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Synthesis and structure of polyhydroxyl rigid triangular nano-macrocyclic imine having multiple hydrogen-bonding sites

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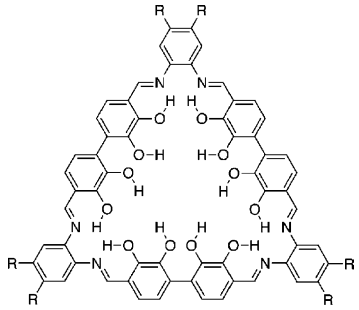
Abstract—42-Membered macrocyclic oligoimines based on the rigid biphenyl framework with 12 hydroxyl groups directing inward were synthesized by six-component cyclization without using a template. In the crystalline state, six dimethylsulfoxide molecules are bound simultaneously in a nano-sized cavity via hydrogen bonds.

Most inter- or intramolecular interactions between biomolecules such as complementary base pairing of DNAs and RNAs or higher order structure of proteins are usually governed by multiple hydrogen bonds. A number of artificial receptors mimicking strong and selective recognition found in nature have been reported to bind a guest molecule via multiple hydrogen bonds.[1] Hosts bearing a larger number of hydroxyl groups are expected to bind a guest molecule strongly via multiple hydrogen bonds or can bind two or more guests because the hydroxyl groups work both as a hydrogen bond donor and as an acceptor. In addition, introduction of many hydroxyl groups into a rigid framework which is suitable for precise control of recognition[2–5] has been extremely limited due to the laborious synthetic methods involved.

We have recently reported high-yield synthesis of a rigid 30-membered macrocyclic imine bearing six hydroxyl groups and, further, that the host nicely binds a water molecule in the crystalline state.[6] Larger analogues of this molecule would provide a cavity of sufficient size and rigidity for binding to organic molecules. In this communication, we report novel 42-membered macrocycles **1** based on three biphenyl units, which have 12 hydroxyl groups directing inward to the cavity.



1a (R = H)
1b (R = OMe)

The key to designing the large and rigid host molecule **1** is the biphenyl unit bearing four hydroxyl groups. We expected that all of the hydroxyl groups direct inward because similar macrocyclic frameworks containing Schiff base moieties are synthesized in high yields due to intramolecular N···H–O hydrogen bonds.[7]

Synthesis of the macrocyclic imines **1** is shown in Scheme 1. 2,2′,3,3′-Tetramethoxybiphenyl (**2**)[8] was dilithiated with *n*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine and subsequent reaction with *N*,*N*-dimethylformamide afforded dialdehyde **3** in 33% yield. Demethylation with boron tribromide in dichloromethane gave bis(salicylaldehyde) **4** in 67% yield. After an equimolar mixture of **4** and *o*-phenylenediamine in DMSO (0.16 M) was allowed to stand for 4 d at ambient temperature, reddish-orange prismatic crystals were precipitated. The IR spectrum of the product shows a C=N stretching band (1609 cm^{-1}) but no C=O band around 1656 cm^{-1} which is observed in the dialdehyde **6**. The ^1H NMR spectrum of **1** in DMF-d_7 exhibits one singlet for the aldimine protons at

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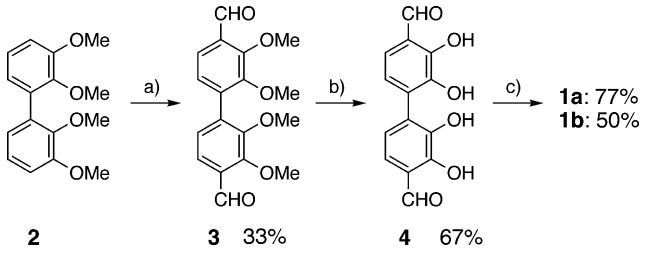

Scheme 1. Synthesis of macrocyclic imines **1a** and **1b**. Reagents and conditions: (a) (i) *n*-BuLi, TMEDA, hexane; (ii) DMF; (iii) H_2O; (b) BBr_3, $CH_2Cl_2H_2O$, (c) *o*-phenylenediamine, DMSO for **1a** and 4,5-dimethoxy-1,2-phenylenediamine, DMF/acetonitrile (9:1) for **1b**.

9.06 ppm, two broad signals at 9.27 and 13.55 ppm for the hydroxyl protons, and four aromatic signals (6.88–7.63 ppm). This simple spectrum indicates a highly symmetric cyclic structure. The [3+3] macrocyclic structure of **1a** is confirmed by ESI mass spectroscopy ($m/z = 1061.4$ [**1a**·Na]$^+$). Elemental analysis also supports the cyclic imine structure.[9] Methoxy analogue **1b** was also synthesized in a similar fashion.

