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Synthesis and study of a new diamidodipyrromethane macrocycle. An anion receptor with a high sulfate-to-nitrate binding selectivity†

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A new 2,6-diamidopyridinedipyrromethane hybrid macrocycle (1) has been synthesized that shows a high selectivity for dihydrogen phosphate and hydrogen sulfate relative to nitrate in acetonitrile solution as judged from UV-vis spectrophotometric titrations; this leads to the suggestion that this or related systems might find use in nuclear waste remediation applications requiring the selective removal of hydrogensulfate from nitrate-rich waste mixtures.

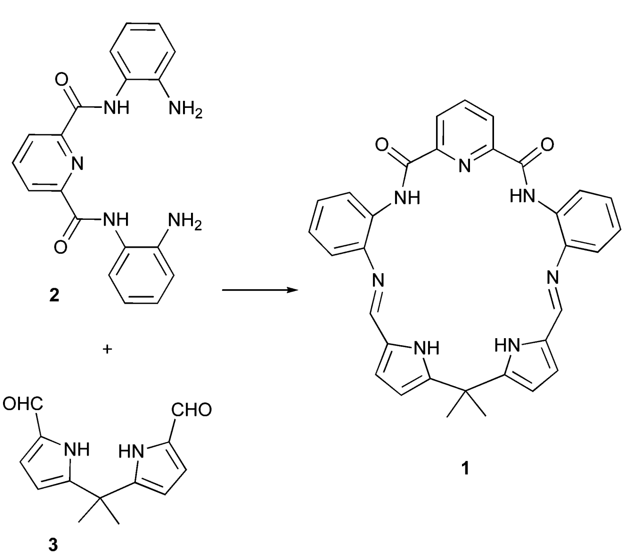
One of the current challenges in anion recognition[1] chemistry involves the preparation of receptors that show high sulfate/nitrate selectivity.[2] The desire to produce such systems comes from an appreciation of the role they could play in radioactive waste remediation. Intensive use of nuclear energy and the Cold War era have left a worrisome legacy of radioactive waste, much of it in the form of low-activity waste (LAW). One proposed means of tackling the problem posed by these latter species involves vitrification, wherein the crude waste would be subject to evaporation and, after addition of suitable additives, high temperature glass formation. This produces "logs" that are easier to transport and less prone to leaching than other proposed storage forms. Unfortunately, the vitrification process is sensitive to slight variations in the chemical and physical parameters of the system. Sulfate anions, in particular, have been shown to influence adversely the vitrification process.[3,4]‡ Nitrate anions, which are generally the dominant anionic species present in LAW from the Hanford waste site, as well as other anions such as phosphate and chloride (present at $\leq$ 0.5 and 0.25–2.8 of the sulfate concentration, respectively), do not interfere appreciably with the vitrification process.[3] Accordingly, considerable effort has been devoted of late to the synthesis of receptors that might allow the removal of sulfate from the highly basic nitrate-rich mixtures produced by pretreatment of the original radioactive waste with NaOH,[4] including *via* selective binding, anion exchange,[4a] extraction,[4b] precipitation, and other means.[4c] While some of these approaches show considerable promise, this problem is far from solved. In this communication we present the synthesis of a novel macrocycle incorporating a pyridine-2,6-dicarboxamide moiety within a dipyrromethane-based macrocycle and show that, in acetonitrile solution, it binds sulfate anion with high selectivity relative to nitrate anion.

Pyridine-2,6-dicarboxamides are well known[5] anion binding motifs. Less studied in this regard, dipyrromethane fragments, a key component of calixpyrroles,[6] also show promise for anion recognition. It was therefore thought that a combined system, incorporating both these elements within a single macrocyclic framework, would prove effective as an anion receptor.

The synthesis of macrocycle **1** is summarized in Scheme 1. It begins with bis(2-aminophenyl)pyridine-2,6-dicarboxamide[7] (**2**). Reaction of this known species with diformyldimethyldipyrrolylmethane[8] (**3**) in the presence of a Brønsted acid catalyst yields the target compound **1** as the corresponding acid salt. The best results (yields on the order of 90%) were obtained using trifluoroacetic acid in methanol, followed by treatment with triethylamine. Under these conditions, no precipitation was observed. By contrast, the use of other acid catalysts (HCl, CH_3COOH, HNO_3, H_2SO_4, and H_3PO_4) led to precipitation and yielded protonated salts of **1** contaminated with various oligomeric products. As a general rule, these precipitates displayed low solubility and could not be readily purified.

The interaction of **1** with several representative anions was studied in acetonitrile solution using UV-vis spectroscopy. The host–guest stoichiometries were determined *via* Job plots or mole-ratio plots. Standard curve fitting protocols, as used previously by our group[9] (and others), were used in both cases. In analogy with previous studies all the anions were used as their tetrabutylammonium salts.

