Regioselective P-O(3′) Cleavage of 2′,3′-Cyclic Monophosphates of Ribonucleosides Catalyzed by β- and γ-Cyclodextrins†,1

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The 2′,3′-cyclic monophosphates of adenosine (Ia) and guanosine (Ib) are regioselectively cleaved to the corresponding 2′-monophosphates (IIa,b) by β- and γ-cyclodextrins (β- and γ-CyDs) as catalysts. The ratio of IIa to the 3′-monophosphate (IIIa) as byproduct at pH 11.0, 30 °C, is 7.3 at the concentration 0.015 M of β-CyD, with a maximal selectivity of 99% for the β-CyD–Ia complex. γ-CyD also enhances the P–O(3′) cleavages of the 2′,3′-cyclic phosphates of cytidine and uridine. In the absence of CyDs, concurrent cleavages of the P–O(2′) bonds largely take place and the II/III ratios are about 1.0. Significantly, the regioselective P–O(3′) cleavages by β- and γ-CyDs are in stark contrast with the regioselective catalyses by α-CyD for P–O(2′) cleavage. The results of ^{1}H NMR and circular dichroism (CD) spectroscopies as well as competitive inhibition kinetics show that the purine residues of Ia,b are included in the cavities of β- and γ-CyDs. The predominant effect of the molecular size of CyD on the regioselective catalysis is interpreted in terms of the structures of the complexes between I's and CyDs. Ribonucleotide dimers, ApA, ApG, ApC, and ApU, are also regioselectively cleaved by β-CyD to adenosine 2′-phosphate.

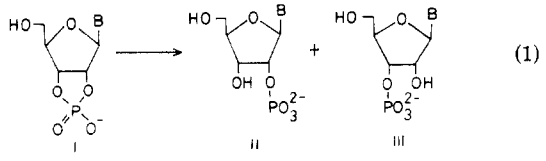
Introduction

Recently many attempts to mimic the functions of enzymes by artificial systems have been made, and large rate-accelerating effects, which are almost comparable to enzymes, have been accomplished.[2-4] However, reports of nonenzymatic systems showing regioselective catalyses, another important feature of the enzymes, have been scarce.

Breslow reported that a cyclic monophosphate of catechol is regioselectively cleaved by use of modified cyclodextrins attached with two imidazolyl groups.[5]

In a previous paper,[6] one of the authors showed that the regioselective catalysis by ribonuclease[7] is successfully mimicked by α-cyclodextrin (α-CyD), a cyclic oligomer of six glucose units.[8] The P–O(2′) bonds of the 2′,3′-cyclic monophosphates of ribonucleotides, intermediates for the enzymatic cleavages of ribonucleic acids, are regioselectively cleaved.

This paper reports that reversed regioselectivity (selective P–O(3′) cleavage of 2′,3′-cyclic monophosphates) is achieved by use of β- and γ-CyDs (the glucose units 7 and 8). The 2′,3′-cyclic monophosphates of adenosine, guanosine, cytidine, and uridine (Ia–d) are selectively cleaved to the corresponding 2′-monophosphates (IIa–d) (eq 1). The results of ^{1}H NMR and CD spectroscopies on the CyD–I complexes are presented, and the marked dependence of the regiospecific catalysis on the molecular size of CyD is inferred from these results.



(1)

B = Ia, adenine; Ib, guanine; Ic, cytosine; Id, uracil

Experimental Section

Materials. CyDs from Tokyo Kasei Kogyo Co. were recrystallized from water. Ia–d, adenylyl(3′–5′)adenosine (ApA), adenylyl(3′–5′)guanosine (ApG), adenylyl(3′–5′)cytidine (ApC), and adenylyl(3′–5′)uridine (ApU) were obtained from Sigma Chemical Co. All other chemicals were purified by the usual methods.

† Dedicate by M.K. to the memory of his teacher Prof. Myron L. Bender and Mrs. Muriel S. Bender.

