Computational Chemistry

Competitive Halide Binding by Halogen Versus Hydrogen Bonding: Bis-triazole Pyridinium

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Abstract: The binding of F^- , Cl^- , Br^- , and I^- anions by bis-triazole-pyridine (BTP) was examined by quantum chemical calculations. There is one H atom on each of the two triazole rings that chelate the halide via H bonds. These H atoms were replaced by halogens Cl, Br, and I, thus substituting H bonds by halogen bonds. I substitution strongly enhances the binding; Br has a smaller effect, and Cl weakens the interaction. The strength of the interaction is sensitive to the

overall charge on the BTP, rising as the binding agent becomes singly and then doubly positively charged. The strongest preference of a halide for halogenated as compared to unsubstituted BTP, as much as several orders of magnitude, is observed for I^- . Both unsubstituted and I-substituted BTP could be used to selectively extract F^- from a mixture of halides.

Introduction

Although the attractive interaction between a halogen and another electronegative atom was first pointed out many years ago,^[1–4] our understanding of the halogen bond has recently undergone a rapid acceleration.^[5–12] It is now generally understood that when a halogen atom, X, is covalently bound to another atom, for example, C, the electrostatic potential around X becomes highly anisotropic. While there exists a belt or equator of negative potential as might be anticipated for an electronegative halogen, a pole of positive potential develops along the extension of the C–X bond. This so-called σ -hole can attract an electronegative atom of a neighboring molecule. This Coulombic attraction is supplemented by the transfer of charge from the neighboring molecule's lone electron pairs into the C–X σ^* antibonding orbital under the rubric of polarization or induction energy. Additional attraction arises by way of London dispersion forces. It is worthwhile to note that this bonding mechanism is not limited to halogen atoms, but has been observed for chalcogen,^[13–21] pnictogen,^[12, 22–28] and tetrel^[29–36] atoms in the eponymous bonds.

Halogen bonding (XB) has been widely recognized and utilized in crystal engineering over the years.^[37–40] But the applications of this phenomenon are diverse, encompassing catalysis,^[41–44] biology,^[45–48] macromolecular self-assembly,^[49, 50] and transmembrane transport^[51] among numerous others. Due to the fundamental nature of halogen bonding, it may represent an attractive alternative to hydrogen bonding (HB) as a means of selectively coordinating anions in aqueous solution.^[52, 53]

Particularly intriguing results^[54, 55] have recently indicated that the binding of halide ions to a bis-triazole-pyridinium (BTP^+) species in aqueous solution is greatly enhanced when a H atom is replaced by I on each of the two triazole rings. The authors attributed this selectivity to the superiority of halogen over hydrogen bonds in this environment. These results lead to some very interesting questions which have important implications for the rational design of new halide-binding agents. In the first place, what are the geometries of the H-bonded and halogen-bonded complexes with the halides? How much more strongly bound are the latter as compared to the former in a quantitative sense? How does the binding depend upon the nature of the halide being captured, and what might be the effect of replacing the I atoms on the triazoles by smaller halogen atoms Br and Cl? How important is the charge on the triazole-containing binding agent: would a neutral or dicationic species function in the same manner? These questions can perhaps best be addressed by quantum chemical calculations, which is the subject of the present work.

Computational Details

Most of the calculations were carried out with the Gaussian 09 set^[56] of codes, using the M06-2X functional^[57] within the context of the aug-cc-pVDZ basis set. For the heavy halogen atoms Br and I, the aug-cc-pVDZ-pp pseudopotential basis set was taken from the EMSL library.^[58, 59] Binding energies were calculated as the difference between the energy of the complex and the sum of the monomers, in their optimized geometries. Binding energies were corrected for the basis set superposition error with the counterpoise^[60] method. Measures of charge transfer were estimated by the natural bond orbital^[61] method (NBO), as implemented in the Gaussian 09 software. Aqueous environment was simulated with the conductor-like polarizable continuum model (CPCM)^[62] with water as solvent. The molecular electrostatic potential (MEP) was analyzed with the WFA-SAS program.^[63]

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The bis-triazole-pyridine (BTP) binding agents tested here are illustrated in Scheme 1. X atoms were varied among H, Cl, Br, and I. The neutral molecule was transformed to a monocation by placement of a $-\text{CH}_3^+$ on the pyridine N, and to a dication by addition of a methyl to each of the two triazole rings, as indicated.

