Dinuclear Barium(II) Complexes Based on a Calix[4]arene Scaffold as Catalysts of Acyl Transfer

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Abstract: Two novel regioisomeric calix[4]arene derivatives (**2** and **3**), decorated with two aza[18]crown-6 units at vicinal (1,2) or diagonal (1,3) positions of the upper rim, were synthesized. The catalytic activities of their dinuclear Ba^{2+} complexes were investigated in the ethanolysis of esters **8**–**11**, endowed with a carboxylate anchoring group. Major results are as follows: 1) the two metal ions in the dinuclear catalysts work together in a cooperative fashion; 2) the vicinal calix[4]arene catalyst **2** is far superior to its diagonal regioisomer **3** in the reactions of all of the investigated esters; and 3) the distance between the carboxylate and ester carbonyl, which increases regularly from **8** to **11**, influences reactivity of catalytic ester cleavage in a way that is decidedly suggestive of the importance of a good match between ester size and metal-to-metal distance. However, the superiority of the vicinal catalyst **2** relative to **3** cannot be explained on the basis of the putative match of ester size to intermetal distance, thus providing an indication that additional, still poorly understood effects may contribute significantly to catalytic efficiency.

Keywords: calixarenes · crown compounds · effective molarity · metallocatalysts · supramolecular chemistry

Introduction

Dinuclear metal complexes endowed with biomimetic hydrolytic activity have been extensively investigated in recent years.[1] In many instances such dinuclear metallocatalysts have been obtained from homoditopic receptors composed of two identical metal-complexing units connected by a suitable molecular spacer.

Previous reports[2] show that the basic ethanolysis of esters equipped with a distal carboxylate is effectively catalyzed with turnover by a number of dinuclear Ba^{2+} and Sr^{2+} complexes of bis-crown homoditopic ligands, by means of a mechanism in which one of the metal ions serves as an anchoring group for the carboxylate, and the other delivers an activated ethoxide to the substrate carbonyl (Scheme 1). Since the target substrate and catalyst must form a well-matched pair in terms of size and geometrical features, catalytic efficiency was found to critically depend on the choice of the spacer unit.[2c]

Dinuclear Zn^{II} and Cu^{II} complexes of ditopic receptors, composed of two nitrogen ligand units at the diagonal positions of a calix[4]arene scaffold fixed in the *cone* conformation, proved to behave as quite efficient phosphodiesterases models, as a result of a good compromise between preorganization and flexibility.[1b] To widen the scope of calixarenes in supramolecular catalysis,[3] it seemed of interest to investigate the catalytic activity in the cleavage of carboxylate esters of dinuclear Ba^{2+} complexes of bis-crown ligands built on a calix[4]arene platform.

In this paper we report on the synthesis of the regioisomeric ligands **2** and **3**, in which two azacrown units have been implanted on the calix[4]arene upper rim in vicinal and diagonal positions, respectively. We also report on an extensive investigation of the catalytic activity of their dinuclear Ba^{2+} complexes in the basic ethanolysis of esters **8**–**11**, in which the distance between the carboxylate anchoring

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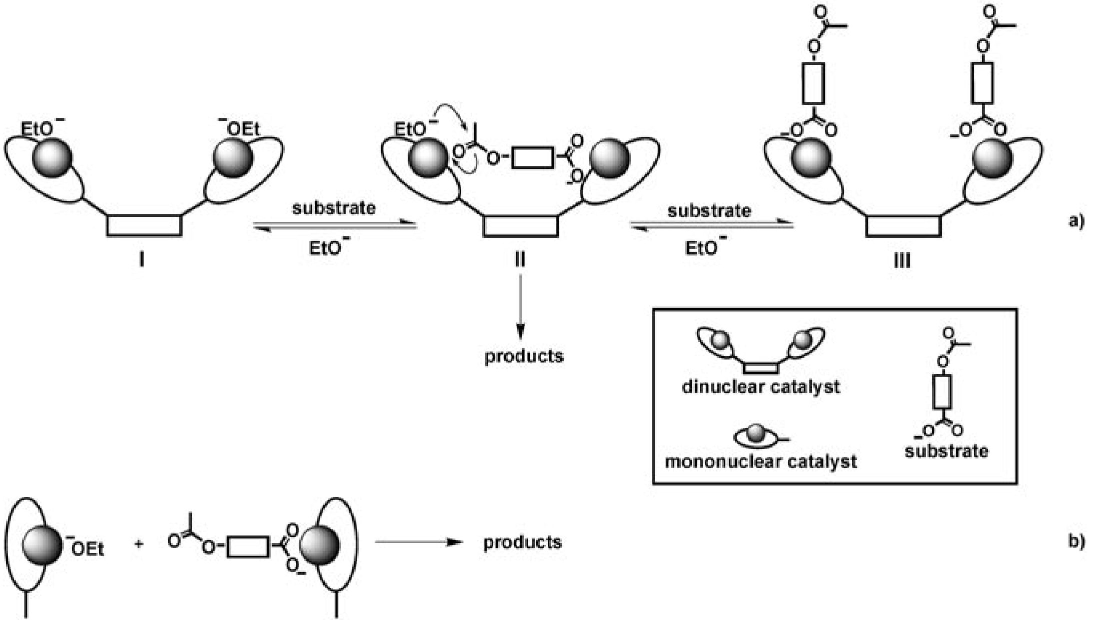
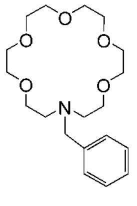


