Hydrogen bond directed synthesis of pyridazine and naphthyridine containing macrocycles†

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Received (in Columbia, MO, USA) 18th July 2005, Accepted 12th September 2005
First published as an Advance Article on the web 20th October 2005
DOI: 10.1039/b510118b

This work describes a high-yielding, one-step synthesis of pyrizadine and naphthyridine containing macrocycles directed by intramolecular H-bonding.

Inspired by the prevalence of cyclic macromolecules in nature, including cyclic antibiotics, cyclodextrins and ionophores, chemists are interested in synthesizing macrocycles with preorganized binding sites and cavities large enough to complex organic or inorganic guest molecules.[1] Macrocycles are commonly synthesized by reactions of bifunctional monomers but the kinetic competition between macrocyclization and polymerization often plagues synthetic yields.[1] To overcome these deleterious polymerization reactions, chemists use high-dilution and templating techniques.[2,3] In some cases dynamic (reversible) covalent chemistry provides an attractive synthetic strategy to yield thermodynamically favored macrocyclic products.[4–7]

Directed conformational preorganization is a powerful approach for macrocyclization reactions.[8] Hunter *et al.* developed a series of macrocycles and catenanes to evaluate the role of hydrogen bonding in macrocycle synthesis.[9,10] By taking advantage of hydrogen bonding, macrocycles can be prepared from one-step irreversible reactions without the need for external templates. For example, Gong and co-workers recently reported highly efficient, one-step macrocyclization reactions assisted by the folding and preorganization of precursor oligomers.[11] Likewise, Huc and co-workers attribute the high yield obtained for the cyclization of oligoamide macrocycles to precursor preorganization.[12] Finally, the naphthyridine macrocycles described in this communication were inspired by the high-yielding macrocyclization of analogous 2,6-diaminopyridine with 1,1′-carbonyldiimidazole or triethyl orthoformate reported by Böhme *et al.*[13,14]

Herein, we report the one-step, high-yielding synthesis and characterization of naphthyridine and pyridazine containing macrocycles. The naphthyridine moieties are connected *via* urea (**1**) or formamidine (**2**) linkages, and the pyridazine moieties are connected to either tolyl (**3**) or phenyl (**4**) groups *via* urea linkages (Fig. 1). These irreversible macrocyclization reactions were not carried out under high-dilution conditions (typical concentrations of the limiting reagent ranged from 0.6 to 1.0 M for macrocycles **1** and **2**, and from 30 to 110 mM for macrocycles **3a**, **3b**, **3c** and **4**).

The general procedure for the synthesis of both **1** and **2** was adapted from Böhme *et al.*[13,14] Macrocycle **1** was formed in a one-step condensation reaction of 2,7-diamino-1,8-naphthyridine[15,16] and 1,1′-carbonyldiimadazole in 64% isolated yield. In 2001, Zimmerman proposed related naphthyridinylurea oligomers designed to switch between an unfolded β-sheet and folded helical structure.[15] Macrocycle **2** was formed by the condensation reaction of 2,7-diamino-1,8-naphthyridine and triethyl orthoformate in 75% isolated yield. Macrocycles **3** and **4** were synthesized from a series of N-substituted 3,6-diaminopyridazines reacting with either tolylene-2,6-diisocyanate to give **3a–c** or 1,3-phenylene diisocyanate to give **4**. The isolated yields of **3a**, **3b**, **3c** and **4** were 64, 67, 64 and 46%, respectively.

Both isobutyl derivatives of the pyridazine macrocycles (**3c** and **4**) and **2** produced single crystals suitable for X-ray analysis and the crystal structures are shown in Fig. 2 (ESI†§). Macrocycle **2** adopts a near planar structure in a manner that points the formamidine C–H hydrogen atoms towards the interior of

