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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 DMol^3 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 noncovalent 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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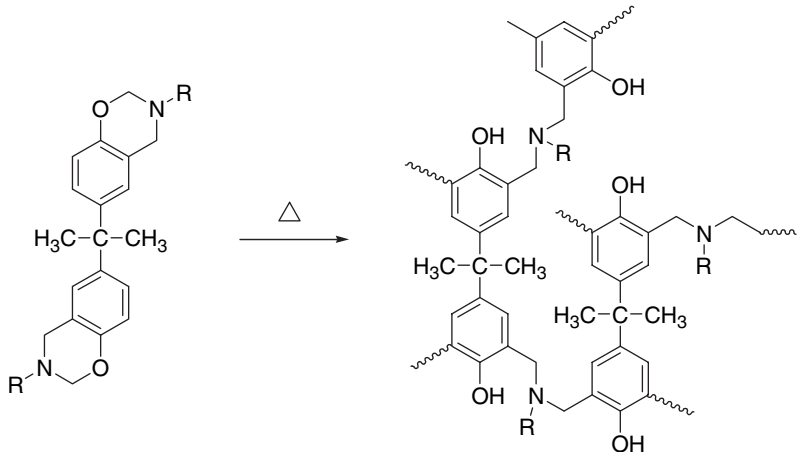
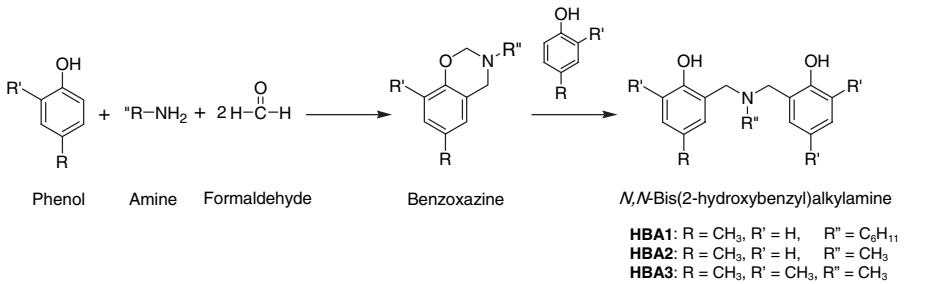


Scheme 1.

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 intramolecular 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.

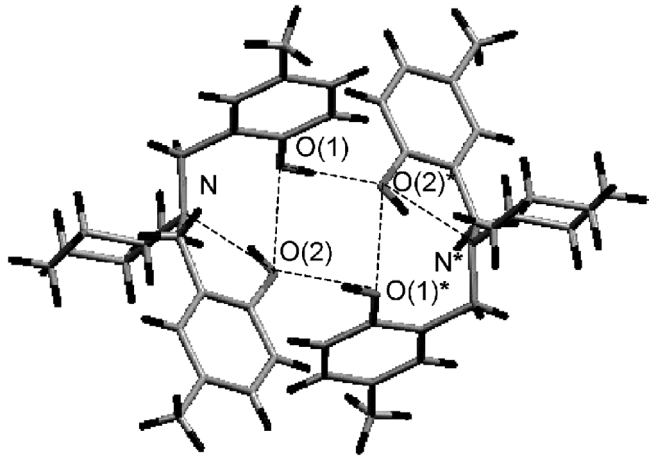


Figure 1.
Crystal structure of *N*,*N*-bis(2-hydroxy-5-methylbenzyl)cyclohexylamine (**HBA1**).

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, ^{1}H NMR and ^{1}H-^{1}H 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 ($–CH_2–N$) suggests that the nitrogen atoms play an important role in interacting with copper ions. ^{1}H-^{1}H NOESY is useful for determining the interaction of the nearby ^{1}H-^{1}H 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

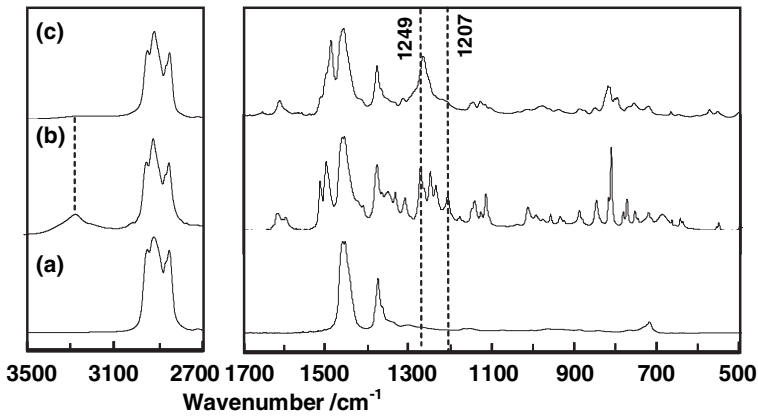


Figure 2.
FTIR spectra of (a) Nujol, (b) **HBA2**, (c) **HBA2**-Cu.

