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Very Strong ⁻N-X⁺•••⁻O-N⁺ Halogen Bonds

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A new ⁻N-X⁺•••⁻O-N⁺ paradigm for halogen bonding is established by using oxygen atom as an unusual halogen bond acceptor. The strategy yielded extremely strong halogen bonded complexes with very high association constants characterized in either $CDCl_3$ or acetone-d_6 solution by ^{1}H NMR titrations and in the solid-state by single crystal X-ray analysis. The obtained halogen bond interactions, R_{XB}, in the solid-state are found to be in the order of strong hydrogen bonds, *viz.* $R_{XB} \approx R_{HB}$.

Halogen bond (XB) has been recently defined[1] as a highly directional non-covalent interaction, and is one of the emerging areas in supramolecular chemistry.[1] However, the ambiguity and difficulty in studying such interactions in solution has severely limited their applicability in supramolecular architechtures.[2] Although, both XB and hydrogen bond (HB) share similar energetic and geometric features,[3] the true nature of halogen bonding and the factors influencing it are yet to be fully explored. The XB can contain contributions from both charge transfer and electrostatic interactions between a polarized Z-X bond (XB donor) and Y, a nucleophile (XB acceptor). Polyfluoroalkyl or polyfluorobenzene molecules as Z have been widely used to polarize the X, which is typically iodine or bromine.[4] In dihalogen X_2 systems the ultimate polarization by a strong XB acceptor can lead to the heterolytic fission of the X-X bond resulting in a halonium ion (X^+) XB complex stabilized with X_3^- counter ion.[5] Nonetheless, the strength of the XB very strongly depends on the nature of X and Y. To rule out the size-effect of the interacting atoms, the interaction can be described by calculating the normalized interaction ratio, R_{DA}, as ($R_{DA} = d_{DA}/D_{vdw}+A_{vdw}$), where d_{DA} [Å] is the distance between the donor atom (D) and the acceptor atoms (A) and divided by the sum of vdW radii [Å] of D and A. The typical values for strong interaction,

e.g. for hydrogen bonds, where the donor atom is hydrogen, is defined as R_{HB} and the values range between 0.55 and 0.65. The interaction ratio for halogen bond is defined as R_{XB} (where X = halogen) and it is typically has larger values ranging from 0.75 to 0.90.[1d,1g]

Among various XB acceptors, nitrogen remains the most popular, generating strongest XB in symmetrical N•••X⁺•••N complexes such as [bis(pyridine)iodine]X (X = tetrafluoroborate, perchlorate, hexafluorophosphate, hexafluoroantimonate, triflate, tosylate, nitrate or trifluoroacetate)[6] with distances around 2.25 Å (I⁺•••N)[5b] and 2.12 Å (Br⁺•••N),[5b] and R_{XB} values of 0.643 and 0.629, respectively. Also similar S•••X⁺•••S motif in [bis-(2-imidazolidinethione)iodine]triiodide with R_{XB} of 0.695 has recently been reported by us.[5a] These short halonium ion mediated XB's are defined *as three center halogen bonds[6] or 'halogen bonds with coordinative nature'*.[5] On the other hand, although oxygen, sulphur, selenium and tellurium can act as potential XB acceptors, they typically yield longer X•••Y distances, and R_{XB} ratios compare to corresponding nitrogen complexes, yet halonium ions do not form halogen bond to oxygen atoms.[5b] In light of recent XB investigations, very strong (OC)₂N-I•••N halogen bonds were reported by us using *N*-iodosuccinimide (NIS) as the XB donor and hexamethylenetetramine (HMTA) as the XB acceptor,[7] where the iodine at the N atom is strongly polarized by the two electron withdrawing carbonyl groups. Inspired by the strong N-I polarization in NIS, and in an endeavour to polarize the N-I bond even further, an analogues *N*-iodosaccharin (NISac) was used as the other XB donor in the current study.

