Oxacalixarenes and oxacyclophanes containing 1,8-naphthyridines: a new class of molecular tweezers with concave-surface functionality†

Jeffrey L. Katz,* Bram J. Geller and Peter D. Foster

Received (in Austin, TX, USA) 29th October 2006, Accepted 17th January 2007
First published as an Advance Article on the web 2nd February 2007
DOI: 10.1039/b615336d

The first examples of oxacalix[4]arenes and [1$_4$]oxacyclophanes bearing 1,8-naphthyridine units are reported, and these systems function as molecular tweezers containing inner-cavity hydrogen bond acceptors.

There is continued interest in the design of host molecules for solution-phase aromatic guest binding and detection.[1] Whitlock's seminal work[2] describing a molecular tweezer outlined design criteria for hosts specifically suited for aromatic guest binding. Such compounds would contain two aromatic walls separated by a rigid spacer at a distance of approximately 7 Å, permitting a bound guest to experience favorable π–π interactions simultaneously with both walls of the receptor cavity. Based on this model, a variety of molecular tweezers have been developed,[3] along with related systems bearing more flexible linkers.[4] The specific geometric and spatial constraints required for construction of these hosts has generally required multistep synthetic sequences. Additionally, many reported molecular tweezers contain unfunctionalized concave surfaces that favor binding of electron-deficient π-systems; the synthesis of tweezers containing inner-cavity functionality that imparts increased substrate selectivity to the host–guest recognition event remains a significant challenge. A bisacridine receptor containing an interior carboxylic acid moiety has been developed by Zimmerman, and this system exhibits selectivity for binding adenine in organic media.[5] More recently, Klärner has shown that norbornane-derived tweezers bearing methyl phosphonates proximal to the recognition cavity bind arginine and lysine in aqueous solution.[6]

Oxacalix[4]arenes hold great potential as platforms for molecular recognition. We have previously shown that oxacalix[4]arenes incorporating benzenes and azaheterocycles are formed in high yield by cyclocondensation of electrophilic *meta*-dihalogenated aromatics with substituted resorcinols.[7] The ring formation is general with respect to the functional group profile of both coupling partners, providing diverse macrocyclic systems in a single step. Our group[7] and others[8] have determined that oxacalix[4]arenes adopt a distorted 1,3-alternate conformation[9] regardless of the functional groups appended to the aromatic rings. This conformation orients the nucleophilic component aromatic rings co-parallel and eclipsing, with a centroid–centroid distance of approximately 4.5 Å (Fig. 1(a)). The tight spacing precludes guests from accessing the concave surface between the co-parallel aromatic walls, limiting the capacity of these systems to act as molecular hosts.

We envisioned that creation of oxacalix[4]arenes bearing larger electrophilic component arene spacers would expand the distance between nucleophilic component aromatic rings in the macrocyclic architecture. Molecular modeling revealed that naphthalene units would create a separation of approximately 7.0 Å between nucleophilic component rings (Fig. 1(b)). In analogy to our previous work with dichlorinated azaheterocycles,[7a,10] we chose to investigate 2,7-dichloro-1,8-naphthyridine[11] (**1**) as an electrophile for oxacalixarene formation. As an added design feature, upon formation of the macrocyclic framework the nitrogen atoms present on **1** should be oriented on the interior of the binding pocket, placing potential hydrogen bond acceptors at the base of the recognition cavity.

Reaction optimization was conducted for the cyclocondensation of 2,7-dichloro-1,8-naphthyridine (**1**) and orcinol (**2**) (eqn (1)). As observed for oxacalixarene formation with alternative electrophiles, higher temperatures were found to favor the cyclic tetramer due to thermodynamic product control.[7a,8e,8f] The maximum yield of oxacalix[2]benzene[2]naphthyridine **3** was obtained at 100 °C (Cs_2CO_3, DMSO, 18 h).

Crystals suitable for X-ray analysis of **3**·2CH_2Cl_2 were obtained by slow evaporation from CH_2Cl_2 (Fig. 2).[12] As predicted,

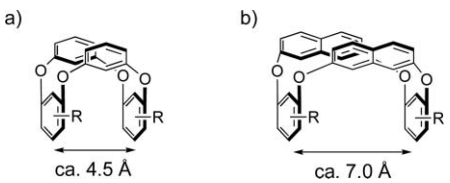


Fig. 1 1,3-Alternate conformations of oxacalix[4]arenes with approximate distances enforced by (a) benzene-type and (b) naphthalene-type spacers.

