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Carbon−Fluorine Activation in the Gas Phase: The Reactions of Benzyl C−F Bonds and Silyl Cations

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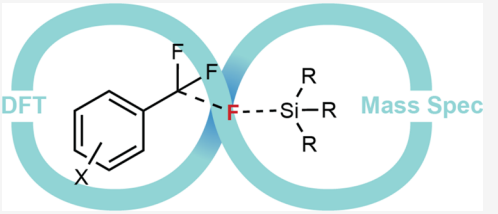
ABSTRACT: The activation of C−F bonds figures largely in both fundamental and applied chemical processes. Herein the activation of benzyl C−F bonds by silyl cations is examined both computationally and experimentally in the gas phase. The experimental rate constant values obtained herein have not heretofore been measured and provide insight into the intrinsic ability of silyl cations to activate C−F bonds. Trends in reactivity and correlations between theoretical and experimental data are discussed in the context of C−F bond cleavage.



INTRODUCTION

The carbon−fluorine bond is the strongest covalent single bond that carbon forms with any element.[1−6] The C−F bond's singular nature is attributed to fluorine's small size and high electronegativity, which result in a short, highly polar bond that has low polarizability.[3] The unique nature of the C−F bond has both advantages and disadvantages. The high stability of the bond makes it feature prominently in many areas of synthetic chemistry, including in the design of new materials, polymers, drugs, and pesticides.[7−13] However, the reverse side of such stability is the persistence in the environment of compounds containing C−F bonds. Hydrofluorocarbons are potent greenhouse gases, and fluorochlorocarbons are known to deplete the ozone layer.[14−16] Furthermore, the prevalence of poly- and perfluoroalkyl substances (PFAS) has also raised concerns about the environmental and human health impact of PFAS exposure.[17−19] Thus, the activation of C−F bonds is of interest from both fundamental and practical points of view.

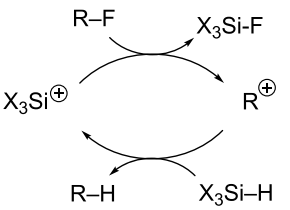
The simplest transformation to remove a C−F bond would be to convert it to a C−H bond, in a hydrodefluorination reaction (HDF, eq 1). However, the use of hydrogen gas yields hydrogen fluoride as a product, which is highly toxic and difficult to handle.

$$R{-}F + H_2 \rightarrow R{-}H + HF \quad (1)$$

One way around this was discovered by Aizenberg and Milstein, who used rhodium catalysts and organosilicon compounds, which led to a more thermodynamically favorable reaction, as well as a less toxic byproduct (eq 2, X = alkyl, aryl).[20]

$$R{-}F + X_3Si{-}H \xrightarrow{\text{catalyst}} R{-}H + X_3Si{-}F \quad (2)$$

Subsequent early HDF work focused on catalysis with transition metals; more recently, a novel approach using Lewis acids was developed independently by Ozerov and Müller.[21,22] These groups proposed utilizing Lewis acid abstraction of fluoride instead of a redox reaction to effect the challenging C−F cleavage. They successfully carried out nonredox C−F activation under ambient conditions using a silylium Lewis acid catalyst (eq 3). Ozerov and co-workers



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have noted, "It is a matter of some debate what should be considered a "free" X_3Si^+ cation in the condensed phase"; finding a counterion that is both weakly coordinating yet stable enough not to decompose in the presence of the strong silylium Lewis acid proved challenging.[21] Ozerov and co-workers ultimately utilized $[B(C_6F_5)_4]^-$ and halogenated monocarboranes as weakly coordinating anions that could support silyl cation C−F activation.[21,23,24] Thus, with condensed phase HDF, the generation of a stabilized cationic silicon catalyst with a suitable counteranion was key.[5,25−28]

Because of the challenges associated with generating a stable silyl cation and a weakly coordinating counteranion in solution, we became intrigued with the prospect of generating a true "free" silyl cation in the gas phase and utilizing it for C−F activation. Prior gas phase work is limited to a study by Krause and Lampe in the 1970s, wherein the reactions of CF_4 and

