

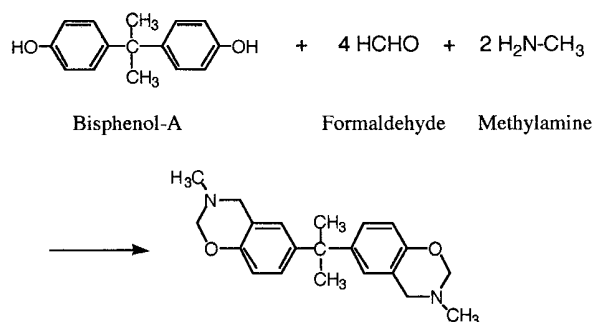
Scheme 1 Benzoxazine local structure.

sponding salts in water. Picric acid at a concentration of $10^{-2}M$ and an additional $2 \times 10^{-2}M$ of an ion salt were dissolved in deionized water. The concentration of each ion stock solution was diluted to obtain 1 absorbance unit at the wavelength of 354 nm as observed by UV spectroscopy, which is equal to 6.89×10^{-5} mol/L. The monomer and oligomers were dissolved in methylene chloride, chloroform, and toluene at the concentration of 0.200, 2.00, and 20.0 g/L, respectively. To study the effect of the organic phase on the ion extraction property of the BA-m monomer, in the liquid-liquid separation system, other solvents, i.e., anisole, trichloroethylene, and 1,2-dichloropropane, were also used.

The ion extraction phenomenon was observed using the Pedersen's technique in liquid-liquid systems.¹⁴ Five milliliters of ionophore in organic solution and 5 mL of ion solution were mixed vigorously for 3 min, followed by centrifuge for 1 min. The ion concentration of the aqueous phase was determined by a UV-Vis spectrophotometer at 354 nm. Ion extraction was accomplished at room temperature by varying the organic phase.

RESULTS AND DISCUSSION

Figure 1 shows the FTIR spectra of BA-m before and after polymerization. The hydrogen bonded



Bis(3,4-dihydro-2H-3-methyl-1,3-benzoxazinyl) isopropane (BA-m)

Scheme 2 Preparation of BA-m.

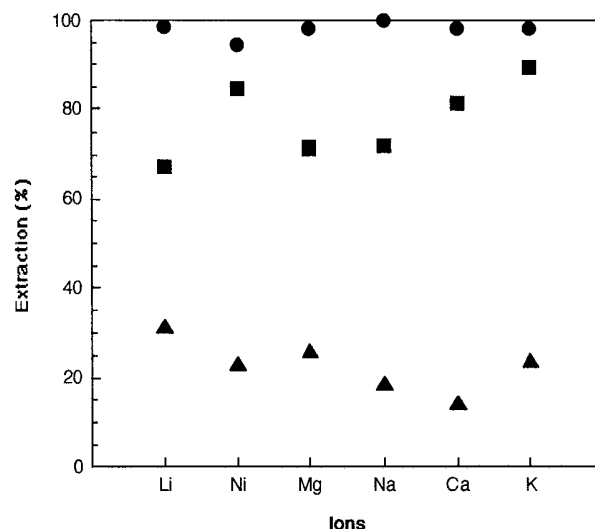


Figure 2 Extraction efficiency of various metal picrates by the BA-m oligomers. Ionophore concentration in CH_2Cl_2 as the organic solvent: ●, 20 g/L; ■, 2 g/L; and ▲, 0.2 g/L.

hydroxyl peaks are observed while the characteristic oxazine ring band is changed (1499 cm^{-1}) as reported elsewhere.⁷

To identify oligobenzoxazine as an ionophore and explore the inclusion phenomenon, it is necessary to study some structural factors of host-guest compounds. In the present work, the following factors are investigated: type of organic phase in liquid-liquid systems, variation of metal ions, and the concentration of both BA-m monomer and ion.

According to Pedersen's¹⁴ technique, the picrate ion will be shifted from the aqueous phase to the organic phase where the ionophore is present and act as an ionophore to entrap the metal ion. Here, when the oligobenzoxazine provides a structure as a host molecule and acts as an ionophore, the metal ion will transfer to the organic phase as soon as the oligobenzoxazine is added to the system and an ion complex is formed. Thus, ion extraction can be investigated by determining the change of picrate concentration in the aqueous phase and its concentration can be quantitatively determined by UV spectroscopy at the absorption wavelength of the picrate. Ion extraction was studied by varying the organic phase in the liquid-liquid system to observe the ion interaction with BA-m.

Figure 2 indicates that when the concentration of BA-m oligomers is higher, the ion extraction is more significant. When the oligomer concentra-

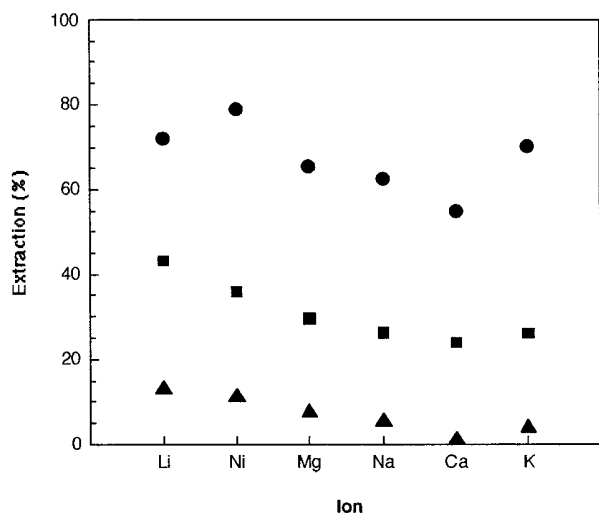


Figure 3 Extraction efficiency of various metal picrates by the BA-m oligomers. Ionophore concentration in CHCl_3 as the organic solvent: ●, 20 g/L; ■, 2 g/L; and ▲, 0.2 g/L.

tion is 20 g/L in CH_2Cl_2 , the ion extraction is nearly 100% of which the ion concentration is 6.89×10^{-5} mol/L. The BA-m oligomers show ion sensitivity to all types of metal ions. Figures 2–4 show the ion entrapment efficiency of the BA-m oligomers when the organic phase is varied from CH_2Cl_2 , CHCl_3 , and toluene. At the same oligomer concentration, the efficiency of ion extraction is highest in CH_2Cl_2 , followed by CHCl_3 , and

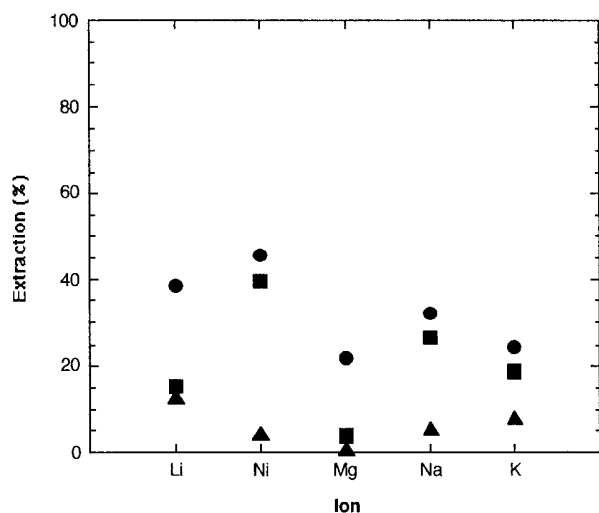


Figure 4 Extraction efficiency of various metal picrates by the BA-m oligomers. Ionophore concentration in toluene as the organic solvent: ●, 20 g/L; ■, 2 g/L; and ▲, 0.2 g/L.

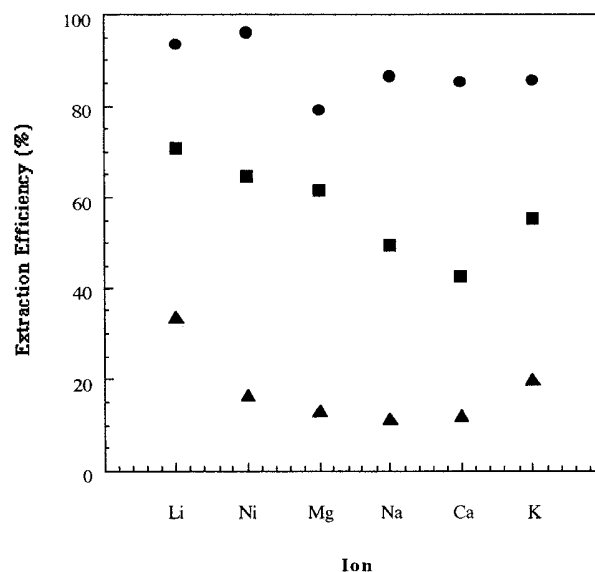


Figure 5 Extraction efficiency of various metal picrates by the BA-m monomer. Ionophore concentration in CH_2Cl_2 as the organic solvent: ●, 20 g/L; ■, 2 g/L; and ▲, 0.2 g/L.

finally toluene. When the oligomer concentration is increased, the percentage of ion extraction increases for all types of metallic ions. This suggests that the BA-m oligomers interact with ion species and act as ionophores. Similar to Figure 2, both Figures 3 and 4 show little selectivity toward any specific ions but high ion sensitivity to all types of metal ions.

To clarify the ion interaction mechanism, the BA-m monomer was studied as an ionophore because of its well defined structural unit. The results from the $\text{H}_2\text{O}-\text{CH}_2\text{Cl}_2$ system are shown in Figure 5. Here, it is clear that the monomer also performs as an ionophore. Ion extraction in a liquid-liquid phase system is significant in CH_2Cl_2 but is low for a toluene organic phase (Figures 5–7). In the case of the BA-m monomer, it is found that the percentage of ion extraction is nearly as high as that of the BA-m oligomers. Figure 5 shows that the BA-m oligomers can trap almost 100% of the sodium ion whereas the BA-m monomer shows a slightly lower (90%) extraction affinity when the BA-m concentration is 2.00 g/L in CH_2Cl_2 . It suggests that the lone pair electrons of the oxygen and/or nitrogen might be involved because there are no hydroxyl groups in the BA-m monomer.

The amount of ion entrapped increases nonlinearly as a function of the monomer concentration

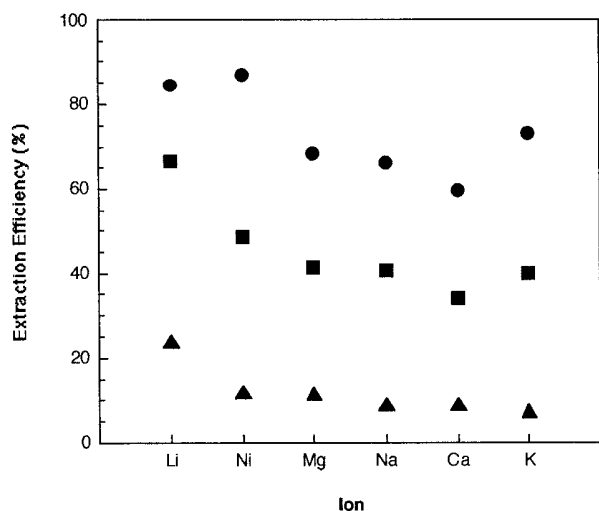


Figure 6 Extraction efficiency of various metal picrates by the BA-m monomer. Ionophore concentration in CHCl_3 as the organic solvent: ●, 20 g/L; ■, 2 g/L; and ▲, 0.2 g/L.

as shown in Figure 8 where the percent entrapment of the calcium ion is plotted as a function of the BA-m monomer concentration in CH_2Cl_2 . As the ion entrapment efficiency increases, the efficiency approaches an asymptotic value. It should be noted that the ion extraction property of benzoxazine is accomplished through various sizes of benzoxazines, oligomers, and even the monomer whereas the ion extraction percentage of metal

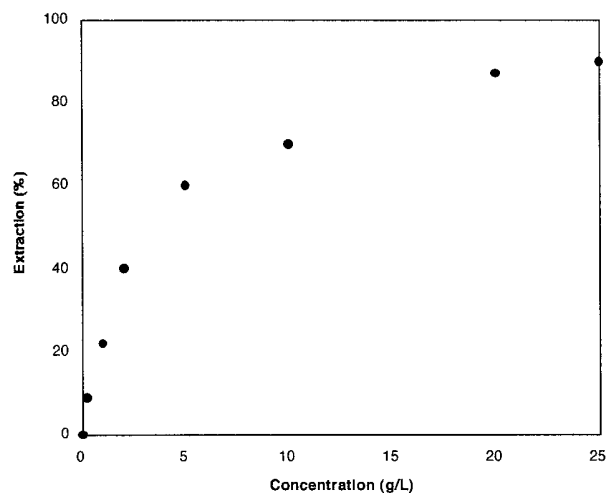


Figure 8 Extraction efficiency of the Ca^{2+} ion as a function of the BA-m monomer concentration in CH_2Cl_2 .

ions studied shows little variation as a function of the ion size. Thus, we propose that the ion extraction mechanism for the ionophore is due to a molecular assembly of host and guest compounds, rather than specific sizes of cage-like structures of cyclic compounds, such as calixarene and cyclodextrin. Yamagishi et al.¹³ proposed that the ionic affinity of the cavity which is present in the molecular assembly can be based on the pseudocyclic conformation. In this study, it is presumed that the assemblies of the benzoxazine oligomers may be flexible, thus the ion extraction can be performed efficiently with various metal ions but the selectivity is not obvious.

Generally, host compounds will provide a specific cavity for guest molecules depending on its molecular assembly structure. In this study, the ionophore was varied to investigate the guest responsive structure due to the assembly formation of the BA-m monomer and oligomers. Alkali, alkaline earth, and transition metal ion (Ni) are used for the observation of ion extraction. Six kinds of metallic ions were used to observe the ion extraction ability of the BA-m monomer. It is expected that there will be an appropriate ion size that fits the cavity of the ionophore if the configuration of the ionophore is fixed. As shown in Figures 5–7, among alkali and alkali earth ions, lithium and potassium ions tend to show slightly higher ion extraction efficiencies than other ions. It should be noted that the size of the potassium ion is twice the size of the lithium ion, whereas the ion extraction percentages are similar. This is

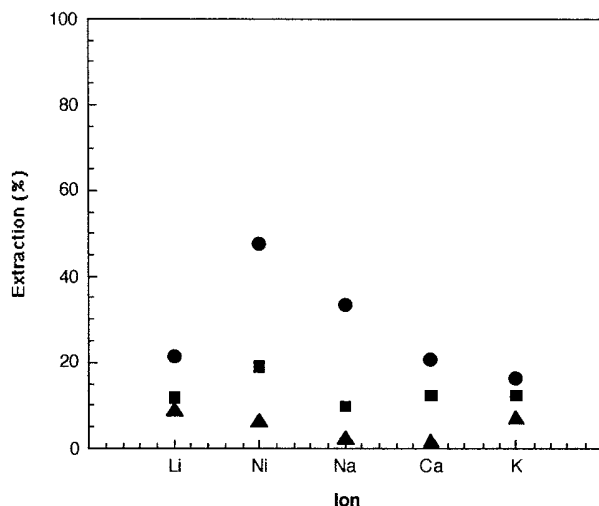


Figure 7 Extraction efficiency of various metal picrates by the BA-m monomer. Ionophore concentration in toluene as the organic solvent: ●, 20 g/L; ■, 2 g/L; and ▲, 0.2 g/L.

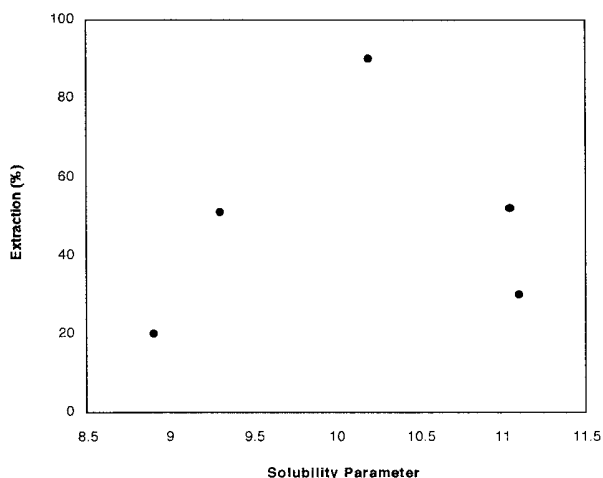


Figure 9 Percent extraction of Ca^{2+} ion by varying solubility parameter of the organic phase when BA-m monomer concentration is 2 g/L.

yet another indication of ion entrapment by the molecular assembly rather than the cavity of fixed size and shape. Miyata et al.¹⁷ reported that when the host molecule acts as a flexible structure for the guest, various types of guest molecules will be allowed in the cavity, as seen in the case of the cholic acid molecular assembly system. Accordingly, the various observations stated above indicate that the BA-m monomer and oligomers provide the guest responsive structure, while the inclusion phenomenon with the low size selectivity takes place.

It is well known that the inclusion phenomenon is related to the interaction of the host and guest molecules. When the host concentration is in excess of the guest molecules, a greater amount of guests will be included in the host compound. It is found that in the case of CHCl_3 and CH_2Cl_2 , when the ionophore (both the BA-m oligomers shown in Figures 2–4, and the BA-m monomer shown in Figures 5–7) concentrations are increased by 100 times from 0.200 to 20.0 g/L, the ion extraction efficiencies are increased only by 60%. In the case of a toluene organic phase, in which the ion extraction percentages are relatively low, the relationship of the ionophore concentration and ion extraction ability is not significant, ranging from 10 to 30%.

The organic phase in a liquid-liquid system plays an important role in the ion extraction step. Tsurubou et al.¹⁵ reported that the host guest assembly can be controlled by the surrounding organic solvent molecules in the liquid-liquid

phase system. Thomas et al.¹⁶ reported that size of the solvent affects the ion transfer across the liquid-liquid phase because of the hydrodynamic continuum effect. The ion extraction selectivity can be established when the appropriate solvent is applied under a certain hydrodynamic continuum atmosphere. In the present work, methylene chloride, chloroform and toluene, which differ in molecular size, clarify the factor of organic phase in the interaction between ionophore and metal ions.

It can be concluded that benzoxazines act as an ionophore to form the ion complexes whereas the organic solvent molecules provide the preferable assembly in the host-guest formation.¹⁶ The solubility parameter of the BA-m monomer, $\delta = 9.99$, is much closer to that of CH_2Cl_2 than to that of toluene. Therefore, the ion entrapment efficiency was suspected to be influenced by the benzoxazine monomer-solvent interaction. This can be examined by varying the solubility parameter of organic phase. As shown in Figure 9, when BA-m monomer is used as an ionophore, the percent extraction is high when the solubility parameter of the organic phase is close to that of the BA-m monomer. To quantitatively evaluate the effect of the interaction, the Flory-Huggins χ_{ab} parameter as defined below was calculated.

$$\chi_{ab} = 0.34 + V_r (\delta_a - \delta_b)^2 / RT$$

where V is the molar volume of the solvent; δ , the solubility parameter; R , gas constant; and T , temperature.

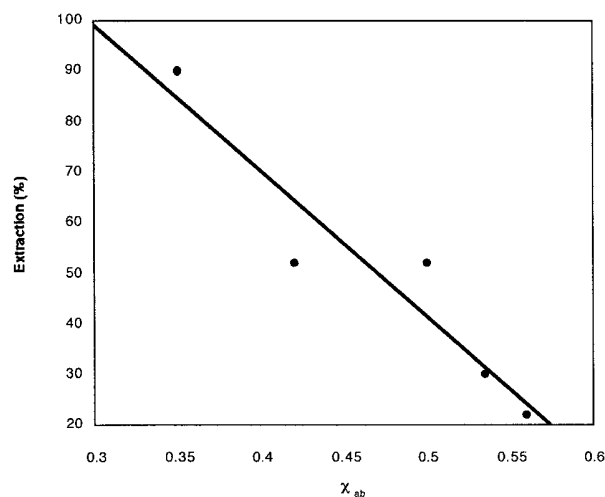


Figure 10 Extraction efficiency of the Ca^{2+} ion in various solvents. The extraction efficiency is plotted against the Flory-Huggins χ_{ab} parameter of the BA-m monomer/solvent system.

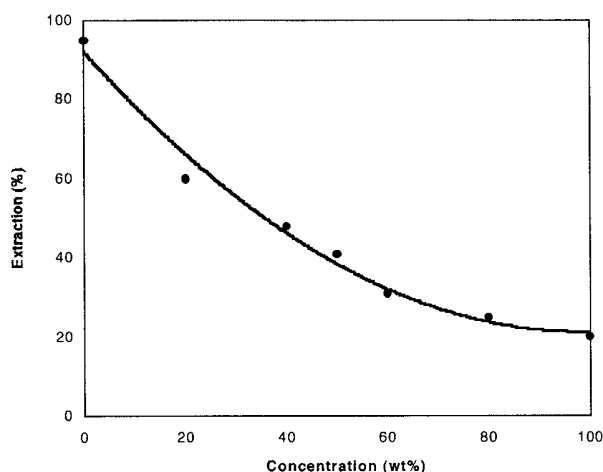


Figure 11 Extraction efficiency of the Ca^{2+} ion in CH_2Cl_2 /toluene mixtures. The extraction efficiency is plotted against the concentration of toluene in the mixtures.

The observed ion entrapment efficiency was plotted as a function of the χ_{ab} parameter of the system as shown in Figure 10. An excellent correlation is observed in which the smaller the χ_{ab} parameter, the greater the ion entrapment. It indicates that the solvation of the benzoxazine monomer is related to the ion entrapment efficiency. This supports that the molecular assembly enhancement by organic solvent molecules plays an important role in ion entrapment.

To study the relationship of the solubility parameter and the ion interaction with the ionophore, the solubility parameter was changed by systematically varying the composition of CH_2Cl_2 and toluene mixtures. Assuming that the Flory-Huggins χ_{ab} parameter can be averaged for the mixture system, the ion entrapment efficiency is again plotted as a function of the toluene concentration as shown in Figure 11. Here, it is found that the ion extraction efficiency is decreased when the solubility parameter is varied by the composition of toluene. Similar to Figure 10, where various solvents are used to vary the χ_{ab} parameter, it is observed that the smaller the χ_{ab} parameter (the lower the concentration of toluene), the higher the ion entrapment efficiency. Accordingly, the solubility of the benzoxazine systems is an important parameter for influencing the ion entrapment efficiency.

Calixarenes, crown-ether, and cyclodextrin are well known inclusion compounds and some practical applications are established. The ion extraction ability of 18-crown-6, calix[4]arene,

calix[6]arene, and calix[8]arene for the calcium, lithium, and sodium ions¹⁸ is compared with that of benzoxazine monomer as shown in Figure 12. To compare the ion extraction ability to the mentioned ionophores, experiments were performed under the same conditions as those reported in the literature. The concentration of the benzoxazine monomer was $2.7 \times 10^{-3}M$, which is also the same as the ionophore concentration reported in the cited reference.

The preliminary study shows that, in the case of lithium and calcium, the ion extraction is in the range of 20–50% for the calixarenes and crown-ether, whereas the extraction efficiency of the benzoxazine is quite high at nearly 80%. The high ion extraction ability of benzoxazines suggests that the benzoxazine can be an effective ionophore based on each phenolic-like repeat unit structure combined with the local structure of the assembly under the preferable condition of the organic phase.

CONCLUSIONS

Benzoxazine, BA-m monomer, and its oligomer perform as an ionophore to show a significant ion interaction among alkali and alkaline earth ions in the liquid-liquid phase. The ion extraction

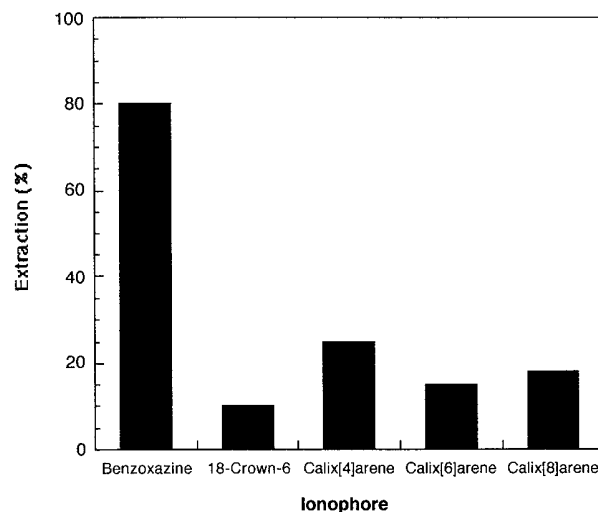


Figure 12 Comparison of the extraction efficiency of lithium picrate of the BA-m monomer with the published results on calix[4]arenes, calix[6]arenes, calix[8]arenes, and 18-crown-6 ether.¹³ The ionophore concentration of all the systems was $2.7 \times 10^{-3}M$ in CH_2Cl_2 as the organic solvent.

study clarifies that benzoxazines entrap all types of ions studied but shows little selectivity for ion size. The ion entrapment is found to proceed via molecular assembly formation under the preferable structure provided by the organic phase molecule in the liquid-liquid system. The ion entrapment efficiency shows a good correlation with the Flory-Huggins c_{ab} parameter of the benzoxazine/organic solvent system studied.

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Asymmetric Mono-oxazine: An Inevitable Product from Mannich Reaction of Benzoxazine Dimers

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Abstract: The Mannich reaction is detailed, which was carried out on benzoxazine dimers under various conditions, that is, temperature, reaction time, and solvents. Against our expectation, in any condition, instead of generating a disubstitution oxazine compound, the reaction gives a product with only a single oxazine ring, a mono-oxazine benzoxazine dimer, as characterized by FT-IR, ^1H NMR, ^{13}C NMR, 2D-NMR (^1H – ^1H COSY, ^1H – ^{13}C HMQC, and ^1H – ^{13}C HMBC), and EA. The asymmetrical reaction is found to be based on the original structure of the benzoxazine dimer which has two phenol rings in a different stability as clarified by X-ray structure analysis of the single crystal. All types of benzoxazine dimers indicate the specific structure with a pair of inter- and intramolecular hydrogen bonds. The bond distance indicates that the intramolecular hydrogen bonding is very strong, while the packing structure emphasizes the high stability of the dimer unit and implies the deactivation of one phenol ring in the benzoxazine dimer. In this contribution, we demonstrate one of the quite rare examples, showing how the stereostructure of the reactant molecule is an important factor to control the reaction and give an asymmetric product which we never expected when considering only the chemical formula.

Introduction

Polybenzoxazine is known as a polymer with a chemical structure of aza-methylene phenol repeating unit (Scheme 1, eq 1) obtained from the ring-opening polymerization of benzoxazine monomers.^{1–5} Benzoxazine monomers, thus, can provide linear or cross-linked polymers, depending on the reaction occurring at ortho and additional para positions. In the cases of some unique monomers, that is, bisphenol-based benzoxazines (Scheme 1, eq 2), Ishida et al. showed a successful polymerization to obtain a series of thermosetting polymers and proposed a novel phenolic resin.^{2–3} When it comes to the simple phenol-based benzoxazine monomers, it is interesting to find that few studies have been done. For example, in the case of para-substituted phenol based benzoxazines (Scheme 1, eq 3), it can be expected to obtain linear polymers. However, on the basis of the kinetic studies, Riess et al. found that the polymerization of *p*-cresol proceeded with a limit of four to six repeating units.⁵ In addition, this number of repeating units might not be quantitatively exactly determined. Until now, the involved factors and the mechanisms controlling this polymerization have not been clarified.

Recently, to propose a novel supramolecular structured benzoxazine our group focused on the unique structures of polybenzoxazines which resemble those of calixarenes.⁶ Here, to achieve our molecules as calixarenes, we came to the point of preparing a well-defined structured benzoxazine, such as a linear or cyclic oligobenzoxazine, based on the ring-opening polymerization of benzoxazine monomers. In such cases, the work can be simplified if we start from the para-substituted phenol in the preparation of benzoxazine monomer followed by the polymerization. However, to our surprise, the para-substituted phenol-based benzoxazine monomers gave us neither the linear oligomer nor the polymer but mainly the dimer in the polymerization process even though the reaction conditions were varied.⁷ It is important to clarify the reasons why benzoxazine dimers show the self-termination in the polymerization process, which will be reported elsewhere.⁷ To achieve our designed molecules as mentioned above, we must overcome the problems of self-termination at the dimer level. In other words, the preparation of linear oligobenzoxazines ($n > 2$) needs other unique strategies to process the reaction to obtain a linear oligobenzoxazine. Previously, Ishida et al. reported multistep reactions to obtain a linear chain using bromo-substituted phenols.⁸ Although the linear benzoxazines were achieved, the reaction was rather complicated, and the final product yield was low while the costs of the synthesis are high.⁸ Thus, the method does not seem to be practical to obtain our required product.

Since we can obtain the benzoxazine dimers in a high yield (80–90%),⁷ it is one of the approaches to apply these dimers

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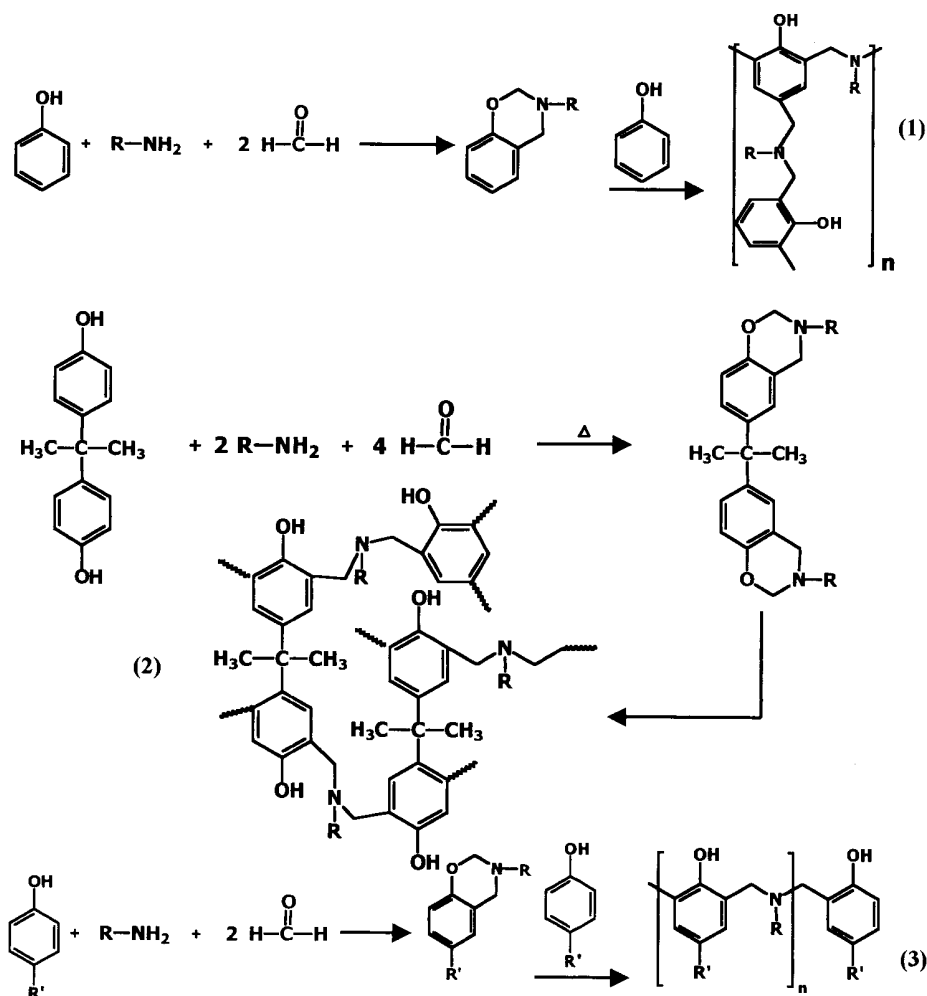
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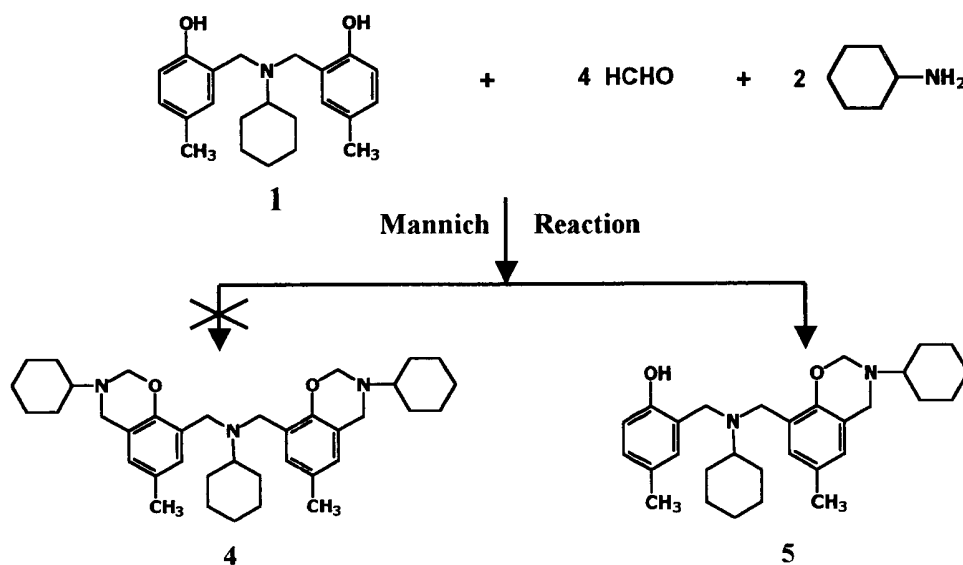
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Scheme 1



Scheme 2



as a starting material. We propose alternative steps of an oxazine cyclization and a ring-opening reaction of benzoxazine dimers to obtain a well-defined cyclic compound. As will be described in the present work, to our surprise again, a Mannich reaction of benzoxazine dimer does not proceed to give dioxazine compounds as expected in Scheme 2 (compound 4) but gives

an asymmetric product with the single oxazine ring at an alternative phenol (Scheme 2, compound 5). Even when the reaction conditions are varied, we obtain only an asymmetric mono-oxazine dimer as a product. At this point, without clarification of the reaction of dimers and the key factors involved, we cannot continue our strategies to obtain a well-

Scheme 3

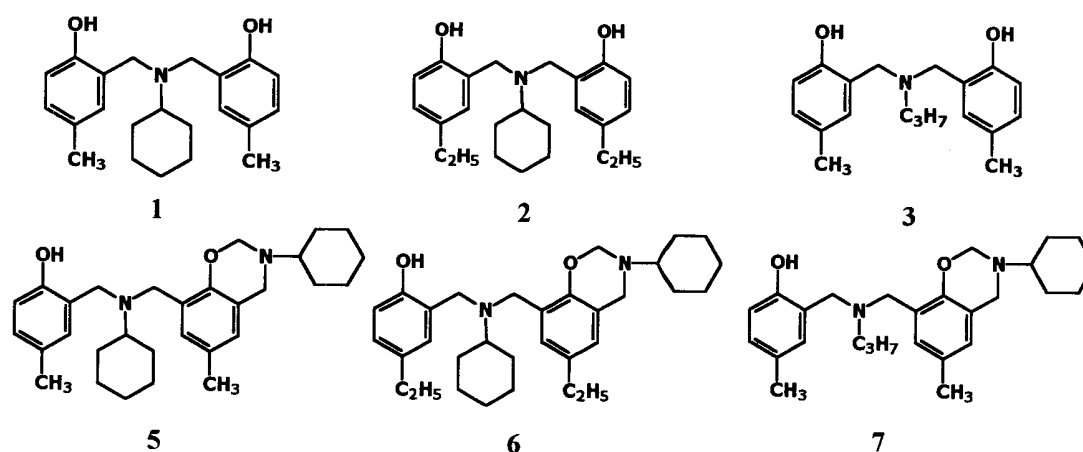
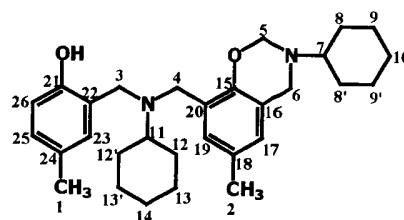


Table 1. NMR Data for Mono-oxazine Benzoxazine Dimer 5



position	^1H δ_{H} , multi. [J (Hz)]	^{13}C δ_{C}	^1H – ^1H COSY	^1H – ^{13}C HMBC
1	2.21, 3H, s	20.47	H26, H23	C23, C24, C26
2	2.20, 3H, s	20.59	H17, H19	C17, C18, C19
3	3.78, 2H, s	52.89	—	C1, C4, C11, C15, C21, C22, C23
4	3.57, 2H, s	47.87	—	—
5	4.98, 2H, s	80.19	—	C2, C6, C7, C15, C21
6	4.03, 2H, s	47.38	—	C2, C5, C7, C15, C16, C17, C18, C21
7	2.68, 1H, m	58.47	H8, H8'	C8, C8'
8	1.25, 2H, m	31.59	H7, H8, H9, H9', H10	C7
8'	1.98, 2H, d, br	31.59	H7, H8', H9, H9'	C7
9	1.58, 2H, m	26.30	H8, H8', H9', H10	C8, C8'
9'	1.74, 2H, m	25.94	H8, H8', H9, H10	—
10	1.12, 2H, m	25.50	H8, H9, H9'	C9'
11	2.62, 1H, tt (11.81, 3.30)	57.99	H12, H12'	C12, C12'
12	1.40, 2H, qd (12.09, 2.75)	27.64	H11, H12', H13, H14	C11
12'	1.92, 2H, d, br	27.64	H11, H12, H13, H13', H14	C11, C13
13	1.60, 2H, m	26.30	H12', H13', H14	C12, C12'
13'	1.76, 2H, m	26.01	H12, H12', H13, H14	C11, C13
14	1.16, 2H, m	25.50	H12, H12', H13, H13'	C13'
15	—	151.58	—	—
16	—	121.91	—	—
17	6.66, 1H, d (1.51)	126.76	H19	C2, C6, C15, C16, C19
18	—	128.71	—	—
19	6.83, 1H, d (1.51)	130.18	H17	C2, C6, C15, C17
20	—	124.91	—	—
21	—	155.94	—	—
22	—	122.44	—	—
23	6.74, 1H, d (1.94)	129.04	H26	C1, C3, C21, C26
24	—	127.48	—	—
25	6.64, 1H, d (8.24)	115.63	H26	C1, C21, C24
26	6.89, 1H, dd (8.24 and 1.94)	128.52	H23, H25	C1, C21, C23

defined benzoxazine structure. We have to clarify the reason the imbalance-structured compound is obtained inevitably. In another words, it is important to note that this asymmetric mono-oxazine product is always produced without any specific condition or catalyst.

Thus, in the present contribution, we (i) maintain that our basic studies on the Mannich reaction of benzoxazine dimer clarifying the structure of the compound obtained based on various aspects of analyses, especially the 2D-NMR, (ii) identify the factor that originates the asymmetric reaction, and (iii) show how the factor studied can be applied in the mechanism to

explain the inevitable generation of mono-oxazine compounds. The clarification of the specific reaction occurring in benzoxazine dimers will be a useful guideline for a reasonable molecular design to obtain a well-defined supramolecular benzoxazine in the future.

Results and Discussion

Mannich Reaction of the Benzoxazine Dimer. Compound **1** (Scheme 3) was used as a model dimer to react with formaldehyde and cyclohexylamine via the Mannich reaction. From FT-IR data, the compound obtained gives rise to a broad

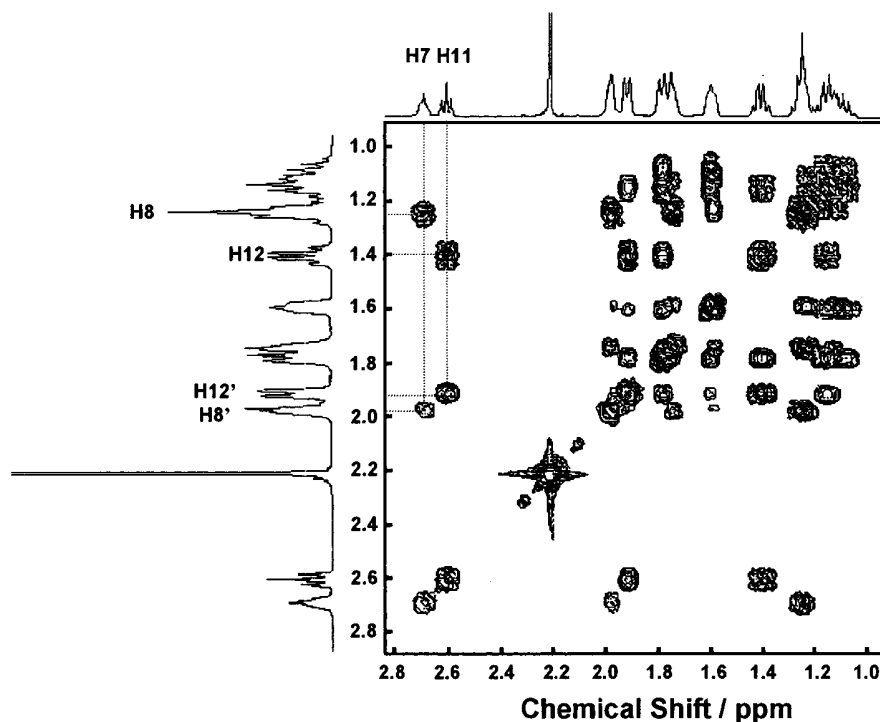


Figure 1. ^1H – ^1H COSY correlation spectra of mono-oxazine benzoxazine dimer **5**.

band at $3000\text{--}2800\text{ cm}^{-1}$, similar to **1**, implying the existence of strong hydrogen bonds. In fact, Daimay et al.⁹ reported that the cyanuric acid shows an infrared band corresponding to the strong OH–N hydrogen bond in the frequency region of $3200\text{--}2600\text{ cm}^{-1}$. The band at 3215 cm^{-1} due to the intermolecular hydrogen bond is observed for compound **1** but cannot be observed in the compound obtained. The bands at 1514 and 1500 cm^{-1} , which are intrinsic to the dimer, were changed to a singlet at 1498 cm^{-1} which is attributed to the vibration mode of the oxazine.

