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Journal of Molecular Catalysis A: Chemical 118 (1997) L5–L7

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

Letter

Lanthanide metal complexes for the hydrolysis of ribonucleoside 3′,5′-cyclic phosphate and deoxyribonucleoside 3′,5′-cyclic phosphate

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Received 9 April 1996; accepted 16 July 1996

Abstract

Ytterbium(III) and praseodymium(III) complexes of 2-carboxyethylgermanium sesquioxide (Ge-132) can hydrolyze the phosphodiester linkage of 3′,5′-cyclic adenosine monophosphate (cAMP) and 3′,5′-cyclic deoxyadenosine monophosphate (dcAMP). Both cAMP and dcAMP are hydrolyzed with high selectivity, yielding predominantly 3′-monophosphates. The selectivity and activity for hydrolyzing cAMP and dcAMP by lanthanide metal(III) complexes and lanthanide metal ions are compared.

Keywords: 3′,5′-cyclic adenosine monophosphate (cAMP) and 3′,5′-cyclic deoxyadenosine monophosphate (dcAMP) hydrolysis; Lanthanide(III) complexes; Lanthanide(III) ion

Non-enzymatic hydrolysis of RNA and DNA has been attracting increasing interest, mainly because it is essential for the preparation of artificial restriction enzymes which are applicable to molecular biology, medication, therapy, and other fields [1–5]. Lanthanide ions and their complexes have recently been shown to be highly reactive for hydrolyzing phosphate diester including RNA and DNA [6–8]. However, lanthanide ions precipitate readily under basic conditions due to the formation of insoluble hydroxide gels which is the major obstacle to their use in aqueous solution. So homogeneous hydrolytic system showing large activities and selectivities for the fission are required.

The phosphodiester bond of cAMP did not hydrolyze to any observable extent even when the reaction solution was heated at 100°C for one month [9]. We now report that lanthanide metal(III) complexes of Ge-132 can selectively hydrolyze cAMP and dcAMP (Fig. 1) [1], the selectivity and activity for hydrolyzing cAMP and dcAMP by lanthanide metal(III) complexes at pH 5.5 and by lanthanide metal(III) at pH 8 are compared.

Figs. 2 and 3 depict the HPLC patterns for

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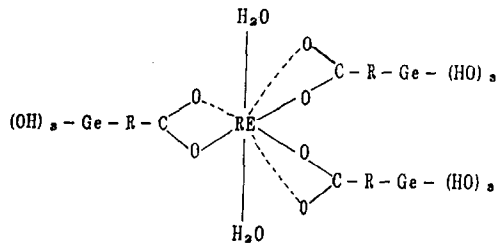
[1] The Ln^{3+}–Ge-132 complexes were prepared in our laboratory [10].

PII S1381-1169(96)00354-8



R = (CH_2)

RE = Yb(III). Pr(III)

Fig. 1. Structures of the lanthanide metal complexes Yb^{3+}–Ge-132 and Pr^{3+}–Ge-132.

the lanthanide metal complex catalyzed hydrolyses of cAMP and dcAMP at pH 5.5, 50°C. 18% of dcAMP and 8% of cAMP are converted to 3′-dAMP and 3′-AMP respectively after 60 h, the catalytic activity is in the following order: dcAMP > cAMP, interestingly, this result is on the contrary for the cleavage of cAMP and dcAMP by lanthanide ions in basic conditions. Figs. 4 and 5 display the HPLC patterns for the lanthanide ion catalyzed hydrolyses of cAMP and dcAMP at pH 8 and 37°C. In only 30 s, 37% of cAMP is converted to adenosine-3′-

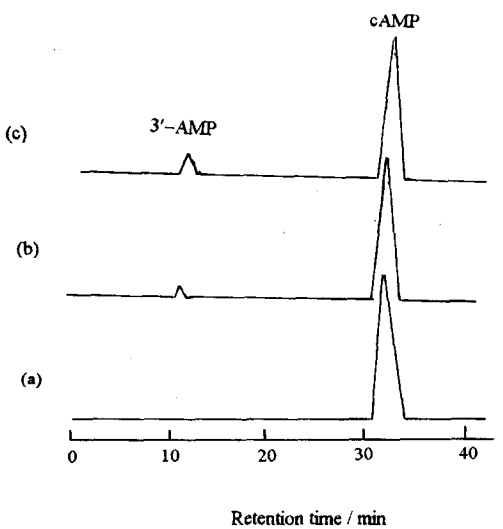


Fig. 2. HPLC patterns for the cleavage of cAMP (2.4 mmol dm^{-3}) by Yb^{3+}–Ge-132 (9.3 mmol dm^{-3}) at pH 5.5 and 50°C. (a) 0 h, (b) 20 h, (c) 60 h.

