

Effect of Substituents on the Strength of N–X (X = H, F, and Cl) Bond Dissociation Energies: A High-Level Quantum Chemical Study

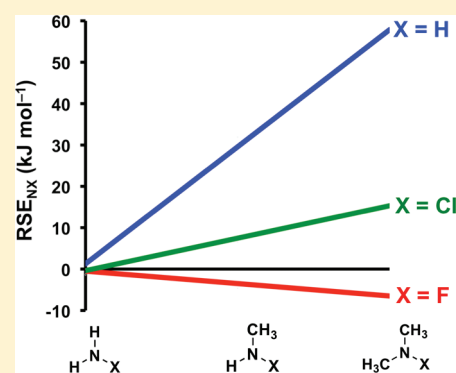
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Supporting Information

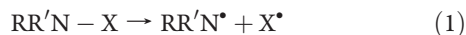
ABSTRACT: The effect of substituents on the strength of N–X (X = H, F, and Cl) bonds has been investigated using the high-level W2w thermochemical protocol. The substituents have been selected to be representative of the key functional groups that are likely to be of biological, synthetic, or industrial importance for these systems. We interpreted the effects through the calculation of relative N–X bond dissociation energies (BDE) or radical stabilization energies (RSE_{NX}). The BDE and RSE_{NX} values depend on stabilizing/destabilizing effects in both the reactant molecule and the product radical of the dissociation reactions. To assist us in the analysis of the substituent effects, a number of additional thermochemical quantities have been introduced, including molecule stabilization energies (MSE_{NX}). We find that the RSE_{NH} values are (a) increased by electron-donating alkyl substituents or the vinyl substituent, (b) increased in imines, and (c) decreased by electron-withdrawing substituents such as CF_3 and carbonyl moieties or through protonation.

A different picture emerges when considering the RSE_{NF} and RSE_{NCl} values because of the electronegativities of the halogen atoms. The RSE_{NX} s differ from the RSE_{NH} values by an amount related to the stabilization of the *N*-halogenated molecules and given by MSE_{NX} . We find that substituents that stabilize/destabilize the radicals also tend to stabilize/destabilize the *N*-halogenated molecules. As a result, N–F- and N–Cl-containing molecules that include alkyl substituents or correspond to imines are generally associated with RSE_{NF} and RSE_{NCl} values that are less positive or more negative than the corresponding RSE_{NH} . In contrast, N–F- and N–Cl-containing molecules that include electron-withdrawing substituents or are protonated are generally associated with RSE_{NF} and RSE_{NCl} values that are more positive or less negative than the corresponding RSE_{NH} .



INTRODUCTION

The strength of a bond with respect to radical formation is defined as the homolytic bond dissociation energy (BDE) of that bond, and for N–X species (X = H, F, and Cl) this is given by the energy change for the reaction



The formation of nitrogen-centered radicals via the homolysis of N–Cl bonds in *N*-chlorinated species represents a specific example of such bond cleavage and is of great importance. From a biological perspective, such processes can lead to the damage of important species such as nucleobases and proteins, via fragmentation of their *N*-chlorinated derivatives.¹ Thus, production of a nitrogen-centered radical via homolysis of the N–Cl bond in *N*-chloroadenine has been shown to initiate covalent binding of the nucleobase to proteins and other nucleobases,² while uridine–dimer formation has been observed upon fragmentation of the N–Cl bond in the monomer.³ Chloramine/amide formation within proteins has been demonstrated to facilitate degradation of proteins⁴ and extracellular matrix.⁵ Pulse radiolysis investigations have been performed in order to understand rates of formation of radicals produced via degradation of biologically

relevant *N*-chlorinated amines and amides, and cleavage of the N–Cl bonds has been found to occur with great facility.⁶

Due to the use of monochloramine (NH_2Cl) as a treatment agent for municipal water supplies, there has been significant interest in the stability of this species. The radiolytic reactions of NH_2Cl have been investigated in aqueous solution, and NH_2Cl is shown to react rapidly with hydrated electrons, resulting in formation of $\bullet NH_2$ radical.⁷ Monochloramine has been shown to transfer chlorine to other amines,⁸ and formation of *N*-chloroamines⁹ has also been observed. EPR investigations have also been used to study the production of nitrogen-centered radicals via homolysis of the N–Cl bond in chloramine-T, a powerful disinfectant used in places such as hospitals and kitchens.¹⁰

Nitrogen-centered radicals (derived from *N*-chloro species) are also of synthetic importance,¹¹ where they have been used in a number of cyclization processes¹² and homolytic amination reactions of aromatic molecules.¹² From an industrial perspective, *N*-chloro derivatives of amides, lactams, carbamates, and

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imides have been shown to be effective initiators for the metal-catalyzed living radical polymerization of methacrylates.¹³

Compounds containing N–F bonds are frequently employed as fluorinating agents. On the other hand, the fluorine transfer is generally assumed to occur via electrophilic processes, rather than involving fluorine atoms. As a result, investigation of the effect of substituents on the homolytic bond strength of N–F bonds has generally been somewhat neglected.

Given the importance of N–X bonds (X = H, F, and Cl) in biological, industrial, and synthetic settings, understanding the effect of substituents on their strength is highly desirable. In this regard, we note that the factors governing the strength of the N–H bonds of amines and amides have been previously investigated in detail using quantum chemical methods.¹⁴ However, much less attention has been given to the N–H bonds of imines.¹⁵ There have been relatively few investigations of the effects of substituents on the strength of N–Cl bonds,¹⁶ while the literature on N–F bonds is scarce.

In the present study, we examine the effect of substituents on the homolytic BDEs of a number of N–X-containing molecules, in which the key functional groups that are likely to be of biological/synthetic/industrial importance are represented. The high-level W2w method is employed.¹⁷ We compare and contrast the effect of substituents on the strength of N–H, N–F, and N–Cl bonds and examine the effect of the substituents on both the stabilities of the molecular precursors and the product radicals. It is important to note that in light of previous investigations in which it has been shown that the effects of substituents on the dissociation energies of R–X bonds depend both on the stabilities of R• and on the nature of X,¹⁸ we might equally expect that the N–X BDEs of RR'N–X molecules will depend both on the stability of the RR'N• radicals and on the nature of X.

