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Pre-organization-mediated macrocylization: efficient synthesis and structural investigations of BINOL-*m*-phenylenediamine-derived macrocycles

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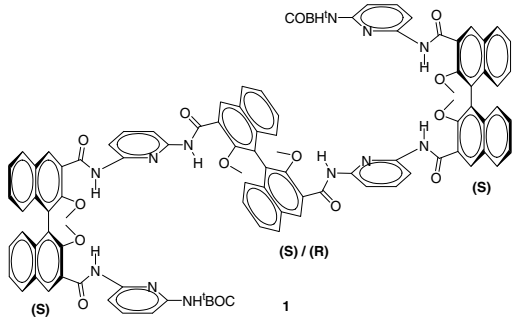
Abstract

This letter describes a serendipitous discovery of an efficient synthetic route to BINOL-*m*-phenylenediamine-derived macrocycles. These macrocycles are quickly accessible in an one-pot procedure by the direct condensation of (*R*) and (*S*) BINOL bis-acids with suitably substituted *m*-phenylenediamine analogs. Structural investigations by single crystal X-ray crystallography and solution-state NMR studies provided convincing evidence of their intramolecular hydrogen bonding arrangement and rigid structural architecture. The striking feature of these macrocycles is their ready accessibility in optically pure form coupled with their ease of synthesis.

1. Introduction

Encouraged by the intriguing structural architecture of the synthetic oligomer **1**,[1] a foldamer[2] obtained from hybrid sequences derived from optically pure BINOL and 2,6-diamino pyridine residues as subunits, we set out to generate larger oligomers derived from similar building blocks, but without protecting the terminal amino groups during synthesis, contrary to the ^{t}BOC protecting strategy we adopted earlier.[1] Work from the laboratories of Lehn[3] and Huc[4] has shown that synthetic oligomers of considerable size can be obtained by segment doubling strategy without resorting to the protection of the terminal amino groups of the building blocks. 2-Methoxy-5-methyl-benzene-1,3-diamine, a *m*-phenylene diamine analog, having similar H-bonding directional effect as that of 2,6-diamino pyridine was chosen due to its improved nucleophilicity as compared to its pyridine analog.



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In accordance with this plan, we first synthesized diamine **3**, both enantiomers (*R*) and (*S*), by reacting excess 2-methoxy-5-methyl-benzene-1,3-diamine with optically pure BINOL bis-acid chloride (Scheme 1). Iteration of the same sequence, however, gave an unexpected result, which was extensively investigated further.

Instead of furnishing a longer oligomer, as we anticipated, this reaction afforded a cyclic product **4**, despite the fact that excess of amine **3** was used for the linear

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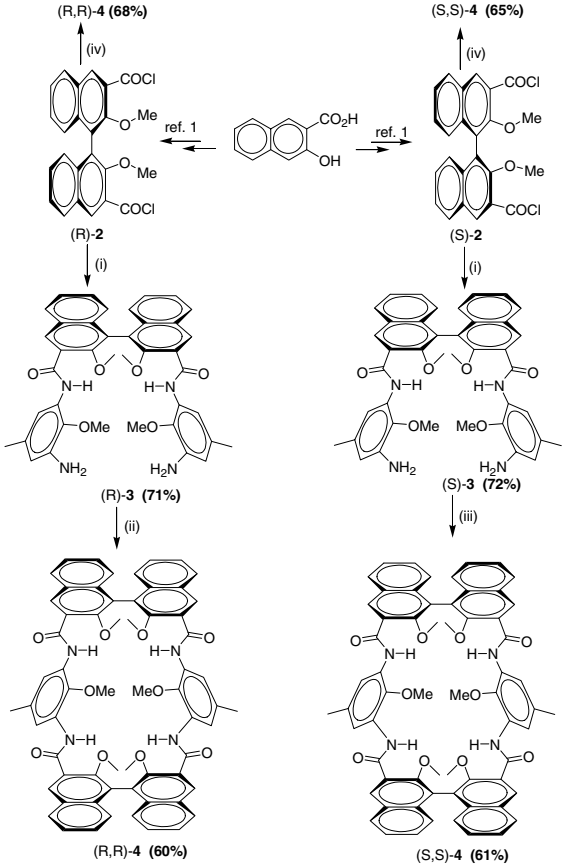

