ORGANIC
LETTERS

2013
Vol. 15, No. 9
2210–2213

# Enabling Nucleophilic Substitution Reactions of Activated Alkyl Fluorides through Hydrogen Bonding

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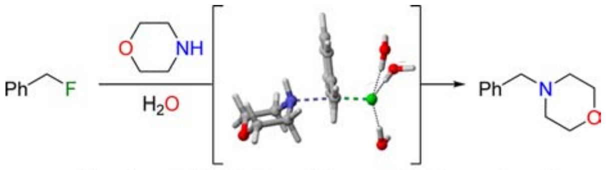
**Received March 21, 2013**

## ABSTRACT



***activation of the C-F bond through hydrogen bonding***

**It was discovered that the presence of water as a cosolvent enables the reaction of activated alkyl fluorides for bimolecular nucleophilic substitution reactions. DFT calculations show that activation proceeds through stabilization of the transition structure by a stronger F···$H_2O$ interaction and diminishing C–F bond elongation, and not simple transition state electrostatic stabilization. Overall, the findings put forward a distinct strategy for C–F bond activation through H-bonding.**

Fluoride has the worst leaving group ability of the halogen series in bimolecular nucleophilic substitution ($S_N2$) reactions on alkyl halides (leaving group ability: $I^- > Br^- > Cl^- \gg F^-$). In fact, relationships between the reaction rate and both the bond strength and the anion stability have been established.[1] The carbon–fluorine bond is the strongest single carbon–halogen bond (the bond dissociation energy for $CH_3$–F is 115 kcal/mol compared to 57.6 kcal/mol for $CH_3$–I),[2] and fluoride is the least stable anion of the halogen series, as estimated by the p$K_a$ of its conjugated acid (p$K_a$ ($H_2O$) HF = 3.2 compared to p$K_a$ ($H_2O$) HI ≈ −10).[1b,3] As such, alkyl fluorides are virtually inert toward nucleophiles under neutral or basic reaction conditions.[4,5] Nonetheless, reactions through activation with strong Brønsted acids, Lewis acids, and carbocations or silylium ions have been described, although most of them seem to proceed through an ionization mechanism, i.e. a unimolecular nucleophilic substitution ($S_N1$) reaction.[4b] Finally, the use of transition metals has also been shown to be a viable approach for the activation of C–F bonds, although in these cases, mechanisms are often substrate-dependent.[4b] Therefore, the metal-free activation of C–F bonds under mild and neutral conditions remains a formidable yet unmet challenge for organic chemistry.

A fluorine atom, when bonded to a carbon, can behave as a Lewis base. As such, interaction of C–F bonds with other Lewis acidic atoms such as Li, Al, B, Si, and others has been characterized.[6] Occasionally, these interactions

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have been used either as a stereocontrol element or to facilitate the departure of the fluoride.[6] One controversial interaction of C−F bonds is the H-bond[7] where the fluorine atom acts as a H-bond acceptor.[6,8] While explorations of crystal structure databases have yielded only rare examples of short contacts which are consistent with C−F···H bond,[9] recent spectroscopic[10] and computational[11] evidence suggest that H-bonds with organic fluorine are possible in solution. In any case, C−F···H bonds would be considered weak interactions,[8,12] as a C($sp^3$)−F···H−O H-bond has been calculated to be ca. 2.4 kcal/mol (compared to ca. 4.8 kcal/mol for a C−O···H−O interaction).[9a]

In light of these studies, we wondered if H-bond donor (HBD) solvents such as water could be used to facilitate the departure of the fluoride in substitution reactions. In addition, it is well-known that fluoride forms a strong H-bond with water (ca. 24 kcal/mol), which would assist in increasing the stability of the fluoride ion.[13] Overall, this could enable the nucleophilic substitution reaction of alkyl fluorides using H-bonding as a distinct activation strategy.[14] Herein, we report our initial findings that the use of water, as a cosolvent, can be used to activate C−F bonds and, thus, allow activated alkyl fluorides to participate in substitution reactions.

