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Original article

Synthesis and characterization of macrocyclic compounds with a hydroxyl functional group

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ABSTRACT

A novel [1+1] Schiff-base macrocyclic compound **3** has been synthesized from precursor **1**, 1,3-bis(2′-formylphenoxy)-2-propanol, and precursor **2**, resorcinol-bis(4-aminophenyl)ether, *via* condensation and cyclizaction using Ba^{2+} as template. The macrocycle **3** was further reduced giving saturated macrocycle **4**. The structures of **3** and **4** were characterized by elemental analysis, ^{1}H NMR, IR, and MS spectra, and their structures were determined *via* single crystal X-ray diffraction studies. X-ray diffraction analysis revealed that the macrocyclic compound **3** has a folded conformation, and the corresponding reduced product **4** adopts a twisted and folded conformation due to its flexible nature.

1. Introduction

Over the past few decades, macrocyclic compounds have become important synthetic targets due to their wide applications in molecular recognition, supramolecular structures, catalysis, and material chemistry [1–6]. One representative group of macrocycles is the Schiff-base macrocyclic compound family. The Schiff macrocycles are synthesized by the reaction of dicarbonyl compounds with diamines by well understood mechanisms [7,8]. The macrocyclic systems can be functionalized by inserting appropriate groups in the aliphatic and/or aromatic chains of the formyl- or keto- and amine-precursors. Furthermore, the Schiff bases can be reduced to the related polyamine derivatives by reaction with an appropriate reducing agent. These polyamine compounds are less sensitive to hydrolysis and more flexible, which may greatly influence the ability to discriminate among the different charged or neutral species [9–12].

In this paper, the new Schiff-base macrocycle **3** was synthesized by the condensation reaction of 1,3-bis(2′-formylphenoxy)-2-propanol and resorcinol-bis(4-aminophenyl)ether. Furthermore, the macrocycle **3** was reduced to the corresponding saturated macrocycle **4** in order to increase its flexibility (Scheme 1). The alkoxyl chain of compounds **3** and **4** contain a hydroxyl functional group, which may be further functionalized by appropriate synthetic procedures.

2. Experimental

2.1. Synthesis of the Schiff-base macrocycle 3

Precursor dialdehyde **1** [1,3-bis(2′-formylphenoxy)-2-propanol] was prepared using the reported procedure [13]. The solid product was dried under vacuum before analysis. Yield: 37%, mp 116–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.40 (s, 2H, CHO), 7.81 (d, 2H, ArH), 7.57 (t, 2H, ArH), 7.03–7.18 (m, 4H, ArH), 4.33 (d, 4H, CH_2), 4.20 (s, 1H, CH), 3.30 (s, 1H, OH).

Precursor diamine **2** [resorcinol-bis(4-aminophenyl) ether] was synthesized using the reported procedure [14]. Resorcinol-bis(4-nitrophenyl)ether was obtained as a pale yellow solid in 65% yield, mp 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.116–7.157 (t, 1H, Ar–H), 6.849–6.880 (m, 4H, ArH), 6.649–6.688 (m, 4H, ArH),6.529–6.554 (t, 3H, ArH), 3.579 (s, 2H, NH_2), 1.646 (s, 2H, NH_2).

[1,3-Bis(2′-formylphenoxy)-2-propanol (0.151 g, 0.5 mmol)] in methanol (50 mL) was added slowly, with stirring, to resorcinol-bis(4-aminophenyl)ether (0.146 g, 0.5 mmol) and $BaCl_2$ (0.105 g, 0.5 mmol) in methanol (100 mL). The mixture was stirred for 12 h at room temperature; the bright yellow precipitate was collected by filtration and washed with ethanol, and dried at room temperature to give **3** as a yellow solid in 75.7% yield, mp 271–273 °C. The solid was dissolved in excess methanol at room temperature; slow evaporation of this solution yielded white block-shaped single crystals that proved suitable for X-ray analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 2H, CH=N), 7.83–7.86 (d, 2H, ArH), 7.39–7.46 (m, 3H, ArH), 7.169–7.191 (d, 4H, ArH), 7.082–7.119 (t, 2H, ArH), 6.951–7.072 (d, 8H, ArH), 6.575 (t, 1H, ArH), 4.519 (t, 1H, CH), 4.31–4.339 (d, 2H, CH_2), 4.00 (t, 1H, OH),

