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Carboxylate complexation by 1,1′-(1,2-phenylene)bis(3-phenylurea) in solution and the solid state†

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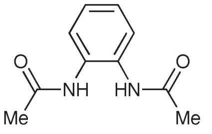
A simple bis-urea containing anion receptor, synthesised from *ortho*-phenylenediamine, has been shown to have excellent selectivity for carboxylates in solution, with a crystal structure elucidation of the benzoate complex showing four hydrogen bonds between the receptor and anion in the solid state.

Receptors for carboxylate anions are important for the recognition of a variety of biomolecules and in particular amino acids.[1] An important sub-class of these receptors are those which contain urea (or thiourea) groups and many systems containing either one[2] or two[3] have been reported and shown to be excellent carboxylate receptors and sensors.

Over the last five years we have investigated the anion binding properties of structurally simple receptors containing amide,[4] urea[5] and pyrrole[6] groups. Little work has been done on anion receptors based upon *ortho*-phenylenediamine or analogous diamines.[7] The potential carboxylate complexation properties of these systems has so far yet to be exploited. In 2000, Reinhoudt and co-workers reported the anion binding ability of cyclic and acyclic receptors containing two *ortho*-phenylenediamine based bis-urea units.[8] This work showed that these receptors were selective for dihydrogen phosphate in DMSO. We wished to 'extract' the bis-urea unit and investigate the intrinsic anion binding properties of 1,1′-(1,2-phenylene)bis(3-phenylurea) (**3**) and those of the structurally related compounds **1** and **2**. Whilst this work was in progress, the anion (but not carboxylate) binding properties of **2** were reported by Cheng and co-workers.[9]

Compound **1** was synthesised according to literature procedures[10] whilst compound **2** was synthesised by the same method reported by Cheng.[9] Compound **3** was originally reported in 1966 (see the ESI for details of the synthesis and characterisation of this compound†).[11]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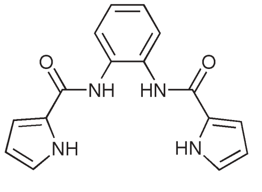
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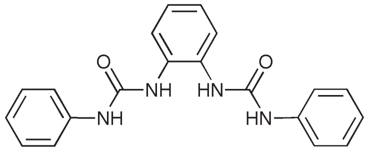
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The anion complexation properties of **1–3** were studied using ^{1}H NMR titration techniques in DMSO-d_6–0.5% water. Stability constants were obtained using the EQNMR computer program.[12] The results are shown in Table 1 and reveal that compound **3** is selective for carboxylate anions under these experimental conditions (binding acetate with a stability constant of 3210 M^{-1} and benzoate with a stability constant of 1330 M^{-1}). A comparison of the shift of the central NH protons of compounds **1**, **2** and **3** upon addition of acetate is shown in Fig. 1 illustrating the higher affinity of the bis-urea for acetate as compared to the bis-amidopyrrole **2** or bis-amide **1**. Presumably the more open binding site offered by the bis-urea receptor allows the receptor to form four hydrogen bonds to the anion in solution (Fig. 2) which is possibly further stabilised by intramolecular CH···O hydrogen bonds. Amidopyrroles form a convergent binding site and presumably, in the case of receptor **2**, the four hydrogen bond donor NH groups cannot efficiently coordinate the two oxygen atoms present in the anion.[6]

In 1995, Umezawa and co-workers reported the carboxylate binding properties of bis-thiourea **4** and bis-urea **5**. Compound **5** was reported to bind tetrabutylammonium acetate in a 1 : 1 stoichiometry with a stability constant of 43 M^{-1} in DMSO-d_6 solution whilst the bis-thiourea **4** bound acetate with a stability constant of 470 M^{-1} under the same conditions.[13] The higher stability constant observed for the **3**–acetate complex (measured under slightly different experimental conditions) may be due to the lower degree of flexibility in the *ortho*-phenylenediamine system as compared to **4** and **5** and hence a higher degree of preorganization. However it must be noted that Umezawa's systems contain pendant butyl groups whereas **3** contains pendant phenyl moieties and hence this comparison must be qualified.

