Mechanistic Insights for Aniline-Catalyzed Halogenation Reactions

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Lewis base catalyzed electrophilic aromatic halogenation using \( N \)-halosuccinimides (NsX; \( X = \text{Cl, Br, I} \)) under mild conditions has attracted much attention, but the detailed mechanism remains elusive. Using the aniline MesNH\(_2\) and anisole PhOMe as the typical base catalyst and aromatic substrate, respectively, a novel mechanism is revealed by extensive DFT calculations. The autogenic protonation of imine XMes\(_{-}\)NH (via Mes\(_{-}\)NH\(^{+}\) mediated dimerization of MesNH\(_2\)) is crucial to initialize the electrophilic halonium X\(^{+}\) transfer to nucleophilic substrates. It is shown that the aniline MesNH\(_2\) and more basic imine XMes\(_{-}\)NH may act as efficient halonium X\(^{+}\) and proton H\(^{+}\) shuttles, respectively, connected by the arenium XMesNH\(_{2}^{+}\). Non-coordinating MesNH\(_2^{+}\) salts are suggested as efficient catalyst for electrophilic iodination. Without suitable stabilization of the highly basic anion Ns\(^{-}\), the generally accepted concept of Lewis base catalyst as simple X\(^{+}\) shuttle will never work efficiently due to a high thermodynamic barrier. In general, autogenic or additional acid additives should be used for more efficient Lewis base catalyzed halogenation.

Aromatic halogenation/C–H functionalization is one of the most important organic transformations. Halogenated aromatic compounds are very useful and attractive building blocks for which many well-developed methods exist for numerous subsequent transformations.[1] They are extensively used as precursors for the synthesis of organometallic reagents while aromatic halides are particularly important for the synthesis of complex molecules via transition-metal-catalyzed coupling reactions.[2] Halogen functionalities can widely modulate the electronic, lipophilic, and steric properties of the attached frameworks, and aryl halides are important in many research fields[3] such as pharmaceutical and material science as both functional and functionalizable molecules.[4]

In classical electrophilic aromatic halogenation, reactive chlorine (Cl\(_{2}\)) and bromine (Br\(_{2}\)) are widely used as halogenating reagents for the synthesis of many aryl halides despite their high toxicity and handling difficulties.[5,6] Substantially less reactive halogenating reagents such as \( N \)-halosuccinimides and 1,3-dihalo-5,5-dimethylhydantoin (NsX and DhX\(_{2}\), respectively, with \( X = \text{Cl, Br, I} \)) are practically useful halogen sources considering their stability and availability, but usually require highly nucleophilic substrates and harsh reaction conditions. Bresnsted[7] or Lewis[8] acid catalysts have been used to activate NsX and DhX\(_{2}\) via protonation or complexation of the carbonyl groups for efficient halonium X\(^{-}\) transfer. More recently, Lewis bases such as phosphines, sulfides, disulfides, indoles and anilines are also found to be active catalysts for the halogenation, presumably via halonium X\(^{-}\) abstraction from the halogenating reagents to generate catalytically active halonium or neutral haloamine (R\(_{2}\)NX) complexes.[9] Although the Lewis base activation[10] is generally less powerful than the acid catalysis for the halogenation of deactivated aromatic compounds, it is proven particularly practical and useful in halonium-induced cyclization of olefinic substrates[11] to provide valuable (poly)cyclic compounds.[12] Recently, the protic hexafluorisopropanol solvent is also found to be able to activate NsX,[11] while transition-metal-catalyzed aromatic halogenation has also emerged for the synthesis of aryl halides.[12]

It is generally accepted that Lewis base catalysts may act as halonium X\(^{-}\) shuttle between halogenating reagents and substrates in catalytic electrophilic halogenation reactions. However, up to now, the detailed catalytic mechanism (even the actual catalytic species) remains unclear. In particular, when the aniline MesNH\(_{2}\) (Mes=mesityl, the 2,4,6-trimethylphenyl group) was applied as the catalyst for electrophilic halogenation using NsX, the \( N \)-halo aniline MesNHX was proposed as the catalytic reactive species (Scheme 1), as the result of deprotonation by highly basic anion Ns\(^{-}\) after initial X\(^{-}\) transfer from NsX.[14]

