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Computational Study of the Amination of Halobenzenes and Phenylpentazole. A Viable Route to Isolate the Pentazolate Anion?

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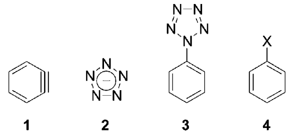
Abstract: Amination of halobenzenes, which proceeds via the benzyne intermediate (**1**), has been studied using quantum chemical methods. The computational data are in agreement with experimentally observed trends in reactivity and provide a qualitative explanation for the observed hydrogen isotope effects. To investigate if this is a viable way to isolate the pentazolate anion (**2**), the reactivities of the halobenzenes have been compared to phenylpentazole (**3**). The reaction energetics for phenylpentazole become favorable after complexation with Zn^{2+}.

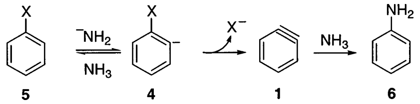
Amination of halobenzenes is a well-known reaction in organic chemistry. In its original form, halobenzenes are treated with excess sodium or potassium amide in liquid ammonia at −33 °C to produce anilines. A number of studies have been published concerning this reaction and on the properties of the benzyne intermediate (**1**), which is formed during the reaction.[1−5]

The first complete mechanistic study of the amination reaction was conducted by Roberts et al. in 1956.[3] On the basis of observed isotope effects, they argued that the amination reaction could proceed by two different mechanisms. The formation of **1** from bromobenzene was thought to proceed via a concerted mechanism, while chlorobenzene reacts through a stepwise mechanism. Bunnet et al. refuted this in 1979[2] when they proved the existence of the *o*-bromophenyl anion, thereby ruling out the concerted mechanism. Today, all halobenzenes are believed to react by the same mechanism (Scheme 1). First, the basic amide abstracts a proton ortho to the halogen (halobenzenes without an *ortho*-hydrogen fail to react). In the following step of the reaction the halogen leaves the intermediate anion (*o*-halobenzene anion, **4**), producing the highly reactive intermediate **1**. Finally, **1** reacts with ammonia to form the product aniline.

CHART 1



SCHEME 1



Roberts et al. reported the reactivity order for the halogens, Br > I > Cl ≫ F, with no product observed when the halogen is fluorine.[3] This order of reactivity was explained by two factors. First, the *ortho*-hydrogen is removed as a positive ion (proton) and the rate for this reaction step is believed to follow the electronegativity of the halogens (F > Cl > Br > I). Second, the halide must depart, and the rate order for this process is suggested to be I > Br > Cl ≫ F, i.e., in the opposite order. The proton-transfer step is rate determining for bromobenzene, while for chlorobenzene the benzyne formation influences the rate. For fluorobenzene the rate of departure of the halide is believed to be too slow for the reaction to proceed.

One of the reasons for our interest in this reaction is the possibility to use it as a route to isolate the elusive pentazolate anion (*cyclo*-N_5^-, **2**) from phenylpentazole (**3**). In recent years, there has been a large interest in polynitrogen compounds such as N_4[6−9] and the ions of N_5[10−16] as potential high energy−density materials. The N_5^+ ion was first synthesized in 1999, and Christe and co-workers have since then reported the preparation and isolation of several N_5^+ salts.[10,11,17] As early as in the late 1950s, Ugi and Huisgen synthesized and studied the stability of arylpentazoles[18,19] and tried to isolate **2** from them.[20] The formation of **2** from arylpentazoles in independent mass spectrometry experiments has recently been reported.[13,14,16] In a recent communication, the generation of **2** from arylpentazoles by treatment with Ceric(IV) ammonium nitrate in a methanol−water solu-

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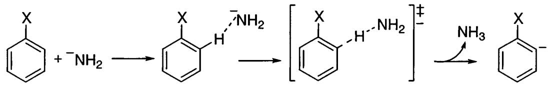
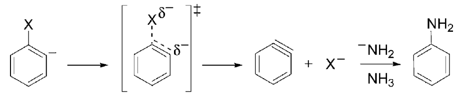
SCHEME 2



7 **8** **9TS** **4**

SCHEME 3



4 **10TS** **1** **6**

tion was presented.[15] In their original work, Ugi and Huisgen used the amination reaction as one of their attempts to obtain **2**.[21] One can only speculate whether the reason for their negative results was the limited detection techniques available at the time or the unsuitability of the reaction. The amination of arylpentazoles may still be an interesting route to obtain **2** in solution. A better understanding of the mechanism and reaction energetics for the amination reaction would be helpful in the quest to reach this goal.

