ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 2228–2230

www.rsc.org/chemcomm

COMMUNICATION

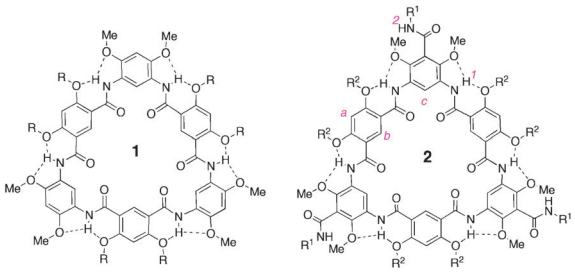
Non-aggregational aromatic oligoamide macrocycles†

Xiangxiang Wu,[ae] Guoxing Liang,[a] Gang Ji,[c] Hoong-Kun Fun,[d] Lan He*[b] and Bing Gong*[af]

Received 8th November 2011, Accepted 19th December 2011
DOI: 10.1039/c2cc16912f

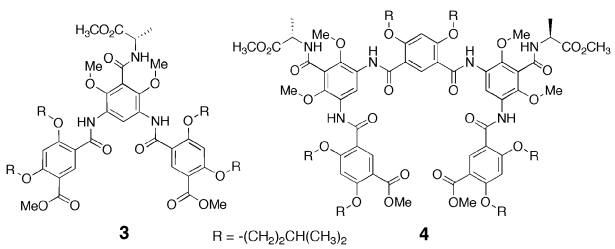
Attaching peripheral amide groups to the backbone of cyclic aromatic oligoamides 1 leads to new macrocycles 2 that show drastically changed behavior including modest yields of formation and no tendency to aggregate while maintaining a rigid backbone and a defined, guest-binding internal cavity.

Macrocyclic molecules have long attracted wide attention.[1] Rigid macrocycles,[2] such as those with arylene ethynylene,[3] aromatic amide,[4,5] aromatic hydrazide,[6] Schiff base,[7] and other[8] backbones, offer advantages including shape-persistency unaffected by synthetic modifications, lumens of defined sizes, and the ability to present functional groups at defined locations.[2] Many rigid macrocycles are now available based on efficient synthetic methods reported in recent years.[3–7] We have described the highly efficient formation of macrocycles **1**,[4] their larger analogs,[9] and those with different backbones,[6] based on either one-pot[4,9] or segment condensation.[9,10] The observed high efficiencies are attributed to the folding of uncyclized oligomeric precursors.[9] These macrocycles have exhibited novel properties. For example, the non-collapsible cavity of **1** is selective for the guanidinium ion.[12] Highly conducting transmembrane single ion channels are formed as a result of the columnar stacking of **1**.[13] Besides, macrocycles **1** were recently found to undergo unusually strong and directional columnar aggregation.[14] Macrocycles **1** and their larger analogs, with their side chains and peripheral aromatic hydrogens, provide multiple sites for structural variation. Herein we report the design, synthesis, and study of macrocycles **2**, which can be regarded as being derived by replacing three exterior aromatic hydrogen atoms of **1** with secondary amide groups.



Macrocycles **2** were designed to probe the possibility of tuning the aggregation propensity of the cyclic oligoamide backbones *via* structural modification.[5] It was conceived that by incorporating H-bonding groups onto the periphery of **1**, the resultant macrocycles **2** would exhibit changed aggregation behavior due to the H-bonding capability, steric hindrance and backbone electronic property endowed by the amide side chains. The R1 side chain was chosen to impart chiral elements into the macrocycles to monitor the formation of chiral assemblies. The resultant macrocycles could associate *via* H-bonding interaction, and may thus exist as well dispersed molecular species in polar media. Molecularly dispersed **2** should avoid the complications caused by the strong stacking of **1** and facilitate structural characterization and monitoring of intermolecular interaction. If the backbone-rigidifying three-center H-bonds of **1** also persist in **2**, the peripheral amide groups should not affect the persistent shapes of the macrocyclic backbone and the internal cavity.

