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On the Mechanism of Halogen Atom Transfer from C–X Bonds to α -Aminoalkyl Radicals: A Computational Study

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Generation of carbon centered radicals from organic halides represents a powerful tool in modern organic chemistry, especially in the context of photoredox catalysis. However, activation of carbon–halogen bonds is usually promoted by toxic and hazardous tin reagents. Alternatively, α -aminoalkyl radicals have emerged as a cheap and efficient halogen atom transfer (XAT) reagents, although the activation mechanism is still underexplored with respect to hydrogen atom transfer

(HAT) chemistry. Herein, we report a computational systematic evaluation of four different α -aminoalkyl radicals on the Halogen Atom Transfer (XAT) mechanism. We have evaluated up to 32 reactions, including two different types of substrates (Ph–X and Cy–X). This systematic study aims to provide a big picture on the key effects in this reactivity including the hybridization of carbon, the nature of the halogen, and the electronics/sterics of the α -aminoalkyl radical.

Introduction

In recent years, photoredox catalysis has emerged as a powerful tool in organic chemistry to achieve new synthetic transformations based on new activation modes using light as the energy source, including functional groups with low reactivity.^[1] The use of visible light absorbing photocatalysts, like transition-metal complexes^[2] and organic photocatalysts,^[3] enables the generation of radical intermediates. Its combination with Hydrogen Atom Transfer (HAT) catalysts expands the selectivity control with respect to classic photochemical approaches, where undesired side reactions are usually obtained.^[4] As a result, the fast development of photoredox catalysis has boosted the discovery of new chemical transformations using visible light irradiation.

Generation of carbon centered radicals has been traditionally performed by activation of different organo-boron, -sulfur, -nitride and carboxylic acids containing groups.^[5] However, organic halides, which are useful building blocks in organic and organometallic chemistry, have not been extensively studied in one-electron activation processes, where only some activated iodine derivatives have been used.^[6] Recently, different research

groups have focused on the mild activation of carbon-halogen bonds using photoredox catalysis,^[7] using a new class of transformations, beyond classical tin or silicon radical chemistry^[8] to generate carbon centered radicals. As discussed by Leonori and co-workers in a recent review,^[9] the activation of C–X bonds to generate carbon centered radicals can be classified into three main types: C–X bond photolysis, reduction through Single Electron Transfer (SET) and Halogen Atom Transfer (XAT) (Scheme 1A).

However, photolysis requires high-energy light sources and it is generally not practical for synthetic applications.^[10] Also, reduction of organic halides through SET processes followed by the fragmentation of the bond is generally limited to activated compounds due to the highly negative reduction potential of these species.^[11] On the other hand, XAT reactions have played a central role in radical chemistry for organic halides, which are typically activated by tin and silicon radicals.^[8] As pointed above, Leonori and co-workers have recently discovered a complementary and safer activation strategy using α -aminoalkyl radicals.^[7a,12] They can be easily generated *via* photoredox catalysis using commercially available and cheap amines. The XAT and HAT activation mechanisms are differentiated by the polarities and the charge motion along the reaction coordinate (Scheme 1B) but the polar effects play a crucial impact on the reactivity for both types of atom transfer mechanisms.^[9]

Understanding the fundamentals of the mechanism behind the XAT and HAT steps and the trends in their reactivity regarding the organic species and the radicals involved, will be key for the further development of this chemistry. In this context, Density Functional Theory (DFT) calculations have demonstrated to be very effective in understanding the thermodynamic and kinetic effects on radical chemistry,^[13] despite the complex character of this reactivity. Following our interest in photoredox catalysis reactivity during the last years,^[14] we aim to perform here a systematic study on the Halogen Atom Transfer step.

