Evidence for Halogen Bond Covalency in Acyclic and Interlocked Halogen-Bonding Receptor Anion Recognition

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ABSTRACT: The synthesis and anion binding properties of novel halogen-bonding (XB) bis-iodotriazole-pyridinium-containing acyclic and [2]catenane anion host systems are described. The XB acyclic receptor displays selectivity for acetate over halides with enhanced anion recognition properties compared to the analogous hydrogen-bonding (HB) acyclic receptor. A reversal in halide selectivity is observed in the XB [2]catenane, in comparison to the acyclic XB receptor, due to the interlocked host’s unique three-dimensional binding cavity, and no binding is observed for oxoanions. Notable halide anion association constant values determined for the [2]catenane in competitive organic–aqueous solvent mixtures demonstrate considerable enhancement of anion recognition as compared to the HB catenane analogue. X-ray crystallographic analysis of a series of halide catenane complexes reveal strong XB interactions in the solid state. These interactions were studied using Cl and Br K-edge X-ray Absorption Spectroscopy (XAS) indicating intense pre-edge features characteristic of charge transfer from the halide to its bonding partner (σ_{Br−X} ← X1s), and providing a direct measure of the degree of covalency in the halogen bond(s). The data reveal that the degree of covalency is similar to that which is observed in transition metal coordinate covalent bonds. These results are supported by DFT results, which correlate well with the experimental data.

INTRODUCTION

Halogen bonding (XB) refers to the attractive noncovalent interaction arising between the electron-deficient σ-hole of a polarized halogen atom, such as bromine or iodine, and an electron-rich Lewis base. 1−4 While XB has been well-developed in the context of solid-state crystal engineering 5,6−8 and in the design of functional materials, 9,10−12 the utilization of XB in solution is relatively underexploited with seminal applications in the areas of reactivity, 16,17 catalysis, 19,20 self-assembly, 21,22 transport, 23 and medicinal chemistry only recently being reported. 24 Anion supramolecular chemistry has experienced rapid growth over the past few decades stimulated by the crucial roles that anions play in many chemical, biological, and environmental processes. 25−37 While supramolecular interactions such as hydrogen bonding (HB) have dominated the field of anion coordination, recognition, and transport, 21,22,38−51 halogen bonding (XB) has only recently begun to emerge as a powerful alternative interaction capable of coordinating anions in competitive solvent media. 21,52−60 The strength of XB in solution has been demonstrated to be comparable to HB, 53 while the stringent linear directionality of XB and pH-independence is advantageous for the design of selective receptors for anions with particular geometries. It is noteworthy that the relatively few examples of acyclic and macrocyclic XB anion receptors reported to date all display significantly contrasting anion recognition behavior compared to HB analogues. Furthermore, rotaxane interlocked host structural frameworks containing convergent XB triazolium donor groups have been demonstrated to selectively recognize and sense halide anions in highly competitive aqueous media. 59,61,62

Herein we report a bis-iodotriazole-pyridinium motif, incorporated within both an acyclic and a novel catenane-based receptor, capable of binding anions via two convergent R−I−X− halogen bonds. The [2]catenane host structural framework, prepared via chloride anion templation, is demonstrated to bind halide anions with impressive selectivity in competitive organic–aqueous solvent mixtures.

In addition, we report for the first time Cl and Br K-edge XAS analysis of the interactions observed in these receptors with anions, revealing significant charge transfer from the halides to the iodonitroazole XB donors, and the first measure of covalency in these systems. These data allow for the first quantitative evaluation of the degree of covalency in halogen-bonded species. Pre-edge features in the XAS spectra are modeled and supplemented with DFT calculations and TDDFT simulations of the XAS data which reproduce the experimentally observed pre-edge features.

