Gas-Phase Reactions

An Unusually Fast Nucleophilic Aromatic Displacement Reaction: The Gas-Phase Reaction of Fluoride Ions with Nitrobenzene**

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Dedicated to Professor Nicola Petragnani on the occasion of his 75th birthday

Nucleophilic displacement reactions in aromatic systems play an important role in organic chemistry and become possible when the aromatic ring is activated by electron-withdrawing substituents.[1] The most common mechanism for aromatic nucleophilic substitution (S_NAr) involves a multistep addition–elimination pathway[2] through the rate-determining formation of well-characterized σ-complex intermediates.[3] Although benzyne-type processes and electron-transfer mechanisms[4] can also mediate nucleophilic reactions in aromatic compounds, direct displacement by means of a backside attack has long been argued to be an energetically demanding pathway for monosubstituted aromatic substrates and thus regarded as very unfavorable.

Unlike S_N2 reactions, aromatic nucleophilic substitution reactions have not been well characterized in the gas phase, in which intrinsic reactivity can be assessed unequivocally.[5,6] The fact that the acidity of simple halobenzenes is comparable to that of methanol in the gas phase[7] (see Supporting Information) has precluded detailed gas-phase studies, because proton abstraction becomes the dominant reaction for some of the usual strong gas-phase nucleophiles.[8] Although multiple fluorine substitution has been shown to give rise to very diverse chemistry,[5a,c–e] the role of σ complexes in gas-phase reactions remains controversial.[9] For example, recent ab initio calculations for the symmetric $X^- + C_6H_5X$ ($X = F$, Cl, Br, I) gas-phase reactions led to the conclusion that σ complexes are stable intermediates for $X = F$, but local transition states in the other cases.[9c] Herein we report the observation of very fast gas-phase aromatic nucleophilic substitution reactions with nitrobenzene as substrate [Eq. (1)].

$$F^- + C_6H_5NO_2 \rightarrow NO_2^- + C_6H_5F \qquad (1)$$

The kinetics of this reaction were studied by FT ICR mass spectrometry[10,11] at typical pressures ($< 10^{-7}$ mbar), and the rate constants were determined from kinetic plots obtained for different partial pressures of nitrobenzene at 335 K (average temperature of the cell due to heating by the ionizing filament). These experiments lead to a bimolecular rate constant for [Eq. (1)]:

$$k_1 = (3.05 \pm 0.10) \times 10^{-9}\,\mathrm{cm^3\ molecule^{-1}\,s^{-1}}.$$

This value, when compared with that estimated for the ADO (average dipole orientation) collision rate constant,[12] indicates that 69 % of the ion–molecule collisions are reactive and yield the products shown above. This remarkably high efficiency (fraction of collisions that yield products) is indeed surprising and several aspects should be noted:

a) Although [Eq. (1)] is exothermic by 28.7 kcal mol^{-1} at 298 K,[13] its high efficiency is unusual considering the type of reaction and the leaving group involved. This efficiency is, in fact, comparable to that of other barrier-free gas-phase ion–molecule reactions proceeding through a double-minimum potential such as gas-phase S_N2 reactions.[14]
b) The possibility of a benzyne mechanism can be discarded because the resulting neutral products, namely HF and C_6H_4, would make the displacement significantly endothermic.[13]
c) No other product ions were observed for this system under our experimental conditions.

To characterize the mechanism of [Eq. (1)], DFT calculations were carried out at the B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory using the Gaussian98 suite of programs.[15] Frequency calculations were carried out

