this slope from unity loses more significance when we recall that the pK_a values used are those of a different standard state.

This Brønsted slope of close to unity confirms the model derived from kinetic data that the transition state for exchange resembles closely the equilibrium carbanion. A similar situation has been found for polyhalobenzenes[26] and may be general for carbon acids with localized carbanions. In ionic media these systems are characterized by weak primary isotope effects in proton exchange. Another property of the proton exchange of such carbon acids, referred to as normal in the Eigen[27] sense by Margolin and Long,[11] is specific base catalysis as demonstrated by them for chloroform.[28] It should also be emphasized that for such compounds we do not anticipate the "anomalous" Brønsted slopes discovered by Bordwell et al.[29] Such Brønsted α values, outside the normal range of 0–1, are expected only for delocalized carbanions having polar substituents in which the charge distribution at the proton transfer transition state differs significantly from that in the equilibrium anion.[30,31]

Available kinetic data on other compounds expected to belong to the "normal" class of carbon acids with localized carbanions allow the assignment of pK_{CsCHA} values from Figure 3. Some examples are summarized in Table IV. The derived pK values are the cesium ion pair pK values for CHA solution; thus, for example, bromoform is expected to be about as acidic towards CsCHA as fluorene. Attempted direct measurements with chloroform in CsCHA failed because of rapid decomposition and it was not possible to evaluate these predicted pK_{CsCHA} values. Nevertheless, the halogenated alkanes form a closely related system to the reference bicyclics in that their carbanions are expected to be localized and pyramidal; correspondingly, the derived values for pK_{CsCHA} are expected to be reliable to a few tenths of a pK unit.

Pentafluorobenzene is significant because both methanol kinetic data[36] and direct pK measurement with CsCHA[26] are available. The pK_{CsCHA} derived from Figure 3 is 1.6 units lower than the direct pK_{CsCHA} measurement. This result implies that the Brønsted correlation for the halobenzenes differs from that of the halogenated alkanes. The difference, which may be associated with the hybridization change at the acidic carbon, is not large. The difference observed, however, does suggest that the pK_{CsCHA} values in Table IV for the halogenated ethylenes derived from the kinetic data of Viehe[37] may also, therefore, be low by ~1.5 pK units.

Table IV. Equilibrium Acidities of Carbon Acids

Carbon acid	log $k_2^{T h}$	$pK_{CsCHA}{}^{i}$	Ref
$CF_3(CF_2)_6H$	-9.55^a	29.7	33
CF_3CF_2H	-7.7^{a-c}	28.2	34
$(CF_3)_2CFH$	−4.21	25.2	33
$(CF_3)_3CH$	$\sim 0.6^a$	~21	33
CHF_3	$-10.4^{a,c}$	30.5	33
$CHCl_3$	−3.19	24.4	32
$CHBr_3$	−1.14	22.7	32
CHI_3	−0.90	22.5	32
CF_3CHCl_2	-3.19^d	24.4	35
$CF_3CHBrCl$	−2.78	24.0	35
CF_3CHBr_2	−2.38	23.7	35
CF_3CHI_2	−2.85	24.1	35
C_6F_5H	−2.99	24.2 $(25.8)^e$	36
$CCl_2{=}CHBr$	$(-0.23)^f$	24.6	37
	$(-0.56)^f$	24.9	37
$CCl_2{=}CHCl$	$(-0.68)^f$	25.0	37
$CF_2{=}CHCl$	$(\sim -1.07)^f$	25.3	37
	$(-1.25)^f$	25.45	37
t-$CHBr{=}CHBr$	$(-1.96)^f$	26.0	37
$CCl_2{=}CHF$	$(-2.3)^f$	26.3	37
c-$CHCl{=}CHCl$	$(-2.85)^f$	26.8	37
t-$CHCl{=}CHCl$	$(-3.00)^f$	26.3	37
$CF_2{=}CHF$	$(-3.36)^f$	27.2	37
Fluorene	−6.11	26.8 $(23.0)^g$	30
9-Phenylfluorene	−4.24	25.3 $(18.5)^g$	30
Triphenylmethene	-12.92^a	32.6 $(31.5)^g$	39

[a] Extrapolated or estimated from results at other temperatures. [b] Assumed $k(CH_3OD)/k(CH_3OH)$ = 2.2 (ref 30). [c] Assumed k_H/k_D = 2.0, k_D/k_T = 1.4 (ref 33). [d] Assumed k_D/k_T = 1. [e] Experimental value, ref 26. [f] Log rate relative to $CHCl_3$ extrapolated to 0 °C. [g] Experimental value, ref 38. [h] $NaOCH_3$, MeOH, 0 °C. [i] From Figure 3.