RESULTS AND DISCUSSION

Acyclic Receptors. Synthesis. The synthesis of the acyclic bis-triazolyl-pyridinium receptors is shown in Scheme 1. 3,5-
Diethylnpyridine 1 was prepared by deprotecting 3,5-bis-(trimethylsilyl)ethyl) pyridine, with KOH in methanol, while azides 2a–c were prepared via a modification of a literature procedure. The bidentate bis-triazole-pyridinium acyclic precursor, 3a, was prepared via a CuAAC “click” reaction between 1 and 2.2 equiv of hexylazide, prepared in situ from the corresponding bromide. The bidentate bis-iodotriazole-pyridinium acyclic receptor precursors, 3b and 3c, were prepared using a modification of a CuAAC “click” reaction literature procedure using various azides. Subsequent methylation with CH₃I afforded acyclic receptors 4a–c-I which were characterized by high-resolution ESI mass spectrometry, ¹H, ¹³C NMR, and ¹⁹F as well as ³¹P NMR spectroscopy where appropriate. Acyclic receptors 4a and, for solubility reasons, 4b were anion exchanged to their corresponding noncoordinating hexafluorophosphate salts in preparation for anion titration experiments, while 4c-X was used in X-ray crystallographic structure analysis (X = Cl⁻) and X-ray absorption spectroscopic analysis (X = Cl⁻, Br⁻, PF₆⁻).

¹H NMR Anion Recognition Studies. The anion recognition properties of acyclic receptors 4a-PF₆ and 4b-PF₆ were investigated using ¹H NMR anion titration experiments by adding aliquots of anions as their tetrabutylammonium salts to solutions of the receptor. Initial titrations with TBA-Cl in acetone-d₆ determined 1:1 stoichiometric association constants of >10⁴ M⁻¹ for both receptors. Consequently, titrations were repeated in the more competitive CD₃CN affording the data in Table 1 for HB receptor 4a-PF₆; however, association constants for XB receptor 4b-PF₆ were still >10⁴ M⁻¹. As a result, titrations for 4b-PF₆ were performed in the even more competitive solvent DMSO-d₆ indicating the superior anion-binding capability of the XB receptor. Addition of anions typically caused downfield perturbations of 4a-PF₆ triazolate proton d, directly involved in anion coordination, and the 4b-PF₆ pyridinium proton c incumbent on anion binding (Figure 1). WinEQNMR2 analysis of the titration data determined the 1:1 stoichiometric association constants shown in Table 1.

The anion binding selectivity of prototriazole receptor 4a-PF₆ follows anion basicity trends, as would be expected for an anion receptor in an aprotic solvent, with the larger halides complexed more weakly than chloride.

Similarly, for the XB acyclic receptor 4b-PF₆ selectivity follows anion basicity trends for the halides, with OAc⁻ being the most strongly associated anion; the association constant, Kᵢ, is 2.5 times larger in magnitude than chloride. Interestingly, no binding was observed for H₂PO₄⁻ and NO₃⁻, while SO₄²⁻ was bound at >10⁴ M⁻¹, presumably due to the greater negative charge. To the best of our knowledge, this is only the second example of an XB oxoanion-selective anion receptor.

Figure 1. Anion binding titrations with 4b-PF₆ following proton c in DMSO-d₆: experimental titration data (circles) with fitted binding isotherms indicated as lines (298 K).
using CH$_3$I, and thereafter, the vinyl-appended bis-iodotriazole-pyridinium-containing macrocycle precursor was anion exchanged to the corresponding chloride salt by repeated washing with NH$_4$Cl(aq) to afford 7·Cl.

Synthesis of [2]catenane 9·Cl was accomplished using chloride templation via a ring-closing metathesis strategy. An initial interpenetrated assembly was prepared by mixing equimolar amounts of macrocycle 8·71 with 7·Cl in dry CH$_2$Cl$_2$. Addition of Grubbs’ II ring-closing metathesis catalyst afforded the [2]catenane in 41% yield following purification by preparative thin layer chromatography.

Catenane 9·Cl was characterized by $^1$H, $^{13}$C and 2D COSY NMR experiments and high-resolution mass spectrometry. Notable shifts in the pyridinium and isophthalamide protons c and 3, respectively, were observed in addition to the splitting and upfield perturbation of the hydroquinone protons 5 and 6 consistent with inter-ring donor–acceptor interactions between the electron-rich hydroquinone groups and the electron-deficient pyridinium group, which confirms the interlocked nature of the catenane (Figure 3). Further evidence for the interlocking of the two macrocyclic components was obtained by 2D ROESY NMR which revealed through-space interactions including those between hydroquinone and pyridinium protons of the two macrocycles (see Supporting Information (SI)).