COMPUTATIONAL PROCEDURES

The geometries of all structures have been obtained at the B3-LYP/A'VTZ level of theory, where A'VnZ indicates the combination of the standard correlation-consistent cc-pVnZ basis sets¹⁹ on H with aug-cc-pVnZ basis sets²⁰ on first-row atoms and aug-cc-pV(n+d)Z basis sets²¹ on Cl. To confirm that the optimized geometries correspond to equilibrium structures, we performed harmonic vibrational analyses, which showed that all frequencies are real. Zero-point vibrational energies (ZPVEs) have been obtained from such calculations and have been corrected using the literature scaling factor of 0.9884.²² All geometry optimizations and frequency calculations were performed using the Gaussian 09 program.²³

In order to obtain reliable relative energies, high-level ab initio calculations have been carried out using the W2w thermochemical protocol with the Molpro 2009.1 program.²⁴ W2w theory represents a layered extrapolation to the relativistic, all-electron CCSD(T) basis set limit and can achieve an accuracy in the kJ mol⁻¹ range for molecules whose wave functions are dominated by dynamical correlation. The computational protocol of W2w theory has been specified and rationalized in ref 17 (see also ref 25). It differs from the older W2 procedure²⁶ through the use of aug'-cc-pV(n+d)Z basis sets, rather than aug'-cc-pV-(n+2d1f)Z basis sets for the extrapolations of the HF, and valence CCSD and (T) components. In brief, the ROHF component is obtained from the results with the A'VQZ and A'VSZ basis sets using the $E(L) = E_\infty + A/L^5$ two-point extrapolation

formula. The valence ROCCSD correlation energy is obtained using the same basis sets with the $E(L) = E_\infty + A/L^3$ two-point extrapolation formula. The (T) valence correlation component is obtained from the same extrapolation formula using the A'VTZ and AV'QZ basis sets. The inner-shell correlation contribution is obtained at the CCSD(T) level using the MTsmall core-correlation basis set.²⁷ The scalar-relativistic contribution is obtained from second-order Douglas–Kroll–Hess CCSD(T)/MTsmall calculations.²⁸ Atomic spin–orbit corrections of 1.61 and 3.52 kJ mol⁻¹ have been applied to F• and Cl•, respectively. The percentage of the total atomization energy accounted for by parenthetical connected triple excitations, %TAE_c[(T)], has been shown to be a reliable energy-based diagnostic for the importance of nondynamical correlation effects.²⁹ It has been suggested that %TAE_c[(T)] < 2% indicates systems that are dominated by dynamical correlation, while 2% < %TAE_c[(T)] < 5% indicates systems that include mild nondynamical correlation. All systems considered in the present study are characterized by %TAE_c[(T)] values smaller than 4.3%. Thus, the W2w BDEs for these systems might be expected to lie close to the full CI limit (typically within 1 kJ mol⁻¹ or better).

RESULTS AND DISCUSSION

N–X BDE Data Set (X = H, F, and Cl) and General Overview.

We calculated a total of 31 N–H, 31 N–F, and 31 N–Cl BDEs for molecules that include the key functional groups that are relevant to synthetic, industrial, and biological settings (Table 1).

We begin by comparing a number of our calculated W2w N–X BDEs with those obtained experimentally or at higher levels of theory. Our calculated value of 443.7 kJ mol⁻¹ for the N–H BDE of NH₃ agrees well with the experimental 0 K value of 444.0 ± 0.2 kJ mol⁻¹³⁰ and with the value of 443.6 ± 0.7 kJ mol⁻¹ derived from high-level W4 energies.^{29,31,32} For the aromatic heterocycles, our calculated N–H BDEs of 398.2 and 393.5 kJ mol⁻¹ for imidazole and pyrrole are in close agreement with the experimentally determined values of 397.9 ± 2.1 and 393.0 ± 0.5 kJ mol⁻¹, respectively.^{33,34} Analogously, the W2w N–H BDE for H₂C=NH of 363.2 kJ mol⁻¹ agrees well with the value of 361.7 ± 0.7 kJ mol⁻¹ derived using energies from the highly accurate W4-08 data set.³¹

Our calculated N–Cl BDE for NH₂Cl of 251.3 kJ mol⁻¹ is 4.0 kJ mol⁻¹ higher than the experimentally derived value of 247.3 kJ mol⁻¹ (after correction to 0 K).³⁵ Although this discrepancy is relatively small, we examined it more closely through performing higher-level calculations for NH₂Cl using the W4 protocol.²⁹ This produces an N–Cl BDE (250.8 ± 0.7 kJ mol⁻¹) just 0.5 kJ mol⁻¹ from the W2w value. A re-evaluation of the experimental BDE of NH₂Cl would be desirable in light of these findings. Additionally, we note that W2w performs well for the N–F BDE of NH₂F, with a calculated value of 284.7 kJ mol⁻¹ compared with the W4 result of 285.4 ± 0.7 kJ mol⁻¹.

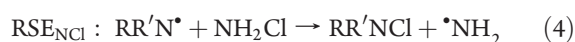
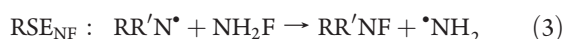
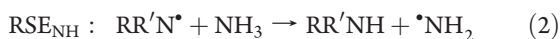
From a broad perspective, we note that for the neutral N–X species, the N–H, N–F, and N–Cl BDEs span from 363.2 to 494.5 kJ mol⁻¹, 219.6 to 311.7 kJ mol⁻¹, and 185.4 to 294.0 kJ mol⁻¹, respectively, corresponding to ranges of 131.3, 92.1, and 108.6 kJ mol⁻¹. The largest BDEs for all X are found for the imide molecules (CHO)₂NX. The smallest N–H BDE occurs for H₂C=NH (363.2 kJ mol⁻¹), while the smallest N–F BDE occurs for N-fluoroimidazole (219.6 kJ mol⁻¹). For the N–Cl-containing species, N-chlorovinylamine (which is the

