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Bis[squaramido]ferrocenes as electrochemical sulfate receptors†

Jakob D. E. Lane,[a] William J. H. Greenwood, [iD][b] Victor W. Day,[c]
Katrina A. Jolliffe, [iD] *[ad] Kristin Bowman-James [iD] *[c] and Louis Adriaenssens [iD] *[b]

1,1′-Bis[squaramido]ferrocenes (FcSq$_2$) are introduced as electrochemically active scaffolds for sulfate recognition. FcSq$_2$ display high sulfate-binding affinity and selectivity in aqueous DMSO mixtures. Among tested anions, sulfate elicits a unique electrochemical response in FcSq$_2$, enabling selective detection.

The key roles played by sulfate in processes essential to industry[1] and healthcare[2] have inspired molecular strategies to selectively bind and report sulfate.[3] Among these, the synthetic challenges and toxicity issues[4] associated with charged species make neutral and discrete receptor molecules a leading choice. These molecules comprise a binding site intended to employ weak non-covalent interactions that interact specifically with sulfate. In this context, the polar and often aqueous environments in which anions are typically found severely challenge the binding ability of receptors. Of the commonly targeted anions, this issue is arguably most significant for sulfate, an anion that features a particularly high hydration energy ($\Delta G_\mathrm{h}^{\circ}{}_{\mathrm{SO_4^{2-}}} = -1090$ kJ mol^{-1}, *cf.* $\Delta G_\mathrm{h}^{\circ}{}_{\mathrm{Cl^-}} = -347$ kJ mol^{-1}).[5]

Among the effective recognition motifs known for binding sulfate in competitive media,[6] squaramides, comprising two NH hydrogen bond donors that act as a "mini-chelate",[7] have proven promising.[8] Within these studies, and in the larger field of anion recognition, an intriguing paradox is raised. While an ideal receptor should comprise a binding site whose size, shape and electronics exclusively promote interaction with the anion of interest, exclusivity must often be balanced with the freedom

needed to adapt receptor structure during the entry and exit of the anion from the binding pocket. In this context, previously unreported 1,1′-bis(squaramido)ferrocenes (FcSq$_2$) intrigued us as a simultaneously rigid and flexible receptor scaffold for sulfate binding (Fig. 1).[9]

Within FcSq$_2$, direct attachment of the squaramide unit to the cyclopentadienyl (Cp) ligand creates a conjugated system, compelling each Cp-squaramide 'arm' of the receptor to adopt a planar structure.[10] Attachment of these arms through the ferrocenyl 'core' of the scaffold presents the two squaramide units upon stacked and parallel planes separated by ≈ 3.4 Å, as defined by the Cp–Cp geometry of ferrocene. We note, in certain prior work, squaramide units bound to the same sulfate anion are shown to stack with a squaramide–squaramide distance between 3.3 and 3.5 Å.[8b,e] To the best of our knowledge, a similar relationship between squaramide motifs is absent from all reported structures involving other singly and doubly charged anions. Thus, it may be expected that the constrained component of the geometrical relationship between squaramide units within FcSq$_2$ engenders sulfate-selective binding. In concert with constraint, a single degree of large-amplitude freedom, characterized by rotation about the central axis of the ferrocenyl 'core' of the molecule, balances rigidity with flexibility. Finally, in addition to structural features suitable for binding sulfate, FcSq$_2$ are built around the robust
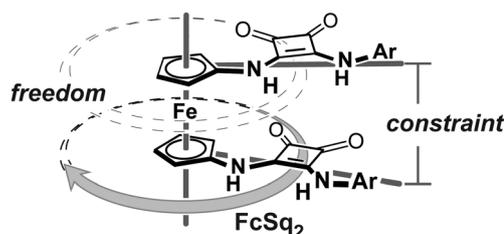
[a] *School of Chemistry, The University of Sydney, NSW, 2006, Australia.*
 E-mail: kate.jolliffe@sydney.edu.au
[b] *School of Chemistry, The University of Lincoln, Lincoln, LN6 7DL, UK.*
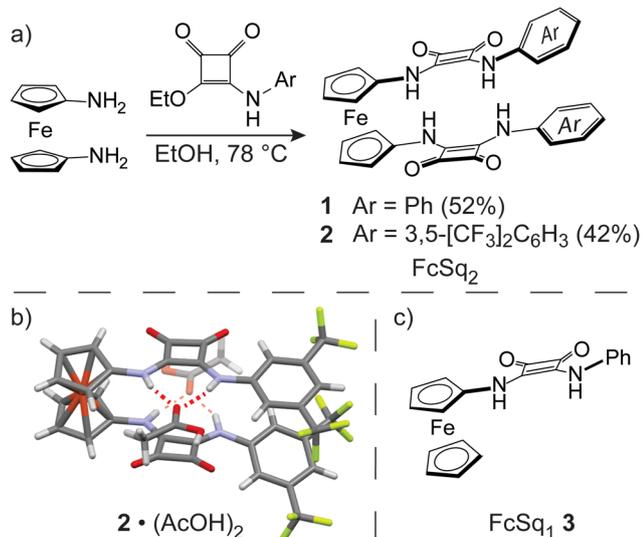 *E-mail: ladriaenssens@lincoln.ac.uk*
[c] *Department of Chemistry, University of Kansas, Lawrence, Kansas, 66045, USA.*
 E-mail: kbjames@ku.edu
[d] *The University of Sydney Nano Institute (Sydney Nano), The University of Sydney, NSW, 2006, Australia.*