Herein, we report the XB formation using oxygen of pyridine *N*-oxides[8] (PyNOs) as unusual XB acceptors for the strongest non-halonium ion based XB complexes. The NIS and NISac skeletons are responsible for the strong polarisation of the N-I bond leading to a ⁻N•••X⁺•••⁻O-N⁺ motif approaching the XB distances found in the N•••X⁺•••N or S•••X⁺•••S XB complexes.[5,6] The Fig. 1 shows the chemical structures of pyridine *N*-oxide (**1**), 2-methylpyridine *N*-oxide (**2**), 4-phenylpyridine *N*-oxide (**3**), 2-methyl-4-nitropyridine *N*-oxide (**4**), and NIS and NISac, that were used as XB acceptors and donors, respectively. The corresponding *N*-oxide HB complexes with

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saccharin (**1**•NHSac and **2**•NHSac) were investigated in the solid-state for comparison.
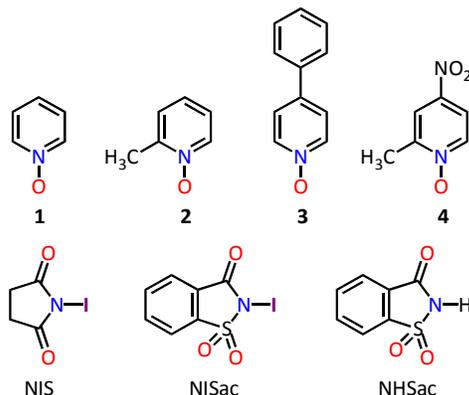
Fig. 1 The chemical structures of the XB and HB acceptor and donor molecules: pyridine N-oxide (**1**), 2-methylpyridine N-oxide (**2**), 4-phenylpyridine N-oxide (**3**), 2-methyl-4-nitropyridine N-oxide (**4**), N-iodosuccinimide (NIS) and N-iodosaccharin (NISac) and saccharin (NHSac).

To quantify the binding strength between the *N*-oxides (**1-4**) and XB donors, a series of ^{1}H NMR titration experiments in both non-competitive $CDCl_3$ and competitive acetone-d_6 solutions were carried out. The XB has been studied in solution only recently.[9] The chemical shifts for selected nuclei in the XB donors were followed as a function of increasing concentrations of *N*-oxide XB acceptors **1-4**, and the binding constants were obtained by non-linear least square fitting using the HypNMR2008 program.[10] The association constants (K_a) obtained from $CDCl_3$ for NISac complexes were extremely high, *viz.* >10000 M^{-1} (Table 1). However, the very strong binding resulted in high fitting errors, and the association constants obtained in $CDCl_3$ should not be considered reliable. For this reason the titrations were repeated in acetone-d_6 resulting in the K_a values ranging from 435 M^{-1} for **1**•NISac to 2774 M^{-1} for **2**•NISac. To have a better insight into the role of the ring substituents on the XB formation, a less nucleophilic XB acceptor **4**, with electron withdrawing NO_2 at *para* position, was used as a control. As expected, a decrease in electron density on oxygen resulted in the lowest association constants (Table 1). These values are still outstandingly high considering the competitive nature of acetone in halogen bonding and were found to follow the same trend **2**•NISac > **3**•NISac > **1**•NISac > **4**•NISac as in $CDCl_3$ (Table 1).
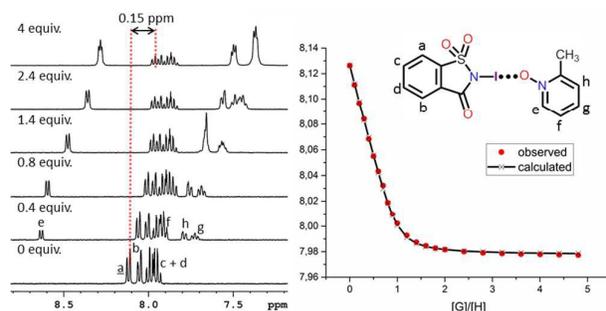
Fig. 2 ^{1}H NMR (acetone-d_6, 298 K) spectral changes observed from the strongest complex of NISac with different equivalents of **2** (K_a = 2774 ± 70).