In this mechanistic work, state-of-the-art DFT calculated free energies at the PW6B95-D3+COSMO-RS/TPSS-D3+ COSMO level in \( \text{CH}_2\text{Cl}_2 \) solution (see below for computational details) are used to explore the detailed catalytic mechanism of the MesNH\(_{2}\)-catalyzed halogenation of anisole PhOMe (PoH, with H highlighting the para-hydrogen atom) using NsX (\( X = \text{Cl, Br, I} \)) as halogenating reagents (Scheme 1). In contrast to previous mechanistic proposal,[14] the autogenic protonation of \( C \)-halo imine XMes\(_{-}\)NH is crucial to initialize efficient halonium X\(^{-}\) transfer from the arenium XMesNH\(_{2}^{+}\), while the aniline MesNH\(_{2}\)
and more basic imine XMes=NH may act as efficient halonium X⁺ and proton H⁺ shuttles, respectively, connected by the arenium XMesNH⁺ in catalytic halogenation reactions.

Two halonium X⁻ transfer reactions may occur in solution from the halogenating reagent NsX (X = Cl, Br, I) to the aminyl nitrogen or the mesityl para-carbon sites of MesNH₂ directed by the moderate intermolecular N−X−C and N−X−N noncovalent (halogen bond) interactions, respectively. As shown in Figure 1A, our DFT calculations show that such Cl⁺, Br⁺ and I⁺ transfers are 11.5, 14.5 and 21.2 kcal/mol endergonic to the para-carbon of MesNH₂ to form the C-halo arenium XMesNH⁺, respectively, along with the separated anion Ns−. The corresponding Cl−, Br− and I− transfers to the aminyl nitrogen of MesNH₂ are 28.3, 20.7 and 13.6 kcal/mol more endergonic (see ESI) and thus can be safely excluded. As shown in Figure 1B, mediated by the electrophilic cation N⁺ autogenic protonation of XMes=NH to reactive arenium XMesNH⁺ for further halonium X⁻ transfer to nucleophilic substrates.

In CHCl₃ solution, C-halo imines XMes=NH may easily dissociate via heterolytic C−X cleavage into separated Mes−NH⁺ and X⁻ ions that are only 11.3, 8.2 and 8.3 kcal/mol higher in free energy for X = Cl, Br and I, respectively. Barrierless N−X recombination then lead to N-halo anilines MesNHX that are 3.3 and 0.4 kcal/mol less stable than imines XMes=NH for X = Cl and Br but −5.0 kcal/mol more stable for X = I. It is thus clear that in the reactions of NsX and MesNH₂, facile formation of imines XMes=NH can be expected for X = Cl and Br; the formation of more stable Mes−NHI is however endergonic by 0.8 kcal/mol over a sizable barrier of 21.2 kcal/mol thus much less efficient.

Direct halonium X⁻ transfer from neutral XMes−NH and MesNHX complexes to the substrate PoH is more than 50 kcal/mol endergonic (see ESI) and thus can be safely excluded. As shown in Figure 1B, mediated by the electrophilic cation Mes−NH⁺ that is easily accessible from imines XMes=NH, further dimerization of MesNH₂ as well as imines XMes=NH (X =
Cl, Br, I) may occur via new N–N bond formation. Due to additional barriers of more than 8 kcal/mol for the imines XMes=NH (via transition structures TS1X), the barrierless association between Mes=NH− and MesNH₂⁺ is kinetically much more efficient, which is −1.8 kcal/mol exergonic to form the cation (MesNH₂⁺)H⁺. Further deprotonation with imines XMes=NH as the most basic species accessible in the reaction eventually lead to the facile formation of arylens XMesNH₂⁺ (and the dimeric (MesNH₂⁺) by-product) for X=Cl and Br. The formation of IMesNH₂⁺ via similar autogenic protonation of IMes=NH is 2.8 kcal/mol endergonic and further disfavored by 11.6 kcal/mol due to the endergonic formation of two equivalents of IMes−NH₂⁺, effectively exerting an additional thermodynamic barrier of 14.4 kcal/mol to further 1° transfer from IMesNH₂⁺.

