CHAPTER III
[1+1] AND [2+2] CROWN ETHERS DERIVED FROM *N,N*-BIS(2-HYDROXYALKYLBENZYL)ALKYLAMINE AND THEIR INCLUSION PHENOMENA WITH METAL IONS

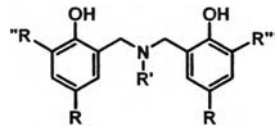
Abstract

N,N-Bis(2-hydroxyalkylbenzyl)alkylamine (HBA) is a derivative obtained from a single time ring opening of benzoxazines. For HBA with methyl group at ortho and para positions, and at N atom, the reaction between this derivative and ditosylated compound gives [1+1] dibenzo-monoaza-crowns. For HBA without methyl group at ortho position, the compound gives [2+2] macrocyclic ethers. The studies on inclusion phenomena using Pedersen's and molar ratio techniques clarify the alkali metal ion guest inclusion to be 2:1 for [2+2] and 5:2 for [1+1] macrocycles.

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

Introduction

For the past few decades, crown ethers and their various derivatives have been well-known macrocyclic host compounds showing the inclusion properties with metal ions [1-3]. In general, macrocyclization needs the dilute condition with or without using a template [4-5]. Previously, our group has been carrying out a series of ring opening of benzoxazine monomers prepared from substituted phenols to find that the reaction tends to self-terminate and gives the substituted benzoxazine ring opening products, i.e., *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine (HBA) (Chart 3.1) after a single ring opening [6-8]. These derivatives consist of two phenol units linked with aza-methylene linkage under the strong networks of inter- and intramolecular hydrogen bonds.



1: R = CH_3, R' = CH_3, R" = CH_3
2: R = CH_3, R' = CH_3, R" = H

Chart 3.1 Chemical structure of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine (HBA) derivatives.

Recently, based on the structure of these derivatives, we succeeded in the preparation of a series of simple selective and effective macrocyclization. For example, we carried out the preparation of [2+2] macrocycles via HBA with para-substitional group [9-10]. These macrocycles performed inclusion phenomena with alkali ions at the different host-guest stoichiometric ratios depending on the type of metal ion. It is important to note that the ortho-substituted group of phenol might play an important role in macrocyclization.

The present work, thus, focuses on an investigation of ortho-substituted group in phenol unit belonging to HBA in macrocyclization. Here, we chose a series of HBA with and without methyl group at ortho position as representative compounds. Furthermore, we investigate the inclusion phenomena of these macrocycles with alkali ions.

Experimental

Chemicals

Paraformaldehyde, methylamine, 2,4-dimethylphenol, *p*-cresol, sodium sulfate anhydrous, diethylene glycol, triethylene glycol ditosylated, and *p*-toluenesulfonyl chloride were purchased from Fluka, Switzerland. Sodium hydroxide and isopropanol were obtained from Carlo Erba, Italy. Diethyl ether, 1,4-dioxane, acetonitrile, ethanol, chloroform, and dichloromethane were provided from Labscan, Ireland. Deuterated chloroform was purchased from Aldrich, Germany. All chemicals were used as received.

Instruments

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 4 cm^{-1}. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were obtained from a Varian Mercury-400BB spectrometer. Mass spectroscopy was analyzed by a PerSeptive. Biosystems/Vestec matrix-assisted laser desorption ionization time-of-flight mass spectrometer (MALDI-TOF MS) and a micrOTOF electrospray ionization mass spectrometer (ESI-MS). Elemental analysis was carried out by using a YANACO CHN Corder MT-5. Single crystal X-ray analysis was done by using a Rigaku RAXIS-RAPID imaging-plate diffractometer and CrystalStructure crystallographic software.

Syntheses

HBA derivatives

N,N-Bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **1**, and *N,N*-bis(2-hydroxy-5-methylbenzyl)methylamine, **2** were prepared from 3,4-dihydro-3,6,8-trimethyl-2H-1,3-benzoxazine and 3,4-dihydro-3,6-dimethyl-2H-1,3-benzoxazine, respectively, via the ring-opening reaction with 2,4-dimethyl phenol [8, 11].

[1+1] Macrocycles

Dibenzo-monoaza-17-crown-5, **3**, and dibenzo-monoaza-14-crown-4, **4** were accomplished by etherification between **1** and ditosylated derivatives as follows.

Ditosylated triethylene glycol (0.458 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 of **3**. The crude product was recrystallized in a mixed

solvents of isopropanol and chloroform (2:1, v/v). The single crystals were characterized by X-ray single crystal analysis [12]. Similarly, **4** was carried out by using the same procedures as **3**. However, ditosylated diethylene glycol (0.414 g, 1 mmol) was used instead of ditosylated triethylene glycol (0.458 g, 1 mmol).

