COMMUNICATION

ChemComm
www.rsc.org/chemcomm

A modular ditopic crown-shielded phosphate ion-pair receptor†

Patrick Gunning,[a] Andrew C. Benniston*[b] and Robert D. Peacock*[a]

[a] *Department of Chemistry, Joseph Black Building, University of Glasgow, Glasgow, UK G12 8QQ. E-mail: bob@chem.gla.ac.uk; Fax: +44 (0)141 330 4888; Tel: +44 (0)141 330 4375*

[b] *Molecular Photonics Laboratory, University of Newcastle, Newcastle upon Tyne, UK NE1 7RU. E-mail: a.c.benniston@ncl.ac.uk; Fax: +44 (0)191 222 6929; Tel: +44 (0)191 222 5706*

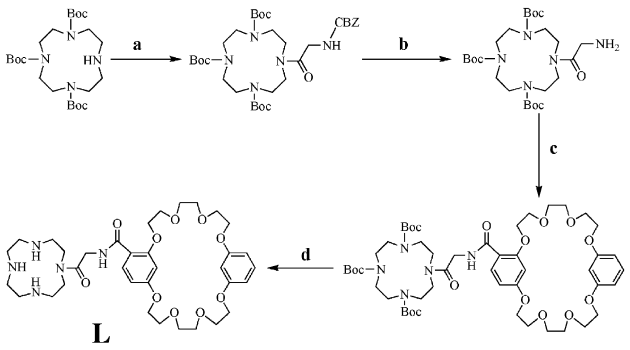
Received (in Cambridge, UK) 17th June 2004, Accepted 16th July 2004
First published as an Advance Article on the web 20th August 2004

The synthesis of a modular hybrid receptor containing both an aza macrocycle and crown ether is described; a complete thermodynamic characterisation of the binding properties, in water, of the zinc(II) complex of the receptor towards phosphate is presented and the parameters are compared to those of the aza macrocycle precursor.

Mimicking natural enzymes using artificial systems has been the impetus for many research groups[1–7] over the past twenty years. In seminal work by Kimura and co-workers[8] it was shown that zinc(II) complexes of the azamacrocycles 1,5,9-triazacyclododecane and 1,4,7,10-tetraazacyclododecane (cyclen) bind a water molecule with a pK_a value that is dramatically reduced when compared to that of a free water molecule. Owing to the generation of this nucleophilic centre these complexes catalytically hydrolyse the ester groups of simple substrates.[9]

More recently the next stage in the development of artificial enzymes has included secondary structures such as cyclodextrins,[10] dendrimers,[11] and cavitands[12] attached to the macrocyclic core. These groups tend to mimic the second coordination sphere and beyond and serve to protect reactants, bind substrates and promote reactions. However, these secondary host sites generally do not possess multiple specific groups that could promote simultaneous H-bonding, π–π stacking and dipole–dipole interactions which is more reminiscent of the protein structure of enzymes. At the heart of many artificial enzyme mimics is an anion receptor. For this reason both anion and ion pair receptors are currently of great interest.[13]

In this communication we report the synthesis and binding properties of a hybrid anion receptor in which an aza macrocycle moiety is attached to an aromatic crown ether polycycle *via* an amino acid bridging unit. The synthetic approach (Scheme 1) is modular allowing all three parts of the molecule to be varied giving access to a wide variety of receptors. A number of tri- and tetra-aza macrocycles are commercially available or may be synthesized and a wide range of amino acids (or dipeptide units) can be used as the linker. The dibenzocrown-8-carboxylic acid was synthesized by a modification of standard methods[14] which allow variation of the number of oxygen atoms in the crown and the position of the carboxylic acid unit on the aromatic ring. Chiral receptors may also be synthesized using enantiopure linking groups such as glutamic acid.



Scheme 1 (a) N-Cbz-glycine, DCC, DMAP, DCM, rt; (b) 10% Pd/C, 1,4-cyclohexadiene, EtOH, rt; (c) dibenzocrown-8-carboxylic acid, DCC, DMAP, DCM, rt; (d) TFA–DCM, rt.

The receptor described here (L) consists of cyclen joined to the dibenzo-24-crown-8 unit *via* a glycine bridge. The zinc(II) complex was prepared by the addition of equimolar quantities of zinc triflate and NMR titration experiments confirmed that the zinc ion binds to the aza and not the oxa crown in a 1 : 1 ratio. Molecular modeling of Zn(H_2O)L clearly demonstrates the zinc(II) macrocycle and crown residing in close proximity, ideal for substrate binding (see Electronic Supplementary Information†). Potentiometric pH titrations determined the pK_a of the attached water to be 7.4 (± 0.1). This value is in good agreement with previous and more recent work by Mareque-Rivas using tetraaza-ligand systems.[15]

The ability of Zn(H_2O)L to bind phosphate and substituted phosphates was assessed by ^{1}H NMR, UV–visible and isothermal calorimetry (ITC).† In order to identify the effect of the attached crown ether, the binding ability of Zn(H_2O)cyclen was measured under identical experimental conditions (pH 7.4 HEPES buffer (10 mM) in aqueous solution; 0.25 mM substrate, 5 mM ligand). We chose to use mono sodium (and potassium) dihydrogen phosphate in order to have one mole of the cation per phosphate available for binding to the crown ether. However at pH 7.4 the phosphate is in the dianionic form $[HPO_4]^{2-}$ and is thus bound as the 2− ion. The results are presented in Table 1.

