Dramatic Ligand Effect in Copper(II) Complex Promoted Transesterification of a Phosphate Diester

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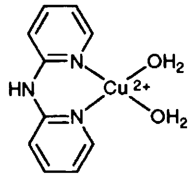
A *cis*-diaqua copper(II) complex has been shown to promote the transesterification of a phosphate diester with second-order dependence on the metal complex.

It was recognized early on that *cis*-diaqua copper(II) complexes efficiently hydrolyze phosphonate esters.[1] More recently, it was shown that *cis*-diaqua cobalt(III) complexes hydrolyze esters,[2] amides,[3] nitriles,[4] and phosphate esters[5] by a combination of Lewis acid activation and metal–hydroxide activation.[6] However a major problem with *cis*-diaqua metal complexes is that they form inactive dimers. It is well known that with increasing concentrations of *cis*-diaqua metal complexes, the reactivity levels off due to dimerization of the metal complexes.[7] Here we report for the first time on a *cis*-diaqua copper(II) complex that becomes more reactive with increasing concentrations for cleaving a phosphate diester.

We compared the reactivities of three *cis*-diaqua copper(II) complexes **1–3** for promoting the intramolecular transesterification of 2-hydroxypropyl-*p*-nitrophenylphosphate (hpnp). The phosphate diester has been used extensively as an RNA model.[8] The *cis*-diaqua copper(II) complexes were generated by dissolving the corresponding dichlorides in water. The dichlorides for **1**,[9] **2**,[10] and **3**[11] were prepared according to literature procedures. The cleavage of the barium(II) salt of hpnp was followed by monitoring the increase in the visible absorbance at 400 nm caused by release of the *p*-nitrophenolate ion. In a typical kinetic experiment, 5 μl of a 0.01 mol dm^{-3} stock solution of hpnp in water ws added to 1 ml of a mmol dm^{-3} solution of the copper(II) complex at 25 °C.† The products of the cleavage of hpnp as detected by ^{1}H and ^{31}P NMR, are *p*-nitrophenol and the cyclic phosphate.‡ Potentiometric titration reveals that the first pK_a values of the metal bound water molecules in **1**, **2** and **3** are 7.2, 8.2 and 6.8 respectively. In Fig. 1, the reactivities of **1**, **2** and **3** are compared at pH values close to the pK_a of the metal complexes.



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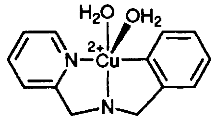

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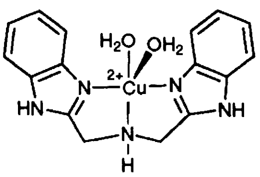

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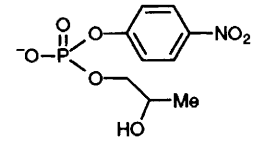


hpnp

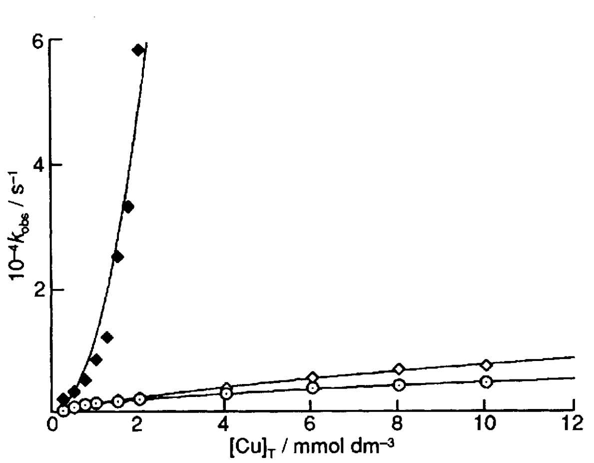


Fig. 1 Rate-concentration profile for **1** (○), **2** (◇) and **3** (◆) catalysed transesterification of hpnp at 25 °C (pH 8 for **2** and pH 7 for **1** and **3**)

