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Spontaneous macrocyclization via recombination of a Schiff-base linkage

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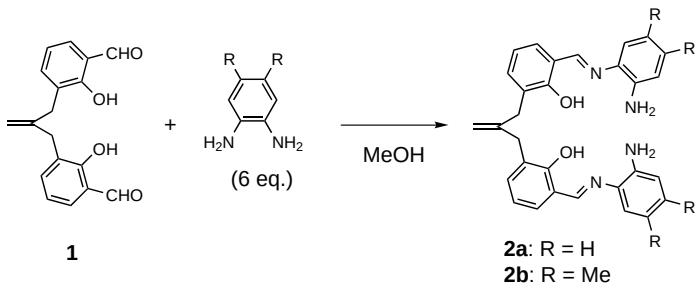
Abstract—A macrocyclic compound that has two salenH_2 moieties was synthesized via recombination of an acyclic Schiff base in quite high yield, and was characterized by X-ray crystallography. The recombination occurred in a slow diffusion system of chloroform–methanol, where the starting material may spontaneously form a molecular assembly suitable for the subsequent reaction. This assumption was supported by the crystal structure of an analogue of the acyclic Schiff base.

2-Hydroxybenzylideneamine ligands, for example salenH_2, are still actively studied and applied to metal complexes with various functions, such as catalysis.[1] During this time, attention has been paid to macrocyclic ligands having plural metal-binding sites, leading to homo- or hetero-bimetallic complexes.[2,3] We have already reported that bis-hydroxybenzaldehyde **1** reacts with a variety of diamines to give the 2:2 macrocyclic polyimines, including salenH_2-type compounds.[4] However, because of the difficulty in purification and recrystallization of these compounds, their crystal structures have not been clarified. Recently, we discovered a new method of preparing one of these macrocyclic compounds and succeeded in elucidating its single crystal X-ray structure.

Compound **1** was prepared according to the reported procedure,[4] and was allowed to react with *o*-phenylenediamine (6 equiv.) in methanol (0.04 M for **1**) without stirring (Scheme 1). After 3 h, acyclic Schiff base **2a** was obtained as a bright yellow precipitate (yield: 86%).[5] Acyclic diamine **2a** (95.2 mg, 0.2 mmol) was dissolved in chloroform (3 ml) in a sample bottle and then methanol (12 ml) was gently added to achieve a slow diffusion condition. By keeping the solution such that the chloroform/methanol interface was not disturbed for 5 days, we obtained a yellow precipitate containing single crystals suitable for X-ray structure analysis.

X-Ray structure analysis revealed that the compound is the 2:2 macrocycle (**3a**) composed of **1** and *o*-phenylenediamine. Fig. 1(b) shows the ORTEP drawing of **3a**.[6] The hydrogen atoms attached to the oxygen atoms were not completely found by differential Fourier transformation processes. As can be seen from the molecular structure, there are two possible tau-



Scheme 1.

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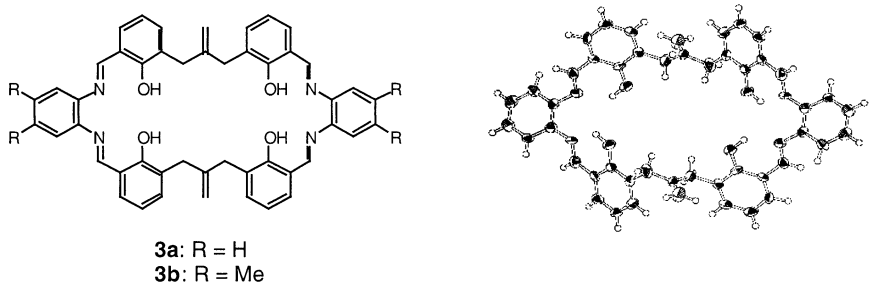
(a) (b)



3a: R = H
3b: R = Me

Figure 1. (a) The molecular structure of **3a** and **3b**, and (b) an ORTEP drawing of **3a**.

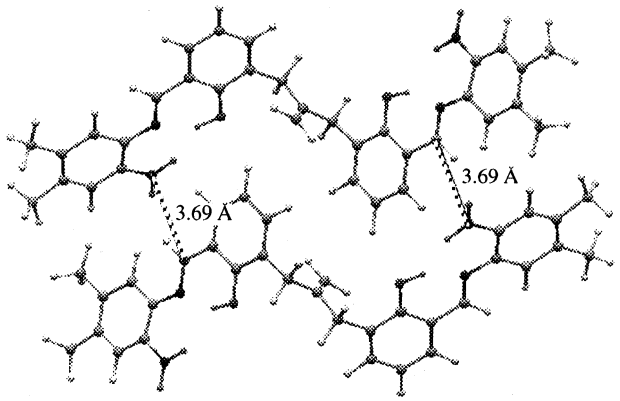


Figure 2. The crystal structure of two neighboring molecules of **2b**. Dotted lines indicate the distance between an azomethyne carbon atom of one molecule and an amine nitrogen atom of another.