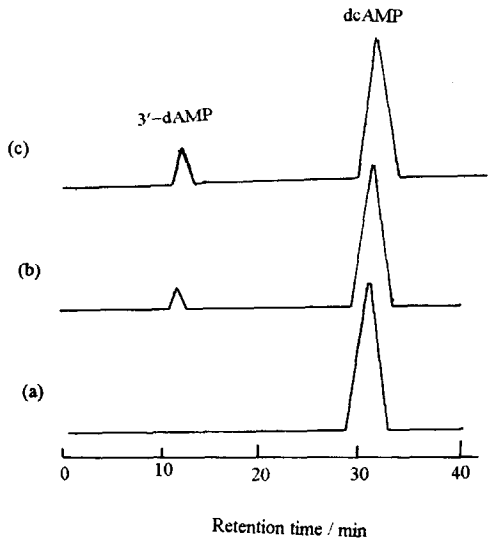


Fig. 3. HPLC patterns for the cleavage of dcAMP (2.4 mmol dm^{-3}) by Yb^{3+}–Ge-132 (9.3 mmol dm^{-3}) at pH 5.5 and 50°C. (a) 0 h, (b) 20 h, (c) 60 h.

phosphate (3′-AMP), only small adenosine-5′-phosphate (5′-AMP) and adenosine (A) are detected. The conversion at 1 min is 6% for stereospecific cleavage of dcAMP to the 3′-monophosphate was observed. The catalytic activity is in the following order: cAMP > dcAMP. In addition to this, the same result was also observed by the complex of Pr–Ge-132, the main products are 3′-monophosphates.

The hydrolytic character of scission is evidenced by reversed-phase HPLC on the hydrolysis of cAMP and dcAMP. Apparently the P–

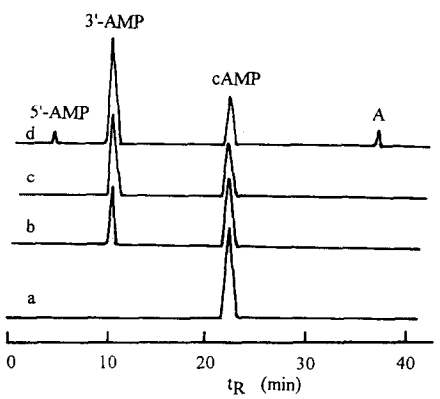


Fig. 4. HPLC patterns for the cleavage of cAMP (2.4 mmol dm^{-3}) by $CeCl_3$ (10 mmol dm^{-3}) at pH 8 and 37°C. (a) 0 min, (b) 0.5 min, (c) 1 min, (d) 2 min.

O(5′) bond in the phosphodiester linkage, rather than the P–O(3′) bond, is selectively cleaved by the lanthanide ions. However, the selectivity for cleaving cAMP by lanthanide complexes and lanthanide ions is different slightly. The main product of 3′-AMP was formed and small 5′-AMP and A were detected after 2 min by lanthanide ion, but in 60 h, neither 5′-AMP and A nor the other products were detected at all except for 3′-AMP by lanthanide complexes. It indicated preferential scission of the P–O(5′) bond over the P–O(3′) bond, and reflecting the high selectivity for cleaving cAMP by lanthanide complexes.

Ge-132 is soluble in water to about 0.98% and in solution this compound is hydrolyzed and dissociated to the monomer, trihydroxygermylpropanoic acid. This fact was clarified from the ^{17}O-NMR spectrum of [^{17}O]-labeled Ge-132 and ^{13}C-NMR spectrum of Ge-132 in the solid state and in solution [11]. The proposed mechanism for the cleavage involves coordination of the phosphate of cAMP to the lanthanide complex, as depicted in Scheme 1, and weaken the P–O bond, then the hydroxide ions on the complex functions as a nucleophilic,

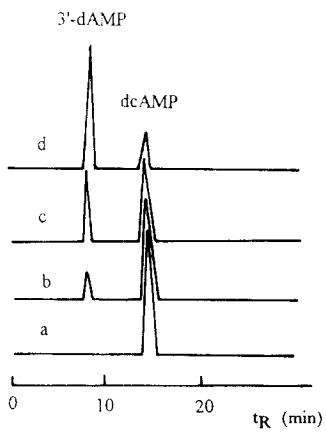
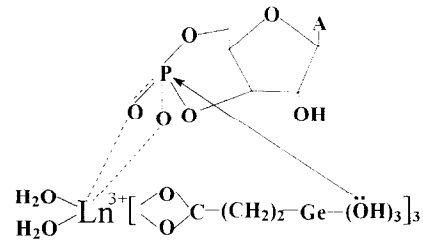


Fig. 5. HPLC patterns for the cleavage of dcAMP (2.4 mmol dm^{-3}) by $CeCl_3$ (10 mmol dm^{-3}) at pH 8 and 37°C. (a) 0 min, (b) 1 min, (c) 6 min, (d) 30 min.



Scheme 1. Proposed mechanism for the Ln^{3+}–Ge-132 cleavage of cAMP.

intramolecular nucleophilic attack phosphorus atom of cAMP, it results in the cleavage of phosphate diester linkage of mononucleosides.

The present findings indicate that the Yb^{3+}–Ge-132 and Pr^{3+}–Ge-132 complexes are a homogeneous hydrolytic system for cleavage of nucleotides and is crucially important for the molecular design of artificial hydrolytic nucleases.

Acknowledgements

This work was supported by the National program "The Basic Research of Rare Earth Science of China" and the Fundamental Bureau of Chinese Academy of Science.

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