Table 1. N–X BDEs (X = H, F, Cl) Obtained at the W2w Level of Theory (0 K, kJ mol⁻¹)

structure	N–H BDE	N–F BDE	N–Cl BDE
NH ₂ X	443.7	284.7	251.3
MeNHX	411.6	289.2	244.6
Me ₂ NX	387.1	290.7	235.6
(XNH)CH ₂ CO ₂ H	417.7	286.0	242.8
F ₃ C–NHX	454.5	282.8	250.3
H ₂ C=CH–NHX	367.7	223.0	185.4
N-XImidazole	398.2	219.6	201.9
N-XPyrrole	393.5	222.2	200.5
NH ₃ X ⁺	516.7	267.9	266.9
MeNH ₂ X ⁺	454.4	248.2	226.6
Me ₂ NHX ⁺	415.8	242.8	203.9
HCONHX	473.6	296.4	271.6
MeCONHX	466.3	297.8	267.6
FCONHX	478.7	286.8	264.2
(NC)CONHX	482.9	290.7	274.8
HCONMeX	450.8	292.7	264.3
(CHO) ₂ NX	494.5	311.7	294.0
(H ₂ N)(HNX)C=O	451.4	294.5	260.1
(XNH)HC=NH	419.3	256.9	225.3
(XNH)(NH ₂)C=NH	418.1	264.6	229.9
H ₂ C=NX	363.2	272.9	216.3
MeHC=NX	371.5	279.3	226.1
(H ₂ N)CH=NX	401.2	298.8	256.5
H(OH)C=NX	413.1	294.8	254.1
FHC=NX	420.6	278.9	243.6
(NC)HC=NX	386.6	276.9	227.5
Me ₂ C=NX	373.3	282.2	229.3
Me(OH)C=NX	409.2	299.4	257.3
(H ₂ N) ₂ C=NX	409.0	299.4	261.3
F ₂ C=NX	441.5	275.9	248.3
F(OH)C=NX	440.2	292.4	259.8

higher energy tautomer of *N*-chloroacetaldimine) has the smallest BDE (185.4 kJ mol⁻¹). Let us now try to understand these results.

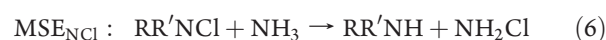
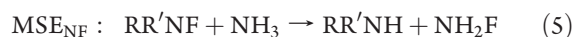
Analysis of Stabilization Effects. It is useful to begin by defining a number of quantities that will assist us in analyzing the effect of substituents on the N–X BDEs.³⁶ Of immediate importance in this respect are the *relative* N–X BDEs. These are the BDEs calculated relative to the BDEs of appropriate parent molecules and are commonly referred to as radical stabilization energies (RSEs). They are given by the energy changes for the hydrogen-atom-transfer reactions



Despite the fact that we are considering the RSE of a *single* radical (RR'N[•]) in reactions 2–4, there are *three* relevant RSEs depending on whether the closed-shell precursor is RR'NH, RR'NF, or RR'NCl. These are accordingly labeled as RSE_{NH}, RSE_{NF}, or RSE_{NCl}. The RSE_{NX} values measure the effect of substituents on

the stabilities of the nitrogen-centered radicals (RR'N[•]) relative to the same effects in the corresponding closed-shell parent molecules (RR'NX). A positive RSE_{NH}, RSE_{NF}, or RSE_{NCl} value implies that the substituents stabilize the radical more than they stabilize the corresponding closed-shell molecule, relative to the parent species. It also means that the N–H, N–F, and N–Cl BDEs of the substituted molecules will be lower than those of parent molecules NH₃, NH₂F, and NH₂Cl, respectively.

Due to the different electronic behavior of H, F, and Cl, the values of RSE_{NH}, RSE_{NF}, and RSE_{NCl} are not expected to be equal for a given substituent(s). The differences for the F and Cl systems are given simply by the N–X molecule stabilization energies (MSE_{NF} and MSE_{NCl}), which are obtained as the energy changes for the halogen-transfer reactions 5 and 6, respectively



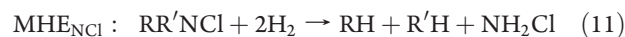
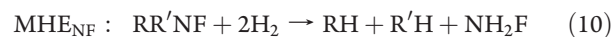
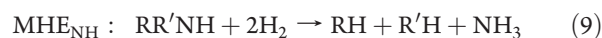
The MSEs measure the stability of RR'NF or RR'NCl compared with RR'NH (relative to the corresponding parent molecules). Equivalently, MSE_{NF} and MSE_{NCl} may be expressed in terms of RSEs according to eqs 7 and 8

$$MSE_{NF} = RSE_{NH} - RSE_{NF} \quad (7)$$

$$MSE_{NCl} = RSE_{NH} - RSE_{NCl} \quad (8)$$

Equations 7 and 8 indicate that RSE_{NX} = RSE_{NH} when MSE_{NX} = 0 (X = F or Cl).

Despite being termed *radical* stabilization energies, variations in RSE_{NH}, RSE_{NF}, and RSE_{NCl} do not reflect the stability of the radicals in absolute terms but instead refer to their *relative* stabilization compared with their closed-shell parents. To separate out the two effects, we define the molecule hydrogenolysis energy (MHE_{NX}) for N–H-, N–F-, and N–Cl-containing molecules as the energy changes for the formal reactions



The MHEs measure the effect of substituents on the stability of RR'NX (X = H, F, or Cl) compared with their effect in RH and R'H. A positive value for MHE_{NX} indicates a relative stabilization by the substituents in RR'NX. For the calculation of the MHE_{NX} values for imines RR'C=NX, the RR'C group is treated as a single substituent and the energy is calculated relative to RR'CH₂ plus NH₂X.

In a similar manner, we measure the effect of substituents on the stability of RR'N[•] or RR'C=N[•] compared with their effects in RH/R'H by the energy changes associated with the radical hydrogenolysis energy (RHE)



Again, for radicals RR'C=N[•] derived from imines, the RR'C group is treated as a single substituent and the energy is calculated relative to RR'CH₂ plus [•]NH₂.