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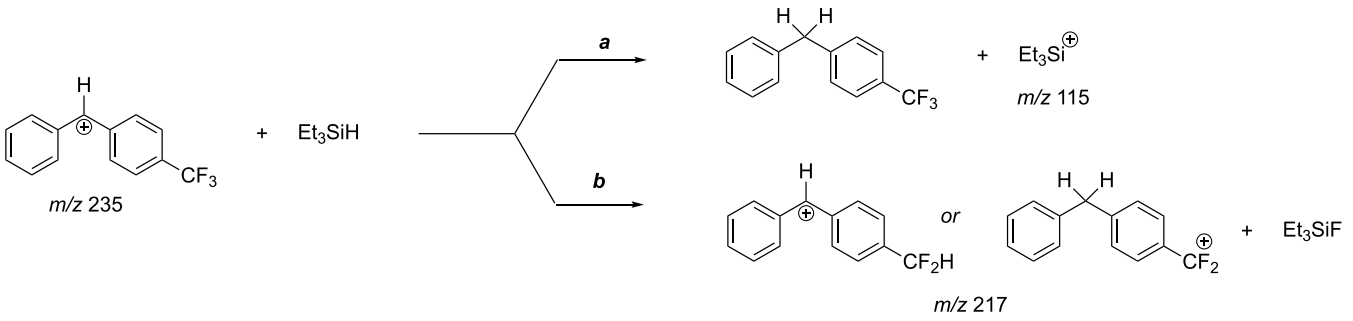

Figure 1. Reactivity of trifluoromethylbenzhydryl cation with triethylsilane.

SiH_3^+, as well as CF_3^+ and SiH_4 were examined *in vacuo*, establishing that silicon has a higher affinity than carbon for the fluorine in this system.[29] This result lends support to the idea that C−F activation by silyl cations should be possible in the gas phase. Furthermore, in the absence of solvent or counterion, the intrinsic reactivity of the free silyl cation as an effective C−F activator could be examined.

As a first step toward understanding intrinsic C−F activation, we examine herein the reactions of a series of (trifluoromethyl)benzene substrates with various silyl cations, to assess the facility of gas phase C−F activation, using both calculations and experiments.

RESULTS AND DISCUSSION

Our C−F activation studies started serendipitously, while examining gas phase hydricity.[30,31] In these studies, we followed the reaction of trifluoromethyl benzhydryl cation with triethylsilane, in order to track abstraction of hydride from the silane by the benzhydryl cation (path a, Figure 1).[30,31] However, in addition to this hydride transfer, we also observed the mass-to-charge ratio (m/z) 217, which corresponds to cations formed by F/H exchange from the cation to the silane (path b, Figure 1). Evidence of subsequent hydrodefluorinations was also found.

This result piqued our interest greatly, especially in light of the prior condensed phase work utilizing silyl cations to catalyze HDF.[21,22] In the condensed phase, one can never generate a free silyl cation; there must always be a counteranion, which will decrease how "cationic" the silylium is.[21] We were intrigued by the tantalizing possibility of generating the bare silyl cation in the gas phase and assessing its inherent reactivity.[29,32]

To this end, we designed a study that would probe the first step of HDF, whereby the silyl cation enables C−F bond breakage (Figure 2). In choosing substrates to show proof-of-

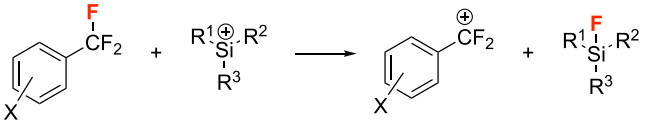

Figure 2. Reactions studied herein.

concept, we focused on a series of (trifluoromethyl)benzenes (Figure 3), which would allow us to track trends in reactivity through 3- and 4-aryl substitution. The silyl cations in Figure 4 were chosen as probable reactive species that could help us understand alkyl substitution effects.

