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Selective and tuneable recognition of anions using C_{3v}-symmetrical tripodal urea-amide receptor platforms†

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The synthesis and binding investigations of first generation C_{3v}-symmetrical hydrogen bonding urea-amide based tripodal receptors, 1–6, with various anions such as acetate, phosphate, sulfate and chloride in DMSO-d_6 are presented. Analysis of the ^{1}H NMR titrations of 1–6 showed on all occasions the selective formation of 1 : 1 stoichiometries.

The design and synthesis of receptors for the selective recognition and sensing of anions, through the use of weak interactions such as hydrogen bonding, is an active area of research within supramolecular chemistry.[1–4] Structures based on urea and thiourea recognition sites are of particular interest due to their strong, and tuneable hydrogen binding abilities,[4–7] and their relatively easy syntheses, which facilitates their use in both simple and complex systems.[8] Incorporation of such moieties into the tripodal molecular platform can give rise to the formation of preorganised structures,[9] which can allow for cooperative hydrogen bonding interactions to take place from several binding sites.[10] Hence, such systems have also been employed for studying transport of anions[11] such as sulfate across lipid bilayers.[12] To date, only a limited number of tripodal anion receptors have been reported in the literature, but these are highly attractive for the formation of anion receptors that possess high coordination requirements such as halides, sulfates and phosphates.[13,14] We have recently demonstrated that simple amido-urea[15] and thiourea[16] receptors can be designed that enable positive cooperative binding of anions. Herein we present the synthesis and anion binding studies of six new tripodal receptors, **1–6**, Fig. 1. Each receptor consists of three urea moieties, connected to a central C_{3v} symmetrical phenyl platform *via* amide linkage. This central *N*-arylbenzamide motif has previously been identified by Lewis *et al.*,[17] as a candidate for developing extended geometries[18] for molecular recognition, but to the best of our knowledge, have not been used as part of an anion receptor platform of the kind presented here. We anticipated that for **1–6**, this central platform would enable cooperative or synergetic binding of anions by all three urea sites. We also foresaw that this binding would affect the chemical shifts of the amide protons in the ^{1}H NMR due to the conformational changes that these structures would undergo. While **1** and **2** possess electron withdrawing groups, **3–6** all have long alkyl chains which we hoped would facilitate the use of these structures as potential membrane transporters.

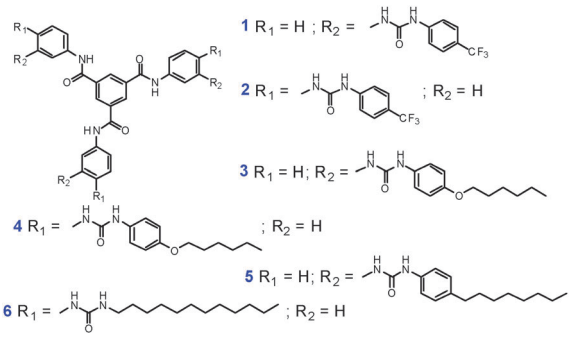

Fig. 1 Structures **1–6** employed in the current study.

The synthesis of receptors **1–6** (see Scheme S1 in ESI†) was achieved in a few steps from 1,3,5-benzenetricarbonyl trichloride. In general, these were first reacted with either *meta* or *para* nitroaniline, followed by reduction to the corresponding amines, using 10% Pd/C and hydrazine monohydrate. The final receptors **1–6** were then formed by suspending these amines into hot CH_3CN followed by the addition of the desired isocyanates, and heating the resulting mixtures at reflux under an inert atmosphere overnight. This resulted in the formation of precipitates, which were filtered and washed with cold CH_3CN giving **1–6** in 91%, 85%, 89%, 95%, 91% and 67% yields respectively (see ESI†).

In order to evaluate the binding affinity of **1–6** for various anions, we initially carried out UV-Vis absorption studies using acetate (AcO^-), sulfate (SO_4^{2-}), dihydrogen phosphate ($H_2PO_4^-$) and chloride (Cl^-), respectively, as their TBA (tetrabutyl ammonium) salt solutions. However, to our surprise, the changes in the absorption spectra were minor, and it was difficult to assess the binding affinity of these receptors for the above anions accurately. Consequently, the anion recognition of **1–6** was instead examined by using ^{1}H NMR titrations

