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A Dinuclear Strontium(II) Complex as Substrate-Selective Catalyst of Ester Cleavage

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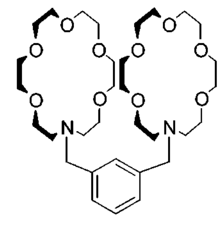
Introduction

In their attempts to mimic the modes of action of hydrolytic enzymes that make use of two metal centers in their active sites, several workers have developed dinuclear metal complexes in which the two metal centers act synergetically in a more or less efficient fashion. Frequently used metals are transition metals (e.g., Zn^{II}, Cu^{II}, Co^{III})[1] and lanthanides (III).[2]

Less common are examples involving block 1s metal ions. The couples Zn^{II}−Sr^{II} and Zn^{II}−Ba^{II} have been used by Canary et al.[3] in the construction of heteronuclear complexes that catalyze the hydrolysis of an activated phosphodiester with moderate synergism between the metal centers. In our ongoing studies of the catalytic properties of block 1s metal ions, we have recently reported that the bis-barium (II) complex of the dinucleating ligand **1** catalyzes with turnover the cleavage of esters and activated amides endowed with a distal carboxylate group.[4] Mechanistic evidence has been collected that whereas one of the metal ions serves as a binding unit for the carboxylate anchoring group, the other binds to ethoxide and activates its addition to the ester carbonyl, as depicted in **I**.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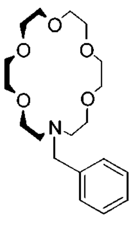
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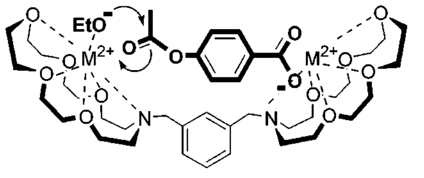
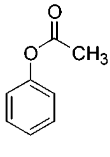


I

In a series of exploratory experiments aimed at defining the range of action of our dinuclear catalysts, we subjected the bicarboxylate ester **6** to basic ethanolysis in the presence of the bis-strontium (II) complex of **1**.[5] We found that a bimetallic catalyst concentration as low as 30 μM increases the rate of cleavage of **6** by a remarkable 5700-fold, but only by 9.5-fold the rate of cleavage of the monocarboxylate ester **4**. To shed light into the origin of the widely different behaviors of the two esters and to find an explanation for the surprisingly high selectivity toward **6**, we have carried out an extensive kinetic investigation of the catalyzed ethanolysis of esters **3**−**6**. The results of such an investigation are reported herein.



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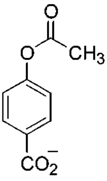

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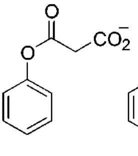

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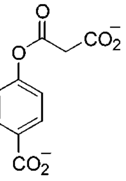

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Results and Discussion

The kinetics of the ethoxide-induced ethanolyses of substrates **3**−**6** were investigated at 25 °C on very dilute substrate solutions (15 μM) in the presence of excess EtONMe$_4$ (1.00 mM). The **1**·[Sr]$_2$ - catalyzed reactions were carried out at two different catalyst concentrations, namely, 30 and 100 μM, respectively. To assess the degree of synergism of the two metal centers in **1**·[Sr]$_2$, a complete set of kinetic experiments was carried out also in the presence of the mononuclear catalyst **2**·[Sr] at concentrations of 60 and 200 μM, respectively. Clean first-order kinetics were observed in all cases. The results are summarized in Table 1.

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[5] Slightly lower rate-enhancements were observed in the presence of the bis-barium (II) complex.

