

Aromatic Nucleophilic Substitution

Competition between Nucleophilic Substitution of Halogen (S_NAr) versus Substitution of Hydrogen (S_NArH)—A Mass Spectrometry and Computational Study

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Abstract: The mechanism of intramolecular gas-phase reactions of *N*-(2-X-5-nitrophenyl)-*N*-methylacetamide carbanions (X = H, F, Cl) has been studied using negative ion electrospray mass spectrometry ((–)ESI-MS) technique and modelled computationally. It was proven that all three anions form cyclic σ^{H} adducts, which undergo elimination of water. In the case of X = F, formation of the σ^{F} adduct, leading to S_NAr reaction, was a competing process. This is the first proof that also in the gas phase formation of σ^{H} adduct proceeds faster than σ^{X} adduct and only when X = F, rates of these two processes are comparable. The experimental results are in full agreement with quantum chemical calculations.

Nucleophilic reagents can react with nitroarenes in a variety of ways, as recently discussed.^[1] The most important ways are aromatic nucleophilic substitution of halogen (S_NAr)^[2] and nucleophilic substitution of hydrogen (S_NArH).^[3] Both of these processes have found wide application in organic synthesis.^[2,3] Both reactions proceed through the formation of anionic σ adduct: σ^{X} adduct in the first case and σ^{H} adduct in the second one (Scheme 1).

In extensive experimental work, it was unambiguously shown that the formation of $\sigma^{\rm H}$ adduct is a much faster process compared with the formation of $\sigma^{\rm X}$ adduct.^[1-3] However, further transformation of the $\sigma^{\rm H}$ adduct requires special reaction conditions and/or specific structure of the attacking nucleophile, because hydride anion cannot depart spontaneously as the leaving group. When these conditions are not fulfilled, the formation of $\sigma^{\rm H}$ adduct is ineffective and, due to reversibility of its formation, $S_{\rm N}Ar$ reaction can proceed. In the case when both reactions are possible, their relative rates depend on the reaction conditions and can be precisely controlled.^[4]

To get deeper insight into the factors governing the relative rates of the S_NAr and S_NArH reactions, and to avoid the effects of the solvent and counter-ion accompanying the attacking nucleophile, these processes should be studied in the gas



Scheme 1. Relation of rates of nucleophilic addition at the position occupied by halogen and hydrogen.

phase. As demonstrated by our group^[5] and other researchers,^[6] strongly electrophilic nitroarenes can form anionic σ adducts in the gas phase. In the case when σ^{X} adduct is formed, it reacts further, finally yielding an anion of the resulting S_NAr reaction product.^[5a] There are no published proofs for the formation of the stable σ^{X} adducts in the gas phase. However, much information concerning relations of the rates of formation of σ^{H} and σ^{X} adducts can be generated by density functional theory (DFT) calculations. Calculations performed for some simple models show that σ^{x} adduct can be either an intermediate or a transition state in the gas-phase S_NAr reaction, depending on the structures of the substituted arene and the attacking nucleophile.^[7] Formation of σ^{H} adducts was not postulated in these calculations. However, according to recent calculations, σ^{H} adducts of enolates are formed faster than isomeric σ^{X} adducts.^[8]

In mass spectrometry studies, the most common way to obtain structural information about an ion is to fragment it and measure the masses of the resulting fragmentation ions. Unfortunately, our extensive studies have shown that it was not possible to distinguish between σ^{H} and σ^{X} adducts, because the former show no specific fragmentation patterns except for the dissociation, yielding the starting nitroarene and nucleophile. This is because the dissociation of the σ^{H} adduct into substrates is the reaction channel with the lowest activation energy. To overcome this problem, we decided to study the formation of σ^{H} and σ^{X} adducts in intramolecular reactions in the gas-phase. This should significantly increase the probability of σ^{H} adduct formation due to geometrical reasons and, consequently, give chance for fragmentation channels other than simple reversion of the adduct formation.

Searching for the best model to study direct competition between the formation of σ^{H} and σ^{X} adducts in the intramolec-

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ular reactions, we chose *N*-(2-X-5-nitro-phenyl)-*N*-methyl-acetamides (**1a**-**c**, X = H, F, Cl). The compounds **1b** and **1c** should, after deprotonation, yield an appropriate carbanion that subsequently attacks either position 6, yielding σ^{H} adduct, or position 2, yielding σ^{X} adduct. The unsubstituted *N*-(3-nitrophenyl)-*N*-methyl-acetamide **1a** was selected as the reference compound.

$$\mathbf{NO}_{2}$$

$$\mathbf{O}$$

$$\mathbf{NO}_{2}$$

$$\mathbf{O}$$

The reaction of compounds 1a and 1c with a strong base has already been studied in solution.^[9] It was found that in the case of chloro derivative 1c, the only observable reaction is the oxidative nucleophilic substitution of hydrogen (ONSH) and no S_NAr reaction product was detect-

ed (Scheme 2). For compound **1 a**, two ONSH products, in the *ortho* and *para* positions to the nitro group, were formed.

Unfortunately, all our attempts to generate the desired carbanions by deprotonation of compounds 1a-c in the gas phase failed. We decided therefore to use the mono-*N*-methyl-



Scheme 2. Reaction of *N*-(2-chloro-5-nitrophenyl)-*N*-methyl-acetamide with *t*BuOK in DMSO.



Scheme 3. Reactions of the anions of compounds 1 a-c in the gas phase.

