90%). ^{1}H NMR ($CDCl_3$): $\delta = 4.85$ (d, 2H, $J = 11.5$ Hz, 2 × OC*H*Ph), 4.61 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.55 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.48, 4.43 (2d, 2H, $J = 11.5$ Hz, OCH_2Ph), 4.32 (d, 1H, $J = 10.0$ Hz, H1), 4.15 (d, 1H, $J = 2.5$ Hz, H4), 3.86 (dd, 1H, $J = 10.5$, 2.5 Hz, H3), 3.79 (br, 4H, N(CH_2Ph)$_2$), 3.65–3.58 (m, 2H, 2 × H6), 3.47 (m, 1H, H5), 3.45 (t, 1H, $J = 10.0$ Hz, H2), 1.90 (s, 3H, SMe); selected ^{13}C NMR data ($CDCl_3$): $\delta =$ 85.39, 82.22, 76.64, 74.27, 73.68, 72.21, 70.58, 68.87, 58.15, 12.15; HR-MS (ES): m/z: 660.3146 $[M+H]^+$.

8: Compound **4** (190 mg, 0.56 mmol), NaH (85 mg, 95%, 3.36 mmol), and Bu_4NI (1.24 g, 3.36 mmol) in DMF (20 mL) were stirred for 30 min at room temperature, and then BnBr (0.4 mL, 3.36 mmol) was added. After 4 h the mixture was worked up and purified by column chromatography to give **8** (300 mg, 88%). ^{1}H NMR ($CDCl_3$): $\delta = 5.14$ (d, 1H, $J = 10.5$ Hz, H1), 4.98 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.85 (t, 1H, $J = 10.5$ Hz, H2), 4.60 (d, 2H, $J =$ 12.0 Hz, 2 × OC*H*Ph), 4.51, 4.46 (2d, 2H, $J = 11.5$ Hz, OCH_2Ph), 4.39 (dd, 1H, $J = 11.0$, 2.8 Hz, H3), 4.32 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.10 (d, 1H, $J = 2.8$ Hz, H4), 3.83 (t, 1H, $J = 6.5$ Hz, H5), 3.66 (m, 2H, 2 × H6), 2.15 (s, 3H, SMe); selected ^{13}C NMR data ($CDCl_3$): $\delta = 80.76$, 77.53, 77.39, 74.53, 73.55, 72.37, 71.51, 68.50, 51.04, 11.05; HR-MS (ES): m/z: 610.2188 $[M+H]^+$.

General procedure for glycosylation and deprotection: A mixture of glycosyl donor (2 equiv), alcohol acceptor (1 equiv), and 4-Å molecular sieves in dichloromethane was stirred for 1 h at room temperature, cooled to −30 °C, and treated with $DMTSBF_4$ (4 equiv). The temperature was increased to 0 °C over 2 h. Thin-layer chromatography (TLC) showed complete disappearance of starting alcohol. After workup and chromatographic purification, disaccharides **9**, **10**, **16**, **18**, **20**, and **22** were obtained. The yields and β:α ratios are shown in Table 1. Protected disaccharides **10**, **16**, **18**, **20**, and **22** were subjected to hydrogenolysis over $Pd(OH)_2$/C (10%) in EtOH with HCl (0.2%) for 3 h. The mixture was then filtered through a Millex-GV filter unit. The residue was purified with a C-18 Sep-Pak cartridge to give **11**, **17**, **19**, **21**, and **23**, respectively. The yields are shown in Scheme 2. Selected physical data are given in the following:

9: ^{1}H NMR ($CDCl_3$): $\delta = 5.14$ (d, 1H, $J = 3.5$ Hz, H1), 5.23 (d, 1H, $J =$ 8.5 Hz, H1′).

10: ^{1}H NMR ($CDCl_3$): $\delta = 5.03$ (d, 1H, $J = 2.0$ Hz, H1), 4.36 (d, 1H, $J =$ 7.8 Hz, H1′); ^{13}C NMR ($CDCl_3$): $\delta = 101.40$ (C1′), 97.13 (C1), 59.05 (C2′).