Table 1 Stability constants (M^{-1}) of compounds **1**, **2** and **3** with a variety of putative anionic guests (added as tetrabutylammonium salts) at 298K in DMSO−d_6/0.5% water.[a] In all cases 1 : 1 receptor : anion stoichiometry was observed.

	Compounds		
Anion	**1**	**2**[b]	**3**
Cl^-	13	12	43
Br^-	—	—	<10
$CH_3CO_2^-$	98	251	3210
$C_6H_5CO_2^-$	43	113	1330
$H_2PO_4^-$	149	295	732
HSO_4^-	—	—	10

[a] Errors estimated to be no more than ± 10%. [b] We have repeated the anion complexation studies with compound **2** under slightly different experimental conditions from those originally reported,[9] however our results are broadly similar.

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† Electronic supplementary information (ESI) available: Synthesis and characterisation of compound **3** and ^{1}H NMR titration profiles. See http://dx.doi.org/10.1039/b508144k

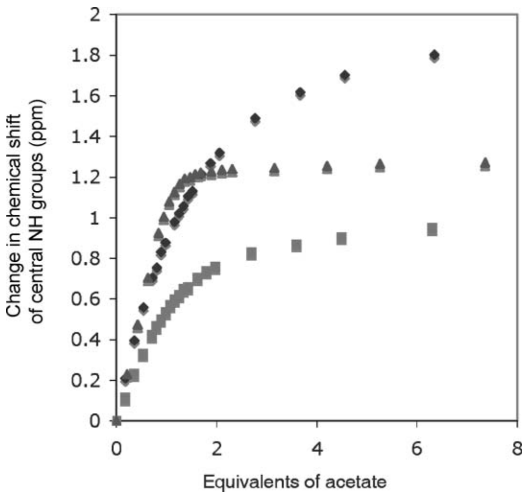
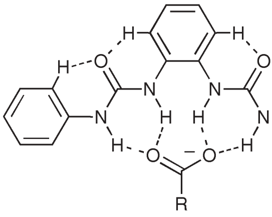
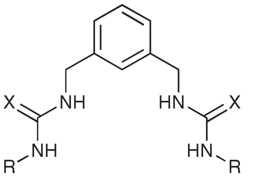


Fig. 1 Shift of the resonance of the central NH groups in compounds **1** (◆), **2** (■) and **3** (▲) upon addition of tetrabutylammonium acetate in DMSO-d_6–0.5%.



3 - carboxylate

Fig. 2 A proposed hydrogen bonding array formed between compound **3** and carboxylate anions in solution.



4 X = S, R = Bu
5 X = O, R = Bu

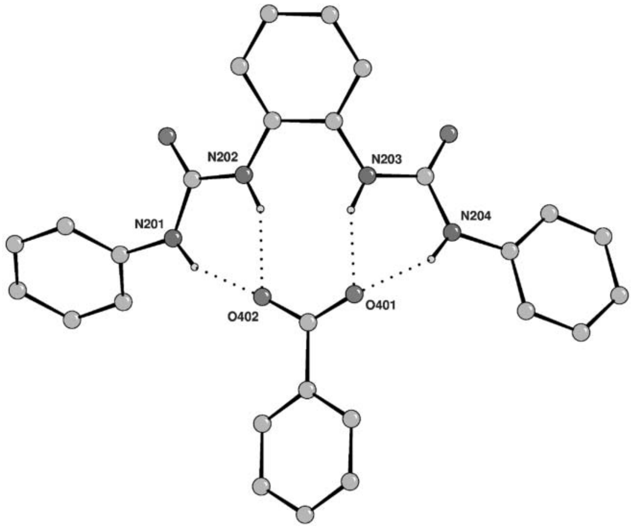


Fig. 4 The benzoate complex of receptor **3** showing the formation of four hydrogen bonds between the receptor and carboxylate anion in the solid state. One of the two independent complexes in the asymmetric unit is shown. Tetrabutylammonium counter cations and non-acidic hydrogen atoms have been omitted for clarity.