Scheme 1. Diagrams of BTP and its charged derivatives.

Results

In most cases, the optimized geometry of the complex of the anion with the binding agent placed the anion Y^- equidistant between the two binding atoms X. These structures are illustrated for $\text{X}=\text{H}$ with the monocationic BTP⁺ in Figure 1.

Figure 1. Optimized geometries of the complexes of halides with monocationic BTP⁺ with $\text{X}=\text{H}$. The bold number indicates the counterpoise-corrected binding energy [kcal mol^{-1}]; distances are in Å.

It may be noted that in these cases, the central CH of the pyridine ring also comes close to the anion, in what may be described as a trifurcated $\text{CH}\cdots\text{Y}^-$ H bond. Indeed, for the fluoride and chloride anions, the central HB is shorter than the two peripheral HBs, although the opposite is the case for the larger anions. On the opposite end of the spectrum, the much larger $\text{X}=\text{I}$ atoms keep the central pyridine H from approaching close enough to the anion to engage in a HB, as is evident in Figure 2. In fact, even for the smaller $\text{X}=\text{Cl}$ complexes, there is no pyridine $\text{CH}\cdots\text{Y}^-$ HB present. The structures of the complexes for $\text{X}=\text{Cl}$ and Br are similar, and are illustrated explicitly in Figure S1 in the Supporting Information.

Figure 2. Optimized geometries of the complexes of halides with monocationic BTP⁺ with $\text{X}=\text{I}$. The bold number indicates the counterpoise-corrected binding energy [kcal mol^{-1}]; distances are in Å.

As illustrated in Scheme 1, removal of the $-\text{CH}_3$ group from the pyridine ring leads to an electrically neutral anion binder. The dicationic binder is formed by adding methyls to each of the two triazole rings. The structures of the resulting complexes, displayed in Figures S2 and S3 in the Supporting Information, are similar to those of the monocation, but with respectively longer and shorter intermolecular distances.

The $\text{X}\cdots\text{Y}$ distances for all the complexes are compiled in Table 1 where certain trends are in evidence. For any given binding agent, the intermolecular $\text{X}\cdots\text{Y}$ distance increases down a column, in the order $\text{Y}^- = \text{F}^- < \text{Cl}^- < \text{Br}^- < \text{I}^-$, consistent with the growing radius of the anion Y. The increasing size of the halogen atom X attached to the BTP does not have the same effect. In most cases, $\text{X}=\text{Cl}$ results in a slightly longer $\text{X}\cdots\text{Y}$ distance than do $\text{X}=\text{Br}$ or I, although the latter two are quite similar to one another. Not surprisingly, $R(\text{X}\cdots\text{Y})$ is considerably shorter when $\text{X}=\text{H}$, due to the much smaller radius of the H atom. With regard to the overall charge on the BTP, the increase from 0 to +1 and then to +2 yields a small but pro-

Table 1. Optimized distances [Å] from anion to H or halogen atoms^[a] of neutral, singly and doubly charged BTP with different halide anions.^[b]

Anion Y ⁻	2H	2Cl	2Br	2I
neutral BTP				
F ⁻	2.030	2.697	2.612	2.614
Cl ⁻	2.579	3.314	3.199	3.226
Br ⁻	2.729	3.458	3.355	3.390
I ⁻	2.955	3.643	3.577	3.610
monocation BTP ⁺				
F ⁻	2.013	2.652	2.577	2.582
Cl ⁻	2.538	3.264	3.166	3.185
Br ⁻	2.695	3.416	3.322	3.352
I ⁻	2.891/2.942	3.607	3.536	3.568
dication BTP ²⁺				
F ⁻	1.075/2.835	2.577	2.492	2.519
Cl ⁻	2.442	3.169	3.093	3.109
Br ⁻	2.657	3.346	3.247	3.262
I ⁻	2.903	3.551	3.458	3.480

[a] Both distances shown for appreciably asymmetric structures. [b] 2H indicates H-bonding anion receptors and 2Cl, 2Br, and 2I refer to corresponding halogen-substituted systems.

gressive shortening of R(X...Y), indicative of a growing binding strength.