Our study[9] suggests that folding of uncyclized oligomer precursors into crescent shapes is responsible for the efficient formation of **1**, with yields from 85% to over 90%,[4] based on one-pot[4,9] or segment condensation.[10] If the uncyclized precursors of **2** also fold, similar folding-assisted cyclization could lead to **2** in high yields. To probe the effect of the incorporated amide groups on the conformations of the uncyclized precursors of **2**, oligoamides **3** and **4** were designed and prepared† based on what we described before.[10,11] Single crystals of **3** from methanol/pyridine (1/1, v/v) and those of **4** from $CHCl_3$/toluene (1/2, v/v) were then obtained by slow evaporation of solvents at room temperature.‡



[a] *College of Chemistry and College of Resources Science and Technology, Beijing Normal University, Beijing 100875, China*
[b] *National Institutes for Food and Drug Control, Beijing 100050, China. E-mail: helan1961@hotmail.com*
[c] *Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China*
[d] *X-Ray Crystallography Unit, School of Physics, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia*
[e] *Henan University of Traditional Chinese Medicine, Zhengzhou 450008, China*
[f] *Department of Chemistry, University at Buffalo, State University of New York, Buffalo, NY 14260, USA. E-mail: bgong@buffalo.edu; Fax: +1 716 645 6963; Tel: +1 716 645 4307*

† Electronic supplementary information (ESI) available: Synthetic procedures; analytical data; additional NMR and mass spectra; method for determining association constants. CCDC 852892 (**3**) and 852893 (**4**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc16912f

The solid-state structures of **3** and **4** show that the peripheral amide groups do not interfere with the backbone three-center H-bonds (Fig. 1). Both **3** and **4** have crescent shapes that are enforced by these three-center H-bonds. The peripheral amide group of **3** has a dihedral angle of $\sim 55^{\circ}$ with the benzene ring it attaches to, and those of **4** are nearly perpendicular to the benzene rings to which they connect. Consequently, these amide groups do not participate in intramolecular H-bonding interaction with the adjacent O atoms. Such an observation demonstrates that modifying backbone-rigidified crescent oligoamides[15] at the peripheral positions does not disturb the folded conformations. Therefore, it was reasoned that these peripheral amide side chains, which do not change the rigidity of the oligoamide backbone, should not change the overall persistent shape of **2**.

The folding of **3** and **4** indicates that the precursors of **2** must also fold into similar shapes, which suggests that **2**, like **1**, could form in high yields. Surprisingly, repeated attempts to prepare **2** by treating the corresponding diacid chlorides with diamines led to a mixture containing cyclic and noncyclic oligomers of 4 to 12 residues†, which is in sharp contrast to the "cleanness" observed in the formation of **1**.[4] By coupling trimers **5** and **6** under dilution, macrocycles **2** were obtained in moderate crude yields (Scheme 1). Purification using column chromatography led to **2a** and **2b** as yellow or white solids in yields of 15% and 17%.† Thus, in comparison to the high yields of **1**, introducing amide side chains drastically lowers the yields of **2**. The modest yields of **2** have raised very interesting mechanistic questions about the formation of **1**. Additional factors besides folding of precursors, such as intermolecular stacking, may also contribute to the unusually high yields of **1**.

In both **3** and **4**, the side-chain amide protons are H-bonded to the ester carbonyl oxygens of another molecule, while the oxygen atoms of these peripheral amide groups do not engage in any H-bonding. Thus, the peripheral amide groups of **2**, being in the same local environment as those of **3** and **4**, should not be "consumed" by intramolecular H-bonding and may be predisposed for intermolecular H-bonding, leading to H-bonded aggregates.

