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Concave reagents: Part 40[†]—The copper(II) complex of a concave reagent as a selective catalyst for ester methanolysis

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ABSTRACT: We have shown that the Cu^{II} complexes of the concave ligand **1** and its model compound **2** are efficient catalysts of ester methanolysis under conditions close to neutrality. Turnover catalysis without product inhibition was demonstrated by the clean first-order release of a greater than stoichiometric amount of product. Compared with background methanolysis, the metal catalysts give greater rate accelerations for methyl acetate methanolysis than for the *p*-nitrophenyl acetate methanolysis.

Analysis of electronic and steric effects on rates of metal-mediated vs metal-free methoxide addition to the esters has provided compelling evidence that transfer of methoxide from the metal to the carbonyl carbon is accompanied by extensive Lewis acid activation of the carbonyl via a four-membered chelate transition state that includes the metal ion. Copyright © 2004 John Wiley & Sons, Ltd.

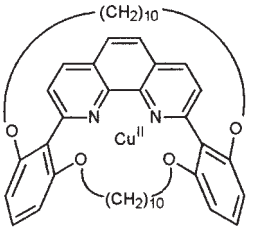
KEYWORDS: concave reagents; 1,10-phenanthroline ligands; ester methanolysis; mechanism of metal catalysis; homogeneous catalysis; selectivity

INTRODUCTION

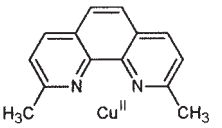
Attempts at mimicking the concave geometry of enzyme active sites that are crucial for the high substrate selectivity of their reactions led to the development of concave reagents whose shape was inspired by a simple model, the light bulb in a lamp shade.[1] Cyclophane structures incorporating a 2,9-diaryl-1,10-phenanthroline unit (e.g. **1**) constitute an important family of concave reagents, in which the role of the light bulb is played by a 1,10-phenanthroline-bound metal ion. Concave 1,10-phenanthrolines proved to be selectivity-inducing ligands in a number of synthetically useful reactions, such as transition metal-catalyzed Diels–Alder reactions,[2] Pd^{II}-catalyzed allylations[3] and Cu^{I}-catalyzed cyclopropanations.[4]

The catalytic activity of Cu^{II} complexes in the hydrolysis of carboxylic and phosphoric acid esters is well documented,[5] and 1,10-phenanthrolines are known to form strong complexes with Cu^{II} salts.[6] To widen the scope of 1,10-phenanthroline-based concave reagents, we undertook an exploratory investigation aimed at ascertaining the influence of a 1,10-phenanthroline-based concave ligand on reactivity and selectivity in the Cu^{II}-catalyzed cleavage of esters.

We report here the results of a kinetic investigation of methanolysis of esters **3**–**7** catalyzed by **1**[Cu] and by the model complex **2**[Cu]. The choice of methanol as reaction medium was dictated by the insolubility of **1** and of its Cu^{II} complex in water. Neocuproine (**2**) was used as a model ligand because the steric effect of the two methyl groups[5d] prevents the formation of unreactive dimeric complexes.[5f]



1[Cu]



2[Cu]

RESULTS

Copper(II) complexes of **1** and **2** were freshly generated in methanol solution from $CuCl_2$. The UV–visible titration experiment in Fig. 1 indicates the existence of a strong ($K > 10^6\ M^{-1}$) complexation between Cu^{II} and the

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[†]Part 40 of the series Concave Reagents. For part 39, see Storm O, Lüning U. Eur. J. Org. Chem. 2003; 3109–3116.

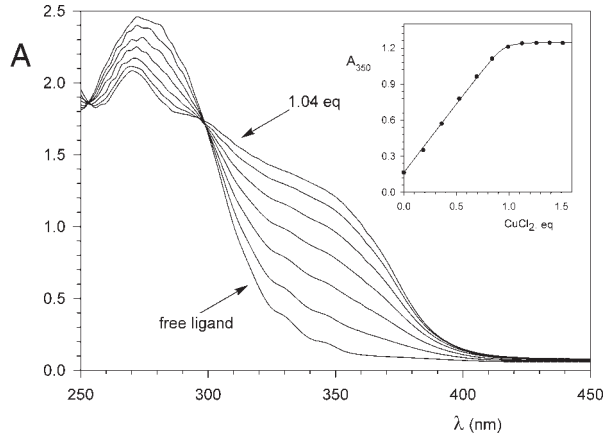


Figure 1. Variations of the UV–visible spectrum of 0.080 mM **1** on addition of increasing amounts of $CuCl_2$ in CH_3OH at 25 °C. A titration plot at 350 nm is shown in the inset