Table I. Selectivities and Rate Constants for the Cleavage of Ia in the Presence and Absence of CyDs[a]

CyD	rate constant (10^{-4} min^{-1})	selectvty (IIa/IIIa)
β-CyD	13	7.3
	11[b]	4.0[b]
γ-CyD	4.9	2.0
α-CyD	3.0	0.45
hepta-2,6-dimethyl-β-CyD	2.9	0.89
hepta-2,3,6-trimethyl-β-CyD	2.7	0.85
none	2.8	0.85

[a] At pH 11.0, 30 °C. The concentration of CyD is 0.015 M unless otherwise noted. [b] $[\beta\text{-CyD}]_0$ = 0.005 M.

Kinetics. The cleavages of the monoribonucleotide phosphates (Ia–d) were carried out at pH 11.0 (sodium hydrogen bicarbonate buffer, I = 0.1 M), 30 °C, and the cleavages of the ribonucleotide dimers (ApA, ApG, ApC, and ApU) were at pH 11.1, 50 °C. The reaction mixtures were periodically analyzed by HPLC, as described previously.[6] All the reactions followed first-order kinetics and the ratios of II to III were constant throughout the reactions. The assignments of the peaks as well as the quantitative analyses in HPLC were achieved by the use of authentic samples.

The rate constants (k_c) for the cleavages of Ia–d in the CyD–I complexes and the equilibrium constants (K_d) for the dissociation of the complexes were evaluated by the usual method.[9] For the competitive inhibition experiments, the dissociation constant of the complex between β-CyD and 4-nitrophenolate as inhibitor was independently determined by absorption spectroscopy (4.4×10^{-3} M).

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Table II. Selectivities and Rate Constants for the Cleavage of Ib–d in the Presence and Absence of CyDs[a]

substra	CyD	rate constant (10^{-4} min^{-1})	selectvty (II/III)
Ib	β-CyD	2.2	1.4
	γ-CyD	2.7	1.3
	α-CyD	3.1	0.59
	none	2.0	0.82
Ic	β-CyD	2.0	1.4
	γ-CyD	1.7	1.1
	α-CyD	3.6	0.15
	none	1.7	1.1
Id	β-CyD	1.5	1.5
	γ-CyD	1.3	1.0
	α-CyD	1.8	0.32
	none	1.3	1.0

[a] At pH 11.0, 30 °C. The concentration of CyD is 0.015 M.

The partial rate constants (k_{II}(complex) and k_{III}(complex)) for the formation of II and III from the CyD–I complex were determined by use of eq 2.[10] Here, k_{II}(free) and k_{III}(free) are the

$$[k_{III}(\text{free}) - k_{II}(\text{free})/R]/F = -k_{III}(\text{complex}) + k_{II}(\text{complex})/R \quad (2)$$

rate constants for the formation of II and III from free I, F is the molar ratio of the CyD–I complex to free I, and R is the ratio of III to II in the product.

Spectroscopy. All spectroscopy was carried out at pH 10.0 (or pD 9.1 for NMR) at 30 °C, where the rates of the cleavages are sufficiently small. The instruments were as follows: ^{1}H NMR spectra, Bruker AM-500 spectrometer; CD spectra, JASCO J-600 spectrometer; absorption spectra, JASCO Ubest-50 spectrophotometer.

Results

Regioselective P–O(3′) Cleavages of Ia–d Catalyzed by β- or γ-CyD. Table I shows the selectivities (the ratios of IIa to IIIa) for the formation of IIa by the cleavage of the P–O(3′) bond of Ia. In the absence of CyDs, the P–O(2′) cleavage is dominant, and the IIa/IIIa ratio is only 0.85.

The selectivity for the formation of IIa as well as the rate of the cleavage of Ia increases asymptotically with increases in the concentration of β-CyD. At the concentration of 0.015 M, the IIa/IIIa ratio is 7.3. Regioselective P–O(3′) cleavages of Ib–d to IIb–d are also achieved by β-CyD (Table II).