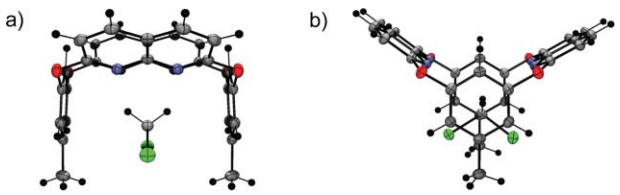
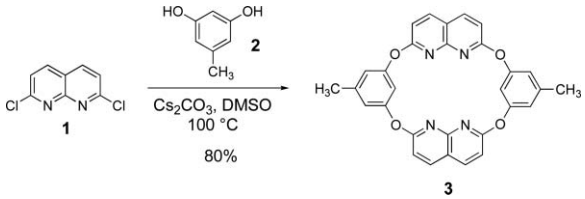


Fig. 2 X-Ray crystal structure of **3**·2CH_2Cl_2. One solvated CH_2Cl_2. molecule has been removed for clarity (thermal ellipsoids at the 30% probability level; oxygen = red, nitrogen = blue, chlorine = green, carbon = grey, hydrogen = black).

Department of Chemistry, Colby College, 5754 Mayflower Hill, Waterville, ME, 04901, USA. E-mail: jlkatz@colby.edu; Fax: (207) 859-5760; Tel: (207) 859-5754

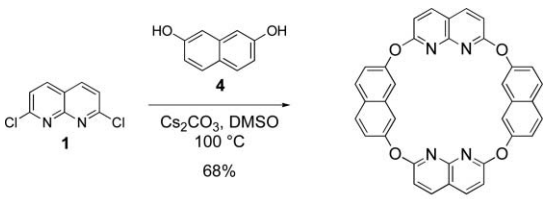
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, copies of NMR spectra, and X-ray crystallographic data for compounds **3**, **6** and **7**. Experiment details and data from ^{1}H NMR titration experiments for binding constant determination. See DOI: 10.1039/b615336d

macrocycle **3** adopts a distorted 1,3-alternate conformation in the solid-state. The benzene rings are nearly parallel and eclipsing (4.8° angle between ring planes), and a 114.5° angle is observed between naphthyridine ring planes. The benzene rings are separated at a centroid–centroid distance of 6.8 Å. This creates a concave surface capable of containing small molecules; one of the two solvated CH_2Cl_2 molecules is found in this cavity.

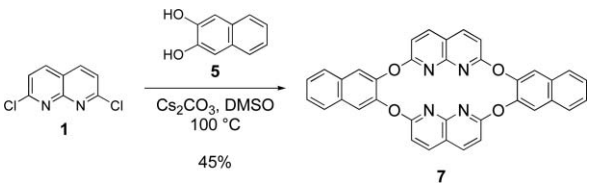


(1)

To increase the size of the recognition cavity, we next investigated macrocyclizations using nucleophilic coupling partners 2,7-dihydroxynaphthalene (**4**) and 2,3-dihydroxynaphthalene (**5**) (eqn (2) and (3)).



(2)



(3)

Under the optimized conditions for formation of macrocycle **3**, cyclocondensation of **1** with **4** or **5** provided oxacalix[2]naphthalene[2]naphthyridine **6** and [1$_4$]oxacyclophane **7** in 68 and 45% yields, respectively. We speculate that the more modest yield obtained for **7** reflects increased rigidity and/or steric congestion relative to **3** and **6** created by the *ortho*-linkages (*vide infra*).

X-Ray crystal structures of **6**·0.5CH_2Cl_2·0.5H_2O and **7**·2CH_3CN were obtained, and a 1,3-alternate conformation is observed for both systems (Fig. 3).[12] Macrocycle **6** adopts a π-stacked "dimer" in the solid state (Fig. 3(a), (b)). The naphthalene walls are tilted 12.5° from co-planarity and twisted 14.8° from fully eclipsing. The twisting, likely due to both crystal packing forces and maximization of intermolecular π–π interactions, creates a cavity with a centroid–centroid distance of 6.9 Å between naphthalene rings and a 103.5° angle between naphthyridine ring planes.

The *ortho*-linkages in oxacyclophane **7** place the naphthyridine rings in very close proximity, with a 3.06 Å transannular N···N distance and a 34.1° angle between naphthyridine ring planes (Fig. 3(c), (d)). The naphthalene units that define the tweezer cavity are separated by 7.0 Å as measured centroid-to-centroid, and deviate 5.6° from co-planarity with a 6.0° twist from fully eclipsing. Further, one of the two solvated CH_3CN molecules is found inside the tweezer cavity and is in π-contact with the cavity walls.

