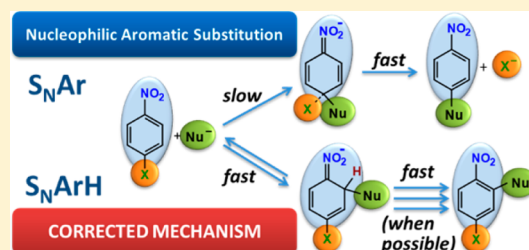# How Does Nucleophilic Aromatic Substitution Really Proceed in Nitroarenes? Computational Prediction and Experimental Verification

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S *Supporting Information*

ABSTRACT: The aim of this paper is to present a correct and complete mechanistic picture of nucleophilic substitution in nitroarenes based on the results obtained by theoretical calculations and experimental observations coming from numerous publications, reviews, and monographs. This work gives the theoretical background to the very well documented experimentally yet still ignored observations that the addition of nucleophiles to halo nitroarenes resulting in the formation of σ^H adducts, which under proper reaction conditions can be transformed into the product of the S_NArH reaction, is faster than the competing process of addition to the carbon atom bearing a nucleofugal group (usually a halogen atom) resulting in the "classic" S_NAr reaction. Only when the σ^H adduct cannot be transformed into the S_NArH reaction product, S_NAr reaction is observed.

INTRODUCTION

Nucleophilic aromatic substitution of halogens in electron-deficient arenes, particularly halonitroarenes, known for more than 150 years, is a process of great importance and wide applications in organic synthesis and industry.[1] The addition–elimination mechanism of this reaction, initially formulated by Bunnett,[2] was subsequently confirmed in thorough mechanistic studies and presently is generally accepted.[3] The reaction proceeds via addition of nucleophiles to the electron-deficient ring at position *ortho* or *para* to the nitro group occupied by halogens, X, to form adducts σ^X, followed by spontaneous departure of X^- resulting in formation of the products. Since the addition is connected with dearomatization, the departure of X^- from the σ^X adduct, connected with rearomatization, proceeds usually faster than the addition, thus as a rule, an addition is the slow, rate-limiting step (Scheme 1a). Nucleophiles add to nitroarenes due to the electron withdrawing effect of the nitro group; thus the addition can proceed at all activated positions (*ortho* and *para*), regardless whether they are occupied by halogens or hydrogen. In recent years, it was shown that anionic C, N, O, and P nucleophiles, as a rule, add to halonitroarenes faster at positions occupied by hydrogen to form σ^H adducts than at those, equally activated, occupied by halogens.[4] Since hydride anions often are unable to spontaneously depart from these initially formed σ^H adducts, they usually dissociate back to the reactants; thus this addition is a fast and reversible process, and σ^H adducts are often considered to be "unproductive" intermediates. Subsequent slower addition of nucleophiles at positions occupied by halogens followed by fast departure of X^- from the σ^X adducts results in S_NAr reaction; hence, the initial formation of the σ^H adducts is generally overlooked.

Scheme 1. (a) Nucleophilic Substitution of Chlorine in *p*-Chloronitrobenzene via Slow Addition of a Nucleophile at the Position Occupied by Chlorine Followed by Fast Departure of Cl⁻ and (b) Fast and Reversible Addition of a Nucleophile at the Position Occupied by Hydrogen To Form σ^H Adduct That Can Be Converted into Products of S_NArH or Dissociate to Substrates
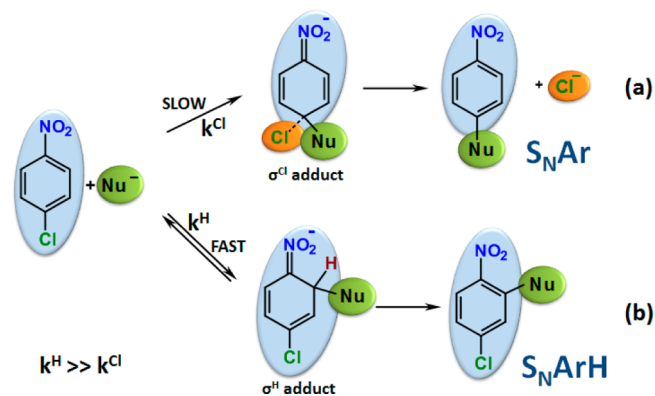