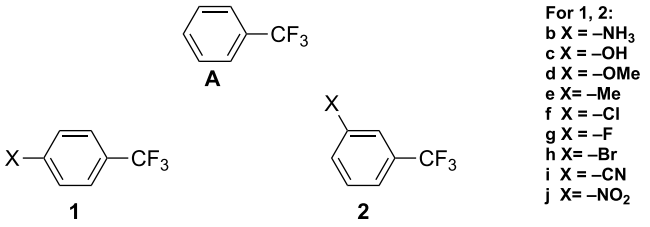

Figure 3. Substituted (trifluoromethyl)benzenes studied herein.

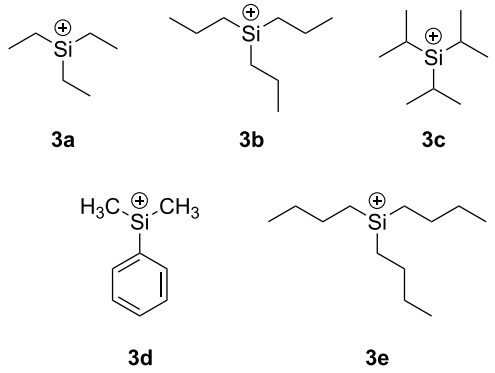

Figure 4. Silyl cations studied herein.

Calculations. We first calculated the enthalpy of reaction to assess whether the thermochemistry of these reactions would be favorable. These results are compiled in Table 1.

4-Substituted (Trifluoromethyl)benzenes. The 4-substituted (trifluoromethyl)benzenes **1** have the same trend in ΔH regardless of which silylium is used; that is, the exothermicity of **1** with any of the silyl cations **3** follows the trend **1b** (−NH_2) > **1d** (−OMe) > **1c** (−OH) > **1e** (−Me) > **A** (−H) > **1 f,g,h** (−Cl, − F, − Br) > **1i** (−CN) > **1j** (−NO_2), where **1b** produces the most exothermic reaction and **1j** is the least exothermic (Table 1). This trend is commensurate with expectations based on electron-withdrawing versus electron-donating ability; as the product of the reaction is a (difluoromethyl)benzyl cation (Figure 2), one would expect electron donating groups to favor reaction. Indeed, the (trifluoromethyl)benzenes with more electron donating groups (e.g., −NH_2, −OMe) yield reactions that are more favorable enthalpically, while those with more electron withdrawing groups (e.g., halides, −NO_2) are less favorable enthalpically. Plots of the ΔH values versus Hammett σ^+ constants are generally linear, as would be expected; one example, with Et_3Si^+ (**3a**) is shown in Figure 5.[33,34]

3-Substituted (Trifluoromethyl)benzenes. We also calculated the enthalpy of reaction for the 3-substituted

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Table 1. Calculated Enthalpies of Reaction between Substituted (Trifluoromethyl)benzenes and Silyl Cations[a]

	ΔH_{calc} (kcal/mol)[b]				
reactants	3a	3b	3c	3d	3e
A	−19.1	−15.5	−15.7	−13.9	−10.3
1b (−NH_2)	−39.8	−36.1	−36.3	−34.6	−31.0
1c (−OH)	−28.7	−25.0	−25.2	−23.5	−19.9
1d (−OMe)	−32.2	−28.5	−28.7	−27.0	−23.4
1e (−Me)	−25.0	−21.3	−21.5	−19.8	−16.2
1f (−Cl)	−18.3	−14.7	−14.9	−13.2	−9.6
1g (−F)	−18.6	−14.9	−15.1	−13.4	−9.8
1h (−Br)	−18.6	−14.9	−15.2	−13.4	−9.8
1i (−CN)	−8.0	−4.3	−4.5	−2.8	0.8
1j (−NO_2)	−5.2	−1.5	−1.8	0.0	3.6
2b (−NH_2)	−23.8	−20.2	−20.4	−18.6	−15.0
2c (−OH)	−19.0	−15.4	−15.6	−13.9	−10.3
2d (−OMe)	−21.3	−17.7	−17.9	−16.1	−12.6
2e (−Me)	−21.9	−18.3	−18.5	−16.7	−13.1
2f (−Cl)	−14.2	−10.6	−10.8	−9.1	−5.5
2g (−F)	−13.6	−10.0	−10.2	−8.4	−4.8
2h (−Br)	−14.7	−11.0	−11.2	−9.5	−5.9
2i (−CN)	−7.4	−3.7	−4.0	−2.2	1.4
2j (−NO_2)	−6.8	−3.2	−3.4	−1.7	1.9

[a]ωB97X-D/6−311++G(2d,p). [b]At 298 K.