3: 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), 3.95-3.99 (m, 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 **3**: $C_{25}H_{35}NO_4$, 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. X-ray data for **3** has been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 671195. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/ retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

4: 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, J_1 = 3.52 Hz), 4.07 (4H, t, Ar-O-CH_2, J_1 = 3.52 Hz), 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%

[2+2] Macrocycles

[2+2] Difunctional 34-membered macrocyclic ethers, **5** was obtained by using the same procedures as **3**, but using **2** (0.271 g, 1 mmol) instead of **1** (0.299 g, 1 mmol) as the starting compound. For [2+2] Difunctional 28-membered macrocyclic ethers, **6**, the macrocycle was carried out as reported previously [10].

5: 78% yield; mp 206.5 °C; FTIR (KBr, cm^{-1}): 1484 (vs, tri-substituted benzene), 1223 (vs, C-N stretching), 1058 (s, C-O-C); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ_H 2.21 (6H, s, N-CH_3), 2.29 (12H, s, Ar-CH_3), 3.58 (8H, s, Ar-CH_2-N), 3.69 (8H, s, Ar-O-CH_2-CH_2-O-CH_2), 3.82 (8H, t, Ar-O-CH_2-CH_2, J_1 = 4.68 Hz), 4.07 (8H, t, Ar-O-CH_2, J_1 = 4.68 Hz), 6.69 (4H, d, Ar-H, J_2 = 7.53 Hz), 6.95 (4H, d, Ar-H, J_2 = 7.53 Hz), 7.24 (4H, s, Ar-H). MALDI-TOF MS: m/z 771.30 ($M+H^+$). Anal. Calcd for $C_{46}H_{62}N_2O_8$: C, 71.66; H, 8.11; N, 3.63; O, 16.60%. Found: C, 71.69; H, 8.05; N, 3.64%.

6: 85% yield; mp 185 °C; FTIR (KBr, cm^{-1}): 1504 (vs, tri-substituted 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, Ar-CH_3), 3.59 (8H, s, Ar-CH_2-N), 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; N, 4.11; O, 14.08%. Found: C, 73.86; H, 7.93; N, 4.07%.

Metal Ion Extraction and Host-Guest Ratio

Metal ion extraction was studied by Pedersen's technique [1-2]. Alkali metal picrate aqueous solutions (sodium picrate, potassium picrate, and cesium picrate) were prepared at the concentration of $7x10^{-5}$ M. An equimolar concentration of **3** in chloroform was prepared and mixed with 5 ml of picrate salt aqueous solution. The solution was vigorously shaken for 1 min and left for 30 min. The picrate salt concentration in aqueous phase was determined by a Perkin Elmer UV-Vis

spectrophotometer Lambda 16 at 356 nm and the extraction percentage was calculated as eq. 1.

$$\text{Extraction percentage} = (A_0\text{-}A)/A_0 \times 100 \qquad \text{(eq. 1)}$$

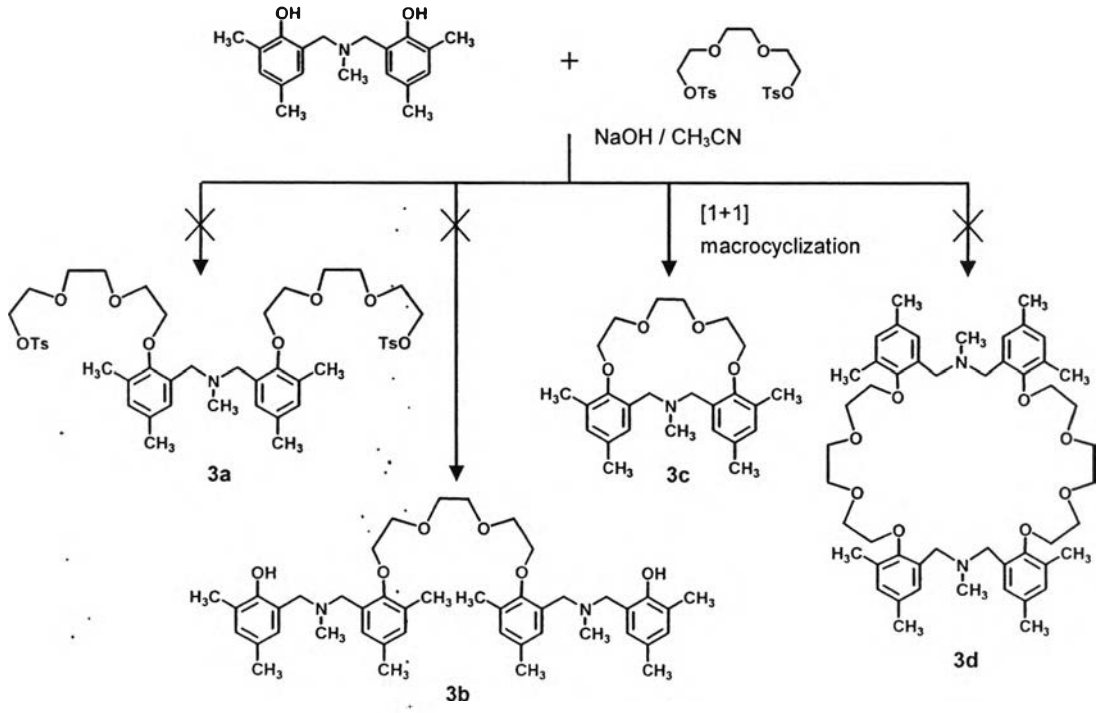
In order to verify the host-guest ratio, the molar ratio method was studied [13]. The molar ratios of **3**:sodium picrate in ethanol solution (with a constant sodium picrate concentration at 5.32×10^{-5} M) are varied from 0 to 6. The absorbance of the mixture at maximum wavelengths as a function of molar ratios of the mixture was plotted.

