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Neutral iodotriazoles as scaffolds for stable halogen-bonded assemblies in solution†

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The halogen bond (XB) donor properties of neutral 1,4-diaryl-5-iodo-1,2,3-triazoles are explored using a combination of computational and experimental results and are shown to be competitive in halogen bonding efficiency with the classic pentafluoriodobenzene XB donor. The S_NAr reactivity of these donors permits the facile assembly of an iodotriazole functionalised with a 3-oxypyridine XB acceptor, thus generating a molecular scaffold capable of undergoing dimerisation through the formation of two halogen bonds. The formation of this halogen-bonded dimer is demonstrated by 1H and DOSY NMR experiments and a plausible structure generated using DFT calculations.

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Introduction

The non-covalent interaction between an electron deficient halogen atom and an electron donor has found¹ a clear definition in the term halogen bonding. Halogen bonds (XBs) have proven to be a powerful tool in a wide range of chemistries. The contribution of Metrangolo, Resnati and co-workers has revolutionised² the conception of XB, making it a valuable tool in all the areas of chemistry where molecular recognition plays a central role.³ A significant effort has also been invested in unravelling the fundamental structural and energetic features of XBs. Computational⁴ and experimental⁵ studies made significant contribution to the understanding of the so-called “ σ -hole”^{4b} – a zone of low electron density displaying a positive electrostatic potential. Simplifying XBs to merely electrostatic interactions is, however, reductive: the factors contributing to the stability of a XB are a convolution of electrostatic,^{4a} polarisation,⁶ charge transfer⁷ and dispersion⁸ forces and the role played by each of these factors is influenced significantly by the molecular components involved and the medium where the interaction takes place. It is generally recognised though that the ability of a halogen atom to participate in a XB increases with the electron withdrawing effect of the group to which the halogen is attached. The plethora of halogenated molecules

constitutes a huge set of XB donors. Among these, a simple demarcation in XB ability can be made between cationic and neutral XB donors. Cationic XB donors are generally halogenated (mainly Br and I) five or six membered nitrogen heterocycles, where one of the nitrogen atoms is quaternarised with an alkyl group. The interaction of such XB donors with XB acceptors is in fact defined⁹ as ‘charge-assisted XB’ and these interactions are significantly stronger than those between two neutral XB partners. Beer and co-workers, for example, have designed and synthesised¹⁰ a variety of macrocycles, catenanes and rotaxanes incorporating halotriazolium and haloimidazolium units able to perform anion sensing in organic and aqueous media *via* charge-assisted XB. Pyridinium¹¹ and imidazolium^{12,13} XB donors have been used extensively by the group of Huber to catalyse C–Br bond cleavage reactions in organic media.

On the other hand, when a polarisable halogen atom is bonded to a neutral organic backbone, its ability to act as a XB donor depends greatly on the electronic properties of the organic residue. It is, therefore, not surprising that the most common neutral XB donors are perfluorohalocarbons (PFHCs). Whether aromatic or aliphatic, these compounds are now considered ‘iconic’ XB donors. In 2002, Metrangolo, Resnati *et al.* reported¹⁴ the first semiquantitative evaluation of XB in solution using 1,2-dibromo and 1,2-diiodo tetrafluoroethanes as the XB donors. Taylor *et al.* have successfully measured¹⁵ the strength of XBs formed by a set of variously substituted iodo-perfluorobenzenes XC_6F_4I in solution using ^{19}F NMR spectroscopy. The association strength could be correlated to the σ Hammett parameter for the X substituent. More recently multivalent PFHC-based XB donors have been successfully exploited in molecular recognition¹⁶ and catalysis.¹⁷

The quest for new and less conventional organic XB donors has been tackled¹⁸ by several research groups and haloalkenes,¹⁹