Table 2. N–X (X = H, F, Cl) Radical Stabilization Energies (RSE_{NH} , RSE_{NF} , RSE_{NCl}), N–X Molecule Stabilization Energies (MSE_{NF} , MSE_{NCl}), and Hydrogenolysis Energies (RHE , MHE_{NF} , MHE_{NCl}) Obtained at the W2w Level of Theory (0 K, kJ mol^{-1})

structure	RSE_{NH}	RSE_{NF}	RSE_{NCl}	MSE_{NF}	MSE_{NCl}	RHE	MHE_{NH}	MHE_{NF}	MHE_{NCl}
NH_2X	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MeNHX	32.1	−4.5	6.7	36.7	25.4	−66.4	−98.5	−61.8	−73.1
Me_2NX	56.6	−6.0	15.7	62.6	40.9	−120.1	−176.7	−114.1	−135.8
$(\text{XNH})\text{CH}_2\text{CO}_2\text{H}$	26.1	−1.3	8.5	27.4	17.6	−53.4	−79.5	−52.1	−61.9
F_3CNHX	−10.8	1.9	1.0	−12.6	−11.8	−32.8	−22.0	−34.7	−33.8
$\text{H}_2\text{C}=\text{CHNHX}$	76.1	61.7	65.9	14.4	10.2	28.7	−47.4	−33.0	−37.2
N-XImidazole	45.6	65.1	49.4	−19.5	−3.8	43.3	−2.3	−21.8	−6.1
N-XPyrrole	50.2	62.5	50.8	−12.3	−0.6	14.6	−35.6	−47.9	−36.2
NH_3X^+	−72.9	16.8	−15.6	−89.7	−57.3				
MeNH_2X^+	−10.6	36.5	24.8	−47.1	−35.4				
Me_2NHX^+	28.0	41.9	47.5	−13.9	−19.5				
HCONHX	−29.8	−11.7	−20.3	−18.1	−9.6	5.0	34.8	16.8	25.2
MeCONHX	−22.6	−13.1	−16.3	−9.5	−6.4	3.4	26.0	16.5	19.6
FCONHX	−34.9	−2.1	−12.9	−32.8	−22.0	−19.7	15.2	−17.6	−6.8
$(\text{NC})\text{CONHX}$	−39.2	−6.0	−23.5	−33.2	−15.7	−5.2	34.0	0.8	18.3
HCONMeX	−7.0	−8.0	−13.0	5.4	5.9	−45.8	−38.8	−33.4	−32.9
$(\text{CHO})_2\text{NX}$	−50.8	−27.0	−42.7	−23.8	−8.1	4.8	55.6	31.8	47.4
$(\text{H}_2\text{N})(\text{HNX})\text{C}=\text{O}$	−7.7	−9.8	−8.8	2.2	1.1	−7.2	0.5	2.6	1.6
$(\text{XNH})\text{HC}=\text{NH}$	24.5	27.8	26.0	−3.3	−1.6	21.6	−2.9	−6.2	−4.5
$(\text{XNH})(\text{NH}_2)\text{C}=\text{NH}$	25.6	20.1	21.4	5.6	4.2	4.6	−21.0	−15.4	−16.7
$\text{H}_2\text{C}=\text{NX}$	80.5	11.8	35.0	68.8	45.5	−121.9	−202.4	−133.6	−156.9
$\text{MeHC}=\text{NX}$	72.2	5.4	25.2	66.8	46.9	−92.2	−164.5	−97.6	−117.5
$(\text{H}_2\text{N})\text{CH}=\text{NX}$	42.6	−14.1	−5.2	56.7	47.7	−64.3	−106.8	−50.1	−59.1
$\text{H}(\text{OH})\text{C}=\text{NX}$	30.7	−10.1	−2.8	40.8	33.4	−66.8	−97.5	−56.7	−64.1
$\text{FHC}=\text{NX}$	23.2	5.8	7.7	17.4	15.5	−101.8	−125.0	−107.6	−109.5
$(\text{NC})\text{HC}=\text{NX}$	57.2	7.8	23.8	49.4	33.4	−144.7	−201.9	−152.5	−168.6
$\text{Me}_2\text{C}=\text{NX}$	70.5	2.5	22.0	68.0	48.4	−71.5	−142.0	−74.0	−93.6
$\text{Me}(\text{OH})\text{C}=\text{NX}$	34.5	−14.7	−6.0	49.2	40.4	−49.2	−83.7	−34.4	−43.2
$(\text{H}_2\text{N})_2\text{C}=\text{NX}$	34.8	−14.7	−10.0	49.5	44.7	−31.4	−66.1	−16.6	−21.4
$\text{F}_2\text{C}=\text{NX}$	2.3	8.8	3.0	−6.5	−0.8	−125.0	−127.3	−133.9	−128.1
$\text{F}(\text{OH})\text{C}=\text{NX}$	3.5	−7.7	−8.5	11.2	12.0	−94.5	−98.1	−86.9	−86.1

The RSE_{NH} , RSE_{NF} , and RSE_{NCl} values may be determined as the difference between RHE and MHE_{NX} values

$$RSE_{NH} = RHE - MHE_{NH} \quad (13)$$

$$RSE_{NF} = RHE - MHE_{NF} \quad (14)$$

$$RSE_{NCl} = RHE - MHE_{NCl} \quad (15)$$

This shows that $RSE_{NX} = 0$ when the radical hydrogenolysis energy is equal to the molecule hydrogenolysis energy.

We should emphasize that quantities such as RHE and MHE_{NX} are relative quantities. However, by examining the differences between them through this approach, it becomes feasible to perform a breakdown of the contribution of both the radical and the closed-shell molecular precursor to RSE_{NH} , RSE_{NF} , and RSE_{NCl} .

We note finally that

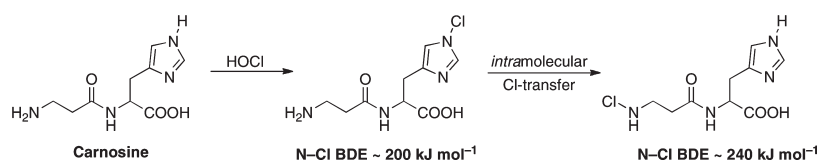
$$MSE_{NF} = MHE_{NF} - MHE_{NH} \quad (16)$$

$$MSE_{NCl} = MHE_{NCl} - MHE_{NH} \quad (17)$$

Effect of Substituents on the N–X (X = H, F, and Cl) BDEs of Amines. Introduction of one or two methyl substituents in

amines gives rise to positive RSE_{NH} values for MeNH_2 and Me_2NH (+32.1 and +56.6 kJ mol^{-1} , respectively) (Table 2), i.e., the BDEs are less than that, of NH_3 (Table 1). We find that although these substituents destabilize both the radical and the closed-shell parents compared with their effects in RH and R'H, they destabilize the radicals to a smaller extent (i.e., the RHE values are less negative than the corresponding MHE_{NH} values). The smaller destabilizing effects may partly be attributed to the existence of stabilizing hyperconjugative electron donation from the σ_{CH} orbitals of the alkyl groups to the half-filled 2p orbital at the nitrogen radical center, which is not possible in the corresponding closed-shell molecules. This appears to be more important than the stabilizing hyperconjugative donation from the nitrogen lone pair to the σ_{C-H}^* orbitals of the parent amines.