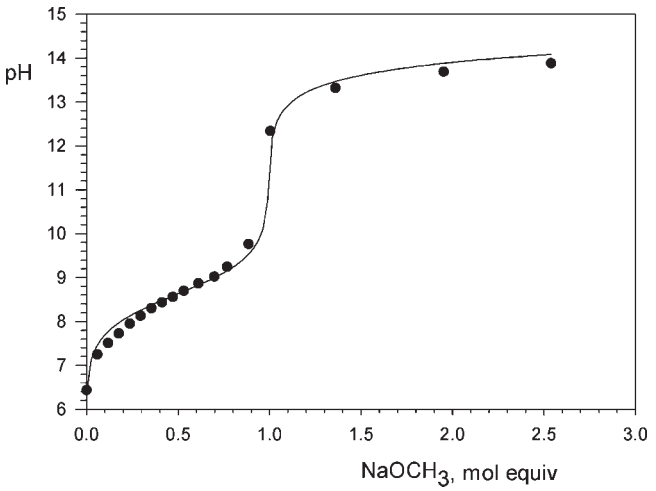
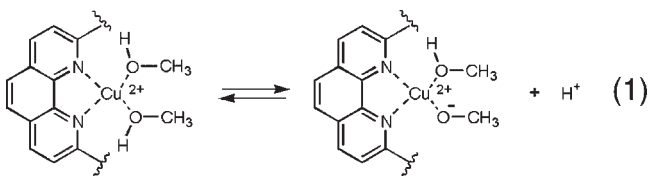
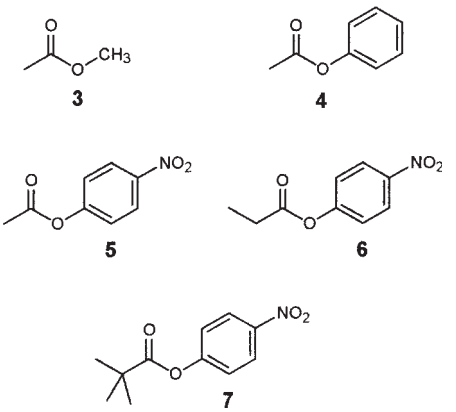


Figure 2. Potentiometric titration of a 1.30 mM 1:1 mixture of **1** and $CuCl_2$ in CH_3OH at 25 °C

1,10-phenanthroline unit in **1**. Potentiometric titration[7] (Fig. 2) reveals that the complex of **1** with $CuCl_2$ behaves as a weak monoprotic acid with $pK_a = 8.6 \pm 0.1$ (the molar autoprotolysis constant of CH_3OH is $K_{ap} = 10^{-16.77}$,[8] which implies that in this solvent the pH value corresponding to neutrality is 8.39 and that the pK_a of CH_3OH is 18.16). A pK_a value of 7.6 ± 0.1 was measured in a similar way for the corresponding complex of neocuproine (**2**). By analogy of the acid–base behaviour of Cu^{II} complexes of 1,10-phenanthrolines and other bidentate nitrogen ligands in aqueous solution,[5b–d] the above data are interpreted as the pK_a values of a metal-bound methanol molecule [Eqn (1)].



The acidity-enhancing effect of the concave reagent **1**[Cu] is an order of magnitude lower than that of the corresponding neocuproine species **2**[Cu]. This is most likely related to steric repulsion between the methoxide ligand and the rim of the lamp shade. [X-ray molecular structures of complexes between $CuCl_2$ and 2,9-disubstituted-1,10-phenanthrolines reveal distorted tetrahedral species, intermediate between tetrahedral and square.[5d,6b] Whereas neutral tetracoordinated Cu^{II} complexes with chelate ligands usually have a planar coordination, distorted tetrahedral coordination is well documented in the presence of bulky substituents.[9] We assume that similar distorted Cu^{II} occurs in complexes of Eqn (1).] Interestingly, the increase in acidity of methanol[8] on coordination to the neocuproine species **2**[Cu] ($\Delta pK_a = -10.6$) is nearly two orders of magnitude higher than the corresponding increase in acidity of water ($\Delta pK_a = -8.7$).[5d]