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suggest that iodotriazole **1** should interact strongly with suitable electron donors. Indeed, the calculated geometries for the complexes formed between the three pyridines shown in Fig. 2b and compound **1** all possess N...I distances much shorter than the sum of the van der Waals radii and significantly negative enthalpies of complexation at 298 K (Fig. 2b). These structural and energetic parameters are all similar to those for the complexes formed between the well-known halogen bond donor **2** and the same set of pyridines. Natural bond order (NBO) analyses (see ESI† for details) demonstrated that, in all six complexes, there are significant interactions between the nitrogen lone pair and the σ^* orbital associated with the C-I bond present in the donor. Intermolecular interaction isosurfaces, generated²⁶ through an analysis of the reduced gradient of the electron density, have been used²⁷ extensively to identify non-covalent interactions that stabilise intermolecular complexes. Analyses of the complexes [1·5] (Fig. 2c) and [2·5] (Fig. 2d) using this method (see ESI† for details) reveal significant low density, low gradient regions that are consistent with the presence of a halogen bond between the interacting partners in both complexes. The similarities between the results for [1·5] and [2·5] suggest that the neutral iodotriazole might be used interchangeably with the perfluorinated iodobenzene as a halogen bond donor.

Encouraged by these computational results, we examined the interaction of iodotriazole **1** and the pyridine-based XB acceptors **3** and **5** in solution. Initially, we examined the interaction of **1** and 4-methylpyridine **3** in d_8 -toluene. Titration of increasing amounts of **3** into a solution of **1** in d_8 -toluene did not result in any significant chemical shift changes in the ¹⁹F NMR spectrum of **1**. However, when the titration was performed again, this time titrating increasing amounts of **1** into a solution of **3** in d_8 -toluene at 293 K, a series of ¹H-¹⁵N HMBC experiments revealed significant upfield ¹⁵N chemical shift changes for the pyridine ring nitrogen atom. The ¹⁵N chemical shift data were fitted²⁸ to a 1 : 1 binding model for the complex [1·3] affording (see ESI† for details) a stability constant for this complex in d_8 -toluene at room temperature of $1.67 \pm 0.55 \text{ M}^{-1}$. For comparison purposes, we repeated this analysis, this time using pentafluoroiodobenzene **2** as the halogen bond donor. The ¹⁵N chemical shift data from this experiment were once again fitted²⁸ to a 1 : 1 binding model for the complex [2·3] (see ESI† for details) affording a stability constant for this complex in d_8 -toluene at 293 K of $2.67 \pm 0.69 \text{ M}^{-1}$. These results confirm experimentally the outcome of our calculations – iodotriazole **1** and pentafluoroiodobenzene **2** have similar halogen bond donor abilities towards pyridine acceptors.

From the set of pyridine XB acceptors studied computationally, DMAP **5** was predicted to form the most stable complexes. When we performed an experiment where increasing amounts of **5** were titrated into a solution of **1** in d_8 -toluene, significant chemical shift changes in the 376.4 MHz ¹⁹F NMR spectrum of **1** were observed (Fig. 3a). In particular, the resonance for the fluorine atom *para* to the iodotriazole ring exhibited a significant upfield shift (Fig. 3a, dotted line) from $\delta -148.7$ to $\delta -149.6$, consistent with the formation of the [1·5] complex. However, this chemical shift data could not be fitted to a 1 : 1 binding model for the [1·5] complex