The large association constants for NISac complexes in $CDCl_3$ can be accounted for the formation of an extremely strong N-I•••O XB due to more strongly polarized N-I bond in NISac compared to NIS (the hydrolysis of NIS in moist acetone-d6 to *N*-hydroxysuccinimide, NOHS, is excluded in the calculation of the NIS association constants, see ESI, Fig. S9, S11 and S13). The association constants obtained for NIS complexes from both solvent systems follow the same trend, yet in the NISac complexes the pyridine-*N*-oxide (**1**) showed remarkably weaker binding in both solvents when compared to **2** and **3** (Table 1.) Of all the XB acceptors, the 2-methylpyridine *N*-oxide (**2**) formed the strongest halogen bonds (Fig. 2) both in $CDCl_3$ and in acetone-d_6.

Table 1. The association constants K_a (M^{-1})[†] of the XB complexes in $CDCl_3$ and in acetone.

Complex	$CDCl_3$	Acetone	Complex	$CDCl_3$	Acetone
1•NIS	660	54	**1**•NISac	3121	435
2•NIS	779	65	**2**•NISac	16338	2774
3•NIS	325	42	**3**•NISac	14200	2099
4•NIS	17	*	**4**•NISac	543	*

[†]The corresponding fitting errors are shown in ESI section II. *No chemical shift changes were observed.

Due to the strong nucleophilic nature of the O atom in the N-O group, it is evident that the aromatic N-oxides can act both as halogen and hydrogen bond acceptors. Thus growing single crystals of the both XB and HB complexes provides an opportunity to compare the solid-state complexes with N-H and N-I donors for detailed structural information about the bond parameters (Table 2) in the solid-state by single crystal X-ray analysis. The PyNOs are known to form tridentate coordination complexes with certain metal cations,[11] however, mono- and bidentate coordination modes are most commonly observed.

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Table 2. Solid-state bond parameters for XB complexes

Complex	Bond parameters			
	N-I(Å)	I•••O(Å)	N-I•••O (°)	R_{XB}
1•NIS	2.094(2)	2.453(2)	178.71(7)	0.700
2•NIS	2.102(3)	2.383(2)	178.12(9)	0.680
3•NIS	2.094(8)	2.404(7)	176.9(2)	0.686
4•NIS	N/A	N/A	N/A	N/A
1•NISac	2.139(8)	2.328(8)	177.2(3)	0.665
2•NISac	2.135(3)	2.316(3)	178.08(10)	0.662
3•NISac	2.141(4)	2.317(3)	176.86(13)	0.662
4•NISac	N/A	N/A	N/A	N/A
N1•••X$^+$•••N2	2.241(3)/2.268(3)[6]	-	178.75(8)	0.648

N/A: Crystal structures not available for the bond parameters and calculation of R_{XB}

The crystallization of **1** and **2** with NHSac by slow evaporation of $CHCl_3$ solution resulted in 1:1 **1**•NHSac and **2**•NHSac complexes with N-H••• $^-$O-N$^+$ distances of 1.614 Å and 1.575 Å [d(N•••O), 2.614 Å and 2.575 Å], respectively (Fig. 3a and 3b), with R_{HB} values of 0.597 and 0.583. Subsequently, the XB donors **1**-**3** were crystallized with NIS and NISac in 1:1 ratios to investigate the XB formation. As shown in Table 2, **1**-**3** forms 1:1 XB complexes with remarkably short $^-$N-X$^+$••• $^-$O-N$^+$ distances with the lowest observed non-halonium ion R_{XB} values, and which are very close to corresponding R_{HB} values. The N-I•••O-N distances in NISac complexes are shorter than in NIS complexes, supporting the results from the solution studies (Table 1). The presence of electron withdrawing C=O and -SO_2 groups in the NISac causes stronger polarization of the N-I bond than the two C=O groups in the NIS. Hence, the N-I bonds are longer in the NISac complexes, and the halogen bonds are shorter than in the corresponding NIS complexes. In all three NISac XB complexes, the N-I bond distances (2.14 Å) are relatively close to the shortest reported N•••X$^+$ distances (ca. 2.25 Å) in N•••X$^+$•••N systems[5,6] while the I•••O XB distance is longer (2.32 Å) forming of a new $^-$N-X$^+$••• $^-$O-N$^+$ XB motif. The $^-$N-X$^+$••• $^-$O-N$^+$ angles are nearly linear varying from 176.9(2)° to 178.71(7)°, and from 177.2(2)° to 178.08(10)° for NIS and NISac complexes, respectively.

