A Simple, Effective, and Selective Synthesis Route without Template Effect (Part II) for [2 + 2] Difunctional 28-Membered Macrocyclic Ethers Based on Benzoxazine Dimers and Its Inclusion Phenomena with Metal Ions

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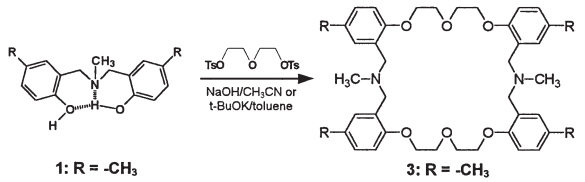
A macrocyclic ether produced from benzoxazine dimers and ditosylated diethylene glycols is a model to show that the cyclization occurs when intramolecular hydrogen bond of benzoxazine dimer is eliminated in the strong basic condition via a selective [2 + 2] pathway without metal template effect. Macrocyclic ethers perform inclusion phenomena at host-guest stoichiometric ratios of 1:1, and 2:1 depending on the type of metal ion, as clarified by UV and ^{1}H NMR.

For the past decades, macrocyclics such as, crown ethers, cyclodextrins, calixarenes, have received much attention for their molecular recognition.[1–3] We proposed the open ring benzoxazines as aza-methylene linkage type of calixarenes[4–7] and reported that bisphenol A-based benzoxazines perform host–guest phenomena with metal ions.[4] In order to establish a well-defined structure of benzoxazine host compound, a series of dimers (Scheme 1) are considered owing to the ease of preparation with high yield (>85%) and without by-products. It is also important to note that the benzoxazine dimer is a difunctional molecule consisting of two active phenol groups. However, the two phenol units are partially deactivated due to the intra- and intermolecular hydrogen bonding. As a result, the benzoxazine dimer performs the reaction differed from the theoretical pathway. For example, recently, we reported a simple Mannich reaction on the benzoxazine dimers to produce a unique asymmetric monooxazine compound inevitably.[6] Based on the molecular design using benzoxazine dimers, we aim to synthesize a series of cyclic compounds using some specific conditions to overcome the hydrogen bond network and activate the difunctional benzoxazine dimers. Previously, we succeeded in obtaining difunctional [2 + 2] 30–membered macrocyclic esters and linear oligoesters selectively from the reaction of benzoxazine dimers with terephthloylchloride.[7] Herein, we present another ''simple, effective, and selective synthesis route'' for benzoxazine dimers based macrocyclic ethers, which leads us to the answer about the way to overcome the specific structure of benzoxazine dimer to form macrocyclic compounds. Furthermore, we clarify the inclusion phenomena of these macrocyclic compounds with metal ions.



Scheme 1.

Benzoxazine dimers (Scheme 1), i.e., *N*,*N*-bis(2-hydroxy-5-methylbenzyl)methylamine (**1**), and *N*,*N*-bis(2-hydroxy-5-ethylbenzyl)methylamine (**2**), were prepared as reported previously.[6] Compound **1** (0.271 g, 1 mmol) was mixed with NaOH (0.080 g, 2 mmol) in 150 mL acetonitrile (CH_3CN). A solution of ditosylated diethyleneglycol (0.414 g, 1 mmol) in CH_3CN (50 mL) was added dropwise and refluxed for 2 days. The solution obtained was collected, washed by water, and dried over anhydrous sodium sulfate. The solvent was removed and the crude product was recrystallized in isopropanol to obtain a white crystal for 85% yield.

Compound **1** gives the peaks at 3251 cm^{-1} (intermolecular H-bond), 3000-2800 cm^{-1} (intramolecular H-bond), 1599 cm^{-1} (N···H–O, intramolecular H-bond)[8] and 1499 cm^{-1} (tri-substituted benzene). The disappearance of the peaks at 3251 and 3000–2800 cm^{-1} is related to the structure without the inter- and intramolecular H-bonds of dimers, implying that the hydroxyl groups were consumed in the reaction. ^{1}H NMR (Figure 1) gives the three different methylene protons, of which the first two peaks at $\delta_H = 3.85$ and 4.02 ppm belong to two methylene groups of diethylene oxide unit and the other one at $\delta_H = 3.59$ refers to aza linkage, indicating the symmetric structure. The integration ratio of these three methylene protons is clarified to be 1:1:1, suggesting that the etherification occurred at both hydroxyl groups as shown in Scheme 1. The precise structure is further studied by the elemental analysis and matrix-assisted laser desorption ionization time-of-flight mass spectrometer (MALDI-TOF MS) to find the molecular ion signal at $M^+ = 682$ corresponding to **3**.[9] Similar reaction is carried out for **2** to obtain **4**.[9]

We extended our work to clarify the template effect by changing from NaOH to potassium tert-butoxide (t-BuOK), which may give us different macrocyclic owing to the size of template (K^+). The compound obtained was found to be **3** in si-

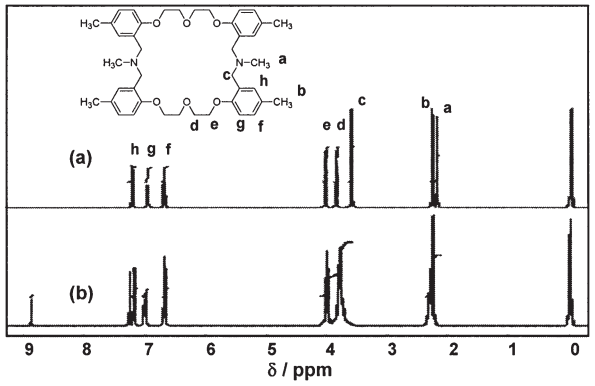


Figure 1. ^{1}H NMR spectra of (a) **3**, and (b) complex of **3** and cesium picrate.

milar yield without by-products. This suggested that the reaction was controlled rather by the dimer structure, where the strong intramolecular hydrogen bond is existed, than the template. In addition, when we used Na_2CO_3/acetone or K_2CO_3/CH_3CN, we obtained only dimer. This might be due to the weak basic condition. Taking these results into our consideration, we speculated that the reaction might occur by 2 steps, (i) phenoxide generation by strong base, and (ii) nucleophilic addition onto ditosylated diethylene glycol. It is important to note that the reaction gives a single product without any by-products implying that the reaction is simple and effectively proceeded in a selective route.

