CHAPTER IV
SELECTIVE CROWN ETHER BASED MACROCYCLIZATION: A MODEL CASE STUDY FROM *N,N*-BIS(2-HYDROXYALKYLBENZYL)ALKYLAMINE

Abstract

A model case of selective crown ether based macrocycles, i.e. [1+1] or [2+2] macrocycles, obtained from a simple reaction of *N,N*-bis(2-hydroxyalkylbenzyl) alkylamine, HBA, and ditosylated compounds is proposed. For HBA with the methyl group at ortho and para position, and at N atom, **1**, the reaction between this derivative and the ditosylated compound with three, four, five, or eight atomic chain lengths gives only a [1+1] macrocycle. For HBA with the methyl group at ortho and para position, but the cyclohexyl group at N atom, **2**, the reaction gives both [1+1] and [2+2] macrocyclic types when reacting with the ditosylated compound. The present work declares that the structure of HBA induces selective macrocyclization to provide both [1+1] and [2+2] macrocycles.

Keywords: benzoxazine, macrocycle, *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine, ditosylated compound

Introduction

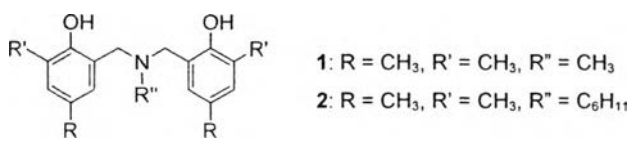
In general, macrocycles are obtained by the cyclization of two or more different molecules under dilute conditions and/or the use of a metal template [1-4]. For example, 18-crown-6 and 15-crown-5 were obtained by using potassium and sodium ion as a template [3]. Hydrogen bond networks of pyridazine- and naphthyridine- containing macrocycles were carried out via condensation [4].

Among many reports on the macrocyclization of crown ethers, cyclization with tosyl derivatives under the presence of a base was a good approach to obtain macrocycles [5-8]. For example, Charbonnière *et al.* proposed the synthesis of novel

crown ethers, i.e. cyclic di[(o-polyethyleneglycoxy)phenyl]amine by treating diarylamine with ditosylated tri-, tetra-, or penta-ethyleneglycol using Cs_2CO_3 as the base [7]. Ágai *et al.* reported on the preparation of dibenzo-monoaza crown ethers from the cyclization of phenol-aza-phenol derivatives with an appropriate ditosylated compound under the presence of K_2CO_3 [8]. In both cases it should be noted that the cyclization of the crown ring with various chain lengths of ditosylated compounds gave only a single type of macrocycle, i.e. [1+1] macrocycle, with modest yields (22-68%). However, in such cases, purification, especially column chromatography, was needed.

Previously, our group focused on *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine (HBA) obtained from benzoxazine derivatives and phenol compounds as a unit for macrocyclization (Scheme 4.1) [9-12]. Considering the structure of these derivatives, the single crystallography analysis pointed out the unique structures with an inter- and intramolecular hydrogen bond network to provide an asymmetric reaction and molecular assembly framework for complex compounds [13-16]. Currently, we find that the reaction of HBA with ditosylated compound not only gives the [1+1] macrocycle, but also a [2+2] one, depending on the HBA derivatives. For example, as shown in Table 4.1, the reaction of **1** gives the [1+1] macrocycle, whereas that of **2** gives the [2+2] macrocycle when it is macrocyclized with 1,3-bis(tosyloxy)propane. It is important to note that the selective macrocycles are obtained in high yield (65–80%) via simple reaction without complicated purification steps. This simple, effective, and selective macrocyclization might be due to the synergistic effects of hydrogen-bonded HBA and the metal template used in the reaction [17].

The present work, therefore, focuses on an investigation of the selective crown ether based macrocyclization of HBA with ditosylated compounds by varying the chain lengths of ditosylated compounds, as well as the HBA derivatives, to declare the factors involved with the selectivity of macrocyclization.



Scheme 4.1 *N,N*-Bis(2-hydroxyalkylbenzyl)alkylamine (HBA)

Experimental

Chemicals

Paraformaldehyde, methylamine, cyclohexylamine, 2,4-dimethylphenol, sodium sulfate anhydrous, diethylene glycol, triethylene glycol ditosylated, and *p*-toluenesulfonyl chloride were purchased from Fluka, Switzerland. The 1,3-bis(tosyloxy)propane and 1,4-butanediol were obtained from TCI, Japan. Sodium hydroxide and isopropanol were obtained from Carlo Erba, Italy. Diethyl ether, 1,4-dioxane, acetonitrile, chloroform, dichloromethane, and tetraethylene glycol ditosylated were obtained from Labscan, Ireland. Deuterated chloroform and ethylene di(*p*-toluenesulfonate) were purchased from Aldrich, Germany. All chemicals were used as received.

Instruments and equipment

Melting points were measured by a YANACO micro melting point apparatus. Fourier transform infrared spectra (FTIR) were recorded by a HORIBA FT-720 infrared spectrophotometer in the range 4000–400 cm^{-1} at a resolution of 4 cm^{-1}. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were obtained from a Varian Mercury-400BB spectrometer. Mass spectra were analyzed by a PerSeptive Biosystems/Vestec matrix-assisted laser desorption ionization time-of-flight mass spectrometer (MALDI-TOF MS) or a JEOL JMS-HX100 fast atom bombardment mass spectrometer (FAB-MS). Elemental analysis was carried out using a YANACO CHN Corder MT-5. Single crystal X-ray analysis was done by using a Rigaku RAXIS-RAPID imaging-plate diffractometer and the CrystalStructure3.8 crystallographic software package.

