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Syntheses of large-membered macrocycles having multiple hydrogen bonding moieties

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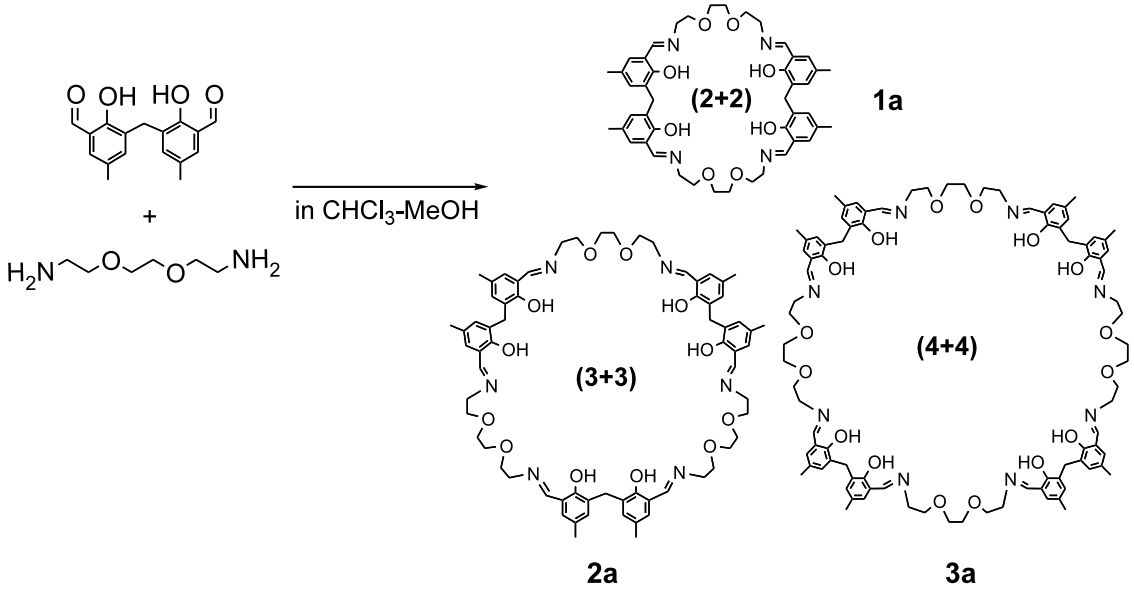
Abstract—New macrocyclic compounds have been synthesized by Schiff-base condensation reaction with methylenebis(4,4′-methyl-6,6′-salicylaldehyde) and 1,2-bis(2-aminoethoxy)ethane based on a high dilution method. [2+2], [3+3], and [4+4]-Cyclocondenced products were effectively isolated and characterized by ^{1}H NMR and HR mass (FAB) spectroscopies as well as X-ray analyses. Reduction of the macrocycles with $NaBH_4$ afforded the corresponding multi-amino, multi-phenolic macrocyclic compounds. The reduced molecules have low energy barriers for conformation change, which are estimated by variable-temperature (VT) ^{1}H NMR study.

Much attention has been focused on the recognition of guest molecules by artificial macrocycles in order to mimic specific functions of naturally occurring supramolecular hosts, such as enzymes and receptors.[1] Furthermore, the formation of medium- and large-sized cyclic systems is a continuing challenge for synthetic chemists as such systems are widespread, ranging from naturally occurring compounds to macrocyclic synthetic receptors or ligands. For the purpose of such study, a large number of macrocyclic host molecules have been synthesized.[2] In many cases, template-controlled synthetic methods are widely used as an elegant access to fascinating macrocyclic structures.[3] Recently, we have reported effective [2+2] cyclocondensation



Scheme 1.

Keywords: macrocyclic compound; Schiff-base; hydrogen bonding; X-ray crystallography.

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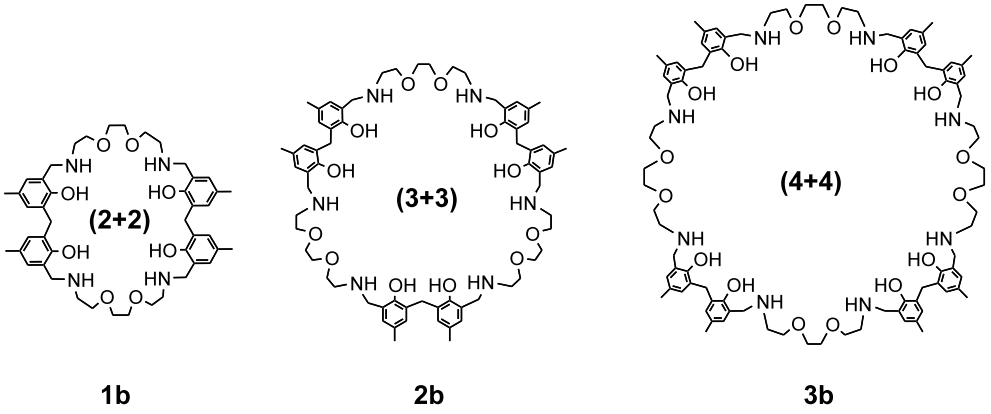