We have thus studied the first two important steps of the amination reaction for chlorobenzene, bromobenzene, and fluorobenzene leading to the formation of the benzyne intermediate. The results for the halobenzenes have been compared to those for **3** to evaluate if this is a possible route to isolate **2**.

Methods and Procedure. All stationary points, minima, and transition states of the first part of the reaction, the proton transfer (Scheme 2), were fully optimized and characterized by vibrational frequency analysis at the B3LYP/6-31+G* level. The average error in calculations of reaction energetics with B3LYP and large polarized basis sets can be estimated to ca. 3.5 kcal/mol.[22] For comparison, we have also computed MP2/6-31+G* energies at the B3LYP/6-31+G* optimized geometries. It is generally considered that MP2 produces relative energies for closed-shell systems of similar accuracy as B3LYP. Solvent effects were estimated by the polarizable continuum model (PCM).[23,24] Single-point calculations were performed at the PCM-B3LYP/6-31+G* level, utilizing the Bondi van der Waals radii with standard scaling factors for the cavity generation and the experimental dielectric constant of liquid ammonia (22.4 at −33 °C). This approach was found to reproduce reasonably well the experimental solvation energies of the halide ions, Cl^-, and Br^- in liquid ammonia.[25−27] All characterization of the stationary points concerning the first part of the reaction was performed using the Gaussian 98 suite of programs.[28]

The second part of the reaction, the formation of **1** (Scheme 3), has a solvent-induced transition state that we were not able to locate using the PCM algorithm of Gaussian 98. Instead, the Poisson−Boltzmann method of Jaguar 4.1[29] with default settings and the experimental dielectric constant for liquid ammonia was used. To locate the transition state, the carbon−halogen distance was increased stepwise from the equilibrium bond-distance by increments of 0.1 Å, and at each distance the system was fully optimized (except for the bond constraint) in the presence of the solvent. This process was continued until the energy started to decrease, and the structure with the highest energy along the scan was taken as the transition state. The solvation method of Jaguar was found to perform slightly worse than the PCM method for prediction of the halide ion solvation energies in liquid ammonia and overestimated the solvent effects by around 10% (6−8 kcal/mol). The geometry optimizations with Jaguar was performed at the B3LYP/6-31+G* level, except for bromine where we used the LACVP+* basis set, which describes the inner electrons by an effective core potential.[30]

Reaction Mechanism. In the computational model system, the reaction starts from the reactants halobenzene and amide ion (**7**), and in the first step an initial complex (**8**) is formed (see Scheme 2). The reaction proceeds through a transition state (**9TS**) to the intermediate, an *o*-halobenzene anion (**4**). This step involves the loss of a proton ortho to the halogen/pentazole. Through the departure of the halide ion (or the pentazolate anion in the case of phenylpentazole) from **4**, the second intermediate, **1**, is formed (see Scheme 3). The strained triple bond in benzyne makes it a highly reactive species that should react quickly with amide/ammonia to form the product **6**. This step is independent of the reactant, i.e., if the reactant is a halobenzene or phenylpentazole, and is therefore omitted from this study.

Proton Transfer. When discussing the energetics of the proton-transfer reaction we will start with B3LYP energies that are not corrected for zero-point or thermal effects. All energies discussed are relative the free reactants (**7**). The formation of the reaction complex (**8**) is a very exothermic process in the absence of solvation effects. For bromobenzene, which forms the strongest complex out of the halobenzenes (see Table 1), the change in energy is −17.3 kcal/mol. It can also be mentioned that MP2 predicts more stable reaction complexes with 1−2.4 kcal/mol than B3LYP for the different species. The transition state (**9TS**) is only slightly higher in energy than the reaction complex for all studied species (see Table 2). The difference ranges from 0.7 kcal/mol for bromobenzene to 1.5 kcal/mol for flurobenzene. This

