JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2006; **19:** 630–636
Published online 6 November 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.1101

Catalysis and inhibition of ester hydrolysis in the presence of resorcinarene hosts functionalized with dimethylamino groups†

Giorgio Cevasco,[1] Sergio Thea,[1]* Daniele Vigo,[1]‡ Andrew Williams[2] and Flora Zaman[2]

[1]Dipartimento di Chimica e Chimica Industriale dell'Università di Genova, C.N.R., Consiglio Nazionale delle Ricerche, Via Dodecaneso, 31,16146 Genova, Italy
[2]University Chemical Laboratory, Canterbury, Kent CT2 7NH, UK

Received 15 February 2006; revised 18 May 2006; accepted 29 May 2006

ABSTRACT: Complexation and catalysis of two calixresorcinarene (**RES**) derivatives with nucleophilic *N,N*-dimethylamino functions attached to their upper rims in the hydrolysis of carboxylate and sulfonate esters of 4-nitrophenol and 2,4-dinitrophenol have been investigated. Rate constants obey the complexation equation:

$$k_{obs} = \frac{k_b \times K_S + k_c[\text{Host}]}{K_S + [\text{Host}]}$$

Values of the dissociation constant (K_s) of the complexes are within the range exhibited by other systems such as cyclodextrins–ester complexes. The reactions of sulfonate esters only exhibit inhibition by the macrocyclic hosts. The reactions of the carboxylate esters exhibit catalysis and inhibition depending on the pH of the system. It is proposed that the dimethylamino function in **RES3** and **RES5** behaves as a nucleophile to form a reactive acylammonium species which subsequently decomposes and regenerates the catalytic amine.

In the reaction of substituted phenyl acetates with **RES3** the effective charge on the leaving oxygen in the complexed state (+0.88) is slightly more positive than that in the free ester (+0.70). The effective charge on the leaving oxygen in the transition structure is substantially more positive (+0.04 units) than in a model intramolecular reaction of tertiary dimethylamines with aryl esters (−0.53 units). The influence of the host on the reaction in the complex includes an electronic component which is ascribed to solvation of the transition structure of the rate-limiting step by water molecules located within the cavity of the host. It is suggested that this solvation is stronger than that occurring in the transition state for the model intramolecular reaction. Copyright © 2006 John Wiley & Sons, Ltd.
Supplementary electronic material for this paper is available in Wiley Interscience at http://www.interscience.wiley.com/jpages/0894–3230/supplmat/

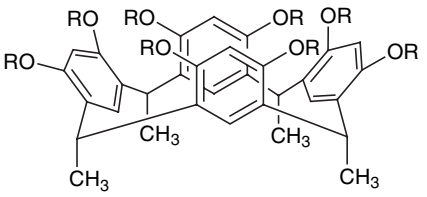
KEYWORDS: calixresorcinarenes; molecular receptors; catalysis; esterolysis

INTRODUCTION

The study of concave, macrocyclic molecules as host analogs of enzymes has enjoyed considerable success, particularly of those derived from cyclodextrins[1] and calixarenes.[2] In this paper we describe the synthesis of water soluble cyclophane derivatives, that is, calixresorcinarenes **RES3** and **RES5**, which possess a concave region suitable to act as a receptor for substrate complexation and hold functions which are potential nucleophilic catalysts, and their employment in structure-reactivity investigations. The reason for choosing this cyclophane structure is that it has the potential of being modified easily on its rims with a variety of catalytic and binding groups which could be useful in a future combinatorial approach. Moreover, it can be cheaply and easily prepared in large quantity. We believe that design of highly active and selective artificial enzymes could in future be assisted by combinatorial studies of structural libraries of potential catalysts and identification of the structure giving optimum activity.

The scope of the catalytic activity of **RES3** and **RES5** (structures are shown in Chart 1 together with those of their precursors **RES1**, **RES2**, and **RES4**) is measured against the fission of the carboxylate and sulfonate esters displayed in Chart 2 (identity of substituted phenyl acetates is shown in Table 3).

**Correspondence to:* S. Thea, Dipartimento di Chimica e Chimica Industriale dell'Università di Genova, C.N.R., Consiglio Nazionale delle Ricerche, Via Dodecaneso, 31,16146 Genova, Italy.
E-mail: sergio.thea@chimica.unige.it
†Dedicated to the memory of Professor Carlo Dell'Erba (1933–2005).
‡In partial fulfillment of his PhD thesis.



RES1 R = H

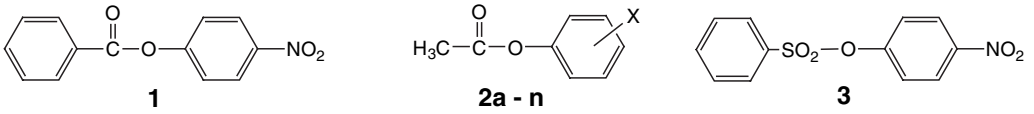
RES2 R = $CH_2CO_2C_2H_5$

RES3 R = $CH_2CONH(CH_2)_3N(CH_2)_2$

RES4 R = $(CH_2)_3CO_2C_2H_5$

RES5 R = $(CH_2)_3CONH(CH_2)_3N(CH_3)_2$

Chart 1.