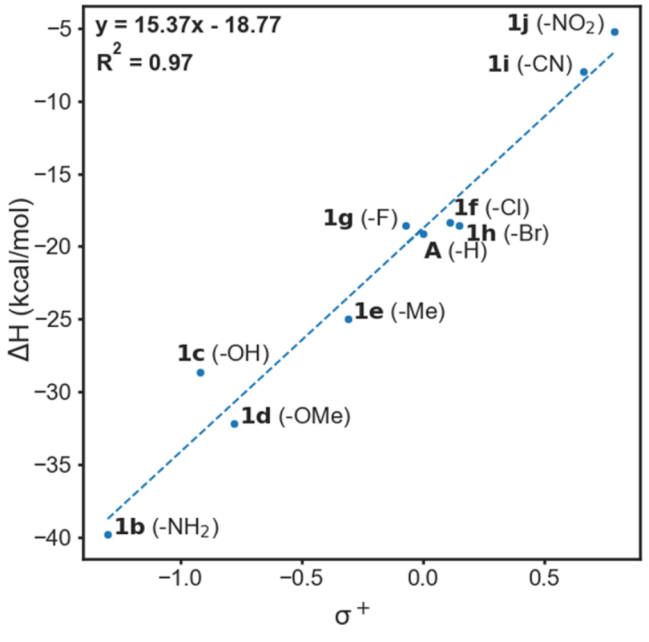

Figure 5. Calculated ΔH versus Hammett σ^+ constants for reaction of silyl cation **3a** with 4-substituted (trifluoromethyl)benzenes **1b**−**1g**.

(trifluoromethyl)benzenes. We find that the ΔH trend from most to least exothermic is **2b** (−NH_2) > **2e** (−Me) > **2d** (−OMe) > **A**, **2c** (−H, − OH) > **2f**, **2h** (−Cl,−Br) > **2g** (−F) > **2i** (−CN) > **2j** (−NO_2) (Table 1). These trends also make sense in that the more electron donating groups lead to reactions that are generally more exothermic.

One other overall trend to discuss is that of the reactions of silyliums **3** with 4-substituted (trifluoromethyl)benzenes **1** versus with their 3-substituted counterparts **2** (Table 1). For substitution with −NH_2 (**1b, 2b**), −OH (**1c, 2c**), and −OMe (**1d, 2d**), the reactions with the 4-substituted benzenes **1** are more exothermic than those with the 3-substituted series **2**. This makes sense, as the reaction of the (trifluoromethyl)-benzenes with the silyl cation yields a (trifluromethyl)benzyl cation (Figure 2). The $ArCF_2^+$ product is inductively stabilized by the −NH_2 substituent, whether this moiety is on the 3- or 4-position. However, the 4-substituted cation will have the added benefit of resonance stabilization by −NH_2, rendering this reaction even more favorable than its 3-substituted counterpart. For −OH and −OMe 3-substitution, the oxygen is inductively electron withdrawing, disfavoring the (trifluoromethyl)benzyl cation product. However, in the 4-position, the alcohol and alkoxy moieties can resonate into the cation, thus favoring these reactions over their 3-substituted counterparts. Substitution by methyl (**1e**, **2e**) also stabilizes the cation, but resonance plays a smaller role, since there is no free lone pair on the substituent, so the reaction is still more favorable with 4-substitution, though by a smaller amount. For halide substitution (**1e,f,g** and **2e,f,g**), the moieties are inductively electron withdrawing but can still stabilize the 4-$ArCF_2^+$ ions via resonance, thus favoring the reactions of **1**, as reflected by the more exothermic ΔH values for **1e,f,g** as compared to **2e,f,g**. The C−F activation to form $ArCF_2^+$ is not favored by highly electron withdrawing groups; therefore, all reactions of 3- and 4- substituted (trifluoromethyl)benzenes with −CN or −NO_2 (**1i,j** and **2i,j**) have fairly comparable ΔH values that are relatively low in absolute magnitude.

