A New Water-Soluble Bowl-shaped Host by Metal-Induced Self-Assembly

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Abstract: A water-soluble bowl-shaped host, **M3M**, which possesses a hydrophobic binding cavity for apolar guests was prepared by metal-induced self-assembly through complexation of L-serine derived hydroxy acid groups with metals. Compound 5 without a xylenic linker was synthesized to investigate the entropy effect on the formation of the self-assembled host. **M3M** guest association constants for three aromatic hydrocarbons were measured by solubility titrations. No extraction of any guests through [5' + M^{2+}] aqueous solution indicated the entropic disadvantage in the formation of the self-assembled structure. The transport of neutral arenes through an aqueous phase of **M3M** was studied in a U-type cell.
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Since the late 1980s, incorporation of metal-ligand interaction into synthetic macromolecules has triggered the development of an entirely new area of self-assembly.[1,2] Some of them showed host-like characters.[1b,2b] For example, Schwabacher and co-workers reported that a hydrophobic binding site self-assembled by metal-ligand interactions promoted transport of pyrene from an isooctane solution through an aqueous layer in 1:1 ligand and metal salt.[1b] In this macrocyle, in spite of strong metal-amino acid interactions, all the monomeric ligands did not seem to participate in the formation of the self-assembled macrocycle presumably due to entropically unfavorable intermolecular binding site organization by two metal templates. We present herein an intramolecular binding site organization approach to show entropy effect[3] on the formation of the self-assembled host and its recognition property.

Figure 1 shows the metal complex designed as a new water-soluble host with a hydrophobic binding cavity. A novel aspect of the design is the use of a xylenic linker to overcome the entropic disadvantage in the formation of the self-assembled structure. Furthermore, we replaced -NH$_2$ groups as ligands used in Schwabacher's system with -OH groups to make better investigation into the entropy effect by means of decreasing the entalpy effect in the self-assembly process.
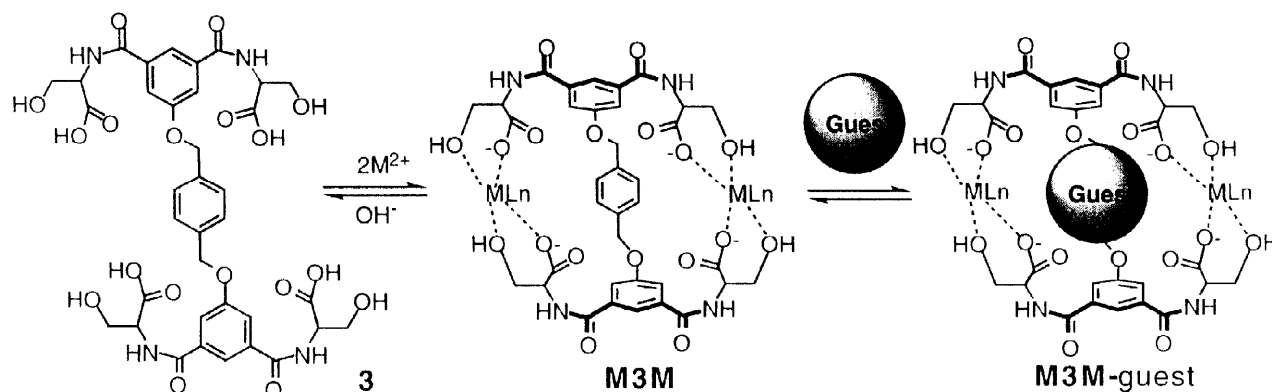

Figure 1

Compound 3 was prepared as shown in Scheme 1.[4] Metal complexes were prepared by addition of 2 equivalent metal salt to 3 in the presence of aqueous NaOH solution. Formation of **M3M**'s was proved by MALDI mass spectrometry: the signals of [Cu3Cu]$^+$, [Ni3Ni]$^+$, [Zn3Zn]$^+$, and [Pd3Pd]$^+$ appeared at 941, 935, 943, and 1026, respectively. Solid-liquid extraction and U-tube transport experiments by UV-Vis

spectrophotometer were used to investigate their binding and transport properties for hydrophobic aromatic substrates.

