

Mechanism of Direct Electrophilic Aromatic Amination: an Electrophile is Found by Quantum-Chemical Study --Manuscript Draft--

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Mechanism of Direct Electrophilic Aromatic Amination: an Electrophile is Found by Quantum-Chemical Study

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Abstract

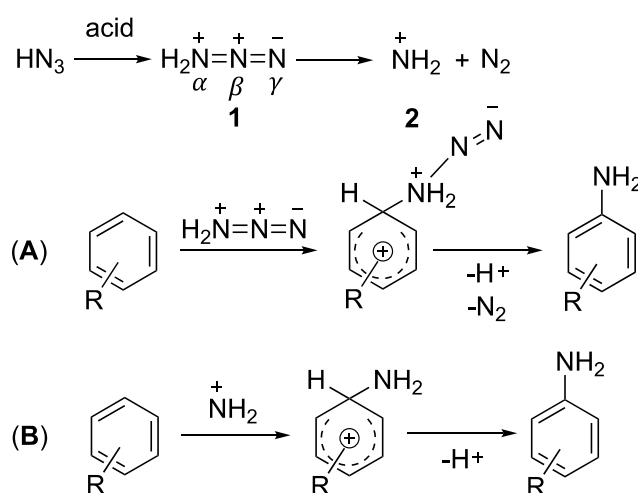
Direct amination is an extremely valuable reaction, allowing for the one-step preparation of aromatic amines. However, its mechanism was poorly studied. Here, for the first time, using quantum chemical calculations, we have shown that direct amination of arenes by hydrazoic acid follows the classical S_EAr mechanism with aminodiazonium cation $H_2N_3^+$ as electrophile. The peculiarity of $H_2N_3^+$ electronic structure has been described using our novel method for tracing the molecular orbitals. The located stationary points and transition states allowed us to define direct amination as S_EAr reaction, which rate is determined by early transition state between π - and σ -complexes. Considering the calculated reaction constant ρ and an early transition state we placed

direct amination of arenes by HN_3 somewhere in-between nitration and halogenations. Our results explain the accumulated experimental data and open a prospect for the development of the new aminating agents working in milder conditions.

Introduction

Aromatic amines are highly valuable building blocks in fine and industrial organic synthesis. Many biologically active compounds, dyes, agrochemicals, and polymers bear aromatic amino moieties. [1] Usually, anilines as well as heteroaromatic amines are prepared via nitration of the corresponding substrate, followed by the reduction of nitro group [2,3] or by other two- or multistep routes. [4-6] Considering an extremely high practical importance of aromatic amines, numerous attempts have been done to directly introduce amino group into aromatics via one-step route. For that purpose such nitrogen-containing compounds as ammonia [7,8], hydroxylamine, its salts and derivatives [9-11], and hydrazoic acid [12-17] were used. However, ammonia and hydroxylamines showed low aminating ability. For instance, in recent studies the yield of aniline from benzene using ammonia generated from ammonium carbonate was 10% at 300 °C and 300 bar in the presence of Rh/Ni-Mn/K-TiO₂ [8]. Amination of toluene by hydroxylammonium salts yielded in at most 65% of aminotoluidines using $(\text{NH}_2\text{OH})_2\cdot\text{H}_2\text{SO}_4/\text{AlCl}_3$. [9] The amination of arenes with organic and inorganic azides in the presence of very strong protic or Lewis acids gave slightly better results. [12-15] In these conditions generated hydrazoic acid (HN_3) acts as the actual aminating agent. However, in this case satisfactory yields can be achieved with a limited number of aromatic substrates such as benzene and its derivatives with moderate electron-donating (e.g., alkylbenzenes) and electron-withdrawing (e.g., chlorobenzene) substituents. Nitrobenzene does not undergo amination by hydrazoic acid with practically significant yields. [13] Among benzenes with strong electron-donating substituents amination was reported for anisole [12,13], whereas no data is available for aniline. Only a few examples of successful direct amination of heterocyclic arenes are known. In instance, the amination of tetrazoles with hydroxylamine-O-sulfonic acid in weakly alkaline aqueous solutions resulted in a mixture of 1- and 2-N-aminotetrazoles in total yield of 38%. [18] N-alkylcarbazoles were aminated in 3,6-positions by NaN_3 in H_2SO_4 (yields are not given). [19] Perimidine reacted with NaN_3 in polyphosphoric acid at 80-90 °C giving 6(7)-aminoperimidines in 62-76% yield. [20] Thus, unfortunately there is no general method of direct amination of arenes to date. First, it is due to fact that the described amination approaches use strong acidic and superacidic conditions, which are inapplicable to the majority of the desired substrates. The other reason for such unimpressive practical results in direct amination of aromatics is a lack of understanding of the possible reaction mechanisms. Unlike most other

important electrophilic substitution reactions direct amination began to be studied much later. Therefore, not only have not been understood the details of the mechanism of this reaction, but even there is no unity in determining possible principal routes of aromatic amination. The understanding of mechanism of direct amination with hydrazoic acid and its derivatives is crucial to broaden the range of suitable substrates and increase preparative yields. Thus, the aim of the study is to investigate possible pathways of electrophilic aromatic amination in nonpolar and polar media using quantum chemical calculations and identify the opportunities and limitations. Overall, there are only several hypotheses regarding the mechanism of direct amination of arenes. According to the current knowledge, direct amination with HN_3 refers to electrophilic aromatic substitution reactions. It starts with the protonation of hydrazoic acid by a stronger acid giving aminodiazonium ion **1** ^[14] (Scheme 1). Considering previous studies, this step can be then followed by two different pathways. In the first one, the aminodiazonium cation **1** (H_2N_3^+) acts as an electrophile itself (pathway **A**), whereas in the second one it decomposes to nitrenium ion **2** (NH_2^+) and nitrogen (pathway **B**) (Scheme 1). ^[12–14,21] In the latter case, the highly reactive nitrenium ion **2** acts as an electrophile. The available experimental results ^[12–14,21] do not allow to distinguish between the pathways **A** and **B**, thus both directions remain equally possible.