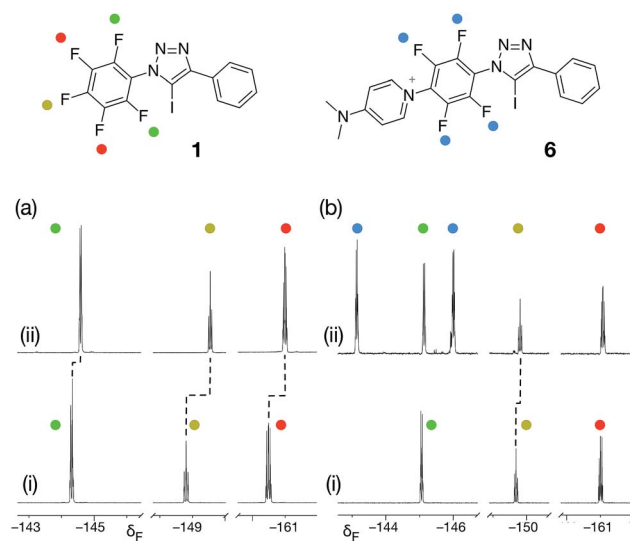


Fig. 3 (a) Partial 376.4 MHz ¹⁹F NMR spectra of (i) a solution of **1** in d_8 -toluene and (ii) the same solution after the addition of 10 equivalents of DMAP **5**. (b) Partial 376.4 MHz ¹⁹F NMR spectra of (i) a solution of **1** in CD_3CN and (ii) the same solution after the addition of 10 equivalents of DMAP **5**. In both case, dashed lines indicate resonances that show chemical shift changes between (i) and (ii).

and close examination of the NMR samples revealed that a precipitate had formed in all samples. Clearly, the formation of the [1·5] complex was accompanied by a concomitant chemical transformation.

Intrigued by the presence of this precipitate, we repeated this titration experiment using CD_3CN as the solvent. In this case, no precipitate was formed. However, the 376.4 MHz ¹⁹F NMR spectrum revealed a new set of resonances at $\delta -143.1$ and $\delta -145.9$ (Fig. 3b, blue circles) that were consistent with the presence of a 1,4-disubstituted tetrafluorobenzene ring. We attributed these resonances to the presence of the insoluble pyridinium salt **6**. This product arises from the nucleophilic aromatic substitution^{29,30} ($\text{S}_{\text{N}}\text{Ar}$) of the fluorine *para* to the triazole ring in **1** by DMAP **5** and analysis of the precipitate formed in d_8 -toluene confirmed its identity as the pyridinium salt **6**.

Although DMAP **5** is potentially the best halogen bond acceptor, it is clearly much too reactive towards the perfluorinated aromatic ring present in **1**. We therefore turned to alkoxyppyridines as halogen bond acceptors. We performed a series of calculations examining the interaction of iodotriazole **1** with 3-methoxyppyridine at the TPSSh/def2-TZVP level of theory. These calculations reveal (Fig. 4a, left) a complex that is very similar in structure ($r(\text{N}\cdots\text{I}) = 2.836 \text{ \AA}$, $\angle \text{C-I}\cdots\text{N} = 179.5^\circ$) and with a similar calculated enthalpy of complexation at 298 K ($-23.6 \text{ kJ mol}^{-1}$) to that formed between **1** and 4-methylpyridine **3**. Titration of **7**, a more soluble variant of **1**, into a solution of 3-pentyloxyppyridine **8** in d_8 -toluene at 298 K resulted in small, but significant, chemical shift changes in the 700.1 MHz ¹H NMR spectrum for the resonances arising from the pyridine ring protons of **8**. A series of ¹H-¹⁵N HMBC experiments (Fig. 4b), performed on the same sample set, also reveal significant ¹⁵N chemical shift changes for the pyridine ring nitrogen