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TABLE 1. Proton Transfer: Energies for the Reaction Complex (8) Relative to Free Reactants (7) (kcal/mol)[a]

X	ΔE (B3LYP)	ΔE (MP2)	$\Delta H°_{g.}$	$\Delta G°_g$	$\Delta G°_{sol}$
Br	−17.3	−18.7	−16.9	−11.1	13.4
Cl	−16.4	−18.5	−15.9	−10.5	12.4
F	−15.8	−18.2	−15.3	−10.0	11.7
cyclo-N_5	−23.5	−24.5	−23.5	−17.9	12.8

[a] ΔE = classical energy, $\Delta H°_g = \Delta E(\text{B3LYP}) + \Delta\Delta H_g$, where $\Delta\Delta H_g$ is the enthalpy correction. $\Delta G°_g = \Delta E(\text{B3LYP}) + \Delta\Delta G_g$, where $\Delta\Delta G_g$ is the free energy correction. $\Delta\Delta G_g$ and $\Delta\Delta H_g$ are calculated at 240.15 K and 1 atm. $\Delta G°_{sol} = \Delta G°_g + \Delta\Delta G_{sol} + \Delta\Delta G(1\ \text{atm} \rightarrow 1\ \text{M})$. $\Delta\Delta G_{sol}$ = PCM solvation free energy correction. $\Delta\Delta G(1\ \text{atm} \rightarrow 1\ \text{M})$ is the correction factor for changing the standard state from 1 atm to 1 M solution in liquid ammonia (40 M).

TABLE 2. Proton Transfer: Energies for the Transition State (9TS) Relative to Free Reactants (7) (kcal/mol)[a]

X	$\Delta E^{\ddagger}$ (B3LYP)	$\Delta E^{\ddagger}$ (MP2)	$\Delta H°_g{}^{\ddagger}$	$\Delta G°_g{}^{\ddagger}$	$\Delta G°_{sol}{}^{\ddagger}$
Br	−16.6	−16.0	−18.4	−11.7	15.7
Cl	−15.2	−14.8	−17.2	−10.8	16.6
F	−14.3	−14.8	−16.4	−10.1	16.6
cyclo-N_5	−22.5	−25.0	−24.5	−17.5	16.4

[a] For definition of energetics see Table 1.

TABLE 3. Proton Transfer: Energies for the Products (4, NH_3) Relative to Free Reactants (7) (kcal/mol)[a]

X	ΔE (B3LYP)	ΔE (MP2)	$\Delta H°_g$	$\Delta G°_g$	$\Delta G°_{sol}$
Br	−20.1	−19.9	−19.3	−20.3	7.9
Cl	−18.7	−17.8	−18.0	−18.9	7.8
F	−17.0	−19.4	−16.3	−17.1	7.1
cyclo-N_5	−29.0	−33.0	−28.2	−29.2	4.7

[a] For definition of energetics see Table 1.

indicates that the potential energy surface is relatively flat in the vicinity of the transition state. Relative to the separated reactants, the MP2 transition state energies for the halobenzenes are in all cases within 1 kcal/mol of the B3LYP values. The formation of the *o*-halobenzene anions is strongly exothermic in the gas phase with reaction energies ranging from −17.0 to −20.1 kcal/mol (see Table 3).

Additions of zero-point and enthalpy corrections have relatively small effects on the reaction energetics. The main effect is a lowering of the energy of the transition state relative to the reaction complex by about 2.5 kcal/mol, due to one less real frequency. Much greater effects are seen when adding free energy corrections. The reaction complex and transition-state energies are raised by around 5.5 kcal/mol, mainly due to the loss in translational entropy upon bringing the two reactants together.