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Table 1. Catalysis by Mononuclear 2·[Sr] and Dinuclear 1·[Sr]$_2$ Metal Complexes on the Basic Ethanolysis of Esters 3−6[a,b]

k_o, s^{-1}	$k_{ditopic}$, s^{-1} ($k_{ditopic}/k_o$) (**1**·[Sr]$_2$, 30 μM)	$k_{monotopic}$, s^{-1} ($k_{monotopic}/k_o$) (**2**·[Sr], 60 μM)	$k_{ditopic}/k_{monotopic}$	$k_{ditopic}$, s^{-1} ($k_{ditopic}/k_o$) (**1**·[Sr]$_2$, 100 μM)	$k_{monotopic}$, s^{-1} ($k_{monotopic}/k_o$) (**2**·[Sr], 200 μM)	$k_{ditopic}/k_{monotopic}$
3; 1.4×10^{-3}	1.7×10^{-3} (1.2)	1.7×10^{-3} (1.2)	1.0	3.2×10^{-3} (2.2)	5.4×10^{-3} (3.7)	0.6
4;[c] 9.1×10^{-4}	8.7×10^{-3} (9.5)	2.9×10^{-3} (3.2)	3.0	0.95[d] (1000)	1.4×10^{-2} (15)	68
5; 1.1×10^{-4}	0.10 (910)	9.5×10^{-2} (850)	1.1	0.17[d] (1600)	0.19[d] (1700)	0.9
6; 1.8×10^{-4}	1.0[d] (5700)	0.11 (600)	9.5	1.8[d] (10000)	0.61[d] (3400)	3.0

[a] Reaction conditions: 15 μM substrate, 1.00 mM Me_4NOEt, EtOH, 25 °C. [b] Error limits of rate constants on the order of ±3−5%, unless otherwise stated. [c] $k_{monotopic} = 8.42 \times 10^{-3}$ s^{-1} in the presence of 120 μM **1**·[Sr]$_2$ and $k_{ditopic} = 0.19$ s^{-1} in the presence of 240 μM **2**·[Sr]; ($k_{ditopic}/k_{monotopic} = 23$). [d] Error limits on the order of ±10%.

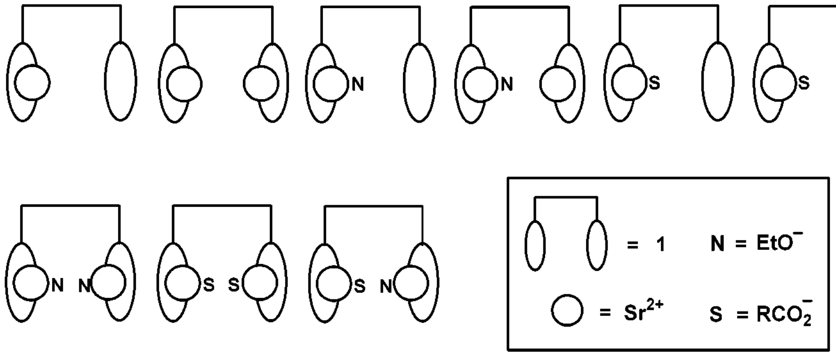

Figure 1. Schematics of the crown-complexed metal species occurring in solutions of ligand **1**, strontium ion, ethoxide nucleophile, and carboxylate substrate.

Solutions containing the metal complexes showed in all cases enhanced rates of ethanolysis relative to solutions containing $EtONMe_4$ alone, as shown by the relative rates reported in Table 1 as parenthesized figures. The magnitude of these rate enhancements is markedly dependent on substrate nature, as well as on catalyst identity and concentration. Very low rate accelerations and no significant differences between dinuclear and mononuclear catalyst, are observed with the parent phenyl acetate (**3**), where no carboxylate anchoring group is present. Comparison of k_o and $k_{monotopic}$ values in the reactions of **3** and **4** shows that binding of the metal cation to the latter substrate transforms a slightly rate-retarding carboxylate into a moderately rate-enhancing carboxylate−metal ion pair. The largest accelerations are seen in the ethanolysis of substrate **6**, when carried out in the presence of dinuclear complex **1**·[Sr]$_2$. The synergism between the two metal centers in **1**·[Sr]$_2$, as measured by the $k_{ditopic}/k_{monotopic}$ ratio, increases significantly when the catalyst concentration decreases.

Contrasting behaviors are observed with the monocarboxylate model substrates **4** and **5**. Both the $k_{ditopic}$ and $k_{ditopic}/k_{monotopic}$ values of the ethanolysis of **4** drop dramatically when the catalyst concentration decreases. High rate enhancements are observed in the ethanolysis of **5**, with very little influence of catalyst concentration, and practically no difference between mononuclear and dinuclear catalyst.

