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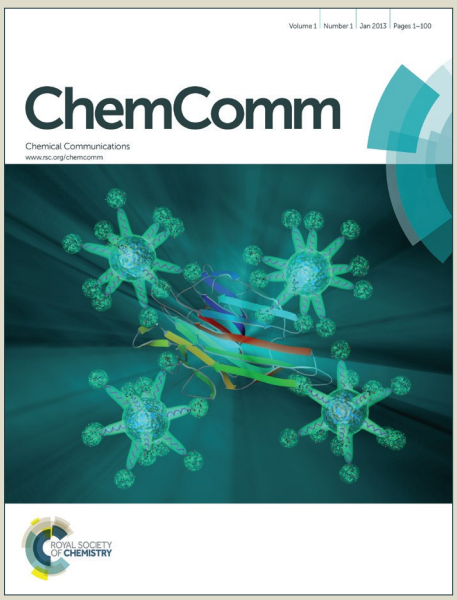

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Harnessing solid-state packing for selective detection of chloride in a macrocyclic anionophore

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We report the synthesis of an inherently fluorescent macrocyclic receptor for chloride. The use of a disulphide tether provides for an excellent yield in the macrocyclization step. This compound binds chloride in the solution and solid state, and whle unstable over time in aqueous solution, shows a selective response toward chloride over other anions in the solid state due to intermolecular interactions between fluorophore backbones. Surprisingly, the optoelectronic response to anions differs in solution and the films, with a distinct colorimetric response observed only in the film.

Classically, macrocyclic scaffolds have been used in a variety of applications, ranging from pharmaceuticals to synthetic receptors and materials for organic electronics. Macrocycles in drug design have been extensively employed due to their conformational rigidity, with their locked structure yielding a higher theoretical ligand efficiency.[1–4] Synthesis of macrocycles is a difficult task, with extensive synthetic techniques utilized to prepare these compounds in good yield over competing oligomer formation.[5–7] These methods can utilize either high dilution/pseudo-high dilution, pre-organization, or templation by a suitable guest. There are a number of reactions that lend themselves to macrocycle formation under thermodynamic control, such as ring-closing metathesis and disulphide bond formation. These have benefits over other methods such as peptide bond formation as the symmetric nature of the bond allows facile synthesis of the cycle.

Preorganization represents an important tool in macrocyclization reactions, wherein the entropic cost of cyclization is alleviated by organizing the scaffold into a curved form to allow macrocyclization to occur preferentially.[8] There are salient examples of high-yielding macrocyclic hosts prepared through exceedingly simple synthetic techniques;[9] in many cases these scaffolds are, by necessity, quite symmetric, and the formation of these scaffolds is thus sensitive to specific functionality present. Such simple, direct macrocyclization routes represent an elegant example of synthetic design and the potential for complex products arising from structurally simple starting materials. A related route to high-yield macrocyclization employs a final ring closing step run under thermodynamic control, such as that used in ring-closing metathesis.[5,8] Such routes allow for modular design that accommodates varying functionality, including electron-rich and electron-poor regions, into the scaffold design to tune physical properties, host-guest chemistry, etc.

In our group we have extensively utilized a 1,3-bis(2-anilinoethynyl)arene scaffold as an effective, tunable fluorescent host for a variety of anionic analytes.[10–21] We found that this backbone provides a facile receptor for the halides, phosphate, sulphate, and nitrate in our examinations of conjugated hosts for biologically and environmentally relevant analytes. It was posited that use of a pre-organized macrocyclic receptor such as one containing a disulphide tether, as in **1**, or an alkoxy-aryl tether, such as **2**, with our scaffold could pay some of the entropic costs of the binding event, creating a much more favourable association (Fig. 1). Although we successfully obtained such a system previously