Scheme 1. a) Mechanism of ester ethanolysis catalyzed by dinuclear barium complexes, showing productive (**II**) and non-productive (**I** and **III**) species and b) the corresponding intermolecular model reaction based on monomolecular complexes.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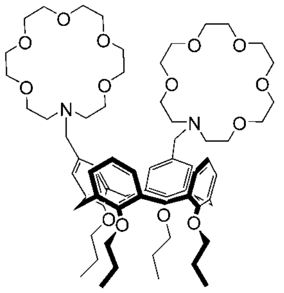
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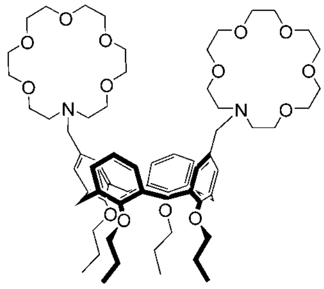
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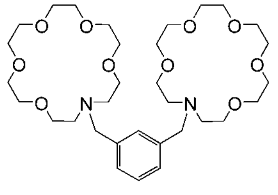
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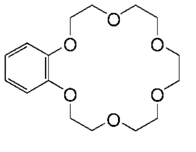
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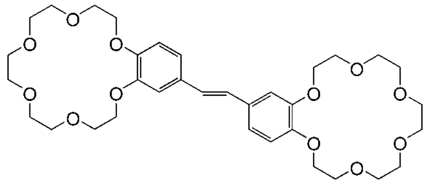
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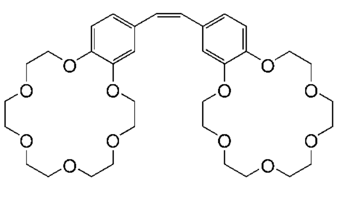
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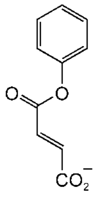
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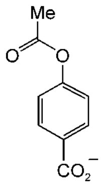
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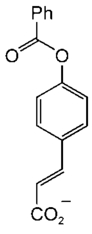
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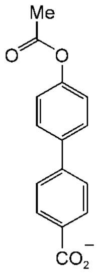
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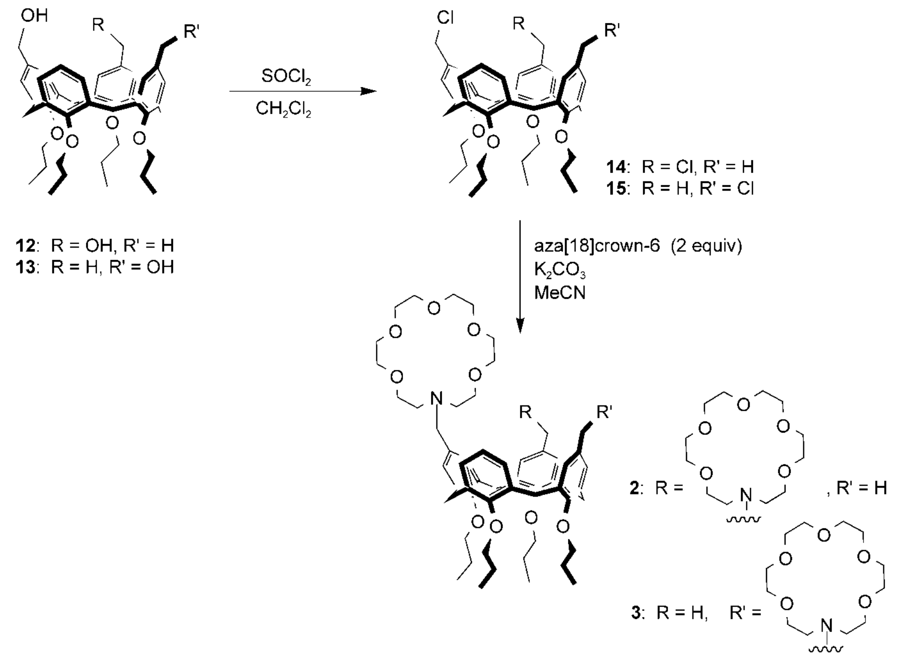
group and the reaction site increases in the given order. The goal of such an investigation has been an assessment of the relative catalytic efficiencies of the isomeric catalysts **2**·(Ba)$_2$ and **3**·(Ba)$_2$, as well as a comparison with the dinuclear Ba^{2+} complexes of the closely related ligand **4**,[2a] and of the isomeric ligands **6** and **7** based on the benzo[18]crown-6 complexation unit.[2c] The monometallic complexes **1**·(Ba) and **5**·(Ba) have also been investigated as reference catalysts to assess the synergism of the two metal ions in the corresponding bimetallic complexes.

