Synthesis and crystal structure of [2 + 2] calixsalens

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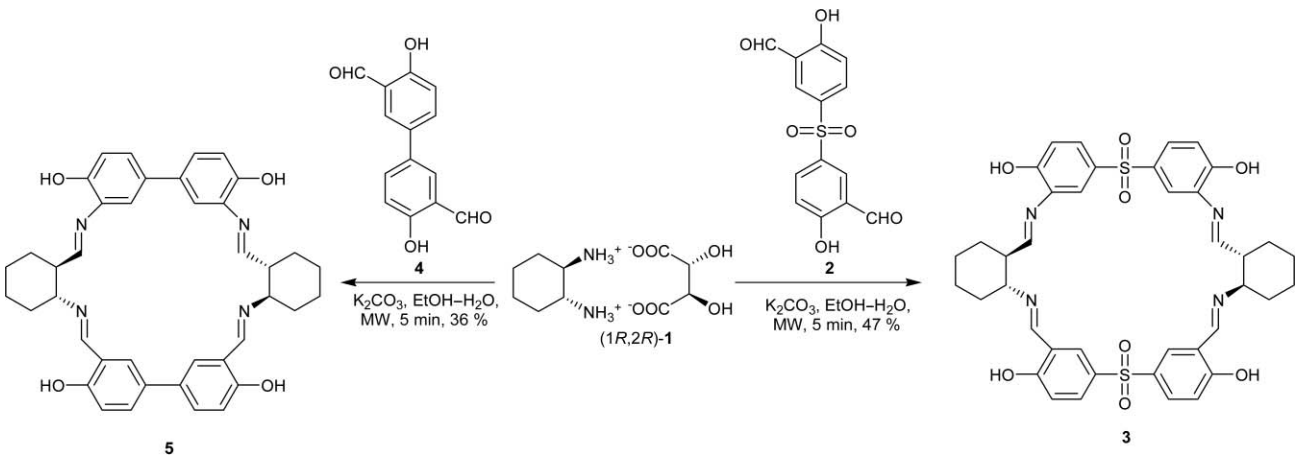
Efficient synthesis of chiral [2 + 2] macrocyclic tetraimines which display calixarene-like crystal structures has been described, with short reaction times under microwave irradiation.

Macrocyclic compounds have been studied extensively for their applications in molecular recognition, host–guest chemistry, supramolecular structures, material chemistry and catalysis.[1] In this regard, structural features of the macrocycles (such as functionalities for the binding of guest molecules and tunable central cavities) are particularly significant. The synthesis of most of the macrocyclic compounds is challenging as it involves a large number of steps.[2] Among the many macrocycles that act as efficient host compounds, macrocyclic Schiff-bases possess the advantage that they can be obtained in different ring sizes and can be further functionalized.[3] Chiral macrocyclic hexaimines and tetraimines have been synthesized by Gawronski *et al.* (and others) from chiral diamines and dialdehydes in moderate to good yields by employing [3 + 3] and [2 + 2] Schiff-base condensation strategy.[4] Chiral salen-based macrocyclic Schiff bases derived from bis(hydroxyaldehydes) possess multi-metal binding N_2O_2 sites and exhibit excellent enantiorecognition properties and catalytic activities.[5] Although a few reports of the synthesis of such macrocycles are known, not much is known about the crystal structure of such systems. [3 + 3] Macrocycles derived from chiral diamines and hydroxydialdehydes display vase-like structures[6] (hence named calixsalens) resembling the cone conformation of calixarene. The hydroxyl groups of these macrocycles point in the direction of the lower rim whereas the upper rim is formed by the alkyl-substituted benzene fragments. Similarly, [2 + 2] macrocycles derived from bis(hydroxyaldehydes) adopt a 1,3-dialternate conformation[7] with a striking calixarene-like structure. [2 + 2] macrocycles formed from different bis(hydroxyaldehydes) can therefore display interesting macromolecular structures.