Syntheses

HBA derivatives (**1-2**)

N,N-Bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **1**, and *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)cyclohexylamine, **2**, were prepared from 3,4-dihydro-3,6,8-trimethyl-2H-1,3-benzoxazine and 3,4-dihydro-6,8-dimethyl-3-cyclohexyl-2H-1,3-benzoxazine, respectively, via the ring-opening reaction with 2,4-dimethyl phenol [16, 18].

[1+1] Macrocycles (**3-6**)

[1+1] Macrocycles (**3-6**) were obtained by the etherification of **1** with ditosylated derivatives as follows.

1,3-Bis(tosyloxy)propane (0.385 g, 1 mmol) was dropwisely added into the solution of **1** (0.299 g, 1 mmol) with sodium hydroxide (0.084 g, 2.1 mmol) in acetonitrile (150 mL) and refluxed at 105 °C for 3 days. The solvent was removed to obtain the crude product, **3**, which was recrystallized in a mixed solvent of isopropanol and chloroform (2:1, v/v). The single crystals were characterized by X-ray single crystal analysis [19]. Similarly, **4**, **5**, and **6** were prepared by using the same procedures as **3** [20-21]. However, 1,4-bis(tosyloxy)butane (0.398 g, 1 mmol), ditosylated diethylene glycol (0.414 g, 1 mmol), and ditosylated triethylene glycol (0.458 g, 1 mmol) were used instead of 1,3-bis(tosyloxy)propane (0.385 g, 1 mmol) to obtain **4**, **5**, and **6**, respectively. The products were analyzed by FTIR, ^{1}H- NMR, MALDI-TOF MS, EA, and X-ray single crystal analysis.

3: 80% yield; mp = 124.5 °C; FTIR (KBr, cm^{-1}): 1480 (vs, tri-substituted benzene), 1213 (vs, C-N stretching), 1053 (s, C-O-C); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ_H 1.94 (3H, s, N-**CH$_3$**), 2.11 (2H, t, CH_2-**CH$_2$**-CH_2), 2.25 (12H, s, Ar-**CH$_3$**), 3.62 (4H, s, Ar-**CH$_2$**-N), 4.11 (4H, t, Ar-O-**CH$_2$**), 6.79 (2H, s, Ar-**H**), 6.91 (2H, s, Ar-**H**). MALDI-TOF MS: m/z 340.23 ($M+H^+$); Anal. Calcd for $C_{22}H_{29}NO_2$: C: 77.84, H:

8.61, N: 4.13, O: 9.42%. Found: C: 77.63, H: 8.40, N: 4.12%. Crystal data for **3**: $C_{22}H_{29}NO_2$, M = 339.48, triclinic, a = 9.2230(3) Å, b = 10.2768(3) Å, c = 11.4606(4) Å, α = 111.6953(10)°, β = 95.7124(11)°, γ = 99.7462(10)°, V = 979.04(5) Å^3, T = 296 K, space group $P\bar{1}$ (no.2), Z = 2, $\mu(M_oK_\alpha)$ = 0.726 cm^{-1}, 3491 reflections measured, 599 unique (R_{int} = 0.025) which were used in all calculations. The final $R1$ = 0.0336 and $wR2$ = 0.0999.

4: 76% yield; mp = 172.8 °C; FTIR (KBr, cm^{-1}): 1481 (vs, tri-substituted benzene), 1213 (vs, C-N stretching), 1076 (vs, C-O-C); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ_H 1.96 (3H, s, N-**CH$_3$**), 2.00 (4H, t, O-CH$_2$-**CH$_2$**), 2.25 (12H, s, Ar-**CH$_3$**), 3.55 (4H, s, Ar-**CH$_2$**-N), 4.01 (4H, t, O-**CH$_2$**-CH$_2$), 6.85 (2H, s, Ar-**H**), 6.92 (2H, s, Ar-**H**). MALDI-TOF MS: m/z 354.13 (M+H$^+$); Anal. Calcd for $C_{23}H_{31}NO_2$: C: 78.15, H: 8.84, N: 3.96, O: 9.05%. Found: C: 77.35, H: 8.82, N: 3.88%. Crystal data for **4**: $C_{23}H_{31}NO_2$, M = 353.50, monoclinic, a = 8.8186(3) Å, b = 8.9144(3) Å, c = 12.8234(4) Å, β = 92.9630(17)°, V = 1006.73(5) Å^3, T = 213 K, space group $P2_1$ (no.4), Z = 2, $\mu(CuK_\alpha)$= 5.708 cm^{-1}, 10556 reflections measured, 3577 unique (R_{int} = 0.068) which were used in all calculations. The final $R1$ = 0.1097 and $wR2$ = 0.3422.

5: 70% yield; mp 90.8 °C; FTIR (KBr, cm^{-1}): 1481 (vs, tri-substituted benzene), 1221 (vs, C-N stretching), 1053 (s, C-O-C); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ_H 2.10 (3H, s, N-**CH$_3$**), 2.30 (12H, s, Ar-**CH$_3$**), 3.79 (4H, s, Ar-**CH$_2$**-N), 3.95 (4H, t, **CH$_2$**-O-**CH$_2$**), 4.07 (4H, t, Ar-O-**CH$_2$**), 6.84 (2H, s, Ar-**H**), 6.93 (2H, s, Ar-**H**). MALDI-TOF MS: m/z 370.32 (M+H$^+$); Anal. Calcd for $C_{23}H_{31}NO_3$: C: 74.47, H: 8.40, N: 3.79, O: 13.34%. Found: C: 74.47, H: 8.41, N: 3.87%.