Investigations on the effect of the solvent were performed using 4-phenylbenzyl fluoride (**1a**) as the substrate and morpholine as the nucleophile, at 70 °C with a fixed reaction time of 4 h (Figure 1). Using pure water, a low but gratifying conversion of 7% was obtained. Performing the reaction in anhydrous ethanol or *i*-PrOH also gave low but quantifiable conversions of 7% and 5% respectively. Our results can be rationalized using the α scale of solvent H-bond donor acidities which describes the ability of the solvent to donate a proton in a solvent-to-solute H-bond.[15] In this case, even though water is a better HBD ($\alpha = 1.17$) than EtOH ($\alpha = 0.83$) or *i*-PrOH ($\alpha = 0.76$), the reaction was heterogeneous due to poor solubility of the substrate in water, which may explain the low conversion observed. Using *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), and acetonitrile ($CH_3CN$), three commonly used aprotic polar solvents for $S_N2$ reactions, no conversion was observed. Notably, in pure DMF, no reaction was noticeable even after 7 days at 70 °C. However, since DMF and DMSO are not HBDs ($\alpha = 0$) and $CH_3CN$ is a very poor HBD ($\alpha = 0.19$), these results were anticipated. As a point of comparison, both the corresponding benzyl chloride and bromide reacted completely under the same reaction conditions in DMF.[16]

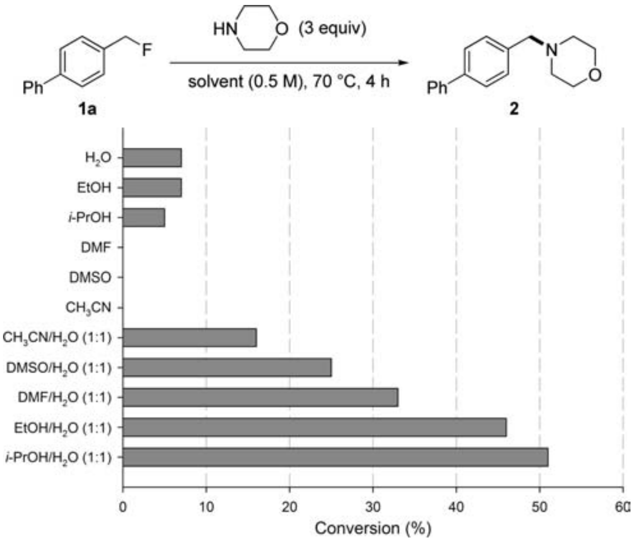

**Figure 1.** Evaluation of the effect of the solvent on the $S_N2$ reaction of benzyl fluoride **1a** with morpholine. Conversions of **1a** to **2** were estimated by $^1H$ NMR of the crude mixture.[16]

To circumvent the solubility issue encountered with water, mixtures of organic solvent/water were next explored. Interestingly, aprotic polar solvents, when mixed with equal amounts of water, provided significant conversions (16−33%). Unexpectedly, as protic solvents are usually regarded as inferior solvents for $S_N2$ transformations, alcohol/$H_2O$ (1:1) mixtures gave the best conversions over 4 h with 46% and 51% for EtOH and *i*-PrOH, respectively. Exploration of other ratios of alcohol/$H_2O$ did not provide any improvement. Finally, increasing the reaction time to 18 h resulted in a complete conversion and an excellent isolated yield of 96%.[16]

After observing this superb enhancement of the fluoride leaving group ability, we wondered if the effect was applicable to all halogens (i.e., no specific C−F activation). We therefore conducted a competition experiment (eq 1) between chloride and fluoride. Typically, fluoride is considered unreactive under $S_N2$ conditions; we thus expected to be able to compare the approximate reactivities of those

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(14) For the activation of a C($sp^3$)−F bond resulting from an intramolecular $S_N2$ process assisted by noncovalent interactions, see: Gonzalez-Duarte, P.; Nova, A.; Mas-Balleste, R.; Ujaque, G.; Lledos, A. *Chem. Commun.* **2008**, 3130.