γ-CyD enhances the P–O(3′) cleavages of Ia,b to IIa,b. However, no effect of γ-CyD on the cleavage of Ic,d could be detected.

The regioselective catalysis by β- and γ-CyDs for P–O(3′) cleavage contrasts with the suppression of P–O(3′) cleavage (thus the relative enhancement of P–O(2′) cleavage) by α-CyD. The II/III ratios from the cleavage of Ia–d in the presence of 0.015 M of α-CyD are only 0.45, 0.59, 0.15, and 0.32. The number of the glucose units composed of CyD has a predominant effect on the regioselectivity.

Hepta-2,6-dimethyl-β-CyD and hepta-2,3,6-trimethyl-β-CyD showed no measurable effects either on the selectivity or on the hydrolysis rate for Ia–d. The hydroxyl groups of CyDs are definitely essential for the present regioselective catalysis.

pH–Rate-Constant Profile for the β-CyD-Catalyzed Cleavage of Ia. The pH-rate-constant profile for the β-CyD-catalyzed cleavage of Ia was a fairly straight line of slope 1.0 in the pH 9.5–11.6 region. This shows that the reaction proceeds by alkaline hydrolysis. The contribution of the water-catalyzed reaction is negligible. The kinetically determined K_d value was virtually constant at (2.4 ± 0.2) × 10^{-2} M up to pH 11.6.

At the higher pH, however, the slope in the pH–rate-constant profile was considerably smaller than 1.0. In addition, the K_d value gradually increased with pH (3.7 × 10^{-2} M at pH 12.0 and 4.8 × 10^{-2} M at pH 12.2). Thus the dissociation of the secondary hydroxyl groups of β-CyD (pK_a around 12)[8] had significant effects both on the regioselective catalysis and on the complex formation.

Spectroscopy of the CyD–I Complexes. On the complex formation between β-CyD and Ia, the NMR signals for the H-3 and the H-5 protons of β-CyD shifted considerably toward the higher magnetic field (0.045 and 0.070 ppm when the charged concentrations of β-CyD and Ia were 10^{-2} and 2 × 10^{-2} M). The changes of the chemical shifts for all the other protons of β-CyD were marginal.

Complex formation of β-CyD with Ia was also confirmed both by the increase of the absorbance in the 255–270-nm region and by the positively induced CD in the 245–280-nm region. The K_d (2.8 × 10^{-2} M at pH 10.0) determined by use of the absorbance change agrees fairly well with the kinetically determined value (2.3 × 10^{-2} M). The β-CyD–Ib system also exhibited positively induced CD in the 240–280-nm region.

IIIa, one of the products for the cleavage of Ia, effectively forms a complex with β-CyD: the K_d (4.0 × 10^{-3} M) is seven times as small as that of the β-CyD–Ia complex. In contrast, IIa does not form a complex with β-CyD to a detectable extent, as estimated by absorption and CD spectroscopy. The stability order of the β-CyD complexes (IIIa > Ia ≫ IIa ~ 0) is consistent with the results in the literature.[11]

No measurable changes of the ^{1}H NMR chemical shifts occurred on complex formation between β-CyD and Ic.

Effect of Competitive Inhibitor on the β-CyD-Catalyzed Regioselective Cleavage of Ia. The addition of 4-nitrophenolate decreased both the rate constant and the selectivity for the β-CyD-catalyzed cleavage of Ia. The magnitudes of the decrease agree satisfactorily with the assumption that 4-nitrophenolate acts as a competitive inhibitor and its complex with β-CyD has no catalytic activity.

β-CyD-Catalyzed Regioselective Cleavage of Ribonucleotide Dimers. When ApA, ApG, ApC, and ApU were cleaved at pH 11.1, 50 °C, in the presence of 0.1 M β-CyD, IIa was predominantly formed (the IIa/IIIa ratios 4.9, 5.3, 5.3, and 4.9), together with adenosine, guanosine, cytidine, and uridine, respectively. In its absence, however, the ratio of IIa to IIIa is about 1:1. Here, Ia was formed as an intermediate, the P–O(3′) bond of which was regioselectively cleaved by β-CyD catalysis.