The chloride anion template was removed by repeated washing with NH$_4$PF$_6$(aq) to afford 9·PF$_6$ for anion recognition studies and was similarly fully characterized (Scheme 3).

$^1$H NMR Anion Recognition Studies. Association constants for the formation of 1:1 stoichiometric host/guest complexes of catenane 9·PF$_6$ with various anions were determined using $^1$H NMR titration experiments, monitoring shifts in the internal isophthalamide proton 3 upon addition of aliquots of anions added as their tetrabutylammonium salts (Figure 4). A preliminary titration of 9·PF$_6$ with TBA·Cl in 1:1 CDCl$_3$/$^4$D$_2$OD resulted in an association constant $K_a > 10^4$ M$^{-1}$, much greater than the value obtained for the previously reported analogous prototriazole-containing HB catenane (Table 2). Consequently, all subsequent titrations were conducted in the aqueous solvent mixture 10:45:45 D$_2$O/
CDCl₃/CD3OD, which is more competitive. The association constants shown in Table 2 were determined by WinEQNMR268 analysis of the titration data.

Very strong binding of the halides is observed for 9·PF₆ in this aqueous solvent mixture. Indeed, association constants determined for Br⁻ and I⁻ are both >10⁴ m⁻¹ which highlights the fact that binding is dramatically enhanced in the XB catenane when compared to the HB catenane analogue.⁷³

Furthermore, in contrast, the XB host demonstrates a preference for the larger halides despite the voluminous iodine XB donors. Indeed, a reversal in selectivity for the halides is observed for 9·PF₆ in comparison to the acyclic receptor 4b·PF₆ due to the interlocked host’s unique three-dimensional binding cavity.

Despite the OAc⁻ selectivity observed for the acyclic XB receptor 4b·PF₆, no evidence for oxoanion binding was discerned for OAc⁻ or H₂PO₄⁻ for the XB catenane 9·PF₆. This may be attributed to the oxoanions’ large size and unfavorable geometry to bind and be encapsulated by the unique interlocked catenane host cavity (vide infra).

**X-ray Crystallography.** Crystals suitable for X-ray diffraction structural analysis were obtained for catenane 9⁺ with chloride, bromide, iodide, dihydrogen phosphate, and sulfate counter-anions. All structures crystallize in P1̅ with 1:1 complexes obtained for chloride (Figure 5), bromide, and iodide, which are isomorphous, and 2:1 complexes were obtained for dihydrogen phosphate and sulfate, which in turn are isomorphous. While both hydrogen and halogen bonds are observed between the host 9⁺ and the anionic guest, the catenane curiously adopts an "open" conformation in the solid state rather than completely encapsulating the anion; presumably this is due to the large iodo-substituted triazole and the most energetically favorable conformation for crystallization. While a varying degree of disorder for the polyether ends of the macrocycles is observed in each complex, it does not affect the anion-binding cavity of the catenane and is omitted for clarity here.

Examining the halide anion structures, strong halogen bonds are observed indicated by bond lengths significantly shorter than the sum of the van der Waals radii and are summarized in Table 3.⁷⁰

Table 2. Association Constants, $K_a$ (m⁻¹)⁴ for 9·PF₆

| anion     | HB catenane²ₓᵧ | 9·PF₆ |
|-----------|----------------|-------|
| Cl⁻       | 680(20)        | 1850(224) |
| Br⁻       | 630(50)        | >10⁴   |
| I⁻        | 510(10)        | >10⁴   |
| OAc⁻      | "             | NB⁴    |
| H₂PO₄⁻    | 49(4)          | NB⁴    |

"Calculated using WinEQA²ₓᵧNmR2⁶⁸ monitoring the internal pyridinium proton; estimated standard errors given in parentheses (293 K, solvent: 10:45:45 D₂O/CDCl/CD₃OD). ²¹:1 CDCl₃/CD₃OD, 298 K.