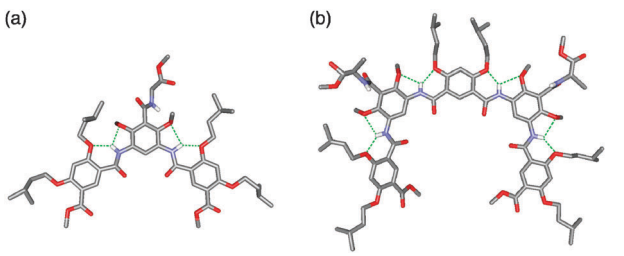
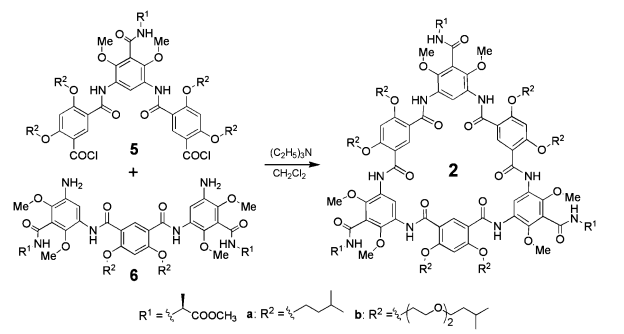


Fig. 1 The solid-state structures of (a) compound **3** and (b) compound **4**. The backbone amide groups are involved in intramolecular three-center H-bonds (dashed green lines). Hydrogen atoms, except those of amide groups, are omitted for clarity.



Scheme 1

However, in contrast to the severely broadened ^{1}H NMR signals of **1** due to strong aggregation,[4,14] no obvious line-broadening was revealed by the ^{1}H NMR spectra of **2a** in $CDCl_3$, CD_3OD or DMSO-d_6†, suggesting that **2a** underwent insignificant aggregation in these solvents. Examination of the presence of intermolecular H-bonding by following concentration-dependent shifts of protons 2 of **2a** was hampered by the limited solubility ($\leq$1 mM in $CDCl_3$) of this compound. Macrocycle **2b**, with its greatly enhanced solubility, also gave sharp ^{1}H NMR signals. The ^{1}H NMR spectra of **2b** recorded in $CDCl_3$ from 10 mM to 0.3 mM indicated no meaningful shifts of the aromatic and amide proton resonances†, which suggests that, like **2a**, macrocycle **2b** does not undergo noticeable aggregation. The lack of concentration-dependent shift of protons 2 of **2b** points to insignificant intermolecular H-bonding interaction in $CDCl_3$. These results demonstrate that, compared to the strongly aggregating **1**, macrocycles **2** have a very low propensity for aggregation in solution.

Our study revealed that the internal cavity of **1** had a very high affinity toward the guanidinium (Gua) ion.[11] As shown in Fig. 2a, the presence of one equivalent of GuaCl leads to significant changes in both the chemical shifts and line-width of the ^{1}H NMR signals of **2b**. The strong binding of the Gua ion to **1b** was indicated by the noticeably different ^{1}H spectra of **2b** with or without added GuaCl in CD_3OD (Fig. 2b). That the Gua ion indeed binds into the cavity of **2b** is shown by the ROESY spectrum of **2b** (2 mM) and GuaCl (2 mM) in $CDCl_3$, which reveals a strong ROE contact between the proton signal of the Gua ion and that of proton *c* of **2b**.†

Attempts to determine the association constant (K_a) between **1** and the Gua ion were hampered by the strong aggregation of **1**.[12,14] The well-resolved ^{1}H NMR spectra of **2b** should allow the K_a values to be determined based on concentration-dependent shifts of ^{1}H NMR signals. However, in $CDCl_3$, the association constant between **2b** and the Gua ion could not be determined because diluting the solution from 10 mM to 0.2 mM led to no detectable shift of ^{1}H signals.† K_a values of $(1.2 \pm 0.1) \times 10^6$ M^{-1} and $(2.2 \pm 0.2) \times 10^6$ M^{-1} between **2b** and the Gua ion in pure $CDCl_3$ were obtained by extrapolating K_a's obtained from $CDCl_3$ with 5%, 10%, 15%, and 20% DMSO-d_6 or CD_3OD.†[16] Thus, like **1**, macrocycle **2b** strongly complexes the Gua ion, which demonstrates that the peripheral amide side chains do not change the recognition ability and likely, the shape of the internal cavity.