11: ^{1}H NMR (D_2O): $\delta = 4.98$ (d, 1H, $J = 1.7$ Hz, H1), 4.38 (d, 1H, $J =$ 8.3 Hz, H1′), 2.90 (dd, 1H, H2′); ^{13}C NMR (D_2O): $\delta = 102.80$ (J(C1′,H1′) = 160.6 Hz, C1′), 98.20 (J(C1,H1) = 170.7 Hz, C1); HR-MS (ES): m/z: 454.6257 $[M+H]^+$.

16: ^{1}H NMR ($CDCl_3$): $\delta = 5.01$ (d, 1H, $J = 8.0$ Hz, H1′), 4.51 (d, 1H, $J =$ 7.8 Hz, H1); ^{13}C NMR ($CDCl_3$): $\delta = 102.60$, 97.95 (C-1′, C1).

17: ^{1}H NMR (D_2O): $\delta = 4.51$ (d, 1H, $J = 7.9$ Hz, H1′), 3.0 (dd, 1H, H2′); HR-MS (ES): m/z: 454.2695 $[M+H]^+$.

18: ^{1}H NMR ($CDCl_3$): $\delta = 5.06$ (d, 1H, $J = 8.0$ Hz, H1′), 4.58 (d, 1H, $J =$ 8.0 Hz, H1); ^{13}C NMR ($CDCl_3$): $\delta = 103.00$, 101.00 (C1′, C1).

19: ^{1}H NMR (D_2O): $\delta = 4.53$ (d, 1H, $J = 8.1$ Hz, H1′), 4.43 (d, 1H, $J =$ 8.1 Hz, H1), 2.93 (dd, 1H, H2′); ^{13}C NMR (D_2O): $\delta = 103.10$ (J(C1,H1) = 160.2 Hz, C1), 105.90 (J(C1′,H1′) = 160.3 Hz, C1′); HR-MS (ES): m/z: 454.2652 $[M+H]^+$.

20: ^{1}H NMR ($CDCl_3$): $\delta = 5.08$ (d, 1H, $J = 7.8$ Hz, H1′), 4.36 (d, 1H, $J =$ 8.0 Hz, H1); ^{13}C NMR ($CDCl_3$): $\delta = 103.86$, 100.88 (C1′, C1).

21: ^{1}H NMR (D_2O): $\delta = 4.52$ (d, 1H, $J = 8.2$ Hz, H1′), 4.41 (d, 1H, $J =$ 7.9 Hz, H1), 2.90 (dd, 1H, H2′); ^{13}C NMR (D_2O): $\delta = 103.50$ (J(C1,H1) = 160.4 Hz, C1), 105.50 (J(C1′,H1′) = 161.7 Hz, C1′); HR-MS (ES): m/z: 454.2654 $[M+H]^+$.**22**: ^{1}H NMR ($CDCl_3$): $\delta = 4.76$ (d, 1H, $J = 8.0$ Hz, H1′), 4.42 (d, 1H, $J = 7.7$ Hz, H1); ^{13}C NMR ($CDCl_3$): $\delta = 104.10$, 102.49 (C1′, C1).

23: ^{1}H NMR (D_2O): $\delta = 4.72$ (d, 1H, $J = 8.6$ Hz, H1′), 4.42 (d, 1H, $J =$ 8.1 Hz, H1), 3.22 (dd, 1H, H2′); HR-MS (ES): m/z: 454.2652 $[M+H]^+$.

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Supramolecular Catalysis of Ester and Amide Cleavage by a Dinuclear Barium(II) Complex**

Roberta Cacciapaglia,* Stefano Di Stefano, Erik Kelderman, and Luigi Mandolini*

A most exciting development in supramolecular chemistry has been the design, synthesis, and evaluation of abiotic catalysts that share with natural enzymes a number of features related to efficient catalysis.[1] Our research efforts are aimed at the development of prototype supramolecular catalysts by means of a modular approach in which an efficient catalytic unit for a given reaction and a receptor unit that is complementary to a nonreacting part of the substrate are covalently connected by means of a suitable spacer.