Results and discussion

Simple, Selective, and Effective Macrocyclization

The reaction of **1** with ditosylated triethylene glycol provides various possible products ((**3a**)-(**3d**)), as shown in Scheme 3.1. Compound **1** showed the broad peak of hydroxyl group and the C-N stretching at 3399 and 1243 cm^{-1} [8]. In the case of **3**, the FTIR spectrum showed the disappearance of the hydroxyl group at 3300-3500 cm^{-1}, the peak shift of C-N stretching to 1209 cm^{-1} referring to the change in vibrational mode, and the new ether peak at 1057 cm^{-1}. This implies the successful etherification. The ^{1}H-NMR spectrum showed the chemical shifts at 3.80-3.83, and 3.97 for methylene protons of CH_2-O-CH_2 and Ar-O-CH_2, respectively. The results indicate the etherification occurred at two hydroxyl groups of **1**. Moreover, ESI-MS and MALDI-TOF MS result showed the parent peak ($M+H^+$) at m/z = 414.26. This leads to the answer that the compound obtained is **3c** of which the structure consists of a molecule of **1** and a molecule of ditosylated triethylene glycol. The elemental analysis result also confirmed the proposed structure of **3c**. All results indicate that the preparation conditions gave **3c** in high yield (80%) with high purity after recrystallization. Other 20% yields were probable by-products as shown in Scheme 3.1. Since the results of [1+1] compound obtained from both ^{1}H-NMR and mass spectra did not show any minor peaks belonging to **3a**, **3b**, and **3d** by-products, we

suspect that the reaction was quite a selective one. It is important to note that the calculated C, H, and N percent of **3c** were exactly equal to that of the found data as evaluated by CHN analyzer, this also supports the selectivity of the reaction to give only **3c**.



Scheme 3.1 Etherification between **1** and ditosylated triethylene glycol.

In order to identify the precise structure of our macrocycles, single crystallography analyses were carried out. The results reveal that **3** consists of a molecule of **1** linked with a molecule of ditosylated triethylene glycol (Figure 3.1). The structure of **3** is orthorhombic, space group *Pna2₁* (no.33), and $Z = 4$. This implies that **1** and ditosylated triethylene glycol arrange themselves to favor the final structure of [1+1] macrocycle.

It might be the case that there are many types of single crystals obtained after recrystallization; thus, to ensure that the compound obtained was only **3c**, the single crystal X-ray analyses were repeated several times by selecting the crystals randomly. All crystals showed the structure of **3c**. Here, we confirmed that the [1+1] macrocyclization is simple, selective, and effective which is relevant to our previous works [9-10].

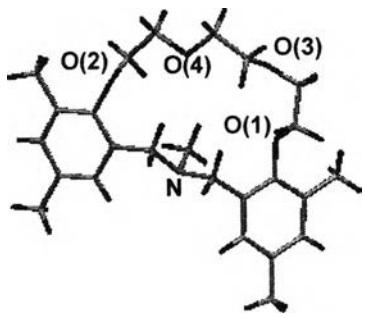
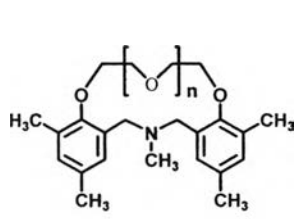


Figure 3.1 Crystal structure of **3**.

