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β-Cyclodextrin Bearing Diethylenetriamine As Highly Active Phosphodiester Hydrolyzing Agent

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β-Cyclodextrin bearing a diethylenetriamino residue exhibits a remarkable catalysis for the hydrolysis of bis(2,4-dinitrophenyl) hydrogenphosphate and bis(4-nitrophenyl) hydrogenphosphate. The catalytic activity is almost comparable to the value of quite an active catalyst $[Co(ethylenediamine)_2(OH)(H_2O)]^{2+}$.

Recently considerable interest has been focusing onto the efficient catalysts for the hydrolysis of phosphodiesters. Artificial nucleases are prepared by the attachment of them to sequence-recognizing moieties.[1] A number of studies on the catalysis by metal complexes have been made.[2-5] However, information on the catalysis by organic molecules has been relatively scarce.[6,7] Molecular design of highly active organic catalysts is required for the further development of the field.

Here we report that β-cyclodextrin bearing a diethylenetriamino residue (CyD-N_3) at the primary hydroxyl side significantly catalyzes the cleavage of bis(2,4-dinitrophenyl) hydrogenphosphate (1) and bis(4-nitrophenyl) hydrogenphosphate (2). The catalytic rate constants of CyD-N_3, which has both a substrate-binding site (β-cyclodextrin) and a catalytic site (diethylenetriamine), are almost comparable to the values of one of the most active metal complex catalysts previously reported.

The modified β-cyclodextrin CyD-N_3 as well as β-cyclodextrin attached with an N,N-diethylamino residue (CyD-N_1) was prepared by the reaction of 6-O-monotosyl-β-cyclodextrin with the corresponding amine according to the literature (see Fig.

1).[8] The cleavage of 1 and 2 at 50°C was followed at 400 nm. In the catalysis by CyD-N_3, the rate of the formation of the 4-nitroaniline derivative as byproduct (about 2-3%) by the aromatic substitution with the primary amine of the catalyst [9] was subtracted from the apparent reaction rate.

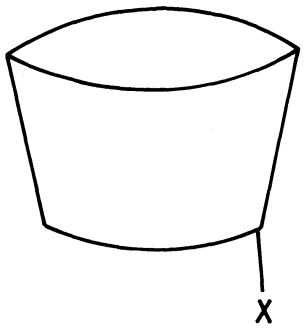

Fig. 1. Structures of the catalysts:
CyD-N_3: X = $-NH(CH_2)_2NH(CH_2)_2NH_2$
CyD-N_1: X = $-N(C_2H_5)_2$

Table 1 shows the pseudo first-order rate constants for the hydrolysis of 1 and 2 in the presence of various catalysts (0.01 mol dm^{-3}). CyD-N_3 exhibits a remarkable catalysis either at pH 11.0 or at pH 7.0 for the hydrolysis of both 1 and 2. This is highly in contrast with the fact that the $[Co(en)_2(OH)(H_2O)]^{2+}$ complex (en: ethylenediamine), one of the quite active catalysts hitherto studied for the cleavage of phosphodiesters, exhibits the largest activity around pH 7.[3-5] The activity of CyD-N_3 largely surpasses the activity of the complex at pH 11.0, whereas the activity is close to the value of the complex at pH 7.0.

The catalysis by 0.01 mol dm^{-3} CyD-N_3 for the cleavage of 1 is 120 fold more effective than that by 0.01 mol dm^{-3} N,N,N',N'-tetramethylethylenediamine at pH 11.0, and is 54 fold more effective at pH 11.0. Thus, the role of the cyclodextrin residue is significant.

In contrast with the significant catalysis by CyD-N_3, the catalytic activity of CyD-N_1, which has a monoamino residue in place of diethylenetriamine, is marginal. Thus the effective catalysis by CyD-N_3 is definitely attributable to the intramolecular cooperation of the amino residues in the diethylenetriamino moiety. The cooperation at pH 11.0 involves two (or three) neutral amino residues, whereas the cooperation at pH 7.0 involves one neutral amino residue and one (or two) ammonium cation(s). The diethylenetriamino residue exists mostly as a neutral species at pH 11.0 and as a dication (the two terminal nitrogen atoms are protonated) at pH 7.0. The titrimetrically determined pK_a values for the first, the second, and the third protonation of diethylenetriamine are 10.2, 9.9, and 4.9, respectively.