Scheme 1. Proposed mechanisms of direct electrophilic amination of arenes

Computational Details

All the calculations were performed in Gaussian 09 (Revision-D.01-SMP) ^[22] and ORCA 3.0.2 ^[23] software.

Quantum Chemical Calculations

The structures of neutral molecules, ions, sigma complexes and transition states were fully optimized with Kohn–Sham density functional theory (DFT) using global-hybrid GGA functional B3LYP^[24,25] and aug-cc-pVDZ^[26,27] basis set. The stationary points were confirmed by harmonic frequency calculations. The transition states were characterized by imaginary vibrational mode and verified by intrinsic reaction coordinate calculation. The neutral molecules, ions, sigma complexes and transition states were solvated using conductor-like polarizable continuum model (CPCM).

Method for tracing the molecular orbitals (MTMOs)

The energy dynamics and spatial distribution of the individual molecular orbitals (MOs) during the decomposition of singlet H_2N_3^+ **1** were studied by relaxed potential energy surface (PES) scan by increasing the N-NH₂ distance from 0.900 Å to 20 Å with a high resolution of 800 steps. The calculations were performed by DFT at B3LYP/aug-cc-pVDZ level of theory using ORCA 3.0.2 software. According to the data obtained, the dependences of the energies of all MOs on the N-NH₂ distance during the process of spatial separation of NH₂⁺ and N₂ were found. The number of orbitals in the initial molecular system (H_2N_3^+) exactly corresponded to the total number of orbitals of the fragments formed (NH₂⁺ and N₂). By revealing the correspondence between the MOs of the H_2N_3^+ and the MOs of the decomposition products (NH₂⁺ and N₂), the energy diagram of the MOs transition was constructed. Then, the contribution of each MO and the total contribution of each fragment to the formation of the H_2N_3^+ were calculated. To perform the tracing, comparing and visualizing of the spatial distribution of the electronic density, the special software was developed and applied.^[28]

Calculation of rate constants

The reaction rate constants were calculated using Eyring–Polanyi Equation 1:

$$k = \frac{\kappa k_B T}{h} \cdot e^{\frac{-\Delta G^\ddagger}{RT}} \quad (1)$$

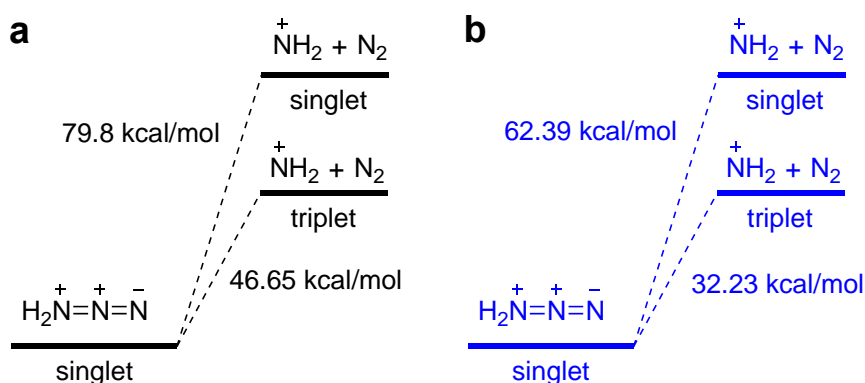
where ΔG^\ddagger is the Gibbs energy of activation, κ is the transmission coefficient ($\kappa = 1$), k_B is Boltzmann's constant, h is Planck's constant, R is gas constant, and T is absolute temperature ($T = 298.15$ K).

Results and discussion

Mechanism of direct amination: Pathway B

Herein, we consider two possible pathways **A** and **B** of direct amination (Scheme 1) proposed earlier elsewhere. [12–14,21] Both of them refer to electrophilic aromatic substitution. However, in the first one the **1** H_2N_3^+ acts as electrophile (pathway **A**), while in the second one the **1** H_2N_3^+ decomposes giving **2** NH_2^+ , which then acts as electrophile (pathway **B**) (Scheme 1).

If we assume that direct amination follows the pathway **B** we need to assess the energy required for the NH_2^+ generation.



Scheme 2. Thermodynamic characteristics of NH_2^+ formation from H_2N_3^+ calculated at B3LYP/aug-cc-pvdz level of theory in (a) gas phase and (b) water (CPCM solvation model).

As can be seen from Scheme 2 (a), the energy of bare **2** NH_2^+ formation from **1** H_2N_3^+ is 79.8 kcal/mol. Solvation decreases the energy of NH_2^+ formation to 62.39 kcal/mol (Scheme 2 (b)).

For a deeper understanding of N- NH_2 bond nature in **1** H_2N_3^+ we used a method for tracing the molecular orbitals (MTMOs), developed by us. [28] Using MTMOs we have found the correspondence between the MOs of the H_2N_3^+ and the MOs of its decomposition products - NH_2^+ and N_2 (Figure 1-2S, Table 1-3S). The analysis showed that occupied MO 11 of H_2N_3^+ is derived from N_2 HOMO, while unoccupied MO 14 of H_2N_3^+ is derived from NH_2^+ LUMO. An important notice is that N_2 HOMO energy (-0.438559 Ha) is higher than the NH_2^+ LUMO energy (-0.610093 Ha). This causes a very strong interaction between these orbitals leading to their slow separation during an increase in N- NH_2 distance (Figure 1 a, b). The analysis of MO energy changes during H_2N_3^+ formation showed that the main contribution to reducing the total energy of all occupied MOs of H_2N_3^+ is made by MOs derived from N_2 (Table 3S). These MOs significantly reduce their energy, while H_2N_3^+ orbitals derived from NH_2^+ MOs change their energy slightly and in different directions. Thus, apparently, the main reason for the interaction between NH_2^+ and N_2 with a decrease in energy and the formation of a very strong chemical bond is the possibility of additional

delocalization of electrons of the N_2 molecule on the nuclei of the nitrogen and hydrogen atoms of NH_2^+ .