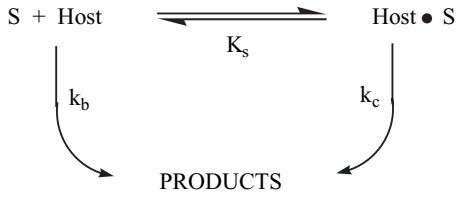
1 **2a - n** **3**

Chart 2.

RESULTS AND DISCUSSION

The kinetics of the reactions of the esters **1–3** (S in Scheme 1) at *ca* 0.01 mM in aqueous buffered solutions containing an excess of the potential host molecule (Host, i.e., **RES3** and **RES5**) exhibited good pseudo first order rate dependencies in the concentration of ester over at least 90% of the total reaction. Generally the kinetics obeyed a rate law (Eqn (1)) which is consistent with the mechanism shown in Scheme 1.

$$k_{obs} = \frac{k_b \times K_S + k_c[\text{Host}]}{K_S + [\text{Host}]} \qquad (1)$$



Scheme 1.

In some instances, however, (when [Host] $\ll K_S$, where K_S is the dissociation constant of the host-guest complex) the rate constant, k_{obs}, was linear in host concentration.

In the case of the 4-nitrophenyl carboxylate esters, lowering the pH changed the effect from inhibition (Fig. 1A) to catalysis (Fig. 1B), due to the background hydrolysis (k_b) becoming slower than the **RES3** catalyzed hydrolysis as the hydroxide ion concentration decreased, as shown in Fig. 2.

The observed effect implies that the kinetic studies at the pH where inhibition changes to catalysis are subject to substantial error in measuring K_S because Eqn (1) predicts that changing [Host] has no effect on the observed rate constant (when $k_b = k_c$). On the contrary, in the hydrolysis of 4-nitrophenyl benzenesulfonate the effect of **RES3** was only inhibition. Although experiments were carried out in a reduced pH range (11.70–13.01), it may be predicted that, in this latter case, rate inhibition will prevail also at lower pHs, owing to the slope of the linear dependence of log k_{OH} versus pH being unit.

Previous work has shown that the values of K_S for dissociation of the 4-nitrophenyl ester complexes with **RES3** depend on the nature of the acyl function.[3] However, the values of K_S for **RES** hosts measured in this

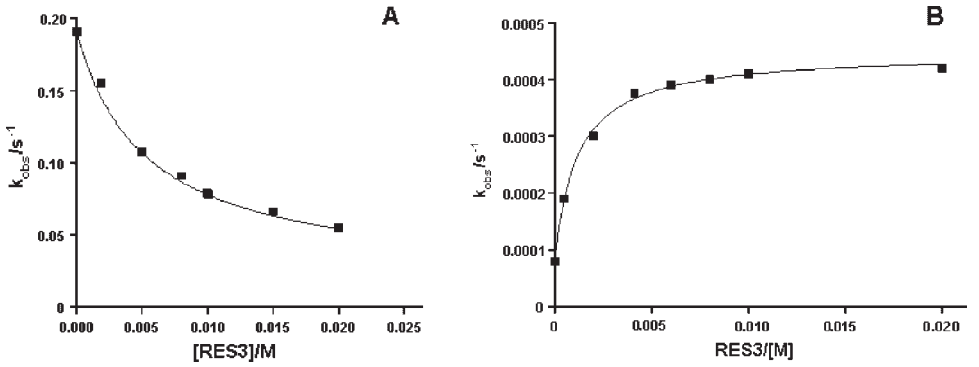


Figure 1. Reaction of **RES3** and 4-nitrophenyl benzoate **1** with increasing concentrations of **RES3** at pH 12.7 (A) or pH 9.6 (B), at 25 °C and 0.1 M ionic strength (made up with KCl)

