Catalysis of Acyl Group Transfer by a Double-Displacement Mechanism: The Cleavage of Aryl Esters Catalyzed by Calixcrown – Ba^{2+} Complexes

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Abstract: The scope of the barium salt of *p-tert*-butylcalix[4]arene-crown-5 as a transacylation catalyst has been defined by evaluating its efficiency in the methanolysis of a series of aryl acetates at 25.0 °C in MeCN/MeOH 9:1 (*v*/*v*) under slightly basic conditions. In this system a phenolic hydroxyl is the acyl-receiving and -releasing unit in a double-displacement mechanism. The complexed barium ion acts both as a nucleophile carrier and a built-in Lewis acid in providing electrophilic assistance to the ester carbonyl both in the acylation and deacylation step (nucleophilic – electrophilic catalysis). Turnover capability is ensured by the acylated intermediate reacting with the solvent more rapidly than the original ester, but a serious drawback derives from the incursion of back-acylation of the liberated phenol. A gradual shift from rate-determining deacylation (*p*-nitrophenyl acetate) to rate-determining acylation (phenyl acetate) is observed along the investigated series. It is shown that the scope of the catalyst is restricted to acetate esters whose reactivity lies in the range approximately defined by the phenyl acetate – *p*-nitrophenyl acetate pair, with a maximum efficiency for *p*-chlorophenyl acetate. Moreover, the catalyst effectively promotes ester interchange between phenols, showing that its activity is not limited to solvolysis reactions. The very high sensitivity of the rate of acylation of the catalyst to leaving group basicity has been interpreted as due to rate-determining decomposition of the tetrahedral intermediate, which is believed to arise from the presumably low basicity of the metal ion stabilized nucleophile. The turnover frequency was in the range of 3.8×10^{-4} min^{-1} for phenyl acetate to 7.4×10^{-3} min^{-1} for *p*-nitrophenyl acetate ($[ArOAc]_0 = 4.0$ mM]). A first attempt to enhance the rate of acylation of the catalyst through intramolecular general acid catalysis is also described.

Keywords: acid – base catalysis · acyl transfer · barium · calixarenes · nucleophilic catalysis

Introduction

Many enzymic transacylation processes, such as those catalyzed by the serine and cysteine proteases,[1] proceed via a double-displacement mechanism (nucleophilic catalysis), where a first step consisting of the formation of an acylated enzyme intermediate is followed by a subsequent transfer of the acyl group to a receiving nucleophile.

Notable examples of nucleophilic catalysis in non-enzymic systems are provided, inter alia, by the imidazole-catalyzed hydrolysis of aryl esters[2] and the acylation of alcohols by activated carboxylic acid derivatives catalyzed by pyridines.[3] Additional examples are provided by a number of synthetic transacylation catalysts (artificial esterases) designed in such a way that an OH/SH group[4–6] covalently linked to the catalyst backbone is deputed to act as acyl-receiving and -releasing unit.

A major problem inherent in studies of artificial esterases designed to proceed via a nucleophilic catalysis mechanism is that the acylated intermediate must react with the receiving nucleophile more rapidly than the original ester. This is not always the case, as shown by the fact that many investigated systems show little or no turnover capability. Another important problem is related to the partition of the tetrahedral intermediate between reactant and product [Equation (1), see below], that is ruled by the relative leaving abilities of Nu^- and $R'O^-$.[2] The very poor leaving group ability of the strongly basic alkoxides explains why nucleophilic catalysis is rarely encountered with alkyl esters, whereas it is much more common with aryl esters.[7] This concept provides a useful basis for understanding the etiology of the

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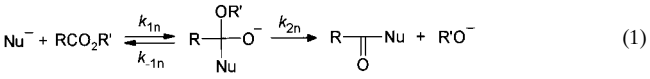
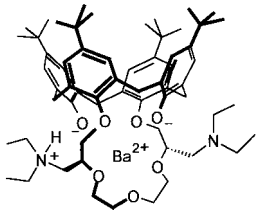
widespread *p*-nitrophenyl ester syndrome[8] in studies of α-chymotrypsin models and other synthetic catalysts of ester cleavage.



(1)

Our preliminary study[5b] of the barium salt of *p-tert*-butylcalix[4]arene-crown-5, **3**·[Ba], as turnover catalyst of ester cleavage is no exception. Its catalytic properties were evaluated using *p*-nitrophenyl acetate (pNPOAc) as a convenient substrate. In the present work we define the scope of our catalyst by evaluating the influence of changes in the basicity of the aryloxide leaving group on the catalytic efficiency. We also establish that **3**·[Ba] effectively catalyzes acyl transfer between different phenols. Finally, we have synthesized calixcrown **6**, possessing two diethylaminomethyl side arms at the polyether bridge, and investigated the catalytic activity of its barium salt **8**·[Ba] with the idea that the monoprotonated form **8**H$^+$·[Ba] could possibly exhibit enhanced acylation rates due to general acid assistance to the departure of the aryloxide leaving group. Compared with the



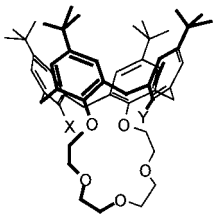
8H$^+$·[Ba]

barium complex of **3**, the protonated form of the barium complex of **8** represents an extension from bifunctional nucleophilic–electrophilic catalysis to trifunctional nucleophilic–electrophilic general acid catalysis.

Abstract in Italian: *Si sono definite le potenzialità del sale di bario del* p-terz-*butilcalix[4]arene-corona-5 quale catalizzatore di processi di transacilazione valutandone l'efficienza nella metanolisi di una serie di acetati arilici a 25.0 °C in MeCN/MeOH 9:1* (v/v)*, in ambiente debolmente alcalino. In questo sistema l'unità in grado di ricevere e rilasciare l'acile, secondo un meccanismo di doppia sostituzione, è un ossidrile fenolico. Lo ione bario complessato agisce sia da trasportatore di nucleofilo che da acido di Lewis in grado di fornire un'assistenza di tipo elettrofilo al carbonile estereo sia nella fase di acilazione che di deacilazione (catalisi nucleofila–elettrofila). La capacità di dare "turnover" è assicurata dal fatto che l'intermedio acilato reagisce con il solvente più velocemente di quanto non faccia l'estere di partenza. Dalla elevata reattività dell'intermedio acilato deriva comunque anche un contropproducente fenomeno di retro-acilazione del fenolo prodotto. Nell'ambito della serie degli esteri presi in considerazione, si ha un passaggio graduale da una situazione in cui lo stadio lento è la deacilazione (acetato di* p-*nitrofenile) ad una situazione in cui lo stadio lento è la acilazione (acetato di fenile). Si è inoltre stabilito che l'attività del nostro catalizzatore è limitata alla scissione di esteri la cui reattività è approssimativamente compresa nell'intervallo definito dalla coppia acetato di fenile–acetato di* p-*nitrofenile, con un massimo di efficienza in corrispondenza dell'acetato di p-clorofenile. Il sale di bario del* p-terz-*butilcalix[4]arene-corona-5 catalizza inoltre efficientemente anche lo scambio di acile tra fenoli, dimostrando in tal modo che il suo campo di azione non è limitato ai soli processi di solvolisi. L'elevata sensibilità della velocità di acilazione del catalizzatore alla basicità del gruppo uscente è stata attribuita ad una decomposizione lenta dell'intermedio tetraedrico. Ciò si ritiene derivi dalla interazione stabilizzante del fenossido con lo ione metallico nella forma attiva del catalizzatore e dalla conseguente ridotta basicità del nucleofilo. Si descrive inoltre un primo tentativo di promuovere l'acilazione del catalizzatore mediante catalisi acida generale intramolecolare.*