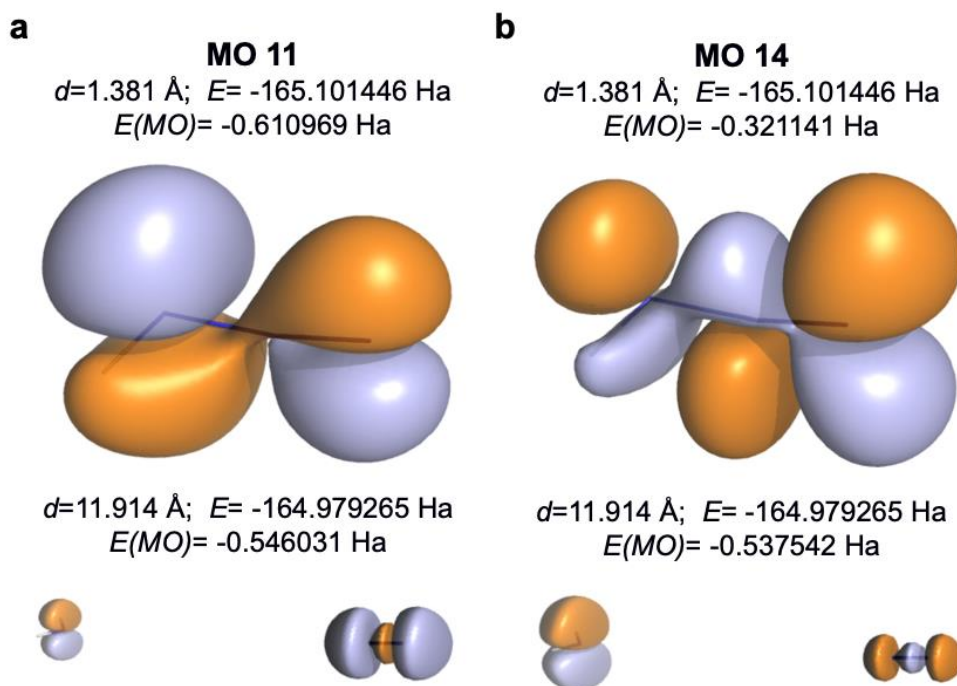


Figure 1. A special case of $H_2N_3^+$ (a) 11 and (b) 14 MOs transformation into N_2 MO and NH_2^+ MO, respectively. The MOs separation is very slow and continues up to a N-NH₂ distance of 50 Å. The videos of all MO transformations are given in Supporting.

Mechanism of direct amination: Pathway A

If we now consider pathway A for direct amination we need to locate the structures and free energies of stationary points on the potential energy surface (PES) of the reaction. Using benzene as an example, we followed the classical electrophilic aromatic substitution mechanism and found the structures and free energies of π -complex, σ -complex, and corresponding transition states (Figure 2, Scheme 3).

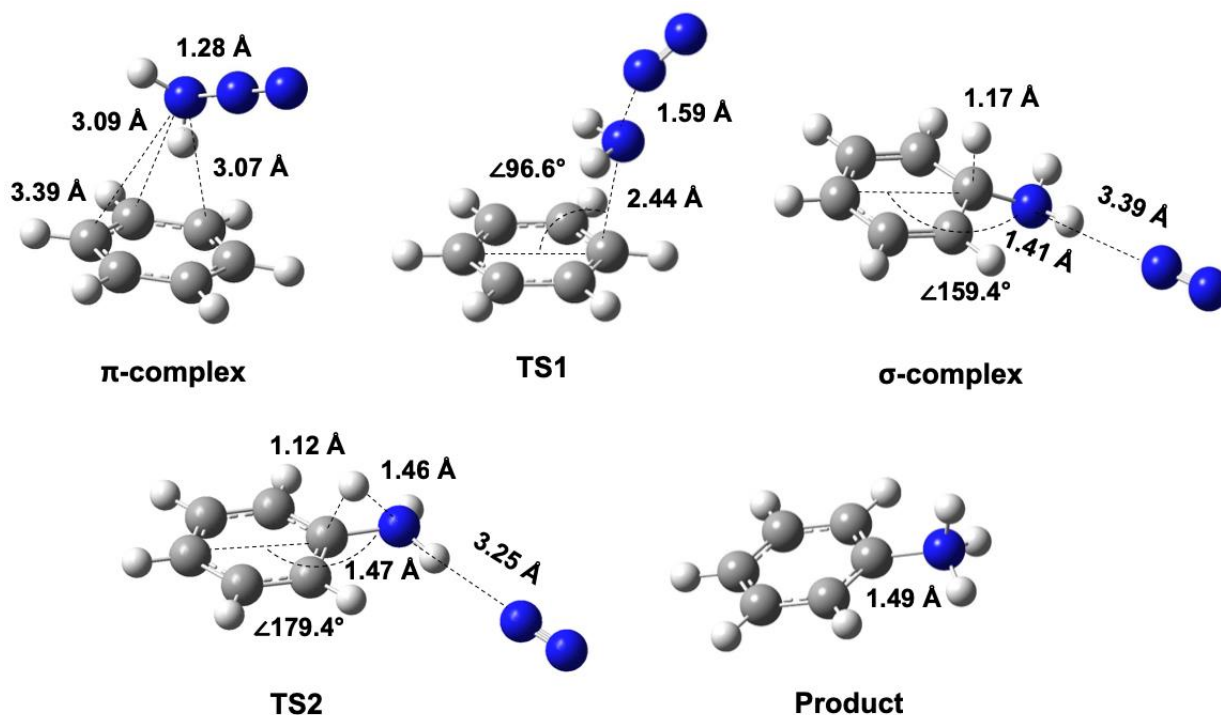
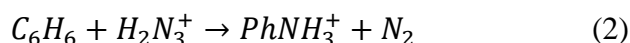


Figure 2. Structures of the stationary points on the potential energy surface in the direct amination of benzene by H_2N_3^+ . The bond distances (angstroms) and bond angles (degrees) are shown according to the results of calculations at B3LYP/aug-cc-pvdz level of theory.