Solvation effects influence the energetics of the proton-transfer reaction greatly. The main effect comes from the cost of desolvating the amide ion upon bringing the reactants together. The free energies of both the reaction complex and the transition state are raised by 22−28 kcal/mol upon addition of solvation effects for the halobenzenes. Due to this large energy increase, it is questionable if the reaction complex exists as a true minimum on the potential energy surface in solution. The computed B3LYP free energy of activation is close to 16 kcal/mol for all the studied species. This is in relatively good agreement with the experimental free energy of activation for fluorobenzene, which can be estimated to 14.4 kcal/mol from the rate constant of proton exchange for amide anions in liquid ammonia.[4] The discrepancy of 2.2 kcal/mol between theory and experiment is within the expected error of the B3LYP method. The result is even more encouraging considering that we are likely to overestimate the entropy cost of bringing the reactants together by a few kcal/mol by using the gas-phase expression in the calculation of the translational and rotational entropies.[31,32] The overall proton-transfer reaction is endergonic by 7−8 kcal/mol for the halobenzenes after consideration of solvent effects (see Table 3), which is consistent with the fact that the *ortho*-halobenzene anion has not been detected as a stable intermediate.

Looking at the substituent effects on the proton-transfer we note that the gas-phase free energy of activation increases in the order Br < Cl < F. This is opposite to the order predicted by Roberts on the basis of the electronegativities of the elements.[3] An alternative explanation could be that the reactivity is determined by the charge capacity of the halogens, which follows the same order as the reactivity.[33] The substituent effects are largely diminished after consideration of solvation effects. However, bromobenzene remains more reactive than chlorobenzene. This is also consistent with the experimentally observed reactivity order for the amination reaction.[3] Still, the computed difference in activation free energy is only 0.9 kcal/mol, and as we shall see, other factors may influence the reactivity for chlorobenzene.

Comparing the energetics for **3** with those of the halobenzenes shows that **3** is considerably more reactive in the gas phase. This can be attributed to the large electron-withdrawing capacity of the pentazole substituent, which also has been observed previously.[34,35] The difference in energetics compared to the halobenzenes is essentially absent after consideration of solvation effects. The activation free energy in solution of 16.4 kcal/mol is almost identical to that of chlorobenzene and fluorobenzene. However, the overall reaction is less endergonic for **3** than for the halobenzenes by around 3 kcal/mol. Interestingly, in contrast to the results for the halobenzenes, we find significant differences between the B3LYP and MP2 relative energies. The latter method lowers the activation energy by 2.5 kcal/mol and the reaction energy by 4.0 kcal/mol. Taken together, the B3LYP and MP2 results strongly indicate that the proton transfer reaction should be equally or even more favorable for **3** than for the halobenzenes. It is even possible that the *ortho*-phenylpentazole anion is sufficiently stable to facilitate its detection, particularly if the reaction is performed in a less polar solvent than liquid ammonia.

Benzyne Formation. The second part of the amination reaction, the formation of **1** (see Scheme 3) is highly dependent on solvent effects. The halogen/pentazole leaves the benzene ring in concert with the formation of a triple bond. This step is driven by the solvation of the

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TABLE 4. Free Energies (kcal/mol) of Activation for Benzyne Formation in Liquid Ammonia[a]

X	$\Delta G_{sol}^{\ddagger}$	X	$\Delta G_{sol}^{\ddagger}$
Br	2.9	N_5	25.3
Cl	5.4	*cyclo*-$N_5 \cdots Zn^{2+}$ [b]	19.2
F	29.0		

[a] See Methods and Procedure for computational details. [b] Phenyl pentazole in complex with Zn^{2+}.

leaving negative ion, and it is not possible to find a gas-phase transition state. Instead we have estimated the solution transition state directly using a stepwise constrained solvent optimization, as described previously. The free energy of activation increases in the order Br < Cl ≪ F with values 2.9, 5.4, and 29.0 kcal/mol, respectively (see Table 4). The very high activation energy for fluorobenzene is consistent with the observation that this reaction does not proceed to products.

