

Cite this: *Chem. Commun.*, 2012, **48**, 1458–1460

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COMMUNICATION

Symmetry of $[\text{N}-\text{X}-\text{N}]^+$ halogen bonds in solution†‡Anna-Carin C. Carlsson,^a Jürgen Gräfenstein,^a Jesse L. Laurila,^a
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Received 20th September 2011, Accepted 10th October 2011

DOI: 10.1039/c1cc15839b

The first investigation of halogen bond symmetry is presented. In contrast to related hydrogen bonds, the iodous halogen bond is symmetric in solution and in the crystal. The bromous analogue is symmetric in solution, but shows asymmetry in the solid state. NMR results are in agreement with DFT predictions.

Halogen bonding (XB)¹ observed first in the nineteenth century² and subsequently explored in the solid-state by Odd Hassel³ has recently been rediscovered and emerged as a potential tool for controlling molecular recognition processes.⁴ Gaseous phase⁵ and *in silico*⁶ investigations provided the basis for the theoretical understanding of this yet unexploited noncovalent interaction of halogens and electron donating nucleophiles. Over the past decade, using X-ray crystallographic methods the applicability of XB in crystal engineering and in supramolecular chemistry has been thoroughly investigated,⁷ and its ability to stabilize protein–ligand complexes of pharmaceutical relevance has been shown.⁸ Recent studies indicated the powerfulness of NMR spectroscopy for its detection in solution.⁹ A strong resemblance of the previously largely overlooked XB with hydrogen bonding (HB) has been earlier emphasized⁴ and motivates the high expectations for its broad applicability. To date, HB is by far the most frequently used tool for governing molecular recognition processes and crystal engineering. Besides recognition of wide similarities, the detailed understanding of the differences between XB and HB¹⁰ is essential for the exploration of the scopes of XB and its use as a complementary molecular tool to HB.

A classic concern regarding HB is its symmetry. Originating from its proposed relevance for enzyme catalysis, HB symmetry has been the matter of intense debate for decades,¹¹ providing the conclusion that hydrogen bonds that are symmetric in crystals are asymmetric in solutions.¹² Despite the frequently stressed analogy of HB and XB^{4,10} and the likely impact of XB symmetry on its applications in catalytic halonium transfer and molecular recognition processes, it is assessed here for the very first time.

Molecular systems comprised of an electropositive atom located in-between two identical electron donors might either be symmetric, having a single-well energy potential, or asymmetric, having a double-well potential.¹² A low energy barrier of a double-well describes rapidly equilibrating tautomers (Fig. 1b) that give rise to coalesced NMR signals even at low temperatures,¹² whereas a high barrier may result in distinct species with separate sets of NMR signals.^{13,14} Following previous evidences for direct transferability of methods developed for investigation of HB to the examination of XB,^{1,4–9} and for straightforward comparability of the observations on the two types of interactions, the NMR spectroscopic method Isotopic Perturbation of Equilibrium (IPE)^{12,15} is used here for assessment of the XB symmetry. IPE has previously been successfully applied to symmetry judgments of *e.g.*, carbocations, O–H...O and N–H...N hydrogen bonds, thiapentalenes, and metal chelating complexes.¹⁶ For evaluation of the symmetry of XB in systems encompassing nitrogeneous XB acceptors¹⁷ and the common iodous or bromous XB donors ($\text{N}-\text{X}^+\cdots\text{N} \rightleftharpoons \text{N}\cdots\text{X}^+-\text{N}$, contra $[\text{N}\cdots\text{X}\cdots\text{N}]^+$), the model systems bis(pyridine)bromonium (**1**) and iodonium (**2**) triflates were investigated. This choice is motivated by the available vast knowledge of pyridines,^{14,18} and the well-defined and for XB optimal^{4,6} linear geometry¹⁹ of the comparably small bis(pyridine) model systems that are also known as synthetic reagents.²⁰ It should be emphasized here that **1** and **2** (Fig. 1) should not be confused with iodonium or bromonium salts as they do not consist of halonium ions and pyridines donating their lone pair of electrons, but of a halogen and two pyridines contributing to the $\text{N}\cdots\text{X}$ bond by a single electron each.²¹ As a consequence, the $\text{N}\cdots\text{X}$ interaction shows rather a covalent than

