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Tetraureas versus Triureas in Sulfate Binding

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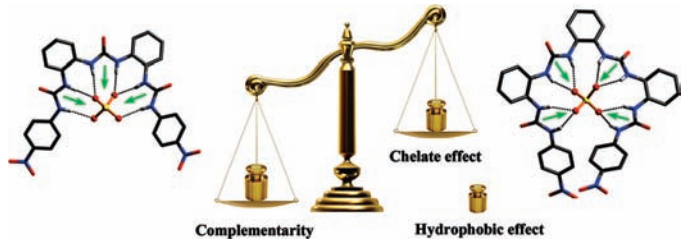
ABSTRACT



By mimicking the scaffolds of oligopyridine-based ligands, triurea and tetraurea receptors have been developed for sulfate binding. The triureas (L^1, L^2) show stronger binding of sulfate than tetraureas (L^3, L^4) in DMSO because of their better conformational complementarity with sulfate, while the tetraureas display better "water tolerance" benefiting from the chelate effect and hydrophobic effect.

The design of sulfate receptors is a focus in anion receptor chemistry[1] due to their promising applications in anion templated synthesis,[2] transmembrane anion transport,[3] and nuclear waste remediation.[4] In recent years, various sulfate receptors have been developed with the macrocyclic,[2,5] helical,[6] tripodal,[7] or podant backbones,[8] and metal ion-assisted frameworks.[9] As required in environmentally and biologically related applications, selective binding of sulfate

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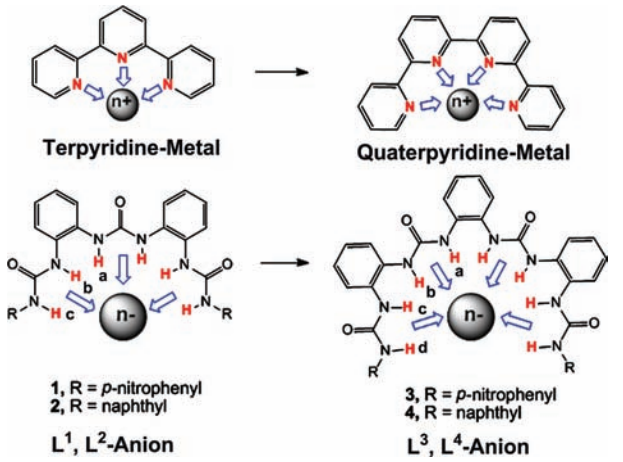
Scheme 1. The Design Strategy of Triurea and Tetraurea Based Anion Receptors



in aqueous environment is attracting more attention.[10] This is much more challenging than in organic solvents due to the severe energetic penalty paid to overcome the high hydration energy ($\Delta G_h = -1080$ kJ mol^{-1})[11] of sulfate. For a long time, it was generally believed that only the receptors bearing multiple charges or charged by coordinated metal ions are able to overcome anion hydration.[10a] However, recent works[5a,b,7a,8a,10b,12] have demonstrated that some neutral receptors, which bind guests only via hydrogen bonds, can also possess considerable binding affinity with anions, even the greatly hydrophilic sulfate ion. The overcoming of anion hydration by these receptors was proven to benefit from either chelate effect, conformational complementarity, or hydrophobic effect.

In the pursuit of sulfate receptors with high binding affinity and selectivity,[7a−d,8a] we have designed some tripodal triurea and tripodal hexaurea ligands which show excellent sulfate recognition properties. Recently, inspired from the similarities between classical metal coordination and anion coordination,[13] a triurea receptor (**L**^{1}) for sulfate/phosphate was developed by mimicking the scaffold of 2,2′:6′,2″-terpyridine (tpy) (Scheme 1).[8a] The receptor displays a fully complementary conformation with sulfate, which results in strong binding in DMSO. However, the binding affinity decreases dramatically as the solvent is mixed with water (v/v, 25%, vide infra) due to the strong competition of sulfate hydration. To improve the "water tolerance" ability of such receptors, several factors could be considered such as the aforementioned ligand conformational complementarity, chelate effect, or hydrophobic effect. A possible way to increase the chelate effect and hydrophobic effect is extending the triurea to tetraurea, which can be viewed as the counterpart of 2,2′:6′,2″:6″,2‴-quaterpyridine (qtpy). As long as all the binding sites are involved in sulfate binding, there will be two more binding sites (positive chelate effect) in the tetraurea than in the triurea. On the other hand, the prolonged receptor is very likely to fold up, creating a helical cavity that would bring in positive hydrophobic effect by more effective encapsulation of the anion.[14] The present work aims to study these issues. The triurea **L**^{2} and tetraureas (**L**^{3}, **L**^{4}) (Scheme 1) functionalized with *p*-nitrophenyl or naphthyl chromophores were thus synthesized by reaction of *p*-nitrophenylisocyanate or 1-naphthylisocyanate with corresponding diamines as reported previously for the ligand **L**^{1} (see the Supporting Information for details).[8a,15]