Results

Synthesis: The synthesis of the novel homoditopic ligands **2** and **3** is outlined in Scheme 2. Dialcohols **12**[4] and **13**,[5] and dichloro derivative **15**[5] were prepared as described in the literature. Dialcohol **12** was treated with SOCl$_2$ in CH$_2$Cl$_2$ to give dichloride **14**. Reaction of **14** and **15** with two equivalents of 1-aza[18]crown-6 in the presence of K$_2$CO$_3$ in MeCN gave ligands **2** and **3**, respectively, in good yields.



Scheme 2. Synthesis of ligands **2** and **3**.

Kinetics: All catalytic experiments were carried out under a standard set of experimental conditions. Metal catalysts were prepared in situ by mixing calculated amounts of the components. Solutions for rate measurements contained 0.20 mM monotopic or 0.10 mM ditopic ligand, plus 0.20 mM $Ba(SCN)_2$ and 1.00 mM $EtONMe_4$. As shown in previous work,[2a,c] under the given conditions complexation of Ba^{2+} to the crown ether moieties was virtually complete, as was pairing of EtO^- to the metal ion; this implies that the metal complex was fully saturated with EtO^-, (structure **I** in Scheme 1), or very nearly so. Addition of a substrate endowed with a carboxylate anchoring group converts **I** into the productive (Michaelis) complex **II**, with an equilibrium constant of 65.[2a] Since in all of the kinetic experiments the substrate concentration was 0.025 mM, the conditions of the kinetic runs were close to saturation, with no less than 90% of the substrate bound to the catalyst, and with a negligible formation of the 2:1 substrate–catalyst unproductive complex **III**. Furthermore, the low substrate/catalyst ratio ensured that product inhibition was unimportant. Consistently the spectrophotometrically monitored kinetics showed good adherence to first-order time dependence in all cases. Typical kinetic runs are plotted in Figure 1.

Catalytic rate constants (k_{obs}) for the ethanolysis of esters **8**–**11** obtained in the presence of catalysts based on aza[18]-crown-6 are listed in the first column of Table 1. The other quantities listed in Table 1 are different measures of catalytic efficiency. The $k_{\text{obs}}/k_{\text{o}}$ ratios are the rate accelerations over background brought about by the various catalysts, whereas the degree of synergism between metal centers in the dinuclear catalysts is measured by the $k^{\text{di}}_{\text{obs}}/k^{\text{mono}}_{\text{obs}}$ ratios. Since the dinuclear catalysts transform an otherwise intermolecular reaction between ester and ethoxide into an intramolecular (intracomplex) reaction, the effective molarity (EM) concept,[6] defined by the ratio $k_{\text{intra}}/k_{\text{inter}}$, strictly applies to the catalytic process at hand. Calculation of the EMs listed in the last column of Table 1 was based on the assumption that $k_{\text{intra}} \approx k_{\text{obs}}$ (see above) and on a set of k_{inter} values measured under conditions such as to approach as close as possible to the intermolecular model reaction between the ternary complexes depicted in Scheme 1b.[7] Unlike the other quantities, the EM is independent of reactant concentrations and its numerical value is solely determined by the choice of molarity as concentration units.

Table 2 summarizes the corresponding data obtained in the presence of the benzo[18]-crown-6 catalysts. Rate data for esters **8**–**10** were available from a previous investigation,[2c] whereas those for ester **11** were measured in this work under the same conditions for the sake of completeness.

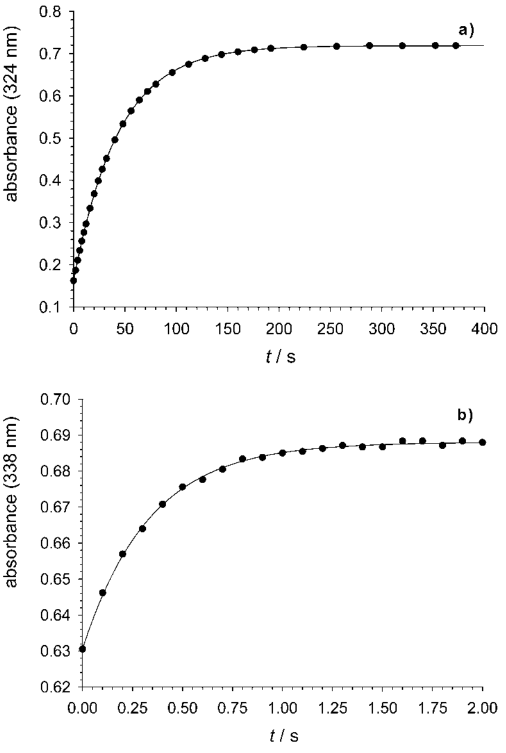


Figure 1. UV-visible-monitored product formation for the basic ethanolysis of a) **11** in the presence of **5**·(Ba), and b) **10** in the presence of **2**·(Ba)$_2$, showing close adherence to first-order time dependence.