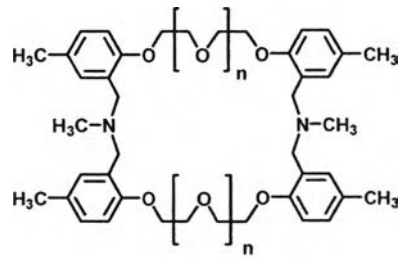
It is known that the general approaches to effectively obtain the macrocyclic compounds are to use metal templates [4]. The condensation through H-bond is also another approach when the backbone molecules are in H-bond network [5]. Based on this viewpoint, we focus on how the substitutional groups of HBA derivatives play their role in selective macrocyclization. To answer this question, **1** and **2** which have different ortho-substitutional groups were applied. When **1** was reacted with ditosylated triethylene glycol, the reaction possibly gives various products (**(3a)-(3d)**), (Scheme 3.1). As clarified above, we found that the reaction gives us only [1+1] macrocycle, **3c**. Similarly, the reaction of **1** with ditosylated diethylene glycol also gives [1+1] macrocycle of **4** (Chart 3.2).

Comparing with the results obtained from **2**, the compound provides [2+2] macrocycle when it was reacted with ditosylated compound. For example, **5** and **6** (Chart 3.2) were achieved when **2** was reacted with ditosylated triethylene glycol and ditosylated diethylene glycol [10], respectively, as clarified by FTIR, ^{1}H-NMR, EA, and MALDI-TOF MS. Although the single crystal analysis to support [2+2] macrocyclization is in progress, the structural characterizations clearly show the effect of ortho-substitutional group. In other words, Chart 3.2 summarizes important information about the selective macrocyclization. That is, it is possible to obtain as desired [1+1] or [2+2] macrocycles by simply choosing the HBA with or without substitutional group at ortho position. The effect of substitutional group is so significant that even the ditosylated compounds were changed from ditosylated alkyl glycol to ditosylated oxyalkane, the reaction still gives the similar selective macrocyclization.



3: n = 2

4: n = 1



5: n = 2

6: n = 1

Chart 3.2 Chemical structures of [1+1] dibenzo-monoaza-crowns (**3** and **4**) and [2+2] macrocyclic ethers (**5** and **6**).

Metal Ion Extraction and Host-Guest Ratio

To determine the ion extraction abilities of the macrocycles obtained, the liquid-liquid extraction via Pedersen's technique was applied. Alkali metal picrate aqueous solutions give a maximum peak at 356 nm. When the host which is in organic phase forms complex with alkali metal picrate in aqueous, this peak intensity will decrease. Here, the decrease of this peak after adding **3-6** was traced. As shown in Figure 3.2, in the case of [2+2] macrocyclic ethers, **5** shows about 50% extraction for all studied ions, i.e., Na^+, K^+, and Cs^+, corresponding to 2:1 host-guest ratio. Similarly, **6** shows the ions extraction percentage at about 50% which refers to 2:1 host-guest ratio [10]. This implies that the increase of methylene chain and oxygen atom as in **5** hardly affects the inclusion properties of [2+2] macrocycles. However, in the case of [1+1] dibenzo-monoaza-crowns, i.e., **3** and **4**, the extraction was approximately 40%. The simple calculation brings us to the host-guest ratio of 5:2. In order to verify this non-integer host-guest ratio, the single crystal analyses of these host-guest compounds are needed and it is in our progress.

Although the single crystal analysis is the most direct evidence to show the host-guest complexation, there are cases that the single crystals can not be obtained easily. For example, Božić *et al.* could not obtain a single crystal of 15-membered O_2N_2 macrocycle to show the direct evidence of proton to ligand complexation including its host-guest ratio [14]. They applied indirect evidences based on FTIR, NMR and ESI-MS to conclude that the host guest ratio is 2:3. Pouretedal *et al.*

showed the molar ratio method to clarify the host-guest ratio of aza-15-crown-5 with quinone derivatives instead of using single crystal information [13].