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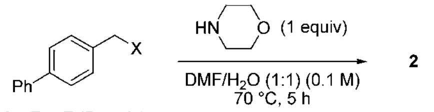
two leaving groups for the first time. NMR analysis of the crude reaction mixture suggests a $k_{Cl}/k_F \approx 5$. This contrasts drastically from the same experiment performed in the absence of water, where a $k_{Cl}/k_F > 49$ was estimated, as no conversion of the fluoride was noticeable even when chloride had reacted completely. These results with benzylic substrates suggest a significant change in the reactivity profile of fluoride under our conditions. Since C−Cl bonds are very weak hydrogen-bond acceptors,[12] we postulate that the observed change in reactivity is mostly due to the increase of reaction rate of the benzylic fluoride (*vide infra*). Together, our numbers would imply an increase of reactivity of at least 10-fold for **1a** in the presence of water.



**1a**; R = F (5 equiv)
**1b**; R = Cl (5 equiv)

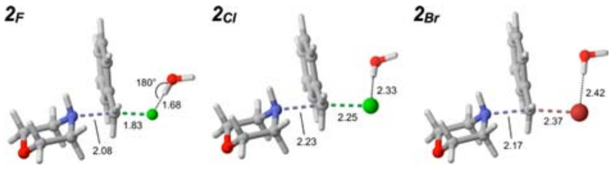
(1)

To gain more insight into the precise role of water in activating the C−F bond, we performed DFT calculations. For the investigation of the activation of C($sp^3$)−F bonds by water, we selected DFT model M06-2X.[17] This functional was found to accurately model noncovalent interactions and activation barriers. All the structures presented were optimized at the M06-2X/6-31+G(d,p) level. To account for the importance of the solvation effect in the reaction and to obtain realistic structures, we performed the geometry optimizations by including the SMD implicit solvation model[18] for *i*-PrOH, which has been found experimentally to be the best cosolvent.

Due to fluorine having a higher electronegativity than other halogens, we might expect the $S_N2$ transition structures to present a larger charge separation. To assess this, the transition structures of the $S_N2$ reaction of morpholine with the different benzyl halides were calculated using the described method, and the solvation free energies for the corresponding benzyl halide and transition structure were evaluated for *i*-PrOH, $H_2O$, and DMF. Unsurprisingly, larger solvation free energies in all solvents were found for the transition structure involving benzyl fluoride ($\Delta G_{solv}$ TS$^\ddagger$ > −24.9 kcal/mol). In contrast, almost identical solvation free energies were found for the different benzyl halide reagents.[16] Interestingly, almost identical relative solvation energies ($\Delta\Delta G$) are found for the benzyl fluoride in all solvents ($\Delta\Delta G_{solv}$ = ca. −21.7 kcal/mol), despite the drastic difference in reactivity of organofluorides in *i*-PrOH/$H_2O$ compared to DMF. These results indicate that the reactivity enhancement does not simply originate from electrostatic stabilization of the transition structures through the dielectric properties of the reaction solvent(s).

To evaluate the actual effect of HBD solvents on activation, we optimized the transition structures by including an explicit water molecule. Then we performed an activation strain analysis using the gas phase energies (Table 1). This model has been developed to understand some factors controlling different chemical reactions.[19]

**Table 1.** DFT Analysis of the $S_N2$ Reaction of Benzyl Halides with Morpholine: Strain Model Analysis of the $S_N2$ Reaction Transition Structures Including Explicit Water Molecules[a]



| TS$^\ddagger$ | $\Delta E_{gas}{}^\ddagger$ | $\Delta E_{dist}$ BnX | $\Delta E_{dist}$ NuH | $\Delta E_{dist}$ $H_2O$ | $\Delta E_{int}$ BnX−NuH | $\Delta E_{int}$ BnX−$H_2O$ |
|---|---|---|---|---|---|---|
| $\mathbf{1_F}$ | 34.8 | 39.6 | 1.0 | | −5.9 | |
| $\mathbf{2_F}$ | 21.7 | 36.1 | 1.0 | 0.2 | −4.6 | −11.1 |
| $\mathbf{1_{Cl}}$ | 18.9 | 22.8 | 1.0 | | −4.8 | |
| $\mathbf{2_{Cl}}$ | 10.9 | 21.3 | 0.9 | 0.1 | −4.4 | −7.0 |
| $\mathbf{1_{Br}}$ | 14.6 | 21.5 | 1.0 | | −7.8 | |
| $\mathbf{2_{Br}}$ | 7.0 | 19.3 | 1.0 | 0.1 | −7.0 | −6.4 |