Table 1. Basic ethanolysis of esters **8**–**11** catalyzed by the Ba^{2+} complexes of ligands **1**–**4**.[a]

Substrate	Entry	Catalyst	k_{obs} [s^{-1}]	$k_{\mathrm{obs}}/k_{\mathrm{o}}$[b]	$k^{\mathrm{di}}_{\mathrm{obs}}/k^{\mathrm{mono}}_{\mathrm{obs}}$	EM[c] [M]
8	1	**1**·(Ba)	0.040	300		
	2	**2**·(Ba)$_2$	4.7	35100	120	0.036
	3	**3**·(Ba)$_2$	0.18	1340	4.5	0.0014
	4	**4**·(Ba)$_2$	0.37	2760	9.2	0.0028
9	5	**1**·(Ba)	0.018	20		
	6	**2**·(Ba)$_2$	20	22000	1100	0.51
	7	**3**·(Ba)$_2$	0.38	420	21	0.010
	8	**4**·(Ba)$_2$	1.1	1220	61	0.028
10	9	**1**·(Ba)	0.0078	52		
	10	**2**·(Ba)$_2$	3.0	20000	385	0.21
	11	**3**·(Ba)$_2$	0.086	570	11	0.0061
	12	**4**·(Ba)$_2$	0.64	4240	82	0.046
11	13	**1**·(Ba)	0.016	12		
	14	**2**·(Ba)$_2$	0.22	170	14	0.0026
	15	**3**·(Ba)$_2$	0.032	24	2	0.0004
	16	**4**·(Ba)$_2$	0.40	300	25	0.0047

[a] Runs carried out in EtOH at 25 °C on 0.025 mM substrate in the presence of 1.00 mM EtONMe$_4$, 0.20 mM monotopic or 0.10 mM ditopic ligand, and 0.20 mM Ba(SCN)$_2$. [b] k_{o} is the pseudo-first-order rate constant observed in the presence of 1.00 mM EtONMe$_4$ alone. Ester **8**, $k_{\mathrm{o}} = 1.34 \times 10^{-4}$ s^{-1}; ester **9**, $k_{\mathrm{o}} = 9.1 \times 10^{-4}$ s^{-1}; ester **10**, $k_{\mathrm{o}} = 1.51 \times 10^{-4}$ s^{-1}; ester **11**, $k_{\mathrm{o}} = 1.32 \times 10^{-3}$ s^{-1}. [c] Calculated as $k_{\mathrm{obs}}/k_{\mathrm{inter}}$. The k_{inter} values [M^{-1}s^{-1}] listed below for the various substrates were measured under the set of conditions given in reference [7]: **8**, 130; **9**, 39; **10**, 14; **11**, 85 M^{-1}s^{-1}.

Table 2. Basic ethanolysis of esters **8**–**11** catalyzed by the Ba^{2+} complexes of ligands **5**–**7**.[a]

Substrate	Entry	Catalyst	k_{obs} [s^{-1}]	$k_{\mathrm{obs}}/k_{\mathrm{o}}$[b]	$k^{\mathrm{di}}_{\mathrm{obs}}/k^{\mathrm{mono}}_{\mathrm{obs}}$	EM[c] [M]
8[d]	1	**5**·(Ba)	0.030	206		
	2	**6**·(Ba)$_2$	0.25	1710	7.6	0.0018
	3	**7**·(Ba)$_2$	0.20	1370	6.0	0.0014
9[d]	4	**5**·(Ba)	0.033	40		
	5	**6**·(Ba)$_2$	0.38	460	12	0.0048
	6	**7**·(Ba)$_2$	3.5	4260	107	0.044
10[d]	7	**5**·(Ba)	0.0098	35		
	8	**6**·(Ba)$_2$	0.24	860	25	0.0045
	9	**7**·(Ba)$_2$	0.69	2450	70	0.013
11	10	**5**·(Ba)	0.023	19		
	11	**6**·(Ba)$_2$	33	27500	1450	1.1
	12	**7**·(Ba)$_2$	3.4	2835	150	0.11

[a] Runs carried out in EtOH/MeCN (85:15, v/v) at 25 °C on 0.025 mM substrate in the presence of 1.00 mM EtONMe$_4$, 0.20 mM monotopic or 0.10 mM ditopic ligand, and 0.20 mM Ba(SCN)$_2$. [b] k_{o} is the pseudo-first-order rate constant observed in the presence of 1.00 mM EtONMe$_4$ alone. Ester **8**, $k_{\mathrm{o}} = 1.46 \times 10^{-4}$ s^{-1}; ester **9**, $k_{\mathrm{o}} = 8.2 \times 10^{-4}$ s^{-1}; ester **10**, $k_{\mathrm{o}} = 2.80 \times 10^{-4}$ s^{-1}; ester **11**, $k_{\mathrm{o}} = 1.20 \times 10^{-3}$ s^{-1}. [c] Calculated as $k_{\mathrm{obs}}/k_{\mathrm{inter}}$. The k_{inter} values [M^{-1}s^{-1}] listed below for the various substrates were measured under the set of conditions given in reference [7]: **8**, 140; **9**, 79; **10**, 53; **11**, 30 M^{-1}s^{-1}. [d] Data from reference [2c].

Discussion

In line with previous observations,[2] solutions containing the metal complexes showed enhanced rates of ethanolysis in all cases relative to solutions containing EtONMe$_4$ alone. Rate-enhancing factors ranged from one to more than four orders of magnitude, with a marked dependence on the individual substrate–catalyst combinations.

