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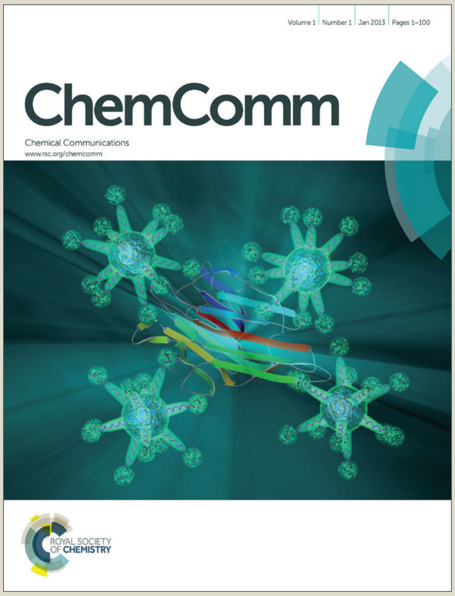

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

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Communication

Nitrate anion templated synthesis of a [2]catenane for nitrate recognition in organic–aqueous solvent media

Matthew J. Langton[a] and Paul D. Beer*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

The first example of a catenane synthesised using a nitrate anion template is demonstrated. Removal of the templating anion reveals a mechanically interlocked molecular host system, which is capable of recognising nitrate selectively over a range of more basic mono-anionic oxoanions in a competitive organic–aqueous solvent mixture.

Stimulated by the important roles anions play in a range of biological, medical and environmental processes, the design of anion receptors capable of strong and selective recognition is an area of supramolecular chemistry of ever increasing interest.[1] The nitrate anion in particular is an important target for binding, sensing and sequestering, due to its role in the eutrophication of natural water courses as a consequence of its over-use in agricultural fertilisers.[2] Furthermore, exposure to increased nitrate levels have been implicated in a number of adverse health conditions such as methemoglobinemia (blue-baby syndrome) in infants.[3] The development of nitrate receptors has been hampered by the low affinity of the anion for hydrogen bonds, in addition to being strongly solvated.[4] As such, receptors reported to date have typically been restricted to operating only in organic solvents.[5–11] Mechanically interlocked molecules, such as rotaxanes and catenanes, have attracted much interest due to their potential in nano-technological and molecular machine applications.[12–15] Such structures, however, also have applications in host-guest chemistry for molecular recognition and sensing, utilising their unique three dimensional topologies to augment guest recognition.[16,17] In particular the use of discrete anion templation has been demonstrated as a means to prepare rotaxane hosts capable of high levels of anion recognition for the templating anion.[18] However, examples of catenane host structures for guest recognition remain relatively rare, especially those capable of binding anionic guests.[19]

Herein we report the first example of a nitrate-templated synthesis of a [2]catenane, which recognises nitrate with impressive selectivity over acetate, dihydrogen phosphate and hydrogen carbonate, in a competitive organic–aqueous solvent mixture (Figure 1).

This communication is dedicated to Prof. Seiji Shinkai on the occasion of his 70th birthday

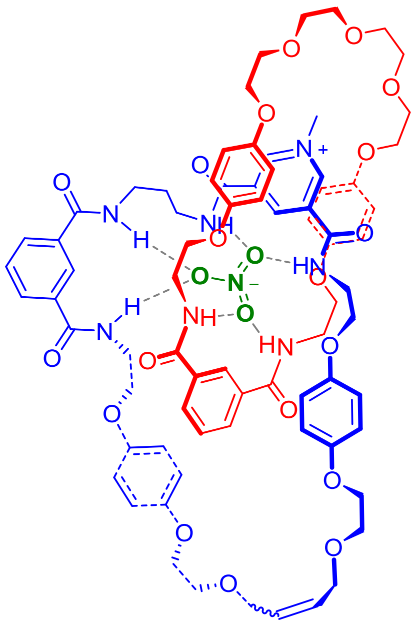

Fig. 1 Catenane nitrate receptor

Previous design strategies to enhance nitrate recognition within synthetic anion receptors have centred around constructing a host in which multiple hydrogen bond donors are arranged in a complementary trigonal arrangement, to favour binding of the trigonal planar nitrate anion over anions of different geometries.[5-11] Recently we reported such a strategy for assembling a nitrate anion selective [2]rotaxane.[20] We reasoned that integrating a bidentate hydrogen bond donor group into one macrocycle and a monodentate hydrogen bond donor group into the other cyclic component would produce a [2]catenane host structural framework containing an interlocked tridentate binding cavity of complementary shape for nitrate recognition.