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2-X-5-nitroanilides of malonic acid, 2a-c, as the carbanion precursors. Under (–)ESI conditions, these compounds yield the respective carboxylate anions, which, after decarboxylation in the medium-pressure region of the ESI ion source, should give the expected carbanions (Scheme 3). This method has been extensively explored in our lab.^[5,10]

(–)ESI spectra of carboxylates 2a-c (see Figure S4–S6 in the Supporting Information) show that the decarboxylation reaction takes place even during standard conditions of ESI measurements. After selection of the $[M-CO_2]^-$ ions, resulting from compounds 2a-c with the first quadrupole of the triple quadrupole mass spectrometer, they were fragmented in a collision cell and the resulting fragment ions were recorded yielding spectra shown in Figure 1. The results can be rationalized by the reactions shown in Scheme 3.



Figure 1. Fragmentation spectra acquired at CE = 10 eV of $[M-\text{CO}_2]^-$ ions obtained from compounds: **2a** (*m*/*z* 193), **2b** (*m*/*z* 211), **2c** (*m*/*z* 227).

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Two fragmentation reactions are common for all three anions **1a**–**c**: an elimination of ketene and water molecules. The first fragmentation is a simple heterolytic C–N bond cleavage and will not be discussed here. Much more interesting is elimination of water molecule. The proposed mechanism for this process is shown in Scheme 3. Anions **1a**–**c** cyclize to yield bicyclic σ^{H} adducts **4a**–**c**, which undergo a proton shift followed by elimination of water molecule, yielding nitroso compounds **6a**–**c** (in anionic form). Such transformation of the σ^{H} adduct to a nitroso compound (or its further transformation products) is well known in solution chemistry,^[3a, b, 1] but has been observed in the gas phase for the first time. Therefore, the observation of an elimination of water from anions **1a**–**c** provides strong evidence that at least a fraction of these ions can exist as σ^{H} adducts **4a–c**.

In the case of fluoro derivative **1 b**, in addition to the reactions mentioned above, elimination of HF is also observed, indicating that a S_NAr reaction takes place (Scheme 3). In contrast to the reaction taking place in solution, the anionic reaction product in the gas phase is not a fluoride anion but an anion of the organic product **8 b**. This is because the fluoride anion is a very strong base in the gas phase (proton affinity $(PA) = 372 \text{ kcal mol}^{-1}$), much stronger than anion **8 b** $(PA = 326 \text{ kcal mol}^{-1})$. This was also proven, both experimentally and computationally, for very similar compounds.^[5a]

The results described above show unequivocally that in the case of the chlorine derivative **1 c**, the formation of σ^{H} adduct is at least two orders of magnitude faster than the formation of σ^{CI} adduct, because no S_NAr reaction product is observed. However, as was shown earlier,^[3b, c, 4] the rates of addition of carbanions to nitroaromatic rings in positions occupied by H

and F are comparable, even though the fluoride ion is known to be the best leaving group in S_NAr reactions.

In an attempt to rationalize the results described above, DFT calculations using Gaussian 09 suite of programs^[12] at PBE1PBE/6-311 + G(2d,p)//PBE1PBE/6-31 + G(d) level of theory (see Section S2 in the Supporting Information for the rationalization of the selection of computational method) have been performed to establish energy profiles of the processes of formation of σ^{X} adducts, leading to the S_NAr reaction products and σ^{H} adducts, followed by the elimination of water molecule. The results are shown in Figure 2. The results obtained show that relative reaction rates of the S_NAr and S_NArH should depend on the activation Gibbs free energy (ΔG^{\dagger}) values for the formation of σ^{H} and σ^{X} adducts. In the case of chlorine derivative **1**c, ΔG^{\dagger} value for the formation of σ^{X} adduct is about 4 kcal mol⁻¹ higher compared with the formation of σ^{H} adduct. Such energy difference indicate that the S_NAr reaction should be slower than the formation of $\sigma^{\!\!\!H}$ adduct by at least two orders of magnitude, which is in perfect agreement with experimental results. ΔG^{\dagger} values for the formation of σ^{H} and σ^{X} adducts from the fluorine derivative 1b differ by only 0.6 kcal mol⁻¹, so both processes should proceed with comparable rates, which again is consistent with experiment. Lower relative intensity of the $[1 b-H_2O]^-$ peak, compared with $[1 b-HF]^-$, can be easily explained, taking into account that the formation of these ions require passing the second activation energy barrier, which is guite significant for the former and negligible for the latter reaction (31.7 versus 0.5 kcal mol⁻¹, see Figure 2).

These preliminary results showed that our approach to study competition between gas-phase S_NAr and S_NArH reactions in the intramolecular mode proved to be very fruitful.

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Figure 2. Calculated Gibbs free energy values and energy profiles for the S_N Ar and S_N Ar H reactions of anions **1a** (X = H; solid line), **1b** (X = F; dotted line), and **1c** (X = Cl; dashed line). PBE1PBE/6-311 + G(2d,p)//PBE1PBE/6-31 + G(d) method; results in kcal mol⁻¹ at 298 K.

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The experiments and calculations necessary to get the full picture of the gas-phase reactions of the anions of mono-*N*methyl-2-X-5-nitroanilides of malonic acids **2a-c** are under progress and their results will be published upon completion.

Conclusion

The first observation of an elimination of water molecule from the gas-phase intramolecular σ^{H} adducts made possible to directly compare the relative rates of the S_NAr and S_NArH gasphase reactions within the same molecule. The results obtained show that, similarly to the reactions taking place in a condensed phase, the formation of σ^{H} adduct is much faster than the formation of σ^{X} adduct when X=Cl. For X=F, these two processes proceed with comparable rates. Experimental observations were supported by the results of the DFT calculations. Our results support the general statement that σ^{H} adduct is an initial, reversibly formed intermediate in the reaction of nitroarenes with carbanions, whereas formation of σ^{X} adducts leading to S_NAr reaction is a slower but irreversible process.

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COMMUNICATION

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