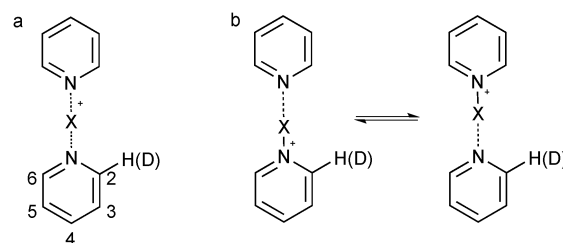


Fig. 1 The symmetric (a) and asymmetric (b) geometries of the investigated compounds. For compound **1**, X = Br, for **2**, X = I and for **3**, X = H. The nondeuterated complex of **1** is abbreviated to **1-d₀**, and the monodeuterium labelled one to **1-d₁**. Abbreviations for **2** and **3** follow the same nomenclature.

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† This article is part of the ChemComm 'Emerging Investigators 2012' themed issue.

‡ Electronic supplementary information (ESI) available: Details of the NMR and computational investigation. See DOI: 10.1039/c1cc15839b

an ionic character. Hence, the chief question studied here is whether the interactions of Br and I to the two coordinating nitrogens are equivalent, interpretable as two identical $N \cdots X$ halogen bonds (Fig. 1a), or if one of the $N-X$ bonds is shorter and thus stronger than the second, yielding an asymmetric complex having one classical covalent and one classical halogen bond (Fig. 1b). In similarity to hydrogen bonded systems, these latter species would be expected to behave as unsymmetrical tautomers.¹² The $[N \cdots X \cdots N]^+$ system studied here is of broad theoretical interest as it provides a simple model for three-center four-electron halogen bonds. For completeness, the properties of **1** and **2** are discussed in comparison with those of the corresponding $[N \cdots H \cdots N]^+$ complex, **3**. Utilizing the IPE technique, isotope effects (IEs) have been measured for the mixture of 2-deutero-pyridine/ X^+ /pyridine (1 : 1 : 1) and pyridine/ X^+ (2 : 1) complexes (Fig. 1, ESI†). As described in detail elsewhere,^{12,15} this technique relies on observation of isotope shifts, which here are induced by deuterium labelling in the C2 position of pyridine ($^n\Delta_{\text{obs}} = \delta_{\text{C(D)}} - \delta_{\text{C(H)}}$). The observed carbon IE, $^n\Delta_{\text{obs}}$, always comprises an intrinsic contribution, $^n\Delta_0$, which falls off quickly with the number of bonds (n) between the reporter carbon and the deuterium. In rapidly equilibrating systems an additional contribution to $^n\Delta_{\text{obs}}$ is observable, commonly named equilibrium IE, $^n\Delta_{\text{eq}}$, which is caused by the perturbation of an equilibrium process as a result of H to D isotope substitution close to the interaction site. As a consequence, for a static, symmetric $[N \cdots X \cdots N]^+$ system $^n\Delta_{\text{obs}} = ^n\Delta_0$ is seen, whereas for a rapidly tautomerizing asymmetric system ($N-X^+ \cdots N \rightleftharpoons N \cdots X^+-N$) the sum of the above components ($^n\Delta_{\text{obs}} = ^n\Delta_0 + ^n\Delta_{\text{eq}}$) is detectable. The magnitude of the term $^n\Delta_{\text{eq}}$ depends on the tautomerization rate following the equation $^n\Delta_{\text{eq}} = D(K - 1)/[2(K + 1)]$,¹² where K is the equilibrium constant of the process and D the chemical shift difference of the halogenated ($N-X^+$) and non-halogenated ($N + X^+$) states. As the equilibrium constant of a process is temperature dependent ($K = \exp[-\Delta G/RT]$), so is the magnitude of $^n\Delta_{\text{eq}}$.¹⁵ In this study, for observation of large IE closest to the $[N \cdots X \cdots N]^+$ interaction site, ^2H was incorporated in the pyridine C2 position as deuteration synperiplanar to the lone pair of the nitrogen is known to efficiently increase its basicity.²² Even if the change is expectably smaller as compared to aliphatic systems, yet it is applicable for the perturbation of equilibrium processes, in which the nitrogen lone pair is involved.

