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Highly selective formation of 2:2 macrocycles from a novel hydroxybenzaldehyde derivative and diamines†

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A hydroxybenzaldehyde derivative which has isobutenyl linkage reacts with a variety of diamines to efficiently result in a 2:2 macrocyclic compound.

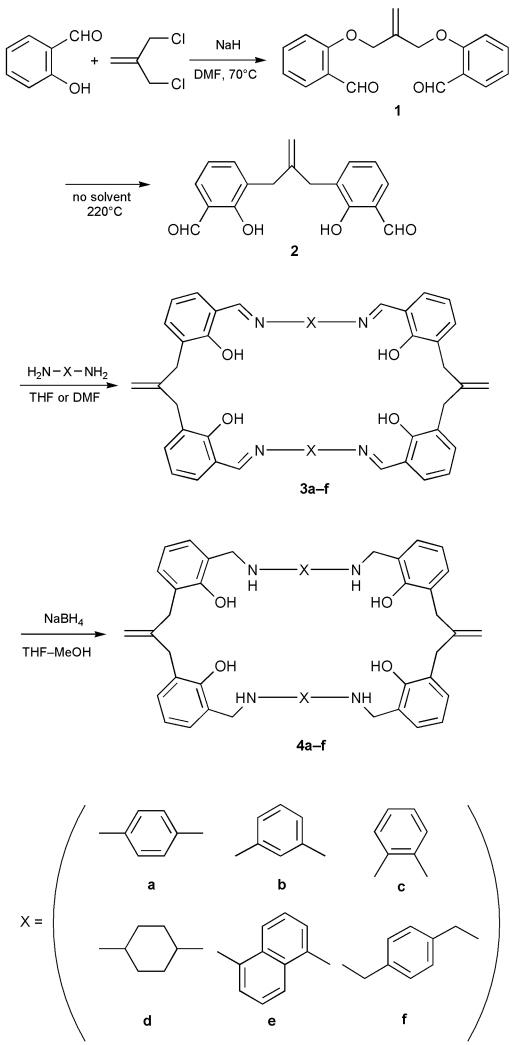
Macrocyclic compounds are extensively studied from the viewpoints of molecular recognition, artificial catalyst, supramolecular structures, and so on.[1] In general, their preparation is not very efficient because competitive reactions may occur, resulting in several kinds of oligomeric compounds. In order to selectively obtain a desired macrocycle, researchers have developed several techniques such as template-assisted or preorganization-assisted syntheses combined with the high dilution method. Since the high dilution method is effective only when an individual reaction is fast enough, each reactant needs to have high activity, which must be maintained during a long period of dropwise addition in a carefully assembled apparatus. In spite of such efforts, the yield usually reaches only 30–60% at most.[2] Even if intramolecular hydrogen bonding works well for the preorganization,[3] stepwise syntheses are necessary to achieve a sufficient yield.

In contrast to kinetic control by, for example, the high dilution method, the concept of self-organization or self-assembly could be useful as another way for an efficient preparation of macrocycles if a desired compound is thermodynamically favoured. In this communication, we report on a hydroxybenzaldehyde derivative that reacts with a variety of diamines to give a 2:2 macrocyclic compound in a good yield under relatively mild and simple conditions. Herein we discuss the role of intramolecular hydrogen bonding that controls the direction of functional groups during the cyclisation step.

A procedure to prepare **1** and **2** is shown in Scheme 1. The second step is a tandem Claisen rearrangement,[4] in which an isobutenyl aryl ether is transformed into the corresponding bisphenol compound. By heating **1** at 220 °C for 10 h under reduced pressure, **2** was obtained in 79% isolated yield. Compounds **1** and **2** were recrystallized from ethyl acetate and MeOH, respectively.‡

Fig. 1(a) and (b) show the X-ray crystal structures of **1** and **2**, respectively,§ which provide information about hydrogen bonding in each compound. In **1**, the aldehyde hydrogen is positioned towards the phenolic ether oxygen, indicating a hydrogen bonded pseudo five-membered ring. In **2**, each carbonyl oxygen is positioned towards the neighbouring hydroxy group to form a hydrogen bonded pseudo six-membered ring. These hydrogen bonding structures are reflected in the ^{1}H NMR spectra: the signal of the aldehyde proton of **1** appears at 10.49 ppm, whereas that of **2** appears at 9.88 ppm. The downfield shift of 0.61 ppm in **1** was caused by the hydrogen bond between ether oxygen and aldehyde hydrogen atoms. For **2**, the relatively lowfield signal of phenolic OH proton (11.27 ppm) implies the hydrogen bonding between the hydroxy group and carbonyl oxygen.