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for all species to establish their nature as local minima or transition states. Enthalpy changes were calculated from the energies of the optimized structures, and thermal corrections included for 298 K without any scaling of the calculated vibrational frequencies (see Supporting Information). The theoretical estimate for the ΔH° of [Eq. (1)] amounts to -28.2 kcal mol^{-1}, which is in very close agreement with the experimental value. Several stable ion–molecule intermediates were found from the interaction of F^- with nitrobenzene as a result of an extensive optimization procedure that included a search for geometries containing in-plane and out-of-plane F^-. The most stable complex, **1a**, results from an F^- ion loosely bound to the *para*-H atom of nitrobenzene, as might be expected when considering the strong ion–dipole interaction. Very stable and similar complexes were also found for F^- ions loosely bound to the *ortho*- and *meta*-H atoms of nitrobenzene. Two different types of stable complexes were also identified as resulting from the out-of-plane attack of F^- at the *para* position of **1b** and at the *ipso* carbon atom of **1c**. Figure 1 summarizes the calculated energy diagram and the important optimized structures. At this stage, we have not searched for the possible local transition states connecting **1a**, **1b**, and **1c**, as our primary interest was to characterize how **1c** evolves into the products of [Eq. (1)]. We can then envision Equation (1) as proceeding initially through the formation of a very stable complex such as **1a** (Figure 1) leading to the prereaction complex **1c**, a stable ion–molecule adduct arising from an out-of-plane attack of F^- at the *ipso* carbon atom. This species is a typical ion–molecule complex in which the calculated C–F bond length (2.24 Å) is well outside the value of covalent bonding. Complex **1c** then proceeds through the local transition state **2** that displays an imaginary frequency corresponding to the NO_2 bond breaking process, and is located only 3.5 kcal mol^{-1} above the reactant-side complex. Finally, the departing NO_2^- gives rise to a stable ion–molecule complex **3** of fluorobenzene and NO_2^-, in which the ion has moved away from the carbon center and rotated around so that the oxygen atoms saddle the *ortho* and *meta* hydrogen atoms of the ring.[16] According to these calculations, the prototype Meisenheimer complex **2**, although below the energy of the reactants, is a *transition state* and not a *local energy minimum*. The calculated potential energy diagram is highly reminiscent of the typical energy diagram for common exothermic gas-phase ion–molecule reactions,[17] and is in agreement with the results obtained from ab initio calculations on the symmetric exchange reactions $X^- + C_6H_5X$ for X = Cl, Br, and I.[9c] Furthermore, our DFT calculations are believed to provide reasonably reliable estimates considering

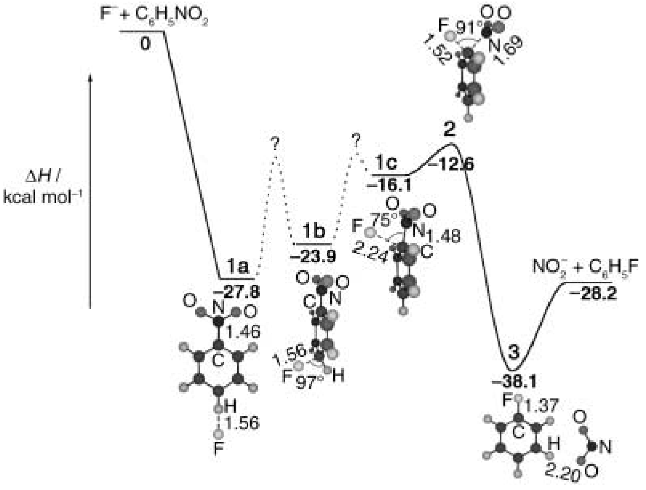

Figure 1. Calculated energy diagram for [Eq. (1)] at the B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) level, including the optimized structures of the different intermediates, and the local transition state for the reaction.