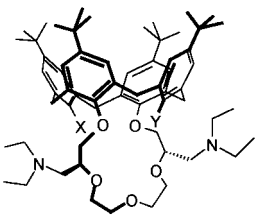
Results

The kinetics of methanolysis of a series of aryl acetates including pNPOAc, *m*-nitrophenyl acetate (mNPOAc), *p*-chlorophenyl acetate (pCPOAc), and phenyl acetate (POAc) were investigated at 25.0 °C in MeCN/MeOH 9:1 (*v*/*v*) containing a 40 mM diisopropylethylamine/perchlorate salt buffer in a [B]/[BH$^+$] ratio of 3:1. Initial concentrations of the ester substrates were as follows: 3.0 mM pNPOAc, 6.1 mM mNPOAc, 0.10 M pCPOAc, 0.20 M POAc. Rate measurements were carried out in the presence of buffer alone (background reactions) and of buffer plus 0.39 mM catalyst. The latter was generated in situ from equimolar amounts of **1** and $Ba(ClO_4)_2$. Whereas **1** remains in its un-ionized form in the given buffer solution, in the presence of 1 mol equivalents of barium salt calixcrown **1** is quantitatively converted into a mixture of barium complexes **2** and **3**, the latter being most likely the



1 X=Y=OH
2 X=OH, Y=O$^-$
3 X=Y=O$^-$
4 X=OH, Y=OAc
5 X=O$^-$, Y=OAc

active form of the catalyst.[5b] Since the present conditions differ slightly from those of the previous report,[5b] a new set of rate measurements was carried out with pNPOAc. For the sake of convenience, these measurements will be described first. Finally, the activity of the extended catalyst generated in situ from equimolar amounts of **6** and $Ba(ClO_4)_2$ was evaluated under the same experimental conditions with pNPOAc and POAc as substrates.



6 X=Y=OH
7 X=OH, Y=OAc
8 X=Y=O$^-$

pNPOAc: The spectrophotometrically determined liberation of *p*-nitrophenol (pNPOH) from pNPOAc in the absence and presence of metal catalyst is shown in Figure 1. The kinetic picture can be summarized as follows:

i) slow background methanolysis (curve a), with an initial rate $v_0 = 2.4 \times 10^{-7}$ M min^{-1}, corresponding to a rate constant $k_{bg} = 8.0 \times 10^{-5}$ min^{-1} ($t_{1/2} = 6.0$ d);

ii) biphasic kinetics for the catalyzed process (curve b), characterized by an initial "burst" of pNPOH release, followed by a slower linear phase.

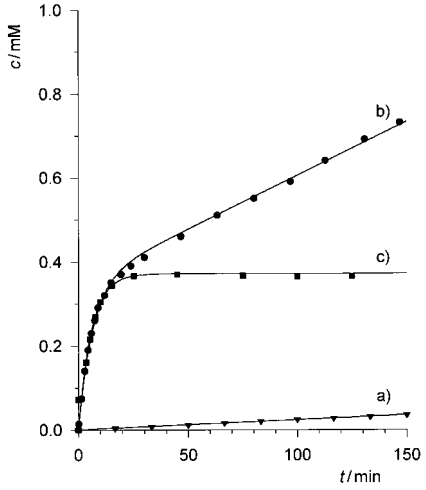
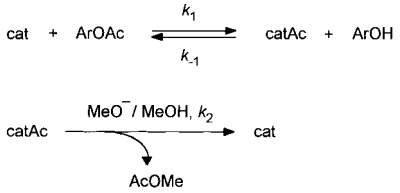


Figure 1. Methanolysis of 3 mM pNPOAc. Liberation of pNPOH (UV/Vis) in the presence of buffer alone (curve a) and of buffer plus 0.39 mM **1** and 0.39 mM $Ba(ClO_4)_2$ (curve b, the points are experimental data corrected for background, and the full line is calculated from Equation (2) with $k_1' = 0.15$ min^{-1} and $k_2 = 7.0 \times 10^{-3}$ min^{-1}). Curve c is a plot of [catAc] (HPLC) obtained under identical experimental conditions. The full line is calculated from Equation (4) with $k_1' = 0.16$ min^{-1} and $k_2 = 7.7 \times 10^{-3}$ min^{-1}.

This behavior is in agreement with a double-displacement mechanism[9] (Scheme 1 with $k_{-1} = 0$, and Equations (2) and (3), with $k_1' = k_1$[ArOAc] and $\tau = (k_1' + k_2)^{-1}$) in which fast acylation of the catalyst (cat) is followed by slower deacylation of the acetylated form (catAc). The solid line is the best fit of data points to Equation (2), with $k_1' = 0.15$ min^{-1} and



Scheme 1. Double-displacement mechanism.

$k_2 = 7.0 \times 10^{-3}$ min^{-1}. Equation (2) is the sum of an exponential (pre-steady state) phase with a first order rate constant τ^{-1} and a linear (steady state) phase obtained when the exponential term dies out and Equation (2) reduces to the form of Equation (3). The intercept $[cat]_0(\tau k_1')^2$ of the linear portion

$$[ArOH] = [cat]_0 \tau k_1' \{\tau k_1' [1 - \exp(-t/\tau)] + k_2 t\} \quad (2)$$

$$[ArOH] = [cat]_0 (\tau k_1')^2 + [cat]_0 \tau k_1' k_2 t \quad (3)$$

defines the "burst" π of ArOH liberation. With pNPOAc we obtain $\pi = 0.35$ mM, corresponding to 90% of $[cat]_0$. The slope of the linear phase $[cat]_0 \tau k_1' k_2$ is 2.6×10^{-6} M min^{-1}, ten times larger than background. The turnover frequency of the catalyst, computed as the quotient of the slope of the linear phase and $[cat]_0$ is 6.7×10^{-3} min^{-1}, which means that the catalyst turns over about ten times per day. An independently prepared sample of the monoacetylated derivative **4** was found to undergo methanolysis in the same buffer solution and in the presence of equimolar amounts of $Ba(ClO_4)_2$[10] (Figure 2) with a first-order rate constant of 7.7×10^{-3} min^{-1}, in good agreement with the value estimated from the two parameter treatment of the catalytic experiment.

