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Note

The Transition State Analog for Metal Catalyzed Hydrolysis of an Ester

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The transition state analog for metal catalyzed hydrolysis of an ester through cooperative interactions between metal ions as Lewis acid and peroxide was discussed.

Key words : *binuclear Co(III) complex, transition state analog, metal catalyzed hydrolysis.*

Phosphinates, phosphonates and phosphonamides are potential transition state analog enzyme inhibitors for esterase and peptidases.[1] More recently, they have been used as antigens for developing catalytic antibodies.[2] Although the abzymes are active for hydrolyzing esters and amides, the level of activity is far below that of real enzymes. Currently there is considerable interest in developing metalloabzymes that are highly reactive for hydrolyzing esters and amides.[3,4] Also of current interest is metal-peroxide cooperativity in hydrolyzing the amide bonds of proteins[5-7] and the phosphate diester bonds of DNA.[8,9] Here, the author report on the transition state analog for metal catalyzed hydrolysis of an ester and amide through the crystal structure of diphenyl phophinate and peroxide both bridged to a binuclear Co(III) complex.

Materials and Method

Compound **1** was synthesized by adding dropwise a methanolic solution of sodium diphenylphosphinate (0.01 M) into a methanolic solutuion of **L** (1 equiv.) and cobalt perchlorate hexahydrate (2 equiv.) with rapid stirring. In a few minutes, black brown rhombic crystals appeared on the bottom of the flask. The product was recrystallized from a solution of acetonitrile and water.

Equimolar amounts of $Co(ClO_4)_2$, sodium diphenyl phosphinate and L in methanol was bubbled with air to yield purple crystals of $[Co_2(\mathbf{L})(O_2P(Ph)_2(O_2)](ClO_4)_2$, **1**.[10] Replacing diphenyl phosphinate with dimethyl phosphinate gave $[Co_2(\mathbf{L})(O_2P(Me)_2(O_2)]\ (ClO_4)_2$, **2**.[11]

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Abbreviations: **L**, 2,6-bis(bis(2-pyridylmethyl)aminomethyl)-4-methylphenol.

Results and Discussion

Over the years, structures of numerous binuclear metal complexes have been determined including those with **L** and bridging carboxylate, peroxide or phosphates.[12,13] Compound **1** represents the first cobalt(III) complex with a bridging phosphate diester analog. Such complexes are potentially valuable as antigen for developing metalloabzymes that hydrolyze esters or amides. Cobalt(III) is the metal of choice for developing metalloabzymes since it is substitutionally inert.

Phosphonates have been used as transition state analog antigens for developing catalytic antibodies that hydrolyze esters and amides (Fig. 1). numerous, several hydrolytic abzymes with remarkable specificities have been developed to date. In an interesting study, a phosphonate ester (**3**) was used as an antigen to develop an abzyme that hydrolyzes the ester bond of cocaine. Although the abzyme is active for hydrolyzing cocaine, a much greater activity would be required in order for it to have any therapeutic effect.

It is well known that metal ions can provide many orders of magnitude rate acceleration for hydrolyzing esters and amides through Lewis acid activation as well as metal-hydroxide activation (Fig. 2). In this example,

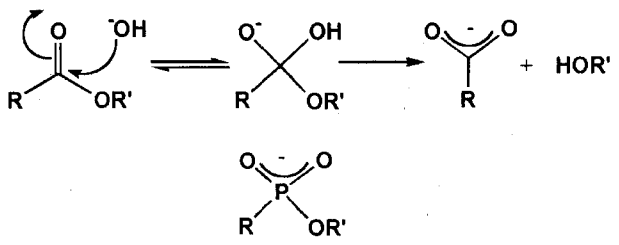

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Fig. 1. Transition state analog for hydrolysis of an ester.

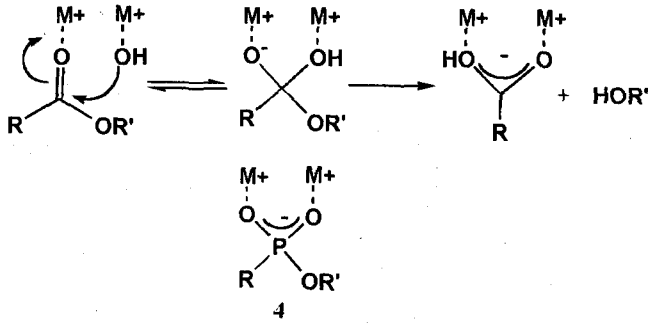

Fig. 2. Transition state analog for metal catalyzed hydrolysis of an ester.

