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Zoramthara Khiangte

`zoramthara.khiangte14@gmail.com`

Mizoram University

Zodinpuia Pachuau

Mizoram University

Moi Phen Phom

Mizoram University

Lalhriatpuia Kawlni

Mizoram University

Lalhruaitluangi Vanchhawng

Mizoram University

Mary Lalmuankimi

Mizoram University

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Mechanistic Origin of Halogen-Dependent Reactivity in Metal-Free C–3 Halogenation of Pyridine N-Oxides: A DFT Study

Zoramthara Khiangte^{1,2*}, Zodinpuia Pachuau^{2,3†},
Moi Phen Phom^{1,2}, Lalhriatpuia Kawlani^{1,3},
Lalhruaitluangi Vanchhawng^{1,4}, Mary Lalmuankimi^{1,5}

^{1*}Department of Chemistry, Mizoram University, Tanhril, Aizawl, 796004, Mizoram, India.

*Corresponding author(s). E-mail(s):

zoramthara.khiangte14@gmail.com;

Contributing authors: zodinpuia@rediffmail.com;

moibuch99@gmail.com; lahriatpuiakawlani@gmail.com;

l.h.tluangivanchhawng@gmail.com; marypachuau543@gmail.com;

[†]These authors contributed equally to this work.

Abstract

Metal-free C–H functionalization of pyridine N-oxides provides a powerful route to regioselective heteroarene derivatization; however, the mechanistic origin of halogen-dependent reactivity remains unclear. Herein, density functional theory (DFT) calculations were employed to investigate the C–3 halogenation of pyridine N-oxides using N-fluoro-, N-chloro-, and N-bromosuccinimides. The computed free-energy profiles reveal stepwise ionic mechanisms involving σ -complex intermediates and two transition states. Solvent effects significantly stabilize charge-separated structures and modulate the rate-determining step across the halogen series. The activation barriers follow the trend **F** > **Cl** > **Br**, consistent with experimental observations. Frontier molecular orbital and conceptual DFT analyses indicate pronounced electronic activation at the first transition state, while NBO analysis highlights strong $n(\text{O}) \rightarrow \sigma^*$ donation as the key stabilizing interaction. These findings demonstrate that halogen-dependent reactivity arises from a balance between halogen polarizability, N–X bond strength, and transition-state stabilization, providing a mechanistic foundation for rational design of metal-free halogenation reactions.

Keywords: Pyridine N-oxides; C-3 halogenation; metal-free functionalization; density functional theory; reaction mechanism

1 Introduction

Heteroaromatic compounds constitute a core structural motif in pharmaceuticals, agrochemicals, functional materials, and natural products. Among them, pyridine and its derivatives occupy a privileged position due to their widespread biological activity and versatile chemical reactivity. Functionalization of the pyridine ring, however, remains challenging because of its intrinsic electron-deficient nature and strong coordination ability toward metals, which often deactivates conventional catalytic systems. In this context, pyridine N-oxides have emerged as particularly valuable synthetic surrogates, as oxidation at nitrogen reverses the electronic character of the ring and enables regioselective C–H functionalization under both metal-catalyzed and metal-free conditions.[1–3]

Over the past two decades, pyridine N-oxides have been employed as key intermediates for regioselective oxygenation, amination, sulfonylation, and halogenation reactions.[4–7] The strong +M effect of the N-oxide group increases electron density at the C-3 and C-5 positions, thereby enabling electrophilic substitution reactions that are otherwise unfavorable for pyridine itself. Among these transformations, halogenation of pyridine N-oxides is particularly important, as halogen atoms serve as versatile synthetic handles for further cross-coupling and diversification reactions.[8–10]

Metal-free halogenation has received increased attention in recent years as part of the broader drive toward sustainable and environmentally benign chemistry.[11, 12] N-Halosuccinimides (NFS, NCS, and NBS) are widely used as practical electrophilic halogen sources because of their operational simplicity, safety, and controlled reactivity.[13] While experimental studies have demonstrated efficient C-3 fluorination, chlorination, and bromination of pyridine N-oxides under mild conditions, the fundamental mechanistic origins of regioselectivity and halogen-dependent reactivity remain incompletely understood at the molecular level. [14–16]

In particular, fluorination stands out as mechanistically distinct from other halogenation reactions. The strong electronegativity of fluorine, the high strength of the C–F bond, and the polarized nature of electrophilic fluorine sources often lead to unusually high activation barriers and strong solvent dependence. [17, 18] Chlorination and bromination, by contrast, typically display lower intrinsic barriers and greater thermodynamic driving forces.[19] Despite these experimentally observed trends, a unified molecular-level explanation that connects reaction energetics, electronic structure, and orbital interactions across the full halogen series is still lacking.

Density functional theory (DFT) has become a powerful and indispensable tool for interrogating reaction mechanisms at the atomistic level. [20–23] Numerous computational investigations have successfully elucidated electrophilic aromatic substitution, σ -complex formation, halogen transfer, and rearomatization steps in both carbocyclic and heterocyclic systems.[24–26] In the case of pyridine N-oxides, DFT

studies have highlighted the essential role of the N-oxide oxygen lone pair in stabilizing σ -complex intermediates and lowering reaction barriers through strong $n(\text{O}) \rightarrow \sigma^*$ and π^* -donor-acceptor interactions.[27–29] However, a systematic computational comparison of fluorination, chlorination, and bromination at the same reactive site remains conspicuously absent.

