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Squaramide-based tripodal receptors for selective recognition of sulfate anion†

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Squaramide-based tripodal anion receptors 1–3 have been prepared and their anion binding properties with various inorganic anions were investigated. Receptor 1 formed a dimeric complex in solid state and a 1 : 1 complex in solution with SO_4^{2-}. All receptors 1–3 could selectively encapsulate SO_4^{2-} *via* hydrogen bonds over other examined anions.

Sulfate anions play important roles in both biological and environmental systems.[1] Therefore, the design and synthesis of artificial receptors bearing amide,[2] pyrrole,[3] urea,[4] thiourea[5] and indole[6] for selective binding of SO_4^{2-} have emerged into considerable interest recently. The (thio)urea based tripodal molecules consisting of three arms with complementary geometric structures could well chelate or encapsulate guests *via* multiple H-bonds, which are employed in consideration of selective recognition for the challenging tetrahedral geometry and high hydrophilicity ($\Delta G_h = -1080$ kJ mol^{-1})[7] of SO_4^{2-} in nature. For example, Custelcean *et al.*[8] and Wu *et al.*[9] developed acyclic tris-(2-aminoethyl)amine (tren)-based tris-urea as receptors or extraction agents for sulfate ions. The Ganguly[10] and Das[11] groups have studied synthetic tris-(thio)urea receptors based on a tren scaffold to encapsulate SO_4^{2-}. Such a tripodal system was also applied for the construction of a triply interlocked capsule with the templated SO_4^{2-} reported by Beer and coworkers.[12]

More recently, squaramide, with the strong hydrogen bond donor ability, has been exploited as a functional group in numerous applications.[13] The aromatic squaramide has shown superiority over urea counterparts due to its stronger H-bond donor ability that was enhanced by its conformationally rigid square-shaped structure upon binding,[14] so it has been employed in the design of new anion receptors.[15] For example, Morey *et al.* have recently reported the squaramide-ammonium based tripodal receptors for the recognition of organic carboxylate anions,[15c,f] and Gale *et al.* have successfully applied squaramides to be potent transmembrane anion transporters which performed better than (thio)urea analogues.[16] Ever since the first tren-based tris-(thio)urea receptors were reported for the anion recognition in 1995,[17] very little work has been reported on the construction of squaramide-based tripodal receptors with a tren scaffold for the anion recognition,[15c,f] especially for the inorganic anion recognition. Therefore, inspired by the stronger H-bond donor ability of squaramide moiety and the reported calculation results[18] that tripodal receptors could effectively bind to tetrahedral inorganic anions such as sulfate and phosphate ion, we prepared a series of squaramide-based tripodal receptors **1–3** (Fig. 1a) to investigate their binding behaviours for inorganic anions in comparison with reported urea-based tripodal receptors.

The synthesis of receptors **1–3** was achieved in one step from tris-(2-aminoethyl)amine using $Zn(OTf)_2$ as a catalyst[19] (see ESI†). Efforts were firstly made to evaluate the recognition of receptors for inorganic anionic guests in solid state. The single crystal X-ray analysis of complex 2TBA-[**1**·SO_4] revealed that unlike those previously reported tripodal capsules with a suitable cavity for hosting a guest,[9e] there was an unusual binding model for sulfate anions (Fig. 1b), where two molecules of tripodal **1** were paired with two sulfate anions to form a dimer. The crystal structure showed that three arms of **1** were in a wide open conformation without C_3 symmetry, and one of two sulfate anions bound two of three squaramide units of one tripodal receptor and one squaramide unit of the other tripodal receptor through N–H···O hydrogen bonding interactions [N···O = 2.652–3.364 Å; ∠N–H···O = 147.21–171.16°], while the other sulfate ion bound in the opposite way.

