The role of charge in 1,2,3-triazol(jum)-based halogen bonding activators†

Alexander Dreger,† Elric Engelage,† Bert Mallick,† Paul D. Beer‡ and Stefan M. Huber†,*

Halogen bonds (XBs) are highly directional non-covalent interactions between the electrophilic region of a covalently bound halogen atom and a Lewis base. For strong halogen bonding, the respective XB donor (i.e., the halogen-based Lewis acid) requires an electron-withdrawing core structure, and often perfluorinated or cationic (hetero)arenes are used. Until now, halogen bonding has been successfully applied in many areas, including crystal engineering, supramolecular chemistry and organocatalysis. 1-4

Halogen bond donors based on triazolium moieties were first introduced in the context of an anion-binding rotasane. 5 Bidentate triazolium-based activators were then used in a benchmark reaction for halide abstraction (the solvolysis of benzhydryl bromide 1 in acetonitrile), and their activating power was found to be similar to that of bidentate imidazolium 7 or pyridinium-based 8 halogen bond donors. Subsequently, neutral bidentate triazole derivatives were investigated as anion receptors, 9,10 but their binding strength to donors. Subsequently, neutral bidentate triazole derivatives were investigated as anion receptors, 9,10 but their binding strength to chloride was found to be markedly lower than that of their dicationic analogues. This is in line with previous findings that charge-assisted XB donors are stronger Lewis acids 11 and are thus preferentially used in organic synthesis. On the other hand, halogen bond donors based on cationic core structures also feature some intrinsic disadvantages, e.g. low solubility in apolar solvents and competition by Lewis basic counterions. 12

In 2015, Beer et al. introduced strong bidentate (but monocationic) halogen bond donors based on a bis(iodotriazolyl)pyridinium motif (3,5-Py(X)R,R/Z, Fig. 1 middle) for anion recognition. 13 Since these compounds represent an interesting compromise between overall charge assistance but neutral halogen-bond-donating moieties, we became interested to test their performance as Lewis acidic activators, especially in comparison to our previous dicationic systems (1,3-Ph(I)Oct,Me/OTf, Fig. 1 left). 6 In doing so, our main goal was to elucidate the relevance of charge on the actual halogen bonding groups. 14

The syntheses of all XB donors employed in this study are shown in Scheme 1. First, a modified Cu(i)-catalysed azide–alkyne 1,3-dipolar cycloaddition reaction of bis-alkyne 4 with benzyl azide or octyl azide and sodium iodide led to the corresponding bis(iodotriazolyl)pyridine derivatives 3,5-Py(i)/Z in good yields (Scheme 1; for nomenclature see Fig. 1). 15 Subsequent regioselective alkylation at the pyridine core with methyl triflate (MeOTf), octyl triflate (OctOTf) or N-methyl bis(trifluoromethylsulfonyl)amide (MeNTf2) provided XB donors 3,5-Py(i)R,R/Z (Z = OTf, NTF2) in good yields (71–98%). 16 In order to include a variant with noncoordinating tetrakis(3,5-bis(trifluoromethyl)-phenyl)boration (BaF4), the corresponding salt 3,5-Py(i)Oct,Me/BaF4 was obtained from salt metathesis of the triflate salt with NMe4BaF4 in chloroform in quantitative yield. 16 Non-iodinated reference compounds were obtained via similar procedures (see the ESI†).

The activity of these XB donors was then tested in the benchmark reaction shown in Scheme 2. 17 Similarly to our previous studies, the XB donor activates the C–Br bond of benzhydryl...
bromide to generate the benzhydryl cation. Deviating from our earlier benchmark reaction, which featured the solvolysis of the intermediate, in this study the cation was quenched with one equivalent of 1,3,5-trimethoxybenzene as an external nucleophile. A stoichiometric amount of the respective XB donor was used and Cs₂CO₃ was added to each reaction to rule out hidden acid catalysis.

The reaction was monitored by ¹H-NMR spectroscopy (see Fig. 2 for kinetic profiles and Table 1 for yields of product). No significant background reaction occurs in the absence of activators (<5% yield after 30 h). Activation by Brønsted acids can also be ruled out, since 5 mol% of triflic acid (HOTf) showed no activation. As a non-iodinated reference compound 3,5-Py(H)Oct,Me/OTf induced no product formation, any activity of iodinated 3,5-Py(I)R₂ compounds cannot be explained by hydrogen bonding or by simple electrostatic interactions and is thus likely based on halogen bonding.