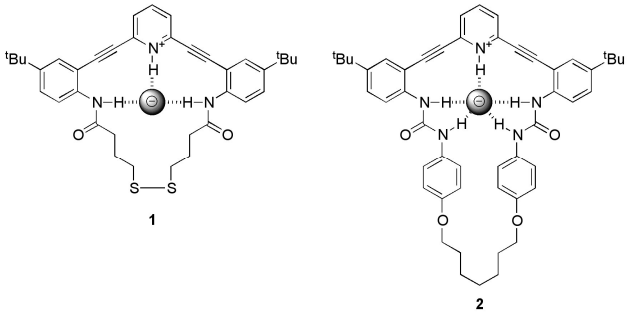

Fig. 1 Comparison of disulphide macrocycle **1** explored in this study and bisurea macrocycle **2** previously reported.

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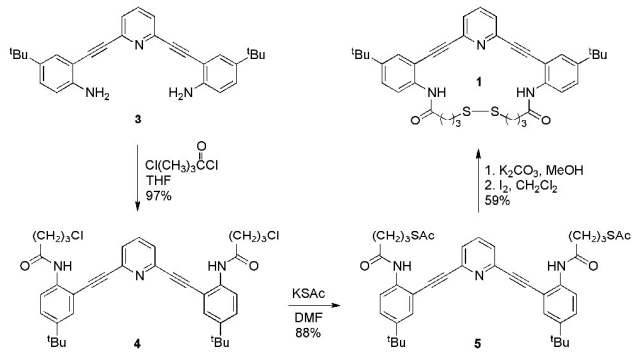
with **2**, it had some limitations: (i) the scaffold showed a poor fluorescence response, (ii) its binding interactions with anions in solution were non-selective, (iii) its synthesis gave a low 11% yield for the key macrocyclization step, and (iv) the final product required extensive purification.[11]

New macrocycle **1** (Fig. 1) possesses suitable functionalities for anionic guest inclusion: hydrogen-bond donors within the cleft, and a pyridine nitrogen atom which when protonated forms a strong, hydrogen-bond donating pocket. To facilitate synthesis, it utilizes a disulphide tether, suitable for late stage cyclization under gentle conditions. We also investigated the size and shape fit of anionic guests within the binding pocket by obtaining solid state structures of both the host and the host-guest complex, and gained insight into the hydrogen bond "anion coordination geometry" in these receptors.[22] Herein we report the synthesis, solid-state structures, and optoelectronic sensing properties of disulphide macrocycle **1**, and we present the surprising result that casting this macrocycle into a film provides a colorimetric indicator for chloride over other anions.

Preparation of **1** started with known key intermediate **3** (Scheme 1).[10] Treatment with 4-chlorobutanoyl chloride provided chloroamide 4 in 97% yield. Subsequent reaction with KSAc gave thioacetyl-functionalized **5** in 88% yield. Under air-free conditions K_2CO_3 unmasked each thioacetate giving a thiolate, which was subsequently oxidized by elemental I_2 after minimal workup, forming target disulphide macrocycle **1** in good isolated yield (59%; 50% over three steps from **3**).



Scheme 1 Synthesis of disulphide macrocycle **1**.

Slow evaporation of a CH_2Cl_2/hexanes solution of **1** provided diffraction quality single crystals, allowing study of the binding cavity within the host. Although the crystallization was performed in hydrophobic solvents, adventitious H_2O was incorporated into the host cavity (Fig. 2). The solid-state structure of **1•H$_2$O** is held together by hydrogen bonds donated by H_2O to an amide oxygen of a neighbouring molecule, forming 1D stacks in the crystal lattice (Fig. 2c). The water guest in **1•H$_2$O** is not centrally held within the cavity, accepting a strong hydrogen bond with only one amide N-H; however, the remaining amide N-H is directed within the cleft still providing weak supporting hydrogen bonds. The remaining hydrogen bond donor of the H_2O guest forms a hydrogen bond with the pyridine nitrogen.