We have now considered the bis-barium(II) complex $\mathbf{1}\cdot(Ba^{2+})_2$ of the homoditopic ligand **1**, in which two aza[18]-

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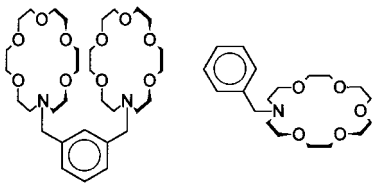
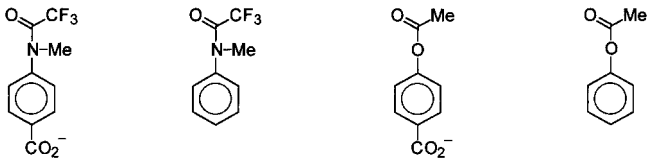
crown-6 units are connected by an *m*-xylylene spacer, as a possible catalyst for the ethoxide-induced cleavage reactions of amide **3** and ester **5**. The two metal ions in the homobimetallic complex are expected to perform different functions, as



1 **2**



3 **4** **5** **6**

depicted in Figure 1. One of the metal ions would bind and activate the ethoxide ion nucleophile,[2] while the other would serve as an anchoring group for the distal carboxylate of the substrate. The synergistic action of two metal centers has been used by several research groups in successful attempts to construct bifunctional enzyme models.[3]

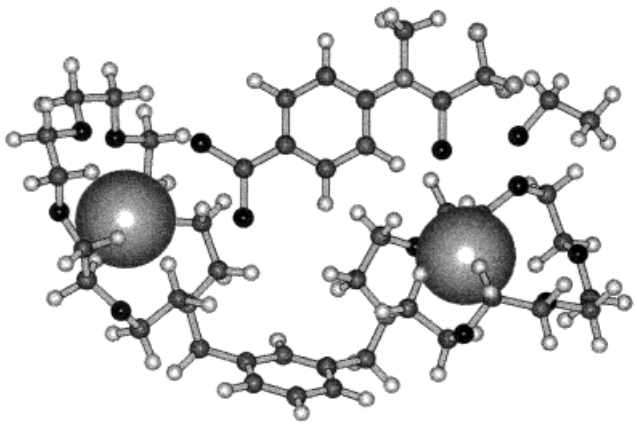


Figure 1. Computer-generated model of the complex between catalyst $\mathbf{1}\cdot(Ba^{2+})_2$, the ethoxide ion nucleophile, and the amide substrate **3** (structure **II** in Scheme 1).

A novel and distinctive feature of our catalyst is that substrate recognition takes place by means of a distal group, rather than the group(s) that undergo reaction.[3] The rationale behind the design of our catalyst is well illustrated by the inhibition experiment plotted in Figure 2. The ethoxide ion of a ternary complex $[(18C6)Ba(OEt)]^+$ (18C6 = [18]crown-6) cleaves trifluoroacetanilide[4] (and phenyl acetate)[5] much more rapidly than free ethoxide ion. Addition of increasing amounts of tetramethylammonium acetate causes a gradual drop of the rate of amide cleavage, until the reactivity of free ethoxide ion is eventually reached. This is consistent with the

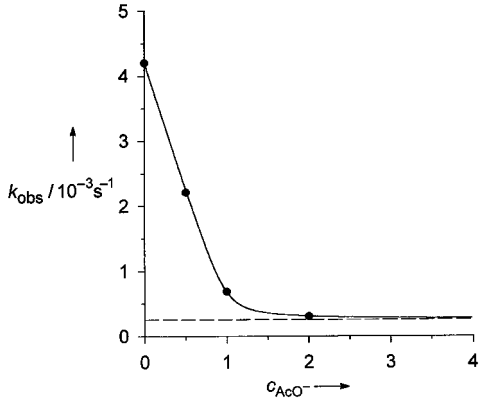


Figure 2. Influence of the amount of tetramethylammonium acetate (c_{AcO^-}, given in molar equivalents) on the rate of ethanolysis k_{obs} of **4** (0.054 mM) at 25 °C and in the presence of a 5.0 mM 1:1:1 mixture of Me_4NOEt, $Ba(SCN)_2$, and 18C6. The solid line is calculated on the basis of the equilibrium of Eq. (1), with $K = 69$. The horizontal dashed line represents the reactivity of free ethoxide ion.