The non-cationic bis(triazole) derivative 1,3-Ph(I)Oct (cf. Fig. 1) showed no activity, indicating that some form of charge assistance is essential for this reaction. The highest rate acceleration was obtained in the presence of 3,5-Py(I)Oct,Me/BArF, yielding 72% of compound 3 after 2.5 h (Table 1, entry 5). However, after 3 h decomposition of the XB donor was observed (reaching ~13% of the decomposed material after 11 h), and thus the interpretation of the observed performance needs some caution. In contrast, no indications of decomposition were obtained for the analogous triflate and NTf₂ salts, but – as could be expected from the more coordinating nature of the counterions – these activators also induced somewhat less product formation (42% for 3,5-Py(I)Oct,Me/OTf after 5 h and 53% for 3,5-Py(I)Oct,Me/NTf₂ after the same time; see Table 1, entries 6 and 7). Variation of the alkylation pattern did not decisively alter the overall outcome: changing the methyl group on the pyridinium to octyl led to a slight increase in yield, which is likely still within the error of experiment (48% yield for 3,5-Py(I)Oct,Oct/OTf after 5 h, entry 8). Substituting the octyl groups on the triazolium moieties with
benzyl groups again led to virtually identical results for the 
N_{Py}–OCT compound 3,5-Py(I)Bn,Me/OTf (41% yield, entry 9). The 
corresponding benzylated N_{Py}–Me compounds showed slightly 
(37% yield for 3,5-Py(I)Bn,Me/NTf₂) to drastically lower performance 
(no yield for 3,5-Py(I)Bn,Me/OTf). At least in the latter 
case, this can be attributed to the low solubility of the XB donor 
in chloroform.

Most importantly, the previously studied⁴ dicationic XB donor 
1,3-Ph(I)Oct,Me/OTf was only slightly more active (54% yield after 
5 h) than its monocationic analogue 3,5-Py(I)Oct,Me/OTf (42%, 
see above).¹⁸ This clearly demonstrates that bidentate charge-
assisted halogen bonding does not automatically also necessitate 
dicationic XB donors. A comparable performance as an activator 
is also feasible for monocationic species. In the current example, 
this is particularly noteworthy since the Lewis structure formalism 
(!) does not indicate the delocalization of the cationic charge 
towards the triazole moieties.

The results of the activation studies are supported by isothermal 
titration calorimetry (ITC) measurements (see Table 2). Both 
the monocationic XB donor 3,5-Py(I)Oct,Me/OTf and its dicationic 
variant 1,3-Ph(I)Oct,Me/OTf feature nearly the same binding strength 
to bromide in chloroform (1.6 × 10⁻⁵ M⁻¹, entries 2 and 10). The 
binding to chloride is also very similar (entries 1 and 9), whereas a 
notable deviation is found for iodide complexation. Somewhat 
surprisingly, the monocationic system 3,5-Py(I)Oct,Me/OTf turned 
out to be the stronger Lewis acid. A clear difference between the 
two types of XB donors is the relative contribution of the enthalpic 
and entropic parts. For the monocationic XB donor, the enthalpic 
part is decidedly more favourable compared to 1,3-Ph(I)Oct,Me/OTf. 
On the other hand, the entropic contribution is negligible for the 
former, but constitutes an important favourable contribution in the 
 latter (similar to the binding of bis(1,2,4-dioxoimidazolium)-derived XB donors).¹⁹

As had already been observed,¹³ the association strength 
decreases in the order chloride > bromide > iodide for all XB 
donors tested. The influence of the counterion could only be 
investigated for the monocationic species, as the dicationic 
ones suffered from solubility issues. As expected, the binding 
strength of the XB donors follows the lesser Lewis basicity of the 
counterions (BARF₂⁻ > NTf₂⁻ > OTf−, entries 1–8). This underlines 
the relevance of ion pairing and may also explain the similar Lewis 
acidity (and activation potential) of mono- and dicationic XB donors: 
ion pairing in the latter is likely stronger, which might compensate 
for their potentially stronger XB donor properties.