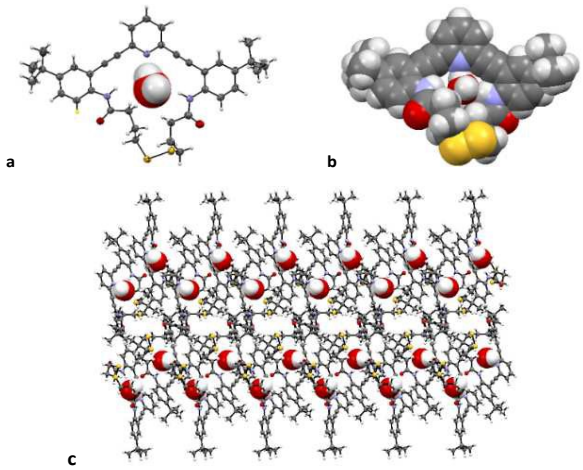


Fig. 2 (a) ORTEP of **1•H$_2$O**, ellipsoids drawn at 50% probability. (b) Space-filling model of solid-state structure of **1•H$_2$O**, showing cavity occupied with water guest. (c) Solid-state crystal packing of **1•H$_2$O**, host molecules drawn as ball-and-stick models, guest drawn in space-filling mode, exemplifying water-assisted intermolecular interactions.

Bubbling HCl gas through a CH_2Cl_2 solution of **1** followed by slow vapour diffusion of pentane afforded single crystals suitable for X-ray diffraction (Fig. 3). The tether flexibility resulted in the crystal structure having four crystallographically independent molecules in the unit cell, each featuring slightly varying cavity sizes. Interestingly, there were two different binding modes in the same solid-state structure. One mode demonstrated a coordination of Cl^- by three hydrogen-bond donors, and the other with only two strong internal N-H hydrogen bonds to a single Cl^-, both with additional support from α-CH donors, an interaction implicated as a feature in tertiary structure stabilization of proteins.[23-26] This packing motif resulted in close spacing between the Cl^- atoms, with a closest distance of 4.035 Å, indicating effective charge screening by the pyridinium, similar to other dimers in our sulphonamide-based hosts (Fig. 3c).[10, 19]

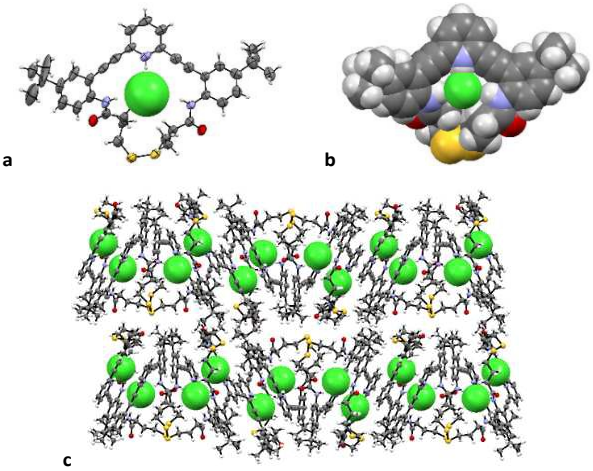


Fig. 3 (a) ORTEP of **1•HCl**, ellipsoids at 50% probability. (b) Space-filling model of **1•HCl**, showing central cavity occupied with Cl^- guest. (c) Solid-state crystal packing of **1•HCl**, host molecules drawn as ball-and-stick models, guest drawn as space-filling spheres. Solvent molecules (CH_2Cl_2) removed for clarity.

To explore the utility of the macrocycle as a solution-state sensor for chloride, the emission spectra of free host and host-guest complexes were compared. Overlaid emission spectra of **1** at the same concentration in both neutral and protonated states is shown in Fig. 4a. When HCl gas is bubbled through a solution of macrocycle **1**, emission red-shifts to ca. 530 nm, indicating facile pyridine protonation and increased charge transfer from acetanilide to pyridinium. Similar emission was reflected in treatment by HBF_4. Interestingly, quenching behaviour is shown not only in the HCl salt, as is expected due to the propensity for halides to undergo collisional quenching, but also in the presence of HBF_4, implicating pyridinium formation as a culprit in the quenching response.