In summary, attaching amide groups onto the backbone of **1** leads to macrocycles **2** that exhibit very different properties. The observed behavior of **2** can be explained by the obstruction of intermolecular stacking due to the presence of the peripheral amide side chains. The low yields of **2** have raised new mechanistic questions that warrant further systematic studies. The determination of the association constant of the guanidinium ion and **1**, which was impeded by the strong aggregation of **1**, has now been accomplished with **2b**. The observed strong binding of the guanidinium ion to **2b** demonstrates that, in spite of the dramatic change of properties caused by the amide side chains,

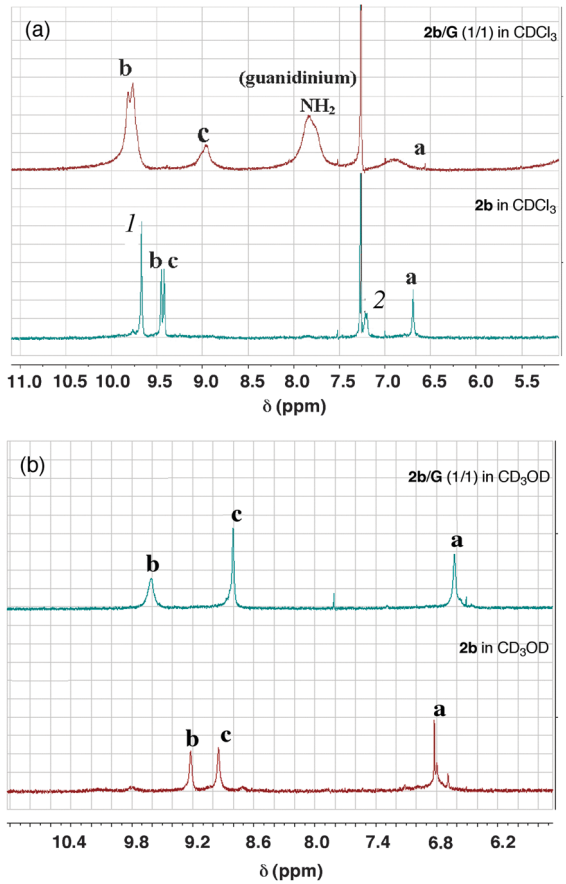


Fig. 2 The partial ^{1}H NMR spectra of (a) **2b** (1 mM)/GuaCl (1/1) (upper) and **2b** (1 mM, bottom) in $CDCl_3$, and (b) **2b** (1 mM)/GuaCl (1/1) (upper) and **2b** (1 mM, bottom) in CD_3OD, recorded at room temperature.

macrocycles **2** still contain a cavity similar to that of **1**. Further modification of **2** could lead us to hosts capable of recognizing a variety of large cations and other polar molecular species.

This work was supported by the Cultivation Fund of the Key Scientific and Technical Innovation Project, Ministry of Education of China Grant 706009 (to BG), the NSFC Grant 21072021 and the Special Fund for Agro-scientific Research in the Public Interest Grant 201103027 (to LH), the US National Science Foundation grants CBET-1036171 and CBET-1066947 (to BG), National Science and Technology Major Projects for Major New Drugs Innovation and Development 2011ZX09307-002-01 (to LH) and the Research University Grant of USM 1001/PFIZIK/811160 (to HKF).