counterion exchange equilibrium [Eq. (1)], in which AcO^- ion favorably competes with EtO^- ion for the crown-complexed metal ion ($K = 69$).

$$[(18C6)Ba(OEt)]^+ + AcO^- \overset{K}{\rightleftharpoons} [(18C6)Ba(AcO)]^+ + EtO^- \quad (1)$$

Since the equilibrium constant for binding of EtO^- ion to $[(18C6)Ba]^{2+}$ is large ($K > 10^4\,M^{-1}$),[5] it is concluded that anchorage of carboxylate ion to the metal ion is virtually quantitative ($K > 10^5\,M^{-1}$) under the conditions of the experiments listed in Table 1. Indeed we find that $\mathbf{1}\cdot(Ba^{2+})_2$ shows efficient catalysis in the ethoxide-induced cleavage reactions of anilide **3** and ester **5**, but not for the corresponding reactions of the parent compounds **4** and **6**. Furthermore, the bimetallic catalyst is superior to the barium complex of the monotopic ligand **2** for **3** and **5**, but for **4** and **6** the two catalysts show very nearly the same activity.[6] Clearly, bifunctional catalysis is observed when the ditopic character of the

Table 1. Effect of additives on the basic ethanolysis of substrates **3**–**6**.[a]

Substrate	$Ba(SCN)_2$ [mM]	**2** [mM]	**1** [mM]	k_{obs}[b] [s^{-1}]	k_{rel}
3	–	–	–	3.54×10^{-5}	1.0
	1.00	–	–	8.28×10^{-4}	23
	2.00	2.00	–	8.04×10^{-4}	23
	2.00	–	1.00	3.06×10^{-2}	865
4	–	–	–	5.10×10^{-5}	1.0
	1.00	–	–	2.16×10^{-4}	4.2
	2.00	2.00	–	2.47×10^{-4}	4.8
	2.00	–	1.00	3.64×10^{-4}	7.1
5	–	–	–	9.12×10^{-4}	1.0
	1.00	–	–	5.17×10^{-2}	57
	2.00	2.00	–	5.53×10^{-2}	61
	2.00	–	1.00	1.14	1250
6	–	–	–	1.44×10^{-3}	1.0
	1.00	–	–	4.80×10^{-2}	33
	2.00	2.00	–	5.86×10^{-2}	41
	2.00	–	1.00	5.07×10^{-2}	35

[a] Reaction conditions: 0.050 mM substrate, 1.00 mM Me_4NOEt, EtOH, 25 °C. [b] First-order rate constants were determined from time-course kinetic studies. Error limits are in the order of ±3–5%.

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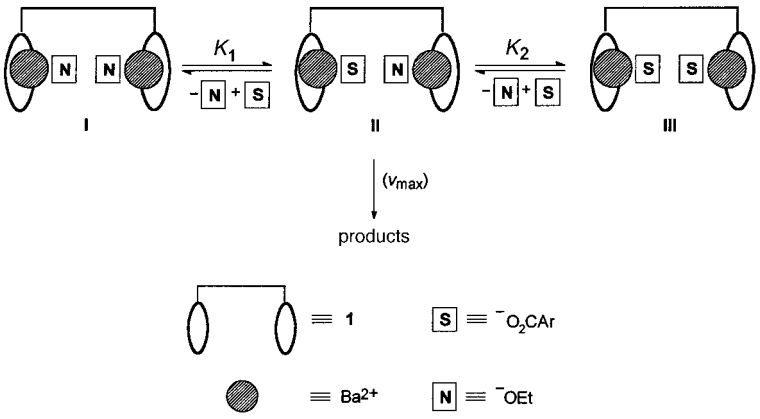
catalyst is combined with the presence of a carboxylate anchoring group.