Nevertheless, under proper conditions, initially formed σ^H adducts can be converted into products of nucleophilic substitution of hydrogen, S_NArH, in several ways (Scheme 1b).[5] The three main ways of conversion of the σ^H adducts into products of S_NArH are (i) oxidation by external oxidants leading to oxidative nucleophilic substitution of hydrogen, ONSH[6] (Scheme 2a), (ii) β-elimination of HL when the

Scheme 2. Examples of Three Major Ways of Conversion of the σ^H Adducts into Products of S_NArH, (a) Oxidation with External Oxidants, (b) Vicarious Nucleophilic Substitution, and (c) Conversion into Substituted Nitrosoarenes
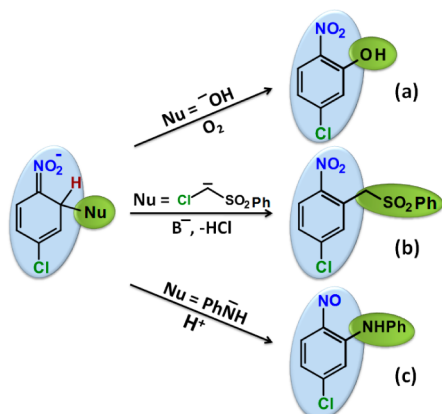
nucleophiles possess leaving groups L at the nucleophilic centers, vicarious nucleophilic substitution, VNS[7] (Scheme 2b), and (iii) conversion into substituted nitrosoarenes upon protonation or action of Lewis acids according to the intramolecular redox stoichiometry[8] (Scheme 2c). Taking into account fast equilibration between σ^H adducts and the reactants, S_NArH can proceed provided conversion of the σ^H adducts is faster than irreversible formation of the σ^X adducts and S_NAr (Curtin–Hammett rule). These three variants of S_NArH reaction are exemplified in Scheme 2.

Thus, the general picture of nucleophilic aromatic substitution in halonitroarenes that emerges from these results is as follows: nucleophiles add initially at positions occupied by hydrogen to form σ^H adducts. When due to the kind of nucleophiles and conditions there are ways for fast further conversion of the σ^H adducts, S_NArH takes place. Otherwise σ^H adducts dissociate, nucleophiles can add at positions occupied by halogens, and S_NAr proceeds.[4–8] This general picture, although confirmed by many experiments with a variety of halonitroarenes and nucleophiles (C^-, N^-, O^-, and P^-) was mostly ignored in text books[9] and numerous mechanistic studies of S_NAr.

Due to the great practical value and interesting mechanistic features of S_NAr reaction, from the very beginning of the computational chemistry, interaction of nucleophiles with electron-deficient arenes was a subject of numerous quantum chemical calculations. However, almost all the reported calculations were limited to analysis of the addition of simple nucleophiles to halonitroarenes, mostly *p*-fluoro- and *p*-chloronitrobenzenes, as well as halodinitrobenzenes, at positions occupied by halogens. Although in recent years level of theory became very high, the reported calculations ignored the alternative reaction pathways, addition of nucleophiles to nitroarenes at positions occupied by hydrogen.[10] This is really surprising because it is evident that nucleophilic addition to nitroarenes is promoted by NO_2 rather than halogens, and in numerous experimental studies, it was unambiguously shown that formation of the σ^H adducts is the fastest process between nucleophiles and nitroarenes (also halonitroarenes) and thus proceeds via transition states of lowest energy.[4] The quantum chemical calculations of any reaction between two partners should find the reaction pathway that proceeds via the transition state of the lowest energy.