The technique chosen for the kinetics to be conveniently monitored was ^1H NMR spectroscopy, which required CD_3OD to be used as reaction medium. To carry out the kinetics around neutrality, a suitable buffer was sought. Whereas the commonly used *N*-2-hydroxyethylpiperazine-*N*′-ethanesulfonic acid (HEPES) buffer is sparingly soluble in methanol, other buffers such as 1-methylimidazole–perchlorate salt and 4-methylmorpholine–perchlorate salt[7] proved to be inappropriate, because of interactions between the buffer components and the Cu^{II} of both **1**[Cu] and **2**[Cu] as revealed by the UV–visible spectra. Therefore, catalyst solutions were prepared *in situ* by mixing stock solutions of phenanthroline ligand (**L**), $CuCl_2$ and CD_3ONa in CD_3OD in the stoichiometric ratio 1:1:0.9. A less than stoichiometric amount of CD_3ONa was used to reduce the concentration of free CD_3O^- and, consequently, the rate of background methanolysis. Typical reactant concentrations in the kinetic runs were 10 mM ester and 4 mM metal catalyst. Kinetic data for the more reactive substrates **5**–**7** were obtained from time-course experiments, whereas an initial-rate technique was conveniently used for the slower substrates **3** and **4**. Typical time–concentration profiles are shown in Figs. 3 and 4.

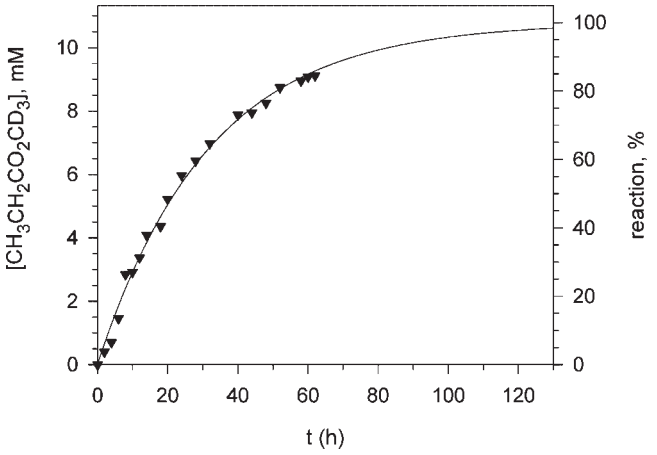


Figure 3. Product concentration–time profile in the basic methanolysis of 10.8 mM *p*-nitrophenyl propanoate (**6**) in the presence of 4.00 mM **1**[Cu]OCD_3 (CD_3OD, 25 °C)

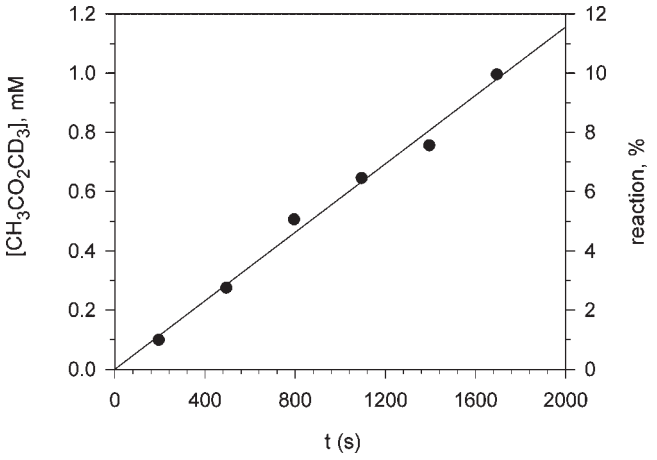


Figure 4. Product concentration–time profile in the basic methanolysis of 10.0 mM phenyl acetate (**4**) in the presence of 4.00 mM **2**[Cu]OCD_3 (CD_3OD, 25 °C)

The pH (pOMe) values of CH_3OH solutions having the same composition as those used in the kinetic runs are 9.5 (7.3) and 8.5 (8.3) for the catalyst solutions based on ligand **1** and **2**, respectively. If the above values are taken as representative of the unknown pD (pOMe) values of the kinetic solutions, the conclusion is reached that phenoxide production is negligibly small even from the more acidic phenol product (*p*-nitrophenol, pK_a in MeOH = 11.30 at 25 °C[10]) liberated in the methanolysis [Eqn (2)] and, consequently, that the concentration of the base catalyst remains constant throughout the entire reaction course. Consistently, only the signals of undissociated phenol products were found in the ^{1}H NMR spectra at the end of reaction and clear first-order behavior was observed in all of the time-course kinetic runs. In these experiments, the release of a greater than stoichiometric amount of product without loss of catalytic activity demonstrates turnover catalysis and lack of product inhibition.