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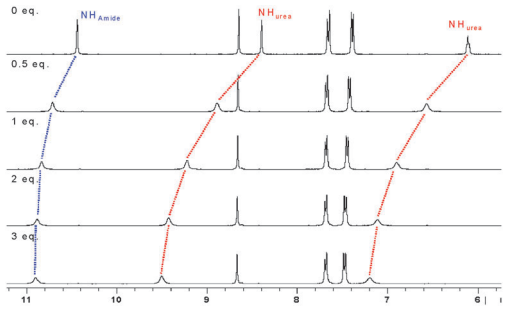

Fig. 2 The ^{1}H NMR (400 MHz) titration of receptor **6** with $H_2PO_4^-$ (0 → 3 eq.) in DMSO-d_6.

in DMSO-d_6, which allowed the changes in the chemical environment of all of the *N–Hs* of **1–6** to be monitored upon anion recognition. An example of such a titration is shown as a stack plot in Fig. 2, for the titration of **6**, where it is clear that the anion binding is in fast exchange on the NMR time scale.[19]

The anion induced changes for the *N–H* resonances of **1–6** were analysed by non-linear regression analysis, and fitted to various host : guest stoichiometries. The changes observed for the urea *N–H* resonances (only one of each shown) of **1** and **2** upon binding of $H_2PO_4^-$ and SO_4^{2-} are shown in Fig. 3, expressed as $\Delta\delta$ *vs.* anion equivalents. From these changes, it can be clearly seen that both structures bind these anions in a 1 : 1 stoichiometry, where the *N–H* protons are shifted by 1.5–2.5 ppm upon hydrogen binding to the anions. Similar behaviour was observed for Cl^- and AcO^- for both receptors (see ESI†), where the largest changes in the ^{1}H NMR were observed upon the addition of one equivalent of these anions. As we had observed in our previous work,[15,16] the amide proton (*meta* to the urea) of **1** also experienced a significant downfield shift upon titration with $H_2PO_4^-$ and Cl^-, being shifted by *ca.* 0.6 ppm within the addition of one equivalent of these anions. In contrast, these chemical shifts were less significant upon titration with SO_4^{2-} and AcO^-, being shifted by *ca.* 0.1 ppm (see ESI†). Moreover, for the structural *para* isomer **2**, only Cl^- gave rise to such shifts, being *ca.* 0.15 ppm, after the addition of one equivalent. Molecular modeling using MM2 of the binding of **1** and **2** (see Graphical Abstract) to these anions showed the formation of closely associated host–guest complexes, where the amide protons are directed away from the anion-binding side (*i.e.* 'receptor pocket'). Hence, these shifts are conformationally induced, signifying the binding of the anions to the urea moieties, and are not due to direct binding of the anions to the amides themselves.

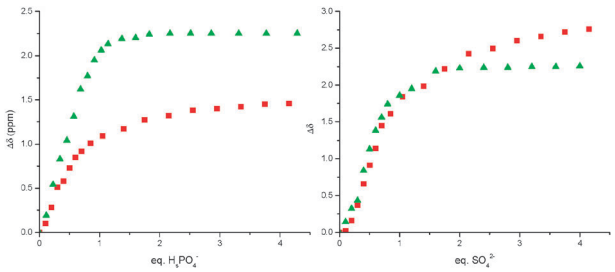

Fig. 3 Changes in the chemical shifts ($\Delta\delta$) of one of the urea protons of **1** (■) and **2** (▲) (7×10^{-3} M) upon titration with $H_2PO_4^-$ (left) and SO_4^{2-} (right) in DMSO-d_6.

Table 1 Binding constants determined for **1–6** from NMR titrations in DMSO-d_6

Receptor	Anion	log $K_{1:1}$ (N–H urea)
1	AcO^-	2.81 ± 0.07
	SO_4^{2-}	2.78 ± 0.05
	$H_2PO_4^-$	**3.10 ± 0.10**
	Cl^-	2.39 ± 0.06
2	AcO^-	2.79 ± 0.07
	SO_4^{2-}	**3.70 ± 0.20**
	$H_2PO_4^-$	**4.20 ± 0.10**
	Cl^-	2.10 ± 0.07
3	AcO^-	**3.70 ± 0.10**
	SO_4^{2-}	2.15 ± 0.08
	$H_2PO_4^-$	**3.19 ± 0.08**
	Cl^-	—[a]
4	AcO^-	**3.25 ± 0.04**
	SO_4^{2-}	2.10 ± 0.10
	$H_2PO_4^-$	**3.50 ± 0.10**
	Cl^-	2.81 ± 0.07
5	AcO^-	**3.70 ± 0.10**
	SO_4^{2-}	2.06 ± 0.09
	$H_2PO_4^-$	**3.20 ± 0.10**
	Cl^-	—[a]
6	AcO^-	—[a]
	SO_4^{2-}	—[a]
	$H_2PO_4^-$	**2.84 ± 0.07**
	Cl^-	2.05 ± 0.04

[a] Isotherm could not be fitted to a 1 : 1 or 1 : 2 binding model.