Under the conditions of the catalytic experiments, strontium ion is involved in many binding processes. The equilibrium constant for association of $SrBr_2$ to the aza-crown ether ligand **2** was determined by UV−vis titration, $K = 1.3 \pm 0.4 \times 10^6$ M^{-1}. A somewhat lower value, namely, $7.0 \pm 1.5 \times 10^5$ M^{-1}, was obtained in the presence of 1 mM Me_4NOEt. This implies that even at the lowest catalyst concentrations used in the catalytic experiments most of the metal ion is bound to the crown-ether ligands. A rough estimate of about 10^4 M^{-1} for the equilibrium constant for pairing of the crown ether complexed strontium ion to the ethoxide ion can be inferred from previous works.[6] This again implies that under the conditions of the catalytic experiments association of the metal ion to ethoxide ion is extensive. The affinity for strontium cation of a carboxylate ion is higher than that of ethoxide, as shown by the fact that a K value of 35 was obtained for the exchange reaction of equilibrium of eq 1.

$$[(18C6)SrOEt]^+ + CH_3CO_2^- \overset{K}{\rightleftharpoons} [(18C6)SrO_2CCH_3]^+ + EtO^- \quad (1)$$

It seems therefore likely that several crown-complexed metal species (Figure 1) occurs simultaneously in solutions containing the dinuclear catalyst **1**·[Sr]$_2$. The fraction of crown uncomplexed metal ion is presumably distributed among Sr^{2+}, $(EtOSr)^+$, and $(RCO_2Sr)^+$ species, with the possible involvement of $(EtO)_2Sr$, RCO_2SrOEt, and RCO_2SrO_2CR neutral ion triplets.[7]

Given the plethora of different species involved in such a complicated system of multiple equilibria and the imperfect and limited knowledge of the relevant equilibrium constants, a quantitative interpretation of the

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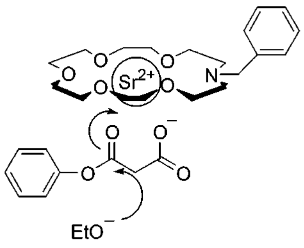
(7) Although care was taken to avoid contamination by atmospheric CO_2, the presence of minute amounts of $EtOCO_2^-$ in the kinetic solutions cannot be excluded. Sequestration of the metal ion by $EtOCO_2^-$ would bring further complications, particularly in the dilute catalyst solutions.

influence of catalyst concentration on ethanolysis rates is beyond the scope of the present work. Nevertheless, the low rate enhancement brought about by the dinuclear complex **1**·[Sr]$_2$ at low concentration in the ethanolysis of **4** is very likely ascribable to a very modest formation of the productive intermediate **1**·[SrOEt][SrO$_2$CR], a supramolecular complex composed of one molecule of ditopic ligand **1**, two Sr^{2+} ions, one ethoxide ion, and one substrate molecule. On the other hand, the absence of any difference between mononuclear and dinuclear catalyst demonstrates that only one metal ion is required in the formation of the productive intermediate in the catalyzed ethanolyses of **5**. Furthermore, the modest influence of catalyst concentration on rates shows that the concentration of the productive intermediate is little affected by dilution, which implies that the malonate-type carboxylate in **5** binds to the metal ion much more strongly than the benzoate-type carboxylate in **4**. We suggest therefore that a chelate interaction of the carboxylate-paired metal ion with the ester carbonyl enhances the binding, and that ethanolysis takes place via nucleophilic addition of a free ethoxide ion to the metal activated ester carbonyl as schematically depicted in **II**.

The malonate moiety of the bicarboxylate substrate **6** should also be involved in a chelate interaction of the same kind. The finding that in the ethanolysis of **6** the catalytic efficiency of the dinuclear complex is higher than that of the mononuclear complex clearly indicates that one of the metal ions is chelated by the malonate moiety, while the other binds to the distal carboxylate. The data are therefore consistent with a productive intermediate in which the dinuclear complex **1**·[Sr]$_2$ acts as a ditopic receptor toward the bicarboxylate substrate. This productive intermediate undergoes rate-limiting nucleophilic addition of a free ethoxide ion, as depicted in **III**. The data in Table 1 show that in the more dilute catalyst solution very nearly 9/10 of the overall reaction takes place via **III**.