Solutions of host-guest complexes of **M3M** with polycyclic aromatic hydrocarbons which are extremely insoluble in water could be prepared by extracting the solid guests with aqueous solution of **M3M**. When a suspension of excess solid guest (naphthalene, anthracene, or pyrene) in a 2.5 x 10^{-4} M aqueous solution of host **M3M** was shaken and exposed to ultrasound sonication for about 6 h, the solution, after centrifugation and filtration, exhibited the intense UV-Vis absorption band of the guest. This is the first evidence for host **M3M**-guest complexations which occur by incorporation of guests in the hydrophobic cavity of **M3M**. By multiple extractions with n-hexane of the aqueous solutions of the complexes obtained by solid-liquid extraction, the aromatic guests were quantitatively transferred into the organic phase. In the combined hexane phases, the total concentration of the guest was determined by UV-Vis spectroscopy. The binding constant and stoichiometry of

Scheme 1
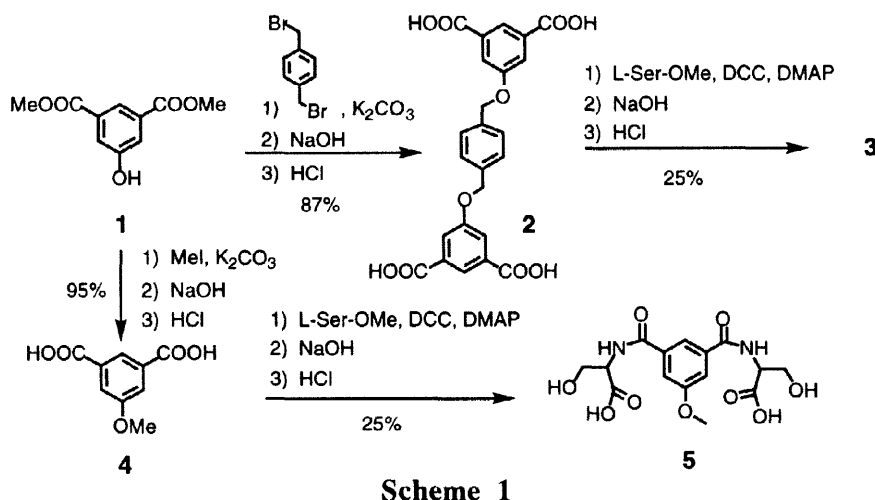
guest to host were determined by measuring the increased solubility of guest in the aqueous solution containing various concentrations of host. From the slopes and intercepts (g_o) of these solubility titration plots (total solubilized guest concentration vs. total host concentration), the standard treatment gives binding constants, K_a.[5] Furthermore, 1:1 complexation was indicated from the good linearity of the plot. Because our system would be

$$K_a = \text{slope} / g_o(1 - \text{slope})$$

in the following dynamic equilibrium, it is very difficult to presume accurately the amount of **M3M** in the aqueous solution. We calculated the binding constant K_a, assuming that the initial concentration of **M3M** was

$$3 + 2M \; \xrightleftharpoons{K_1} \; \text{M3M} + \text{guest} \; \xrightleftharpoons{K_a} \; \text{M3M-guest}$$
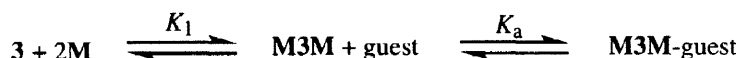
equal to that of compound **3**. Therefore, the calculated K_a would be always smaller than the real K_a.

Table 1 shows the binding constants of **M3M**-guest complexes in water at pH 7, 10, and 12. Pyrene had the largest binding constants regardless of metals. The examination of CPK models led us to predict that pyrene could have the largest contact area for the van der Waals interaction with host **M3M**. It seems that the van der Waals contact area would have the following order: pyrene > anthracene > naphthalene. Thus the magnitude of binding constants could be clearly explained in terms of the contact area and hydrophobicity of guests.[6] In the case of altering metals in **M3M**, Ni^{2+}, Cu^{2+}, and Zn^{2+} are much more effective than Pd^{2+}. These results give the information about K_1 in the above dynamic equilibrium, if the structure and cavity size of **M3M** have little variation as altering metals. That is, K_1 in the case of using Ni^{2+}, Cu^{2+}, and Zn^{2+} can be higher than Pd^{2+} in the aqeuous solution. The above results may be explained by the fact that hard metals Ni^{2+}, Cu^{2+}, and Zn^{2+} bind more strongly with hard oxygen atoms of compound **3** than soft metal Pd^{2+}. This explanation seemed to have