$$RCO_2R' + CD_3OD \xrightarrow{\text{cat}} RCO_2CD_3 + R'OH$$
$$\text{cat} = \mathbf{L}[Cu]OCD_3 \qquad (2)$$

Numerical values of the second-order rate constants (k) for the reaction of the metal-bound CD_3O^- with the ester substrates [Eqn (3)] were calculated as k_{obs}/[cat], where k_{obs} is the directly measured pseudo-first-order rate constant [Eqn (4)] corrected for background methanolysis whenever appropriate (see below).

$$\text{rate} = k[\text{cat}]\,[\text{ester}] \qquad (3)$$
$$k_{obs} = k[\text{cat}] \qquad (4)$$

Rate data are summarized in Table 1. For comparison purposes, Table 1 also lists second-order rate constants for reactions of esters with uncomplexed CD_3O^- ion (Na^+ salt). Combination of the latter data with the pOMe values given above afforded approximate rates of background methanolysis under the conditions of the kinetic experiments. Methanolyses catalyzed by **2**[Cu]OCD_3 were in all cases much faster than background, with ratios of catalyzed to background rates in the range 2600-110, limiting values measured for the reactions of **4** and **5**, respectively. However, lower ratios of catalyzed to background rates were calculated for the reactions catalyzed by **1**[Cu]OCD_3, owing to a combination of a higher basicity of the catalyst solution and a lower catalytic efficiency compared with **2**[Cu]OCD_3. Thus, for ester methanolyses catalysed by **1**[Cu]OCD_3, background rates are likely to be a significant fraction of the

Table 1. Second-order rate constants ($M^{-1}s^{-1}$) for the reactions of esters **3**–**7** with free and Cu^{II}-complexed CD_3O^- anion in CD_3OD at 25 °C

Compound	CD_3O^- k	**1**[Cu]OCD_3 k^1	**2**[Cu]OCD_3 k^2	k/k^1	k/k^2	k^2/k^1
3	0.17	1.3×10^{-4}	4.2×10^{-4}	1300	400	3.2
4	4.4[a]	2.1×10^{-3}	1.6×10^{-2}	2100	270	7.6
5	190	$(2.8–5.5) \times 10^{-3}$[b]	2.9×10^{-2}	$\geq 35\,000$	6600	≥ 5.3
6	90	$(0.4–1.8) \times 10^{-3}$[b]	2.3×10^{-2}	$\geq 50\,000$	3900	≥ 13
7	3.0	$(0–3.5) \times 10^{-5}$[b]	2.1×10^{-3}	$\geq 86\,000$	1400	≥ 60

[a] From Ref. 19.
[b] See text and Table 2.

Table 2. Methanolysis of esters **3**–**7** catalyzed by **1**[Cu]OCD_3 in CD_3OD at 25 °C: correction for background methanolysis (rate constants in s^{-1})

		$(K_a^H/K_a^D) = 6$[a]		$(K_a^H/K_a^D) = 1$[b]	
Compound	k_{obs}	k_{bg}[c]	k^*_{obs}[d]	k_{bg}[c]	k^*_{obs}[d]
3	5.2×10^{-7}	1.2×10^{-8}	5.1×10^{-7}	2.0×10^{-9}	5.2×10^{-7}
4	8.4×10^{-6}	3.2×10^{-7}	8.1×10^{-6}	5.2×10^{-8}	8.3×10^{-6}
5	2.4×10^{-5}	1.3×10^{-5}	1.1×10^{-5}	2.2×10^{-6}	2.2×10^{-5}
6	8.0×10^{-6}	6.5×10^{-6}	1.5×10^{-6}	1.1×10^{-6}	6.9×10^{-6}
7	1.8×10^{-7}	2.2×10^{-7}	0	3.6×10^{-8}	1.4×10^{-7}

[a] pOMe = 7.14.
[b] pOMe = 7.92.
[c] Rate constant of background methanolysis, calculated as $k_{bg} = k \times 10^{-pOMe}$, with k values from Table 1.
[d] $k^*_{obs} = k_{obs} - k_{bg}$.