Scheme 1. Reagents and conditions: (i) 2-methoxy-5-methyl-benzene-1,3-diamine (5 equiv), (*R*)-2/(*S*)-2 (1 equiv), Et_3N, dry dichloromethane, rt, 6 h; (ii) (*R*)-3 (3 equiv), (*R*)-2 (1 equiv), Et_3N, dry dichloromethane, rt, 12 h; (iii) (*S*)-3 (3 equiv), (*S*)-2 (1 equiv), Et_3N, dry dichloromethane, rt, 12 h; (iv) 2-methoxy-5-methyl-benzene-1,3-diamine (1 equiv), (*R*)-2/ (*S*)-2 (1 equiv), Et_3N, dry dichloromethane, rt, 12 h.

oligomerization. Interestingly, a one-pot reaction of 2-methoxy-5-methyl-benzene-1,3-diamine with BINOL acid chloride[5] also furnished the same macrocycles in good yield, without much difficulty of isolation.

The exclusive formation of macrocycles **4** is presumably due to the combined effect of the conformational restrictions of the residues (BINOL and *m*-phenylenediamine units) coupled with the intramolecular hydrogen bonding in their coupled intermediates that preorganizes the structural architecture for macrocyclization. Recent years have witnessed a multitude of reports that reveal such pre-organization-mediated macrocylizations.[5–8]

To gain insights into the structural features of macrocycles **4**, studies were undertaken in solid- and solution-state by single crystal X-ray crystallography and NMR spectroscopy, respectively. Extensive efforts to crystallize the macrocycles **4** gave fruitful results eventually. Good quality crystals could be grown from a solvent mixture comprising dichloromethane:methanol (40:60) (Fig. 1).

Analysis of the crystal data revealed that the amide protons are tightly held by intramolecular bifurcated hydrogen bonding involving synchronized (*S*-5)- and (*S*-6)-type interactions.[9] The aryl amide protons are flanked from

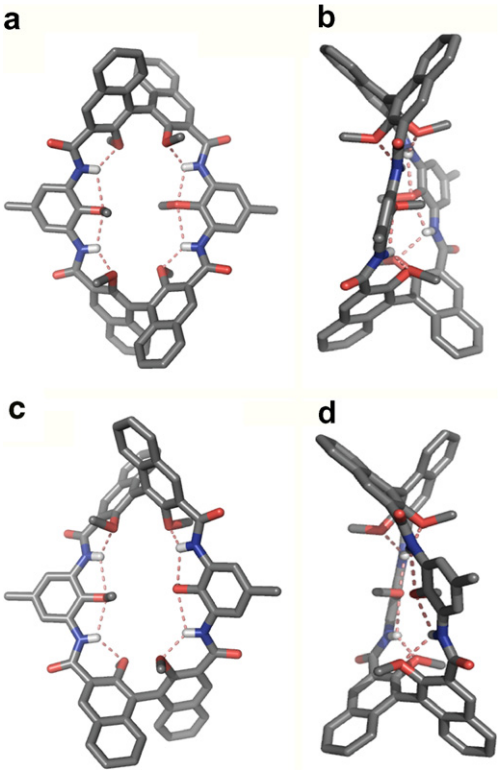

Fig. 1. Various views of the crystal structures of macrocycles **4**. (a,b) Single crystal structures of macrocycle (*R*,*R*)-**4** displayed in two different orientations, and (c,d) Single crystal structures of macrocycle (*S*,*S*)-**4** displayed in two different orientations.

both sides by the alkoxy oxygens from the adjacent *m*-phenylenediamine and BINOL residues, giving these macrocycles a robust structural architecture. Further, the periplanar arrangement of the naphthyl rings in the BINOL rings is clearly observed, which is in agreement with the crystal structures of the common BINOL derivatives.[10] A closer comparison of the crystal structures [(*R*,*R*)-**4** versus (*S*,*S*)-**4**] further reveals their mirror image structural architecture.

Macrocycles (*R*,*R*)-**4** and (*S*,*S*)-**4** were highly soluble in non-polar organic solvents ($\gg$100 mM in chloroform) at ambient temperature. This observation suggested that the polar hydrogen bonding groups of **4** were strongly protected (solvent shielded) by intramolecular hydrogen bonding, preventing the formation of polymeric hydrogen-bonded aggregates.[11,12] To confirm that intramolecular hydrogen bonds are clearly prevalent in solution, we also performed DMSO-d_6 titration study of (*S*,*S*)-**4** (titration graph in Supporting Information). The NH signal that appears at downfield region (10.10 ppm) suggests its involvement in strong hydrogen bonding interactions. Indeed, the NH proton shows little shift when solutions of (*S*,*S*)-**4** are titrated gradually with DMSO-d_6 ($\Delta\delta \sim$ 0.01 ppm) suggesting their strong involvement in intramolecular hydrogen bonding.