In terms of the reactivity of the silyl cations, the trend for exothermicity is **3a** > **3b** ∼ **3c** > **3d** > **3e**, meaning the reaction of any given (trifluoromethyl)benzene with **3a** is more exothermic than the reaction of the same (trifluoromethyl)-benzene with **3b** or **3c**, with **3e** yielding the lowest exothermicities (Table 1). Exothermicity thus tracks inversely with larger alkyl group substitution on **3**. For example, the fluoride abstraction reactions for triethylsilylium **3a**, Et_3Si^+, are more exothermic than those of the tributylsilylium **3e**. Presumably, this is due to the larger alkyl groups providing increased polarizability, which would stabilize the positive charge; therefore, **3e** is a less reactive silyl cation than **3a**.[35]

These results are also consistent with prior studies by Gusev and Ozerov, who calculated the fluoride affinity of various silyl cations.[36] They found that the trimethylsilyl cation Me_3Si^+ has a higher fluoride affinity than Et_3Si^+ (**3a**). That is, the longer chain alkyl group decreased the silylium affinity for fluoride. This is consistent with our results showing that the exothermicity of the reaction of silyl cations with our (trifluoromethyl)benzenes follows the trend Et_3Si^+ (**3a**) > Pr_3Si^+ (**3b, 3c**) > nBu_3Si^+ (**3e**). Ozerov also compared the fluoride affinity of H_3Si^+ with PhH_2Si^+ and found that the addition of the phenyl group decreases the silylium fluoride affinity. We likewise find that the phenyl ring diminishes reactivity; although two of the alkyl groups are methyl, we still find that in our fluoride exchange reactions, $PhMe_2Si^+$ (**3d**) is less favorable than both Et_3Si^+ (**3a**) and Pr_3Si^+ (**3b, 3c**).

Experiments. The experimental gas phase rate constants are compiled in Table 2. Missing data either reflect (trifluoromethyl)benzenes that are not easily vaporized, or, in the case of the methoxy(trifluoromethyl)benzenes (**1d** and **2d**) and the propylsilanes (**3b, c**), the reactant and product *m*/*z* ratios are by coincidence too close to differentiate; this is indicated by (N/A) in the Table.

For the 4-substituted (trifluoromethyl)benzenes **1**, the reactions with the silyl cations follow the trends predicted by our ΔH_{rxn} calculations. The more electron donating groups (**1b, 1d, 1e**) yield higher rate constants than the more electron

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Table 2. Experimental Gas Phase Rate Constants for the Reactions of Substituted (Trifluoromethyl)benzenes with Silyl Cations[a,b,c]

	3a	3b	3c	3d	3e
A	0.95 ± 0.03	1.06 ± 0.02	0.90 ± 0.02	0.82 ± 0.07	0.59 ± 0.10
1b	1.47 ± 0.13	1.51 ± 0.14	1.50 ± 0.12	1.64 ± 0.17	1.43 ± 0.11
1d	1.43 ± 0.08	N/A	N/A	1.60 ± 0.01	1.67 ± 0.06
1e	1.17 ± 0.04	1.43 ± 0.04	1.13 ± 0.04	1.90 ± 0.13	1.77 ± 0.07
1f	0.97 ± 0.01	1.19 ± 0.15	0.68 ± 0.03	0.75 ± 0.003	0.71 ± 0.01
1g	0.47 ± 0.04	0.46 ± 0.07	0.33 ± 0.06	0.55 ± 0.10	0.43 ± 0.07
2b	1.59 ± 0.17	1.32 ± 0.15	1.55 ± 0.22	1.23 ± 0.14	0.91 ± 0.18
2d	1.02 ± 0.13	N/A	N/A	1.13 ± 0.22	1.11 ± 0.18
2e	1.06 ± 0.14	1.35 ± 0.13	1.49 ± 0.02	1.71 ± 0.11	0.91 ± 0.13
2f	0.82 ± 0.13	0.89 ± 0.04	1.04 ± 0.10	0.77 ± 0.06	0.82 ± 0.07
2g	0.51 ± 0.05	0.63 ± 0.03	0.55 ± 0.10	0.75 ± 0.05	0.54 ± 0.03