Further analysis of the catalytic activity of $\mathbf{1}\cdot(Ba^{2+})_2$ was carried out in the presence of a large excess of EtO^- ion, which causes the catalyst to be fully saturated with EtO^- as shown by structure **I** in Scheme 1. According to the mechanism outlined in Scheme 1, addition of the amide substrate **3** would cause the gradual conversion of **I** into the 1:1 productive complex **II**, but further addition of **3** would yield the unproductive 1:2 complex **III**. As expected from this mechanism, a bell-shaped profile is observed in a plot of initial rate v_0 versus substrate concentration (Figure 3). A standard curve-fitting procedure based on Scheme 1 was used to obtain best fit for v_{max} and K_1 values, whereas K_2 was assigned the statistically corrected value of $K_1/4$ to avoid the use of too many variables. The fairly good quality of the fit supports the validity of Scheme 1. Highly significant is the finding that the K_1 value compares very well with the K value determined from the experiment plotted in Figure 2.[7]



Scheme 1. Equilibria leading to the productive and unproductive catalyst–substrate complexes **II** and **III**.

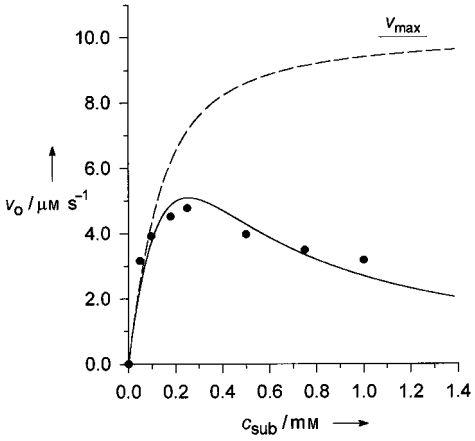
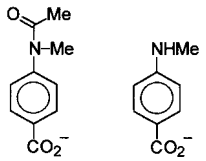


Figure 3. Plot of initial rate versus substrate concentration c_{sub} for the catalyzed ethanolysis of **3**. Reaction conditions: 0.10 mM **1**, 0.20 mM $Ba(SCN)_2$, 5.0 mM Me_4NOEt. Calculation of the solid line is based on Scheme 1, with $v_{max} = 1.0\times10^5\,M\,s^{-1}$, $K_1 = 65$, and $K_2 = K_1/4$ (see text). The dashed line is a Michaelis–Menten plot calculated without the K_2 equilibrium step shown in Scheme 1.

Also consistent with the proposed mechanism is the finding that catalytic ethanolysis of **3** is inhibited by benzoate anion derivatives (Table 2). Anion **8** is a stronger inhibitor than **7**, on account of the presumably higher basicity of the former. Furthermore it is apparent that the affinity of **8** for the catalyst is twice as great as that of **3**. Since **8** is the reaction product, severe product inhibition is expected. Indeed we found that only four to five turnovers are seen in the ethanolysis of **3** before product inhibition shuts down the reaction. The first two turnovers are shown graphically in Figure 4.



7 **8**

In conclusion, the bis-barium complex of **1** catalyzes the cleavage of amide and ester substrates endowed with a carboxylate anchoring group. The catalyst shows high structural recognition of the substrate, induces fairly high reaction rates with catalytic turnover, and is subjected to competitive inhibition by an inert substrate, as well as by the reaction product. Given the extreme structural simplicity of precursor **1**, and the fact that the active form of the catalyst is spontaneously self-assembled when the separate components are mixed, our catalyst represents an extremely parsimonious realization of an artificial amidase/esterase. The function of the binding step is manifold. It selects the substrate, provides electronic activation to the

Table 2. Competitive inhibition of the catalyzed ethanolysis of **3**.[a, b]

Inhibitor[c]	v_0 [M s^{-1}]	v_{rel}
none	3.9×10^{-6}	1.0
7	2.3×10^{-6}	0.59
8	1.3×10^{-6}	0.33

[a] Reaction conditions: 0.10 mM **1**, 0.20 mM Ba^{2+}, 0.10 mM substrate, 5.00 mM Me_4NOEt, EtOH, 25 °C. [b] Determined from measurements of initial rates. Error limits are in the order of ±5–10%. [c] Inhibitor concentration is 0.10 mM.