Mononuclear complexes caused rate accelerations on the order of 10- to 50-fold (entries 5, 9, and 13 in Table 1; entries 4, 7, and 10 in Table 2), with the exception of ester **8**, whose ethanolysis rate increased by 300-fold in the presence of **1**·(Ba) and by 206-fold in the presence of **5**·(Ba) (entry 1 in Tables 1 and 2, respectively). As previously noted,[2a] binding of the metal ion to carboxylate transforms a moderately electron-releasing (rate-retarding) substituent into an electron-withdrawing (rate-enhancing) one. In accordance with this idea, the much higher sensitivity of the reaction of **8** to the electron-withdrawing influence of the Ba^{2+}-paired carboxylate can be attributed to the fact that in **8** the carboxylate–carbonyl distance is the shortest in the series of the investigated esters.

The superiority of dinuclear catalysts compared with their mononuclear counterparts shows that in all cases the two metal ions work together in a cooperative fashion, in accordance with the catalytic mechanism depicted in Scheme 1. The $k^{\mathrm{di}}_{\mathrm{obs}}/k^{\mathrm{mono}}_{\mathrm{obs}}$ ratios range from the very low value of 2, observed in the cleavage of **11** by **3**·(Ba)$_2$ (Table 1, entry 15), to the remarkably high values of 1100 (Table 1, entry 6) and 1450 (Table 2, entry 11) of the reactions of **9** and **11**, catalyzed by **2**·(Ba)$_2$ and **6**·(Ba)$_2$, respectively.

A graphical illustration of the requirements of catalysis in terms of substrate size and catalyst structure, as well as a panoramic view of the varying catalytic efficiency observed for the different substrate–catalyst pairs, is given by plots of EM versus the carboxylate–carbonyl distance in the ester substrate, taken between the carbon atoms of the two functions (Figure 2). The calculation is straightforward for esters **8**, **9**, and **11**, whereas for ester **10** the quoted distance is an average value.

The first observation is that the dinuclear catalyst **2**·(Ba)$_2$, in which the crown ether moieties are linked to vicinal positions of the calix[4]arene scaffold, is not only superior to its diagonal regioisomer **3**·(Ba)$_2$ in all cases, but is also the best catalyst in the reactions of esters **8**–**10**. The EM profile shows that the catalytic efficiency of **2**·(Ba)$_2$ reaches its maximum value in the reaction of ester **9**, and drops dramatically to a very low value in the reaction of the "longest" ester

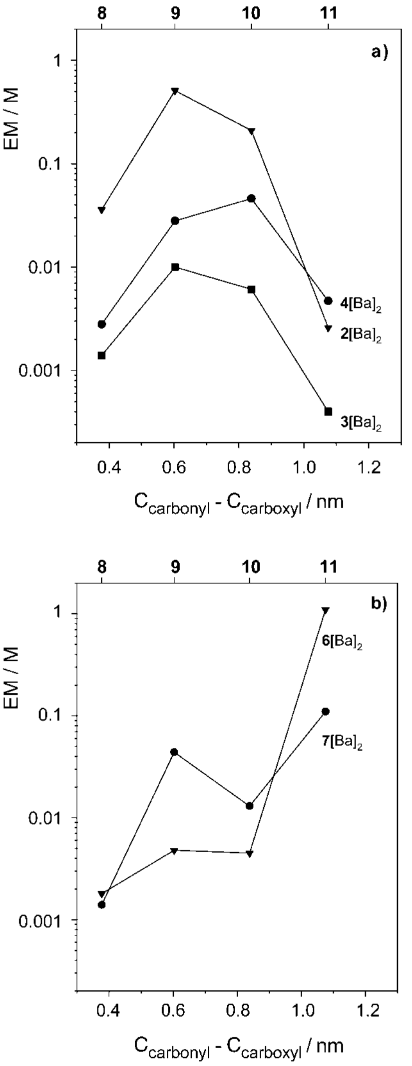


Figure 2. EM profiles for reaction of substrates **8**–**11** in the presence of dinuclear catalysts based on a) aza-crown and b) benzo-crown ligands.

11; this indicates that catalyst **2**$\cdot$(Ba)$_2$ cannot expand its intermetal distance to fit the long carboxylate–carbonyl distance in **11**. On the other hand, there appears to be a good fit to the *trans*-stilbene catalyst **6**$\cdot$(Ba)$_2$, with short distances between the metal ions, and the negative charges of the dianionic tetrahedral intermediate involved in the reaction of **11** (Figure 3). This nicely explains why **6**$\cdot$(Ba)$_2$ is very effective in the cleavage of **11**, but much less so in the cleavage of the shorter esters. Thus, a good match of the ester's carboxylate–carbonyl distance to the catalyst intermetal distance plays a key role in determining catalytic efficiency.