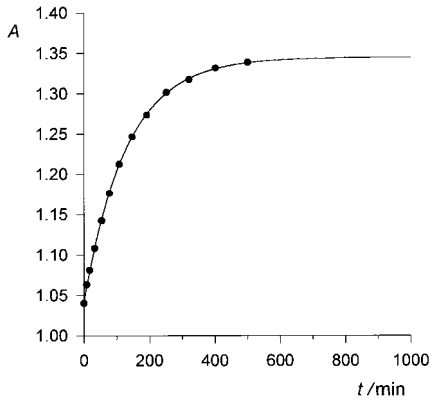


Figure 2. Methanolysis of 0.39 mM **4** in the presence of buffer plus 1 molar equivalent of $Ba(ClO_4)_2$ as monitored by UV/Vis spectrophotometry. The full line is a plot of the first-order equation ($k = 7.7 \times 10^{-3}$ min^{-1}).

A definite proof of the intermediacy of the monoacetylated form of the catalyst was obtained from HPLC analysis of acid-quenched samples of the reaction mixture in a catalytic experiment identical to that corresponding to curve b of Figure 1. Fully consistent with Equations (4) and (5), curve c in Figure 1 shows that **4** builds up until a steady concentration

$$[catAc] = [cat]_0 \tau k_1' [1 - \exp(-t/\tau)] \quad (4)$$

$$[catAc]_{ss} = [cat]_0 \tau k_1' \quad (5)$$

($[catAc]_{ss}$) is reached, corresponding to 95% of $[cat]_0$. Treatment of data points with Equation (4) gave $k_1' = 0.16$ min^{-1} and $k_2 = 7.7 \times 10^{-3}$ min^{-1} as best fit values, in excellent agreement with the values obtained from the independent experiments described above. Thus, the initial "burst" of pNPOH release strictly corresponds to the build-up of the acetylated intermediate, whereas the linear phase corresponds to an exact balance between formation and destruction of the same intermediate.

0947-6539/00/0608-1324 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 8

mNPOAc, pCPOAc, and POAc: Initial rates of background methanolysis of these compounds, suitably measured by a HPLC technique, were translated into the first order rate constants k_{bg} listed in Table 1.

Table 1. Methanolysis of aryl acetates catalyzed by **3**·[Ba] in MeCN/MeOH 9:1 (*v*/*v*) containing diisopropylethylamine perchlorate salt buffer, at 25 °C.[a]

	POAc	pCPOAc	mNPOAc	pNPOAc
k_{bg}/min^{-1}[b]	3.3×10^{-6}	5.4×10^{-6}	4.0×10^{-5}	8.0×10^{-5}
	(1)	(1.6)	(12)	(24)
k_1/M^{-1} min^{-1}[b]	0.10[c]	0.70	8.0	50[d]
	(1)	(7.0)	(80)	(500)
pK_a (XPOH)[e]	9.95	9.38	8.35	7.14
v_{cat}/v_{bg}[f, g]	9.3	15	38	11
v_{cat}/v_{bg}[f, h]	0.96	1.9	11	7.9
Turnover frequency[i, g]/min^{-1}	3.8×10^{-4}	2.0×10^{-3}	6.2×10^{-3}	7.4×10^{-3}
Turnover frequency[i, h]/min^{-1}	2.6×10^{-3}	6.0×10^{-3}	7.6×10^{-3}	7.7×10^{-3}

[a] $k_2 = 7.7\times10^{-3}$ min^{-1} for deacylation of **4** in the presence of buffer plus 1 mol equivalent of $Ba(ClO_4)_2$. [b] Data in parentheses are relative values. [c] $k_1 = 5.0\times10^{-2}$ M^{-1} min^{-1} in the acylation of 0.40 mM **8**·[Ba]. [d] $k_1 = 5.5$ M^{-1} min^{-1} in the acylation of 0.40 mM **8**·[Ba]. [e] In H_2O at 25 °C (data from ref. [2]). [f] Calculated from Equation (10), with $[cat]_0 = 0.40$ mM. [g] $[ArOAc]_0 = 4.0$ mM. [h] $[ArOAc]_0 = 40$ mM. [i] Calculated as $\tau k_1' k_2$.

The results of two identical catalytic experiments carried out with mNPOAc are graphically shown in Figure 3. Here again, the spectrophotometrically monitored liberation of *m*-nitrophenol (mNPOH) (curve a) shows an initial "burst" followed by a slower, apparently linear phase. The "burst" phase coincides with the accumulation of **4** (curve b) whose concentration, after reaching a maximum, unexpectedly decreases somewhat on increasing reaction time. Similar bell-shaped profiles were obtained from catalytic experiments with pCPOAc (Figure 4) and POAc (Figure 5).[11]

In order to explain the above findings, the hypothesis was made that back-acylation of the liberated phenol by catAc (Scheme 1, step k_{-1}) can become significant in the time course of reaction on increasing the phenol concentration. Back-reaction of the liberated phenol with reactive acylated intermediates, such as that formed in the 4-methylpyridine catalyzed hydrolysis of aryl acetates, is a well precedented phenomenon.[12] A confirmation of the validity of the above

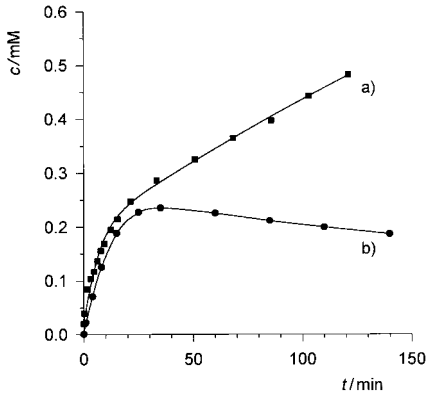


Figure 3. Methanolysis of 6.1 mM mNPOAc in the presence of 0.39 mM **1** and 0.39 mM $Ba(ClO_4)_2$. Plots of [mNPOH] (curve a, UV/Vis, corrected for background) and [catAc] (curve b, HPLC) versus time.

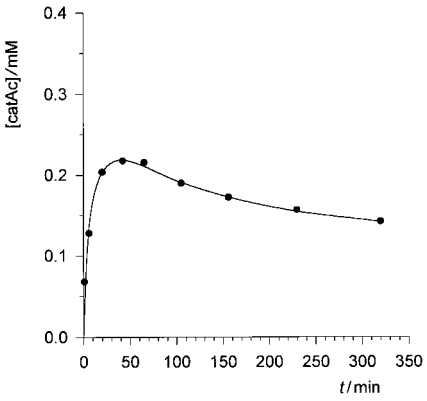


Figure 4. [catAc] (HPLC) versus time in the methanolysis of 0.1 M pCPOAc carried out in the presence of 0.39 mM **1** and 0.39 mM $Ba(ClO_4)_2$.