Indeed, the binding energies in Table 2 reflect the stronger complexes formed by the ionic BTPs. F⁻ is clearly the most strongly bound, with a large gap after which the other halides obey the order by Cl⁻ > Br⁻ > I⁻. Unlike the X...Y distances which are relatively insensitive to the identity of the X atom, the binding energies show that X=I is the most strongly bound, followed by Br and then by Cl; the X=H systems tend to fall between X=Cl and X=Br. Overall, the weakest complex is that between the neutral X=Cl BTP and I⁻, which is bound by 3.2 kcal mol⁻¹. The strongest, bound by 24.1 kcal mol⁻¹, connects the X=I dicationic BTP²⁺ with F⁻.

A more complete thermodynamic treatment of the binding yields the quantities displayed in Table 3. In all cases ΔS is negative which reflects the process which takes two separate entities into a single complex. The values reported for ΔH are similar to the energies in Table 2, differing primarily by the incorporation of vibrational energies into ΔH. The combination of ΔH and ΔS yields the free energies. ΔG is positive for some of the more weakly bound complexes, for example +5.29 kcal mol⁻¹ for 2H...I⁻. It turns negative for the more strongly bound dimers,

Table 2. Counterpoise-corrected binding energies [kcal mol⁻¹] for complexes of neutral, singly and doubly charged BTP with different halide anions.

Anion Y ⁻	2H	2Cl	2Br	2I
neutral BTP				
F ⁻	9.70	4.20	10.18	16.02
Cl ⁻	5.44	3.26	6.77	10.33
Br ⁻	4.77	3.24	6.55	9.88
I ⁻	4.10	3.21	6.30	9.37
monocation BTP ⁺				
F ⁻	13.18	5.93	12.38	18.83
Cl ⁻	7.35	4.34	8.22	12.16
Br ⁻	6.42	4.23	7.88	11.59
I ⁻	5.47	4.10	7.47	10.94
dication BTP ²⁺				
F ⁻	11.12	9.11	16.87	24.13
Cl ⁻	8.57	6.11	10.81	15.49
Br ⁻	7.77	5.82	10.28	14.61
I ⁻	6.74	5.50	9.60	13.66

peaking at -16.3 kcal mol⁻¹ when the dicationic BTP²⁺ with X=I is paired with F⁻.

As has been reported in the literature, the replacement of H by I strongly enhances the attraction of the BTP for halide anions. The enhancement of the binding of each halide that results from halogenation of the BTP is reported in Table 4. More specifically, the quantities were calculated as the equilibrium ratio of (2X...Y⁻)/(2H...Y⁻) assuming a Boltzmann distribution, $K = \exp(-\Delta G/RT)$. It is immediately clear that the replacement of H in the BTP by Cl has little if any enhancement effect. Indeed many of the quantities in the first column of Table 4 are less than unity which corresponds to a preference for X=H over X=Cl. An enhancement is apparent for X=Br, particularly for the iodide anion in the last rows. But the largest

Table 3. Thermodynamic parameters for binding of halide anions by neutral and charged receptors at 25 °C and 1 atm.