Fig. 1 The 1,1′-bis[squaramido]ferrocene scaffold FcSq$_2$ combines flexibility with rigid attributes suitable for sulfate recognition.
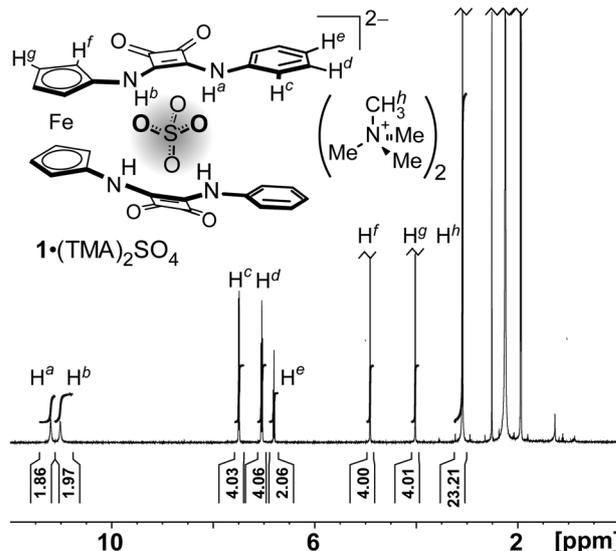
Scheme 1 (a) Synthesis of FcSq$_2$ **1** and **2**. (b) Single crystal structure of acetic acid solvate of **2**. Disorder of the fluorine atoms within two CF$_3$ groups is omitted for clarity. Select hydrogen bonds are denoted with dashed red lines. (c) Structure of FcSq$_1$ **3**.[9a]

Fig. 2 ^{1}H-NMR (500 MHz, MeCN-d_3, 25 °C) of **1**·SO$_4$$^{2-}$ with the TMA counter ion. See Fig. S3 (ESI†) for corresponding ^{13}C-NMR spectrum and Fig. S4 (ESI†) for analogous spectra of **2**·SO$_4$$^{2-}$.

electrochemical manifold of ferrocene. Thus, the FcSq$_2$ scaffold has potential to bind and electrochemically detect sulfate.

FcSq$_2$ were synthesized by reaction of diaminoferrocene with the appropriate squaramate ester (Scheme 1a) with purification achieved by recrystallization from dimethyl sulfoxide (DMSO). The FcSq$_2$ receptors exhibit poor solubility in all solvents, however, solutions could be obtained by heating suspensions of FcSq$_2$ in DMSO to near boiling temperatures. Upon cooling to room temperature, these solutions are kinetically stable for up to 30 minutes, permitting ^{1}H-NMR spectroscopic analysis which showed FcSq$_2$ are isolated as the FcSq$_2$· 2DMSO complexes (Fig. S1 and S2, ESI†). Crystals of 3,5-bis(trifluoromethyl)phenyl substituted FcSq$_2$ **2** suitable for single crystal X-ray diffraction grew from hot acetic acid (AcOH), confirming the structure of **2** as the acetic acid solvate (Scheme 1b).

