Fluoromethylation

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The Nucleophilicity of Persistent α-Monofluoromethide Anions

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Dedicated to Professor George A. Olah

Abstract: *α-Fluorocarbanions are key intermediates in nucleophilic fluoroalkylation reactions. Although frequently discussed, the origin of the fluorine effect on the reactivity of α-fluorinated CH acids has remained largely unexplored. We have now investigated the kinetics of a series of reactions of α-substituted carbanions with reference electrophiles to elucidate the effects of α-F, α-Cl, and α-OMe substituents on the nucleophilic reactivities of carbanions.*

The nucleophilic addition of α-fluorocarbanions to electrophiles is a widely employed synthetic strategy for monofluoromethyl group incorporation.[1,2] It is documented that α-fluorine substitution of carbanions alters their Brønsted basicity,[3,4] thermal stability, nucleophilicity,[5a] as well as the reversibility of their additions to electrophiles.[5] The consequences of these factors, among others, lead to variable fluorine effects that have been described.[6] For example, while the fluoromalonate anion was believed to be a weaker nucleophile than malonate in the reaction with alkyl bromides,[7] the conjugate addition of α-fluorodinitromethide anion to methyl acrylate in water is about 2000 times faster than that of α-chlorodinitromethide or α-alkyldinitromethide.[8] Seminal work by Hu and co-workers showed that α-fluorodi(benzenesulfonyl)methane, $(PhSO_2)_2CFH$, reacts with enones faster than di(benzenesulfonyl)methane, $(PhSO_2)_2CH_2$.[9a] Similarly, the urea-catalyzed reactions between α-fluoro-α-nitro(benzenesulfonyl)methane and chalcones are also more rapid than those of nitro(benzenesulfonyl)methane.[9b,c] Furthermore, despite that the nucleophilic addition of $(PhSO_2)_2CFLi$ to benzaldehyde leads to the corresponding alcohol in high yield, no adduct was obtained in the reaction with $(PhSO_2)_2CHLi$ or $(PhSO_2)_2CClLi$ under similar reaction conditions.[9d] Although these observations provide valuable information on overall fluorine effects in nucleophilic fluoroalkylations, they may not reflect the nucleophilic reactivities of the fluorocarbanions, an intrinsic kinetic property by definition.[10] In particular, one may argue whether conclusions can be withdrawn based on forgoing results as several reactions were not performed under any specified conditions.[6d,e] To the best of our knowledge, no systematic study exists on how the reactivity of α-monofluoromethide derivatives contributes to the overall fluorine effect on nucleophilic fluoromethylating reactions. Herein, we disclose a quantitative evaluation of reactivity in a series of persistent α-monofluoromethide anions by comparing the nucleophilicity of these anions with that of their non-fluorinated analogues.

Therefore, we have studied the kinetics of the reactions of the α-substituted carbanions (**1X**–**4X**; Figure 1) with various reference electrophiles, including quinone methides (**5a**–**5h**, Table 1, for the characterization of strong nucleophiles) and benzhydrylium ions (**5i**–**5m**, for the characterization of weak nucleophiles). The linear free-energy relationship [Equation (1)],[11] where s_N and N are solvent-dependent nucleophile-specific parameters, and E is an electrophile-specific parameter, has previously been used to quantify the reactivities of a large variety of carbanions.[12] From the second-order rate constants determined in this work and the availability of well-established reference electrophiles with known E parameters, the solvent-dependent nucleophile-specific parameters (s_N and N) can be derived based on Equation (1).[12]

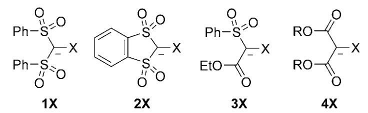

Figure 1. Carbanions **1X**–**4X**.

$$\log k_2\ (20\,^\circ\mathrm{C}) = s_N\,(N + E) \quad (1)$$

The reactions of **1X**–**4X** with **5** can be considered model reactions of widely exploited conjugate additions in nucleophilic fluoroalkylations. The CH acids **1X-H** to **4X-H** were chosen as carbanion precursors because of their synthetic