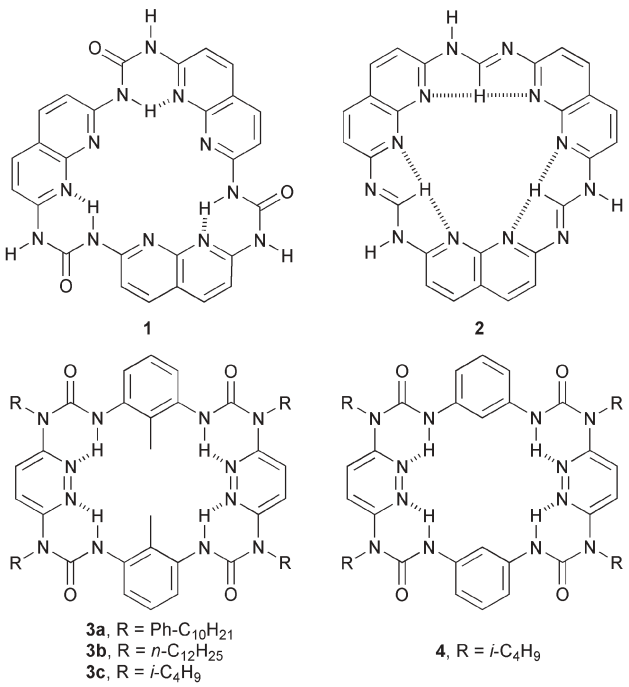

Fig. 1 Macrocycles **1–4** synthesized in one step utilizing the propensity to form intramolecular H-bonding to guide the ring closing reaction.

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† Electronic supplementary information (ESI) available: Synthetic details, NMR data and crystallographic data. See DOI: 10.1039/b510118b
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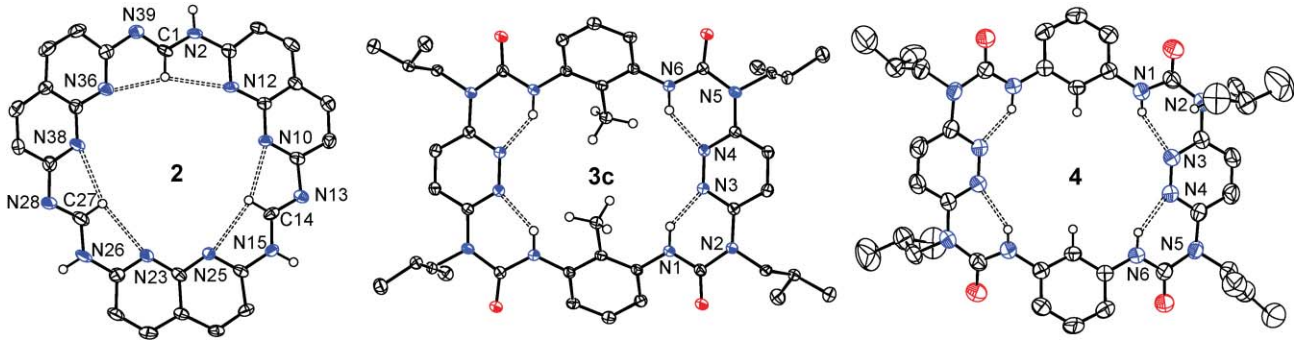

Fig. 2 ORTEP crystal structure views of macrocycles **2**, **3c** and **4**. Thermal ellipsoids are shown at the 50% probability level and solvents and selected hydrogen atoms were removed for clarity.

the cavity and the N–H hydrogen atoms to the exterior. The formamidine C–H hydrogen atoms are believed to participate in three-centered hydrogen bonding with the lone pairs of the naphthyridyl nitrogens as evidenced by the following C–H···N bond distances: C1···N36 2.679(4) Å, C1···N12 2.778(4) Å, C27···N38 2.673(4) Å, C27···N23 2.777(4) Å, C14···N10 2.662(4) Å, C14···N25 2.783(4) Å and C–H···N angles: C1–H1···N36 102°, C1–H1···N12 97°, C14–H14···N10 103°, C4–H14···N10 97°, C27–H27···N38 102°, C27–H27···N23 97°. Interestingly, the crystal structure of macrocycle **2** indicates that the formamidine groups have asymmetric orientations.[17,18] Macrocycle **2** packs into an interdigitated columnar structure with face-to-face aromatic π-stacking (ESI†). It is believed that both hydrogen bonding and steric interactions are involved in macrocyclization and that the formation of these intramolecular H-bonds in the transition state directs the irreversible macrocyclic ring closing reaction to occur at such high yields in the absence of a template.