Experimentally, the broad NH¹H-NMR signal observed at 4.7 ppm (1.2 ppm downfield shifted with respect to MesNH₂⁺) was taken as strong evidence of the formation of N-chloro aniline MesNHCl in the reaction of NsCl and MesNH₂⁺. However, as discussed above, our DFT calculations show such reaction is −5.1 kcal/mol exergonic over a low barrier of 11.5 kcal/mol to form the C-aryl acid IMes=NH that is 3.3 kcal/mol lower in free energy than MesNHCl. Moreover, further autogenic protonation of IMes=NH via Mes=NH− mediated dimerization of MesNH₂⁺ is −3.1 kcal/mol exergonic over a low barrier of 11.4 kcal/mol to form the arenium XMesNH₂⁺ along with separated Cl− dimeric (MesNH₂⁺)ₙ suggesting IMes=NH and (MesNH₂⁺)ₙ as more likely candidates. This is further supported by the DFT-computed ¹H-NMR chemical shifts at 10.5, 7.4 and 5.5 for the NH group of IMesNH₂⁺, MesNHCl and (MesNH₂⁺)ₙ (at 3.6 ppm for the NH₂ group of MesNH₂⁺), respectively, indicating that the observed strong signal at 4.7 ppm and the weak signal at 10.7 ppm are due to the dimeric by-product (MesNH₂⁺)₂ and the imine intermediate IMes=NH, respectively, thus providing further support to our DFT-computed reaction mechanism.

As shown in Figure 2, only low thermodynamic barriers of 16.0, 15.8, and 13.6 kcal/mol are found for further electrophilic halonium X⁺ transfers from arylens XMesNH₂⁺− (X=Cl, Br, I) to the substrate PoH to form the arenium PoHX⁺, followed by highly exergonic proton H⁺ transfer from PoHX⁺ to neutral MesNH₂⁺ and more basic XMes=NH. Consistent with a relatively weak C−I bond, IMesNH₂⁺ is indeed about 2 kcal/mol more reactive than ClMesNH₂⁺ and BrMesNH₂⁺ with respect to halonium X⁺ transfer to PoH. No additional transition structure could be found for such X⁺ and H⁺ transfer reactions. Proton H⁺ transfer from arenium PoHX⁺ to basic MesNH₂⁺ is also exergonic but kinetically less efficient due to an additional barrier of about 11 kcal/mol (see ESI). Coupled with the facile formation of imines XMes=NH and arenium's XMesNH⁺− in the reaction of MesNH₂⁺ and NsX for X=Cl and Br (Figure 1), this eventually completes the catalytic cycle of electrophilic halogenation of PoH, involving MesNH₂⁺ and more basic XMes=NH as efficient X⁺ and H⁺ shuttles, respectively. The presence of imine XMes=NH is also important to avoid the trapping of ammonium MesNH₂⁺ by halide anions X⁻ into more stable salt form of MesNH₂⁺X⁻ that may reduce the catalytic activity of the catalyst MesNH₂⁺. For X=I, due to an additional thermodynamic barrier of 14.4 kcal/mol for the autogenic protonation of imine IMes=NH, such mechanism of electrophilic iodination involving imine IMes=NH as 1° shuttle becomes much less efficient over a high barrier of 28.0 kcal/mol.

Since the formation of imine IMes=NH and arenium IMesNH₂⁺− is disfavored in the reaction of NsX and MesNH₂⁺, the ammonium MesNH₂⁺ becomes the key intermediate for the protic NsX activation to regenerate the reactive arenium IMesNH₂⁺. via formal H⁺/I⁻ exchange over a low thermodynamic barrier of 16.1 kcal/mol, with MesNH₂⁺ acting as both 1° and H⁺ shuttles, very similar to the case of Lewis basic chloride Cl⁻ when the neutral protic acid HCl is used as efficient iodination catalyst (see ESI Figure S1). Such barrier for NsX activation is 2.5 kcal/mol higher than that for further 1° transfer from IMesNH₂⁺ to the substrate PoH (Figure 2), and can be further enhanced by 10.4, 7.6, and 6.4 kcal/mol when MesNH₂⁺ is trapped by 1 M concentrated halide anions for X=Cl, Br and I, respectively. This leads to an sizable barrier of 22.5 kcal/mol for the MesNH₂⁺-catalyzed iodination of PoH using NsX, consistent with the experimentally observed low reaction rate for X=I at room temperature.[54] Non-coordinating MesNH₂⁺ salts should be very helpful for efficient catalytic iodination.

