

Molecule of the Month

A Dicopper (II) Complex Hydrolyzes the Phosphate Diester Bond!

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A dinuclear copper (II) complex is a synthetic catalyst for modelling enzymatic cleavage of RNA.

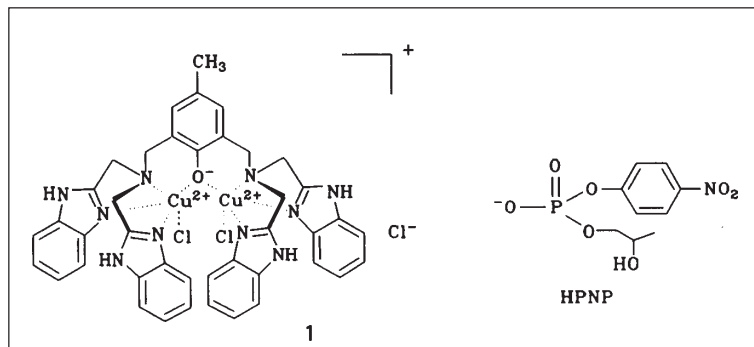
Both DNA and RNA contain phosphodiester linkages in their backbones.¹ The phosphodiester bond is an excellent candidate for this function because of its stability under physiological conditions. However, there are enzymes (nucleases, phosphodiesterases) which can cleave such phosphodiester bonds efficiently. It has been reported that a number of enzymes which hydrolyze phosphate diesters contain two metal ions. Chemists have long been interested in designing synthetic molecules that can mimic or imitate the action of natural enzymes.

¹ DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid; HPNP: 2-Hydroxypropyl-p-nitrophenyl phosphate; Phosphodiester: Di-ester of phosphoric acid.

Before 1993, compound **1** (Figure 1) was only one of a multitude of complexes known to contain two Cu²⁺ ions. However, Chin *et al* (*Angew. Chem. Int. Ed. Engl.*, **1993**, 32, 1633) demonstrated that **1** catalyzes the cleavage of the phosphate diester bond present in HPNP (a simple RNA model) under physiological conditions (pH 7, 25°C). The products of this reaction are the cyclic phosphate ester of propylene glycol and p-nitrophenol (Figure 2).² Since the latter (in the phenolate form) absorbs radiation of 400 nm, it is rather easy to measure the rate of this reaction. In an

² Note that this transformation is really an intramolecular alcoholysis, rather than hydrolysis. A complete hydrolysis will cleave the cyclic phosphate ester.

Figure 1 Structures of the dinuclear copper (II) catalyst **1** and HPNP



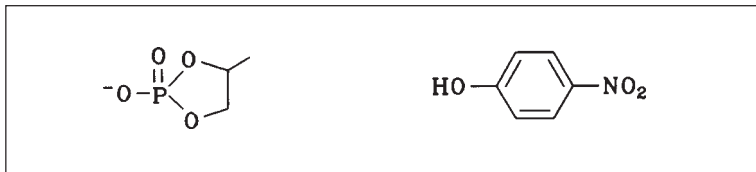


Figure 2 Cleavage products of HPNP

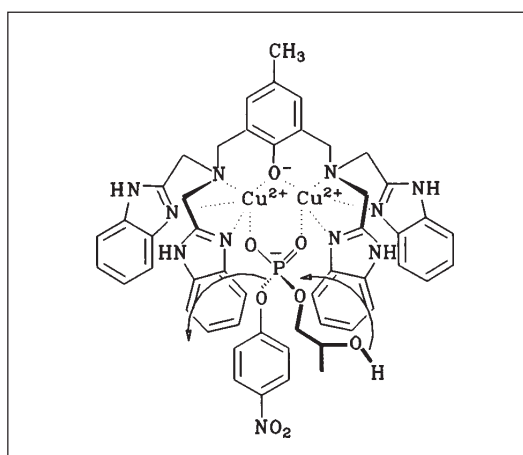
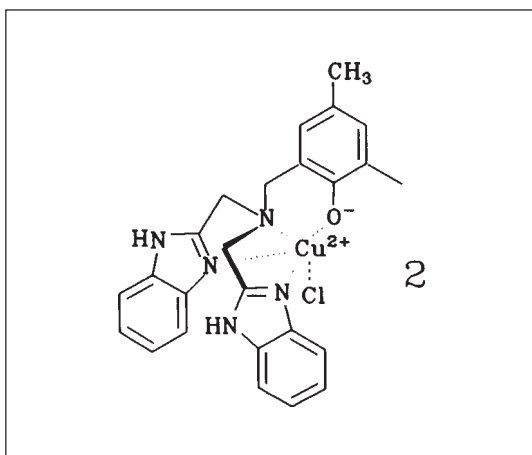
attempt to evaluate the role of the second metal ion in **1**, the mononuclear complex **2** (Figure 3) was also tested for its ability to cleave HPNP. Interestingly, dinuclear complex **1** was found to be almost 50 times more efficient as a catalyst than **2**, suggesting that both the Cu²⁺ ions in **1** cooperate in the catalysis.