In this communication, we report the synthesis and crystal structure of new [2 + 2] macrocyclic Schiff bases (**3** and **5**) formed in a short reaction time from (1*R*,2*R*)-diammoniumcyclohexane mono-(+)-tartrate **1** and achiral bis(hydroxyaldehydes) **2** and **4**, respectively. A facile synthesis of bisbinaphthyl macrocycle **7** from **1** and chiral bis(hydroxyaldehyde) (*S*)-**6** is also described.

Microwave irradiation (5–15 min) of a mixture of bis-(hydroxyaldehydes) and chiral diamines in the presence of potassium carbonate afforded chiral [2 + 2] macrocyclic tetraimines in moderate to good yields.[8]† The cyclocondensation does not require any anhydrous or dilute reaction conditions for the macrocycle synthesis. Moreover, salts of chiral diamines were employed instead of widely-used enantiopure diamines. The cyclocondensation of (1*R*,2*R*)-**1** and 5,5′-sulfonyl-bis-salicylaldehyde **2** afforded the [2 + 2] macrocycle **3** in 47% isolated yield (Scheme 1). Macrocycle **3** formed as the only macrocycle during condensation was isolated in pure form by short path column chromatography. This is in contrast to the template assisted synthesis of similar macrocycles reported by Jablonski and co-workers where the condensation resulted in a mixture of macrocycles.[7] The MALDI-TOF mass spectrum of **3** exhibits the expected single molecular ion at m/z 769 $[M + H]^+$. The single crystal X-ray structure of **3** confirmed the macrocyclic structure (Fig. 1).‡ There are one and half molecules in the crystallographic asymmetric unit with



Scheme 1 Macrocyclic tetraimines derived from achiral bis(hydroxyaldehydes).

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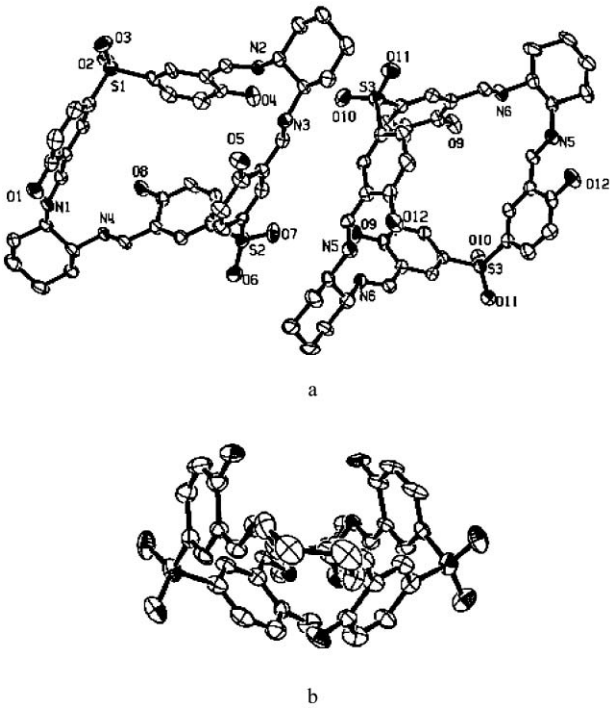


Fig. 1 Molecular structure (from single crystal X-ray diffraction) of macrocycle **3** ($C_{40}H_{40}O_8N_4S_2{\cdot}0.66C_2H_5OH{\cdot}1.33CH_2Cl_2{\cdot}H_2O$). Ortep drawing with thermal ellipsoids at 50% probability is shown. Hydrogen atoms and solvent molecules are omitted for clarity. (a) View from the top of the macrocycle **3**. (b) Lateral view of macrocycle **3**.