Without aniline base catalyst, direct halonium X⁺ transfers from NsX (X=Cl, Br, I) to PoH reactions may occur via a N−X−C halogen bond, which are however 27.5, 30.3, and 34.8 kcal/mol endergonic to form the C-halo arenium PoHX⁺ and the highly basic anion Ns⁻, consistent with slow reactions observed at

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**Figure 2.** DFT computed free energy paths (in kcal/mol, at 298 K and 1 M concentration) for the electrophilic halogenation of anisole PhOMe (PoH) using catalytic arenium XMesNH₂⁺−, coupled with the reaction of NsX and MesNH₂⁺ for the formation of imine XMes=NH to complete the catalytic cycle. For X=I, formal H⁺/I⁻ exchange (red line) between MesNH₂⁺ and NsI is likely involved.
Further proton transfer from PoHX\(^+\) to \(\text{Ns}\) is highly exergonic to form thearyl halide PoX and stable succinimide NH\(_2\), making the overall halogenation reactions thermodynamically favorable. Such high thermodynamic barriers for the \(X^+\) transfer from halogenating reagents to aromatic substrates cannot be reduced by Lewis base catalysts as simple halonium \(X^+\) shuttle. In the case of MesNH\(_2\), Lewis base catalyst autogenic protonation of imine XMesNH may be crucial for the regeneration of reactive arenium XMesNH\(^+\) that is initially deprotonated by the highly basic anion \(\text{Ns}^-\), at the cost of partial catalytic deactivation via dimerization. In general, either autogenic or additional acidic additives should be used in Lewis base catalyzed electrophilic halogenation in order to initialize efficient halonium \(X^+\) transfer to aromatic substrates, providing reasonable rationale of recent experimental studies.\(^{[76-106,113,115]}\)

In summary, for the first time, a detailed mechanistic picture is revealed by extensive DFT calculations for the MesNH\(_2\)-catalyzed electrophilic halogenation of the aromatic substrate PoH using practically useful halogenating reagents NsX (X = Cl, Br). Autogenic protonation is crucial to initialize efficient halonium \(X^+\) transfer to PoH. The aniline MesNH\(_2\) and more basic imine XMesNH may act as efficient \(X^+\) and \(H^+\) shuttles, respectively, connected by the reactive arenium XMesNH\(^+\), suggesting non-coordinating MesNH\(^+\) salts as efficient catalyst. In general, acidic additives should be used to realize more efficient Lewis base catalysis.

**Computational Methods**

All DFT calculations are performed with the TURBOMOLE 7.3 suite of programs.\(^{[14]}\) The structures are fully optimized at the TPSS-D3/def2-TZVP + COSMO(CH\(_2\)Cl\(_2\)) level, which combines the TPSS meta-GGA density functional[19] with the BJ-damped DFT–D3 dispersion correction\(^{[106]}\) and the def2-TZVP basis set,\(^{[15]}\) using the Conductor-like Screening Model (COSMO)\(^{[108]}\) for CH\(_2\)Cl\(_2\) solvent (dielectric constant \(\varepsilon=8.93\) and diameter \(R_{	ext{eq}}=2.94\) Å). The well-established density-fitting RI-J approach\(^{[19]}\) is used, which speeds up semi-locall DFT functional calculations by a factor of 5–20 at practically no loss of accuracy. Chemically reasonable reaction paths are generated manually and tested in DFT calculations. Useful initial guesses of transition structures are obtained from interpolation between optimized reactant/intermediate/product structures and constrained optimizations with appropriate reaction coordinates. The optimized structures are characterized by frequency analysis (no imaginary frequency for true minima and only one imaginary frequency for transition states) to provide thermal free-energy corrections (at 298.15 K and 1 atm) according to the modified ideal gas-rigid rotor-harmonic oscillator model.\(^{[21]}\) The connection of the transition state with reactants and products is checked visually by careful examining the vibrational transition mode.