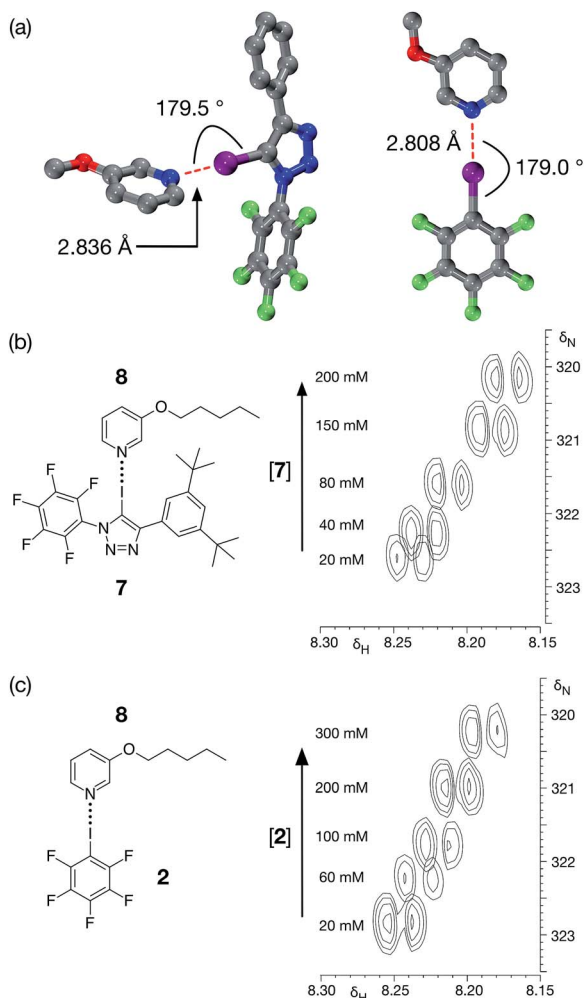


Fig. 4 (a) Calculated structure (TPSSH/def2-TZVP) for the complexes formed between **1** and 3-methoxyiodotriazole (left) and between **2** and 3-methoxyiodotriazole (right). Halogen bonds are marked in red. For the complex of 3-methoxyiodotriazole with **1**: $r(\text{N}\cdots\text{I}) = 2.836 \text{ \AA}$; $\angle \text{C-I}\cdots\text{N} = 180.0^\circ$. For the complex of 3-methoxyiodotriazole with **2**: $r(\text{N}\cdots\text{I}) = 2.808 \text{ \AA}$; $\angle \text{C-I}\cdots\text{N} = 179.0^\circ$. Carbon atoms are coloured grey, nitrogen atoms are coloured blue, fluorine atoms are coloured green and iodine atoms are coloured purple. Hydrogen atoms are not shown. (b) Partial 700.1 MHz ^1H - ^{15}N HMBC correlations of a 20 mM solution of pyridine **8** in d_8 -toluene with increasing amounts (0 to 200 mM) of iodotriazole **7** added to the solution. (c) Partial 700.1 MHz ^1H - ^{15}N HMBC correlations of a 20 mM solution of pyridine **8** in d_8 -toluene with increasing amounts (0 to 200 mM) of pentafluoroiodobenzene **2** added to the solution.

atom. Both the ^1H and the ^{15}N chemical shift data were fitted²⁸ to a 1 : 1 binding model for the complex [7·8] affording (see ESI† for details) a stability constant for this complex in d_8 -toluene at 293 K of $1.44 \pm 0.24 \text{ M}^{-1}$.

For comparison purposes, we also evaluated the stability of the complex formed between pentafluoroiodobenzene **2** and 3-methoxyiodotriazole at the same level of theory. These calculations reveal (Fig. 4a, right) a complex with a halogen bond that is similar in geometry ($r(\text{N}\cdots\text{I}) = 2.808 \text{ \AA}$, $\angle \text{C-I}\cdots\text{N} = 179.0^\circ$) and a similar calculated enthalpy of complexation at 298 K ($-19.6 \text{ kJ mol}^{-1}$) to the complex formed between 3-methoxyiodotriazole

1. Analysis of a titration of **2** into a solution of 3-penthyloxyiodotriazole **8** in d_8 -toluene using a series of 700.1 MHz ^1H - ^{15}N HMBC experiments (Fig. 4c) reveal significant ^1H and ^{15}N chemical shift changes in the pyridine ring. These data were fitted²⁸ to a 1 : 1 binding model for the complex [2·8] affording a stability constant for this complex in d_8 -toluene at room temperature of $1.40 \pm 0.17 \text{ M}^{-1}$ (see ESI† for details).

It is clear from these data that the interactions between both **2** and **8** and **7** and **8** are not particularly strong in d_8 -toluene at 298 K. However, we reasoned that the reactivity observed between **1** and nucleophiles, such as an amino- or hydroxyiodotriazole, should allow us to construct rapidly a molecule that possessed both a pyridine ring and an iodotriazole. Such a molecule would be self-complementary and could, potentially, benefit from cooperative binding³¹ between the self-complementary recognition sites, thus forming a halogen-bonded dimer.