From the Mannich reaction, the structure of the product obtained from **1** can be proposed as either **4** or **5** (Scheme 2). It should be noted that compound **4** consists of three different methylene groups and three cyclohexyl groups, while compound **5** consists of four different methylene groups and two different cyclohexyl groups. ^1H NMR spectra of the product obtained from **1** shows four types of methylene groups at $\delta_{\text{H}} = 3.57$, 3.78, 4.03, and 4.98 ppm as singlet resonances, while the corresponding ^{13}C NMR spectra show carbon resonances at $\delta_{\text{C}} = 47.38$, 47.87, 52.89, and 80.19 ppm. These data suggest the preferability of **5** for the compound in question. Four different methylene groups correlate to two sets at 4.03 and 4.98 ppm and at 3.57 and 3.78 ppm, suggesting the existence of the methylene groups of the aza linkage and of the oxazine ring (Table 1).

In another step, the structure of **5** can be identified by confirming cyclohexyl protons presented in the structure. The number and the position of the cyclohexyl groups on each nitrogen atom were studied by the ^1H – ^1H COSY. Figure 1 shows the two cyclohexyl groups appearing in different position. The cyclohexyl groups can be distinguished clearly into two groups by resonances of methine protons of H7 and H11. However, the protons remaining (H8 to H10, H8' and H9', H12 to H14, H12' and H13') cannot be identified for the exact

position in the structure because of the possibility of being vicinal and geminal protons, including axial and equatorial protons in the cyclohexyl structure. In addition, ^1H – ^{13}C HMBC (Figure 2) shows the interaction between methylene protons, that is, between H5, H6, and C7 of cyclohexyl group, and that between H3 and C11, implying the asymmetric structure of compound **5**.

On the assumption of an asymmetric structure such as **5**, the protons of each aromatic ring can be distinguished into two and three species, which should be observed from the correlation shift and the different coupling constants (J). As shown in Table 1, the values of J for H17, H19, H23, H25, and H26 indicate the different species of protons. This supports the asymmetric structure of **5**. Here, the two equivalent aromatic protons (C17 and C19) are difficult to distinguish. The interaction between methylene groups with aromatic carbons in the HMBC mode helps us clarify. As shown in Table 1 and Figure 3, the methylene protons, H6, show the interaction only with aromatic carbon of C17, while aromatic protons, H17 and H19, interact with aromatic carbon C6 (Table 1). Another set of methylene protons H3 interacts with the aromatic carbon C23, while a set of aromatic protons H23 interacts with C3 of methylene group. This suggests that there is one oxazine ring unit linked by an aza-methylene bridge to the phenyl ring, as shown in structure **5**.

The phenol ring is also confirmed from the presence of the hydroxyl resonance at 11.16 ppm. In addition, the methyl group of the phenol ring appears in the ^{13}C NMR spectrum at 20.47 ppm, while the other of the benzoxazine ring is found at 20.59 ppm. Methyl protons H1 interact with aromatic carbons, C22, C23, C24, and C26, while other methyl protons H2 interact with aromatic carbons, C17 and C19. In this way, all of the data of the NMR spectra support the chemical formula of **5** in Scheme 3 as the compound obtained from the Mannich reaction of **1**.

Another important experimental result to support this conclusion is the data of EA. On the assumption of the dioxazine unit, the EA should give C 77.95, H 9.40, and N 7.18, respectively.

(9) Lin-Vien, D.; Colthup, N. B.; Fateley, G. W.; Grassell, G. J. *Infrared and Raman Characteristic Frequencies of Organic Molecules*; Academic Press: 1991; p 296.

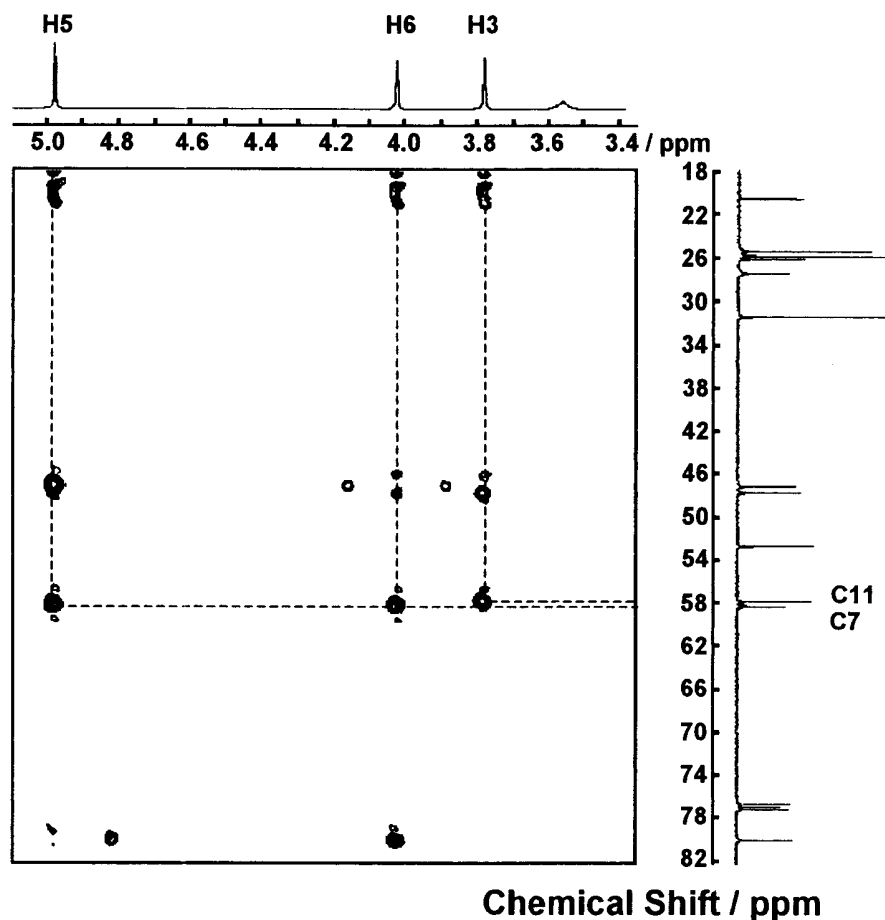


Figure 2. ^1H – ^{13}C HMBC correlation spectra of mono-oxazine benzoxazine dimer **5**.

However, the analyzed result gives C 77.79, H 9.17, and N 6.09, which are quite close to the calculated data for the dimer with a single oxazine unit: C 77.92, H 9.10, and N 6.06. This excellent agreement indicates also that dimer **1** yields only compound **5** and does not give any product such as compound **4**.

Solvent Polarity Effect. In each reaction, dimer **1**, **2**, or **3**, was found to dissolve well in dioxane, resulting in an homogeneous system for benzoxazine preparation. After 6 h at the reflux temperature of dioxane, the reaction was completed to give mono-oxazine with the yield of 75–80%. In contrast to the case of dioxane, the dimer was rather difficult to dissolve in cyclohexane. The reaction started as an heterogeneous system but turned into an homogeneous after the completion of the reaction. The yield obtained in cyclohexane was the same as that obtained from dioxane.

A polar solvent such as methanol was also used. The system gave low yields (20–30%), and the product was a yellowish viscous solution. This implies that the high polarity of the solvent affects the mono-oxazine formation. After recrystallization, the product was identified to be the mono-oxazine one.

To exclude the solvent effect, we attempted the reaction in a neat liquid state. The dimer **1** was heated to a temperature higher than the melting point (135 °C), and formaldehyde and cyclohexylamine were added. The reaction was completed within 15 min. After recrystallization, the yield of the product **5** was found to be 75–80%.

In all the cases, the compounds obtained were mono-oxazine derivatives as characterized by FT-IR and NMR. It should be noted that the mono-oxazine benzoxazine dimer was formed in

high yield even at the diversified reaction conditions, that is, polarity (dioxane, cyclohexane, methanol) and temperature (60 °C for methanol, 80 °C for cyclohexane, 100 °C for dioxane, and 135 °C for molten state systems). This indicates that the mono-oxazine benzoxazine dimer is a stable compound and the reaction is terminated almost always at the stage of the formation of only one oxazine unit, against our earlier prediction.

Molar Ratio of Reactants. It is important to clarify whether the mono-oxazine benzoxazine dimer comes from incomplete reaction or is a product of the inevitable pathway. Judging from the equation of chemical reaction shown in Scheme 2, the production of the compound **5** might be a result of incomplete reaction. The ratio of formaldehyde and amine was increased further to get the dioxazine product.

However, even when the ratio was increased to 1:8:4, the compound **5** was obtained in a similar yield. In contrast, the decrement of the ratio to half, that is, dimer:formaldehyde:amine = 1:2:1 also gave the compound **5** with the yield of 75–85%. In this way, only the mono-oxazine product was obtained irrespective of the molar ratio of reactants. In other words, the benzoxazine with a single oxazine unit is a reaction product of the “inevitable pathway”.

It is also necessary to show that not only dimer **1** but also other benzoxazine dimers give mono-oxazine derivatives. Here, we studied the Mannich reaction on dimers **2** and **3**. The structural studies by FT-IR, NMR, and EA indicate that **2** and **3** give the mono-oxazine compounds of **6** and **7**, respectively.

Crystal Structure and the Stability of Benzoxazine Dimer. We speculated that the asymmetric product might come from the different circumstances of the two phenol groups in a

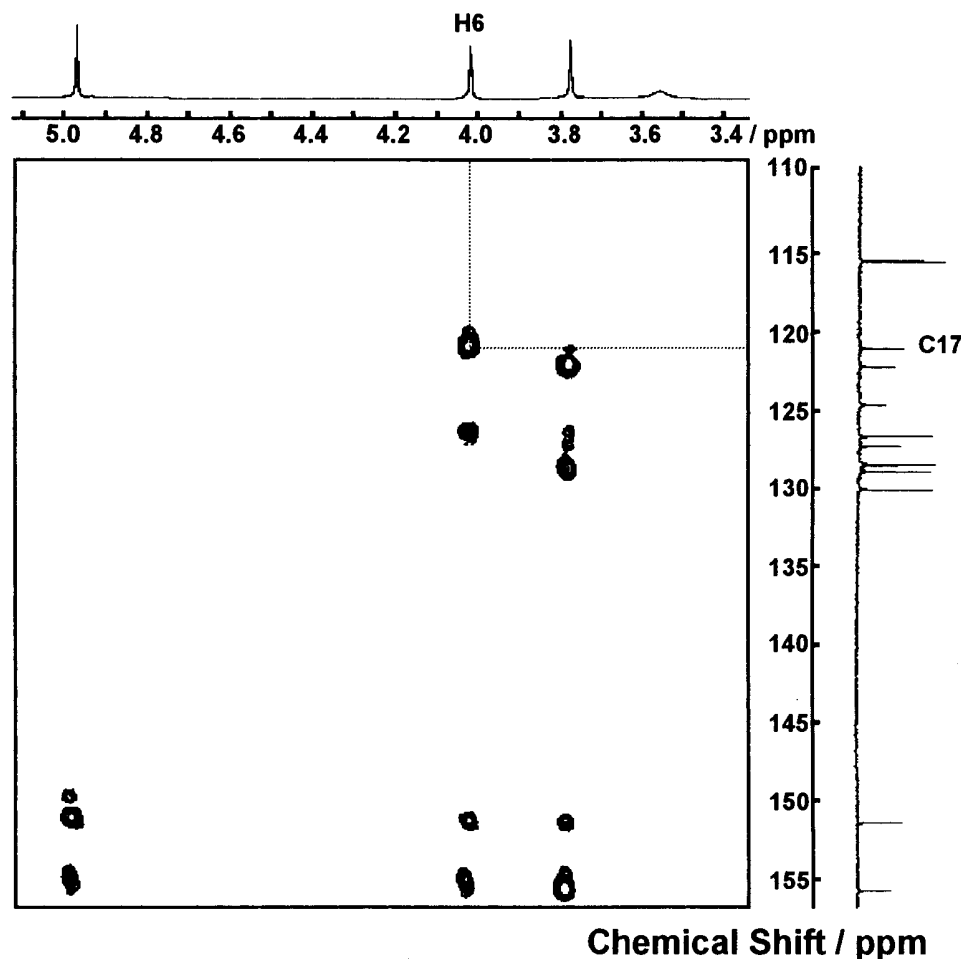


Figure 3. ^1H – ^{13}C HMBC correlation spectra of mono-oxazine benzoxazine dimer **5**.

molecule which induced the different activity. For example, Dunkers et al.¹⁰ and Schnell et al.¹¹ applied *N,N*-bis(3,5-dimethyl-2-hydroxybenzyl)methylamine as a benzoxazine model compound to study the conformation of polybenzoxazine resins and reported the existence of inter- and intramolecular hydrogen bondings between the nitrogen atom of the aza group and the hydroxy group of phenol by using FT-IR data and the X-ray structure analysis. However, the detailed information concerning the bond length and bond angle of the intramolecular hydrogen bond was not clarified at all. Moreover, they did not notice at all an intimate relationship of this intramolecular hydrogen bonding with the reaction of the dimer. As will be mentioned below, we speculated the possibility that the asymmetric reaction might originate from the imbalance reactivity of the phenol group; one phenol group is constrained by an intramolecular hydrogen bond while the other phenol is not.

The X-ray structural analyses of dimers were successfully done for the compounds **1**, **2**, and **3**. The difference synthesis $F_o - F_c$ gave definitely the position of the hydrogen atom participating in the intramolecular hydrogen bond. Figure 4 shows an example of **1** having a strong intramolecular hydrogen bond between the aza group and the phenol with the distance of O–H...N 1.80 Å, O...N 2.62 Å, and O–H...O 2.41 Å. The intermolecular hydrogen bond is formed between the two adjacent dimers with the distance of O–H...O 1.77 Å and

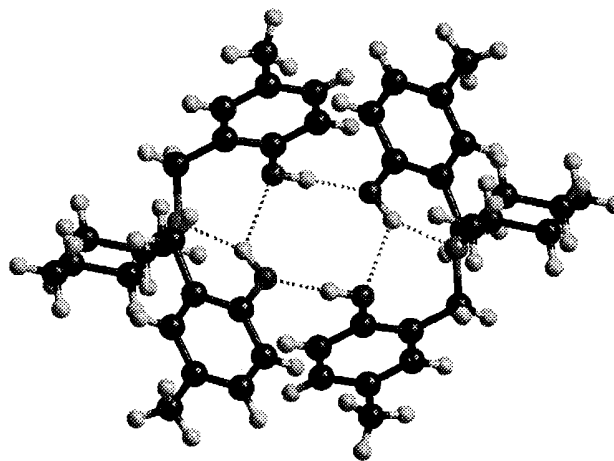


Figure 4. Dimer **1** packing structure.

O...O 3.04 Å. In this way, for all of the dimers investigated here, the strong inter- and intramolecular hydrogen bonds are observed. Table 2 summarizes some of the molecular parameters revealed for compound **1**. Crystallographic data including fractional coordinates of atoms are given in Table 3. The structural analyses for the other compounds will be reported elsewhere.¹²

As mentioned above, the two phenol groups are subjected to quite different circumstances. Although this observation can be

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Table 2. Intramolecular Bond Lengths and Angles of Dimer 1

selected geometry parameters			
(A) Intramolecular Bond Length ^a			
O(1)–C(10)	1.369(2)	O(3)–H(3)	0.93(2)
C(5)–C(10)	1.394(2)	O(1)–H(1)	0.94(2)
C(5)–C(6)	1.510(5)	N(2)–H(1)	1.798(6)
N(2)–C(6)	1.477(2)	O(3)–H(1)	2.405(9)
N(2)–C(9)	1.482(2)	N(2)–O(1)	2.624(1)
C(7)–C(9)	1.506(1)	O(3)–H(1)	3.013(1)
C(7)–C(8)	1.394(2)	O(1)–O(3)	3.040(1)
O(3)–C(8)	1.366(2)		
(B.1) Intramolecular Bond Angles			
N(2)–H(1)–O(1)	144.6(1)		
H(1)–O(1)–C(10)	111.6(1)		
O(1)–C(10)–C(5)	120.9(1)		
C(10)–C(5)–C(6)	120.1(1)		
C(5)–C(6)–N(2)	113.3(4)		
C(6)–N(2)–C(9)	110.5(1)		
N(2)–C(9)–C(7)	111.7(1)		
C(9)–C(7)–C(8)	120.2(2)		
C(7)–C(8)–O(3)	117.3(1)		
C(8)–O(3)–H(3)	112.9(1)		
C(8)–O(3)–H(1)	90.9(1)		
O(3)–H(1)–N(2)	90.4(1)		
H(1)–N(2)–C(6)	93.7(1)		
H(1)–N(2)–C(9)	115.7(1)		
O(3)–H(1)–O(1)	124.5(1)		
(B.2) Intermolecular Non-Bond Angles			
O(1)–H(3)–O'(3)	176.3(1)		
(C) Intramolecular Torsional Angles			
H(1)–O(1)–C(10)–C(5)	12.2(1)		
O(1)–C(10)–C(5)–C(6)	5.6(1)		
C(10)–C(5)–C(6)–N(2)	–38.5(2)		
C(5)–C(6)–N(2)–C(9)	158.1(1)		
C(6)–N(2)–C(9)–C(7)	–73.3(3)		
N(2)–C(9)–C(7)–C(8)	–67.1(1)		
C(9)–C(7)–C(8)–O(3)	–1.2(1)		
C(7)–C(8)–O(3)–H(3)	174.6(4)		
(D) Intermolecular Interatomic Bond Length			
O(1)–H'(3)	1.773(3)	O(1)–O'(1)	4.210(4)
O(1)–O'(3)	2.702(1)	N(2)–N'(2)	7.441(1)

^a The atomic numbering is referred to in Table 3.

made for the solid-state samples, a similar situation may be expected to occur even in the solution where our reaction was proceeded. In fact, Dunker et al.¹⁰ reported the existence of intramolecular hydrogen bonding in the solution of chloroform. The intramolecular hydrogen bonding can be maintained even in the molten state, as reported by Dunker et al.¹⁰ for bisphenol A-based benzoxazine. In this way, the intramolecular hydrogen bonds can be formed stably in the various states of the benzoxazine molecule. Thus, we propose here that the reactive sites of the dimer are reduced to one by stabilization through an intramolecular hydrogen bond. In other words, one of the phenol rings becomes inactive owing to the intramolecular hydrogen bond of O–H...N, giving an asymmetrically structured product. This can be seen for most of the dimers investigated thus far.

Speculated Mechanism. The mechanism proposed by Burke et al.¹³ can be applied to explain the reaction. Owing to the intramolecular hydrogen bonding, a single phenol group in the dimer is stabilized. As a result, the oxazine formation can be achieved only at the other phenol group where the intermolecular hydrogen bond is formed. When one of the phenol rings is deactivated in this way by the intramolecular hydrogen bond, the electrophilic substitution of the iminium ion will occur only

on the alternate phenol ring at its ortho position. The cyclization to form the oxazine ring then occurs after the loss of a water molecule.

Experimental Section

Chemicals. Paraformaldehyde was purchased from Sigma (U.S.A.). 4-Ethylphenol, *p*-cresol, cyclohexylamine, and propylamine were obtained from Fluka Chemicals (Buchs, Switzerland). 1,4-Dioxane, methanol, cyclohexane, sodium hydroxide, sodium sulfate anhydrous, and diethyl ether were products from Ajax chemicals (Australia). All chemicals were AR grade and used without further purification.

Instruments. Fourier transform infrared spectra were measured at a resolution of 4 cm^{–1} by using a Bruker Equinox55/S spectrophotometer equipped with deuterated triglycine (DTGS) detector under the constant purge with dry air. The ¹H- and ¹³C nuclear magnetic resonance (NMR) spectrometers were a Varian UNITYplus 600 with proton frequency of 600 MHz. The coaddition of 64 transients for ¹H NMR spectra and 960 transients for ¹³C NMR spectra gave sufficient signal-to-noise ratio. The repeating time for ¹H experiments was 6 s for obtaining the proper integration value. The repeating time for ¹³C experiments was 3 s. ¹H–¹H correlated spectroscopy (COSY), ¹H–¹³C heteronuclear multiple quantum coherence (HMQC) and ¹H–¹³C heteronuclear multiple-bond coherence (HMBC) were performed. The samples were prepared as solutions using deuterated chloroform solvent with tetramethylsilane (0.1%, w/w) as an internal reference. Elemental analysis (EA) was performed by using a Perkin-Elmer 2400 Series II CHNS/O analyzer with the combustion temperature of 975 °C and a reduction temperature of 500 °C. For single crystals of benzoxazine dimers, that is, compounds **1**, **2**, and **3**, an X-ray imaging plate system DIP3000 (MAC Science Co. Ltd., Japan) was used. The graphite-monochromatized Mo K α line ($\lambda = 0.71073$ Å), which was generated from the SRA-M18XHF rotating anode X-ray generator (50 kV and 200 mA), was used as an incident X-ray source. The data collection was performed by the XDIP software (MAC Science). The sample was oscillated in a range of 3° over a total rotation angle of 0–180° around the ω axis. The exposure time was 30 min for one image. It took about 12 h to collect the 24 images in total. The data were analyzed by using the software DENZO and SCALEPACK.^{14–15} The crystal structure was solved by using a software maXus (NoniusBV, Delft). The direct method was used to find out the initial models, where the software SIR92 developed by Altmar et al. was used.¹⁶ Least-squares refinement was made on the basis of the full matrix method by using the quantity $\sum \omega(|F_o|^2 - |F_c|^2)^2$ as a minimized function with the weight $\omega = \exp[-FA \sin^2 \theta / \lambda^2] / [\sigma^2(F_o) + FB F_o^2]$, where $\sigma^2(F_o)$ was the squared standard deviation of the observed structure factor F_o and the coefficients FA and FB were set to the values 0.0 and 0.03, respectively. The reflections satisfying the cutoff condition of $|F_o| > 3\sigma(|F_o|)$ were used in the least-squares refinement. Because no detectable effect was found, the absorption correction for the observed intensity was not included in the structural refinement. As the measure of the reasonableness of the structural analysis, the reliability factors, R and R_w , were defined by the following equations; $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ and $R_w = [\sum \omega(|F_o| - |F_c|)^2 / \sum \omega |F_o|^2]^{1/2}$.

Syntheses. Symmetric benzoxazine dimers (Scheme 3), *N,N*-bis(2-hydroxy-5-methylbenzyl)cyclohexylamine **1**, *N,N*-bis(2-hydroxy-5-ethylbenzyl)cyclohexylamine **2**, and *N,N*-bis(2-hydroxy-5-methylbenzyl)propylamine **3**, were prepared as reported elsewhere⁷ and used as starting materials.

Preparation of 3,4-Dihydro-3-cyclohexyl-6-methyl-8-((2'-hydroxy-5'-methylbenzyl)cyclohexylaminomethyl)-2H-1,3-benzoxazine, 5. Cyclohexylamine (1.15 mL, 10 mmol) was added dropwise into the solution of paraformaldehyde (0.63 g, 20 mmol) in dioxane (10 mL). Benzoxazine dimer **1** (1.70 g, 5 mmol) in 20 mL of dioxane was further added, and the solution was refluxed for 6 h. The dioxane was removed

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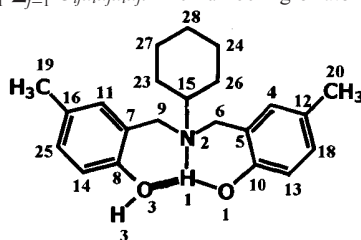
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Table 3.

	X	Y	Z	$U_{eq}(\text{\AA}^2)^a$		X	Y	Z	$U_{eq}(\text{\AA}^2)^a$
O1	0.54290(3)	0.49860(7)	0.61750(4)	0.0653(4)	H9A	0.5349(4)	0.0088(9)	0.6419(5)	0.047(2)
N2	0.57080(3)	0.21790(7)	0.65030(4)	0.0415(3)	H9B	0.5509(4)	0.057(1)	0.5724(5)	0.049(2)
O3	0.49630(3)	0.28420(8)	0.48650(4)	0.0627(4)	H11	0.4306(5)	0.004(1)	0.6167(6)	0.063(3)
C4	0.59230(4)	0.4425(1)	0.81620(5)	0.0492(5)	H13	0.5628(5)	0.750(1)	0.6801(6)	0.067(3)
C5	0.57300(4)	0.40840(9)	0.74190(4)	0.0413(4)	H14	0.3783(5)	0.345(1)	0.4170(6)	0.068(3)
C6	0.55680(5)	0.25140(9)	0.71330(5)	0.0470(5)	H15	0.6557(4)	0.2960(9)	0.7040(5)	0.049(2)
C7	0.46650(4)	0.13210(9)	0.56060(5)	0.0461(5)	H18	0.5951(5)	0.799(1)	0.8100(6)	0.072(3)
C8	0.44990(5)	0.2309(1)	0.50120(5)	0.0505(5)	H19A	0.3136(9)	−0.055(3)	0.571(1)	0.20(1)
C9	0.53340(4)	0.09020(9)	0.60670(5)	0.0483(5)	H19B	0.273(1)	0.034(2)	0.510(1)	0.150(7)
C10	0.56270(4)	0.52510(9)	0.69200(5)	0.0487(5)	H19C	0.3002(9)	0.112(2)	0.584(1)	0.191(9)
C11	0.42000(5)	0.0734(1)	0.57560(6)	0.0557(5)	H20A	0.6238(7)	0.535(2)	0.9558(9)	0.136(6)
C12	0.60040(4)	0.5868(1)	0.84280(5)	0.0564(5)	H20B	0.5988(8)	0.698(2)	0.9286(9)	0.136(7)
C13	0.57160(5)	0.6705(1)	0.71740(6)	0.0636(6)	H20C	0.6542(9)	0.671(2)	0.9442(9)	0.149(7)
C14	0.38830(5)	0.2701(1)	0.45890(6)	0.0630(6)	H23A	0.6533(6)	−0.018(1)	0.6865(8)	0.110(5)
C15	0.63820(4)	0.2055(1)	0.67330(5)	0.0475(5)	H23B	0.6606(6)	0.065(1)	0.7627(7)	0.094(4)
C16	0.35790(5)	0.1111(1)	0.53430(6)	0.0669(6)	H24A	0.7414(6)	0.305(1)	0.6542(7)	0.106(5)
C18	0.58950(5)	0.6995(1)	0.79160(6)	0.0651(6)	H24B	0.7288(7)	0.213(1)	0.5845(8)	0.115(5)
C19	0.61930(9)	0.6187(2)	0.92390(7)	0.090(1)	H25	0.3019(6)	0.239(1)	0.4463(6)	0.074(3)
C23	0.72100(7)	0.2128(2)	0.62890(9)	0.095(1)	H26A	0.6300(6)	0.313(1)	0.5781(7)	0.094(4)
C25	0.34330(6)	0.2104(1)	0.47600(7)	0.0691(7)	H26B	0.6316(6)	0.132(1)	0.5744(7)	0.099(4)
C26	0.65200(6)	0.2164(2)	0.60630(6)	0.0756(8)	H27A	0.7609(7)	−0.001(2)	0.7775(9)	0.132(5)
C27	0.74000(6)	0.0801(2)	0.7445(1)	0.101(1)	H27B	0.7562(7)	0.179(2)	0.7752(9)	0.138(6)
C28	0.75250(8)	0.0812(2)	0.6773(1)	0.105(1)	H28A	0.7976(8)	0.090(2)	0.6967(8)	0.134(6)
H4	0.5997(3)	0.3613(9)	0.8514(4)	0.041(2)	H28B	0.7344(7)	−0.017(2)	0.6446(8)	0.126(5)
H6A	0.5759(4)	0.179(1)	0.7546(5)	0.055(3)	H3	0.4827(6)	0.356(2)	0.4492(7)	0.108(5)
H6B	0.5109(5)	0.2403(9)	0.6948(5)	0.055(3)	H1	0.5460(6)	0.397(2)	0.6080(7)	0.115(5)

^a $T = \exp[2\pi^2 U]$; $U = U_{iso} = U_{eq}$; $U_{eq} = 1/3 \sum_{i=1}^3 \sum_{j=1}^3 U_{ij} a_i a_j a_j$. The numbering of atom is shown below.



in vacuo to obtain a yellowish viscous product. The solution obtained was dissolved in 50 mL of diethyl ether and extracted with 3 N NaOH 10 mL for three times, followed by 10 mL of water washing until the solution became neutral. The product was dried over sodium sulfate, and the solvent was removed. The crude viscous product was left overnight at room temperature, producing a white precipitate. The precipitate was collected and recrystallized by 2-propanol.

To study the solvent effect, the similar reactions were carried out using cyclohexane and methanol as solvents. The reaction in a neat liquid state at 135 °C for 15 min was also performed for comparison. The molar ratios of reactants were also varied, that is, paraformaldehyde (0.32 g, 10 mmol), cyclohexylamine (0.56 mL, 5 mmol) and benzoxazine dimer **1** (1.70 g, 5 mmol).

Compound **5**: 80% yield; $R_f = 0.29$ (5% MeOH in CHCl_3); mp = 130 °C; FT-IR (KBr, cm^{-1}): 3300–3100 (br, OH), 1498 (s, oxazine), 1223 (br s, C–O); ^1H NMR (600 MHz, CDCl_3 , ppm): δ_{H} 1.12 (2H, m, CH_2), 1.16 (2H, m, CH_2), 1.25 and 1.98 (4H, m, CH_2), 1.40 and 1.92 (4H, m, CH_2), 1.58 and 1.74 (4H, m, CH_2), 1.60 and 1.76 (4H, m, CH_2), 2.21 (3H, s, Ar– CH_3), 2.20 (3H, s, Ar– CH_3), 2.62 (1H, tt, CH, $J_1 = 11.81$ Hz and $J_2 = 3.30$ Hz), 2.68 (1H, m, CH), 3.57 (2H, s, Ar– CH_2 –N), 3.78 (2H, s, Ar– CH_2 –N), 4.03 (2H, s, Ar– CH_2 –N), 4.98 (2H, s, O– CH_2 –N), 6.64 (1H, d, Ar–H, $J_3 = 8.24$ Hz), 6.66 (1H, d, Ar–H, $J_4 = 1.51$ Hz), 6.74 (1H, d, Ar–H, $J_5 = 1.94$ Hz), 6.83 (1H, d, Ar–H, $J_4 = 1.51$ Hz), 6.89 (1H, dd, Ar–H, $J_3 = 8.24$ Hz and $J_5 = 1.94$ Hz), 11.16 (1H, br, Ar–OH); ^{13}C NMR (150 MHz, CDCl_3 , ppm): δ_{C} 20.47, 20.55, 25.48, 25.94, 26.01, 26.30, 27.64, 31.60, 47.38, 47.87, 52.89, 57.99, 58.47, 80.19, 115.63, 121.19, 122.45, 124.91, 126.76, 127.48, 128.52, 128.71, 129.04, 130.18, 151.58, 155.94. Anal. calcd for $\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_2$: C, 77.92; H, 9.10; and N, 6.06. Found: C, 77.79; H, 9.17; and N, 6.09.

Preparation of 3,4-Dihydro-3-cyclohexyl-6-ethyl-8-((2'-hydroxy-5'-methylbenzyl)cyclohexylaminomethyl)-2H-1,3-benzoxazine, 6 and

3,4-Dihydro-3-cyclohexyl-6-methyl-8-((2'-hydroxy-5'-methylbenzyl)-propylaminomethyl)-2H-1,3-benzoxazine, 7. Benzoxazine dimer **2** (1.84 g, 5 mmol), paraformaldehyde (0.32 g, 10 mmol), and cyclohexylamine (0.56 mL, 5 mmol) were used to prepare compound **6**, while benzoxazine dimer **3** (1.50 g, 5 mmol), paraformaldehyde (0.32 g, 10 mmol), and propylamine (0.42 mL, 5 mmol) were used to prepare compound **7**. Similarly, the reactions proceeded in a neat liquid state at 135 °C for 15 min. The obtained products were characterized using FT-IR, ^1H NMR, ^{13}C NMR, and EA.

Compound **6**: 80% yield; $R_f = 0.27$ (5% MeOH in CHCl_3); mp = 143 °C; FT-IR (KBr, cm^{-1}): 3300–3100 (br, OH), 1498 (s, oxazine), 1198 (br s, C–O). ^1H NMR (600 MHz, CDCl_3 , ppm): δ_{H} 1.08 (2H, m, CH_2), 1.15 (2H, m, CH_2), 1.19 (6H, t, CH_3 – CH_2 –Ar, $J_1 = 7.69$ Hz), 1.25 and 1.98 (4H, m, CH_2), 1.40 and 1.91 (4H, m, CH_2), 1.58 and 1.75 (4H, m, CH_2), 1.60 and 1.79 (4H, m, CH_2), 2.52 (4H, q, CH_3 – CH_2 –Ar, $J_1 = 7.69$ Hz), 2.63 (1H, tt, CH, $J_2 = 11.97$ Hz and $J_3 = 3.42$ Hz), 2.71 (1H, m, CH), 3.59 (2H, s, Ar– CH_2 –N), 3.81 (2H, s, Ar– CH_2 –N), 4.05 (2H, s, Ar– CH_2 –N), 4.99 (2H, s, O– CH_2 –N), 6.67 (1H, d, Ar–H, $J_4 = 8.12$ Hz), 6.68 (1H, d, Ar–H, $J_5 = 2.14$ Hz), 6.77 (1H, d, Ar–H, $J_6 = 1.71$ Hz), 6.86 (1H, d, Ar–H, $J_5 = 2.14$ Hz), 6.93 (1H, dd, Ar–H, $J_4 = 8.12$ Hz, $J_6 = 1.71$ Hz), 11.22 (1H, br, Ar–OH); ^{13}C NMR (150 MHz, CDCl_3 , ppm): δ_{C} 15.67, 15.92, 25.47, 25.94, 26.02, 26.31, 27.68, 27.99, 28.02, 31.59, 47.48, 47.96, 52.95, 58.05, 58.39, 80.15, 115.65, 121.16, 122.43, 124.93, 125.49, 127.30, 127.82, 128.98, 134.14, 135.24, 151.73, 156.16. Anal. calcd for $\text{C}_{32}\text{H}_{46}\text{N}_2\text{O}_2$: C, 78.36; H, 9.39; and N, 5.71. Found: C, 78.19; H, 9.44; and N, 5.73.

Compound **7**: 75% yield; $R_f = 0.31$ (5% MeOH in CHCl_3); mp = 125 °C; FT-IR (KBr, cm^{-1}): 3350–3100 (br, OH), 1498 (s, oxazine), 1228 (br s, C–O); ^1H NMR (600 MHz, CDCl_3 , ppm): δ_{H} 0.83 (3H, t, N– CH_2 – CH_2 – CH_3 , $J_1 = 7.33$ Hz), 1.13 (2H, m, CH_2), 1.24 and 1.97 (4H, m, CH_2), 1.61 and 1.74 (4H, m, CH_2), 1.65 (2H, qt, N– CH_2 –

$\text{CH}_2\text{-CH}_3$, $J_1 = 7.33$ Hz and $J_2 = 2.06$ Hz), 2.21 (3H, s, CH_3), 2.22 (3H, s, Ar- CH_3), 2.42 (2H, t, N- $\text{CH}_2\text{-CH}_2\text{-CH}_3$, $J_2 = 2.06$ Hz), 2.68 (1H, m, CH), 3.57 (2H, s, Ar- $\text{CH}_2\text{-N}$), 3.68 (2H, s, Ar- $\text{CH}_2\text{-N}$), 4.04 (2H, s, Ar- $\text{CH}_2\text{-N}$), 4.98 (2H, s, O- $\text{CH}_2\text{-N}$), 6.66 (1H, d, Ar-H, $J_3 = 8.01$ Hz), 6.68 (1H, d, Ar-H, $J_4 = 1.49$ Hz), 6.74 (1H, d, Ar-H, $J_5 = 1.60$ Hz), 6.83 (1H, d, Ar-H, $J_4 = 1.49$ Hz), 6.92 (1H, dd, Ar-H, $J_3 = 8.01$ Hz and $J_5 = 1.60$ Hz), 10.83 (1H, br, Ar-OH); ^{13}C NMR (150 MHz, CDCl_3 , ppm): δ_{C} 11.83, 19.33, 20.55, 20.66, 25.56, 26.02, 31.65, 47.55, 52.46, 55.32, 57.59, 58.59, 80.30, 115.75, 121.40, 122.48, 124.16, 127.01, 127.72, 128.72, 128.79, 129.16, 130.22, 151.69, 155.89. Anal. calcd for $\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_2$: C, 76.78; H, 9.00; and N, 6.64. Found: C, 76.83; H, 9.07; and N, 6.57.

Conclusions

Although we expected the dioxazine compound as a product from the Mannich reaction onto benzoxazine dimer, we got only mono-oxazine as characterized by FT-IR, ^1H NMR, ^{13}C NMR, and 2D-NMR. X-ray structure analysis revealed the existence of intramolecular hydrogen bonds with a distance of ca. 1.8 Å. Here, we want to propose the reaction mode of our benzoxazine dimer as a "self-selective reaction" since the reaction occurs at only the single site of phenol, owing to the intramolecular hydrogen bond of the dimer itself. In other words, the mono-oxazine is produced *inevitably* because of this "self-selective reaction" under the various conditions.

In this way, judging from the chemical formula, it is unexpected to achieve the asymmetric molecule. However, as we clarified here, another key factor is involved in the reaction, that is, the unique stereo structure of the reactant molecule by intramolecular hydrogen bonding has to be taken into consid-

eration. We ought to note that the present work gives us a hint to achieve the asymmetrical product by designing the molecule with a strong intramolecular hydrogen bond to deactivate the reactive site. Hence, with this approach we may obtain the desired product in a high yield without multisteps of protecting and deprotecting procedures, and the use of catalysts, and special condition. We are achieving a series of well-defined polybenzoxazines by making mono-oxazine benzoxazine dimer compounds be a useful pathway.

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Supporting Information Available: Additional spectra (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Metal Ion Guest Responsive Benzoxazine Dimers and Inclusion Phenomena of Cyclic Derivatives*

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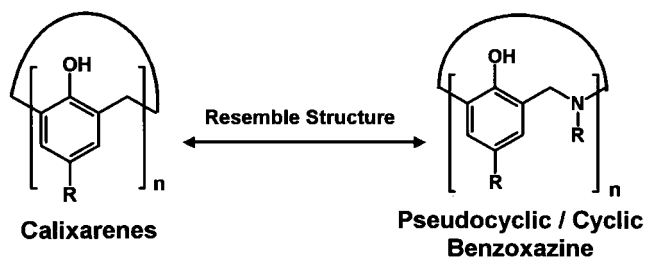
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Key words: benzoxazine dimer, benzoxazine dimer based macrocyclic, metal ion guest responsive properties, Pedersen's technique, stoichiometric host–guest ratio

Abstract

A series of benzoxazine dimers (**1–9**), esterified benzoxazine dimers (**10–18**), and benzoxazine dimer based macrocyclic derivatives (**19–22**) are prepared. The metal ion guest responsive properties of the benzoxazine dimers obtained are clarified by using Pedersen's technique. The ion extractions of the benzoxazine dimers are controlled by the bulkiness of the functional group at the aza position. The ones with cyclohexyl bulky groups at the aza position, **7–9**, are two times higher than those with methyl groups, **1–3**. The extractions are close to 100% for esterified dimers (**10–18**). For the macrocyclic derived dimers, the ether cyclic derivatives, **21–22**, interact with sodium, potassium and cesium ions at stoichiometric ratios 2:1 and 1:1 depending on the metal species, as evidenced from ¹H-NMR.



Introduction

For the past three decades, host–guest compounds or inclusion compounds have received much attention mainly due to the information obtained from interactions at the molecular level [1–2] observed by a variety of characterization techniques. The induced molecular recognition properties are known to be based on non-covalent interactions, or secondary forces, such as van der Waals, dipole–dipole interaction, π – π stacking, and hydrogen bonding between host and guest [1–3]. Many of the host molecules were designed either with specific functional groups to form molecular assemblies or definite macrocyclic structures, in order to achieve novel functional supramolecules.

Polybenzoxazine is a new type of phenolic resin with superb mechanical and thermal properties [4]. Most of the studies on these materials have concentrated on difunctional benzoxazines with the objective of improving the processing

conditions of thermosetting materials. In our studies of open-ring benzoxazines [5], we originally proposed that the basic unit is close to that of calixarenes but with an aza methylene linkage in between (Scheme I). Hence, the open-ring benzoxazines can be expected to have properties similar to that of calixarenes. In order to clarify whether the open-ring benzoxazines show inclusion properties and to understand the phenomena related to the structure, a series of the controlled structure benzoxazines dimers were prepared [6–7]. High yield (80%) was obtained from a single step ring opening reaction of benzoxazine monomer. We also extended the work to the [2+2] macrocyclic dimers via esterification and etherification [7–10].

The benzoxazine dimer is an appropriate model to use since there is no complication due to the chain length. Moreover, a series of derivatives can be prepared which enables systematic studies to be done on the inclusion properties related to the chemical structure. The present article is aimed at exploring host–guest interactions of benzoxazine on the basis of the interaction between aza methylenephénol unit and metal ions.

Experimental

Materials

Barium chloride, lithium hydroxide and deuterated chloroform (CDCl_3) were purchased from Fluka Chemicals (Buchs, Switzerland). Sodium hydroxide, cesium carbonate, potassium hydroxide, chloroform, magnesium chloride, calcium chloride, and picric acid were the products of Ajax

* Supplementary data relating to this article are deposited with the British Library as Supplementary Publication No. 82305 (1 page).

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chemicals (Australia). All chemicals were analytical grade and used without further purification.