Carbon acids having delocalized carbanions constitute an important further class. Fluorenes and polyarylmethanes give Brønsted correlations for methanol kinetics and CsCHA equilibria having slopes much less than unity.[30,39] The results in Table IV show, correspondingly, that the pK's$_{CsCHA}$ from Figure 3 are several units higher than the experimental values; that is, these compounds undergo kinetic proton exchange more slowly than their pK's would warrant, based on the localized systems. The delocalized systems show other characteristic properties, such as strong primary isotope effects, that suggest transition states for proton transfer intermediate between carbon acid and anion. A comparison of the series triphenylmethane, fluorene, and 9-phenylfluorene shows that the difference between the Figure 3 and experimental pK values increases as the pK decreases. This change is in the direction expected if the transition states for the less acidic compounds are more product-like.

Finally, it should be mentioned again that if the interaction of the carbanion with cesium cation is of comparable magnitude to hydrogen bonding in protic solvents, then the pK values derived in Table IV may actually be close to the true aqueous values. In this regard it is interesting that Margolin and Long[11] derive a pK of 24 for chloroform in aqueous solution, a value remarkably close to the 24.4 derived in Table IV.

Some of the compounds in Table IV have been assigned pK values previously. Klabunde and Burton[40] made some assignments based on hydrogen isotope exchange rates in a methanol-Me_2SO mixture. Their values are about 7–9 pK units lower than those in Table IV, but they caution that their assignments are crude and have relative significance only. However, for five compounds in both lists, a plot of the Kla-

Table V. Kirkwood–Westheimer Electrostatic Calculations

Cesium salt of	E_{elect}, kcal mol^{-1}
1	27.06
2	25.68
6	27.29
7	30.31
$(CF_3)_3CH$	29.65

bunde and Burton pK's vs. those in Table IV gives a relatively poor correlation. This result suggests caution in comparing kinetic acidities in aprotic solvents with equilibrium acidities in protic or ion-pair systems.[41] A number of pK values for halogenated carbon acids have also been assigned by Butin et al.[42] based on polarographic reductions of mercury compounds. Their values differ in many cases so radically from those in Table IV that no rational comparison is possible. The validity of the polarographic method for determining carbon acidities remains to be demonstrated.

Kirkwood–Westheimer Treatment. The inductive effect of a nonconjugated C–F bond in stabilizing a carbanion can be regarded to a first approximation as a simple electrostatic interaction between the carbanionic charge and the substituent bond dipole. The complex effects on Coulomb's law of substrate and solvent dielectric constant are reduced to calculable form in the Kirkwood–Westheimer model, in which the charges are imbedded in a continuous dielectric cavity contained within another continuous dielectric medium.[43] In our model calculations of cesium carbanide ion pairs the bicyclic carbon system was centered in a spherical cavity having $\epsilon = 2$ and the external medium was assigned the value $\epsilon = 4$, typical of amines. Separate calculations were made for each type of C–F bond with the anion and cation of the cesium carbanide ion pair. The point unit dipole was approximated by a pair of equal and opposite charges (20.83 units) 0.01 Å apart, located at the fluorine and aligned along the C–F bond. The ion pair was treated as point negative and positive charges 0.4 and 2.7 Å, respectively, from the carbanionic carbon. The spherical cavity was taken as the larger of the two spheres determined by the spherical surface 1.5 Å from the dipole or 1.0 Å from the positive charge (cesium). The calculations were made with a computer program written by Professor C. F. Wilcox[44,45] and subsequently modified by P. H. Owens and J. E. Schafer. The results are summarized in Table V. The results encompass three fluorinated bridgehead carbanions of bicyclo[2,2,1]-heptane derived from **1**, **2**, and **6**, the perfluorobicyclo[2.2.2]-octyl anion from **7**, and $(CF_3)_3C^-$.

The electrostatic energies of Table V are compared with the corresponding pK values in Figure 4. The three points of the bicycloheptyl series, **1**, **2**, and **6**, define a reasonably straight line whose intercept corresponds to a pK of bicyclo[2.2.1]-heptane itself of 51 for the bridgehead hydrogen. This value is in the expected range, since kinetic acidities of cycloalkanes compared to benzene lead to pK's in the 50's.[46] The directions of the deviations of points 1 and 6 from the line can be rationalized on the basis that a unit point dipole was used to represent all C–F bonds. Because of mutual polarization the effective substituent dipole should be greater for an isolated C–F and less for those in a CF_3 group compared to the value appropriate for the ring CF_2 groups. For this reason, calculations were not extended to **4** and **5**, since we were not sure what value to use for the C–Br or C–I substituent dipoles or where to put them. It should also be mentioned that the specific slope found in Figure 4 is of little significance. Other models in which the position of the dipoles was varied along the C–F bond give different slopes, but a similar pattern of points.[45]