The presence of the σ -electron-withdrawing CF_3 substituent leads to a negative RSE_{NH} (−10.8 kJ mol^{-1}) for CF_3NH_2 . This is associated with the existence of a greater destabilizing effect for the CF_3 substituent in the radical ($RHE = -32.8 \text{ kJ mol}^{-1}$) compared with the same effect in the closed-shell parent ($MHE_{NH} = -22.0 \text{ kJ mol}^{-1}$). The radical is destabilized because of electron withdrawal by CF_3 from the electron-deficient radical center.³⁷ In addition, stabilizing hyperconjugative electron donation from the nitrogen lone pair to the σ_{C-F}^* orbitals of the CF_3

Scheme 1. Initial *N*-Chlorination of Carnosine and Subsequent Intramolecular Chlorine-Atom Transfer Affording a Stronger N–Cl Bond


substituent is likely to be more favorable in the closed-shell parent than in the radical.

For the vinylamine system, we calculate a large positive RSE_{NH} value of 76.1 kJ mol⁻¹, which arises because the vinyl substituent stabilizes the radical (RHE = +28.7 kJ mol⁻¹) but destabilizes the parent closed-shell molecule ($MHE_{NH} = -47.4$ kJ mol⁻¹) (relative to ethene plus ammonia). It is of interest that the calculated atomic spin densities indicate the radical to be better described as a carbon-centered radical ($\cdot\text{CH}_2\text{-CH=NH}$) than a nitrogen-centered radical ($\text{CH}_2\text{=CH-NH}\cdot$). The heterocyclic structures imidazole and pyrrole also lead to significantly positive RSE_{NH} values (45.6 and 50.2 kJ mol⁻¹, respectively). They are somewhat smaller than the values for the vinylamine (76.1 kJ mol⁻¹) and Me_2NH (56.6 kJ mol⁻¹) systems. In a similar manner to that observed for vinylamine, we find that, whereas the substituents relatively stabilize the imidazolyl and pyrrolyl radicals (RHE = 43.3 and 14.6 kJ mol⁻¹, respectively), they destabilize the parent-closed-shell species ($MHE_{NH} = -2.3$ and -35.6 kJ mol⁻¹, respectively).

A somewhat different picture emerges regarding the effect of substituents on the N–X BDEs and RSEs in *N*-halogenated amines (X = F and Cl), compared with those for X = H. We can see that for MeNHX systems RSE_{NH} (+32.1 kJ mol⁻¹) > RSE_{NCl} (+6.7 kJ mol⁻¹) > RSE_{NF} (–4.5 kJ mol⁻¹) and for the Me_2NX systems RSE_{NH} (+56.6 kJ mol⁻¹) > RSE_{NCl} (+15.7 kJ mol⁻¹) > RSE_{NF} (–6.0 kJ mol⁻¹). These trends can be rationalized on the basis that both F and Cl are electronegative, and the increased electron density afforded by introduction of the alkyl substituents stabilizes the MeNHX and Me_2NX molecules. The resulting large positive MSE_{NF} and MSE_{NCl} values mean that $RSE_{NX} < RSE_{NH}$. Because of the greater electronegativity of F, such effects are larger in the N–F species, leading to a negative RSE_{NF} . The results show that for the MeNHX and Me_2NX systems with X = Cl, the N–Cl bonds are weakened compared with that for NH_2Cl ($RSE_{NCl} = +6.7$ and $+15.7$ kJ mol⁻¹, respectively), but when X = F, the BDEs of the analogous N–F structures are actually increased relative to that for NH_2F ($RSE_{NF} = -4.5$ and -6.0 kJ mol⁻¹, respectively).

In contrast to the negative RSE_{NH} for the CF_3NH_2 system (–10.8 kJ mol⁻¹), the *N*-halogenated derivatives are associated with slightly positive RSE_{NF} and RSE_{NCl} values (+1.9 and +1.0 kJ mol⁻¹, respectively), i.e., the N–F and N–Cl BDEs of these structures are slightly lower than those for NH_2F and NH_2Cl , respectively. These findings can be attributed to the CF_3 substituent destabilizing the parent molecules CF_3NHX (X = F and Cl) relative to CF_3NH_2 (MSE_{NF} and $MSE_{NCl} = -12.6$ and -11.8 kJ mol⁻¹, respectively) and is again consistent with the electronegativities of both F and Cl.

As a result of the positive MSE_{NF} and MSE_{NCl} values associated with the *N*-halogenated derivatives of vinylamine (MSE_{NF} and $MSE_{NCl} = +14.4$ and $+10.2$ kJ mol⁻¹, respectively), the values of RSE_{NF} and RSE_{NCl} (61.7 and 65.9 kJ mol⁻¹, respectively) are

lower than the RSE_{NH} for the parent vinylamine system (76.1 kJ mol⁻¹). The positive MSE_{NF} and MSE_{NCl} values possibly arise because of enhanced π -donation from the nitrogen lone pair in the π -electron-rich N–F and N–Cl species, compared with the N–H system. In contrast, we find that due to the negative MSE_{NF} and MSE_{NCl} values in *N*-halogenated imidazole ($MSE_{NF} = -19.5$ and $MSE_{NCl} = -3.8$ kJ mol⁻¹) and *N*-halogenated pyrrole ($MSE_{NF} = -12.3$ and -0.6 kJ mol⁻¹), these substituents reduce the N–X BDEs compared with the effects in their N–H counterparts. Thus, the RSE_{NF} and RSE_{NCl} values for *N*-halogenated imidazole (65.1 and 49.4 kJ mol⁻¹, respectively) and *N*-halogenated pyrrole (62.5 and 50.8 kJ mol⁻¹, respectively) are larger than the RSE_{NH} values for the unsubstituted imidazolyl and pyrrolyl radicals (45.6 and 50.2 kJ mol⁻¹, respectively).