Quantum chemical calculations published in numerous reports do not meet this fundamental criterion. It appears that the calculations published earlier, despite the high level of theory, have a conceptual deficiency: they are limited to the commonly accepted reaction pathways of S_NAr reaction proceeding via addition of nucleophiles at positions occupied by halogens. Alternative addition pathways, addition at positions occupied by hydrogen, although it proceeds via the TS of lower energy, were not considered. It is also a reason why nitrobenzene, which does not contain nucleofugal groups, was not considered in these calculations. We have found only one paper mentioning that calculated rates of addition of nucleophiles to halonitrobenzenes is higher at the positions occupied by hydrogen.[11]

The aim of this paper is to present a correct and complete picture of nucleophilic substitution in nitroarenes based on results of experimental studies and unbiased quantum chemical calculations. Results of experimental studies of nucleophilic substitution in nitroarenes, particularly halonitroarenes, that confirm fast initial formation of the σ^H adducts are presented in numerous publications, reviews, and monographs.[3–8]

In this paper, quantum chemical calculations of reactions between selected nucleophiles and nitroarenes will be presented and confronted with published experimental results.

■ RESULTS AND DISCUSSION

For the calculations of the energy profiles for reactions between nucleophiles and nitroarenes, we have selected three model nitroarenes: nitrobenzene **1**, *p*-fluoronitrobenzene **2**, and *p*-chloronitrobenzene **3**. Compounds **2** and **3** are common model nitroarenes used for experimental and computational mechanistic studies of the S_NAr and S_NArH reactions. On the other hand, nitrobenzene **1** is the simplest nitroarene that enters S_NArH reaction and can serve as a reference compound. As the model nucleophile, carbanion of chloromethyl phenyl sulfone ($PhSO_2CHCl^-$, **4**) was chosen. Contrary to the simple nucleophiles, such as OH^-, CH_3O^-, or NH_3, commonly used for the calculations, reactions of carbanion **4**, due to its nature, are much less affected by solvation effects; hence the quantum chemical calculations of reactions of this nucleophile that do not consider solvation or treat it on a basic level (PCM model) better mimic the situation of experiments that are usually carried out in dipolar aprotic solvents. Furthermore, **4** was widely used as the model nucleophile in S_NArH reactions studies; thus comparison of the calculations and experimental results should be facile and reliable. It should be mentioned that simple nucleophiles, such as OH^- or NH_3, also add to chloronitrobenzenes faster at positions occupied by hydrogen and hence similarly to **4** enter S_NArH reactions.[6c,d]

Kinetics and Thermodynamics of the Nucleophilic Addition. Due to the size of the reacting molecules, the only practical choice to get reliable results in a reasonable time was to use one of the density functional (DFT) methods. However, because the number of such methods is very high and there are no reliable indications which methods should be the best in our case, we decided to test four DFT methods in the gas phase and in solution.

The results of these calculations are collected in the Supporting Information (SI). On their basis, we decided to use PBE1PBE/6-311+G(2d,p)∥PBE1PBE/6-31+G(d) method, which as it has been proven in our preceding paper[12] is a reliable source of thermodynamic data of organic reactions. Similar results were obtained using three other DFT methods

(see SI). To see how important the solvent effects are in our calculations, both gas-phase and solvent-phase calculations have been performed. For solvent-phase calculations, the polarizable continuum model (PCM) has been used with N,N-dimethylformamide (DMF) as the solvent. The results are presented in Tables 1 and 2. As it should be expected, in PCM

Table 1. Gibbs Free Energy Values (ΔG in kcal mol^{-1}) for the Reactions of Nitroarenes 1−3 with Anion 4 Calculated at PBE1PBE/6-311+G(2d,p)‖PBE1PBE/6-31+G(d) Level of Theory (Gas Phase)

