Enhanced Alkaline Hydrolysis of Monoesterified 4-*tert*-Butylcalix[4]arenes Involving Intramolecular Electrophilic Catalysis by the Phenolic Hydroxy Group

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Rate enhancements over model systems up to 1600-fold are observed in the alkaline hydrolysis of monobenzoate esters of calix[4]arenes.

Spectrophotometric titration of the mono-benzoate ester over a pH range indicates ionisation of phenolic hydroxy groups at p*K* 6.84, 12.14 and >14.02.

The kinetics of hydrolysis of substituted monobenzoate esters of 4-*tert*-butylcalix[4]arene in 50% (v/v) ethanol–water solvent (at 25 °C) obey pseudo-first-order kinetics which fit the rate law,

$$k_{obs} = (k_1K_w/K'_a + k_2[OH])[OH]/(K_w/K'_a + [OH])$$

where k_1 and k_2 correspond to bimolecular attack of hydroxide ion on monoanion and dianion respectively. The kinetics were measured at pHs at which the calixarene esters are in their monoanionic form. The kinetics of the alkaline hydrolyses (k_{OH}) of substituted benzoate esters of 4-nitrophenol were measured under the same conditions. The following Hammett equations are obeyed.

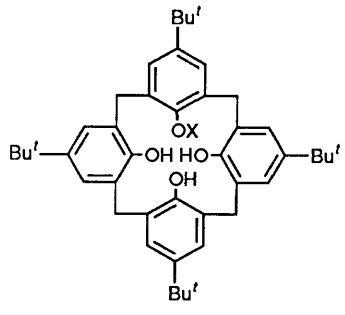
$$\log k_1 = 1.86\sigma + 1.33$$
$$\log k_2 = 2.21\sigma + 0.34$$
$$pK'_a = -2.90\sigma + 11.78$$
$$\log k_{OH} = 2.23\sigma + 0.26$$

The large negative Hammett ρ value for the pK'_a of the calixarenes (determined kinetically) is consistent with a strong interaction between the ester and the ionised hydroxy groups, attributed to formation of an intramolecular tetrahedral adduct. The formation of the adduct means that hydrolysis is retarded and the enhancements observed are lower limits.

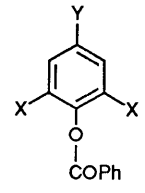
The alkaline hydrolysis of the calixarene esters is due to hydroxide ion attack on monoanion for k_1 and on the dianion for k_2. The substantial negative Hammett ρ values for water attack on dianion and trianion respectively provide unequivocal evidence to exclude these mechanisms in favour of hydroxide ion attack.

An important common structural feature of the active sites of enzymes catalysing hydrolytic and transfer reactions of the carbonyl acyl function is a hydrogen-bonding network;[1] this has been recognised as contributing to the catalytic advantage of the enzyme over model systems.[1] The possibility of electrophilic assistance of nucleophilic attack in proteolytic enzymes has been addressed experimentally by X-ray crystallographic studies of active sites filled with substrate analogues[2] and studies of substituent effects on acylation and deacylation reactions.[3,4]

Calix[4]arenes possess a strongly hydrogen-bonded network of four phenolic hydroxy groups,[5] one of which can be readily acylated.[6] The monoacylated calix[4]arene having three hydroxy groups is a partial model of the active site of an acyl intermediate in the mechanism of a proteolytic enzyme possessing an oxyanion pocket.[2] The hydrogen-bonded network in monoacyl calix[4]arenes has the potential of interacting with the carbonyl or ether oxygen of the acyl group, thus providing a 'preformed' microsolvation environment for the transition state for ester cleavage. A microsolvation effect has been proposed in the mechanism of acylation and deacylation of proteolytic enzymes.[1] It is possible that a similar interaction occurs between the hydroxy groups of the calixarene ester and the oxygens of the ester function.



1a X = C_6H_5CO
b X = 3-CNC_6H_4CO
c X = 4-ClC_6H_4CO
d X = 4-$NO_2C_6H_4CO$
e X = 3-ClC_6H_4CO
f X = 3-$NO_2C_6H_4CO$
g X = 4-MeC_6H_4CO



2a Y = Bu^t; X = H
b Y = H; X = CH_3
c Y = X = CH_3

3 4-$NO_2C_6H_4$ substituted benzoate esters

The purpose of this work is to study the hydrolysis of a series of monobenzoate esters of the 4-*tert*-butylcalix[4]arenes (**1a–g**) in comparison with various model systems (**2**) to try and elucidate the possible role of the hydrogen-bonded network in the calix[4]arene system for acyl group transfer catalysis.

