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Synthesis and structure determination of pyrazine-containing macrocyclic polyazomethines

Liang Chun Wu [a], Long Qing Liu [a], Hai Shan Jin [a], Ming Liang Ma [a], Xiao Li Zhao [b], Ke Wen [a,*]

[a] *Division of Supramolecular Chemistry and Medicinal Chemistry, Key Laboratory of Brain Functional Genomics, MOE, and Shanghai Key Laboratory of Brain Functional Genomics, East China Normal University, Shanghai 200062, China*
[b] *Shanghai Key Laboratory of Green Chemistry and Chemical Processes, and Department of Chemistry, East China Normal University, Shanghai 200062, China*

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Abstract

Two pyrazine-containing macrocyclic polyazomethines **2** and **3** were synthesized by direct [2 + 2] and [3 + 3] condensation reactions between 2,2′-[pyrazine-2,3-diylbis(oxy)]dibenzaldehyde (**1**) and hydrazine. Both **2** and **3** were characterized by NMR, HRMS, and their structures were determined *via* X-ray crystal diffraction studies.

Keywords: Azomethine; Macrocycles; Schiff base; Pyrazine

Macrocyclic compounds such as crown ethers [1], cyclodextrins [2], calixarenes [3], cucurbiturils [4], and macrocyclic bipyridinium ions [5] are intensive research topics in the areas of supramolecular chemistry. Incorporation of functional groups in macrocyclic scaffolds could generate supramolecular systems with specific guest binding and self-assembling abilities, for instance, introduction of heterocyclic rings into aza- and oxa-calixaromatics resulted in heterocalixaromatics capable of interacting with neutral molecular guests [6], selective binding of metal ions [7], and coordination-driven molecular self-assembly [8]. Azomethines are very useful scaffolds for construction of cyclic compounds *via* ring closure between primary amines and aldehydes [9]. Azomethines are also known to have biological activities, such as antitumour [10] and antibacterial [11]. They have also been found in wide application in the areas of dyes and pigments owing to their luminescent properties [12]. However, the number of research reports on the incorporation of azomethines into macrocycles is quite limited [13].

In this communication, two new macrocycles, **2** and **3**, containing both pyrazinyl rings and polyazomethines, were synthesized successfully *via* a two-step reaction sequence. First, aromatic nucleophilic substitution of 2,3-dichloropyrazine by 2-hydroxybenzaldehyde, using K_2CO_3 as a base, under refluxing condition in DMF, resulted in the formation of 2,2′-[pyrazine-2,3-diylbis(oxy)]dibenzaldehyde (**1**) in 83% yield; **1** was then reacted with hydrazine in methanol to give macrocyclic polymethines **2** and **3** in the yields of 8.4% and 11.1% (see Section 1), respectively

* Corresponding author.
E-mail address: kwen@brain.ecnu.edu.cn (K. Wen).

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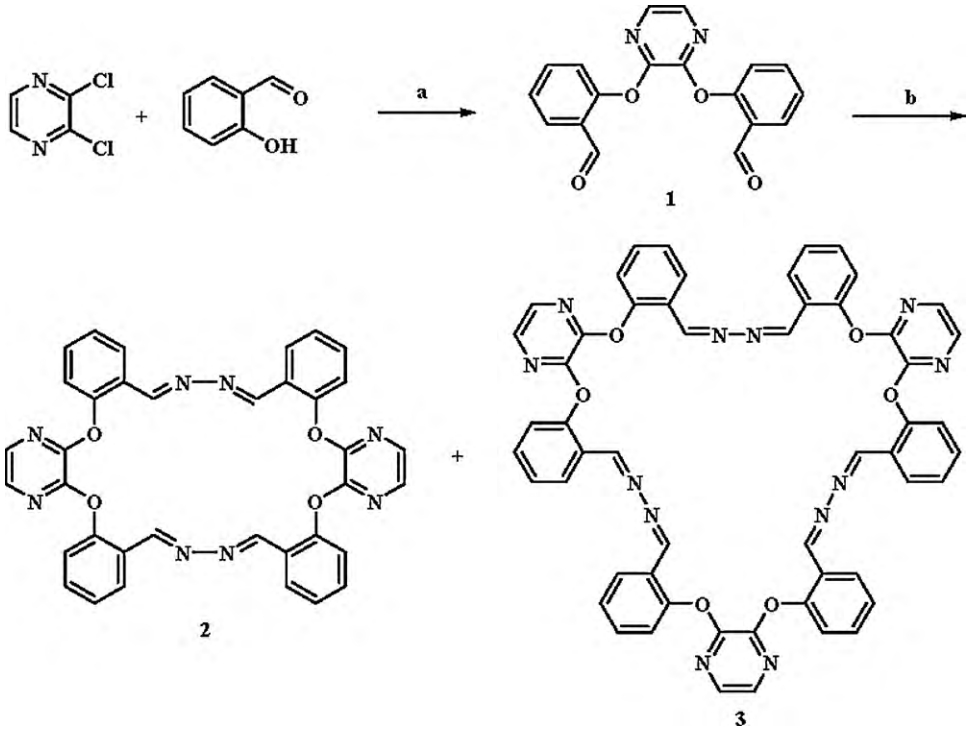

Scheme 1. *Reagents and condition:* (a) K_2CO_3, DMF, reflux, 12 h; (b) hydrazine hydrate, methanol, 24 h.