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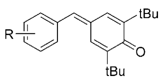
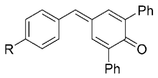
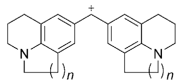
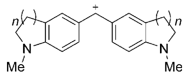
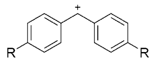
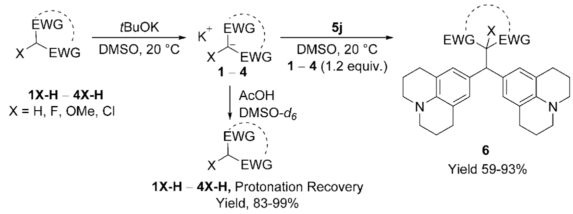
Table 1: Quinone methides **5a–5h** and benzhydrylium ions **5i–5m** employed as reference electrophiles.

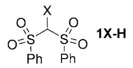
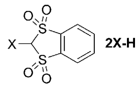
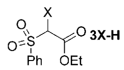
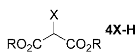
Electrophile			E	λ_{max} [nm]
	R = *p*-NMe$_2$	**5a**	−17.29	486
	R = *p*-OMe	**5b**	−16.11	393
	R = *p*-Me	**5c**	−15.83	371
	R = *m*-F	**5d**	−15.03	354
	R = *p*-NO$_2$	**5e**	−14.36	374
	R = NMe$_2$	**5f**	−13.39	533
	R = OMe	**5g**	−12.18	422
	R = H	**5h**	−11.87	384
	*n* = 1	**5i**	−10.04	630
	n = 2	**5j**	−9.45	635
	*n* = 1	**5k**	−8.76	627
	n = 2	**5l**	−8.22	618
	R = *N*-pyrrolidino	**5m**	−7.69	620

significance[13] and the persistence of the corresponding carbanions. We previously demonstrated the persistence of α-fluorodi(benzenesulfonyl)methide, $(PhSO_2)_2CF^-$, at ambient temperature.[2b] The persistence of the carbanions (**1X–4X**) was also confirmed by the high yield of **1X-H** to **4X-H** recovered after the protonation of the corresponding stock solution of **1X–4X** (83–99 %, determined by NMR spectroscopy; Table 2). The protonation recovery yields of **3F** and **4OMe** are lower than those of their combination reactions with **5j** by 5 % and 4 %, respectively.[14] These results are, to some extent, counterintuitive, as it may be expected that the protonation is a more facile reaction affording higher yields. Although conclusive explanations for this observation cannot be currently provided, the protonation experiments, at least of other anions, presumably provide evidence for the substantial persistence of these anions. It is worth noting that, despite the persistence of α-nitro(benzenesulfonyl)methide, its α-fluorinated counterpart readily decomposed. Thus, nitro(benzenesulfonyl)methide-derived anions were not included in the present study.

Pseudo-first order rate constants k_{obs} (s^{-1}) were obtained by fitting the mono-exponential function $A_t = A_0 \exp(-k_{obs} t) + C$ to the observed time-dependent absorbance A_t. To obtain the second-order rate constants k_2 ($L\,mol^{-1}s^{-1}$), each electrophile–nucleophile combination was measured typically at 3–5 different nucleophile concentrations by stopped-flow techniques (Table 3). Because the adducts of the reactions of **1X–4X** with **5j**-BF_4^- were isolated with relatively high yields (59–93 %, Table 2), the contribution of undesired side reactions to the observed kinetics cannot play a significant role. Moreover, the addition of a stoichiometric amount of 18-crown-6 did not change the reaction kinetics, indicating that potassium cation does not exert a noticeable effect on the observed rate constants (see the Supporting Information for details).[15] N and s_N parameters were derived

Table 2: Recovery of **1X-H-4X-H** from carbanions **1X–4X** and the reactions between carbanions **1X–4X** and benzhydrylium salt **5j**-BF_4^- in DMSO.



