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Chelate effects in sulfate binding by amide/urea-based ligands

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The influence of chelate and mini-chelate effects on sulfate binding was explored for six amide-, amide/amine-, urea-, and urea/amine-based ligands. Two of the urea-based hosts were selective for SO_4^{2-} in water-mixed DMSO-d_6 systems. Results indicated that the mini-chelate effect provided by a single urea group with two NH binding sites appears to provide enhanced binding over two amide groups. Furthermore, additional urea binding sites incorporated into the host framework appeared to overcome to some extent competing hydration effects with increasing water content.

Selectively binding sulfate ion in aqueous solutions is of great significance in environmentally and biologically related applications, but challenging because of the extremely large hydration energy of the ion (G_h = –1080 KJ mol^{-1}).[1-3] One way to attack this problem is to take advantage of extended hydrogen bonding sites, i.e., the chelate effect, in anion host design. In the most favorable scenario this strategy would include not only ligands that are functionalized with the highest possible number of hydrogen bonding sites, but also those that are preorganized in conformations readily positioned for binding a tetrahedral sulfate ion.[4-14] In classical transition-metal coordination, the chelate effect has been extensively studied as a major contributor to enhanced stabilities in transition metal complexes.[15-21] In anion coordination, the chelate effect also plays an important role. The synergistic effect of appropriately positioned multiple hydrogen bonding sites can result not only in more enhanced binding but also in more selective hosts for targeted anions.[22-25]

Urea-based acyclic hosts have previously been studied by one of us (CJ) in order to probe the influence of the chelate effect in anion coordination. Findings from those studies indicated that while to some extent increasing the number of urea groups tends to result in increased binding, this effect can be tempered by steric strain depending on the linkages between the ureas.[5] Nevertheless, hosts with urea groups appear to be capable of maintaining anion binding in mixed aqueous systems, albeit with lower affinities. Previous findings also revealed that while bulky end groups can prevent encircling a single anion (which would capitalize on the chelate influence), they can induce the formation of helical structures, also of interest due to biological implications.[26]

Here we report a comparative study of the influence of the chelate effect on anion binding for two widely used functional groups, amides and ureas (Fig. 1). We further study the effect of covalently linking these groups on their ability to bind anions. In order to circumvent the issues inherent in short or strained connections and bulky end groups, we have used N-methyldiethylene bridges and ethyl termini, respectively.

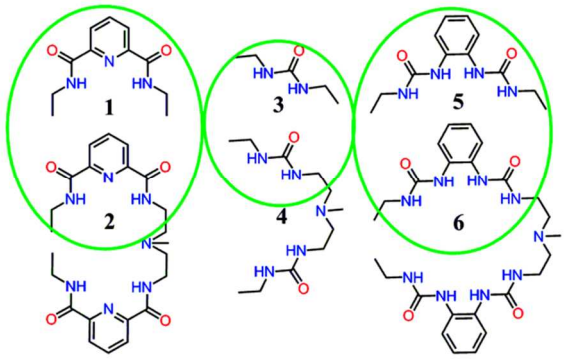

Fig. 1 Amide- and urea-based ligands **1** - **6**.

Six ligands were functionalized with increasing numbers of either amide or urea hydrogen bond donor sites (Fig. 1). Numbers of binding sites ranged from two to eight with the expectation that anion binding would increase along with the number of binding sites.[1,22-25] While both 2,6-dicarboxamides and ureas are can be viewed as chelates, ureas can be considered as "mini chelates" due to the short separation between the two NH groups. Such systematic variations in chelating frameworks provide an opportunity for assessment not only of the similarities and differences between ureas and amides, but also of the influence of increasing numbers of hydrogen bonding sites on binding affinities. Association constants were determined in 0.5% to 50% H_2O-mixed DMSO-d_6 in order to probe whether the power of additional hydrogen bonding sites, and in particular the urea mini-chelating sites, could compete with the large hydration energy of sulfate ion.