6: 80% yield; mp = 99.2 °C; FTIR (KBr, cm^{-1}): 1489 (vs, tri-substituted benzene), 1209 (vs, C-N stretching), 1057 (s, C-O-C); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ_H 2.17 (3H, s, N-**CH$_3$**), 2.24 (12H, s, Ar-**CH$_3$**), 3.71 (4H, s, Ar-**CH$_2$**-N), 3.80-3.83 (8H, m, **CH$_2$**-O-**CH$_2$**), 3.97 (t, 4H, Ar-O-**CH$_2$**), 6.84 (2H, s, Ar-**H**), 7.12 (2H, s, Ar-**H**). MALDI-TOF MS: m/z 414.26 (M+H$^+$); Anal. Calcd for $C_{25}H_{35}NO_4$: C: 72.61, H: 8.53, N: 3.39, O: 15.47%. Found: C: 72.41, H: 8.38, N: 3.38%. Crystal data

for **6**: $C_{25}H_{35}NO_4$, M = 413.56, orthorhombic, a = 18.0895(4) Å, b = 8.9394(2) Å, c = 14.4691(3) Å, V = 2339.79(9) Å^3, T = 296K, space group $Pna2_1$ (no.33), Z = 4, $\mu(M_oK_\alpha)$ = 0.783 cm^{-1}, 7677 reflections measured, 388 unique (R_{int} = 0.019) which were used in all calculations. The final $R1$ = 0.0290 and $wR2$ = 0.0804.

[2+2] Macrocycles (**7-8**)

[2+2] Macrocycles (**7-8**) were prepared from the same procedures as **3** and **4**, respectively, but using **2** (0.271 g, 1 mmol) instead of **1** (0.299 g, 1 mmol) as the starting compound. The crude product was recrystallized by the mixed solvent of isopropanol and chloroform (3:2, v/v).

7: 68% yield; mp = 206.5 °C; FTIR (KBr, cm^{-1}): 1481 (vs, tri-substituted benzene), 1209 (vs, C-N stretching), 1056 (s, C-O-C); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ_H 1.26 (4H, m, **CH$_2$**), 1.90 (4H, m, CH$_2$-**CH$_2$**-CH$_2$), 2.20-2.27 ((24H, s, Ar-**CH$_3$**), and (16H, m, **CH$_2$**)), 2.44 (2H, m, **CH**), 3.66 (8H, s, Ar-**CH$_2$**-N), 3.88 (8H, t, Ar-O-**CH$_2$**), 6.82 (4H, s, Ar-**H**), 7.33 (4H, s, Ar-**H**). FAB-MS: m/z 408.4 (M+H$^+$); Anal. Calcd for $C_{54}H_{74}N_2O_4$: C: 79.56, H: 9.15, N: 3.44, O: 7.85%. Found C: 77.27, H: 9.01, N: 3.99%. Crystal data for **7**: $C_{54}H_{74}N_2O_4$, M = 815.19, triclinic, a = 9.8551(3) Å, b = 9.8809(4) Å, c = 13.7754(4) Å, α = 90.004(2)°, β = 99.8559(18)°, γ = 115.8896(16)°, V = 1184.74(7) Å^3, T = 213 K, space group $P\bar{1}$ (no.2), Z = 1, $\mu(CuK_\alpha)$ = 5.464 cm^{-1}, 12516 reflections measured, 4229 unique (R_{int} = 0.102) which were used in all calculations. The final $R1$ = 0.1297 and $wR2$ = 0.4090.

8: 65% yield; mp = 219.9 °C; FTIR (KBr, cm^{-1}): 1473 (s, tri-substituted benzene), 1209 (vs, C-N stretching), 1051 (s, C-O-C); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ_H 1.97 (4H, m, **CH$_2$**), 2.01 (8H, m, O-CH$_2$-**CH$_2$**), 2.22-2.34 ((24H, s, Ar-**CH$_3$**), and (16H, m, **CH$_2$**)), 2.46 (2H, m, **CH**), 3.56 (8H, s, Ar-**CH$_2$**-N), 4.02 (8H, m, O-**CH$_2$**-CH$_2$), 6.85 (4H, s, Ar-**H**), 6.92 (4H, s, Ar-**H**). MALDI-TOF MS: m/z 844.55 (M+H$^+$); Anal. Calcd for $C_{56}H_{78}N_2O_4$: C: 79.76, H: 9.32, N: 3.32, O: 7.59%. Found C: 77.27, H: 9.03, N: 3.39%. Crystal data for **8**: $C_{56}H_{78}N_2O_4$, M = 843.24, triclinic, a

= 10.1109(5) Å, b = 11.2701(5) Å, c = 11.9581(6) Å, α = 104.883(3)°, β = 90.099(3)°, γ = 109.335(3)°, V = 1237.01(10) Å^3, T = 213 K, space group $P\bar{1}$ (no.2), Z = 1, μ(CuK$_\alpha$) = 5.381 cm^{-1}, 12796 reflections measured, 4399 unique (R_{int} = 0.089) which were used in all calculations. The final $R1$ = 0.1060 and $wR2$ = 0.2719.