The yield (77%) of **1a** is considerably high for nontemplated synthesis of the 42-membered macrocycle from six components probably due to the intramolecular hydrogen bonding. This is supported by the ^{1}H NMR spectrum of the reaction mixture in DMSO-d_6. Several peaks around 13.5 ppm indicative of O–H···N hydrogen bonding appeared in the initial stage. In addition, low solubility of **1a** in DMSO may promote the reaction and facilitates the purification of the product since very pure **1a** precipitated during the reaction. This precipitation is also favorable to shift the reaction equilibrium to the product **1a**. On the other hand, the reaction in DMF-d_7 proceeded more slowly and did not cause any precipitation. In this case, purification of the crude product was extremely difficult.

The structure of the [3+3] macrocycle was finally determined by X-ray crystallographic analysis using a single crystal obtained directly from the reaction mixture (Fig. 1).[10] Interestingly, the crystal contains four crystallographically independent molecules; one D_3-symmetric (one per unit cell, site A in Fig. 1), two C_3-symmetric (four per unit cell, sites B and C), and one C_2-symmetric molecules (three per unit cell, site D) are found. As a result, the unit cell contains eight molecules, although the space group *P*321 has six asymmetric units. Five of the eight molecules (C_3 or D_3 symmetric) lie perpendicular to the crystallographic *c*-axis, parallel to each other. Phenylenediamine units at the apex of the triangle stack at 3.55 Å intervals, which is indicative of π–π stacking interaction between the benzene units. The other three molecules (C_2-symmetric) tilt at about 52° from the crystallographic *ab* plane.

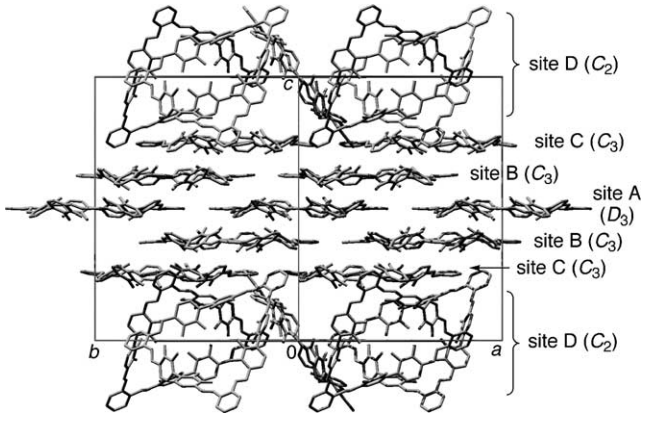

Figure 1. Perspective view along the [110] axis of the crystal of **1a**·8.5DMSO·2.75H_2O. Solvent molecules (DMSO and H_2O) are omitted for clarity.

The structure of the molecule at each site is similar, one of which is shown in Figure 2. The molecule forms a planar equilateral triangle with side length of 2 nm. The two benzene rings of the biphenyl units cross at an angle of about 60–80°, forming the D_3-(or pseudo-D_3-) symmetric structure. The hydroxyl groups of the three H_2 saloph units direct toward an imine nitrogen atom. The distances between oxygen and nitrogen atoms in O–H···N range from 2.5 to 2.6 Å, which indicate strong intramolecular hydrogen bonding. The other hydroxyl