Ligands **1** - **6** can be readily synthesized in one to three steps (see ESI†). Anion binding was studied by ^{1}H NMR titrations in water mixed DMSO-d_6, using the tetra *n*-butylammonium (TBA^+) salts of a broad range of anions (Cl^-, SO_4^{2-}, $H_2PO_4^-$, AcO^-, NO_3^-, ClO_4^-, N_3^-). None of the ligands except for **6** interacted to any measurable extent with NO_3^-, ClO_4^-, and N_3^-, although **1** - **4** were found to bind to some extent with Cl^-, $H_2PO_4^-$, and AcO^- (see ESI†). Notably, **5** and **6** were found to bind a majority of the anions in DMSO-d_6 with 0.5% H_2O (Fig. 2, Table 1). Binding constants were calculated based on 1:1 binding modes, as confirmed for solution binding by Job's plots (see ESI†). Results can probably be attributed to both the larger number of hydrogen

bond donor groups (**6**) and the preorganization provided by the *o*–phenylene group (**5** and **6**). However, **1** – **6** all displayed affinity for SO_4^{2-} over other anions.

Table 1 Binding constants (K, M^{-1})[a] of the SO_4^{2-} (added as tetrabutylammonium salts) complexes of ligands **1** - **6** at 298 K in water-mixed DMSO-d_6 in the presence of increasing percentages of H_2O.[a]

complexes	possible coordination number (C.N.)	DMSO-d_6 (0.5 % H_2O)	DMSO-d_6 (10% H_2O)	DMSO-d_6 (25% H_2O)	DMSO-d_6 (50% H_2O)
1·SO_4^{2-}	2	744	–[c]	–[d]	–[d]
2·SO_4^{2-}	4	5149	52	–[c]	–[d]
3·SO_4^{2-}	2	1405[b]	82	–[c]	–[d]
4·SO_4^{2-}	4	9630	307	68	–[c]
5·SO_4^{2-}	4	$>10^4$	3266	294	–[c]
6·SO_4^{2-}	8	$>10^4$	$>10^4$	7025	47

[a] All errors < 10% except where noted. [b] Error = 12%. [c] Changes in the ^{1}H NMR spectra are too small to calculate the association constants. [d] Not determined.

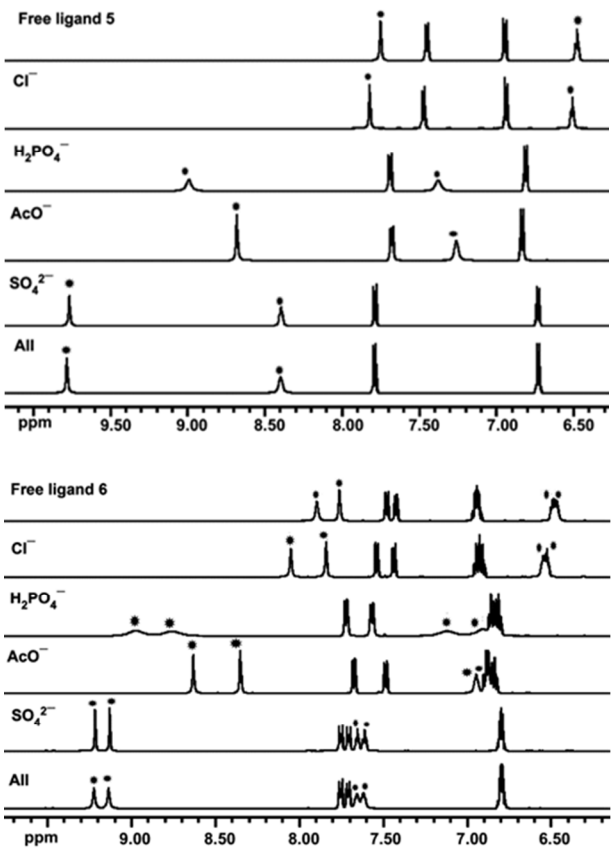

Fig. 2 Partial ^{1}H NMR spectra (500 MHz, 298 K, 0.05% water-mixed DMSO-d_6) of ligands **5** and **6** in the presence of 1 equiv of selected anions and with all anions (NH signals are labelled by asterisks).