[a]Rate constant units are $\times 10^{-9}$ $cm^3/(molecule{\cdot}s)$. [b]Theoretical collisional rate constants are all between 1 to 3×10^{-9} $cm^3/(molecule{\cdot}s)$.[41−43] [c]Details on experimental protocol are in Experimental section.

withdrawing groups (**1f**, **1g**). For example, for the reaction of the 4-substituted (trifluoromethyl)benzenes **1** with **3a** (first column, Table 2), the rate constants for **1b** ($-NH_2$), **1d** (−OMe) and **1e** (−Me) are higher (1.47, 1.43 and 1.17×10^{-9} $cm^3/(molecule{\cdot}s)$) than those for **1f** (−Cl) and **1g** (−F) (0.97 and 0.47×10^{-9} $cm^3/(molecule{\cdot}s)$). This is consistent with the larger calculated exothermicity of **1b**, **1d**, and **1e** (16−31 kcal/mol exothermic) versus that of **1f** and **1g** (∼9−10 kcal/mol exothermic). Although we calculated thermochemical values, yet measured rate constants, the correlation still holds, as would be expected by the Hammond Postulate, where more exothermic reactions would have lower activation barriers, leading to higher rate constants.[37,38] The result also makes sense mechanistically as electron donating groups will stabilize the $ArCF_2^+$ cationic product (Figure 2). The Hammett plots do show this expected trend (example plot for reactions with **3a** shown in Figure 6). The one point that appears to be an outlier is that for reaction of 4-fluoro-(trifluoromethyl)-benzene. For our plots, we utilized the well-known and robust

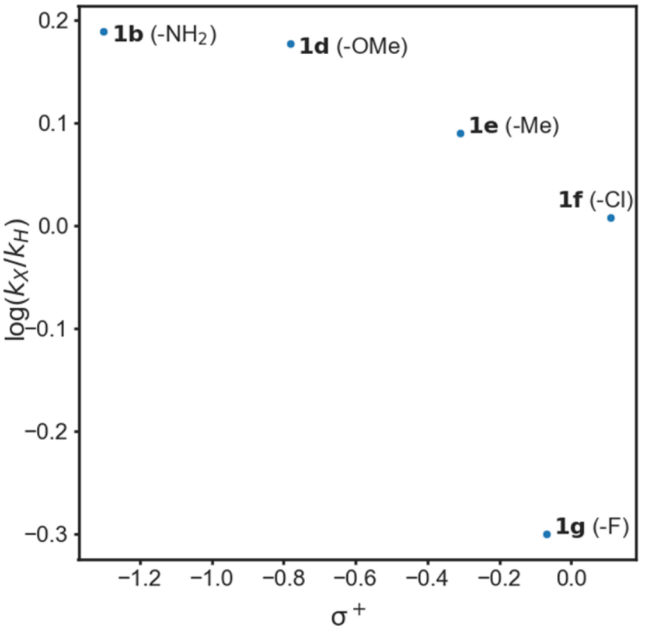

Figure 6. Hammett plot of log (k_{expt}/k_H) for the reaction of silyl cation **3a** with 4-substituted (trifluoromethyl)benzenes **1b-1g**.

σ^+ values obtained in 90% acetone/water; the unexpectedly slow reaction with fluorine substitution may be due to fluorine being an unusually small and electronegative element that may behave differently in nonaqueous environs.[39,40] Our gas phase rate constants thus provide data that are consistent in trends with the computed thermochemistry.

The 3-substituted ((trifluoromethyl)benzenes also react faster with the silyl cations when the aryl substituents are electron donating versus electron withdrawing; again, the experiments benchmark the computational prediction. Thus, for **2b**, **2d**, and **2e** ($-NH_2$, $-OCH_3$ and $-CH_3$), the experimental rate constants are higher with a given silyl cation than the reactions of **2f** and **2g** (−Cl, −F) (Table 2).