^{1}H and ^{13}C NMR (500 and 125 MHz, respectively) spectra of macrocycles (*R*,*R*)-**4** and (*S*,*S*)-**4** in $CDCl_3$ show single set of well-resolved signals[13] suggesting the existence

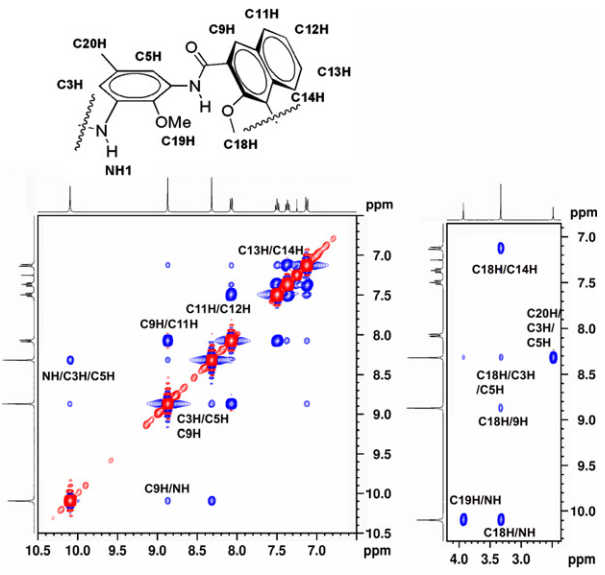

Fig. 2. Partial 2D NOESY NMR spectra of (*S*,*S*)-**4** ($CDCl_3$, 500 MHz) and its partial molecular structure (top).

of a single conformation in solution-state at ambient environments. To provide insights into the conformational features of these macrocycles, 2D NOESY studies were undertaken.

The observed dipolar couplings (NOEs) strongly support the bifurcated hydrogen bonding interaction, as seen in their crystal structures in the solid-state. One of the most characteristic NOEs that would clearly indicate the synchronized (*S*-5)- and (*S*-6)-type[9] bifurcated hydrogen bonding interactions, as observed in the solid-state, would be the requirement of dipolar couplings of both the alkoxy substituents with the NH group that participates in such interactions.[1,14] Analysis of the 2D data set of (*S*,*S*)-**4** clearly reveals that such an interaction (C19H/NH; C18H/NH; Fig. 2) is prevalent that clearly confirms the bifurcated H-bonding arrangement in solution-state as well.

In summary, we have described the novel BINOL-*m*-phenylenediamine-derived macrocycles[15] that feature conformational ordering both in solid- and solution-state. Structural investigations provide convincing evidence of their intramolecular hydrogen bonding arrangement and rigid structural architecture. It is noteworthy that macrocycles consisting of rigid cavities decorated with hetero atoms have proven to be highly versatile receptors and ligands for diverse guest molecules and metals, respectively.[16]

2. Experimental

2.1. Crystal data for (*R*,*R*)-4

$C_{64}H_{52}N_4O_{10}\cdot 2.5(CH_2Cl_2)\cdot CH_3OH$): $M = 1277.42$, crystal dimensions $0.56 \times 0.11 \times 0.07$ mm^3, monoclinic, space group $P2_1$, $a = 17.003(2)$, $b = 9.1398(13)$, $c = 21.745(3)$ Å, $\beta = 108.902(3)°$; $V = 3197.0(7)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.327$ g cm^{-3}, μ(Mo-K$_\alpha$) $= 0.290$ mm^{-1}, $F(000) = 1326$, $2\theta_{max} = 50.00°$, 23,042 reflections collected, 11,122 unique, 9190 observed ($I > 2\sigma(I)$) reflections, 857 refined parameters, R value 0.0821, $wR_2 = 0.2067$ (all data $R = 0.0992$, $wR_2 = 0.2269$), $S = 1.115$, minimum and maximum transmission, 0.8544 and 0.9805; maximum and minimum residual electron densities, +1.037 and −0.825 e Å^{-3}.