Complexes **1**, **2** and **3** (Fig. 1) all gave a single set of ^1H and ^{13}C solution NMR signals (ESI†), indicating either a single symmetric structure or a mixture of tautomers in rapid equilibrium. IEs observed for CD_2Cl_2 solution of mixtures of XB complexes **1-d₀**/**1-d₁** and **2-d₀**/**2-d₁**, and the HB complex **3-d₀**/**3-d₁** are summarized in Table 1. The IEs of pyridine- d_0 /pyridine- d_1 were acquired to provide an estimate for the intrinsic isotope shifts ($^n\Delta_0$)¹² and correlate well in magnitude to previous observations.^{14,23} The small, yet measurable (ESI†) alteration of $^n\Delta_{\text{obs}}$ of **1–3** as compared to pyridine (Table 1) along with an expected $^1\Delta_{\text{eq}} < 40$ ppb corresponding to an estimated $K \approx 1.01$ and an unexpected,¹² but apparent variation of the intrinsic IE upon small structural changes makes it impossible to distinguish between a static symmetric and

Table 1 Observed and calculated isotopic shifts ($^n\Delta_{\text{obs}}$)^a

Structure	Solvent	C2	C3	C4	C5	C6
Pyridine	CD_2Cl_2	−341	−140	0	+14	−15
	<i>Calculated</i>	−358	−154	+2	+1	−21
1	CD_2Cl_2	−307	−139	+17	0	−29
	<i>Symmetric</i>	−301	−141	−6	−2	−19
	<i>Asymmetric</i>	−304	−144	+41	−5	−23
2	CD_2Cl_2	−336	−145	+20	0	−30
	<i>Symmetric</i>	−310	−146	−8	−3	−17
	<i>Asymmetric</i>	−307	−151	+8	−10	−18
3	CD_2Cl_2	−333	−126	+45	+20	−52
	<i>Symmetric</i>	−270	−145	−33	−2	−13
	<i>Asymmetric</i>	−308	−120	+63	+23	−43

^a For 298 K and in ppb. Italics: calculated values (see ESI for details), otherwise: experimental values.

rapidly tautomerizing asymmetric bonds for these systems, based on the observed $^n\Delta_{\text{obs}}$ values only.

For a reliable distinguishment, the temperature coefficients of the IEs ($\Delta^n\Delta_{\text{obs}}/(1/\Delta T)$)¹⁵ were acquired from the slopes of $^n\Delta_{\text{obs}}$ vs. reciprocal temperature plots (Table 2, ESI†). The observed temperature dependence of the intrinsic IEs (Table 2, pyridine), which has previously not been reported, is, however, consistent with theory as $^n\Delta_0$ depends on the amplitude of the molecular vibration, which is temperature-dependent for soft vibrations (*ca.* $\nu < 500 \text{ cm}^{-1}$). In addition, solvent effects may depend on temperature.²⁴ The alteration of $^n\Delta_0$ of pyridine upon temperature change is small, yet significant, and its magnitude correlates to the number of intervening bonds to the point of isotopic substitution (Table 2). Whereas the magnitude of $\Delta^n\Delta_{\text{obs}}/(1/\Delta T)$ of **1** and **2** similarly depends on the number of intervening bonds (n) to the point of H to D isotope substitution (C2), those of the carbons of **3**, importantly, show an additional dependence on their distance to the nitrogen. The fact that the magnitude of the change of $^n\Delta_{\text{obs}}/(1/\Delta T)$ of the hydrogen bonded complex **3** is in absolute value largely symmetric around the $N-C4$ axis is indicative of the involvement of its nitrogens in an equilibrium process. In contrast, the independence of the magnitude of $\Delta^n\Delta_{\text{obs}}/(1/\Delta T)$ of **1** and **2** from the distance of the reporter carbons to the nitrogen is indicative of static, symmetric structures.

As a complement to the NMR experiments, DFT calculations with dichloromethane solvent model were performed to determine the low-energy structures of **1–3**, the ^{13}C NMR shielding tensors and the H/D isotope shifts (details given in the ESI†). DFT calculations predict static, symmetric structures for **1** and **2** (ESI†). For both, two centrosymmetric low energy geometries (D_{2h} and D_{2d} , ESI†) were found to be in thermodynamic equilibrium ($\Delta G < 0.1 \text{ kcal mol}^{-1}$ at 298 K in

Table 2 Temperature coefficients of the isotopic shifts^a

Structure	C2	C3	C4	C5	C6
Pyridine	−4.8	−4.8	0	+1.9	−2.1
1	−3.1	−6.4	+0.4	0	−2.5
2	−4.5	−6.4	+0.6	0	−2.6
3	−6.1	−9.8	−4.5	−5.8	−6.5

^a Values are given in $\text{ppm} \times \text{K}$ for CD_2Cl_2 solutions, as measured for the temperature range of 193 K to 298 K for pyridine, **1**, and **2**, and 273 K to 298 K for **3**.