Syntheses

A series of benzoxazine dimers; *N,N*-bis(3,5-dimethyl-2-hydroxybenzyl)methylamine **1**, *N,N*-bis(5-methyl-2-hydroxybenzyl)methylamine **2**, *N,N*-bis(5-ethyl-2-hydroxybenzyl)methylamine **3**, *N,N*-bis(3,5-dimethyl-2-hydroxybenzyl)propylamine **4**, *N,N*-bis(5-methyl-2-hydroxybenzyl)propylamine **5**, *N,N*-bis(5-ethyl-2-hydroxybenzyl)propylamine **6**, *N,N*-bis(3,5-dimethyl-2-hydroxybenzyl)cyclohexylamine **7**, *N,N*-bis(5-methyl-2-hydroxybenzyl)cyclohexylamine **8**, *N,N*-bis(5-ethyl-2-hydroxybenzyl)cyclohexylamine **9**, were prepared as reported elsewhere [6–7] and used as starting materials (Scheme II).

Preparation of

N,N-bis(2-benzoyl-3,5-dimethylbenzyl)methylamine **10**,
N,N-bis(2-benzoyl-5-methylbenzyl)methylamine **11**,
N,N-bis(2-benzoyl-5-ethylbenzyl)methylamine **12**,
N,N-bis(2-benzoyl-3,5-dimethylbenzyl)propylamine **13**,
N,N-bis(2-benzoyl-5-dimethylbenzyl)propylamine **14**,
N,N-bis(2-benzoyl-5-ethylbenzyl)propylamine **15**,
N,N-bis(2-benzoyl-3,5-dimethylbenzyl)cyclohexylamine **16**,
N,N-bis(2-benzoyl-5-ethylbenzyl)cyclohexylamine **17**,
N,N-bis(2-benzoyl-5-ethylbenzyl)cyclohexylamine **18**

Benzoxazine dimer **1** (5 mmol) was dissolved in dichloromethane (50 mL) followed by the addition of NaOH (20 mmol) in water (50 mL). The mixture was stirred vigorously at room temperature for 30 min and a solution of benzoyl chloride (10 mmol) in dichloromethane (CH₂Cl₂, 50 mL) was added dropwise for 1 h. The reaction was allowed to proceed at room temperature for 6 h. The CH₂Cl₂ phase was collected and extracted with water several times. The product was dried over sodium sulfate and the solvent removed to obtain a white product of **10**. Similarly, **11–18** were prepared as for **10** with the starting materials **2–9**, respectively. The products obtained were characterized by FTIR, ¹H NMR, and EA.

Compound **10**: 95% yield; clear and colorless crystal; mp. 158–159 °C; FTIR (KBr, cm⁻¹): 1737 (vs, C=O), 1484 (s, tetrasubstituted benzene), 1265 (vs, C–N stretching). ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 2.05 (3H, s, N–CH₃), 2.15 (6H, s, Ar–CH₃), 2.30 (6H, s, Ar–CH₃), 3.35 (4H, s, Ar–CH₂–N), 6.98 (2H, s, Ar–H), 7.05 (2H, s, Ar–H), 7.45 (4H, t, Ar–H), 7.62 (2H, t, Ar–H), 8.20 (4H, d, Ar–H). Anal. calcd for C₃₃H₃₃NO₄: C, 78.11; H, 6.51; and N, 2.76. Found: C, 77.99; H, 6.54; and N, 2.78.

Compound **11**: 95% yield; clear and colorless crystal; mp. 151–152 °C; FTIR (KBr, cm⁻¹): 1738 (vs, C=O), 1499 (s, trisubstituted benzene), 1266 (vs, C–N stretching). ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 2.05 (3H, s, N–CH₃), 2.30 (6H, s, Ar–CH₃), 3.45 (4H, s, Ar–CH₂–N), 6.98 (2H, d, Ar–H), 7.05 (2H, s, Ar–H), 7.10 (2H, d, Ar–H), 7.45 (4H, t, Ar–H), 7.62 (2H, t, Ar–H), 8.20 (4H, d, Ar–H). Anal. calcd for C₃₁H₂₉NO₄: C, 77.66; H, 6.05; and N, 2.92. Found: C, 77.71; H, 6.12; and N, 2.89.

Compound **12**: 95% yield; clear and colorless crystal; mp. 153–154 °C; FTIR (KBr, cm⁻¹): 1738 (vs, C=O), 1498 (s, trisubstituted benzene), 1264 (vs, C–N stretching). ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 1.25 (6H, t, Ar–CH₂–CH₃), 2.05 (3H, s, N–CH₃), 2.65 (4H, q, Ar–CH₂–CH₃), 3.45 (4H, s, Ar–CH₂–N), 6.98 (2H, d, Ar–H), 7.05 (2H, s, Ar–H), 7.10 (2H, d, Ar–H), 7.45 (4H, t, Ar–H), 7.62 (2H, t, Ar–H), 8.20 (4H, d, Ar–H). Anal. calcd for C₃₃H₃₃NO₄: C, 78.11; H, 6.51; and N, 2.76. Found: C, 78.12; H, 6.48; and N, 2.73.

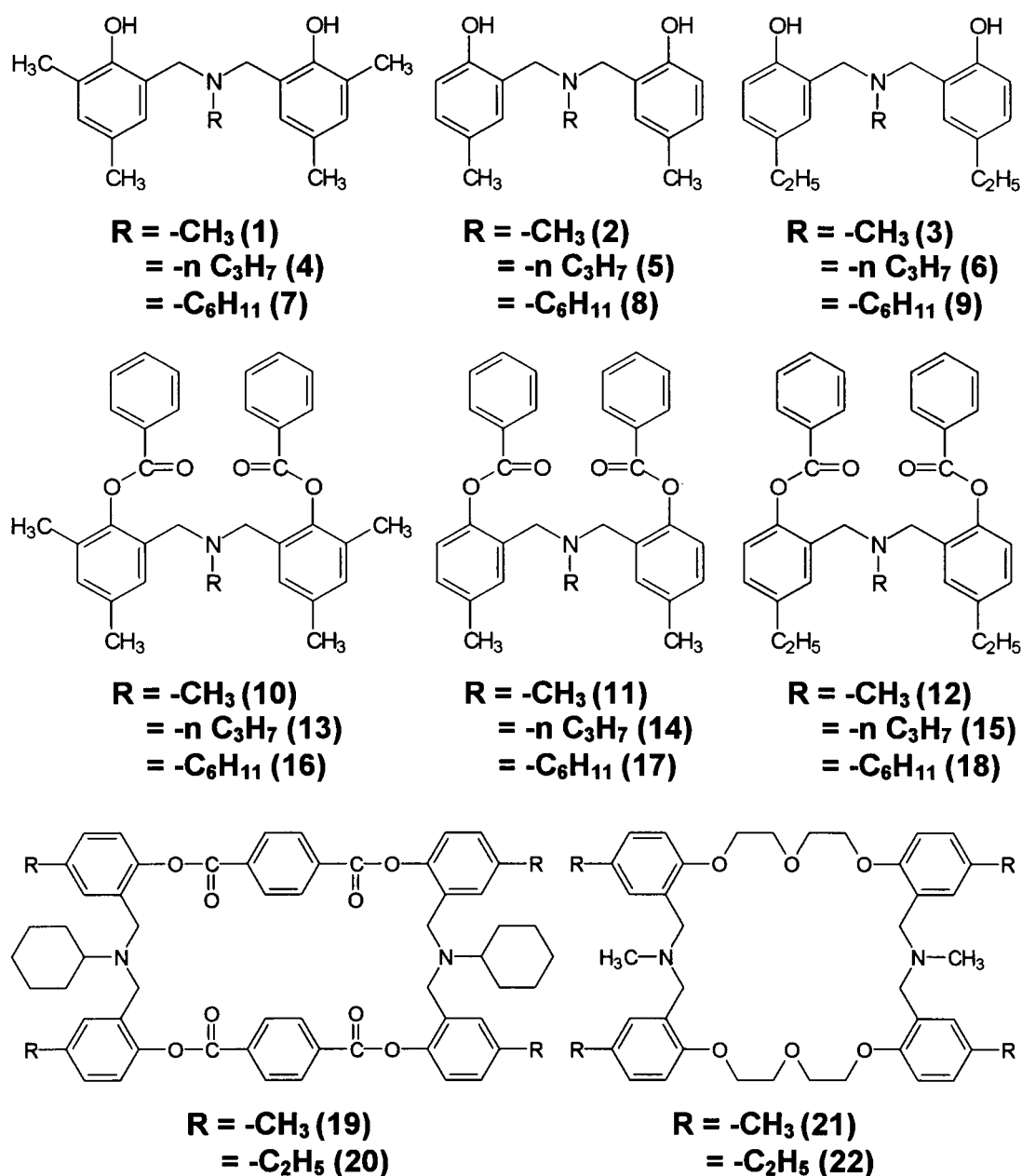
Compound **13**: 95% yield; clear and colorless crystal; mp. 161–162 °C; FTIR (KBr, cm⁻¹): 1734 (vs, C=O), 1498 (m, tetrasubstituted benzene), 1264 (s, C–N stretching). ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 0.75 (3H, t, N–CH₂–CH₂–CH₃), 1.45 (2H, m, N–CH₂–CH₂–CH₃), 2.10 (6H, s, Ar–CH₃), 2.22 (6H, s, Ar–CH₃), 2.35 (2H, t, N–CH₂–CH₂–CH₃), 3.45 (4H, s, Ar–CH₂–N), 6.98 (2H, d, Ar–H), 7.05 (2H, s, Ar–H), 7.10 (2H, d, Ar–H), 7.45 (4H, t, Ar–H), 7.62 (2H, t, Ar–H), 8.20 (4H, d, Ar–H). Anal. calcd for C₃₅H₃₇NO₄: C, 78.50; H, 6.92; and N, 2.62. Found: C, 78.48; H, 6.87; and N, 2.65.

Compound **14**: 95% yield; clear and colorless crystal; mp. 154–155 °C; FTIR (KBr, cm⁻¹): 1737 (vs, C=O of ester), 1497 (m, trisubstituted benzene), 1268 (vs, C–N stretching). ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 0.75 (3H, t, N–CH₂–CH₂–CH₃), 1.45 (2H, m, N–CH₂–CH₂–CH₃), 2.18 (6H, s, Ar–CH₃), 2.35 (2H, t, N–CH₂–CH₂–CH₃), 3.45 (4H, s, Ar–CH₂–N), 6.98 (2H, d, Ar–H), 7.05 (2H, s, Ar–H), 7.10 (2H, d, Ar–H), 7.45 (4H, t, Ar–H), 7.62 (2H, t, Ar–H), 8.20 (4H, d, Ar–H). Anal. calcd for C₃₃H₃₃NO₄: C, 78.11; H, 6.51; and N, 2.76. Found: C, 78.07; H, 6.46; and N, 2.78.

Compound **15**: 95% yield; clear and colorless crystal; mp. 158–159 °C; FTIR (KBr, cm⁻¹): 1734 (vs, C=O), 1497 (m, trisubstituted benzene), 1267 (vs, C–N stretching). ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 0.75 (3H, t, N–CH₂–CH₂–CH₃), 1.25 (6H, t, Ar–CH₂–CH₃), 1.45 (2H, m, N–CH₂–CH₂–CH₃), 2.35 (2H, t, N–CH₂–CH₂–CH₃), 2.65 (4H, q, Ar–CH₂–CH₃), 3.45 (4H, s, Ar–CH₂–N), 6.98 (2H, d, Ar–H), 7.05 (2H, s, Ar–H), 7.10 (2H, d, Ar–H), 7.45 (4H, t, Ar–H), 7.62 (2H, t, Ar–H), 8.20 (4H, d, Ar–H). Anal. calcd for C₃₅H₃₇NO₄: C, 78.50; H, 6.92; and N, 2.62. Found: C, 78.53; H, 6.90; and N, 2.59.

Compound **16**: 95% yield; clear and colorless crystal; mp. 171–172 °C; FTIR (KBr, cm⁻¹): 1731 (vs, C=O), 1482 (s, tetrasubstituted benzene), 1265 (vs, C–N stretching). ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 1.1 (4H, m, CH₂), 1.60 (2H, m, CH₂), 1.82 (4H, dt, CH₂), 2.05 (3H, s, N–CH₃), 2.15 (6H, s, Ar–CH₃), 2.60 (1H, t, CH), 3.35 (4H, s, Ar–CH₂–N), 6.98 (2H, s, Ar–H), 7.05 (2H, s, Ar–H), 7.45 (4H, t, Ar–H), 7.62 (2H, t, Ar–H), 8.20 (4H, d, Ar–H). Anal. calcd for C₃₈H₄₁NO₄: C, 79.30; H, 7.13; and N, 2.43. Found: C, 79.28; H, 7.11; and N, 2.47.

Compound **17**: 95% yield; clear and colorless crystal; mp. 163–164 °C; FTIR (KBr, cm⁻¹): 1738 (vs, C=O), 1497 (m, trisubstituted benzene), 1267 (vs, C–N stretching). ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 1.1 (4H, m, CH₂), 1.60 (2H, m, CH₂), 1.82 (4H, dt, CH₂), 2.40 (6H, s, Ar–CH₃), 2.50 (1H, t, CH), 3.55 (4H, s, Ar–CH₂–N), 6.98 (2H, d, Ar–



Scheme 2.

H), 7.05 (2H, s, Ar-H), 7.10 (2H, d, Ar-H), 7.45 (4H, t, Ar-H), 7.62 (2H, t, Ar-H), 8.20 (4H, d, Ar-H). Anal. calcd for C₃₆H₃₇NO₄: C, 78.98; H, 6.76; and N, 2.56. Found: C, 78.88; H, 6.78; and N, 2.55.

Compound **18**: 95% yield; clear and colorless crystal; mp. 166–167 °C; FTIR (KBr, cm⁻¹): 1737 (vs, C=O), 1498 (m, trisubstituted benzene), 1267 (vs, C–N stretching). ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 1.1 (4H, m, CH₂), 1.25 (6H, t, Ar-CH₂-CH₃), 1.45 (2H, m, N-CH₂-CH₂-CH₃), 1.60 (2H, m, CH₂), 1.82 (4H, dt, CH₂), 2.35 (2H, t, N-CH₂-CH₂-CH₃), 2.50 (1H, t, CH), 2.65 (4H, q, Ar-CH₂-CH₃), 3.55 (4H, s, Ar-CH₂-N), 6.98 (2H, d, Ar-H), 7.05 (2H, s, Ar-H), 7.10 (2H, d, Ar-H), 7.45 (4H, t, Ar-H), 7.62 (2H, t, Ar-H), 8.20 (4H, d, Ar-H). Anal. calcd for C₃₄H₄₁NO₄: C, 79.30; H, 7.13; and N, 2.43. Found: C, 79.27; H, 7.15; and N, 2.44.

Preparation of cyclic benzoxazines

Benzoxazine dimers based cyclic esters, **19–20**, were prepared as reported elsewhere [7–9] while benzoxazine dimers based cyclic ethers, **21–22** were reported previously [9–10].

Ion extraction property of benzoate benzoxazine dimers

Ion extraction was qualitatively and quantitatively analyzed by Pedersen's technique [1]. Benzoxazine derivatives (**1–22**) were dissolved in chloroform at 7×10^{-3} , 7×10^{-2} , 3.8×10^{-2} , 7×10^{-1} , and 3.8×10^{-1} M. Alkali and alkaline earth metal picrate aqueous solutions were prepared at 7×10^{-5} M. Both solutions were mixed and left for 10 min before determining the concentration of metal picrates. The concentration was determined using a UV-Vis Perkin-Elmer Lambda-16 Spectrophotometer at λ_{max} 354 nm (ε =

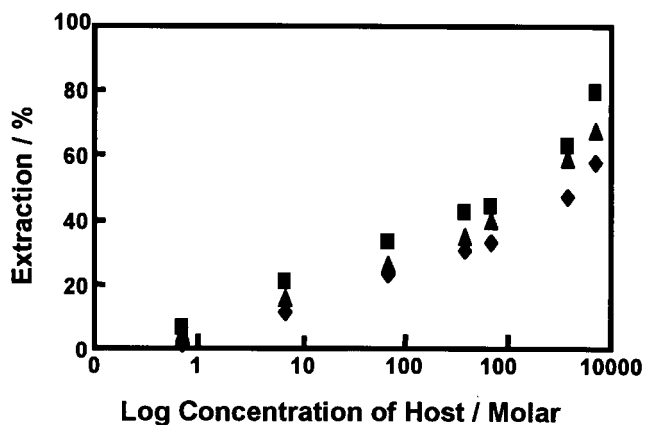


Figure 1. Extraction percentage of potassium picrate at a concentration of 7.5×10^{-5} M by (■) 1, (◆) 2, and (▲) 3 with various concentrations in CHCl_3 at 25° .

$1.45 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$). For cyclic derivatives, the organic phase was collected and further studied for the host–guest ratio by a ^1H NMR ACF 200 MHz of Bruker, Switzerland, using deuterated chloroform as a solvent with a trace amount of tetramethylsilane (TMS).

Results and discussion

Ion extraction

Figure 1 summarizes the ion extraction of 1–3. The host molecules have different substituents at the ortho and para positions, while the substituted groups at the nitrogen is the methyl group. When the concentration of 1–3 increases, the extraction of potassium ion increases gradually. At equimolar concentration of host and guest (7×10^{-5} M), the extraction is $\sim 10\%$. When the concentration of host is increased to 7×10^{-2} M, the extraction accomplished for $\sim 40\text{--}50\%$. Hampton *et al.* [11] reported that a series of hexahomotriazacalix[3]arenes gave ion extraction percentages of less than 0.2% at host and metal picrate concentrations of 5×10^{-3} M, owing to strong intramolecular hydrogen bonding. Recently, our group [7, 12–13] reported a unique inter and intramolecular hydrogen bonded network with the dimers using X-ray structural analysis. The intramolecular hydrogen bond generates a six-membered ring [13–14] via O–H–N and is found to be one of the key factors that provides the asymmetric reaction inevitably [13].

Thus, it is conceivable that intramolecular hydrogen bonding might play an important role for 1–9. Figure 1 also demonstrates that the ion extraction ability of dimers is achieved for only $20\text{--}40\%$ even the host concentration was 1000 times (7×10^{-2} M) higher than that of picrate (7×10^{-5} M). Here, we speculate that the host–guest formation might form a molecular assembly controlled by hydrogen bonding. Here, 1 with two methyl substituted groups at both ortho and para positions might form a loosely assembled structure owing to the steric effect, and consequently, there may be more available space to include the guests.

Sone *et al.* [15] reported that inclusion compounds of phenol–formaldehyde oligomers is enhanced when the

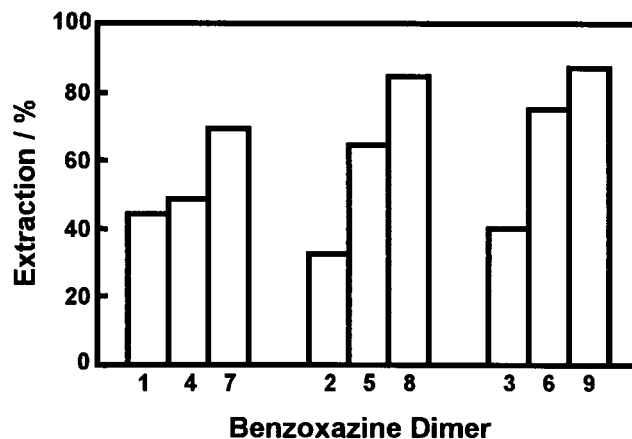


Figure 2. Extraction percentage of potassium picrate at a concentration of 7×10^{-5} M by 1–9 at the concentration of 7×10^{-2} M in CHCl_3 at 25°C .

phenol unit has a bulky group at the para position as observed that the guest was separated from water phase via the function of oligomers. It is, therefore, reasonable to expect that 3, which has more bulky group than 2, shows a higher ion extraction percentage (Figure 1). The electron density of host molecules is another important factor to be considered except the bulkiness of side groups. In terms of the electron donating ability, the order is $1 > 3 > 2$. This directly correlates with the ion extraction percentage. Similarly, it was found that other alkali and alkaline earth metal ions (lithium, sodium, magnesium, calcium, and barium) gave an increase in ion extraction percentage with increasing concentration of 1–3.

Effect of substituent groups on the aza methylene linkage

Chirachanchai *et al.* [12–13] determined the crystal structures of a series of benzoxazine dimers and found that the hydrogen bonding network and the variation of unit cell are both dependent on the substituted group at the aza linkage. Solid-state NMR studies using dimer crystals by Schnell *et al.* [16] supported the idea of hydrogen bonded network formation of dimers.

In order to identify the effect of substituent groups on the aza linkage in ion interaction, a series of dimers (4–9) were studied. As shown in Figure 2, the ion extraction percentage increased gradually when the functional groups changed from methyl to propyl and cyclohexyl groups. Compounds 4–6 (propyl group on aza linkage) show higher extraction ability than those of 1–3. In addition, the dimers 7–9, with cyclohexyl group, show significant extraction percentages up to $70\text{--}80\%$. This suggests that the bulky groups on the aza linkage enhance the ion extraction ability. Comparing 4 with 5 and 7 with 8, it can be concluded that the substituent group on the aza linkage is more important than any other substituent group in benzoxazine dimers. The extraction ability becomes most significant when both para-substituted groups in phenol and aza units are bulky (9).

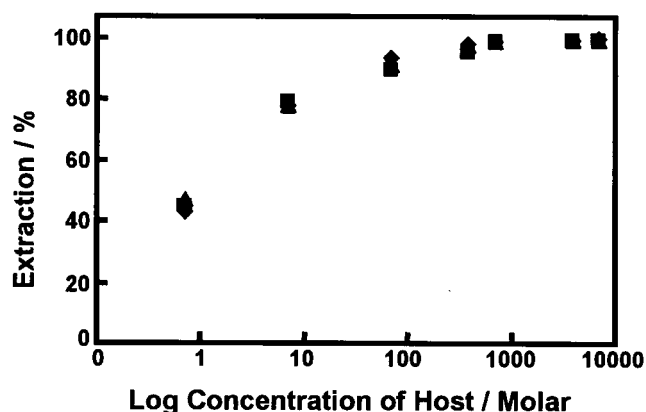


Figure 3. Extraction percentage of potassium picrate at a concentration of 7.5×10^{-5} M by (■), 10, (◆) 11, and (▲) 12 with various concentrations in CHCl_3 at 25 °C.

Symmetrical products of benzoxazine dimers by esterification

In a previous study, it was reported that the intramolecular hydrogen bond between $-\text{OH}$ and $-\text{N}-$ generated in each dimer is so strong that asymmetric products were formed due to the Mannich reaction [13]. In the present study, an attempt to obtain symmetric esters was carried out by using a strong base to deprotonate the hydroxyl group and eliminate the intramolecular hydrogen bond between the aza group and the OH of the phenol ring. Compounds 10–18 (Scheme II) were successfully obtained and confirmed by FTIR, $^1\text{H-NMR}$ and elemental analysis.

Effect of ester group on phenol unit

A series of compounds, 10–18, should provide us information on how the ion extraction ability changes when the hydrogen bonded network of the dimer is eliminated. Figure 3 clearly shows that the esterified dimers 10–12 give a two-fold increase in extraction percentage over those of 1–3. Almost all of the potassium picrate ($\sim 100\%$) is extracted by 10–12 at a concentration of 7×10^{-2} M. The results suggest that the elimination of hydrogen bonds together with an increase in lone pair electrons produces a strong interaction with metal ions.

Figure 4 shows that the extraction ability of each esterified dimer 10–18 is $\sim 100\%$. In other words, the effect of esterification is strong and overcomes that of substituent groups at either the aza or phenol positions.

Speculated ion interaction system

Figures 1–4 show that the ion extraction percentages are in the 30–95% range. In other words, the nearly quantitative extraction proceeds when the concentrations of dimers are higher than those of the metal ions by a factor of 1000. Although the ion extraction ability is clarified, selectivity is rarely observed.

Yamagishi *et al.* [17–18] reported that the metal ion extraction accomplished by acyclic all-ortho *p*-tert-butylphenol-formaldehyde was ~ 10 –80% when the concen-

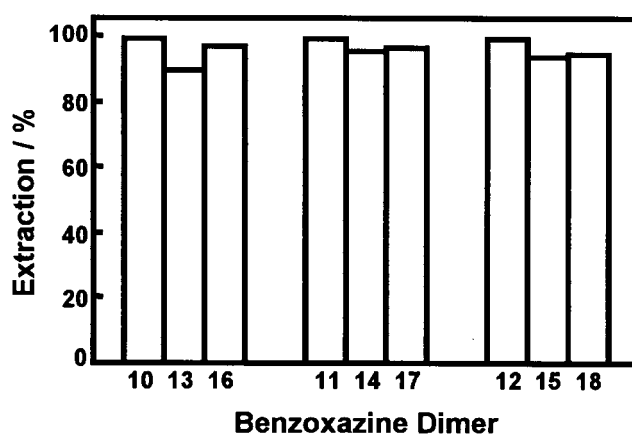


Figure 4. Extraction percentage of potassium picrate at a concentration of 7×10^{-5} M by 10–18 at the concentration of 7×10^{-2} M in CHCl_3 at 25 °C.

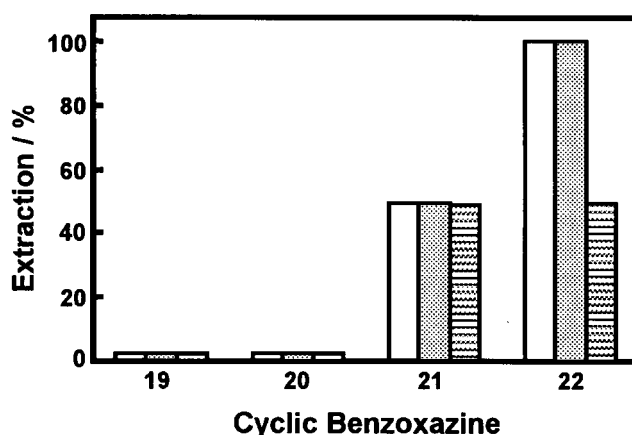


Figure 5. Extraction percentage of (□) sodium picrate, (▤) potassium picrate, and (▨) cesium picrate at a concentration of 7×10^{-5} M by 19–22 in CHCl_3 at 25 °C.

tration of host was 1000 times higher than that of the guest. The proposed host–guest formation was expected to be a pseudo-cyclic molecular assembly. In our case, we speculated that the molecular assembly between metal ions and benzoxazine dimers may form and be influenced by (i) the bulky group at nitrogen, (ii) the hydrogen bonding network, and (iii) the lone electron pairs.

Stoichiometry of ion interaction of benzoxazine dimer based cyclic compounds

Figure 5 shows the extraction percentages of sodium, potassium, and cesium ions using benzoxazine dimer based macrocyclic esters (19–20) and macrocyclic ethers (21–22) determined by Pedersen's technique [1] at equimolar concentration of host and metal species. The metal ion extraction percentages for 19–20 are difficult to observe while those for 21–22 are significant (Figure 5).

Here, the important information is that the extraction percentage for each of 21–22 is either 50 or 100%, which implies a molar ratio basis in integral numbers are 2:1 and 1:1. Thus, the host–guest formations are in stoichiometric ratio.

Table 1. ^1H NMR data of **21** and **21**-metal ion complexes

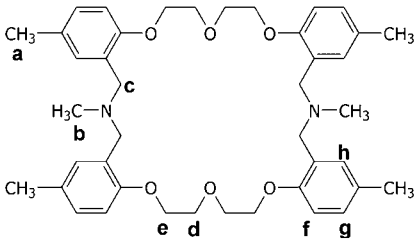
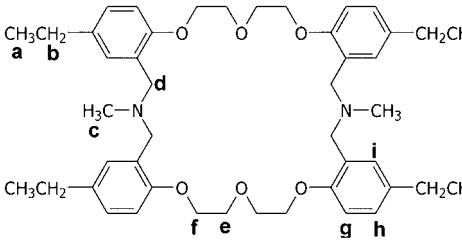
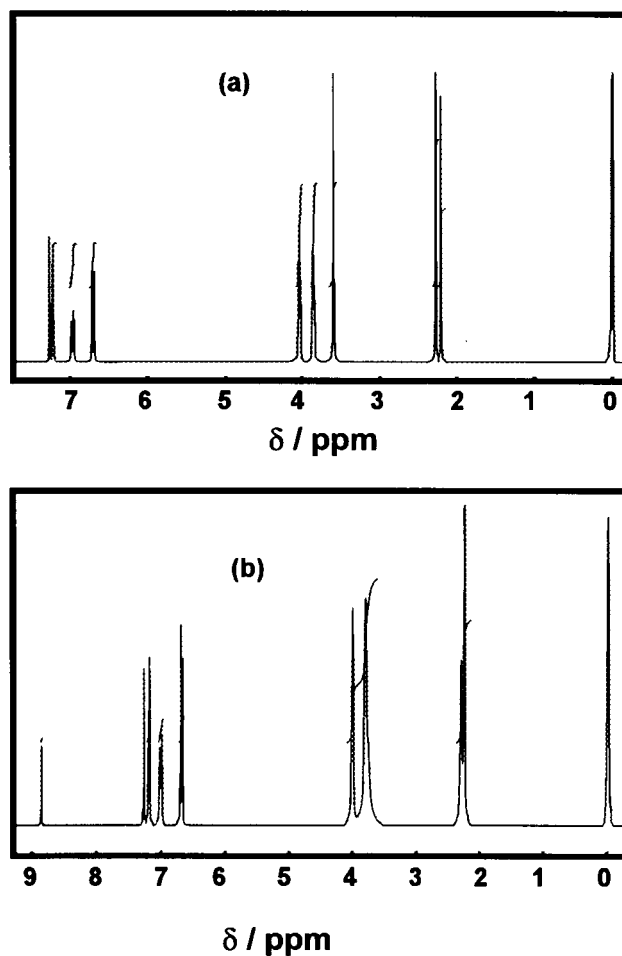
				
Position	Chemical Shift/ppm			
	21	21-Na⁺ complex	21-K⁺ complex	21-Cs⁺ complex
a	2.27	2.32	2.32	2.30
b	2.21	2.25	2.25	2.25
c	3.60	3.78	3.78	3.78
d	3.87	3.85	3.78	3.78
e	4.05	3.98	3.98	4.01
f	6.95	7.02	7.02	7.01
g	6.70	6.68	6.68	6.68
h	7.21	7.15	7.18	7.18

Table 2. ^1H NMR data of **22** and **22**-metal ion complexes

				
Position	Chemical Shift/ppm			
	22	22-Na⁺ complex	22-K⁺ complex	22-Cs⁺ complex
a	1.21	1.15	1.15	1.16
b	2.58	2.52	2.52	2.52
c	2.22	2.44	2.42	2.37
d	3.65	4.15	4.18	3.92
e	3.89	3.69	3.69	3.75
f	4.05	3.91	3.91	3.92
g	6.72	6.68	6.68	6.69
h	6.98	7.11	7.11	7.08
i	7.25	7.21	7.21	7.21

Further, ^1H NMR was applied to qualitatively and quantitatively study the host–guest ratio [19]. Since our studies were achieved using a liquid–liquid extraction system with picrate salt, the picrate peak at 8.8 ppm would be observed if host–metal complexes formed. In addition, the peak shifts indicate the changes of electron density in the host structure. Tables 1 and 2 clarify that δ_{H} values of **21–22** are shifted after extraction with picrate salts, especially the ones belonging to the methylene linkage and diethylene oxide unit. This implies that the host interacts with the metal guest via the lone pair electrons of nitrogen and oxygen atoms. It is important to note that even the type of metal ion changed; the chemical shifts for hosts (either **21** or **22**) appear at nearly the same position. This implies that the inclusion structure does not depend on the type of metal ion for both hosts (**21** and **22**).

To evaluate the molar ratio of host–guest, the peaks of picrate and aromatic protons were investigated. Compound **21** showed host–guest ratio of 2:1 for all studied ions while **22** has a ratio of 1:1 for Na^+ and K^+ , and 2:1 for Cs^+ (Figures 6–7). This indicates that the macrocyclic structure affects the host–metal formation significantly. In other words, **22** with more bulky group in the para position might preferentially form 1:1 type. It was unexpected that **19** and **20** did not show any ion extraction ability. It is speculated that the unpreferable cavity in the host compound could be the reason for the lack of extraction ability; future studies are being carried out to investigate this hypothesis.

Figure 6. ^1H NMR spectra of (a) **21** and (b) complex of **21** and cesium ion.

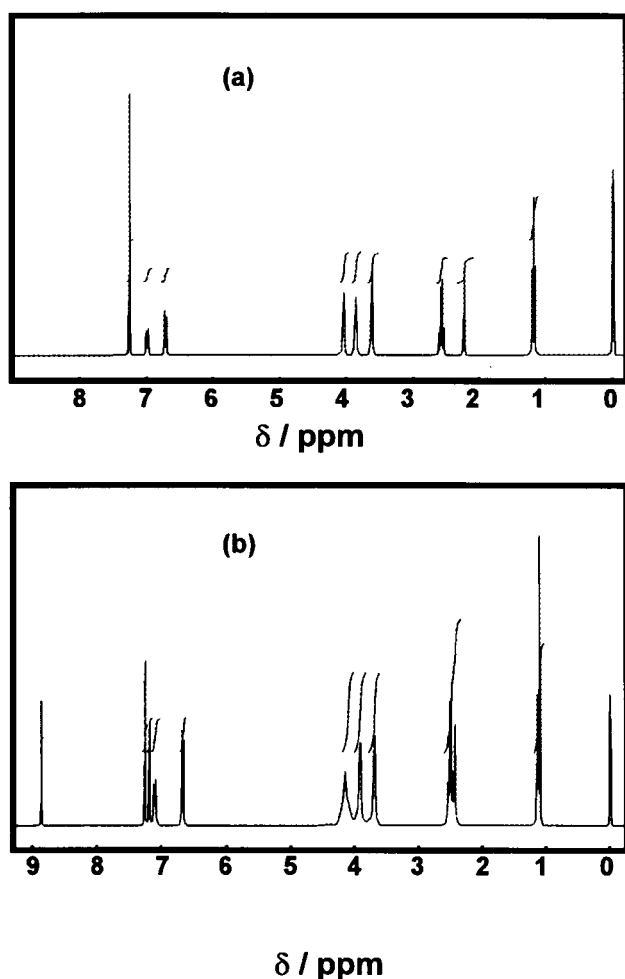


Figure 7. ^1H NMR spectra of (a) **22** and (b) complex of **22** and potassium ion.

Conclusions

Ion extraction studies using a series of benzoxazine dimers (**1–9**) and their esterified derivatives (**10–18**) verified that the ion interaction ability was related to (i) the inter and intramolecular hydrogen bond network (ii) the bulky group at the aza position and (iii) the number of electron lone pairs. A stoichiometric ratio between host-metal ions was observed when benzoxazine dimers were modified to be cyclic compounds. Studies on macrocyclic types (**19–22**) showed that ion interactions were involved with (i) the preferable structure of cyclic molecules, and (ii) the size of metal ions.

Acknowledgements

The authors thank Dr. Buncha Pulpoka (Chulalongkorn University) for his valuable comments. We also acknowledge Prof. Yoshihisa Inoue (Osaka University) for his constructive advice. One of the authors (S.C.) extends his thanks to the Hitachi Scholarship Foundation, Japan. Appreciation is to Mr. John Ellis, The Petroleum and Petrochemical College, Chulalongkorn University, for his linguistic advice. The work was granted by Ratchadaphisek Somphot Endowment, Chulalongkorn University.

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Inclusion Compounds Formed from *N,N*-bis(2-hydroxybenzyl)alkylamine Derivatives and Transition Metal Ions via Molecular Assembly

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A series of *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives (1–5) have been found to form host–guest compounds with transition metal ions. The inclusion phenomena in solution are confirmed from the new peak at 415 nm observed by UV-Vis (ultraviolet-visible) spectroscopy and the aromatic and methylene peak shifts observed by ¹H NMR (proton nuclear magnetic resonance) spectroscopy. Comparative studies on 1–5 by liquid–liquid extraction studies suggest that the bulky group at the aza position of the derivatives obstructs the ion interaction resulting in the decrease in ion extraction ability. Inclusion depends on the interaction of the transition metal ions with the compounds 1–5 at the aza and hydroxyl groups as identified by the two-dimensional nuclear Overhauser enhancement technique (¹H–¹H NOESY). The results from Job's plot and electrospray ionization mass spectroscopy (ESIMS) imply molecular assembly of the host–guest system in a 2:1 ratio. Comparative studies among different ions, i.e., Cu²⁺, Zn²⁺ and Cd²⁺ suggest that the host–guest formation is effective when electron sharing is possible through the outer orbital of the transition metal ions. In the case of inclusion in the solid state, the FTIR (Fourier transform infrared) spectra show the changes in vibrational mode of the functional groups in host molecules whereas the X-ray diffraction (XRD) patterns suggest a change in the packing structure of the host molecules. After host–guest formation, the thermal stability of the host molecules decreases as a result of the change in the packing structure from a hydrogen-bonded network to one of ionic interaction with the guest.

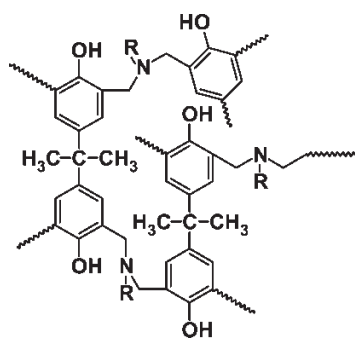
Keywords: Inclusion; Molecular assembly; *N,N'*-bis(2-hydroxybenzyl)alkylamine derivatives; Transition metal ions; Hydrogen bond network; Ionic interaction

INTRODUCTION

For the past few decades, supramolecular chemistry has received much attention with regard to molecular recognition and inclusion [1–5]. With the advance of instrumentation technology, not only cyclic but also acyclic compounds can be involved in host–guest relationships based on non-covalent interactions such as van der Waals [6], dipole–dipole [7], π – π stacking [8] and hydrogen bonding [9]. Many strategies for obtaining supramolecular compounds are challenging from the fundamental molecular designs to synthesis pathways.

Polybenzoxazines are reported as a novel type of phenolic resin with superb mechanical and thermal properties, which make them suitable composite materials [10]. The structure of the repeat unit of polybenzoxazines, the aza-methylene-phenol group, resembles the aza-methylene linkage in azacalixarenes (Scheme 1) [11]. Previously, we reported the conditions for a one-step ring opening reaction of benzoxazine to quantitatively (~90% yield) obtain *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives (Scheme 2) [12]. The structural characterization of the derivatives by single crystal X-ray analysis, NMR, and FTIR proved that the compounds are stabilized by an intra- and intermolecular hydrogen bond network [13]. Considering the uniqueness of *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives, it is important to note that the molecule can be a basic unit for a series of macrocyclic compounds. For example, we succeeded in using this compound

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SCHEME 1

in the synthesis of a variety of macrocycles and established their inclusion phenomena with alkali and alkaline earth metal ions [14–16].

In order to extend their use to organometallic catalysis, the metal ions in the host–metal compounds need to be transition metals. Thus, another practical application for the *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives would be in the generation of inclusion compounds with transition metal ions, and we expected that the electron rich phenol and aza groups might interact with transition metals. The present work thus aims to clarify (i) whether the *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives exhibit inclusion phenomena with the transition metal ions, and what the host–guest ratio is, (ii) how the functional group of the derivatives plays a role in the interaction with transition metal ions, (iii) the effect of inclusion on the thermal stability of the derivatives, and (iv) the effect of solvent molecules in the host–guest system.

RESULTS AND DISCUSSION

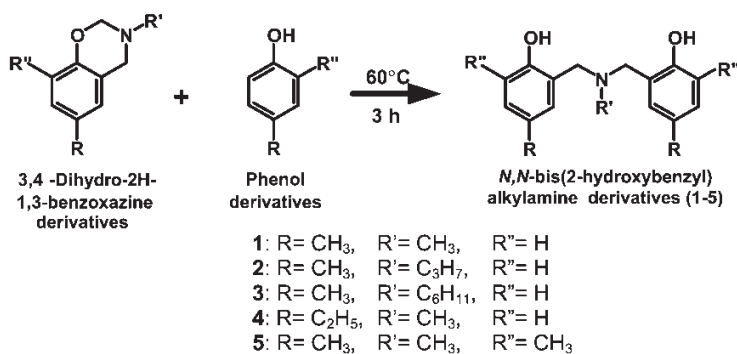
Inclusion Phenomena of *N,N*-bis-(2-hydroxybenzyl)alkylamine Derivatives and Transition Metal Ions

In order to identify whether a host–guest compound between *N,N*-bis(2-hydroxybenzyl)alkylamine

derivatives and various transition metal ions is formed, UV-Vis spectra were obtained to check for peak shift or the new peak generation. Makarska *et al.* reported that porphyrins with copper ions show inclusion phenomena as identified from the peak shifts in UV-Vis spectra [17]. Fig. 1(A) shows UV-Vis spectra of the solution **1** with CuCl₂ in methanol for various ratios. Compound **1** gives a peak maximum at 284 nm whereas CuCl₂ gives a peak at 267 nm. After mixing, a new peak at 415 nm is observed implying that **1** forms an inclusion compound with CuCl₂. Similarly, **2–4** with CuCl₂ gave a new peak at 415 nm, whereas **5** gave a new peak at 435 nm, confirming that *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives act as hosts. Fig. 1(B) was re-plotted from Fig. 1(A) to represent the optimal host–guest ratio for **1** with CuCl₂. The Job's plot obtained from the new peak at 415 or 435 nm indicates that the *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives (**1–5**) incorporate the Cu²⁺ guest in the host–guest ratio of 2:1.