X	σ^H adduct	TS$_{ortho}$−X	TS$_{para}$−X	σ^X adduct
H	−2.1	10.7	9.2	−1.7
F	−6.7	8.0	10.0	−5.6
				[P$_{SNAr}$ + Cl$^-$]
Cl	−7.9	6.2	13.2	−39.9

Table 2. Gibbs Free Energy Values (ΔG in kcal mol^{-1}) for the Reactions of Nitroarenes 1−3 with Anion 4 Calculated at PBE1PBE/6-311+G(2d,p)‖PBE1PBE/6-31+G(d) Level of Theory Using PCM Solvation Model with DMF as the Solvent

X	σ^H adduct	TS$_{ortho}$−X	TS$_{para}$−X	σ^X adduct
H	9.2	22.1	21.8	8.4
F	6.9	20.9	21.4	3.9
				[P$_{SNAr}$ + Cl$^-$]
Cl	6.5	19.9	23.7	−35.5

calculations ΔG values of the σ adducts and activation free energies of the transition states leading to these adducts are shifted up by about 10−12 kcal mol^{-1}, compared with the gas-phase results. This is because the reactants are solvated more strongly by the polar solvent than their adducts and transition states. Despite this effect, the general trends concerning relative stabilities of σ adducts, as well as differences in activation Gibbs free energies, are very similar in both methods. This observation is very important because it shows that qualitatively correct predictions concerning preferred reaction directions can be obtained using much simpler and faster gas-phase calculations, at least for the reactions of medium-sized organic molecules. However, since the results obtained by the solvent-aware PCM method should, by their principle, better reproduce real experiments *in vitro*, this set of results (Table 2) has been selected for further discussion.

Interesting conclusions can be drawn from the comparison of the ΔG values of the σ adducts in the gas and the liquid phase. Calculations show that in the gas phase such adducts should be relatively stable species (negative ΔG values compared with the substrates), while in DMF solution ΔG of the reactions in which they are formed is positive. In fact, the experiments show that at room temperature there is no detectable concentration of σ adducts of nitrobenzene or its halogenated derivatives with carbanion 4. This observation shows again that in the cases in which solvent-aware calculations are technically possible they should be performed to make the results not only qualitatively but also quantitatively more reliable.

The relations of rates of the addition of 4 at various positions of 1, 2, and 3 expressed by values of the Gibbs free energies of the transition states (TS) are shown in Table 2 and Figure 1. Activation barriers correspond to the optimized transition state structures (see SI).
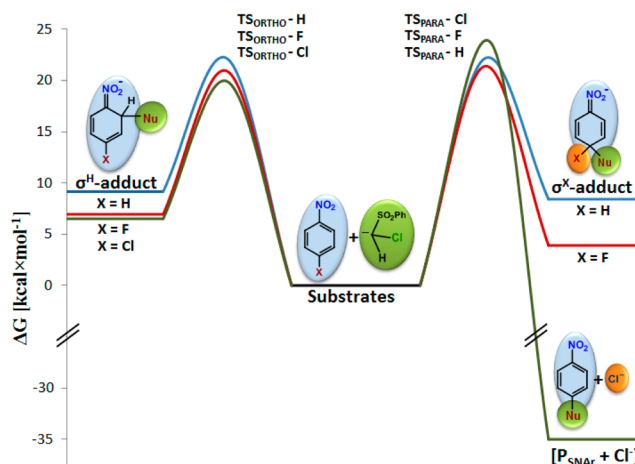

Figure 1. Calculated energy profiles for addition of the model nucleophile 4 at positions *ortho* and *para* of nitroarenes 1−3 to form σ^H, σ^F, and σ^{Cl} adducts in DMF solution (data from Table 2).

