

Cu(II)-Mediated decomposition of phosphorothionate P=S pesticides. Billion-fold acceleration of the methanolysis of fenitrothion promoted by a simple Cu(II)–ligand system

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The kinetics of methanolysis of the title compound (**3**) were studied in the presence of Cu^{2+} , introduced as $\text{Cu}(\text{OTf})_2$, in the presence of 0.5–1.0 eq. of methoxide and in the presence of 1.0 eq. of a ligand such as bipyridyl (**5**), phenanthroline (**6**) or 1,5,9-triazacyclododecane (**4**). In all cases the active species involve $\text{Cu}^{2+}(\text{OCH}_3)$. In the case of added strong-binding ligands **5** or **6**, a plot of the observed rate constant for methanolysis of **3** vs. $[\text{Cu}^{2+}]_{\text{total}}$ gives a curved line modelled by a process having a $[\text{Cu}^{2+}]^{1/2}$ dependence consistent with an active monomeric species in equilibrium with an inactive dimer *i.e.* $\{\text{LCu}^{2+}(\text{OCH}_3)\}_2 \rightleftharpoons 2\text{LCu}^{2+}(\text{OCH}_3)$. In the case of the added strong binding ligand **4**, the plot of the observed rate constant for methanolysis of **3** vs. $[\text{Cu}^{2+}]_{\text{total}}$ gives a straight line consistent with the catalytically active species being $4\text{Cu}^{2+}(\text{OCH}_3)$ which shows no propensity to form inactive dimers. Turnover experiments where the $[\mathbf{3}] > [\text{Cu}^{2+}]_{\text{total}}$ indicate that the systems are truly catalytic. In the optimum case a catalytic system comprising 1 mM of the complex $4\text{Cu}^{2+}(\text{OCH}_3)$ catalyzes the methanolysis of **3** with a $t_{1/2}$ of ~58 s accounting for a 1.7×10^9 -fold acceleration relative to the background reaction at near neutral pH (8.75).

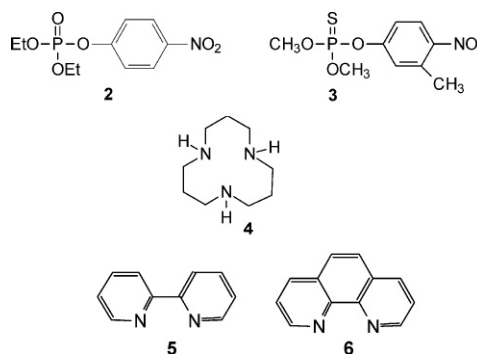
Introduction

Phosphorothionate esters of general structure **1** (X and Y are alkoxo, Z is aryl with HOZ pK_a between 6 and 8) are widely used agricultural pesticides because they exhibit high insecticidal and acaricidal properties but much lower mammalian toxicity than their P=O counterparts.^{1,2} Controlled decomposition of these materials is of both fundamental and practical interest and generally is effected by oxidation or hydrolysis with catalytic methods being especially valuable. For practical applicability a viable catalytic decomposition method must be inexpensive, have high turnovers, occur at relatively neutral pH and ambient temperature, convert the toxic starting material into far less toxic products and proceed rapidly, *e.g.* $t_{1/2} < 1$ min. Transition metal ions and lanthanides and certain mono- and dinuclear complexes thereof are known to promote the hydrolysis of neutral phosphate and/or phosphonate esters.^{3,4} However, the available literature on the hydrolysis of the P=S esters is quite sparse with only the softer metal ions such as Cu^{2+} , Pb^{2+} , Hg^{2+} and some cyclometallated Pt and Pd aryl ketoximes showing significant catalysis.⁵ The lack of reported hydrolytic examples is possibly due to the reduced activity of the P=S esters relative to their P=O counterparts,^{5a,d,e} their poor aqueous solubility and the fact that the anionic hydrolytic products can bind to the metal ions thereby curtailing further catalysis.