Table 1. Pseudo first-order rate constants (in 10^{-4} min^{-1}) for the hydrolysis of 1 and 2 in the presence of 0.01 mol dm^{-3} catalyst

Catalyst	1		2
	pH 7	pH 11	pH 11
CyD-N_3	89	1100	5.0
CyD-N_1	1.8	38	0.18
$[Co(en)_2(OH)(H_2O)]^{2+}$	250 a)	20 b)	0.12 b)
None	1.2	20	0.12

a) Value from Ref. 3.

b) Estimated from the rate constant at pH 7.0 using the pH-rate constant profiles for the catalysis by the similar Co(III) complexes in Ref. 4.

The present catalysis proceeds by the nucleophilic attack of the neutral amino residue in the diethylenetriamino moiety toward the phosphorus atom of the substrate, which is included in the cavity of the β-cyclodextrin moiety. The complex formation prior to the chemical transformation has been clearly confirmed by the asymptotical increase of the observed rate constant of the cleavage with the increasing concentration of the catalyst. The amino residue as base catalyst and the ammonium cation as acid catalyst in the diethylenetriamine, which are adjacent to the neutral amino residue as the nucleophilic center, can cooperatively promote the nucleophilic reaction.[10]

The proposed cooperative catalysis by the diethylenetriamino residue is consistent with the previous finding [11] that the catalytic activities of N,N,N',N'-tetramethylalkylenediamines for the cleavage of 1 and 2 are largely enhanced by the intramolecular cooperation of the two amino residues. The cooperative function of two imidazolyl residues, which are attached to β-cyclodextrin, for the cleavage of cyclic phosphate of catechol was previously shown by Breslow.[7]

CyD-N_3 was successfully recycled as catalyst, as clearly evidenced in the reactions involving excess amount of the substrate. No stable intermediate is

formed in the catalysis. This is certainly an advantage of the present catalysis over the catalysis by the Co(III) complexes, in which the products are hardly released from the complexes.[3-5]

The present finding indicates that organic molecules showing both substrate-binding and cooperative catalysis have a strong potentiality as the catalytic site in the artificial nucleases. Study on the detailed mechanism of the catalysis and on the application of the present finding to the artificial nucleases is currently under way.

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References

1) P. B. Dervan, Science (Washington D. C.), 232, 464 (1986); J. K. Barton, Science (Washington D. C.), 233, 727 (1986).
2) D. R. Jones, L. F. Lindoy, and A. M. Sargeson, J. Am. Chem. Soc., 105, 7327 (1983); S. H. Gellman, R. Petter, and R. Breslow, ibid., 108, 2388 (1986).
3) J. Chin and X. Zou, J. Am. Chem. Soc., 110, 223 (1988).
4) J. Chin, M. Banaszczyk, V. Jubian, and X. Zou, J. Am. Chem. Soc., 111, 186 (1989).
5) J. Chin and M. Banaszczyk, J. Am. Chem. Soc., 111, 4103 (1989).
6) B. Barbier and A. Brack, J. Am. Chem. Soc., 110, 6880 (1988).
7) R. Breslow, J. B. Doherty, G. Guillot, and C. Lipsey, J. Am. Chem. Soc., 100, 3227 (1978); R. Breslow and M. LaBelle, ibid., 108, 2655 (1986).
8) I. Tabushi, N. Shimizu, T. Sugimoto, M. Shiozuka, and K. Yamamura, J. Am. Chem. Soc., 99, 7100 (1977).
9) A. J. Kirby and W. P. Jencks, J. Am. Chem. Soc., 87, 3209 (1965).
10) M. L. Bender, R. J. Bergeron, and M. Komiyama, "The Bioorganic Chemistry of Enzymatic Catalysis," John Wiley & Sons, New York (1984).
11) M. Komiyama and K. Yoshinari, J. Chem. Soc., Chem. Commun., in press.

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