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Cooperation of Alkali Metal Ions and β-Cyclodextrin for the Regioselective Cleavage of Adenosine 2',3'-Cyclic Phosphate

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Sodium(I), potassium(I), rubidium(I), and cesium(I) ions significantly increase both the selectivity and the rate constant for the β-cyclodextrin-induced regioselective cleavage of adenosine 2',3'-cyclic phosphate. The ratio of the 2'-phosphate to the 3'-phosphate in the product is 11.2 with sodium chloride and β-cyclodextrin (3.0 and 0.015 mol dm^{-3}) at pH 11, 30 °C.

Efficient and selective cleavage of nucleic acids has been attracting much interest. Significant developments have been made in the fission of deoxyribonucleic acids.[1)] However, artificial systems for the cleavage of ribonucleic acids have been rather scarce.

In previous papers,[2-5)] the authors succeeded in the regioselective cleavage of ribonucleic acids by use of cyclodextrins, cyclic oligomers of glucose, as catalysts. The P-O(3') bonds of the 2',3'-cyclic phosphates of ribonucleotides, the intermediates for the cleavage of ribonucleic acids, are regioselectively cleaved by β-cyclodextrin (β-CyD).

This paper reports that both the selectivity and the rate in the β-CyD-induced regioselective cleavage of adenosine 2',3'-cyclic phosphate (I) are furthermore promoted by alkali metal ions. Significant dependence of the effect on the kind of metal ions is described.

The cleavage of I was carried out at 30 °C. Required amounts of metal salts were added to aqueous buffer solutions of ionic strength 0.1 mol dm^{-3} (KCl), followed by the adjustment of the pH when necessary. The rate constants of the cleavage as well as the ratios of adenosine 2'-phosphate (II) to the 3'-phosphate (III) in the products were determined by periodical analysis with HPLC (Merck Lichrospher RP-18(e) column, 25 cm; eluent, 97:3 water-acetonitrile mixture). All the reactions followed first-order kinetics and the ratios of II to III were constant throughout the reactions.

Table 1 shows the results for the β-CyD-induced regioselective cleavage of I at pH 9.5. Quite significantly, the ratios (4.6, 7.2, 5.8, and 5.5) of adenosine 2'-phosphate (II) to the 3'-phosphate (III) in the presence of NaCl, KCl, RbCl, and CsCl together with β-CyD (0.01 mol dm^{-3}) are much larger than the ratio (2.5) in the absence of the metal salts. The ratio is increased by β-CyD from 0.6 to 2.5, and is additionally enhanced by the alkali metal salts. The ratio is 8.5, when $[\beta\text{-CyD}]_0$ = 0.016 and $[KCl]_0$ = 3.0 mol dm^{-3}. Furthermore, the rate constants for the β-CyD-induced cleavage with NaCl, KCl, RbCl, and CsCl are 26, 8.2, 5.3, and 5.5 times as large as those in their absence. Thus, the alkali metal salts largely promote both the selectivity and the rate of the β-CyD-induced cleavage of I.

The selectivity and the rate constant increased almost linearly with the increasing concentration of NaCl up to 3.0 mol dm^{-3}, when the concentration of β-CyD was kept constant. Sodium nitrate showed almost the same selectivity-promoting effect as NaCl. Thus, the metal ion has a predominant effect in the present promotion, and the contribution of the counter anion is marginal.

Similar promotion of the selectivity and the rate for the β-CyD-induced cleavage was also observed at pH 11.0. The II/III ratio and the rate constant in the presence of 3.0 mol dm^{-3} of KCl ($[\beta\text{-CyD}]_0$ = 0.015 mol dm^{-3}) were 11.2 and 8.2×10^{-3} min^{-1}. In the absence of KCl, the corresponding values were 5.9 and 1.8×10^{-3} min^{-1}.

The remarkable promotion of both the selectivity and the rate is ascribed to cooperation of the metal ions and β-CyD. In the absence of β-CyD, the alkali metal ions showed only acceleration with no measurable increase in the regioselectivity. In the presence of NaCl (3.0 mol dm^{-3}) at pH 9.5 without the β-CyD catalyst, the II/III ratio and the rate of cleavage were 0.6 and 6.1×10^{-4} min^{-1}, respectively.

Table 1. Effects of metal halides on the rate constants and the regioselectivity for the cleavage of I in the presence of β-CyD (0.01 mol dm^{-3}) at pH 9.5, 30 °C [a)]

Metal halide	Rate constant 10^{-4} min^{-1}	Selectivity (II/III)
LiCl	35.1	1.8
NaCl	15.7	4.6
KCl	4.9	7.2
	7.3	8.5 b)
RbCl	3.2	5.8
CsCl	3.3	5.5
$MgCl_2$ c)	190	0.5
None	0.6	2.5
	0.3 d)	0.6 d)

a) $[\text{Metal halide}]_0$ = 3.0 mol dm^{-3}.

b) $[\beta\text{-CyD}]_0$ = 0.016 mol dm^{-3}.

c) $[MgCl_2]_0$ = 1.0 mol dm^{-3} at pH 8.5.

d) In the absence of both β-CyD and metal halide.

In contrast with the promotion of both the regioselectivity and the reaction rate by NaCl, KCl, RbCl, and CsCl, LiCl considerably decreased the regioselectivity (II/III = 1.8). In the presence of $MgCl_2$ together with β-CyD, the II/III ratio (0.5) is smaller than the value (0.6) in the absence of β-CyD. Lithium and magnesium ions suppress the regioselective catalysis of β-CyD, although the accelerating effects are quite significant.

The promotion of the β-CyD catalysis by the alkali metal ions is probably ascribed to the interactions with the phosphate residues [6)] of I in the β-CyD-I complex. In the complex, the adenine residue penetrates in the cavity of β-CyD, and the phosphate forms hydrogen bonds with the secondary hydroxyl groups of β-CyD.[4)] The regioselective cleavage of the P-O(3') bond by β-CyD has been attributed to the stabilization of the transition state by the strengthened hydrogen bonds. Lithium(I) and magnesium(II) ions, typical hard acids,[7)] mainly interact with the O(1) and the O(2) of the phosphate on which the negative charge is largely located. As a result, the hydrogen bonding between I and β-CyD (and thus the regioselective catalysis by β-CyD) is suppressed by the metal ions, and only the acceleration effects are significant. However, sodium(I), potassium(I), rubidium(I), and cesium(I) ions, which have less hard nature, can interact more favorably with the O(3') atom, facilitating the P-O(3') cleavage.

The cleavage of the 2',3'-cyclic phosphates of guanosine, uridine, and cytidine in the presence of β-CyD (0.01 mol dm^{-3}) was also accelerated by KCl (3.0 mol dm^{-3}): 5.7, 3.3, and 3.9 fold, respectively. The II/III ratios (1.3, 1.0, and 0.7), however, were virtually identical with the values in the presence of β-CyD alone without KCl.

In conclusion, the alkali metal ions (sodium(I), potassium(I), rubidium(I), and cesium(I) ions) show promotion of the selectivity and the rate for the β-cyclodextrin-induced regioselective cleavage of adenosine 2',3'-cyclic phosphate. By the cooperation with the metal ions, β-cyclodextrin cleaves ribonucleic acids in higher selectivity and at lower pH. Spectroscopic study on the interaction between the metal ions and either I or β-CyD is currently under way.

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