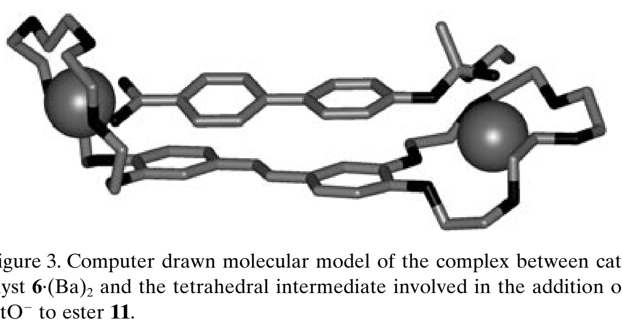


Figure 3. Computer drawn molecular model of the complex between catalyst **6**$\cdot$(Ba)$_2$ and the tetrahedral intermediate involved in the addition of EtO$^-$ to ester **11**.

The EM profiles (Figure 2) of the calixarene-based catalysts are structured much in the same way and display a similar dependence on the carboxylate–carbonyl distance. Ester **9** is the best substrate for both catalysts, yet the reaction catalyzed by the vicinal regioisomer **2**$\cdot$(Ba)$_2$ is 53 times faster than the reaction catalyzed by the diagonal regioisomer **3**$\cdot$(Ba)$_2$. A careful inspection of molecular models of the complexes between the catalysts and the tetrahedral intermediate involved in the methanolysis of **9** fails to reveal the reasons for the catalytic superiority of the vicinal regioisomer. Clearly, in addition to the purely geometrical match of ester size to intermetal distance, there are other factors at work, but their origin defies a simple explanation. They are possibly related to conformational effects in the catalysts and/or steric repulsions in the host–guest complexes between catalyst and transition state.

The EM values in Tables 1 and 2 are much lower than the remarkably high values, amounting to several powers of ten, usually reported for intramolecular processes involving small- and common-sized cyclic species.[6] The number of skeletal single bonds in the bifunctional chain molecules undergoing cyclization has an important influence on the efficiency of intramolecular processes, because a part of the torsional entropy is lost upon cyclization. A general treatment set forth by one of us many years ago relates the entropy loss upon cyclization, and hence the entropic component of the EM, to the number of rotatable bonds in the open chain reactant.[6b] Such a treatment was recently extended to the reactions of supramolecular ternary complexes[8] and is here applied to the catalytic processes described in this work.

If one regards the carboxylate–metal–(crown ether) and ethoxide–metal–(crown ether) moieties as pseudo-single bonds, there are nine rotatable bonds in the productive complex involved in the ethanolysis of **9** catalyzed by **2**$\cdot$(Ba)$_2$, ten rotatable bonds in the reaction of **10** catalyzed by **2**$\cdot$(Ba)$_2$, and eight rotatable bonds in the reaction of **11** catalyzed by **6**$\cdot$(Ba)$_2$. Based on the admittedly rough assumption that the torsional entropy associated to such pseudo-bonds is comparable to that of a covalent bond, the above numbers of rotatable bonds translate into an EM value of 0.67 M for the reaction of the **9**–**2**$\cdot$(Ba)$_2$ pair, 0.47 M for the **10**–**2**$\cdot$(Ba)$_2$ pair, and 1.0 M for the **11**–**6**$\cdot$(Ba)$_2$ pair. These values compare remarkably well with the experimental values of 0.51 M, 0.21 M (Table 1), and 1.1 M (Table 2), respectively.

Although not too much emphasis can be put on the exact figures in view of the many approximations involved, the close adherence of experimental to predicted values strongly suggests that a virtually ideal match between bimetallic catalyst and transition state is achieved in the given catalytic processes, whose efficiency is solely determined by the relatively large entropy losses due to the involvement of several rotatable bonds. In all of the other cases the lower-than-predicted EM values may be taken as a strong indication of the existence of a more or less pronounced mismatch between catalyst and transition state.

Conclusion

Although the catalysts reported in this work are endowed with spacers between the ligand units that have degrees of conformational freedom, the data obtained bear on the important question of the influence of the intermetal distance on the efficiency of catalytic processes in which the two metals act in a cooperative fashion.[1c,d] Reactivity data obtained for the various catalyst–substrate combinations indeed show that a close fit of ester size to intermetal distance is an important prerequisite for catalysis, but other factors, whose origin is still poorly understood, may come into play. This is most likely the case with the calixarene-based catalysts **2** and **3**. The superiority of **2** relative to **3** with all of the esters **8**–**11** can hardly be ascribed to more suitable intermolecular distances in the former.

The number of rotatable bonds in the productive complexes of catalysts and reactants sets upper limits to catalytic efficiency, to be reached under conditions in which strain effects are unimportant. Interestingly, such upper limits imposed by entropic restrictions were practically reached in a number of cases, namely, the reactions of the pairs **9**–**2**·(Ba)$_2$, **10**–**2**·(Ba)$_2$, and **11**–**6**·(Ba)$_2$. The lower EMs recorded for the remaining substrate–catalyst combinations would probably indicate the existence of more or less pronounced distortions from ideal geometry in the productive complexes.