good correspondence with the fact that Pd^{2+} was less influenced by the concentration of hard OH⁻ ion than other metals. In fact, we observed that some solid particles were precipitated in the aqueous solutions of Cu3Cu, Ni3Ni, and Zn3Zn except Pd3Pd at pH 12.0. These precipitates might be $Cu(OH)_2$, $Ni(OH)_2$, and $Zn(OH)_2$. As shown in Table 1, the parenthesized values were obtained by using metal acetate instead of metal chloride and 20 - 30 % greater than those by using metal chloride.

Table 1. Association Constants K_a (x 10^3 M⁻¹) for 1:1 Host-Guest Complexes Formed between M3M and Neutral Arenes in Aqueous Solution, Determined by Solubility Titration[a]

Guest		CuCl₂	ZnCl₂	NiCl₂	PdCl₂
Naphthalene	pH 7	1.6(2.0)[b]	1.4(1.8)	2.1(2.5)	0.63(0.91)
	pH 10	0.89(1.1)	0.69(0.82)	1.2(1.4)	0.49(0.56)
	pH 12	ND[c]	ND	ND	0.39(0.46)
Pyrene	pH 7	101(129)	103(127)	190(221)	34.5(48.8)
	pH 10	47.5(55.9)	43.7(50.5)	98.2(111)	26.0(30.7)
	pH 12	ND	ND	ND	15.0(15.3)
Anthracene	pH 7	35.2(41.6)	39.6(49.5)	54.9(62.8)	21.0(29.1)
	pH 10	15.0(18.9)	16.8(19.4)	26.4(31.2)	12.4(16.1)
	pH 12	ND	ND	ND	8.6(11.2)

a. All experiments were conducted at 298 K
b. Using $M(OAc)_2$ instead of MCl_2.
c. Not detected.

In order to know whether external binding of guest to M3M outside the binding cavity provides an additional amount of guest transferred into the aqueous phase during the solid-liquid extraction, solid guests were extracted with 2 x 10^{-4} M solution of 3. The same guest concentration in the aqueous phase as in the extraction with pure water was obtained. This result indicates that all guests solubilized in the aqueous solutions of M3M are bound inside the cavity of M3M.

Compound 5 was synthesized to investigate the binding property of the self-assembled macrocycle with an intermolecularly organized binding site by two pieces of [5^{2-} + M^{2+}] in the aqueous solution (Scheme 1). Presumably it might be more difficult for [5^{2-} + M^{2+}] to form a hydrophobic binding cavity than M3M because of the absence of a xylenic linker for intramolecular binding site organization and the entropic disadvantage in the formation of the self-assembled structure. In fact, no solid guests were extracted with [5^{2-} + M^{2+}] aqueous solution. This result means that [5^{2-} + M^{2+}] is not able to make the concave hydrophobic binding pocket in the aqueous solution. In contrast, Schwabacher's binding site organized by intermolecular metal-ligand interactions was able to bind aromatic hydrocarbons in water. This will be due to the fact that the formation enthalpy of the self-assembly of a hydrophobic binding site in Schwabacher's system can overcome the entropic disadvantage while that in our system can not do so because of weaker binding of the hydroxy acid to transition metal ions compared with the amino acid ligand. From the above result, it can be deduced that the advantageous entropy effect by a xylenic linker is very large in our self-assembly system in which the enthalpy contribution is small.

