A simple benzimidazole-based receptor for barbiturate and urea neutral guests that functions in polar solvent mixtures†

Matthew G. Fisher, Philip A. Gale* and Mark E. Light

Received (in Durham, UK) 18th April 2007, Accepted 13th July 2007
First published as an Advance Article on the web 23rd July 2007
DOI: 10.1039/b705854c

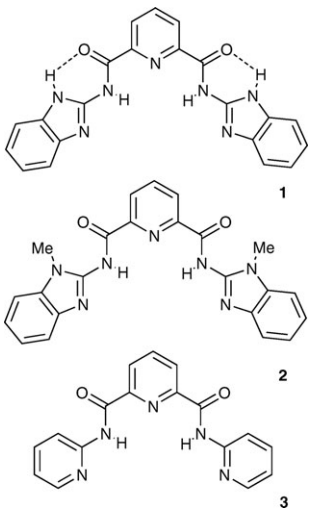
A 2,6-dicarboxamidopyridine cleft with appended benzimidazole groups functions as a receptor for neutral guests in solvent mixtures of DMSO-d_6 and $MeNO_2$-d_3.

Many supramolecular receptors have been reported for urea and barbiturate, consisting of complementary hydrogen bonding arrays incorporated into macrocyclic or acyclic frameworks. Particularly elegant early macrocyclic examples from Hamilton's group[1] inspired work on acyclic systems,[2] electrochemical sensors[3] and receptors for the chiral recognition[4] of neutral guests.

We have recently studied the effect of hydrogen bonding in preorganizing macrocyclic receptors for carboxylate recognition,[5] and, with our collaborators, produced highly efficient acyclic membrane transporters for chloride[6] and HCl.[7] Here, we report a very simple receptor based on a 2,6-dicarboxamidopyridine skeleton with appended benzimidazole[8] groups that employs intramolecular hydrogen bonding interactions to maintain a cleft-like conformation in solution. This receptor binds neutral guests such as urea, imidazolidone and barbital in polar solvent mixtures, whereas model compounds lacking stabilising interactions do not interact with these neutral guests under the same or similar conditions.

Compounds **1** and **2** were synthesised by the condensation of 2-aminobenzimidazole or 2-amino-1-methylbenzimidazole with pyridinedicarbonylchloride in 81 and 54% yield, respectively. Compound **3** was prepared as reported previously.

2,6-Dicarboxamidopyridines adopt predominantly the *syn–syn* conformation in solution.[10] Proton NMR evidence in DMSO-d_6 solution leads us to suggest that the benzimidazole NH group in **1** forms an intramolecular hydrogen bond with the amide oxygen atom, as this NH is shifted downfield to 12.9 ppm compared to the starting 2-aminobenzimidazole, in which the NH group has a chemical shift of 10.7 ppm. Compounds **2** and **3** were designed as models. Compound **2** lacks the benzimidazole NH group and hence possesses a lower degree of preorganization than compound **1**. Compound **3** is a pyridine analogue of compound **1** and again lacks the same degree of preorganization as compound **1**.[9]



Crystals of compound **1** were grown by the slow evaporation of a DMSO solution of the receptor.‡ The structure (Fig. 1) shows the receptor adopting a *syn–syn* conformation with a DMSO molecule bound to the amide NH groups. The intramolecular hydrogen bonding interactions N1···O1 (2.666(2) Å) and N7···O2 (2.741(2) Å) presumably stabilize the solvate in the solid state.[11]

Binding studies were conducted between compounds **1–3** in either $MeNO_2$-d_3/20% DMSO-d_6 or $MeNO_2$-d_3/30% DMSO-d_6 and the neutral guests shown in Fig. 2. Stability constants were determined using the EQNMR computer program.[12] The crystal structure of compound **1** shows that DMSO binds to the amide NH groups. Hence, it is reasonable to expect that, in solution, the neutral guests must compete with this solvent for the guest binding site. In the former solvent mixture, compound **1** was found to bind urea and imidazolidone but precipitate upon the addition of barbital. Switching to the

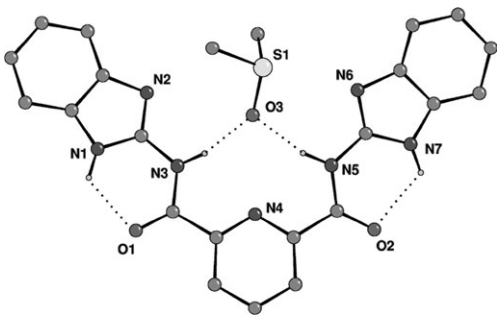


Fig. 1 X-Ray crystal structure of the DMSO solvate of compound **1**. The non-acidic hydrogen atoms have been omitted for clarity.