The 1,8-naphthyridine nitrogen atoms in macrocycles **3**, **6** and **7** are oriented on the interior of the concave surface at the base of

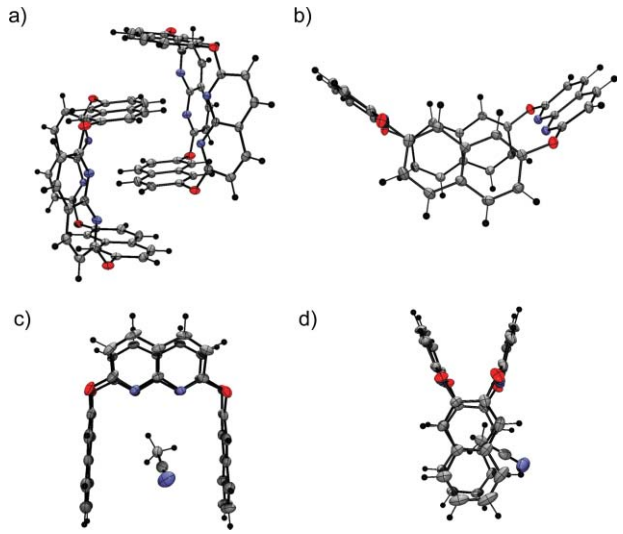


Fig. 3 X-Ray crystal structures of macrocycles **6** (a, b) and **7** (c, d). Some solvent molecules have been removed for clarity (thermal ellipsoids at the 30% probability level; oxygen = red, nitrogen = blue, carbon = grey, hydrogen = black).

the binding pocket, and the transannular N···N distance is dictated by the diphenolic coupling partner. *Meta*-diphenol **2** enforces a transannular N···N distance in **3** of 4.70 Å (Fig. 4(a)). 2,7-Dihydroxynaphthalene (**4**) widens the separation between naphthyridine rings, creating a transannular N···N distance in **6** of 7.17 Å (Fig. 4(b)). *Ortho*-diphenol **5** tightly clusters the nitrogen atoms at the base of the cavity in **7**, with a 3.06 Å transannular N···N distance (Fig. 4(c)). Thus, spatial tuning of the concave surface with respect to the cavity wall dimensions, the positioning of the naphthyridine nitrogen atoms, and the angle between naphthyridine ring planes can be accomplished simply by judicious choice of the diphenolic coupling partner.

Preliminary molecular recognition experiments were conducted using ^{1}H NMR spectroscopy to probe the importance of both cavity size and hydrogen bonding for guest binding by tweezers **3**, **6** and **7**. Guests containing zero, one, or two hydrogen bond-capable functional groups were investigated: toluene (**8**), benzonitrile (**9**), phenol (**10**), benzoic acid (**11**), and *o*-salicylic acid (**12**). We expected to observe host–guest complex formation from upfield ^{1}H chemical shifts of bound guest molecules due to anisotropic shielding from the aromatic cavity walls. Macrocycle **3** contains a relatively small recognition cavity, and no host–guest complexes were observed between **3** and guests **8–12**. Tweezers **6** and **7** also

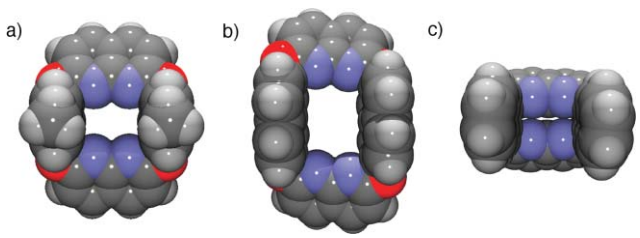


Fig. 4 X-Ray crystal structures of (a) **3**, (b) **6** and (c) **7** shown as space-filling depictions looking into the binding pockets (solvent molecules removed for clarity, oxygen = red, nitrogen = blue, carbon = grey, hydrogen = light grey).