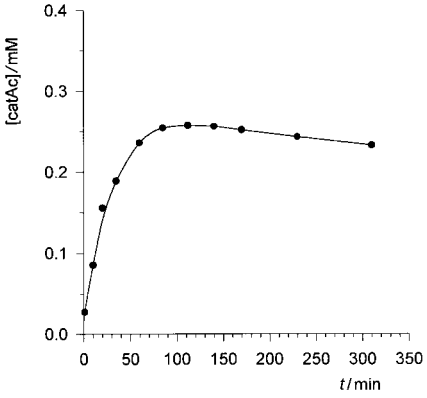


Figure 5. [catAc] (HPLC) versus time in the methanolysis of 0.2 M POAc carried out in the presence of 0.39 mM **1** and 0.39 mM $Ba(ClO_4)_2$.

hypothesis was obtained from a set of experiments in which the adverse mass-law effect of the liberated phenol was magnified by the addition of the phenol product in a 25-fold molar excess with respect to $[cat]_0$, which implies that the phenol concentration remained essentially constant for a reasonably low number of catalytic turnovers. The results of these experiments are graphically shown in Figure 6, where it

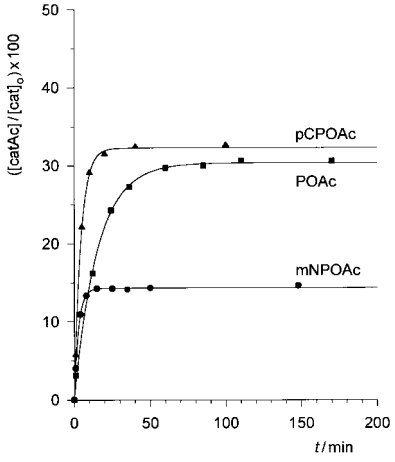


Figure 6. Accumulation of the acetylated intermediate catAc in the methanolyses of mNPOAc (●), pCPOAc (▲), and POAc (■), carried out in the presence of 0.39 mM **1**, 0.39 mM $Ba(ClO_4)_2$, and 10 mM of the corresponding phenol ArOH. The lines are calculated from Equation (7) with $k_2 = 7.7\times10^{-3}$ min^{-1} and the pertinent best fit values of k_1 and k_{-1} (see text).

is seen that in all cases a stationary concentration of catAc is obtained after an initial transient phase. The conversion of cat into catAc at steady state is 14%, 32%, and 30% in the reactions of mNPOAc, pCPOAc, and POAc, respectively. Consistent with expectations, these values are clearly much lower than the maximum values reached in the corresponding profiles given in Figures 3–5. Kinetic analysis of the time-concentration profiles plotted in Figure 6 was carried out as follows. From Scheme 1 one obtains Equation (6), whose integrated form is shown in Equation (7). As long as [ArOH] is constant, Equation (7) represents a simple first-order process whose infinity value is the steady-state concentration of catAc [Equation (8)]. Since $k_2 = 7.7 \times 10^{-3}\,\mathrm{min}^{-1}$ is a known quantity, a two-parameter curve-fitting procedure gave the k_1 and k_{-1} values (both in $\mathrm{M}^{-1}\mathrm{min}^{-1}$) listed in the given order for the different substrates: mNPOAc: 8.0, 28; pCPOAc: 0.70, 14; POAc: 0.10, 3.6.

$$\mathrm{d[catAc]}/\mathrm{d}t = k_1'[\mathrm{cat}] - [\mathrm{catAc}](k_2 + k_{-1}[\mathrm{ArOH}]) \quad (6)$$

$$[\mathrm{catAc}] = [k_1'[\mathrm{cat}]_0/(k_1' + k_2 + k_{-1}[\mathrm{ArOH}])][1 - \exp(-k_1' - k_2 - k_{-1}[\mathrm{ArOH}])t] \quad (7)$$

$$\lim_{t\to\infty}[\mathrm{catAc}] = [\mathrm{catAc}]_{ss} = k_1'[\mathrm{cat}]_0/(k_1' + k_2 + k_{-1}[\mathrm{ArOH}]) \quad (8)$$

Ester interchange between phenols: The very finding that catAc can acetylate a phenol in what is viewed as an undesired back-acylation process when the catalytic methanolysis of an aryl acetate is the target reaction, suggested a simple catalytic experiment of acyl transfer between phenols [Equation (9)].

pCPOH + pNPOAc ⟶ pCPOAc + pNPOH (9)

A mixture of 1.0 mM *p*-chlorophenol (pCPOH) and 3.0 mM pNPOAc in the usual buffer solution shows a hardly perceptible conversion of pCPOH into pCPOAc after 2 h (Figure 7). But on addition of 0.39 mM catalyst, 70% of pCPOH is acetylated during the same amount of time. Clearly, the catalyst takes the acetyl from pNPOAc and gives it to pCPOH in a turnover catalytic process, as confirmed by the fact that two complete turnovers were carried out in the given experiment.

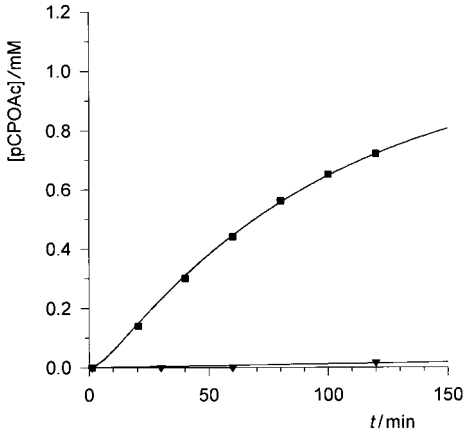
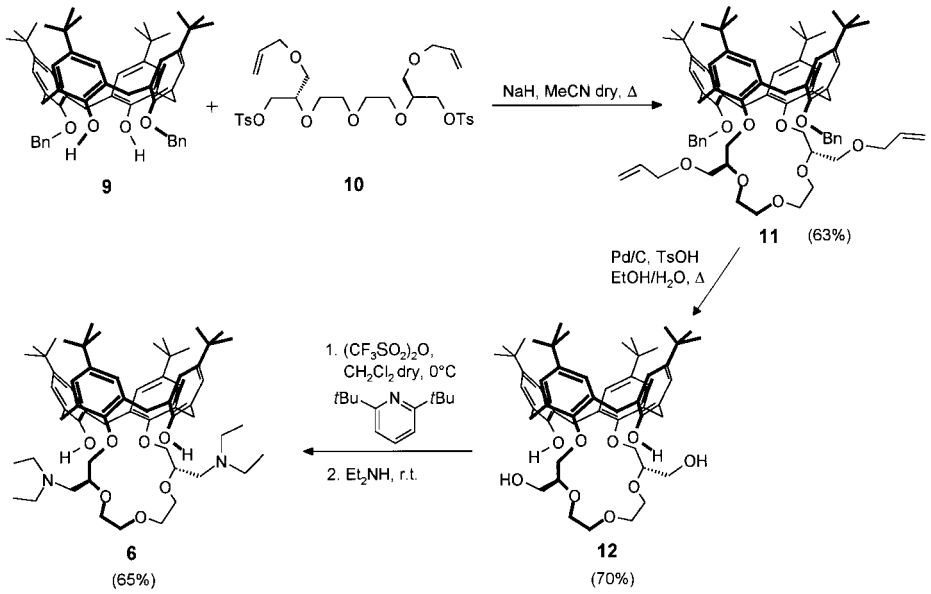


Figure 7. Acetyl transfer from pNPOAc (3 mM) to pCPOH (1 mM) in the presence of buffer alone (▼) and in the presence of buffer plus 0.39 mM **1** and 0.39 mM $Ba(ClO_4)_2$ (■).