"Not conducted. "NB: No binding: Δδ < 0.07 ppm.

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The structure of (9)₂·SO₄ (Figure 6) clearly shows the SO₄²⁻ anion situated between two hosts rather than being encapsulated in the cavity, as it is too large to penetrate the interlocked binding pocket. Furthermore, the anion is on the inversion center in the asymmetric unit allowing it to adopt one of two symmetry-related orientations (see Supporting Information). Two independent S=O···I=C halogen bonds are formed rather than bifurcated halogen bonds from one O to each of the iodine XB donors. The dihydrogen phosphate structure (see Supporting Information), while of lower quality,
shows a very similar structure; i.e., the large oxoanion binds outside of the cavity.

**Donor K-edge X-ray Absorption Spectroscopy.** To establish the nature of the interactions between the halide (Cl\(^{-}\)/Br\(^{-}\)) donor and the iodine acceptor, we have exploited Cl and Br K-edge X-ray Absorption Spectroscopy (XAS). It has been clearly established that Cl K-edge XAS can be used to evaluate the degree of delocalization in chloro-metal bonds.\(^{74-76}\) In such cases, a pre-edge feature is observed in the spectrum that formally corresponds to excitation of a Cl\(^1s\) electron to empty valence d-orbitals on the transition metal acceptor. The intensity of such transitions is directly proportional to the amount of Cl\(^3p\) character mixed into these empty metal acceptor orbitals, providing a convenient method of obtaining a quantitative measure of the degree of mixing between the chloro donor and the metal acceptor. This methodology is equally applicable in cases where nonmetal acceptors are under investigation, although to our knowledge it has not been applied to other types of donor–acceptor systems.

Within the context of this work, one would expect a halide ion (Cl\(^{-}\) and/or Br\(^{-}\)) to exhibit simple K-edge XANES spectra with no pre-edge features. Electric-dipole allowed Cl\(^3p\) ← Cl\(^1s\) (or Br\(^4p\) ← Br\(^1s\)) transitions would not be observed since these valence p-states are filled (n\(^s^2n^p_6\)). Covalent delocalization of the filled Cl\(^3p\) orbital with an empty acceptor orbital (e.g., via hydrogen or halogen bonding) would result in the possibility of a new allowed transition corresponding to charge transfer from the chloride to its bonding partner (σ\(^\text{AX}\) ← Cl\(^{-}\)). Given that the intensity of such transitions is directly proportional to the amount of Cl\(^3p\) in the final state wave function, σ\(^\text{AX}←\text{Cl}^{-}\), the intensity of any observable pre-edge feature provides us a direct measure of the degree of covalency in the halogen bond.

Chlorine K-edge XAS data were obtained for a series of donor–acceptor complexes at beamline 4-3 at the Stanford Synchrotron Radiation Lightsource. The near-edge spectra for 4·Cl and 9·Cl (see Figure 7) each exhibit an intense pre-edge feature that is not present in ionic chloride salts. The presence of this intense feature can only result from charge transfer between the chloro donor and its partners.\(^{74,76}\) Fitting of the pre-edge and edge features allows experimental quantification of the degree of charge donation in each of these species (Table 4).\(^{77-79}\) These results clearly demonstrate charge transfer from the donor via halogen bonding in 4·Cl, and a combination of
The magnitude of charge donation/halogen bonding interaction is possible, we consider when interpreting these results. These XAS data, however, allow us to quantify with previous reports that charge transfer is an important factor in XB bonds. The data indicate the presence of a low-energy shoulder, indicating a pre-edge feature to that observed in the Cl K-edge data. We note that the pre-edge shoulder is larger for the X-bonded systems as compared to the H-bonded system (10 Br). However, quantitative comparisons between the different X-bonded systems are inconclusive due to large errors in the associated fits (see section S6).