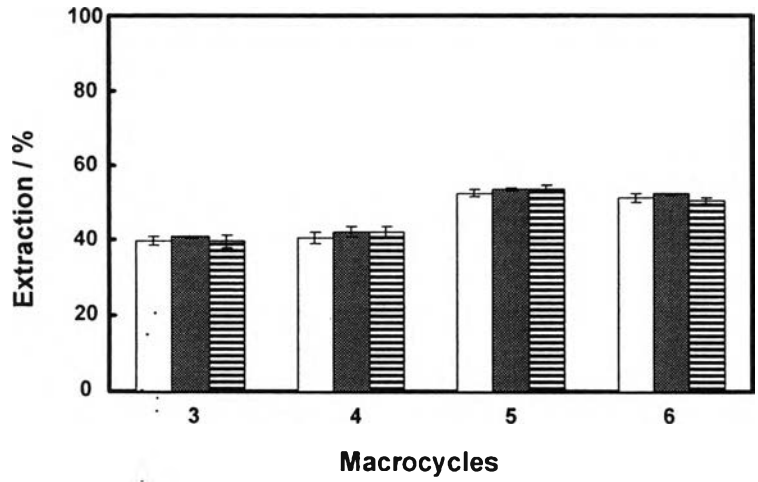


Figure 3.2 Extraction percentage of (▫)sodium picrate, (▪) potassium picrate, and (▭) cesium picrate by **3-6** in $CHCl_3$ at an equimolar concentration of $7x10^{-5}$ M, observed at 356 nm by UV-Vis spectrophotometer.

We extend our studies to clarify host-guest ratio using the molar ratio method as we also could not obtain the single crystal. Here, we applied sodium picrate as guests for **3**. As sodium picrate in ethanol solution shows the UV peak at 356 nm, the shift of this peak can be observed when complexation occurs. When the molar ratio of **3**:sodium picrate was varied from 0 to 6, the maximum peak of sodium picrate gradually shifted to 353 nm. Figure 3.3 shows the plot between the absorbance at the λ_{max} 353 nm and the **3**:sodium picrate ratio. An intercept is identified at the molar ratio of 2.65 or ~5:2. This value implies the incorporation of sodium picrate in **3**. This is relevant to what we obtained from the analysis based on Pedersen's technique mentioned above (Figure 3.2).

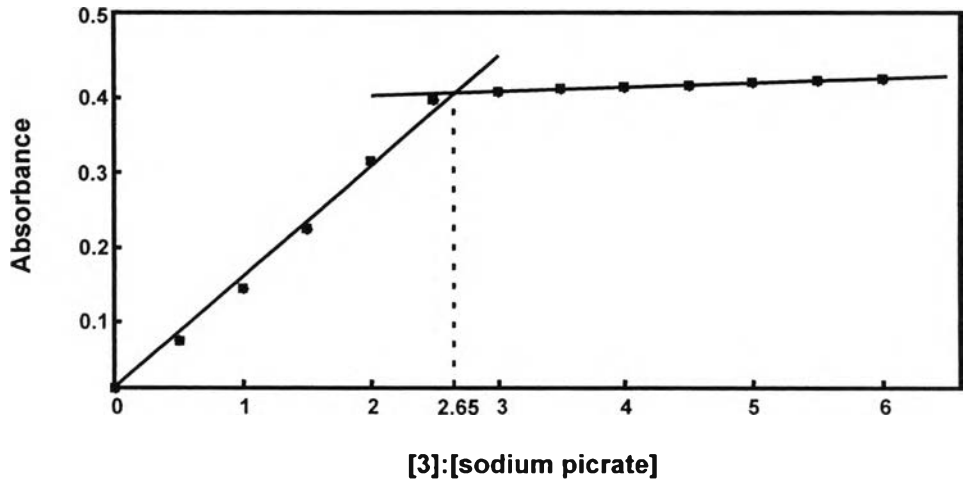


Figure 3.3 Plot of absorbance at λ_{max} = 353 nm vs. [**3**]:[sodium picrate] molar ratio in ethanol solution.

Although, up to now, we have succeeded in determining the non-integer host-guest compound of **3** and **4** based on Pedersen's and the molar ratio techniques, the further investigations, e.g. X-ray stucture of the complex, molecular simulation, etc., are needed and in our progress. Combining the results obtained from both [1+1] and [2+2] macrocycles derived from HBA, it is clear that [1+1] macrocycles favor 5:2, whereas [2+2] macrocycles prefer 2:1 host-guest ratio. This suggests that the type and the size of HBA based macrocyclic compound controls the host-guest ratio.

Conclusions

We succeeded in preparing the selective macrocycles in high yield (70-80%) via the simple reaction without further complicated purification. We found that the ortho-substituted phenol is a key factor to control the macrocyclization of HBA to selectively obtain only [1+1] macrocycles. All macrocycles derived from HBA showed the inclusion phenomena with alkali ions. The ratio between macrocyclic host and alkali metal ion is either 5:2 or 2:1 depending on the structure of macrocycle and whether or not it contains the ortho-substituted group in phenol. At present, further systematic studies on macrocyclization of HBA derivatives, especially HBA with different functional groups at the N atom, are in progress and will be discussed in our up-coming article.

Acknowledgements

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