Finally, X-ray structural analyses helped to shed light on 
the binding mode of the monocationic XB donors to anions. 
The result of the single-crystal X-ray analysis of the XB donor 
3,5-Py(I)Bn,Me/OTf is shown in Fig. 3. Two strong halogen bonds 
between iodine atoms of the XB donor and oxygen atoms of 
triflate can be found in the solid state. The iodine–oxygen bond 
distances (2.78 Å and 2.99 Å) are shorter than the sum of the 
van der Waals radii (3.5 Å)²⁰ and the binding angle C–I–O is 
neatly linear (173° and 166°), as expected for halogen bonding. 
The previously reported crystal structure of the dicaticnic XB 
donor 1,3-Ph(I)Oct,Me/OTf featured halogen bonds to triflate 
anions with I–O distances of 2.88 Å and 2.90 Å.⁶

From a solution of 3,5-Py(I)Br,Me/OTf and benzhydrol bromide 
(1) in acetonitrile, we obtained a single-crystal of 3,5-Py(I)Br,Oct/Br 
(Fig. 4). The bromide is bound in a bidentate fashion by the 

### Table 1 Yields of product 3 in the reaction of Scheme 2 after approx. 5 h and 12 h in the presence of different activation reagents

<table>
<thead>
<tr>
<th>#</th>
<th>Activating reagent</th>
<th>Yield [%] (5 h)</th>
<th>Yield [%] (12 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>2</td>
<td>HOTf</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>3</td>
<td>3,5-Py(I)Oct,Me/OTf</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>4</td>
<td>1,3-Ph(I)Oct</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>5</td>
<td>3,5-Py(I)Oct,Me/Br</td>
<td>81b</td>
<td>87b</td>
</tr>
<tr>
<td>6</td>
<td>3,5-Py(I)Oct,Me/OTf</td>
<td>42</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>3,5-Py(I)Oct,Me/NTf₂</td>
<td>53</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>3,5-Py(I)Oct,Me/OTf</td>
<td>48</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>3,5-Py(I)Oct,Me/NTf₂</td>
<td>44</td>
<td>61</td>
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<tr>
<td>10</td>
<td>3,5-Py(I)Oct,Me/NTf₂</td>
<td>37</td>
<td>52</td>
</tr>
<tr>
<td>11</td>
<td>3,5-Py(I)Oct,Me/OTf</td>
<td>&lt; 5</td>
<td>10b</td>
</tr>
<tr>
<td>12</td>
<td>1,3-Ph(I)Oct,Me/OTf</td>
<td>54</td>
<td>68</td>
</tr>
<tr>
<td>13</td>
<td>1,3-Ph(I)Oct,Me/Br</td>
<td>35b</td>
<td>38b</td>
</tr>
</tbody>
</table>

* Yields according to 1H-NMR analysis. b Partial decomposition of the XB donor. c Low solubility in CDCl₃.

### Table 2 Results of isothermal titration calorimetry experiments of various mono- and di-cationic XB donors with halides in chloroform at 30 °C

<table>
<thead>
<tr>
<th>#</th>
<th>Host</th>
<th>X° K [M⁻¹]</th>
<th>ΔH [kJ mol⁻¹]</th>
<th>ΔS [kJ mol⁻¹ K⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,5-Py(I)Oct,Me/OTf</td>
<td>Cl</td>
<td>1.35 × 10⁻³</td>
<td>-19.34</td>
</tr>
<tr>
<td>2</td>
<td>3,5-Py(I)Oct,Me/OTf</td>
<td>Br</td>
<td>1.59 × 10⁻³</td>
<td>-21.50</td>
</tr>
<tr>
<td>3</td>
<td>3,5-Py(I)Oct,Me/NTf₂</td>
<td>I</td>
<td>9.26 × 10⁻³</td>
<td>-21.77</td>
</tr>
<tr>
<td>4</td>
<td>3,5-Py(I)Oct,Me/NTf₂</td>
<td>Cl</td>
<td>2.53 × 10⁻³</td>
<td>-25.41</td>
</tr>
<tr>
<td>5</td>
<td>3,5-Py(I)Oct,Me/NTf₂</td>
<td>Br</td>
<td>2.59 × 10⁻³</td>
<td>-24.66</td>
</tr>
<tr>
<td>6</td>
<td>3,5-Py(I)Oct,Me/NTf₂</td>
<td>I</td>
<td>1.53 × 10⁻³</td>
<td>-25.66</td>
</tr>
<tr>
<td>7</td>
<td>3,5-Py(I)Oct,Me/Br</td>
<td>Cl</td>
<td>3.16 × 10⁻³</td>
<td>-24.25</td>
</tr>
<tr>
<td>8</td>
<td>3,5-Py(I)Oct,Me/Br</td>
<td>Br</td>
<td>3.57 × 10⁻³</td>
<td>-29.15</td>
</tr>
<tr>
<td>9</td>
<td>1,3-Ph(I)Oct,Me/Br</td>
<td>Cl</td>
<td>9.09 × 10⁻³</td>
<td>-12.45</td>
</tr>
<tr>
<td>10</td>
<td>1,3-Ph(I)Oct,Me/Br</td>
<td>Br</td>
<td>1.60 × 10⁻³</td>
<td>-14.36</td>
</tr>
<tr>
<td>11</td>
<td>1,3-Ph(I)Oct,Me/Br</td>
<td>I</td>
<td>1.82 × 10⁻³</td>
<td>-17.68</td>
</tr>
<tr>
<td>12</td>
<td>1,3-Ph(I)Oct,Me/Br</td>
<td>Cl</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>1,3-Ph(I)Oct,Me/Br</td>
<td>Br</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