Frontier molecular orbital (FMO) theory provides a robust conceptual framework for understanding reactivity trends in terms of HOMO–LUMO interactions, orbital energy gaps, and charge-transfer processes.[30–32] In parallel, conceptual DFT descriptors such as chemical hardness (η), softness (S), electronegativity (χ), and electrophilicity (ω) offer quantitative measures of chemical reactivity and selectivity.[33–35] These descriptors have been widely used to rationalize electrophilic activation, regioselectivity, and reaction kinetics in heteroaromatic chemistry.[36, 37]

Natural Bond Orbital (NBO) analysis further complements these approaches by providing a chemically intuitive description of donor-acceptor interactions, hyperconjugation, and charge delocalization in real molecular systems.[38, 39] In electrophilic halogenation reactions, NBO analysis is particularly powerful for tracking $n \rightarrow \sigma^*$ and $n \rightarrow \pi^*$ interactions that stabilize developing cationic character within σ -complex intermediates and transition states.[40, 41]

By combining free-energy profiles with detailed orbital and bonding analyses, this work delivers a molecular-level explanation for the experimentally observed C-3 regioselectivity and halogen-dependent reactivity trends in pyridine N-oxide halogenation. The mechanistic insights gained from this study are expected to assist in the rational design of new metal-free C–H functionalization strategies for heteroaromatic systems and to guide future experimental development in sustainable halogenation chemistry.

In this context, we hypothesize that halogen-dependent reactivity originates from differences in N–X bond strength, polarizability, and transition-state stabilization. To test this hypothesis, we perform a systematic DFT investigation of fluorination, chlorination, and bromination pathways, aiming to establish a unified mechanistic framework for halogen-dependent reactivity in pyridine N-oxide functionalization.

2 Methods

All quantum chemical calculations were performed using Density Functional Theory (DFT) as implemented in the Gaussian 16 program package.[42] Geometry optimizations of all reactants, intermediates, transition states, and products involved in the C–3 halogenation of pyridine N-oxide with N-fluorosuccinimide (NFS), N-chlorosuccinimide (NCS), and N-bromosuccinimide (NBS) were carried out using the B3LYP hybrid exchange–correlation functional.[43, 44] This functional has been widely employed for studying electrophilic substitution and halogen-transfer reactions in heteroaromatic systems.[45–47]

The 6-31+G(d,p) basis set was used for all atoms. This basis set includes polarization functions and diffuse functions, which are essential for accurately describing charge-separated σ -complex intermediates and polar transition states.[48, 49] For bromine-containing species, the same basis set was consistently applied across all

systems to ensure meaningful comparison of relative energetic trends, despite the availability of larger basis sets or effective core potentials for heavier elements.

All stationary points were fully optimized without symmetry constraints. Harmonic vibrational frequency calculations were performed at the same level of theory to confirm the nature of each structure: minima were identified by the absence of imaginary frequencies, while transition states exhibited one imaginary frequency corresponding to the reaction coordinate. Intrinsic Reaction Coordinate (IRC) calculations were carried out using the Gonzalez–Schlegel algorithm to verify that each transition state connects the appropriate reactants and products.^[50]

Thermal corrections to Gibbs free energies were computed at 298.15 K and 1 atm, including zero-point energy (ZPE), thermal, and entropic contributions. All reported free energies (ΔG) are given relative to the corresponding reactant complexes.

Solvent effects were incorporated using the SMD implicit solvation model with acetonitrile ($\epsilon = 35.688$) as the solvent. Single-point energy calculations were performed on gas-phase optimized geometries to obtain solution-phase free energies. The SMD model has been extensively validated for describing solvation effects in polar and ionic reaction mechanisms.^[51]

Frontier molecular orbital (FMO) energies were obtained from the converged Kohn–Sham orbitals. Based on these energies, global reactivity descriptors—including as chemical hardness (η), softness (S), electronegativity (χ), and electrophilicity (ω)—were calculated using standard conceptual DFT formulations.^[52]

Natural Bond Orbital (NBO) analysis was performed using NBO version 3.1 as implemented in Gaussian 16 to investigate donor–acceptor interactions, hyperconjugation, and charge delocalization. Stabilization energies were evaluated using second-order perturbation theory.^[38]

While the SMD implicit solvation model effectively captures bulk solvent effects, it does not explicitly account for specific solvent–solute interactions or hydrogen-bonding networks. In particular, the deprotonation step may involve direct participation of solvent molecules, which cannot be described within a purely continuum model. Therefore, the computed activation barriers should be interpreted with this limitation in mind.

All molecular structures and orbital visualizations were generated using GaussView 6. Energy profiles and graphical representations were prepared using standard plotting software. Cartesian coordinates, absolute energies, vibrational frequencies, IRC results, and NBO data for all species are provided in the Supporting Information.

3 Results and Discussion

3.1 Fluorination

3.1.1 Energy profile and mechanistic features

The relative Gibbs free energies for the metal-free C-3 fluorination of pyridine N-oxide are summarized in Table 1, and the corresponding energy profile is shown in Figure 1.

In the gas phase, the first transition state TS1 lies $+59.8\text{ kcal mol}^{-1}$ above the reactant complex F1, while the σ -complex intermediate F2 appears at $+32.5\text{ kcal mol}^{-1}$.

Table 1 Relative Gibbs free energies (ΔG , kcal mol⁻¹) for the fluorination pathway in gas phase and acetonitrile.