Compound **9**

Compound **9** was achieved by using the same procedures as **7**, but using ditosylated diethylene glycol (0.414 g, 1 mmol) instead of 1,3-bis(tosyloxy)propane (0.385 g, 1 mmol) as the starting compound.

9: 90% yield; mp = 225 °C; FTIR (KBr, cm^{-1}): 3312 (w, -NH-), 1484 (vs, tri-substituted benzene), 1364 (s, O=S=O), 1221 (s, C-N stretching), 1177 (vs, O=S=O); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ_H 0.70 (4H, m, **CH$_2$**), 0.95 (4H, m, **CH$_2$**), 1.15 (2H, m, **CH$_2$**), 1.68 (2H, m, **CH$_2$**), 2.20 (3H, s, Ar-**CH$_3$**), 2.32 (3H, s, Ar-**CH$_3$**), 2.38 (3H, s, S-Ar-**CH$_3$**), 2.69 (1H, m, **CH**), 3.52 (2H, t, CH$_2$-**CH$_2$**-O), 3.88 (2H, s, Ar-**CH$_2$**-N), 4.02 (2H, t, S-O-**CH$_2$**), 6.72 (1H, s, Ar-**H**), 6.85 (1H, s, Ar-**H**), 7.18 (2H, d, S-Ar-**H**), 7.30 (2H, d, S-Ar-**H**), 7.70 (4H, m, S-Ar-**H**). FAB-MS: m/z 234.2; Anal. Calcd for $C_{22}H_{31}NSO_4$: C: 65.15, H: 7.70, N: 3.45, O: 15.78, S: 7.91%. Found C: 64.74, H: 7.69, N: 3.36, S: 7.05%. Crystal data for **9**: $C_{22}H_{31}NSO_4$, M = 405.55, monoclinic, a = 25.1142(6) Å, b = 10.0918(3) Å, c = 16.3733(4) Å, β = 94.3394(15)°, V = 4137.88(17) Å^3, T = 123 K, space group $C2/c$ (no.15), Z = 8, μ(CuK$_\alpha$) = 16.164 cm^{-1}, 20057 reflections measured, 3777 unique (R_{int} = 0.104) which were used in all calculations. The final $R1$ = 0.0885 and $wR2$ = 0.2845.

[1+1] Macrocycle, **10**

[1+1] Macrocycle, **10** was achieved by using the same procedures as **6**, but using **2** (0.367 g, 1 mmol) instead of **1** (0.299 g, 1 mmol) as the starting compound. The crude product was recrystallized by the mixed solvent of isopropanol and chloroform (3:2, v/v).

10: 79% yield; mp = 117.5 °C; FTIR (KBr, cm^{-1}): 1479 (s, tri-substituted benzene), 1209 (vs, C-N stretching), 1058 (s, C-O-C); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ_H 1.12 (2H, m, **CH_2**), 1.36 (2H, m, **CH_2**), 1.58 (2H, m, **CH_2**), 1.75 (2H, m, **CH_2**), 1.98 (2H, m, **CH_2**), 2.22 (6H, s, Ar-**CH_3**), 2.26 (6H, s, Ar-**CH_3**), 2.44 (1H, m, **CH**), 3.75 (4H, s, Ar-O-CH_2-CH_2-O-**CH_2**), 3.78 (4H, s, Ar-**CH_2**-N), 3.82 (4H, m, Ar-O-CH_2-**CH_2**), 3.92 (4H, m, Ar-O-**CH_2**), 6.79 (2H, s, Ar-**H**), 7.25 (2H, s, Ar-**H**). MALDI-TOF MS: m/z 483.21 ($M+H^+$); Anal. Calcd for $C_{30}H_{43}NO_4$: C: 74.81, H: 9.00, N: 2.91, O: 13.29%. Found C: 71.23, H: 8.57, N: 4.28%. Crystal data for **10**: $C_{30}H_{43}NO_4$, M = 481.67, triclinic, a = 10.2934(5) Å, b = 11.0830(5) Å, c = 13.8177(6) Å, α = 70.900(3)°, β = 79.973(3)°, γ = 74.412(3)°, V = 1428.34(11) $Å^3$, T = 273 K, space group $P\bar{1}$ (no.2), Z = 2, μ(CuK_α) = 5.771 cm^{-1}, 14840 reflections measured, 5091 unique (R_{int} = 0.392) which were used in all calculations. The final $R1$ = 0.1699 and $wR2$ = 0.5297.

Results and discussion

Structural Characterization

In order to initiate a nucleophilic reaction between the phenol and tosyl groups, an excess amount of base, i.e. NaOH (2.1 mmol), was added. Compound **1** provides various possible products, i.e. **3a**, **3b**, **3c**, and **3d**, when it was reacted with 1,3-bis(tosyloxy)propane (Scheme 4.2). Compound **1** showed the broad peak of the hydroxyl group and the C-N stretching at 3399 and 1243 cm^{-1} [16]. In the case of **3**, the FTIR spectrum shows the disappearance of the hydroxyl group at 3300-3500 cm^{-1}, the peak shift of C-N stretching to 1213 cm^{-1}, referring to the change in vibrational mode, and the new ether peak at 1053 cm^{-1}, implying successful etherification (Figure 4.1a). The ^{1}H-NMR spectrum, as shown in Figure 4.1b, indicates the chemical shift of the methylene protons of CH_2-**CH_2**-CH_2 and O-**CH_2**-CH_2 at 2.11 and 4.11, respectively. This shows that the etherification occurred at two hydroxyl groups of **1**. Figure 4.1c shows the parent peak ($M+H^+$) at m/z = 340.23, belonging to **3c**. The elemental analysis result also confirms the proposed structure of **3c**. All