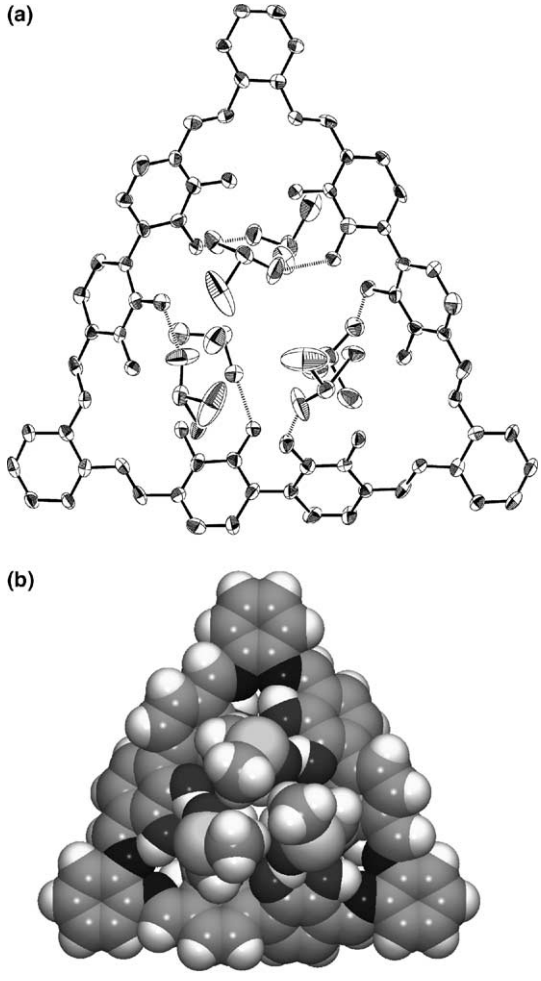

Figure 2. Molecular structure of macrocyclic imine **1a**. (a) ORTEP drawing with thermal ellipsoids plotted at 30% probability level. (b) Space-filling representation. Only one of the four crystallographically independent molecules (site(b)) is shown. Six DMSO molecules interacting with **1a** via hydrogen bonds are also shown.

groups point inward to make a hydrogen bond with the DMSO molecules (O–O distance of O–H···O←SMe_2: 2.48–2.86 Å). Consequently, the six DMSO molecules are bound by **1a** in the solid state (Fig. 2).

It is noteworthy that in the absorption spectra of **1a** in DMF the wavelength of the maximum absorption shifts bathochromically as the concentration decreases (352 nm, 0.2 mM; 376 nm, 0.01 mM). The result suggests that the molecules aggregate in the solution.[11,12] From consideration of the crystal structure, the driving force for the aggregation in solution seems to be π–π stacking of the extended π system rather than intermolecular hydrogen bonding.

Similar aggregation of **1a** may afford a supramolecular channel structure, when the macrocyclic compounds exactly stack on each other. Investigation on the recognition of other organic guests via multiple hydrogen bonding and the metallation[13–15] of H_2saloph[16–18] moieties to convert to the corresponding trinuclear metallohosts is in progress.

Acknowledgements

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9. Synthesis of macrocyclic imine **1a**. A solution of *o*-phenylenediamine (8.6 mg, 0.08 mmol) in DMSO (0.25 mL) was added to a solution of 2,2′,3,3′-tetrahydroxybiphenyl-4,4′-dicarbaldehyde (21.2 mg, 0.08 mmol) in DMSO (0.25 mL) and the resulting solution was stand at rt. After 4 d, reddish-orange precipitates were collected on a suction filter, washed with DMSO, and air-dried to afford macrocyclic imine **1a**. In the TG/DTA analysis of the samples, 30% loss of weight was observed at 138 °C corresponding the loss of some solvent molecules and decomposed at 190 °C with carbonizing. **1a**: reddish-orange crystals; IR (KBr) ν 1609 (C=N), 3422 (O–H) cm^{-1}, ^{1}H NMR (400 MHz, DMF-d_7) δ 6.88 (d, $J = 7.8$ Hz, 6H), 7.27 (d, $J = 7.8$ Hz, 6H), 7.46–7.48 (m, 6H), 7.61–7.63 (m, 6H), 9.06 (s, 6H), 9.2 (brs, 6H), 13.6 (brs, 6H); ^{13}C NMR (100 MHz, DMF-d_7) δ 119.2, 120.3, 121.1, 128.5, 128.9, 130.2, 142.7, 147.6, 151.0, 164.4. Anal. Calcd for $C_{60}H_{42}N_6O_{12}\cdot 8.5C_2H_6SO\cdot 4H_2O$: C, 52.10; H, 5.73; N, 4.73; S, 15.35. Found: C, 52.00; H, 5.89; N, 4.50; S, 14.90.
10. Crystallographic data for **1a**·8.5DMSO·2.75H_2O: $C_{77}H_{98.5}N_6O_{23.25}S_{8.5}$ ($M_r = 1752.63$), reddish-orange crystal, $0.4\times0.4\times0.2$ mm^3, trigonal, space group $P321$ (no. 150), $a = 26.052(5)$, $c = 29.249(7)$ Å, $V = 17192(6)$ Å^3, $Z = 8$, $d_{calcd} = 1.354$ g cm^{-3}, $T = 120$ K, Rigaku Mercury CCD diffractometer, Mo-K$_\alpha$ ($\lambda = 0.71069$ Å), $\mu = 0.295$ mm^{-1}, collected reflections 113,183, unique 20,142 ($R_{int} = 0.0609$), $2\theta_{max} = 50.00°$, $R1 = 0.0964$ ($I > 2\sigma(I)$), $wR2 = 0.2457$ (all data), GOF (F^2) = 1.036.[19] The structure was solved by the direct method.[20] CCDC-225191 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336-033; or e-mail: deposit@ccdc.cam. ac.uk).
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