From the titration profiles in Fig. 3, it is also clear that the recognition of $H_2PO_4^-$ did not result in any further measurable shifts in the urea N–H resonance after the formation of the 1 : 1 host : guest complex. This 1 : 1 stoichiometry was also confirmed using MALDI-TOF mass spectrometry, (see ESI) for the binding of **2** to $H_2PO_4^-$, with a *m*/*z* peak observed at 1138.2332, which had an isotopic distribution pattern matching that calculated for [**2** + H_2PO_4]$^-$. The binding affinity of **1** and **2** for the aforementioned anions was further assessed by fitting the changes in the *N–H* resonances of the urea protons using the program WinEq NMR[19] to 1 : 1 and 1 : 2 binding stoichiometries. On all occasions the best fit was obtained using a 1 : 1 stoichiometry and the binding constants obtained from this analysis (expressed as log $K_{1:1}$) are shown in Table 1, where the binding constants of anions such as $H_2PO_4^-$ which displayed high affinity for these receptors are displayed in bold. Moreover, similar results were obtained for fitting either of the two *N–H* urea protons (see ESI†). With the exception of Cl^-, **2** gave rise to higher binding affinity for these ions than **1**, which in the case of $H_2PO_4^-$ resulted in a log $K_{1:1}$ = 4.20 (±0.10), for **2**, while an order of magnitude lower binding constant, of log $K_{1:1}$ = 3.10 (±0.10), was observed for **1**. This clearly demonstrates the importance of the substituted pattern of the di-aryl urea part (*e.g. meta vs. para*) of these receptors and that **1** and **2** have high affinity for tetrahedral anions. For both, the highest affinity was also found to be for $H_2PO_4^-$ of the anions tested. However, the interaction between **2** and SO_4^{2-} was also strong with log $K_{1:1}$ = 3.70 (±0.20), again, being a magnitude larger than that seen for **1**.

Next the electron donating receptors *m*- and *p*-urea-phenyl-alkoxy chain derivatives, **3** and **4**, were investigated. The interaction with AcO^- and SO_4^{2-} showed very similar results with the urea protons experiencing a large downfield shift of

2.5–3 ppm before reaching a plateau. In contrast, the amide proton of both receptors experienced, however, a significantly smaller shift to that seen for **1** and **2** above. The formation of only the 1 : 1 species for receptor **4** with AcO^- was also evident in the MALDI-TOF mass spectrum (ESI†). Similar shifts were seen for $H_2PO_4^-$. The smallest spectral changes were observed upon titration with Cl^-. The results from these NMR titrations were fitted to 1 : 1 binding, from which log $K_{1:1}$ was determined, Table 1. Here, receptor **4** showed a slightly higher affinity for these anions than **3**; albeit the difference in log $K_{1:1}$ was to a lesser extent than seen for **1** and **2**. Interestingly, the binding of AcO^- was significantly higher for both compared to **1** and **2**. For both, the smallest log $K_{1:1}$ was observed for SO_4^{2-}.

With the view of further investigating the effect that the various substituents had on the anion affinity of these tripodal systems, the *m*-urea-phenyl-alkyl chain and the *p*-urea-alkyl chain based receptors **5** and **6** were also analysed in an analogous manner. Here, **5**, a slightly modified version of **3**, was determined to have higher affinity for the anions than **6**, which is to be expected, as **6** lacks the second aryl group, which through inductive effects makes the protons in **5** more acidic and hence, better hydrogen bonding donors, Table 1. In fact, comparison of **3** and **5** showed that both display similar affinity for these anions. Analysis of the binding of AcO^- and SO_4^{2-} to **6** did not result in a full plateau being reached after the addition of excess anions, making accurate determination of log $K_{1:1}$ difficult. From the analysis of **5**, slightly higher affinity was seen for AcO^-, over $H_2PO_4^-$; the latter being of similar magnitude, to that seen for **1** and **3** above. In contrast the binding of SO_4^{2-} was significantly weaker for **5** than seen for **1**; but of similar to that seen for **3**. Receptor **6** also showed a significant interaction with $H_2PO_4^-$ and Cl^-, but in contrast to that seen for **1–5** it was the lowest in the series.