results indicate that the reaction of **1** with 1,3-bis(tosyloxy)propane gives only [1+1] macrocycle, **3c**, in high yield (80%) after recrystallization. It is possible that other 20% yields were by-products, as shown in Scheme 4.2. The fact that the [1+1] compound obtained did not show any minor peaks belonging to the by-products, in both the NMR and the MALDI-TOF MS spectra, and the calculated data were equal to that of the found data in EA, including the same single crystal results even though we randomly used different crystals. This implies that the reaction yielded a single type of cyclic product with some unreacted species.

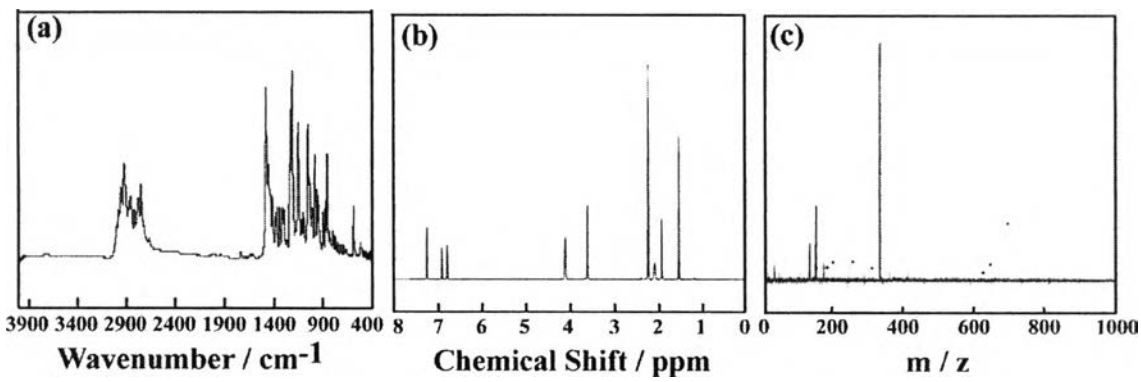
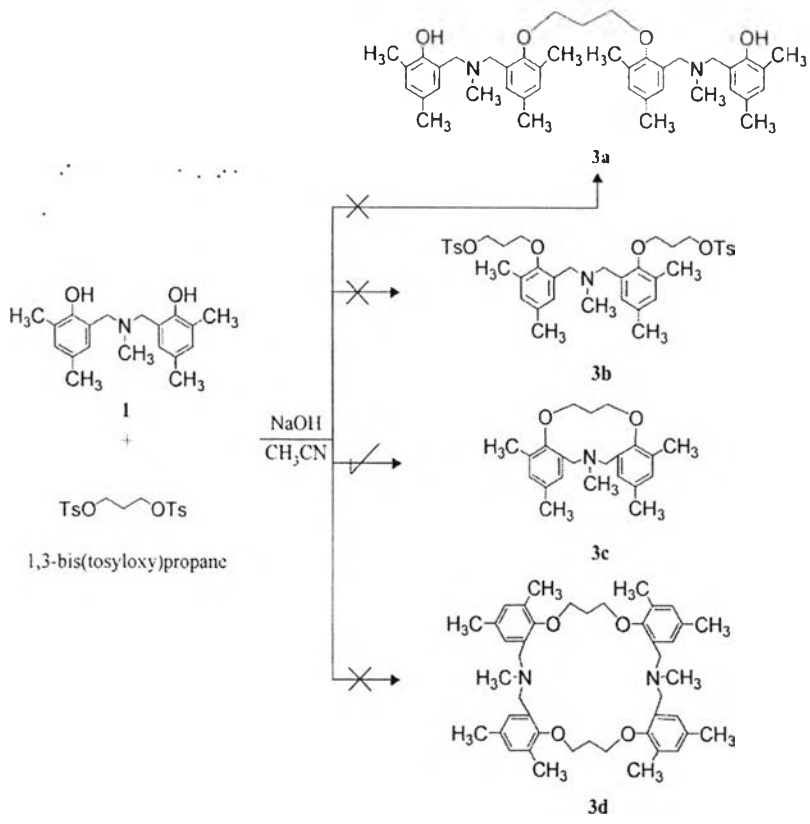


Figure 4.1 Structural characterization of **3c**; (a) FTIR spectrum, (b) ^{1}H NMR spectrum, and (c) MALDI-TOF mass spectrum.

