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Methanesulfonyl-polarized halogen bonding enables strong halide recognition in an arylethynyl anion receptor†

Jessica A. Lohrman, Chun-Lin Deng, Trevor A. Shear, Lev N. Zakharov, Michael M. Haley * and Darren W. Johnson *

A 3,5-bis((2-iodophenyl)ethynyl)pyridinium scaffold was synthesized which introduces the use of methanesulfonyl withdrawing groups to polarize iodine halogen bonding units for anion binding. We investigate the capability of this receptor to bind halides in polar media, while further probing the structure–property relationship of this well-polarized yet under-explored halogen bonding system.

Halogen bonding (XB) forces have emerged in the field of supramolecular chemistry as an attractive alternative to more common reversible interactions (*e.g.*, hydrogen bonding).[1,2] Polarized halogen atoms generate an electron deficient σ-hole capable of forming a highly directional non-covalent bond with nucleophilic species at a near 180° bond angle (R–X···Y).[3] Recently, scaffolds that utilize σ-hole interactions including halogen,[4–11] chalcogen,[12–14] and pnictogen[15] bonding have brought exciting new developments to the field of anion recognition. Initially, halogen bonding had primarily been explored in crystal engineering[16,17] and in the gas phase;[18,19] however, further investigation of these interactions has focused on their efficacy in solution phase as well.[20–23] Halogen bonding interactions are comparable in strength to those of hydrogen bonding, and furthermore, they demonstrate a surprising resilience to interference from competitive, polar solvents.[24–26] These attributes have generated a growing interest in halogen bonding from the supramolecular community over the past 20 years.

The water-resilience of XB interactions is an attractive feature for reversible anion receptors with potential applications in biomedical,[27,28] environmental,[29,30] and agricultural areas,[31,32] where conventional anion sensors meet competition from polar protic media. Previously examined XB-containing scaffolds have utilized perfluoroaryl/alkyl,[33] pyridinium,[34,35] imidazolium,[36–38] and triazolium[39–41] functional groups as electron withdrawing sources to generate the electron deficient σ-hole binding site. While perfluorinated compounds have previously demonstrated significant XB polarization capabilities, they can limit host functionalization. *para*-Positioned withdrawing groups allow for facile functionalization of the receptor's binding moiety while still generating suitable XB donor sites.[42] The size of the σ-hole has been shown to directly correlate to the strength of the polarizing group.[43] To the best of our knowledge, our new scaffold ($\mathbf{1}^+$) is the first to introduce neutral methanesulfonyl polarizing groups for XB donors in anion receptors, which we found surprising given the Hammett sigma parameter for this functional group (σ_p = 0.72)[44] exceeds those of other neutral withdrawing groups such as trifluoromethyl (σ_p = 0.54),[44] suggesting sulfones should be very good at polarizing halogen bond donors as well.

Herein, we report a new bidentate anion receptor ($\mathbf{1}^+$, Scheme 1) with a 3,5-diethynylpyridinium central core coupled to two 2-iodo-5-(methanesulfonyl)phenyl units to yield a binding pocket with two XB donor recognition sites designed to bind and sense anionic guests reversibly. Host $\mathbf{1}^+$ integrates the methanesulfonyl-polarized XB recognition units within a highly conjugated arylethynyl backbone that can generate a spectroscopic response upon binding in solution.[45–47] In addition, the cationic *N*-methylpyridinium core generates a positive potential to the receptor for electrostatic binding and promotes solubility in more polar solvent systems. The computed electrostatic potential surface of $\mathbf{1}^+$ (Fig. 1) illustrates the partial positive charge enhancement from the methanesulfonyl groups on both iodines along the R–X axis and highlights the convergence of the two σ-holes within a single binding pocket with a determined $V_{s,max}$ of +78 kcal mol^{-1}. A computed electrostatic potential surface for the analogous pyridinium receptor without methanesulfonyl groups (instead substituted with H atoms in the *para*-position to the XB donors) demonstrated a $V_{s,max}$ of +74 kcal mol^{-1}. The addition of the sulfone groups in the *para*-position thus leads to a +4 kcal mol^{-1} increase. To assess methanesulfonyl's withdrawing potential in the absence of a charged pyridinium group, electrostatic

Department of Chemistry & Biochemistry and Materials Science Institute, University of Oregon, Eugene, OR 97403-1253, USA.
E-mail: haley@uoregon.edu, dwj@uoregon.edu