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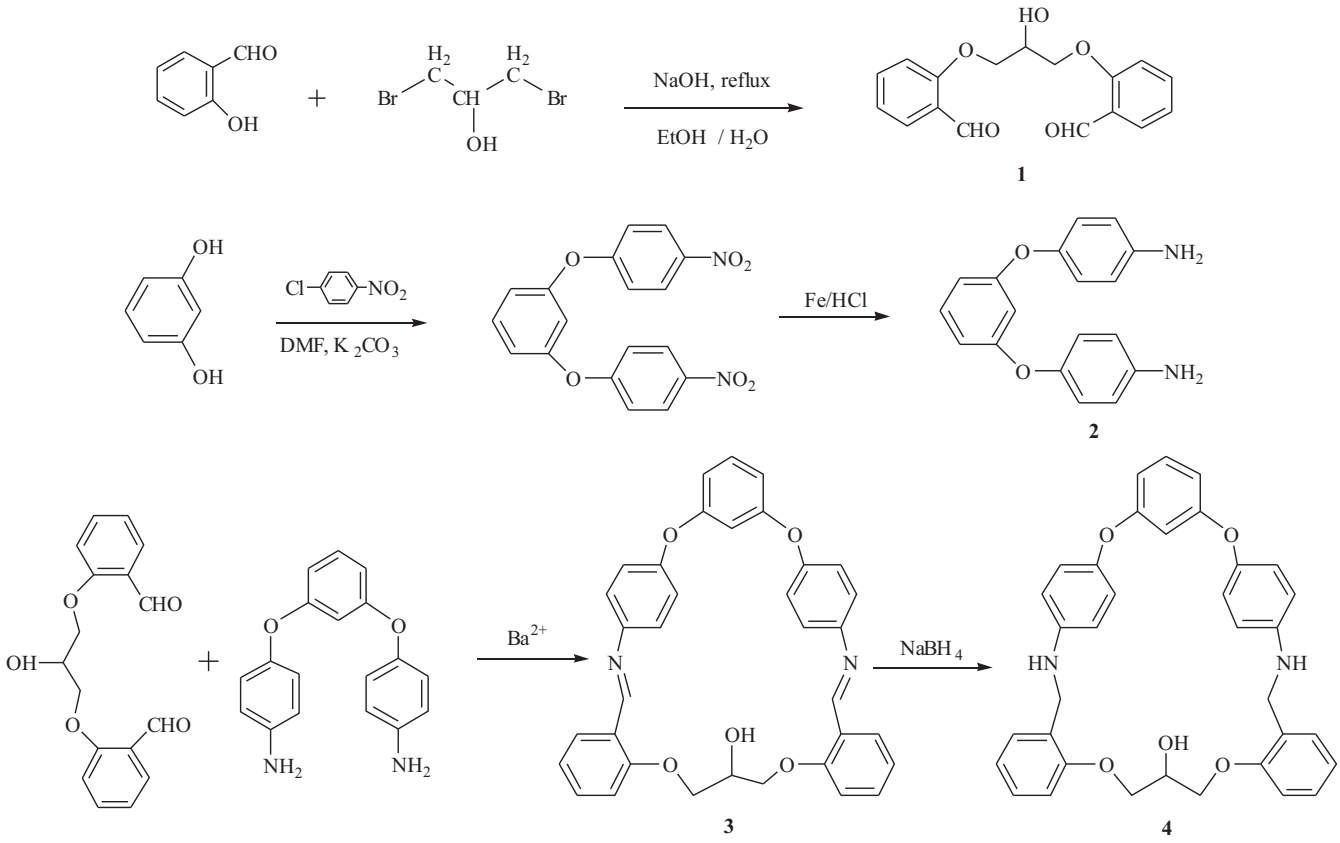

Scheme 1. Syntheses of the Schiff-base macrocycle **3** and the macrocycle **4**.