The sulfate binding properties of **L**^{1}−**L**^{4} were first investigated by ^{1}H NMR experiments performed in DMSO-d_6−0.5% water. In the cases of both the triurea and tetraurea receptors, strong and saturated downfield shifts of all NH signals were induced by addition of 1 equiv of sulfate, indicating that all NH protons are involved in the binding of sulfate (Figure S1, Supporting Information), with a binding stoichiometry of 1:1 that was further confirmed by the Job's plot (Figure S2, Supporting Information). However, the average strength of hydrogen bonds formed by the tetraureas is remarkably weaker than that of the triureas since the downfield shifts of NH signals of the former are considerably smaller than those of the latter (Table 1). These results imply that the tetraureas prefer to adopt the fully chelating binding mode by using all four urea groups, although the spatial complementarity is decreased compared to the triureas as indicated by the weaker hydrogen bonding interactions. This is also consistent with the solid-state structures described below.

Table 1. Downfield Shifts ($\Delta\delta$, ppm) of NH Signals in **L**^{1}−**L**^{4} Induced by 1 equiv of Sulfate in DMSO-d_6−0.5% Water Solution[a]

	NHa	NHb	NHc	NHd	on average
L^1	1.17	1.78	1.31		1.42
L^2	1.48	1.55	1.2		1.41
L^3	0.88	0.84	1.01	0.91	0.91
L^4	0.99	1.16	1.15	0.66	0.99

[a] See Scheme 1 for the labeling of protons.

Single crystals of the sulfate complex of **L**^{3}, $(TBA)_2[\mathbf{L}^3SO_4]$, were obtained from a H_2O/DMSO solution

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of $\mathbf{L^3}$ in the presence of an excess of $(TBA)_2SO_4$. Although attempts to grow crystals of the sulfate complex of $\mathbf{L^1}$ or $\mathbf{L^2}$ failed, a 1:1 structure of $\mathbf{L^1}-SO_4$ could be optimized by DFT computations[16] (see the Supporting Information for details). In both structures, all NH protons are involved in the binding of sulfate with all coordination vectors arranged like that of the corresponding oligopyridines (Figure 1). In the computed

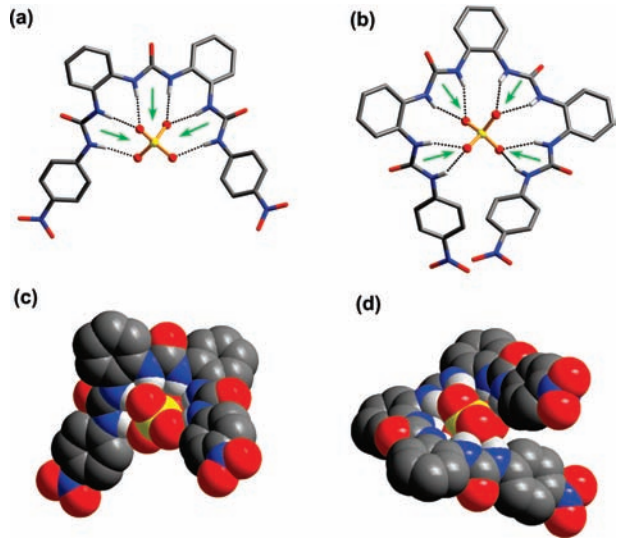

Figure 1. Calculated (a, c) and crystal (b, d) structures of the sulfate complexes of $\mathbf{L^1}$ and $\mathbf{L^3}$, respectively (nonacidic hydrogen atoms and counter cations were omitted for clarity).