Table 2. Transport Rates (x 10^{-6} M/h cm²) of Aromatic Guests through the Aqueous phase of M3M[a]

Guest		CuCl₂	ZnCl₂	NiCl₂	PdCl₂	through water
Naphthalene	pH 7	3.3(2.8)[b]	3.0(2.5)	5.6(4.7)	1.7(1.4)	
	pH 10	2.0(1.7)	1.7(1.4)	2.4(2.0)	1.5(1.3)	1.2
	pH 12	1.2	1.2	1.2	1.2	
Pyrene	pH 7	8.5(370)	7.8(340)	15(650)	4.6(200)	
	pH 10	3.0(130)	2.5(110)	3.9(170)	2.0(90)	0.023
	pH 12	0.028	0.029	0.031	0.043	
Anthracene	pH 7	6.2(160)	5.3(140)	10(260)	3.5(90)	
	pH 10	1.8(46)	1.2(30)	2.7(69)	0.9(23)	0.039
	pH 12	0.039	0.039	0.039	0.039	

a. All experiments were conducted at 298 K by using the U-type cell. A total of 8 mL of doubly distilled water or of an aqueous solution of host M3M (5.0 x 10^{-4} M) was located at the bottom of the cell as phase II. 4 mL of a 1.0 x 10^{-2} M solution of arene in n-octane was placed at source phase I. In the other arm 4 mL of n-octane was placed as receiving phase III. All given rate values were reproducible within 10% under the constant experimental conditions, and constant stirring speed of 1100 rpm at which clear interfaces exist between the three phases.
b. Acceleration factor.

M3M can be used as a molecular carrier for the acceleration of the transport of neutral arenes through an aqueous phase along a concentration gradient.[6,7] In order to determine the transport rate of the guest across the aqueous phase II, the concentration of delivered arenes in the receiving phase was periodically measured by UV-Vis absorption spectroscopy. The transport rate of pyrene through a 5.0×10^{-4} M aqueous solution of Ni3Ni at pH 7.0 turned out to be 650 times higher than the rate of passage through pure water. Investigation into the origin of the high substrate selectivity showed that there is an approximate proportionality between the relative rates of transport in the presence of a carrier or the acceleration factors shown in Table 2 and binding constants of host-guest complexation in Table 1.

In summary, we have developed a new water-soluble bowl-shaped host which possesses a hydrophobic binding cavity for apolar guests by metal-induced self-assembly through complexation of L-serine derived hydroxy acid groups with several transition metals. The binding constants of the self-assembled receptor-guest complexes in water at various pH's were determined by solubility titrations and their relative magnitudes can be rationalized in terms of van der Waals contact area and hydrophobicity of guests. We also found good correlation between the relative rates of transport of neutral arenes in the presence of the self-assembled receptor as a carrier and binding constants of the host-guest complexation.

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4. Spectral Data for **Compound 3**: mp 176-177 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (d, 8H, CHCH_2OH, J = .6.0 Hz), 4.49 (q, 4H, -CH-, J = 6.0 Hz), 5.26 (s, 4H, ArOCH_2Ar), 7.54 (s, 4H, CH$_2$ArCH_2), 7.72 (s, 4H, ArH), 8.03 (s, 2H, ArH), 8.60 (d, 4H, O=CNH, J = 9.0 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 56.6, 62.0, 70.4, 117.5, 120.0, 128.8, 136.4, 137.3, 159.0, 166.5, 172.7; MS (FAB) m/z 815 (M+1)$^+$. **Compound 5**: mp 186-188 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (d, 4H, CHCH_2OH, J = 6.0 Hz), 3.90 (s, 3H, ArOCH_3), 4.51 (q, 2H, -CH-, J = 6.0 Hz), 7.78 (s, 2H, ArH), 8.11 (s, 1H, ArH), 8.63 (d, 2H, O=CNH, J = 9.0 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 55.5, 61.0, 61.5, 127.5, 135.6, 136.4, 160.0, 164.1, 171.5; MS (FAB) m/z 370 (M+1)$^+$. General Experiments: The UV-Vis absorption spectra of aromatic guests used in the solid-liquid extraction and the transport experiments are of importance for the quantitative evaluation of these experiments. The bands which have been used for the determination of concentrations are listed. Pyrene (*n*-octane): λ_{max} (*e*) 335 (56500). Anthracene (*n*-octane): λ_{max} (*e*) 350 (7850). Naphthalene (*n*-octane): λ_{max} (*e*) 275 (5750).
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