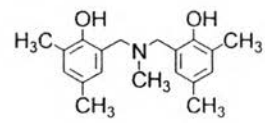
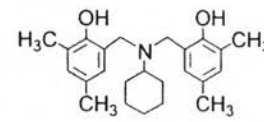
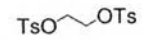
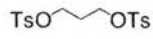
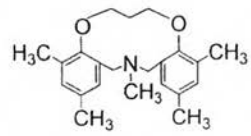
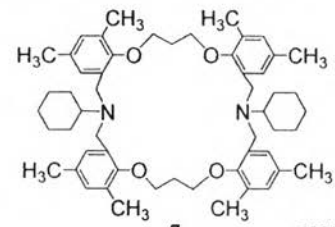
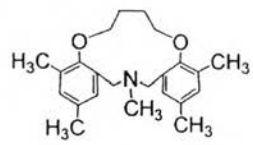
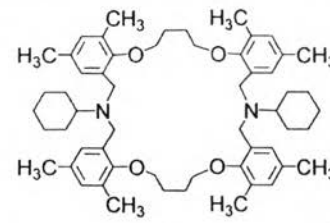
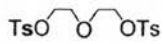
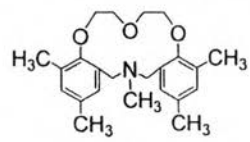
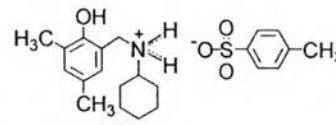
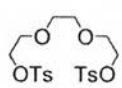
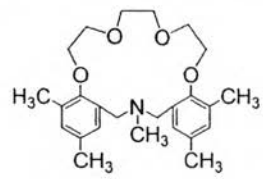
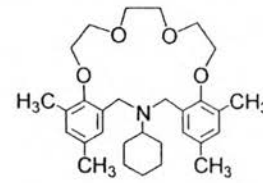
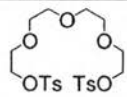
In order to identify how the reaction provides the [1+1] macrocycle, various chain lengths of ditosylated compounds were used. When **1** was reacted with four, five, or eight atomic chain lengths of the ditosylated compound, the reaction gives a single type of [1+1] cyclic compounds, i.e. **4**, **5**, and **6**, respectively (Table 4.1). This suggests that [1+1] macrocyclization is selectively derived from the structure of **1** itself rather than from the chain lengths of the ditosylated compounds. In order to confirm the structure of HBA inducing the selective macrocyclization, **2** was used instead of **1**. Actually, the reaction of **2** was done under the same procedures as in the cases of **1**. However, [2+2] macrocycles, (**7**-**8**), were obtained when **2** was reacted with three or four atomic chain lengths of the ditosylated compound (Table 4.1). In addition, Table 4.1 demonstrates that [1+1] macrocycle, **10**, was achieved by the reaction of **2** with eight ditosylated chain lengths. This implies that **2**, the structure of

which consists of a bulky group at N atom, provides both types of macrocycles, i.e. [1+1] and [2+2] macrocycles. Inevitably, the result from the single crystal analysis shows that compound **9** was obtained by the reaction of **2** with five ditosylated chain lengths (Figure 4.2f). This implies unsuccessful macrocyclization. Combining the results of **1** and **2**, we may conclude that the structure of HBA induces selective macrocyclization to obtain either [1+1] or [2+2] macrocycle (*See a further discussion in Effect of HBA derivatives to Selective Macrocyclization*). Although the macrocyclization of HBA derivatives with three, four, five, or eight atomic chain lengths of the ditosylated compounds was successful, that of HBA derivatives with two or eleven atomic chain lengths of the ditosylated compounds was not successful (Table 4.1). This might be because (i) the preparation conditions are not suitable for these cases and (ii) the chain lengths of the ditosylated compounds are too short or too long for macrocyclization.



Scheme 4.2 Feasible products of reaction of **1** and 1,3-bis(tosyloxy)propane.

Table 4.1 Products obtained when **1** or **2** reacts with various ditosylated chain lengths

HBA / Ditosylated compound	 **1**	 **2**
 **ethylene di(*p*-toluene sulfonate)** **atomic chain lengths = 2**	no cyclization	no cyclization
 **1,3-bis(tosyloxy) propane** **atomic chain lengths = 3**	 **3** **80% yield**	 **7** **68% yield**
 **1,4-bis(tosyloxy) butane** **atomic chain lengths = 4**	 **4** **76% yield**	 **8** **65% yield**
 **ditosylated diethylene glycol** **atomic chain lengths = 5**	 **5** **70% yield**	 **9** **90% yield**
 **ditosylated triethylene glycol** **atomic chain lengths = 8**	 **6** **80% yield**	 **10** **79% yield**
 **ditosylated tetraethylene glycol** **atomic chain lengths = 11**	no cyclization	no cyclization

Single Crystal Analysis

In order to identify the macrocyclic structure, single crystallographic analysis was applied. The single crystals of products derived from **1** or **2** were obtained by slowly cooling over a few days at room temperature under the mixed solvent of isopropanol and chloroform with 2:1 or 3:2 v/v, respectively. For the reaction of **1** with the ditosylated compound, the single crystallographic analysis reveals that cyclic compounds (**3**, **4**, and **6**) consist of one molecule of **1** linked with one molecule of ditosylated compound to be a single type of [1+1] macrocycle (Figure 4.2). Macrocycles **3**, **4**, and **6** are the 12-, 13-, and 17-membered ring, respectively, (Figure 4.2(a-c)). Even though all macrocycles are [1+1] cyclic compounds, their crystal systems are different. The structure of **3** is triclinic, space group $P\bar{1}$ (no.2); that of **4** is monoclinic, space group $P2_1$ (no.4); and that of **6** is orthorhombic, space group $Pna2_1$ (no.33). For the reaction of **2** with the ditosylated compound, the single crystallographic analysis demonstrates that **7** and **8** consist of two molecules of **2** linked with two molecules of ditosylated oxyalkane to form [2+2] macrocycles (Figure 4.2(d-e)), whereas **10** contains one molecule of **2** linked with one molecule of ditosylated triethylene glycol to form the [1+1] macrocycle (Figure 4.2g). All macrocyclic compounds are triclinic, space group $P\bar{1}$ (no.2). This suggests that the reaction of **2** with three, four, or eight ditosylated chain lengths provides both types of macrocycles, i.e. [1+1] and [2+2] macrocycles. In the case of the reaction of **2** with ditosylated diethylene glycol, the crystallographic data identify that **9** forms the combination of a fragment of **2** and the ditosylated group of ditosylated diethylene glycol under ionic bond (Figure 4.2f). This implies that the macrocyclization of **2** with five atomic chain lengths of the ditosylated compound under the presence of NaOH in acetonitrile was not successful.