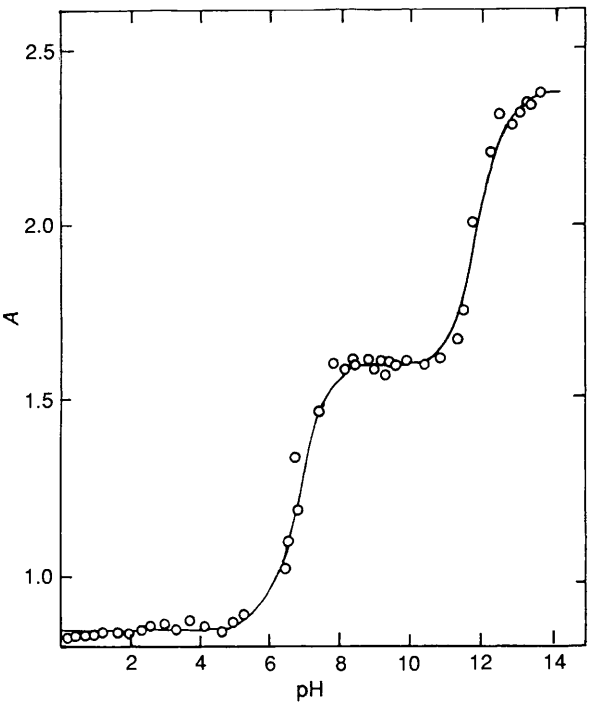


Fig. 1 Spectrophotometric pH-titration of benzoyl tetra-4-*tert*-butylcalix[4]arene in 50% (v/v) ethanol–water at 250 and 1 mol dm^{-3} ionic strength. The line is calculated from the pK'_a values given in the text.

Experimental

Materials.—The calix[4]arene monoesters (**1**) were produced as follows:[6] a solution in acetonitrile (100 cm^3) of 4-*tert*-butylcalix[4]arene (2 g, 3 mmol), *N*-(butyl)imidazole (Fluka) (5.58 g, 45 mmol) and the benzoyl chloride (4 mmol) was stirred at room temp. for 30 h. The product monoesters were precipitated from solution by acidification with HCl, (2 mol dm^{-3}), filtered, washed with water and dried. The esters, obtained in good yields, were recrystallised from chloroform–methanol.

The substituted phenyl benzoate esters (**2**) were synthesised from the acid chloride or from benzoic acid with dicyclohexylcarbodiimide[7] as a coupling agent. The 4-nitrophenyl benzoates were donated by Mr. M. Colthurst.

Tetra-4-*tert*-butylcalix[4]arene was prepared from 4-*tert*-butylphenol and formaldehyde by Gutsche's method.[8] Other materials were of analytical reagent grade or were recrystallised or redistilled from bench grade reagents.[9] Water used in the kinetics was doubly distilled from glass.

Analytical and Physical Data.—Yields were not optimised. M.p.s were determined with a Kofler Thermospan instrument. IR spectra (ν_{max}/cm^{-1}) were recorded using Nujol mulls and KBr discs on a Perkin-Elmer Model 683 spectrometer. ^1H NMR spectra were recorded on a 100 MHz JEOL JNM-PS-100 machine ($CDCl_3$ solvent, tetramethylsilane standard). Microanalyses were carried out by Mr. A. J. Fassam in the UKC Chemical Analysis Centre with a Carlo Erba CHN Analyser.

5,11,17,23-*Tetra*-tert-*butyl*-25-(*substituted-benzoyloxy*)-26,27,28-*trihydroxycalix*[4]*arenes* (**1a–g**). (*a*) Parent (**1a**) yield 76%; m.p. >200 °C; ν_{max}/cm^{-1} 3200br (OH str.) and 1730s (C=O str.); δ_H 9.60 (s, 3 H, OH), 7.20 (s, 13 H, ArH), 3.90 (s, 8 H, $ArCH_2Ar$) and 1.25 (s, 36 H, Bu^t) (Found: C, 81.0; H, 8.3. $C_{51}H_{60}O_5$ requires C, 81.40; H, 7.98%).

(*b*) 3-Cyano ester (**1b**) yield 62%; m.p. >200 °C; ν_{max}/cm^{-1} 3250br (OH str.), 2220m (C≡N str.) and 1740s (C=O str.); δ_H 8.40 (s, 3 H, OH), 7.20 (s, 12 H, ArH), 4.20 (s, 8 H, $ArCH_2Ar$) and 1.40 (s, 36, H, Bu^t) (Found: C, 80.6; H, 7.0; N, 2.1. $C_{52}H_{59}NO_5$ requires C, 80.31; H, 7.59; N, 1.80%).

(*c*) 4-Chloro ester (**1c**) yield 82%; m.p. >200 °C; ν_{max}/cm^{-1} 3200br (OH str.) and 1730s (C=O str.); δ_H 9.85 (s, 3 H, OH), 7.40 (s, 12 H, ArH), 4.10 (s, 8 H, $ArCH_2Ar$) and 1.2 (s, 36 H, Bu^t) (Found: C, 77.4; H, 7.0. $C_{51}H_{59}ClO_5$ requires: C, 77.81; H, 7.50%).