a Tetraoctylammonium salts were used as guests; (guest) = 10 mM; 
c(host) = 1 mM. The guest solution was titrated into the host solution.
b No accurate fitting data could be obtained.

Fig. 3 ORTEP²¹ plot of the X-ray structural analysis of compound 
3,5-Py(I)Br,Me/OTf (ellipsoids at 50% probability). Selected bond distances [Å] 
and angles [°]: 1–O3 = 2.780, I1–O3 = 2.780, I2–O2 = 2.987, I1–C8 = 2.056, I2–C17 = 2.072, 
donor with I–Br distances of 3.19 Å and 3.23 Å. These distances are again significantly shorter than the sum of the van der Waals radii (3.83 Å) and the binding angle C–I–Br is close to linear (171° and 166°). A similar crystal structure of 3,5-Py(I)OTfBr was previously reported by Beer et al. In all reported crystal structures of monocationic XB donors with the 3,5-Py(I)OTfBr/2 core motif, both triazolyl moieties are in plane with the pyridinium ring. In the crystal structure of 1,3-Ph(I)Br,Me/OTf, on the other hand, the triazolium groups are out of plane with the central benzene ring. As a consequence of the planar geometry of the core structure of 3,5-Py(I)OTfBr, π conjugation will allow some delocalization of the cationic charge.

In summary, a comparison of halogen bond donors based on either a bis(iodotriazolium)benzene or a bis(iodotriazolyl)-pyridinium motif allowed elucidation of the influence of charge (dicaticonic vs. monocationic) on the Lewis acidity of these compounds. In a halide abstraction benchmark reaction, the performance of both types of XB donors was very similar. Calorimetric measurements also confirmed that overall the Lewis acidity of the monocationic XB donors is roughly in the same range as the one of the previously studied dicationic bidentate variants. As a consequence of the planar geometry of the core structure of 3,5-Py(I)OTfBr, π conjugation will allow some delocalization of the cationic charge.

These findings may have important implications for the design of strong halogen-bonding-based activators or organocatalysts: apparently, a monocationic backbone is sufficient to ensure strong charge-assisted bidentate halogen bonding. The monocationic species, however, feature some distinct advantages over their respective dicaticionic analogues: complete anion exchange by metathesis is realized more easily, and the solubility in less polar organic solvents is generally superior. This already became apparent in this study, as 3,5-Py(I)OTfBr/2 exibits much better solubility in chloroform than 1,3-Ph(I)Br,Me/OTf (see footnote 18). As a further example, 3,5-Py(I)OTfBr/2OTf exhibits much better solubility in diethylether than 1,3-Ph(I)Br,Me/OTf. As a consequence, the utilization of monocationic motifs like the one studied here might allow to combine the “best of both worlds” in halogen-bonding organocatalysis: the performance of charge-assisted XB donors and the solubility of (generally weaker) fluorinated XB donors in less polar media.

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Conflicts of interest
There are no conflicts to declare.

Notes and references
18. For the corresponding Barf²⁺ compounds, even a slight decrease in activity is observed for the dicaticonic XB donor 1,3-Ph(I)Br,Me/OTf (35% yield after 5 h), again likely due to low solubility.