the first metal is providing the Lewis acid activation while the second metal is providing the metal-hydroxide activation. The transition state analog for the metal catalyzed hydrolysis reaction is represented by **4**. Hence metalloabzymes developed from binuclear metal complexes with bridging phosphinates or phosphonates (eq. **1**, **2**, or **4**) should provide far greater activity than those developed from simple uncoordinated phosphinates or phosphonates (**3**). Although metalloabzymes have been reported, they have not been developed from transition state analog for metal catalyzed hydrolysis reaction.[3,4]

Sequence specific hydrolytic cleavage of the amide bonds in protein molecules through cooperative interactions between metal complexes and hydrogen peroxide has been achieved even though the mechanism of this remarkable reaction is still unclear.[5-7] In a more recent study, cooperativity between Flp recombinase and peroxide in cleaving the phosphate diester bond of DNA has been reported.[8] We have been interested in developing simple systems which cleave amides or phosphate esters through cooperative interactions between metal ions and peroxide.[9,10] Interestingly, compound **1** consists of a diphenyl phosphinate and peroxide, both bridged to a binuclear Co(III) complex. One of the oxygen atoms of the peroxide is only about 2.8 Å away from the phosphorus of the coordinated phosphinate. It remains to be seen whether the peroxide will act as a nucleophile if the bridging phosphinate is replaced with a bridging phosphonate ester or a phosphate ester.

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References

1. Jacobsen, N. E. and Bartlett, P. A. (1981) A phosphonamidate dipeptide analogue as an inhibitor of carboxypeptidase. *J. Am. Chem. Soc.* **103**, 654-657.
2. Lerner, R. A., Benkovic, S. J. and Schultz, P. G. (1991) At the crossroads of chemistry and immunology: Catalytic antibodies. *Science* **252**, 659-667.
3. Iverson, B. L. and Lerner, R. A. (1989) Sequence-specific peptide cleavage catalyzed by an antibody. *Science* **243**, 1184-1188.
4. Iverson, B. L., Iverson, S. A., Roberts, V.A., Getzoff, E. D., Tainer, J. A., Benkovic, S. J. and Lerner, J. A. (1990) Metalloantibodies. *Science* **249**, 659-662.
5. Rana, T. M. and Meares, C. F. (1990) Specific cleavage of a protein by an attached iron chelate. *J. Am. Chem. Soc.* **112**, 2457-2458.
6. Rana, T. M. and Meares, C. F. (1991) Iron chelate mediated proteolysis; protein structure dependence. *J. Am. Chem. Soc.* **113**, 1859-1861.
7. Rana, T. M. and Meares, C. F. (1991) Transfer of oxygen fron an artificial protease to peptide carbon during proteolysis. *Proc. Natl. Acad. Sci. USA* **88**, 10578-10582.
8. Kimball, A. S., Lee, J., Jayaram, M. and Tullius, T. D. (1993) Sequence-specific cleavage of DNA via nucleophilic attack of hydrogen peroxide, assisted by FIP recombinase. *Biochemistry* **32**, 4698-4701.
9. Takasaki, B. K. and Chin, J. (1995) La(III)-hydrogen peroxide cooperativity in phosphate diester cleavage: A mechanistic study. *J. Am. Chem. Soc.* **117**, 8582-8585.
10. Sung, N. D., Seo, J. S., Hynes, R. C., Williams, D. and Chin, J. (1998) Structure and reactivity of dinuclear Cobalt (II) complex with peroxide and phosphate diester and analoges bridging the metal ions. *J. Am. Chem. Soc.* **120**, 9943-9944.
11. 31P NMR spectra were taken on a Varian XL-300 spectrometer. Compound **1**: ^{31}P NMR, DMSO(trimethylphosphate) δ 51.19 ppm. Compound **2**: δ 74.35. ^{31}P NMR shifts for sodium diphenyl phosphinate and sodium dimethyl phosphinate are δ 14.09 and δ 41.77, respectively.
12. Well, M., Hynes, R. C. and Chin, J. (1993) Double Lewis acid activation in phosphate diester cleavage. *Angew. Chem. Int. Ed. Engl.* **32**, 1633-1635.
13. Sung, N. D., Seo, J. S., Hynes, R. C. and Chin J. (1996) Structure and reactivity of dinuclear Cobalt(II) complex with a bridging phosphate monoester. *Inorg. Chem.* **35**, 7472-7273.