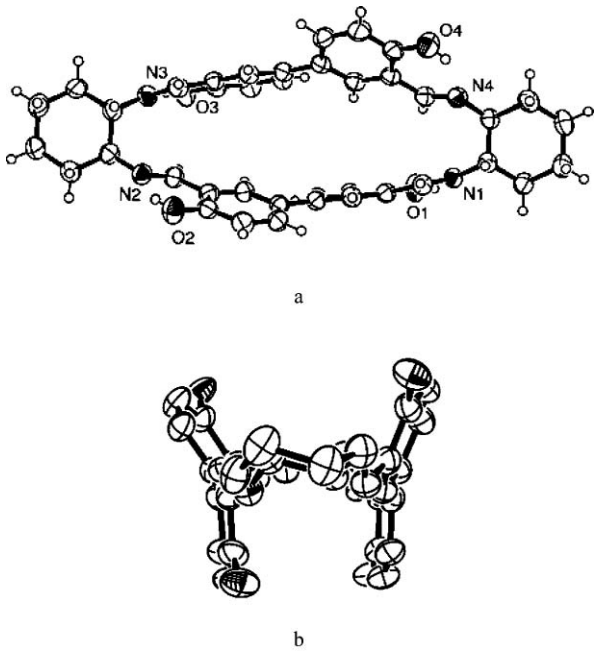


Fig. 2 ORTEP drawing of [2 + 2] macrocycle **5**. The displacement ellipsoids are drawn at 50% probability level. Hydrogen atoms are omitted for clarity. Macrocyle **5** viewed (a) down the *a*-axis and (b) down the *c*-axis.

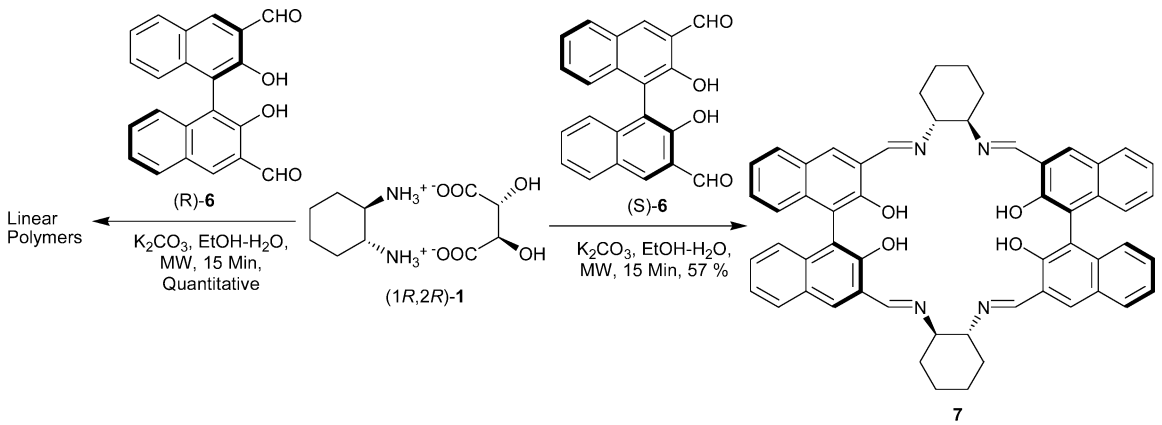
a C_2 space group and the two molecules are conformationally different. In one of these molecules, the two-fold axis parallel to the *y*-axis relates the two halves of the molecule by a two-fold symmetry. The other molecule of the asymmetric unit has no crystallographic symmetry element passing through it. However it has approximate two-fold rotation symmetry (non-crystallographic). The conformational difference can be seen by the presence of different S–S distances in the two molecules. For the ideally symmetric molecule, the dimensions of the cavity are 9.46 × 12.64 Å whereas for the other molecule the dimensions are 8.79 × 13.11 Å. Each hydroxyl group of the molecule points towards the nitrogen of an imine indicating a strong intramolecular hydrogen bond network.