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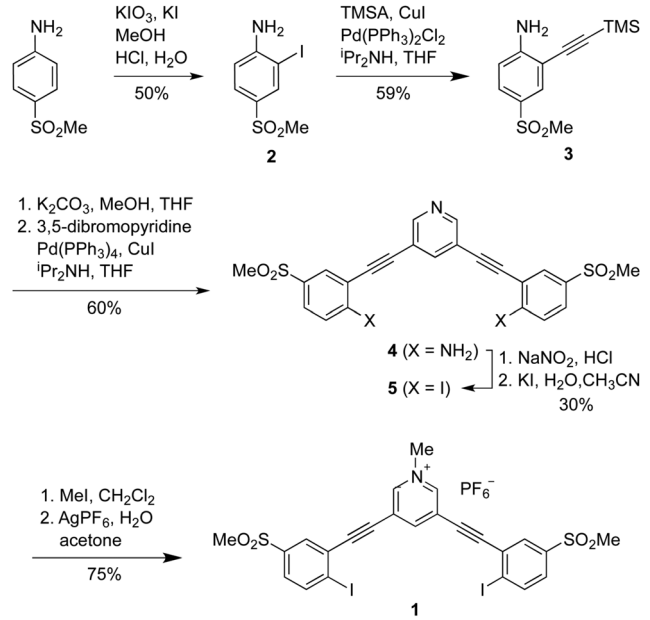

Scheme 1 Synthesis of XB anion recognition scaffold **1·PF$_6$**.

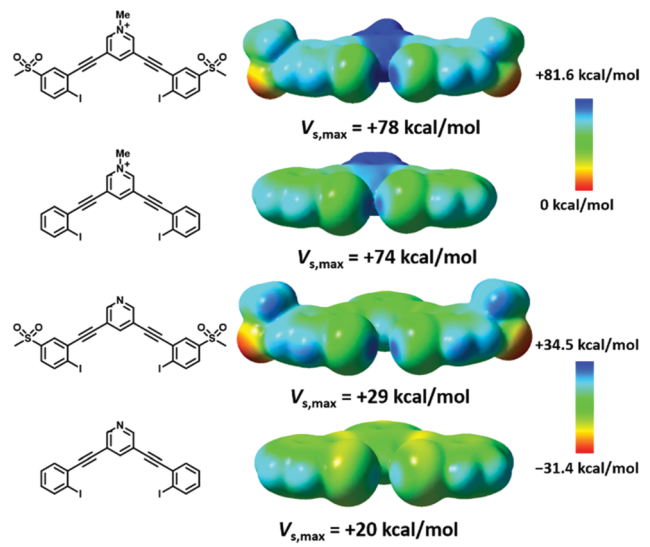

Fig. 1 Molecular electrostatic potential surfaces (isovalue = 0.001 a.u.) calculated at the B97-D3/Def2-TZVP level of theory for compounds **1**$^+$ and **5** along with congeners lacking methanesulfonyl substituents indicate areas of rich electron density (red) and depleted electron density (blue). $V_{s,max}$ values shown for the σ-holes.

potential surfaces were also determined for a non-methylated neutral variant of the receptor scaffold (Fig. 1). The addition of the sulfone groups leads to a +9 kcal mol^{-1} increase in $V_{s,max}$ at the site of the σ-hole, suggesting it is a suitable source of polarization for neutral XB donors as well.

The receptor scaffold was synthesized as shown in Scheme 1. 4-Methanesulfonylaniline[48] was iodinated with KI/KIO_3 to give **2**, which was then cross-coupled with (trimethylsilyl)acetylene (TMSA) to afford **3**.[49] Desilation in mildly basic MeOH and a second Sonogashira cross-coupling with 3,5-dibromopyridine yielded bis-aniline intermediate **4**. Diazotization followed by addition of KI furnished neutral **5**, which was alkylated with MeI to produce the charged pyridinium product **1**$^+$ with iodide (I^-) as the counterion (**1·I**). To assess binding affinities more accurately, the iodide was exchanged for the more labile hexafluorophosphate[7] (PF_6^-) to give **1·PF$_6$**.