As seen from the competitive titration experiments (Fig. 2, spectrum in the presence of all anions), **5** and **6** selectively bind SO_4^{2-}, even in the presence of a mixture that includes several different anions. It should be also noted that all of the N*H* protons seem to participate in the binding to SO_4^{2-}, as suggested by the significant downfield shifts observed for all NH protons in the ^{1}H NMR spectra (Fig. 2). Job's plots indicated that SO_4^{2-} is held in a 1:1 mode in all cases, which was also observed for three of the four crystal structures (*vide infra*). Thus, at least for this series of ligands, SO_4^{2-} appears to be quite suitable as a target anion in an evaluation of the chelate effect with increasing amounts of water.

Association constants for SO_4^{2-} (Table 1) were obtained by fitting ^{1}H NMR titration data with EQNMR (see ESI†). As shown in the Table, the increasingly favorable influence of covalently linked chelates within each pair of hosts (**1**,**2**; **3**,**4**; **5**,**6**) is clearly evident: K(**1**·SO_4^{2-}) < K(**2**·SO_4^{2-}); K(**3**·SO_4^{2-}) < K(**4**·SO_4^{2-}); and K(**5**·SO_4^{2-}) < K(**6**·SO_4^{2-}). In the DMSO-d_6/0.5% H_2O studies, the ratio of binding constants in hosts progressing from two to four binding sites (**1** → **2** and **3** → **4**) indicates an almost seven-fold enhancement for the ligand with the larger number of binding sites in each pair. Binding was so strong with **5** and **6**, it was beyond NMR capabilities (> 10^4) for accurate determination when in DMSO-d_6 0.5% water

A comparison of Table 1 with Fig. 3 illustrates the interdependence of the NMR chemical shifts with binding strengths. Binding precipitously decreased for all hosts in solutions with increasing percentages of H_2O. Even in only 10% H_2O, we found it to be immeasurably small for the very simple pyridine dicarboxamide, **1**. The lessened affinities are reflected in decreases in the magnitudes of the chemical shift. However, the urea-based hosts with four and eight binding sites still displayed at least some binding in 25% H_2O.

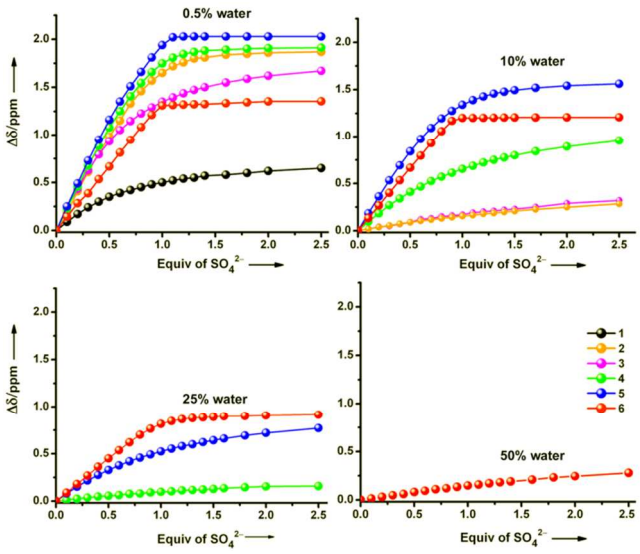

Fig. 3 Chemical shifts of amide NH protons in **1** - **6** upon addition of $(TBA^+)_2SO_4^{2-}$ in DMSO-d_6 containing v/v: (a) 0.5%, (b) 10%, (c) 25% and (d) 50% H_2O.