2.2. Crystal data for (*S*,*S*)-4

$C_{64}H_{52}O_{10}N_4\cdot 2.5(CH_2Cl_2)\cdot H_2O$): $M = 1266.92$, crystal dimensions $0.56 \times 0.11 \times 0.07$ mm^3, monoclinic, space group $P2_1$, $a = 16.933(2)$, $b = 9.1812(11)$, $c = 21.721(2)$ Å, $\beta = 108.712(2)°$; $V = 3198.4(6)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.316$ g cm^{-3}, μ(Mo-K$_\alpha$) $= 0.289$ mm^{-1}, $F(000) = 1317$, $2\theta_{max} = 50.00°$, 38,586 reflections collected, 11,227 unique, 8279 observed ($I > 2\sigma$ (I)) reflections, 834 refined parameters, R value 0.0729, $wR_2 = 0.1888$ (all data $R = 0.1045$, $wR_2 = 0.2170$), $S = 1.060$, minimum and maximum transmission, 0.8478 and 0.9865; maximum and minimum residual electron densities, +0.790 and −0.724 e Å^{-3}.

2.3. (*R*,*R*)-4

To a solution of 2,2′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxylic acid (0.04 g, 0.099 mmol, 1 equiv), in dry DCM (5 mL), oxaloyl chloride (0.05 mL, 0.59 mmol, 6 equiv) and a catalytic amount of dry DMF were added. The reaction mixture was stirred for 2 h at room temperature. The solvent was stripped off under reduced pressure and dried under high vacuum. The resulting acid chloride (*R*)-**2** was dissolved in dry DCM (8 mL) and slowly added to a solution of (*R*)-**3** (0.2 g, 0.29 mmol, 3 equiv) in dry DCM (10 mL) containing triethylamine (0.11 mL, 0.79 mmol, 8 equiv). After stirring overnight, the reaction mixture was diluted with dichloromethane and washed sequentially with water and saturated sodium chloride solution. Drying and concentration of the DCM extract under reduced pressure gave the crude product, which on column chromatography (40% EtOAc/Hexane) afforded macrocycle (*R*, *R*)-**4** (0.063 g, 60%). Mp 292–295 °C; $[\alpha]_D$ −200.0 (*c* 1.0, Chloroform); IR ($CHCl_3$) ν cm^{-1}): 3336, 3020, 1670, 1596, 1508, 1217, 757; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.10 (s, 4H), 8.87 (s, 4H), 8.32 (s, 4H), 8.08 (d, $J = 7.79$ Hz, 4H), 7.50 (m, 4H), 7.37 (m, 4H), 7.13 (d, $J = 8.71$ Hz, 4H), 3.93 (s, 6H) 3.32 (s, 12H), 2.48 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 153.3, 136.5, 135.2, 134.0, 131.1, 130.3, 129.7, 128.8, 126.7, 125.9, 125.3, 125.0, 117.0, 62.1, 61.4, 21.9; ESI Mass: 1052 (M+Na); Anal. Calcd for $C_{64}H_{52}N_4O_{10}$: C, 74.12; H, 5.05; N, 5.40. Found: C, 74.09; H, 4.99; N, 5.38.

2.4. (*R*,*R*)-4 (*One-step formation from BINOL acid chloride and m-phenylenediamine*)

To a solution of 2,2′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxylic acid (0.2 g, 0.49 mmol, 1 equiv), in dry DCM (5 mL), oxaloyl chloride (0.26 mL, 2.98 mmol,

6 equiv) and a catalytic amount of dry DMF were added. The reaction mixture was stirred for 2 h at room temperature. The solvent was stripped off under reduced pressure and dried under high vacuum. The resulting acid chloride (*R*)-**2** was dissolved in dry DCM (8 mL) and slowly added to a solution of 2-methoxy-5-methyl-benzene-1,3-diamine (0.07 g, 0.49 mmol, 1 equiv) in dry DCM (5 mL) containing triethylamine (0.55 mL, 3.97 mmol, 8 equiv). The resulting mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with dichloromethane and washed sequentially with water and saturated sodium chloride solution. Drying and concentration of the DCM extract under reduced pressure gave the crude product, which on column chromatography (40% EtOAc/hexane) afforded the desired pure product (*R*,*R*)-**4** (0.17 g, 68%).

Acknowledgements

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