More accurate solvation free energies in CH\(_2\)Cl\(_2\) are computed with the sophisticated COSMO-RS continuum solvating model\(^{[21]}\) (parametric file: BP_TZVP,C30_1601.ctl) using the COSMOtherm package\(^{[21]}\) based on the TPSS-D3 optimized structures, corrected by +1.89 kcal/mol to account for the 1 mol/L reference concentration in solution. To check the effects of the chosen density functional on the reaction energies and barriers, single-point calculations at both TPSS-D3\(^{[31]}\) and hybrid-meta-GGA PW6B95-D3\(^{[28]}\) levels are performed using the large def2-QZVP\(^{[17]}\) basis set.

Final reaction free energies (\(\Delta G\)) are determined from the electronic single-point energies plus TPSS-D3 thermal corrections and COSMO-RS solvation free energies. The reaction energies from both DFT functionals are in good mutual agreement with average deviations of only \(-1.0 \pm 2.4\) (average \(\pm\) standard deviation) kcal/mol, with the TPSS-D3 functional tends to predict somewhat lower reaction barriers but stronger halogen bond interactions (see ESI).

In the discussion, the more reliable PW6B95-D3 + COSMO-RS free energies (in kcal/mol, at 298.15 K and 1 mol/L standard state concentration) are used unless specified otherwise.

To help experimental \(^1\)H and \(^{13}\)C NMR assignment, magnetic shielding constants for various complexes are also computed using the GIAO (Gauge Including Atomic Orbital) method\(^{[24]}\) at the TPSS/def2-QZVP level. The final \(^1\)H and \(^{13}\)C chemical shifts are referenced to Si(CH\(_3\))\(_4\) (computed shielding constants at 31.60 and 183.68 ppm, respectively). The applied DFT methods in combination with the large AO basis sets provide usually accurate electronic energies with typical errors of 1–2 kcal/mol for chemical energies (including barriers), which has been tested thoroughly for the huge data base GMTKN55,\(^{[25]}\) that is the common standard in the field of DFT benchmarking.

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**Conflict of Interest**

The authors declare no conflict of interest.

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\(^{[1]}\) a) L. G. Voskressensky, N. E. Golantsov, A. M. Maharramov, *Synthesis Stuttgart* 2016, 48, 615–643; b) I. Saikia, A. J. Borah, P. Phukan, *Chem. Rev.* 2016, 116, 6837–7042.

\(^{[2]}\) a) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* 2002, 102, 1359–1469; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* 2005, 44, 4442–4489; *Angew. Chem.* 2005, 117, 4516–4563; c) J. S. Fairlamb, *Chem. Soc. Rev.* 2007, 36, 1036–1045.

\(^{[3]}\) a) M. J. Adam, D. S. Wilbur, *Chem. Soc. Rev.* 2005, 34, 153–163; b) M. L. Tang, Z. Bao, *Chem. Mater.* 2011, 23, 446–453; c) S. L. Pimlott, A. Sutherland, *Chem. Soc. Rev.* 2011, 40, 149–162; d) T. Cernák, K. Dyrkstra, S. Tyagarajan, P. Vachal, S. W. Krksa, *Chem. Soc. Rev.* 2016, 45, 546–576.

\(^{[4]}\) R. A. Rodriguez, C.-M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* 2014, 136, 6908–6911.

\(^{[5]}\) a) K. Rajesh, M. Somasundaram, R. Saigamesh, K. K. Balasubramanian, *J. Org. Chem.* 2007, 72, 5867–5869; b) V. K. Chaikovskii, V. D. Filimonov, V. I. Skorokhodov, V. D. Gogoridze, *Russ. J. Org. Chem.* 2007, 43, 1278–1281; c) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamaneaka, T. Akiyama, *J. Am. Chem. Soc.* 2013, 135, 3964–3970; d) M. M. Cummings, B. C. G. Soederberg, *Synth. Commun.* 2014, 44, 954–958; e) A. J. Close, P. Kemmitt, S. M. Roe, J. Spencer, *Org. Biomol. Chem.* 2017, 15, 6751–6756; f) M. Bergstrom, G. Suresh, V. R. Naidu, C. R. Unelius, *Eur. J. Org. Chem.* 2017, 2017, 3234–3239.