The first point to be taken from the table is the large binding constant for the $[HPO_4]^{2-}$ anion in aqueous solution. Comparable binding constants have been reported recently by Anslyn (2.5×10^4)[1b] and Ren (4.2×10^3 buffered; 2.4×10^4 unbuffered).[16] Secondly potassium phosphate binds approximately twice as strongly to Zn(H_2O)L as does the sodium salt, whereas the binding of sodium and potassium phosphate to Zn(H_2O)cyclen is essentially identical. Since the oxa crown is of such a size as to favor binding K^+ over Na^+,[17] this result strongly suggests that the oxa crown is binding the cation and thus that Zn(H_2O)L is an *ion pair* receptor. This is further supported by ITC evidence that shows Zn(H_2O)L not binding either $NaClO_4$ or $KClO_4$ under identical experimental conditions. Most importantly Zn(H_2O)L binds $[HPO_4]^{2-}$ between three and six times more strongly than the Zn cyclen control demonstrating the enhanced binding provided by the oxa-crown arm. *p*-Nitrophenyl phosphate binds to essentially the same extent to the two substrates within experimental error. Finally the bulkier glycophosphate is bound more strongly by Zn(H_2O)cyclen than by Zn(H_2O)L.

In addition to stability constants, however, ITC provides the ΔH^0 for the interaction of ligand and substrate and thus a complete thermodynamic characterization of the binding process. We believe this is the first time that such an analysis has been performed on a ditopic receptor based on an azamacrocycle and simultaneously on the parent complex. The results clearly show that in every case binding to Zn(H_2O)cyclen is exothermic, whereas binding to

† Electronic supplementary information (ESI) available: details of experimental work, ITC traces, selected ^{1}H NMR data and molecular modelling. See http://www.rsc.org/suppdata/cc/b4/b409132a/

DOI: 10.1039/b409132a

Table 1 Thermodynamic data for the binding of various substrates to $Zn(H_2O)L$ and $Zn(H_2O)$cyclen in HEPES buffer at pH 7.4 at 25 °C

Ligand	Ligand : substrate binding ratio[a]	Substrate	$K \times 10^4$	ΔG^0/ kcal mol^{-1}[b]	ΔH^0/ kcal mol^{-1}	$-T\Delta S^0$/ kcal mol^{-1}
$Zn(H_2O)L$	2 : 1	$Na[H_2PO_4]$	4.93 ± 0.72[c]	−6.39	3.47 ± 0.17	9.86
$Zn(H_2O)L$	2 : 1	$K[H_2PO_4]$	9.32 ± 1.60[c]	−6.78	2.44 ± 0.09	9.22
$Zn(H_2O)$cyclen	1 : 1	$Na[H_2PO_4]$	1.60 ± 0.09[d]	−5.74	−3.25 ± 0.08	2.49
$Zn(H_2O)$cyclen	1 : 1	$K[H_2PO_4]$	1.52 ± 0.19[d]	−5.70	−3.89 ± 0.24	1.81
$Zn(H_2O)L$	1 : 1	Sodium glycerophosphate	0.48 ± 0.06[d]	−5.02	0.48 ± 0.02	5.50
$Zn(H_2O)$cyclen	1 : 1	Sodium glycerophosphate	0.87 ± 0.04[d]	−5.38	−1.63 ± 0.06	3.75
$Zn(H_2O)L$	1 : 1	Disodium 4-nitrophenylphosphate	0.39 ± 0.04[d]	−4.90	0.58 ± 0.04	5.48
$Zn(H_2O)$cyclen	1 : 1	Disodium 4-nitrophenylphosphate	0.51 ± 0.21[d]	−5.05	−0.45 ± 0.19	4.60

[a] Binding stoichiometry was confirmed by ^{1}H NMR titration experiments[19] (see ESI). [b] Calculated from $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$. [c] mol^{-2} dm^6. [d] mol^{-1} dm^3.