Additionally, in order to evaluate the binding affinities of receptors **1–3** with various inorganic anions in solution, ^{1}H NMR titration studies were conducted in DMSO-d_6, where halides (Cl^-, Br^- and I^-) and oxo-anions (SO_4^{2-}, HSO_4^-, $H_2PO_4^-$, AcO^-, NO_3^- and ClO_4^-) were investigated as their tetrabutylammonium salts. The results showed that for

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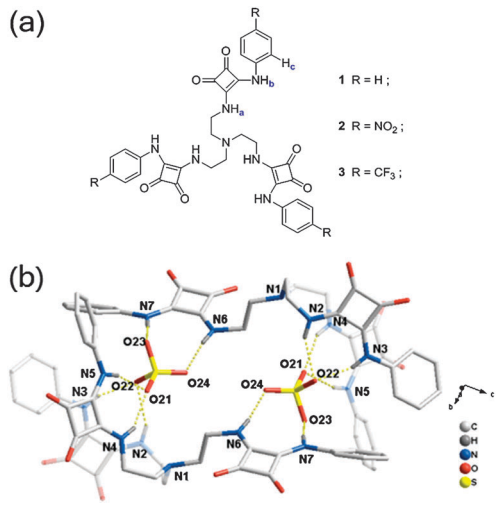

Fig. 1 (a) Molecular structures of tris-(squaramide) receptors **1–3**; (b) the X-ray structure of 2TBA-[**1**·SO_4] depicting the H-binding interactions of two disordered SO_4^{2-} with two tripodal molecules. Only one set of H-bonds are shown for each sulfate cluster and counter cations are omitted for clarity.

receptors **1–3**, chemical shift changes or disappearance of both squaramide N–H_a and N–H_b signals were all observed upon addition of Cl^-, SO_4^{2-}, HSO_4^-, $H_2PO_4^-$ and AcO^-, which, however, were negligible upon addition of Br^-, I^-, NO_3^- and ClO_4^-, indicating that receptors **1–3** showed strong binding affinities or acid–base[4b] interactions to Cl^-, SO_4^{2-}, HSO_4^-, $H_2PO_4^-$ and AcO^-. The ^1H NMR titration experiments of receptor **1** with SO_4^{2-} at different concentrations (0.5, 1.0, 5.0, 10.0 mM) were conducted, and the similar chemical shift changes of squaramide N–Hs were observed (Fig. S7–S10, ESI†) in all cases, indicating the same binding behaviour of receptor **1** with SO_4^{2-} in solutions over a wide range of concentrations. And then the pure receptor **1** and **1**-SO_4^{2-} complex in solution were investigated by 2D NOESY NMR experiments in DMSO-d_6, respectively, to demonstrate the hydrogen bonding formation between N–$H_{a,b}$ of squaramide moieties and SO_4^{2-} (Fig. S28, ESI†).[11,20] The 1 : 1 binding ratio of receptor **1** and SO_4^{2-} in solution was supported by both Job Plot (Fig. S8, ESI†) and HR-ESI-MS experiments (Fig. S35, ESI†). Since the binding stoichiometry of receptor **1** and SO_4^{2-} ion in solid state was 2 : 2, in order to investigate its binding stoichiometry, 1 : 1 or 2 : 2, in solution, a series of DOSY NMR experiments[21] were applied for such investigation. All resulting DOSY NMR spectra (Fig. S29–S33, ESI†) showed that no diffusion coefficient of dimeric complex of 2TBA-[**1**·SO_4] was found, which indicated the dimeric structure does not exist as a stable complex in solution under such conditions, and suggested a 1 : 1 binding stoichiometry between receptor **1** and SO_4^{2-} in solution (Fig. S34, ESI†).

Similar distinct changes of chemical shifts of receptors **2** and **3** upon addition of SO_4^{2-} in DMSO solution from ^1H NMR titration studies were also observed with the case of receptor **1** with SO_4^{2-}, where the downfield chemical shift changes of N–H_a protons were 1.70 ppm and 1.74 ppm, respectively (Fig. S15 and S20, ESI†), which was larger than that of receptor **1** (1.68 ppm, Fig. S8, ESI†) due to the effect of the electron withdrawing groups attached to phenyl groups. Moreover, the addition of Cl^- and HSO_4^- ions into the DMSO solution of receptors **1–3** resulted in moderate chemical shift changes of N–H_a protons of receptors **1–3** by 0.24, 0.35 and 0.39 ppm, and 0.25, 0.88 and 0.88 ppm, respectively, in ^1H NMR titration experiments (see ESI†), which suggested the weaker binding affinities of Cl^- and HSO_4^- to receptors **1–3** than SO_4^{2-}. The addition of tetrahedral $H_2PO_4^-$ and Y shape AcO^- ion into the DMSO solution of receptor **1** caused the significantly downfield chemical shift changes of both squaramide N–H_a and N–H_b protons of receptor **1** by 1.51 (N–H_a) and 1.39 (N–H_b) ppm, and 1.29 ppm (N–H_a) and 1.25 ppm (N–H_b), respectively, indicating the superior complementary geometric tripodal scaffold for better selective recognition of tetrahedral anion than Y shape one. However, in the cases of receptors **2** and **3** in DMSO solution, upon addition of $H_2PO_4^-$ and AcO^- ions, respectively, the ^1H NMR spectra showed that the peak of N–H_b protons became broadened and even disappeared (see ESI†), suggesting that receptors **2** and **3** with $H_2PO_4^-$ and AcO^- in solution underwent a deprotonation process.[22] Furthermore, TBAOH as a much stronger base was titrated into the DMSO solution of receptors **2** and **3**, respectively, to confirm such deprotonation process (Fig. S25–S26, ESI†).