In summary, we have developed six novel tripodal receptors, **1–6**, possessing highly organised urea binding sites, and determined their binding properties with various anions using ^1H NMR titrations. These showed high binding affinities for $H_2PO_4^-$ and AcO^-. Moreover, **2** also showed high affinity for SO_4^{2-}. The results clearly show that our simple design principle facilitates the development of novel anion receptors possessing tuneable cooperative binding. We are currently developing this anion binding motives in greater details.

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Notes and references

1 (*a*) P. A. Gale, *Chem. Soc. Rev.*, 2010, **39**, 3746; (*b*) J. W. Steed, *Chem. Soc. Rev.*, 2010, **39**, 3686; (*c*) B. P. Hjay, *Chem. Soc. Rev.*, 2010, **39**, 3700; (*d*) A.-F. Li, J.-H. Wang, F. Wang and Y.-B. Jiang, *Chem. Soc. Rev.*, 2010, **39**, 3729; (*e*) V. Amendola, L. Fabbrizzi and L. Mosca, *Chem. Soc. Rev.*, 2010, **39**, 3889; (*f*) R. M. Duke, E. B. Veale, F. M. Pfeffer, P. E. Kruger and T. Gunnlaugsson, *Chem. Soc. Rev.*, 2010, **39**, 3936.

2 (*a*) P. Padros and R. Quesada, *Supramol. Chem.*, 2008, **20**, 201; (*b*) P. A. Gale, S. E. Garcia-Garrido and J. Garric, *Chem. Soc. Rev.*, 2008, **37**, 151; (*c*) P. A. Gale and R. Quesada, *Coord. Chem. Rev.*, 2006, **250**, 3219; (*d*) J. W. Steed, *Chem. Commun.*, 2006, 2637.

3 T. Gunnlaugsson, M. Glynn, G. M. Tocci (née Hussey), P. E. Kruger and F. M. Pfeffer, *Coord. Chem. Rev.*, 2006, **250**, 3094.

4 J. L. Sessler, P. A. Gale and W. S. Cho, *Anion Receptor Chemistry*, Royal Society of Chemistry, Cambridge, UK, 2006.

5 (*a*) E. B. Veale, G. M. Tocci, F. M. Pfeffer, P. E. Kruger and T. Gunnlaugsson, *Org. Biomol. Chem.*, 2009, **7**, 3447; (*b*) C. M. G. dos Santos and T. Gunnlaugsson, *Dalton Trans.*, 2009, 4712; (*c*) E. B. Veale and T. Gunnlaugsson, *J. Org. Chem.*, 2008, **73**, 8073; (*d*) R. M. Duke and T. Gunnlaugsson, *Tetrahedron Lett.*, 2007, **48**, 8043; (*e*) C. M. G. dos Santos, T. McCabe and T. Gunnlaugsson, *Tetrahedron Lett.*, 2007, **48**, 3135; (*f*) H. D. P. Ali, P. E. Kruger and T. Gunnlaugsson, *New J. Chem.*, 2008, **32**, 1153; (*g*) A. J. Lowe, F. A. Dyson and F. M. Pfeffer, *Org. Biomol. Chem.*, 2007, **5**, 1343; (*h*) F. M. Pfeffer, K. F. Lim and K. J. Sedgwick, *Org. Biomol. Chem.*, 2007, **5**, 1795.

6 (*a*) P. A. Gale, J. R. Hiscock, S. J. Moore, C. Caltagirone, M. B. Hursthouse and M. E. Leight, *Chem.–Asian J.*, 2010, **5**, 555; (*b*) R. M. Duke, J. E. O'Brien, T. McCabe and T. Gunnlaugsson, *Org. Biomol. Chem.*, 2008, **6**, 4089; (*c*) A. J. Lowe, G. A. Dyson and F. M. Pfeffer, *Eur. J. Org. Chem.*, 2008, 1559; (*d*) L.-H. Wei, Y.-B. He, J.-L. Wu, L.-Z. Meng and X. Yang, *Supramol. Chem.*, 2004, **16**, 561.