Accordingly, we designed compound **9a** (Fig. 5a), which was prepared in two steps, in high yield, from 5-(2-iodoethynyl)-1,3-bis(*tert*-butyl)benzene and 1-azido-2,3,4,5,6-pentafluorobenzene (see ESI† for details). We envisaged that **9a** might be able to form a halogen-bonded dimer in which the pyridine ring of one molecule interacts with the iodotriazole of a second molecule. This expectation was supported by calculations (Fig. 5b) at the TPSSH/def2-TZVP level of theory on compound **9b** – identical to **9a** save for the replacement of the *tert*-butyl groups by hydrogen atoms in the interests of computational efficiency.

A doubly halogen-bonded homodimeric structure was located that possessed approximate C_2 symmetry and in which the tetrafluoroaromatic rings in the two molecules of **9b** are rotated by around 120° with respect to each other. The two halogen bonds showed almost identical lengths and geometries ($r(\text{N}\cdots\text{I}) = 2.887 \text{ \AA}$; $\angle \text{C-I}\cdots\text{N} = 175.2^\circ$ and $r(\text{N}\cdots\text{I}) = 2.890 \text{ \AA}$; $\angle \text{C-I}\cdots\text{N} = 174.7^\circ$). The calculated enthalpy of dimerisation at 298 K for [9b·9b] is -30.6 kJ at this level of theory. Comparison of [9b·9b] with the corresponding monodentate interaction – as represented by the calculated structure of the complex formed between **1** and pyridine **10** at the same level of theory (Fig. 5b, left) – is instructive. The calculated geometry of the halogen bond in [1·10] ($r(\text{N}\cdots\text{I}) = 2.875 \text{ \AA}$; $\angle \text{C-I}\cdots\text{N} = 178.5^\circ$) reveals an interaction that is marginally shorter and more linear than those in [9b·9b]. The geometry of the [1·10] complex, together with the calculated enthalpy of dimerisation at 298 K (-17.9 kJ) – more than half the total for [9b·9b], suggested that a slight structural mismatch may be present in the [9b·9b] complex, preventing it from taking full advantage of both halogen bonds.

Single crystals of **9a**, suitable for analysis by X-ray diffraction, were grown by slow evaporation of a solution of **9a** in toluene. The solid-state structure of **9a** (Fig. 6) reveals antiparallel chains of molecules connected by halogen bonds between the pyridine of one molecule and the iodotriazole of the next. The geometry of these close contacts between the pyridine ring nitrogen atoms and the iodotriazole rings are suggestive of strong halogen bonds – $r(\text{N}\cdots\text{I}) = 2.767 \text{ \AA}$; $\angle \text{C-I}\cdots\text{N} = 176.5^\circ$.

Despite the absence of homodimers in the solid state structure of **9a**, we wished to characterise the stability of the [9a·9a] complex in solution. Accordingly, we performed a dilution experiment in order to assess the stability of the [9a·9a]