Synthesis and evaluation of the trifunctional catalyst 8·[Ba]: Introduction of two diethylaminomethyl side arms in the polyether chain of **1** has been carried out according to the synthetic strategy outlined in Scheme 2. The C_2 symmetry of the target compound **6** avoids any complication arising from non-equivalence of the two faces of the catalyst. The lariat calixcrown derivative **6** was obtained in 28% overall yield starting from the dibenzylated derivative **9** and the enantiomerically pure ditosylate **10**. The ring forming reaction of **9** with **10** was carried out in very good yield (63%) under conditions known to afford only the cone conformation.[13] That only this conformation was present in the isolated product **11** was shown by the two AX systems for the methylene bridge protons[14] in the ^{1}H-NMR spectrum. Simultaneous removal of both allyl and benzyl groups was followed by acylation of the bis-hydroxymethyl derivative **12** with triflic anhydride and subsequent reaction with diethylamine.

The kinetics of acylation of 0.40 mM **8**·[Ba] by pNPOAc and POAc were measured under single turnover conditions by UV/Vis and HPLC initial rate methods, respectively. Initial rates obtained in the presence of 3.0 mM pNPOAc and 0.20 M POAc were translated into second-order rate constants k_1 of $5.5\,\mathrm{M}^{-1}\mathrm{min}^{-1}$ and $5.0 \times 10^{-2}\,\mathrm{M}^{-1}\mathrm{min}^{-1}$, respectively. The presence of the monoacetate **7** was detected by ESI-MS analysis of acid quenched samples of the reaction mixtures.



Scheme 2. Synthesis of lariat calixcrown **6**.

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Discussion

The barium salt formed from equimolar amounts of **1** and $Ba(ClO_4)_2$ in MeCN/MeOH 9:1 (*v*/*v*) under slightly basic conditions catalyzes the methanolysis of a series of aryl acetates by a double-displacement mechanism involving as a common covalent intermediate the barium complex of **5**. Although this mechanism can be safely classified as nucleophilic catalysis, it is important to appreciate that nucleophilic–electrophilic catalysis is actually involved, as the complexed barium ion acts as a built-in Lewis acid in providing electrophilic assistance to the ester carbonyl both in the acylation and deacylation step. This is well in keeping with experimental evidence that hard metal ions can greatly enhance rates of acyl transfer from esters to anionic nucleophiles.[15]

Analysis of rate data according to Scheme 1 provided a complete set of rate constants (Table 1). The complicating interference of the liberated phenol in reactions of mNPOAc, pCPOAc, and POAc[16] was accounted for in terms of a back-reaction with the acetylated intermediate.

From the data listed in Table 1, it is seen that the acylation step (k_1) shows a very high sensitivity to the structure of the ester. By way of example, the pNPOAc/POAc ratio is 500 for the acylation step (k_1), 24 for the background reaction (k_{bg}),[17] 7.5 for the reaction with OH^-/H_2O,[2] and 34 for the reaction with $C_6H_5O^-/H_2O$.[2]

An extensive investigation of the reactivity of nucleophilic reagents towards esters in which the basicities of nucleophiles and leaving groups were varied over wide ranges, led Jencks and Gilchrist[12] to the generalization that "the reactions with oxygen anions exhibit a small sensitivity to the basicity of both the attacking group and the leaving group when the former is more basic than the latter and a large sensitivity to the basicity of both groups in the converse case".

The acidity of **1** is not known, nor is the acidity of its barium complex, but the finding that upon addition of 1 mol equiv barium salt **1** is transformed into a mixture of $(\mathbf{2}\cdot[Ba])^+$ and $\mathbf{3}\cdot[Ba]$ indicates that the basicity of the latter is slightly higher than that of $pNPO^-$, and considerably lower than that of $mNPO^-$. Thus, in keeping with Jencks and Gilchrist's generalization, the high sensitivity exhibited by the acylation step is related to the relatively low basicity of the incoming nucleophile. In terms of the two-step mechanism of Equation (1), the tetrahedral intermediate partitions itself more extensively towards reactants when the leaving group becomes worse (more basic).[18] Consistent with this conclusion is the Brönsted plot of Figure 8, curve a. Although the plot is based on a limited number of data points, a negative curvature is evident, with β values varying approximately from 0.7 to 1.4.[19]

There is a remarkable similarity with the corresponding Brönsted plot (Figure 8, plot b) for reaction of the same esters with imidazole[2] (pK_a 7.21 in H_2O at 25 °C). This is not surprising in view of the close mechanistic analogy between the two reactions and the fact that a change in the rate-determining step occurs approximately with pNPOAc in both series.

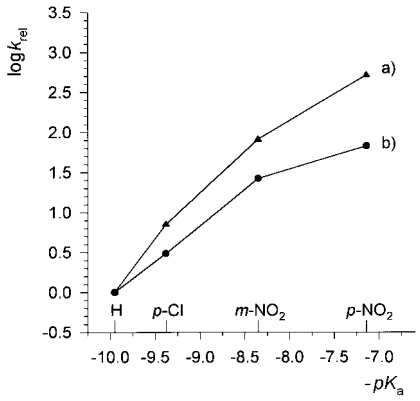


Figure 8. Brönsted plot for the reaction of aryl acetates with $\mathbf{3}\cdot[Ba]$ in MeCN/MeOH 9:1 (curve a) and with imidazole in H_2O (curve b; data from ref. [2]).

Catalytic efficiency versus ester reactivity: A convenient measure of catalytic efficiency for any given ester substrate is provided by the ratio v_{cat}/v_{bg} between the steady-state rate of the $\mathbf{3}\cdot[Ba]$ catalyzed reaction and the rate of background methanolysis, Equation (10).

$$v_{cat}/v_{bg} = ([cat]_0 \tau k_1' k_2)/(k_{bg}[ArOAc]_0) \quad (10)$$

To simplify matters, the back-acylation process k_{-1} was neglected. Since the relative importance of the various terms in Equation (10) varies significantly with the structure and concentration of the ester substrates, the v_{cat}/v_{bg} ratios and turnover frequencies were calculated for two sets of working conditions in which the substrate to catalyst ratio is 10:1 and 100:1, respectively (Table 1).