Crystals of **1**$^+$ with the counteranions PF_6^-, I^-, Br^-, and Cl^- suitable for X-ray diffraction were grown *via* slow evaporation methods.[50] Interestingly, each anion afforded a structure that displayed profound conformational differences in the host with respect to how and where guest binding occurs. As previously seen with the arylethynyl-bisurea hydrogen bonding receptors, the halogen bonding 3,5-bis(2-iodophenyl)ethynylpyridinium scaffold can adopt each of the three possible binding conformations we have observed in this receptor class (W-, S-, and U-shaped) in the presence of each of the aforementioned anions.[45,51]

Crystals of **1·PF$_6$** were grown by slow evaporation of acetone (Fig. 2a). Crystal packing shows the receptor units stacked head-to-tail in off-set pairs in which PF_6^- sits in the pocket of one receptor and over the pyridinium core of a second receptor in a complementary position (Fig. 2b). Notably, the structure reveals the PF_6^- counterion does not halogen bond with the polarized iodine atoms, which are instead twisted out of the central binding pocket toward the external pyridinium, in a W-like conformation. Instead, an acetone molecule forms an XB interaction with one of the externally facing iodine atoms with a R–I···O bond length of 3.021(7) Å, resulting in a 14% reduction of the sum of van der Waals radii and a bond angle of 173.5°, which is near the ideal 180° angle for halogen bonds.[52] The second XB donor interacts with an adjacent receptor's sulfonyl oxygen to a weaker extent at a R–I···O distance of 3.106(6) Å at a 158.0° angle, showing a slight deviation from the idealized 180°.

The molecular structure of **1·Cl**, from crystals grown by evaporation of MeOH, demonstrates a change from the W-shaped structure seen in **1·PF$_6$** to an S-type conformation where one XB donor is pointing inward towards the binding pocket and the other pointed outwards towards the pyridinium. The structure reveals a 1 : 1 stoichiometric ratio of Cl^- to **1**$^+$ in the solid state with two different Cl^- binding modes. Two independent receptors are seen bridging a Cl^- between them through halogen bonds, resulting in a bis-monodentate binding external from the idealized binding pocket near the pyridinium at an R–I···Cl^- distance of 3.241(2) Å and a binding angle of 168.9° (Fig. 2c). A second Cl^- ion is found in the molecular plane forming a hydrogen bond with a pyridinium C(H) on the side opposite to the halogen bond at a C(H)···Cl^- distance of 3.405 Å, thus balancing the complex charge between the two receptors and two anions. The bond distance is seen to exhibit a 15% shortening between the van der Waals and ionic radii.[53] The second XB donor is twisted inward toward the binding pocket and below the molecular plane, forming the S-shape conformation which allows for a XB interaction with the sulfonyl oxygen of a second host **1·Cl** molecule (Fig. 2d) at a distance and angle of 3.146(1) Å and 176.5°, respectively. This interaction between the polarizing methanesulfonyl oxygen and

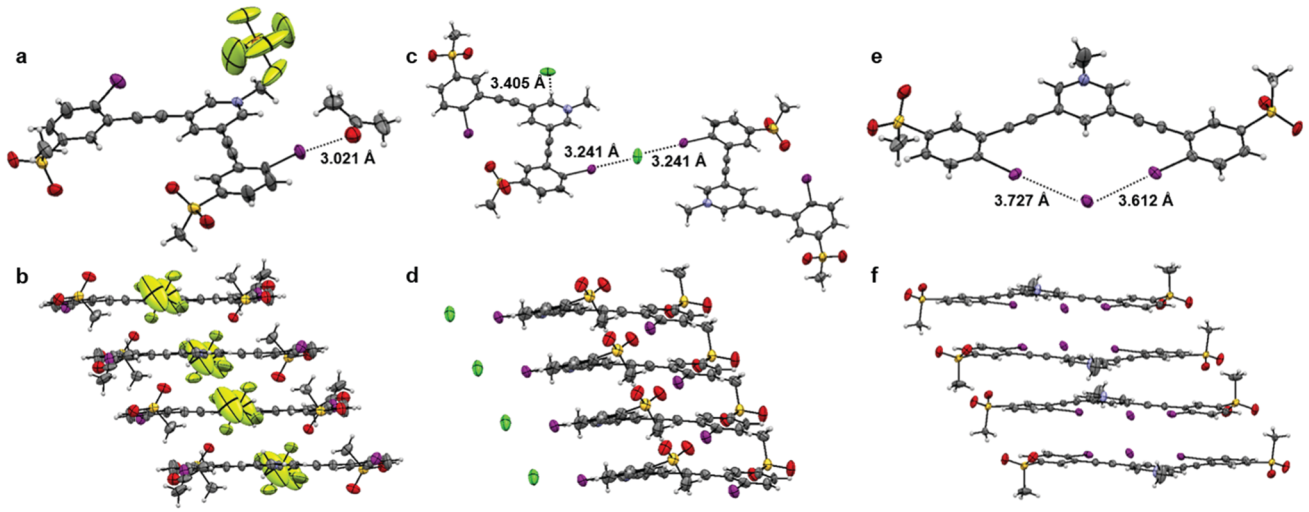

Fig. 2 ORTEP representation (50% probability ellipsoid) of the X-ray crystal structures and stacking of (a and b, W-conformation) **1·PF$_6$**, (c and d, S-conformation) **1·Cl**, and (e and f, U-conformation) **1·I**.