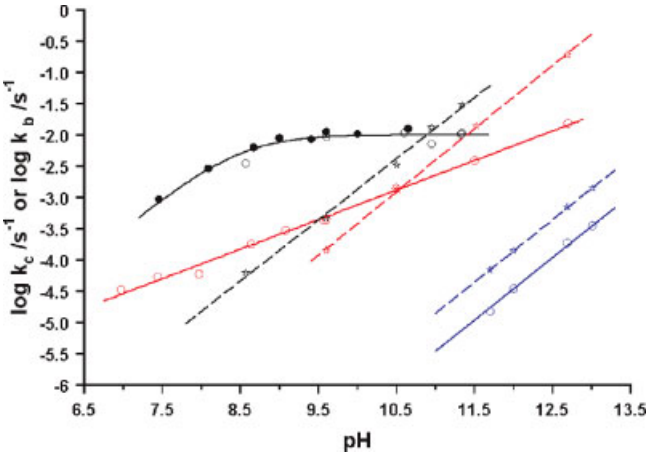


Figure 2. pH-Dependence of the **RES3**-catalyzed (log k_c) and uncatalyzed (log k_b) hydrolyses of esters **1**, **2a**, and **3**. Identification is as follows. Colors, lines and symbols: red, ester **1**; black, ester **2a**; blue, ester **3**; solid lines refer to log k_c (circles); dashed lines refer to log k_b (stars). Open symbols refer to data from present work, closed ones to data from Ref. 3. Line for the acetate/**RES3** reaction is from Eqn (2) with k_c^{max} from Table 3 and p$K_a = 8.49$. k_b values for all three esters agree nicely with values for the hydroxide ion catalyzed fission of the corresponding esters (ester 1: $k_{OH} = 3.95\,M^{-1}\,s^{-1}$, this work, see Table 1; ester **2a**: $k_{OH} = 9.5\,M^{-1}\,s^{-1}$, from Ref. 4; ester **3**: $k_{OH} = 1.6 \times 10^{-2}\,M^{-1}\,s^{-1}$, from Ref. 5) [This figure is available in colour online at www.interscience.wiley.com]

work (shown in Table 1) indicate that in general fairly strong binding takes place in ester complexes.

The pH-dependences of the k_c term for the **RES3**-catalysed fission of 4-nitrophenyl benzoate and acetate should fit Eqn (2), corresponding to a simple ionization taking place within the pH range explored (potentiometric titration of **RES3**, and **RES5** as well, gave good values of the ionization constants K_a, suggesting that no significant interaction occurred among the dimethylamino groups, see Supplementary Material). The results for the 4-nitrophenyl acetate and **RES3** appear to fit Eqn (2) nicely, but the kinetics of the benzoate seem to follow a flattened sigmoid pH dependence with a relatively low slope (0.47) over

$$k_c = \frac{k_c^{max}}{10^{-pH}/K_a + 1} \qquad (2)$$

the entire range studied, at variance with 4-nitrophenyl benzenesulfonate, whose dependence has unit slope. At this stage, it is not possible to advance any simple explanation about this fact; it seems reasonable, however, that in the benzoate reaction specific host-guest interaction take place, most likely involving the dimethylamino groups as nucleophiles. A tentative explanation could be that, upon ionization, the **RES3**/benzoate complex has a different behavior than the free **RES3**, involving interaction between the ionizing functions. As for 4-nitrophenyl benzenesulfonate, results are consistent with its 'simple' encapsulation into **RES3** cavity, followed by slower reaction of the host-guest complex with hydroxide ion. This result is in line with the moderate reactivity of aryl sulfonates toward amines.[6]

The pH-dependences of k_c for the acetate and benzoate esters are consistent with the neutral dimethylamino functions being involved in the catalysis. It is likely that the dimethylamino function in **RES3** and **RES5** behaves as a nucleophile to form a reactive acylammonium species which subsequently decomposes and regenerates the catalytic amine (Scheme 2).

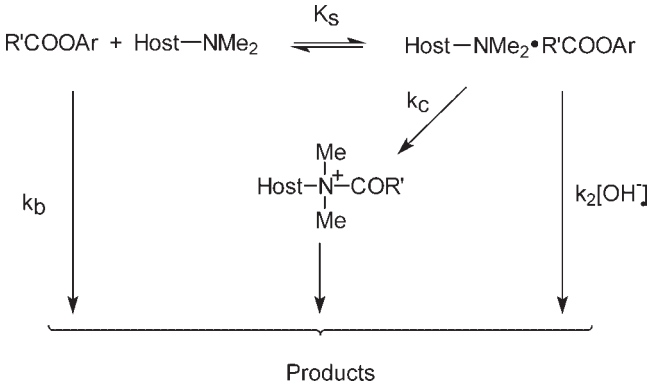
Comparison of macrocycle reactivity with that of a model nucleophile

The catalytic activity of the hosts can be measured by the ratio k_c/K_S which registers the difference in free energy between the transition structure of the rate-limiting step and the reactant state where host and ester substrate are free.[1] This ratio therefore could be compared with k_{Nuc}, the second order rate constant for the model catalyst $CH_3CONH(CH_2)_3N(CH_3)_2$ (1-acetylamino-3-dimethylaminopropane, compound **4**), which also measures the free energy difference between reactants (free ester and catalyst) and the transition state. The reactivities k_{Nuc} of the model **4** against esters **1** and **2a** are shown in Table 2. In a previous report,[3] the reactivity of trimethylamine was employed as a model, suggesting that in the hydrolysis of ester **2a** the reaction flux taken by the intramolecular, **RES3**-catalyzed route (as compared to the intermolecular one) is some 99% of the total. For the dimethylamino group of **4**, pK_a was estimated to be 9.13[7] (a pK_a value of 9.23 has been reported for *N*-(3-dimethylaminopropyl)-acrylamide.[8]) A further refinement of the model was carried out as follows: for the intermolecular reactions of a hypothetical dimethylamino group with a pK_a of 8.49 (the same as that of **RES3**) with ester **2a** the bimolecular rate constant of 6.5×10^{-3} can be calculated from that of **4**, assuming a β_{Nuc} of 0.9,[9] and the respective pK_a values. Supposing that the same β_{Nuc} value holds also for the aminolysis of aryl benzoates (Um *et al.*[10] report a β_{Nuc} of 0.85 for the reaction of 4-nitrophenyl benzoate and secondary alicyclic amines), a rate constant of $1.1 \times 10^{-3}\,M^{-1}\,s^{-1}$ can be reckoned for ester **1** analogously. Table 2 also shows the k_{Nuc}(calc) values calculated for a dimethylamino nucleophile with p$K_a = 8.94$, model for the intermolecular reaction of **RES5**, as well as the k_c(corr) values (k_c(corr) = k_c/8, see footnote *e* in Table 2). The comparison of model with host reactivity is included in Table 2 and the ratio [(k_c(corr)/K_S)/k_{Nuc}(calc)] shows that there are significant rate enhancements in the ester hydrolysis catalyzed by **RES3** and **RES5** as compared with the model nucleophile (in the less favorable case, i.e., the **RES3** catalyzed hydrolysis of 4-nitrophenyl acetate **2a**, the reaction flux taken by the intramolecular route is some 97%).

