

## Remarkably Fast Hydrolysis of 3',5'-Cyclic Adenosine Monophosphate by Cerium(III) Hydroxide Cluster

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Cerium(III) hydroxide cluster hydrolyses 3',5'-cyclic adenosine monophosphate at an unprecedentedly large rate (half-life 35 s at pH 8.0; 30 °C).

3',5'-Cyclic adenosine monophosphate (cAMP) regulates response of cells against external stimulus as second messenger.<sup>1</sup> Thus, efficient catalysts for cAMP hydrolysis are important for clarification of the mechanism of cell-to-cell communication and also for artificial regulation of the process. Although Co<sup>III</sup> complexes show notable catalysis,<sup>2,3</sup> the activities are not sufficient yet to hydrolyse the stable cAMP effectively under physiological conditions.

The present paper reports an enormous catalysis by Ce<sup>III</sup> hydroxide cluster.<sup>4,5</sup> Hydrolysis of cAMP is completed within a few minutes at pH 8.0, 30 °C.

Quite rapid hydrolysis of cAMP by CeCl<sub>3</sub> (0.01 mol dm<sup>-3</sup>) is clearly evident by HPLC (Fig. 1). In only 1 min (b), 70% of cAMP is converted to adenosine 3'- and 5'-phosphates (3'-AMP and 5'-AMP). The 3'-AMP/5'-AMP ratio is 7.6, reflecting preferential scission of the P-O(5') bond over the P-O(3') bond. cAMP disappears soon, and the resultant 3'- and 5'-AMP are then hydrolysed to adenosine (Ado) more slowly (c). No other products are detected.

The pseudo-first-order rate constant for the hydrolysis of cAMP is 1.2 min<sup>-1</sup>.† The acceleration by 0.01 mol dm<sup>-3</sup> CeCl<sub>3</sub> is more than 10<sup>11</sup> fold, decreasing the half-life of cAMP from a half million years in its absence<sup>2</sup> to 35 s. The hydrolysis is by several orders of magnitude faster than any of the cAMP hydrolyses ever reported (the acceleration by 0.01 mol dm<sup>-3</sup> Co<sup>III</sup> complex is 10<sup>8</sup> fold).<sup>3</sup>

The pH-rate constant profile involves quite a steep slope at pH 6.5–8 and a plateau above pH 8 (Fig. 2). This indicates that the cluster [Ce<sub>3</sub>(OH)<sub>5</sub>]<sup>4+</sup> is mostly responsible for the present catalysis: formation of this cluster according to eqn. (1) was previously shown by potentiometric titration.<sup>6,7</sup> All the experimental points satisfactorily fit the theoretical (solid) line calculated by use of the catalytic rate constant 3 dm<sup>3</sup>

† The reaction followed good pseudo-first-order kinetics for at least 3 half-lives.

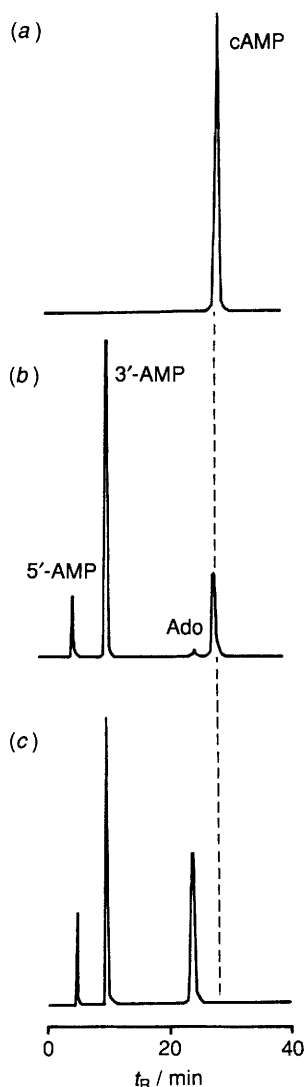


Fig. 1 HPLC patterns for the hydrolysis of cAMP ( $10^{-4}$  mol dm $^{-3}$ ) by CeCl $_3$  ( $10^{-2}$  mol dm $^{-3}$ ) at pH 8.0, 30 °C: (a) 0 min, (b) 1 min, (c) 30 min

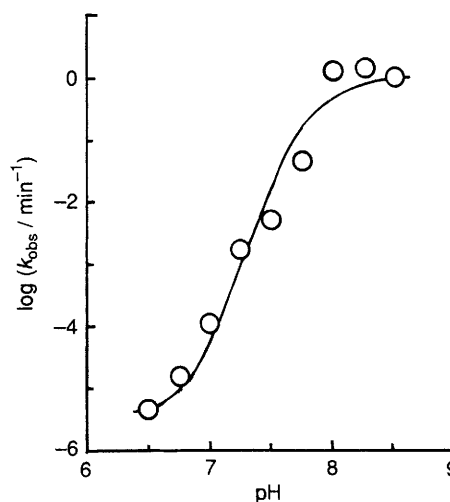


Fig. 2 pH-rate constant profile for the hydrolysis of cAMP in the presence of CeCl $_3$  ( $0.01$  mol dm $^{-3}$ ) at 30 °C: the solid line is the theoretical one calculated in terms of a major contribution from [Ce $_3$ (OH) $_5$ ] $^{4+}$  with a minor contribution from Ce $^{3+}$  (see the text for detail)

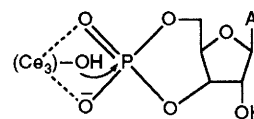
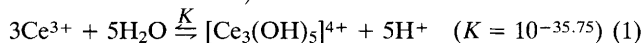


Fig. 3 Proposed mechanism for the cAMP hydrolysis by the Ce $^{III}$  hydroxide cluster: the cluster is represented by (Ce $_3$ ), and the dotted lines refer to the acid catalyses by the Ce $^{3+}$  ions or by the water molecules bound to them

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mol $^{-1}$  min $^{-1}$  for the cluster (the value for free Ce $^{3+}$  ion is  $5 \times 10^{-6}$  dm $^3$  mol $^{-1}$  min $^{-1}$ ).



The  $10^6$  fold larger catalytic activity of [Ce $_3$ (OH) $_5$ ] $^{4+}$  cluster than free Ce $^{3+}$  ion is probably associated with cooperation of the Ce $^{3+}$  ions in the cluster, as schematically depicted in Fig. 3. One of them provides a metal-bound hydroxide ion as the nucleophile for the hydrolysis: a similar mechanism was proposed for the hydrolysis of phosphate esters and RNAs.<sup>4,5</sup> The other two Ce $^{III}$  ions (or water molecules coordinating to them) can promote the nucleophilic reaction as acid catalysts. Cooperative catalysis is required for the prompt hydrolysis of the less reactive cAMP.

Other rare earth metal ions also catalyse the hydrolysis (Pr > Nd > La > Y, Sm, Dy), although less efficiently than Ce $^{3+}$  (< 1/700). In contrast, Al $^{3+}$ , Fe $^{3+}$ , Mg $^{2+}$  and Ca $^{2+}$  are non-active. The superb catalysis is specific for rare earth metal ions.

In conclusion, biologically important cAMP has been for the first time hydrolysed promptly under physiological conditions by use of Ce $^{3+}$  and other rare earth metal ions. Detailed study on the catalytic mechanism is currently under way.

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