Notes and references

‡ Crystal data for **3**: $C_{51}H_{71}N_3O_{15}$, M = 966.11, triclinic, space group $P\bar{1}$, a = 13.8349(5), b = 14.3436(5), c = 15.2208(4) Å, α = 75.917(2), β = 86.728(2), γ = 66.006(2)°, U = 2673.52(15) Å^3, Z = 2, μ(Mo-Kα) = 0.088 mm^{-1}, 17 070 reflections measured (9373 unique, R_{int} = 0.0313). $R_1[I > 2\sigma(I)]$ = 0.0819. The final w$R(F^2)$ was 0.3087 (all data). CCDC 852892. Crystal data for **4**: $C_{82}H_{112}N_6O_{24}{\cdot}0.5C_7H_8$, M = 1611.89, monoclinic, space group $C2/c$, a = 31.4547(10), b = 25.7172(7), c = 26.8169(9) Å, α = 90.00, β = 120.999(2), γ = 90.00°, U = 18594.6(10) Å^3, Z = 8, μ(Cu-Kα) = 0.693 mm^{-1}, 124 790 reflections measured (13 676 unique, R_{int} = 0.0428). $R_1[I > 2\sigma(I)]$ = 0.1536. The final w$R(F^2)$ was 0.4703 (all data). CCDC 852893.