It should be stressed that the reaction of 4 with a variety of nitroarenes, particularly 1, 2, and 3, has been thoroughly studied under various experimental conditions; hence reliable data concerning relative rates and equilibrium of the addition, as well as further conversion of the σ^H adducts, are available.[13]

The results of the experimental studies of reactions of 1, 2, and 3 with 4 are presented in Scheme 3. The addition of 4 to 1 and 2 proceeds at positions *ortho* and *para* to give σ^H_{ortho} and σ^H_{para} adducts of 1 and σ^H_{ortho} adduct and σ^F_{para} adduct of 2, whereas the addition to 3 proceeds exclusively at the position *ortho* to give the σ^H_{ortho} adduct. The σ^H adducts undergo base induced β-elimination of HCl to give final VNS products 1a,b, 2b, and 3b, whereas the σ^F adduct loses the F$^-$ anion to give the product of S$_N$Ar reaction 2a. When a strong base is present in excess, the β-elimination is faster than dissociation of the σ^H adducts and the composition of the products 1a,b and 2a,b reflects the relations of rates of the addition. On the other hand, in the presence of a weak base at low concentration, the β-elimination is a slow process and the systems equilibrate. Hence slower formation of the σ^F adducts followed by departure of the F$^-$ anion and S$_N$Ar reaction becomes possible. The addition of 4 at the *para* position of 3 to form σ^{Cl} adducts is too slow to be observed experimentally.

Thus, using competitive experiments, relative rates of the addition of 4 to nitroarenes were determined. These data for 1, 2, and 3 are shown in Scheme 4 (black numbers).

On the basis of the results of the calculations shown in Table 2, it is possible to compare rates of nucleophilic addition of 4 at various positions *ortho* and *para* of 1, 2, and 3 to form σ^H, σ^F, and σ^{Cl} adducts.

The most interesting is comparison of rates of the addition at positions *ortho* and *para* of 2 and 3, right and left parts of Figure 1. The rates of the additions are determined by value of the Gibbs free energies of the transition states. The differences of the $\Delta G^{\ddagger}$ for 3 are expressed by the following equation:

$$\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{\sigma^{Cl}_{para}} - \Delta G^{\ddagger}_{\sigma^{H}_{ortho}} = 3.8 \text{ kcal mol}^{-1}$$

This relatively large difference in the free energies of the two TS leading to isomeric σ^{Cl} and σ^H adducts, which corresponds to about 1200:1 reaction rates ratio (taking into account the statistical factor, two *ortho* positions versus one *para* position), is in good agreement with experimental results. Indeed, it was

Scheme 3. Results of Experimental Studies of the Reactions between Nitroarenes 1−3 and Carbanion 4
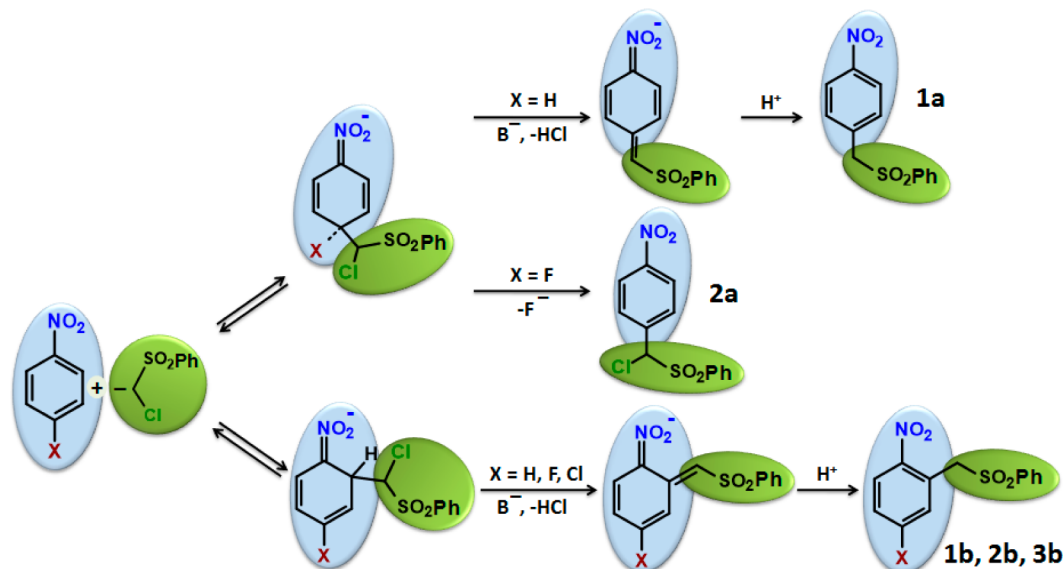
Scheme 4. Relative Rates of the Addition of 4 to 1, 2, and 3, Experimental (Black) and Calculated (Red), Rate of the Addition to Position *ortho* in 1 Taken as the Reference
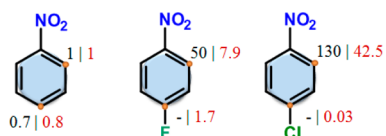
shown that reaction of **4** with **3** proceeds exclusively as S_NArH-VNS. Due to the high energy of TS for the addition of **4** to **3** at the position occupied by chlorine and fast dissociation of the C−Cl bond in the σ^{Cl} adduct, facilitated by rearomatization, according to the calculations, this adduct does not exist, and the TS for the addition (formation of the σ^{Cl} adduct) is in fact the TS for the whole S_NAr reaction (S_NAr proceeds via one TS).