Experimental Section

Instruments and techniques: Kinetics measurements ($k_{obs} < 5\times10^{-2}$ s^{-1}) were carried out in the thermostatted cell compartment of a diode array spectrophotometer (Hewlett Packard HP8453). The fast mixing accessory HI-TECH SCIENTIFIC SFA-12 was used for kinetic runs with $5\times10^{-2} \leq k \leq 0.7$ s^{-1}, while kinetic runs with $k > 0.7$ s^{-1} were carried out on a stopped-flow apparatus. Error limits of kinetic data were in the order of ±5–10%. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Acids **8**·H$^+$–**11**·H$^+$ were converted in situ into their Me_4N^+ salts by neutralization with $EtO^{-}\cdot{}^{+}NMe_4$. Mass spectra by electrospray ionization (ESI) and chemical ionization (CI) methods were recoded on a Micromass ZMD and on a Finnigan Mat SSQ710 spectrometer, respectively.

Materials: Acid **11**·H$^+$ was prepared as described in the literature.[9] Ligands **4**,[2a] **6**,[2c] **7**[2c] and **1**[2a] and acids **8**·H$^+$,[2c] **9**·H$^+$,[2a] **10**·H$^+$,[2c] were available from previous investigations. Benzo[18]crown-6 (**5**) was a commercial sample and was used as such without further purification. Other materials, apparatuses, and techniques were as reported previously.[2a]

Bis(hydroxymethyl)-[4] and bis(chloromethyl)calix[4]arene[5] (**12** and **15**, respectively) were synthesized according to the literature.

5,11-Bis(chloromethyl)-25,26,27,28-tetrapropoxycalix[4]arene (14): Thionyl chloride (2.2 mL, 3.0 mmol) was added to a solution of calix[4]arene **12**[4] (100 mg, 0.153 mmol) in CH_2Cl_2 (8 mL) and the solution was stirred for 3 h. The solvent was removed under reduced pressure to give the dichloromethyl derivative **14** (105 mg, 0.152 mmol, quantitative yield), which was pure enough for further modification. An analytical sample of **14** was obtained free from hydrochloric acid by extraction from saturated $NaHCO_3$ aqueous solution with CH_2Cl_2, subsequently followed by drying over anhydrous Na_2SO_4, filtering and concentration in vacuo. ^{1}H NMR (CDCl$_3$, TMS): δ = 6.65–6.58 (m, 10H; Ar*H*), 4.48 (d, J = 13.3 Hz, 1H; ArC*H*$_2$Ar ax), 4.47 (d, J = 13.4 Hz, 2H; ArC*H*$_2$Ar ax), 4.46 (d, J = 13.4 Hz, 1H; ArC*H*$_2$Ar ax), 4.33 (s, 4H; ArC*H*$_2$Cl), 3.89 (t, J = 7.1 Hz, 4H; ArOC*H*$_2$), 3.87 (t, J = 7.4 Hz, 4H; ArOC*H*$_2$), 3.18 (d, J = 13.4 Hz, 4H; ArC*H*$_2$Ar eq), 2.00–1.88 (m, 8H; ArOCH$_2$C*H*$_2$), 1.03 (t, J = 7.6 Hz, 6H; CH$_2$C*H*$_3$), 1.02 ppm (t, J = 7.5 Hz, 6H; CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, TMS): δ = 156.6, 156.3, 135.6, 135.2, 135.1, 134.7, 130.6, 128.6, 128.4, 128.0, 121.6, 76.6, 46.7, 30.9, 23.1, 10.2 ppm; MS (CI): m/z (%): 688.3 (100) $[M]^+$, 690.3 (65) $[M+2]^+$; elemental analysis calcd (%) for $C_{42}H_{52}O_4Cl_2$ (691.78): C 72.92, H 7.58, Cl 10.25; found: C 72.88, H 7.53, Cl 10.30.