Aromatic dialdehydes with bent structure, such as **2** possessing a $-SO_2$-spacer are expected to produce [2 + 2] cyclocondensation products predominantly. Biaryl based dialdehydes lacking spacers such as 5,5′-*bis*-salicylaldehyde **4** and 3,3′-diformyl-2,2′-dihydroxy-1,1′-binaphthyl[9] **6** are therefore examined for macrocycle synthesis. Under microwave irradiation for 5 min, **4** underwent cyclocondensation with (1*R*,2*R*)-**1** to afford the tetraimine **5** in 36% yield. The structure of the [2 + 2] macrocycle **5** was confirmed by both MALDI-TOF analysis (the molecular ion peak at *m*/*z* 641 correspond to the $[M + H]^+$ ions of the [2 + 2] cyclocondensation product) and single-crystal XRD§ (Fig. 2). The X-ray crystallographic analysis of the unsolvated macrocycle **5** grown from a hexane–ethyl acetate solution confirmed the cyclic nature of the structure. Strong intramolecular hydrogen bonding was found between the hydroxyl groups and the nitrogen of the imines. The molecule has an elongated structure with central cavity dimensions of 4.71 × 13.04 Å. In the case of macrocycle **5**, the imine bonds in the same diaryl group are *anti* oriented as found for macrocycle **3** and other trianglimines. In the crystal structure, the torsion angles around the C_{Ar}–C_{Ar} of the phenyl groups are −26.4 and −36.6°, respectively.

Macrocycles **5** showed interesting crystal packing. The macrocycle stack in an eclipsed manner along the crystallographic *a*-axis, giving rise to infinite columns with micropores.[10] The lateral view of the macrocycle **3** appears to have a bowl-like structure (Fig. 1b) whereas that of **5** has a vase-like structure (Fig. 2b) resembling cyclodextrins and 1,3-alternate conformation[7] of calixarenes.

Bisbinaphthyl macrocyclic Schiff bases derived from chiral biaryl based dialdehydes exhibit excellent enantioselective fluorescent recognition and are used as chiral ligands in asymmetric catalysis.[11] Bisbinaphthyl macrocyclic Schiff base **7** was synthesized under microwave irradiation by employing 3,3′-diformyl-2,2′-dihydroxy-1,1′-binaphthyl[10] **6**. Both racemic and the enantiomers of **6** were used for cyclocondensation with (1*R*,2*R*)-**1**. The synthesis of **7** reported in the literature involves longer reaction time and anhydrous reaction conditions. However under microwave irradiation in aqueous ethanol, the macrocycle **7** was formed in less than 15 min from (*S*)-**6** and (1*R*,2*R*)-**1** in 57% isolated yield (Scheme 2). The MALDI-TOF spectrum of the crude product displayed predominant peaks due to macrocycle **7** (*m*/*z* 840 and *m*/*z* 863 correspond to the $[M]^+$ and $[M + Na]^+$ ions, respectively).

The antipode (*R*)-**6** exhibited a different reactivity with (1*R*,2*R*)-**1**. The condensation of (*R*)-**6** with (1*R*,2*R*)-**1** resulted in the formation of linear polymers[12] as confirmed by MALDI-TOF spectrum. While the macrocycle **7** is freely soluble in ethyl acetate, the linear polymers are insoluble in ethyl acetate but are soluble in



Scheme 2 Chiral macrocyclic tetraimine derived from chiral bis(hydroxyaldehyde).