To investigate the suitability of FcSq$_2$ as receptors for sulfate, 10 equivalents of tetramethylammonium sulfate (TMA)$_2$SO$_4$, were added to a suspension of FcSq$_2$ **1** or **2** in deuterated acetonitrile. Both (TMA)$_2$SO$_4$ and FcSq$_2$ are insoluble in acetonitrile. However, upon sonication of the heterogeneous mixture, the acetonitrile liquid-phase adopted a deep orange colour while the residual solid powder turned from an orange colour to pure white, suggesting full solubilisation of the ferrocene. Following separation of the excess (TMA)$_2$SO$_4$ solid, NMR spectroscopic analysis of the orange solution showed signals indicative of the 1 : 1 FcSq$_2$·SO$_4$$^{2-}$ complex with every carbon and proton environment accounted for (Fig. 2, Fig S3 and S4, ESI†). ^{1}H-NMR signals belonging to squaramide NH protons (H^a and H^b) appear in the far downfield region of the spectrum at 11.20 and 11.01 ppm, respectively, suggesting the participation of these protons in hydrogen bonding interactions with the sulfate anion (cf. 9.56 ppm for H^a and 9.18 ppm

for H^b in the ^{1}H-NMR spectrum of free **1** in DMSO-d_6, Fig. S1, ESI†). Notably, despite exposure of FcSq$_2$ to a large excess of sulfate, the relative integral values for ^{1}H-NMR signals corresponding to FcSq$_2$ **1** (H^{a-g}) and the TMA counter ion (H^h) are indicative of the 1 : 1 FcSq$_2$·SO$_4$$^{2-}$ complex.

To investigate the anion recognition properties of FcSq$_2$, ^{1}H-NMR binding studies were conducted by the addition of the tetrabutylammonium (TBA) salts of various anions to a solution of FcSq$_2$ **1** (2.5 mM) in 1% H$_2$O/DMSO (Table 1, entries 1–7).[11,12] Little to no changes in the spectral characteristics corresponding to **1** were observed with the addition of Cl$^-$, HSO$_4$$^-$ or NO$_3$$^-$, indicating a lack of binding between **1** and these anions. The addition of one equivalent of F$^-$ or AcO$^-$ was accompanied by disappearance of the ^{1}H-NMR signals corresponding to the NH protons, signifying deprotonation occurs in

Table 1 Association constants K_a (M^{-1}) for 1 : 1 adducts of two- and one-arm squaramidoferrocene receptors, **1** and **3**, respectively, with various anions in water/DMSO mixtures^a

Entry	Anion	Receptor	% H$_2$O	K_a (M^{-1})
1	Cl$^-$	**1**	1	2.0×10^{2b}
2	HSO$_4$$^-$	**1**	1	No interaction^c
3	NO$_3$$^-$	**1**	1	No interaction^c
4	F$^-$	**1**	1	Deprotonation^d
5	AcO$^-$	**1**	1	Deprotonation^d
6	H$_2$PO$_4$$^-$	**1**	1	$>10^{4b}$
7	SO$_4$$^{2-}$	**1**	1	$>10^{4b}$
8	H$_2$PO$_4$$^-$	**3**	1	4.0×10^{2b}
9	SO$_4$$^{2-}$	**3**	1	1.2×10^{3b}
10	H$_2$PO$_4$$^-$	**1**	20	1.4×10^{4e}
11	SO$_4$$^{2-}$	**1**	20	3.1×10^{5e}

^{a} Titrations were performed at 298 K. Errors estimated at ±15%. ^{b} ^{1}H-NMR titration. ^{c} Changes in the spectra are too small to calculate association constants. ^{d} Signals corresponding to the squaramide NH protons disappeared following addition of 1 equivalent of anion. ^{e} UV-Vis titration.

the presence of more basic anions. Conversely, the addition of $TBAH_2PO_4$ or $(TBA)_2SO_4$ effected clear changes in the ¹H-NMR spectra that could be ascribed to anion binding.