The finding that the N–Cl BDEs of primary *N*-chloramines are substantially greater than that of *N*-chloroimidazole may be of biological importance. As an example, it is known that HOCl-induced *N*-chlorination of the imidazole moiety of the antioxidant carnosine (Scheme 1) occurs with greater facility than the corresponding reactions with a number of other biologically important targets (e.g., DNA and protein backbones),³⁸ but the N–Cl BDE of the resulting *N*-chloroimidazole is expected to be weak (~200 kJ mol⁻¹). On the other hand, it has been shown experimentally that subsequent to this initial chlorination a rapid intramolecular chlorine-atom transfer occurs, in which the Cl is transferred to the terminal nitrogen (Scheme 1) forming a primary *N*-chloramine.³⁹ Comparison of the MSE_{NCl} value of *N*-chloroimidazole (–3.8 kJ mol⁻¹) with those of the primary *N*-chloramines of methylamine or glycine (25.4 and 17.6 kJ mol⁻¹, respectively) suggests that such a transfer will be thermodynamically favorable. Furthermore, our calculations indicate that the *N*-chloramine derivative that is produced is expected to have a significantly larger BDE (~240.0 kJ mol⁻¹) and therefore a greatly diminished extent of N–Cl dissociation. The favorable secondary chlorine-transfer process is thus likely to enable carnosine to play a critical role in diminishing the extent of host damage by the endogenous oxidant HOCl.

Effect of Substituents on the N–X (X = H, F, and Cl) BDEs of Protonated Amines. We can see (Table 1) that the N–H bond dissociation energies are significantly greater (and the RSE_{NH} values significantly more negative or less positive, Table 2) for the protonated amines than for their corresponding unprotonated parents. This means that the radicals are less stabilized by protonation than the corresponding closed-shell molecules, a result that is consistent with the electron-deficient nature of the radicals. The MSE_{NX} values are large and negative for the protonated species, indicating that protonation of the halogenated amines is less favorable than protonation of the corresponding amines. Again, this would be expected on the basis of the electronegativity of F and Cl. The large negative MSE_{NX} values mean that RSE_{NF} and RSE_{NCl} are less negative or more positive than the corresponding RSE_{NH} s.

Effect of Substituents on the N–X (X = H, F, and Cl) BDEs of Amides. The RSE_{NH} values for all the amides investigated are negative (-7.0 to -39.2 kJ mol^{-1}), i.e., the N–H BDEs are larger than that of NH_3 . The negative RSE_{NH} values mean that the RCO substituents stabilize the parent closed-shell molecules to a greater extent than the resulting amidyl radicals (i.e., $MHE_{NH} > RHE$). For the closed-shell species, delocalization of the nitrogen lone pair into the $\pi^*_{C=O}$ orbital of the RCO moiety results in a stabilizing interaction. There is a reduced stabilizing effect (or even a destabilizing effect) in the corresponding amidyl radicals, as reflected in the less positive or more negative RHEs compared with corresponding MHE_{NH} values. The negative RSE_{NH} values in amidyl radicals have been rationalized previously on the basis that delocalization of the lone pair, which occurs in the parent closed-shell species RCO-NH_2 , is reduced in the resulting RCO-NH^\bullet radicals because, in their pseudo- $^2A'$ electronic ground states, it is the unpaired electron rather than the lone pair that is positioned to allow delocalization into the $\pi^*_{C=O}$ orbital.^{14j}

Of the amide systems investigated, the FCO- and (NC)CO-substituted systems are associated with the most negative RSE_{NH} values (-34.9 and -39.2 kJ mol^{-1} , respectively). This finding may be rationalized on the basis of the greater electron-withdrawing nature of both the F and the NC substituents. In contrast, the HCONHMe and $(\text{H}_2\text{N})_2\text{C}=\text{O}$ systems are associated with the least negative RSE_{NH} values (-7.0 and -7.7 kJ mol^{-1} , respectively). In these cases, the radicals would benefit to a greater extent as a result of the donating effect of the Me substituent and the reduced electron-withdrawing effect of the CONH_2 substituent.

Moving to the only imide structure investigated, namely, $(\text{CHO})_2\text{NH}$, the presence of two CHO substituents induces the largest N–H BDE (494.5 kJ mol^{-1}) and hence the largest negative RSE_{NH} value of the neutral molecules investigated ($RSE_{NH} = -50.8$ kJ mol^{-1}). This arises because of the substantial stabilization in the $(\text{CHO})_2\text{NH}$ system ($MHE = +55.6$ kJ mol^{-1}), which is associated with delocalization of the nitrogen lone pair into the $\pi^*_{C=O}$ orbitals of the two CHO groups in $(\text{CHO})_2\text{NH}$. This is reduced in the 2A ground state of the $(\text{CHO})_2\text{N}^\bullet$ radical ($RHE = +4.8$ kJ mol^{-1}). The effect of the two CHO substituents appears to be less than additive, with the RSE_{NH} of the imide species being slightly less than twice the RSE_{NH} value associated with HCONH₂ (-29.8 kJ mol^{-1}).

Replacing the carbonyl moiety of HCONH₂ and $(\text{H}_2\text{N})_2\text{C}=\text{O}$ with imine groups, as in the structures $\text{HC}(\text{=NH})\text{NH}_2$ and $(\text{H}_2\text{N})_2\text{C}=\text{NH}$, has a dramatic effect on the values of RSE_{NH} , which go from being negative in the case of the carbonyl derivatives ($RSE_{NH} = -29.8$ and -7.7 kJ mol^{-1} , respectively) to being positive in the case of the imine derivatives ($RSE_{NH} = +24.5$ and $+25.6$ kJ mol^{-1}). These findings may be attributed to the fact that, whereas for the amido species the RHE values are less positive or more negative than the corresponding MHE_{NH} values (implying that the substituents have a greater stabilizing effect on the closed-shell parent molecules than in the resulting amidyl radicals), the opposite is the case for the imine-containing species. The imine substituent leads to negative MHE_{NH} values and more positive RHEs than are found for the carbonyls. This in turn may be attributed to the better π -electron-accepting nature of the $\pi^*_{C=O}$ orbital compared with the $\pi^*_{C=N}$ orbital.