Figure 1. Structures of multi-amino, multi-phenolic macrocyclic compounds.

reaction of *o*-phenylenediamine and methylenebis(4,4′-butyl-6,6′-salicylaldehyde) in the presence of a boric ion as a template.[4] In this reaction, the [2+2] cyclocondensation product was selectively formed in high yield. Besides our study, there are some reports in the literature for the syntheses of macrocyclic condensation products.[5] In the course of our study, we have found that a reaction between methylenebis(4,4′-methyl-6,6′-salicylaldehyde) and a linear diamine in the absence of a template affords some cyclocondensation products with large-membered systems. In this letter, we report the syntheses and characterization of the large-membered macocycles.

Macrocyclic compounds (**1a**–**3a**) were synthesized by the condensation reaction of 1,2-bis(2-aminoethoxy)ethane and methylenebis(4,4′-methyl-6,6′-salicylaldehyde) based on a non-templated high dilution method as shown in Scheme 1.† To a mixed solvent, $CHCl_3$ (7.5 mL)–MeOH (7.5 mL), were dropwise added slowly 1,2-bis(2-aminoethoxy)ethane (156 mg, 1.06 mmol) in MeOH (6 mL) and methylenebis(4,4′-methyl-6,6′-salicylaldehyde) (300 mg, 1.06 mmol) in $CHCl_3$ (6 mL) at the same time. The solution changed immediately to yellow and was further stirred overnight at room temperature. The viscous precipitates were collected by decantation and washed with MeOH several times, and dried in vacuo. The yellow products were purified by gel permeation chromatography (GPC) on columns of JAIGEL-1H, 2H, and 2.5H in this sequence with $CHCl_3$ as elute. [2+2], [3+3], and [4+4]-Cyclocondensed products were effectively isolated in yields of 14, 7, and 4%, respectively.‡ Reduced products, **1b**–**3b** (see Fig. 1), were also synthesized in a similar manner with subsequent in situ reduction by $NaBH_4$ as described below. To a solution of the reaction mixture for **1a**–**3a** described above was added $NaBH_4$ (1.2 g, 31.7 mmol) at 45°C. The solution changed rapidly to colorless and was stirred for 10 min, and then the products were extracted with $CHCl_3$. After being dried over anhydrous Na_2SO_4, the $CHCl_3$ solution was concentrated to dryness using a rotary evaporator. The residues were purified by GPC under the same conditions for **1a**–**3a** to isolate **1b**–**3b**.§ The yields of **1b**, **2b**, and **3b** were 54, 19, and 6%, respectively. All of the products were identified by IR, ^1H NMR, and HR-mass (FAB) spectroscopies.

The IR analyses of **1a**–**3a** show intense ν(C=N) bands and broad ν(O–H) bands at 1634 and 3450 cm^{-1}, respectively. The ^1H NMR spectra for **1a**–**3a** at room temperature are similar to each other, and the downfield proton signals at 13.4 ppm for the phenolic hydroxy protons indicate the presence of hydrogen bonds.[6] The IR analyses of **1b**–**3b** show the disappearance of the C=N stretching band which clearly indicates the reduction of the imino groups. In the ^1H NMR spectrum of **1b**, no peak was observed at the imino H