[a] Energies are in kcal/mol. $\Delta E_{gas}{}^\ddagger$ and $\Delta E_{int}$ (BnX−$H_2O$) are BSSE corrected. $\mathbf{1_x}$ refers to the transition states without a water molecule.[16]

In this kind of analysis, the activation energy ($\Delta E^\ddagger$) is decomposed into the amount of energy needed to distort the isolated reactants up to their transition structure (TS$^\ddagger$) geometries (i.e., distortion energy, $\Delta E_{dist}$) and the energy of interaction between these reactants at the TS$^\ddagger$ geometry (i.e., interaction energy, $\Delta E_{int}$). It is clear from the analysis that the distortion energy of the benzylic halides ($\Delta E_{dist}$ BnX) is the major contributing factor in the activation barrier height of the nucleophilic substitution reaction. It is noticeably higher for BnF, in accordance with the relative C−X bond strengths. In all cases, stabilization is observed with the introduction of the water molecule, with the largest amplitude found for $\mathbf{2_F}$ vs $\mathbf{1_F}$. The other general effect observed on the structures is that a longer C−N bond and a shorter C−X bond form, indicative of an earlier transition structure. This is demonstrated clearly by the decrease of the distortion energy of the benzyl halides and interaction energies between morpholine and the benzyl halides ($\Delta E_{int}$ BnX−NuH). The amplitude of the decrease in distortion energy of BnX is the largest for BnF, leading to the most effective stabilization. In contrast, the $\Delta E_{dist}$ of the morpholine (NuH) and the water molecule are almost identical for all the transition structures.

Now, looking at the interaction energies, we can find more insight into the role of water in the activation of the C($sp^3$)−F bond. Indeed, one can notice that the interaction between BnX and the water molecule is dependent on the

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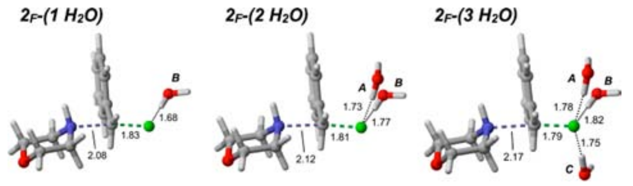
nature of X, being more important for BnF ($\Delta E_{\text{int}} = -11.1$ kcal/mol) than for BnCl ($\Delta E_{\text{int}} = -7.0$ kcal/mol) and BnBr ($\Delta E_{\text{int}} = -6.4$ kcal/mol). As a point of interest (i.e., BnF), the $F \cdots O(H_2O)$ distance is 2.66 Å and the $F \cdots H{-}O(H_2O)$ angle is 180°, indicative of a medium-to-strong H-bond. The H-bond strength in transition state $\mathbf{2_F}$ is 2-fold greater than that calculated for the equivalent $F \cdots H_2O$ interaction in the starting material (−4.6 kcal/mol). To evaluate the potential of stabilization of multiple HBD molecules, transition structures involving 1 to 3 water molecules were computed. The results are summarized in Table 2. These molecules bind with similar strength to the leaving fluoride atom in the transition structure, effectively reducing the distortion energy required for BnF down to 31.6 kcal/mol (Table 2).[16] Unsurprisingly, similar stabilization is observed using explicit *i*-PrOH molecules. However, considering the more intricate H-bonding network of water molecules, it is understandable that the latter is a better HBD solvent. This is further supported by the lower free energy of solvation of the parent fluoride anion in water in comparison to a protic solvent such as methanol and ethanol.[20]