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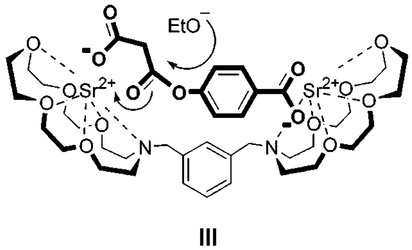

III

In summary, the results of the present work, while emphasizing again the importance of carboxylate anchoring groups in the catalysis, demonstrate that the mode of action of a malonate carboxylate is different from that of a benzoate carboxylate. Whereas the latter acts essentially as a mere anchoring group,[14] the former acts both as anchoring group and activator of the proximal ester function through a chelated metal ion.

The high affinity of the malonate monoester moiety toward the metal ion explains why a high catalytic efficiency is observed even in the presence of very low catalyst concentrations. The finding that in the reaction of the bicarboxylate substrate **6** the synergism between the metal centers in the dinuclear catalyst increases when the catalyst concentration decreases points to a sort of template effect exerted by the bicarboxylate substrate on the formation of the ring-shaped productive intermediate **III** from its separate components.

Experimental Section

Instruments and Materials. ^{1}H and ^{13}C NMR spectra were recorded at 200 and at 50 MHz, respectively. Chemical shifts are reported in ppm from tetramethylsilane, added as internal standard. Ligands **1**[8] and **2**[9] and compounds **4**·H$^+$ [10] and **5**·H$^+$ [11] were prepared according to published procedures.

Malonic Acid Mono(4-carboxyphenyl) Ester (6·(H$^+$)$_2$). Malonyl half-chloride[11] (0.704 g, 5.71 mmol) prepared as described in the literature and *p*-hydroxybenzoic acid (0.82 g, 5.0 mmol) were reacted in 14 mL of benzene at reflux for 7 h. The heterogeneous mixture was filtered, and the solid residue, containing reactant and product in a 1:2 ratio, was purified by medium-pressure chromatography on a RP-8 (particle size 40−63 μm) pre-packed (600 mm length × 16 mm i.d.) glass column (eluent: H$_2$O/MeOH from 70:30 (v/v) to 60:40 (v/v)) to give **6**·(H$^+$)$_2$ (0.092 g, 0.41 mmol, 8.2% yield) as a white solid (mp > 250 °C). ^{1}H NMR (CD$_3$COCD$_3$): 8.12 (2H, d, J = 9 Hz), 7.31 (2H, d, J = 9 Hz), 3.74 (2H, s). ^{13}C NMR (CD$_3$COCD$_3$): 167.83, 166.88, 165.89, 155.28, 132.08, 129.27, 122.66, 41.83. Anal. Calcd for C$_{10}$H$_8$O$_6$: C, 53.58; H, 3.60. Found: C, 53.44; H, 3.75.

Substrates **4**−**6** were generated in situ by neutralization of the parent acids with Me$_4$NOEt.

Other materials, apparatuses, and techniques were as reported previously.[12]

Equilibrium and Rate Measurements. The value of the equilibrium constant of the counterion-exchange process given in eq 1 was obtained by measuring the effect of added tetramethylammonium acetate on the rate of ethanolysis at 25 °C of 0.054 mM *N*-methyl-2,2,2-trifluoroacetanilide[12] in the presence of a 5.0 mM 1:1:1 mixture of Me$_4$NOEt, SrBr$_2$, and 18-crown-6, according to a previously reported[4] procedure. Spectrophotometric determination of the association constant of strontium(II) ion with ligand **2** was carried out as previously described.[13] Kinetic measurements were carried out as previously reported[12] in the thermostated cell compartment of a photodiode array spectrophotometer.

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(14) Binding of the metal ion to carboxylate transforms a moderately electron-releasing substituent into an electron-withdrawing one, with the net result that the reactivity of the ester function toward nucleophilic addition is increased to some extent (see ref 4).