Recently we presented an alternative methodology for the decomposition of phosphorus triesters such as paraoxon (**2**),⁶ namely metal-ion catalyzed alcoholysis.⁷ Several reports have listed alcohols as co-solvents for the metal-catalyzed hydrolysis of phosphate triesters to enhance the solubility of the reactants without altering very much the overall kinetics, but as far as we know, none, other than our own studies,⁷ has reported the pure alcohol as a reactive medium. The catalytic alcoholysis methodology offers decided advantages over hydrolysis mainly from the perspective of substrate solubility, enhanced M^{+} :substrate pre-equilibrium complexation leading to increased reaction rates, and the fact that the products are also neutral triesters which are non-inhibitory. We have shown that the methanolysis of paraoxon (**2**) at essentially neutral pH

conditions (in methanol) is accelerated by 10^9 -fold at ambient temperature in the presence of 2 mmol dm^{-3} $\text{La}(\text{OTf})_3$ along with 1 eq. of NaOCH_3 .^{7a} However La^{3+} shows no propensity to accelerate the methanolysis of the P=S triester fenitrothion (**3**), probably due to the “hardness” of this metal ion which resists binding to the “soft” sulfur of that substrate. More recent studies have shown that a “softer” system, $\text{Zn}^{2+}(\text{OCH}_3)$, when complexed to some N-containing ligands, reacts with both **2** and **3**, although less effectively with the latter than with **2** by a factor of 17.^{7b} Herein we report that the softer metal ion system comprising $\text{Cu}^{2+}(\text{OCH}_3)$ at 25 °C either alone or in the presence of equimolar 1,5,9-triazacyclododecane (**4**), bipyridyl (**5**) or phenanthroline (**6**) shows both greater catalytic efficacy and specificity toward the P=S derivatives. In the optimum case a catalytic system comprising 1 mM of the complex $4\text{Cu}^{2+}(\text{OCH}_3)$ catalyzes the methanolysis of **3** with a $t_{1/2}$ of ~58 s accounting for a 1.7×10^9 -fold acceleration relative to the background reaction at near neutral pH (8.75).^{8,9}



Results

(a) Kinetics of methanolysis of **2** and **3**

Shown in Figs. 1 and 2 are plots of k_{obs} for the methanolysis of **3** (**3** and **2** in the case of Fig. 2) vs. total amount of Cu^{2+} ion ($[\text{Cu}^{2+}]_{\text{t}}$) which fall into two categories depending on the nature of the ligand employed. In order to self-buffer the pH of the solutions, in all cases the $[\text{OCH}_3]/[\text{Cu}^{2+}]_{\text{t}}$ ratio was kept at 0.5 corresponding to the half neutralization point for titration of the first metal-bound HOCH_3 . In the absence of any ligand or in the presence of equimolar **5** or **6**, the plots shown in Fig. 1 are bowed, not due to any pre-

Table 1 Kinetic constants for the methanolysis of **2** and **3** catalyzed by Cu²⁺ in the absence and presence of ligands **4–6**, T = 25 °C

Catalyst	pH at 0.5 eq. of base	K _{dis} ^a /mmol dm ⁻³	k _m (2)/dm ³ mol ⁻¹ s ⁻¹	k _m (3)/dm ³ mol ⁻¹ s ⁻¹	Relative selectivity ^b
⁻ OCH ₃		N.A.	1.1 × 10 ⁻²	(7.2 ± 0.2) × 10 ⁻⁴	1
Cu ²⁺ (⁻ OCH ₃) ^c	6.86 ± 0.2	<0.005	0.22 ± 0.02	0.79 ± 0.03	55
5Cu ²⁺ (⁻ OCH ₃) ^d	7.8 ± 0.2	<0.005	<0.2	4.48 ± 0.12	342
6Cu ²⁺ (⁻ OCH ₃) ^e	7.45 ± 0.2	<0.005	<0.2	2.44 ± 0.06	186
4Cu ²⁺ (⁻ OCH ₃) ^f	8.75 ± 0.1	N.A.	2.76 ± 0.17	12.2 ± 0.4	67
4Zn ²⁺ (⁻ OCH ₃) ^g	9.3	N.A.	0.85 ± 0.01	(4.8 ± 0.2) × 10 ⁻²	0.86
La ³⁺ ₂ (⁻ OCH ₃) ₂ ^h		N.A.	47.2 ± 2.3	ⁱ	~0