The difference in activation energies for the bromo and chloro compounds provides at least a qualitative explanation for the observed hydrogen isotope effects on the total reaction. Chlorobenzene has been found to react with an *ortho*-deuterium kinetic isotope effect of 2.7 in solutions of KNH_2 in ammonia and 5.7 for $LiN(C_2H_5)_2$ in ether, while the isotope effect for bromobenzene is close to 5.7 (5.4−5.8) in both reaction systems.[3] The lower isotope effect for chlorobenzene in liquid ammonia has been ascribed to a competition between the backward proton-transfer reaction, i.e., the *ortho*-chloro phenyl anion abstracts a proton from the solvent and reverts to chlorobenzene, and the forward formation of **1**. A total isotope effect of 2.7 corresponds to a quota between the two rate constants of 1.5. This is qualitatively consistent with our computational results, which indicate that the two corresponding activation free energies are of similar magnitude. For bromobenzene, on the other hand, the activation free energy for the formation of **1** is only half of that for chlorobenzene, which suggests that this reaction is so fast that the proton abstraction from the solvent will not be of importance. The kinetic isotope of 5.7 is consistent with a reaction where a proton transfer step is rate determining. (We computed the kinetic isotope effect from the B3LYP harmonic frequencies to 6.2 for the proton transfer reaction for both chloro- and bromobenzene.) Thus, our results show that the observed isotope effects are consistent with a single reaction mechanism, and not two as was originally proposed.[3] The high isotope effect for chlorobenzene solutions of $LiN(C_2H_5)_2$ in ether is also consistent with this interpretation, since there are no sufficiently acidic hydrogens to facilitate a backward proton-transfer reaction.

The estimated free energy of activation for the formation of **1** from **3** is 25.3 kcal/mol. This is probably too high to make the reaction useful for synthesis, considering that the proton transfer step is slightly endergonic (4.7 and 0.7 kcal/mol at the B3LYP and MP2 levels, respectively). However, it should be noted that we do not account for the vibrational effects on the activation energy for this reaction step. These usually lower the activation energy by a few kcal/mol, due to the conversion of one vibrational degree of freedom to a translation upon passing the transition state. There is also some uncertainty in the computed energies, and it is not unlikely that we in total may overestimate the overall activation energy by 4−5 kcal/mol. This could make the reaction feasible, especially with an alternative solvent to liquid ammonia that would allow a higher reaction temperature. However, the solvent needs to be of equal or higher polarity than ammonia in order not to raise the free energy of activation. The activation energy for this step could also be influenced by a substituent on the phenyl group, preferably an electron-donating substituent such as NH_2, which would be expected to lower the energy of the transition state relative to the intermediate. However, after the potential energy for the *p*-NH_2-substituted phenylpentazole was scanned, a similar activation energy was obtained.

The most promising way to use the amination reaction for the isolation of the all-nitrogen anion is to add a complexing metal ion. The very polar phenylpentazole has most of its negative charge centered around the pentazole, making this an attractive target for complexing metal cations such as Fe^{2+} and Zn^{2+} as suggested in a recent article.[15] The Zn cation binds in the plane of the ring and coordinates to one of the end nitrogens 3 or 4. The idea is that the metal cation could help **2** to leave in the second step, lowering the activation energy. It also has the added benefit of producing a complexed pentazolate anion, which would be easier to isolate and/or detect. We investigated the benzyne formation with a Zn^{2+} complexed to the 3 position of the pentazole ring. This resulted in a reduction of the free energy by 6 kcal/mol for this step. The activation free energy of 19.2 kcal/mol is sufficiently low to make the reaction of interest for synthesis, in particular if it is performed in an alternative solvent that allows a higher reaction temperature.

Conclusion. The first two important steps in the amination reaction of halobenzenes have been studied. The computed order of reactivity was found to be in agreement with that observed experimentally. For the first step of the reaction, the proton transfer, we also found a good agreement between theoretical and experimentally derived free energies of activation. On the basis of the experimental hydrogen kinetic isotope effects and our computed activation energies, we conclude that the initial proton-transfer step is rate-determining for bromobenzene, while the second step, the benzyne formation, contributes to the rate for chlorobenzene. In the case of flourobenzene, the second step is too slow for the reaction to proceed at measurable rates.

For **3**, the first reaction step is slightly more favorable than the same step for the halobenzenes. However, the second step is rate-determining and the overall free energy of activation energy is estimated to be 26−30 kcal/mol depending upon the computational level. This shows that the reaction without modifications is probably too slow to be useful for synthesis of **2**. The reaction rate can be enhanced by reaction engineering such as changing the solvent or with the addition of a catalyzing metal ion. Our studies indicate that addition of Zn^{2+} lowers the free energy of activation by more than 6 kcal/mol, and this may be sufficient to make the reaction useful for synthesis.

Supporting Information Available: Coordinates for optimized structures and absolute energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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