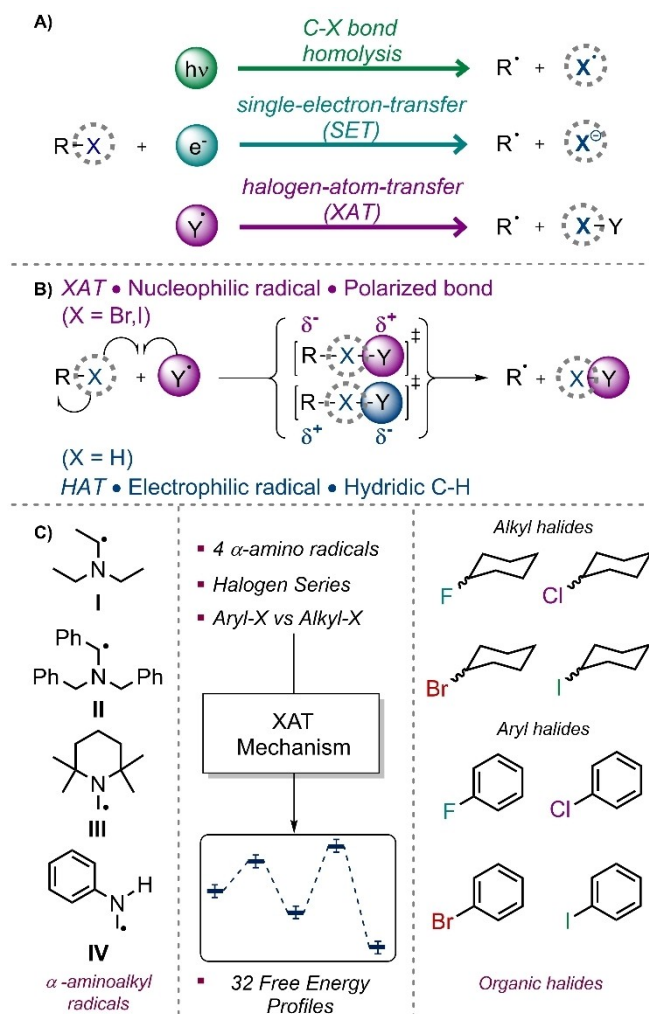
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Scheme 1. A) Activation modes of organic carbon halide species. B) Halogen-Atom Transfer (XAT) vs Hydrogen Atom Transfer (HAT) mechanisms. C) This work.

Thus, in this work, we have systematically studied, by means of DFT calculations, a series of XAT activations. Using a set of aryl and alkyl halides, in combination with α -amino carbon centered radicals (Scheme 1C), we have evaluated up to 32 reaction pathways to shed light into 1) the halogen effect in the XAT mechanism; 2) the influence of the carbon-centered radical (aryl or alkyl) in the mechanism and 3) the effect of the

α -amino carbon focused in both the thermodynamics and the kinetics of the process.

Results and Discussion

In our computational study, we have initially selected a variety of amines, which have been recently reported as efficient XAT radicals in experimental photoredox reactions,^[7a] including three α -aminoalkyl radicals (Scheme 1C I, II, III) whose preparation has been successfully reported by Leonori and co-workers.^[7] Additionally, another α -aminoalkyl radical (*N*-phenylaminomethyl) was also integrated to the whole set (Scheme 1C, IV) to analyze the effect of the secondary character of the amine in the overall mechanism considering that the generation of the radical is achievable via photochemical activation. We were particularly interested in understanding the effect of the substrate type (alkyl vs aryl) and the impact of the halogen reactive atom in the halogen abstraction step. In addition, all the bond dissociation energies (BDE) were also calculated for the purpose of understanding the possible enthalpic effects of the bond strength into the reaction mechanism.