Carbanion precursors		Protonation recovery yield [%][a]	Reaction yield [%][b]
	X = H	–[c,d]	59
	X = F	91[d]	71
	X = OMe	89	83
	X = H	–[c]	73
	X = F	99	93
	X = OMe	93	70
	X = H	90	89
	X = F	83	88
	X = OMe	88	83
	X = F, R = Et	92	92
	X = Cl, R = Et	97	91
	X = OMe, R = Me	87	91

[a] The protonation was performed by adding AcOH to **1X–4X** in [D$_6$]DMSO. The yield of recovered material was determined by ^{19}F NMR or ^{1}H NMR spectroscopy using $PhCF_3$ or $PhCH_3$ as internal references, respectively (see the Supporting Information for details). [b] Isolated yield. [c] The persistency of the carbanions has been illustrated by the isolation of potassium carbanions (see the Supporting Information for details). [d] The persistency of the carbanions has been corroborated with single X-ray crystal structures in earlier work (Ref. [2b]).

from $\log k$ vs. E plots (Figure 2) according to the free energy relationship of Equation (1).[15]

In most cases, the s_N values vary only slightly for the different carbanions (second values in Figure 3) implying that their relative reactivities do not depend strongly on the nature of the electrophilic reaction partner. Thus, a typical ordering of reactivity can be established based on the magnitude of the nucleophilicity parameters N. Figure 3 illustrates the general

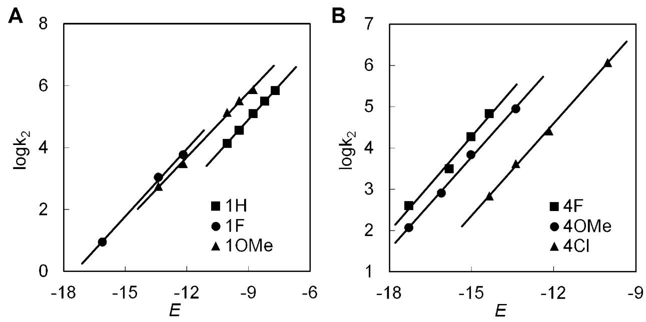
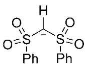
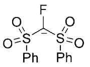
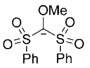
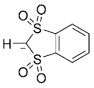
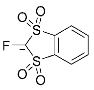
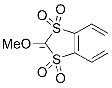
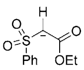
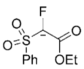
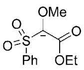
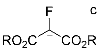
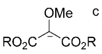
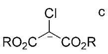


Figure 2. Plots of $\log k_2$ (DMSO, 20 °C) for the reactions of carbanions **1X** (A) and **4X** (B) with benzhydrylium ions **5** against the electrophilicity parameters E of **5**.

Table 3: Second-order rate constants k_2 for the reactions of carbanions **1X–4X** with reference electrophiles **5** in DMSO at 20°C.

1X–4X[a]	N (s_N)[b]	Electrophile	k_2 [$\mathrm{L\,mol^{-1}\,s^{-1}}$]
 **1H**	15.68 (0.74)	**5i**	1.38×10^{4}
		5j	3.68×10^{4}
		5k	1.27×10^{5}
		5l	3.22×10^{5}
		5m	7.01×10^{5}
 **1F**	17.46 (0.73)	**5b**	8.95×10^{0}
		5f	1.10×10^{3}
		5g	5.87×10^{3}
 **1OMe**	17.29 (0.70)	**5f**	5.59×10^{2}
		5g	3.07×10^{3}
		5i	1.38×10^{5}
		5j	3.27×10^{5}
		5k	7.44×10^{5}
 **2H**	16.06 (0.69)	**5i**	1.57×10^{4}
		5j	3.69×10^{4}
		5k	6.79×10^{4}
		5l	2.19×10^{5}
		5m	7.24×10^{5}
 **2F**	19.03 (0.58)	**5f**	1.78×10^{3}
		5g	9.45×10^{3}
		5i	1.76×10^{5}
		5j	3.10×10^{5}
		5k	8.73×10^{5}
 **2OMe**	17.36 (0.71)	**5f**	3.30×10^{2}
		5g	1.24×10^{4}
		5i	1.75×10^{5}
		5j	2.72×10^{5}
 **3H**	18.81 (0.59)	**5f**	1.43×10^{3}
		5g	9.65×10^{3}
		5i	1.41×10^{5}
		5j	3.05×10^{5}
		5k	9.13×10^{5}
 **3F**	20.51 (0.64)	**5c**	9.15×10^{2}
		5e	1.41×10^{4}
		5f	2.49×10^{4}
		5g	2.47×10^{5}
 **3OMe**	19.15 (0.59)	**5f**	2.53×10^{3}
		5i	2.20×10^{5}
		5j	5.30×10^{5}
 [c] **4F**	20.63 (0.76)	**5a**	3.98×10^{2}
		5c	3.13×10^{3}
		5d	1.89×10^{4}
		5e	6.84×10^{4}
 [c] **4OMe**	20.08 (0.74)	**5a**	1.19×10^{2}
		5b	8.05×10^{2}
		5d	6.80×10^{3}
		5f	8.89×10^{4}
 [c] **4Cl**	18.19 (0.74)	**5e**	6.80×10^{2}
		5f	4.17×10^{3}
		5g	2.60×10^{4}
		5i	1.18×10^{6}