The asymmetric macrocycle precursor $\mathbf{12{\cdot}NO_3}$ incorporates two hydrogen bond donor motifs: the positively charged 3,5-bis-amide pyridinium and neutral isophthalamide, to coordinate to two of the nitrate anion's oxygen atoms. The precursor is functionalised with vinyl groups to facilitate "clipping" ring closing metathesis (RCM) catenane formation when threaded via

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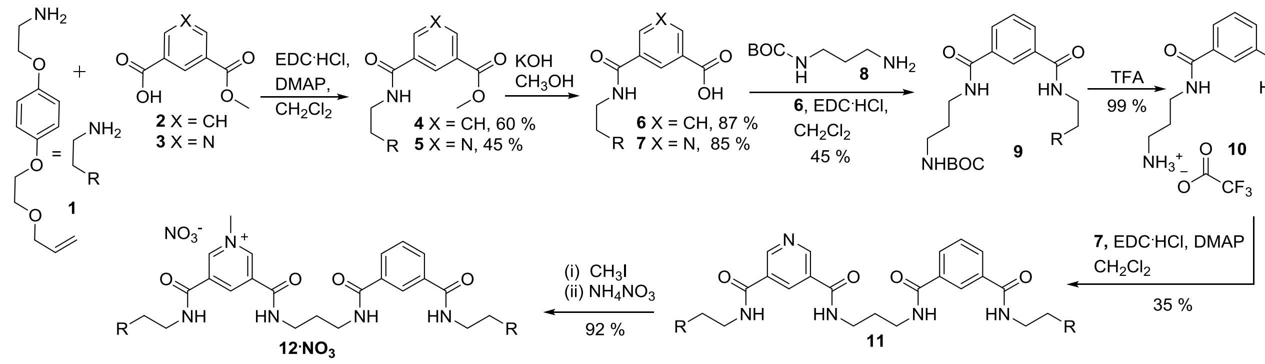
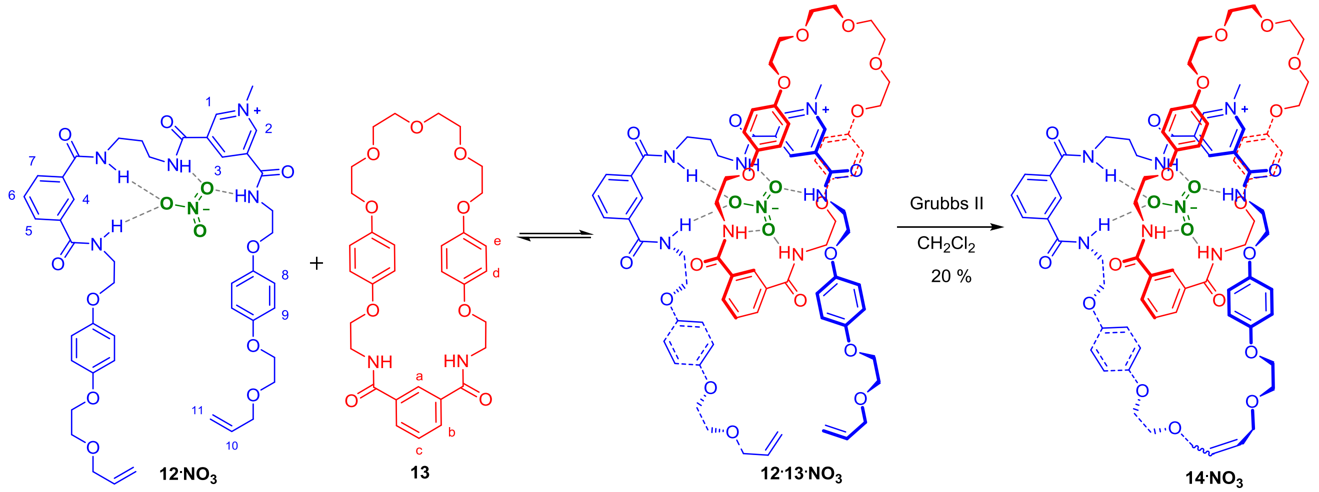
Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford, OX1 3TA (UK), Fax: (+44) 1865-272-690, E-mail: paul.beer@chem.ox.ac.uk
†Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/