5,11-Bis[*N*-(monoaza[18]crown-6)]methyl-25,26,27,28-tetrapropoxycalix[4]arene (2): Potassium carbonate (53 mg, 0.383 mmol) and 1-aza[18]-crown-6 (100 mg, 0.380 mmol) were added to a solution of the dichloro derivative **14** (80 mg, 0.116 mmol) in dry MeCN (5 mL). The reaction mixture was heated at 60 °C for three days under nitrogen atmosphere. The solvent was evaporated under reduced pressure and the crude product dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with 0.1 M LiOH and the aqueous layer was extracted with additional CH_2Cl_2 (50 mL). The combined organic phases were evaporated under vacuum, and the residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH/NEt$_3$ 8.4:1.6:0.1). The fractions containing the product were collected, evaporated and the product dissolved again in CH_2Cl_2 and washed with 0.1 M LiOH. After evaporation of the organic solvent under vacuum the ditopic ligand **2** was obtained as a colorless oil (75 mg, 0.066 mmol, 57% yield). ^{1}H NMR (CDCl$_3$, TMS): δ = 6.63–6.50 (m, 10H; Ar*H*), 4.44 (d, J = 13.1 Hz, 1H; ArC*H*$_2$Ar ax), 4.41 (d, J = 13.1 Hz, 2H; ArC*H*$_2$Ar ax), 4.38 (d, J = 13.1 Hz, 1H; ArC*H*$_2$Ar ax), 3.83 (t, J = 7.3 Hz, 4H; ArOC*H*$_2$), 3.81 (t, J = 7.3 Hz, 4H; ArOC*H*$_2$), 3.68–3.60 (m, 32H; OC*H*$_2$C*H*$_2$O), 3.52 (t, J = 5.8 Hz, 8H; NCH$_2$C*H*$_2$O), 3.38 (d, J_{AB} = 13.9 Hz, 2H; ArC*H*$_A$H$_B$N), 3.33 (d, J_{AB} = 13.9 Hz, 2H; ArCH$_A$*H*$_B$N), 3.12 (d, J = 13.1 Hz, 1H; ArC*H*$_2$Ar eq), 3.10 (d, J = 13.1 Hz, 2H; ArC*H*$_2$Ar eq), 3.06 (d, J = 13.1 Hz, 1H; ArC*H*$_2$Ar eq), 2.59 (t, J = 5.8 Hz, 8H; NC*H*$_2$CH$_2$O), 1.98–1.85 (m, 8H; ArOCH$_2$C*H*$_2$), 0.98 ppm (t, J = 7.4 Hz, 12H; CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, TMS): δ = 156.4, 155.4, 135.1, 134.9, 134.4, 128.6, 128.5, 128.0, 127.9, 121.7, 76.7, 70.7, 70.3, 70.2, 69.9, 59.3, 53.3, 30.9, 23.1, 10.2 ppm; MS (CI): m/z (%): 1143.8 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{66}H_{98}N_2O_{14}$ (1143.51): C 69.32, H 8.64, N 2.45; found: C 69.27, H 8.70, N 2.40.

5,17-Bis[*N*-(monoaza[18]crown-6)methyl]-25,26,27,28-tetrapropoxycalix[4]arene (3): Potassium carbonate (85 mg, 0.615 mmol) and 1-aza[18]-crown-6 (0.21 g, 0.794 mmol) were added to a solution of the dichloro derivative **15**[5] (0.2 g, 0.290 mmol) in dry MeCN (6 mL). The reaction mixture was heated at 60 °C overnight under a nitrogen atmosphere. The solvent was evaporated under reduced pressure and the crude product dissolved in CH_2Cl_2 (100 mL). The organic layer was washed with 0.1 M LiOH and the aqueous layer was extracted with additional CH_2Cl_2 (100 mL). The combined organic phases were evaporated under vacuum and the product was obtained as a pale yellow oil (232 mg, 0.203 mmol, 70% yield) upon column chromatography (neutral Al_2O_3, eluent: CH_2Cl_2/MeOH 9.2/0.8). An analytical sample was obtained as a white solid by crystallization from cold methanol. M.p. 99.6–100 °C; ^{1}H NMR (CDCl$_3$, TMS): δ = 6.92 (s, 4H; Ar*H*), 6.26–6.17 (m, 6H; Ar*H*), 4.40 (d, J = 3.2 Hz, 4H; ArC*H*$_2$Ar ax), 3.93 (t, J = 7.9 Hz, 4H; ArOC*H*$_2$), 3.72–3.59 (m, 48H; ArOC*H*$_2$, ArC*H*$_2$N, NCH$_2$(C*H*$_2$OC*H*$_2$)$_5$), 3.09 (d, J = 13.2 Hz, 4H; ArC*H*$_2$Ar eq), 2.81 (brs, 8H; OCH$_2$C*H*$_2$NC*H*$_2$CH$_2$O), 1.94 (q, J = 7.9 Hz, 4H; ArOCH$_2$C*H*$_2$), 1.86 (q, J = 7.5 Hz, 4H; ArOCH$_2$C*H*$_2$), 1.06 ppm (t, J = 7.5 Hz, 6H; ArOCH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, TMS): δ = 156.6, 155.3, 136.0, 133.6, 129.4, 127.3, 121.9, 76.7, 76.4, 70.8, 70.7, 70.3, 69.9, 59.8, 53.7, 30.8, 23.3, 22.9, 10.6, 9.9 ppm; MS-ES: 602.3 $[M+Na^++K^+]/2$, 594.4 $[M+2Na^+]/2$, 583.4 $[M+Na^++H^+]/2$, 572.4 $[M+2H^+]/2$; elemental analysis calcd (%) for $C_{66}H_{98}N_2O_{14}$ (1143.52): C 69.32, H 8.64, N 2.45; found: C 69.26, H 8.72, N 2.40.

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[7] The intermolecular model is the second-order reaction between the ester substrate bound through its distal carboxylate to a crown-complexed Ba^{2+} ion and ethoxide ion cation-paired to a crown-complexed Ba^{2+} ion, as shown in Scheme 1b. Since under the conditions of excess EtO^- adopted for the measurement of k_{obs} values possible contributions to the overall rate from the reaction of the substrate-containing ternary complex with free EtO^- ion cannot be ruled out, a new set of kinetic runs was carried out with the following reactant concentrations: monotopic ligand, 1.00 mM; $Ba(SCN)_2$, 1.00 mM; $EtONMe_4$, 1.00 mM; ester substrate, 0.025 mM. Under this new set of reaction conditions any contribution from free EtO^- can be ruled out.

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