	ΔS ^[a]	2H ΔH ^[b]	ΔG ^[b]	ΔS ^[a]	2Cl ΔH ^[b]	ΔG ^[b]	ΔS ^[a]	2Br ΔH ^[b]	ΔG ^[b]	ΔS ^[a]	2I ΔH ^[b]	ΔG ^[b]
neutral BTP												
F ⁻	-29.63	-9.76	-0.93	-29.07	-4.00	4.67	-28.74	-10.09	-1.52	-34.34	-16.29	-6.05
Cl ⁻	-27.10	-5.27	2.81	-25.03	-3.31	4.15	-24.88	-6.78	0.64	-31.16	-10.33	-1.04
Br ⁻	-30.07	-5.31	3.65	-23.49	-3.32	3.68	-23.92	-6.52	0.61	-30.45	-9.86	-0.78
I ⁻	-33.48	-4.70	5.29	-23.92	-3.11	4.02	-23.65	-6.23	0.82	-28.39	-9.34	-0.88
monocation BTP ⁺												
F ⁻	-28.13	-13.32	-4.94	-30.04	-5.57	3.38	-27.86	-12.42	-4.11	-30.23	-19.01	-10.00
Cl ⁻	-23.74	-7.35	-0.27	-26.11	-4.22	3.56	-25.32	-8.07	-0.52	-28.08	-12.18	-3.81
Br ⁻	-30.74	-7.05	2.11	-26.25	-4.07	3.76	-22.31	-7.84	-1.19	-27.53	-11.65	-3.45
I ⁻	-33.82	-6.14	3.94	-31.89	-4.57	4.94	-22.02	-7.48	-0.92	-26.97	-10.97	-2.92
dication BTP ²⁺												
F ⁻	-24.10	-13.56	-6.38	-33.84	-9.86	0.23	-31.09	-16.83	-7.56	-24.68	-23.66	-16.31
Cl ⁻	-25.85	-8.58	-0.87	-27.16	-5.88	2.22	-26.35	-10.89	-3.04	-22.74	-15.00	-8.22
Br ⁻	-25.49	-7.92	-0.32	-25.39	-5.76	1.81	-25.04	-10.52	-3.05	-20.62	-14.22	-8.08
I ⁻	-18.14	-6.86	-1.45	-24.75	-5.54	1.84	-22.70	-9.92	-3.15	-18.50	-13.20	-7.69

[a] ΔS is in cal mol⁻¹ K⁻¹. [b] ΔH and ΔG are in units of kcal mol⁻¹.

Table 4. Preference of halide anion for halogenated versus H-bonding agent expressed as equilibrium ratio.

	2Cl	2Br	2I
neutral BTP			
F ⁻	7.92E-05	2.70E+00	5.62E+03
Cl ⁻	1.04E-01	3.88E+01	6.60E+02
Br ⁻	9.51E-01	1.68E+02	1.76E+03
I ⁻	8.51E+00	1.88E+03	3.30E+04
monocation BTP ⁺			
F ⁻	8.07E-07	2.47E-01	5.08E+03
Cl ⁻	1.57E-03	1.52E+00	3.91E+02
Br ⁻	6.19E-02	2.61E+02	1.18E+04
I ⁻	1.85E-01	3.62E+03	1.06E+05
dication BTP ²⁺			
F ⁻	1.44E-05	7.31E+00	1.87E+07
Cl ⁻	5.46E-03	3.88E+01	2.41E+05
Br ⁻	2.75E-02	9.98E+01	4.82E+05
I ⁻	3.90E-03	1.76E+01	3.71E+04

preference of halide for halogenated BTP over H-bonding BTP is observed for X=I. The enhancement ranges from a factor of 400 up to 1.9×10^7 .

It was noted above that F⁻ forms much stronger complexes with any of the BTPs than do the other halides. These systems could thus be used to selectively bind fluoride in competition with the other halides. The level of selectivity, again expressed as a ratio of equilibrium populations is exhibited in Table 5. The X=Cl BTPs show very little selectivity, with values hovering around unity. X=Br represents an improvement, with ratios between 40 and 2000. H-bonding BTPs are superior to Br, but the largest selectivity is exhibited by X=I. Even the uncharged BTPs are characterized by a F⁻ selectivity of roughly 5000. This quantity grows larger as charge is placed on the BTP. Consequently, the equilibrium F⁻/Y⁻ population ratio of the dicationic BTP²⁺ with X=I is on the order of 10^6 .

There is a crystal structure with which some of our calculated data may be compared. When complexed with Cl⁻, a molecule very similar to our monocation with two I atoms con-

tained a R(I...Cl⁻) distance^[55] in the 3.121–3.195 Å range, which compares well with our optimized value of 3.185 Å in Table 1. When its two H atoms were replaced by I, other measurements showed that the cationic system displayed an enhancement in its binding of the I⁻ anion in water,^[54] consistent with our calculated stronger binding.