¹H NMR was applied to study the interaction between host–metal ion and the effect of the metal ion. In order to avoid complicated conditions, methanol was selected as a good solvent for both *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives and transition metal chloride salts. As shown in Fig. 2, in the case of **1**, when CuCl₂ was added into the system, the peak at 3.636 (–CH₂–N) ppm is significantly shifted and splits into two broad peaks at 4.118 and 4.310 ppm. The peak of CH₃–N is also substantially deshielded by 0.481 ppm. The shifting and splitting of these specific peaks imply that the proton environment at the aza and methylene groups has changed. It can be speculated that the metal ion withdraws electrons from the aza and methylene groups resulting in a decrease in electron density of these protons in the host–guest system. It was found that the other derivatives (**2–5**) gave the similar results suggesting host–guest formation via interaction through the aza and methylene groups.

Up to now, most reports on inclusion phenomena are for macrocyclic host compounds.



SCHEME 2

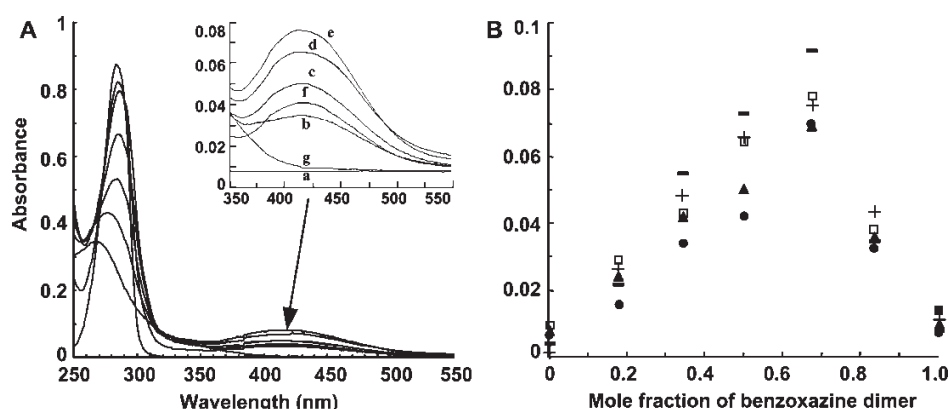


FIGURE 1 (A) UV-Vis spectra of **1**-CuCl₂ in methanol at various volumetric ratios; a) 0:6, b) 1:5, c) 2:4, d) 3:3, e) 4:2, f) 5:1, and g) 6:0. (B) Job's Plot as a function of mole fraction of (□) **1**, (+) **2**, (●) **3**, (–) **4** at 415 nm, and (▲) **5** at 435 nm.

However, there are cases where oligomers and small molecules can also form inclusion compounds by molecular assembly as seen in pseudocalixarenes [18], oligobenzoxazine [11] and cholic acid [19]. Ganem *et al.* demonstrated that ESIMS provide important information on the host-guest complexation of macrolides [20]. A number of host-guest molecular assembly compounds, either cyclic or noncyclic, especially calixarenes and β -cyclodextrins, were also elucidated by ESIMS [21–23]. Here, we applied ESIMS to determine how *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives accept transition metal ions.

Compound **4** gives the peak ($M + H$) at $m/z \sim 300$ which is equal to its molecular weight (Fig. 3(a)). Moreover, a series of peaks appear at the $m/z = 300$, 600, and 899 implying that **4** tends to form an assembly structure of two and three molecules. This might be related to the inter- and intramolecular hydrogen-bond network in the solution state.

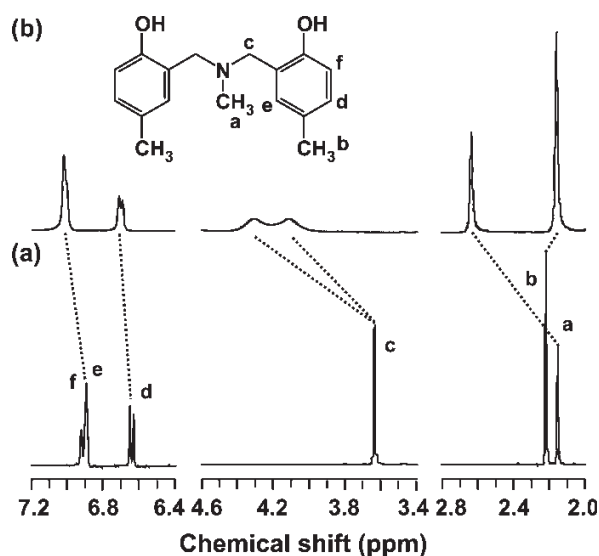


FIGURE 2 ¹H NMR spectra of (a) **1** and (b) **1**-CuCl₂ in methanol-*d*₄ with a 1:1 host-guest ratio.

The hydrogen bonding of the host structure in solution might resemble that in the solid state [13]. After complexation, the spectrum shows m/z peaks in the range of 300–370, 590–670, 890–970, 1180–1260, and 1490–1560 (Fig. 3(b)). It is important to point out that these values are close to the total of m/z of **4** and Cu²⁺. This implies that in solution, **4** interacts with CuCl₂ as clusters in the host-guest ratios of 1 : 1 ~ 5 : 1, which is significantly different from the results in Fig. 1 where the host-guest ratio for each compound in solution observed by UV-Vis was 2:1. The difference might arise from the rapid solvent evaporation *in vacuo* during ESIMS characterization.

Ion Extraction Ability of *N,N*-bis-(2-hydroxybenzyl)alkylamine Derivatives

To evaluate the efficiency of metal ion interaction, liquid-liquid extraction containing aqueous metal ions and *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives dissolved in chloroform was studied. In general, the extraction percentages refer to the equilibrium between host and metal in the form of complex and free molecules existing in the solution.

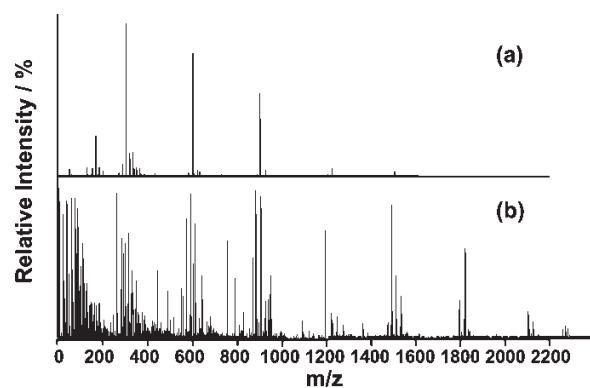


FIGURE 3 ESIMS spectra of (a) **4** and (b) **4**-CuCl₂ with an orifice of 35 V.

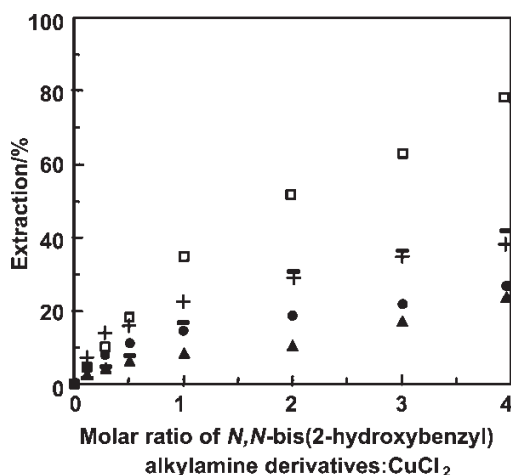


FIGURE 4 Extraction percentages of (□) 1, (+) 2, (●) 3, (○) 4, and (▲) 5 as a function of molar ratio to CuCl_2 .

Among 1–5, 1 gives the highest extraction percentage (up to 80%) whereas 5 gives the lowest (24%) (Fig. 4). In addition, the extractions of 2–5 are less than that of 1 (between 50% and 70% at all ratios). Here, the differences in extraction percentage might be due either to the electrical effect or the bulkiness of substituted groups. Considering the substituent group at the phenol ring, although the ethyl group donates electrons to the phenol ring, the ion extraction of 4 was not higher than that of 1 as would be expected. It should be noted that when substituent group adjacent to the nitrogen atom is a propyl or cyclohexyl group as in 2 and 3, the extraction percentages decreased remarkably compared to 1. Here, the bulkiness must be affecting the suitability of the *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives for ion extraction. As seen in 1–5, an increase in bulkiness at the aza group leads to a decrease in ion extraction. We speculate that the bulky group might occupy the space and obstruct the metal in interacting with the host molecule. At present, we are studying the crystal structure to confirm our speculation.

Inclusion Compounds Formed between *N,N*-bis-(2-hydroxybenzyl)alkylamine Derivatives and Transition Metals in the Solid State

It is important to clarify the solid state of inclusion compounds as this leads to the understanding of host–guest interactions without the solvent effect. Here, the solid state of the host–guest complex was prepared and the host–guest ratio was confirmed to be 2:1. The FTIR and XRD techniques were used to identify the changes in vibrational mode of the functional group in the host molecule and the packing structure. Spectra were recorded in Nujol in order to observe the host–guest formation with the least disturbance by moisture and water molecules.

Fig. 5 shows the FTIR spectra of 1, 3, and 4 before and after inclusion with CuCl_2 compared to the Nujol reference spectrum. In all inclusions with CuCl_2 , a trace amount of OH is observed suggesting a weak intermolecular hydrogen bond among the host molecules. The doublet peaks at 1617 and 1597 cm^{-1} resulting from the stretching mode of $\text{C}=\text{C}$ in the aromatic ring become a singlet implying an effect from the metal ion. The other peaks, especially, 1249 ($\text{C}-\text{N}$) and 1207 cm^{-1} ($\text{C}-\text{N}-\text{C}$) due to the aza-methylene group, become insignificant reflecting that the vibration of the functional group might be obstructed by interaction with the metal ion.

To our surprise, in the case of 3, there was little change in FTIR spectra after complexation. This suggests that the structure of 3 might have some limitations in rearranging to accept metal guests. We speculate that there might be two types of the structure when compounds 1–5 encounter the metal ion, i.e., one in which metal ion interaction occurs through the hydroxyl group of the phenol unit and the aza-methylene group (the cases of 1, 2 and 4) and one with very weak interaction (the case of 3 and 5). This is also relevant to the liquid–liquid extraction studies, where 3 and 5 gave lower extraction percentages than the others (Fig. 4). It is important to note that Fig. 1 shows 2:1 complex formation for 3 or 5 whereas Fig. 4 demonstrates their low extraction ability. This implies a solvent effect, which favors the complexation of 3 and 5 in methanol (Fig. 1). In other words, when the solvent is evaporated, it is difficult to maintain the host–guest interaction in solid state (Fig. 4).

The X-ray diffraction patterns indicate the packing structures and support the FTIR results. For example, the XRD pattern of 1– CuCl_2 (Fig. 6(c)) is drastically changed compared to that of 1 (Fig. 6(a)), whereas the pattern of 3– CuCl_2 (Fig. 6(e)) is similar to that of 3 (Fig. 6(d)). In the case of 1– CuCl_2 , the compound gives a series of new peaks around $2\theta = 5-8^\circ$, especially at 5.58, 6.36 and 6.98° with little changes at 11–30°. This suggests that copper ions are aligned in the packing structure of 1. For 3– CuCl_2 , the results from extraction percentages and the FTIR, all suggest an unchanged packing structure of the host (Fig. 6(d) and (e)).

Stability of *N,N*-bis(2-hydroxybenzyl)alkylamine Derivatives in the Host–metal Compound

The thermal properties of inclusion compounds are studied to assess the effect of the guest on the thermal stability of the host molecule. Rossel *et al.* reported on studies of cyclodextrin and acyclovir inclusion compounds by TGA and DSC [24]. Here, we applied DSC to assess the stability of the *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives

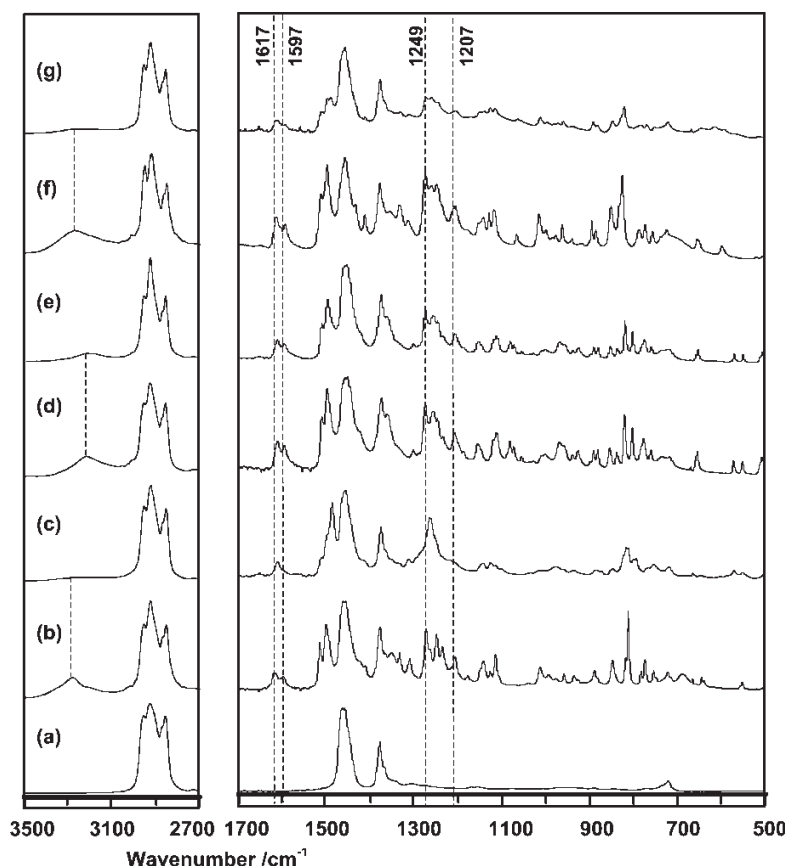


FIGURE 5 FTIR spectra of (a) Nujol, (b) **1**, (c) **1**-CuCl₂, (d) **3**, (e) **3**-CuCl₂, (f) **4** and (g) **4**-CuCl₂.

upon changing the hydrogen bond network after inclusion of the metal ion.

Fig. 7(a) shows that in the case of **1** with no metal guest, the melting temperature is 161°C. Here, the melting of the *N,N*-bis(2-hydroxybenzyl)alkylamine derivative reflects the stability afforded by the hydrogen-bond network as shown by the single crystal analysis [13]. However, **1**-CuCl₂ (2:1) shows a broad melting temperature at 130–150°C (Fig. 7(b)). This implies that the hydrogen-bond network of **1** might be obstructed after inclusion. The host–guest interactions in the solid state as evidenced from FTIR, XRD and DSC (Figs. 5–7) are relevant to those in solution shown by ¹H NMR (Fig. 2). We speculate that the hydrogen-bond network of **1** changes to ionic interactions with metal ions both in solution and in the solid state.

Effect of Solvent on Inclusion of *N,N*-bis-(2-hydroxybenzyl)alkylamine Derivatives

In solution, the interaction of solvent molecules may either enhance or reduce the stability and possibility of host–guest formation. In the present work, the effects of protic solvent (methanol) and aprotic solvent (DMSO and chloroform) on the inclusion

compounds were observed by ¹H NMR. Since the host–guest ratio is 2:1 (Fig. 1), here, an excess of guest was added to the host solution in order to provide the condition that most hosts interact with guests. The CuCl₂ was added in deuterated solvent in an equimolar amount to the host compound.

Comparing Fig. 2 with Fig. 8, it is important to note that **1** shows an OH peak in DMSO. This implies that there are free hydroxyl groups of **1** in DMSO since the interactions in DMSO might be based on polar–polar interactions. However, after inclusion, the hydroxyl peak splits into one broad peak and one sharp peak. This suggests two structures in equilibrium, i.e., one with a hydrogen-bond network (broad peak) and one with a free hydroxyl group (sharp peak). Furthermore, the –CH₂–N peak becomes broader with splitting and shifts to low field. This suggests a decrease in electron density as a result of metal ion interaction. Another significant change in the ¹H NMR is that two species of methyl protons appear at the same chemical shift suggesting an identical environment.

The chloroform system was also studied. After formation of the inclusion compound of **1** with CuCl₂ (Fig. 9(b)), the methylene protons (3.71 ppm) were slightly deshielded by 0.03 ppm. The hydroxyl

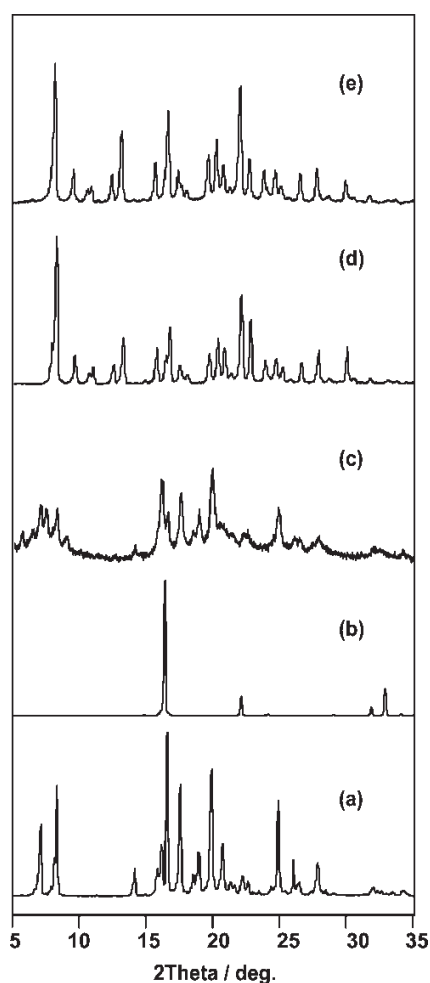


FIGURE 6 Diffraction patterns of (a) **1**, (b) CuCl_2 , (c) 1-CuCl_2 , (d) **3** and (e) 3-CuCl_2 .

protons of **1** appearing at 9.4 ppm (Fig. 9(a)) reflect the inter and intramolecular hydrogen-bond network of **1** in CDCl_3 . The upfield shifting of these hydroxyl protons from 9.4 to 8.2 ppm (Figure 9(b)) suggests that

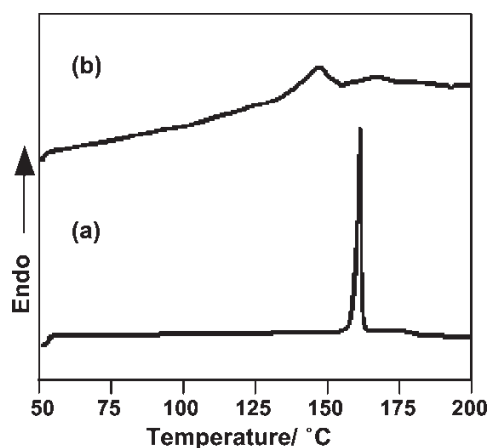


FIGURE 7 DSC thermograms of (a) **1** and (b) 1-CuCl_2 .

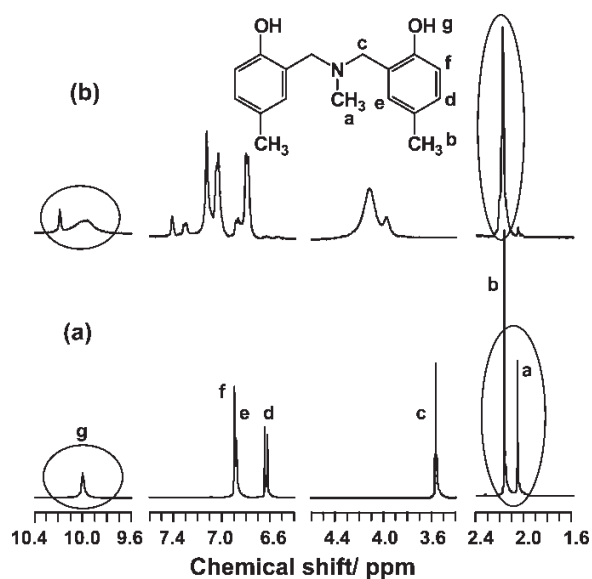


FIGURE 8 ^1H NMR spectra of (a) **1** and (b) 1-CuCl_2 in $\text{DMSO-}d_6$.

when complexation occurs, the hydrogen bonding ($\text{O-H}\cdots\text{N}$) might be changed to $\text{H-O}\cdots\text{metal}\cdots\text{N}$. The changes in the peaks due to the aromatic protons also support formation of an inclusion compound since those due to the phenol group are broader after complexation (Fig. 9(b)).

Here, $^1\text{H}\text{-}^1\text{H}$ NOESY was also carried out to obtain more information on the inclusion process [25]. Compound **1** shows the peaks involved in the interaction between protons of the hydroxyl group (H1, H2) and protons of methylene group (H7, H9) (Fig. 10(a)). In the case of 1-CuCl_2 (Fig. 10(b)), the disappearance of those peaks supports our speculation about the interaction of **1** with the metal ion via the lone pair of electrons on the oxygen and nitrogen atoms. Upon inclusion, the intramolecular interaction (H1, H2 to H7, H9) decreased

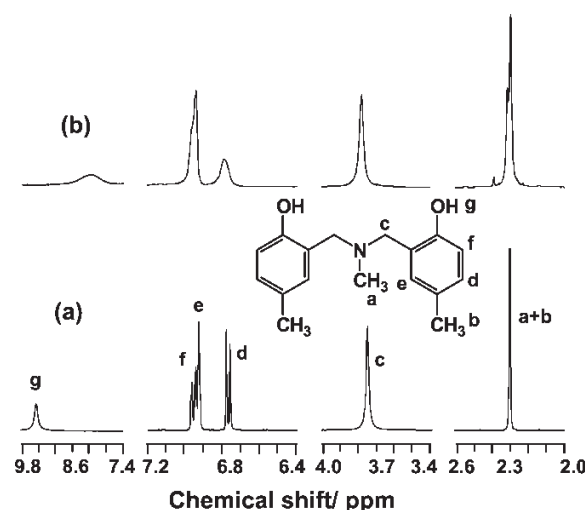
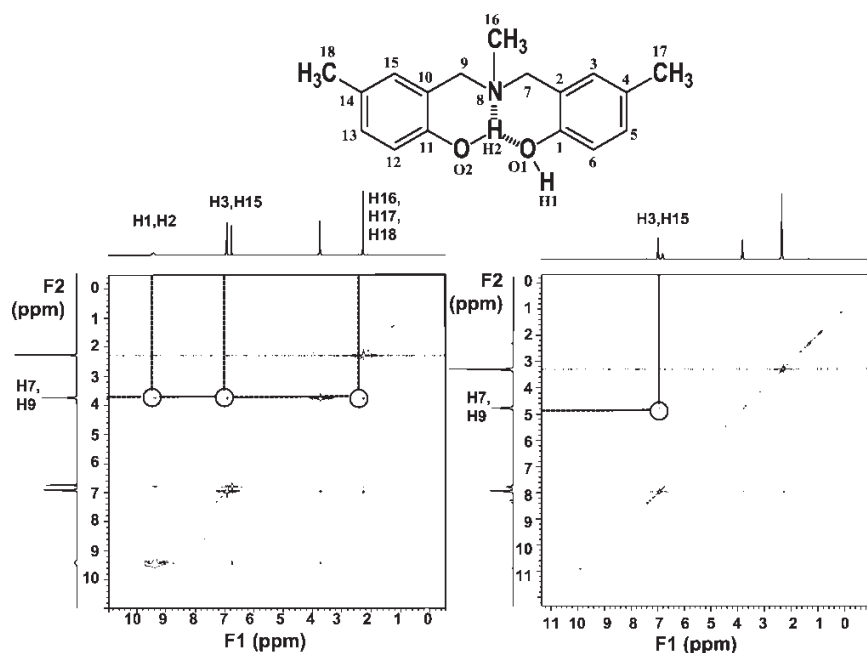


FIGURE 9 ^1H NMR spectra of (a) **1** and (b) 1-CuCl_2 in CDCl_3 .

FIGURE 10 ^1H - ^1H NOESY spectra of (a) **1** and (b) **1**- CuCl_2 in CDCl_3 .

while the interaction with metal ions was dominant. The peak resulting from the interaction of the methylene protons (H7, H9) with the methyl protons (H16) disappeared whereas that of the methylene protons (H7, H9) with the aromatic protons (H3, H15) became weaker, implying the effect of the metal ion on **1** during host-guest formation.

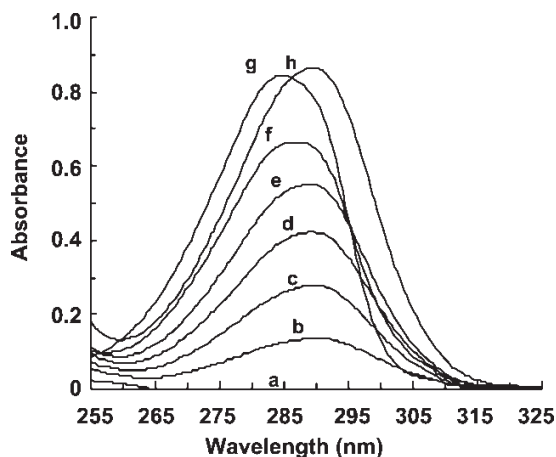
Inclusion Compounds of *N,N*-bis-(2-hydroxybenzyl)alkylamine Derivatives with other Transition Metal Ions

Another question of interest was to what extent a different transition metal *d*-orbital system would

affect the inclusion phenomena. For example, the successful inclusion phenomena of Cu^{2+} ($3d^9$) might be due to an empty $4s$ orbital being available to accept electrons from *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives. A study of the formation of complexes of **1** with other transition metal ions was therefore carried out.

Figure 11 shows UV-Vis spectra of solutions of **1** with zinc ions in methanol with ratios of 1:5 to 5:1. In methanol, **1** gives a peak maximum at 284 nm (Fig. 11(g)) whereas ZnCl_2 does not show any peak (Fig. 11(a)) over the range 255–325 nm. This is different from the CuCl_2 system since there is no new peak from the solution of ZnCl_2 and **1** but a bathochromic effect. For example, in the case of **1**- ZnCl_2 for 1:5, the peak is shifted from 284 to 290 nm, implying a host-guest system. A saturated system of ZnCl_2 -**1** shows a significant peak at 290 nm (Fig. 11(h)). This implies that the high concentration of ZnCl_2 increases the metal ion interaction with the host molecules resulting in a hyperchromic effect. Considering the peaks b–f, the apparent peak shift might come from the overlap of the two peaks, i.e. 284 nm (due to the host) and 290 nm (due to the host-guest complex).

^1H NMR measurements were also undertaken to confirm inclusion of Zn^{2+} with **1**. Considering the electronic orbital of Zn^{2+} , we speculate that the fully filled $3d^{10}$ orbital with no available *s*-orbital might prevent electron sharing with **1**. A series of spectra of **1**- ZnCl_2 show all protons deshielded similar to **1**- CuCl_2 (Figs. 2 and 12(c)–(e)). The methylene peak shows only

FIGURE 11 UV Spectra of **1** (1.65×10^{-4} M) mixed with ZnCl_2 (1.65×10^{-4} M) in methanol at the volumetric ratios of a) 0:6, b) 1:5, c) 2:4, d) 3:3, e) 4:2, f) 5:1 and g) 6:0, and h) 1.65×10^{-4} M solution of **1** mixed with ZnCl_2 at the molar ratio of 1:8.

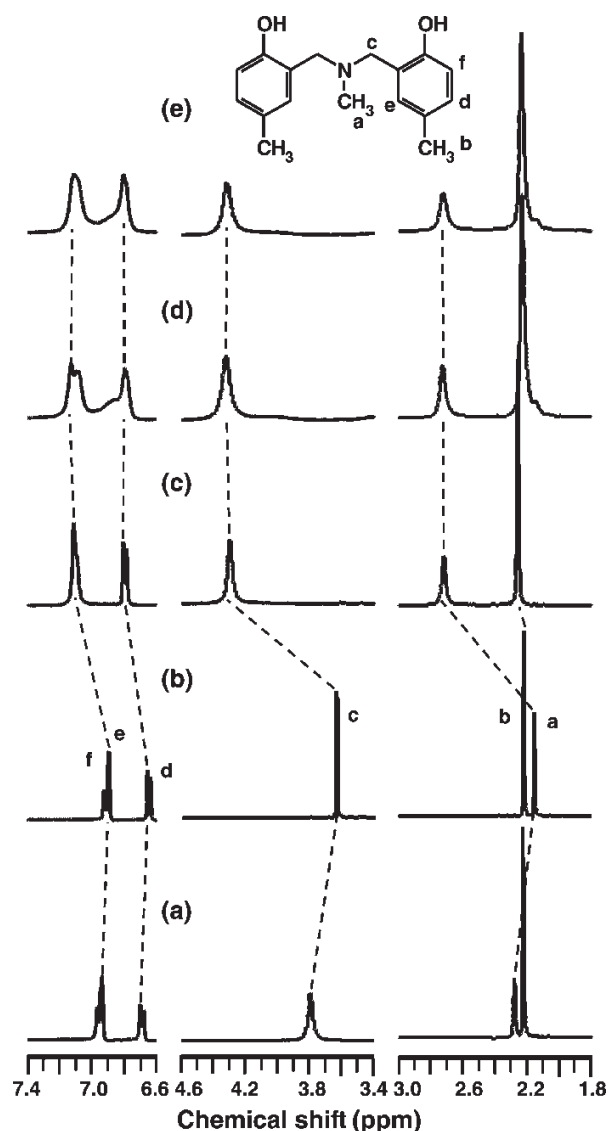


FIGURE 12 ^1H NMR spectra of (a) 1- CdCl_2 , (b) 1 and 1- ZnCl_2 at the ratios of (c) 1:1, (d) 1:8 and (e) 1:15 in methanol- d_4 .

peak shifting without splitting. This implies that the Zn^{2+} maintains the equivalent structure of the two $-\text{CH}_2-$ groups (adjacent to the N atom) even upon host-guest formation. In other words, the fully filled d -orbital in Zn^{2+} might obstruct the sharing of the lone pair electrons of OH and N in the host-guest compound. When the ratio of 1- ZnCl_2 was as high as 1:8 or 1:15, the aromatic peaks were significantly broad. This suggests that there are various averaging aromatic proton environments in the inclusion complex formed between 1 and ZnCl_2 .

In order to confirm the electronic orbital involved in the inclusion process, CdCl_2 was also studied. We expected that CdCl_2 with the outer orbital $5s^2$ would show similar results to ZnCl_2 .

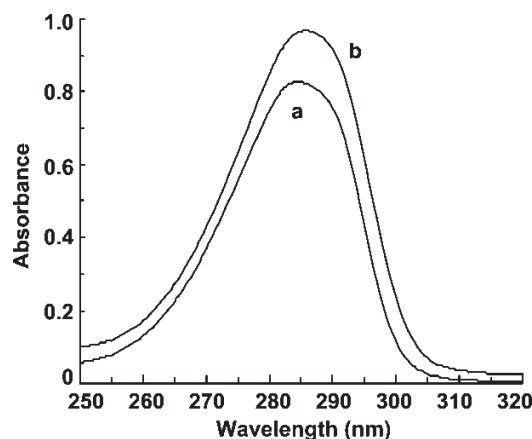


FIGURE 13 UV Spectra of (a) 1.65×10^{-4} M solution of 1 and (b) 1- CdCl_2 (1:8).

The mixing of a solution of 1 with CdCl_2 was observed by UV (Fig. 13) and gave a peak with a hyperchromic shift similar to that of ZnCl_2 , implying that inclusion had occurred. The ^1H NMR spectrum of 1- CdCl_2 shows a shift in the methylene protons but the change is small compared to that of 1- ZnCl_2 (Fig. 12(a)). This implies a difficulty in interaction with the host. The small changes in ^1H NMR and UV also imply that the size of the metal ions also has an effect on complexation.

CONCLUSION

The present work clarifies the inclusion compound of N,N -bis(2-hydroxybenzyl)alkylamines with transition metals by using copper, cadmium and zinc as model ions. In solution, the host-guest ratios of N,N -bis(2-hydroxybenzyl)alkylamine derivatives with CuCl_2 were found to be 2:1. Although the host-guest formation is dependent on the structure of the host, the interaction might form at the hydroxyl and aza-methylene group as suggested from UV-Vis, ^1H NMR and $^1\text{H}-^1\text{H}$ NOESY. The ESIMS showed cluster patterns indicating inclusion phenomena by the molecular assembly of N,N -bis(2-hydroxybenzyl)-alkylamines. The studies on the interaction with metal ions in various solvents suggested that the inclusion might be enhanced by either hydrogen bonding or polar-polar interaction. For the solid-state host-guest compound, the DSC clarified that the N,N -bis(2-hydroxybenzyl)alkylamine derivatives lost some thermal stability after forming inclusion compounds with metal ions. Overall, we found that with respect to the nature of N,N -bis(2-hydroxybenzyl)alkylamine derivatives, the larger the bulky group at the aza position is, the lower the metal ion acceptance of the host will be, whereas with regard to the transition metals, the vacant electron orbital was an important factor for inclusion.

EXPERIMENTAL

Chemicals

Paraformaldehyde, methylamine, 4-ethylphenol, 2,4-dimethylphenol, and anhydrous sodium sulfate were purchased from Fluka, Switzerland. *p*-Cresol, propylamine, cyclohexylamine, and methanol-*d*₄ were obtained from Merck, Germany. Sodium hydroxide and isopropanol were provided from Carlo Erba, Italy. Copper(II) chloride and zinc(II) chloride were purchased from Shimadzu's Pure Chemicals, Japan, and Ajax Finechem, Australia, respectively. 1,4-Dioxane, diethyl ether, isopropanol, dichloromethane, and *N,N*-dimethylsulfoxide (DMSO) were from Labscan, Ireland. Chloroform-*d*, and methyl sulfoxide-*d*₆ (DMSO-*d*₆) were purchased from Aldrich, Germany. All chemicals were used without further purification.

Instruments

Fourier transform infrared spectra (FTIR) were recorded in Nujol in the range 4000–400 cm⁻¹ with 64 scans at a resolution of 2 cm⁻¹ on a Bruker Equinox55/S spectrophotometer using a deuterated triglycinesulfate detector (DTGS) with a specific detectivity, *D*^{*}, of 1 × 10⁹ cm Hz^{1/2} W⁻¹. Differential scanning calorimetry analysis (DSC) was carried out by a Perkin Elmer DSC7 from 50°C to 200°C at a heating rate of 10°C/min. X-ray diffraction (XRD) patterns were obtained from a Rigaku RINT 2000, using CuK_α (λ = 0.154 nm) as an X-ray source with 2θ of 5–50° operating at 40 kV and 30 mA with Ni filter. Proton nuclear magnetic resonance (¹H NMR) spectra and two-dimensional nuclear Overhauser enhancement (¹H–¹H NOESY) spectra were obtained using a Varian Mercury-400BB spectrometer. The host–guest ratio was studied by electrospray ionization mass spectrometry (ESIMS), using a PE SCIEX API III Biomolecular Mass Analyzer. UV-Vis absorbance data were obtained on a Perkin Elmer UV-VIS spectrometer Lambda 16.

Synthesis

A series of the derivatives, i.e., *N,N*-bis(2-hydroxy-5-methylbenzyl)methylamine, **1**, *N,N*-bis(2-hydroxy-5-methylbenzyl)propylamine, **2**, *N,N*-bis(2-hydroxy-5-methylbenzyl)cyclohexylamine, **3**, *N,N*-bis(2-hydroxy-5-ethylbenzyl)methylamine, **4**, and *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **5**, were prepared from a ring-opening reaction of the relevant benzoxazine and phenol derivatives. Mixtures of 3,4-dihydro-3,6-dimethyl-2H-1,3-benzoxazine and *p*-cresol (1:1) were prepared and stirred at 60°C. The mixtures were allowed to react until viscous and left for

precipitation. The precipitates obtained were collected, and washed with diethyl ether before vacuum drying. The compounds were recrystallized in chloroform before use. Similarly, 3,4-dihydro-6-methyl-3-propyl-2H-1,3-benzoxazine, 3,4-dihydro-6-methyl-3-cyclohexyl-2H-1,3-benzoxazine, 3,4-dihydro-6-ethyl-3-methyl-2H-1,3-benzoxazine, and 3,4-dihydro-3,6,8-trimethyl-2H-1,3-benzoxazine were reacted with *p*-cresol, *p*-cresol, 4-ethylphenol, and 2,4-dimethylphenol, respectively. The compounds obtained were qualitatively analyzed by FTIR, ¹H NMR and EA.

***N,N*-bis(2-hydroxy-5-methylbenzyl)methylamine (1)**: 90% yield; *R*_f = 0.24 (5% MeOH in CHCl₃); clear and colorless solid; mp = 163°C; FTIR (KBr, cm⁻¹): 3271 (br, OH), 1499 (vs, C–C), 1456 (m, N–CH₃), 1249 (s, C–N), 1209 (m, C–N–C), 815 (vs, C–N–C); ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 2.23 (6H, s, Ar–CH₃), 2.23 (3H, s, N–CH₃), 3.69 (4H, s, Ar–CH₂–N), 6.70 (2H, d, Ar–H), 6.83 (2H, s, Ar–H), 6.86 (2H, d, Ar–H). Anal.calcd. for C₁₇H₂₁NO₂: C, 75.28; H, 7.75; and N, 5.17. Found: C, 75.31; H, 7.77; and N, 5.19%.

***N,N*-bis(2-hydroxy-5-methylbenzyl)propylamine (2)**: 80% yield; *R*_f = 0.22 (5% MeOH in CHCl₃); clear and colorless solid; mp = 149°C; FTIR (KBr, cm⁻¹): 3251 (br, OH), 1501 (vs, C–C), 1467 (m, N–CH₃), 1276 (s, C–N), 1210 (s, C–N–C), 819 (s, C–N–C); ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 0.87 (3H, t, CH₃–CH₂–CH₂–N), 1.65 (2H, m, CH₃–CH₂–CH₂–N), 2.22 (6H, s, Ar–CH₃), 2.50 (2H, t, CH₃–CH₂–CH₂–N), 3.70 (4H, s, Ar–CH₂–N), 6.68 (2H, d, Ar–H), 6.85 (2H, s, Ar–H), 6.90 (2H, d, Ar–H). Anal.calcd. for C₁₉H₂₅NO₂: C, 76.25; H, 8.36; and N, 4.69. Found: C, 76.28; H, 8.31; and N, 4.70%.

***N,N*-bis(2-hydroxy-5-methylbenzyl)cyclohexylamine (3)**: 80% yield; *R*_f = 0.30 (5% MeOH in CHCl₃); clear and colorless solid; mp = 181°C; FTIR (KBr, cm⁻¹): 3226 (br, OH), 1500 (vs, C–C), 1449 (m, N–CH), 1249 (s, C–N), 1210 (m, C–N–C), 819 (s, C–N–C); ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 1.1 (2H, m, CH₂), 1.45 (4H, m, CH₂), 1.82 (4H, m, CH₂), 2.22 (6H, s, CH₃–Ar), 2.70 (1H, m, CH), 3.72 (4H, s, Ar–CH₂–N), 6.68 (2H, d, Ar–H), 6.85 (2H, s, Ar–H), 6.90 (2H, d, Ar–H). Anal.calcd. for C₂₂H₂₉NO₂: C, 77.88; H, 8.55; and N, 4.13. Found: C, 77.90; H, 8.56; and N, 4.16%.

***N,N*-bis(2-hydroxy-5-ethylbenzyl)methylamine (4)**: 90% yield; *R*_f = 0.34 (5% MeOH in CHCl₃); clear and colorless solid; mp = 130°C; FTIR (KBr, cm⁻¹): 3301 (br, OH), 1499 (vs, C–C), 1460 (m, N–CH₃), 1251 (s, C–N), 1207 (m, C–N–C), 821 (s, C–N–C); ¹H NMR (200 MHz, CDCl₃, ppm): δ_H 1.17 (6H, t, Ar–CH₂–CH₃), 2.25 (3H, s, N–CH₃), 2.54 (4H, q, Ar–CH₂–CH₃), 3.72 (4H, s, Ar–CH₂–N), 6.73 (2H, d, Ar–H), 6.87 (2H, s, Ar–H), 6.94 (2H, d, Ar–H). Anal.calcd. for

$C_{19}H_{25}NO_2$: C, 76.26; H, 8.36; and N, 4.68. Found: C, 76.24; H, 8.35; and N, 4.65%.

***N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine (5)**: 80% yield; $R_f = 0.39$ (5% MeOH in $CHCl_3$); clear and colorless solid; mp = 123°C; FTIR (KBr, cm^{-1}): 3399 (br, OH), 1484 (vs, C–C), 1427 (m, N–CH₃), 1243 (m, C–N), 1214 and 1201 (m, C–N–C), 847 (m, C–N–C); 1H NMR (200 MHz, $CDCl_3$, ppm): δ_H 2.22 (12H, s, Ar–CH₃), 2.25 (3H, s, N–CH₃), 3.68 (4H, s, Ar–CH₂–N), 6.72 (2H, s, Ar–H), 6.81 (2H, s, Ar–H). Anal. calcd. for $C_{19}H_{25}NO_2$: C, 76.26; H, 8.36; and N, 4.68. Found: C, 76.27; H, 8.34; and N, 4.69%.

Complexation in Solution

Methanolic solutions of each derivative and copper chloride (1.65×10^{-4} M) were made up and the two solutions were mixed in the following ratios: (1–5)-copper chloride, 1:5, 2:4, 3:3, 4:2, and 5:1, respectively. The mixtures were shaken vigorously for 1 min and left for 12 h, UV-Vis absorbance at the maximum peak position was measured and plotted as Job's plot. Zinc chloride was also used instead of copper chloride. Each chloride salt of copper, zinc, and cadmium was mixed with the *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives to give a 1:1 molar ratio, and dissolved in methanol- d_4 for analysis by 1H NMR. Similarly, DMSO- d_6 and $CDCl_3$ were used as solvents to study the solvent effect.