School of Chemistry, University of Southampton, Southampton, UK SO17 1BJ. E-mail: philip.gale@soton.ac.uk; Fax: +44 2380596805; Tel: +44 23 80593332

† Electronic supplementary information (ESI) available: Details of the syntheses of **1** and **2**, and NMR titration data. See DOI: 10.1039/b705854c.

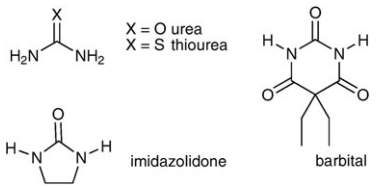


Fig. 2 The neutral guests used in this binding study.

Table 1 Binding constants K_a ($/M^{-1}$) for receptors **1–3** with a selection of neutral guests in 20% DMSO-d_6/$MeNO_2$-d_3, unless otherwise noted, at 298 K

	1	**1**[a]	**2**	**3**
Thiourea	0	0	0	0
Urea	28	<10	0	0
Imidazolidone	45	13	0	0
Barbital	Precipitate	59	0[a]	0[a]

[a] In 30% DMSO-d_6/$MeNO_2$-d_3. All errors are estimated to be <10%.

latter mixture allowed a stability constant of 59 M^{-1} to be determined for the formation of the **1**–barbital complex under these more polar solvent conditions (Table 1). Compounds **2** and **3** showed no interaction with the guests under these conditions. Interestingly, thiourea does not interact with compound **1** under either set of solvent conditions, whereas urea is bound (albeit weakly). This is presumably due to the poor hydrogen bond acceptor ability of the thiourea sulfur atom compared to the urea oxygen.

Crystals of the barbital complex of receptor **1** were grown by the slow evaporation of a DMSO solution of the complex (Fig. 3).§ The barbital is held by four hydrogen bonds N2···N9 (2.7700(4) Å), N3···O3 (2.9769(4) Å), N5···O3 (2.172(3) Å) and N6···N8 (2.7406(4) Å). Intramolecular hydrogen bonds N1···O1 (2.6906(3) Å) and N7···O2 (2.7198(4) Å) are present in the complex and, interestingly, each benzimidazole NH group also forms a hydrogen bond to a DMSO molecule.

We have shown that a structurally simple bis-benzimidazole-functionalised 2,6-dicarboxamidopyridine, **1**, is capable of binding neutral guests in 30% DMSO-d_6/$MeNO_2$-d_3 solution, whereas compounds possessing similar hydrogen bonding arrays but lacking some of the intramolecular hydrogen bonding interactions present in compound **1** do not, under these conditions, interact with the neutral guests studied. In 20% DMSO-d_6/$MeNO_2$-d_3, the barbital complex of compound **1** precipitates from solution. We are continuing to study receptors and transport agents stabilised by intramolecular hydrogen bonding interactions. The results of this work will be published in due course.

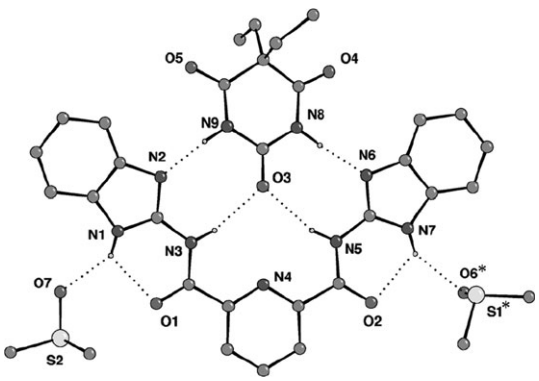


Fig. 3 X-Ray crystal structure of the barbital complex of receptor **1**. The non-acidic hydrogen atoms have been omitted for clarity. * These atoms are at equivalent positions (1 + x, −1 + y, z).