The calculation results predict amination to be thermodynamically favorable. The Gibbs free energy change in the reaction of anilinium ion and nitrogen formation from benzene and H_2N_3^+ is -85.75 kcal/mol (Equation 2). The data for the substituted arenes are given in Table 1 and will be discussed further.



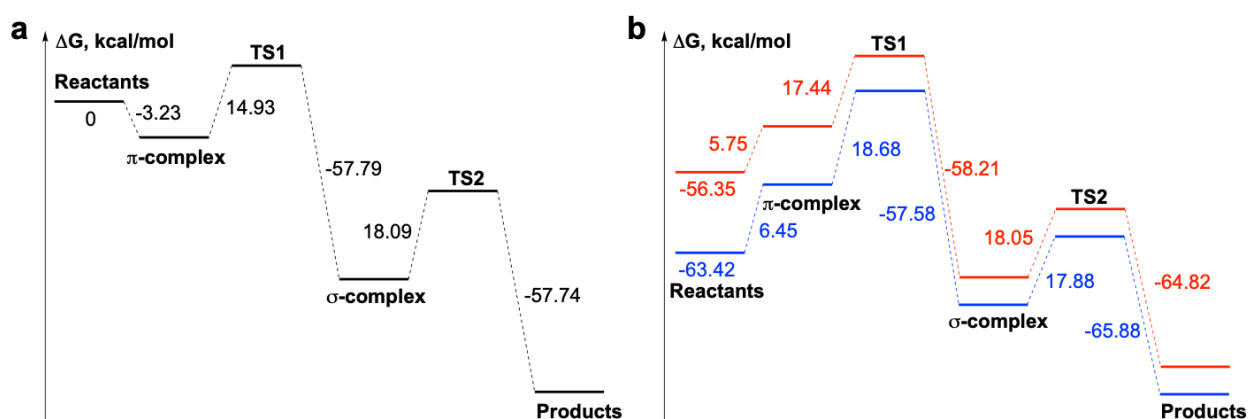
As can be seen from Figure 2, benzene and H_2N_3^+ form a C atom coordinated π -complex with a C-N distances of 3.07-3.39 Å. The strong interaction and charge transfer between H_2N_3^+ and benzene in π -complex facilitate the further decomposition of H_2N_3^+ observed in TS1 (-523.52 cm^{-1}). The geometry of TS1 shows an increased N-NH₂ bond length of 1.59 Å in H_2N_3^+ specie and decreased C_{Ar}-N _{α} distance of 2.44 Å indicating that N-NH₂ bond cleavage in H_2N_3^+ is accompanied by simultaneous formation of C-N _{α} bond between appearing NH_2^+ and benzene. In σ -complex the C-N _{α} distance reduces to 1.41 Å, whereas N-NH₂ distance increases to 3.39 Å demonstrating the final appearance of C-N _{α} bond and release of nitrogen. A comparison of the C-N distance in π -complex, TS1, and σ -complex shows that TS1 has a structure more similar to π -complex. Thus, according to the Hammond postulate the direct amination has an earlier transition state than halogenations since halogenations show a closer structural similarity between the σ -complex and corresponding transition state. [29-31]

1 The PESs for the direct amination of benzene by **1** H₂N₃⁺ in gas phase, dichloromethane and water
2 are shown in Scheme 3. According to the data, free Gibbs energies of π -complex and TS1 increase
3 in polar aqueous medium versus non-polar (Scheme 3). Specifically, the formation of the π -
4 complex in gas phase is an exergonic process by -3.23 kcal/mol (Scheme 3, a), whereas in aqueous
5 solution it is endergonic by 6.45 kcal/mol (Scheme 3, b). Such a difference can be explained by
6 the strongest solvation of **1** H₂N₃⁺ (-61.75 kcal/mol in water) as specie with the smallest size and
7 highest charge density among the other amination intermediates. Indeed, the structure of the π -
8 complex in gas phase shows the distance between carbon and N _{α} of 3.07 Å, whereas in water it
9 increases up to 3.27 Å. At the same time, the opposite pattern is observed for TS1 with the C-N _{α}
10 distance decreased in water (2.35 Å) and increased in gas phase (2.44 Å) leading to an increased
11 free energy of TS1 in aqueous phase. The similar changes in energy were observed for the
12 formation of the π -complex in aqueous and gas phase in nitration.^[29] The rest of the PES profile
13 is similar for the gas phase and water.
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16 As we can see in both gas phase and water the rate determining step in benzene amination by **1**
17 H₂N₃⁺ is the transition state TS1 between π - and σ -complexes, which formation from π -complex
18 in gas phase requires 14.93 kcal/mol (Scheme 3). In TS1 the energy of the N-NH₂ bond cleavage
19 is compensated by the energy of new C-N bond formation between the appearing **2** NH₂⁺ and
20 benzene (Figure 2). The stabilization of **2** NH₂⁺ facilitates the release of nitrogen and reduces the
21 energy required for the **1** H₂N₃⁺ decomposition from 79.8 kcal/mol (pathway **B**, Scheme 2) to 14.93
22 kcal/mol (comparing to the energy of **1** H₂N₃⁺ decomposition with formation of bare **2** NH₂⁺). As
23 a result, the energy required for electrophile generation in the pathway **B** is significantly higher
24 than the energy of rate determining step in pathway **A**, hence the pathway **B** can be ruled out as
25 less thermodynamically favorable.
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28 Very little experimental data are known on the effect of solvent polarity on electrophilic aromatic
29 amination. The calculations predict the non-polar media to be the most convenient for this reaction
30 (Scheme 3) and provide a rational explanation to the fact that the amination of the mesitylene by
31 NaN₃/AlCl₃/HCl in solvents with low polarity results in better yields of the amination products.
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Scheme 3. Free energies for the stationary points on the PES in the direct amination of benzene by H_2N_3^+ calculated at B3LYP/aug-cc-pvdz level of theory in (a) gas phase (black), (b) dichloromethane (red) and water (blue) (CPCM solvation model). The indicated energies of reactants in dichloromethane and water are presented comparing to gas phase.