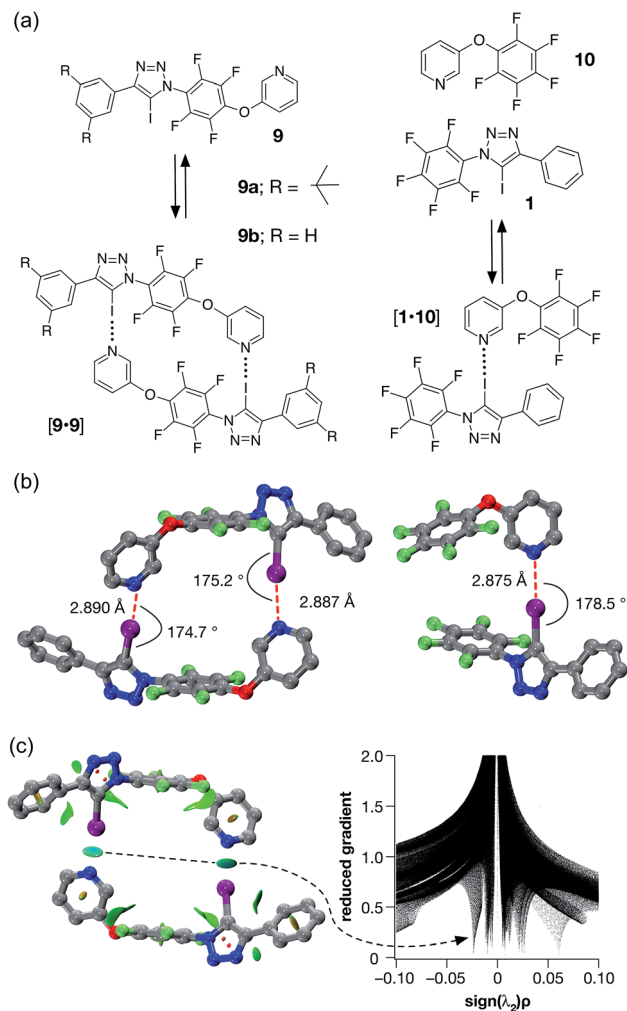


Fig. 5 (a) Iodotriazole **9b** provides a computational model for **9a**, which was prepared synthetically. Both iodotriazoles can dimerise through two halogen bonds to form homodimers. Complex **[1·10]** provides a computational model for the halogen bonds found in the dimers. (b) Comparison of the calculated structures (TPSSH/def2-TZVP) of the **[9b·9b]** dimer and the complex **[1·10]**. (c) Left: intermolecular interaction isosurfaces for the **[9b·9b]** dimer, generated by NCIPLOT,²⁶ for $s = 0.5$ and $-0.05 < \text{sign}(\lambda_2)\rho < 0.05$ (colour scale: attractive (blue) \rightarrow repulsive (red)). Right: plot of $\text{sign}(\lambda_2)\rho$ vs. reduced gradient highlighting the favourable interaction corresponding to the halogen bonds at $\text{sign}(\lambda_2)\rho \sim -0.035$. Atom colouring in molecular structures: C atoms = grey, N atoms = blue, O atoms = red, F atoms = light green, I atoms = purple. H atoms are omitted for clarity.

dimer in C_6D_6 solution. From a starting concentration of 200 mM, progressive dilution of a solution of **9a** resulted in chemical shift changes in the ^1H NMR spectrum for the resonances associated with the pyridine ring. These chemical shift changes were fitted²⁸ (see ESI† for details) to a dimerisation binding model, affording a stability constant for the **[9a·9a]** dimer in C_6D_6 of $3.4 \pm 0.7 \text{ M}^{-1}$. This value was disappointingly low and indicated that the **[9a·9a]** dimer benefits from little, if any, cooperativity³¹ arising from the connection of the halogen bond donor and acceptor within the same molecule.

In order to characterise the association of **9a** in C_6D_6 solution further, we turned to DOSY NMR experiments to assess the

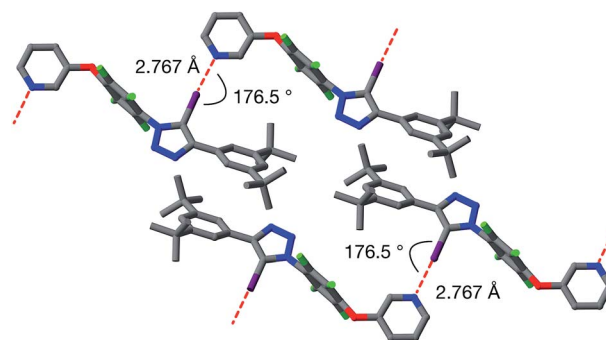


Fig. 6 Solid state structure of **9a** determined from single crystal X-ray diffraction data. Potential halogen bonds are marked in red ($r(\text{N}\cdots\text{I}) = 2.767 \text{ \AA}$; $\angle \text{C-I}\cdots\text{N} = 176.5^\circ$). Atom colouring: C atoms = grey, N atoms = blue, O atoms = red, F atoms = light green, I atoms = purple. Hydrogen atoms are omitted for clarity.

nature of the assembly formed. A series of DOSY experiments were performed (Fig. 7a) on sample **9a** in C_6D_6 , at concentrations ranging from 200 mM down to 1.0 mM. The diffusion coefficients of **9a** and that of the solvent were measured at each concentration. The observed variations of the diffusion coefficient of the solvent were interpreted as a variation in the viscosity of the sample.