**Table 2.** Effect of Water Molecules on the Stabilization of the Transition Structure of $S_N2$ Reaction with BnF[a]



| | TS‡ | | | |
|---|---|---|---|---|
| | $\mathbf{1_F}$ | $\mathbf{2_F}$-(1 $H_2O$) | $\mathbf{2_F}$-(2 $H_2O$) | $\mathbf{2_F}$-(3 $H_2O$) |
| $\Delta H^{\ddagger}$ | 22.4 | 16.8 | 12.3 | 8.8 |
| $\Delta E_{\text{dist}}$ BnX | 39.6 | 36.1 | 33.7 | 31.6 |
| $\Delta E_{\text{int}}$ $H_2O_A$ | – | – | −11.1 | −9.2 |
| $\Delta E_{\text{int}}$ $H_2O_B$ | – | −11.1 | −10.0 | −8.7 |
| $\Delta E_{\text{int}}$ $H_2O_C$ | – | – | – | −8.6 |

[a] Energies are in kcal/mol. Distances are reported in Å. $\mathbf{1_F}$ refers to the transition state without a water molecule.[16]

Overall, the combination of stabilization from the lowering of the distortion energy for BnF in synergy with the stronger $F \cdots H_2O$ interactions in the transition structure compared to the starting material is a valid rationale to explain the activation effect of water as a cosolvent.

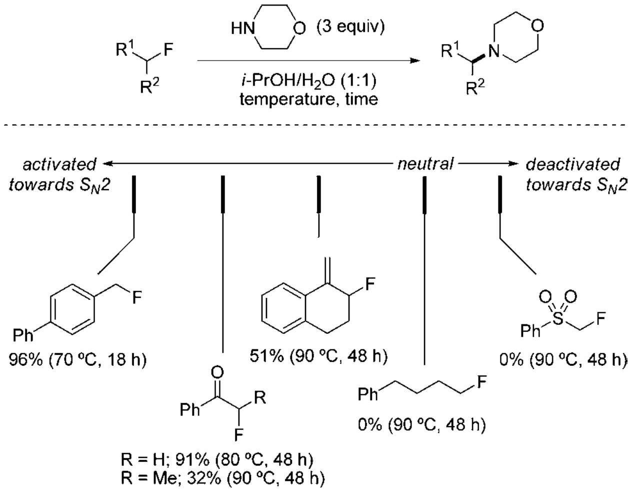


**Figure 2.** Establishing the reactivity of various alkyl fluorides.[16]

Finally, we evaluated the reactivity of other alkyl fluorides toward morpholine under our reaction conditions in order to establish a reactivity profile (Figure 2).[16] The observed reactivity for the various alkyl fluorides parallel the order of reactivity established for α-substituted alkyl halides in $S_N2$ reactions where the order has been shown to be benzyl halides > α-haloketones > allylic halides > alkyl halides > α-halosulfone.[21] As such, our results suggest that, under the current reaction conditions, only activated alkyl fluorides may be used. Interestingly, this trend is also reflected in the experimental conditions employed since, for a less activated system, more forcing conditions were required. Preliminary studies indicate that nucleophiles other than morpholine can also be employed. Indeed, benzyl fluoride **1a** reacted successfully with a number of *N*-, *O*-, *S*-, and *C*-nucleophiles.[16]

In conclusion, we have discovered that the presence of water as a cosolvent enables the reaction of activated alkyl fluorides in bimolecular nucleophilic substitution reactions. DFT calculations show that activation proceeds through stabilization of the transition structure by a stronger $F \cdots H_2O$ interaction and diminishing C−F bond elongation, and not simple transition state electrostatic stabilization. Overall, our findings put forward a distinct strategy for C−F bond activation through H-bonding. We are presently exploring practical applications of our findings and exploring the effect of using stronger HBDs.

**Acknowledgment.** This work was supported by the Canada Research Chair Program, the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation, the FRQNT Centre in Green Chemistry and Catalysis, PROTEO, the Université Laval and the University of Sherbrooke. Computational resources were provided by Calcul Québec and Compute Canada.

**Supporting Information Available.** Full experimental details, DFT calculations, and $^{1}H$, $^{13}C$, and $^{19}F$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.