Thus, for the first time we have clearly shown that the pathway **A** is thermodynamically favored over the pathway **B** and direct amination of arenes by hydrazoic acid proceeds via H_2N_3^+ as electrophile. Also, we demonstrated that direct amination refers to electrophilic aromatic substitution reactions, which rate is determined by the transition state TS1, and better proceeds in non-polar media.

In order to study the influence of the substitution in aromatic ring on the structure and energies of the stationary points on amination PES we took six monosubstituted benzenes: toluene, aniline, anisole, chlorobenzene, nitrobenzene and anilinium ion.

Taking *para*- isomer as an example, we may see that with an increase of ionization potential (PI) of the corresponding substituted benzene the distance between the *para*-carbon (C_4) and N_α in π -complex increases. The shorter $\text{C}_4\text{-N}_\alpha$ distance in π -complexes of benzenes with electron-donating substituents indicates stronger interaction and a more significant charge transfer between H_2N_3^+ and a substrate.

Table 1. *Para*-carbon and N_α distances in π -complexes (d_π), TS1 (d_{TS1}) and σ -complexes (d_σ) and differences in free energies between TS1 and π -complexes ($\Delta G_{\text{TS1}-\pi}$) and σ -complexes and TS1 ($\Delta G_{\sigma\text{-TS1}}$) for *para*-substituted anilines.

PhX; X=	PI [eV] [33]	d_π [Å]	d_{TS1} [Å]	d_σ [Å]	$\Delta d_{\text{TS1}-\pi}$ [Å]	$\Delta G_{\text{TS1}-\pi}$ [kcal/mol]	$\Delta d_{\text{TS1}-\sigma}$ [Å]	$\Delta G_{\sigma\text{-TS1}}$ [kcal/mol]
NH ₂	7.7	-	2.60	1.46	-	-	1.136	-71.88
OMe	8.22	2.89	2.53	1.46	0.353	12.18	1.083	-67.60
Me	8.82	2.97	2.47	1.44	0.504	13.61	1.035	-61.81

H	9.245	3.07	2.44	1.41	0.626	14.93	1.030	-57.79
Cl	9.07	-	2.47	1.44	-	-	1.033	-58.84
NO ₂	9.92	3.28 ^a	2.41	1.38	0.867	14.56	1.032	-51.19

^a In case of nitrobenzene no specific carbon orientation was observed in π -complex

The opposite relationship is observed between the PI and C4-N_α distance in TS1: with a decrease of PI the C4-N_α distance increases (Table 1). Indeed, the more activating substituent is the earlier rate determining TS1 is observed as the reaction rate increases ^[29]. Therefore, the structures and energies of rate determining TS1 of substrates with electron-donating substituents is further away from the corresponding σ -complexes. The length of the C4-N_α bond in σ -complexes decreases with an increase of PI (Table 1). Obviously, the stronger electron-withdrawing substituent stimulates the more pronounced electron donating effect of amino group resulting in a higher conjugation of appearing amino group and aromatic ring and shorter C4-N_α bond length.

It could be seen that reaction rate increases with an increase of the substrate activity: the highest rate is observed for aniline, while the lowest - for nitrobenzene (Table 2). The calculated $k_{\text{substrate}}/k_{\text{benzene}}$ ratio for toluene is 9.3/1 for *para*- and 7.1/1 for *ortho*- position (Table 2). These results are overall in agreement with the experimental data obtained by Olah et al, where $k_{\text{substrate}}/k_{\text{benzene}}$ rate for toluene was 4/1 (25 °C, H₂N₃⁺AlCl₄⁻) ^[14] or 3/1 (55 °C, Me₃SiN₃, TfOH) ^[34] depending on amination conditions. Considering the $k_{\text{substrate}}/k_{\text{benzene}}$ rate found for other arenes (Table 2), we can conclude that both calculations and experiments show that amination has low substrate selectivity.

Table 2 shows the free energies of the stationary points on the PES for the direct amination of toluene, aniline, anisole, chlorobenzene and nitrobenzene by **1** H₂N₃⁺.

Toluene is activated in *S_EAr* and *ortho*-/ *para*- directing. The formation of *ortho*- and *para*- oriented π -complexes between toluene and H₂N₃⁺ is thermodynamically favorable with *para*- position preferred over *ortho*-. For toluene the formation of TS1 is a rate determining step with the lowest activation energy for *para*- position. The thermodynamics of σ -complexes and TS2 formation shows that in both cases *para*- isomer is the most favorable and *meta*- isomer is the least favorable. However, among the products the most thermodynamically favorable is *meta*- toluidinium ion and the least thermodynamically favorable is *ortho*- toluidinium ion (Table 2).