(Scheme 1), along with some inseparable by-products. Prolonged reaction time and high reaction temperature have not improved the yields of compounds **2** and **3**. Additionally, catalytic amount of $Zn(OAc)_2$ could accelerate the reaction, but did not change the yields of products **2** and **3** and product distribution. Refluxing the reaction mixture in methanol under $Zn(OAc)_2$ overnight resulted in the improvement of the yield of compound **2** to 14%, but significantly decreased the yield of compound **3** (only traces could be detected in TLC). Attempts to reduce the azomethines in compounds **2** and **3** with both $NaBH_4$ and H_2 (under Pd/C) failed to give the corresponding hydrazines.

Both macrocyclic products **2** and **3** give very simple ^1H and ^{13}C NMR spectra, indicating symmetrical structure in solution; or compounds **2** and **3** are very fluxional in solution, and the rates of interconversion of various conformational structures are very rapid relative to the NMR time scale.

The macrocyclic structures of **2** and **3** were unambiguously established by single crystal X-ray diffraction analysis. As shown in Fig. 1, compound **2** adopts an 1,3,5-alternate conformation with a non-planer C_2 symmetric structure in the solid state. Judging from the C–O bond lengths, conjugation between the bridging oxygen atoms and the pyrazine rings exists (C–O distances: 0.1360 and 0.1374 nm), while the bridging oxygen atoms do not conjugate to the phenyl

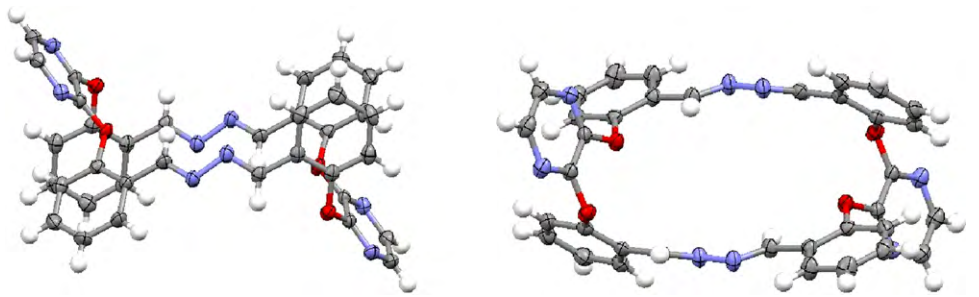

Fig. 1. Crystal structure of **2**: (left) side view, (right) top view. Color code: O (red), N (blue), C (gray), H (white). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of the article.)

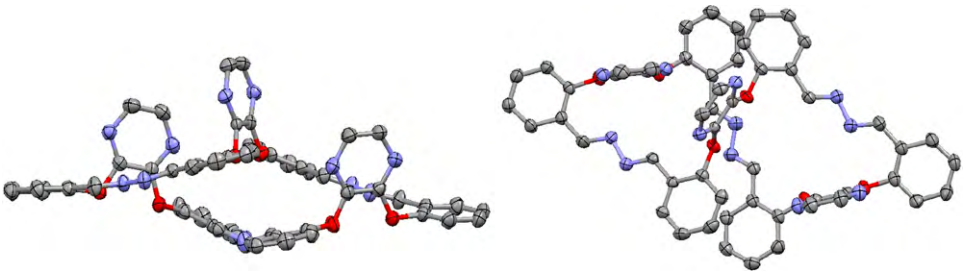

Fig. 2. Crystal structure of **3**, all hydrogen atoms are emitted for clarity; (left) side view, (right) top view. Color code: O (red), N (blue), C (gray). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of the article.)

rings (C–O: 0.1404 and 0.1406 nm). Two CH=N groups (C=N distances: 0.1265 and 0.1271 nm) connected to each N–N function adopt *trans*-configuration with the N–N bond length of 0.1408 nm, and the hydrogen atoms of the CH=N groups are oriented out of the cycle hole. The diameter of the macrocycle hole is 0.5438 nm (distance between the two N–N bonds), and no guest molecules (solvents) were found being included in the macrocyclic cavity. Shown in Fig. 2, compound **3** reveals a 36-member macrocycle ring. Due to its highly flexible nature, no macrocyclic hole could be defined for **3** in the solid state. The molecule **3** folded in a way that its hole space was occupied by part of the molecule itself. Similar to compound **2**, the bridging oxygen atoms in compound **3** conjugate to the pyrazine rings, but not the phenyl components. The pairs of CH=N groups connected to each N–N function are arranged in *trans*-configuration with the C=N bond distances varied from 0.1259 nm to 0.1274 nm, and the three N–N bond distances of 0.1404 nm, 0.1411 nm and 0.1414 nm, respectively.