**Computational.** To further explore the details of the covalent nature of X-bonding in these systems, we performed a series of density functional calculations, and TD-DFT simulations of the XAS data. Optimized geometries (Table 5) are in good agreement with experimental data. For example, the r_{CI-I} in 4Cl are calculated to be 3.18(3) Å, which compare favorably with that observed crystallographically (3.120(2)–3.195(2) Å). TD-DFT simulations of the Cl K- and Br K-edge XAS data reproduce the low energy pre-edge feature assigned to the σ_{AX-X} → X_{CI} transition in each case. The relevant σ_{AX-X} orbitals for 11Cl and 4Cl are shown in Figure 8. In each case, these antibonding acceptor orbitals reflect the covalent nature of the X → I bond(s). Two relevant acceptor orbitals are present in 4Cl since two X → I interactions are possible; the splitting of these two orbitals in 4Cl is small (~0.3 eV), and thus the resulting transitions cannot be resolved experimentally.

[XB and HB interactions in 9-Cl. For comparison, data were also collected on the H-bonding analogue of 4Cl (10Cl) as well as a simple X-bonded adduct 5-iodo-3-methyl-1,4-dioctyl-1H-1,2,3-triazol-3-ium chloride (11Cl) (Figure 7; see SI for the synthesis of 10Cl and 11Cl). These data provide a measure of the total donation from the chloride anion to all of its bonding partners, and thus the number of interactions must be considered when interpreting these results.

It is apparent that, with a chloride donor, X-bonding interactions are significantly more covalent in character than comparable H-bonding interactions. These data are consistent with previous reports that charge transfer is an important factor in XB bonds. These XAS data, however, allow us to quantify the degree of covalency in the XB bond and thus compare the degree of charge transfer in different systems, which to our knowledge is unprecedented. In 11Cl, where only a single halogen bonding interaction is possible, we find that the degree of donation is consistent with ~6% charge transfer to the iodinated triazole acceptor. The magnitude of charge donation/covalent character in the XB bond is notable in that it is a similar magnitude to that which is commonly observed in transition metal complexes, where covalent contributions are considered to be of great importance in defining chemical properties. For example, in simple divalent metal chlorides ([MCl^2+], where M = Cu, Ni, Co, Fe), bond covalencies have been determined to range from 6% to 9%.

In the bis-triazole 4-Cl, the total charge donation from the halide ion almost doubles to ~11%, which implies that each of the halogen bonds are independent from each other and additive. By contrast, replacement of the iodine acceptors for protons in the bis-triazole (10-Cl) leads to an almost complete loss of intensity in the Cl K-edge XAS pre-edge feature, reflecting very poor charge donation through H-bonding in this system.

Data for the catenane 9-Cl, where both H- and X-bonds are present, indicate that charge donation from the chloride anion decreases substantially (as compared to 4-Cl). This presumably reflects weakened halogen bonding due to competition with amide H-bond interactions.

Qualitatively similar data were obtained for the bromide donor complexes 11Br, 4Br, 10Br, and 9Br (see Figure 7). Unfortunately, lifetime broadening at the higher energy Br K-edge, as well as smaller energy separation between features, leads to poorer resolution of the pre-edge features of interest. The data indicate the presence of a low-energy shoulder, indicating a pre-edge feature to that observed in the Cl K-edge data. We note that the pre-edge shoulder is larger for the X-bonded systems as compared to the H-bonded system (10 Br). However, quantitative comparisons between the different X-bonded systems are inconclusive due to large errors in the associated fits (see section S6).

**Table 4. Experimentally Obtained Pre-edge Intensities and the Corresponding % Charge Donation of Chloride Donor Complexes**

| compd | Cl− ·· X | Cl− ·· H | pre-edge energy (eV) | normalized pre-edge intensity | total % Cl_{CI-p} |
|-------|---------|----------|---------------------|-----------------------------|------------------|
| 11-Cl | 1       | 2        | 2816.9(1)           | 0.90(5)                     | 6.4(2.1)         |
| 4-Cl  | 2       | 2        | 2817.3(1)           | 1.59(4)                     | 11.3(2.0)        |
| 10-Cl | 2       | 2        | 2816.2(2)           | 0.13(3)                     | 0.9(1.9)         |
| 9-Cl  | 2       | 2        | 2818.4(2)           | 1.00(6)                     | 7.1(2.3)         |

*Calculated errors (parentheses) are obtained from statistical distribution of fit results for >50 fits for each data set. See section S1 for further details. Total donation is calculated in comparison with Cl K-edge XAS data on a CuCl_{Cl−} reference, errors include an estimate of the error in charge transfer of this reference compound.