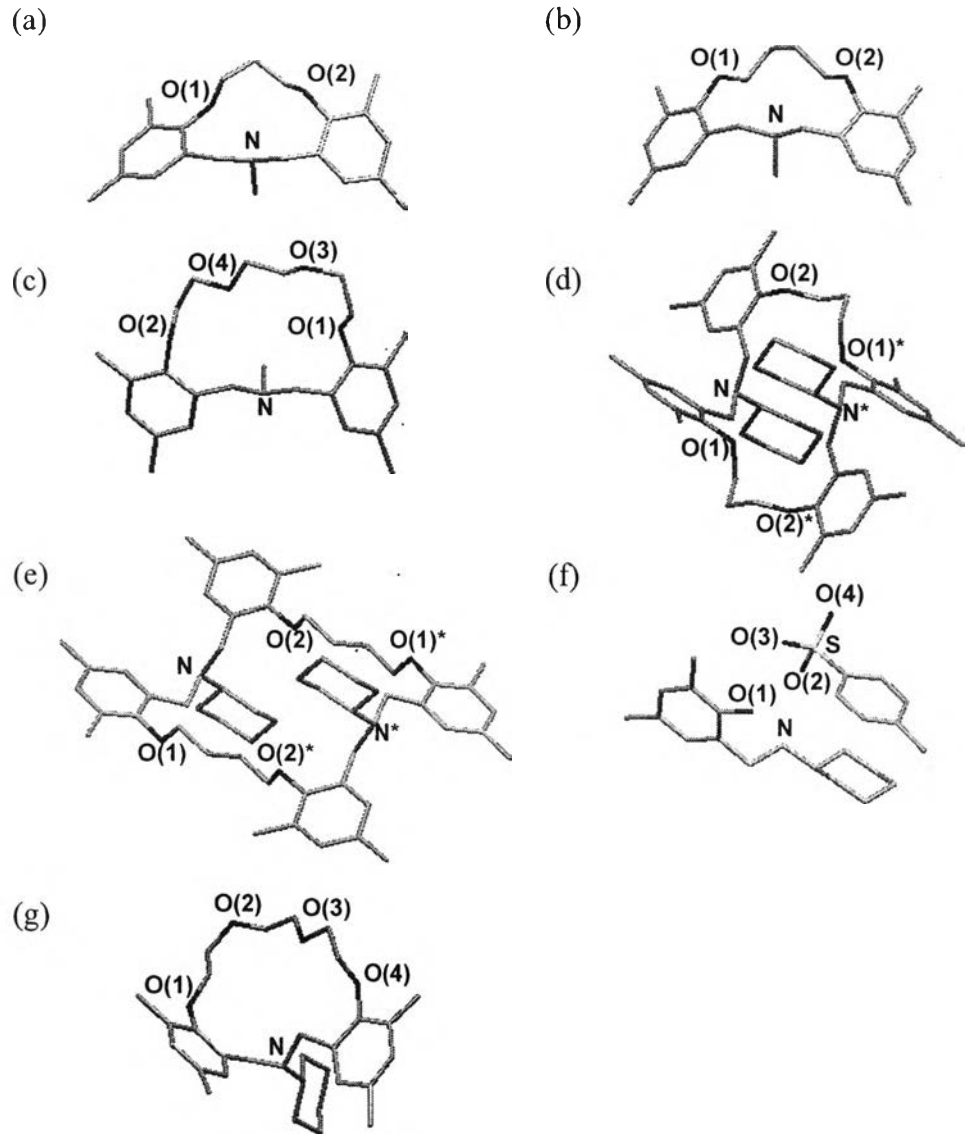


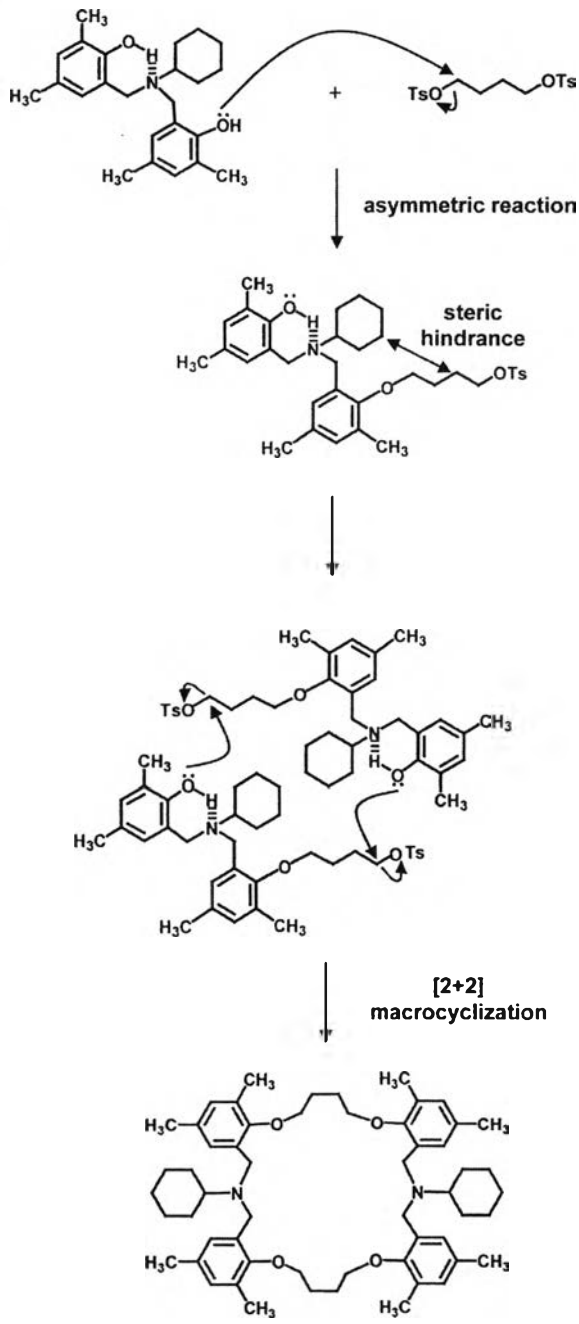
Figure 4.2 Crystal structures of (a) **3**, (b) **4**, (c) **6**, (d) **7**, (e) **8**, (f) **9**, and (g) **10**.

Effect of HBA derivatives to Selective Macrocyclization

To study the selective macrocyclization of the HBA derivative systematically, we control the basic structure of HBA by using a phenol derivative with methyl substitutional group at ortho and para position, but varying the substitutional group at N atom. Here, we chose **1** and **2**, of which the substitutional group at N atom is methyl and cyclohexyl groups, respectively, as representative compounds for the study. Table 4.1 shows that **1** gives only [1+1] macrocycles (**3-6**), even though it was

reacted with three, four, five, or eight ditosylated chain lengths. This implies that the chain lengths of the ditosylated compound are not the factor to induce the selective macrocyclization. In other words, the structure of HBA itself controls the reaction to provide only a single type of macrocycle. Based on the previous report, we infer that the [1+1] macrocyclization may be carried out via the synergistic effects of the alkoxide metal template and the hydrogen bonded HBA [17]. In addition, Table 4.1 demonstrates that **2** gives both [1+1] and [2+2] macrocycles. For example, the reaction of **2** with three or four ditosylated chain lengths gives [2+2] macrocycle, (**7-8**), whereas [1+1] macrocycle, **10**, was obtained in the case of eight ditosylated chain lengths. Although it is difficult to prove how the reaction gives [1+1] or [2+2] cyclic compounds, since there are no intermediates during the one pot reaction, we speculate that the reaction between **2** and short chain lengths of the ditosylated compound prefers to form [2+2] macrocycles due to the combined effects of i) the bulkiness of the cyclohexyl group and ii) the shortness and stiffness of the ditosylated chain leading to the obstruction of [1+1] macrocyclization. Additionally, our group already reported the unique structures of the inter- and intramolecular hydrogen bond network of HBA causing the asymmetric reaction [13-14]. Taking this into consideration, we suspect that only