Attempts to crystallize **4** with NIS and NISac were unsuccessful; however, the association constants, K_a = 17 and 543 M^{-1}, respectively, obtained in $CDCl_3$ indicates the existence of a XB complex. On the other hand, the lack of chemical shift changes in acetone-d_6 indicate very weak binding as previously observed in some of the *N*-oxide XB complexes even in very non-competitive solvents like fluoroalkanes,[4e] suggesting that acetone•NIS/NISac XB complex competes with the formation of the **4**•NIS/NISac XB complex.
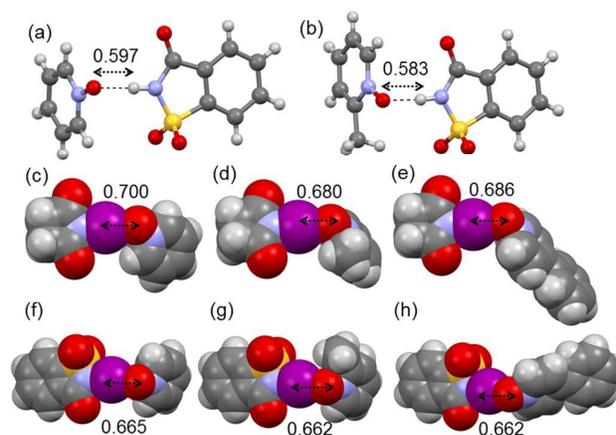
Fig. 3 The HB complexes of (a) **1**•NHSac and (b) **2**•NHSac in ball and stick models. The XB complexes of (c) **1**•NIS (d) **2**•NIS (e) **3**•NIS (f) **1**•NISac (g) **2**•NISac (h) **3**•NISac in CPK models. Values above double headed broken lines represent R_{HB} and R_{XB} values. [N-H distances are normalized to 1.0 Å]

The halogen bonds in the studied complexes (Fig. 3) are very strong based on their R_{XB} values, yet it is truly unprecedented that the association constants are very high in a highly competitive acetone solvent, which always contains small amounts of water. Thus it is evident that the $^-$N-X$^+$••• $^-$O-N$^+$ XB motif persists in moist acetone, and the pyridine *N*-oxide oxygen is better XB acceptor than the water or acetone oxygen. The robustness of the $^-$N-X$^+$••• $^-$O-N$^+$ XB motif is evident in the X-ray structure of the complex **2**•NIS, where besides the XB formation the co-crystallized water molecule bridges two **2**•NIS complexes generating a dimeric assembly held together with concerted XB and HB interactions as shown in Fig. 4. The carbonyl oxygen atoms act as weak HB acceptors indicating tolerance of the XB complex even under moist conditions.
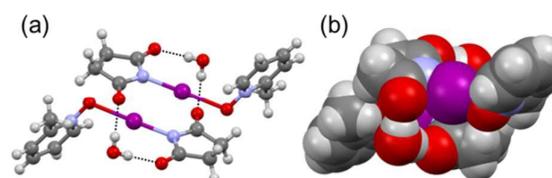
Fig. 4 The water molecule mediated **2**•NIS dimer represented in (a) ball and stick, and (b) CPK model.

In conclusion, we have shown extremely strong halogen bonds both in solution and in the solid-state utilizing oxygen of PyNOs as the XB acceptor with the NIS and NISac as XB donors. Oxygen being unusual XB acceptor, the elongated N-I bond distances in the donor part, and the very short halogen bond interaction distance can be best described as a new $^-$N-X$^+$••• $^-$O-N$^+$ XB motif, structurally very close to the strongest N•••X$^+$•••N XB motif.[12] The R_{XB} values of the XB complexes are remarkably close to those of the corresponding HB complexes. The strength and extent of interaction of N-I with N-O groups depends on the extent of polarization by C=O and SO_2 groups in donor molecules. The nature of the resulting halogen bond between the ultra-polarized iodine and the highly nucleophilic