Table 1. Rate parameters for the hydrolysis of 4-nitrophenyl esters in the presence of calixresorcinarene hosts. Solvent water, ionic strength maintained at 0.1 M with KCl, 25 °C[a]

[Host]/mM[b]	Host/ester	pH	k_b (s^{-1})	k_c (s^{-1})	K_s (mM^{-1})	Effect[c]	k_c/K_S ($M^{-1}\,s^{-1}$)
	RES3						
0–60	**1**[d]	6.97		$(3.30 \pm 0.03) \times 10^{-5}$	—[e]	C	
0–60		7.44		$(5.37 \pm 0.02) \times 10^{-5}$	—[e]	C	
0–60		7.97		$(5.89 \pm 0.01) \times 10^{-5}$	—[e]	C	
0–60		8.64		$(1.76 \pm 0.19) \times 10^{-4}$	—[e]	C	
0–60		9.08		$(2.95 \pm 0.01) \times 10^{-4}$	—[e]	C	
0–60		9.57		$(4.40 \pm 0.02) \times 10^{-4}$	—[e]	C	
5–20		9.60	$(1.41 \pm 0.03) \times 10^{-4}$	$(4.41 \pm 0.08) \times 10^{-4}$	1.09 ± 0.13	C	0.40
2.5–20		10.51	$(1.32 \pm 0.02) \times 10^{-3}$	$(1.39 \pm 0.01) \times 10^{-3}$	—[f]	—[f]	
2.5–20		11.52	$(1.39 \pm 0.01) \times 10^{-2}$	$(3.89 \pm 0.26) \times 10^{-3}$	3.60 ± 0.30	I	1.08
2.5–20		12.69	$(1.91 \pm 0.02) \times 10^{-2}$	$(1.53 \pm 1.14) \times 10^{-2}$	6.24 ± 1.08	I	2.45
2.5–20	**2a**	8.57	$(6.21 \pm 0.01) \times 10^{-5}$	$(3.48 \pm 0.78) \times 10^{-3}$	43 ± 15	C	0.081
2.5–20		9.60	$(4.72 \pm 0.01) \times 10^{-4}$	$(9.30 \pm 1.40) \times 10^{-3}$	28 ± 7	C	0.33
2.5–20		10.60	$(3.34 \pm 0.01) \times 10^{-3}$	$(1.08 \pm 0.13) \times 10^{-2}$	15 ± 6	C	0.69
2.5–20		10.95	$(1.30 \pm 0.02) \times 10^{-2}$	$(7.19 \pm 0.15) \times 10^{-3}$	2.5 ± 1.2	I	2.90
2.5–20		11.34	$(3.02 \pm 0.01) \times 10^{-2}$	$(1.07 \pm 0.06) \times 10^{-2}$	5.8 ± 1.1	I	1.84
5–20	**3**[e]	11.70	$(6.91 \pm 0.04) \times 10^{-5}$	$(1.04 \pm 0.01) \times 10^{-5}$	4.06 ± 0.01	I	0.00256
5–20		12.00	$(1.38 \pm 0.01) \times 10^{-4}$	$(3.47 \pm 0.12) \times 10^{-5}$	3.06 ± 0.15	I	0.0113
5–20		12.69	$(7.79 \pm 0.03) \times 10^{-4}$	$(1.87 \pm 0.09) \times 10^{-4}$	2.56 ± 0.19	I	0.073
5–20		13.01	$(1.38 \pm 0.01) \times 10^{-4}$	$(3.54 \pm 0.22) \times 10^{-4}$	3.62 ± 0.25	I	0.098
	RES5						
5–20	**1**	10.51	$(1.40 \pm 0.01) \times 10^{-3}$	$(5.21 \pm 1.43) \times 10^{-4}$	9.7 ± 3.6	I	0.053
2.5–20		11.48	$(1.39 \pm 0.01) \times 10^{-2}$	$(8.51 \pm 1.7) \times 10^{-4}$	4.8 ± 1.4	I	0.177
2.5–20		12.03	$(4.05 \pm 0.02) \times 10^{-2}$	$(3.19 \pm 1.85) \times 10^{-3}$	3.5 ± 0.6	I	0.091
2.5–20		12.69	$(1.90 \pm 0.01) \times 10^{-1}$	$(1.12 \pm 0.48) \times 10^{-2}$	3.7 ± 0.3	I	3.02
5–20	**2a**	10.51	$(4.18 \pm 0.01) \times 10^{-3}$	$(1.39 \pm 0.60) \times 10^{-2}$	34 ± 30	C	0.41
2.5–20		11.48	$(4.16 \pm 0.02) \times 10^{-2}$	$(3.09 \pm 0.05) \times 10^{-2}$	2.5 ± 0.4	I	12.4
2.5–20		12.03	$(1.29 \pm 0.01) \times 10^{-1}$	$(9.28 \pm 0.94) \times 10^{-2}$	1.9 ± 2	I	48.8
2.5–20		12.69	$(5.16 \pm 0.02) \times 10^{-2}$	$(3.30 \pm 0.20) \times 10^{-1}$	13 ± 3	I	25.6