Structure	ΔG (Gas phase)	ΔG (Solvent)
F1	0.0	0.0
TS1	59.8	26.2
F2	32.5	11.0
TS2	48.9	32.5
F3	-23.8	-21.8

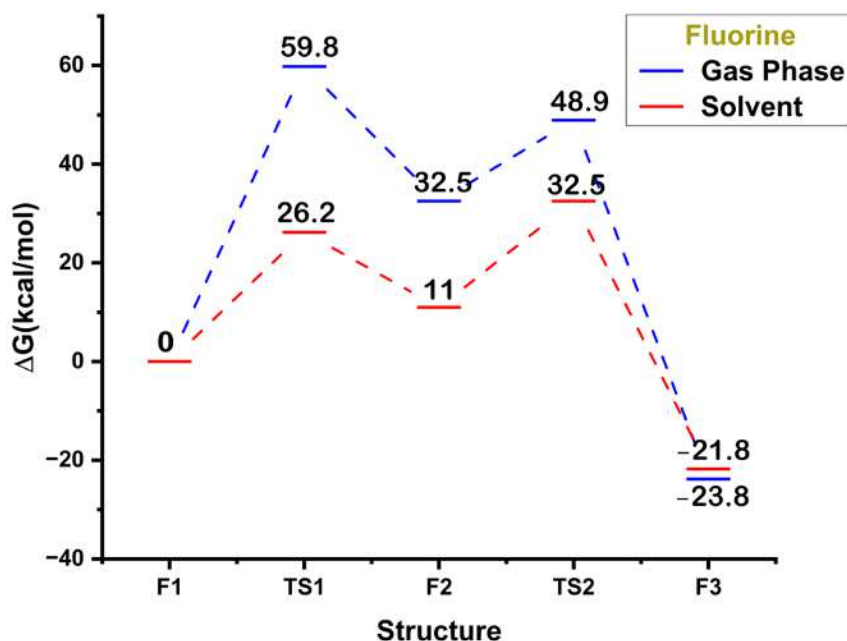


Fig. 1 Computed Gibbs free-energy profile for the metal-free C-3 fluorination of pyridine N-oxide with N-fluorosuccinimide in the gas phase and in acetonitrile

The second transition state TS2 is located at +48.9 kcal mol⁻¹, and the final product F3 is significantly stabilized at -23.8 kcal mol⁻¹ relative to F1. These values indicate a strongly exergonic overall transformation but very high gas-phase barriers, implying that the uncatalyzed fluorination would be kinetically inaccessible under ambient conditions.

In acetonitrile, the reaction profile changes markedly. TS1 is strongly stabilized by the polar medium, dropping to +26.2 kcal mol⁻¹, whereas F2 and TS2 appear

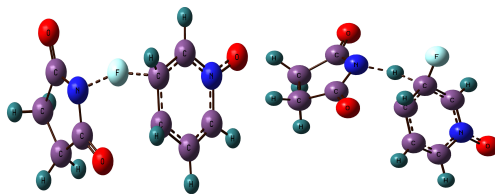


Fig. 2 Optimized structure of TS1 and TS2 for C-3 fluorination of pyridine N-oxide

at +11.0 and +32.5 kcal mol⁻¹, respectively. The product remains highly exergonic (-21.8 kcal mol⁻¹). Under these conditions TS2 becomes the highest point on the free-energy surface and is therefore predicted to be the rate-determining step in solution. Overall, the computed landscape is fully consistent with a stepwise ionic mechanism: initial electrophilic activation by NFS leads to a highly polar σ -complex, followed by a second barrier associated with deprotonation and rearomatization, culminating in a thermodynamically favored C-3 fluorinated pyridine N-oxide. The optimized geometries of TS1 and TS2 involved in the fluorination pathway are shown in Figure 2.

3.1.2 Frontier molecular orbitals and global reactivity descriptors

The HOMO–LUMO gaps for the fluorination pathway are collected in Table 2.

Table 2 Frontier molecular orbital energies and HOMO–LUMO gaps for the C-3 fluorination pathway.

Structure	HOMO	LUMO	Gap (Hartree)	Gap (eV)
F1	-0.23512	-0.05882	0.17630	4.796
TS1	-0.25868	-0.19568	0.06300	1.715
F2	-0.23890	0.19541	0.04349	1.183
TS2	-0.21950	-0.09398	0.12552	3.416
F3	-0.24372	-0.06725	0.17647	4.801

The reactant F1 and product F3 display large HOMO–LUMO gaps (0.17630 and 0.17647 Hartree, ≈ 4.80 eV), characteristic of electronically stable, closed-shell aromatic systems. In contrast, TS1, F2, and TS2 exhibit significantly reduced gaps of 0.06300 (1.72 eV), 0.04349 (1.18 eV), and 0.12552 Hartree (3.42 eV), respectively. The very small gaps for TS1 and F2 identify these species as the most electronically activated along the pathway and coincide with the high-lying transition state and reactive σ -complex. TS2 partially restores the gap as the system approaches the rearomatized product, reflecting partial recovery of aromatic character at this stage.

Global reactivity descriptors (Table 4) provide a complementary quantitative picture. The reactant F1 is relatively hard ($\eta = 2.40$ eV) and soft only to a modest degree ($S \approx 0.42$ eV⁻¹), with moderate electrophilicity ($\omega = 1.67$ eV), consistent with a stable aromatic substrate. TS1, by contrast, shows the smallest hardness ($\eta = 0.86$ eV), largest softness ($S = 1.16$ eV⁻¹), and a very large electrophilicity index ($\omega = 11.15$ eV), clearly identifying it as the most electron-accepting, highly activated species along the profile. The σ -complex F2 is unusually hard ($\eta = 5.91$ eV)

and nearly non-electrophilic ($\omega = 0.02$ eV), suggesting a transient but electronically stabilized adduct where charge has been effectively delocalized. TS2 has intermediate softness and electrophilicity ($\eta = 1.71$ eV, $\omega = 5.32$ eV), in line with its role in the rearomatization step. Finally, F3 regains high hardness ($\eta = 2.40$ eV) with moderate electrophilicity, in agreement with its characterization as a thermodynamically stable C-3 fluorinated product.

Table 3 Global reactivity descriptors for the C-3 fluorination pathway calculated using frontier molecular orbital energies.

Structure	η	$S = 1/\eta$	χ	ω
F1	2.40	0.417	3.99	1.67
TS1	0.86	1.163	6.19	11.15
F2	5.91	0.169	0.59	0.02
TS2	1.71	0.585	4.27	5.32
F3	2.40	0.416	4.23	3.73

Overall, the FMO and global descriptor analyses dovetail with the free-energy profile: species with small HOMO–LUMO gaps and high softness (TS1 and F2) correspond to the key reactive configurations, whereas large gaps and high hardness are associated with the stable minima (F1, F3).