Discussion

Kinetic Analysis of the β-CyD-Catalyzed Regioselective Cleavage of I. The plot of the data for the β-CyD-catalyzed cleavage of Ia according to eq 2 is depicted in Figure 1. The linearity is fair, and the ratio of the partial rate constants is determined as follows:

$$k_{II}(\text{complex}):k_{III}(\text{complex}):k_{II}(\text{free}):k_{III}(\text{free}) = (6.3 \pm 0.3):(0.08 \pm 0.08):1.0:1.1$$

The formation of IIa is accelerated 6.3-fold by complex formation with β-CyD, whereas the formation of IIIa is decelerated by about 90%. As a result, the ratio of k_{II}(complex) to k_{III}(complex) is 79, corresponding to a max-

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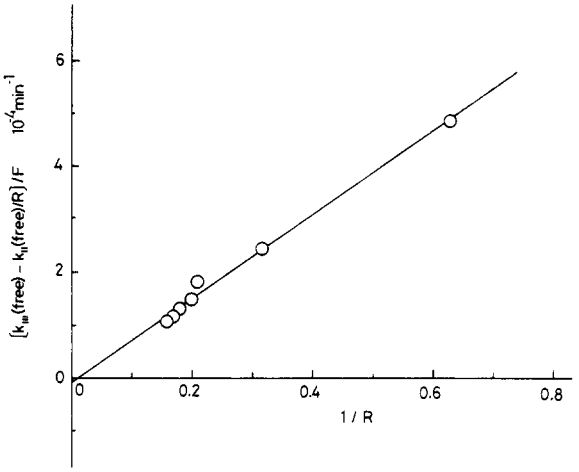

Figure 1. Plot of $[k_{III}(free) - k_{II}(free)/R]/F$ vs $1/R$ according to eq 2 for the β-CyD-catalyzed cleavage of Ia at pH 11.0, 30 °C.

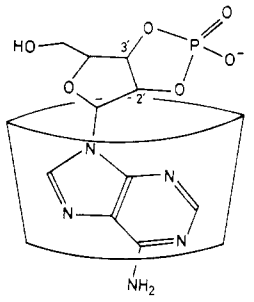

Figure 2. Proposed structure of the complex between β-CyD and Ia.

imal selectivity of 99% for the P–O(3′) cleavage of the β-CyD–Ia complex.

Structure of the β-CyD–I Complex. The upfield shifts for the H-3 and the H-5 protons of β-CyD on complex formation with Ia are attributable to the anisotropic shielding effects of the adenine residue of Ia, which is included in the cavity of β-CyD. The larger shift for the H-5 protons than that for the H-3 protons (ratio 1.6:1.0) shows that the penetration of the adenine residue into the cavity is deep so that the H-5 protons are efficiently shielded by the ring current effect.[12] The small shifts observed for the other protons, which are in the exterior of the cavity, are consistent with this conclusion.

The positively induced CD in the 245–280-nm region indicates that the long axis of the adenine residue of Ia is located nearly perpendicular to the longitudinal axis of the cavity. Here the corresponding transition dipole moment[13] is almost parallel to the axis of the cavity, resulting in the positively induced CD as estimated by the Kirkwood–Tinoco equation.[14] Thus the structure of the complex is proposed as schematically depicted in Figure 2.

The considerably larger K_d values of the β-CyD–Ia complex above pH 11.6 support the proposed structure of the complex. Here the dissociation of the secondary hydroxyl groups of β-CyD (pK_a 12)[8] to the negatively charged alkoxide ions largely suppresses complex formation (as well as the regioselective catalysis), since they are located near the phosphate residue of Ia and the electrostatic repulsion between these negative charges is significant.

The inclusion of the adenine residue of Ia in the cavity of β-CyD is further confirmed by the competitive inhibition of the regioselective catalysis by 4-nitrophenolate.