N-oxide oxygen in the ⁻N-X⁺••• ⁻O-N⁺ motif is markedly influenced by this polarization. Prior to this work only a few reports about the use of *N*-oxides in XB chemistry have been published, yet none of them combine both solution and solid-state studies. Very high XB based association constants have been reported in the literature[13] which are the product of either the cooperativity between cavity containing XB donor and XB acceptor molecules or increasing the XB strength between donor-acceptor molecules within confined spaces. However these extremely strong halogen bonds, irrespective of the chemical environment and solvent effects, solely depends on electronic properties of the XB donor and acceptor molecules, and when properly tuned will result in very high association constants in solution. In our study this observation is also supported by the X-ray crystal structures of the corresponding systems. We are currently carrying out a systematic study with different XB donors and *N*-oxides to get further information about the nature of the halogen bond in the ⁻N-X⁺••• ⁻O-N⁺ complexes.

Acknowledgements

References

1 (a) G. R. Desiraju, P. S. Ho, L. Kloo, A. C. Legon, R. Marquardt, P. Metrangolo, P. Politzer, G. Resnati, K. Rissanen, *Pure Appl. Chem.*, 2013, **85**, 1711; (b) P. Metrangolo, G. Resnati, T. Pilati, S. Biella, *Halogen Bonding: Fundamentals and Applications*: Springer, 2008; (c). R. Wilcken, M. O. Zimmermann, A. Lange, A. C. Joerger and F. M. Boeckler, *J. Med. Chem.*, 2013, **56**, 1363–1388; (d). K. Rissanen, *CrystEngComm*, 2008, **10**, 1107–1113; (e). C. B. Aakeröy, M. Baldrighi, J. Desper, P. Metrangolo and G. Resnati, *Chem. – Eur. J.*, 2013, **19**, 16240–16247; (f). F. Meyer and P. Dubois, *CrystEngComm*, 2013, **15**, 3058–3071; (g). R. W. Troff, T. Mäkelä, F. Topić, A. Valkonen, K. Raatikainen and K. Rissanen, *Eur. J. Org. Chem.*, 2013, **2013**, 1617–1637.

2 (a) P. Hobza, K. Müller-Dethlefs, *Non-covalent Interactions: Theory and Experiment*, RSC Pub., 2010; (b). G. R. Desiraju, *Angew. Chem., Int. Ed.*, 1995, **34**, 2311–2327.

3 (a) A. R. Voth, P. Khuu, K. Oishi and P. S. Ho, *Nat. Chem.*, 2009, **1**, 74–79; (b). C. B. Aakeröy, C. L. Spartz, S. Dembowski, S. Dwyre and J. Desper, *IUCrJ*, 2015, **2**, 498–510.

4 (a) P. Metrangolo, F. Meyer, T. Pilati, D. M. Proserpio and G. Resnati, *Cryst. Growth Des.*, 2008, **8**, 654–659; (b).A. Casnati, R. Liantonio, P. Metrangolo, G. Resnati, R. Ungaro and F. Ugozzoli, *Angew. Chem., Int. Ed.*, 2006, **45**, 1915–1918; (c). G. Cavallo, P. Metrangolo, T. Pilati, G. Resnati, M. Sansotera and G. Terraneo, *Chem. Soc. Rev.*, 2010, **39**, 3772–3783; (d). M. Fourmigué, *Curr. Opin. Solid State Mater. Sci.*, 2009, **13**, 36–45; (e) V. Mugnaini, C. Punta, R. Liantonio, P. Metrangolo, F. Recupero, G. Resnati, G. F. Pedulli and M. Lucarini, *Tetrahedron Lett.*, 2006, **47**, 3265–3269.

5 (a) L. Koskinen, P. Hirva, E. Kalenius, S. Jaaskelainen, K. Rissanen and M. Haukka, *CrystEngComm*, 2015, **17**, 1231–1236; (b) K. Rissanen and M. Haukka, in *Halogen Bonding II SE-587*, Eds. P. Metrangolo and G. Resnati, Springer International Publishing, 2015, **359**, 77–90.