Compound **1** had been shown to be active for hydrolyzing unactivated esters and amides.[9] It is well known that *cis*-diaqua metal complexes dimerize at neutral pH and that the dimer is not active for cleaving phosphate esters (Scheme 1) where L represents di- or tri-amine ligands.[1,7]

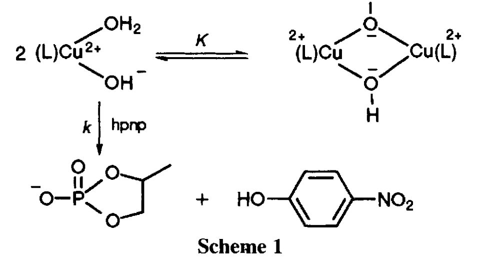
The observed pseudo-first order rate constants (k_{obs}) for **1** and **2** promoted transesterification of hpnp were fit according to eqn. (1) which was derived from Scheme 1 where k and K are as in the scheme $\{K = [\{CuL(OH)\}_2]/[CuL(H_2O)(OH)]^2\}$ and $[Cu]_T$ is the total concentration of the metal complex used (Fig. 1).§

$$k_{obs} = k\left(\frac{-1 + (1 + 8K[Cu]_T)^{1/2}}{4K}\right) \qquad (1)$$

The values of k and K for **1** are 1.9×10^{-2} dm^3 mol^{-1} s^{-1} and 5.7×10^2 dm^3 mol^{-1} respectively while those for **2** are 1.3×10^{-2} dm^3 mol^{-1} s^{-1} and 6.0×10^1 dm^3 mol^{-1} respectively..

The observed pseudo-first order rate constants for **3** promoted transesterification of hpnp cannot be fit according to eqn. (1). Compound **3** becomes more reactive with increasing concentrations unlike **1** and **2** which become less reactive (Fig. 1). It is particularly interesting that **3** is so much more reactive than **2** considering that the two metal complexes are closely related electronically. The pK_a value of pyridinium (5.2) is comparable to that of benzimidazolium (5.4). The solid state structure of $[CuL^1Cl_2]$ [L^1 = bis(2-benzimidazolylmethyl)amine] reveals that one of the chlorides is in a highly hindered environment (Fig. 2).¶ Therefore, it should be difficult for **3** to form a dihydroxy bridging dimer (Scheme 1) even though it might form a monohydroxy bridging dimer. We propose that **3** dimerizes to a highly reactive monohydroxy bridging complex in contrast to **1** and **2** that dimerize to inactive dihydroxy bridging complexes (Scheme 1).

The observed pseudo-first order rate constants (k_{obs}) for **3** promoted transesterification of hpnp were fit according to eqn. (2) where K is the equilibrium constant for dimerization of the metal complex to form the monohydroxy bridging complex ($K = [\{CuL^1(H_2O)\}_2(OH)][OH]/[CuL^1(H_2O)(OH)]^2$) and k is the rate constant for the dimer promoted cleavage of hpnp.|| The value of Kk obtained from the best fit of the experimental points is 1.2×10^2 dm^6 mol^{-2} s^{-1}.



Scheme 1

$$k_{obs} = 0.013[\mathrm{Cu}]_T + kK[\mathrm{Cu}]_T^2 \qquad (2)$$

Below pH 7, the rate of **3** promoted transesterification of hpnp increases with increasing pH. The rate levels off at about pH 7 indicating that the aqua-hydroxy form of **3** or its kinetic equivalent is the active species. A mechanism that is consistent with the pH dependence as well as the rate-concentration profile for **3** promoted transesterification of hpnp is shown in Scheme 2. Such double Lewis-acid activation mechanisms had recently been proposed for dinuclear metal complex promoted cleavage of phosphate diesters[12]

The concentration of the dimer in Scheme 2 is expected to peak at the solution pH equal to the pK_a of **3**. However, the rate of specific base-catalysed ring closure in Scheme 2 is expected to increase with increasing pH. The net effect is that the overall rate of **3** promoted transesterification of hpnp should increse with increasing pH and and level off at the solution pH equal to the pK_a of **3**. The transesterification reaction should result in formation of a trigonal-bipyrimidal intermediate or transition state. The O–P–O bond angle in the six-membered ring (Scheme 2) is expected to increase to about 120° as the trigonal-bipyrimidal intermediate or transition state is formed.

