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Dynamics of Molecular Recognition of Multi-point Host–Guest Complex

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Abstract: The rates for association and dissociation of complexes between functionalized zinc porphyrin and amino acid esters in $CDCl_3$ at 30 °C were determined by ^1H NMR relaxation time studies. The association rate increased with increasing the number of recognition groups, indicating that the hydrogen bonding catalyzes the association process. Copyright © 1996 Elsevier Science Ltd

Molecular recognition via complementary multi-point interactions has been successfully developed and to the design of a highly specific host for a given guest.[1] As the number of recognition groups increases the specificity of recognition becomes higher.[2] However the effects of the number of recognition groups on the dynamics of molecular recognition process are rarely investigated.[3] In enzymatic processes, importance of acceleration of association process has been emphasized.[4] In the previous study,[2] we reported that the trifunctionalized porphyrin binds amino acid esters with a polar side chain group via three pairs of attractive forces, one coordinative and two hydrogen bonding interactions, between the polar recognition groups (Figure 1). In this paper we aim at elucidating the dynamics of this multi-point recognition system, focusing on the catalytic effects of the auxiliary recognition groups on the association and dissociation processes.

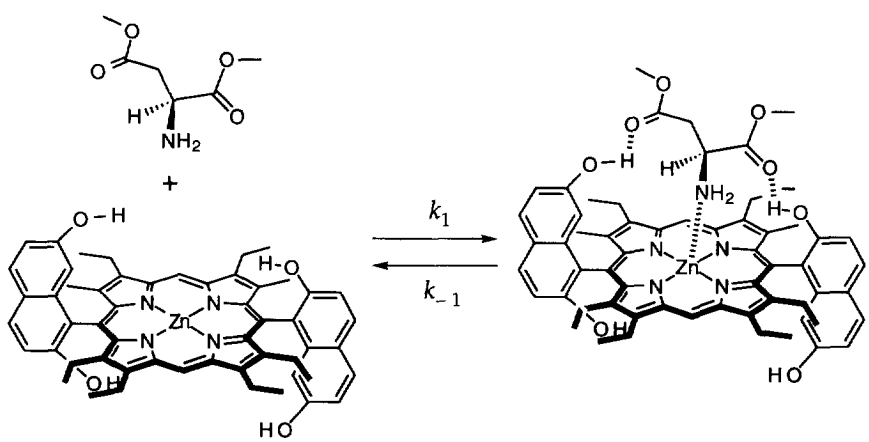
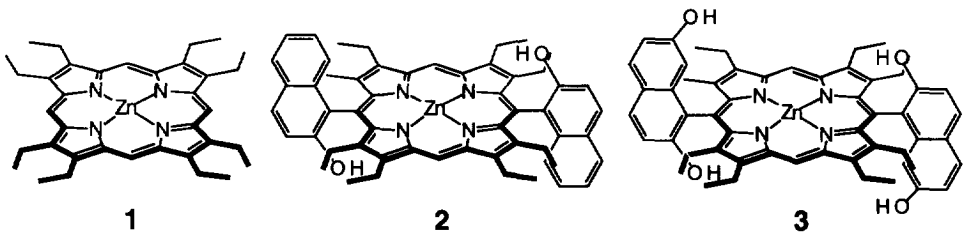


Figure 1. Three-point recognition of Asp-$(OMe)_2$ by the trifunctionalized zinc porphyrin.



1 2 3

Three zinc porphyrins, [OEP[5]]zinc **1**, [trans-5,15-(2-hydroxynaphthyl)OEP]zinc **2**, and [trans-5,15-(2,7-dihydroxynaphthyl)OEP]zinc **3**, were used as host molecules for amino acid esters. Their preparations and binding features have been reported elsewhere.[2,6] Host **1** binds amino acid esters with one-pair interaction (Zn-NH_2 coordination), host **2** binds them with two-pair interactions (coordination of NH_2 to Zn and one hydrogen bond between OH and O=C), and host **3** binds Asp-$(OMe)_2$ via three-pair interactions (coordination of NH_2 to Zn and two hydrogen bonds between OH and O=C). As the number of recognition pairs increases, the binding constants also increased: the binding constants for Asp-$(OMe)_2$ by **1**, **2** and **3** in $CHCl_3$ at 30°C were 290, 2250, and 45800 M^{-1}, respectively, and those for Leu-OMe by **1**, **2** and **3** were 500, 7380, and 13600 M^{-1}, indicating that the complementary recognition interaction constructively leads to the larger binding constants.