[a] Concentration of esters *ca* 0.01 mM.
[b] Each determination from at least four data points.
[c] C = catalysis; I = inhibition.
[d] Second order rate constant for hydroxide ion attack on the benzoate ester measured in the range of [KOH] 0.05–0.1 M is $(3.95 \pm 0.04)\ M^{-1}s^{-1}$ at 0.1 M ionic strength maintained with KCl, 25 °C.
[e] The rate constants $k_{obs} - k_b$ at [**RES3**] = 60 mM were normalized to the value $k_c = 4.4 \times 10^{-4}\ s^{-1}$ for pH 9.60. It is assumed that $K_S << [\mathbf{RES3}]$ under these conditions.
[f] No effect of host concentration in the range studied.



Scheme 2. Proposed mechanism for catalysis by **RES3** and **RES5**

Effective charges during reactions in the presence of RES3

The values of K_S, k_c^{max} and k_c^{max}/K_S for reaction of substituted phenyl acetates corresponding to the plateau region of the pH-dependence of the reaction of **RES3** are recorded in Table 3 together with k_{OH} for the non-catalyzed reaction.

K_S, k_c^{max} and k_c^{max}/K_S obey Brønsted Eqns (3)–(6):

$$\log k_{OH} = -0.34 \pm 0.10\ pK_a^{ArOH} + 3.63 \pm 0.67 \quad (3)$$

$$\log K_S = -0.18 \pm 0.10\ pK_a^{ArOH} + 0.73 \pm 0.69 \quad (4)$$

$$\log k_c^{max} = -0.84 \pm 0.11\ pK_a^{ArOH} + 4.25 \pm 0.80 \quad (5)$$

$$\log\left(\frac{k_c^{max}}{K_S}\right) = -0.67 \pm 0.16\ pK_a^{ArOH} + 4.97 \pm 1.16 \quad (6)$$

The effective charge maps[11] of the reaction of **RES3** and hydroxide ion with substituted phenyl acetates may be derived from Eqns (3)–(6) and are illustrated in Scheme 3. The effective charges for the hydroxide ion reaction with free acetate esters are similar to those determined from previous measurements.[12] The com-

Table 2. Rate parameters for the hydrolysis of substituted 4-nitrophenyl esters **1** and **2a** in the presence of hosts or their model **4**[a]

Ester	Model or host	N[b]	Range of [**4**] (M^{-1})	k_{Nuc}(exp)[c] ($M^{-1}s^{-1}$)	k_{Nuc}(calc)[d] ($M^{-1}s^{-1}$)	pH	k_c(corr)[e] (s^{-1})	k_c(corr)/K_S	(k_c(corr)/K_S)/k_{Nuc}(calc)
1	**4**	7	0–0.4	4.21×10^{-3}	1.1×10^{-3}[f] 2.84×10^{-3}[g]				
2a	**4**	3	0–0.5	2.43×10^{-2}	6.5×10^{-3}[f], 1.64×10^{-2}[g]				
1	**RES3**					11.52	4.86×10^{-4}	0.135	123
2a	**RES3**					11.34	1.34×10^{-3}	0.231	36
1	**RES5**					12.03	3.99×10^{-4}	0.114	40
2a	**RES5**					11.48	3.86×10^{-3}	1.54	94

[a] Water solvent, ionic strength maintained at 0.1 M with KCl, 25 °C.
[b] Number of data points.
[c] Measured rate constant.
[d] Calculated for the pK_as indicated in footnotes f and g.
[e] $k_c/8$ to allow for the equivalent eight dimethylamino groups in the RES (data are from Table 1).
[f] Calculated for pK_a = 8.49.
[g] Calculated for pK_a = 8.94.

plexation step exhibits only a small β_{eq} corresponding to only a slight increase in positive effective charge on the phenolic oxygen; this implies that only a small component of the driving force of the complexation process involves an electrophilic interaction with the complexed ester.

The effective charge measured for the transition structure of the rate limiting step (+0.04) is substantially more positive than that found in the intramolecular attack by the dimethylamino group on the ester in substituted phenyl 4-*N,N*-dimethylaminobutyrates and 5-*N,N*-dimethylaminovalerates and the intermolecular reaction between phenyl acetates and trimethylamine.[13] The difference in effective charge of 0.57 units between **RES3** (+0.04) catalysis and that of the intramolecular reaction (−0.53) corresponds to 34% of the total charge change on the phenolic oxygen (1.7 units) from reactant to product states.