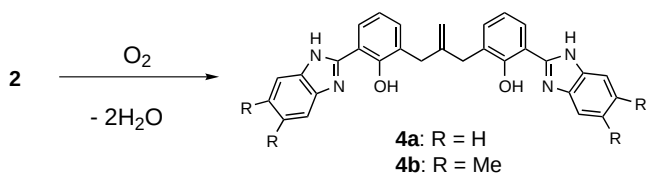
tomeric forms, i.e. OH- and NH-forms, for the O–C–C–C–N framework. By comparison with the reported values of the bond lengths of the salicylideneaniline moiety,[7] it was suggested that each moiety adopts the OH-form for the present case.

This result indicates that a recombination reaction of **2a** occurs in the system, together with the removal of *o*-phenylenediamine. All of the precipitate was collected and examined by FT-IR, resulting in essentially the same spectrum as that of the single crystal.[8] This indicates that all of the precipitate was a single compound (**3a**) and the total yield of **3a** was 71%.

As a by-product, a benzimidazole derivative **4a**, which was generated via oxidative intramolecular cyclization (Scheme 2), was isolated from the solution phase in 13% yield.

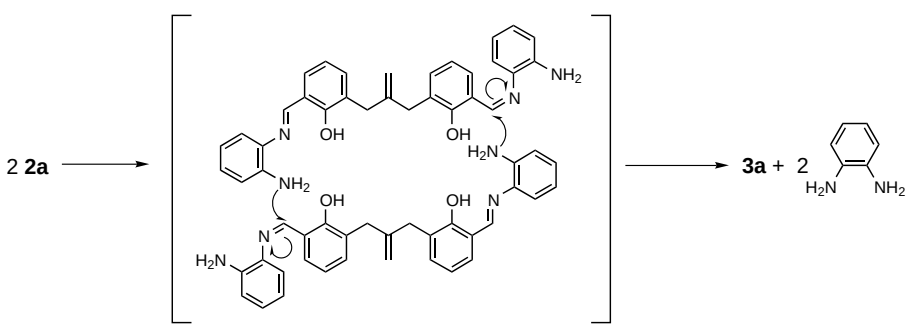
In a similar manner to **2a**, a dimethyl derivative **2b** was synthesized (Scheme 1).[9] The crystal structure of **2b** was successfully analyzed.[10] Fig. 2 is a close-up of two neighboring molecules in the crystal, where one molecule is the mirror image of another. As can be seen, each nitrogen atom of the amino group is located in the proximity of the azomethyne carbon atom of the neighboring molecule. The C–N distance is only 3.69 Å (indicated by a dotted line), comparable to a usual van der Waals contact distance. This structure implies that the preferable arrangement of the molecules could assist the attack of the nitrogen lone pair on the azomethyne carbon. In fact, after slow diffusion treatment, the corresponding 2:2 macrocycle **3b** was obtained in 37% yield.[11] The yield of a by-product **4b** was 23%.

We can presume that **2a** has a crystal structure similar to that of **2b**[12] and, thereby, results in an efficient conversion to **3a** (Scheme 3). Namely, during the slow



4a: R = H
4b: R = Me

Scheme 2.



Scheme 3.

diffusion process in the chloroform–methanol system, two molecules of **2a** (or **2b**) spontaneously assembled to form an enantiomeric pair similar to one shown in Fig. 2. This assumption was supported by ESI-MS measurements: the spectra of **2a** and **2b** both show a moderate peak corresponding to twice that of their molecular weight other than their strong parent peak. For the efficient condensation reaction of this molecular pair, a small amount of proton existing in the system could act as a catalyst. In addition, the reaction may be promoted as **3a** separates out. For **2b**, which gave **3b** in a relatively low yield, the intramolecular reaction (Scheme 2) would take precedence due to the steric repulsion among the methyl groups on the phenyl ring (cf. Fig. 2).

There have been several studies on the thermodynamic and kinetic control of macrocyclization.[13] In this study, we found a new method of preparing a macrocyclic compound in a 'non-equilibrated system'. This is an interesting example of a reaction that was initiated by self-assembly of the starting materials. Moreover, compound **3a** and its derivatives are promising macrocyclic metal ligands and can be applied to the development of various functional complexes.