The rates for the dissociation of the complexes of these hosts and amino acid esters (Leu-OMe and Asp-$(OMe)_2$) were determined by the ^1H NMR relaxation time (T_1 and T_2) measurements of the methoxy signal[7] of the guests as a function of host concentrations according to the procedure reported by Meiboom[8] and modified by Sykes:[9]

$$\frac{1}{T_2} - \frac{1}{T_1} = \frac{[H]_0}{K_D + [G]_0}\left(\frac{1}{k_{-1}}\right)\Delta^2$$

where $[H]_0$ and $[G]_0$ are the concentrations of added host and guest, respectively, K_D and k_{-1} are the dissociation equilibrium constant and the dissociation rate constant, respectively, and Δ is the chemical shift displacement in radian/s of the methoxy signal upon complexation.

Table 1. The rate constants for association (k_1) and dissociation (k_{-1}) of complexes between zinc porphyrin hosts **1** – **3** and amino acid methyl esters.[a]

	Leu-OMe		Asp-$(OMe)_2$	
	k_1 / 10^9 s^{-1}•M^{-1}	k_{-1} / 10^5 s^{-1}	k_1 / 10^9 s^{-1}•M^{-1}	k_{-1} / 10^5 s^{-1}
1 (OEP•Zn)	0.75	15.0	0.72	25.0
2	2.5	3.3	1.2	5.3
3	1.6	1.2	16.0	3.6

[a]At 30 °C, in $CDCl_3$. Estimated errors are 10%.

The rate constants are listed in Table 1. The dissociation rate constants, k_{-1}, are in the range: $\Delta / 2\pi < k_{-1} < \omega$, where ω is the resonance frequency (500 MHz) of ^{1}H NMR, which is the necessary condition for the above equation to be valid. The association rate constants, k_1, are in the order of 10^9-10^{10} $M^{-1}s^{-1}$, being close to the diffusion controlled limit.[10] Pasternack *et al.*[11] determined the association rate constant of deoxyribonucleotide to a porphyrin in water at 23 °C to be 1.9×10^9 $M^{-1}s^{-1}$ by the temperature-jump experiment. In their host-guest complex, π-stacking and attractive Coulombic forces are the driving forces of association. The association rates of aromatic guests and anionic guests to cyclodextrins[12] are comparable or slower than those determined in this work.

The larger binding constants of Leu-OMe and Asp-$(OMe)_2$ for host **2** compared to those for host **1** are ascribed to the additional hydrogen bonding interaction between the naphthyl hydroxy group and the carbonyl group on the basis of the thermodynamic studies.[6] Kinetically, the hydrogen bonding accelerates the association and decelerates the dissociation, as seen for the enhanced k_1 and reduced k_{-1} of **2** compared to those of **1** for both Leu-OMe and Asp-$(OMe)_2$. The effects of the second hydrogen bonding seem to be somewhat different. The larger binding constant for Asp-$(OMe)_2$ by host **3** than that by host **2** is attributable to the faster association rate. The dissociation rate for **3** – Asp$(OMe)_2$ complex is similar to that for **2** – Asp$(OMe)_2$ complex. Thus, in this multi-point recognition host-guest system, the second hydrogen bonding lowers the activation energy of association without significantly affecting the activation energy of dissociation.

A strong binding can be achieved either by one strong interaction between host and guest or by a combination of weak interactions (multi-point recognition). The latter mode of molecular recognition is preferred since it leads to high selectivity for a guest. Either a faster association rate or a slower dissociation rate leads to a larger association constant, that is a necessary condition for a high selectivity. However a decrease in the dissociation rate would be disadvantageous for some biological functions since it results in the slow dissociation process and retards the subsequent processes, as seen in the product inhibition in enzymatic reactions. The larger rate of association without retarding the dissociation process observed for **3** – Asp-$(OMe)_2$ complexation indicates that the multi-point recognition can results in high selectivity without expense of the fast dissociation process.

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