[a] Carbanions were pregenerated by treating **1–4** with KO*t*Bu in DMSO. [b] Nucleophile-specific reactivity parameters N and s_N derived according to Equation (1). [c] R = Et for **4F** and **4Cl**, R = Me for **4OMe**.

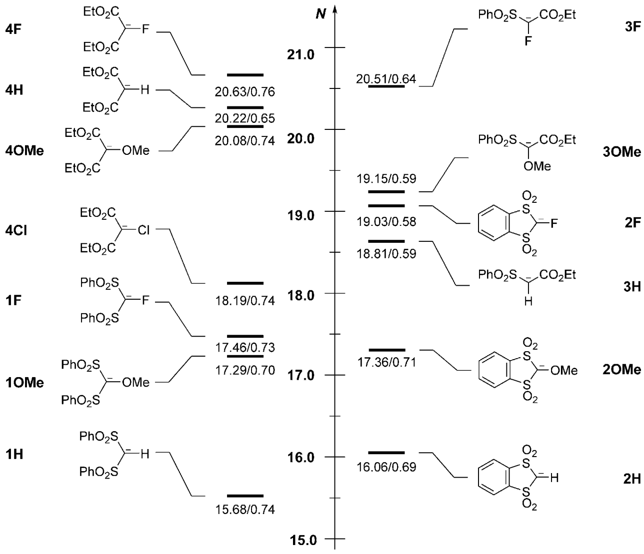


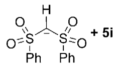
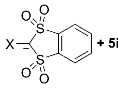
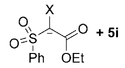
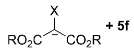
Figure 3. N and s_N of carbanions **1X–4X** according to Equation (1). The parameters were determined by applying $\log k_2 = s_N(N+E)$ with 3–5 proper reference electrophiles (Table 3, see the Supporting Information for details).

reactivity order $N_{4X} > N_{3X} > N_{2X} > N_{1X}$. Although the N of **4OMe** is slightly lower than that of **4H,** the higher s_N of **4OMe** implies that this species is more reactive than **4H** towards strong nucleophiles. Replacement of one benzenesulfonyl group in **1X** by an ester group (**3X**) in general increases the nucleophilic reactivity by approximately 3 units. Malonate anions (**4X**) are more reactive than the corresponding di(benzenesulfonyl)methide anions (**1X**). The influence of anionic carbon geometry on nucleophilicity was also observed as the cyclic di(sulfonyl)methide anions (**2X**) are more reactive than their acyclic analogues **1X**. The relative nucleophilicities of the parent anions, **4H** (20.22) > **1H** (15.68), is in agreement with their corresponding Brønsted basicities in DMSO (pK_{aH}(**4H**) = 16.4 vs. pK_{aH}(**1H**) = 12.2).[3]

In all series **1X** to **4X**, an increase of N is observed by replacing X = H with X = F. Because the reactivity of a nucleophile toward an electrophile is related to both N and s_N, we also compared the measured rate constants (k_2) of α-substituted carbanions with respect to a specific electrophile. Table 4 shows that in all reaction series α-fluorine substitution activates nucleophiles by approximately one order of magnitude, while α-methoxy substitution exerts a similar effect in the di(sulfonyl)-substituted carbanions **1X** and **2X** and a significantly smaller activation in series **3X** and **4X**. α-Chlorine substitution was only studied for compounds **4X** and results in a 7-fold decrease in the reaction rate. Thus the activation Gibbs energy ($\Delta G^{\neq}$) varies less than ±2 kcal mol^{-1} when X = H is replaced by F, Cl, or OMe in the anions **1X** to **4X**.