The preorganization effect of the *o*-phenyl group appears to

enhance binding significantly (**5** and **6**). Doubling the potential number of donor groups from four to eight resulted in an almost 25-fold increase in the binding of SO_4^{2-} for **6** over **5** for 25% water in DMSO-d_6 solution (K(**6**·SO_4^{2-})/K(**5**·SO_4^{2-}) = 23.9). Comparatively, the dicarboxamide hosts were not nearly as effective in binding SO_4^{2-} as the percentage of H_2O was increased. These findings tend to suggest the superior binding capabilities of the almost adjacent "mini-chelating" hydrogen bond donors in the urea hosts, at least in this instance. It should be kept in mind, however, that in urea (and thiourea) functionalities, the NH groups are always oriented in the same direction, plus they are stronger acids than amides and thus more effective at hydrogen bonding. An additional influence, also a result of the proximal position of the urea NH groups, solvation/hydration of the anion may well be blocked, as noted by Hamilton in a seminal paper.[27] For the pyridine dicarboxamide ligands, the two amide groups are not constrained to be pointed in the same direction, but are frequently preorganized for chelation due to intramolecular hydrogen bonding interactions with the pyridine nitrogen atom.[28]

Crystal structure results for the SO_4^{2-} complexes of the urea hosts **4**, **5**, and **6** tend, for the most part, to support the binding conclusions. Crystals of the TBA^+ salts of **4**-SO_4^{2-}, **5**-SO_4^{2-}, and **6**-SO_4^{2-} were obtained by slow evaporation of DMSO solutions of the ligands in the presence of excess $(TBA^+)_2SO_4^{2-}$. The structural results for the $(TBA^+)_2SO_4^{2-}$ complex with the simple diurea acycle **4** nicely illustrates the conformational flexibility of a host that is not preorganized for binding (Fig. 4(**a**)). The two urea binding sites of a single ligand are associated with two different SO_4^{2-} ions. Each SO_4^{2-} is also linked via hydrogen bonding to a neighboring host, resulting in the formation of a host-guest chain that extends throughout the crystal lattice. Although not shown in the Figure for ease of viewing purposes, the single oxygen atom that is not hydrogen bonded with a host appears to be cushioned by the bulky TBA^+ groups. Hence, as a result of the greater conformational flexibility in **4**, the two urea groups do not surround a single SO_4^{2-}, as seen in the structures of the other, more preorganized ligands, **5** and **6**.

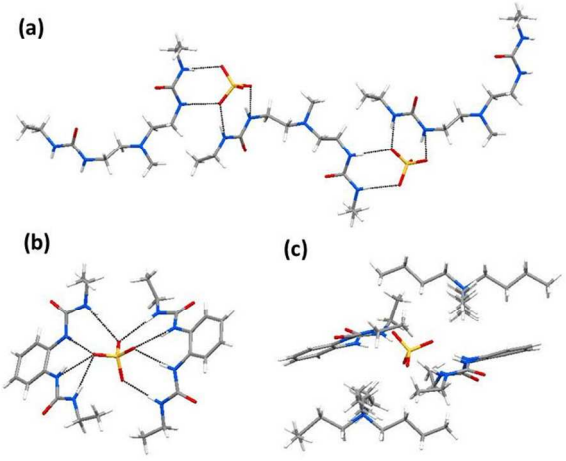

Fig. 4 Perspective views of the crystal structures of **(a)** $(TBA^+)_2$[**4**·(SO_4^{2-})] without the TBA^+ counterions; **(b)** overhead view of [$\mathbf{5}_2$·(SO_4^{2-})] without the counterions, and **(c)** side view of [$\mathbf{5}_2$·(SO_4^{2-})] with the two hosts on the left and right of the SO_4^{2-} and with the TBA^+ counterions above and below.