References

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5. Analytical data for **2a**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.42 (s, Ar-CH_2-C(=CH$_2$)-, 4H), 4.74 (s, -C(=CH_2)-, 2H), 5.04 (s, Ar-NH_2, 4H), 6.63 (t, N-ArH-N, 2H), 6.78 (d, N-ArH-N, 2H), 6.95 (t, ArH-OH, 2H), 7.01 (t, N-ArH-N, 2H), 7.14 (d, N-ArH-N, 2H), 7.29 (d, ArH-OH, 2H), 7.50 (d, ArH-OH, 2H), 8.84 (s, -CH=N-, 2H), 13.44 (s, ArH-OH, 2H).
6. Crystal data for **3a**: $C_{48}H_{40}N_4O_4$, M_w = 736.84, crystal system = monoclinic, space group = $P2_1/n$ (no. 14), Z = 2 in a cell with the following dimensions: a = 7.3369(2), b = 20.7770(9), c = 12.0310(3) Å, β = 95.1956(7)°, V = 1826.5(1) Å^3, D_{calcd} = 1.340 g cm^{-3}. The data were collected at −80°C on a Rigaku RAXIS-RAPID imaging plate diffractometer, λ (Mo Kα) = 0.7107 Å, μ = 0.86 cm^{-1}, 14752 measured and 4106 unique reflections ($2\theta_{max}$ = 55.0, R_{int} = 0.066). R = 0.075, R_w = 0.128.
7. (a) Ogawa, K.; Kasahara, Y.; Ohtani, Y.; Harada, J. *J. Am. Chem. Soc.* **1998**, *120*, 7107; (b) Ogawa, K.; Harada, J.; Tamura, I.; Noda, Y. *Chem. Lett.* **2000**, 528.
8. Analytical data for **3a**: FT-IR: 1611, 1574, 1447, 1280, 1208, 751 cm^{-1}; ESI-MS (positive mode): m/z 743 assigned to **3a**+Li (a sample was prepared by dissolving **3a** in a saturated DMSO solution of LiI, followed by diluting with acetonitrile). Elemental analysis calculated for $C_{48}H_{40}N_4O_4 \cdot 0.5H_2O$: C, 77.29; H, 5.54; N, 7.51. Found: C, 77.17; H, 5.43; N, 7.89.
9. Analytical data for **2b**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.12 (s, CH_3-Ar, 12H), 3.41 (s, Ar-CH_2-C(=CH$_2$)-, 4H), 4.72 (s, Ar-NH_2, 4H), 4.77 (s, -C(=CH_2)-, 2H), 6.59 (s, N-ArH-N, 2H), 6.92 (t, ArH-OH, 2H), 6.99 (s, N-ArH-N, 2H), 7.26 (d, ArH-OH, 2H), 7.48 (d, ArH-OH, 2H), 8.84 (s, -CH=N-, 2H), 13.61 (s, ArH-OH, 2H).
10. Crystal data for **2b**: $C_{17}H_{18}N_2O$, M_w = 368.43, crystal system = monoclinic, space group = $C2/c$ (no. 15), Z = 4 in a cell with the following dimensions: a = 27.784(2), b = 8.2459(5), c = 12.9377(9) Å, β = 109.719(2)°, V = 2790.3(3) Å^3, D_{calcd} = 1.268 g cm^{-3}. The data were collected at −80°C on a Rigaku RAXIS-RAPID imaging plate diffractometer, λ (Mo Kα) = 0.7107 Å, μ = 0.80 cm^{-1}, 13803 measured and 3193 unique reflections ($2\theta_{max}$ = 55.0, R_{int} = 0.033). R = 0.135, R_w = 0.222.
11. Analytical data for **3b**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.32 (s, CH_3-Ar, 12H), 3.35 (s, Ar-CH_2-C(=CH$_2$)-, 8H), 4.76 (s, -C(=CH_2)-, 4H), 6.92 (t, ArH-OH, 4H), 7.29 (d, ArH-OH, 4H), 7.38 (s, N-ArH-N, 4H), 7.51 (d, ArH-OH, 4H), 8.98 (s, -CH=N-, 4H), 13.71 (s, ArH-OH, 4H); ESI-MS (positive mode): m/z 815 assigned to **3b**+Na (a sample was prepared by dissolving **3b** in $CHCl_3$, followed by diluting with acetonitrile).
12. We have also examined a variety of **2a** derivatives, which show a similar conformation in the crystalline state. The results will be described elsewhere.
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