THF solutions of **2** (0.1 M) and *p*-phenylenediamine (0.1 M) were mixed and stirred over 30 h at rt. Then, MeOH was slowly



Scheme 1

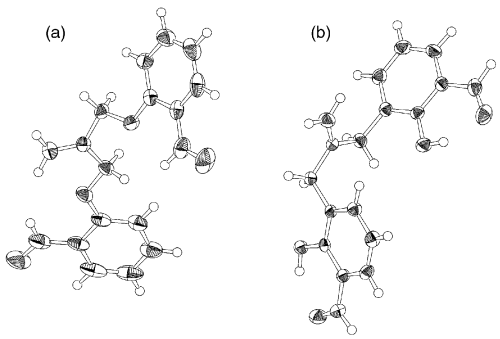


Fig. 1 X-ray crystal structures of (a) **1** and (b) **2**.

† Electronic supplementary information (ESI) available: characterisation data for new compounds. See http://www.rsc.org/suppdata/cc/b0/b005536k/ for crystallographic files in .cif format.

Table 1 The yields (%) of tetraimine (**3a**–**f**) and tetramine (**4a**–**f**) from a variety of diamines (**a**–**f**)

	3a–**f**[a]	**4a**–**f**[b]
a *p*-phenylenediamine	76–89	47–69
b *m*-phenylenediamine	58–64	61–81
c *o*-phenylenediamine	90–97	53–59
d *trans*-1,4-cyclohexanediamine	57–79	87
e naphthalene-1,5-diamine	80–90	70–79
f *p*-xylylenediamine	33	75

[a] Yields of crude solid. [b] Yields of **4a**–**f** from **3a**–**f**.

added to the solution until a yellowish orange solid precipitated (crude yield >80 %). FAB MS and ^{1}H NMR measurements revealed that the solid was 2:2 adduct **3a**, and that the amount of higher oligomeric compounds was too small to accurately determine their structures and yields. Since it was difficult to purify **3a** by recrystallisation or column chromatography due to its low solubility, it was used for the next step after washing with $CHCl_3$. To a THF–MeOH suspension (v/v = 7/3) of **3a** (0.736 g/50 ml), four equiv. of sodium borohydride were added at rt, resulting in cyclic polyamine **4a** as a colorless solid (69 %).‡ Similarly, by using *o*-phenylenediamine, *m*-phenylenediamine, *trans*-1,4-cyclohexanediamine, naphthalene-1,5-diamine, and *p*-xylylenediamine instead of *p*-phenylenediamine, **4b**–**f** were prepared respectively (Scheme 1).‡ In the case of naphthalene-1,5-diamine, DMF was used as solvent in the cyclisation step. In some cases, a catalytic amount of hydrochloric acid was used for the Schiff base formation. The yields are summarized in Table 1.

It is noteworthy that the reaction selectively affords the 2:2 compounds in a relatively concentrated solution. For *p*-phenylenediamine, it is confirmed that a major product in an early stage of this reaction is the linear imine **5** (see Fig. 2) resulting from 1:1 condensation of **2** and the diamine, suggesting that the reaction proceeds as illustrated in Scheme 2. This scheme can be applied to the cases of the other diamines. For aromatic amines (X = **a**, **b**, **c**, and **e**), the Schiff base formation is slow enough so that the reaction can proceed stepwise, resulting in high yields of the 2:2 macrocycles. Similarly, *trans*-1,4-cyclohexanediamine (X = **d**), which has aliphatic amine groups, afforded the 2:2 compound in a good yield. On the other hand, the yield for *p*-xylylenediamine (X = **f**), which also has aliphatic amine groups, was relatively low.

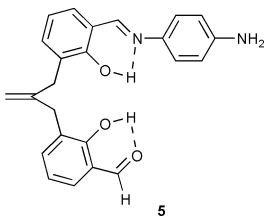


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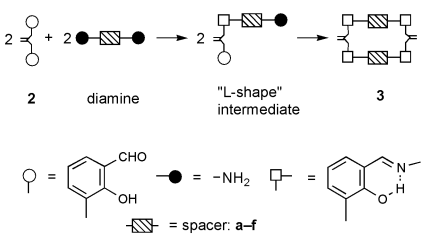
Fig. 2 Presumptive hydrogen bonding for *p*-phenylenediamine Schiff base of **2**.



Scheme 2

These results imply that the yield is much affected by the flexibility of the amine rather than its reactivity.