Both compounds **2** and **3** showed maximal adsorption at 302 nm and emission at 471 nm. No changes were observed in their adsorption and emission spectra when C_{60} was added to their benzene solution, indicating no molecular interaction between the polyazomethine macrocycles (**2** and **3**) and C_{60} in benzene. Attempts to create metal (Ag^+, Cu^{2+}, Zn^{2+}) complexes with compounds **2** and **3** failed to give any positive results.

In summary, two macrocyclic polymethines **2** and **3** were synthesized in a two-step reaction sequence. X-ray crystallographic analysis revealed that the 24-member ring (**2**) has a defined macrocyclic hole, while no defined macrocyclic hole could be observed for the 36-member ring (**3**) due to its high flexible nature in the solid state. No molecular interactions were found between the two macrocyclic compounds and C_{60} in benzene. Additionally, the polymethine and pyrazinyl functions in the two macrocyclic compounds were found not to form metal complexes with Ag^+, Cu^{2+}, Zn^{2+} ions. Works on the synthesis, molecular interaction and metal coordination of macrocyclic polymethines are currently ongoing in our laboratory; the results will be reported in due course.

1. Experimental

*Synthesis of compound **1**:* 2,3-Dichloropyrazine (2.98 g, 20 mmol), 2-hydroxybenzaldehyde (5.86 g, 48 mmol), and K_2CO_3 (11.06 g, 80 mmol) were mixed in 100 mL DMF, the reaction mixture was heated to reflux for 12 h. After cooling down, the reaction mixture was poured into 300 mL water and neutralized with 1 mol/L HCl, extracted with ethyl acetate for three times (3 × 100 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by FC (PE/AcOEt 6:1) to give pure **1** (5.31 g, 83%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.27 (s, 2H), 8.00 (d, 2H, J = 10 Hz), 7.73 (t, 2H, $J_1 = J_2$ = 10 Hz), 7.71 (2H, s), 7.46 (t, 2H, $J_1 = J_2$ = 10 Hz), 7.40 (d, 2H, J = 10 Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 188.83, 154.27, 150.10, 135.59, 134.91, 130.65, 128.44, 126.24, 123.23; HRMS: $[M+Na]^+$, $C_{18}H_{12}N_2O_4Na^+$ *m/z* calcd. 343.0689, found 343.0771.

*Synthesis of compounds **2** and **3**:* Compound **1** (960 mg, 3 mmol) and hydrazine hydrate (80%, 156.25 mg, 3.6 mmol) were dissolved in 30 mL methanol, and the reaction mixture was stirred and kept in room temperature for 24 h. The solvent was then evaporated and redissolved in 40 mL ethyl acetate, washed with water and brine, dried over Na_2SO_4. The ethyl acetate was evaporated and the crude products were purified by FC (PE/AcOEt, 4:1–1:1) in neutral Al_2O_3 to give pure **2** (94 mg, 8.4%) and **3** (123 mg, 11.1%). ^{1}H NMR (500 MHz, $CDCl_3$) for **2**: δ 8.55 (4H, s), 7.82 (d, 4H, J = 7.75 Hz), 7.78 (4H, s), 7.46 (t, 4H, J_1 = 6.5 Hz, J_2 = 7.45 Hz), 7.28 (d, 4H, J = 7.25 Hz), 7.16 (d, 4H, J = 8.15 Hz,); ^{13}C NMR (500 MHz, $CDCl_3$): δ 157.18, 152.63, 150.32, 135.31, 131.90, 130.73, 126.10, 125.38,

121.64; HRMS: $[M+Na]^+$, $C_{36}H_{24}N_8O_4Na^+$ *m/z* calcd. 655.1813, found 655.1984. ^1H NMR (500 MHz, $CDCl_3$) for **3**: δ 8.63 (s, 6H), 7.83 (d, 6H, J = 7.25 Hz), 7.42 (s, 6H), 7.30 (t, 6H, J_1 = 7.3 Hz, J_2 = 7.1 Hz), 7.10 (m, 12H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 157.45, 152.06, 150.46, 133.75, 131.88, 129.33, 126.89, 125.79, 123.04; HRMS: $[M+Na]^+$, $C_{54}H_{36}N_{12}O_6Na^+$ *m/z* calcd. 971.2773, found 971.2792.

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