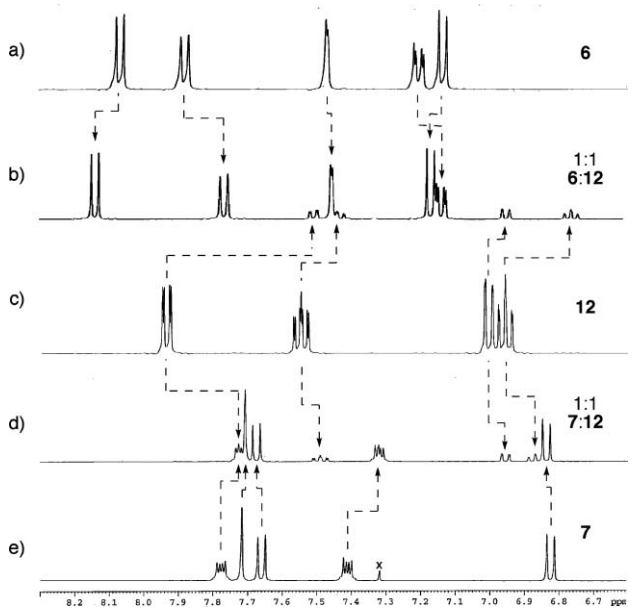


Fig. 5 Partial ^{1}H NMR spectra (8.3–6.6 ppm, 400 MHz, CD_2Cl_2, 298 K) of (a) **6**, (b) equimolar mixture of **6** and *o*-salicylic acid (**12**), (c) **12**, (d) equimolar mixture of **7** and *o*-salicylic acid (**12**), (e) **7**.

failed to form observable host–guest complexes with toluene (**8**) or benzonitrile (**9**); these guests lack hydrogen-bond donors and the ability to interact with the naphthyridine nitrogen atoms inside the tweezer cavities. Addition of phenol (**10**) or benzoic acid (**11**) to hosts **6** or **7** resulted in only small upfield shifts (<0.05 ppm) for host and guest ^{1}H NMR resonances, suggesting weak host–guest interactions.[13] Substantially larger shifts were observed for 1 : 1 mixtures of *o*-salicylic acid (**12**) and either **6** or **7** (Fig. 5). Mutual anisotropic shielding shifts the protons on **12** and the naphthalene protons on **6** and **7** upfield, while hydrogen bonding causes the downfield shifts observed for the protons on the naphthyridine rings of **6** and **7**. Association constants (K_a) were measured in 9 : 1 CH_2Cl_2:CD_2Cl_2[14] using ^{1}H NMR, and were found to be 45 and 306 M^{-1} for the **6**·**12** and **7**·**12** host–guest complexes, respectively.[15] While the magnitudes of these binding constants are modest, it is evident that both π–π and hydrogen bonding interactions play a role in guest binding by **6** and **7**, and that such macrocycles are promising scaffolds for molecular recognition of neutral aromatic compounds.

In conclusion, we have synthesized the first examples of oxacalix[4]arenes and [1$_4$]oxacyclophanes bearing 1,8-naphthyridine units. Due to the preferred 1,3-alternate conformations, these systems are molecular tweezers capable of binding aromatic guests in solution. Additionally, the inner-cavity naphthyridine nitrogen atoms are able to impart substrate selectivity to the recognition event. We continue to explore the synthesis and recognition properties of this new class of molecular tweezers, and our findings will be reported in due course.

The authors are grateful to Research Corporation (CC6665), the Petroleum Research Fund (45440-B1), and Colby College for financial support of this work. Special thanks are due to the Bowdoin College MALDI HRMS facility funded by the NSF (MRI-0116416).

Notes and references

1 (*a*) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, 1995; (*b*) J. H. Hartley, T. D. James and C. J. Ward, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3155–3184; (*c*) A. Arduini, A. Pochini, A. Secchi and F. Ugozzoli, *Calixarenes 2001*, Kluwer Academic Publishers, Dordrecht, Netherlands, 2001, pp. 457–475.

2 C.-W. Chen and H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, 1978, **100**, 4921–4922.

3 (*a*) R. P. Sijbesma, S. S. Wijmenga and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1992, **114**, 9807–9813; (*b*) S. C. Zimmerman, *Top. Curr. Chem.*, 1993, **165**, 71–102; (*c*) R. N. Warrener, D. Margetic, A. S. Amarasekara, D. N. Butler, I. B. Mahadevan and R. A. Russell, *Org. Lett.*, 1999, **1**, 199–202; (*d*) R. D. Sommer, A. L. Rheingold, A. J. Goshe and B. Bosnich, *J. Am. Chem. Soc.*, 2001, **123**, 3940–3952; (*e*) H. Kurebayashi, T. Haino, S. Usui and Y. Fukazawa, *Tetrahedron*, 2001, **57**, 8667–8674; (*f*) F.-G. Klarner and B. Kahlert, *Acc. Chem. Res.*, 2003, **36**, 919–932; (*g*) J. N. H. Reek, J. A. A. W. Elemans, R. de Gelder, P. T. Beurskens, A. E. Rowana and R. J. M. Nolte, *Tetrahedron*, 2003, **59**, 175–185; (*h*) M. Harmata, *Acc. Chem. Res.*, 2004, **37**, 862–873; (*i*) A. Wu, P. Mukhopadhyay, A. Chakraborty, J. C. Fettinger and L. Isaacs, *J. Am. Chem. Soc.*, 2004, **126**, 10035–10043; (*j*) T. Mas, C. Pardo and J. Elguero, *Helv. Chim. Acta*, 2005, **88**, 1199–1207; (*k*) H. Iwamoto, N. Takahashi, T. Maeda, Y. Hidaka and Y. Fukazawa, *Tetrahedron Lett.*, 2005, **46**, 6839–6842; (*l*) H. Huang and D. G. Drueckhammer, *Chem. Commun.*, 2006, 2995–2997.