The β-CyD–Ib complex has a similar structure as estimated from the positively induced CD in the 240–280-nm region.[15]

Reaction Mechanism of Regioselective Catalyses. The β-CyD-catalyzed cleavage of Ia–d proceeds via nucleophilic attack of hydroxide ion at the phosphorus atoms, as clearly shown by the pH–rate-constant profile (slope 1.0). Nucleophilic attack of the secondary alkoxide ions of CyDs at the phosphorus atoms of I's is unlikely, since the total rates of the appearance of the products are exactly identical with the rates of the disappearance of I.

The regioselective catalysis by β- and γ-CyDs is definitely due to the fact that in the complex between CyD and Ia–d the chemical environments of the P–O(2′) bonds and the P–O(3′) bonds of I's, which are otherwise almost identical with each other, are largely differentiated. In the β-CyD–Ia complex, the O(2′) atoms are located in or near the apolar cavity of the β-CyD (Figure 2). Thus the cleavage of the P–O(2′) bonds is highly suppressed, since the formation of the O(2′) alkoxide ions in the apolar environment is energetically unfavorable. In contrast, the formation of the O(3′) alkoxide ions for the P–O(3′) cleavages is facilitated by effective solvation of the ions with water molecules.

Efficient P–O(3′) cleavage is also promoted by the increasing proximity of the phosphate residues of Ia–d to the secondary hydroxyl groups of β-CyD as the reactions proceed. This should strengthen the hydrogen bonds between the phosphate residues and the hydroxyl groups and stabilize the transition state. In the P–O(2′) cleavage, however, the distance between the two groups gradually increases and the transition state is destabilized.

The possibility that the regioselective catalyses arise from the stronger binding of II than III is ruled out by the absorption and CD spectroscopy.

The significantly different regioselectivities of β- or γ-CyD (the selective P–O(3′) cleavages) and of α-CyD (the selective P–O(2′) cleavages) are attributable to the difference in the structure of the complexes. α-CyD forms hydrogen-bonding complexes with I, in which the secondary hydroxyl groups of α-CyD interact with the heterocyclic base and the phosphate residues.[6] As a result, the O(3′) oxygen atom of I is located near the cavity of α-CyD, in contrast with the complexes of β- and γ-CyDs involving the O(2′) atoms near the cavity (see Figure 2).

These conclusions are confirmed by the fact that 4-nitrophenolate acts as a competitive inhibitor and effectively inhibits the regioselective catalysis by β- and γ-CyDs, although the effect on the catalysis by α-CyD is much smaller than that expected from the competitive inhibition.[6] The catalysis by α-CyD does not require the cavity of α-CyD, and thus the α-CyD–inhibitor complex still has some catalytic activity. For the regioselective catalysis by β- and γ-CyDs, however, the cavities are absolutely necessary.

Conclusion

The regioselective cleavage of the P–O(3′) bonds of I's by β- and γ-CyDs is ascribed to the formation of inclusion complexes in which the heterocyclic bases are accommo-

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(15) The direction of the transition dipole moment is similar to that of Ia: ref 13a.

dated in the cavity. The environments of the O(2′) and the O(3′) atoms are substantially different upon the complex formation, resulting in the selective cleavage of the P–O(3′) bonds. The regioselective catalysis is applicable to the cleavage of ribonucleotide dimers.

The regioselectivity of β- and γ-CyD is opposite to the selectivity (the P–O(2′) cleavage) of ribonuclease, whereas the specificity of α-CyD is parallel to that of the enzyme. The remarkable dependence of the regioselectivity on the kind of CyD originates from the difference of the structure of the CyD–substrate complex (the inclusion type for β- and γ-CyDs and the hydrogen-bonding type for α-CyD).