For the N–X BDEs of the *N*-fluoro and *N*-chloroamide derivatives, we note that although the values of RSE_{NF} and RSE_{NCl} are negative they are generally less negative than the corresponding RSE_{NH} . This arises because of destabilizing effects

present in the *N*-halogenated parent structures (i.e., MSE_{NF} and MSE_{NCl} are negative), which can be explained on the basis of the electronegativities of F and Cl and the electron-withdrawing nature of the carbonyl group. Owing to the greater electronegativity of F vs Cl, the values of MSE_{NF} are generally more negative than the corresponding MSE_{NCl} values. There are two exceptions to this, namely, the HCONMeX and $(\text{H}_2\text{N})(\text{HXN})\text{C}=\text{O}$ species where, by virtue of the electron-donating nature of the Me and NH_2 substituents, MSE_{NF} and MSE_{NCl} have small positive values and RSE_{NF} and RSE_{NCl} are slightly more negative than the corresponding RSE_{NH} .

For the *N*-halogenated imides, we note the existence of destabilizing effects in the closed-shell species ($MSE_{NF} = -23.8$ kJ mol^{-1} and $MSE_{NCl} = -8.1$ kJ mol^{-1}) compared with $(\text{CHO})_2\text{NH}$. This leads to less negative values of RSE_{NF} and RSE_{NCl} (-27.0 and -42.7 kJ mol^{-1} , respectively) compared with the corresponding RSE_{NH} for the parent $(\text{CHO})_2\text{NH}$ system (-50.8 kJ mol^{-1}).

Effect of Substituents on the N–X (X = H, F, and Cl) BDEs of Imines. For the N–H dissociations in imines, we find that the radicals are generally destabilized to a smaller extent than the closed-shell precursor parent molecules (i.e., the RHE values are less negative than the corresponding MHE_{NH} values), and hence, all of these systems are associated with positive RSE_{NH} values (Table 2). It is interesting to note that out of all of the neutral N–H-containing molecules (amines, amides, imides, and imines) investigated, the $\text{H}_2\text{C}=\text{NH}$ system is associated with the smallest N–H BDE (363.2 kJ mol^{-1}) and hence the largest RSE_{NH} (80.5 kJ mol^{-1}). The significantly smaller destabilization in the $\text{H}_2\text{C}=\text{N}^\bullet$ radical ($RHE = -121.9$ kJ mol^{-1}) compared with the $\text{H}_2\text{C}=\text{NH}$ parent ($MHE_{NH} = -202.4$ kJ mol^{-1}) may be partly attributed to the existence of a powerful hyperconjugative stabilizing effect in the radical, which does not exist in the closed-shell parent. This hyperconjugative interaction involves electron donation from the σ_{C-H} orbitals to the half-filled 2p orbital at the nitrogen radical center.⁴⁰ According to Ingold and co-workers,^{40b} such hyperconjugative interactions will be favored when the R/R' substituents are σ -electron donating while σ -electron-withdrawing substituents would disfavor such interactions. We find that the RSE_{NH} values become less positive for all the substituents that we examined, and the origin of this effect is now discussed. For ease of discussion, we analyze the effects in terms of differences (denoted ΔRSE_{NH} , ΔRHE , and ΔMHE_{NH}) in RSE_{NH} , RHE, and MHE_{NH} values in the substituted system compared with those in the parent imine ($\text{H}_2\text{C}=\text{NH}$) (Table 3).

For the monosubstituted imine systems, we see that values of ΔRSE_{NH} become successively more negative as we move along the sequence of substituents Me, NH_2 , OH, and F. On the other hand, the pattern of ΔRHE values is less regular. To examine why this is so, we look also at the ΔRHE and ΔMHE_{NH} values. We note that substituents that stabilize the radicals also stabilize the closed-shell parents (relative to the effects in $\text{H}_2\text{C}=\text{N}^\bullet$ and $\text{H}_2\text{C}=\text{NH}$, respectively), but the magnitude of the stabilizing effects in the parent imines is much greater than the effect in the corresponding radicals (i.e., ΔMHE_{NH} values are more positive or less negative than the corresponding ΔRHE values). Thus, stabilization effects in the parent imines contribute substantially to the RSE_{NH} values and lead to the irregular relationship between ΔRSE_{NH} and ΔRHE .

For specific monosubstituted imines, we find that $\text{FCH}=\text{NH}$ has the most negative ΔRSE_{NH} value (-57.3 kJ mol^{-1}). The cyano-substituted system has a substantially less negative ΔRSE_{NH} value (-23.3 kJ mol^{-1}), and in this case it is interesting to note

Table 3. Changes in RSE_{NH} , RHE, and MHE_{NH} Associated with Substitution in Imines and Iminyl Radicals (kJ mol^{-1})^a

molecule	ΔRSE_{NH}^a	ΔRHE^a	ΔMHE_{NH}^a
$\text{H}_2\text{C}=\text{NH}$	0.0	0.0	0.0
$\text{MeHC}=\text{NH}$	-8.3	29.7	37.9
$(\text{H}_2\text{N})\text{CH}=\text{NH}$	-37.9	57.6	95.6
$\text{H}(\text{OH})\text{C}=\text{NH}$	-49.8	55.1	104.9
$\text{FHC}=\text{NH}$	-57.3	20.1	77.4
$(\text{NC})\text{HC}=\text{NH}$	-23.3	-22.8	0.5
$\text{Me}_2\text{C}=\text{NH}$	-10.0	50.4	60.4
$\text{Me}(\text{OH})\text{C}=\text{NH}$	-46.0	72.7	118.7
$(\text{H}_2\text{N})_2\text{C}=\text{NH}$	-45.7	90.5	136.3
$\text{F}_2\text{C}=\text{NH}$	-78.2	-3.1	75.1
$\text{F}(\text{OH})\text{C}=\text{NH}$	-77.0	27.4	104.3

^a Values calculated relative to $\text{H}_2\text{C}=\text{NH}$ and $\text{H}_2\text{C}=\text{N}^\bullet$.

that the ΔRHE value associated with the resulting radical is negative compared with that of $\text{H}_2\text{C}=\text{N}^\bullet$ ($-22.8 \text{ kJ mol}^{-1}$). For the disubstituted species, $\text{F}_2\text{C}=\text{N}^\bullet$ has the most negative ΔRSE_{NH} value ($-78.2 \text{ kJ mol}^{-1}$) while $\text{Me}_2\text{C}=\text{N}^\bullet$ has the least negative ΔRSE_{NH} value ($-10.0 \text{ kJ mol}^{-1}$).