CD₂Cl₂). The lowest symmetric N–X stretch vibration frequencies are 173 cm^{−1} (**1**) and 182 cm^{−1} (**2**), respectively, whereas the lowest asymmetric N–X stretch vibration frequencies are 162 cm^{−1} (**1**) and 167 cm^{−1} (**2**). The frequencies of the N–X stretch vibrations indicate that **1** and **2** are stable against both dissociation and breaking of the N–X–N symmetry. In contrast, **3** is predicted to be asymmetric (C_{2v}) and twisted, with N–H bond lengths of 1.082 Å and 1.648 Å, respectively, an inversion barrier of $\Delta G^\ddagger = 1.10$ kcal mol^{−1} at 298 K, and an imaginary frequency of 1996 cm^{−1} for the asymmetric N–H stretch vibration of the transition state. The low barrier height and the high imaginary frequency indicate high likelihood for rapid interconversion between the stable geometries by thermal effects and by proton tunnelling. Isotope shifts were calculated both for the calculated symmetric (**1**, **2**, **3**) and asymmetric (**3**) equilibrium structures and for hypothetical asymmetric structures of **1** and **2** (see ESI† for details), using the local mode zero-point level (LMZPL) approach recently proposed by Yang and Hudson²⁵ and are given in Table 1. These estimates of ν_{obs} are immensely better than those of other methods used in previous studies.²⁶ Whereas ν_{obs} at C2 is slightly overestimated for pyridine, it is underestimated for **1–3**. This difference may be caused by several features that distinguish **1**, **2** and **3** from pyridine, for example the presence of counter ions and the soft interfragment vibration modes in **1**, **2** and **3**, both of which are neglected in the local-mode approach, or the electronic interactions between the lone pairs and the solvent. For **3**, the calculated IEs for the asymmetric structure agree significantly better with the experimental IEs than those of the symmetric structure, indicating rapid interconversion between asymmetric tautomers of **3** (Fig. 1b), which is in excellent agreement with the previously described general asymmetry of hydrogen bonds in solution.¹² For **1** and **2**, the measured IEs are compatible with those calculated for the symmetric structure (Table 1 and Fig. 1a); however, it should be emphasized that the difference between the magnitude of the calculated values for the symmetric and asymmetric geometries is within the range of the error bounds, a fact depriving from the possibility of an unambiguous symmetry assignment. The small difference (~ 0.2 Å) between the N–X bond lengths of the symmetric and hypothetical asymmetric structures of **1** and **2** as compared to that of **3** (0.6 Å) provides a plausible explanation for this observation.

An important and previously not reported²⁷ observation is that the intrinsic IE is slightly altered upon secondary chemical interactions, here to halogens or protons, which is here qualitatively reproducible by the applied theory.

In the solid state, compounds **1** and **2** show linear [N⋯X⋯N]⁺ arrangements. Whereas **1** is asymmetric, **2** is symmetric in the crystal with the pyridines slightly deviating from coplanarity.²⁸ The asymmetry of **1** in the solid state is likely to originate from packing forces and might be indicative of a lower energetic gain in forming symmetric bromous halogen bonds than iodosous ones. Complex **3** shows symmetric [N⋯H⋯N]⁺ arrangement in the solid state,²⁸ whereas its here observed asymmetry in solution compares well with previous observations on hydrogen bonding asymmetry in solution.¹²

In conclusion, whereas N⋯H⋯N-type HBs are asymmetric in solution, but symmetric in crystals,¹² analogous iodosous and

bromous halogen bonded systems prefer symmetric arrangements in solution and a XB-donor dependent symmetry in the solid state. The observed stability of the symmetric halogen bonded structures in solution is well-supported by theory (DFT).

This research was supported by the Swedish (2007-4407, 621-2008-3562) and the European Research Council (259638) as well as by the Carl Tryggers and the Åke Wibergs Foundation. We thank the C3SE, Gothenburg, and the NSC, Linköping, for generous allotments of CPU time.

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