Inspection of Table 1 reveals that receptor **1** binds hydrogen sulfate in a strong, 1 : 1 fashion in acetonitrile.§ By contrast it displays no detectable affinity for nitrate anion. Weak binding interactions were also seen in the case of cyanide, chloride, and bromide. This is rationalized in terms of the geometries of these anions (spherical: Cl^-, Br^-; linear: CN^-; and trigonal planar: NO_3^-)[10] and leads us to propose that **1** has a deep cavity that favors the formation of well-oriented, directional NH–anion hydrogen bonds (Fig. 1). Consistent with this supposition is the finding that acetate and phosphate, anions not particularly germane to the LAW remediation problem, are bound with appreciable affinity. In fact this latter anion interacts with receptor **1** in a strong, stepwise 2 : 1 (anion–receptor) fashion. Such a sequential binding process is thought to reflect the presence of a second binding site external to the macrocycle core that is not directly involved in sulfate recognition. Support for this conclusion comes from DFT (PBE non-empirical functional, TZ2p basis set) calculations (*cf.* Supporting Information) and from the fact that the equilibrium constant for



Scheme 1 Synthesis of macrocycle **1**. *Reagents and conditions*: MeOH, 2.5 equiv. TFA, 15 min, followed by Et_3N.

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† Electronic supplementary information (ESI) available: detailed experimental data and UV-vis spectrophotometric titration data. See http://www.rsc.org/suppdata/cc/b4/b403665d/

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the second phosphate binding process is not appreciably reduced upon the addition of excess hydrogen sulfate. In particular, when a standard UV-vis titration involving dihydrogen phosphate was carried out in acetonitrile solution containing receptor **1** and 10 molar equivalents of hydrogen sulfate, no evidence of a 2 : 1 binding process was seen. Rather, spectroscopic changes analogous to those seen at high dihydrogen phosphate in the absence of sulfate are observed; fitting these changes to a 1 : 1 binding profile gave a K_a of 15,000 mol dm^{-3}. An analogous, albeit reversed, competition study was also performed wherein hydrogen sulfate was titrated into an acetonitrile solution containing **1** and 11 molar equivalents of dihydrogen phosphate. Fits to the observed UV-vis spectroscopic changes confirmed the low binding affinity (K_a = 204 mol dm^{-3}) of hydrogen sulfate to the presumed secondary binding site present in **1**.

In summary, this novel diamidopyridinedipyrromethane macrocycle opens the door to a new type of hybrid systems that show promise as selective anion receptors. The main feature of this new macrocycle is its ability to bind selectively hydrogensulfate in the presence of nitrate, bromide, chloride and cyanide. This attractive property, coupled with its ease of synthesis, leads us to suggest that it may prove useful for removing sulfate from nitrate-rich nuclear wastes. Studies along these lines are in progress.

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Table 1 Affinity constants for the binding of anions by receptor **1** as determined from UV-vis spectroscopic titrations in CH_3CN. The anions studied were in the form of their tetrabutylammonium salts

Anion	K_a (mol dm^{-3})[a]
Br^-	[b]
NO_3^-	[b]
Cl^-	2000 ± 23
CN^-	12,000 ± 2500
CH_3COO^-	38,000 ± 3000
HSO_4^-	64,000 ± 2600
$H_2PO_4^-$	342,000; 26,000[c]

[a] The R^2 values for the curves fits used to determine the affinity constants range between 0.959 and 0.999. [b] No apparent binding as reflected in the lack of changes observed in the UV-vis spectral titrations upon anion addition. [c] Stepwise, 2 : 1 (anion : receptor) binding observed; the values refer to those for the first and second binding events, respectively.

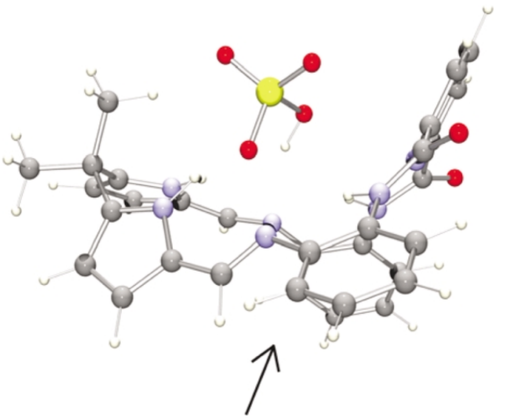

Fig. 1 Proposed binding mode of HSO_4^- by **1**. The arrow indicates a possible secondary binding mode, as suggested by DFT calculations.¶

Notes and references

‡ U.S. National Laboratories reports are available for download from: http://www.osti.gov/bridge/search.easy.jsp

§ While a 1 : 1 binding profile was inferred from Job plots in the case of the sulfate, acetate, and cyanide anions, a slight deviation from isosbestic behavior was seen during the early portions of the UV-vis spectroscopic titrations. This is ascribed to a competition with internal amide NH–pyridine hydrogen bonding interactions. This produces a slight cooperative effect. For instance, fitting the data set for hydrogen sulfate to a 1 : 1 binding profile gave a K_a of 50,000 mol dm^{-3}, while fitting the portion of the isotherm that shows clean isosbestic behavior in an analogous way gives a K_a = 64,000 mol dm^{-3}.

¶ For more information and additional figures generated as the result of the DFT calculations, please see the supporting information.

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