Moving next to the N–F and N–Cl BDEs of the N-halogenated imine derivatives, we note that the values for RSE_{NF} and RSE_{NCl} are nearly always smaller than the corresponding RSE_{NH} values. Furthermore, in contrast to RSE_{NH} values of the N–H species (which are always positive), the RSE_{NF} and RSE_{NCl} values are often negative (Table 2). These results arise because the N-halogenated molecules are generally associated with large positive MSE_{NF} and MSE_{NCl} values, with the former being of generally greater magnitude. These positive MSE values indicate the existence of stabilizing effects in the $\text{RR}'\text{C}=\text{NX}$ molecules compared with $\text{RR}'\text{C}=\text{NH}$, relative to the corresponding parent molecules. Alternatively, this may be associated with more favorable (or less unfavorable) interactions in molecules such as $\text{H}_2\text{C}=\text{NF}$ compared with NH_2F (relative to $\text{H}_2\text{C}=\text{NH}$ vs NH_3). The unfavorable interactions in NH_2F include repulsion between the lone pairs on N and F, which is much less important in $\text{H}_2\text{C}=\text{NF}$. This difference in interactions does not exist for the $\text{H}_2\text{C}=\text{NH}$ vs NH_3 comparison. The only exceptions to the positive MSE_{NX} values are the $\text{F}_2\text{C}=\text{NF}$ and $\text{F}_2\text{C}=\text{NCl}$ systems, where the MSE_{NF} and MSE_{NCl} values are -6.5 and -0.8 kJ mol^{-1} , respectively. The largest RSE_{NF} and RSE_{NCl} values occur for the $\text{H}_2\text{C}=\text{NX}$ systems (11.8 and 35.0 kJ mol^{-1} , respectively) and are substantially reduced compared with the RSE_{NH} value for $\text{H}_2\text{C}=\text{NH}$ (80.5 kJ mol^{-1}). For the N-fluorinated imines, the $\text{Me}(\text{OH})\text{C}=\text{NF}$ and $(\text{H}_2\text{N})_2\text{C}=\text{NF}$ systems are associated with the most negative RSE_{NF} values ($-14.7 \text{ kJ mol}^{-1}$). For the N-chlorinated imines, the most negative RSE_{NCl} values occur in the case of the $(\text{H}_2\text{N})_2\text{C}=\text{NCl}$ and $\text{F}(\text{OH})\text{C}=\text{NCl}$ systems (-10.0 and -8.5 kJ mol^{-1} , respectively).

CONCLUSIONS

The strength of N–X (X = H, F, and Cl) bonds has been investigated from the point of view of the effect of functional group and substitution using the high-level W2w method. A number of important conclusions emerge:

- We used the W2w method to provide benchmark-quality thermochemistry with which to analyze the effect of substituents on the strength of N–X (X = H, F, and Cl) bonds.

- For the neutral N–X species, we find that the BDEs span from 363.2 to $494.5 \text{ kJ mol}^{-1}$ (N–H), 219.6 to $311.7 \text{ kJ mol}^{-1}$ (N–F), and 185.4 to 294.0 (N–Cl) kJ mol^{-1} , corresponding to ranges of 131.3 , 92.1 , and $108.6 \text{ kJ mol}^{-1}$, respectively.
- The analysis of the results is facilitated through introduction of thermochemical quantities in addition to bond dissociation energies (BDEs) and radical stabilization energies (RSE_{NX}). These include molecule stabilization energies (MSE_{NX}), radical hydrogenolysis energies (RHE), and molecule hydrogenolysis energies (MHE_{NX}).
- With respect to the effects of substituents on the relative strengths of N–X bonds, it is important to consider stabilizing/destabilizing effects in both the reactant molecule and the product radical.
- The presence of donor alkyl substituents in alkylamines results in positive RSE_{NH} values. For the corresponding N–Cl species, the values of RSE_{NCl} are still positive but to a diminished extent. Donor alkyl substituents result in negative RSE_{NF} values. These findings arise because of the existence of stabilizing effects in the parent N-halogenated amines. The effects are larger in the case of the N–F species because of the greater electronegativity of F vs Cl.
- Electron-withdrawing substituents (e.g., CF_3) or protonation lead to larger N–H BDEs but not necessarily larger N–X (X = F and Cl) BDEs because the presence of such substituents generally leads to increased destabilizing effects in the closed-shell parent as well as the radical.
- For amides, we find that RSE_{NH} , RSE_{NF} , and RSE_{NCl} adopt negative values, i.e., the BDEs of such structures are greater than those of NH_3 , NH_2F , and NH_2Cl , respectively. Negative RSE_{NH} values arise because the RCO substituents stabilize the parent closed-shell molecules to a greater extent than the resulting amidyl radicals. Owing to the generally negative MSE_{NF} and MSE_{NCl} values for the N-halogenated species, the corresponding RSE_{NF} and RSE_{NCl} values are typically less negative than the corresponding RSE_{NH} values.
- The N–H BDEs of all the imines investigated are smaller than that of NH_3 , which may be attributed to the fact that the radicals are destabilized to a smaller extent than the closed-shell parent species, as reflected in MHE_{NH} values being more negative than the RHE values. We do not find a correlation between the RSE_{NH} and RHE values, indicating that the RSE_{NH} values are not always a good indicator of relative radical stability. For the N–X (X = F and Cl) species, we note that MSE_{NF} and MSE_{NCl} are in almost all cases large and positive. Such positive MSE values may be associated with more favorable (or less unfavorable) interactions in molecules such as $\text{H}_2\text{C}=\text{NF}$ compared with NH_2F (relative to $\text{H}_2\text{C}=\text{NH}$ vs NH_3). As a result, RSE_{NF} and RSE_{NCl} are smaller than the corresponding RSE_{NH} values and can even become negative if the MSEs are greater than the corresponding RSEs.

ASSOCIATED CONTENT

S Supporting Information. W2w energies and their components at 0 K (Table S1), W4 total atomization energies at 0 K (TAE_0) and their components (Table S2), and B3-LYP/aug'-cc-pV(T+d)Z-optimized geometries (Table S3). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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