one hydroxyl group of HBA was conjugated with the ditosylated compound, whereas another hydroxyl group was still maintained under the intramolecular hydrogen bond, leading to intermediate compounds, as shown in Scheme 4.3. Consequently, two intermediate compounds were reacted together to form [2+2] macrocycles (**7-8**). On the other hand, in the case of **10**, [1+1] macrocyclization was carried out. This might be because the appropriate chain lengths, i.e. eight atomic chain lengths, together with four oxygen atoms of the ditosylated compound, provide a flexible chain to exactly match one molecule of **2** and one molecule of the ditosylated compound, leading to the [1+1] macrocyclization (Figure 4.2g). It should be noted that when the ditosylated compound has five atomic chain lengths, the cyclization was not accomplished, as seen in the case of **9** (Table 4.1). Although the outcome makes us curious about how this happened, one possible explanation is that the five ditosylated chain lengths is flexible but too short for the [1+1] macrocyclization of **2.** Therefore, the structure of macrocycle might be distorted, resulting in cleavage of the macrocycle and finally

giving the final product of **9** (Figure 4.2f). Combining the results derived from **1** and **2**, we identify that both types, [1+1] and [2+2] macrocycles, were controlled by the structure of HBA. For HBA consisting of a methyl group at ortho and para position, and at N atom, the reaction gives only the [1+1] macrocycle. For HBA with the methyl group at ortho and para position, but a cyclohexyl group at N atom, the reaction gives both [1+1] and [2+2] macrocycles.



Scheme 4.3 Proposed mechanism of [2+2] macrocyclization.

Conclusions

The present work presents the achievement of the selective crown ether based macrocyclization of HBA with ditosylated compounds to obtain selective macrocycles in high yield via a simple reaction. The structure of HBA is the key factor to induce selective macrocycles. An understanding of the effect of the substituted group of HBA on the selective macrocyclization will help in molecular design to obtain the as-desired macrocycle.

Acknowledgements

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