Unlike the k_{bg} and k_1 values that increase regularly on decreasing the leaving group basicity, the v_{cat}/v_{bg} ratios exhibit maximum values for the reaction of pCPOAc. This is graphically shown in Figure 9, where the catalytic efficiencies are plotted against ester reactivity, as measured by the log k_{bg} values. It is apparent that an increase in the substrate to

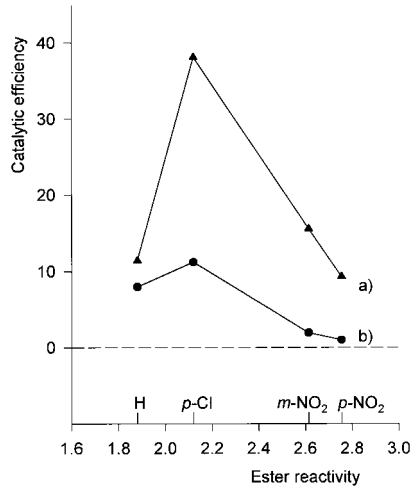


Figure 9. Catalytic efficiency of $\mathbf{3}\cdot[Ba]$ [Equation (10)] in the methanolysis of aryl acetates calculated for a substrate to catalyst ratio of 10:1 (curve a) and 100:1 (curve b) versus ester reactivity (as measured by the log k_{bg} values).

catalyst ratio dramatically decreases the catalytic efficiency for the pNPOAc reaction, but affects only slightly the POAc reaction. This is easily understood with reference to Equations (11) and (12), that are the simple forms to which Equation (10) reduces when the rate-determining step is acylation of cat ($k_1' \ll k_2$) and deacylation of catAc ($k_1' \gg k_2$), respectively.

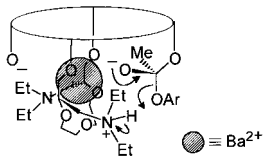
$$v_{cat}/v_{bg} = k_1[cat]_0/k_{bg} \quad \text{rate-determining acylation} \quad (11)$$

$$v_{cat}/v_{bg} = k_2[cat]_0/k_{bg}[ArOAc]_0 \quad \text{rate-determining deacylation} \quad (12)$$

The reaction of pNPOAc, for which the rate-determining step is mainly deacylation, approaches a situation in which the catalytic efficiency varies inversely to the ester concentration [Equation (12)], whereas the reaction of POAc, for which acylation is mainly rate determining, is nearly independent of substrate concentration [Equation (11)]. Extrapolation of the above considerations to acetate esters less reactive than POAc, that is, with leaving groups more basic than PO^-, leads to the prediction of lower catalytic efficiencies because k_1 is expected to decrease much more rapidly than k_{bg}. On the other hand, when the leaving group is less basic than $pNPO^-$, an increased rate of background methanolysis will practically obscure the catalyzed reaction. Thus, for one reason or another, the scope of the catalyst is restricted to acetate esters whose reactivity lies in the range approximately defined by the POAc – pNPOAc pair. Additional limitations are provided by the need of using not too high substrate to catalyst ratios and by the incursion of back-acylation processes.

The trifunctional catalyst: The search for enhanced catalysis in the three-catalyst versus two-catalyst system has not been as fruitful as desired, for the presence of the two diethylaminomethyl pendant groups did not result in improved activity when compared with the parent catalyst. The rate of acylation of **8**·[Ba] by pNPOAc is 1/9 as that of **3**·[Ba], and the corresponding figure with POAc is 1/2 (see Table 1, footnotes (c) and (d)). This can reasonably be explained by assuming that, in both cases, acylation of the catalyst is hindered by the sterically demanding diethylaminomethyl side arms. However, the fact that the two esters respond quite differently to the presence of the side arm, is a strong evidence that the protonated diethylaminomethyl group participates to the catalytic process. In fact, given that the protonated nitrogen in **8**H^+·[Ba] is deputed to help departure of the aryloxide leaving group of the tetrahedral intermediate of the acylation step, the rate-enhancing effect due to intramolecular general acid catalysis should be significant with the more basic PO^- ion (worse leaving group), but much smaller or even negligible, with the less basic $pNPO^-$ (better leaving group). Unfortunately, the pK_a of the diethylaminomethyl group in the reaction medium is unknown, but if one makes the reasonable assumption that its basicity is the same as that of the diisopropylethylamine buffer,[20] and considers that the B/BH^+ ratio in the buffer is 3:1, the conclusion is reached that only 1/4 of the pendant nitrogens of **8**·[Ba] are protonated. If this fraction is taken into account in the calculation of the pNPOAc/POAc ratio for the trifunctional catalyst one obtains a value of 110/4 or 28, which is practically coincident with the value of 24 of the background methanolysis, that can be viewed as a normal value in the given medium for a reaction in which formation of the tetrahedral intermediate is rate limiting. This contrasts with the exceedingly high pNPOAc/POAc ratio of 500 obtained with **3**·[Ba] and indicates that with the trifunctional catalyst **8**·[Ba] only the reaction with POAc benefits from intramolecular general acid catalysis.

To sum up, we believe that there is circumstantial evidence that the protonated side arm of **8**H^+·[Ba] does not fail in its duty to assist departure of the lazy leaving group of POAc as schematically depicted in **13**, but the catalytic efficiency is spoiled by unfavorable steric factors.



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Conclusion

In conclusion, this work precisely defines merits and limitations of a synthetic transacylation catalyst in which an ionized calix[4]arene hydroxyl acts as acyl-receiving and -releasing unit. A serious limitation comes from the relatively low basicity of the aryloxide nucleophile, which is held responsible for the low reaction rates with acetate esters of the less acidic phenols. It has been shown that, in principle, it is possible to accelerate the acylation step by going to a higher order catalytic process, namely, one in which a neighboring protonated amino group helps departure of a poor leaving group. In the given example, however, the advantage of the additional catalytic group is overshadowed by the steric hindrance of the side-arm bearing the catalytic group itself. Here as elsewhere, synthesis of designed multifunctional catalysts may lead to unsuccessful results, and awareness of imperfections and drawbacks in the design comes only a posteriori. The progress towards a higher order multifunctional catalysis requires a most careful design of intra- and intermolecular interactions for optimal positioning of catalytic units in a molecular framework. The results obtained in this work are useful in this direction.

Experimental Section

Instruments and general methods: Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on Bruker AC100, Bruker AC300 and Bruker AMX400 spectrometers. Chemical shifts are reported as δ values in ppm from tetramethylsilane as internal standard. Analytical thin-layer chromatography was carried out on silica gel plates (SiO_2, Merck 60 F_{254}). Optical rotations were measured on a Autopol III Rudolph Research Polarimeter. Mass spectra were performed with FINNIGAN MAT SSQ 710 (CI, CH_4), or with a Fisons Instruments VG-Platform Benchtop LC-MS (positive ion electrospray mass spectra). Melting points have been obtained in a nitrogen-sealed capillary on an

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electrothermal apparatus. Spectrophotometric measurements were carried out on Varian Cary 219 and diode array Hewlett Packard 8452A spectrophotometers. HPLC analyses were performed on a Hewlett Packard 1050 liquid chromatograph fitted with a UV/VIS detector operating at 230 nm. Samples were analyzed on a Supelcosil LC-18 DB column (25 cm × 4.6 mm I.D., particle size 5 μm).

Error limits of rate constants are in the order of ±5% (time course kinetics) and ±10% (initial rate method). Nonlinear least-squares calculations were carried out using the program Sigma Plot for Windows 1.02 (Jandel Scientific).