Using this data, the diffusion coefficients of solute **9a** were corrected for viscosity changes using the diffusion coefficient

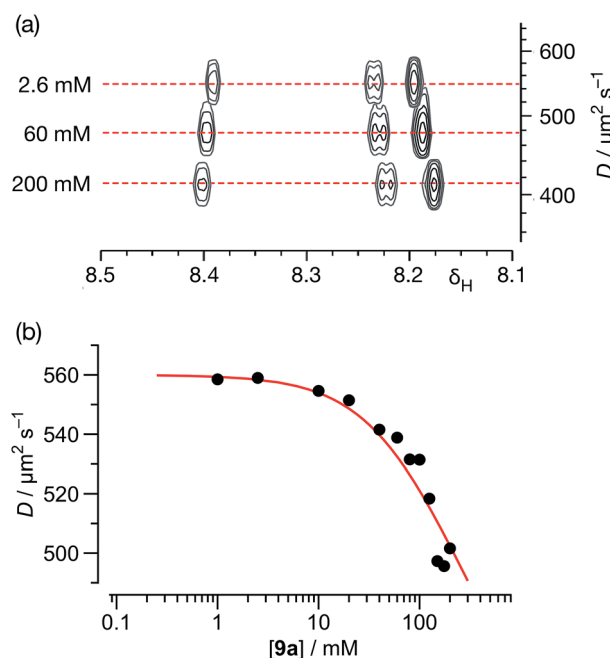


Fig. 7 (a) A series of 500.1 MHz ^1H DOSY NMR experiments, performed on solutions of **9a** in C_6D_6 at 298 K, illustrating the decrease in the measured diffusion coefficient (D) for **9a** with increasing concentration. (b) Variation of diffusion coefficients (D), corrected for viscosity, with respect to the concentration of **9a** in C_6D_6 solution at 298 K. The red line shows the best fit of these data to a monomer \rightleftharpoons dimer equilibrium model with a K_a for the **[9a·9a]** homodimer of $2.1 \pm 0.4 \text{ M}^{-1}$ (see ESI† for details).



for the solvent (C_6D_6) measured on the same samples. The variation of these corrected diffusion coefficients for **9a** across the concentration range studied were then fitted (Fig. 7b, see ESI† for further details) to a simple dimerisation model, using the model³² of Morris and co-workers for estimating the diffusion of the dimer. The results of this fitting procedure confirm the presence of dimer [**9a**·**9a**] in solution, and the estimated value of the stability constant for [**9a**·**9a**] at 298 K – $2.1 \pm 0.4 M^{-1}$ – was in good agreement with that obtained using the more conventional NMR titration method.

Conclusions

We have demonstrated that 1,4-diaryl-5-iodo-1,2,3-triazoles possess XB properties that make them reliable, neutral XB donors in organic solvents, able to interact with pyridine XB acceptors with efficiencies similar to those displayed by the iconic XB donor iodopentafluorobenzene. The synthetic versatility of these molecular scaffolds allowed the facile construction a self-complementary molecular module, incorporating both an XB donor and an XB acceptor, that was capable of forming a homodimer through the formation of two neutral XB interactions. The stability of this dimeric assembly was evaluated by means of DFT calculations and in C_6D_6 solutions using 1H NMR and DOSY experiments. The results of these investigations showed that, despite the increased stability of the dimeric assembly, full exploitation of the chelate effect could not be achieved as a result of a partial structural mismatch between the two monomeric units. Nevertheless, the application of chelate cooperativity represents a valid strategy to reinforce XB interactions between two neutral partners in solution and further studies directed towards the optimisation of the monomer design are currently underway in our laboratory.

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