In **5**·SO_4^{2-}, two of the ligands form a bis-chelate around a single SO_4^{2-} ion, resulting in a 2:1, **5**:SO_4^{2-}, binding mode (contrary to the results of the Job plot) (Fig. 4**(b)** and **(c)**). The bis-chelate formation is reminiscent of an earlier report by one of us (CJ) of anion-templated dimeric host associations. fomr structureThe crystals were twinned and three of the four independent SO_4^{2-} complexes were disordered (see ESI†). Nonetheless, all four independent complexes displayed the bis-chelate structures, but with varying hydrogen bond distances, some less strongly "coordinated" than others. Obviously, the *o*-phenyl group plays a major role in the complex formation by virtue of the preorganized urea groups. Just one of the independent units is displayed in the Figure with its associated hydrogen bond contacts. In this complex the SO_4^{2-} is held by eight hydrogen bonds from the two surrounding **5** hosts with N···O distances ranging from about 2.8 Å to just under 3.0 Å. The two TBA^+ counterions form axial shields above and below the complex. This axial positioning of the counterion essentially boxes in the SO_4^{2-} ion and serves to isolate it from neighboring anions (Fig. 4**(c)**). The other three crystallographically-independent $(TBA)_2$[$\mathbf{5}_2$·(SO_4)] moieties have similar local arrangements.

In the crystal structure of the most extended host ligand, **6**, with SO_4^{2-}, the asymmetric unit contains three independent [**6**·(SO_4^{2-})] complexes (Fig. 5). Each of the independent ligands encircles a single SO_4^{2-} anion and forms six hydrogen bonds with N···O separations between 2.70 and 3.07 Å. Each ligand uses the remaining two amide hydrogen atoms to form three longer H-bonds with N···O separations between 3.13 and 3.33 Å. Shorter hydrogen bond distances are seen for the urea NH groups closest to the phenyl rings. These *ortho*-substituted NH groups are pulled in closer by the small bite of the five-membered ring assisted by the other hydrogen bonded NH groups. As in the crystal structure with **5**, the TBA^+ counterions are located in the axial positions, above and below the extended chelate complex (Fig 5**(b)**.

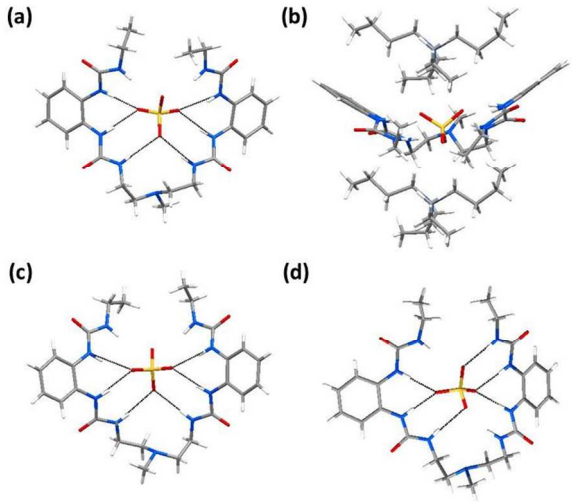

Fig. 5 Perspective views of the crystal structures of the three independent sulfate complexes of $(TBA^+)_2$[**6**·(SO_4^{2-})]: **(a)** and **(b)**, a selected complex without and with the TBA^+ counterions, respectively; **(c)** and **(d)**, the other two structurally independent complexes without the TBA^+ cations.

Conclusions

In summary, results indicate that the chelate effect in anion coordination appears to be alive and well as anticipated. In this comparison study of 2,6-dicarboxamide pincer-based frameworks with similar urea-based anion hosts, we used non-bulky ethyl groups for the chelate termini, and, in three of the hosts, used flexible N-methyldiethylene bridges to link chelate units. As expected, we found enhanced sulfate binding as the number of NH donor groups increased. The urea mini-chelate hosts appeared to be superior to the amide systems, attributed to the double binding power of a single urea compared to a single amide. This is especially striking in a comparison of **1** with **3** and **2** with **4**. In both cases the urea host, with the same number of NH groups as the amide corollary, displayed almost twice the affinity for sulfate ion. Furthermore, the urea hosts continued to be effective, although to increasingly lesser extents, with increasing percentages of water. The host with the largest number of urea groups, **6**, binds most effectively, a tribute to the extended chelate influence. In his review several years ago, Fabbrizzi asked the question, "Is there anything better than urea?"[25] These studies add to the evidence that at the very least urea is extremely good.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, X-ray data, spectral data, NMR spectra, binding studies. See DOI: 10.1039/b000000x/

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