**Table 5. DFT-Calculated Parameters Obtained for Halide Adducts**

| distances (Å) | X−I | X−H | average bond | total % Cl_{CI-p} in σ_{AX-X} | 10^{3}f_{osc} for σ_{AX-X} → X_{CI} |
|---------------|-----|-----|--------------|-------------------------------|----------------------------------|
| 11-Cl         | 3.00| −   | 6.9          | 1.292                         |                                  |
| 4-Cl          | 3.18| −   | 7.7          | 1.862                         |                                  |
| 10-Cl         | 2.54| 1.1  | 0.213        |                               |                                  |
| 9-Cl          | 2.62| −   | 6.1          | 0.945                         |                                  |
| 11Br          | 3.21| −   | 6.4          | 0.286                         |                                  |
| 4Br           | 3.40| −   | 8.0          | 0.045                         |                                  |
| 10Br          | 2.76| 1.7  | 5.6          | −                             |                                  |

*All calculated values are for fully optimized structures at the B3LYP/def2-TZVP+ZORA level of theory.
The bromide adducts show similar trends as those observed in the chlorides; the TDDFT simulations are also in reasonable agreement with the Br K-edge experimental data. The calculated degree of charge donation is very similar between the two halides, suggesting that the degree of covalent mixing is similar in both cases. Investigations are currently underway to further evaluate the specific factors that affect the covalency of these XB interactions and the resultant binding affinities in the catenanes.

**CONCLUSION**

In conclusion, the XB bis-iodotriazole-pyridinium motif is shown to be a potent anion-coordinating motif in competitive aqueous media, especially when incorporated into a [2]-catenane host structural framework. The acyclic XB receptor displays a marked enhancement in anion recognition over the HB analogue and the first instance of acetate selectivity. Moreover, the XB [2]catenane notably exhibits further augmentation of anion recognition ability over its HB analogue, selectively binding halides very strongly in competitive aqueous media with no binding of oxoanions which is the reverse acetate selectivity trend of the acyclic XB receptor. This suggests the NB catenane’s unique interlocked host binding cavity is of complementary size and shape for halides, whereas the oxoanions are too large and are of the wrong geometry for encapsulation.

Single crystal X-ray structural analysis provided solid-state evidence for the association of anions with the [2]catenane host framework where halide anions are able to penetrate the cavity of the [2]catenane. By contrast oxoanions (H2PO4\(^-\) and SO4\(^{2-}\)) are found outside the three-dimensional binding pocket in support of the solution-state anion recognition binding observations.

Cl and Br K-edge XAS revealed the presence of intense pre-edge features characteristic of charge transfer between the halide donor and the XB acceptor. Quantitative fitting of these pre-edge features provided a direct measure of the degree of covalency in the halogen bonding interaction, which is comparable to that observed in transition metal complexes. Furthermore, we confirm that perpendicular XB interactions are independent and additive, but that the degree of XB covalency can be mitigated through the presence of HB donors. These conclusions are well supported and substantiated by TDDFT simulations of the XAS data, which indicate that the degree of covalency is essentially the same for both Cl\(^-\) and Br\(^-\) donors.

Most importantly, these results offer the first evidence of this kind for covalency\(^5\) in halogen bonds of anion receptors with halide anions. Furthermore, the presence of both XB and HB donors in the [2]catenane host framework provides interesting insight into the interplay between these two competing interactions in a single anion receptor system.

**ASSOCIATED CONTENT**

5 Supporting Information

Experimental procedures and spectroscopic data for all new compounds, titration protocol and data, full crystallographic data, XAS data and fitting details, and DFT and TDDFT computational details are available. This material is available free of charge via the Internet at http://pubs.acs.org.
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