3.1.3 NBO analysis

NBO second-order perturbation analysis for the fluorination system reveals an extensive network of donor→acceptor interactions that rationalize the stabilization of intermediates and transition states (see Figure 4 and detailed data in the Supporting Information; selected values are listed in the NBO tables above). Within unit 1, π - and σ -bonding orbitals act as important donors into neighboring antibonding orbitals. Interactions such as $\text{BD}(\text{C3}–\text{C4}) \rightarrow \text{BD}^*(\text{C1}–\text{C2})$ ($E(2) = 21.47$ kcal mol^{−1}) and $\text{BD}(\text{C3}–\text{C4}) \rightarrow \text{BD}^*(\text{C5}–\text{N6})$ ($E(2) = 27.09$ kcal mol^{−1}) attest to strong conjugation across the ring backbone, which helps delocalize developing charge density during electrophilic attack. Mild hyperconjugative donations (e.g., $\text{BD}(\text{C1}–\text{H8}) \rightarrow \text{BD}^*(\text{C2}–\text{C3})$ and $\text{BD}(\text{C2}–\text{C3}) \rightarrow \text{BD}^*(\text{C4}–\text{F12})$, $E(2) \approx 3–5$ kcal mol^{−1}) provide additional $\sigma \rightarrow \sigma^*$ stabilization.

The N-oxide oxygen plays a particularly central role. Lone-pair donation $\text{LP}(\text{O11}) \rightarrow \text{BD}^*(\text{C5}–\text{N6})$ exhibits a very large stabilization energy ($E(2) = 59.88$ kcal mol^{−1}, $\Delta E = 0.17$ a.u., $F = 0.095$ a.u.), indicating powerful $n(\text{O}) \rightarrow \sigma^*$ delocalization that supports the accumulation and distribution of positive charge in the vicinity of the C–N bond as the reaction proceeds. Additional $\text{LP}(\text{O11}) \rightarrow \text{BD}^*(\text{C1}–\text{N6})$ and $\text{LP}(\text{O11}) \rightarrow \text{RY}^*(\text{N6})$ interactions ($E^{(2)} \approx 3–9$ kcal mol^{−1}) corroborate the role of the N-oxide oxygen as a key stabilizing center. Fluorine also participates through $\text{LP}(\text{F12}) \rightarrow \text{BD}^*(\text{C3}–\text{C4})$ interactions ($E(2)$ up to 18.20 kcal mol^{−1}), which reflect through-bond polarization and contribute to electronic fine tuning of the aromatic core.

Several large $\text{BD}^* \rightarrow \text{BD}^*$ couplings, such as $\text{BD}^*(\text{C5-N6}) \rightarrow \text{BD}^*(\text{C3-C4})$ ($E(2) = 84.72 \text{ kcal mol}^{-1}$) and $\text{BD}^*(\text{C5-N6}) \rightarrow \text{BD}^*(\text{C1-C2})$ ($E(2) = 35.35 \text{ kcal mol}^{-1}$), are observed. Such unusually high $E(2)$ values result from near-degenerate antibonding orbitals and should be interpreted qualitatively as evidence of extensive mixing within the antibonding manifold rather than as simple pairwise stabilizations. Taken together, the NBO results demonstrate that strong lone-pair donation from the N-oxide oxygen and extensive $\text{BD} \rightarrow \text{BD}^*$ conjugation stabilize the high-energy σ -complex and facilitate the C-3 fluorination process.

3.2 Chlorination

3.2.1 Energy profile and mechanistic features

The computed Gibbs free energies for the C-3 chlorination of pyridine N-oxide are summarized in Table 4, and the corresponding energy profile is shown in Figure 3.

Table 4 Relative Gibbs free energies (ΔG , kcal mol^{-1}) for the chlorination pathway in the gas phase and in acetonitrile (ACN).

Structure	ΔG (Gas phase)	ΔG (Solvent)
Cl1	0.0	0.0
TS1	57.4	59.9
Cl2	9.7	18.4
TS2	51.7	55.2
Cl3	-24.1	-30.2

Using Cl1 as the reference ($0.0 \text{ kcal mol}^{-1}$), the gas-phase TS1, Cl2, and TS2 are located at $+57.4$, $+9.7$, and $+51.7 \text{ kcal mol}^{-1}$, respectively, while the product Cl3 is exergonic at $-24.1 \text{ kcal mol}^{-1}$. As in the fluorination case, the gas-phase barriers are prohibitively high, indicating that chlorination is also kinetically inaccessible without solvent or additional activation.

The TS2 structures are found at $+59.9$ and $+55.2 \text{ kcal mol}^{-1}$, whereas Cl2 lies at $+18.4 \text{ kcal mol}^{-1}$. The product Cl3 is substantially more stable in solution at $-30.2 \text{ kcal mol}^{-1}$, confirming that chlorination is thermodynamically highly favorable. The increased solution-phase barriers relative to the gas-phase values may arise from differential stabilization of the reactant complex relative to the transition states within the continuum solvation model. In this profile TS1 remains the highest point in solution and thus represents the predicted rate-determining step in chlorination under the modeled conditions. Overall, the mechanism again follows a stepwise sequence involving formation of a σ -complex followed by rearomatization, but now the initial electrophilic halogen transfer remains the rate-determining step, whereas the subsequent deprotonation step proceeds with a lower activation barrier.