Upon addition of sub-stoichiometric $TBAH_2PO_4$, ¹H-NMR signals corresponding to the squaramide NH protons (H^a and H^b) became broad to the point of disappearance (Fig. S7, ESI†). In the presence of 0.5 to 2.0 equivalents $TBAH_2PO_4$, ¹H-NMR signals that we ascribe to H^a and H^b within the 1:1 $1 \cdot H_2PO_4^-$ complex appeared at 11.30 and 11.25 ppm, respectively (cf. H^a at 9.56 ppm and H^b at 9.18 ppm in the ¹H-NMR spectrum of the free receptor). Observation that the 1:1 complex is fully formed after addition of 1 equivalent $TBAH_2PO_4$ indicates that $K_{a(1 \cdot H_2PO_4^-)} > 10^4 \text{ M}^{-1}$ under these conditions. Then, as the amount of $TBAH_2PO_4$ exceeded 2.5 equivalents, the ¹H-NMR signals belonging to H^a and H^b shifted further downfield, suggesting the formation of a putative 1:2 $1 \cdot (H_2PO_4^-)_2$ complex in the presence of excess dihydrogen phosphate. Finally, beyond the addition of 5 equivalents $TBAH_2PO_4$, ¹H-NMR signals belonging to H^a and H^b disappeared, indicating deprotonation.

Addition of ≤1 equiv. $(TBA)_2SO_4$ to $FcSq_2$ 1 provoked a similar response as observed during the titration with dihydrogen phosphate (Fig. 3). ¹H-NMR signals corresponding to the squaramide NH protons (H^a and H^b) initially broadened to the point of disappearance, and then reappeared at 11.75 and 11.65 ppm, respectively, as the ratio of $1:(TBA)_2SO_4$ neared 1:1. Remarkably, as further equivalents of $(TBA)_2SO_4$ were added, the signals corresponding to 1 remained unchanged. Despite the ability of $FcSq_2$ to adopt an opposed conformation, whereby the two squaramide motifs are presented on opposite sides of the molecule as separate binding sites (cf. titration with H_2PO_4), it appears that the 1:1 $1 \cdot (TBA)_2SO_4$ complex is exceptionally stable and robust, even in the presence of large excesses of sulfate.

To quantify K_a for the $1 \cdot SO_4^{2-}$ and $1 \cdot H_2PO_4^-$ complexes, binding studies monitored by UV-vis spectroscopy were initially run in 1% water/DMSO. However, in this medium, the data could not be fit to any simple binding model. We propose that intermolecular hydrogen bonding facilitates $FcSq_2$ homo-oligomerization processes which combine with anion-binding processes to create a complex equilibrium that cannot be properly fit with a simple model. To minimise hydrogen bonding between $FcSq_2$ units, titrations were run in 20% water/DMSO; in this competitive aqueous medium, the data fit well to a simple 1:1 binding model (Table 1, entries 10 and 11). Notably, $FcSq_2$ 1 was shown to bind SO_4^{2-} strongly ($K_a = 3.1 \times 10^5 \text{ M}^{-1}$) and with a significant preference for SO_4^{2-} vs. $H_2PO_4^-$ ($K_{a(SO_4^{2-})}/K_{a(H_2PO_4^-)} = 22$), suggestive that the $FcSq_2$ scaffold does indeed present an excellent and selective fit for the sulfate anion.

To probe the role of $FcSq_2$ structure in selective interaction with sulfate, the binding behaviour of the analogous one-arm derivative $FcSq_1$ 3[9a] (Scheme 1c) was quantified through ¹H-NMR binding studies in 1% water/DMSO-d_6 (Table 1, entries 8 and 9). From these studies, two key observations were made: (1) one-arm $FcSq_1$ 3 shows a preference for binding SO_4^{2-} vs. $H_2PO_4^-$ ($K_{a(SO_4^{2-})}/K_{a(H_2PO_4^-)} = 3$) that is seven times lower than observed for two-arm $FcSq_2$ 1, (2) sulfate binding with one-arm analogue 3 in moderately competitive 1% water/DMSO is over two orders of magnitude weaker than sulfate binding with two-arm $FcSq_2$ 1 in highly competitive 20% water/DMSO! These notable differences in binding behaviour between one- and two-arm analogues are strong evidence that the stacked presentation of two planar Cp-squaramide arms is a key factor in the sulfate-selectivity of the $FcSq_2$ scaffold.