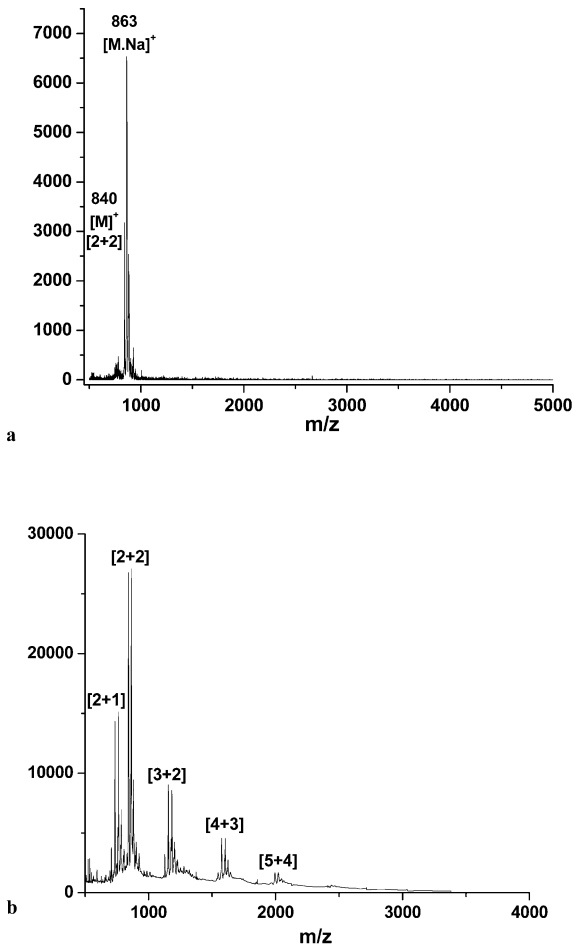


Fig. 3 MALDI-TOF spectra of products from condensation of (1*R*,2*R*)-**1** with (a) (*S*)-**6** and (b) racemic **6**.

dichloromethane. The solubility difference among the products of condensation together with the use of readily available (1*R*,2*R*)-diammoniumcyclohexane mono-(+)-tartrate as a condensation component can be applied as a method for easy synthesis of optically pure macrocycle **7** from racemic **6** and (1*R*,2*R*)-**1** and can be further extended as a method for optical resolution of racemic **6**.[13] Thus when racemic **6** was used for cyclocondensation with (1*R*,2*R*)-**1**, the ethyl acetate soluble fraction was found to contain [2 + 2] macrocycle **7** as the major product. However, the MALDI-TOF spectrum showed the presence of minor amounts of linear oligomers complicating the purification of the macrocycle **7**. The MALDI-TOF spectra of ethyl acetate fractions obtained from condensation of (1*R*,2*R*)-**1** with (*S*)-**6** and racemic **6** are shown in Fig. 3. Formation of linear oligomers in the case of racemic **6** is a result of the stepwise nature of four-component condensation with (1*R*,2*R*)-**1**.

In summary, we have described an efficient method for the synthesis of chiral [2 + 2] macrocycles from chiral and achiral bis(hydroxyaldehydes) and chiral diamines. The crystal structure of the macrocycles resembles that of calixarenes and exhibits columnar stacking in the solid state. In the case of binaphthyl-based dialdehyde **6**, the reactivity difference between the enantiomeric and racemic dialdehyde with chiral diamine is used to synthesize chiral macrocycle **7** from racemic **6**.