6 (a) M. Bedin, A. Karim, M. Reitti, A.-C. C. Carlsson, F. Topic, M. Cetina, F. Pan, V. Havel, F. Al-Ameri, V. Sindelar, K. Rissanen, J. Grafenstein and M. Erdelyi, *Chem. Sci.*, 2015, **6**, 3746–3756.

7 (a) K. Raatikainen and K. Rissanen, *CrystEngComm*, 2011, **13**, 6972–6977; (b) K. Raatikainen and K. Rissanen, *Chem. Sci.*, 2012, **3**, 1235–1239.

8 (a) A. Albini, *Heterocyclic N-oxides*, Taylor & Francis, 1991; (b). A. R. Katritzky, *Handbook of heterocyclic chemistry*, Pergamon Press, 1985; (c) M. T. Messina, P. Metrangolo, W. Panzeri, T. Pilati and G. Resnati, *Tetrahedron*, 2001, **57**, 8543–8550; (d) C. B. Aakeroy, T. K. Wijethunga, J. Benton and J. Desper, *Chem. Commun.*, 2015, **51**, 2425–2428; (e).C. B. Aakeroy, T. K. Wijethunga and J. Desper, *CrystEngComm*, 2014, **16**, 28–31.

9 (a) A.-C. Carlsson, A. Veiga and M. Erdélyi, in *Halogen Bonding II SE-607*, Eds. P. Metrangolo and G. Resnati, Springer International Publishing, 2015, **359**, 49–76; (b). M. Erdelyi, *Chem. Soc. Rev.*, 2012, **41**, 3547–3557; (c).T. M. Beale, M. G. Chudzinski, M. G. Sarwar and M. S. Taylor, *Chem. Soc. Rev.*, 2013, **42**, 1667–1680; (d). A.-C. C. Carlsson, J. Gräfenstein, A. Budnjo, J. L. Laurila, J. Bergquist, A. Karim, R. Kleinmaier, U. Brath and M. Erdélyi, *J. Am. Chem. Soc.*, 2012, **134**, 5706–5715; (e) S. Castro-Fernández, I. R. Lahoz, A. L. Llamas-Saiz, J. L. Alonso-Gómez, M.-M. Cid and A. Navarro-Vázquez, *Org. Lett.*, 2014, **16**, 1136–1139.

10 C. Frassineti, L. Alderighi, P. Gans, A. Sabatini, A. Vacca and S. Ghelli, *Anal. Bioanal. Chem.*, 2003, **376**, 1041–1052.

11 (a) R. Puttreddy and P. J. Steel, *Inorg. Chem. Commun.*, 2014, **41**, 33–36; (b). R. Puttreddy and P. J. Steel, *CrystEngComm*, 2014, **16**, 556–560.

12 (a) A. S. Batsanov, J. A. K. Howard, A. P. Lightfoot, S. J. R. Twiddle and A. Whiting, *European J. Org. Chem.*, 2005, **2005**, 1876–1883; (b). A. A. Neverov, H. X. Feng, K. Hamilton and R. S. Brown, *J. Org. Chem.*, 2003, **68**, 3802–3810; (c). T. Okitsu, S. Yumitate, K. Sato, Y. In and A. Wada, *Chem. – Eur. J.*, 2013, **19**, 4992–4996.

13 (a) M. G. Sarwar, D. Ajami, G. Theodorakopoulos, I. D. Petsalakis and J. Rebek, *J. Am. Chem. Soc.*, 2013, **135**, 13672–13675; (b). S. M. Walter, F. Kniep, L. Rout, F. P. Schmidtchen, E. Herdtweck and S. M. Huber, *J. Am. Chem. Soc.*, 2012, **134**, 8507–8512; (c). S. H. Jungbauer, S. Schindler, E. Herdtweck, S. Keller and S. M. Huber, *Chem. – Eur. J.*, 2015, **21**, 13625–13636; (d). M. J. Langton, S. W. Robinson, I. Marques, V. Félix and P. D. Beer, *Nat. Chem.*, 2014, **6**, 1039–1043; (e). B. R. Mullaney, A. L. Thompson and P. D. Beer, *Angew. Chem., Int. Ed.*, 2014, **126**, 11642–11646.