The electrochemistry of $FcSq_2$ was investigated through cyclic wave voltametry. In DMSO, voltammograms reported multiple and overlapping oxidation processes. Switching the solvent to 20% water/DMSO revealed a single oxidation wave (Fig. 4), suggesting that the complexity of the voltamograms obtained in pure DMSO is due to similar aggregation processes that hampered data-fitting during binding studies. Oxidation occurs at $E_{1/2} = -63$ mV for 1 (compared to $E_{1/2(ferrocene)} = 0$ V)[13] and is irreversible. 80–100 mV separation is observed between anodic and cathodic peaks in addition to an anodic current that is approximately 3× more intense than the cathodic current.[14]
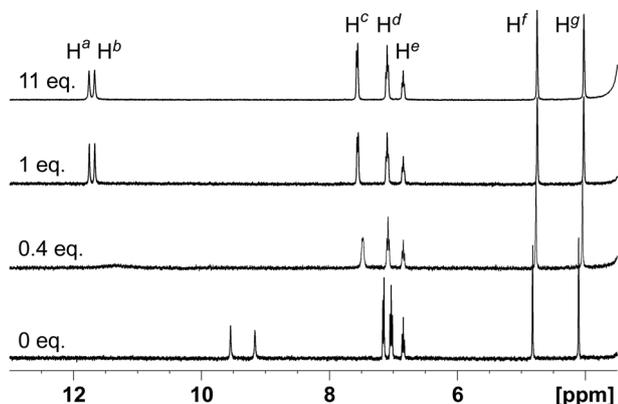

Fig. 3 Selected spectra from the ¹H-NMR titration of $FcSq_2$ 1 with $(TBA)_2SO_4$ in 1% H_2O/DMSO-d_6 at 25 °C. Proton assignments from Fig. 2.
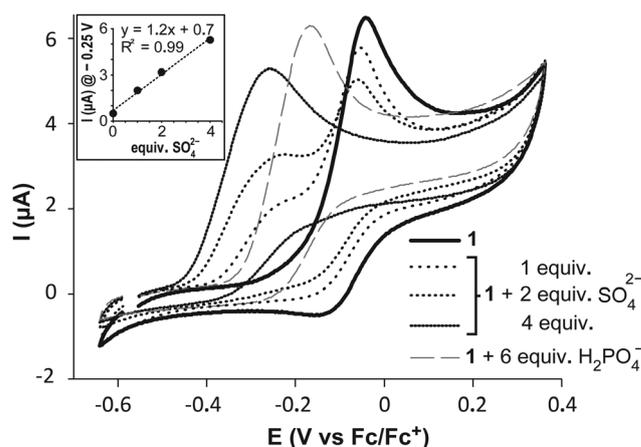

Fig. 4 CV response of 1 (0.25×10^{-3} M) in 20% water/DMSO before and after addition of $(TBA)_2SO_4$ or $TBAH_2PO_4$; supporting electrolyte, 0.1 M $TBAClO_4$; scan rate, 100 mV s⁻¹; $T = 80$ °C. Inset: Linear electrochemical response of 1 to sulfate addition at −0.25 V vs. Fc/Fc⁺.