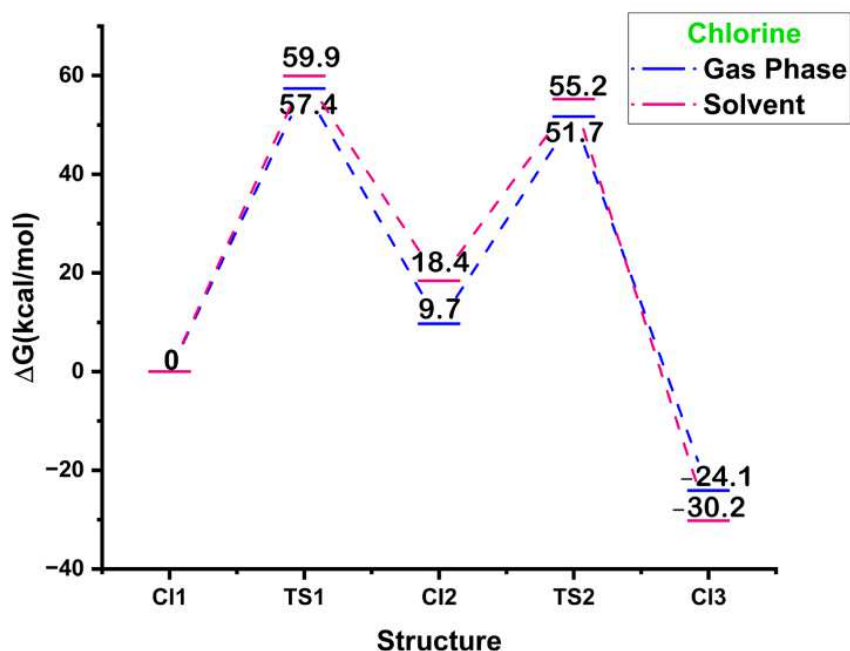


Fig. 3 Computed Gibbs free-energy profile for the metal-free C-3 chlorination of pyridine N-oxide with N-chlorosuccinimide in the gas phase and in acetonitrile.

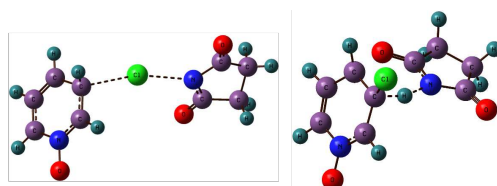


Fig. 4 Optimized structure of TS1 and TS2 for C-3 chlorination of pyridine N-oxide

3.2.2 Frontier molecular orbitals and global reactivity descriptors

HOMO–LUMO gaps along the chlorination pathway (Table 5) display trends analogous to those seen in fluorination.

The reactant Cl1 and product Cl3 possess large gaps (0.17375 and 0.17573 Hartree; 4.73 and 4.78 eV), indicative of stable aromatic species. At TS1 the gap narrows sharply to 0.06646 Hartree (1.81 eV), highlighting a highly activated, charge-redistributed structure corresponding to the first electrophilic chlorination step. The σ -complex Cl2 largely restores the gap (0.17076 Hartree, 4.65 eV), suggesting a well-defined, electronically relaxed intermediate. TS2 again shows an intermediate gap

Table 5 Frontier molecular orbital energies and HOMO–LUMO gaps for the chlorination pathway.

Structure	HOMO	LUMO	Gap (Hartree)	Gap (eV)
Cl1	−0.23541	−0.06166	0.17375	4.726
TS1	−0.25814	−0.19168	0.06646	1.808
Cl2	−0.23491	−0.06415	0.17076	4.647
TS2	−0.22540	−0.11645	0.10895	2.966
Cl3	−0.24416	−0.06843	0.17573	4.780

(0.10895 Hartree, 2.97 eV), consistent with a second, less severe activation associated with rearomatization.

Global descriptor analysis (Table 5) reinforces this picture. Cl1 and Cl3 are relatively hard ($\eta \approx 2.3$ – 2.4 eV) and moderately electrophilic ($\omega \approx 3.5$ – 3.8 eV). TS1 displays very low hardness ($\eta = 0.90$ eV), high softness ($S = 1.11$ eV^{−1}), and a very large electrophilicity index ($\omega = 20.71$ eV), marking it as the most reactive, strongly electron-accepting species along the chlorination profile and consistent with its role as the rate-determining transition state. The σ -complex Cl2 regains hardness and low electrophilicity, while TS2 shows intermediate softness and electrophilicity, again matching a rearomatization step.

Table 6 Global reactivity descriptors for the chlorination pathway calculated using frontier molecular orbital energies.

Structure	η	$S = 1/\eta$	χ	ω
Cl1	2.36	0.42	4.04	3.46
TS1	0.90	1.11	6.12	20.71
Cl2	2.32	0.43	4.07	3.56
TS2	1.48	0.67	4.65	7.30
Cl3	2.39	0.42	4.25	3.78

3.2.3 NBO analysis

The NBO analysis for chlorination reveals donor–acceptor patterns closely paralleling those observed for fluorination. In unit 1, strong $n(\text{N})/n(\text{O}) \rightarrow \sigma^*$ interactions such as $\text{LP}(\text{N}9) \rightarrow \text{BD}^*(\text{C1}–\text{O10})$ ($E^{(2)} = 49.80$ kcal mol^{−1}) and $\text{LP}(\text{O10}) \rightarrow \text{BD}^*(\text{C1}–\text{N9})$ ($E^{(2)} = 29.64$ kcal mol^{−1}) indicate efficient delocalization of electron density from the *N*-oxide and the adjacent oxygen atom into antibonding orbitals. Additional $\text{BD} \rightarrow \text{BD}^*$ interactions across the aromatic ring, including $\text{BD}(\text{C2}–\text{C3}) \rightarrow \text{BD}^*(\text{C1}–\text{O10})$ and $\text{BD}(\text{C2}–\text{C3}) \rightarrow \text{BD}^*(\text{C4}–\text{O11})$ ($E^{(2)} \approx 4$ – 5 kcal mol^{−1}), further contribute to the stabilization of the σ -complex intermediate, further support extended conjugation and charge delocalization.