We would like to thank the EPSRC for a studentship (M. G. F.) and the EPSRC, together with Professor Mike Hursthouse, for access to the crystallographic facilities at the University of Southampton. We would also like to thank Dr Jim Tucker (University of Birmingham) for the sample of barbital used in these studies.

References

‡ Crystal data for the DMSO solvate of **1**: $C_{23}H_{21}N_7O_3S$, M_r = 475.53, T = 120(2) K, monoclinic, space group $P2_1/n$, a = 19.3932(4), b = 5.87740(10), c = 19.4872(4) Å, β = 102.8420(10)°, V = 2165.62(7) Å^3, ρ_{calc} = 1.458 g cm^{-3}, μ = 0.193 mm^{-1}, Z = 4, reflections collected: 29 058, independent reflections: 4975 (R_{int} = 0.0594), final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0505, w$R2$ = 0.1252, R indices (all data): $R1$ = 0.0681, w$R2$ = 0.1377. CCDC 651652. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b705854c.

§ Crystal data for the barbital complex of **1**: $C_{33}H_{39}N_9O_7S_2$, M_r = 737.85, T = 120(2) K, triclinic, space group P-1, a = 9.9882(4), b = 14.1537(5), c = 14.7208(8) Å, α = 64.158(2), β = 86.751(3), γ = 70.732(3)°, V = 1758.73(13) Å^3, ρ_{calc} = 1.393 g cm^{-3}, μ = 0.213 mm^{-1}, Z = 2, reflections collected: 20 558, independent reflections: 7607 (R_{int} = 0.0609), final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0561, w$R2$ = 0.1274, R indices (all data): $R1$ = 0.0976, w$R2$ = 0.1467. CCDC 651651. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b705854c.

1 (*a*) S.-K. Chang and A. D. Hamilton, *J. Am. Chem. Soc.*, 1988, **110**, 1318; (*b*) S.-K. Chang, D. van Engen, E. Fan and A. D. Hamilton, *J. Am. Chem. Soc.*, 1991, **113**, 7640.
2 (*a*) C.-Y. Hung, T. Höpfner and R. P. Thummel, *J. Am. Chem. Soc.*, 1993, **115**, 12601; (*b*) P. V. Mason, N. R. Champness, S. R. Collinson, M. G. Fisher and G. Goretzki, *Eur. J. Org. Chem.*, 2006, 1444; (*c*) B. Chetia and P. K. Iyer, *Tetrahedron Lett.*, 2006, **47**, 8115.
3 (*a*) J. Westwood, S. J. Coles, S. R. Collinson, G. Gasser, S. J. Green, M. B. Hursthouse, M. E. Light and J. H. R. Tucker, *Organometallics*, 2004, **23**, 946; (*b*) S. R. Collinson, T. Gelbrich, M. B. Hursthouse and J. H. R. Tucker, *Chem. Commun.*, 2001, 555.
4 B. S. Ramussen, U. Elezcano and T. Skrydstrup, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1723.
5 (*a*) S. J. Brooks, S. E. García-Garrido, M. E. Light, P. A. Cole and P. A. Gale, *Chem.–Eur. J.*, 2007, **13**, 3320; (*b*) See also: S. J. Brooks, P. A. Gale and M. E. Light, *Chem. Commun.*, 2006, 4344.
6 P. V. Santacroce, J. T. Davis, M. E. Light, P. A. Gale, J. C. Iglesias-Sánchez, P. Prados and R. Quesada, *J. Am. Chem. Soc.*, 2007, **129**, 1886.
7 P. A. Gale, J. Garric, M. E. Light, B. A. McNally and B. D. Smith, *Chem. Commun.*, 2007, 1736.
8 Recently, benzimidazolium groups have been used as components of receptors for carboxylates. See: M. Mazik and H. Cavga, *J. Org. Chem.*, 2007, **72**, 831 and references cited therein.
9 H. Hou, Y. Wei, Y. Song, L. Mi, M. Tang, L. Li and Y. Fan, *Angew. Chem., Int. Ed.*, 2005, **44**, 6067.
10 C. A. Hunter and L. D. Sarson, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2313.
11 Please see the ESI for the crystal structure of compound **2**†.
12 M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311.