Although in the solution state there was no noticeable sensing response selectively for Cl^-, we undertook association constant determinations to explore this scaffold as a receptor for halides. As initial experiments indicated that the association with chloride was exceedingly large in non-competitive $CHCl_3$ solvent, we proceeded to measure association constants via UV/Vis for the macrocycle **1•TFA** in MeCN/15% H_2O. We were able to obtain a reasonable fit using a 2:1 binding model and were pleased to confirm robust complexation even in a competitive solvent system (see ESI). However, the macrocycles were poorly behaved in aqueous solutions, and their performance changed over time suggesting that disulphide shuffling occurred and oligomers were being formed. With a lack of selective sensing response, and poor long-term stability in aqueous solution, exploration of the performance of **1** as a solution-state anionophore was not pursued further.

As we possessed solid-state structural data for the host **1**, we decided to explore its emissive and potential sensing behaviors in the solid-state as drop cast films. Host **1,** when dissolved in CH_2Cl_2 and drop-cast onto glass slides, formed an amorphous film (see ESI) displaying significantly red-shifted fluorescence compared to the solution state. When neutral films were treated with acid, the emission further red-shifted and displayed differing emission between HCl and TFA (Fig. 5). Two degenerate first excited states exist in the bis(2-ethynylacetanilido)pyridine scaffold, corresponding to transfer of electron density to the central pyridine/pyridinium from acetanilide rings. As a result, the transition dipole moment of the fluorophore backbone can be viewed as two separate vectors, originating in the pyridine and terminating in the centroid of the acetanilides.

The solid state structures demonstrate a partially parallel alignment between transition moment dipole vectors, indicative of J-aggregate dimer formation.[27,28] J-aggregates are exemplified by red-shifted emission in the solid-state compared to solution state, and somewhat sharp emission bands. This is verified by a 91 nm red-shift in the solid state versus solution state for **1** (emission – solution state: 389 nm, solid state: 480 nm, Fig. 4). In the protonated state, the red-shift due to film formation is only 36 nm, a less dramatic change. Comparison to the vector alignment in the solid state again agrees with J-aggregate formation, as the vectors are less parallel in the **1•HCl** complex compared to **1•H_2O** (Fig. 5).

This sensing behavior was intriguing, so to test the use of these films as a method to indicate the presence of Cl^-, the neutral film was exposed to TFA to form the protonated species, and the film was then dipped into a 2M aqueous solution of KCl. Upon exposure to the solution for one hour,

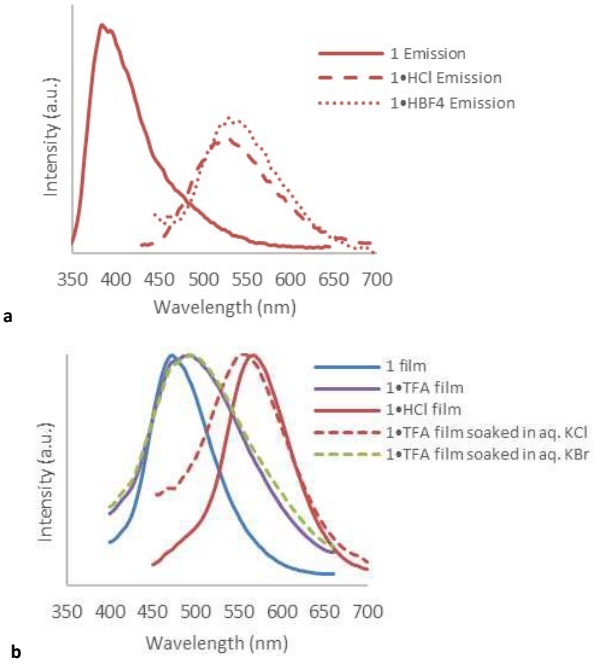


Fig. 4 (a) Emission spectra of equimolar solutions of **1** in $CHCl_3$, neutral and in the presence of HCl and HBF_4, demonstrating the difference in emission intensities as a function of added anion in the solution state. (b) Normalized emission spectra of **1** films and their response to acids and anionic analytes. Films prepared by drop casting 1 mL of a 1M solution of macrocycle in CH_2Cl_2 on glass slide. To obtain protonated films, neutral cast films were exposed to vapours of the relevant acid.