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Ferroelectric Liquid Crystals. 6. Synthesis of Nonracemic Aryl Cyanohydrin Ethers

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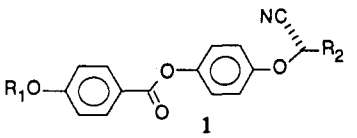
In connection with our project directed toward the design and synthesis of high-performance ferroelectric liquid crystals, we have developed a generally applicable synthetic route to chiral nonracemic aryl cyanohydrin ethers. The synthesis is illustrated herein by preparation of the arylbenzoate **1** (R_1 = *n*-decyl, R_2 = *n*-pentyl), which results in a straightforward manner from benzoylation of the key phenol intermediate **7**. Phenol **7** derives from Mitsunobu coupling of *p*-(benzyloxy)phenol (**3**) with nonracemic *N*-(α-hydroxyacyl)oxazolidone **2** prepared by the method of Evans. It is shown that this coupling proceeds predominantly with inversion of configuration. Conversion of the resulting *N*-(α-(aryloxy)acyl)oxazolidone **4** to amide **5** by treatment with dimethylaluminum amide, dehydration to nitrile **6** by the action of trimethylsilyl polyphosphoric acid, and then debenzylation promoted by trimethylsilyl iodide gives **7** in 51% overall yield from **2**.

Introduction

In connection with a project directed toward the design and synthesis of high-performance ferroelectric liquid crystals (FLCs),[1] we required an efficient route to nonracemic aryl cyanohydrin ethers of type **1**, where R_1 and R_2 are branched or straight-chain alkyl groups. Access to both enantiomers of the target materials in high enantiomeric purity was required, and a high degree of structural flexibility in the alkyl grouping R_2 was considered desirable.



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We report herein a simple solution to this problem[2] based upon chiral oxazolidone chemistry recently reported by Evans,[3] as illustrated in Scheme I for R_1 = *n*-decyl and R_2 = *n*-pentyl. The route involves Mitsunobu coupling of a phenol with nonracemic α-hydroxy-*N*-acyloxazolidones such as **2**. Aminolysis of the *N*-acyloxazolidone, followed by dehydration of the resulting amide, leads to the key aryl cyanohydrin ethers of type **7**. Details of the illustrative synthesis of compound **1** (R_1 = *n*-decyl, R_2 = *n*-pentyl) follow.

Mitsunobu Coupling of *p*-(Benzyloxy)phenol (3) with Alcohol 2. The starting material, nonracemic α-hydroxyoxazolidone **2**, is easily prepared using the Evans protocol.[3] Coupling of alcohol **2** with *p*-(benzyloxy)phenol (**3**) under standard Mitsunobu conditions[4] (diethyl azodicarboxylate (DEAD)/triphenylphosphine, THF, room temperature) is extremely slow, presumably due to the hindered nature of the secondary alcohol substrate. While benzene has been shown to be an excellent solvent for the inversion of hindered hydroxyl groups in steroids using the Mitsunobu procedure,[5] phenol **3** is only slightly soluble in benzene, and coupling in this solvent is very sluggish. Efficient coupling could be achieved, however, using dichloromethane as solvent, affording the target aryl ether **4** in 73% yield, along with a minor amount (3–5%) of diastereomeric product.[6] The major product was purified by chromatography.

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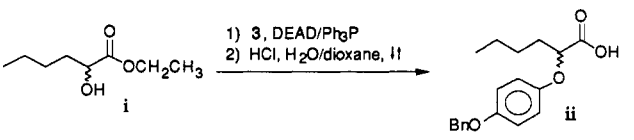
(6) In the case of the Mitsunobu coupling of alcohol **2** with phenol **3**, the minor diastereomer was tentatively identified as a component of the crude reaction mixture by ^{1}H NMR. This assignment is quite firm, however, since in the homologous series leading to compounds **1**, R_2 = *n*-butyl, the minor diastereomer was isolated from a coupling reaction and was shown to be identical by ^{1}H NMR with one of the diastereomers produced by coupling of the racemic acid **ii** (prepared from ethyl α-hydroxypentanoate (**i**) as shown) with the norephedrine-derived oxazolidone. The other diastereomer deriving from the latter process was, of course, identical with the major product of the Mitsunobu coupling.



i **ii**

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