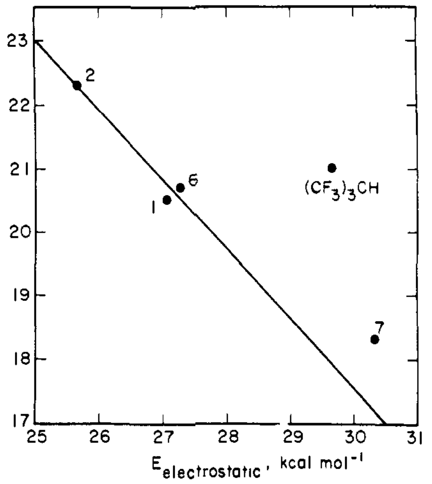


Figure 4. Comparison of pK_{CsCHA} values of fluorinated carbon acids with electrostatic ion-pair energies. The straight line shown is p$K_{\text{CsCHA}} = 1.102E_{\text{elect}} + 50.57$.

Although **7** is the most acidic compound measured in this study, it is still about 1 pK less acidic than predicted by Figure 4. The difference may well be due to a hybridization difference at the bridgehead carbons. For the corresponding bicyclic hydrocarbons the difference in s character of the two bridgehead C–H bonds as determined by $J_{^{13}C-H}$[47] corresponds to a ΔpK of at least 1.8, according to a kinetic acidity correlation.[48] The additional deviation from the line in Figure 4 of the point for $(CF_3)_3CH$ may stem in part from the greater uncertainty of the experimental pK for this compound, based as it is on a single approximate kinetic measurement, but also from the mutual polarization of fluorines in a CF_3 group, which reduces their effective substituent dipole. In this compound the effect is magnified compared to that in **6** because of the greater number of CF_3 groups and their closer proximity to the carbanionic carbon. The Kirkwood–Westheimer model is still a relatively crude model with important limitations; however, within these limitations, we conclude that a classical field effect interpretation is adequate to understand the qualitative effects of fluorine substituents in stabilizing this group of carbanions and there would appear to be no need to invoke any special effects of C–F no-bond resonance or "anionic hyperconjugation" or their MO equivalent of conjugation of lone pairs with C–F antibonding orbitals.[49]

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References and Notes

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(45) A more detailed description with mathematical derivations and parameter modifications may be found in ref 10. In particular, change in the location of the substituent point dipole, for example, from fluorine to the center of the C–F bond, changed the absolute values of the electrostatic energies but not their proportional relation as a function of structure. The results are also relatively insensitive to the dielectric constant of the outer medium; calculations using the dielectric constant of methanol for the outer medium gave similar relative ionization energies.
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Method for Estimating the Magnitude of Equilibrium Constants for Covalent Addition of Nucleophilic Reagents to Heteroaromatic Molecules[1]

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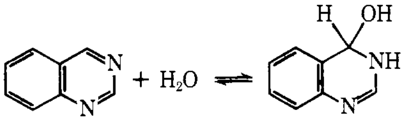
Abstract: A linear correlation is shown to exist between the first half-wave potentials for reduction at a dropping mercury electrode in 1 M HCl of quinazoline, purine, acridine, pyrimidine, 2-aminopyrimidine, and 2-amino-4-methylpyrimidine, and the logarithms of the equilibrium constants for covalent addition of HSO_3^- or SO_3^{2-} to a $>C{=}N^+<$ group of their conjugate acids. This correlation is used as the basis for a method of estimating the magnitude of the equilibrium constants for a wide variety of covalent additions to heteroaromatic molecules.

The covalent addition of nucleophilic reagents such as water,[2] bisulfite ion (HSO_3^-),[3-7] cysteine,[8] and electron-rich functionalities in enzymes[9,10] across a double bond in heteroaromatic molecules has been implicated as the initial step in a variety of chemical and biochemical processes. Typical covalent addition reactions are illustrated in Scheme I. Arriving at decisions about the operational probability of these reactions would be facilitated if ways could be found for predicting the value of the equilibrium constants for specific covalent addition reactions.

This paper discusses a correlation which is shown to exist between the first half-wave potentials for reduction at a dropping mercury electrode in 1 M HCl of a variety of heteroaromatic molecules which contain a $>C{=}N-$ group and

Scheme I

Covalent Addition of Water to Quinazoline[11]



Covalent Addition of HSO_3^- to Uracil[3]