The increased positive charge in the transition structure of catalysis by the **RES3** could be due to an electrophilic component providing a stronger interaction than that in the transition state in the non-host reaction. It is possible that the negative charge developing in the oxyanion-like transition structure (Scheme 4) interacts with electrophiles (E) in the host-guest complex causing a net reduction of observed negative charge. The reduced negative charge on the departing ether oxygen in the transition structure of the intramolecular reaction has precedence in the proteinase catalyzed hydrolysis of esters which are proposed to arise from electrophilic interactions between peptide NH groups in the protein architecture and the oxyanion-like transition structure.[14] The identity of the electrophilic interacting group (E) could be the NH of the amido function of **RES3** but it could equally well be non-bulk water molecules accompanying the ester in the host-guest complex. In either case the results suggest that such interaction is more effective at withdrawing electrons than in the transition structure of the reaction in free solution.

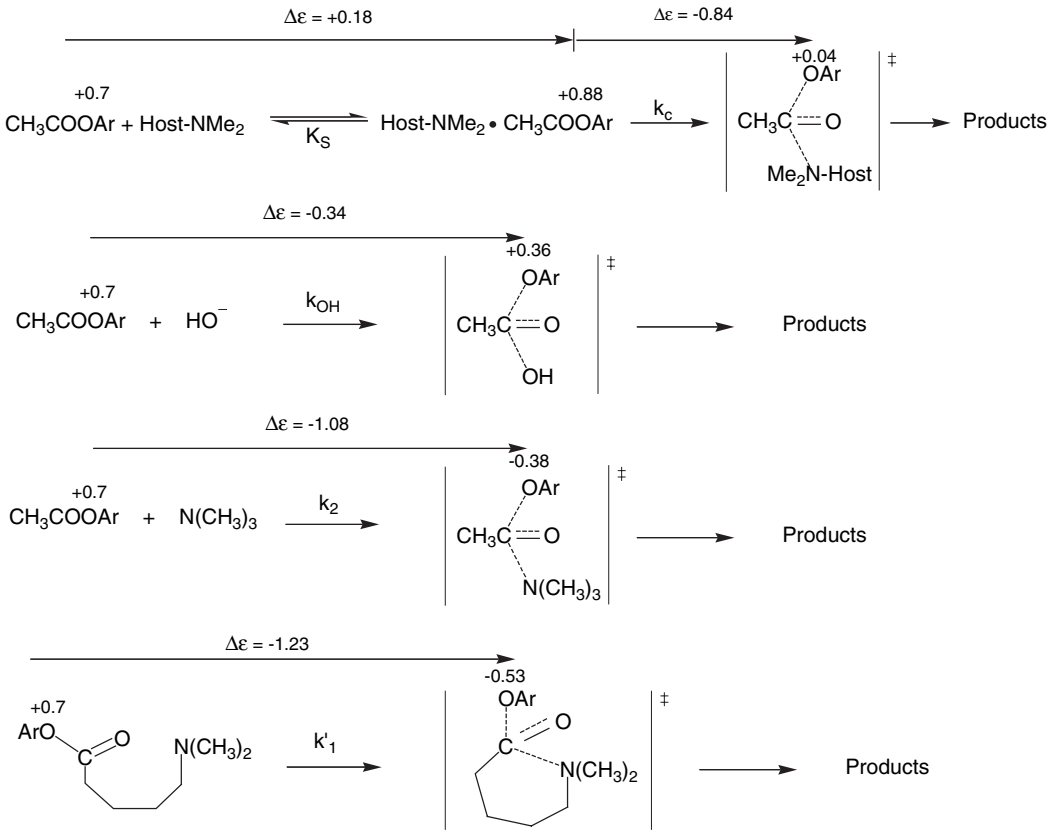
Positive increases in charge are observed in transition structures during hydrolysis of esters in the presence of xanthines (+0.54 compared with +0.3 in the non-catalyzed reaction).[15] This smaller positive increase in charge is probably due to the xanthines not possessing suitable structure to accept water molecules and thus not providing a significant solvation difference from that in the non-catalyzed reaction. There is even less difference in solvation between the transition state of the reaction in water and that of the reaction of ester complexed with micelle[16] where the ester function reacts in a water-like region of the micelle.

It is interesting to compare results for **RES3** with those for the other poly-dimethylamino substituted resorcinarene (**RES5**) investigated here. In principle, the overall length of the chains bearing the catalytic dimethylamino groups (which is reflected in their distance from the hydrophobic cavity of the host) could influence their

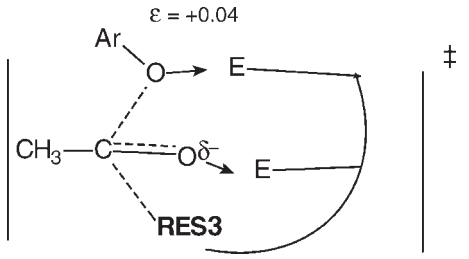
Table 3. Rate and equilibrium parameters for the hydrolysis of substituted phenyl acetates in the presence of **RES3** host[a]