In contrast to **2**, attempts to prepare macrocycles from **1** were not successful. Although the products have not been characterised in detail, the reaction might give a mixture of several oligomeric compounds. Although there is a difference in substitution position between **1** and **2**, these results suggest that the hydroxy groups of **2** play an important role in selectively forming the 2:2 macrocycles.

A typical ^{1}H chemical shift of such an hydroxy group for **3a**–**f** was 13–14 ppm, indicating a strong interaction between the hydroxy and imine groups by making a pseudo six-membered ring even in solution. For **5**, the corresponding ^{1}H NMR peak was observed at 13.88 ppm, indicating similar hydrogen bonding. Such a hydrogen bond can fix this molecule into an 'L-shape' (Fig. 2), and thereby prevents it from making an intramolecular Schiff base linkage to give a 1:1 macrocycle. As shown in Scheme 2, if two L-shaped molecules are present in high concentration, the probability of the formation of 2:2 macrocycles will increase. For the Schiff base of **1**, however, one can not expect so strong a hydrogen bond that the conformational freedom of the molecule is reduced. This would be a reason why a selective macrocyclisation of **1** and diamine is not successful.

In summary, a novel bishydroxybenzaldehyde that we synthesized *via* tandem Claisen rearrangement is a useful building block for preparation of a new series of macrocyclic polyamine compounds. These compounds can be regarded as derivatives of salophane,[5] and therefore are expected to act as good metal ligands. Furthermore, taking advantage of hydrogen bonding interactions, these cyclic salophanes might act as molecular hosts, artificial catalysts, and so on. In fact, recently **4a** has been found to react selectively with *p*-quinones to reduce them into hydroquinones. We will describe an electrochemical study on this system elsewhere.[6]

Notes and references

‡ Compound **1**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.80 (s, Ar-O-CH_2-), 5.53 (s, -C(=CH_2)-), 7.02 (d, -O-*Ar*-), 7.07 (t, −O-*Ar*-), 7.55 (m, -O-*Ar*-), 7.84 (m, -O-*Ar*-), 10.49 (s, Ar-C*H*O). Precise MS calcd. for $C_{18}H_{16}O_4$ 296.1048, found 296.1069.

Compound **2**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.42 (s, Ar-CH_2-C(=CH_2)), 4.81 (s, -C(=CH_2)-), 6.97 (t, -*Ar*(OH)-), 7.44 (d, -*Ar*(OH)-), 7.44 (d, -*Ar*(OH)-), 9.88 (s, Ar-C*H*O), 11.27 (s, -Ar(O*H*)-). Precise MS calcd. for $C_{18}H_{16}O_4$ 296.1048, found 296.1098.

§ Crystal data for **1**: $C_{18}H_{16}O_4$, *M*w = 296.32, crystal system = monoclinic, space group $P2_1/n$(#14), Z = 4 in a cell of dimensions: a = 7.7307(3), b = 13.7793(6), c = 14.5413(4) Å, β = 101.431(1)°, V = 1519.50(10) Å^3, D_{calcd} = 1.29 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 = 0.91 cm^{-1}, 3572 measured and 3427 unique reflections ($2\theta_{max}$ = 55.00, R_{int} = 0.023). R = 0.103, R_w = 0.073.

Crystal data for **2**: $C_{18}H_{16}O_4$, *M*w = 296.32, crystal system = monoclinic, space group $P2_1/a$(#14), Z = 4 in a cell of dimensions: a = 7.9346(4), b = 14.3035(8), c = 13.3949(7) Å, β = 102.18(2)°, V = 1486.0(1) Å^3, D_{calcd} = 1.32 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 = 0.93 cm^{-1}, 3555 measured and 3410 unique reflections ($2\theta_{max}$ = 55.00, R_{int} = 0.021). R = 0.085, R_w = 0.078. CCDC 182/1801.

1 J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VHC, Weinheim, 1995.
2 *Macrocycle Synthesis*, ed. D. Parker, Oxford University Press, New York, 1996.
3 F. J. Carver, C. A. Hunter and R. J. Shannon, *J. Chem. Soc., Chem. Commun.*, 1994, 1277.
4 K. Hiratani, K. Kasuga, M. Goto and H. Uzawa, *J. Am. Chem. Soc.*, 1997, **119**, 12 677.
5 D. A. Atwood, *Coordination Chem. Rev.*, 1997, **165**, 267.
6 H. Houjou, S.-K. Lee, Y. Nagawa and K. Hiratani, in preparation.