^aDimer dissociation constant (K_{dis}) and conditional second order rate constant (k_m) for reaction with monomer defined as in text. N.A. means non-applicable since there is no observable dimerization under the specific conditions. A K_{dis} of <0.005 indicates very strong dimerization and is quoted as an upper limit based on an iterative fitting procedure which provided the lowest standard deviations. ^bdefined as (k_m(**3**)/k_{OCH}(**3**))/(k_m(**2**)/k_{OCH}(**2**)). ^cBased on fits of k_{obs} vs. [Cu²⁺]_i data to eqn. (1) at a [methoxide]/[Cu²⁺]_i ratio of 0.5. ^dBased on fits of k_{obs} vs. [5Cu²⁺]_i data to eqn. (1) at a [methoxide]/[Cu²⁺]_i ratio of 0.5. ^eBased on fits of k_{obs} vs. [6Cu²⁺]_i data to eqn. (1) at a [methoxide]/[Cu²⁺]_i ratio of 0.5. ^fBased on linear fits of k_{obs} vs. [4Cu²⁺(⁻OCH₃)]_i data at a [methoxide]/[Cu²⁺]_i ratio of 0.5. ^gFrom ref. 7b. ^hFrom ref. 7a. ⁱNo catalysis observed.

equilibrium substrate–Cu²⁺ saturation binding process but rather to a monomer–dimer equilibrium behaviour of the free or ligand bound Cu²⁺(⁻OCH₃) species. Such a monomer/dimer behaviour requires a square-root dependence^{3i,n,u,7b,10} for the k_{obs} vs. [Cu²⁺]_i data which can be fit via a standard NLLSQ treatment to eqn. (1) derived from the assumptions that: (a) when present, all the ligand is bound to Cu²⁺,^{4f} and (b) an inactive dimer is in rapid equilibrium (dissociation constant K_{dis}) with an active (rate constant k_m) monomeric species LCu²⁺(⁻OCH₃) as shown in eqn. (2). The goodness of fit of the rate constant data to this model is shown as the computed lines through the Fig. 1 data and the best fit constants are given in Table 1. Also in Table 1 are the measured p₃H values over the entire [Cu²⁺]_i range under the self-buffering conditions described above which deviate by an acceptable 0.2 or less units. In the case of 5Cu²⁺(⁻OCH₃) and 6Cu²⁺(⁻OCH₃) mediated methanolysis of paraoxon (**2**), the catalyzed reactions were sufficiently slow that we have placed upper limits on the rate and equilibrium constants.

$$k_{\text{obs}} = \{k_m K_{\text{dis}} (\sqrt{1 + 8[\text{Cu}^{2+}]_i / K_{\text{dis}}} - 1) / 4\} \quad (1)$$

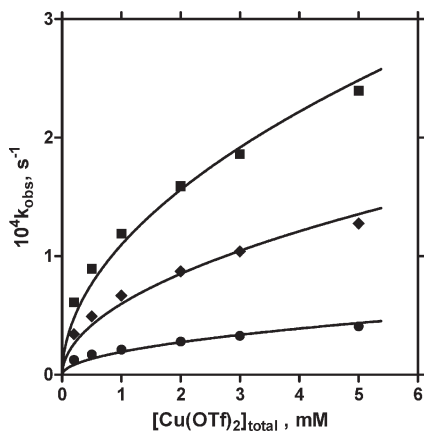
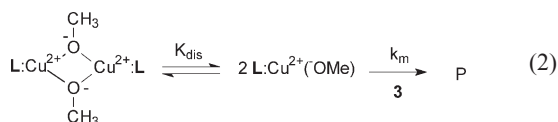


Fig. 1 Plot of the k_{obs} vs. total [Cu(OTf)₂]_{total} for the methanolysis of fenitrothion (**3**) catalyzed by various species conducted at T = 25 °C, [⁻OCH₃]/[Cu²⁺]_i = 0.5; when ligand is used, [Cu²⁺]_i = [L]: Cu²⁺(⁻OCH₃) (●), 5Cu²⁺(⁻OCH₃) (◆), 6Cu²⁺(⁻OCH₃) (■). Lines through the data are computed on the basis of fits to eqn. (1).