On the other hand, the calculated differences of the free energies of TS for the addition of **4** at positions *ortho* and *para* of **2** are much lower, although they still indicate that addition at positions *ortho* occupied by hydrogen should proceed faster.

$$\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{\sigma^{F}_{para}} - \Delta G^{\ddagger}_{\sigma^{H}_{ortho}} = 0.5 \text{ kcal mol}^{-1}$$

The σ^H adduct is thermodynamically less favorable ($\Delta\Delta G = \Delta G_{\sigma^{F}_{ortho}} - \Delta G_{\sigma^{H}_{ortho}} = -3.0 \text{ kcal mol}^{-1}$) than the isomeric σ^F adduct. Also in this case there is an excellent correlation with experiments. Under conditions that ensure fast further conversion (β-elimination of HCl) of the initially formed σ^H, S_NArH-VNS is the only observed reaction. On the other hand, under conditions that favor equilibrium, that is, the transformation of the σ^H adduct to the VNS product is slow, S_NAr of fluorine can compete with VNS or be even an exclusive process.[13a,b]

For the addition of **4** to nitrobenzene (**1**), activation free energy of the reaction leading to the formation of the *para* σ^H adduct is 0.3 kcal mol⁻¹ lower than $\Delta G^{\ddagger}$ of the addition at positions *ortho* indicating that addition at position *para* should proceed faster than at *ortho*. Also the σ^H_{para} adduct is more stable by 0.8 kcal mol⁻¹ than the isomeric σ^H_{ortho} adduct. Taking into account that there are two positions *ortho* and one position

para, the addition reaction should be slightly faster in the *ortho* position, as is shown in Scheme 4. This result is in perfect agreement with the experiment conducted under conditions that ensure fast β-elimination of HCl from the σ^H adduct indicating that, indeed, addition at the *ortho* position proceeds faster under kinetic conditions. On the other hand, when equilibration is possible, *para* substitution is the only process.[13a] Very low calculated differences between the $\Delta G^{\ddagger}$ values, as well as between relative stabilities of σ^H_{ortho} and σ^H_{para} adducts, indicate that the reaction conditions (e.g., solvent, temperature, cation, and base concentration) can change dramatically its direction.