1 Q. C. Meng and M. Hesse, *Top. Curr. Chem.*, 1992, **161**, 107; J. L. Sessler and A. K. Burrell, *Top. Curr. Chem.*, 1992, **161**, 177; P. V. Bernhardt and E. G. Moore, *Aust. J. Chem.*, 2003, **56**, 239.
2 U. H. F. Bunz, Y. Rubin and Y. Tobe, *Chem. Soc. Rev.*, 1999, **28**, 107–119; J. L. Sessler, N. A. Tvermoes, J. Davis, P. Anzenbacher, K. Jursikova, W. Sato, D. Seidel, V. Lynch, C. B. Black, A. Try, B. Andrioletti, G. Hemmi, T. D. Mody, D. J. Magda and V. Kral, *Pure Appl. Chem.*, 1999, **71**, 2009–2018; C. Grave and A. D. Schluter, *Eur. J. Org. Chem.*, 2002, 3075–3098; W. Zhang and J. S. Moore, *Angew. Chem., Int. Ed.*, 2006, **45**, 4416–4439; M. J. MacLachlan, *Pure Appl. Chem.*, 2006, **78**, 873–888; S. Höger, *Pure Appl. Chem.*, 2010, **82**, 821–830.
3 S. Höger, K. Bonrad, A. Mourran, U. Beginn and M. Moller, *J. Am. Chem. Soc.*, 2001, **123**, 5651–5659; W. Zhang and J. S. Moore, *J. Am. Chem. Soc.*, 2004, **126**, 12796; S. H. Seo, T. V. Jones, H. Seyler, J. O. Peters, T. H. Kim, J. Y. Chang and G. N. Tew, *J. Am. Chem. Soc.*, 2006, **128**, 9264.
4 L. H. Yuan, W. Feng, K. Yamato, A. R. Sanford, D. G. Xu, H. Guo and B. Gong, *J. Am. Chem. Soc.*, 2004, **126**, 11120–11121.
5 H. Jiang, J. M. Leger, P. Guionneau and I. Huc, *Org. Lett.*, 2004, **6**, 2985; F. Campbell, J. Plante, C. Carruthers, M. J. Hardie, T. J. Prior and A. J. Wilson, *Chem. Commun.*, 2007, 2240–2242; Y. Y. Zhu, C. Li, G. Y. Li, X. K. Jiang and Z. T. Li, *J. Org. Chem.*, 2008, **73**, 1745–1751; B. Qin, X. Y. Chen, X. Fang, Y. Y. Shu, Y. K. Yip, Y. Yan, S. Y. Pan, W. Q. Ong, C. L. Ren, H. B. Su and H. Q. Zeng, *Org. Lett.*, 2008, **10**, 5127–5130; F. Li, Q. Gan, L. Xue, Z. M. Wang and H. Jiang, *Tetrahedron Lett.*, 2009, **50**, 2367–2369; B. Qin, C. L. Ren, R. J. Ye, C. Sun, K. Chiad, X. Y. Chen, Z. Li, F. Xue, H. B. Su, G. A. Chass and H. Q. Zeng, *J. Am. Chem. Soc.*, 2010, **132**, 9564–9566.
6 J. S. Ferguson, K. Yamato, R. Liu, L. He, X. C. Zeng and B. Gong, *Angew. Chem., Int. Ed.*, 2009, **48**, 3150–3154.
7 P. D. Frischmann, G. A. Facey, P. Y. Ghi, A. J. Gallant, D. L. Bryce, F. Lelj and M. J. MacLachlan, *J. Am. Chem. Soc.*, 2010, **132**, 3893–3908.
8 Y. Yamaguchi and Z.-I. Yoshida, *Chem.–Eur. J.*, 2003, **9**, 5430–5440; L. Y. Xing, U. Ziener, T. C. Sutherland and L. A. Cuccia, *Chem. Commun.*, 2005, 5751–5753; L. He, Y. An, L. H. Yuan, W. Feng, M. F. Li, D. C. Zhang, K. Yamato, C. Zheng, X. C. Zeng and B. Gong, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 10850–10855; A. M. Zhang, Y. H. Han, K. Yamato, X. C. Zeng and B. Gong, *Org. Lett.*, 2006, **8**, 803–806; J. L. Sessler, E. Tomat and V. M. Lynch, *Chem. Commun.*, 2006, 4486–4488; J. M. Holub, H. J. Jang and K. Kirshenbaum, *Org. Lett.*, 2007, **9**, 3275–3278.
9 W. Feng, K. Yamato, L. Q. Yang, J. Ferguson, L. J. Zhong, S. L. Zou, L. H. Yuan, X. C. Zeng and B. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 2629–2637.
10 L. Q. Yang, L. J. Zhong, K. Yamato, X. H. Zhang, W. Feng, P. C. Deng, L. H. Yuan, X. C. Zeng and B. Gong, *New J. Chem.*, 2009, **33**, 729–733.
11 L. H. Yuan, A. R. Sanford, W. Feng, A. M. Zhang, J. Zhu, H. Q. Zeng, K. Yamato, M. F. Li, J. S. Ferguson and B. Gong, *J. Org. Chem.*, 2005, **70**, 10660–10669.
12 A. R. Sanford, L. H. Yuan, W. Feng, K. Yamato, R. A. Flowers and B. Gong, *Chem. Commun.*, 2005, 4720–4722.
13 A. J. Helsel, A. L. Brown, K. Yamato, W. Feng, L. H. Yuan, A. Clements, S. V. Harding, G. Szabo, Z. F. Shao and B. Gong, *J. Am. Chem. Soc.*, 2008, **130**, 15784–15785.
14 Y. A. Yang, W. Feng, J. C. Hu, S. L. Zou, R. Z. Gao, K. Yamato, M. Kline, Z. H. Cai, Y. Gao, Y. B. Wang, Y. B. Li, Y. L. Yang, L. H. Yuan, X. C. Zeng and B. Gong, *J. Am. Chem. Soc.*, 2011, **133**, 18590–18593.
15 L. H. Yuan, H. Q. Zeng, K. Yamato, A. R. Sanford, W. Feng, H. Atreya, D. K. Sukumaran, T. Szyperski and B. Gong, *J. Am. Chem. Soc.*, 2004, **126**, 16528–16537.
16 Receptors with binding constants (most measured in methanol) ranging from a few hundreds to 10^5 M^{-1} range were reported for guanidinium ions: A. V. Eliseev and M. I. Nelen, *J. Am. Chem. Soc.*, 1997, **119**, 1147–1148; T. W. Bell, A. B. Khasanov and M. G. B. Drew, *J. Am. Chem. Soc.*, 2002, **124**, 14092–14103.