In the case of ligand **4** the behaviour is markedly different, and the k_{obs} vs. [Cu²⁺]_i plots for methanolysis of both **2** and **3** shown in Fig. 2 are strictly linear, indicative of complete formation of a kinetically active monomeric form 4Cu²⁺(⁻OCH₃). The k_m(**2**) and k_m(**3**) second-order rate constants are evaluated as the gradients of the linear plots and are given in Table 1.

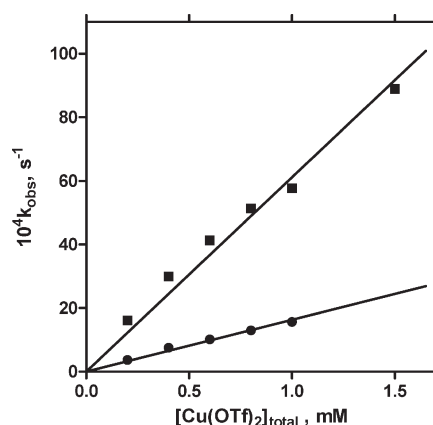


Fig. 2 Plots of the k_{obs} vs. total [Cu(OTf)₂] for the methanolysis of paraoxon (**2**, ●) and fenitrothion (**3**, ■) catalyzed by 4Cu²⁺(⁻OCH₃) conducted at T = 25 °C, [⁻OCH₃]/[Cu²⁺]_i = 0.5, [Cu²⁺]_i = [4].

(b) NMR turnover experiment

To test for true catalysis, NMR experiments were performed on a CD₃OD–CH₃OH (9 : 1) solution containing 3.6 mg (23 mmol dm⁻³) of **3** and 1.78 mmol dm⁻³ in each of Cu(OTf)₂, Bu₄N⁺OCH₃⁻ and ligand **4**, so that the final concentration of **3** was 12.9 times in excess of Cu²⁺. Almost immediately the solution became a bright yellow colour which intensified further with time. The ¹H and ³¹P NMR spectra were recorded after 100 min and showed no traces (<1%) of starting material. The only signals present belonged to the product *O,O,O*-trimethyl phosphorothionate (or *O,O*-dimethyl *O*-trideuteriomethyl phosphorothionate): ³¹P NMR signal at δ 73.28 ppm (lit.¹¹ 73.91 ppm). By way of reference, the ³¹P NMR signal for unreacted **3** occurs at δ 66.11 ppm.¹¹ After 100 min the ¹H NMR spectrum showed no (<1%) characteristic signals for fenitrothion (aromatic protons δ 8.04, 7.14 and CH₃O– δ 3.89 ppm) but did show the characteristic signal for the product CH₃O–; δ 3.735 ppm, J_{H-P} = 13.39 Hz (lit.¹² δ 3.72 ppm, J_{H-P} = 13.45 Hz). The signals for the aromatic protons were shifted upfield from the starting material and were reminiscent of those for 3-methyl-4-nitrophenol but with significant broadening, probably due to transient coordination with Cu²⁺ ions.

(c) Electrospray mass spectrometric (ES-MS) study of Cu(OTf)₂ solutions with or without complexing ligands and base

A solution containing 2 mmol dm⁻³ of Cu(OTf)₂ in methanol without added base was analyzed by ES-MS methods at cone voltages varying from 12 to 61 V. Peaks corresponding to monomeric (Cu(OTf))⁺ and dimeric forms with different numbers of solvating molecules of methanol (Cu₂(OTf)₂(CH₃OH)_n)⁺ were found to be present with n = 1–4 (at 29 V cone voltage) and n = 3–5 (at 12 V cone voltage).