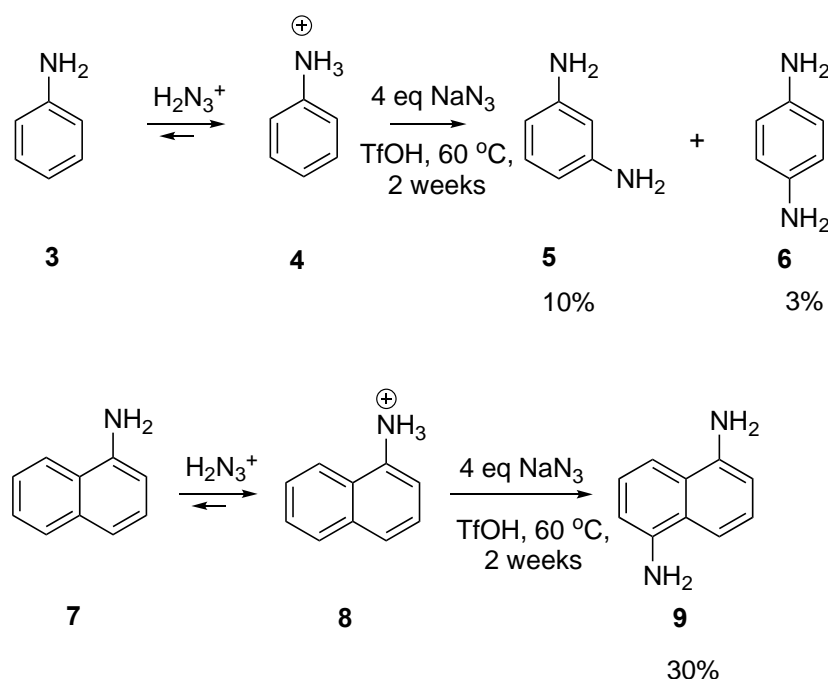
Anisole is activated in *S_EAr* and *ortho*-/ *para*- directing. The formation of *para*- oriented π -complex between anisole and H₂N₃⁺ requires -7.21 kcal/mol and is more thermodynamically favourable than for toluene. The energy required for TS1 formation for anisole is also reduced comparing to benzene and toluene with *para*- position preferred over *ortho*-. The same is observed in σ -

complexes, whereas in TS2 and products *ortho*- isomer is thermodynamically favoured over *para*- (Table 2).

Chlorobenzene is deactivated in S_EAr , but *ortho*-/*para*- directing. The formation of π -complex between chlorobenzene and $H_2N_3^+$ is less thermodynamically favourable than for benzene and toluene. Same as for toluene, for chlorobenzene the TS1 is a rate determining step with the lowest activation energy for *para*- position. In σ -complexes and TS2 of the chlorobenzene *para*- isomer is also the most thermodynamically favorable and *meta*- isomer is the least thermodynamically favorable.

Nitrobenzene is strongly deactivated in S_EAr and *meta*- directing. The π -complex formation between nitrobenzene and $H_2N_3^+$ requires 7.82 kcal/mol. Unfortunately, we were not able to find TS1 for *meta*- isomer, but σ -complexes energies indicate *meta*- position as the most thermodynamically favorable one (Table 2). Indeed, the experiments showed, that the amination of nitrobenzene resulted in trace amount of *meta*- isomer ^[13].

The amination of aromatic amines is a special case. On the one hand, aniline **3** is evidently the most active aromatic substrate in the amination (Tables 1, 2). At the same time, there are no successful experimental results on its amination to date. The calculations show that the formation of π -complex found for aniline **3** should proceed easily and is followed by TS1 with the lowest activation energies among the studied compounds. The *para*- position is thermodynamically favored in TS1, TS2 and products, whereas in σ -complexes the *ortho*- isomer is preferable (Table 2). Thus, the amination of aniline **3** is thermodynamically possible, however, it has not been reported experimentally. It could be explained by the different reasons. On the one hand, aniline **3** is obviously a stronger base than $H_2N_3^+$, thus it would replace it from its salt leading to a decrease in electrophile concentration. On the other hand, in the strong acidic media there is an equilibrium between aniline **3** and anilinium ion **4** (Scheme 4). The latter is deactivated in S_EAr reactions due to the electron-withdrawing effect of NH_3^+ . Calculations predict anilinium ion to be even more deactivated than nitrobenzene (Table 2). To identify the actual reason of aniline sluggishness in direct amination, we aminated aniline **3** and, for the first time, 1-aminonaphthalene **7** in the same conditions using NaN_3 in CF_3SO_3H .



Scheme 4. Direct amination of aniline and 1-aminonaphthalene by NaN_3/TfOH

As a result of aniline **3** direct amination, we have obtained the reaction mixture containing aniline **3** (87%), *meta*- phenylene diamine **5** (10%) and *para*- phenylene diamine **6** (3%) according to the GC and GC-MS (Figure 3S) data (Scheme 4). Positional selectivity for phenylene diamines was identified by comparing their retention times and R_f to pure compounds. The observed positional selectivity indicates that the major process is amination of anilinium ion. Experimental results are supported by calculations that predict only *meta*- and *para*- isomers to be thermodynamically favorable among the products of anilinium ion amination (Table 2). The 1-aminonaphthalene **7** amination in the same conditions resulted in 1,5-diaminonaphthalene **9** as a major product with 30% yield (Scheme 4). It is known that naphthalenes with electron-withdrawing group in 1 position undergo electrophilic substitution in 5 position. For example, electrophilic bromination of 1-nitronaphthalene yielded in 30% of 1-bromo-5-nitronaphthalene.^[35] At same the time, nitration of 1-aminonaphthalene in non-acidic conditions led in a mixture of 1-amino-2-nitronaphthalene and 1-amino-4-nitronaphthalene in a ratio 22:71%.^[36] Therefore, our data indicate that product **9** is obtained as a result of naphthalene-1-aminium **8** amination. Thus, even if the H_2N_3^+ is partially deactivated due to the proton exchange with anilines as the bases, the remaining amount of electrophile is still able to aminate anilinium ion.

Table 2. Free energies difference from reactants and rate constant ratios for the direct amination of aniline, anisole, toluene, benzene, chlorobenzene, nitrobenzene and anilinium ion by **1** H_2N_3^+ .