Last, how do these reactions overall compare to their condensed phase counterparts? In terms of the reactivity of the 3- versus 4-substituted (trifluoromethyl)benzenes, and the reactivity of the various silyl cations **3**, in general, the reactions herein are all quite fast, and differentiating, for example, across a row (Table 2) is difficult, especially as many of the rate constants overlap, within experimental error. The rate constants range from 0.33×10^{-9} to 1.90×10^{-9} $cm^3/(molecule{\cdot}s)$; the gas phase collisional rate constants are around 1 to 3×10^{-9} $cm^3/(molecule{\cdot}s)$, making these quite fast gas phase reactions.[41−44] These experimental results thus indicate that C−F activation is favorable with a "naked" reactive silyl cation, across a wide range of (trifluoromethyl)-benzenes.[29]

CONCLUSIONS

Calculations and experiments were used to examine the reaction of a series of substituted (trifluoromethyl)benzenes with silyl cations. The rate constants reported herein were heretofore unknown. Trends in reactivity of *meta*− versus *para*−substituted (trifluoromethyl)benzenes, in terms of both the nature and the position of the substituent are discussed. Overall, the reactions are quite fast, indicating the continued promise of cationic silyliums for C−F activation. These data establish the ability of "bare" silyl cations (without solvent or counterion) to activate a wide range of benzyl C−F bonds.

EXPERIMENTAL SECTION

The (trifluoromethyl)benzenes **A, 1b−j, 2b−j** and silanes (precursors for the silyl cations **3a−e**) are all commercially available and were used as received.

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A Fourier transform ion cyclotron resonance mass spectrometer (FTMS) equipped with a dual cell setup was used to measure rate constants, as described previously.[31,45,46] The magnetic field is 3.3 T, with a baseline pressure of 1×10^{-9} Torr within the cells. Neutral substances can be added to either cell independently, via heatable batch inlets. Hydronium ions were formed by pulsing water into the cell and ionizing it using an electron beam (ranging from 20−30 eV, 4−6 μA, 0.5 s). Under our conditions, hydronium ions react with silanes to produce silyl cations (Figure 7).

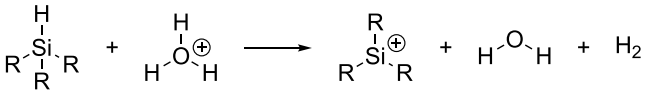

Figure 7. Generation of silyl cations.

To run the reaction, silyl cations were generated in one cell then transferred to the other, through a 2 mm-wide hole in the middle trapping plate, by briefly dropping the central trapping plate voltage to 0 V. Transferred ions were cooled with argon.[47,48] Then, gas-phase rate constants were measured using pseudo-first order conditions, where the concentration of the neutral substituted (trifluoromethyl)-benzene in the second cell was kept in excess relative to the concentration of the silyl cations; this has also been described previously.[31,45,46] The concentration, or pressure, of the neutral substituted (trifluoromethyl)benzene in the analyzer cell was measured by using a fast control reaction (hydronium with the (trifluoromethyl)benzenes), since the pressure measurement from the ion gauges were not always accurate; this has also been described previously.[31,41,42,45] The rate constant was measured a minimum of three times; the errors listed in Table 2 represent the standard deviation of the multiple measurements. Theoretical collision rates were calculated using the parametrized trajectory method of Su and Chesnavich.[41]

All density functional calculations were conducted using Gaussian 16[49] utilizing the ωB97X-D/6−311++G(2d,p) level of theory.[50,51] Additional calculations were also conducted using M06−2X and B3LYP-D3(BJ), with the 6−311++G(2d,p) basis set, to ensure consistency of results.[51−57] For reactant geometry optimization of structures that could have multiple low-lying conformers, bonds were manually rotated for conformational searching, to find the lowest energy structure. All ground state geometries were fully optimized and the resulting structures had no negative frequencies. No scaling factor was applied. Reported values are at 298 K.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01775.

Cartesian coordinates and further details for all calculated species (PDF)

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Notes

The authors declare no competing financial interest.

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