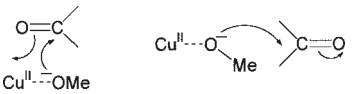
overall rates, and corrections are required. Since the exact pOMe value of the catalyst solution is unavailable, an approximate treatment was adopted, based on the isotope effect of $K_{ap}^H/K_{ap}^D = 5$ for the autoprotolysis of pure methanol,[11] and on the assumption that $1 \leq K_a^H/K_a^D \leq 6$ for the ionization of Cu^{II}-bound methanol. This assumption was based on the analogy of the ionization of weak acids in water, for which the K_a^H/K_a^D values are mostly in the range 3–6, but drop to values very close to 1 for the aquo complexes of thallium(III) and iron(III).[12] Thus, the two sets of rate constants of background methanolysis (k_{bg}) listed in Table 2 represent upper and lower estimates, but it seems likely that values based on the assumption $K_a^H/K_a^D = 1$ are a better approximation.

DISCUSSION

As shown in Table 1, the reactivity orders **3** < **4** < **5** and **5** > **6** > **7** expected on the basis of electronic effects in the alkyl (aryl) portion and steric effects in the acyl portion of the esters, respectively, are experienced not only by free CD_3O^- ion, but also by the Cu^{II}-complexed species. Not surprisingly, the more stable, less basic Cu^{II}-complexed species are in all cases much less reactive than free CD_3O^- ion, which is well in keeping with published data on the hydrolysis catalyzed by hydroxo complexes of Cu^{II} and Zn^{II}.[5b,13]

It has been pointed out by several workers that catalysts which are highly effective at hydrolyzing activated esters are sometimes either much less effective or not effective at all towards unreactive esters.[5b,14] This is clearly not the case with our metal catalysts. Free methoxide ion reacts with *p*-nitrophenyl acetate (**5**) 1100 times more rapidly than with methyl acetate (**3**), but the corresponding reactivity ratio drops to 69 in the reaction with **2**[Cu]OCD_3 and to a value lying somewhere in the range 22–42 in the reaction with **1**[Cu]OCD_3. Thus, compared with background methanolysis, the metal catalysts give greater rate accelerations for methyl acetate than for *p*-nitrophenyl acetate.

The neocuproine catalyst **2**[Cu]OCD_3 is more effective than the concave catalyst **1**[Cu]OCD_3 in the cleavage of all of the esters investigated (Table 1, last column), in spite of the higher basicity and, presumably, higher nucleophilicity of the latter. This finding points to the existence of steric repulsion between the ester undergoing nucleophilic attack and the rim of the concave catalyst. The resulting adverse effect on catalytic rate is already apparent in the cleavage of the sterically unhindered acetate esters **3**–**5**, and becomes very significant on increasing the steric bulk of the acyl portion of *p*-nitrophenyl esters in the order **5** < **6** < **7**.



A **B**

The catalytic mechanism involves transfer of the methoxide nucleophile from the metal ion to the carbonyl carbon either with (**A**) or without (**B**) Lewis acid activation of the carbonyl group.[15] The two mechanisms are kinetically equivalent, but are conceptually different in that they proceed via valence isomeric transition states, whose structures are characterized by the presence (**A**) or absence (**B**) of an interaction between the metal ion and the carbonyl oxygen of the altered substrate in the transition state.

Application of the Hammond postulate[16] to the mechanism involving nucleophile delivery without electrophilic assistance (**B**) leads to the conclusion that the more stable, less reactive Cu^{II}-bound methoxide species should be more selective than the more reactive free methoxide in attacking an activated rather than a deactivated substrate. Our data are markedly at variance with the above conclusion. For example, *p*-nitrophenyl acetate (**5**) reacts with free CD_3O^- ion 43 times more rapidly than with phenyl acetate (**4**), but with the Cu^{II}-bound species the reactivity ratio drops to factors of about 2. Such an extremely low sensitivity to the electronic activation of the *p*-NO_2 group is clearly inconsistent with mechanism **B**, but is well