3.485–3.498 (d, 2H, CH_2); IR (KBr, cm^{-1}): ν 2925(CH_2), 1618 (C=N), 1497, 1482, 1451 (C=C), 1283 (C–O); FABMS (*m/z*): 579 $[M+Na]^+$; Anal. Calcd. for $C_{35}H_{28}N_2O_5$: C 75.52, H 5.07, N 5.03; Found: C 75.50, H 5.10, N 5.09.

2.2. Synthesis of the macrocycle **4**

$NaBH_4$ (0.3 g, 6.7 mmol) in ethanol (30 mL) was added dropwise, with stirring, to Schiff-base macrocycle **3** (0.8 g, 1.43 mmol) in THF (60 mL) and the reaction solution heated at reflux for 12 h. The solution was concentrated to a volume of *ca.* 10–15 mL in a rotary evaporator whereupon distilled water (30 mL) was added, and reaction solution was extracted with methylene chloride. The retained organic phase was dried with Na_2SO_4 before removal of solvent in a rotary evaporator. The residue was purified by recrystallization from methylene chloride/ethyl acetate (2/1, v/v) to give pale yellow solid 0.45 g, yield in 56%, mp 96–98 °C. The solid was dissolved in excess ethanol at room temperature; slow evaporation of this solution yielded white needle-shaped single crystals that proved suitable for X-ray analysis. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28–7.32 (m, 5H, ArH), 6.978 (t, 2H, ArH), 6.910–6.926 (d, 2H, ArH), 6.77–6.82 (m, 6H, ArH), 6.598–6.616 (d, 4H, ArH), 6.214 (t, 1H, ArH), 4.433 (t, 1H, CH), 4.254 (t, 4H, $ArOCH_2$), 4.198 (s, 1H, NH), 4.174 (s, 1H, NH), 4.078 (t, 4H, N–CH_2); IR (KBr, cm^{-1}): ν 3422 (N–H), 3040 (Ar–H), 2927 (CH_2), 1448, 1508, 1598 (C=C), 1245(C–N). FABMS (*m/z*): 583 $[M+Na]^+$; Anal. Calcd. for $C_{35}H_{32}N_2O_5$: C 74.98, H 5.75, N 4.99; Found: C 74.95, H 5.71, N 5.01.

3. Results and discussion

3.1. Characterization of macrocyclic compounds **3** and **4**

The reaction of 1,3-bis(2′-formylphenoxy)-2-propanol and resorcinol-bis(4-aminophenyl)ether using Ba^{2+} as template in