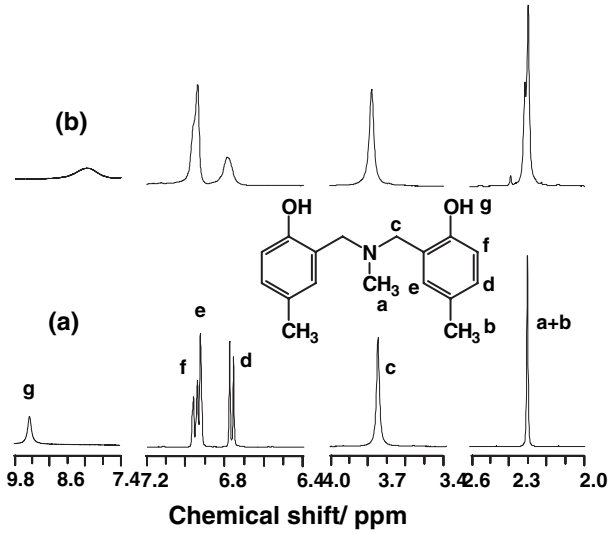


Figure 3.
^{1}H NMR spectra of (a) **HBA2** and (b) **HBA2**-Cu in $CDCl_3$.

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

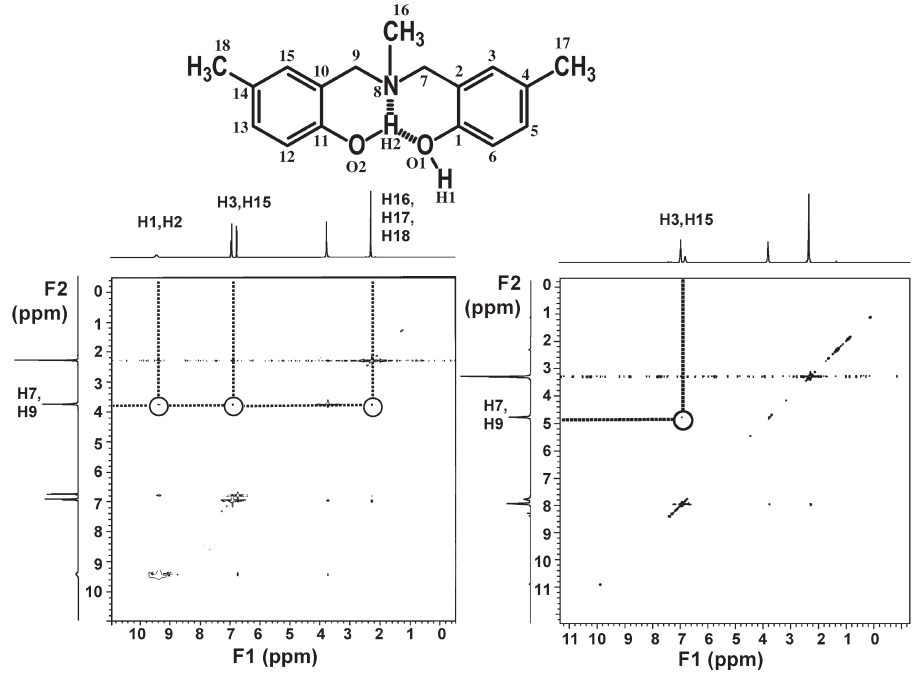
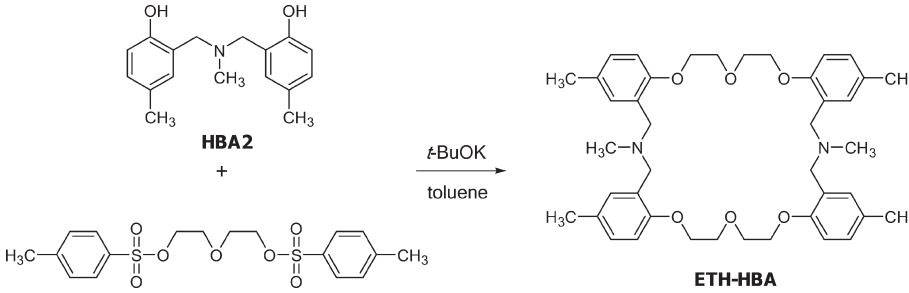


Figure 4.
^{1}H-^{1}H NOESY spectra of (a) **HBA2** and (b) **HBA2**-Cu in $CDCl_3$.