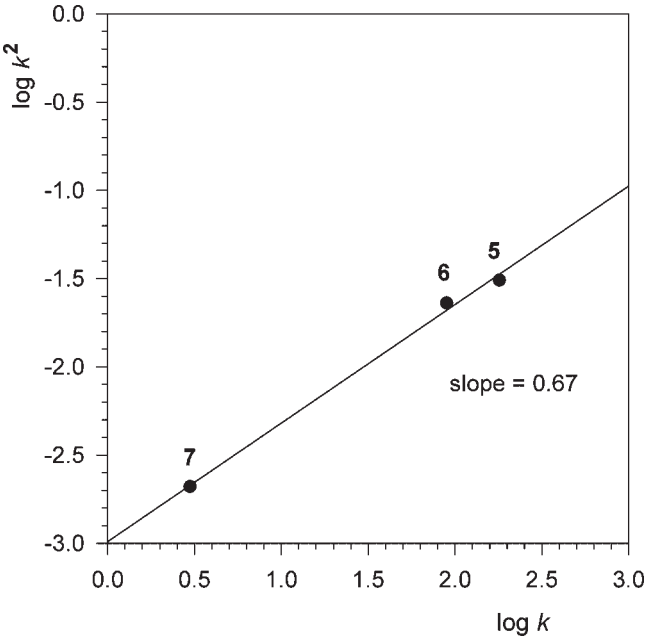


Figure 5. Logarithmic plot of the second-order rate constant (k^2) for the reaction of **2**[Cu]OCD_3 with *p*-nitrophenyl esters **5**–**7** against the second-order rate constant (k) for the corresponding reaction of uncomplexed CD_3O^- ion in CD_3OD, 25 °C (data from Table 1)

accommodated by mechanism **A**. The *p*-NO_2 substituent favours nucleophilic attack at the carbonyl carbon, but decreases the Lewis basicity of the carbonyl oxygen of the altered substrate in the transition state, with nearly complete cancellation of the two opposing effects.

It is remarkable that the sensitivity to steric effects in the acyl portion of *p*-nitrophenyl esters **5**–**7** is much lower in the reactions of the bulkier **2**[Cu]OCD_3 than in those of free CD_3O^-, as shown by the slope of 0.67 of a plot of log k^2 vs log k (Fig. 5). Again, this finding strongly argues against the operation of mechanism **B**, which predicts a higher degree of nucleophile–carbon bond formation in the transition state of the metal complex reaction and, consequently, a higher sensitivity to steric effects. Owing to the chelate structure of the four-membered ring-shaped transition state that includes the metal ion (mechanism **A**), the angle between the nucleophile and the ester carbonyl should be $\sim 90°$, i.e. much smaller than in the transition state of the metal-free reaction, in which a tetrahedral geometry is approached. The resulting reduction in steric repulsion between the metal-bound nucleophile and the substituent attached to the carbonyl carbon provides a reasonable explanation for the lower sensitivity of the reaction of **2**[Cu]OCD_3 to steric effects.

In conclusion, the different sensitivity to electronic and steric effects exhibited by the Cu^{II}-catalyzed reactions compared with the reactions of free methoxide is fully consistent with a catalytic mechanism involving concerted nucleophile transfer and Lewis acid activation.

EXPERIMENTAL

Instruments and general methods

Reactions of CD_3ONa with substrates **4**–**7** were monitored by UV–visible spectrophotometry. In all other cases kinetics were monitored by ^1H NMR spectroscopy on either a 300 or 200 MHz Bruker spectrometer in the presence of cyclohexane as an internal standard.

An initial rate technique was used for reactions of **3**, **4** and **7** with **L**[Cu]OCD_3 and of **3** with CD_3ONa (error ± 20%), whereas time-course kinetic experiments were carried out for reactions of **5** and **6** with **L**[Cu]OCD_3 and **4**–**7** with CD_3ONa (error ± 10%). In the kinetic runs the following ^1H NMR signals were monitored: **3**, reaction with CD_3O^- and with **L**[Cu]OCD_3, $\delta = 3.343$ (singlet, CH_3OD); **4**, reaction with **L**[Cu]OCD_3, $\delta = 2.018$ (singlet, $CH_3CO_2CD_3$); **5**, reaction with **L**[Cu]OCD_3, $\delta = 2.018$ (singlet, $CH_3CO_2CD_3$); **6**, reaction with **L**[Cu]OCD_3, $\delta = 2.330$ (quartet, $CH_3CH_2CO_2CD_3$); **7** reaction with **L**[Cu]OCD_3, $\delta = 1.181$ (singlet, $(CH_3)_3CO_2CD_3$).

Potentiometric titrations were carried out with a Crison GLP22 pH meter under an argon atmosphere. Potentiometric data were elaborated with Hyperquad 2000 version 2.1 (NT).

Materials

Ligand **2** and substrates **3**–**5** and **7** were commercial samples. Substrate **6** was prepared by reaction of *p*-nitrophenol with propanoic acid in dioxane in the presence of DCC.[17] Ligand **1** was synthesized according to literature procedures.[18] CD_3OD and $CuCl_2$ were purchased from Aldrich and used as received. CD_3ONa solutions were prepared from sodium metal and CD_3OD and subsequently titrated using a Normex 0.01 M HCl standard solution.

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