$\mathbf{L^1}-SO_4$ complex, the ligand $\mathbf{L^1}$ binds sulfate in a crescent mode through six hydrogen bonds (N···O distances ranging from 2.768 to 2.811 Å, 2.790 Å on average; N−H···O angles from 168° to 171°, 169° on average), and each coordination vector points to one O−S−O edge of the anion. In the crystal structure of $[\mathbf{L^3}SO_4]^{2-}$, sulfate is encapsulated in a helical cavity through eight hydrogen bonds with four ureas (N···O distances ranging from 2.802(7) to 2.927(6) Å, 2.882 Å on average; N−H···O angles from 151° to 162°, 156° on average), and each coordination vector points to one vertex of the anion. It has also been demonstrated by theoretical studies that this binding mode is less stable than the former.[17] As a result, the average hydrogen bond length of $\mathbf{L^1}-SO_4$ is 0.092 Å shorter than that of $\mathbf{L^3}-SO_4$, and the average N−H···O angle 13° larger than that of $\mathbf{L^3}-SO_4$. Thus, the results further proved the superiority of chelate effect over the conformational complementarity in the binding of sulfate by the tetraurea receptors, and the loss of complementarity might, at least in part, be compensated by the formation of two more hydrogen bonds.

To evaluate the overall effect resulting from the two aspects, association constants were determined by UV−vis ($\mathbf{L^1}$) or fluorescence titration experiments ($\mathbf{L^2}$, $\mathbf{L^4}$) with the data fitted by the Dynafit program[18] to the 1:1 binding mode (errors are less than 10% in all cases, Figure S3, Supporting Information). Unfortunately, the colorimetric changes of $\mathbf{L^3}$ induced by SO_4^{2-} were too small to allow for the determination of the association constant. The value was alternatively obtained by fitting the ^1H NMR titration data by EQNMR,[19] which is more than 10^4 M^{-1} in the presence of 10% D_2O (more D_2O will induce disappearance of the NH signals, Figure S4, Supporting Information). The sulfate binding affinities (Figure 2) of the triureas $\mathbf{L^1}$ and $\mathbf{L^2}$ are larger than

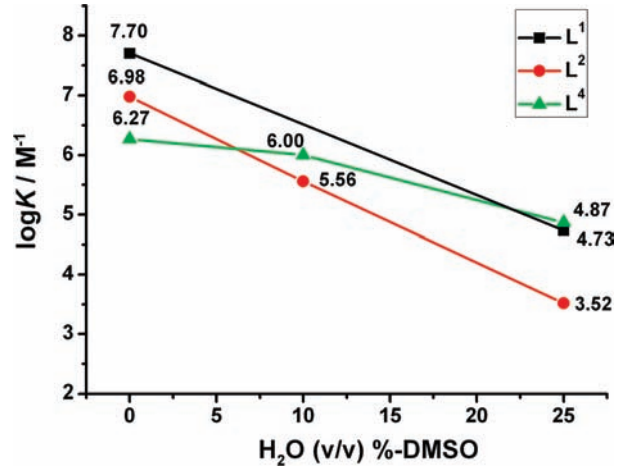

Figure 2. Plots of the sulfate association constants $K(\mathbf{L^1})$, $K(\mathbf{L^2})$, and $K(\mathbf{L^4})$ against the percentage of water (v/v % DMSO) in the solvent.

those of the tetraurea $\mathbf{L^4}$ in DMSO [$K(\mathbf{L^1})/K(\mathbf{L^4}) = 26.9$, $K(\mathbf{L^2})/K(\mathbf{L^4}) = 5.1$], indicating that the superiority in conformational complementarity of triureas exceeds their inferiority in chelate effect in the nonaqueous environment. However, $\mathbf{L^1}$ and $\mathbf{L^2}$ displayed remarkably decreased binding affinities as the solvent was mixed with increasing amounts of water. As a result, the sulfate binding affinity of $\mathbf{L^4}$ finally surpassed that of $\mathbf{L^1}$ and $\mathbf{L^2}$ in the presence of 25% (v/v) water ($K(\mathbf{L^4})/K(\mathbf{L^1}) = 1.4$, $K(\mathbf{L^4})/K(\mathbf{L^2}) = 22.4$). Thus the tetraurea $\mathbf{L^4}$ is more "water-tolerant" than the triureas $\mathbf{L^1}$ and $\mathbf{L^2}$. Besides the favorable chelate effect, the tetraurea $\mathbf{L^4}$ probably gained an additional benefit of hydrophobic effect over the triureas. As shown in Figure 1, sulfate is better encapsulated by the tetraurea in a helical cavity that is protected by hydrophobic aromatic rings, while it is only partially encapsulated by the triurea in a crescent cleft, which will thus suffer from more hydration effect than the former. On this point, Kubik[10a] has recently summarized the positive hydrophobic effect in anion binding. In the present aqueous environment (25%, v/v, water−DMSO), the superiorities of tetraurea $\mathbf{L^4}$ in chelate effect and hydrophobic effect exceed its inferiority in conformational complementarity, which results in the stronger binding with sulfate.