Ion extraction was studied by using Pedersen's technique.[2] The solutions of **3**, and **4** in chloroform and alkali metal picrate in water were prepared at equimolar concentration (7×10^{-5} M). The host-guest interaction was quantified by UV spectrophotometer at λ 354 nm. Compound **3** shows approximately 50% extraction for Na^+, K^+, and Cs^+, whereas **4** shows nearly 100% for Na^+ and K^+ but 50% for Cs^+ (Table 1). Here, ^{1}H NMR was further used for clarification of the inclusion phenomena in qualitative and quantitative aspects. A series of picrate salts (i.e., sodium, potassium and cesium) were dissolved in the solution of **1** in $CDCl_3$ and the picrate salt peak at 8.8 was focused. Figure 1b gives two important informations of **3** about the interaction with potassium picrate, which are (i) the change of chemical shifts before and after metal ion complexation (Table 2), and (ii) the proton of picrate implying the existence of picrate salt in the cavity of **3**. Here, the host-metal ratio of **3** and Cs^+ can be calculated from the peak integration of picrate and aromatic protons to be 2:1. Similarly, other ^{1}H NMR and UV results indicated the host–guest ratio of **3** for Na^+, and K^+ to be 2:1. In the case of **4**, the host–guest ratios were found to be 1:1 for Na^+, K^+ and 2:1 for Cs^+. At present, we are studying the factors to control the host–metal inclusion phenomena.

Table 1. Extraction percentage of picrate guest by **3**, and **4** in $CHCl_3$ at 25 °C at an equimolar concentration (7×10^{-5} M) of host and guest, observed at 354 nm by UV-Vis spectrophotometer

3-Na^+ Complex	**3**-K^+ Complex	**3**-Cs^+ Complex	**4**-Na^+ Complex	**4**-K^+ Complex	**4**-Cs^+ Complex
49.50	52.40	49.79	98.90	99.20	51.70
51.30	51.90	50.70	98.70	99.70	50.90
51.70	52.30	51.30	99.40	98.40	49.79
52.10	51.80	49.80	99.80	99.40	51.40

Table 2. Chemical shift of **3** before and after complexation with Na^+, K^+, and Cs^+

Position	Chemical Shift/ppm			
	3	**3**-Na^+ Complex	**3**-K^+ Complex	**3**-Cs^+ Complex
a	2.21	2.25	2.25	2.25
b	2.27	2.32	2.32	2.30
c	3.60	3.78	3.78	3.78
d	3.87	3.85	3.78	3.78
e	4.05	3.98	3.98	4.01
f	6.70	6.68	6.68	6.68
g	6.95	7.02	7.02	7.01
h	7.21	7.15	7.18	7.18

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9 Spectroscopic results of compounds, **3**-**4**, were shown as follows. Compound **3**: 85% yield; mp 185 °C; FTIR (KBr, cm^{-1}): 1504 (vs, trisubstituted benzene), 1253 (vs, C-N stretching), 1140 (s, C-O-C); ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ_H 2.20 (6H, s, N-CH_3), 2.27 (12H, s, CH_3-Ar), 3.59 (8H, s, N-CH_2), 3.85 (8H, t, CH_2-O, $J_1 = 4.57$ Hz), 4.02 (8H, t, CH_2-O, $J_1 = 4.57$ Hz), 6.69 (4H, d, Ar-H, $J_2 = 8.25$ Hz), 6.95 (4H, d, Ar-H, $J_2 = 8.25$ Hz), 7.20 (4H, s, Ar-H). MALDI-TOF MS (m/z): 682. Anal. Calcd for $C_{42}H_{54}N_2O_6$: C, 73.90; H, 7.91; and N, 4.11%. Found: C, 73.86; H, 7.93; and N, 4.07%. Compound **4**: 85% yield; mp 186 °C; FTIR (KBr, cm^{-1}): 1503 (vs, trisubstituted benzene), 1248 (vs, C-N stretching), 1133 (s, C-O-C); ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ_H 1.20 (12H, t, Ar-CH_2-CH_3, $J_1 = 7.51$ Hz), 2.22 (6H, s, N-CH_3), 2.58 (8H, q, Ar-CH_2-CH_3, $J_1 = 7.51$ Hz), 3.65 (8H, s, N-CH_2), 3.89 (8H, t, CH_2-O, $J_2 = 4.47$ Hz), 4.05 (8H, t, CH_2-O, $J_2 = 4.47$ Hz), 6.72 (4H, d, Ar-H, $J_3 = 8.23$ Hz), 6.98 (4H, d, Ar-H, $J_3 = 8.23$ Hz), 7.25 (4H, s, Ar-H). MALDI-TOF MS (m/z): 738. Anal. Calcd for $C_{46}H_{62}N_2O_6$: C, 74.80; H, 8.40; N, 3.79%. Found: C, 74.78; H, 8.39; N, 3.81%.

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