A stronger α-fluorine effect was previously observed among dinitromethides: α-fluorinated species reacts with methyl acrylate approximately 2000 times faster than α-chloro- and α-alkyl-dinitromethides.[8] This reactivity enhancement has been ascribed to the increased pyramidalization of the anionic carbon induced by the electron-with-

Table 4: Rate constants k_2 [$L\,mol^{-1}\,s^{-1}$] of the reactions of the carbanions **1X**–**4X** with the reference electrophiles **5i** or **5f** in DMSO at 20 °C.

		 **1X**		 **2X**		 **3X**		 **4X**	
X	σ_I[a]	$k_2/10^4$	$\Delta\Delta G^{\ddagger}$ kcal mol^{-1}	$k_2/10^4$	$\Delta\Delta G^{\ddagger}$ kcal mol^{-1}	$k_2/10^4$	$\Delta\Delta G^{\ddagger}$ kcal mol^{-1}	$k_2/10^4$	$\Delta\Delta G^{\ddagger}$ kcal mol^{-1}
H	0.00	1.38	0.00	1.57	0.00	14.1	0.00	2.96[c]	0.00
F	0.50	24.2[b]	−1.67	17.6	−1.41	502[b]	−2.08	30.9[b]	−1.37
OMe	0.23	13.8	−1.34	17.5	−1.40	22.0	−0.26	8.89	−0.64
Cl	0.47	–[d]		–[e]		–[e]		0.417	+1.14

[a] Polar substituent constant measuring the inductive effect (Ref. [16]). [b] The value is calculated by applying the known *E*-value of the reference electrophile to the established Equation (1). [c] The k_2 of **4H** is obtained from Ref. [12b]. [d] Undesired α-hydrodechlorinated product formed likely through nucleophilic attack on Cl (see the Supporting Information for details). [e] Not determined due to the limited synthetic availability.

drawing effect of the α-substituent,[8,17] which, however, cannot account for the decreased reactivity of **4Cl** (Table 4, $\sigma_{I(Cl)} = 0.47$). Such an observation indicates the likely participation of both steric and electronic effects in the overall α-substituent effect. The limited number of α-substituents investigated in the present study, however, refrains us from providing a conclusive evaluation of the importance of each component.

To explain the origin of the α-substituent effect, density functional theory (DFT) calculations were performed at the PCM-B3LYP/6-311++G(2d,2p)//6-31+G(d,p) and the PCM-ωB97xD/6-311++G(2d,2p)//6-31+G(d,p) levels of theory in conjunction with an implicit model for DMSO solvent effects (via Gaussian 09's standard PCM model, see the Supporting Information for details). The calculated relative activation energies, although showing a trend consistent with the experimental outcomes, do not linearly correlate with observed $\Delta\Delta G^{\ddagger}$ (Supporting Information, Figure S2). Considering the significant computational challenges associated with reliably pinning down the small energy differences (ca. 1 kcal mol^{-1}) responsible for the observed α-substituent effect, a meaningful mechanistic insight may not be feasibly gained by routinely used DFT calculations. Similar challenges have been encountered in the mechanistic investigation of the closely related α-effect.[18]

In conclusion, the reactivity of a series of α-heteroatom-substituted carbanions has been investigated through kinetic experiments. Despite the high electronegativity of fluorine, α-fluorine substitution enhances the reactivity of several α-monofluorinated carbanions. In contrast, α-chlorine substitution reduces the nucleophilic reactivity of **4H**. Different overall fluorine effects are still expected if, for example, deprotonation of pronucleophiles is rate determining or incomplete (due to the use of weak bases) or when thermal decomposition of carbanions becomes significant. Related phenomena have been intensively investigated in the seminal work by Hu and co-workers. Currently, it cannot be predicted whether α-monofluorine substitution increases the reactivity of other carbanions, such as fluoro(benzenesulfonyl)methide and even simpler fluoromethide.

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