The analysis of the ES-MS of a 2 mmol dm⁻³ solution of Cu(OTf)₂ in the presence of 2 mmol dm⁻³ Bu₄N⁺OCH₃⁻ showed that the major

species are dimeric forms $(\text{Cu}_2(\text{OCH}_3)_2(\text{OTf})(\text{CH}_3\text{OH})_n)^+$ with $n = 2$ at 14 V and $n = 1$ at 29 V. No monomeric species $(\text{Cu}(\text{OTf}))^+$ or $(\text{Cu}(\text{OCH}_3))^+$ were observed.

The ES-MS of a sample containing 1 mmol dm^{-3} in each of $\text{Cu}(\text{OTf})_2$ and bipyridyl **5** showed the presence of the dimeric species $(\text{Cu}_2(\mathbf{5})_2(\text{OTf})_3)^+$ as the major component and the monomeric forms $(\text{Cu}(\mathbf{5})(\text{OTf}))^+$ and $(\text{Cu}(\mathbf{5})(\text{OCH}_3))^+$ as minor components at a cone voltage of 59 V; also present at this high cone voltage was $(\text{Cu}(\mathbf{5}))^+$ indicating some reduction of the metal ion under these conditions. The ES-MS of second solution formulated as above but with 1 mmol dm^{-3} of added Bu_4NOCH_3 was also determined at 59 V and showed the presence of $(\text{Cu}_2(\mathbf{5})_2(\text{OCH}_3)_2(\text{OTf}))^+$ and $(\text{Cu}_2(\mathbf{5})(\text{OCH}_3)_2(\text{OTf}))^+$ and $(\text{Cu}(\mathbf{5})(\text{OCH}_3))^+$. It is of note that in the presence of ligand one does not see the presence of methanol solvated forms which are observed in the absence of ligand.

Discussion

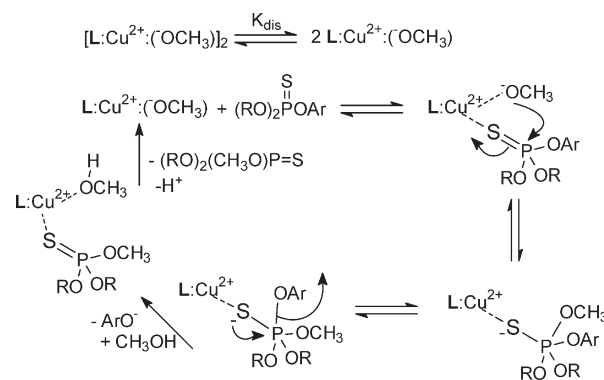
There are several points of note revealed by the present study that pertain to the rapid rate of catalyzed methanolysis of the P=O and P=S substrates and to the stoichiometry of the catalytically active forms. First, as is the case for uncatalyzed attack of HO^- on paraoxon (**2**) vs. parathion (the P=S analogue of **2**),¹³ uncatalyzed attack of methoxide on **2** is faster (by some 15 times) than on **3**. However all the $\text{Cu}^{2+}(\text{OCH}_3)$ catalysts are more effective for **3** than **2**. We quantify this by the relative selectivity (RS) parameter given in Table 1 which compares the relative reactivity of the $\text{Cu}^{2+}(\text{OCH}_3)$ reaction and free methoxide attack on the P=S and P=O substrates. The RS parameters clearly correlate with the hard/soft properties of the metal ion. The "hard" ion La^{3+} exhibits exclusive selectivity for the P=O substrate ($\text{RS} \sim 0$), while the softer Zn^{2+} ion shows almost equal affinity for P=O and P=S substrates ($\text{RS} \sim 1$). Of the three ions Cu^{2+} is softest and exhibits very high selectivities for the P=S substrates with RS values of ~ 55 – 340 , the highest values being exhibited in the case of the aromatic ligands. Interestingly, the best combination of selectivity and overall high catalytic activity is achieved with $4\text{Cu}^{2+}(\text{OCH}_3)$ because its extant coordination appears to prevent the undesirable dimerization exhibited by the other Cu^{2+} -containing catalysts.