† **1a** [2+2]: Yield, 59 mg (14%); ^1H NMR ($CDCl_3$, 500 MHz): $\delta=2.20$ (s, 12H, C$\underline{H}_3$), 3.40 (t, 8H, -C$\underline{H}_2$-), 3.53 (s, 8H, -C$\underline{H}_2$-), 3.59 (t, 8H, -C$\underline{H}_2$-), 3.93 (s, 4H, Ph-C$\underline{H}_2$-Ph), 6.71 (d, 4H, Ph), 7.04 (d, 4H, Ph), 7.89 (s, 4H, N=C$\underline{H}$), 13.40 (br, 4H, O$\underline{H}$]; HRMS (FAB, m/z) calcd for $C_{46}H_{57}N_4O_8$: [MH]$^+$, 793.4176. Found: [MH]$^+$, 793.4141. **2a** [3+3]: Yield, 29 mg (7%); ^1H NMR ($CDCl_3$, 500 MHz): $\delta=2.15$ (s, 18H, C$\underline{H}_3$), 3.52 (s, 12H, -C$\underline{H}_2$-), 3.57 (t, 12H, -C$\underline{H}_2$-), 3.63 (t, 12H, -C$\underline{H}_2$-), 3.96 (s, 6H, Ph-C$\underline{H}_2$-Ph), 6.79 (d, 6H, Ph), 6.96 (d, 6H, Ph), 8.12 (s, 6H, N=C$\underline{H}$), 13.43 (br, 6H, O$\underline{H}$]; HRMS (FAB, m/z) calcd for $C_{69}H_{85}N_6O_{12}$: [MH]$^+$, 1189.6225. Found: [MH]$^+$, 1189.6250. **3a** [4+4]: Yield, 16 mg (4%); ^1H NMR ($CDCl_3$, 500 MHz): $\delta=2.16$ (s, 24H, C$\underline{H}_3$), 3.53 (s, 16H, -C$\underline{H}_2$-), 3.57 (t, 16H, -C$\underline{H}_2$-), 3.64 (t, 16H, -C$\underline{H}_2$-), 3.96 (s, 8H, Ph-C$\underline{H}_2$-Ph), 6.79 (d, 8H, Ph), 6.96 (d, 8H, Ph), 8.14 (s, 8H, N=C$\underline{H}$), 13.43 (br, 8H, O$\underline{H}$]; HRMS (FAB, m/z) calcd for $C_{92}H_{113}N_8O_{16}$: [MH]$^+$, 1585.8275. Found: [MH]$^+$, 1585.8340. In this reaction, template effect of the boric ion is not observed.

‡ [5+5], [6+6], and [7+7]-Cyclocondensation products were also formed in this reaction which is deduced from the desirable GPC peak and MALDI-TOF MS (dithranol matrix), m/z 1983 [5+5], 2380 [6+6], 2778 [7+7].

§ **1b** [2+2]: Yield, 228 mg (54%); ^1H NMR ($CDCl_3$, 500 MHz): $\delta=2.16$ (s, 12H, C$\underline{H}_3$), 2.67 (t, 8H, -C$\underline{H}_2$-), 3.52 (t, 8H, -C$\underline{H}_2$-), 3.55 (s, 8H, -C$\underline{H}_2$-), 3.74 (s, 8H, -C$\underline{H}_2$-), 3.82 (s, 4H, Ph-C$\underline{H}_2$-Ph), 5.3 (br, 8H, O$\underline{H}$, N$\underline{H}$), 6.60 (d, 4H, Ph), 6.83 (d, 4H, Ph]; HRMS (FAB, m/z) calcd for $C_{46}H_{65}N_4O_8$: [MH]$^+$, 801.4802. Found: [MH]$^+$, 801.4816. **2b** [3+3]: Yield, 80 mg (19%); ^1H NMR ($CDCl_3$, 500 MHz): $\delta=2.14$ (s, 18H, C$\underline{H}_3$), 2.74 (t, 12H, -C$\underline{H}_2$-), 3.54 (m, 24H, -C$\underline{H}_2$-), 3.84 (s, 12H, -C$\underline{H}_2$-), 3.86 (s, 6H, Ph-C$\underline{H}_2$-Ph), 6.62 (d, 6H, Ph), 6.79 (d, 6H, Ph]; HRMS (FAB, m/z) calcd for $C_{69}H_{97}N_6O_{12}$: [MH]$^+$, 1201.7164. Found: [MH]$^+$, 1201.7203. **3b** [4+4]: Yield, 25 mg (6%); ^1H NMR ($CDCl_3$, 500 MHz): $\delta=2.14$ (s, 24H, C$\underline{H}_3$), 2.75 (t, 16H, -C$\underline{H}_2$-), 3.55 (m, 32H, -C$\underline{H}_2$-), 3.85 (s, 16H, Ph), 3.86 (s, 8H, Ph), 6.62 (d, 8H, Ph), 6.78 (d, 8H, Ph]; HRMS (FAB, m/z) calcd for $C_{92}H_{129}N_8O_{16}$: [MH]$^+$, 1601.9527. Found: [MH]$^+$, 1601.9523.