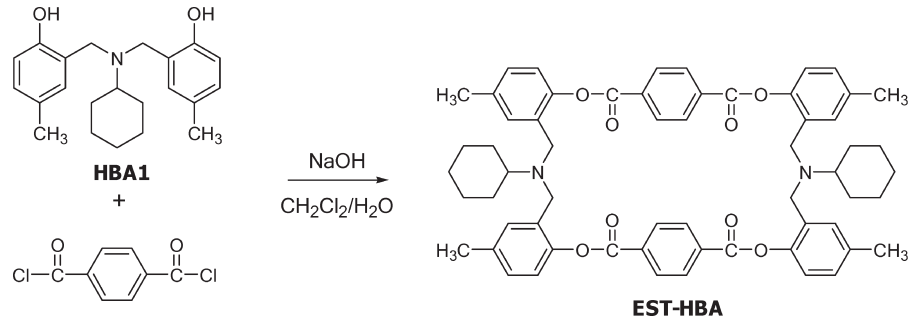
Scheme 3.

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. ^{1}H NMR spectrum shows the peaks at 3.8 and 4.2 ppm for –C**H**$_2$–C**H**$_2$–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 ^{1}H 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.

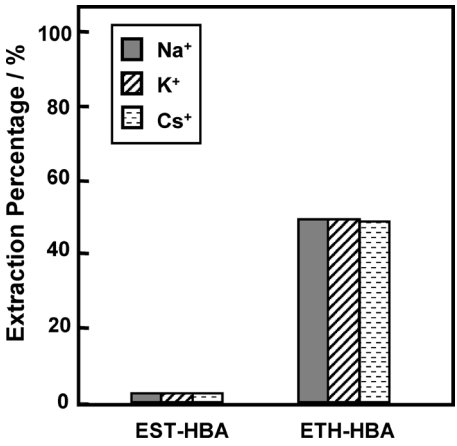


Figure 5.
Extraction percentages of **EST-HBA** and **ETH-HBA**.

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 ($3200 \sim 3400$ cm^{-1}) in the case of the **HBA**-Cu complex.

The atomic charge distribution was calculated on the basis of density function theory with DMol[3] (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 ($Cu(CH_3COO)_2$) 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.

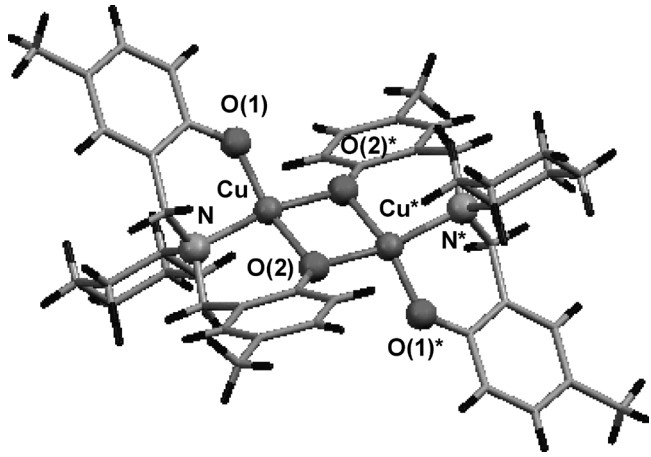
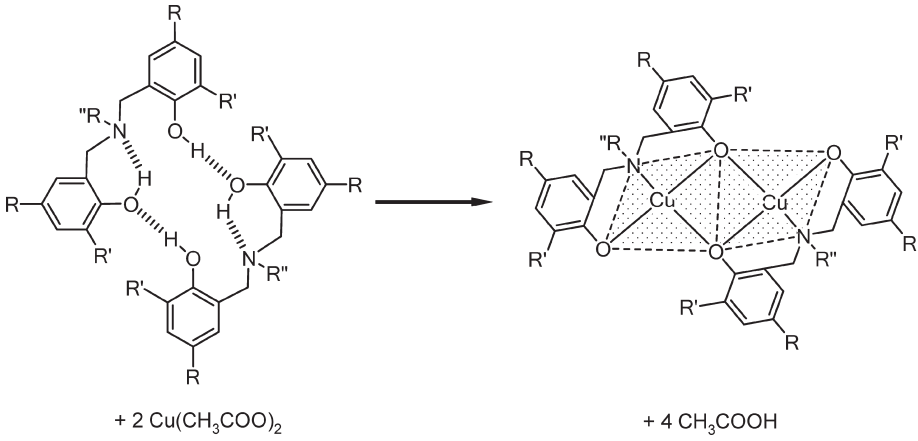


Figure 6.
Coordination compound of **HBA1**-Cu.