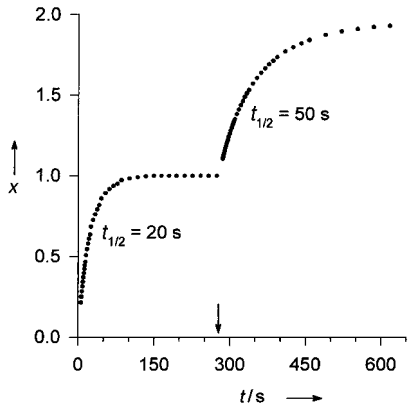


Figure 4. Turnover catalysis with product inhibition in the ethanolysis of **3** under the conditions outlined in Figure 3. One molar equivalent of **3** is added at time zero. A second molar equivalent is added at the time indicated by the arrow. Further portions of **3** (1 mol equiv) solvolyze with increasingly lower rates (not shown in the plot). x = turnover number.

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amide/ester group undergoing reaction,[6] and converts reacting groups into neighboring groups. Based on the assumption that, under the conditions of the experiments listed in Table 1, only half of the catalyst is in the active form of a 1:1 ethoxide complex, rate enhancements for reactions catalyzed by the bimetallic vs. monometallic catalyst translate into an effective molarity (EM)[8] value of 0.08 M for the reaction of **3** and one of 0.04 M for the reaction of **5**. We believe that the loss of entropy associated with torsional motions around two C–C and two C–N bonds is largely responsible for these relatively low EM values.[8] Current work is aimed at the construction of more preorganized, and hopefully more efficient, catalysts.

Experimental Section

Ligands **1**[9] and **2**[10] and compounds $\mathbf{3}\cdot H^+$,[11] **4**,[12] $\mathbf{5}\cdot H^+$,[13] and $\mathbf{7}\cdot H^+$[13] were prepared according to published procedures (melting points and/or spectral data in agreement with literature data). The compound $\mathbf{8}\cdot H^+$ was a commercial sample. Acids $\mathbf{3}\cdot H^+$, $\mathbf{5}\cdot H^+$, $\mathbf{7}\cdot H^+$, and $\mathbf{8}\cdot H^+$ were converted in situ into the Me_4N^+ salts by neutralization with Me_4NOEt. Spectrophotometric rate measurements were carried out in the thermostatted cell compartment of a Hewlett Packard HP 8452A diode array spectrometer. For initial rate measurements, a fast mixing accessory, HI-TECH SCIENTIFIC SFA-12, was connected to the spectrometer and the process was monitored at the isosbestic point for the free and the Ba^{2+}-paired reaction product ($\lambda = 276$ nm). Other materials, apparatus and techniques were as reported previously.[4, 5]

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[7] The close similarity of the two values would indicate that the higher affinity for the monometallic complex of the more basic AcO^- ion is substantially counterbalanced by the statistical factor 2 which operates in the binding of the less basic **3** to the bimetallic complex. The fact that the ligand is not exactly the same in the two cases is presumably unimportant.

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Continuous Amination of Propanediols in Supercritical Ammonia**

Achim Fischer, Tamas Mallat, and Alfons Baiker*

The heterogeneously catalyzed amination of alcohols has been established as the most important industrial process for the manufacture of a variety of aliphatic and aromatic amines.[1–6] However, the yields and selectivities are usually rather low in the synthesis of primary aliphatic diamines from the corresponding diols and ammonia. The transformation of a simple aliphatic alcohol to the corresponding amine on a metal catalyst includes three major reaction steps (Scheme 1): 1) dehydrogenation to a carbonyl compound; 2) condensation with ammonia or an amine to form an imine or an enamine; and 3) hydrogenation to the corresponding amine.[7, 8] Each intermediate and the product amine can undergo various side reactions such as condensation, decarbonylation, disproportionation, and hydrogenolysis.[4, 9–11] The direct transformation of an aliphatic diol to the corresponding diamine requires the repetition of steps 1–3, which favors the formation of the by-product. In addition, the bifunctional intermediates extend the scope of possible side reactions (for example, oligomerization and cyclization).[12, 13] However, reasonable yields have still been reported for the amination of alkanediols with secondary amines, as the tertiary amine product is moderately reactive.[7, 14] Unfortunately, the situation is the reverse in aminations with ammonia, as the reactivities of the inter-

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