4 (*a*) K. D. Shimizu, T. M. Dewey and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1994, **116**, 5145–5149; (*b*) O. Molt, D. Rübeling and T. Schrader, *J. Am. Chem. Soc.*, 2003, **125**, 12086–12087; (*c*) A. Petitjean, R. G. Khoury, N. Kyritsakas and J.-M. Lehn, *J. Am. Chem. Soc.*, 2004, **126**, 6637–6647.

5 (*a*) S. C. Zimmerman and W. Wu, *J. Am. Chem. Soc.*, 1989, **111**, 8054–8055; (*b*) S. C. Zimmerman, Z. Zeng, W. Wu and D. E. Reichert, *J. Am. Chem. Soc.*, 1991, **113**, 183–196.

6 M. Fokkens, T. Schrader and F.-G. Klärner, *J. Am. Chem. Soc.*, 2005, **127**, 14415–14421.

7 (*a*) J. L. Katz, B. J. Geller and R. R. Conry, *Org. Lett.*, 2006, **8**, 2755–2758; (*b*) J. L. Katz, M. B. Feldman and R. R. Conry, *Org. Lett.*, 2005, **7**, 91–94.

8 (*a*) R. D. Chambers, P. R. Hoskin, A. R. Kenwright, A. Khalil, P. Richmond, G. Sandford, D. S. Yufit and J. A. K. Howard, *Org. Biomol. Chem.*, 2003, **1**, 2137–2147; (*b*) M.-X. Wang and H.-B. Yang, *J. Am. Chem. Soc.*, 2004, **126**, 15412–15422; (*c*) E. Hao, F. R. Fronczek and M. G. H. Vicente, *J. Org. Chem.*, 2006, **71**, 1233–1236; (*d*) F. Yang, L. Yan, K. Ma, L. Yang, J. Li, L. Chen and J. You, *Eur. J. Org. Chem.*, 2006, 1109–1112; (*e*) H. Konishi, K. Tanaka, Y. Teshima, T. Mita, O. Morikawa and K. Kobayashi, *Tetrahedron Lett.*, 2006, **47**, 4041–4044; (*f*) W. Maes, W. V. Rossom, K. V. Hicke, L. V. Meervelt and W. Dehaen, *Org. Lett.*, 2006, **8**, 4161–4164.

9 C. D. Gutsche, *Calixarenes Revisited*, Royal Society of Chemistry, London, 2000.

10 J. L. Katz, K. J. Selby and R. R. Conry, *Org. Lett.*, 2005, **7**, 3505–3507.

11 (*a*) A. E. M. Boelrijk, T. X. Neenan and J. Reedijk, *J. Chem. Soc., Dalton Trans.*, 1997, 4561–4570; (*b*) G. R. Newkome, S. J. Garbis, V. K. Majestic, F. R. Fronczek and G. Chiari, *J. Org. Chem.*, 1981, **46**, 833–839.

12 CCDC 624760–624762. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b615336d.

13 In all cases, guest exchange is rapid on the NMR timescale and the observed chemical shift changes are averages of bound and unbound states.

14 **6** and **7** have low solubility in $CHCl_3$, but are soluble in CH_2Cl_2.

15 Attempts to determine host–guest binding stoichiometries *via* Job plots were frustrated by modest binding constants and unavoidable guest speciation at the concentration ranges dictated by the host solubility limits.[16] Nonlinear regression fitting of the host–guest titration chemical shift data to binding isotherm models that include both the known host speciation and specific binding stoichiometry assumptions revealed probable **6**:monomer-**12** and **7**:dimer-**12** associations. Molecular mechanics calculations support these host–guest stoichiometries. See ESI† for details.

16 (*a*) V. M. S. Gil and N. C. Oliveria, *J. Chem. Educ.*, 1990, **67**, 473–478; (*b*) W. Likussar and D. F. Boltz, *Anal. Chem.*, 1971, **43**, 1265–1272.