Ester	pK_a	pH	λ[b]	k_b[c]	K_s[d]	k_c^{max}[c]	k_c^{max}/K_s[e]	Effect[f]	k_{OH}[g]
4-NO_2(**2a**)	7.11	—[i]	400	—	28 ± 7	11.0 ± 0.4	0.33	C	9.53[j]
2,4-$(NO_2)_2$(**2b**)	4.11	7.01	356	0.0635 ± 0.0072	71 ± 22	$(1.2 \pm 0.3) \times 10^4$	199	C	620
2-Cl-4-NO_2(**2c**)	5.45	10.58	396	9.26 ± 1.20	12.4 ± 0.9	1980 ± 6	160	C	24.4
2,3,5-Cl_3(**2d**)	6.43	11.00	305	11.2 ± 0.3	—[h]	—[h]	—[h]	C[h]	11.4
4-Cl-2-NO_2(**2e**)	6.46	9.58	428	0.565 ± 0.069	11.9 ± 0.5	19.3 ± 0.33	1.62	C	172
2,4,5-Cl_3(**2f**)	6.72	11.00	312	10.8 ± 0.2	3.4 ± 1.3	8.17 ± 0.29	2.38	I	10.8
2,5-Cl_2(**2g**)	7.51	10.52	300	17.8 ± 0.3	11.7 ± 3.2	7.77 ± 1.3	0.667	I	53.8
4-CHO (**2h**)	7.66	10.58	327	3.35 ± 0.05	—[h]	—[h]	—[h]	I[h]	6.58
2,3-Cl_2(**2i**)	7.70	10.52	300	13.5 ± 0.2	12.5 ± 3.3	4.56 ± 1.1	0.365	I	40.7
4-Cl-3-NO_2(**2j**)	7.75	9.58	400	0.30 ± 0.17	12.7 ± 9.4	3.22 ± 1	0.254	C	8.00
3,4,5-Cl_3(**2k**)	7.68	11.00	310	11.4 ± 0.3	4.6 ± 1.4	5.15 ± 0.59	1.13	I	11.4
3-CHO (**2l**)	8.00	11.52	351	13.2 ± 0.2	2.1 ± 0.7	7.66 ± 0.44	3.74	I	4.0
4-CH_3CO (**2m**)	8.05	10.58	321	2.50 ± 0.02	38 ± 19	0.953 ± 0.5	0.0247	I	6.6
2,3,4-Cl_3(**2n**)	7.63	11.00	312	8.58 ± 0.09	5.1 ± 0.6	4.01 ± 0.18	0.782	I	8.6

[a] Ester concentration $= 2.5 \times 10^{-5}$ M, temperature 25 °C, ionic strength 0.1 M (KCl), [**RES3**] = 0–20 mM. For each substrate at least seven data points were obtained.
[b] Monitoring wavelength of reaction in nm.
[c] $\times 10^3\ s^{-1}$; except for 4-NO_2-phenyl acetate, k_c^{max} values were calculated from k_c values assessed at the indicated pHs through the relationship $k_c^{max} = k_c/FB$, where FB is the fraction of host present in its free base form calculated on the basis that p$K_a = 8.49$, on the assumption that only the unprotonated form of **RES3** is catalytically active (see footnote i).
[d] $\times 10^3\ M^{-1}$.
[e] $M^{-1}\ s^{-1}$.
[f] C = catalysis; I = inhibition.
[g] $M^{-1}\ s^{-1}$. Second order rate constant for attack of hydroxide ion on free ester ($k_b/[OH^-]$).
[h] Very little change in k_{obs} with increase in [**RES3**] ($k_b \triangleq k_c$).
[i] Data from Table 1 for a range of pHs. k_c fitted to $\log k_c = \log k_c^{max} - \log(1 + 10^{8.49\text{-pH}})$ from which k_c^{max} was obtained.
[j] Literature value:[3] 570 $M^{-1}\ min^{-1}$, that is, 9.5 $M^{-1}\ s^{-1}$ at 25 °C.



Scheme 3. Effective charge map for the reaction of substituted phenyl acetate esters with **RES3** compared with those for model reactions



Scheme 4. Cartoon of the transition structure in the reaction of **RES3** with acetate esters; 'E' could be either NH of the component amide or the proton from water molecules present in the cavity

complexing and/or catalytic ability. Comparison of k_c and K_s values for **RES3** and **RES5** displayed in Table 1 suggests that catalytic and complexing properties are similar for both. A possible explanation is that the aliphatic chains are flexible enough to allow the dimethylamino groups to approach the ester function of the guest molecule in a similar way; moreover, the difference in length is also comparatively unimportant as far as their complexing ability is involved. In any case, values of the dissociation constants (K_s) of the complexes are within the range exhibited by other systems such as cyclodextrin-ester complexes.[1]

EXPERIMENTAL

The macrocycles described here possess, in general, very high melting points and in some cases the temperature characteristics were determined by differential scanning calorimetry (DSC).