Materials: Most of the solvents and all reagents were obtained from commercial supplies and used without further purification. Dichloromethane and acetonitrile employed in the syntheses were freshly distilled and stored over 3 Å molecular sieves. 1,3-Dibenzyloxy-*p-tert*-butylcalix[4]-arene[21] and ditosylate **10**[22] have been prepared according to literature procedures. *p-tert*-Butylcalix[4]arene-crown-5 (**1**)[23] and monoacetoxy derivative **4**[24] were available from previous investigations. pNPOAc (Fluka) and POAc (Fluka) were purified as reported in the literature.[12] mNPOAc and pCPOAc were prepared according to a standard procedure.[25] Solutions of pNPOAc and mNPOAc were freshly prepared and stored at 5 °C. $Ba(ClO_4)_2$ (Aldrich) was used without further purification after determination of the water content of the commercial sample by thermogravimetric analysis. Other materials were as reported previously.[6a]

Warning! Care was taken when handling diisopropylethylammonium perchlorate and barium perchlorate because they are potentially explosive.[26] No accident occurred in the course of the present work.

25,27-Dibenzyloxy-*p-tert*-butylcalix[4]arene-26,28-[2,10-bis(allyloxymethyl)]-crown-5 (11): A solution of calixarene **9** (0.45 g, 0.54 mmol), ditosylate **10** (0.42 g, 0.65 mmol), and NaH (0.05 g, 1.09 mmol) in dry MeCN (270 mL) was refluxed for one day. The solution was then acidified with HCl (200 mL, 1N), the acetonitrile was removed under reduced pressure, and the aqueous layer extracted with CH_2Cl_2 (2 × 100 mL). The organic extract was washed with water and dried over anhydrous $MgSO_4$. After removal of the solvent, the pure product was obtained as a white solid by flash chromatography on silica gel (diethyl ether/hexane 2:1). Yield: 63%; m.p. 143 °C (MeOH); $[\alpha]_{598}^{25} = -10.5$ ($c = 0.0343$ in MeOH/$CHCl_3$ 6:4); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): $\delta = 0.82$ (s, 18H; $C(CH_3)_3$), 1.34 (s, 18H; $C(CH_3)_3$), 2.95 (d, $^2J = 12.4$ Hz, 2H; H_{eq}), 3.10 (d, $^2J = 13.1$ Hz, 2H; H_{eq}), 3.17 – 3.21 (m, 2H; CH_2=CHCH$_2$OCH*H*), 3.40 – 3.44 (m, 2H; CH_2=CHCH$_2$OC*H*H), 3.40 – 3.67 (m, 8H; ArOCH$_2$CHROCH_2CH_2), 3.69 – 3.76 (m, 4H; CH_2=CHCH_2), 3.96 – 4.03 (m, 4H; ArOC*H*HC*H*OR), 4.28 (d, $^2J = 12.4$ Hz, 2H; H_{ax}), 4.47, (d, $^2J = 13.1$ Hz, 2H; H_{ax}), 4.66 (d, $^2J = 10.8$ Hz, 2H; C*H*HPh), 4.68 – 4.70 (m, 2H; ArOCH*H*CHOR), 4.79 (d, $^2J = 10.8$ Hz, 2H; CH*H*Ph), 5.02 – 5.10 (m, 4H; CH_2=CH), 5.60 – 5.67 (m, 2H; CH_2=C*H*), 6.37 (s, 4H; Ar-H), 7.03 – 7.07 (m, 4H; Ar-H), 7.31 – 7.40 (m, 10H; Ph-H); ^{13}C NMR (75.5 MHz, $CDCl_3$, 300 K): $\delta = 31.0$, 31.6 (q, $C(CH_3)_3$), 31.6 (t, ArCH$_2$Ar), 33.0, 33.4 (s, $C(CH_3)_3$), 70.4, 70.9, 71.0, 72.1, 72.3, 78.1, 78.8 (t, ArOCH$_2$CH(CH$_2$OCH$_2$CH=CH$_2$)OCH$_2$CH$_2$, ArOCH$_2$Ph; 2s, CHRO), 116.3 (t, CH_2=CH), 124.2, 124.6, 125.0, 126.6 (d, *m*-Ar), 127.9, 128.3, 129.9 (d, *o*-, *m*-, *p*-Ph), 131.3, 131.6, 133.8, 134.1 (s, *o*-Ar), 137.1 (s, *i*Ph), 137.3 (d, CH_2=CH), 144.4, 146.0 (s, *p*-Ar), 154.9, 157.2 (s, *i*Ar); MS (CI, CH_4): *m*/*z* (%): calcd for $C_{74}H_{94}O_9$ 1126.7; found 1127.2 (100) $[M]^+$.

25,27-Dihydroxy-*p-tert*-butylcalix[4]arene-26,28-[2,10-bis(hydroxymethyl)]-crown-5 (12): A suspension of the bis-allyloxymethyl derivative **11** (0.39 g, 0.34 mmol), Pd/C (0.39 g) and TsOH (0.39 g, 4.11 mmol) in a mixture of ethanol/H_2O 7:1 (21 mL) was heated to reflux. After 6 h, the catalyst was filtered off on a bed of celite, the filter was washed with CH_2Cl_2 (2 × 4 mL) and ethyl acetate (2 × 4 mL) and the solvents were removed under reduced pressure. The residue was then dissolved in ethyl acetate (15 mL), the organic layer was washed with water (4 × 10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, pure compound **12** was obtained as a white solid with no need for further purification (70%). M.p. > 300 °C; $[\alpha]_{598}^{25} = +2.46$ ($c = 0.0203$ in MeOH/CH_2Cl_2 7:3); ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): $\delta = 1.08$ (s, 18H; $C(CH_3)_3$), 1.26 (s, 18H; $C(CH_3)_3$), 3.32 (d, $^2J = 12.4$ Hz, 2H; H_{eq}), 3.40 (d, $^2J = 13.1$ Hz, 2H; H_{eq}), 3.69 – 3.73 (m, 2H, ArOCH$_2$C*H*OR), 3.92 – 4.24 (m, 18H; ArOCH_2-CHORCH_2CH_2, *H*OCH_2), 4.13 (d, $^2J = 13.1$ Hz, 2H; H_{ax}), 4.42, (d, $^2J = 12.4$ Hz, 2H; H_{ax}), 6.90 (d, $^4J = 2.3$ Hz, 2H; Ar-H), 6.98 (d, $^4J = 2.7$ Hz, 2H; Ar-H), 6.99 (d, $^4J = 2.7$ Hz, 2H; Ar-H), 7.08 (d, $^4J = 2.3$ Hz, 2H; Ar-H), 7.95 (s, 2H; ArOH); ^{13}C NMR (75.5 MHz, $CDCl_3$, 300 K): $\delta = 29.6$, 31.0 (q, $C(CH_3)_3$), 31.0, 31.6 (t, ArCH$_2$Ar), 33.7, 34.0 (s, $C(CH_3)_3$), 64.5, 68.6, 70.8, 75.6 (t, ArOCH$_2$CH(CH$_2$OH)OCH$_2$CH$_2$), 79.7 (d, CHRO), 125.0, 125.2, 125.4, 126.3 (d, *m*-Ar), 126.7, 128.1, 132.4, 133.2 (s, *o*-Ar), 141.6, 147.2 (s, *p*-Ar), 149.3, 150.1 (s, *i*Ar); MS (CI, CH_4): *m*/*z* (%): calcd for $C_{54}H_{74}O_9$ 867.2; found: 866.5 (100) $[M]^+$.