Addition of up to 10 equiv. TBACl or TBANO$_3$ exerted little to no effect on the electrochemistry of FcSq$_2$ **1**.[13] Conversely, upon progressive addition of TBAH$_2$PO$_4$ or (TBA)$_2$SO$_4$, two-wave behaviour was observed (Fig. 4), whereby the wave corresponding to free **1** diminished in intensity while a cathodically shifted second wave appeared which presumably corresponds to the **1**·anion complex. Addition of TBAH$_2$PO$_4$, affected appearance of the new wave at $E_{1/2} = -170$ mV ($\Delta E_{1/2} = 107$ mV *vs.* free **1**). The corresponding wave induced by addition of (TBA)$_2$SO$_4$ appears at a significantly more negative potential ($E_{1/2} = -305$ mV, $\Delta E_{1/2} = 242$ mV *vs.* free **1**). In addition, fewer equivalents of SO$_4^{2-}$ are required to achieve the maximum response (4 equiv. SO$_4^{2-}$ *vs.* 6 equiv. H$_2$PO$_4^-$), a behaviour we ascribe to the higher affinity of FcSq$_2$ for SO$_4^{2-}$ *versus* H$_2$PO$_4^-$. The electrochemical response, measured as the maximum anodic current (at -0.25 V *vs.* Fc/Fc$^+$), is linear with respect to the concentration of sulfate up to 4 equiv. (Fig. 4, inset). Concentrations of sulfate less than 1 equiv. *vs.* [**1**] were not trialled, so 0.25 mM is the lowest detection limit we can claim.

Conclusions

In summary, two receptors built around the previously unreported 1,1′-bis(squaramido)ferrocene (FcSq$_2$) scaffold have been prepared. Binding studies showed that FcSq$_2$ receptors overcome the high hydration energy of sulfate and make strong 1 : 1 complexes with this anion in highly competitive aqueous media. Notably, despite FcSq$_2$ presenting two independent squaramide units, the 1 : 1 complex with sulfate is robust and, contrary to the analogous complex with H$_2$PO$_4^-$, does not break to form the 1 : 2 receptor·(anion)$_2$ complex, even in the presence of excess sulfate. Furthermore, FcSq$_2$ **1** binds selectively to sulfate *versus* nitrate, acetate, bisulfate, chloride and dihydrogen phosphate. Comparison to the one-arm analogue **3** provides evidence for the importance of the stacked two arm structure of FcSq$_2$; whereby excision of one arm results in 7× lower selectivity for binding SO$_4^{2-}$ *versus* H$_2$PO$_4^-$ and a 1 : 1 complex with sulfate that is over two orders of magnitude weaker. Cyclic wave voltammetry revealed that FcSq$_2$ present an irreversible oxidation that is cathodically shifted relative to ferrocene. In the presence of H$_2$PO$_4^-$ or SO$_4^{2-}$ two-wave behaviour is observed with the new wave featuring a large cathodic shift. Notably, the shift induced by sulfate is separated from that induced by H$_2$PO$_4^-$ by over 130 mV. The electrochemical response of FcSq$_2$ **1** to sulfate is easily distinguishable and proportional to [SO$_4^{2-}$], underlining the promise of FcSq$_2$ as a tool to bind and detect sulfate.

Conflicts of interest

There are no conflicts ro declare.

Acknowledgements

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7 We adapt the term ''mini-chelate'', originally coined for the related urea-binding motif (ref. 6d), to squaramides.

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10 Within the group of carbonyl-conjugated N–H hydrogen bond donors, aryl-substituted squaramides are exceptionally planar. For the 39 organic diarylsquaramides reported in the Cambridge Structural Database, the average angle between planes defined by the diaminocyclobutyl component and either aryl group is 21°. The average angle between analogous planes within 861 reported diarylureas is 30° and 9451 N-aryl amides is 23.5°.

11 Binding of **1** with TBANO$_3$ followed by UV-Vis spectroscopy.

12 Titrations involving the 3,5-(CF$_3$)$_2$-C$_6$H$_3$ FcSq$_2$ derivative **2** were complicated by poor fits and disappearance of ^{1}H-NMR signals corresponding to the NH protons and are not discussed here.

13 Section S5 of the ESI† reports all details of the electrochemistry of FcSq$_2$ **1** and the electrochemistry of the free receptor **2**.

14 The redox behaviour of ferrocenes, including both the amide- and urea-analogues of FcSq$_2$ (see ref. 15 and 16, respectively), is known to be robust. Therefore, it is somewhat surprising that FcSq$_2$ **1** and **2** both show irreversible electrochemical behaviour. See Section S5 of the ESI† for more details and discussion on the irreversible component of the electrochemical manifold of FcSq$_2$.

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