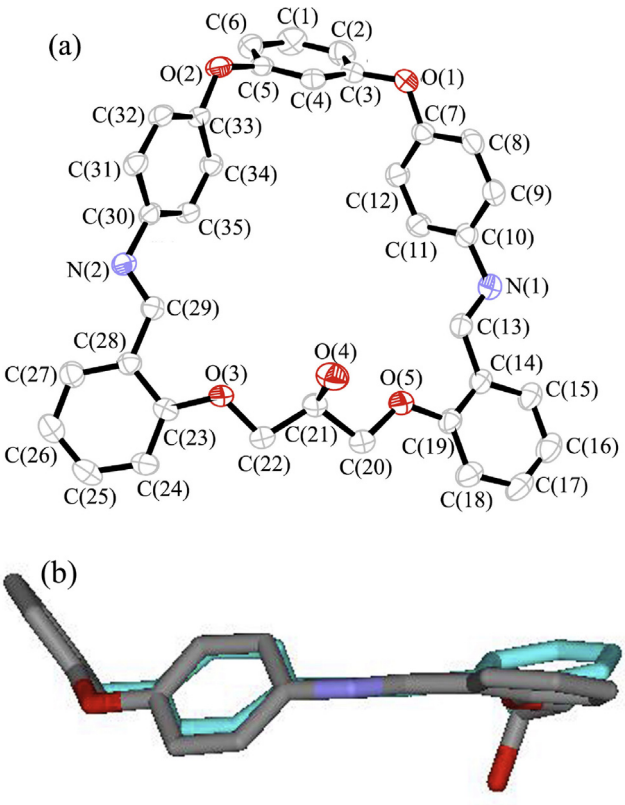

Fig. 1. (a) Molecular structure of the compound **3** (probability of ellipsoid is 30%); (b) molecular structure viewed along side chain. Hydrogen atoms have been omitted for clarity.

ethanol solution yields the Schiff base macrocycle **3**, isolated as an air-stable yellow solid in 75.7% yield. In order to increase the flexibility of macrocycle **3**, the Schiff base macrocycle **3** was reduced to the corresponding saturated macrocycle 4 *via* $NaBH_4$ in THF ethanol solution, and the pale yellow solid **4** was extracted from the reaction solution in a 56% yield.

The two macrocycles were characterized by elemental analysis, FAB MS, IR, and ^1H NMR spectra. The FAB mass spectrum of **3** shows the parent ion peak at *m/z* 579 $[M+Na]^+$, confirming the [1+1] nature of the Schiff-base compound, and the peak of molecular ion corresponding to the reduced macrocycle **4** at *m/z* 583 $[M+Na]^+$ is shown in the FAB mass spectrum of **4**. The FAB mass spectra and ^1H NMR spectra of **3** and **4** can be found in the Supporting information.

The ^1H NMR spectrum of **3** in $CDCl_3$ solution is complicated and shows more than the expected number of signals with the signal at δ 8.70 attributed to the CH=N– proton. Comparison of the ^1H NMR spectra of the macrocycles **3** and **4** reveals the disappearance of the signal at δ 8.70 due to the imino-protons and the appearance of two new singlets at δ 4.174 and 4.198 corresponding to the $NHCH_2$ amine protons of **4** (see Supporting information). Crystallographic data for structures reported in this article have been deposited in the Cambridge Crystallographic Data Centre, CCDC: 934142 for **3**, and 934143 for **4**.

The IR spectrum of the Schiff-base macrocycle **3** features a strong band at 1618 cm^{-1} attributable to the azomethine group, while the IR spectrum of the macrocycle **4** features a secondary amine N–H stretching band at *ca.* 3422 cm^{-1} and no C=N band at *ca.* 1618 cm^{-1}. The absorption band due to C=N stretching at 1618 cm^{-1} for **3** and the absorption band due to N–H stretching at 3422 cm^{-1} for **4**, are also in good agreement with the molecular structures (see below).

3.2. Crystal structures of the compounds 3 and 4

The macrocyclic structures of **3** and **4** were determined by single crystal X-ray analysis. Crystal data, structural refinements and selective bond lengths or angles for the two compounds are shown in Tables S1 and S2 (Supporting information).

According to X-ray analysis, compound **3** has a [1+1]-condensation 26-membered macrocyclic structure (Fig. 1a). In the resorcinol-bis(4-iminophenyl)ether subunit, the dihedral angles between the two benzene rings located in the two "arms" of the central phenolic-ring (top) are 102° and 94°, respectively. The dihedral angles of the two pairs of benzene rings (lying in the same side chain) bridged by the Schiff base C=N are 118° and 129°, respectively. The dihedral angle of the two benzene rings linked *via* the alkyl bridge is 158°, and the macrocycle **3** adopts a folded conformation (Fig. 1b). Bond lengths of the two C=N groups are 0.1264(4) nm and 0.1271(4) nm, respectively (a typical C=N, *ca.* 0.1269 nm) [15]. The diameter of the macrocycle hole is 0.9378 nm [distance between N(1) and N(2)], and no solvent molecules were found included in the macrocyclic cavity.