Crystals of the tetrabutylammonium acetate complex of receptor **2** were grown by slow evaporation of an acetonitrile solution of the receptor in the presence of excess tetrabutylammonium acetate.‡ The structure (Fig. 3) shows the acetate anion bound by two amide NH groups (N···O 2.751(3) and 2.731(3) Å) and one pyrrole NH group (N···O 2.781(3) Å). The other pyrrole NH group is oriented out of the cavity forming an intermolecular hydrogen bond to an adjacent complex (N···O 2.874(3) Å).

Crystals of the tetrabutylammonium benzoate complex of receptor **3** were grown by slow evaporation of an acetonitrile solution of the receptor in the presence of excess tetrabutylammonium benzoate.§ The asymmetric unit contains two complexes with each benzoate anion bound between the two urea groups *via* four hydrogen bonds in the range 2.740(4)–2.939(4) Å (Fig. 4). To the best of our knowledge this is the first crystallographically characterized complex of a single carboxylate bridging between two urea groups in a bis-urea based organic anion receptor.

The crystal structure of compound **2** binding acetate shows the anion is bound in a non-symmetrical arrangement by three hydrogen bonds whilst the solution studies show that **2** does not possess as high an affinity for carboxylates as compound **3**. The solution studies illustrate the selectivity of compound **3** for carboxylate anions in DMSO-d_6–0.5% water whilst the crystal structure of the benzoate complex of **3** shows the anion is bound to the four urea NH groups. This relatively simple yet highly effective hydrogen bonding motif may find application in receptors for amino acids and we are currently working towards that goal.

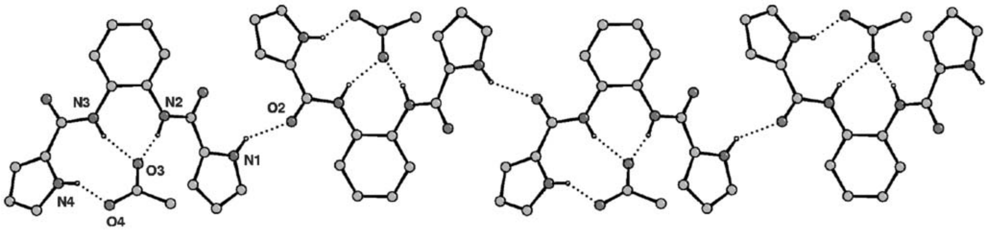


Fig. 3 Hydrogen bonded chains in the acetate complex of receptor **2**. In the solid state the acetate anion is bound by three hydrogen bonds from the receptor with one pyrrole group oriented to form an intermolecular hydrogen bond to an adjacent molecule. Tetrabutylammonium counter cations and non-acidic hydrogen atoms have been omitted for clarity.

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Notes and references

‡ Crystal data for **2**–tetrabutylammonium acetate $C_{34}H_{53}N_5O_4$, Mr = 595.81, T = 120(2) K, monoclinic, space group $P2_1/c$, a = 9.577(3), b = 19.020(8), c = 18.309(5) Å, β = 93.73(3)°, V = 3328.0(18) Å^3, ρ_{calc} = 1.189 g cm^{-3}, μ = 0.078 mm^{-1}, Z = 4, reflections collected: 37336, independent reflections: 6567 (R_{int} = 0.1337), final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0683, w$R2$ = 0.1406, R indices (all data): $R1$ = 0.1754. w$R2$ = 0.1791. CCDC 278725.

§ Crystal data for **3**-tetrabutylammonium benzoate $C_{43}H_{58}N_5O_4$, Mr = 708.94, T = 120(2) K, monoclinic, space group $P2_1/n$, a = 8.478(2), b = 38.654(10), c = 24.402(7) Å, β = 93.68(3)°, V = 7980(4) Å^3, ρ_{calc} = 1.180 g cm^{-3}, μ = 0.076 mm^{-1}, Z = 8, reflections collected: 60181, independent reflections: 15477 (R_{int} = 0.1747), final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0795, w$R2$ = 0.1442, R indices (all data): $R1$ = 0.2583. w$R2$ = 0.2035. CCDC 278726. See http://dx.doi.org/10.1039/b508144k for crystallographic data in CIF or other electronic format.

1 For an excellent comprehensive review see: R. J. Fitzmaurice, G. M. Kyne, D. Douheret and J. D. Kilburn, *J. Chem. Soc., Perkin Trans. 1*, 2002, 841.