PhX; X=	NH ₂ position	ΔG difference from reactants, kcal/mol					$k_{\text{subst}}/k_{\text{benzene}}$
		π -complex	TS1	σ -complex	TS2	Products	
NH ₂	<i>ortho</i> -	-9.38	2.60	-73.90	-35.54	-90.45	147
	<i>meta</i> -	- ^a	- ^a	- ^b	-41.12	-91.53	-
	<i>para</i> -	- ^b	-0.13	-72.01	-41.55	-91.75	1·10 ⁵
OMe	<i>ortho</i> -	- ^b	6.20	-61.37	-91.97	-36.80	13
	<i>meta</i> -	- ^a	- ^a	- ^b	- ^b	-35.77	-
	<i>para</i> -	-7.21	4.98	-62.63	-83.06	-36.16	100
Me	<i>ortho</i> -	-4.34	9.42	-51.96	-31.15	-86.71	7.1
	<i>meta</i> -	- ^a	9.65	-49.21	-30.70	-87.59	-
	<i>para</i> -	-5.25	8.36	-53.46	-32.47	-86.78	9.3
H	-	-3.23	11.70	-33.24	-28.01	-85.75	-
Cl	<i>ortho</i> -	-0.31	14.04	-43.73	-24.55	-83.31	2.7
	<i>meta</i> -	0.65	- ^a	-40.41	-22.78	-80.92	-
	<i>para</i> -	- ^c	13.63	-45.21	-25.00	-81.21	-
NO ₂	<i>ortho</i> -	7.82	18.03	-28.66	-14.82	-80.91	5·10 ⁻³
	<i>meta</i> -		- ^d	-31.25	-14.52	-74.92	-
	<i>para</i> -		22.39	-28.80	-14.27	-74.33	3·10 ⁻⁶
NH ₃ ⁺	<i>ortho</i> -	- ^c	- ^b	45.58	70.83	11.80	-
	<i>meta</i> -		86.36	- ^b	58.26	-7.59	-
	<i>para</i> -		85.72	- ^b	56.08	-10.69	-

^a During optimization *meta*- position converged to *para*-

^b Proton transfer was observed

^c We were not able to find a π -complex

^d We were not able to find TS1

Direct amination among the *S_EAr* reactions

In attempt to compare the direct amination with the other *S_EAr* reactions we calculated the rate constants for the amination of studied compounds using Eyring–Polanyi Equation (1). The free energies of TS1 formation were taken as activation free energies. The rate constants were then correlated with the σ_p and σ_p^+ values of the corresponding substituents ^[37] (-NH₂, -OMe, -Me, -H, -Cl, -NO₂). The plot showed good correlation between $\lg k_{\text{substrate}}/k_{\text{benzene}}$ and σ_p ($R^2 = 0.997$, $\rho = -$

7.2) and weaker correlation between $\lg k_{\text{substrate}}/k_{\text{benzene}}$ and σ_p^+ ($R^2 = 0.899$, $\rho = -4.9$). In contrast, if free energies of σ -complex formation were used for the rate constants calculation the correlation was much better with σ_p^+ ($R^2 = 0.988$, $\rho = -8.5$) than with σ_p ($R^2 = 0.908$, $\rho = -10.7$). The overall similar results were observed in [29], where authors correlated computed activation free energies and free energies of σ -complex formation with σ_m/σ_p and σ_m^+/σ_p^+ for nitration. For amination as well as for nitration the correlations are consistent with early rate-determining TS when the positive charge is located on electrophile and bond between nitrogen and aromatic carbon has not been formed. In contrast, in σ -complex there is a resonance interaction between the substituent and the positive charge in substitution site, [29] which explains better correlation with σ_p^+ . As authors of [29] we have also observed that the substituent effect on the free energy for σ -complex is more pronounced compared to TS1 (Table 2).

Table 3. The reaction constants for different S_EAr reactions

Reaction	ρ
Bromination (CH_3COOH) [37]	-13.1
Chlorination ($\text{CH}_3\text{COOH}+\text{H}_2\text{O}$) [37]	-13.0
Acylation (CH_3COCl , AlCl_3 , $\text{C}_2\text{H}_2\text{Cl}_2$) [37]	-8.6
Amination (HN_3)	-4.9^a / -8.5^b
Nitration ($\text{H}_2\text{SO}_4+\text{HNO}_3$) [37]	-6.4
Amination (PhXN_3 , AlCl_3) [38]	-6.0
Amination (PhXN_3 , CF_3COOH , $\text{CF}_3\text{SO}_3\text{H}$) [39]	-4.5

^a found using the free energies of TS1 formation for the rate constants calculation

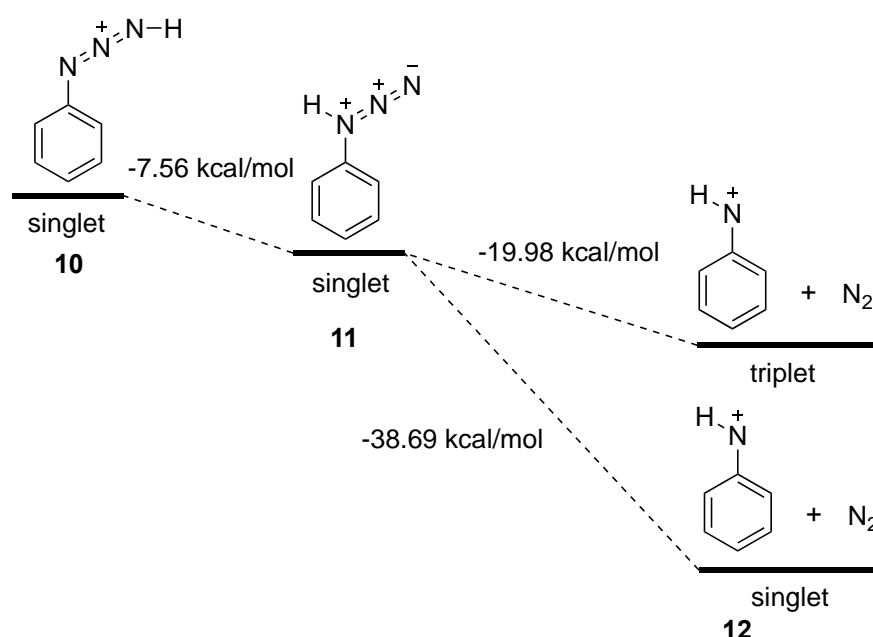
^b found using the free energies of σ -complex formation for the rate constants calculation