Scheme 1 Synthesis of asymmetric macrocycle precursor **12·NO$_3$**



Scheme 2 Nitrate-templated synthesis of [2]catenane **14·NO$_3$**

nitrate anion templation through an isophthalamide containing macrocycle. The multistep synthesis of **12·NO$_3$** is shown in Scheme 1. The convergent synthesis commenced with the EDC-mediated coupling of amine **1**[21] with the asymmetrically de-esterified acids **2** and **3**, to yield compounds **4** and **5**. These were subsequently deprotected to the acid forms (**6** and **7** respectively) using KOH. Coupling of compound **6** with mono BOC-protected 1,3-diaminopropane **8** afforded compound **9**, from which the BOC protecting group was cleaved using trifluoroacetic acid to afford amine **10**, as the ammonium salt. This was then coupled to **7** to give the neutral pyridine compound **11**, which was methylated using CH$_3$I to produce the asymmetric pyridinium-isophthalamide macrocycle precursor **12·I**. Anion exchange using a nitrate-loaded Amberlite® anion exchange resin afforded the nitrate salt, **12·NO$_3$**.

The synthesis of the [2]catenane was achieved using nitrate templation, via a RCM strategy (Scheme 2). An initial pseudorotaxane assembly was prepared by mixing **12·NO$_3$** with macrocycle **13**[22] in dry CH$_2$Cl$_2$. Addition of Grubbs' second generation RCM catalyst afforded the [2]catenane. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed that the catenane was formed in approximately 25% yield; the other products being the cyclised form of **12**$^+$ and non-interlocked macrocycle **13**. Catenane **14·NO$_3$** was isolated in an overall yield of 20% following purification by silica gel chromatography, and fully characterised by ^{1}H, ^{13}C and ^{1}H ROESY NMR, and high resolution mass spectrometry (see Figure 2 and ESI†). The ^{1}H NMR spectra of macrocycle **13**, catenane **14·NO$_3$**, and macrocycle precursor **12·NO$_3$** are compared in Figure 2A. Of particular note is the upfield shift and splitting of the hydroquinone protons *d* and *e*, which is diagnostic of aromatic donor–acceptor interactions between the hydroquinones in macrocycle **13** and the electron-deficient pyridinium motif in the other macrocycle, and confirms the interlocked nature of the catenane. Further confirmation of the interlocked structure is obtained in the ^{1}H ROESY NMR spectrum of **14·NO$_3$**, which reveals multiple through space interactions between the two interlocked macrocycles (see ESI†). Synthesis of the catenane was also attempted using both the chloride and hexafluorophosphate (PF$_6^-$) salts of **12**$^+$. ^{1}H NMR analysis of the crude reaction mixtures revealed a catenane yield of <10% with chloride[23] and no interlocked product in the case of PF$_6^-$, highlighting the crucial templating role of the nitrate anion in the synthesis of the catenane. In order to investigate the anion recognition properties of the new catenane, it was necessary to anion exchange to the non-coordinating PF$_6^-$ salt by washing with aqueous NH$_4$PF$_6$. ^{1}H NMR anion binding titration experiments were conducted in the competitive aqueous solvent mixture of 45:45:10 CDCl$_3$–CD$_3$OD–D$_2$O. Binding of nitrate, added as the tetrabutylammonium salt, results in strong upfield perturbation of the internal pyridinium proton *3* ($\Delta\delta = 0.21$ ppm after 10 equiv.), which is diagnostic of the anion binding within the catenane's interlocked binding cavity. Addition of other mono-charged oxoanions led to significantly smaller perturbations of this proton