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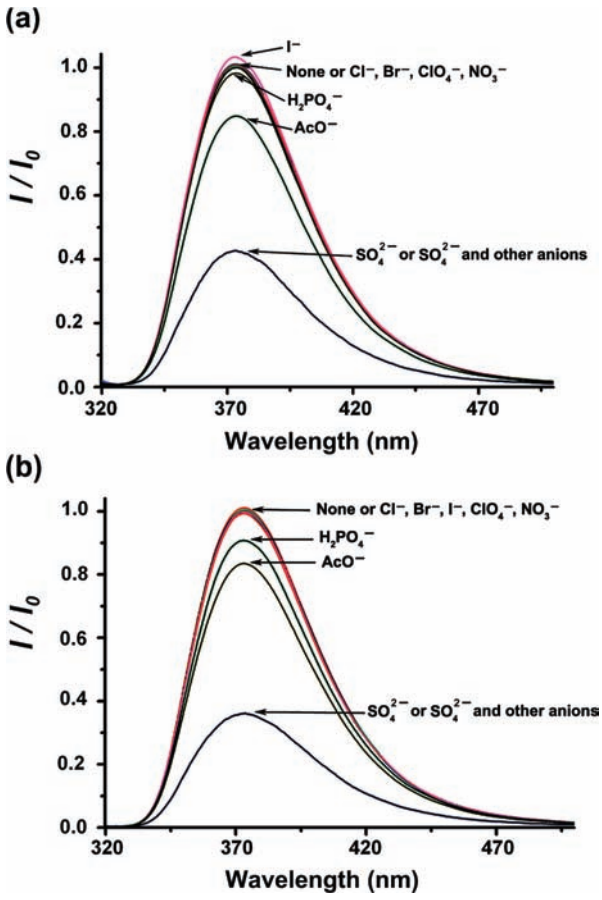

Figure 3. Fluorescence spectra of 10 μM 10% (v/v) $H_2O-DMSO$ solution of (a) $\mathbf{L^2}$ and (b) $\mathbf{L^4}$, alone and in the presence of 1 equiv of various anions (added as TBA salts, other anions = Cl^-, Br^-, I^-, ClO_4^-, NO_3^-, $H_2PO_4^-$, AcO^-).

The anion selectivity of $\mathbf{L^2}$ and $\mathbf{L^4}$ was also assessed by competitive titrations performed in a 10% (v/v) $H_2O-DMSO$ solution, and the results revealed a good selectivity for sulfate. As shown in Figure 3, 1 equiv of sulfate led to remarkable quenching of the fluorescence of both receptors, while an equal amount of other anions induced much less or no quenching effect. In the presence of equal amounts of all studied anions, both $\mathbf{L^2}$ and $\mathbf{L^4}$ can selectively bind sulfate. Since the fluorescence quenching induced by sulfate is remarkable and selective, the receptors may be potentially utilized as sulfate sensors functioning in an aqueous environment.

In summary, two oligourea (triurea and tetraurea) sulfate receptors have been developed by mimicking the scaffolds of the well-known tpy and qtpy ligands. Triureas possess superiority in conformational complementarity (with sulfate), whereas tetraureas benefit from both chelate effect and hydrophobic effect, resulting in stronger binding affinity in DMSO or aqueous environments, respectively.

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Supporting Information Available: Experimental details, X-ray data, spectral data, NMR spectra, binding studies, DFT calculation data, and full citation of Gaussian 03 program. This material is available free of charge via the Internet at http://pubs.acs.org.

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