Kinetics were followed spectroscopically by using host solution at a series of concentrations and constant pH and ionic strength prepared by dilution of a stock solution of host in buffer with an identical solution of buffer without added host. Buffer reagents were of analytical grade. In a number of instances, pH was maintained constant by mechanical buffering achieved with a Radiometer pH-Stat. Water was double distilled from glass and degassed *in vacuo*. The reactions were initiated by adding a stock solution of the ester (25 μL) to host solution (2.5 mL) in a silica cuvette in the thermostatted cell holder of a UV–VIS spectrometer. The progress of the reaction was monitored at constant wavelength and the change in absorbance with time was fitted to a pseudo-first order rate law by use of standard fitting techniques.

Calix-4-resorcinarene **RES1** in the cone conformation was prepared according to Hogberg's method.[17] Derived calixarenes (**RES2–5**) were prepared as described in the supplementary material, available in Wiley Interscience. Substituted esters (1–3, Chart 1) were obtained from previous work from these laboratories.

Acknowledgements

The authors are grateful to Marco Civardi for help with DSC measurements. Financial support from SERC for a quota award (92301379 to F.Z.), the Royal Society of Chemistry for a travel grant (S.T.) and the Compagnia di San Paolo (Torino, Italy) for the acquisition of a gradient NMR probe (GC, ST) is also acknowledged.

REFERENCES

1. For reviews on cyclodextrins, see: (a) Tee OS. *Adv. Phys. Org. Chem*. 1994; **29**: 1–85; (b) Breslow R, Dong SD. *Chem. Rev.* 1998; **98**: 1997–2011.
2. Reviews on this topic are: (a) Sansone F, Segura M, Ungaro R. Calixarenes in Bioorganic and Biomimetic Chemistry. In *Calixarenes*, Asfari Z, Böhmer V, Harrowfield J, Vicens J (eds). Kluwer: Dordrecht, 2001; pp 496–512. (b) Cacciapaglia R, Mandolini L. Calixarene Based Catalytic Systems. In *Calixarenes in Action*; Mandolini L, Ungaro R (eds). Imperial College Press: London, 2000; pp 241–264. (c) Molenveld P, Engbersen JF, Reinhoudt DN. Chem. Soc. Rev. 2000; **29**: 75–86 and references cited. (d) Vicens J, Bohmer A. In *Topics in Inclusion Science:Calixarenes: A Versatile Class of Macrocyclic Compounds*, **Vol. 3**. Kluwer Academic Press: Dordrecht, 1991.
3. Pirinccioglu N, Zaman F, Williams A. *J. Chem. Soc. Perkin Trans 2*, 1996; 2561–2562.
4. Kirsch JF, Jencks WP. *J. Amer. Chem. Soc*. 1964; **86**: 837–846.
5. Bruice TC, Benkovic SJ. *J. Amer. Chem. Soc*. 1963; **85**: 1–8.
6. Davy MB, Douglas KT, Loran JS, Steltner A, Williams A. *J. Amer. Chem. Soc*. 1977; **99**: 1196–1206.
7. Perrin DD, Dempsey B, Serjeant EP. *pK_a Prediction for Organic Acids and Bases*. Chapman and Hall: London, 1981; p. 40.
8. Kazantsev OA, Shirshin KV, Kazakov SA, Danov SM. *Russ. J. Gen. Chem*. (EN) 1966; **66**: 1958–1962 (Zh. *Obsch. Khim*, 1996; **66**: 2014–2018).
9. Satterthwait AC, Jencks WP. *J. Am. Chem. Soc*. 1974; **96**: 7018–7031.
10. Um IH, Yeom ES, Kwon HJ, Kwon DS. *Bull. Korean Chem. Soc*. 1997; **18**: 865–868.
11. For significance, assessment and application in mechanistic studies of effective charges see: (a) Williams A. *Acc. Chem. Res.* 1984; **17**: 425–430; (b) Williams A. *Free Energy Relationships in Organic and Bio-organic Chemistry.* The Royal Society of Chemistry: Cambridge, 2003; 55–74.
12. (a) Bruice TC, Mayahi MF. *J. Amer. Chem. Soc*. 1960; **82**: 3067–3071; (b) Jencks WP, Gilchrist M. *J. Amer. Chem. Soc*. 1968; **90**: 2622–2627.
13. Bruice TC, Benkovic SJ. *J. Amer. Chem. Soc*. 1963; **85**: 1–8.
14. (a) Williams A, Lucas EC, Rimmer AR. *J. Chem. Soc. Perkin Trans 2* 1972; 621–627; (b) Williams A, Salvadori G. *J. Chem. Soc. B* 1971; 2401–2406; (c) Williams A, Woolford G. *J. Chem. Soc. Perkin Trans 2* 1972; 272–275; (d) Williams A. *Biochemistry* 1970; **9**: 3383–3390; (e) Hawkins HC, Williams A. *J. Chem. Soc. Perkin Trans 2* 1976; 723–729.
15. Pirinccioglu N, Williams A. *J. Chem. Soc., Perkin Trans 2* 1998; 37–40.
16. (a) Pirinccioglu N, Zaman F, Williams A. *J. Org. Chem*. 2000; **65**: 2537–2543; (b) Al-Awadi N, Williams A. *J. Org. Chem*. 1990; **55**: 2001–2004.
17. Hogberg SA. *J. Org. Chem*. 1980; **45**: 4498–4500.