Solid State of Host–metal Ion Complex

Solutions of *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives in chloroform (7×10^{-3} M) and copper chloride in deionized water (0.7 M) were prepared, vigorously mixed and left for 3 d. The organic phase was collected, dried by anhydrous Na_2SO_4 , and evaporated to obtain a green powder, which was characterized by FTIR, DSC, and XRD. The concentration of copper chloride in the aqueous phase was determined (to establish the host–guest ratio) by UV-Vis spectroscopy. The powder was dissolved in $CDCl_3$ for analysis by 1H – 1H NOESY NMR.

Percentage Metal Ion Extraction

Solutions of copper chloride in deionized water (2.5×10^{-2} M) and the *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives in chloroform (0.1 , 7.5×10^{-2} , 5.0×10^{-2} , 2.5×10^{-2} , 1.25×10^{-2} , 6.25×10^{-3} , and 2.5×10^{-4} M) were prepared; 5 ml of each solution were mixed together, vigorously shaken for 1 min, and left overnight. The absorbance at 815 nm was measured and calculated for percentage extraction by the equation $[(A_0 - A)/A_0] \times 100$ where A_0 is the initial absorbance, and A is the absorbance after

extraction with the *N,N*-bis(2-hydroxybenzyl)alkylamine derivative.

Acknowledgements

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Supramolecular Structure of *N,N*-Bis(2-hydroxybenzyl)alkylamine: Flexible Molecular Assembly Framework for Host without Guest and Host with Guest

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N,N-Bis(2-hydroxybenzyl)alkylamine derivatives form a cage-like assembly consisting of two molecules via inter- and intramolecular hydrogen bonds. The derivatives exhibit themselves as host to accept copper-ion guests under the double-oxygen-bridged dimeric system. Quantum chemical calculation suggested that the host–guest interaction is based on a charge-transfer coordination. Comparison of the crystal structures before and after complexation clarifies a rare example of a host–guest compound where the hosts maintain their cage framework through the change of hydrogen bonds to coordination bonds.

Introduction

Benzoxazine is a unique heterocyclic compound obtained from cyclization between phenol, formaldehyde, and amine.¹ As shown in Scheme 1, theoretically the ring-opening reaction of *p*-substituted phenol-based benzoxazine with phenol derivatives gives a linear aza-methylene-linked phenol-based polymer. We found, however, that the actual reaction tends to terminate at the dimer formation stage, which might be due to the fact that reactive hydroxyl groups are stabilized by inter- and intramolecular hydrogen bonds as reported previously.² The thus-created dimer, *N,N*-bis(2-hydroxybenzyl)alkylamine, hereinafter referred to as **HBA**, takes a cage structure to induce a supramolecular assembly by accepting other molecules or ionic species (Figure 1). As host–guest complexes are known as organometallic catalysts,³ biomimetic metalloproteins,⁴ and enzymatic complex systems,⁵ establishment of **HBA** for supramolecular chemistry might bring useful applications.

In previous papers,^{6,7} we clarified the inclusion phenomena of **HBA** with various guests in either solution or the solid state. It is important to note that parallel to our work there are some reports on **HBA** derivatives with metal ions. For example, Tshuva et al. reported on the zirconium complex of amine-bis-(phenolate) as a candidate catalyst for 1-hexene polymerization.⁸ Malathy Sony et al. showed a biomimetic model complex of *N*-[(2-hydroxylato-5-methyl)benzyl-(2'-hydroxylato-3',5'-dimethylbenzyl)]ethylamine dicopper(II).⁹ Although those complexes demonstrated the precise crystal structures of the **HBA** derivative and metal ions, the role of **HBA** self-assembly and its development to form a complex were not clarified. As we succeeded in preparing a series of **HBA** derivatives via a simple, effective, and selective ring-opening reaction of benzoxazines², it is possible to carry out systematic work on the supramolecular

complex structure under variations of host molecules to establish the supramolecular chemistry of the **HBA**.

In the present article, we focus on two types of benzoxazine dimer derivatives (*N,N*-bis(2-hydroxy-5-methylbenzyl)cyclohexylamine, **HBA1**, and *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **HBA2**) and on their copper-ion complexation (Scheme 1). On the basis of the information obtained from crystal structure analysis, thermal analysis, vibrational spectroscopy, and quantum chemical calculation, the derivatives have been found for the first time to show their uniqueness in accepting guests without destroying the host framework. This is a rare example among many already revealed hosts. In the present paper, we describe various unique behaviors concerning the specific supramolecular structure of **HBA** on the basis of the following significant experimental findings: (i) the double-oxygen-bridged charge-transfer host–metal complex, (ii) the well-superimposition structure of the hydrogen-bond network of **HBA** and coordination systems of **HBA** with metal guest, and (iii) the existence of multiguest species, i.e., ion and neutral molecules, in a single host–guest framework.

Experimental Section

Preparation of HBA Derivatives. *p*-Cresol, 2,4-dimethylphenol, formaldehyde, methylamine, and cyclohexylamine were obtained from Merck, Germany. Copper(II) acetate monohydrate and sodium hydroxide were purchased from Fluka, Switzerland. 1,4-Dioxane, diethyl ether, 2-propanol, and methanol were from Labscan, Ireland. All chemicals and solvents used for synthesis were of reagent grade and used without purification. *N,N*-Bis(2-hydroxy-5-methylbenzyl)cyclohexylamine (**HBA1**) and *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine (**HBA2**) were prepared from a ring-opening reaction of the relevant benzoxazine and phenol derivatives as reported previously.⁷ Mixtures of 3,4-dihydro-6-methyl-3-cyclohexyl-2*H*-1,3-benzoxazine and *p*-cresol (1:1) were prepared and stirred at 60 °C. The mixtures were allowed to react until the solution became viscous, and they were left for precipitation. The precipitates obtained were collected and washed with diethyl

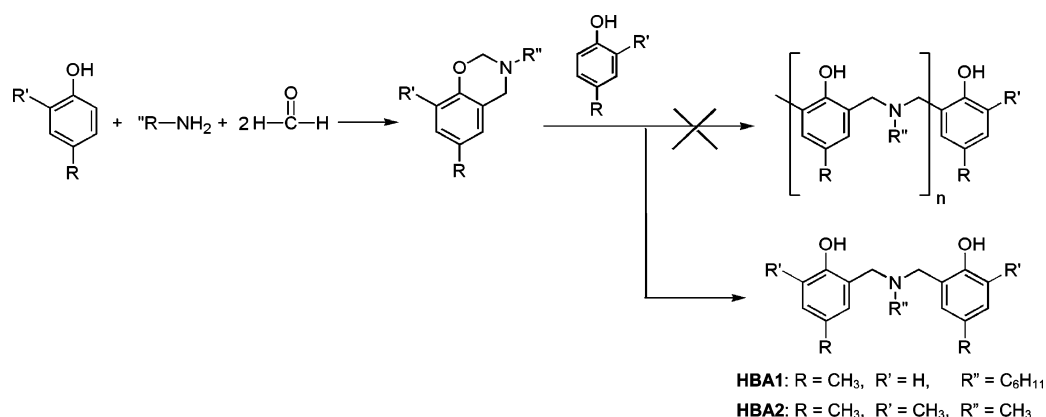
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SCHEME 1



ether before vacuum drying. **HBA1** was recrystallized in chloroform to prepare single crystals. Similarly, 3,4-dihydro-3,6,8-trimethyl-2*H*-1,3-benzoxazine was reacted with 2,4-dimethylphenol to obtain **HBA2**.

N,N-Bis(2-hydroxy-5-methylbenzyl)cyclohexylamine (**HBA1**): 80% yield; $R_f = 0.30$ (5% MeOH in CHCl_3); clear and colorless solid; mp = 181 °C; FTIR (KBr, cm^{-1}) 3226 (br, OH), 1500 (vs, C—C), 1449 (m, N—CH), 1249 (s, C—N), 1210 (m, C—N—C), 819 (s, C—N—C); ^1H NMR (200 MHz, CDCl_3 , ppm) δ_{H} 1.1 (2H, m, CH_2), 1.45 (4H, m, CH_2), 1.82 (4H, m, CH_2), 2.22 (6H, s, CH_3 —Ar), 2.70 (1H, m, CH), 3.72 (4H, s, Ar— CH_2 —N), 6.68 (2H, d, Ar—H), 6.85 (2H, s, Ar—H), 6.90 (2H, d, Ar—H). Anal. Calcd for $\text{C}_{22}\text{H}_{29}\text{NO}_2$: C, 77.88; H, 8.55; N, 4.13. Found: C, 77.90; H, 8.56; N, 4.16.

N,N-Bis(2-hydroxy-3,5-dimethylbenzyl)methylamine (**HBA2**): 80% yield; $R_f = 0.39$ (5% MeOH in CHCl_3); clear and colorless solid; mp = 123 °C; FTIR (KBr, cm^{-1}) 3399 (br, OH), 1484 (vs, C—C), 1427 (m, N— CH_3), 1243 (m, C—N), 1214 and 1201 (m, C—N—C), 847 (m, C—N—C); ^1H NMR (200 MHz, CDCl_3 , ppm) δ_{H} 2.22 (12H, s, Ar— CH_3), 2.25 (3H, s, N— CH_3), 3.68 (4H, s, Ar— CH_2 —N), 6.72 (2H, s, Ar—H), 6.81 (2H, s, Ar—H). Anal. Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_2$: C, 76.26; H, 8.36; N, 4.68. Found: C, 76.27; H, 8.34; N, 4.69.

Instrumentation. Fourier transform infrared spectra (FTIR) were recorded by the Nujol mull method in the range 4000–400 cm^{-1} at a resolution of 2 cm^{-1} using a HORIBA FT-720 infrared spectrometer. Thermogravimetric-differential thermal analysis (TG-DTA) was performed with a Rigaku Thermoplus TG8120 from 50 to 300 °C at a heating rate of 5 °C/min under a nitrogen atmosphere.

Structural Analysis. Single crystals of **HBA** with copper ions were prepared by dropping the methanolic copper acetate

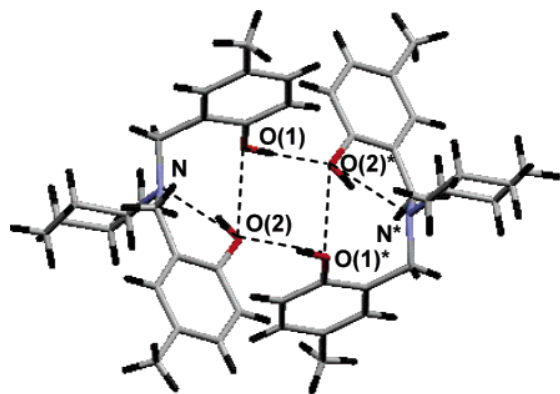


Figure 1. Cage structure of **HBA1** consisting of two **HBA1** molecules (the broken line represents the hydrogen bonds).

solution into methanol solutions of **HBA1** and **HBA2** and leaving them for several days. The single crystals of **HBA** derivatives are colorless, whereas those of the copper inclusions are dark green. X-ray diffraction measurement of **HBA1** and **HBA2** was carried out using an X-ray imaging plate system DIP3000 (MAC Science Co., Ltd., Japan). The graphite monochromatized Mo $\text{K}\alpha$ line ($\lambda = 0.71073$ Å), which was generated from the SRA-M18XHF rotating anode X-ray generator (50 kV and 200 mA), was used as an incident X-ray source. Data correction was performed with XDIP software (MAC Science). The sample was oscillated in a range of 3° over a total rotation angle of 0–180° around the ω axis. The exposure time was 30 min for one image. It took about 12 h to collect the 24 images in total. Data were analyzed using DENZO and SCALEPACK software.^{10,11} The crystal structure was solved using maXus (NoniusBV, Delft) software. The direct method was used to find out the initial models, where the SIR92 software developed by Altomare et al. was used.¹² Least-squares refinement was made on the basis of the full-matrix method using the quantity $\sum \omega(|F_o|^2 - |F_c|^2)^2$ as a minimized function with weight $\omega = \exp[FA \sin^2 \theta / \lambda^2] / [\sigma^2(F_o) + FBF_o^2]$, where $\sigma^2(F_o)$ is the squared standard deviation of the observed structure factor F_o and coefficients FA and FB were set to 0.0 and 0.03, respectively. The reflections satisfying the cutoff condition of $|F_o| > 3\sigma(|F_o|)$ were used in the least-squares refinement. Because no detectable

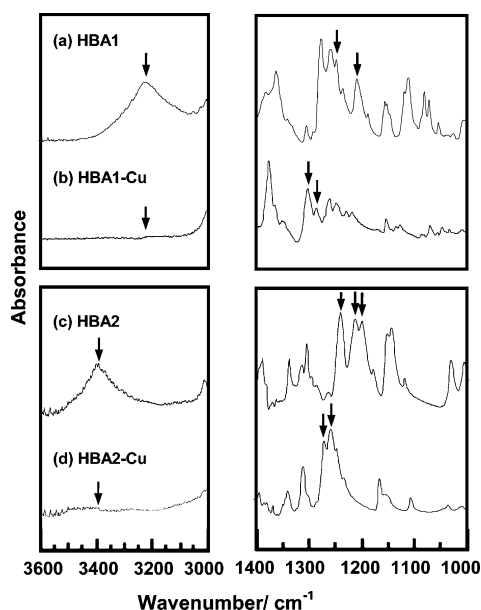


Figure 2. FTIR spectra of (a) **HBA1**, (b) **HBA1**—Cu, (c) **HBA2**, and (d) **HBA2**—Cu after Nujol peaks were subtracted.

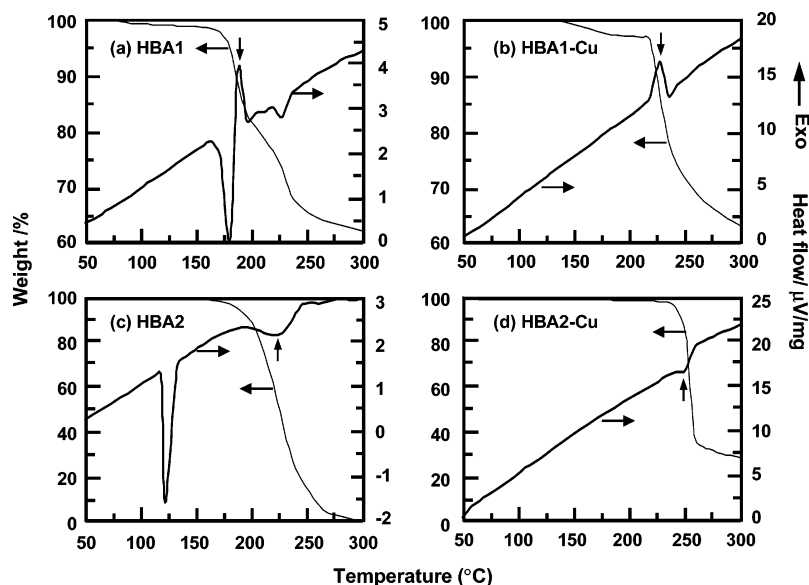


Figure 3. TG and DTA thermograms of (a) **HBA1**, (b) **HBA1**–Cu, (c) **HBA2**, and (d) **HBA2**–Cu.

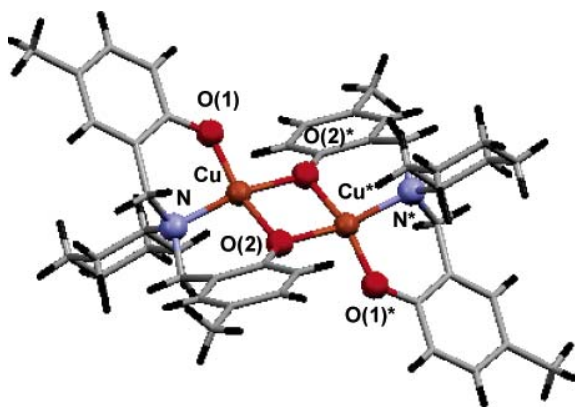


Figure 4. Coordination compound of **HBA1**–Cu.

effect was found, the absorption correction for the observed intensity was not included in the structural refinement. As a measure of the reasonableness of the structural analysis, the reliability factors, R and R_w , were defined by the following equations: $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$. X-ray diffraction measurement of **HBA1**–Cu and **HBA2**–Cu was performed using a Rigaku R-Axis RAPID/FS diffractometer with graphite-monochromated Mo $K\alpha$ radiation at 296 K. The structure was solved by direct methods (SIR92)¹² and refined by the full-matrix least-squares procedure on $|F|^2$. All non-hydrogen atoms were refined for anisotropic thermal parameters as well as the coordinates. Hydrogen atoms were detected from the different Fourier map, and positions were refined assuming isotropic thermal parameters. All calculations were performed using the TEXSAN crystallographic software package.¹³

Molecular Modeling. The electron density distribution was calculated for the original cage structure and the complex with Cu ions utilizing DMol³ software (Material Studio, version 3.0, Accelrys) on the basis of density function theory. The atomic orbital basis set was DND (double numerical plus d-functions), and the type of exchange-correlation potential was a local LDA. The molecular structures were transferred directly from the X-ray analysis results, and electron densities were calculated for the isolated molecules without energy optimization.

Results and Discussion

Infrared Spectral Change by Cu Complexation. Green crystals of **HBA1** and **HBA2** including copper ions, abbreviated as **HBA1**–Cu and **HBA2**–Cu, were characterized by FTIR to observe the vibrational spectral changes caused by copper inclusion. Since metal-ion exchange might occur relatively easily when KBr powder is mixed with **HBA1**–Cu and **HBA2**–Cu complexes, samples for IR measurements were prepared by the Nujol mull method. Figure 2 shows the FTIR spectra of the single crystals of **HBA1**, **HBA2**, and their copper inclusions where the contribution of Nujol bands was already subtracted. Although **HBA1** and **HBA2** give the peak positions and width of the bands differently, due to the strength and environment of the hydrogen bonds, the OH peaks are clearly observed before complex formation for both compounds (Figure 2a and 2c). After entrapping copper ions, the significant decrease of the OH band intensity was observed, as shown in Figure 2b and 2d, corresponding to loss of inter- and intramolecular hydrogen bonds. This implies that **HBA1** and **HBA2** form a complex with copper ions. The newly observed peaks for **HBA1**–Cu (Figure 2b) are at 1305 and 1289 cm^{-1} , whereas for **HBA2**–Cu (Figure 2d) they are at 1267 and 1255 cm^{-1} .¹⁴ These bands may be assigned to the C–N vibrational modes. However, these are different from the usual ones at 1249 and 1210 cm^{-1} for **HBA1** and at 1243, 1214, and 1201 for **HBA2**. This result indicates the change of the vibrational mode of the aza group after copper-ion inclusion. In this way, the OH and C–N groups of **HBA** were affected remarkably by introducing copper ions.

Thermal Stability of Complex. Thermal stabilities of the compounds before and after inclusion of the copper ion were investigated. As shown in Figure 3a, **HBA1** gives a sharp melting at 177 °C followed by an exothermic peak at 185 °C and an endothermic peak at 225–240 °C with a remarkable weight loss. As the measurement was done in a nitrogen atmosphere, the endothermic peak reflects the continuous thermal degradation in nonoxidative conditions. However, in the case of **HBA1**–Cu, the melting peak was difficult to detect and only an exothermic peak due to thermal degradation was observed (Figure 3b). For **HBA2**, the melting peak was located at 125 °C and it disappeared after complexation (Figure 3c and 3d). Thermal degradation of **HBA2** was observed at 225 °C, whereas that of **HBA2**–Cu was identified at 250 °C. The

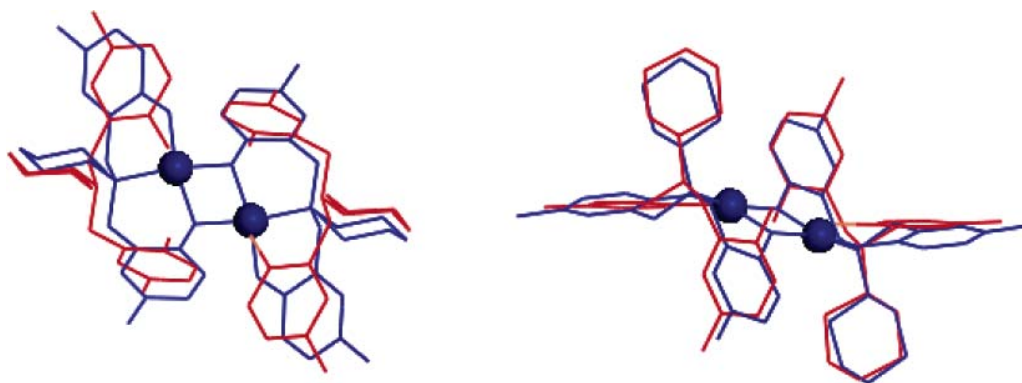
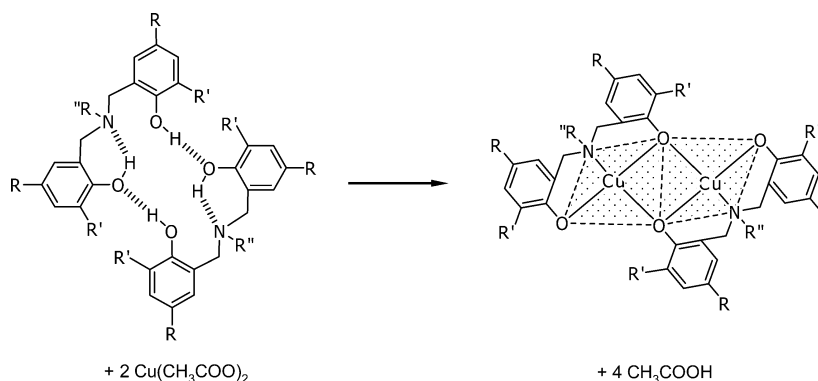


Figure 5. Comparison of cage structure between **HBA1** (red color) and **HBA1**–Cu complex (blue color) viewed from different directions.

SCHEME 2



increase in thermal degradation indicates a remarkable thermal stability of the **HBA1** and **HBA2** complexes.

Crystal Structures. To clarify the crystal structures of the **HBA**–copper complexes, single-crystal X-ray analysis was performed. Figure 4 shows the inclusion structure of **HBA1**–Cu with doubly bridged Cu–oxygen linkages. Each copper is bridged by three phenoxy oxygens and an amine donor. The bond lengths of Cu–O(1), Cu–O(2), Cu–O(2)*, and Cu–N are almost identical (1.85–2.05 Å). These distances are in the range suitable for stable Cu–O and Cu–N coordination bonds.¹⁵ The bond angles of O(1)–Cu–N, O(2)–Cu–N, O(1)–Cu–O(2)*, and O(2)–Cu–O(2)* are nearly 90°, as illustrated in Scheme 2, and therefore, the inclusion structure appears in a distorted square-planar geometry. Similar coordination is also identified for other types of asymmetric hydroxybenzylalkylamine with different substituted groups (R, R', and R'' in Scheme 1) including the derivatives reported previously.⁹ This type of molecular geometry was reported also by Malathy Sony et al.⁹ It is important to note that the square-planar geometry is a unique characteristic of the **HBA** derivatives, which form coordination bonds with metals.

Although, in general, it is difficult to determine the proton positions by single-crystal X-ray analysis, we succeeded in extracting the protons of OH groups for **HBA1** and **HBA2** with reasonable bond distances. In the case of **HBA1**–Cu, however, the hydrogen atoms could not be detected but the oxygen atoms were found to be directly linked to Cu atoms, as shown in Figure 4. Here, we could not identify the acetate counteranions, although there were reports that inclusion complexes occasionally show their counterions.¹⁶ This causes us to speculate that the hydrogen atoms of the hydroxyl groups might perform as proton donors for acetate anions, resulting in formation of acetic acid molecules after complexation (Scheme 2). This speculation is consistent with the infrared spectrum (Figure 2) in which

O–H stretching at 3200–3400 cm^{−1} is hardly observed for the **HBA1**–Cu complex.

As shown in Figure 1, the **HBA** derivatives form the inter- and intramolecular hydrogen bonds between N atoms and OH groups (O(1)–H···O(2)* and N···H–O(2)), resulting in an assembly of two **HBA** molecules.² As for the **HBA** with and without guest ions, the point to be raised here is that the cage is formed between the two **HBA** molecules either before or after complex formation (Scheme 2). As described later, the electron density distribution was calculated for the original cage structure and the complex with Cu ions on the basis of density function theory utilizing DMol³ software. As demonstrated in Figure 5, the size and shape of the cage structure composed of two **HBA** molecules are maintained even after complexation with Cu ions, although the O–H···O and O–H···N inter- and intramolecular hydrogen bonds, respectively, are replaced with coordination linkages of Cu–O and Cu–N types. This geometrical relation between the **HBA** and **HBA**–Cu complex may allow us to speculate on the mechanism of benzoxazine–copper complex formation (as discussed later).

Stabilization of Supramolecular Structure by Solvent Molecules. Such a reservation of cage structure can also be seen for **HBA2**–Cu complexation (Figure 6). However, it is important to note that complexation of **HBA2** is a little different from that of **HBA1**.¹⁷ As shown in Figure 7, three water molecules are coexistent with the dimeric **HBA2**–Cu molecules in the crystal lattice. The distances between the phenoxy oxygens (O(3)–H···O(1)) and water oxygens (O(4)–H···O(3)) are 2.70 and 2.82 Å, respectively. The positions of the hydrogen atom belonging to the water molecules were extracted successfully from the difference Fourier synthesis map. The O(1)···H distance is 1.78 Å, which is acceptable for the interatomic distance of the hydrogen bond, as found for cases of phenol and water (1.80 Å).¹⁸ The structure reveals that **HBA2**–Cu

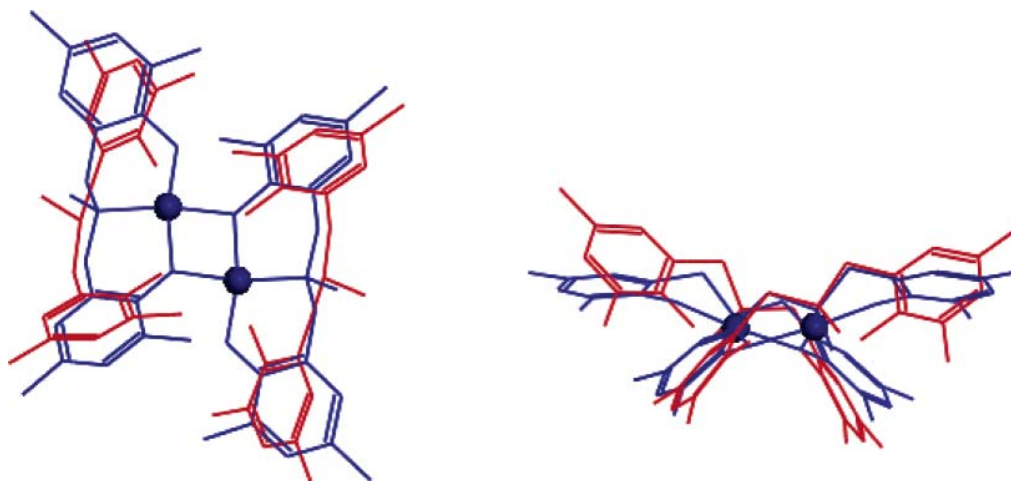


Figure 6. Comparison of cage structure between **HBA2** and **HBA2**–Cu viewed from different directions.

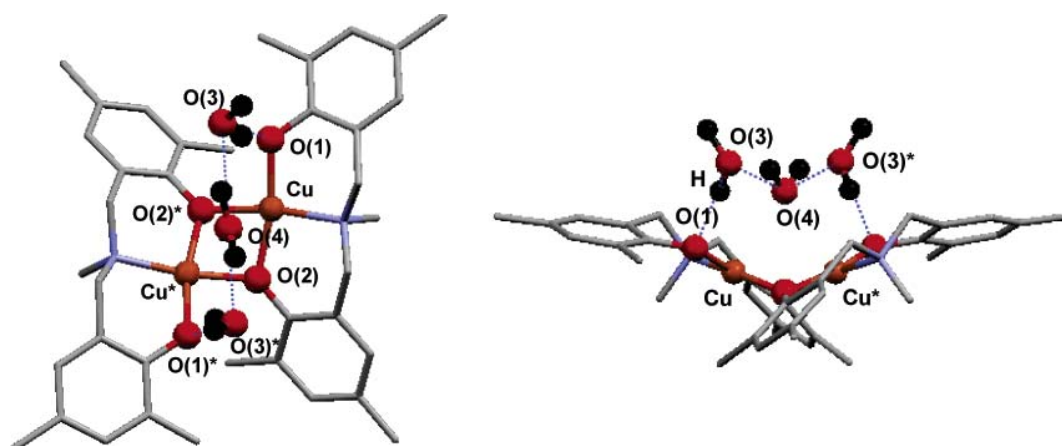


Figure 7. Structure of **HBA2**–Cu complex coordinated by water molecules. (Hydrogen atoms are omitted for clarity.)

complex takes a unique bowl-shaped network structure and accepts those small solvent molecules to stabilize the whole structure.

Comparison of crystal volumes also supports this concept about the role of the water molecules in formation of **HBA2**–Cu complex. For **HBA2**–Cu, one complex framework composed of the two **HBA2** molecules has a volume of 963.6 Å³ whereas a single **HBA2** framework has a volume of 859.1 Å³. This volume increment after Cu-complex formation is different from that of **HBA1**, showing a decrease in volume after complexation from 974.1 to 959.9 Å³.

Essential Features of Benzoxazine–Copper Complexes.

The characteristic features of these copper complexes of **HBA** are seen in the formation of the double square planes connected by common oxygen atoms. To reveal the characteristic features, the atomic charge distribution was calculated on the basis of density function theory with DMol³ (Material Studio Version 3.0, Accelrys). The atomic orbital basis set was DND (double numerical plus d-functions), and the type of exchange-correlation potential was a local LDA. In the calculation the X-ray-analyzed structure was used without any further optimization. Of course, it is more ideal to take the intermolecular interactions into account in the geometrical calculation, but the DFT calculation of the whole crystal lattice is quite a hard task for such a complicated structure, as in the present case. The calculation was made for a rough estimation of the atomic charge distribution in this characteristic complex structure. More detailed and accurate calculation will be made in the future to clarify the

essence of the charge distribution change in the formation process of the complex crystal, and it is also expected that the infrared frequencies and intensities obtained from the calculation will support the results in Figure 2.

Figure 8 shows the calculated electrostatic potential (ESP) charges. In the case of **HBA1**, the typical charge distribution is observed for the O–H···O hydrogen bond. After complexation (Figure 8b), the charges of oxygen atoms connected directly to the Cu atom change from –0.47 and –0.58 to –0.53 and –0.78 eV. At the same time the charges of nitrogen atoms decrease from –0.34 to –0.55 eV. The phenol carbon atoms connected to oxygen also change their charges. As for the Cu atom, the charge decreases from +2 (Cu²⁺ of Cu(CH₃COO)₂) to +1.02 is shown in Figure 8b. The changes in the atomic charge distribution suggest that the electrons flow from carbon (or aromatic rings) to oxygen and nitrogen and to copper atoms. Referring to the case of π -conjugated oligo(phenylene ethynylene),¹⁹ we speculate that our complex might be formed by the charge-transfer mechanism. Considering the assembly networks of **HBA1** and **HBA2**, it is natural to emphasize that the charge-transfer coordination networks of **HBA1**–Cu and **HBA2**–Cu are formed with only a minor destruction of the original packing structure. In other words, the charge-transfer complex is initiated smoothly by substituting the hydrogen atoms with Cu atoms. This type of dimeric charge-transfer complexation is, to our knowledge, quite rare to find in general complexation.

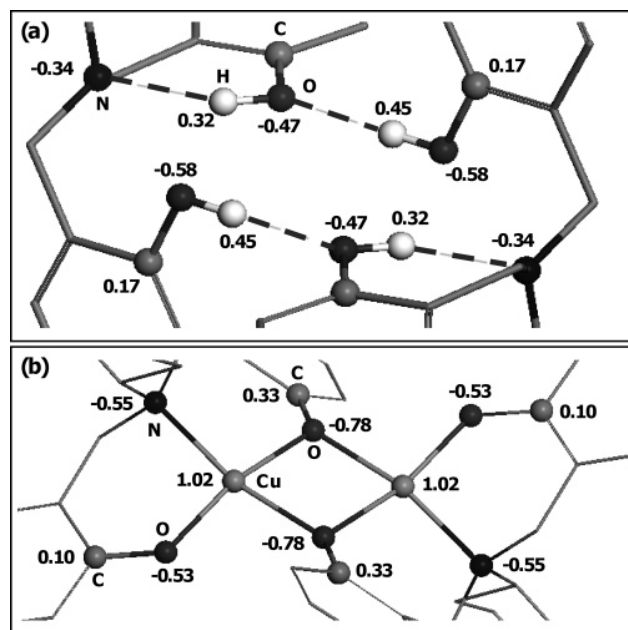


Figure 8. Calculated atomic charges of (a) HBA1 and (b) HBA1-Cu.

Conclusions

In general, a host molecule accepts a guest species under the interaction induced by favorable conditions, e.g., solvent dissolution, melting, and irradiation. To date, it is known that the host likely dissolves its original framework and establishes its new channel to incorporate the guest. The present work clarified a unique type of complex formation in that the host retains its framework even after accepting guests: HBA1 and HBA2 form complexes with copper ions without losing the cage-like structure through modification from a hydrogen-bonded self-assembly to a coordination-bonded host-guest system, as illustrated in Scheme 2. The energy calculation suggested formation of an HBA-copper complex through the atomic charge transfer among the phenoxy oxygen atom, aromatic ring, and aza methylene group, leading to a double-oxygen-bridged network.

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Supporting Information Available: Crystallographic information files (CIF); HBA1, HBA2, HBA1-Cu; CCDC 258998, and HBA2-Cu; CCDC 258999. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Supramolecular Structure of *N,N*-Bis(2-hydroxybenzyl)alkylamine: From Hydrogen Bond Assembly to Coordination Network in Guest Acceptance

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Summary: *N,N*-Bis(2-hydroxybenzyl)alkylamine (**HBA**) was described as a model to simplify the supramolecular system of polybenzoxazines. The single crystal X-ray analysis revealed that **HBA** forms a dimeric assembly based on its simultaneous inter- and intramolecular hydrogen bond network. When the **HBA** accepted the copper ion, the dimeric assembly **HBA** changed its primary hydrogen bond network to charge transfer coordination as clarified by the single crystal analysis as well as the superimposed structure based on DMol³ calculation. The supramolecular structure of **HBA** and copper also exhibited the role of solvent molecules in the packing structure which is a rare example showing the host accepts not only the metal ions but also the neutral molecules in the same time. The cyclization of **HBA** with esters or ethers to macrocyclic compounds was also an important model reaction to show how the backbone molecules self-stabilized with the hydrogen bond network initiate the simple, effective and efficient macrocyclic reaction.

Keywords: benzoxazine; coordination; crystal structure; host-guest system; hydrogen bonding; supramolecule

Introduction

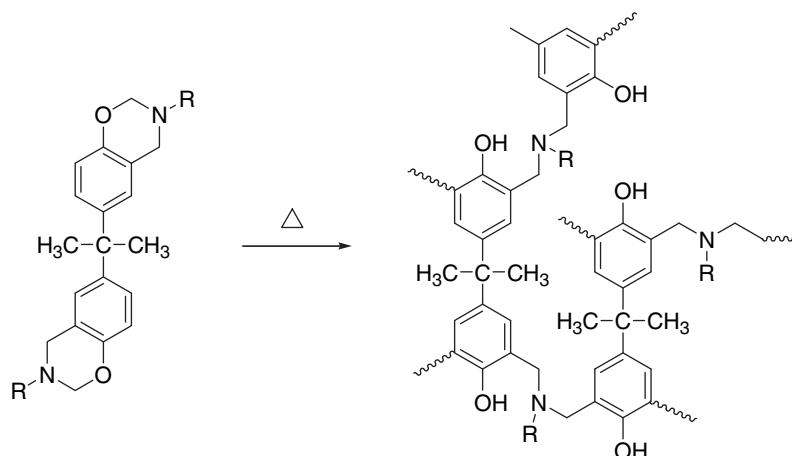
Supramolecular chemistry has received much attention for the unique molecular recognition and the related inclusion phenomena for decades. Various kinds of molecules, not only cyclics but also acyclics, are clarified for supramolecular structure to accept guest species based on either non-covalent interactions such as van der Waals, dipole-dipole, π - π stacking, or hydrogen bonding. Up to now, various host molecules such as urea, cholic acid, cyclodextrin, crown ether, calixarene, and their derivatives have been developed and clarified for the molecular recognition.

Polybenzoxazine is known as one of thermosetting polymer which has similar structure to phenolic resin. It can be obtained from the ring opening reaction of difunctional benzoxazine monomer which was synthesized from bisphenol, formaldehyde, and amine (Scheme 1). For decades, it has been proposed as composite material with the good physical and mechanical properties.^[1] As the structure of this polymer consists of the hydroxyl groups and nitrogen atoms, it can be expected for an effective electron donating system which might be developed as a host compound similar to the cases of phenolic resins and calixarenes.

For the past few years, we have focused on the supramolecular structure and its interaction with various metal ions. Although the metal ion entrapment has been identified, the question about how benzoxazines and metal ions interact at the molecular level is still left unanswered. Recently, we succeeded in preparing a

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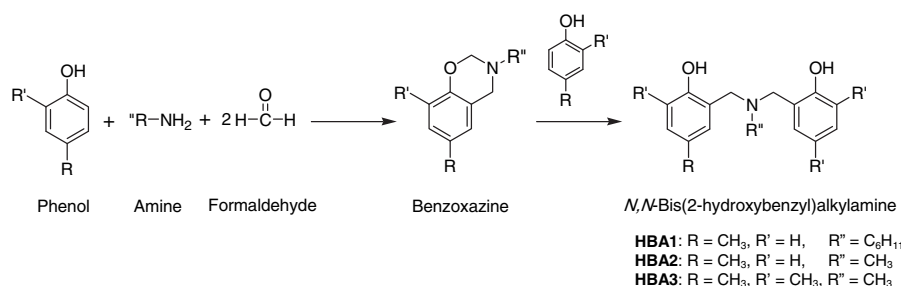
Scheme 1.

series of model compound consisting of two phenols linked with azamethylene linkage, *N,N*-bis(2-hydroxybenzyl)alkylamine (**HBA**), which can be easily obtained from the ring opening reaction of *p*-phenol based benzoxazines (Scheme 2). Our basic investigation on **HBA** using the single crystal analysis proves to us that the **HBA** forms the dimeric network with inter- and intra-molecular hydrogen bonds (Figure 1).^[2] The present work is, thus, focused on the investigation of supramolecular structure of **HBA** derivatives with copper ion based on the single crystal analysis as it will be a good model to explain how polybenzoxazines perform the host-guest phenomena. The work is also extended to the reaction of **HBA** as it is quite rare example that the macrocyclization can be achieved in very

simple steps without complicated purification steps.

Host-Guest Phenomena of HBA in Solution State

As the structure of **HBA** is similar to the repeat unit of azacalixarenes, the inclusion phenomena with various types of metal ions might be the good information to relate to those of polybenzoxazines and oligobenzoxazines.^[3,4] By using Pedersen's technique or, in other words, the liquid-liquid extraction between copper in aqueous solution and **HBA** in chloroform solution, the color of chloroform phase was changed to dark green implying the copper ion was entrapped by the host. The chloroform phase was collected and dried in vacuum to obtain dark green precipitates. Here, the



Scheme 2.

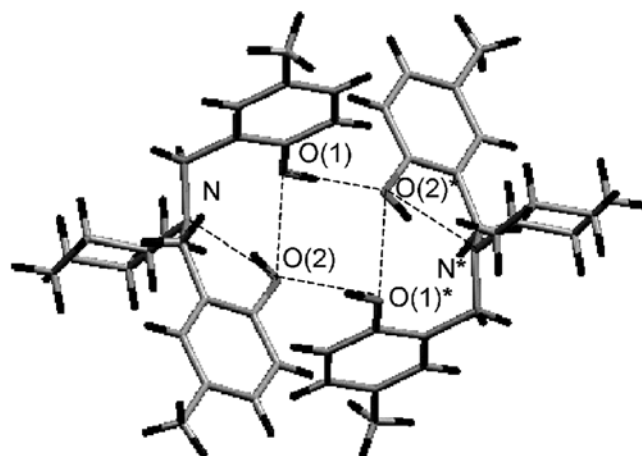


Figure 1.
Crystal structure of *N,N*-bis(2-hydroxy-5-methylbenzyl)cyclohexylamine (**HBA1**).

host-guest formation was identified by Fourier transform infrared spectroscopy (FTIR) using Nujol mull method to avoid the disturbance of water peaks. Figure 2 shows that after the copper ions were entrapped in **HBA2** (**HBA2-Cu**), the OH peak is hardly observed implying the hydrogen bonds were eliminated after the interaction with metal ions. The change of C–N peak (1249 and 1207 cm^{-1}) is the information suggesting that the aza group might take part in the metal interaction. To confirm the structure of host-metal,

^1H NMR and ^1H - ^1H NOESY techniques were applied (Figure 3 and 4). In the case of **HBA2-Cu**, the significant shift of methyl protons adjacent to the nitrogen atoms including peak shift of methylene protons ($-\text{CH}_2-\text{N}$) suggests that the nitrogen atoms play an important role in interacting with copper ions. ^1H - ^1H NOESY is useful for determining the interaction of the nearby ^1H - ^1H species. As seen in the case of **HBA2-Cu** (Figure 4), the disappearance of the hydroxyl proton peak (H1, H2) and the decrease in intensity of the peak belonging

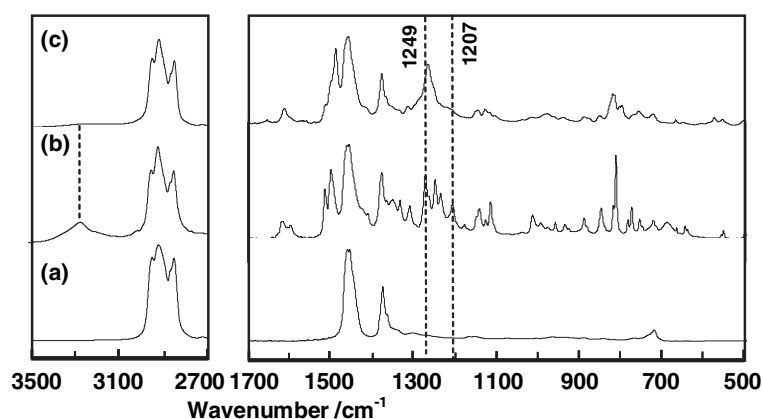


Figure 2.
FTIR spectra of (a) Nujol, (b) **HBA2**, (c) **HBA2-Cu**.