25,27-Dihydroxy-*p-tert*-butylcalix[4]arene-26,28-[2,10-bis(*N*,*N*-diethylaminomethyl)]-crown-5 (6): Triflic anhydride (0.18 mL, 1.05 mmol) was added to an ice-bath cooled solution of compound **12** (0.19 g, 0.21 mmol) and 2,6-di-*tert*-butylpyridine (0.24 mL, 1.05 mmol) in dry CH_2Cl_2 (15 mL). The mixture was stirred for 30 min under nitrogen, then was poured in a separatory funnel containing a saturated solution of $NaHCO_3$ in water (10 mL). After vigorous shaking the organic layer was separated, washed with water (2 × 8 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product was carefully dried under high vacuum, then dissolved in CH_2Cl_2 (15 mL) under nitrogen and diethylamine (0.19 mL, 1.89 mmol) was added to the solution. The reaction proceeded at r.t. overnight and was then quenched by adding a saturated solution of $NaHCO_3$ in water (10 mL). After vigorous shaking the organic layer was separated, washed with water (2 × 8 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the pure product was obtained by flash chromatography on silica gel (gradient from hexane/ethyl acetate 9:4 to hexane/ethyl acetate/triethylamine 9:4:0.5). Yield: 65%; m.p. 161 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): $\delta = 0.87$ (s, 18H; $C(CH_3)_3$), 0.99 (m, 12H; NCH$_2$CH_3), 1.32 (s, 18H; $C(CH_3)_3$), 2.48 – 2.65 (m, 12H; NCH_2CH$_3$, NCH_2CHOR), 3.26 (d, $^2J = 13.0$ Hz, 2H; H_{eq}), 3.30 (d, $^2J = 13.0$ Hz, 2H; H_{eq}), 3.79 – 3.82 (m, 2H; ArOCH$_2$C*H*OR), 3.94 – 4.08 (m, 12H; ArOCH_2CHROCH_2CH_2), 4.32 (d, $^2J = 13.0$ Hz, 2H; H_{ax}), 4.46 (d, $^2J = 13.0$ Hz, 2H; H_{ax}), 6.69 (s, 4H; Ar-H), 6.98 (s, 2H; ArOH), 7.07 – 7.09 (m, 4H; ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$, 300 K): $\delta = 11.9$ (q, NCH$_2$CH_3), 30.9, 31.7 (q, C(CH_3)$_3$), 30.9, 31.3 (t, ArCH$_2$Ar), 33.7 (s, $C(CH_3)_3$), 47.6 (t, NCH$_2$CH$_3$), 54.1 (t, NCH$_2$CHOR), 69.1, 70.9, 77.7 (t, ArOCH$_2$CHROCH$_2$CH$_2$), 79.0 (d, CHRO), 124.7, 124.9, 125.1, 125.3 (d, *m*-Ar), 127.6, 128.1, 132.0, 133.4 (s, *o*-Ar), 141.0, 146.5 (s, *p*-Ar), 150.0, 150.8 (s, *i*Ar); MS (CI, CH_4): *m*/*z* (%): calcd for $C_{62}H_{92}O_7N_2$ 976.7; found: 976.8 (100) $[M]^+$.

Kinetic measurements: Spectrophotometric and HPLC rate measurements were carried out as previously reported.[6a] Eluent and flow rate are indicated in the given order for HPLC monitoring of the following processes: liberation of mNPOH in the background methanolysis of mNPOAc and liberation of phenol (POH) in the background methanolysis of POAc (MeOH/H_2O 40:60, 0.6 mL min^{-1}), liberation of pCPOH in the background methanolysis of pCPOAc and acetyl transfer from pNPOAc to pCPOH (MeOH/H_2O 1:1, 0.6 mL min^{-1}), accumulation of catAc in the catalyzed methanolysis of pNPOAc, mNPOAc, pCPOAc, POAc carried out in the presence of **3**·[Ba] (MeOH, 1 mL min^{-1}), liberation of POH in the methanolysis of POAc carried out in the presence of calixcrown **8**·[Ba] (MeOH/H_2O 1:1, *v*/*v*) containing 10 mM sodium 1-heptanesulfonate and 17.5 mM NaH_2PO_4/H_3PO_4 buffer, pH 3, 0.50 mL min^{-1}). The latter mobile phase was prepared daily and stored at 4 °C when unused.

Acknowledgement

Financial contribution from MURST (Progetto Dispositivi Supramolecolari) is greatly acknowledged. We also thank C.I.M. (Centro Interdipartimentale Misure) of the Parma University for the use of the NMR and mass spectrometry instruments.

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[10] Evidence was obtained (see ref. [5b]) that a significant fraction of **4** is in the form $(\mathbf{5}\cdot[\mathrm{Ba}])^{+}$ in the reaction medium.
[11] In these cases the time concentration profiles of the liberated phenols were not obtained because the spectrophotometric technique was not applicable due to the negligible dissociation of the liberated phenols in the reaction medium.
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[16] A moderate mass-low retardation effect due to the liberated pNPOH might well have gone undetected in the [catAc] versus time profile shown as curve c in Figure 1, because the steady-state value of [catAc] is very close to the saturation value $[\mathrm{cat}]_0$.
[17] Evidence was obtained (see ref. [5b]) that MeO^- is the active nucleophile under the given conditions.
[18] As pointed out by Kirsch and Jencks (ref. [2]), a discrete intermediate with definite stability is not strictly required for the argument. An equally acceptable description can be based on a skewed transition state, the nature of which changes as the leaving group becomes worse. For a discussion of a concerted mechanism for nucleophilic reactions of esters, see: a) J. P. Guthrie, *J. Am. Chem. Soc.* **1991**, *113*, 3941 – 3949; b) A. Williams *Adv. Phys. Org. Chem.* **1992**, *27*, 1 – 55.
[19] A β value larger than 1 is not surprising. The equilibrium for the addition of an acyl group from a constant acyl donor has a β value of 1.7 (see ref. [12]). Thus a β value of 1.4 means that in terms of change of the charge of the leaving group the reaction has proceeded some 1.4/1.7 of the way toward completion.
[20] This assumption is probably optimistic. A lower basicity may result from electrostatic repulsion between the protonated nitrogen and the divalent metal cation.
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Received: April 16, 1999
Revised version: October 3, 1999 [F1731]

  0947-6539/00/0608-1330 $ 17.50+.50/0