2 (*a*) P. J. Smith, M. V. Reddington and C. S. Wilcox, *Tetrahedron Lett.*, 1992, **41**, 6085; (*b*) E. Fan, S. A. van Arman, S. Kincaid and A. D. Hamilton, *J. Am. Chem. Soc.*, 1993, **115**, 369; (*c*) T. R. Kelly and M. H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072; (*d*) R. Kato, S. Nishizawa, T. Hayashita and N. Teramae, *Tetrahedron Lett.*, 2001, **42**, 5053; (*e*) B. Linton and A. D. Hamilton, *Tetrahedron*, 1999, **55**, 6027; (*f*) T. Gunnlaugsson, P. E. Kruger, T. C. Lee, R. Parkesh, F. M. Pfeffer and G. M. Hussey, *Tetrahedron Lett.*, 2003, **44**, 6575; (*g*) For a seminal early paper describing the hydrogen bonding ability of ureas with other hydrogen bond acceptors in the solid state see: M. C. Etter, Z. Urbañczyk-Lipkoska, M. Zia-Ebrahimi and T. W. Panunto, *J. Am. Chem. Soc.*, 1990, **112**, 8415.

3 (*a*) B. C. Hamann, N. R. Branda and J. Rebek, Jr, *Tetrahedron Lett.*, 1993, **34**, 6837; (*b*) D. H. Lee, H. Y. Lee, K. H. Lee and J. I. Hong, *Chem. Commun.*, 2001, 1188.

4 (*a*) C. R. Bondy, P. A. Gale and S. J. Loeb, *Chem. Commun.*, 2001, 729; (*b*) S. J. Coles, J. G. Frey, P. A. Gale, M. B. Hursthouse, M. E. Light, K. Navakhun and G. L. Thomas, *Chem. Commun.*, 2003, 568; (*c*) S. J. Brooks, L. S. Evans, P. A. Gale, M. B. Hursthouse and M. E. Light, *Chem. Commun.*, 2005, 734; (*d*) L. S. Evans and P. A. Gale, *Chem. Commun.*, 2004, 1286.

5 C. R. Bondy, P. A. Gale and S. J. Loeb, *J. Am. Chem. Soc.*, 2004, **126**, 5030.

6 For an overview see: (*a*) P. A. Gale, *Chem. Commun.*, 2005, 3761; (*b*) Also see: P. A. Gale, M. E. Light, B. McNally, K. Navakhun, K. E. Sliwinski and B. D. Smith, *Chem. Commun.*, 2005, 3773; (*c*) I. E. D. Vega, S. Camiolo, P. A. Gale, M. B. Hursthouse and M. E. Light, *Chem. Commun.*, 2003, 1696.

7 For an example of a 1,2-urea functionalised anthraquinone see: (*a*) D. A. Jose, D. K. Kumar, B. Ganguly and A. Das, *Org. Lett.*, 2004, **6**, 3445; (*b*) For a macrocyclic system containing a ferrocene and naphthalene see: F. Otón, A. Tárraga, M. D. Velasco, A. Espinosa and P. Molina, *Chem. Commun.*, 2004, 1658; (*c*) For a naphthalene based system see: G. Xu and M. A. Tarr, *Chem. Commun.*, 2004, 1050.

8 B. H. M. Snellink-Ruël, M. M. G. Antonisse, J. F. J. Engbersen, P. Timmerman and D. N. Reinhoudt, *Eur. J. Org. Chem.*, 2000, 165.

9 Z. Yin, Z. Li, A. Yu, J. He and J.-P. Cheng, *Tetrahedron Lett.*, 2004, **45**, 6803.

10 A. Shivanyuk, K. Rissanen, S. K. Körner, D. M. Rudkevich and J. R. Rebek, Jr., *Helv. Chim. Acta*, 2000, **83**, 1778.

11 M. I. Bruce and J. A. Zwar, *Proc. R. Soc. London, Ser. B.*, 1966, **165**, 245.

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

13 S. Nishizawa, P. Bühlmann, M. Iwao and Y. Umezawa, *Tetrahedron Lett.*, 1995, **36**, 6483.