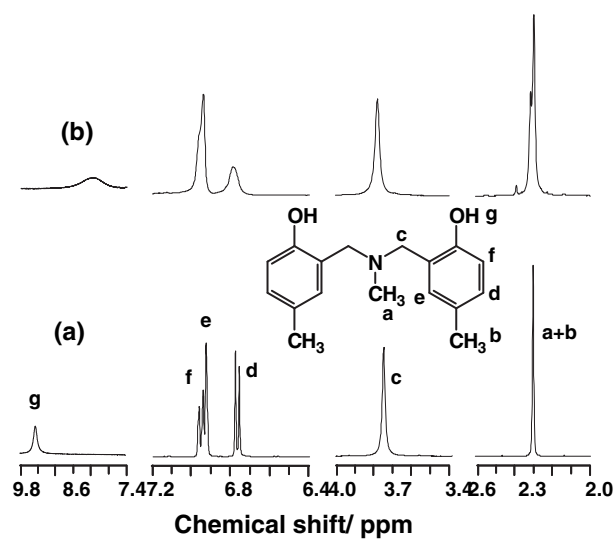


Figure 3.

^1H NMR spectra of (a) **HBA2** and (b) **HBA2-Cu** in CDCl_3 .

to the interaction between aromatic protons and methylene protons suggested that the metal ion might be in between the hydroxyl group and azamethylene unit.^[4]

Host-Guest Phenomena of Macrocyclic Compounds Based on HBA

Considering the structure of **HBA**, we shift our viewpoint to the reaction of hydroxyl

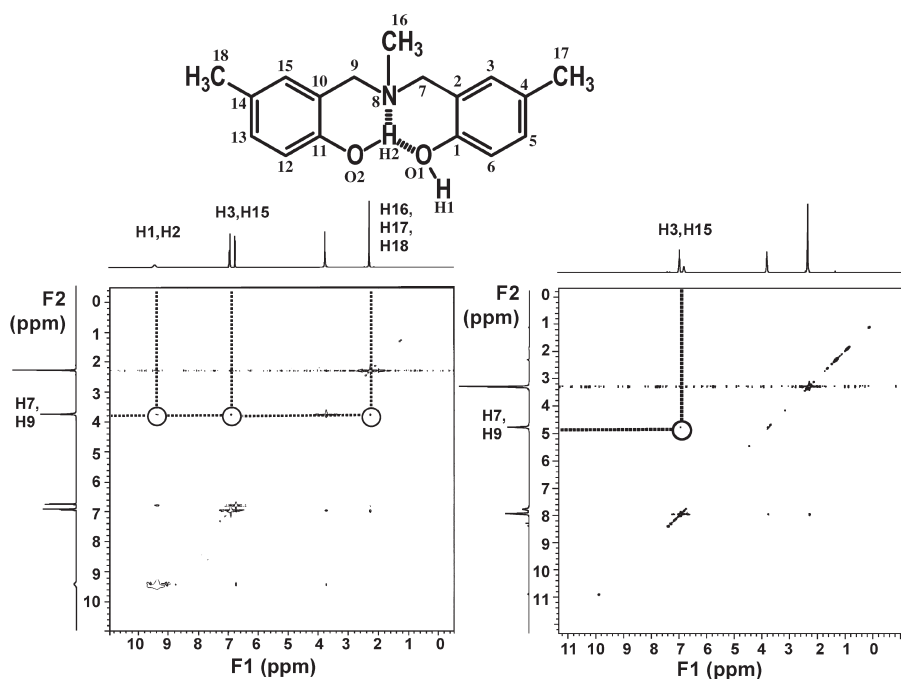
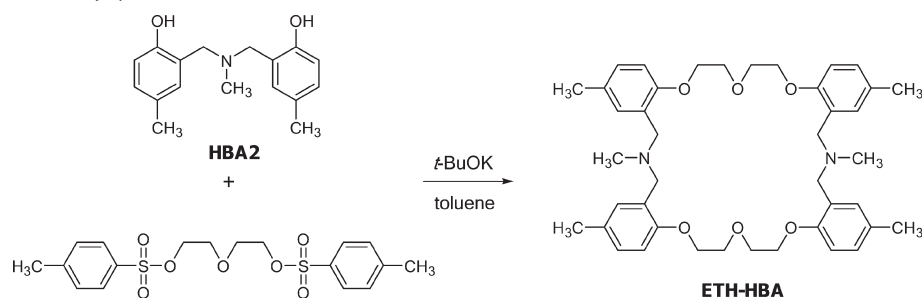


Figure 4.

^1H - ^1H NOESY spectra of (a) **HBA2** and (b) **HBA2-Cu** in CDCl_3 .



Scheme 3.

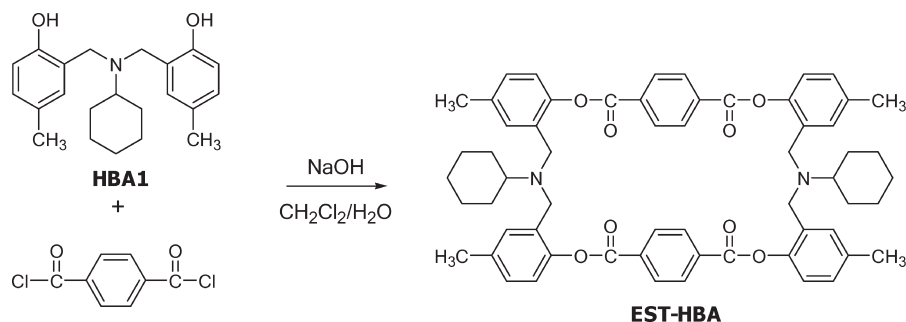
group and investigate the interaction with guest species. It should be noted that some reactions such as etherification and esterification might proceed at two hydroxyl groups. Macrocyclic compounds were synthesized by using the simple, effective, and selective synthesis routes as shown in Schemes 3^[5] and 4^[6] to obtain **ETH-HBA** and **EST-HBA**, respectively. The FTIR showed the disappearance of OH peak implying the successful reaction of hydroxyl group with the acid chloride. ¹H NMR spectrum shows the peaks at 3.8 and 4.2 ppm for $-\text{CH}_2-\text{CH}_2-\text{O}-$ in the product. This confirms the **HBA** reaction with benzoyl chloride. The result from mass spectra suggested the 2+2 cyclization with the molecular weight of 682.^[5] For **EST-HBA**, the 2+2 macrocyclization was accomplished as clarified by FTIR, NMR and MALDI-TOF MS.^[6]

The ion extraction studies of **ETH-HBA** and **EST-HBA** were investigated by using

UV-Vis and ¹H NMR spectrometers. **ETH-HBA** shows the significant ion extraction ability with alkali metal ions (Figure 5) and the host guest ratio was 2:1. In addition, **EST-HBA** showed very little ion extraction percentage. This implied that the size and the lone pair electrons of oxygen atom might play an important role in ion recognition.

Supramolecular Structure of HBA

As demonstrated in Figure 1, the dimeric packing of **HBA1** is stabilized by inter- and intramolecular hydrogen bonds. Here, **HBA1** and **HBA3** with different bulky substitution group were used as model compounds to observe the supramolecular structure with metal ions formed. Although it is difficult to determine the proton positions by single crystal X-ray analysis, we could extract the protons of hydroxyl groups for **HBA1** and **HBA3** with reasonable bond distances. However, in the case



Scheme 4.

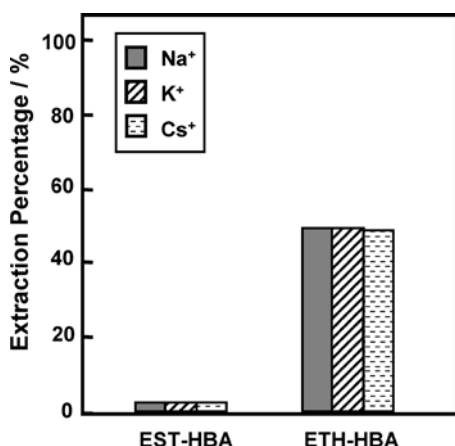


Figure 5.
Extraction percentages of **EST-HBA** and **ETH-HBA**.

of **HBA1-Cu** and **HBA3-Cu**, the hydrogen atoms could not be detected whereas the oxygen atoms were found to be directly linked to Cu atoms as seen in Figure 6. In addition, we could not observe those acetate counter anions. This leads us to a speculation that the hydrogen atoms of hydroxyl groups might perform as proton donors for acetate anions, resulting in the formation of acetic acid molecules after complexation (Scheme 5). FTIR spectra also supported this speculation

since there was no O–H stretching band ($3200\sim3400\text{ cm}^{-1}$) in the case of the **HBA-Cu** complex.

The atomic charge distribution was calculated on the basis of density function theory with DMol³ (Material Studio Version 3.0, Accelrys) in order to reveal the characteristic features of these copper complexes of **HBA**. The atomic orbital basis set was DND (Double Numerical plus d-functions), and the type of exchange-correlation potential was a local LDA. In the calculation, the structure obtained from X-ray analysis was used without any further optimization. The calculation was made for the rough estimation of the atomic charge distribution in this characteristic complex structure.

Figure 7 shows the calculated electrostatic potential (ESP) charges. After complexation, the charges of oxygen atoms were bound over Cu atom obviously; resulting in the changes of the charges of nitrogen atoms and carbon atoms in aromatic rings. The charge of Cu atom was decreased from +2 ($\text{Cu}(\text{CH}_3\text{COO})_2$) to +1.02. The changes in atomic charge distribution suggested that the electrons migrated from carbon (or aromatic rings) to oxygen and nitrogen and to copper atoms. This indicated the charge transfer system.

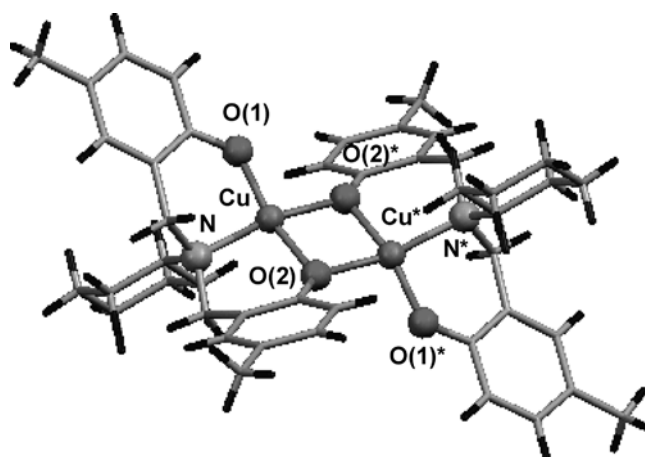


Figure 6.
Coordination compound of **HBA1-Cu**.


$$+ 4 \text{CH}_3\text{COOH}$$

Superimposition of HBA and HBA-Cu

Considering the assembly networks of **HBA1** and **HBA3**, it is important to clarify how the charge-transfer coordination networks of **HBA1**-Cu and **HBA3**-Cu affect the original packing structure. It was found that the two **HBA** molecules either before or after the complex formation gave the similar dimeric assembly. As shown in Scheme 5, the size and shape of the cage structure composed of two **HBA** molecules are maintained even after the complexation with Cu ions. At that time, the O-H...O and O-H...N for the inter- and intramolecular hydrogen bonds, respectively, are replaced with the coordination linkages of Cu-O and

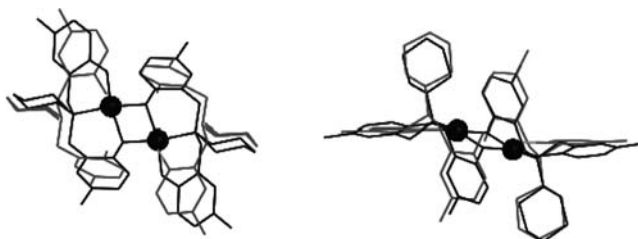
Cu-N types as demonstrated in Figures 8 and 9.

Simultaneous Inclusion of Guest Species

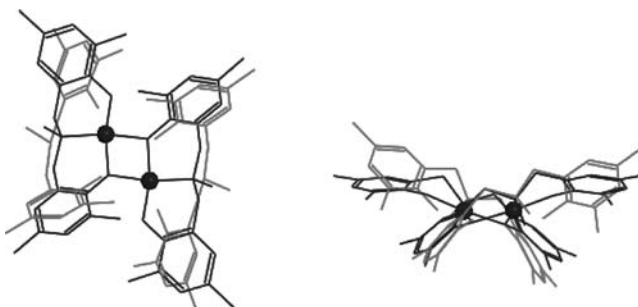
It is important to point out that **HBA3**-Cu complex showed the simultaneous inclusion of two guest species in a single host frame.^[7] The framework of **HBA** under the hydrogen bonded structure was so strong that the **HBA** with Cu remained the same host framework by changing its hydrogen bonds to coordination bonds as clarified from the superimposition structure. As seen in Figure 10, the **HBA3**-Cu complex also entraps neutral molecules such as water, methanol, and ethanol in the unit cell. A



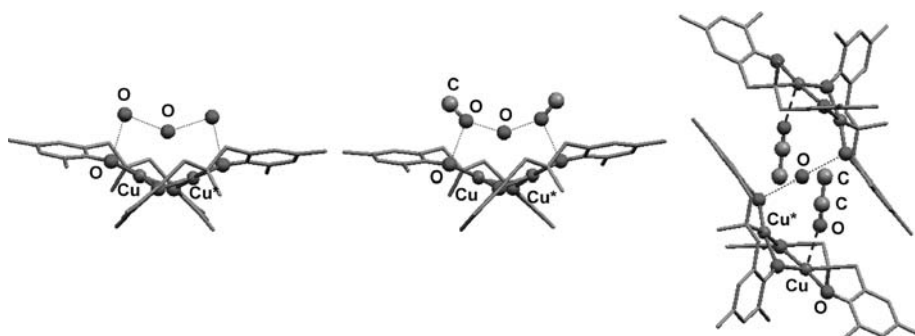
Figure 7.
Calculated atomic charges of **HBA1** and **HBA1-Cu**.

**Figure 8.**

Comparison of cage structure between **HBA1** (red color) and **HBA1-Cu** complex (blue color) viewed from different directions.

**Figure 9.**

Comparison of cage structure between **HBA3** (red color) and **HBA3-Cu** (blue color) viewed from the different directions.

**Figure 10.**

Structure of **HBA3-Cu** complex coordinated by solvent molecules. (Hydrogen atoms are omitted for clarity.)

unique bowl shape network structure of **HBA3-Cu** favors the acceptance of those small solvent molecules to stabilize the whole structure. This symmetrical structure and the availability of hydrogen bonds including the lone pair electron system might be key factors to allow simultaneous coordinated and hydrogen bonded molecular assembly.

Conclusion

In previous, our group proposed polybenzoxazines as host system for metal ions, especially alkali and alkaline earth ones. Due to the complicated structure of the polymer chain, it was hard to identify the host-guest structure. The present work focused on a model compound of poly-

benzoxazine which is **HBA** derivatives to clarify the host-guest phenomena at molecular level. In solution, the compound showed the host-guest phenomena with various types of metal ions. The single crystal of **HBA** with Cu ion clarified us that the **HBA** in solid state shared its lone pair electrons of nitrogen atom and oxygen atom in accepting the Cu ion. The framework of **HBA** was so strong that the **HBA**-Cu was in the same host framework but changed from the hydrogen bonds to coordination bonds as clarified from the superimposition structure. The extension studies on **HBA** proved that the hydrogen bonded structure of **HBA** favored the macrocyclization to accomplish a series of ether- or ester-typed macrocyclic compounds by the simple, effective, and selective reactions. The **HBA**-based macrocyclic compounds also showed the host-metal interaction.

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Structural Effects of Acyclic Benzoxazine in Building Nanochannel for Ion Guest

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Abstract

A series of benzoxazine monomer derivatives, i.e., 3,4-dihydro-2H-1,3-benzoxazines, *O,O'*-Bis(3,4-dihydro-alkyl-2H-1,3-benzoxazine)ethylene glycol, and ***N,N*-bis(3,4-dihydro-alkyl-2H-1,3-benzoxazine)tetramethylene diamine**, with different functional groups at ortho and/or para positions on the phenol ring and amine groups were prepared. Ion interaction properties of the monomer derivatives for alkali metal were studied by using Pedersen's technique and characterized by UV/Vis. Ion extraction percentage depended on main factors; concentrations, the substituent group at ortho and para position of benzene ring, and the substituent group at aza group of benzoxazine monomers. Benzoxazine monomer derivatives increased ion extraction ability when (i) the concentration of benzoxazines was increased. (ii) the benzene ring has the bulky group but the aza group of benzoxazines have less steric effect. Moreover, they were proved that only their own benzoxazine structures performed the inclusion phenomena by interacting with alkali ions. The chain attached at aza group of the oxazine ring hardly affected to the inclusion properties.

Keywords: benzoxazine structure, benzoxazine monomer, host molecule, guest species, alkali metal ion, 3,4-dihydro-2H-1,3-benzoxazines, *O,O'*-Bis(3,4-dihydro-alkyl-2H-1,3-benzoxazine)ethylene glycol, ***N,N*-bis(3,4-dihydro-alkyl-2H-1,3-benzoxazine)tetramethylene diamine**, Pedersen's technique, inclusion properties, aza group.

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Introduction

Chemistry of inclusion compounds have received much attention owing to their unique molecular assembly between host and guest species stabilized by the secondary forces, i.e., van der Waals, hydrophilic and/or hydrophobic interaction, ionic interaction, dipole-dipole interaction, etc.¹ Structural characterization in liquid and solid states proved that host compounds provide the concave structure for guests of which can either be neutral molecules or ion species.²⁻⁴ It has been known that crown ethers⁵, cyclodextrins⁶, and calixarenes⁷, the related compounds exhibit inclusion properties for decades. The practical applications can be raised as the improvement of solubility of particular organic species, the exclusion of impurity from the mixtures, the ionic catalyst, the inclusion polymerization, etc.⁸

In previous, our group focused on benzoxazines and the open ring oligobenzoxazine derivatives and proposed them as a novel type of host compound via the resemble structure to calixarenes and/or pseudocyclic calixarenes.⁹⁻¹¹ In the preliminary studies, it was found that benzoxazine monomers and their derivatives perform inclusion phenomena by interacting with alkali and alkaline earth metal ions. Due to the unique structure of benzoxazines, electron rich position N and O atoms are the attracted position to occur interaction with metal ion. Therefore, from this main reason it is interesting to study the host-guest chemistry of benzoxazines. However, the inclusion phenomena induced by the benzoxazine structures are still unknown.

Thus, the present work was designed to clarify the effect of benzoxazine structure itself to the inclusion phenomena with ion species in host-guest system. A series of monomers were prepared and studied by varying the structure of starting materials, phenol derivatives and amine types, systematically. The host-metal interactions were characterized by means of Pedersen's technique.

Experimental

Chemicals

Paraformaldehyde, *p*-cresol, 2,4-dimethyl phenol (99%), methylamine (w/w 40%), propyl amine, cyclohexylamine, sodium sulfate anhydrous, 2,2'-(ethyldioxy)diethylamine, and 1,6-diaminohexane were the product of Fluka, Switzerland. 4-Ethylphenol and picric acid were purchased from Merck, Germany. 1,4-Diaminobutane was provided from Acros, Belgium. Sodium hydroxide, isopropanol were obtained from Carlo Erba, Italy. Diethyl ether, 1,4-dioxane, dichloromethane, methanol, chloroform, potassium hydroxide and dichloromethane were provided from Labscan, Ireland. Chloroform-d was purchased from Aldrich, Germany. All chemicals were analytical grade and used without purification.

Instruments and equipment

Fourier transform infrared spectra (FTIR) were recorded on a Bruker Equinox55/S spectrometer with 64 scans at a resolution 4 cm^{-1} in the frequency range of $4,000\text{--}400\text{ cm}^{-1}$. Proton nuclear magnetic resonance spectra (^1H NMR) were analyzed from a Bruker ACF 200 MHz Fourier transform NMR spectrometer in deuterated chloroform (CDCl_3) with tetramethylsilane (TMS) as an internal standard. Mass spectroscopy was obtained by Electrospray Mass Spectrometer PE SCIEX API III Biomolecular Mass Analyzer. Vigorous shaking of the mixture between organic and aqueous solution was performed using GENIE-2 Scientific Industries Vortex mixer. UV-Vis absorbance data were recorded by a Perkin Elmer UV-Vis spectrophotometer Lambda 16.

1. Preparation of Benzoxazine Monomer Derivatives (1-15).

A series of 3,4-dihydro-2H-1,3-benzoxazines; (3,4-dihydro-3,6,8-trimethyl-2H-1,3-benzoxazines, **1**, 3,4-dihydro-3,6-dimethyl-2H-1,3-benzoxazines, **2**, 3,4-dihydro-6-ethyl-3-methyl-2H-1,3-benzoxazines, **3**, 3,4-dihydro-6-*t*-butyl-3-methyl-2H-1,3-benzoxazines, **4**, 3,4-dihydro-3-methyl-2H-1,3-benzoxazines, **5**, 3,4-dihydro-6,8-dimethyl-3-propyl-2H-1,3-benzoxazines, **6**, 3,4-dihydro-6-methyl-3-propyl-2H-1,3-benzoxazines, **7**, 3,4-dihydro-6-ethyl-3-propyl-2H-1,3-benzoxazines, **8**, 3,4-dihydro-6-*t*-butyl-3-propyl-2H-1,3-benzoxazines, **9**, 3,4-dihydro-3-propyl-2H-1,3-benzoxazines, **10**, 3,4-dihydro-6,8-dimethyl-3-cyclohexyl-2H-1,3-benzoxazines, **11**,

3,4-dihydro-6-methyl-3-cyclohexyl-2H-1,3-benzoxazines, **12**, 3,4-dihydro-6-ethyl-3-cyclohexyl-2H-1,3-benzoxazines, **13**, 3,4-dihydro-6-*t*-butyl-3-cyclohexyl-2H-1,3-benzoxazines, **14**, 3,4-dihydro-3-cyclohexyl-2H-1,3-benzoxazines, **15**)

Benzoxazine monomers **1-15** were synthesized (Scheme 1) as referred to Ishida *et al.*¹²⁻¹³ The structures of the obtained monomers were studied by FTIR, ¹H NMR, and MS.

A series of *O,O'*-Bis(3,4-dihydro-alkyl-2H-1,3-benzoxazine)ethylene glycol; (*O,O'*-Bis(3,4-dihydro-3-ethyl-6-methyl-2H-1,3-benzoxazine)ethylene glycol, **16**, *O,O'*-Bis(3,4-dihydro-3,6-diethyl-2H-1,3-benzoxazine)ethylene glycol, **17**)

Benzoxazine monomers **16-17** were synthesized (Scheme 2) as follows.

***O,O'*-Bis(3,4-dihydro-3-ethyl-6-methyl-2H-1,3-benzoxazine)ethylene glycol, 16**

2,2'-(ethyldioxy)diethylamine (1.46 mL, 10 mmol) was added dropwise into the solution of paraformaldehyde (1.23 g, 41 mmol) in 1,4-dioxane (10 mL), followed by adding *p*-cresol (2.1 mL, 21 mmol) in 1,4-dioxane (20 mL). The solution was refluxed for 6 h. The solution obtained was dissolved in 50 mL of diethyl ether and extracted with 3 N sodium hydroxide (10 mL) for 3 times, followed by washing with water. The product was dried over sodium sulfate anhydrous. The solvent was evaporated out. The product was collected and recrystallized with isopropanol. The product obtained was characterized by FTIR, ¹H NMR, and MS.

Compound **16**: 75% yield; $R_f = 0.66$ (5% methanol in chloroform); FTIR (KBr, cm^{-1}): 1121 (s, C-O-C), 1231 (vs, C-N stretching), 1500 (s, oxazine); ¹H-NMR (200 MHz, CDCl_3 , ppm): δ_H 2.25 (6H, s, Ar-**CH₃**), 2.95 (4H, t, N-**CH₂**-CH₂-O, $J_1 = 5.86$ Hz), 3.65 (4H, s, N-CH₂-CH₂-O-**CH₂**-), 3.75 (4H, t, -N-CH₂-**CH₂**-O, $J_1 = 5.86$ Hz), 4.05 (4H, s, Ar-**CH₂**-N-), 4.85 (4H, s, O-**CH₂**-N-), 6.65 (2H, d, Ar-**H**, $J_2 = 8.06$ Hz), 6.75 (2H, d, Ar-**H**, $J_3 = 1.46$ Hz), 6.95 (2H, dd, Ar-**H**, $J_2 = 8.06$ and $J_3 = 1.46$ Hz). MS (m/z): 412.

***O,O'*-Bis(3,4-dihydro-3,6-diethyl-2H-1,3-benzoxazine)ethylene glycol, 17**

4-Ethylphenol (2.44 g, 21 mmol), paraformaldehyde (1.23 g, 41 mmol), and 2,2'-(ethyldioxy)diethylamine (1.46 mL, 10 mmol) were used for preparing compound **17**. Similarly, the reactions were proceeded as compound **16**. The product obtained was then qualitatively analyzed by using FTIR, ¹H NMR, and MS.

Compound **17**: 80% yield; $R_f = 0.65$ (5% methanol in chloroform); FTIR (KBr, cm^{-1}): 1121 (s, C-O-C), 1230 (vs, C-N stretching), 1500 (s, oxazine); ¹H-NMR

(200 MHz, CDCl₃, ppm): δ_{H} 1.31 (6H, t, Ar-CH₂-CH₃, $J_1 = 7.32$ Hz), 2.55 (4H, s, Ar-CH₂-CH₃, $J_1 = 7.32$ Hz), 2.95 (4H, t, N-CH₂-CH₂-O, $J_2 = 5.86$ Hz), 3.65 (4H, s, N-CH₂-CH₂-O-CH₂-), 3.75 (4H, t, -N-CH₂-CH₂-O, $J_2 = 5.86$ Hz), 4.05 (4H, s, Ar-CH₂-N-), 4.85 (4H, s, O-CH₂-N-), 6.65 (2H, d, Ar-H, $J_3 = 8.06$ Hz), 6.79 (2H, d, Ar-H, $J_4 = 1.46$ Hz), 6.95 (2H, dd, Ar-H, $J_3 = 8.06$ and $J_4 = 1.46$ Hz). MS (m/z): 440.

A series of *N,N*-bis(3,4-dihydro-alkyl-2H-1,3-benzoxazine)tetramethylene diamine; (*N,N*-bis(3,4-dihydro-3-ethyl-6-methyl-2H-1,3-benzoxazine) tetramethylene diamine, **18**, *N,N*-bis(3,4-dihydro-3,6-diethyl -2H-1,3-benzoxazine)tetramethylene diamine, **19**)

Benzoxazine monomers **18-19** were synthesized (Scheme 3) as follows.

N,N-bis(3,4-dihydro-3-ethyl-6-methyl-2H-1,3-benzoxazine)tetramethylene diamine, **18**

Similarly, compound **18** was prepared as procedure of **16** by replacing 2,2'-(ethyldioxy)diethylamine with 1,4-diaminobutane (1 mL, 10 mmol).

Compound **3**: $R_f = 0.81$ (5:95 methanol:dichloromethane); FTIR (KBr, cm⁻¹): 1121 (s, C-O-C), 1225 (vs, C-N stretching), 1501 (s, oxazine); ¹H-NMR (200 MHz, CDCl₃, ppm): δ_{H} 1.60 (6H, s, Ar-CH₃), 2.24 (4H, t, N-CH₂-CH₂), 2.72 (4H, t, -CH₂-CH₂), 3.96 (4H, s, =C-CH₂-N-), 4.96 (4H, s, -O-CH₂-N-), 6.68 (2H, d, Ar-H), 6.76 (2H, s, Ar-H), 6.92 (2H, d, Ar-H). MS (m/z): 352.

N,N-bis(3,4-dihydro-3,6-diethyl -2H-1,3-benzoxazine)tetramethylene diamine, **19**

Similarly, compound **19** was prepared as procedure of **18** by using 4-ethylphenol (2.44 g, 21 mmol) instead of *p*-cresol.

Compound **4**: $R_f = 0.77$ (5:95 methanol:dichloromethane); FTIR (KBr, cm⁻¹): 1121 (s, C-O-C), 1225 (vs, C-N stretching), 1500 (s, oxazine); ¹H-NMR (200 MHz, CDCl₃, ppm): δ_{H} 1.12 (6H, t, -CH₂-CH₃), 1.56 (4H, t, N-CH₂-CH₂), 2.48 (4H, q, -CH₂-CH₃), 2.72 (4H, t, -CH₂-CH₂), 3.92 (4H, s, =C-CH₂-N-), 4.80 (4H, s, -O-CH₂-N-), 6.68 (2H, d, Ar-H), 6.76 (2H, s, Ar-H), 6.92 (2H, d, Ar-H). MS (m/z): 380.

2. Ion Interaction Properties.

2.1 Preparation of Metal Picrate Solution.

Sodium and potassium picrate were prepared by recrystallization of picric acid with NaOH and KOH, respectively, in methanol. The metal picrate was dissolved in water at concentration 7×10^{-5} M and used as a metal picrate solution.

2.2 Ion Extraction Studies.

Five mL of picrate (concentration 7×10^{-5} M) and benzoxazine solution (concentration 7×10^{-5} , 7×10^{-4} , and 7×10^{-3} M) were taken and mixed vigorously for 1 min. The mixture was left at room temperature till the aqueous and organic phases were completely separated. The decrease of picrate salt concentration in aqueous phase was determined by UV-Vis spectrophotometer at 354 nm.

Results and Discussion

1. Preparation of Benzoxazine Monomer Derivatives (1-15).

Synthesis and structural characterization of monomers **1-15** were previously reported elsewhere.^{10, 14}

The synthesis of monomers **16-19** was carried out via Mannich reaction shown in (Scheme 2) and (Scheme 3), respectively.

Structural characterization of monomer **16**. The characteristic peaks found in FT-IR spectra were at 1121 and 1500 cm^{-1} that belonged to C-O-C bond and oxazine ring, respectively. The important peak of **16** found in ^1H -NMR spectra was at 4.85 that referred to O-CH₂-N bond. The parent peak of product found in MS at m/z 412.

Monomers **17-19** were characterized as follows.

2. Ion Interaction Properties of Benzoxazine Monomer Derivatives (1-19).

Benzoxazine monomers (**1-19**) are expected to give a specific conformation as a host compound to form complexes with ion guests. The effects of their own benzoxazine structures to ion extraction abilities were studied by variation of concentrations, the substituent group at ortho and para positions in the benzene ring, the substituent group at aza position, and the chain attached at aza group of the oxazine ring of these benzoxazine monomers.

2.1 Effect of Benzoxazine Monomers Concentration.

Figure 1 shows that when the concentration of **1-5**, **16**, **18** increases, the sodium picrate extraction percentage are also increased. In the case of **1** and **4**, the extraction percentage is nearly 100% while in the case of **5** the extraction percentage is only 10%. It could be mentioned that the monomers with side groups on benzene ring such as methyl, ethyl, or *t*-butyl gave the higher ion extraction percentage than the monomers without those groups. The result implied that the structure of benzoxazine monomers should play an important role in the ion extraction. Since benzoxazine monomers could not provide the specific cavity by their own monomer units, the ion entrapment ability might come from the unique molecular assembly.

Considering benzoxazine monomers, the molecular assembly should be formed by stacking conformation between benzene ring. However, the oxygen and nitrogen atoms would make the oxazine ring repulsion owing to the electronegativity. It suggested that the bulky group in oxazine gave the loose packing to provide more space than guests.

2.2 Effect of the Substituent Group at Ortho and Para Positions in the Benzene Ring and the Substituent Group at Aza Position of Benzoxazine Monomers.

In order to clarify the effects of the structure of benzoxazine monomers to metal ion interaction, a series of monomers were prepared. The ion interaction properties were studied by variation host-guest ratio.

As shown in Figure 2, monomers **5**, **10**, and **15**, which are based on phenol, show ion extraction percentage, either Na^+ or K^+ , less than 20% even the host concentration is higher than guest for 100 times. The results suggested that the benzene ring has no side group, the ion extraction percentage is insignificant.

In contrast, Figure 3 suggests that **3**, **8**, and **13** having the same basic unit of ethyl phenol, extract high percent of ion when the amine group is methyl group, **3**. The results implied the effect of aza group that when aza group has no bulky group, the ion extraction percentage is significant.

Figure 4 demonstrates that benzoxazine monomers with a series of 2,4 dimethylphenol have also nearly 100% of ion extraction. Similarly as monomer **3**, the one with methyl group at N (monomer **1**) show higher percent extraction than the one with propyl or cyclohexyl group at N (monomer **6**, and **11**). The results suggested that the ion interaction ability is increased when the nitrogen atom at oxazine ring has less steric group. In the case of benzoxazine monomers with a series of methyl phenol (monomer **2**, **7**, and **12**) and *t*-butyl phenol (monomer **4**, **9**, and **14**), the results showed the same trend as monomer **3** and monomer **1**. Therefore, the results informed that benzoxazine monomers increased ion interaction ability when the benzene ring has the bulky group but the nitrogen and oxygen at oxazine ring has less steric effect.

2.3 Effect of the Chain Attached at Aza Group of the Oxazine Ring.

Monomer **3** can extract sodium ion approximately 70% whereas monomer **16-17**, and **18-19**, are 40, and 20%, respectively, at the concentration 7×10^{-3} M of host molecules (Figure 5). Although, monomer **16** and **17** consist of more O atom at the chain attached at aza group that should be electron rich position to improve host-guest formations, the ion extraction percentage was similar to the monomers which have bulky group at the aza group. What's a more, the long chain of methylene group attached at aza group of monomer **18** and **19** were insignificant for increasing the ion extraction ability. The results found that not only short and long

chain of methylene group, but also ether chain attached at aza group of the oxazine ring are hardly affect to the inclusion properties with alkali metal ion guest species. It proved that only their own benzoxazine structures performed the inclusion phenomena by interacting with alkali ions. The chain attached at aza group of the oxazine ring hardly affected to the inclusion properties.

Conclusion

Benzoxazine monomers exhibited the host-guest properties controlled only their own benzoxazines. The high concentration, the bulky group at ortho and para position in benzene ring, and the less steric aza group of benzoxazine monomers were the factors to enhance ion interaction ability. Not only short and long chain of methylene group, but also ether chain attached at aza group of the oxazine ring hardly affected to the inclusion properties with alkali metal ion guest species.

Acknowledgements

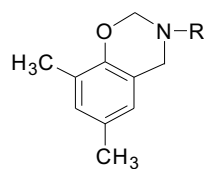
S.C. acknowledges financial support from The Thailand Research Fund (grant no. RSA4680025).

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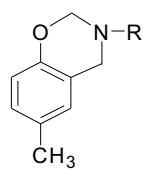
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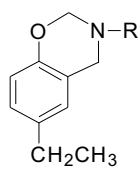
Scheme 1



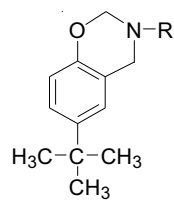
R = CH₃ (**1**)
 = CH₂CH₂CH₃ (**6**)
 = C₆H₁₁ (**11**)



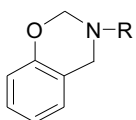
R = CH₃ (**2**)
 = CH₂CH₂CH₃ (**7**)
 = C₆H₁₁ (**12**)



R = CH₃ (**3**)
 = CH₂CH₂CH₃ (**8**)
 = C₆H₁₁ (**13**)

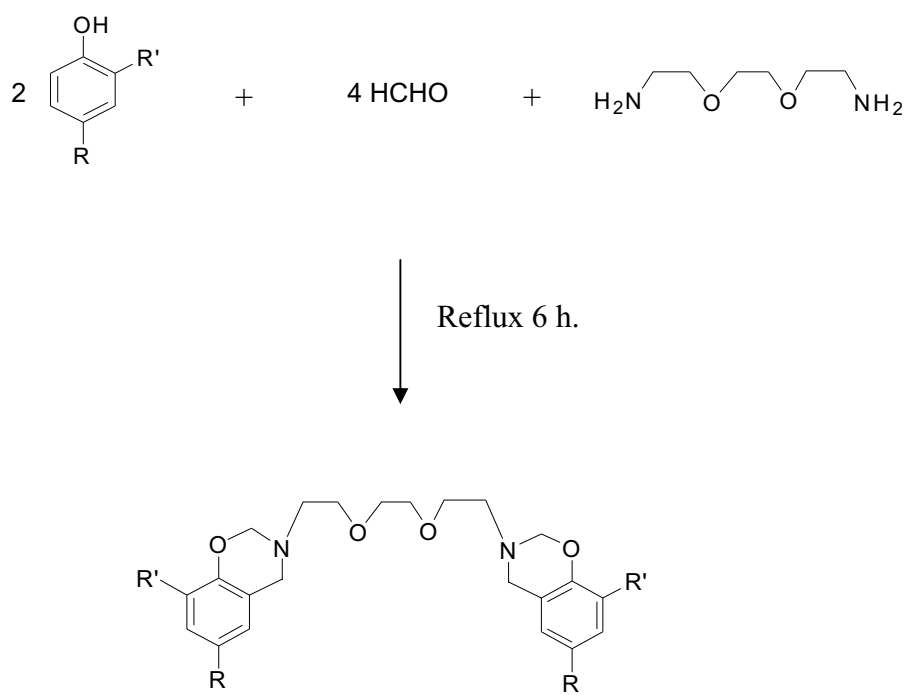


R = CH₃ (**4**)
 = CH₂CH₂CH₃ (**9**)
 = C₆H₁₁ (**14**)



R = CH₃ (**5**)
 = CH₂CH₂CH₃ (**10**)
 = C₆H₁₁ (**15**)

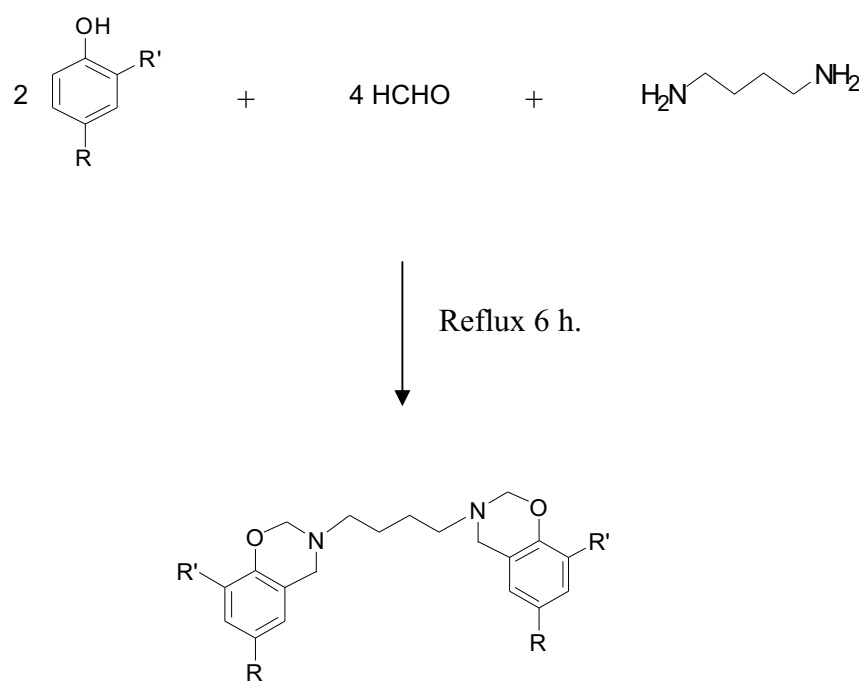
Scheme 2



R = CH₃, R' = H (**16**)

R = C₂H₅, R' = H (**17**)

Scheme 3



R = CH₃, R' = H (**18**)

R = C₂H₅, R' = H (**19**)

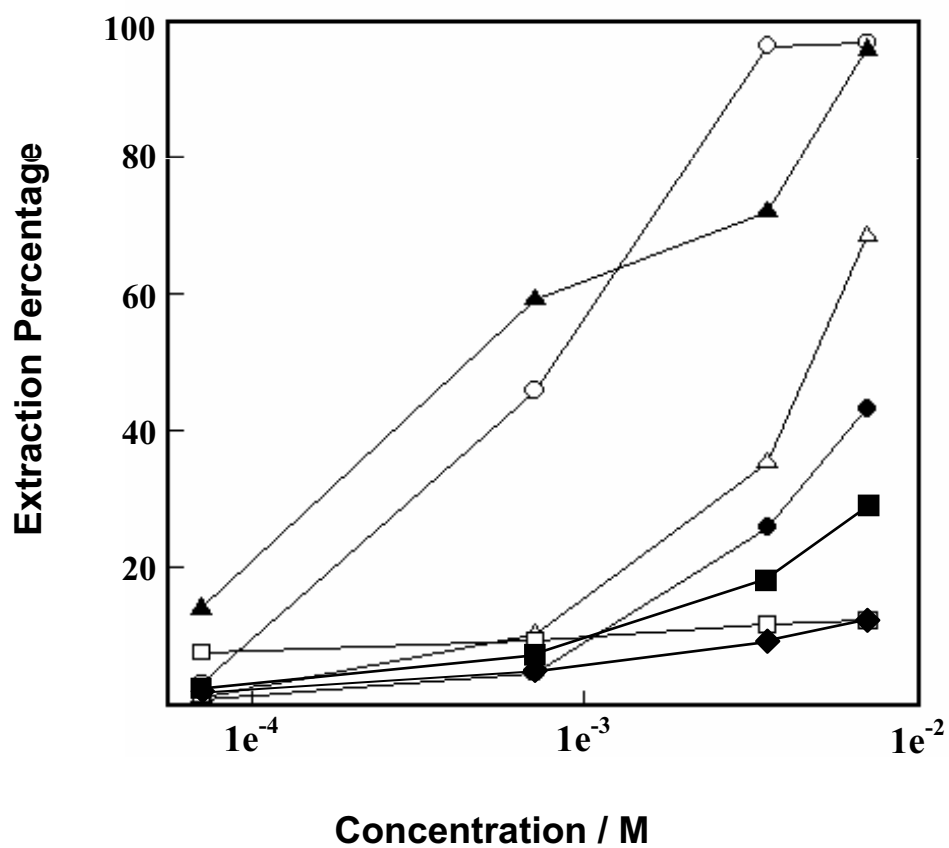


Figure 1. Ion extraction of benzoxazine monomers of ○) 1 ; ●) 2 ; △) 3 ; ▲) 4 ; □) 5 ; ■) 16 ; and ◆) 18 at monomer concentration of 7×10^{-5} , 7×10^{-4} , 3.5×10^{-3} , and 7×10^{-3} M sodium picrate salt at concentration 7×10^{-5} M.