the XB donor shows the susceptibility for individual host molecules to interact with one another to form dimerized complexes. An almost identical binding mode was observed in the crystal structure of **1·Br**. While the adopted conformation remains the same, the Br^- is held at a distance and angle of 3.407(2) Å and 167.2°, respectively, resulting in a 14% reduction of the sum of the ionic and van der Waals radii (Fig. S4, ESI†).[53]

Complex **1·I** demonstrates another notable change in the structural conformation to the U-shape, producing a bidentate binding pocket (Fig. 2e) within a 1 : 1 host : iodide complex. The complex again packs in a head-to-tail paired pattern, with receptors slightly offset from one another (Fig. 2f). Both XB donor units are pointing inward toward the central binding pocket, coordinating a lone I^- with a high degree of planarity. The I^- anion is held in the central pocket at I···I^- distances of 3.727(6) and 3.612(8) Å, a shortening in the sum of the ionic and van der Waals radii of 11% and 14%, respectively.[53] While the lengthening of the interaction distance typically denotes weaker binding, the second XB interaction provides an additional stabilizing force in binding I^- over the monodentate Cl^- bound system. Additionally, the R–I···I^- bond angles are 172.2° and 174.5°, further confirming the highly directional XB interaction elicited from the σ-hole created by the *p*-methanesulfonyl substituents.

The strength of the anion binding interactions of **1·PF$_6$** with a range of halides was determined by UV-vis spectroscopy. UV-vis titrations were performed with 30 μM solutions of **1·PF$_6$** in DMSO–1.5 ± 0.5 wt% water (see ESI†), with the anions introduced as tetrabutylammonium salts. DMSO was chosen in order to assess binding in a competitive solvent and as a stepping stone for future binding studies in water mixtures. Association constants (K_a) were determined by fitting the change in the absorbance to a 1 : 1 binding model using Bindfit.[54] As chloride, bromide, or iodide were titrated into the solution, the absorption band at 300 nm decreased and the bands at 380 and 430 nm increased (Fig. S3, ESI†), generating an isosbestic point at 345 nm. Despite the competitive nature of the polar solvent, and possible competitive halogen bonding between the C–I donor and sulfonyl oxygen, receptor **1·PF$_6$** binds Cl^-, Br^-, and I^- with K_a values of 940, 690, and 3900 M^{-1}, respectively (Table S1, ESI†).

As expected from the bidentate binding shown in the solid-state, **1·PF$_6$** exhibited the greatest affinity for I^- over the other halide anions, with a K_a three times larger than that of the more basic Cl^- guest. This preference is attributed to the size of the binding pocket coupled with the constraints of the near-180° XB bonding angle. Crystal structures for **1·Cl** and **1·Br** demonstrated monodentate binding of the smaller Cl^- and Br^- anions outside of the pocket. To effectively bind inside the pocket would require a greater deviation from the 180° bonding angle thus generating repulsion from the electron belt surrounding the σ-hole. The larger sized ionic radius of I^- allows the host to better coordinate it using both XB donors while still maintaining nearly 180° angles from both of the R–I···X^- positions, making I^- clearly the best fit for the binding pocket.[55] Overall, given the pocket dimensions and required bite angles for the target anion to XB donors, I^- is the most effectively coordinated between the two XB donors in the scaffold. These structural features as well as possible solvation effects result in the observed binding preferences.

In conclusion, we have synthesized a new ditopic 3,5-bis((2-iodophenyl)ethynyl)pyridinium receptor $\mathbf{1}^+$ with XB anion recognition sites that showcase the utility of the electron-withdrawing methanesulfonyl group to polarize XB donors. Crystal structures revealed both an external monodentate and internal bidentate binding model for Cl^- and I^-, respectively. These differences in binding modes can be attributed to the receptor's rigid architecture and large pocket size coupled with the highly directional 180° XB interactions that make the binding pocket more suitable for the larger I^- anion. This is supported by binding data that revealed an inherent selectivity for I^- over the more basic, yet smaller Cl^- and Br^- anions. These attributes suggest the XB-based anion-binding receptor **1·PF$_6$** will open new avenues for anion detection in highly competitive media.

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Conflicts of interest

There are no conflicts to declare.

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