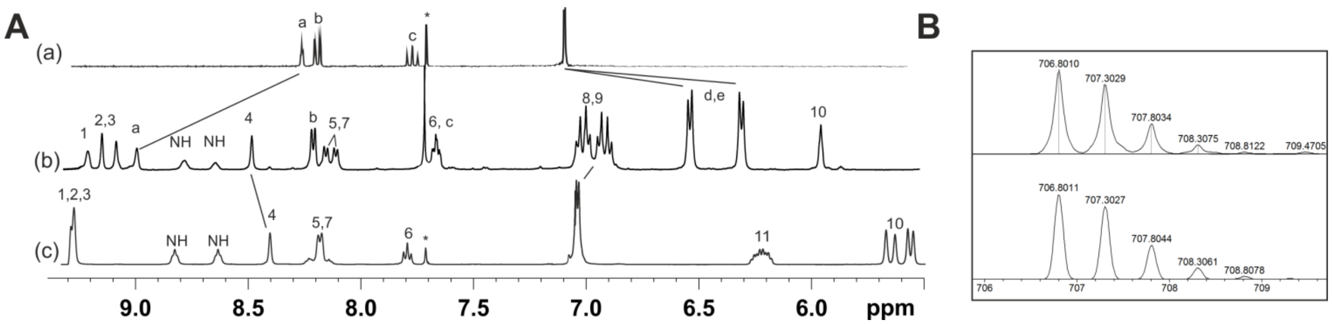


Fig.2 (A) Partial ^{1}H NMR spectra of (a) Macrocycle **13**, (b) Catenane **$14{\cdot}NO_3$** and (c) Macrocycle precursor **$12{\cdot}NO_3$** in 1:1 $CDCl_3$–CD_3OD (500 MHz, 298 K). For atom labels see Scheme 2, *denotes residual solvent peak. **(B)** High resolution electrospray ionisation mass spectrum of catenane **$14{\cdot}NO_3$** (top) with theoretical isotope model for $[M\text{-}NO_3^- + Na^+]^{2+}$ (bottom).

Table 1 Anion association constants of catenane **$14{\cdot}PF_6$** in 45:45:10 $CDCl_3/CD_3OD/D_2O$ and anion complexation induced chemical shift changes of proton *3*.

Anion[a]	NO_3^-	HCO_3^-	$H_2PO_4^-$	AcO^-	Cl^-
K_a (M^{-1})[b]	250	80	-[c]	-[c]	200
$\Delta\delta(3)$[d]	0.21	0.10	0.04	0.04	0.19

T = 298 K. [a] Anions added as TBA salts, except for HCO_3^- which was added as the TEA salt. [b] Calculated using chemical shift data of proton *3*. Errors estimated to be <10%. [c] Binding too weak to be quantified. [d] Chemical shift change of proton *3* after addition of 10 equiv. of anion.

(see Table 1). WinEQNMR2[24] analysis of the titration data determined the 1:1 stoichiometric association constants shown in Table 1.

The trigonal, tridentate binding cavity of the catenane host is highly selective for nitrate, over the other mono-charged oxoanions. The selectivity over acetate is particularly noteworthy, which despite being five orders of magnitude more basic, is not bound by the catenane. Dihydrogenphosphate is also not bound, and only weak binding was observed for hydrogen carbonate. This observed selectivity for nitrate over more basic oxoanions can be attributed to the excellent size and geometry match of the catenane's complementary binding cavity with the trigonal planar nitrate anion. For comparison, the association constant with the spherical chloride anion, which lacks the trigonal geometric preference, was determined in the same solvent mixture and found to be lower than that of nitrate, albeit by a modest amount. It has previously been demonstrated that analogous acyclic receptors, bearing the same bidentate hydrogen bond donating functionality as **12^+**, bind chloride exclusively in the same solvent mixture, with no nitrate association being observed.[20] This serves to highlight the crucial role that the three-dimensional tridentate binding cavity of catenane **$14{\cdot}PF_6$** plays in enhancing the recognition and selectivity of the host towards the nitrate anion.

In conclusion, we have demonstrated the first example of nitrate-templated catenane formation. Removal of the templating nitrate anion results in an interlocked catenane host which displays impressive selectivity for nitrate over a range of more basic oxoanions, even in a highly competitive organic–aqueous solvent mixture. The utilisation of templating anions for the synthesis of interlocked molecular architectures for recognition and sensing applications is continuing in our laboratories.

M.J.L would like to thank the EPSRC for a DTA studentship.