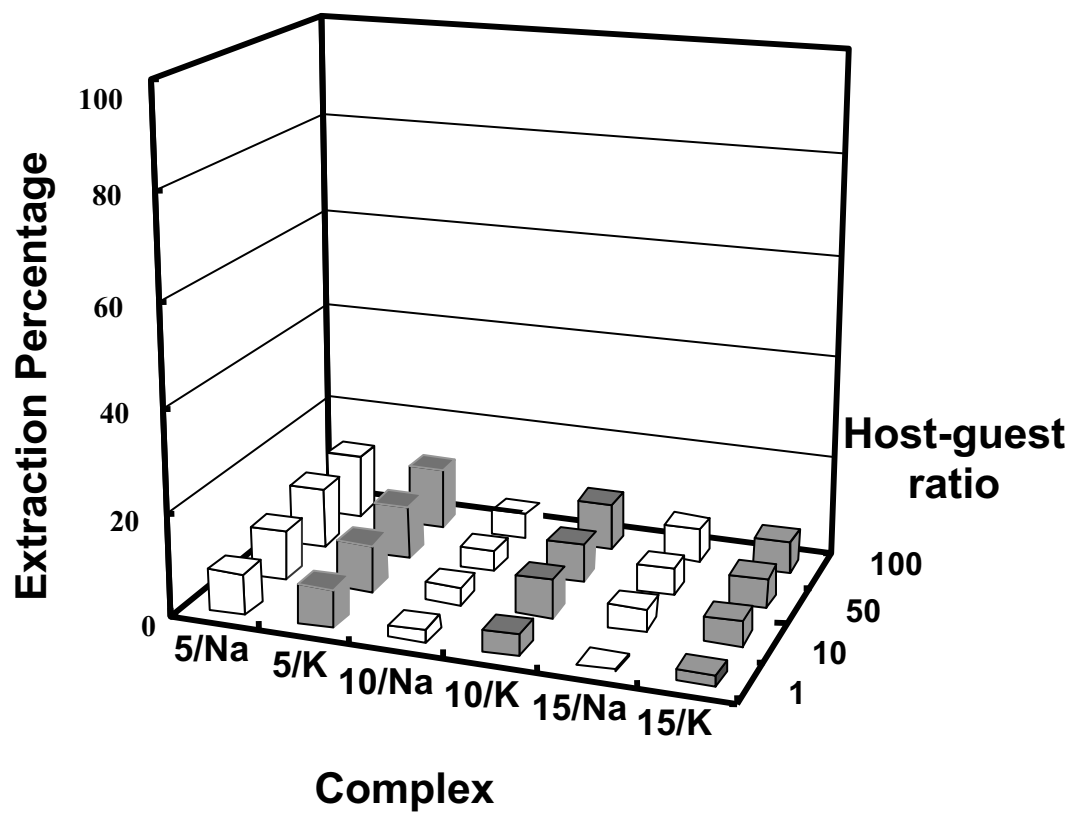


Figure 2. Ion extraction percentage of benzoxazine monomers **5**, **10**, and **15** by varying host guest ratio using picrate salt of Na^+ and K^+ at the concentration $7 \times 10^{-5} \text{M}$.

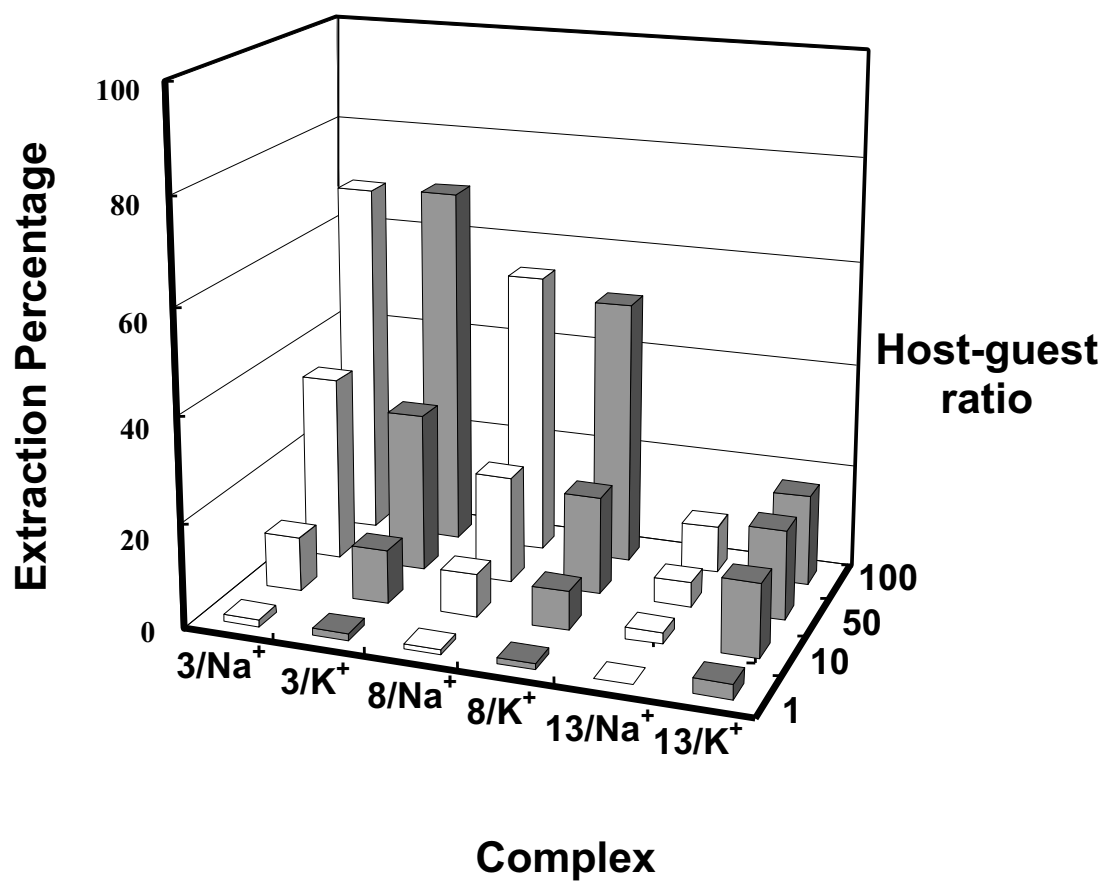


Figure 3. Ion extraction percentage of benzoxazine monomers **3**, **8**, and **13** by varying host guest ratio using picrate salt of Na⁺ and K⁺ at the concentration $7 \times 10^{-5} \text{M}$.

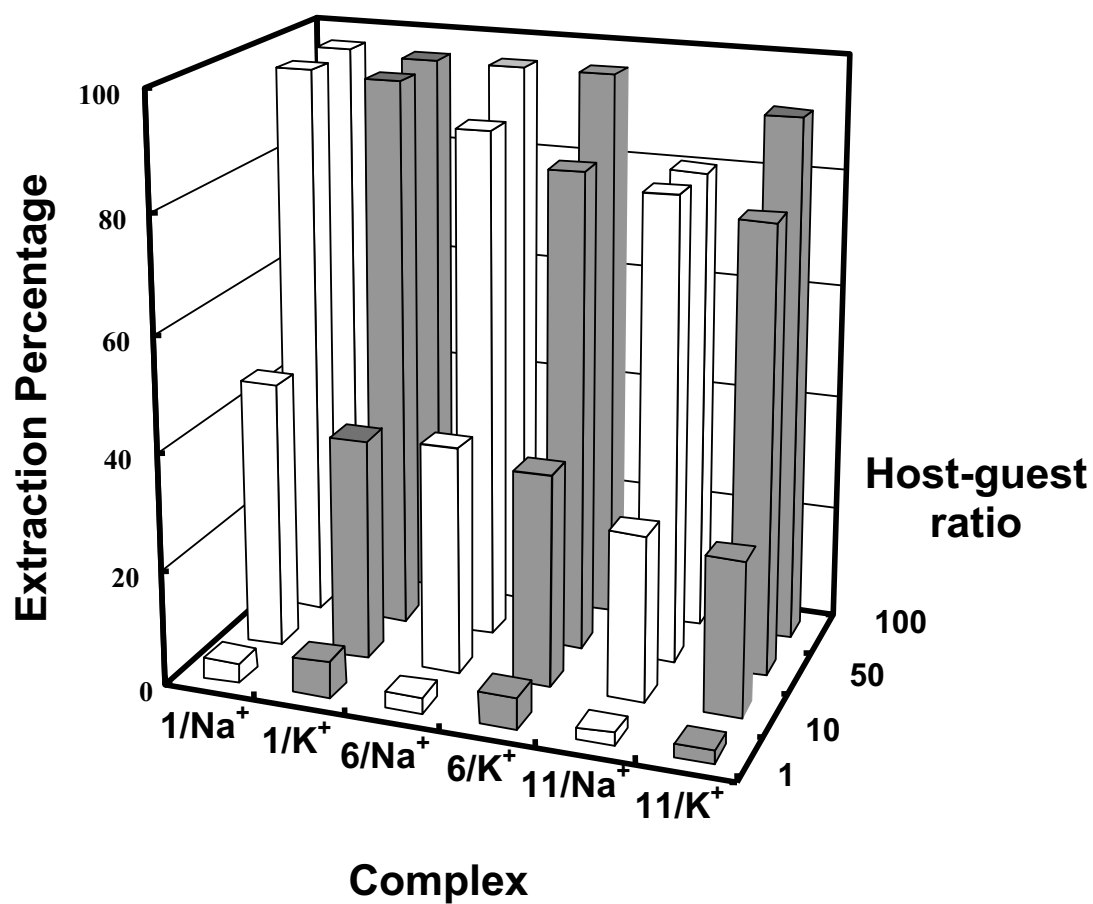


Figure 4. Ion extraction percentage of benzoxazine monomers **1**, **6**, and **11** by varying host guest ratio using picrate salt of Na⁺ and K⁺ at the concentration 7x10⁻⁵M.

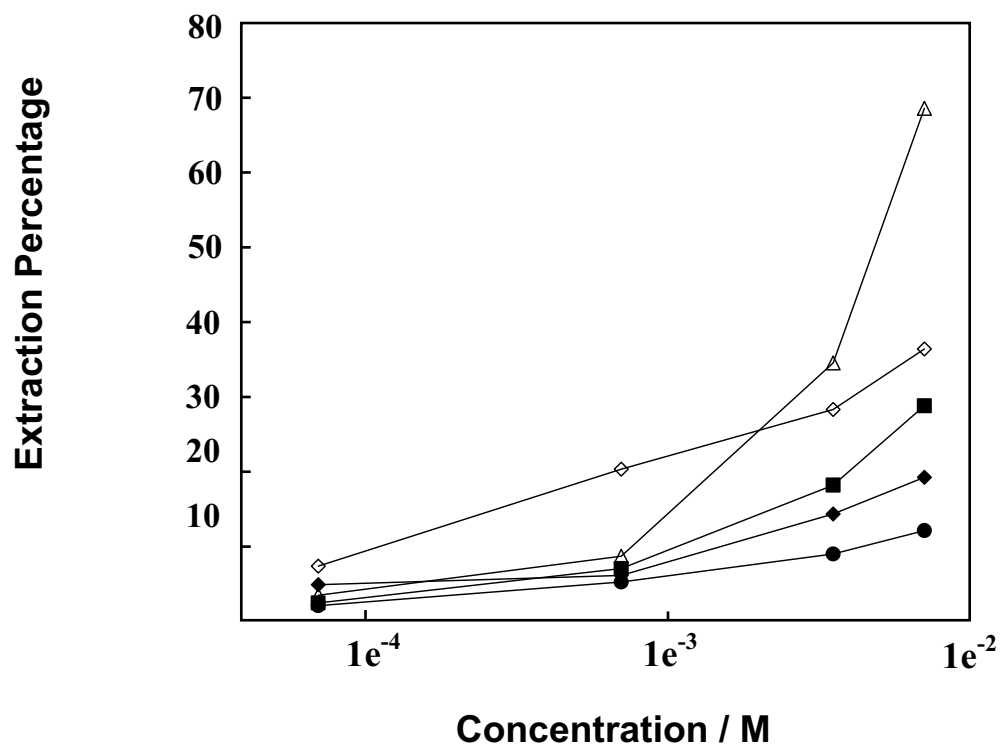


Figure 5. Ion extraction of benzoxazine monomers of Δ) **3** ; $\blacksquare$) **16** ; $\diamond$) **17** ; $\blacklozenge$) **18** ; and $\bullet$) **19** at monomer concentration of 7×10^{-5} , 7×10^{-4} , 3.5×10^{-3} , and 7×10^{-3} M sodium picrate salt at concentration 7×10^{-5} M.

Novel Supramolecular Assembly Structures of Acyclic Benzoxazines

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Abstract

Novel supramolecular assembly containing acyclic benzoxazines (**1-6**) are prepared and characterized with FTIR, NMR and MS. The alkaline metal ion guest responsive properties of the acyclic benzoxazines are studied by using Pedersen's technique. The ion extraction ability of the acyclic benzoxazines are affected by their structures.

Keywords: Novel Supramolecular Assembly Structures, Acyclic Benzoxazines, Nanomaterials, Metal Ion Guest Responsive Properties, Pedersen's Technique, Ion Extraction Ability

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Introduction

Nowadays, nanomaterials have received much interest owing to the ability of functionalization in molecular level, and the significant mechanical performances.⁽¹⁾ The development and molecular design at molecular level from the small molecules of angstrom size to be the macromolecules of nanometer size are focused to achieve nanomaterials such as macrocyclic compounds⁽²⁾, molecular assembly⁽³⁾, etc.. Most of these nanomaterials show the unique properties that have never found in the small molecules. For example, *N*-adamantylaza-crown ethers can form complexation with K^+ and Rb^+ higher than the parent aza 18-crown-6 and *N*-benzylaza-18-crown-6.⁽⁴⁾

Inclusion or host-guest have been also received much interest according to their unique properties on the molecular recognition.⁽⁵⁾ Various types of host compounds, such as crown ether⁽⁶⁾, calixarene⁽⁷⁾, cyclodextrin⁽⁸⁾, etc., are well-known to be model showing inclusion property. The induced molecular interactions between host-guest compounds are known as non-covalent interactions or secondary forces, for examples, ionic interaction⁽⁹⁾, dipole-dipole interaction⁽¹⁰⁾, hydrogen bonding⁽¹¹⁾, and etc.. Hence, many host compounds have been focused on molecular design to carry out the novel supramolecules which have specific functional groups can form either molecular assemblies or macrocyclic structure.⁽¹²⁾

Polybenzoxazine, a new type of phenolic resin with superb mechanical and thermal properties has been proposed and mainly studied on the processing conditions to improve their properties for using as composite materials.⁽¹³⁾ In our studies, novel supramolecular assembly structures of acyclic benzoxazines are objected to obtain the material for the advanced applications such as molecular ionic devices, photo-electronic molecules, and etc. by means of host-guest structured benzoxazines. We therefore focused on the unique structure of the open ring polybenzoxazine resembled to a unit of azamethylene linked calixarenes (Scheme 1) for applications as ion extraction materials.⁽¹⁴⁾ By using molecular design and synthesis pathway, the novel supramolecular assembly structures of acyclic benzoxazines have been proposed. For the past few years, our group has succeeded the fruitful results to declare benzoxazines as supramolecules either macrocyclics or molecular assemblies with specific properties via molecular recognition.⁽¹⁵⁻¹⁷⁾

Apparently, acyclic host compounds are interesting in their induced property to form metal ion complex as well as cyclic host compounds.⁽¹⁸⁻¹⁹⁾ In this present article, we aim to propose the possibility to develop novel supramolecular assembly structures

of acyclic benzoxazines for preference structure to form complexation with metal ion especially alkaline metal ions. Besides, the effects of the structure to metal ion extraction ability of these host compounds have been also studied in order to understand clearly about the appropriate structure to form inclusion phenomena with metal ion species. Moreover, the preliminary study of ion interaction property via Pedersen's technique has been done to declare the supramolecular structured benzoxazines.

Experimental

Chemicals

Paraformaldehyde, *p*-cresol methylamine, sodium sulfate anhydrous, 2,2'-(ethyldioxy)diethylamine, 1,6-diaminohexane and cesium carbonate were purchased from Fluka, Switzerland. 4-Ethylphenol and picric acid were provided from Merck, Germany. 1,4-Diaminobutane was purchased from Acros, Belgium. Sodium hydroxide, isopropanol were obtained from Carlo Erba, Italy. Diethyl ether, 1,4-dioxane, dichloromethane, ethanol, potassium hydroxide and dichloromethane were provided from Labscan, Ireland. Chloroform-*d* was purchased from Aldrich, Germany. All chemicals were analytical grade and used as received.

Instruments and equipment

Fourier transform infrared spectra (FTIR) were recorded on a Bruker Equinox55/S spectrometer with 64 scans at a resolution 4 cm⁻¹. Proton nuclear magnetic resonance spectra (¹H NMR) were obtained from a Fourier transform NMR spectrometer ACF 200 MHz in deuterated chloroform (CDCl₃) with tetramethylsilane (TMS) as an internal standard. Mass spectroscopy was analyzed by FAB⁺-MS 707 VG Autospec-ultima mass spectrometer employing a direct probe inlet and using Cs gun to ionize sample. UV-Vis absorbance data were recorded by a Perkin Elmer UV-Vis spectrophotometer Lambda 16.

1. Preparation of Supramolecular Assembly Structures of Acyclic Benzoxazines (1-6).

A series of *O,O'*-Bis(3,4-dihydro-alkyl-2H-1,3-benzoxazine)ethylene glycol (Scheme 2), ***N,N*-bis(3,4-dihydro-alkyl-2H-1,3-benzoxazine)tetramethylene diamine** (Scheme 3), and ***N,N*-bis(3,4-dihydro-alkyl-2H-1,3-benzoxazine)hexamethylene diamine** (Scheme 4), i.e., *O,O'*-Bis(3,4-dihydro-3-ethyl-6-methyl-2H-1,3-benzoxazine)ethylene glycol (1), *O,O'*-Bis(3,4-dihydro-3,6-diethyl-2H-1,3-benzoxazine)ethylene glycol (2), ***N,N*-bis(3,4-dihydro-3-ethyl-6-methyl-2H-1,3-benzoxazine)tetramethylene diamine** (3), ***N,N*-bis(3,4-dihydro-3,6-diethyl-2H-1,3-benzoxazine)tetramethylene diamine** (4), ***N,N*-bis(3,4-dihydro-3-ethyl-2H-1,3-benzoxazine)hexamethylene diamine** (5), and ***N,N*-bis(3,4-dihydro-3,6-diethyl-2H-1,3-benzoxazine)hexamethylene diamine**, 6 were prepared as follows.

***O,O'*-Bis(3,4-dihydro-3-ethyl-6-methyl-2H-1,3-benzoxazine)ethylene glycol, 1**

2,2'-(ethyldioxy)diethylamine (1.46 mL, 10 mmol) was added dropwise into the solution of paraformaldehyde (1.23 g, 41 mmol) in 1,4-dioxane (10 mL), followed by adding *p*-cresol (2.1 mL, 21 mmol) in 1,4-dioxane (20 mL). The solution was refluxed for 6 h. The solution obtained was dissolved in 50 mL of diethyl ether and extracted with 3 N sodium hydroxide (10 mL) for 3 times, followed by washing with water. The product was dried over sodium sulfate anhydrous. The solvent was evaporated out. The product was collected and recrystallized with isopropanol. The product obtained was characterized by FTIR, ^1H NMR, and FAB^+ -MS.

Compound **1**: 75% yield; $R_f = 0.66$ (5% methanol in chloroform); FTIR ($\text{KBr}, \text{cm}^{-1}$): 1121 (s, C-O-C), 1231 (vs, C-N stretching), 1500 (s, oxazine); ^1H -NMR (200 MHz, CDCl_3 , ppm): δ_{H} 2.25 (6H, s, Ar-**CH**₃), 2.95 (4H, t, N-**CH**₂-CH₂-O, $J_1 = 5.86$ Hz), 3.65 (4H, s, N-CH₂-CH₂-O-**CH**₂-), 3.75 (4H, t, -N-CH₂-**CH**₂-O, $J_1 = 5.86$ Hz), 4.05 (4H, s, Ar-**CH**₂-N-), 4.85 (4H, s, O-**CH**₂-N-), 6.65 (2H, d, Ar-**H**, $J_2 = 8.06$ Hz), 6.75 (2H, d, Ar-**H**, $J_3 = 1.46$ Hz), 6.95 (2H, dd, Ar-**H**, $J_2 = 8.06$ and $J_3 = 1.46$ Hz). FAB^+ -MS (m/z): $M+1 = 413$; $M = 412$.

***O,O'*-Bis(3,4-dihydro-3,6-diethyl-2H-1,3-benzoxazine)ethylene glycol, 2**

4-Ethylphenol (2.44 g, 21 mmol), paraformaldehyde (1.23 g, 41 mmol), and 2,2'-(ethyldioxy)diethylamine (1.46 mL, 10 mmol) were used for preparing compound **2**. Similarly, the reactions were proceeded as compound **1**. The product obtained was then qualitatively analyzed by using FTIR, ^1H NMR, and FAB^+ -MS.

Compound **2**: 80% yield; $R_f = 0.65$ (5% methanol in chloroform); FTIR ($\text{KBr}, \text{cm}^{-1}$): 1121 (s, C-O-C), 1230 (vs, C-N stretching), 1500 (s, oxazine); ^1H -NMR (200 MHz, CDCl_3 , ppm): δ_{H} 1.31 (6H, t, Ar-CH₂-**CH**₃, $J_1 = 7.32$ Hz), 2.55 (4H, s, Ar-**CH**₂-CH₃, $J_1 = 7.32$ Hz), 2.95 (4H, t, N-**CH**₂-CH₂-O, $J_2 = 5.86$ Hz), 3.65 (4H, s, N-CH₂-CH₂-O-**CH**₂-), 3.75 (4H, t, -N-CH₂-**CH**₂-O, $J_2 = 5.86$ Hz), 4.05 (4H, s, Ar-**CH**₂-N-), 4.85 (4H, s, O-**CH**₂-N-), 6.65 (2H, d, Ar-**H**, $J_3 = 8.06$ Hz), 6.79 (2H, d, Ar-**H**, $J_4 = 1.46$ Hz), 6.95 (2H, dd, Ar-**H**, $J_3 = 8.06$ and $J_4 = 1.46$ Hz). FAB^+ -MS (m/z): $M+1 = 441$; $M = 440$.

***N,N*-bis(3,4-dihydro-3-ethyl-6-methyl-2H-1,3-benzoxazine)tetramethylene diamine, 3**

Similarly, compound **3** was prepared as procedure of **1** by replacing 2,2'-(ethyldioxy)diethylamine with 1,4-diaminobutane (1 mL, 10 mmol).

Compound **3**: R_f = 0.81 (5:95 methanol:dichloromethane); FTIR (KBr, cm^{-1}): 1121 (s, C-O-C), 1225 (vs, C-N stretching), 1501 (s, oxazine); $^1\text{H-NMR}$ (200 MHz, CDCl_3 , ppm): δ_{H} 1.60 (6H, s, Ar-**CH**₃), 2.24 (4H, t, N-**CH**₂-CH₂), 2.72 (4H, t, -CH₂-**CH**₂), 3.96 (4H, s, =C-**CH**₂-N-), 4.96 (4H, s, -O-**CH**₂-N-), 6.68 (2H, d, Ar-**H**), 6.76 (2H, s, Ar-**H**), 6.92 (2H, d, Ar-**H**). FAB⁺-MS (m/z): $M+1$ = 353; M = 352.

***N,N*-bis(3,4-dihydro-3,6-diethyl-2H-1,3-benzoxazine)tetramethylene diamine, 4**

Similarly, compound **4** was prepared as procedure of **3** by using 4-ethylphenol (2.44 g, 21 mmol) instead of *p*-cresol.

Compound **4**: R_f = 0.77 (5:95 methanol:dichloromethane); FTIR (KBr, cm^{-1}): 1121 (s, C-O-C), 1225 (vs, C-N stretching), 1500 (s, oxazine); $^1\text{H-NMR}$ (200 MHz, CDCl_3 , ppm): δ_{H} 1.12 (6H, t, -CH₂-**CH**₃), 1.56 (4H, t, N-CH₂-**CH**₂), 2.48 (4H, q, -**CH**₂-CH₃), 2.72 (4H, t, -CH₂-**CH**₂), 3.92 (4H, s, =C-**CH**₂-N-), 4.80 (4H, s, -O-**CH**₂-N-), 6.68 (2H, d, Ar-**H**), 6.76 (2H, s, Ar-**H**), 6.92 (2H, d, Ar-**H**). FAB⁺-MS (m/z): $M+1$ = 381; M = 380.

***N,N*-bis(3,4-dihydro-3-ethyl-2H-1,3-benzoxazine)hexamethylene diamine, 5**

Similarly, compound **5** was prepared as procedure of **1** by replacing 2,2'-(ethyldioxy)diethylamine with 1,6-diaminohexane (1 mL, 10 mmol).

***N,N*-bis(3,4-dihydro-3,6-diethyl-2H-1,3-benzoxazine)hexamethylene diamine, 6**

Similarly, compound **6** was prepared as procedure of **5** by using 4-ethylphenol (2.44 g, 21 mmol) instead of *p*-cresol.

2. Ion Extraction Property of Supramolecular Assembly Structures of Acyclic Benzoxazines (1-6).

The metal ion extraction of compound **1-6** was qualitative and quantitative analyzed by Pedersen's technique. Compound **1**, **2** were dissolved in chloroform whereas compound **3**, **4** were dissolved in dichloromethane at 7×10^{-3} , 7×10^{-4} , and 7×10^{-5} M. Metal picrate aqueous solutions (sodium picrate, potassium picrate, and

cesium picrate) were prepared at concentration of 7×10^{-5} M. Five milliliters of each solution were mixed together, followed by vigorously shaken for 1 min and left at room temperature until each phase was separated completely. The aqueous phase was collected to determine the concentration of metal picrate solution by using a Perkin Elmer UV-Vis spectrophotometer Lambda 16 at λ_{max} 354 nm. Extraction percentage was calculated as eq. 1.

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

The organic phase was collected. The solvent was removed out to obtain the complex salts of benzoxazine monomer derivatives and metal picrate. The salts obtained were analyzed by ^1H NMR spectroscopy using deuterated chloroform as a solvent with a trace amount of tetramethylsilane (TMS).

Results and Discussion

1. Preparation of Supramolecular Assembly Structures of Acyclic Benzoxazines (1-6).

The synthetic route to prepare supramolecular assembly structures of acyclic benzoxazines, i.e., (Compound **1**, **2**), (Compound **3**, **4**), and (Compound **5**, **6**) by Mannich reaction are shown in (Scheme 2), (Scheme 3), and (Scheme 4), respectively. The FT-IR spectra of compound (**1**, **2**), (**3**, **4**), and (**5**, **6**) are shown in Figure 1, Figure 2, and Figure 3, respectively. Figure 1 shows the characteristic peaks of benzoxazine monomers at 1500 cm^{-1} whereas Figure 2, and Figure 3 show at 1501, and 1501, respectively.

The parent peak of products (M+1) found in the mass fragmentation spectra were at m/z 413, and 441, respectively. The characterization results were confirmed the structures of products as **1-2** shown in Scheme IV.

2. Ion Extraction Property of Supramolecular Assembly Structures of Acyclic Benzoxazines (1-6).

Acknowledgements

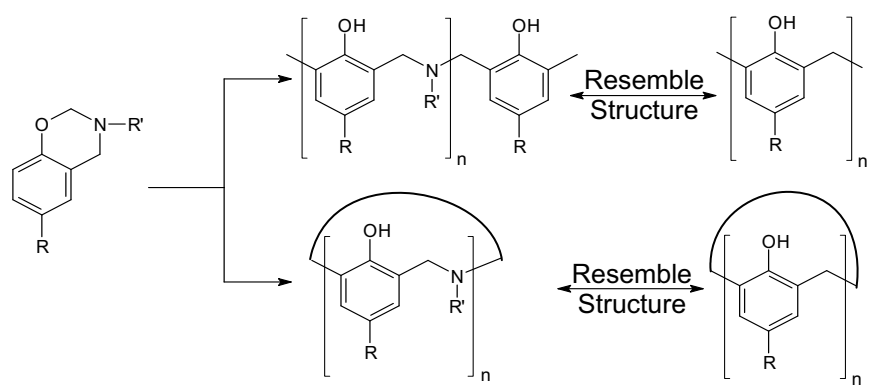
S.C. acknowledges financial support from The Thailand Research Fund (grant no. RSA4680025).

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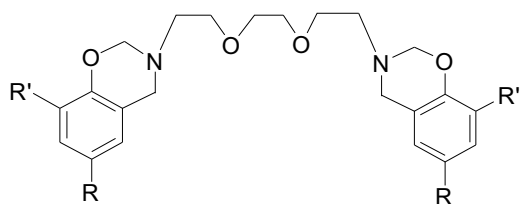
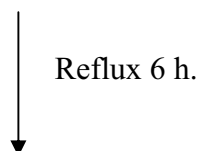
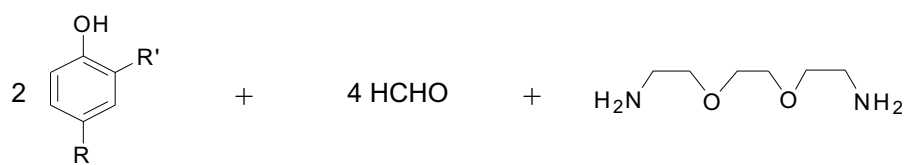
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Scheme 1



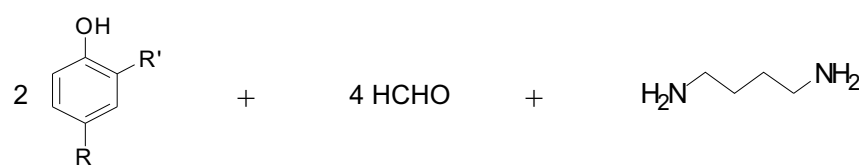
Scheme 2



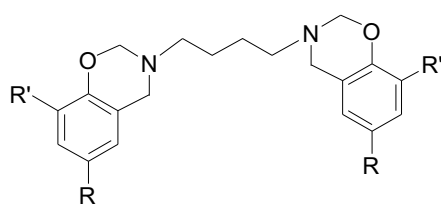
R = CH₃, R' = H (**1**)

R = C₂H₅, R' = H (**2**)

Scheme 3



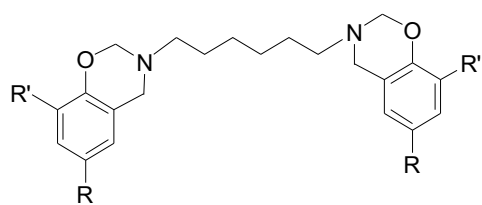
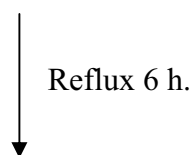
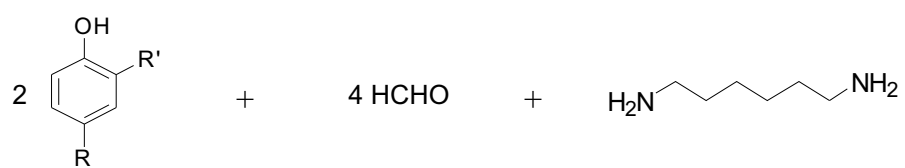
Reflux 6 h.



R = CH₃, R' = H (**3**)

R = C₂H₅, R' = H (**4**)

Scheme 4



R = CH₃, R' = H (**5**)

R = C₂H₅, R' = H (**6**)

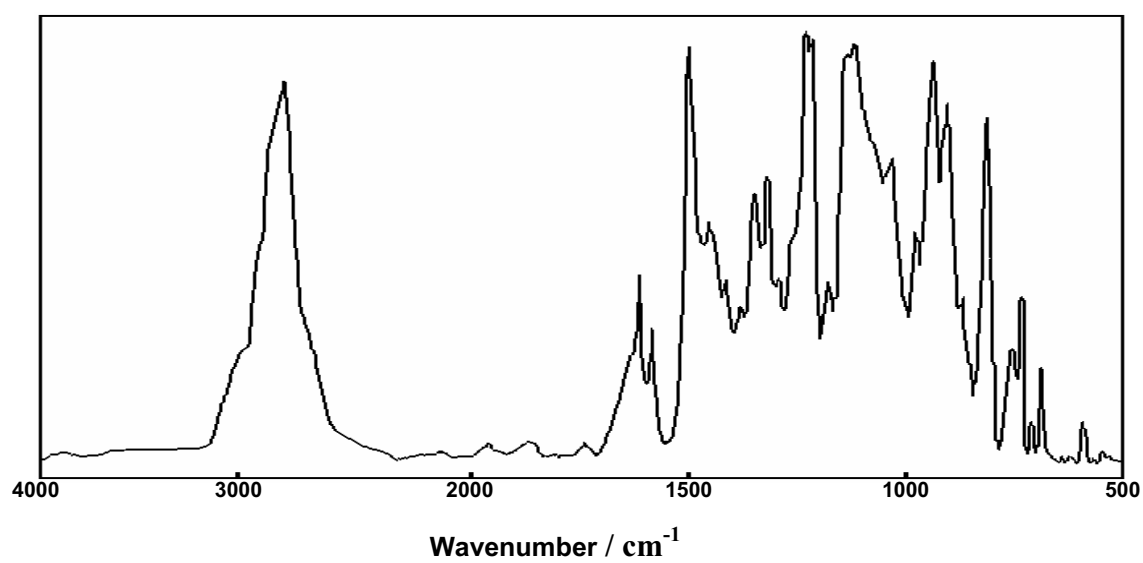


Figure 1. FTIR spectra of **1**.

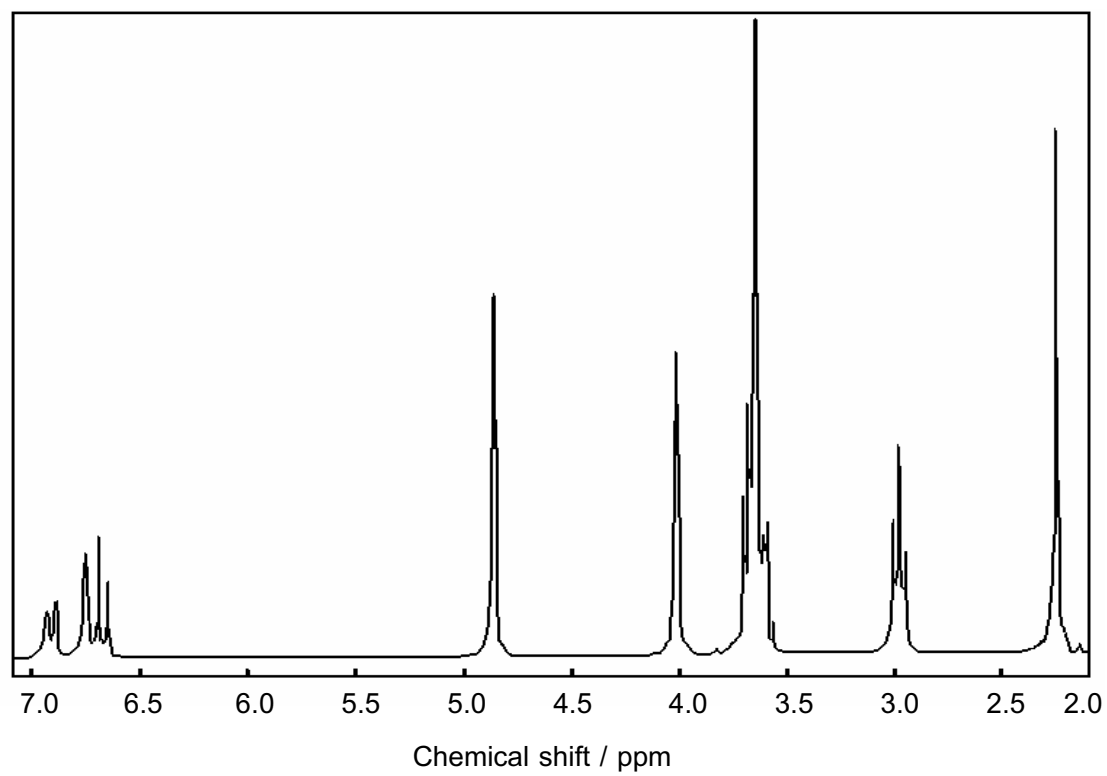


Figure 2. ^1H NMR spectra of **1**.

Role of H-bond in Controlling the Macrocyclization: A Model Case of Dibenzo-monoazacrown Ethers from *N,N*-Bis(2-hydroxybenzyl)alkylamine Derivatives

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In principle, supramolecular phenomena¹ are achieved from either self-assemblies or macrocyclic compounds. In the case of self-assemblies, the key points deal with a molecular design with significant non-covalent bonded host framework and favorable conditions to initiate host-guest interaction.² For macrocyclics, the specific ring size with functional group brings the inclusion properties as seen in crown ethers, calixarenes, etc.³ As macrocyclization is a random reaction between two backbone molecules, the dilute system⁴ is known as the basic requirement to initiate the reaction between these two different molecules. At final, steps of purification (i.e., by chromatography and/or recrystallization) are always needed, which consume time and initiate loss of the yield. Although the use of metal template is a good way for selective cyclization⁴, in most cases, the yield is limited at about 30-40%. Thus, it is a challenging theme to develop an ideal macrocyclization of which the reaction is not only simple but gives the as-designed macrocyclic molecules with the high yield and the high purity. Here, we demonstrate for the first time that the structure of the backbone molecule itself, especially the H-bond network, plays an important role in controlling the selective, effective and efficient macrocyclization.

N,N-bis(2-hydroxybenzyl)alkylamine derivative is the good model compound as it has a unique simultaneous inter- and intramolecular hydrogen bonds in a dimeric system as clarified by the single crystal analysis (Figure 1).⁵ Considering the reaction between *N,N*-bis(2-hydroxybenzyl)alkylamines and 1,3-bis(tosyloxy)propane⁶, one may recognize the feasible reactions of linear polymerization and macrocyclization, either the [1+1] and/or [2+2], as shown in Scheme 1.

To answer the question about which compound in Scheme 1 was obtained; the structural characterizations were carried out as follows. From FTIR, compound **1** gave the peaks at 3240 cm⁻¹ (intermolecular H-bond), 3200-2600 cm⁻¹ (intramolecular H-bond), 1612 cm⁻¹ (trisubstituted benzene), 1350 cm⁻¹ (C-N-C stretching), and 1242 cm⁻¹ (C-N stretching). After the reaction with 1,3-bis(tosyloxy)propane, a new peak at 1065 cm⁻¹ due to Ar-O-CH₂ stretching was clarified while the broad OH peak was disappeared implying the successful etherification. The peak shifts, especially the 1350 to 1327 and 1242 to 1250 cm⁻¹, referring to the changes in vibrational mode of C-N-C and C-N stretching were also observed. The results implied that the cyclization of **1** might be **4a**, **4b**, or **4c** as detailed in Scheme 1. The ¹H NMR of **4** declares the proton positions of 2, 3, 5, 7, 8, and 9 (as indicated in Scheme 1) in **4** and of propyl chain (the positions of 10 and 11).⁷ In addition, ¹H-¹³C HMBC allows us to confirm the significant interaction between C1 and H10. ¹H-¹H NOESY demonstrates the strong interaction of H7 with H10 and H11.⁸ Taking the results in our consideration, the most possibility of cyclization was the [1+1].