The predicted ρ values and observed similarities allowed us to put amination of arenes by H_2N_3^+ somewhere close to nitration (Table 3). As we stated above, amination is characterized by an earlier transition state than halogenations since TS1 in amination shows more similarity to the π -complex, whereas TS in halogenations is more similar to the σ -complex. [30,31] Nitration was also shown to have an earlier transition state than halogenations. [29] It is quite complicated to compare nitration and amination in terms of TS location. On the other hand, it is well known that nitration of aniline gives a mixture of *para*- and *meta*- isomers in a ratio of 51% to 47% with 95% yield, while amination of aniline results in only traces of *meta*- (10%) and *para*- (3%) phenylenediamines. In both cases, aniline forms a conjugated acid due to strong acidic conditions and becomes deactivated. However, it still undergoes nitration in rigorous conditions, while is more sluggish to amination. We may observe the same situation for nitration and amination of

nitrobenzene. From this point we may say that amination is quite similar to a Friedel-Crafts alkylation and acylation, which also almost do not proceed with strongly deactivated substrates. Thus, direct amination refers to electrophilic substitution reactions with an early transition state.

Future of direct amination

Strong acidic conditions required for amination of arenes by HN_3 significantly reduce the number of substrates suitable for amination. To overcome this problem, the derivatives of HN_3 such as arylazides can be used. For comparison, we found the thermodynamic characteristics of **12** PhNH^+ formation from **10** (**11**) PhHN_3^+ (Scheme 5).



Scheme 5. Thermodynamic characteristics of PhNH^+ formation from PhHN_3^+ in gas phase (B3LYP/aug-cc-pVDZ).

The conjugation between of NH^+ and aromatic ring stabilizes the appearing nitrenium ion **12** and significantly decreases the energy of nitrogen cleavage. It makes the process of **12** PhNH^+ formation thermodynamically favourable that, in turn, makes **10** (**11**) PhHN_3^+ totally different from **1** H_2N_3^+ . The calculation results are supported by the fact that arylazides react with benzene giving diphenylamines in the presence of CF_3COOH ,^[39] i.e. in much less acidic conditions than required for direct amination of arenes with HN_3 . However, the mechanism of direct amination of arenes by **10** (**11**) PhHN_3^+ and its derivatives require special investigation.

Apparently, the use of organic azides for amination might be promising as reaction would proceed in milder conditions.

Conclusions

Overall, for the first time, using quantum chemical calculations we have shown that direct amination of arenes by hydrazoic acid follows the classical S_EAr mechanism with aminodiazonium cation $H_2N_3^+$ as electrophile. Using method for tracing of the molecular orbitals we have shown that the peculiarity of the $H_2N_3^+$ electronic structure is that the N_2 HOMO energy (-0.438559 Ha) is higher than the NH_2^+ LUMO energy (-0.610093 Ha), which leads to a very slow separation of these orbitals during the nitrogen elimination. The located stationary points allowed us to define direct amination as S_EAr reaction, which rate is determined by the transition state between π - and σ -complexes. The structural similarity between the transition state and π -complex shows that direct amination has an early transition state. The comparison of amination and other S_EAr reactions in terms of transition state location allowed us to place it somewhere in-between nitration and halogenations closer to nitration and Friedel-Crafts alkylation/acylation. We also argue that using organic azides, such as phenylazide, instead of HN_3 for the amination of arenes, can be energetically more beneficial and safer.

Supporting Information Summary

The following data is provided in supporting information: the energies of individual MO over increasing N_α - N_β distance during N_2 elimination from $H_2N_3^+$ (Figure 1S), the energy diagram of the formation of $H_2N_3^+$ from NH_2^+ (Figure 2S), the structural parameters of species $[NH_2 + N_2]^+$ (Table 1S), the thermodynamics of various pathways of $H_2N_3^+$ decomposition (Table 2S), the energy changes of each MO during the formation of $H_2N_3^+$ from NH_2^+ and N_2 (Table 3S), the videos of all MO transformations, and experimental section including NMR, IR and GC-MS spectra of the synthesized compounds (Figure 3-9S).

Acknowledgments

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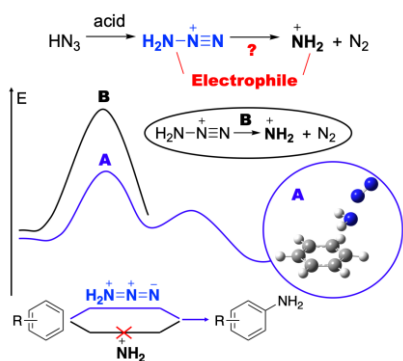
Keywords: amination, density functional theory, electrophilic substitution, hydrazoic acid, tracing the molecular orbitals

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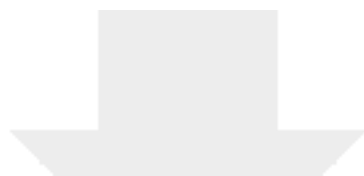
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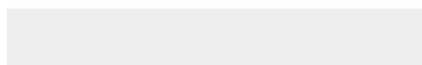
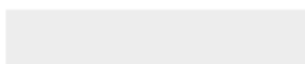
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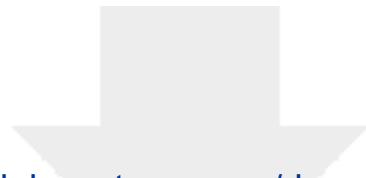


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