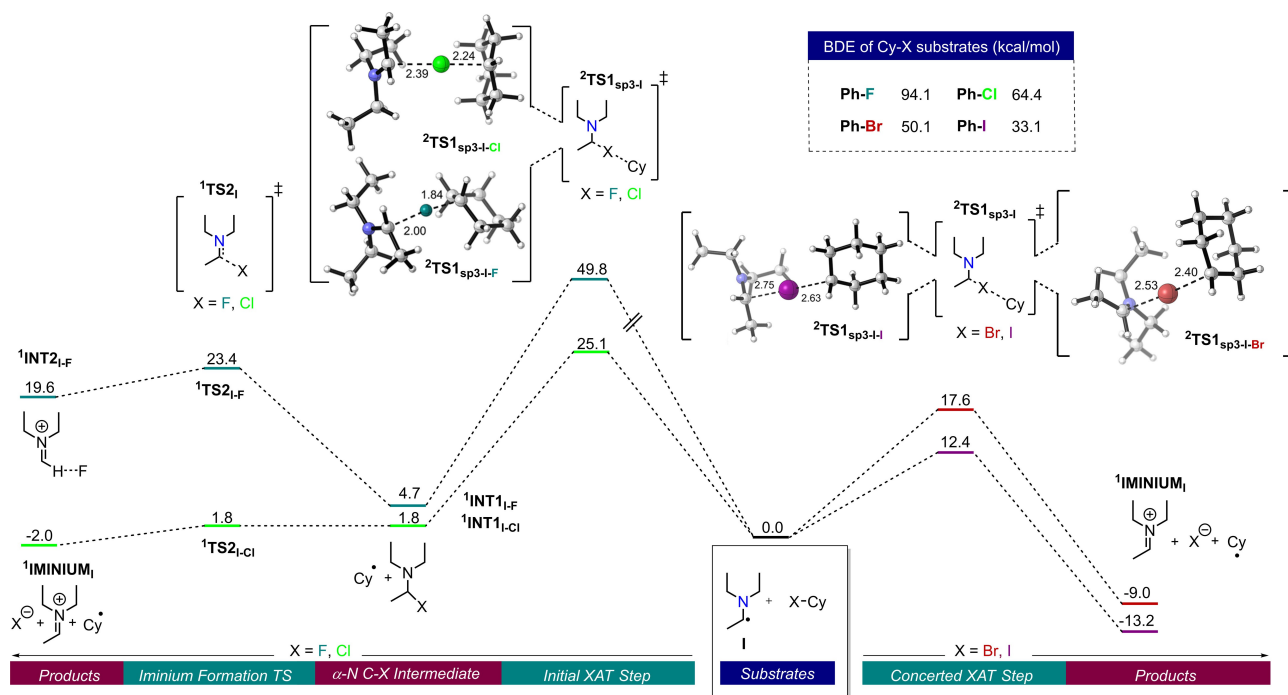
Cyclohexyl halide activation

We began our investigation with the triethylamine derived radical I and the whole series of cyclohexyl derivatives (Cy-X; X=F, Cl, Br, I). The free energy profile was evaluated for the XAT step for each case and we rapidly identified two different mechanisms (Scheme 2), based on the stability of the α -aminoalkyl halide generated, depending on the nature of the X group. On the right-hand side, both Cy-I and Cy-Br, which are the halogens mostly used experimentally, exhibit a low free energy barrier. Interestingly, the process is concerted and the formation of the final iminium product and the C-X bond breaking occurs simultaneously. This is in line with the preliminary computational study performed by Constantin *et al.*^[7a] where they could not identify the α -aminoalkyl iodide intermediate in solution. The large polarizability of the C-X bonds and the σ -hole on the halogen center promote an early transition state in both Cy-I and Cy-Br substrates. The α -aminoalkyl radical attacks in a collinear trajectory in which the attacking and leaving groups form an angle close to 180° with respect to the C-X bond. After the transition state, the formation of the iminium is highly exergonic (−9.0 from CyBr and −13.2 for CyI, in kcal/mol) acting as the thermodynamic driving force of this process.