Notes and references

† Typical experimental procedure: to a solution of (1*R*,2*R*)-diammoniumcyclohexane mono-(+)-tartrate **1** (104 mg, 0.392 mmol) and K_2CO_3 (108 mg, 0.784 mmol) in 3 mL of water was added a solution of 5,5′-sulfonyl-bis-salicylaldehyde **2** (100 mg, 0.328 mmol) in 5 mL of ethanol. This homogeneous mixture was irradiated in an unmodified domestic microwave oven at low power setting for 5 min. The reaction mixture was cooled to room temperature and the solid material formed was filtered off. The solid material was dissolved in ethyl acetate and the undissolved material was removed by filtration. The filtrate was dried over sodium sulfate, concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel using 20% EtOAc–hexane to afford pure yellow [2 + 2] macrocyclic tetraimine **3** (59 mg, 47%). $[a]_D^{28} = -246$ (*c* 0.17, THF); IR (KBr) : *ν* 3440, 1632, 1376 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 1.43–1.49 (m, 1H), 1.69–1.71 (m, 1H), 1.88–1.91 (m, 2 H), 3.31–3.33 (m, 1H), 6.88–6.90 (d, *J* = 8.8 Hz, 1H), 7.6 (d, *J* = 1.96 Hz, 1H), 7.87–7.89 (dd, *J* = 2 & 8.8 Hz, 1H), 8.18 (s, 1H), 13.97 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 23.9, 33.0, 72.9, 118.2, 118.6, 131.1, 131.6, 132.2, 163.4, 165.4. MALDI-TOF MS: *m/z* 769 $[M + H]^+$, 792 $[M + Na]^+$. Macrocyclic tetraimine **4**. Yield. 36%. $[a]_D^{28} = -570$ (*c* 0.22, $CHCl_3$); IR (KBr): *ν* 3435, 1628 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 1.49–1.54 (m, 1H), 1.89–1.92 (m, 2H), 2.25–2.83 (m, 1H), 3.06–3.08 (m, 1H), 6.60–6.61 (d, *J* = 1.78 Hz, 1H), 6.88–6.90 (d, *J* = 8.47 Hz, 1H), 7.18–7.21 (dd, *J* = 1.88 Hz & 8.48 Hz, 1H), 7.73 (s, 1H), 12.78 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 24.1, 31.9, 71.3, 117.1, 117.8, 128.7, 130.0, 130.8, 160.1, 167.3. MALDI-TOF MS: *m/z* 641 $[M + H]^+$. Macrocyclic tetraimine **7**. Yield 57%. $[a]_D^{28} = -70$ (*c* 0.50, $CHCl_3$); IR (KBr): *ν* 3425, 1631 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 1.56–1.58 (m, 1H), 1.88–1.90 (m, 1H), 2.01–2.07 (m, 2H), 3.41–3.44 (m, 1H), 7.11–7.20 (m, 3H), 7.54–7.57 (d, *J* = 12.88 Hz, 1H), 7.60 (s, 1H), 8.56

(s, 1H), 12.45 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 24.7, 32.5, 70.2, 116.1, 121.2, 122.6, 124.6, 127.2, 127.5, 128.7, 132.9, 135.1, 154.6, 164.6. MALDI-TOF MS: m/z 840 $[M]^+$, 863 $[M + Na]^+$.

‡ Crystal data for **3**. $C_{42}H_{50}N_4O_{10}S_2$, yellow crystal, monoclinic, space group C2 (no.), a = 27.55 (2), b = 10.928 (8), c = 23.154 (9) Å, V = 6971 (8) Å^3, Z = 6, d_{calcd} = 1.348 mg m^{-3}, T = 293 (2) K, Enraf Nonius CAD4 diffractometer, Mo Kα (λ = 0.71069 Å), μ = 0.328 mm^{-1}, collected reflections 7159, unique 6480 (R_{int} = 0.0169), $2\theta_{max}$ = 25.01°, Final R indices [$I > 2\sigma(I)$]: R_1 (observed) = 0.0799, wR_2 = 0.2078, R (all data): R_1 = 0.1417, wR_2 = 0.2281, GOF (F^2) = 1.020. CCDC reference number 296811. For crystallographic data in CIF format see DOI: 10.1039/b604003a

§ Crystal data for **5**. $C_{40}H_{40}N_4O_4$, yellow crystal, orthorhombic, space group P212121 (no.), a = 10.0407 (13), b = 15.0369 (16), c = 22.816 (3) Å, V = 3444.7 (7) Å^3, Z = 4, d_{calcd} = 1.236 mg m^{-3}, T = 293 (2) K, Enraf Nonius CAD4 diffractometer, Mo Kα (λ = 0.71069 Å), μ = 0.642 mm^{-1}, collected reflections 3516, unique 3516 (R_{int} = 0.0000), $2\theta_{max}$ = 67.96°, Final R indices [$I > 2\sigma(I)$]: R_1 (observed) = 0.0350, wR_2 = 0.0945, R (all data): R_1 = 0.0433, wR_2 = 0.1006, GOF (F^2) = 1.052. CCDC reference number 296813. For crystallographic data in CIF format see DOI: 10.1039/b604003a

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