Second, the fact that all the Cu^{2+} -catalyzed reactions proceed with computed second-order rate constants larger than those for the attack of methoxide on **2** or **3** indicates that there is a dual role for the metal ion. As in other M^{n+} -promoted hydrolytic^{3,4} and methanolytic⁷ reactions the metal ion is reasonably proposed to simultaneously deliver a M^{n+} -coordinated OH^- or CH_3O^- and act as a Lewis acid to polarize a P=S or P=O unit which provides both rate and selectivity enhancement. As far as we know the 17000-fold enhancement of attack of $4\text{Cu}^{2+}(\text{OCH}_3)$ vs. free OCH_3^- on **3**, even though uncoordinated methoxide is $\sim 10^8$ -fold more basic,¹⁴ represents the largest acceleration reported for any metal-ion catalyzed phosphoryl transfer reactions to solvent, and is even larger than the 4300-fold enhancement that we reported earlier for attack of $\text{La}^{3+}_2(\text{OCH}_3)_2$ vs. free OCH_3^- on paraoxon.^{7b}

It is also of note that we have, through turnover experiments, demonstrated that this is a truly catalytic system which, at concentrations of 1 mmol dm^{-3} , can provide 1.7×10^9 -fold acceleration of the methanolysis of **3** at neutral pH and ambient temperature. This has been demonstrated unambiguously by the NMR experiments on the $4\text{Cu}^{2+}(\text{OCH}_3)$ system which is capable of at least 12 turnovers under the conditions employed. These findings supplement our previous studies⁷ that effective true catalysts for alcoholysis of phosphate triesters can be generated *in situ* from metal triflate salts, an appropriate ligand, and the addition of up to one eq. of methoxide per M^{n+} .

Presented in Scheme 1 is a proposed mechanism for the catalytic methanolysis reaction of **3** promoted by $\text{LCu}^{2+}(\text{OCH}_3)$. Depending on the ligand chosen, for example, bipyridyl **5** or phenanthroline **6**, the predominant form in solution is an unreactive dimer which must dissociate to an active monomer $\text{LCu}^{2+}(\text{OCH}_3)$ which is probably square planar with a weakly associated HOCH_3 which can be replaced by the $\text{X}=\text{P}$ of the substrate to form a transient complex

during the catalytic cycle. When the ligand is the triazacrown **4**, we do not see evidence of any inactive dimeric forms and the kinetics indicate that the great bulk of the material is an already active monomer ($4\text{Cu}^{2+}(\text{OCH}_3)$) which may be four-coordinate in the resting state and at least five-coordinate in the transition state formed after the transient coordination of the substrate. In Scheme 1 the transition state involves both a Lewis acid role for the Cu^{2+} and simultaneous delivery of a coordinated methoxide. Breakdown of the pentacoordinated phosphorus intermediate may or may not involve assistance through coordination of the leaving group to the metal ion: departure of a good leaving group such as *p*-nitrophenoxy probably does not require such assistance.¹⁵



Scheme 1 L = **4**, **5** or **6**.

Conclusion

With due consideration for matching the hard/soft characteristics of the substrate and the metal ion, dramatic rate and selectivity can be achieved in the methanolysis of P=O vs. P=S phosphates. The $\text{Cu}^{2+}(\text{OCH}_3)$ systems herein provide spectacular catalysis of the decomposition of fenitrothion. Thus, a 1 mmol dm^{-3} solution of complex $4\text{Cu}^{2+}(\text{OCH}_3)$, simply formulated *in situ* by sequential addition of 1 mmol dm^{-3} each of $\text{Cu}(\text{OTf})_2$, ligand **4** and methoxide (added either as NaOCH_3 or Bu_4NOCH_3) catalyzes the methanolysis of **3** with a $t_{1/2}$ of ~ 58 s accounting for a 1.7×10^9 -fold acceleration of the reaction at near neutral pH (8.75). In systems where the hydrolysis of neutral *p*-nitrophenyl phosphates was reported to be catalyzed by metal ions the rate enhancements are considerably less, in some cases being only 10-fold and in the best cases no more than 10^4 – 10^6 -fold, and many of these systems are not entirely catalytic due to lack of turnover.^{3,4} There are, to our knowledge, only two studies where the hydrolysis of phosphorothionates is reported to have billion-fold catalysis relative to the background, namely when promoted by cycloplatinated or cyclopalladated aryl ketoximes.^{5d,e}