$Zn(H_2O)L$ is endothermic. The binding of substrate to $Zn(H_2O)L$ is driven by the large positive entropy term. If a simple subtraction is made between the parameters for $Na[H_2PO_4]$ bound to $Zn(H_2O)$cyclen and to $Zn(H_2O)L$ it is apparent that on going from the simple aza macrocycle to the receptor, this results in a $\Delta\Delta H^0$ of +6.72 kcal mol^{-1} and a $\Delta T\Delta S^0$ of +7.37 kcal mol^{-1} producing an overall $\Delta\Delta G^0$ of −0.65 kcal mol^{-1}. We propose that the explanation for this effect is that there is a "pocket" of hydrogen-bonded water trapped between the $[OH]^-$ ion (at pH 7.4) attached to the zinc ion, and the oxa crown ether. Binding of an anion to the zinc results in the expulsion of the water requiring an input of energy but generating a large amount of entropy. This explanation has been put forward to explain binding in natural systems,[18] and to account for substrate binding in a copper-based artificial system.[1b]

The $\Delta T\Delta S^0$ for binding sodium and potassium phosphate to both receptors are essentially the same within experimental error while the $\Delta\Delta H^0$ is significantly less positive for the potassium salt suggesting that the K^+ ion is being bound to some extent in the oxa crown cavity.

In conclusion, we have shown that hybrid azamacrocycle-crown polycycle receptors offer a new dimension in anion recognition and binding. Since the modular approach gives us flexibility in the design and functionality of the receptor, there is great scope to bind other phosphate-based substrates such as organophosphates found in nerve gases and insecticides. Furthermore, optimization of the crown polycycle size and number of azamacrocycle metal ion sites should lead to enhanced binding of substrates and reactivity, which will be explored in second-generation models.

We thank the EPSRC for a studentship (to PG) and Prof A. Cooper and Margaret Nutley for help with the ITC measurements. Molecular modeling calculations performed by Ben Allen (MPL) are greatly appreciated.

Notes and references

1 (*a*) S. L. Tobey and E. V. Anslyn, *J. Am. Chem. Soc.*, 2003, **125**, 14807–14815; (*b*) S. L. Tobey and E. V. Anslyn, *J. Am. Chem. Soc.*, 2003, **125**, 10963–10970.
2 (*a*) B. N. Trawick, A. T. Daniher and J. K. Bashkin, *Chem. Rev.*, 1998, **98**, 939–960; (*b*) W. H. Jr. Chapman and R. J. Breslow, *J. Am. Chem. Soc.*, 1995, **117**, 5462–5469.
3 I. Iranza, Y. A. Kovalevsky, J. R. Morrow and J. P. Richard, *J. Am. Chem. Soc.*, 2003, **125**, 1988–1993.
4 A. Ojida, M. Inoue, Y. Mito-oka and I. Hamachi, *J. Am. Chem. Soc.*, 2003, **125**, 10184–10185.
5 M. S. Han and D. H. Kim, *Angew. Chem., Int. Ed.*, 2002, **41**, 3809–3811.
6 J. L. Sessler, S. Camiolo and P. A. Gale, *Coord. Chem. Rev.*, 2003, **240**, 17–55.
7 B. R. Linton, M. S. Goodman, E. Fan, S. A. Van Arman and A. Hamilton, *J. Org. Chem.*, 2001, **66**, 7313–7319.
8 S. Aoki and E. Kimura, *Chem. Rev.*, 2004, **104**, 769–787.
9 O. Iranzo, T. Elmer, J. P. Richard and J. R. Morrow, *Inorg. Chem.*, 2003, **42**, 7737–7746.
10 D. K. Leung, J. H. Atkins and R. Breslow, *Tetrahedron Lett.*, 2001, **42**, 6255–6258.
11 (*a*) M. Enomoto and T. Aida, *J. Am. Chem. Soc.*, 1999, **121**, 874–875; (*b*) L. Lui and R. Breslow, *J. Am. Chem. Soc.*, 2003, **125**, 12110–12111.
12 H. Boerrigter, L. Grave, J. W. M. Nissink, L. Chrisstoffels, J. H. Van der Maas, W. Verboom, F. De Jong and D. N. Reinhoudt, *J. Org. Chem.*, 1998, **63**, 4174–4180.
13 P. D. Beer and P. A. Gale, *Angew. Chem., Int Ed.*, 2001, **40**, 486–516.
14 J. W. Jones, L. N. Zakharov, A. L. Rheingold and H. W. Gibson, *J. Am. Chem. Soc.*, 2002, **124**, 1378–1379.
15 J. C. Mareque-Rivas, R. Prabaharan and R. T. Martín de Rosales, *Chem. Commun.*, 2004, 76–77.
16 J. E. Barker, Y. Lui, N. D. Martin and T. Ren, *J. Am. Chem. Soc.*, 2003, **125**, 13332–13333.
17 H. K. Frensdorff, *J. Am. Chem. Soc.*, 1971, **93**, 600–606.
18 D. B. Smithrud, T. B. Wyman and F. Diederich, *J. Am. Chem. Soc.*, 1991, **113**, 5420–5426.
19 M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311–312.