The only chemical difference between **3c** and **4** is the presence of the tolyl groups in **3c** *vs.* the phenyl groups in **4**. Expectedly, the crystal structures of **3c** and **4** are similar with the urea hydrogen atoms pointed towards the interior participating in intramolecular hydrogen bonds with the pyridazine nitrogen atoms while the urea carbonyls point towards the exterior of the macrocycle. The two pyridazine rings of **3c** and **4** are coplanar with each other while the non-heterocyclic rings, which are also coplanar to each other, are tilted out of plane with respect to the pyridazine rings. Macrocycles **3c** and **4** contain the following hydrogen bonding distances: **3c**: N1···N3 2.607(3) Å, N6···N4 2.619(3) Å; **4**: N1···N3 2.765(4) Å, N6···N4 2.606(4) Å. The remaining hydrogen bond distances shown in Fig. 2 are created by symmetry operations. Along the C_2 symmetry axis of macrocycles **3c** and **4**, a columnar pattern is formed by face-to-face aromatic π-stacking. Previously, Yagi *et al.* have shown that steric repulsion between a tolyl methyl and an adjacent urea carbonyl are important, and our work exploits this steric repulsion to direct macrocyclization.[19] This is supported by the difference in yield of the tolyl-containing macrocycles **3a**, **3b** and **3c** (64, 67 and 64%, respectively) as compared to the phenyl-containing macrocycle (46%).

The ^{1}H NMR spectra of all the urea-based macrocycles show a singlet at *ca.* 12 ppm that is characteristic of an intramolecularly hydrogen bonded proton and the simple signal pattern suggests a high degree of symmetry. The assigned proton spectra for **1** and **2** are included in the ESI.† Deuterium exchange was carried out for **1** to probe the location of the urea protons. H/D exchange occurred readily with the urea N–H's that point to the exterior of the macrocycle. Interior N–H's are characterized and differentiated from exterior N–H's by large downfield shifts. The upfield urea protons were completely exchanged with deuterons within 5 min whereas the downfield N–H's took much longer (>30 min) to exchange, suggesting that the interior urea protons are "locked" into an intramolecular hydrogen bonding pattern that is consistent with the structure shown in Fig. 1. Variable-temperature NMR studies for **2** indicate that the outward pointing formamidine N–H's are capable of intermolecular hydrogen bonding where disruption of this network results in a temperature-dependent chemical shift. Formamidine C–H's that point inwards did not show temperature-dependent chemical shifts (ESI†). The presence of extensive intermolecular hydrogen bonding is consistent with the poor solubility of **1** which precluded concentration studies. The relative position of the urea protons of **3c** was confirmed by NOESY, which showed the expected cross-peak between the tolyl methyl protons and the inward-pointing urea protons. A similar cross-peak was observed for **4** between the interior phenyl protons and the adjacent urea protons (ESI†).

The ESI-TOF mass spectra for **1**–**4** show *m*/*z* $[M + H]^+$ parent ions found (calc.) of: 559.171 (559.170), 511.191 (511.186), 1433.99 (1433.96), 1241.99 (1241.96), 793.473 (793.462) and 765.432 (765.431), respectively. All macrocycles were found to form protonated dimers $[2M + H]^+$ and metal ion associates $[2M + Na]^+$ (MALDI-TOF-MS).[20]

Compound **3b** showed self-assembly properties on a liquid/highly ordered pyrolitic graphite (HOPG) interface as revealed by scanning tunneling microscopy (STM) (Fig. 3). Lamellar structures can be observed with alternating bright and dark stripes, which we assign to the aromatic and aliphatic moieties, respectively. The stripes themselves are substructured and in the high-resolution image (Fig. 3(b)) the aliphatic chains can be noticed to some extent. The experimentally determined periodicities correspond well to the proposed model (Fig. 3(c)) with interdigitating alkyl chains. Additional stabilization of the 2D self-assembly may be provided by weak C–H···O intermolecular interactions between the carbonyl group and a phenyl hydrogen atom. Such weak hydrogen bonds are known to stabilise 2D assemblies.[21–25] These patterns will be further investigated to exploit their potential function as templates for the construction of hybrid organic–inorganic nanostructures.