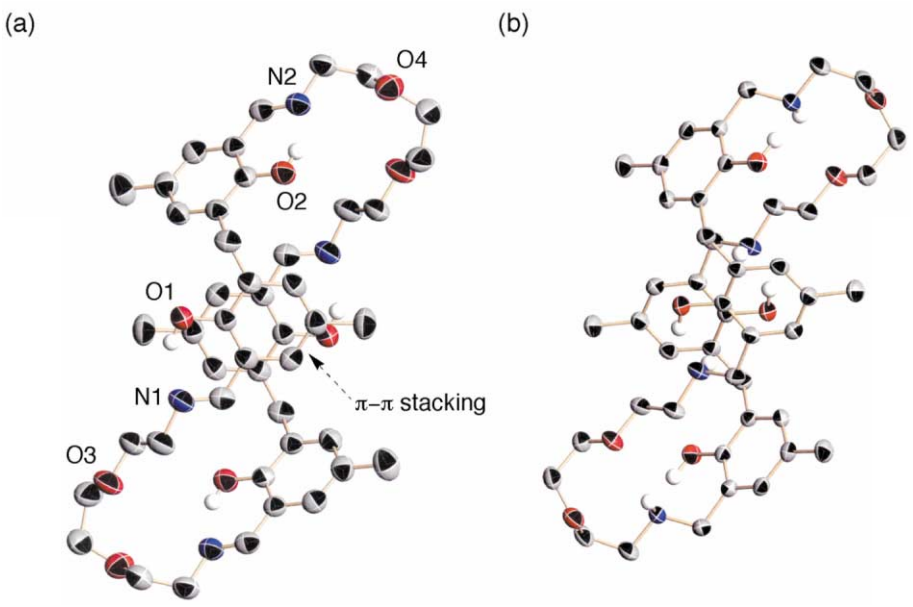

Figure 2. ORTEP drawings of (a) **1a** and (b) **1b** with thermal ellipsoids at 50% probability. Parts of hydrogen atoms have been omitted for clarity.

region. Furthermore, a broad peak around 5 ppm assigned to O–H and N–H disappeared upon D_2O exchange. Thus, the phenolic hydroxy protons of **1b** do not form hydrogen bonds at room temperature in $CDCl_3$.

The structures of **1a** and **1b** were also identified by X-ray crystallographic analyses. ORTEP drawings of **1a** and **1b** are shown in Fig. 2(a) and (b), respectively.¶ Both of the compounds have a macrocyclic structure, and each of the phenol groups linked to the methylene spacer is oriented in opposite direction as shown in Fig. 2(a) and (b). Intramolecular π–π stacking between the phenolic rings is observed with 3.3 Å distance for **1a**. Existence of intramolecular hydrogen bondings between the phenolic hydroxy protons and adjacent imino nitrogen atoms of **1a** is also deduced from the atom–atom distance (-OH···N = 1.86 and 1.89 Å). The phenolic hydroxy protons of **1b** also form intramolecular hydrogen bondings in solid state (-OH···N = 1.78 and 1.75 Å) as shown in Fig. 2(b) in contrast with the ^1H NMR analysis at room temperature described above.

Thus, VT ^1H NMR study for the conformation dynamics was carried out in CD_2Cl_2. There was little change in the ^1H NMR spectra of **1a** in the temperature range between 203 and 293 K, while the coalescence of the two methyl groups was observed for **1b** as shown in Fig. 3. The nonequivalence of the methyl groups is ascribed to the fact that the rotation of the phenol groups about the C–N bond is restricted at low temperature. A free energy of activation ($\Delta G^{\ddagger}$) calculated by the Eyring equation is 47.7 kJ/mol for **1b**.‖ Adding a protic solvent such as CD_3OD greatly changed the VT NMR spectra of **1b**. The spectra changed to broad ones as the temperature lowered, and no coalescence of the methyl groups was observed even at 203 K. Therefore, it is expected that hydrogen bondings play an important role for the dynamics of **1b** in solution. In fact, the appearance of a D_2O exchangeable proton signal at 15.3 ppm at 203 K indicates the formation of hydrogen bonding below the coalescence temperature in CD_2Cl_2. In any event, **1b** has a more flexible structure with multiple hydrogen bonding moieties (OH and NH) compared to **1a** and it is anticipated to have unique molecular recognition behavior.