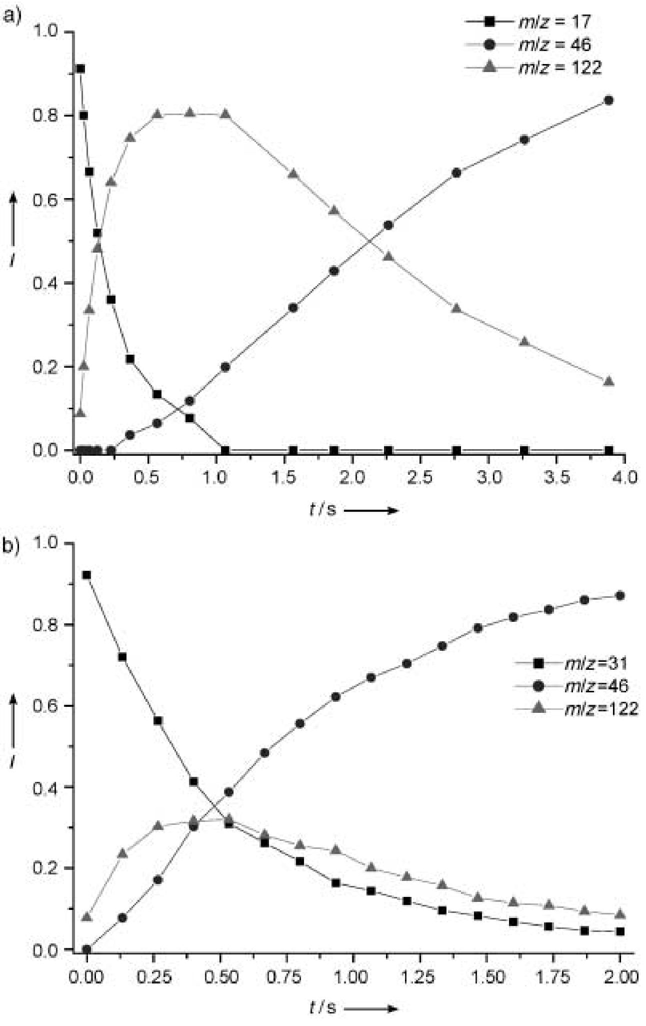

Figure 2. a) Kinetic plot of the gas-phase reaction of OH^- ($m/z = 17$) with nitrobenzene reveals rapid proton transfer to yield $C_6H_4NO_2^-$ ($m/z = 122$) and H_2O. The subsequent reaction of the $C_6H_4NO_2^-$ ion with neutral H_2O yields NO_2^- ($m/z = 46$) and phenol. This secondary reaction is clearly observed from the delay in the appearance of the NO_2^- ion. b) A similar kinetic plot of the gas-phase reaction of MeO^- ($m/z = 31$) with nitrobenzene reveals competition between proton transfer (to yield $C_6H_4NO_2^-$ ($m/z = 122$) and methanol) and NO_2^- ($m/z = 46$) displacement (with formation of anisole). $C_6H_4NO_2^-$ ($m/z = 122$) then undergoes a subsequent reaction with neutral H_2O (used to generate MeO^- from the reaction of OH^- with MeOH) to yield NO_2^- ($m/z = 46$) and phenol as in Figure 2a.

the agreement obtained in reference [9c] for the complexation energies calculated at different levels of theory. Finally, the low local energy barrier found for the nucleophilic displacement suggests that [Eq. (1)] should be fast, and its efficiency dictated by the density of states of the transition state.[18]

The displacement of NO_2^- from nitrobenzene by other nucleophiles other than F^-[19] was also observed for alkoxide ions, RO^- (R = Me, Et, *i*Pr), and OH^-. Nitrobenzene reacts rapidly with hydroxide ion by proton transfer to yield $C_6H_4NO_2^-$ at $m/z = 122$, and this product ion then undergoes secondary reactions with neutral water (used to generate the OH^- ions) to yield NO_2^- and phenol.[20] A similar behavior is observed with MeO^-, although the direct displacement becomes competitive with proton abstraction. The behavior of OH^- and MeO^- is illustrated in Figure 2. The corresponding reaction with EtO^- yields primarily NO_2^- and very little proton abstraction, whereas *i*PrO^- yields exclusively the aromatic displacement reaction. In the last two cases, the observed nucleophilic displacement reactions are not as fast as that reported for **1** but the reactions do proceed readily under our experimental conditions.

The present combined experimental and theoretical results show for the first time that direct aromatic nucleophilic displacement can, in fact, be an extremely facile process in the gas phase, and can proceed through a potential energy surface similar to those observed for other gas-phase ion-molecule reactions. Furthermore, the present observations open up a range of possibilities regarding the experimental study of these reactions and the role of σ complexes in the gas phase, as well as theoretical studies dealing with the dynamics of these reactions.

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Keywords: ab initio calculations · aromatic substitution · gas-phase reactions · ion–molecule reactions · nucleophilic substitution

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[10] In these studies, F^- ions ($m/z = 19$) were generated inside the cell of our FT ICR spectrometer by dissociative electron attachment of NF_3 at pressures of the order of 3.7×10^{-8} mbar. In the presence of nitrobenzene (typical pressures $\approx 3.7 \times 10^{-8}$ mbar), the fluoride ions react rapidly to yield NO_2^- ions ($m/z = 46$), and these NO_2^- ions were observed to disappear completely upon pumping away NF_3. Absolute pressures were obtained from an independent calibration of the ion gauge sensitivity and position against a capacitance micromanometer by using a procedure developed in these laboratories.

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[16] This product side complex is identical to that found in the ab inito study of the aromatic nucleophilic substitution reaction of MeS^- with 2,4-dinitrochlorobenzene.[9b]

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[20] This behavior is similar to that observed with the halobenzenes; the halophenide ions, $C_6H_4X^-$, undergo exchange reactions with H_2O (or D_2O), and the nascent OH^- in the collision complex promotes nucleophilic substitution (see, for example, reference [5h] and references therein). In fact, reaction of $C_6H_4NO_2^-$ with D_2O yields both NO_2^- and the whole family of $C_6H_{4-n}D_nNO_2^-$ ($n = 1$–4) as product ions.