In conclusion, **3** represents the first metal complex that cleaves hpnp by second-order kinetics. Furthermore, it is the most reactive mononuclear metal complex reported to date for promoting the transesterification reaction.

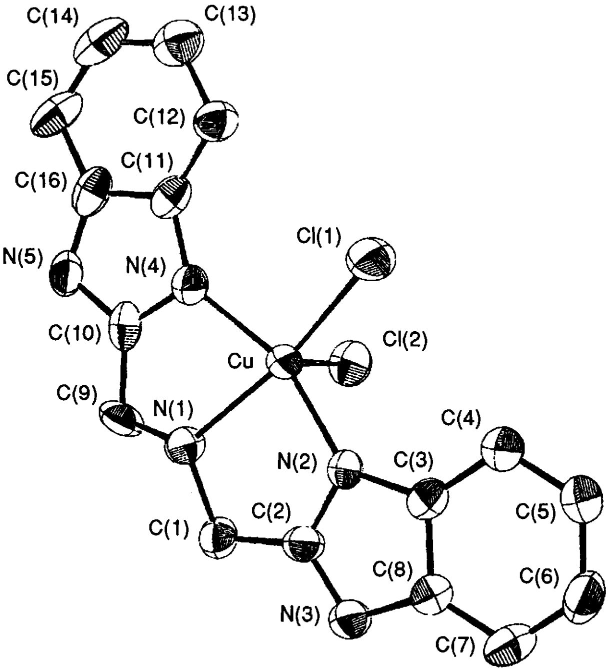
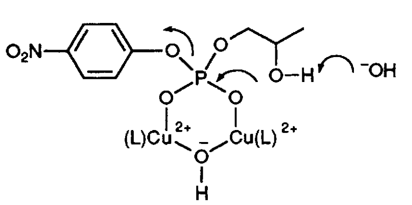


Fig. 2 View of [CuL^1(Cl)$_2$] (ORTEP ellipsoids at the 50% probability level). Selected bond distances (Å) and angles (°): N(1)–Cu 2.119(19), Cu–Cl(1) 2.2674(21), Cu–Cl(2) 2.6027(22), N(1)–Cu–Cl(1) 178.4(5), N(1)–Cu–Cl(2) 80.9(5).



Scheme 2

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Footnotes

† The rate constants were obtained by fitting the first three half-lives of the reaction to a first-order rate law. Each kinetic run was reproducible to within 3% error. The pH of the reaction solution did not change appreciably during the course of the transesterification as a result of the buffering effect of the metal complex solution.

‡ Since the copper(II) complex is paramagnetic, it was first coordinated with excess ethylenediamine before recording the NMR spectrum.

§ The rate constants were obtained by fitting the experimental points according to eqns. (1) and (2) using a commercially available (Kaleidograph Inc) non-linear least-square curve fitting program. Derivations of eqn. (1) and (2) are available as supplementary material.

¶ *Crystal structural data of* [CuL^{1}Cl$_2$]: orthorhombic, space group *Pbca*, a = 14020(4), b = 14.380(3), c = 8.268(4) Å, V = 3683.0(15) Å^3, Z = 8; 2626 measured reflections, 1458 with $I > 2.5\sigma(I)$, 235 refined parameters, R = 0.048, R_w = 0.044. Atomic coordinates, bond distances and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‖ Eqn. (2) was derived with the assumption that the equilibrium favours the monomer under our experimental conditions and that the reactivity of the monomer is the same as that for **2**.

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