In conclusion, new large-membered macrocycles have been synthesized and characterized by various spectroscopic methods. Molecular recognition behaviors for

¶ Vapor diffusion of Et_2O into the $CHCl_3$ solution of **1a** afforded pale yellow crystals. Crystal data for **1a**: $C_{46}H_{56}N_4O_8$, $M_w = 792.95$, crystal system = triclinic, space group = $P\bar{1}$, $Z = 1$ in a cell with the following dimensions: $a = 9.6731(10)$, $b = 10.6378(11)$, $c = 11.0123(12)$ Å, $\alpha = 98.088(2)$, $\beta = 105.067(2)$, $\gamma = 98.244(2)°$, $V = 1063.96(19)$ Å^3, $D_{calcd} = 1.238$ g cm^{-3}. The data were collected at 273 K on a Bruker SMART APEX CCD diffractometer, λ (Mo Kα) = 0.71073 Å, $\mu = 0.085$ mm^{-1}, 6012 measured and 3609 unique reflections ($2\theta_{max} = 49.42$, $R_{int} = 0.0149$). $R = 0.0496$, $R_w = 0.1371$. Vapor diffusion of Et_2O into the $CHCl_3$ solution of **1b** afforded white crystals. Crystal data for **1b**: $C_{46}H_{64}N_4O_8$, $M_w = 801.01$, crystal system = monoclinic, space group = $P2(1)/c$, $Z = 2$ in a cell with the following dimensions: $a = 11.2711(8)$, $b = 21.5525(15)$, $c = 8.9423(6)$ Å, $\beta = 99.3930(10)$, $V = 2143.1(3)$ Å^3, $D_{calcd} = 1.241$ g cm^{-3}. The data were collected at 223 K on a Bruker SMART APEX CCD diffractometer, λ (Mo Kα) = 0.71073 Å, $\mu = 0.085$ mm^{-1}, 22017 measured and 5316 unique reflections ($2\theta_{max} = 56.56$, $R_{int} = 0.0273$). $R = 0.0559$, $R_w = 0.1488$. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 191283 (**1a**) and 191284 (**1b**).

‖ In this case, the coalescence temperature is 239 K and the frequency separation is 119.3 Hz.

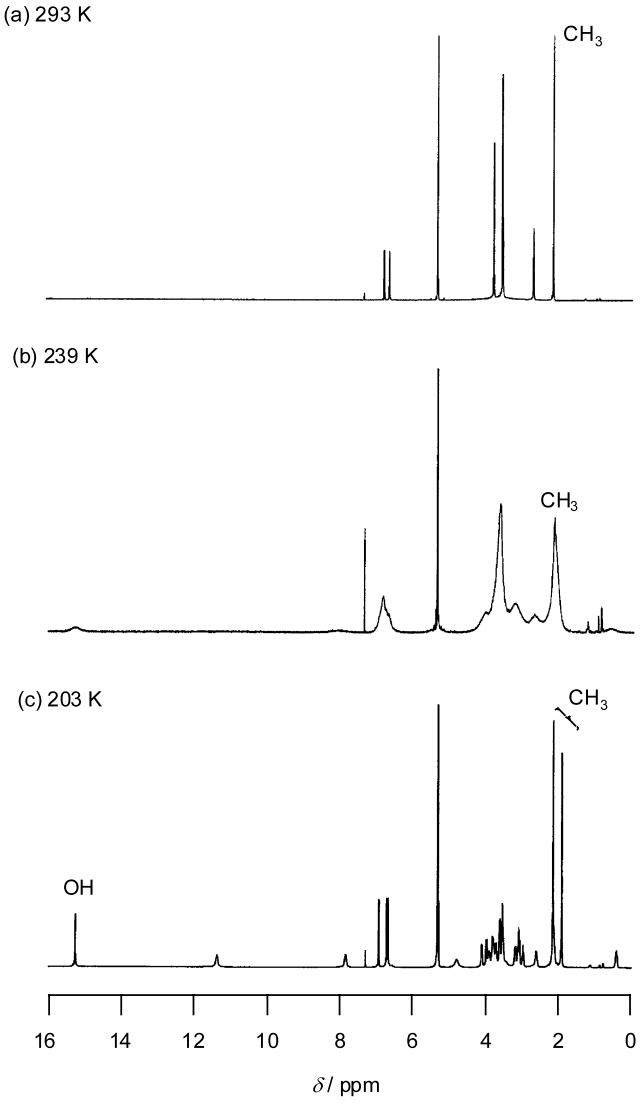

Figure 3. Variable-temperature ^{1}H NMR spectra (500 MHz, CD_2Cl_2) of **1b** at (a) 293 K, (b) 239 K, and (c) 203 K.

guest molecules by these macrocycles are now under investigation in our laboratory.

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