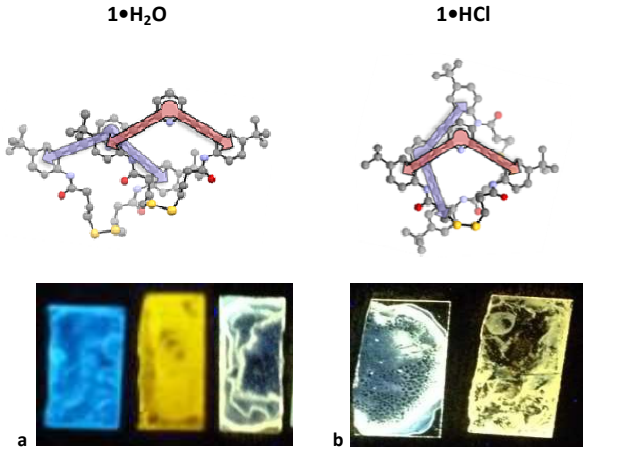


Fig. 5 (top) Illustration demonstrating the alignments of π-stacked dimers in the solid state structures of **1•H_2O** (left) and **1•HCl** (right). Hydrogen atoms, solvent, and guests omitted for clarity, models shown as ball and stick. The two degenerate transition dipole moment vectors are shown for two molecules in each dimer, with the two sets of vectors coloured red and blue as a visual aid. (bottom) Demonstration of emission change of **1** in the solid state as a film on glass slides. (a) Left, neutral compound film. Middle, neutral compound film exposed to HCl vapours. Right, neutral compound film exposed to TFA vapours. (b) **1** as a film protonated by TFA, (left) and a TFA-protonated film soaked in a solution of KCl (right). Films illuminated under broadband UV-light.

the change in emission due to Cl^- incorporation was apparent (Figs. 4b, 5b). It should be noted that the peak for **1•TFA** after soaking in KCl solution does not redshift quite as far as does the peak for the cast **1•HCl** film, likely due to incomplete incorporation of Cl^- within the films; the peak of the film's emission possesses a shoulder that extends to 450 nm, representative of remaining **1•TFA** in the film. Interestingly, performing the same test with a 2M solution of KBr yielded no spectroscopic change compared to that seen with Cl^-, demonstrating the sensitivity of solid-film emission toward the nature of anionic guest (Figs. 4b and 5a,b). This lack of a response of **1** in the solid state to Br^- as opposed to Cl^- (Fig 4b) is integral to its use as a sensing film for Cl^-. The structural arrangements resulting in the red shift in response to Cl^- are thus not amenable to the larger bromide, lending halide detection selectivity through the solid-state structure. Although there are a number of notable examples in the literature of solid-state anion sensors using either thin films or anionophores loaded onto a solid support,[29–35] to the best of our knowledge this is the first example of an optical anion sensing mechanism in a film selective for Cl^- over Br^-, with spectroscopic changes visible to the naked eye.

In summary, a fluorescent disulphide-based macrocycle was synthesized using the facile disulphide bond formation as a mechanism for macrocyclization. Application of this ring-closing strategy allowed for the formation of large rings in a relatively high yield. This fluorescent host, though it did not display detection capabilities in the solution state, displayed a stark difference in solid state emission upon chloride incorporation. The films are being investigated as a solid state sensor for chloride, and have demonstrated proficiency in the application as solid-state sensors for the detection of chloride in the presence of other anions, including bromide.

Acknowledgements

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