Within unit 2, strong lone-pair donations from O22 and N21 into neighboring antibonding orbitals, e.g. $\text{LP}(\text{O22}) \rightarrow \text{BD}^*(\text{C12}–\text{N21})$ ($E^{(2)} = 58.14$ kcal mol^{−1}), and significant $\text{BD}(\text{C15}–\text{C16}) \rightarrow \text{BD}^*(\text{C12}–\text{N21})$ ($E^{(2)} = 29.00$ kcal mol^{−1}) establish a highly

conjugated heteroatomic fragment capable of stabilizing charge and polarizing bonds during electrophilic substitution. Several very large $\text{BD}^* \rightarrow \text{BD}^*$ contributions (e.g. $\text{BD}^*(\text{C12}-\text{N21}) \rightarrow \text{BD}^*(\text{C15}-\text{C16})$ ($E^{(2)} = 77.49 \text{ kcal mol}^{-1}$); $\text{BD}^*(\text{C15}-\text{C16}) \rightarrow \text{BD}^*(\text{C13}-\text{C14})$ ($E^{(2)} = 216.16 \text{ kcal mol}^{-1}$)) again reflect near-degenerate antibonding orbitals and should be interpreted qualitatively as indicators of extensive antibonding mixing. Altogether, the NBO results confirm that N-oxide and carbonyl lone pairs, together with conjugated C-C/C-N frameworks, play a decisive role in stabilizing the chlorination transition states and σ -complex.

3.3 Bromination

3.3.1 Energy profile and mechanistic features

The computed Gibbs free energies for the bromination pathway are summarized in Table 7,

Table 7 Relative Gibbs free energies (ΔG , kcal mol^{-1}) for the bromination pathway in the gas phase and in acetonitrile.

Structure	ΔG (Gas phase)	ΔG (Solvent)
Br1	0.0	0.0
TS1	44.2	41.0
Br2	25.4	19.0
TS2	40.2	45.0
Br3	-24.7	-24.7

and the corresponding energy profile is shown in Figure 5.

Taking Br1 as the reference ($0.0 \text{ kcal mol}^{-1}$), the gas-phase TS1, Br2, TS2, and Br3 are found at +44.2, +25.4, +40.2, and $-24.7 \text{ kcal mol}^{-1}$, respectively. In the gas phase TS1 has the highest energy and therefore represents the rate-determining barrier, consistent with an initial electrophilic activation step.

In acetonitrile TS1 and Br2 are located at +41.0 and +19.0 kcal mol^{-1} , while TS2 rises to +45.0 kcal mol^{-1} and the final product Br3 remains strongly exergonic ($-24.7 \text{ kcal mol}^{-1}$). Under these conditions TS2 slightly exceeds TS1 in energy, indicating a shift in the rate-determining step from the first activation barrier in the gas phase to the second, rearomatization step in solution. As in the fluorination and chlorination cases, the overall reaction is thermodynamically favorable and proceeds through a stepwise process involving a σ -complex intermediate whose energy is significantly lower than that of the preceding TS. The optimized geometries of TS1 and TS2 for the bromination pathway are shown in Figure 6.

3.3.2 Frontier molecular orbitals and global reactivity descriptors

The HOMO-LUMO gaps for the bromination pathway (Table 8) again display the characteristic alternation between stable and activated species.

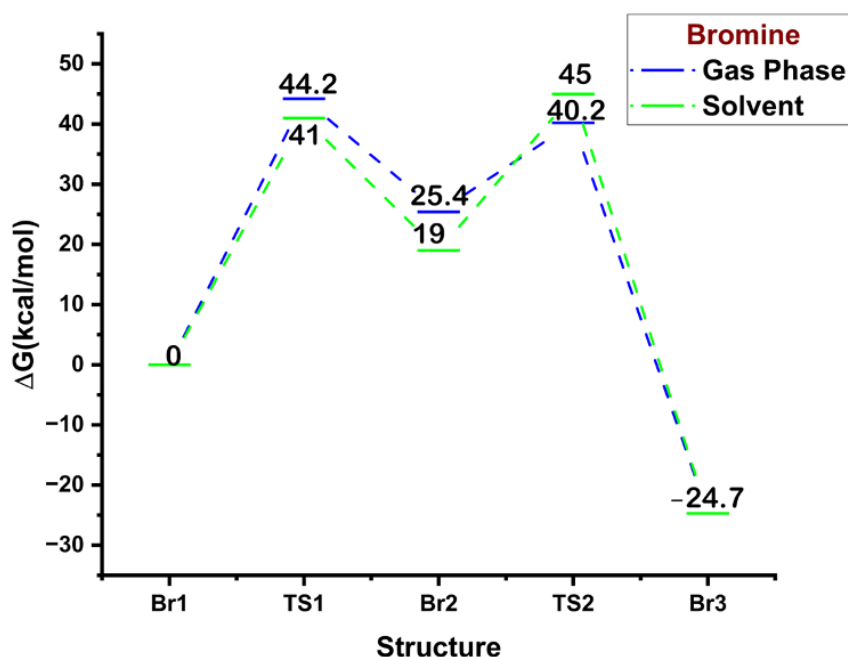


Fig. 5 Computed Gibbs free-energy profile for the metal-free C-3 bromination of pyridine N-oxide with N-bromosuccinimide in the gas phase and in acetonitrile.