The binding affinities of receptors **1–3** with those different anions were assessed (Table 1) using WinEQN MR2[23] software by fitting the largest chemical shift of the N–H proton resonance of the squaramide moieties (see ESI†).[22] Generally, in all cases of receptors **1–3**, the binding constants obtained for SO_4^{2-} ($\log K > 4.75$) were higher than $H_2PO_4^-$ and HSO_4^-, and much higher than AcO^- and Cl^-, demonstrating the advantage of such tripodal scaffold to selectively chelate SO_4^{2-}. In receptors **1–3**, receptors **2** and **3** demonstrated the better binding affinity for SO_4^{2-} than receptor **1** due to the electron withdrawing group attached to their phenyl groups. These obtained strong binding affinity from receptors **1–3** showed obvious superiority for SO_4^{2-} recognition compared to reported urea-based tripodal receptors, such as phenyl-substituted tripodal urea ($\log K = 3.48$)[17] or *p*-cyanophenyl-substituted tripodal urea ($\log K = 4.70$).[20] Receptor **1** could also more strongly bind to tetrahedral $H_2PO_4^-$ ion with the binding constant $\log K = 4.15$ compared to reported phenyl-substituted tripodal urea receptor ($\log K = 4.04$),[17] while receptors **2** and **3** underwent the deprotonation process with $H_2PO_4^-$ ion. Considering the significant differences in the anion binding behaviours between our squaramide-based tripodal receptors **1–3** and those well-explored urea tripodal receptors, such receptors **1–3** appeared to show evident improvement for the inorganic anion

Table 1 Binding constants ($\log K/M^{-1}$) of receptors **1**, **2** and **3** with various anions determined from NMR titrations in DMSO-d_6[a]

Anion[b]	Receptor **1**	Receptor **2**	Receptor **3**
SO_4^{2-}	4.75 ± 0.11	4.95 ± 0.12	4.87 ± 0.07
$H_2PO_4^-$	4.15 ± 0.14	N/A[c]	N/A[c]
HSO_4^-	3.65 ± 0.12	3.78 ± 0.05	3.65 ± 0.14
AcO^-	2.82 ± 0.07	N/A[c]	N/A[c]
Cl^-	2.58 ± 0.08	2.61 ± 0.11	2.65 ± 0.09

[a] Data was best fitted in 1 : 1 binding stoichiometry and see ESI† for experimental details. [b] Anions used as tetrabutylammonium salts. [c] Deprotonation behavior was observed.

recognition, which could be related to the H-bond donor abilities of squaramide moieties, complementary geometry of tripodal scaffold, and the Hofmeister series.[24]

Furthermore, the competitive experiments of receptor **1** and SO_4^{2-} with various other anions were also conducted by ^{1}H NMR experiments (Fig. S27, ESI†). The results confirmed receptor **1** selectively binds SO_4^{2-} over equal amounts of various competitive inorganic anions.

In conclusion, we have developed three squaramide-based tripodal anion receptors **1–3**, and receptor **1** formed dimeric complex in solid state and 1 : 1 complex in solution with SO_4^{2-}. All receptors **1–3** could selectively encapsulate SO_4^{2-} *via* hydrogen bonds over other examined anions. This work will facilitate the potential applications of such receptors in various fields such as anion transporters and extraction agents.

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