7 (*a*) C. Jia, B. Wu, S. Li, X. Huang and X.-J. Yang, *Org. Lett.*, 2010, **12**, 5612; (*b*) R. Yang, W.-X. Liu, H. Shen, H.-H. Huang and Y.-B. Jiang, *J. Phys. Chem. B*, 2008, **112**, 5105; (*c*) F. M. Pfeffer, P. E. Kruger and T. Gunnlaugsson, *Org. Biomol. Chem.*, 2007, **5**, 1894; (*d*) E. Quinlan, S. E. Matthews and T. Gunnlaugsson, *J. Org. Chem.*, 2007, **72**, 7497.

8 (*a*) C. Jia, B. Wu, S. Li, X. Huang, Q. Zhao, Q.-S. Li and X.-J. Yang, *Angew. Chem., Int. Ed.*, 2011, **50**, 486; (*b*) M. Li, B. Wu, C. Jia, X. Huang, Q. Zhao, S. Shao and X.-J. Yang, *Chem.–Eur. J.*, 2011, **17**, 2272; (*c*) M. Alajarín, R. A. Orenes, J. W. Steed and A. Pastor, *Chem. Commun.*, 2010, **46**, 1394; (*d*) D. R. Turner, M. J. Paterson and J. W. Steed, *J. Org. Chem.*, 2006, **71**, 1598; (*e*) F. M. Pfeffer, T. Gunnlaugsson, P. Jensen and P. E. Kruger, *Org. Lett.*, 2005, **7**, 5357.

9 (*a*) D. R. Turner, M. J. Paterson and J. W. Steed, *Chem. Commun.*, 2008, 1395; (*b*) N. Singh and D. O. Jang, *Org. Lett.*, 2007, **9**, 1991; (*c*) C. R. Bondy, P. A. Gale and S. J. Loeb, *J. Am. Chem. Soc.*, 2004, **126**, 5030; (*d*) S. J. Brooks, P. A. Gale and M. E. Light, *Chem. Commun.*, 2006, 4344; (*e*) J. Nelson, M. Nieuwenhuyzen, I. Pál and E. M. Town, *Dalton Trans.*, 2004, 2303; (*f*) S. Yun, H. Ihm, H. G. Kim, C.-W. Lee, B. Indrajit, K. S Oh, Y. J. Gong, J. W. Lee, J. Yoon, H. C. Lee and K. S. Kim, *J. Org. Chem.*, 2003, **68**, 2467; (*g*) H. Ihm, S. Yun, H. G. Kim, J. K. Kim and K. S. Kim, *J. Org. Chem.*, 2002, **4**, 2897.

10 (*a*) S. Hussain, P. R. Brotherhood, L. W. Judd and A. P. Davis, *J. Am. Chem. Soc.*, 2011, **133**, 1614; (*b*) J. T. Davis, O. Okunola and R. Quesada, *Chem. Soc. Rev.*, 2010, **39**, 3583.

11 (*a*) N. J. Andrews, C. J. E. Haynes, M. E. Light, S. J. Moore, C. C. Tong, J. T. Davis, W. A. Harrell and P. A. Gale, *Chem. Sci.*, 2011, **2**, 256; (*b*) J. T. Davis, P. A. Gale, O. A. Okunola, P. Prados, J. C; Iglesias-Sáanchez, T. Torroba and R. Quesada, *Nat. Chem.*, 2009, **1**, 138; (*c*) N. Busschaert, P. A. Gale, C. J. E. Haynes, M. E. Light, S. J. Moore, C. C. Tong, J. T. Davis and W. A. Harrell, *Chem. Commun.*, 2010, **46**, 6252.

12 P. A. Gale, J. R. Hiscock, C. Jie Zhu, M. B. Hursthouse and M. E. Light, *Chem. Sci.*, 2010, **1**, 215.

13 H. R. Seong, D.-S. Kim, S.-G. Kim, H.-J. Choib and K. H. Ahn, *Tetrahedron Lett.*, 2004, **45**, 723.

14 C. M. G. dos Santos, T. McCabe, G. W. Watson, P. E. Kruger and T. Gunnlaugsson, *J. Org. Chem.*, 2008, **73**, 9235.

15 E. M. Boyle, T. McCabe and T. Gunnlaugsson, *Supramol. Chem.*, 2010, **22**, 586.

16 F. D. Lewis, T. M. Long, C. L. Stern and W. Liu, *J. Phys. Chem. A*, 2003, **107**, 3254.

17 P. Ballester, *Chem. Soc. Rev.*, 2010, **39**, 3810.

18 Examples of such large changes in the ^1H NMR: T. Gunnlaugsson, A. P. Davis, J. E. O'Brien and M. Glynn, *Org. Lett.*, 2002, **4**, 2449.

19 M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311.