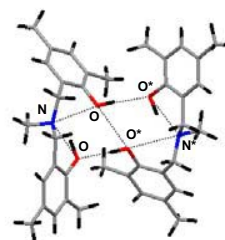
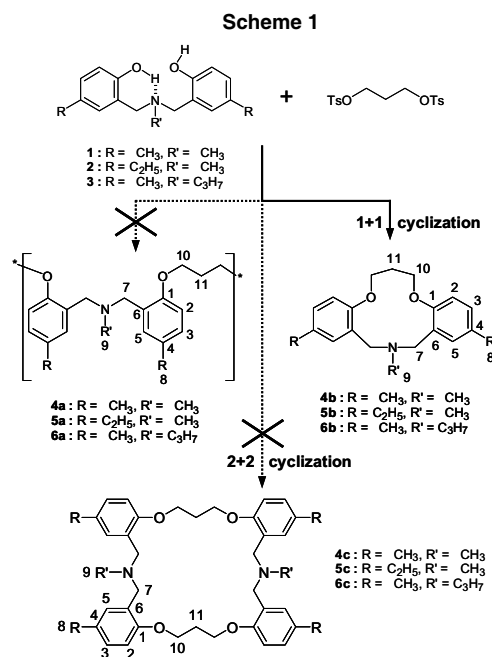


Figure 1. Crystal structure of **1**.



The matrix-assisted laser desorption ionization time-of-flight mass spectrometer (MALDI-TOF MS) gives a single peak at *m/z* = 312.6 which precisely equals to the [1+1] type or **4b**.⁷

Further analysis was done by recrystallizing the compound in methanol and the colorless cubic crystals were obtained. The single crystal analysis using a Rigaku RAXIS-RAPID imaging plate with a TEXSAN software was carried out. The orthorhombic space group *Pnma* with the *R*1 value of 4.7% clearly identifies that the product from the reaction was **4b** with a [1+1] symmetrical structure.⁹ Figure 2 shows an ORTEP view declaring a 12-membered ring macrocyclic of **4b** from the TEXSAN. As there might be the possibility of the mixtures of [1+1] and [2+2] macrocycles, we, then, repeated our single crystal X-ray analysis using various crystals to find that all of the crystals showed the structure of **4b** without any by-products of **4a** and **4c**.

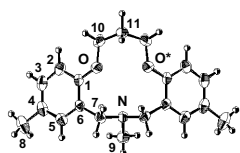


Figure 2. ORTEP view of **4b**.

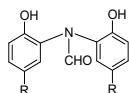


Figure 3. Chemical structure of 2,2'-dihydroxydiphenylamine.

The similar work by Agai *et al.*¹⁰ using 2,2'-dihydroxydiphenylamine (Figure 3) as a backbone molecule leads us to the following discussion. In their work, the reaction was succeeded in the specific conditions such as the high temperature (120°C) with alkylating agent, K_2CO_3 and KI to obtain [1+1] monoaza-12-crown-4 with the yield range of 7-40%, depending on the concrete condition details. As the only difference between 2,2'-dihydroxydiphenylamine and **1** is a unit of methylene in aza-methylene linkage (Scheme 1), we suspect that a six-membered ring of the intramolecular hydrogen bond formed by the methylene unit and the OH of phenol together with the consequence intermolecular hydrogen bond network of dimeric of **1** might play an important role in the macrocyclization. In other words, our simple condition to obtain only **4b** with as high as 75% yield might relate to the H-bonds. Acetonitrile was the good solvent to give **4b** in the good yield as compared to other solvents such as methanol, dioxane, toluene, etc. This implied that acetonitrile might maintain the H-bonded dimeric system as in the crystal state to favor the selective macrocyclization. The use of KOH base was also important since we found that the reaction with other bases such as sodium hydroxide, triethylamine hardly gave any of **4** (either **4a**, **4b**, or **4c**). Taking all into our consideration, we speculated the mechanism in macrocyclization as follows (Figure 4); (i) the weakening of intermolecular hydrogen bond of the dimeric system of **1** by KOH to initiate a phenoxide ion at a single phenol group (at this time the other phenol group is maintained its intramolecular hydrogen bond with aza-methylene unit in acetonitrile), (ii) the nucleophilic substitution of a single tosyl group from the ditosylated compound at this phenoxide position, and (iii) the nucleophilic addition between the terminal tosylated group and the other phenol group (which is remained by the intramolecular H-bond) resulting in the controlled macrocyclization to obtain a single type of [1+1]. In the case of 2,2'-dihydroxydiphenylamine with no H-bond network, the step of nucleophilic addition of ditosylated compound might occur randomly on the two phenoxide groups and lead to various by-products and the low yield.

To confirm the role of hydrogen bond of **1** and the mechanism as mentioned above, a series of *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives, i.e., *N,N*-bis(2-hydroxy-5-ethylbenzyl)methylamine, **2**, and *N,N*-bis(2-hydroxy-5-methylbenzyl)propylamine, **3**, were also applied in the similar reaction condition. The compounds obtained were **5b**¹¹ and **6b**¹² in the yields above 75%. We found that the concentration of **1** to give the highest yield was 5 mM.

As shown in this work, we conclude that it is possible to obtain a single type of macrocyclic in high yield if only the backbone macromolecule has its favorable structure in controlling the macrocyclization, for example the H-bond network. At present, we are studying more conditions involved with the role of hydrogen bond in **1** and its derivatives by varying the solvents, the substituent groups, etc., to achieve the various types of macrocyclics.

ACKNOWLEDGMENT The present work was supported by the Thailand Research Fund (Grant No. RSA4680025). Thanks to Prof. Mikiji Miyata, Graduate school of engineering, Osaka University, for the helps in single crystal structure analysis.

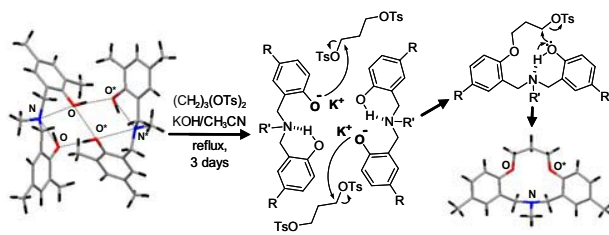
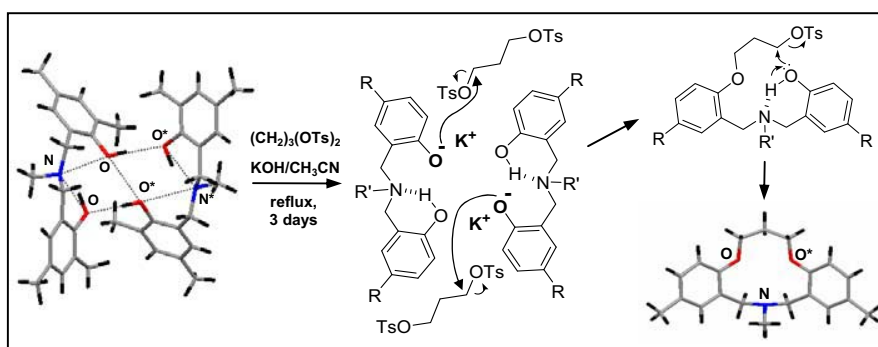


Figure 4. Proposed mechanism of **4b**.

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- (6) *N,N*-bis(2-hydroxy-5-methylbenzyl)methylamine¹³, **1**, (0.27 g, 1 mmol) was refluxed in acetonitrile (150 mL) with potassium hydroxide (0.11 g, 2 mmol) for 1 h. A solution of 1,3-bis(tosyloxy)propane (0.38 g, 1 mmol) in acetonitrile (70 mL) was added dropwisely and refluxed continuously for 3 days before removing solvent. The crude product was dissolved in dichloromethane, washed several times with water, before drying over anhydrous sodium sulfate. The solvent was removed to obtain the white product in 75% yield.
- (7) The characterization for **4b**: $C_{20}H_{25}NO_2$; 75% yield; mp = 203°C; FTIR (KBr, cm^{-1}): 1504 (vs, trisubstituted benzene), 1327 (vs, C-N stretching), 1250 (vs, C-N stretching), 1065 (s, Ar-O-CH₂); ¹H NMR (600 MHz, CDCl₃): δ 2.137 (s, 3H, N-CH₃), 2.217 (qu, 2H, C-CH₂-C, $J_1 = 4.86$ Hz), 2.259 (s, 6H, Ar-CH₃), 3.614 (s, 4H, N-CH₂-Ar), 4.204 (t, 4H, CH₂-O, $J_2 = 5.02$ Hz), 6.736 (d, 2H, Ar-H, $J_3 = 7.90$ Hz), 6.977 (s, 2H, Ar-H), 6.984 (d, 2H, Ar-H, $J_4 = 8.56$ Hz); ¹³C NMR (600 MHz, CDCl₃): δ 20.495, 28.524, 40.959, 58.224, 67.789, 111.638, 128.125, 128.379, 128.802, 131.901, 155.586; MALDI-TOF MS: m/z 312.6 (M+H⁺); Anal. Calc. for $C_{20}H_{25}O_2N$: C: 77.14, H: 8.09, N: 4.50, O: 10.28. Found: C: 76.38, H: 7.69, N: 4.46.
- (8) ¹H-¹³C HMQC for **4b** (600 MHz, CDCl₃): H2:C1,C3,C4,C5,C6; H3:C1,C2,C4,C5,C6; H5:C1,C2,C3,C4,C6; H7:C1,C5,C6,C9; H8:C1,C2,C3,C4,C5,C6; H9:C7; H10:C1,C11; H11:C10. ¹H-¹H NOESY: H2:H3,H10; H3:H2,H8; H5:H7,H8,H9; H7:H5,H9,H10; H8:H3,H5; H9:H5,H7; H10:H2,H7,H11; H11:H10.
- (9) Crystal data for **4b**: $C_{10}H_{12.5}NO_0.5$, $M = 155.71$, orthorhombic, $a = 9.3556(7)$, $b = 15.341(1)$, $c = 11.8139(8)$ Å, $V = 1695.6(4)$ Å³, $T = 296$ K, space group $Pnma$ (no.62), $Z = 8$, $\mu(Mo-K\alpha) = 0.78$ cm⁻¹, 12579 reflections measured, 1616 unique ($R_{int} = 0.032$) which were used in all calculations. The final $R1 = 0.047$ and $Rw = 0.121$. X-ray data for compound **4b** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 258583. Copies of the data may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033. e-mail: deposit@ccdc.cam.ac.uk).
- (10) Agai, B.; Nemeth, V.; Bocskei, Z.; Simon, K.; Bitter, I.; Toke, L. *Tetrahedron* **1996**, *52*, 6713-6724.
- (11) The characterization for **5b**: $C_{22}H_{29}NO_2$; 76% yield; FTIR (KBr, cm^{-1}): 1503 (vs, trisubstituted benzene), 1248 (vs, C-N stretching), 1057 (s, Ar-O-CH₂); ¹H NMR (400 MHz, CDCl₃): δ 1.106 (6H, t, Ar-C-CH₃, $J_1 = 7.622$ Hz), 2.069 (3H, s, N-CH₃), 2.170 (2H, qu, C-CH₂-C, $J_2 = 4.837$ Hz), 2.484 (4H, q, Ar-CH₂-C, $J_3 = 7.622$ Hz), 3.571 (s, 4H, N-CH₂-Ar), 4.141 (t, 4H, CH₂-O, $J_4 = 4.984$ Hz), 6.679 (d, 2H, Ar-H, $J_5 = 8.209$ Hz), 6.911 (s, 2H, Ar-H), 6.936 (d, 2H, Ar-H, $J_6 = 8.208$ Hz); MALDI-TOF MS: m/z 338.85.
- (12) The characterization for **6b**: $C_{22}H_{29}NO_2$; 78% yield; FTIR (KBr, cm^{-1}): 1505 (vs, trisubstituted benzene), 1253 (vs, C-N stretching), 1054 (s, Ar-O-CH₂); ¹H NMR (400 MHz, CDCl₃): δ 0.804 (3H, t, CH₃-C-C-N, $J_1 = 7.329$ Hz), 1.440 (2H, m, C-CH₂-C-N, $J_2 = 7.622$ Hz), 2.028 (qu, 2H, C-CH₂-C, $J_3 = 4.984$ Hz), 2.220 (6H, s, Ar-CH₃), 2.345 (2H, t, C-C-CH₂-N, $J_4 = 7.327$ Hz), 3.557 (s, 4H, N-CH₂-Ar), 4.166 (t, 4H, CH₂-O, $J_5 = 4.984$ Hz), 6.718 (d, 2H, Ar-H, $J_6 = 8.209$ Hz), 6.926 (d, 2H, Ar-H, $J_7 = 8.208$ Hz), 7.076 (s, 2H, Ar-H); MALDI-TOF MS: m/z 340.75.
- (13) Phontamrug, S.; Pulpoka, B.; Chirachanchai, S. *Supra. Chem.* **2004**, *16*, 269-278.

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ABSTRACT FOR WEB PUBLICATION The possible compounds obtained from the macrocyclization of dihydroxy backbone molecules and ditosylated compounds are linear, [1+1], and [2+2] cyclics. Herein, we demonstrate that if the backbone molecules have a favorable hydrogen bond network, the macrocyclization results in a single type of macrocyclic in high yield.

A Simple, Effective, and Selective Synthesis Route for [1+1] Dibenzo-Monoaza-Crown Ethers Based on *N,N*-Bis (2-hydroxy-3,5-dimethylbenzyl)methylamine and Their Inclusion Phenomena with Metal Ions

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Abstract

Synthetic route for dibenzo-monoaza-crown ethers is carried out by a simple etherification of a *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine and ditosylated derivatives. A selective [1+1] pathway without using catalysts for multistep reactions in specific conditions and purification with column chromatography gives dibenzo-monoaza-14-crown-4 and dibenzo-monoaza-12-crown-3 in high yield. These macrocyclic ligands show the inclusion phenomena with metal ions as clarified by UV-Vis Spectroscopy and ¹H-NMR Measurement. The inclusion phenomena between these ligands and metal ions declare the novel supramolecular structured compounds.

Keywords: Dibenzo-monoaza-crown ether, Etherification, *N,N*-Bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, Inclusion phenomena, Macrocyclic ligand, Metal ion

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Introduction

For the past decades, crown ethers¹, cyclodextrins², and calixarenes³ are well known macrocyclics exhibiting the inclusion properties. The practical applications can be used as the building blocks to induce a metal-ion-selective function in supramolecular systems⁴, the exclusion of impurity from the mixtures, the improvement of solubility of particular organic species, the ionic catalyst, the inclusion polymerization, etc.⁵ Crown ethers were first recognized for their molecular recognition with cations by Pedersen¹. Various crown ethers have been prepared and their cation binding properties have been studied continuously. For example, the synthesis of novel dibenzo-monoaza-crown ethers based on phenol-aza-phenol derivatives was proposed.⁶ In this case, dibenzo-monoaza-12-crown-4 was the small crown ether obtained in 30% yield from [1+1] cyclization of tosylated derivatives under the basic condition. Besides, a series of bis(12-crown-3) derivatives with malonate spacers⁷ and several benzocrown amino ethers⁸ were also prepared. According to the compounds consist of 12-crown-3 macrocyclic ring, we may term these compounds as the smallest macrocyclic compounds. However, these compounds were obtained in low yield by using expensive catalysts for multistep reactions in severe conditions, and by the need for chromatographic separation. Similarly, monoazatrithia-12-crown-4 was also obtained in low yield (only 10 to 39%) from cyclization of diethanolamine derivatives with 3-thiapentane-1,5-dithiol.⁹ Diazacrown ethers, which were used as intermediates for the synthesis of nitrogen-pivot lariat crown ether and cryptands¹⁰, i.e *N,N'*-bis(4-substituted phenyl)-1,7-diaza-12-crown-4, and *N,N'*-bis(4-substituted phenyl,)-1,10-diaza-18-crown-6 were obtained in low yield (only 11 to 18%), isolated by column chromatography by cyclization of a ditosylate with the appropriately substituted diol.

Previously, we succeeded to synthesize [2+2] 28-membered macrocyclic ethers based on benzoxazine dimers via a simple, effective, and selective synthesis route.¹¹ Besides, we reported *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine was obtained from a ring opening reaction of benzoxazine with 2,4 dimethylphenol.¹² Considering the basic structure of *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, there are also many possibilities to proceed the reaction through the hydroxyl group such as etherification. Herein, we aim to present the synthesis of the small [1+1] dibenzo-monoaza-crown ethers via a simple etherification reaction of a

N,N-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine and ditosylated derivatives in high yield without column chromatography purification. Furthermore, we clarified the inclusion phenomena of these macrocyclic ligands with metal ions to propose novel supramolecular structured compounds.

Experimental

Chemicals

Paraformaldehyde, methylamine, 2,4-dimethylphenol, sodium sulfate anhydrous, diethylene glycol, *p*-toluenesulfonyl chloride and cesium carbonate were purchased from Fluka, Switzerland. 1,3-Bis(tosyloxy)propane was the product of TCI, Japan. Picric acid was provided from Merck, Germany. Sodium hydroxide, isopropanol were obtained from Carlo Erba, Italy. Diethyl ether, 1,4-dioxane, acetonitrile, ethanol, potassium hydroxide and dichloromethane were provided from Labscan, Ireland. Chloroform-*d* was purchased from Aldrich, Germany. All chemicals were used without further purification.

Instruments and equipment

Fourier transform infrared spectra (FTIR) were recorded on a Nicolet NEXUS 670 with 32 scans at a resolution 4 cm⁻¹. Proton nuclear magnetic resonance spectra (¹H NMR) were obtained by using a Varian Mercury-4400BB spectrometer. Elemental analysis (EA) was carried out by a Perkin Elmer 2400 CHN. UV-Vis absorbance data were recorded by a Perkin Elmer UV-Vis spectrophotometer Lambda 16. Mass spectroscopy was analyzed by a PerSeptive Biosystems/Vestec matrix-assisted laser desorption ionization time-of-flight mass spectrometer (MALDI-TOF MS).

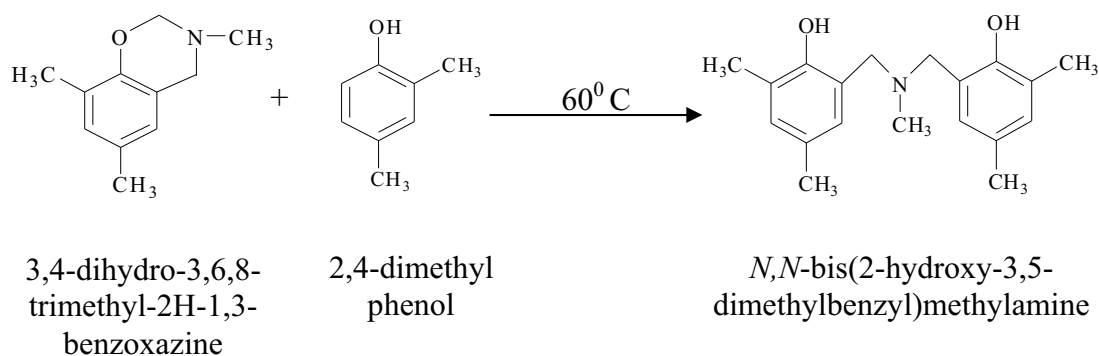
Synthesis

N,N-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **1**

N,N-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **1** was prepared from a ring-opening reaction of 3,4-dihydro-3,6,8-trimethyl-2H-1,3-benzoxazine and 2,4-dimethylphenol¹³ (**Scheme 1**). In brief, the mixtures of 3,4-dihydro-3,6,8-trimethyl-2H-1,3-benzoxazine and 2,4-dimethylphenol (1:1) were stirred at 60°C to obtain white precipitates. The precipitates obtained were washed with diethyl ether before drying

in vacuo. The compound was recrystallized with isopropanol to obtain white crystal of **1**. The compound obtained was determined with FTIR, ^1H NMR, and EA.

Scheme 1

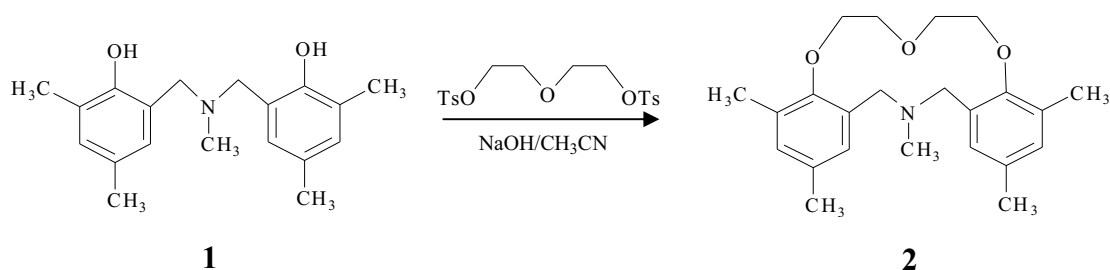


N,N-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **1**: 80% yield; $R_f = 0.40$ (5% methanol in chloroform); white solid; FTIR (KBr, cm^{-1}): 3399 (br, OH), 1484 (vs, C-C), 1427 (m, N-CH₃), 1243 (m, C-N), 1215 and 1200 (m, C-N-C), 847 (m, C-N-C); ^1H NMR (400 MHz, CDCl₃, ppm): δ_{H} 2.22 (12H, s, Ar-CH₃), 2.24 (3H, s, N-CH₃), 3.68 (4H, s, Ar-CH₂-N), 6.73 (2H, s, Ar-H), 6.83 (2H, s, Ar-H). Anal. calcd. for C₁₉H₂₅NO₂: C, 76.26; H, 8.36; and N, 4.68%. Found: C, 76.27; H, 8.34; and N, 4.69%.

Dibenzo-monoaza-14-crown-4 based on *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **2**

N,N-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **1** (0.299 g, 1 mmol) and sodium hydroxide (0.084 g, 2.1 mmol) were mixed in acetonitrile (150 mL), followed by adding ditosylated diethyleneglycol (0.414 g, 1 mmol) in acetonitrile (50 mL) dropwisely and refluxed for 3 days (**Scheme 2**). The solution obtained was washed 5 times with water and dried with sodium sulfate anhydrous. The solvent was evaporated out. The product was collected and recrystallized with isopropanol to obtain white crystal of **2**. The product obtained was qualitatively analyzed by FTIR, ^1H NMR, EA, and MALDI-TOF.

Scheme 2

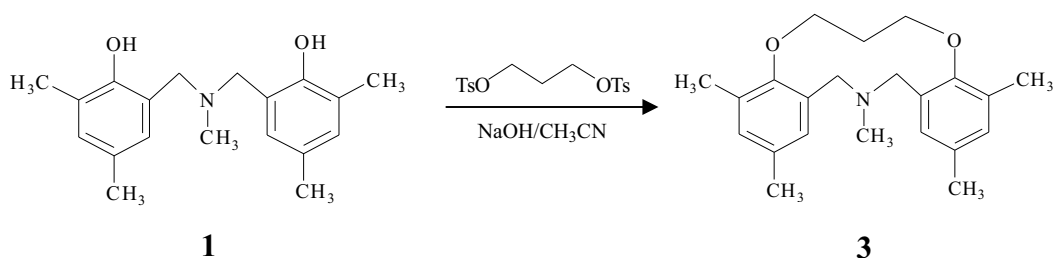


Dibenzo-monoaza-14-crown-4 based on *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **2**: $R_f = 0.03$ (5% methanol in chloroform); white crystal; FTIR (KBr, cm^{-1}): 1481 (vs, tri-substituted benzene), 1221 (vs, C-N stretching), 1139 (s, C-O-C); $^1\text{H-NMR}$ (400 MHz, CDCl_3 , ppm): δ_{H} 2.10 (3H, s, N-**CH₃**), 2.30 (12H, s, Ar-**CH₃**), 3.79 (4H, s, Ar-**CH₂-N**), 3.95 (4H, t, **CH₂-O**), 4.07 (4H, t, **CH₂-O**), 6.84 (2H, s, Ar-**H**), 6.93 (2H, s, Ar-**H**). MALDI-TOF MS (m/z): 369.32. Anal.calcd. for $\text{C}_{23}\text{H}_{31}\text{NO}_3$: C, 74.469; H, 8.401; and N, 3.794%. Found: C, 74.469; H, 8.408; and N, 3.873%.

Dibenzo-monoaza-12-crown-3 based on N,N-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, 3

Similarly, compound **3** was prepared as procedure of **2** by replacing ditosylated diethyleneglycol (0.414 g, 1 mmol) with 1,3-Bis(tosyloxy)propane (0.385 g, 1 mmol) (**Scheme 3**).

Scheme 3



Dibenzo-monoaza-12-crown-3 based on *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **3**: $R_f = 0.08$ (5% methanol in chloroform); white crystal; FTIR (KBr, cm^{-1}): 1480 (vs, tri-substituted benzene), 1213 (vs, C-N stretching), 1150 (s, C-O-C); $^1\text{H-NMR}$ (400 MHz, CDCl_3 , ppm): δ_{H} 1.94 (3H, s, N-**CH₃**), 2.10 (2H, m, **CH₂-CH₂-CH₂**), 2.25 (12H, s, Ar-**CH₃**), 3.61 (4H, s, Ar-**CH₂-N**),

4.11 (4H, t, O-CH₂-CH₂), 6.79 (2H, s, Ar-H), 6.91 (2H, s, Ar-H). MALDI-TOF MS (m/z): 339.23.

Metal ions-Dibenzo-monoaza-crown ethers Interaction

Metal ion extraction was studied by Pedersen's technique. Alkali metal picrate aqueous solutions (sodium picrate, potassium picrate, and cesium picrate) were prepared at concentration of 7×10^{-5} M. Equimolar concentration of dibenzo-monoaza-crown ethers 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 absorbance at 356 nm was measured by a Perkin Elmer UV-Vis spectrophotometer Lambda 16. Extraction percentage was calculated. The organic phase was collected and analyzed by UV-Vis and ¹H-NMR spectroscopy.

Results and Discussion

Synthesis

The benzoxazine dimer, **1**, for dibenzo-monoaza-crown ethers synthesis was prepared as shown in Scheme 1. A single step reaction of tosyl derivatives with **1** in the basic condition gave **2** and **3** in high yield via a selective [1+1] pathway. The products obtained were white crystal. The structure of **2** was confirmed as follows. The FTIR spectrum showed the disappearance of the hydroxyl group and the new ether peak at 1139 cm⁻¹ as compared to **1** (Figure 1). The ¹H-NMR showed the protons of CH₂-O linkage at 3.95 and 4.07 ppm (Figure 2). The parent peak of **2** in MALDI-TOF was at 369.32 (Figure 3). Similarly, the structure of **3** showed the new ether peak at 1150 cm⁻¹. The ¹H-NMR showed the protons of CH₂-O linkage at 3.95 and 4.07 ppm. The parent peak of **3** was at 339.23.

Metal ions-Dibenzo-monoaza-crown ethers Interaction

The metal ion extraction percentage of dibenzo-monoaza-crown ethers was determined by UV measurement. The initial absorbance of sodium picrate, potassium picrate, cesium picrate aqueous solutions at 25°C concentration (7×10^{-5} M) at 356 nm was 0.96, 1.00, and 0.99, respectively. The alkali ion extraction property of **2**, **3** were determined from the decrease in the picrate aqueous solution concentration as calculated. as eq. 1.

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

Compound **2** shows approximately 40% whereas compound **3** shows 15% extraction (Figure 4). So, it is important to note that **2**, **3** perform as the small macrocyclic host molecules in accepting alkali metal ions.

In order to clarify the interaction between dibenzo-monoaza-crown ethers and metal ions, the organic phase was collected and analyzed by UV-Vis and ¹H-NMR. When the small macrocyclic host molecule(or dibenzo-monoaza-crown ether) absorbs light at different wavelengths in free and complexed states, the peak shift or the new peak generation may suffice for estimation of molecular recognition. In free state, the host molecule absorbs light at ...nm and nm. After complexation, we observed the peak shift from nm to 284 nm and the new peak at 356 nm that belongs to alkali metal ion (Figure 5). It seems that the interaction between the host molecule and the guest species are occurred. This might be due to the host molecules can form complex with alkali ions. We can also confirmed the interaction between the host molecules and the guest species by using ¹H-NMR spectroscopic measurement. A series of picrate salts (i.e., sodium, potassium, and cesium) were dissolved in the solution of **2** in CDCl₃. Table 1 shows the chemical shift of **2** before and after complexation with Na⁺, K⁺, and Cs⁺. Figure 6 shows ¹H-NMR spectra of **2** before and after potassium ion complexation. The chemical shift of **2** before and after complexation with K⁺ is observed. This indicates that the interaction between **2** and potassium picrate were occurred. The picrate salt peak at 8.82 is also focused to confirm the existence of picrate salt in the solution of **2** in CDCl₃. This implies that the inclusion phenomena were succeeded.

From UV and ¹H-NMR, we declares **2**, **3** perform as the novel supramolecular structured compounds.

Conclusions

The present work showed the [1+1] selective and effective macrocyclization of *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine with tosyl derivatives via the etherification. The studies on alkali metal ions extraction by UV technique suggested that the alkali ions extraction property of dibenzo-monoaza-14-crown-4 based on *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine is higher than dibenzo-monoaza-12-crown-3 based on *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine. The

inclusion phenomena as clarified by UV-Vis and ^1H -NMR suggested that these compounds performed as a host in accepting metal ion guests.

Acknowledgements

S.C. acknowledges financial support from The Thailand Research Fund (grant no. RSA4680025).

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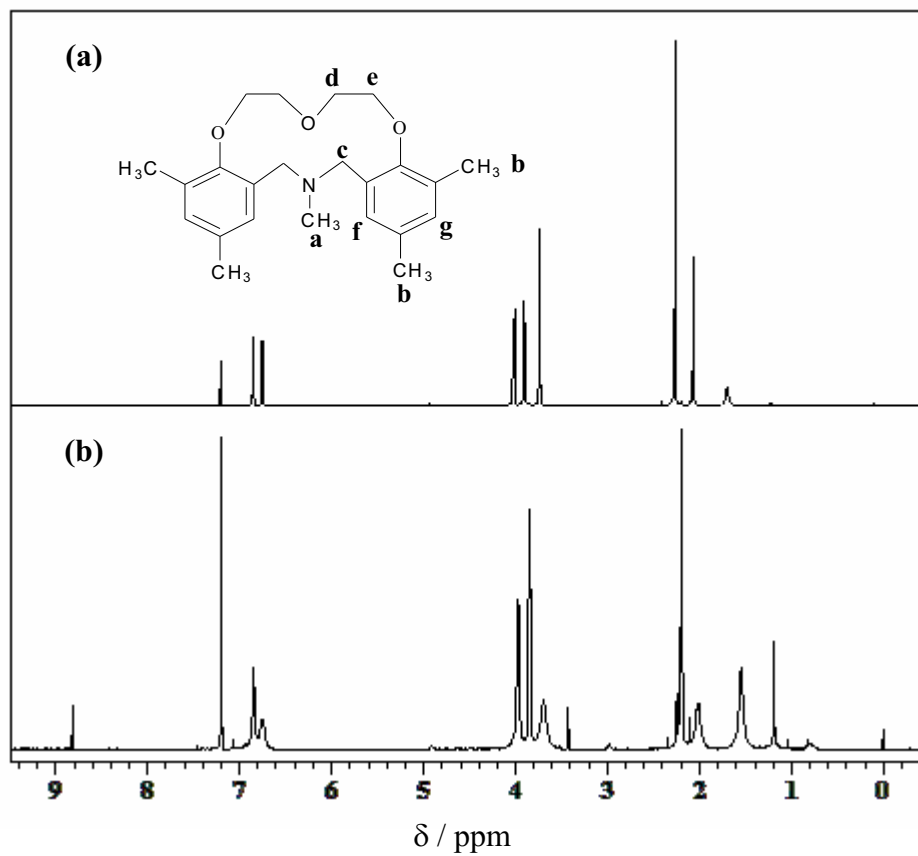


Figure 2. ^1H -NMR spectra of (a) **2**, and (b) complex of **2** and potassium picrate

Synthesis, characterization, and single crystal of the novel dibenzo-monoaza-17-crown-5 based on N,N-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine

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The etherification between N,N-bis(2-hydroxy-3,5-dimethyl)methylamine and ditosylated triethylene glycol give the single crystal exhibiting the insertion of methyl group at aza position into the cavity of the ring of dibenzo-monoaza-17-crown-5 with the high yield without column chromatography purification.

For the past decades, macrocyclic compounds, e.g., calixarenes¹, crown ethers², and their analogous compounds have been received much attention for their inclusion properties. However, the synthesis of macrocyclic compounds related to the multi-steps reaction and complicated condition such as dilute condition³, metal template⁴, and column chromatography purification. For example, the synthesis of cage-functionalized diaza(17-crown-5) lariat crown ethers were obtained from the multi-steps reaction that related to catalytic hydrogenolysis.⁵

This, we have focused on the molecular design to obtain the high yield macrocyclic compound from the simple reaction. In previous, we succeeded to propose the synthesis route without template effect for [2+2] difunctional 28-membered macrocyclic ether based on benzoxazine dimers.⁶ These compounds were obtained from the reaction between benzoxazine dimers and ditosylated diethylene glycol under basic condition.

According to the successful in the past about the synthesis route for the high yield macrocyclic ethers via the simple condition⁶, at present, we aim to synthesize the novel macrocyclic ether from the one pot reaction between benzoxazine dimer and ditosylated triethylene glycol. Moreover, we demonstrate the single crystal structure of the macrocyclic ether.

A white powder of N,N-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine⁷, **1**, (0.299g, 1 mmol) and sodium hydroxide (0.084g, 2.1 mmol) were mixed in acetonitrile (150 mL), followed by adding ditosylate triethylene glycol (0.458g, 1 mmol) in acetonitrile (50 mL) dropwisely and refluxed for 3 days (Scheme 1). The solution obtained was washed 5 times with

water and dried with sodium sulfate anhydrous. The solvent was evaporated out. The product was collected and recrystallized with isopropanol to obtain white crystal of **2**.

When the reaction between **1** and ditosylated triethylene glycol were proceeded, the product obtained should be possible the one of all compounds as shown in Scheme 1. To answer the question about what type of product we obtained, the characterizations were done as follows.

Compound **1** gave the peaks at 3399 cm⁻¹ (intermolecular H-bond), 3200-3600 cm⁻¹ (intramolecular H-bond), 1484 cm⁻¹ (trisubstituted benzene), 1214 cm⁻¹ and 1201 cm⁻¹ (C-N-C stretching).⁷ After **1** reacted with ditosylated triethylene glycol, the broad peak of OH group was disappeared together with a peak of Ar-O-CH₃ was occurred. This implies the compound **1** should be changed to the compound **2**. Besides, the peak shifts (1484 to 1480 and 1214 to 1209 cm⁻¹) that belong to the vibrational mode of trisubstituted benzene and C-N stretching suggested the change in the structure. From these data, we conclude the reaction is proceeded completely. However, there are many possibilities of the product obtained, **2a-2d**.

The ¹H NMR spectra of **2** show the characteristic peaks of **2b** and **2c** at the range of chemical shift from 2.719 to 7.124. This implies that the reaction between N,N-bis(2-hydroxy-3,5-dimethyl benzyl)methylamine and ditosylated triethylene glycol should give only macrocyclic compound. Nevertheless, there are two possibilities of the product obtained, **2b** or **2c**.

The matrix-assisted laser desorption ionization time-of-flight mass spectrometer (MALDI-TOF MS) shows a single peak at m/z = 414.26 that equalizes to the molecular weight of the [1+1] type of macrocyclic compound. So, we conclude that our compound is [1+1] macrocyclic compound that is called dibenzo-monoaza-17-crown-5, **2b**.

The colorless crystal of **2b** after recrystallization with isopropanol was clarified the structure by single crystal analysis. The results give us the orthorhombic space group Pna2₁ belonging to the dibenzo-monoaza-17-crown-5. The R₁ value is 2.9% that suggests the accuracy of [1+1] symmetrical macrocyclic compound. Surprisingly, the TEXSAN software demonstrates an ORTEP view (Fig. 1) declaring the insertion of methyl group at aza group of macrocyclic ring inside the cavity of the ring. This phenomenon shows clearly different structure from tradition macrocyclic crown ethers that have alkyl group stay on the outside of the cavity of the ring.⁸ According to the single crystal structure, it brings us to the question about its inclusion properties with metal ions. We imply that this structure

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See <http://dx.doi.org/10.1039/b000000x/>

maybe obstruct the entrance of the metal ion guest species into the macrocyclic ring of **2b** host molecule. The alkaline metal ions extraction ability of **2b**, the interaction of complexation, and the single crystal of host-guest molecules are now in progress.

In conclusion, we have developed the novel supramolecule **2b** by combining N,N-bis(2-hydroxy-3,5-dimethyl)methylamine **1** and ditosylated triethylene glycol exhibiting high yield without column chromatography purification. The single crystal of **2b** shows the insertion of methyl group at aza group of macrocyclic ring inside the cavity of the ring. We believe that this structure might affect to its metal ion extraction abilities. At present, we are studying its inclusion properties together with the molecular design to produce the novel supramolecules for using in many applications in the future.

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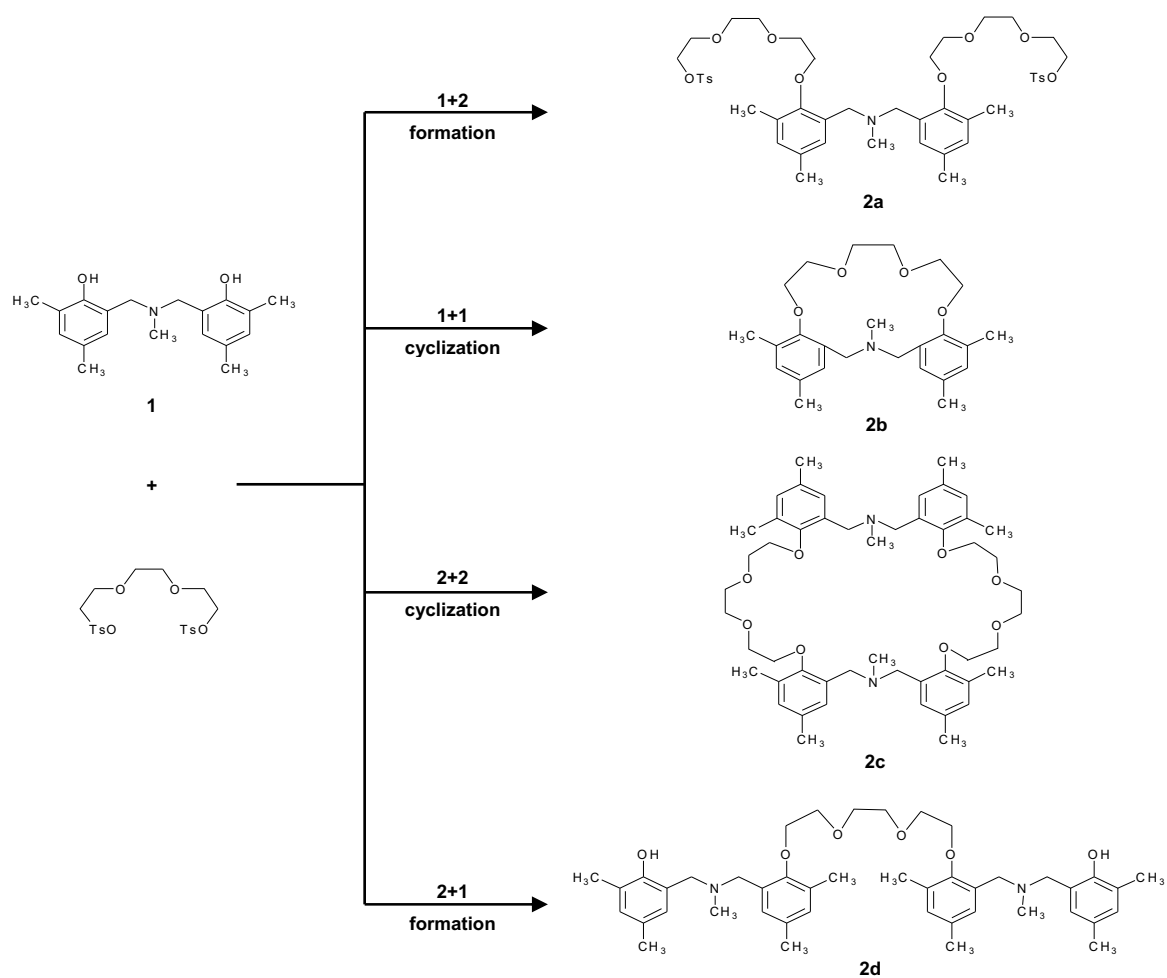
Notes and references

† The characterization for **2** (0.331 g, 80%): FTIR (KBr, cm^{-1}): 1489 (s, trisubstituted benzene), 1209 (vs, C-N stretching), 1112 (vs, Ar-O-CH₂); ¹H NMR (400 MHz, CDCl₃): δ 2.179 (s, 3H, N-CH₃), 2.245 (s, 12H, Ar-CH₃), 3.714 (s, 4H, C-CH₂-N), 3.801-3.833 (t, 8H, C-CH₂-O-CH₂), 3.970 (t, 4H, O-CH₂-CH₂), 6.848 (s, 2H, Ar-H), 7.124 (s, 2H, Ar-H); MALDI-TOF MS: m/z 414.26 (M+H⁺).

‡ Crystal data for **2**: C₂₅H₃₅NO₄, orthorhombic, $a = 18.0895(4)$, $b = 8.9394(2)$, $c = 14.4691(3)$ Å, $V = 2339.79(9)$ Å³, space group Pna2₁ (no.33), $Z = 4$, $\mu(\text{Mo-K}\alpha) = 0.078 \text{ mm}^{-1}$, 53806 reflections measured, 5327 unique ($R_{\text{int}} = 0.019$) which were used in all calculations. The final $R_1 = 0.029$ and $R_w = 0.080$.

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Double column figure/scheme (below)



Scheme 1

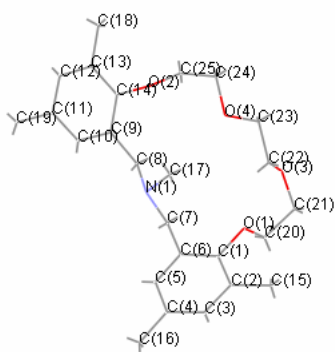


Fig. 1 ORTEP view of 2b with the atomic numbering scheme.