Experimental

(a) Materials

Methanol (99.8% anhydrous), sodium methoxide (0.5 M solution in methanol), Bu_4NOH (1 M solution in methanol: at the diluted mmol dm^{-3} concentrations used in our experiments, we assume that the water content can be ignored and that the active base is Bu_4NOCH_3), copper perchlorate ($\text{Cu}(\text{ClO}_4)_2$), paraoxon (**2**), bipyridyl (**5**), phenanthroline (**6**) and 1,5,9-triazacyclododecane (**4**) were purchased from Aldrich and used without any further purification. Copper triflate ($\text{Cu}(\text{OTf})_2$) was purchased from Strem Chemicals Inc. HClO_4 (70% aqueous solution) was purchased from BDH. Fenitrothion (**3**) was a gift from Prof. Erwin Buncel of this department. **CAUTION:** paraoxon and fenitrothion are acetylcholinesterase inhibitors, with oral LD_{50} values of 1.8 and 250 mg kg^{-1} , respectively, in rats.¹⁶

(b) Methods

^1H NMR spectra were determined at 400 MHz and referenced to the CD_2H peak of d_4 -methanol appearing at δ 3.31 ppm. ^{31}P NMR spectra were referenced to an external standard of 70% phosphoric

acid in water, and upfield chemical shifts are negative. Mass-spectra of 1–2 mmol dm⁻³ solutions of Cu(OTf)₂ in methanol in the presence of ligands and base were determined using a VG Quattro mass spectrometer equipped with an electrospray source operating at cone voltages between 12 and 60 V. The CH₃OH₂⁺ concentration was determined using an auto-titrator equipped with a Metrohm 6.0255.100 combination (glass/calomel) electrode calibrated with standardized aqueous buffers (pH = 4.00 and 10.00) as described in our recent papers.^{7,17} Values of pH^{M} were calculated by subtracting a correction constant of -2.24 from the experimental meter reading as reported by Bosch *et al.*¹⁸

(c) Kinetics

The kinetics of methanolysis were monitored at 25 °C in anhydrous methanol by observing the rate of appearance of *p*-nitrophenol or 3-methyl-4-nitrophenol between 312 and 335 nm at [2] or [3] = (4–12) × 10⁻⁵ mol dm⁻³ under pseudo-first-order conditions of excess Cu(OTf)₂ ((0.2–5.0) × 10⁻³ mol dm⁻³). All reactions were followed to at least three half lives and found to exhibit good pseudo-first order rate behavior and the first-order rate constants (*k*_{obs}) were evaluated by least squares fitting the Abs. vs. time traces to a standard exponential model. The kinetics were all determined under self-buffered conditions where the pH^{M} was controlled by a constant Cu²⁺/Cu²⁺(⁻OCH₃) ratio and in the cases with ligands 4–6, these were added in amounts equivalent to the [Cu²⁺]_{total}. Under these conditions, the observed pH^{M} values correspond to the apparent pH_a value for ionization of the LCu²⁺(HOCH₃) ⇌ LCu²⁺(⁻OCH₃) + ⁺H₂OCH₃ system. A turnover experiment was conducted using 0.4 mM Cu(OTf)₂ along with equimolar 4 and 0.5 eq. of NBu₄OCH₃. The methanolysis of 2 mM 3 was monitored by UV/vis kinetics and showed 10 turnovers relative to the active catalyst (0.2 mM 4Cu²⁺(⁻OCH₃)) within 100 min.

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- The difference in basicity of the coordinated vs. free ⁻OCH₃ is judged on the basis of the autoprotolysis constant of methanol ($\text{p}K = 16.77$) and the pH^{M} of half neutralization of 4Cu²⁺(HOCH₃) ⇌ 4Cu²⁺(⁻OCH₃) + H₂O⁺CH₃ which is 8.75.
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