Interestingly, the free energy profiles differ considerably for the rest of the Cy-X series. In these cases, the concerted formation of the iminium product from the first transition step does not occur. In fact, a stable intermediate could be optimized in both cases (¹INT_{1,Cl}, ¹INT_{1,F}). Additionally, the stronger C-X bond, as well as the reduced polarizability of the bond are related to a higher energy barrier for Cy-Cl (25.1 kcal/mol) and a prohibitive barrier for Cy-F (49.8 kcal/mol). It is



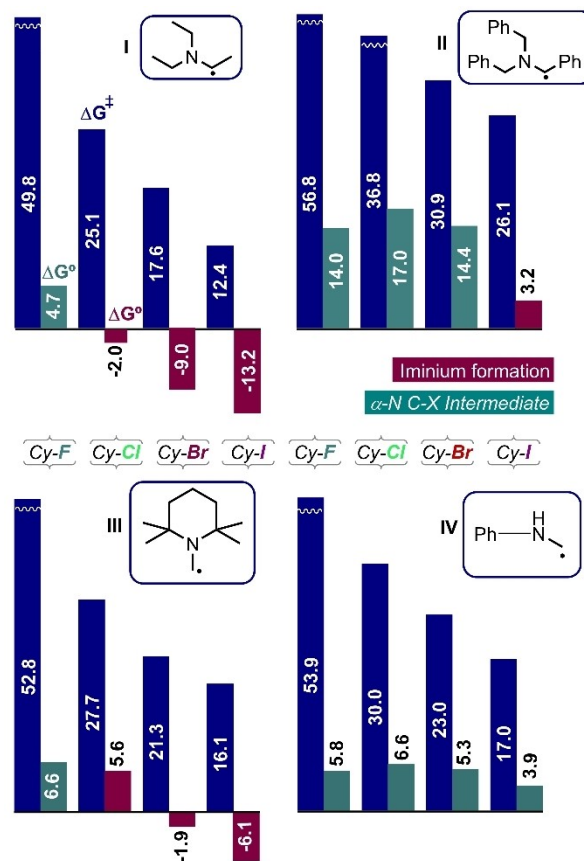
Ignacio Funes-Ardoiz got his PhD in 2017 in computational homogeneous catalysis at ICIQ in Spain. In 2018, he moved to RWTH Aachen as an Alexander von Humboldt postdoctoral fellow. He then joined the photochemistry group at the University of La Rioja in 2020, where he is currently a Juan de la Cierva Incorporación fellow. His research topics cover computational photoredox catalysis, machine learning applied to chemistry and cross-coupling mechanistic studies.



Scheme 2. Free energy profiles of XAT reaction mechanisms between I and Cy-F (dark green), Cy-Cl (light green), Cy-Br (dark red) and Cy-I (purple). Energies in kcal/mol.

important to notice that the three different intermediates resulting from the initial XAT step are more energetic than the initial substrate and only in the case of Cy-Cl, the system can evolve towards the formation of a stable iminium species in an exergonic way. Overall, the type of halogen atom becomes a key effect that controls the outcome of the XAT reactions, both for the transition state barrier (ΔG^\ddagger) and for the thermodynamic reaction feasibility (ΔG^\ominus).