\(^{[6]}\) a) C.-Y. Zhou, J. Li, S. Pediashvili, D. Romo, *Org. Lett.* 2010, 12, 2104–2107; b) D. Leboeuf, J. Ciesielski, A. J. Frontier, *Synlett* 2014, 25, 399–402; c) D. T. Racy, C. E. Warnillo, S. L. Pimlott, A. Sutherland, *Org. Lett.* 2015, 17, 4782–4785; d) D. T. Racy, S. A. I. Sharif, S. L. Pimlott, A. Sutherland, J.
[7] a) G. Jakab, A. Hosseini, H. Hausmann, P. R. Schreiner, Synthesis-Stuttgart 2013, 45, 1635–1640; b) S. M. Maddox, C. J. Nalbandian, D. E. Smith, J. L. Gustafson, Org. Lett. 2015, 17, 1042–1045; c) P. Bovonombat, P. Sophanpanichkul, A. Pandey, S. Tungsirisurp, K. Chobtumskul, P. Kuhataparuk, S. Sathityatiwat, P. Teecomegaet, Chem. Int. Ed. 2016, 55, 16101–16105; d) R.-J. Tang, T. Milcent, B. Crousse, Angew. Chem. 2016, 128, 16335–16339; e) X. Xiong, F. Tan, Y.-Y. Yeung, Org. Lett. 2017, 19, 4243–4246; f) P. Bovonombat, P. Teecomegaet, P. Kulvaranon, A. Pandey, K. Chobtumskul, S. Tungsirisurp, P. Sophanpanichkul, S. Losuwakanul, D. Soimaneewan, P. Kanjanwongpaisan, P. Siricharomsang, S. Choosakoonyiart, Tetrahedron 2017, 73, 6564–6572; g) X. Xiong, Y.-Y. Yeung, ACS Catal. 2018, 8, 4033–4043; h) Y. Hirose, M. Yamazaki, M. Nagata, A. Nakamura, T. Maegawa, J. Org. Chem. 2019, 84, 7405–7410; i) K. Iida, S. Ishida, T. Watanabe, T. Arai, J. Org. Chem. 2019, 84, 7411–7417; j) Y. Shi, Z. H. Ke, Y. Y. Yeung, Green Chem. 2018, 20, 4448–4452.

[8] a) S. E. Denmark, G. L. Beutner, Angew. Chem. Int. Ed. 2008, 47, 1560–1638; b) Angew. Chem. 2008, 120, 1584–1663; c) S. E. Denmark, W. E. Kuester, M. T. Burk, Angew. Chem. Int. Ed. 2012, 51, 10938–10953; d) Angew. Chem. 2012, 124, 11098–11113; e) S. Guha, I. Kazi, A. Nandy, G. Schreckenbach, T. Ziegler, Chem. Eur. J. 2017, 23, 5197–5213.

[9] a) S. A. Snyde, D. S. Treitler, A. P. Brucks, Aldrichimica Acta 2011, 44, 27–40; b) A. Sakakura, K. Ishihara, Chem. Rec. 2015, 15, 728–742; c) W. J. Chung, C. D. Vanderwal, Angew. Chem. Int. Ed. 2016, 55, 4396–4434; d) Angew. Chem. 2016, 128, 4470–4510.

[10] a) M. Terazaki, K.-i. Shiomoto, H. Mizoguchi, A. Sakakura, Org. Lett. 2019, 21, 2073–2076; b) S. E. Denmark, M. T. Burk, PNAS USA 2010, 107, 20655–20660; c) A. Sakakura, A. Ukai, K. Ishihara, Nature 2007, 445, 900–903; d) R. C. Samanta, H. Yamamoto, J. Am. Chem. Soc. 2017, 139, 1460–1463.

[11] R.-J. Tang, T. Milcent, B. Crousse, J. Org. Chem. 2018, 83, 930–938.