As mentioned earlier, the replacement of H by Cl weakens the interaction of the BTP with any anion, while I substitution leads to a stronger binding energy; the effect of Br is intermediate between Cl and I. This pattern is not consistent with a purely electrostatic effect. The molecular electrostatic potential surrounding each of the monocations is reproduced in Figure 3. These maps indicate that the potential is most positive in the unsubstituted BTP⁺ monocation; halogen substitution lessens the positive potential. Moreover, the potential in the binding region is not obviously affected by the nature of the halogen, whether Cl, Br, or I. This insensitivity runs counter to the observation of a clear strengthening pattern as the halogen becomes heavier. The electrostatic potential does, though, offer an explanation for the preference of the halide anion Y⁻ for a position midway between the two halogen X atoms of the BTP⁺; the potential is most positive (blue) in this region.

Figure 3. Molecular electrostatic potentials of monocationic BTP⁺. Potential is illustrated on an isocount equal to 1.5 times the van der Waals radius of each atom. Most positive potential shown (blue) is 0.15 au, and most negative (red) is 0.0 au.

These trends can be quantitatively assessed by the evaluation of the maximum of the electrostatic potential on a fixed isodensity contour of 0.001 au, roughly equivalent to the surface envisioned in Figure 3. Consistent with this Figure, Table 6 indicates that the unsubstituted 2H BTP⁺ has a more positive potential than do the halogenated species. There is a trend for higher potential in the order 2Cl < 2Br < 2I, although this trend is weaker than that exhibited by the total binding energies in Table 2. Table 6 also obeys the expected pattern that increasing positive charge on the binding agent raises the potential at the maximum, quite dramatically so. Indeed the placing of a single or double positive charge on BTP roughly doubles or triples the potential maximum, respectively. This strong

Table 5. Selectivity of binding agent for F⁻ over other halogen anions, expressed as equilibrium ratio.

	2H	2Cl	2Br	2I
neutral BTP				
Cl ⁻	5.48E+02	4.16E-01	3.82E+01	4.67E+03
Br ⁻	2.26E+03	1.88E-01	3.63E+01	7.24E+03
I ⁻	3.59E+04	3.34E-01	5.17E+01	6.11E+03
monocation BTP ⁺				
Cl ⁻	2.63E+03	1.35E+00	4.26E+02	3.41E+04
Br ⁻	1.46E+05	1.90E+00	1.38E+02	6.26E+04
I ⁻	3.19E+06	1.39E+01	2.17E+02	1.53E+05
dication BTP ²⁺				
Cl ⁻	1.08E+04	2.87E+01	2.04E+03	8.41E+05
Br ⁻	2.74E+04	1.44E+01	2.01E+03	1.06E+06
I ⁻	4.08E+03	1.51E+01	1.70E+03	2.05E+06

Table 6. Maximum of molecular electrostatic potential, evaluated on the 0.001 au isodensity contour, at the M06-2X/6-311G* level.

	2H	2Cl	2Br	2I
neutral BTP	60.7	38.2	44.5	51.1
monocation BTP ⁺	129.0	90.2	96.6	101.6
dication BTP ²⁺	189.8	151.9	157.6	160.5

dependence is not mirrored by the binding energies which rise with increasing charge, but much less dramatically.

Induction appears to offer a better explanation of the observed behavior of the binding energy. In particular, the strongest element of the induction in a halogen bond is associated with charge transfer from the halide lone pairs to the C–X σ^* antibonding orbitals. The energetic manifestation of this transfer can be evaluated by the NBO method, and is presented as $E(2)$ in Table 7. These values properly reflect the progressively stronger binding from Cl to Br to I. The data also correctly indicate the much stronger binding of F[−] than of the other anions, which are not very different from one another. On the other hand, the charge transfer in the H-bonding systems is disproportionately higher than that of the halogen-bonded complexes, so one cannot draw the conclusion that the binding energy is strictly correlated with $E(2)$ for both sorts of bonds. The failure of electrostatic effects to fully account for the differential binding presents a plausible argument that these interactions are better represented as H bonds or halogen bonds, albeit ionic ones, rather than as simple Coulombic charge-pair interactions.