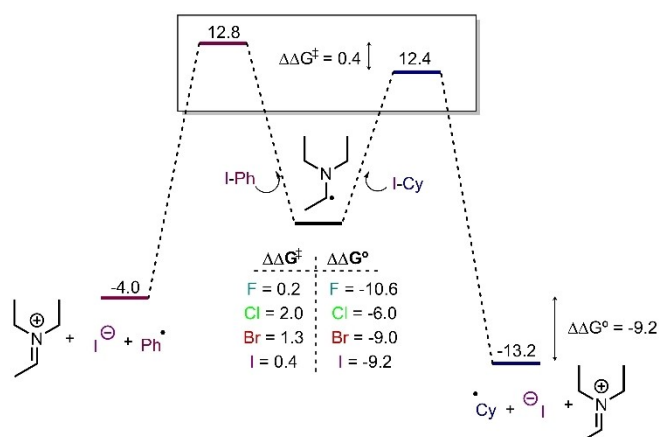
To complete the reaction picture, the free energy barrier (ΔG^\ddagger) and the thermodynamic driving force (ΔG^\ominus) were also calculated for all the α -aminoalkyl radicals I-IV reacting with the cyclohexyl-X series (Scheme 3, see Table S1 in the supporting information for further details). As expected, the activation energy values increase from iodine to fluorine following the general trend $\text{I} > \text{Br} > \text{Cl} > \text{F}$ which mirrors the strength of the C-halogen bonds. Radical III shows a very similar performance with respect to the reference triethylamine radical studied in Scheme 2. Overall, both the reaction barriers and the thermodynamic driving force are uphill by 2–6 kcal/mol, due to the lower stability of the primary radical and the larger steric hindrance in the transition state because of the crowded α -N positions in the ring. Unlike I and III, IV does not show any exergonic pathway due to the lack of stability of the resulting protonated iminium, which is never favored in this case. Finally, radical II shows the most different behavior. The benzyl character of the reactive radical increases its stability considerably, raising the free energy barrier up to 26.1 kcal/mol even for Cy-I. However, the iminium product can be formed, suggesting that under very polar conditions, this low-reactive radical could be used to fine-control the reactivity in sensitive species.



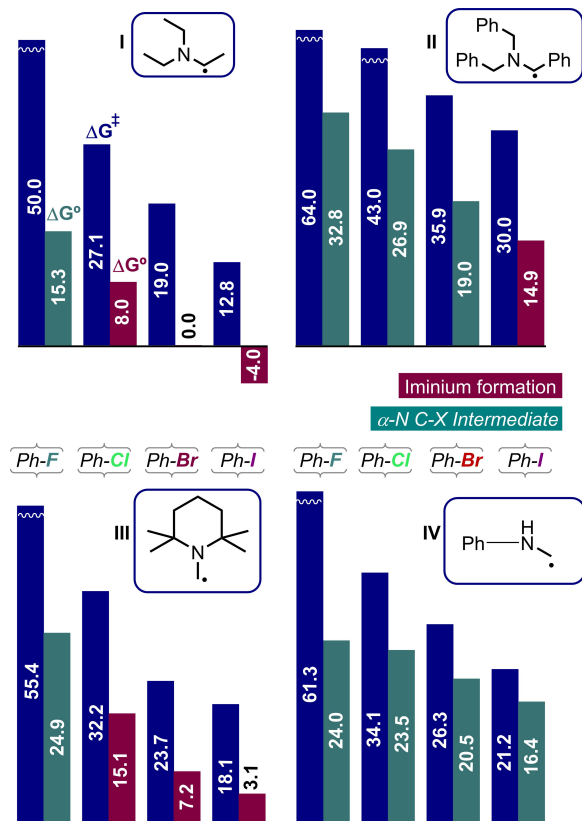
Scheme 3. Simplified reaction profiles of Cy-X XAT mechanism with α -aminoalkyl radicals I-IV. ΔG^\ominus in green or dark red bars. ΔG^\ddagger in blue bars. Energies in kcal/mol.

Phenyl halide activation

Once the big picture of the XAT mechanism using alkyl halides was obtained, the substrate scope was extended towards aryl halides. Firstly, the free energy profile of the triethylamine derived radical was explored (see Figure S2). The mechanism shows similarities with the Cy-X mechanism regarding the



Scheme 4. Comparison between Ph-X and Cy-X kinetic and thermodynamic values for the whole halogen series mechanism using triethylamine derived radical as the halogen abstractor. Free energies in kcal/mol.