Computational results presented in this work concern only the relative rates of the σ^H adduct formation in the reaction of **1** with **4** and their relative stabilities. It has to be noticed, however, that in the case when the rate of the consecutive reaction step, base-induced β-elimination of HCL, is relatively low, this step determines the rate of the entire reaction. Elimination of HCl from the σ^H adducts requires antiperiplanar arrangement of the ring hydrogen and chlorine. For the σ^H_{para} adduct, such conformation can be easily adopted without steric hindrance. The situation is different for *ortho* addition. The addition of **4** at the *ortho* position creates two stereogenic centers; hence two diastereoisomeric σ^H adducts are formed. For one of the diastereomers, antiperiplanar arrangement of H and Cl atoms is difficult to attain because of steric repulsion of the phenylsulfonyl and the nitro group. The elimination from this diastereomer should be preceded by its epimerization. Formation of two diastereoisomeric σ^H adducts *ortho* to the nitro group and the epimerization of the unfavorable adduct before the β-elimination was shown experimentally.[14] Our calculations fully confirm this observation. Indeed, two diastereoisomeric σ^H_{ortho} adducts can be formed and only one of them can adopt the antiperiplanar conformation required for HCl elimination.

Very interesting is comparison of the calculated rates of the addition of **4** at the *ortho* positions of **1**, **2**, and **3** expressed by the Gibbs free energies of the TS (Figure 1, left side) with the relative rates of this addition determined experimentally (Scheme 4, SI2). Calculated values of relative rates leading to formation of σ^H_{ortho} adducts for **1**, **2**, and **3** are 1:7.9:42.5 and are

in good qualitative correlation with the relative rates (**1** as a standard) of the addition determined experimentally, 1:50:130.[13a] Although fluorine is considered to exert a stronger electron-withdrawing effect than chlorine, back-donation of the p-electron pairs of fluorine to the electron-deficient nitro-aromatic ring is more efficient; hence the overall electron withdrawing activating effect of fluorine is weaker than that of chlorine.

To explain the differences between calculated and experimental relative reaction rates, it is helpful to compare them with those calculated for the gas-phase reactions. These values are 1:91:2050, so they are much higher than the experimental ones. It appears that the PCM model changes these values in the correct direction but overestimates somewhat the solvation effects.

CONCLUSIONS

For the first time, unbiased quantum chemical calculations of nucleophilic aromatic substitution are presented. Calculations of the addition pathways of a nucleophile to nitrobenzene and p-fluoro- and p-chloronitrobenzenes revealed that for both halonitroarenes the addition at positions *ortho* to form σ^H adducts is faster than at positions *para* to form σ^X adducts. The difference is relatively high for p-chloronitrobenzene ($\Delta\Delta G^\ddagger$ = 3.8 kcal mol^{-1}) and very small for p-fluoronitrobenzene ($\Delta\Delta G^\ddagger$ = 0.5 kcal mol^{-1}). In the former case, due to fast elimination of Cl$^-$, the σ^{Cl} adduct does not exist, so the TS for the addition is in fact the TS of the whole S$_N$Ar reaction, which in this case is a one step process. In the case of p-fluoronitrobenzene, calculated free energies of σ^H_{ortho} and σ^F_{para} adducts indicate that the former is thermodynamically preferred. The results of calculations are in good agreement with experimental results. The generally accepted mechanistic picture of the fundamental process of S$_N$Ar should be therefore corrected: in the majority of cases, the addition of nucleophiles at positions occupied by leaving groups, the key first step of S$_N$Ar, is preceded by reversible addition at positions occupied by hydrogen to form σ^H adducts. Moreover, numerous previous calculations limited to only one reaction pathway leading to S$_N$Ar of halogens are conceptually biased and do not reflect real processes. Even the newest chapter on theoretical treatment of S$_N$Ar reaction suffers from this deficiency.[10l] Thus, the full and complementary mechanistic outlook of nucleophilic substitution in nitroarenes has been described. Additionally, the presented results show that for qualitatively correct predictions of the preferred reaction directions gas-phase calculations are sufficient while for more quantitative results the PCM solvent model is required. The comparison of these two sets of results leads to important conclusions concerning the solvation effects on the studied reactions.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13365.

> Description of computational procedures and method selection, geometries, and energies of the studied structures (PDF)

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Notes

The authors declare no competing financial interest.

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