The crystal structure of **4** is shown in Fig. 2a. In the resorcinol-bis(4-iminophenyl)ether subunit, the dihedral angles between the two benzene rings located in the two "arms" of the central phenolic-ring (top) are 111° and 107°, respectively. The dihedral angles of the two pairs of benzene rings (lying in the same side chain) bridged by the Schiff base C=N are 95° and 94°, respectively. The dihedral angle of the two benzene rings linked *via* the alkyl bridge is 129°. This is reinforced by intramolecular O–H···N hydrogen-bond interaction (O–H: 0.082 nm, O···N: 0.3053 nm, O–H···N: 155°). The lengths of the two C–N bands are 0.1438(4) nm and 0.1457(4) nm, respectively, and the bond length of carbon–nitrogen single bond is longer than the typical C=N double bond.

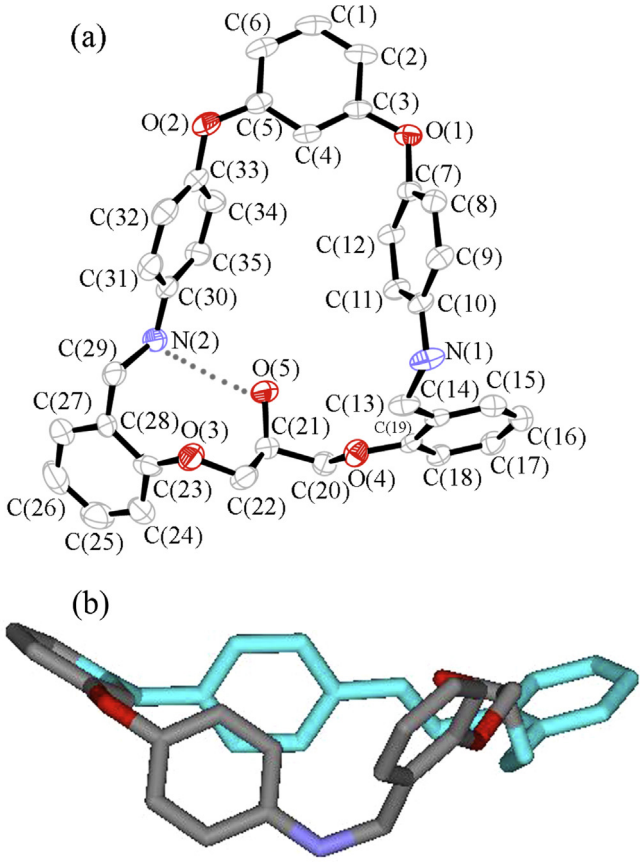

Fig. 2. (a) Molecular structure of the compound **4** (probability of ellipsoid is 30%); (b) molecular structure viewed along side chain. Hydrogen atoms have been omitted for clarity, the O–H···N hydrogen bond is shown as dashed line.

The diameter of the macrocycle hole is 0.7231 nm [distance between N(1) and N(2)], and no solvent molecules were found included in the macrocyclic cavity. Unlike the structure of **3**, the flexibility of the macrocycle **4** allows it to adopt a twisted and folded conformation (Fig. 2b).

Both macrocyclic products **3** and **4** exhibited maximal adsorption at 327 nm and 309 nm, respectively, and no changes were observed in their adsorption spectra when C60 was added to their benzene solution. Attempts to create some transitional metal (Cu^{2+}, Zn^{2+}, Cd^{2+}, Fe^{3+}) complexes with macrocycles **3** or **4** failed to give any positive results.

4. Conclusion

A 26-membered Schiff-base macrocycle **3** with a hydroxyl functional group was synthesized and macrocycle **3** was further reduced giving macrocyclic compound **4**. X-ray crystallographic analysis revealed that the macrocyclic compound **3** has a folded conformation, and the corresponding reduced product **4** adopts a twisted and folded conformation due to its flexible nature.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2013.06.014.

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