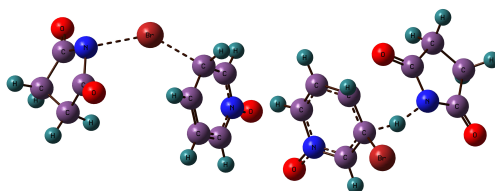


Fig. 6 Optimized structure of TS1 and TS2 for C-3 bromination of pyridine N-oxide

The reactant Br1 and product Br3 exhibit relatively large gaps (0.15254 and 0.17528 Hartree; 4.15 and 4.77 eV), indicating electronically stable species with restored aromatic character. At TS1 the gap narrows to 0.07036 Hartree (1.91 eV), marking a highly activated electronic configuration associated with the initial electrophilic bromination step. The intermediate Br2 regains a large gap (0.16986 Hartree, 4.62 eV), comparable to that of the product, and can thus be regarded as a well-defined, electronically robust σ -complex. TS2 again lies between these extremes (0.11613 Hartree, 3.16 eV), in line with its role as a second transition state required for rearomatization and product formation.

Table 8 Frontier molecular orbital energies and HOMO–LUMO gaps for the bromination pathway.

Structure	HOMO	LUMO	Gap (Hartree)	Gap (eV)
Br1	−0.23624	−0.08370	0.15254	4.15
TS1	−0.24808	−0.17772	0.07036	1.91
Br2	−0.23276	−0.06290	0.16986	4.62
TS2	−0.23050	−0.11437	0.11613	3.16
Br3	−0.24200	−0.06672	0.17528	4.77

Table 9 Global reactivity descriptors for the bromination pathway calculated using frontier molecular orbital energies.

Structure	η	$S = 1/\eta$	χ	ω
Br1	2.08	0.48	4.35	4.57
TS1	0.96	1.04	5.80	17.53
Br2	2.31	0.43	4.02	3.51
TS2	1.58	0.63	4.69	6.97
Br3	2.38	0.42	4.20	3.70

Global reactivity descriptors show the same pattern. Br1 is relatively hard ($\eta = 2.08$ eV) with moderate electrophilicity ($\omega = 4.57$ eV). TS1 is the softest and most electrophilic species ($\eta = 0.96$ eV, $S = 1.04$ eV^{−1}, $\omega = 17.53$ eV), clearly identifying it as the most reactive configuration on the bromination surface, especially in the gas phase. Br2 and Br3 regain higher hardness and lower electrophilicity ($\eta \approx 2.3$ – 2.4 eV, $\omega \approx 3.5$ – 3.7 eV), consistent with stabilization after electrophilic attack and in the final product. TS2 exhibits intermediate softness and electrophilicity ($\eta = 1.58$ eV, $\omega = 6.97$ eV), consistent with a rearomatization transition state.

3.3.3 NBO analysis

Natural bond orbital (NBO) second-order perturbation analysis was performed for the optimized product structures in order to gain qualitative insight into the electronic delocalization and donor–acceptor interactions associated with C–3 halogenation of pyridine N-oxides. Since reliable NBO convergence could not be obtained for all transition states and short-lived intermediates, the present discussion is intentionally restricted to the electronic features of the thermodynamically stable products, which nevertheless reflect the cumulative electronic effects operative along the reaction pathway.

The NBO results reveal that the N-oxide oxygen plays a dominant stabilizing role in the halogenated products through strong lone-pair donation into adjacent antibonding orbitals. In particular, pronounced $n(\text{O}) \rightarrow \sigma(\text{C–N})^*$ and $n(\text{O}) \rightarrow \pi(\text{C–C})^*$ interactions are observed, confirming efficient charge redistribution across the heteroaromatic framework after C–X bond formation. These interactions provide a robust electronic basis for the enhanced stabilization of the C-3 substituted N-oxide products relative to the reactant complexes.

Significant $\pi \rightarrow \pi^*$ and $\sigma \rightarrow \sigma^*$ delocalization within the aromatic ring further indicates extensive conjugation in the halogenated systems, consistent with the recovery of aromatic stabilization following σ -complex formation and rearomatization. In addition, for the fluorinated product, measurable $\text{LP}(\text{F}) \rightarrow \pi(\text{C}-\text{C})^*$ interactions highlight the strong polarization of the C-F bond and its participation in through-bond electronic communication with the ring.

Although NBO analysis of the transition states was not included, the product-level donor-acceptor interactions observed here are fully consistent with the trends inferred from the free-energy profiles, frontier molecular orbitals, and global reactivity descriptors. Convergence difficulties associated with brominated transition-state wavefunctions prevented reliable second-order perturbation analysis. In particular, the strong involvement of the N-oxide lone pair provides indirect support for its key role in stabilizing cationic character during electrophilic attack at C-3.

Overall, the partial NBO analysis confirms that lone-pair donation from the N-oxide oxygen and extensive aromatic delocalization are fundamental electronic factors governing the stability of the halogenated products, and they complement the mechanistic picture derived from energetic and conceptual DFT analyses. The omission of transition-state NBO analysis does not affect the mechanistic conclusions, which are primarily supported by the computed free-energy profiles and IRC calculations.

3.4 Comparative halogen trends

Taken together, the fluorination, chlorination, and bromination profiles reveal a coherent mechanistic picture for metal-free C-3 halogenation of pyridine N-oxide. In all cases the reaction proceeds via a stepwise ionic pathway involving (i) an initial electrophilic activation step that generates a σ -complex, followed by (ii) a second barrier associated with rearomatization and product formation. The overall transformations are strongly exergonic in solution ($\Delta G \approx -22$ to -30 kcal mol⁻¹).