Notes and references

1. J. L. Sessler, P. A. Gale, and W.-S. Cho, *Anion Receptor Chemistry*, RSC, Cambridge, 2006; P. D. Beer and P. A. Gale, *Angew. Chem. Int. Ed.*, 2001, **40**, 486-516; P. A.Gale, N. Busschaert, C. J. E. Haynes, L. E. Karagiannidis and I. L. Kirby, *Chem. Soc. Rev.*, 2014, **43**, 205-241; S. Kubik, *Chem. Soc. Rev.*, 2010, **39**, 3648-3663; K. Zhu, S. Li, F. Wang and F.Huang, *J. Org. Chem*, 2009, **74**, 1322-1328; G.Yu, Z. Zhang, C. Han, M. Xue, Q. Zhou and F. Huang, *Chem. Comm.*, 2012, **48**, 2958-2960.
2. V. H. Smith and D. W. Schindler, *Trends Ecol Evol*, 2009, **24**, 201–207.
3. R. F. Follett and J. L. Hatfield, *Nitrogen in the environment sources, problems, and management*,, Elsevier, New York, 2001.
4. J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, Wiley, Chichester, UK, 2nd Edition., 2009.
5. A. P. Bisson, V. M. Lynch, M.-K. C. Monahan, and E. V. Anslyn, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 2340–2342.
6. K. Choi and A. D. Hamilton, *J. Am. Chem. Soc.*, 2001, **123**, 2456–2457.
7. R. Herges, A. Dikmans, U. Jana, F. Köhler, P. G. Jones, I. Dix, T. Fricke, and B. König, *Eur. J. Org. Chem.*, 2002, **17**, 3004–3014.
8. P. Blondeau, J. Benet-Buchholz, and J. de Mendoza, *New J. Chem.*, 2007, **31**, 736–740.
9. A. S. Singh and S.-S. Sun, *J. Org. Chem.*, 2012, **77**, 1880–1890.
10. J. Romański and P. Piątek, *J. Org. Chem.*, 2013, **78**, 4341–4347.
11. M. M. Watt, L. N. Zakharov, M. M. Haley and D. W. Johnson, *Angew. Chem. Int. Ed.*, 2013, **52**, 10275–10280.
12. S. F. M. van Dongen, S. Cantekin, J. A. A. W. Elemans, A. E. Rowan, and R. J. M. Nolte, *Chem. Soc. Rev.*, 2014, **43**, 99–122.
13. V. Balzani, A. Credi, S. Silvi, and M. Venturi, *Chem. Soc. Rev.*, 2006, **35**, 1135–1149.
14. E. R. Kay, D. A. Leigh, and F. Zerbetto, *Angew. Chem. Int. Ed.*, 2007, **46**, 72–191.
15. L. Fang, M. A. Olson, D. Benítez, E. Tkatchouk, W. A. G. Iii, and J. F. Stoddart, *Chem. Soc. Rev.*, 2009, **39**, 17–29.
16. M. J. Langton and P. D. Beer, *Acc. Chem. Res.*, 2014, DOI: 10.1021/ar500012a
17. C. G. Collins, E. M. Peck, P. J. Kramer, and B. D. Smith, *Chem. Sci.*, 2013, **4**, 2557–2563.
18. G. T. Spence and P. D. Beer, *Acc. Chem. Res.*, 2013, **46**, 571–586.
19. N. H. Evans and P. D. Beer, *Chem. Soc. Rev.*, 2014, DOI: 10.1039/c4cs00029c
20. M. J. Langton, L. C. Duckworth, and P. D. Beer, *Chem. Commun.*, 2013, **49**, 8608–8610.
21. J. A. Wisner, P. D. Beer, M. G. B. Drew, and M. R. Sambrook, *J. Am. Chem. Soc.*, 2002, **124**, 12469–12476.
22. J. A. Wisner, P. D. Beer, and M. G. B. Drew, *Angew. Chem. Int. Ed.*, 2001, **40**, 3606–3609.
23. Chloride templation leads to the predominant formation of the non-interlocked cyclised form of **12^+**: presumably the bidentate nature of **12^+** fulfils the coordination of chloride and competes with association of macrocycle **13**.
24. M. J. Hynes, *J. Chem. Soc. Dalton Trans.*, 1993, **2**, 311–312.