Scheme 5. Simplified reaction profiles of Ph-X XAT mechanism with α -aminoalkyl radicals I-IV. ΔG° in green or dark red bars. ΔG^\ddagger in blue bars. Energies in kcal/mol.

concerted or step-wise character. However, the activation of Ph-X is thermodynamically more challenging, due to the stronger BDE of the Ph-X bond. This is shown in Scheme 4, where the difference in the reaction barriers between Cy-X and Ph-X remains always below 2 kcal/mol, but the thermodynamics is much less favored for the formation of the phenyl radical with respect to the formation of the cyclohexyl radical. This fact, in line with the experimental observations, explains the easy engage in XAT reactivity of alkyl halides, which is much more limited for aryl halides. Regarding the halogen effect and the electronic properties of the α -aminoalkyl radicals, the reactivity of Ph-X follows the same trends than in the case of Cy-X (Scheme 5). Interestingly, only trimethylamine-derived radical I provides the driving force to make the process exergonic in the case of Ph-I or isoenergetic for Ph-Br. However, the similar barriers with respect to Cy-X suggest that these systems could be used if the phenyl radical is quickly trapped in the reaction media.

As in Scheme 3, the evaluation of ΔG^\ddagger highlights a slight increase in the energy barriers for the first step of II compared to I, III and IV. However, radical nucleophilicity is not severely distorted because energy differences between C_{sp^3} and C_{sp^2} in the C-X activation step are quite small (Scheme 5).

Conclusions

In this computational study, we have systematically analyzed the free energy profiles associated with the Halogen Atom Transfer step from phenyl and cyclohexyl halides towards four different α -aminoalkyl radicals. As shown in the mechanistic study, stability of the formed radical is crucial for the driving force of the reaction as well as the formation of stable iminium salt species, which are favored for R-X when X = Cl, Br and I and the iminium is fully alkylated. In addition, the halogen character determines the activation free energy barrier of the process, being accessible for X = Br and I, supporting the experimental observations. Finally, the electronic and the steric properties of the α -aminoalkyl radicals are not as important as the stability of the radical itself, being the benzylic radical II the least reactive. We envision that this mechanistic study will help in the understanding and development of further XAT processes in the future.

Computational Details

All the Density Functional Theory calculations were carried out using the Gaussian16 program package.^[15] All the structures were optimized using the ω B97x-D functional^[16] combined with the Def2SVP basis set. The nature of the stationary points was confirmed by frequency calculations as minima (no imaginary frequencies) or transition states (one imaginary frequency). Transition states were further verified by relaxing the imaginary frequency towards the reactant and the product and doing IRC calculations when needed. In addition, single point calculations using the M06-2X functional^[17] and the Def2TZVPP basis set were performed to further refine the potential energies. Solvation was included in both optimizations and single point calculations using

the CPCM implicit solvent model^[18] and acetonitrile as solvent, generally used in this chemistry.^[7a] Finally, a comparison between ω B97x-D/Def2TZVPP, PBE0/Def2TZVPP and M06-2X/Def2TZVPP methods was performed to validate the results and all the methods yield very similar results (See Supplementary Information for details). 3D structures were illustrated using the CYLview 1.0 program.^[19]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

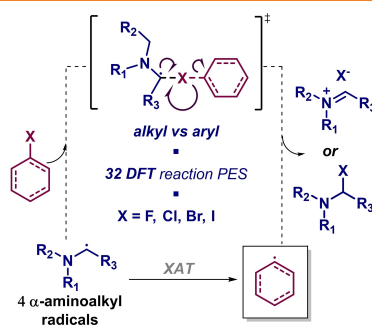
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RESEARCH ARTICLE

A comprehensive computational study of the Halogen Atom Transfer (XAT) mechanism is reported. Up to 32 α -aminoalkyl radical/organic halide combinations are explored to understand the effect of the C–X bond, the influence of α -aminoalkyl radical properties and the alkyl or aryl character of the reactive C center in the reactivity.



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1 – 6

On the Mechanism of Halogen Atom Transfer from C–X Bonds to α -Aminoalkyl Radicals: A Computational Study