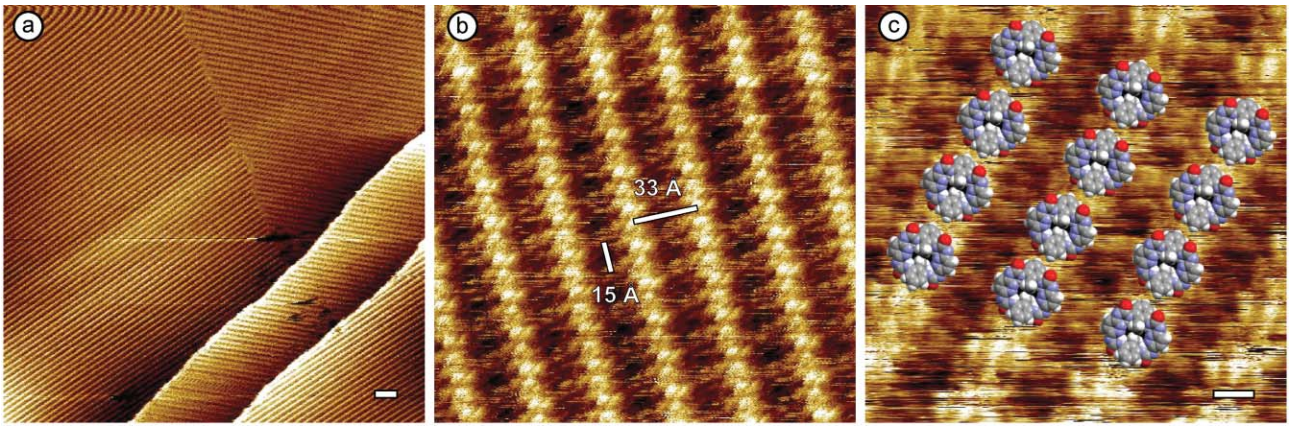

Fig. 3 STM image of **3b** self-assembly on HOPG from 1,2,4-trichlorobenzene in constant current mode using a Pt/Ir tip. (a) Large scan area with step edges and grain boundaries: I_{set} = 26.9 pA, V_{set} = −564 mV, scale bar is 10 nm. (b) Lamellar structure with periodicities of 33 Å (lamellae) and 15 Å (substructure in each lamella), respectively: I_{set} = 95.5 pA, V_{set} = −1.00 V. (c) A CPK model of **3b** superimposed onto the STM image, alkyl chains are omitted for clarity, same conditions as (b), scale bar is 1 nm.

In summary, this work has detailed the efficient one-step synthesis of '*self-templated*' naphthyridine and pyridazine containing macrocycles whereby the starting materials are predisposed to form closed cyclic structures rather than oligomers by intramolecular hydrogen bonding. Both urea and formamidine linkages were investigated and the presence of intra- and intermolecular hydrogen bonds was shown. We believe that the strong conformational preference of the building blocks, once the urea or formamidine linkage is formed, gives rise to a thermodynamic preference for macrocyclization.[4] Future work will focus on ion binding studies, self-assembly behavior and the synthesis of larger self-templated macrocycles and their related foldamers.

We thank N. Tang for assistance in the synthesis of 2,7-diamino-1,8-naphthyridine, L. Zhang, S. Bohle and F. Bélanger for crystallography, A. Tessier and N. Saade for mass spectrometry, S. Robidoux for NMR, and I. Huc, A. Petitjean and R. B. Lennox for useful discussions. The authors are grateful to NSERC, FQRNT, CFI, Concordia University and the German Science Foundation ("Deutsche Forschungsgemeinschaft") within the Research Center 569 ("Sonderforschungsbereich 569") for the generous support of this work. We also acknowledge our membership in the FQRNT-supported, multi-university Centre for Self-Assembled Chemical Structures (CSACS). This manuscript is dedicated to the memory of Dr Bernard Dietrich.

Notes and references

§ CCDC 267802 (**2**), 267803 (**3c**) and 267804 (**4**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b510118b

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