Table 7. NBO values of $E(2)$ [kcal mol^{−1}] for interaction of halide anion with monocationic receptors.^[a]

Anion	2H	2Cl	2Br	2I
F [−]	43.19	8.64	21.57	36.82
Cl [−]	25.38	4.42	12.91	22.77
Br [−]	22.06	4.10	11.88	21.17
I [−]	18.50	4.10	11.14	19.98

[a] Charge transfers from all halide lone pairs to the C–H/X σ^* antibonding orbitals.

The results presented here were obtained using a DFT formalism. It would be worthwhile to ensure that the values are consistent with a higher level of theory. For this reason, the energetics were recomputed at the ab initio MP2 level, with the same aug-cc-pVDZ basis set, and also in water as solvent. Geometries were taken from the prior M06-2X optimizations, and binding energies were again corrected by the counterpoise procedure. These MP2 calculations were performed for both neutral and monocationic chelating agents, for 2H and 2I, with all four halide ligands. MP2 binding energies for the H-bonded complexes were quite similar to M06-2X quantities, in most cases within 5%. Larger deviations were observed when the H-bonding chelating agents were bound to F[−], where there was a 20% drop. There was also a smaller binding

energy of the iodosubstituted chelating agents at the MP2 level, but this change was a fairly uniform decrease of 18–28% for all four halides. Most importantly, none of the trends observed with the M06-2X calculations were altered. The cationic chelator binds the halides more strongly than does its neutral analogue. The energetic order of binding, whether H bonding or I bonding, remains F[−] > Cl[−] > Br[−] > I[−]. Also, the 2I chelator binds each halide much more strongly than does 2H.

The symmetrical, largely planar, geometries are not the only ones on the potential energy surface of each complex, although they do generally represent the global minimum. Other minima are displayed in Figure S4 in the Supporting Information. One sort of structure that appears with the neutral BTP places the anion well out of the binder's plane, engaged primarily in a CH...Y[−] H bond with the pyridine CH. This HB is a distorted one, with $\theta(\text{CH}\cdots\text{Y})$ angles usually less than 150°. (Geometries such as these do not occur for X=H, however.) Like the neutral BTPs, the monocations also display H-bonded minima. In a few cases, their energies are competitive, or even slightly more stable than the symmetric structures. Slightly greater stability is restricted to X=Cl, with Y=Cl[−], Br[−], and I[−], where the energies are within 1 kcal mol^{−1} of the symmetrical structures. There are no secondary minima in the case of any of the dicationic binders.

Conclusion

Halide anions generally prefer a location midway between the two H or halogen atoms of the binding agent, whether the latter is neutral or positively charged. The binding energy is largest for the dicationic BTP²⁺, followed by the monocation and the neutral BTP. The halide binding strength decreases with the size of the anion: F[−] > Cl[−] > Br[−] > I[−]. Replacement of the pair of H atoms of BTP by halogens has a strong effect: the binding is weakened for Cl replacement and strengthened by I substitution; effects with Br are mixed. As a result, the binding of BTP, or any of its charged counterparts, to a halide is strongly enhanced by replacement of H atoms by I. In terms of equilibrium populations, this enhancement can be as large as 10⁷. These binding agents, whether cationic or neutral, exhibit a strong preference for F[−]. The selectivity for F[−] over other halides can be as large as 10⁶, for the dicationic BTP²⁺ substituted by I.

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FULL PAPER

Enhanced binding via halogen bonds:

Bis-triazole-pyridine (BTP) binds halide anions in solution via multiple $\text{CH}\cdots\text{X}^-$ H bonds. Substitution of the relevant H atoms by halogen atoms, particularly I, changes these H bonds to halogen bonds, and can lead to much stronger binding (see figure). The strongest preference, as much as several orders of magnitude, of a halide for halogenated rather than unsubstituted BTP is observed for iodine.

Computational Chemistry

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Competitive Halide Binding by Halogen Versus Hydrogen Bonding: Bis-triazole Pyridinium