Scheme 5.

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

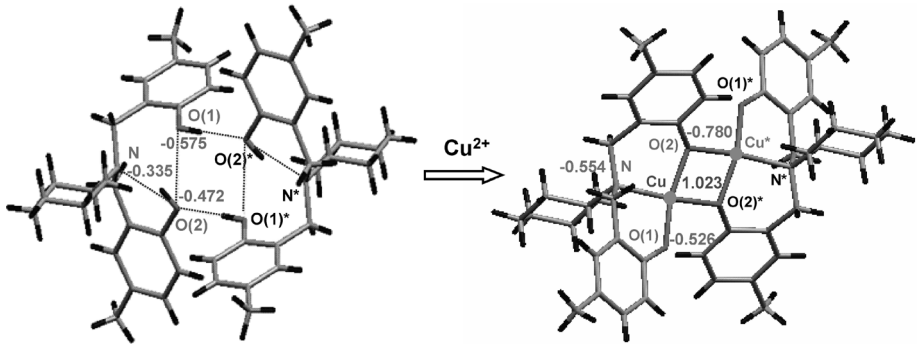


Figure 7.
Calculated atomic charges of **HBA1** and **HBA1**-Cu.

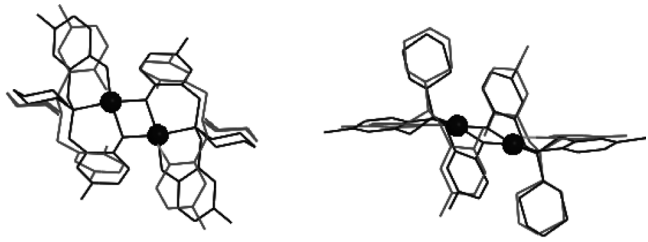


Figure 8.
Comparison of cage structure between **HBA1** (red color) and **HBA1**-Cu complex (blue color) viewed from different directions.

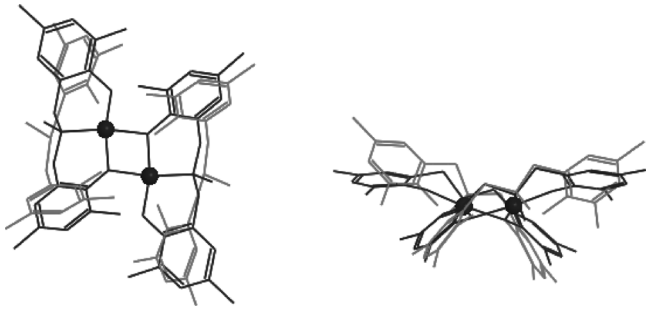


Figure 9.
Comparison of cage structure between **HBA3** (red color) and **HBA3**-Cu (blue color) viewed from the different directions.

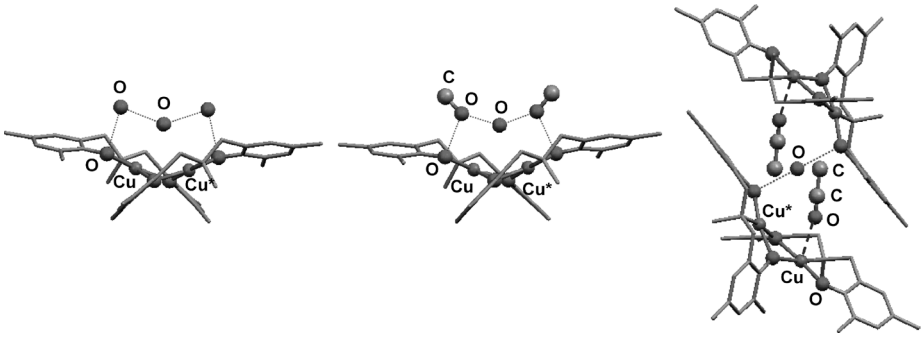


Figure 10.
Structure of **HBA3**-Cu complex coordinated by solvent molecules. (Hydrogen atoms are omitted for clarity.)

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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