Solvent effects are pronounced for the more charge-separated species. For fluorination, solvation dramatically lowers the first barrier and renders TS2 rate-determining. For chlorination, TS1 remains the highest point both in the gas phase and in solution, while for bromination the RDS shifts from TS1 in the gas phase to TS2 in solution. This halogen-dependent change in rate-determining step reflects a subtle interplay between intrinsic bond strengths, charge distribution in the σ -complex, and differential solvent stabilization. The relatively high computed activation barriers may partly reflect the absence of explicit solvent molecules and the simplified model system employed in the present study. Explicit solvent participation, particularly during the deprotonation step, could provide additional stabilization that is not captured by the continuum SMD model. Across the series, TS1 consistently shows the smallest hardness, largest softness, and highest electrophilicity, indicating strongly electron-accepting, highly activated species that correlate with the experimentally expected electrophilic halogen transfer step. The σ -complex intermediates are electronically stabilized with large HOMO-LUMO gaps and relatively high hardness, while the final products recover gaps comparable to or larger than the reactants, confirming that C-3 halogenation preserves or even enhances aromatic stabilization. NBO analyses consistently point to N-oxide and carbonyl/heteroatom lone pairs as the dominant donors

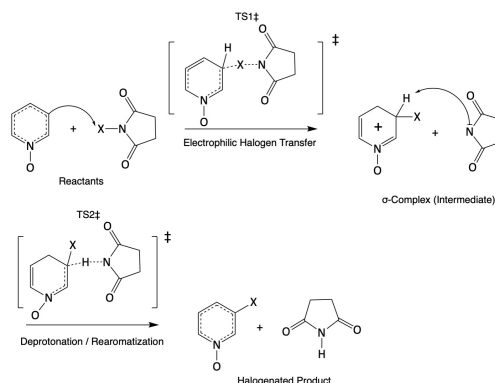


Fig. 7 Proposed DFT-supported stepwise ionic electrophilic substitution mechanism for the C-3 halogenation of pyridine N-oxide using N-halosuccinimides (NXS; X = F, Cl, Br). Electrophilic halogen transfer via TS1 forms a σ -complex intermediate, which undergoes deprotonation and rearomatization through TS2 to afford the corresponding halogenated pyridine N-oxide.

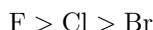
that delocalize charge into σ^* and π^* orbitals during electrophilic attack, explaining the strong directing effect of the N-oxide group and the robustness of the σ -complex intermediates.

Based on the computed free-energy profiles, IRC analyses, and NBO results, a common stepwise ionic electrophilic substitution mechanism is proposed for all three halogenation reactions (Figure 7). The reaction proceeds through electrophilic halogen transfer to form a σ -complex intermediate, followed by deprotonation and rearomatization. The observed halogen-dependent reactivity arises from differences in N–X bond strength, halogen polarizability, and transition-state stabilization.

3.5 Comparison with Experimental Observations

Although the present study is theoretical in nature, the computed reactivity trends are in good agreement with reported experimental studies on N-halosuccinimide-mediated halogenation of pyridine N-oxides and related heteroaromatic systems. N-halosuccinimides such as N-chlorosuccinimide (NCS) and N-bromosuccinimide (NBS) are widely employed as efficient electrophilic halogenating agents under mild and metal-free conditions, enabling regioselective functionalization of heteroarenes.^[53–55] In contrast, electrophilic fluorination reactions are generally more challenging and often require more forcing conditions or specialized reagents, which has been attributed to the strong N–F bond and the low polarizability of fluorine.^[17]

The computed activation free energies obtained in the present work follow the trend:



which is fully consistent with experimental observations indicating that fluorination is kinetically less favorable than chlorination and bromination.^[18] In particular, bromination is known to proceed more readily due to the higher polarizability of bromine and the relatively weaker N–Br bond, which facilitates electrophilic halogen transfer. This trend is accurately reproduced in the present DFT calculations,

where bromination exhibits lower activation barriers compared to fluorination and chlorination. Furthermore, the calculated thermodynamic profiles indicate that all halogenation reactions are strongly exergonic ($\Delta G \approx -22$ to -30 kcal mol⁻¹), which is consistent with the experimentally observed irreversibility of electrophilic aromatic substitution processes following σ -complex formation and rearomatization.[56]

Experimental studies have also demonstrated that the N-oxide functionality plays a crucial role in directing substitution to the C-3 position of the pyridine ring.[25] This directing effect is well reproduced in the present calculations, where stabilization of the σ -complex intermediate is achieved through significant lone-pair donation from the N-oxide oxygen into adjacent antibonding orbitals, as revealed by NBO analysis.

Overall, the strong agreement between computed activation barriers, thermodynamic trends, and regioselectivity with available experimental data supports the validity of the proposed stepwise ionic mechanism and provides a consistent molecular-level explanation for halogen-dependent reactivity in pyridine N-oxide halogenation.

4 Conclusion

A comprehensive density functional theory investigation of the metal-free C-3 halogenation of pyridine N-oxide with N-fluoro-, N-chloro-, and N-bromosuccinimide has been carried out to unravel the mechanistic origin of halogen-dependent reactivity and selectivity. The computed free-energy profiles consistently support stepwise ionic pathways involving σ -complex intermediates and two sequential transition states. Solvent effects exert a decisive influence by stabilizing polar transition structures and modulating the rate-determining step across the halogen series.

Frontier molecular orbital analysis reveals pronounced HOMO-LUMO gap compression at TS1 in all three cases, while global reactivity descriptors unequivocally identify TS1 as the softest and most electrophilic species along each reaction pathway. Natural bond orbital analysis demonstrates that strong $n(\text{O}) \rightarrow \sigma^*$ donation from the N-oxide oxygen and extended π -delocalization across the heteroaromatic system are the dominant electronic factors governing σ -complex stabilization and halogen transfer.

Overall, this study establishes that halogen-dependent reactivity in pyridine N-oxide halogenation arises from a synergistic interplay between halogen polarizability, N-X bond strength, and transition-state stabilization. The combined energetic, orbital, and bonding analyses provide a consistent mechanistic framework that aligns with experimental observations and offers predictive insight for the rational design of metal-free heteroarene functionalization reactions.

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- Author contribution : Zoranthara performed the calculations and drafted the manuscript. Zodinpuia Pachuau supervised the work and revised the manuscript. All authors contributed to data analysis and approved the final version.

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