The key mechanistic feature of the HPNP cleavage by **1** can be understood as follows. The phosphate group of HPNP binds to the two copper (II) centres of **1** as shown in Figure 4. This activates³ the phosphate ester, or in other words, makes the phosphorus more electrophilic. Subsequently, the internal hydroxyl group attacks the phosphorus atom, and finally *p*-nitrophenolate is liberated. Since the attack of the hydroxyl group increases the charge on the oxygen atoms attached to phosphorus, it is easy to see why compound **1** acts as a better catalyst than **2** (Figure 5). Evidence for the mechanism shown in Figure 4 comes from the analysis of the crystal structure of **1** complexed with dibenzyl phosphate (phosphate replacing the Cl atoms), in which the phosphate was shown forming a bridge between the two Cu²⁺ centers through oxygen atoms.

³ This is an example of Lewis acid activation.

Figure 3 (bottom left) Structure of the mononuclear Cu(II) complex **2**.

Figure 4 (bottom right) Mechanistic feature for double Lewis acid activation for the cleavage of HPNP by **1**.



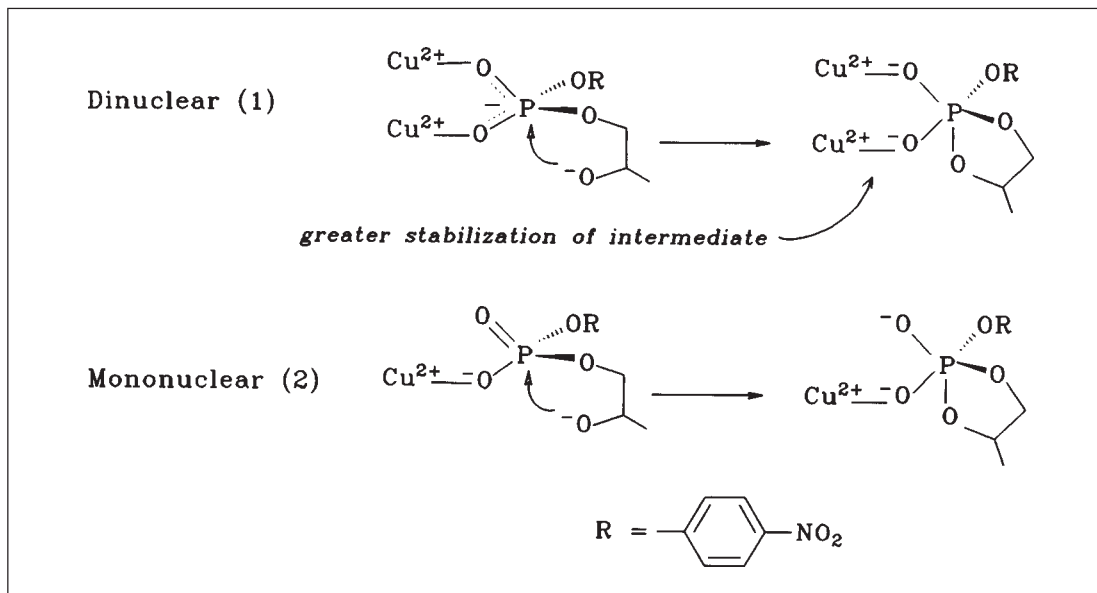


Figure 5 Comparison of the stabilization of the intermediate by 1 and 2.

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Molecules **1** and **2** demonstrate that properly designed synthetic metal complexes can provide valuable information for understanding the chemistry involved in the action of enzymes catalyzing the cleavage of phosphodiester bonds at a molecular level. This kind of biomimetic study can eventually provide subtle insights into the design of more efficient functional nucleolytic agents.



The Second Pauli Principle ... Students in physics and chemistry encounter the Pauli Exclusion Principle (the commonly stated chemistry version: no two electrons in an atom can have the same set of quantum number, including spin; the physics counterpart: total wave functions of fermions are antisymmetric with respect to exchange of any pair of particles). There is also the less well known Second Pauli Principle. This one is simpler. It was widely believed that the presence of Wolfgang Pauli, the Swiss theoretician, in the vicinity of a research laboratory inexplicably caused apparatus to break down. One interpretation is that experimentalists became nervous whenever Pauli entered the laboratory, and consequently made silly mistakes. But what can one say about the explosion which devastated the Physics Department of the University of Berne, which people link to the fact that at that very instant Pauli halted at the Berne railway station on his way to Zurich?