(*d*) 4-Nitro ester (**1d**) yield 78%; m.p. >200 °C; ν_{max}/cm^{-1} 3200br (OH str.), 1730s (C=O str.), 1530s (NO_2 str.) and 870s (C–N str); δ_H 9.85 (s, 3 H, OH), 7.40 (s, 12 H, ArH), 4.15 (s, 8 H, $ArCH_2Ar$) and 1.40 (s, 36 H, Bu^t) (Found: C, 76.4; H, 7.8; N, 1.9. $C_{51}H_{59}NO_7$ requires C, 76.79; H, 7.40; N, 1.76%).

(*e*) 3-Chloro ester (**1e**) yield 72%; m.p. >200 °C; ν_{max}/cm^{-1} 3200br (OH str.) and 1735s (C=O str.); δ_H 9.80 (s, 3 H, OH), 7.35 (s, 12 H, ArH), 4.20 (s, 8 H, $ArCH_2Ar$) and 1.40 (s, 36 H, Bu^t) (Found: C, 77.75; H, 8.0. $C_{51}H_{59}ClO_5$ requires C, 77.81; H, 7.50%).

(*f*) 3-Nitro ester (**1f**) yield 67%; m.p. >200 °C; ν_{max}/cm^{-1} 3200br (OH str.), 1730s (C=O str.) and 870s (CN str.); δ_H 8.40 (s, 3 H, OH), 7.10 (s, 12, ArH), 3.95 (s, 8 H, ArCHAr) and 1.20 (s, 36 H, Bu^t) (Found: C, 76.2; H, 7.1; N, 1.5. $C_{51}H_{59}NO_7$ requires C, 76.79; H, 7.40; N, 1.76%).

(*g*) 4-Methyl ester (**1g**) yield 72%; m.p. >200 °C; ν_{max}/cm^{-1} 3300br (OH str.) and 1740s (C=O str.); δ_H 9.00 (s, 3 H, OH), 7.15 (s, 12 H, ArH), 4.05 (s, 8 H, $ArCH_2Ar$), 2.20 (s, 3 H, $ArCH_3$) and 1.25 (s, 36 H, Bu^t) (Found: C, 81.6; H, 8.3. $C_{52}H_{62}O_5$ requires C, 81.46; H, 8.09%).

Substituted phenyl benzoate esters. (*a*) 4-*tert*-Butylphenyl benzoate yield 51%; m.p. 80–82 °C; ν_{max}/cm^{-1} 1730s (C=O str.) and 1590s (C=C str.); δ_H 8.20 (d, 2 H, *J* 12, ArH), 7.40 (m, 3 H, ArH), 6.80 (dd, 4 H, *J* 14, ArH) and 1.60 (s, 9 H, Bu^t) (Found: C, 80.3; H, 7.0. $C_{17}H_{18}O_2$ requires: C, 80.31; H, 7.09%).

(*b*) 2,6-Dimethylphenyl benzoate yield 65%; m.p. 41–42 °C; ν_{max}/cm^{-1} 1730s (C=O str.) and 1590s (C=C str.); δ_H 8.20 (d, 2 H, *J* 12, ArH), 7.40 (m, 3 H, ArH), 6.80 (m, 3 H, ArH) and 2.10 (s, 6 H, CH_3) (Found: C, 79.4; H, 6.1. $C_{15}H_{14}O_2$ requires: C, 79.65; H, 6.19%).

(*c*) 2,4,6-Trimethylphenyl benzoate yield 67%; m.p. 58–60 °C; ν_{max}/cm^{-1} 1730s (C=O str.) and 1590s (C=C str.); δ_H 8.20 (d, 2 H, *J* 12, ArH), 7.40 (m, 3 H, ArH), 6.70 (d, 2 H, *J* 12, ArH) and 2.10 (s, 9 H, CH_3) (Found: C, 79.7; H, 7.0. $C_{16}H_{16}O_2$ requires: C, 80.00; H, 6.67%).

Methods.—The kinetics were followed spectrophotometrically with a Perkin-Elmer Lambda 5 spectrophotometer. An aliquot (10–50 mm^3) of a stock solution of the ester in acetonitrile (*ca.* 20 mmol dm^{-3}) was placed on the flattened tip of a glass rod and introduced into the buffer solution (2.5 cm^3) in a 1 cm pathlength silica UV cell in the thermostatted cell compartment of the spectrophotometer. Two or three vertical strokes of the glass rod effected mixing and the reaction was followed by repetitively scanning the spectrum to obtain the best wavelength for following the reaction kinetics. The absorbance changes at the single wavelength were fitted to a first-order rate law by use of a desk-top microcomputer.

Strongly basic solutions were made up by serial dilution of KOH stock solutions in 50% (v/v) ethanol–water solution and KOH was standardised by titration. Buffers with pHs below 11 were made up with carbonate buffers. The pH meter employed in this study (Radiometer Model PHM 62) was calibrated for the solvent employed by use of standard HCl and KOH solutions. The value of p*K* obtained in this way was 14.14 for 50% (v/v) ethanol–water at 25 °C.

Spectrophotometric titration of the benzoate ester of tetra-4-*tert*-butylcalix[4]arene was carried out with ethanol–water solvent by use of a 0.75 mmol dm^{-3} solution and a wavelength at 280 nm. The ester was titrated from pH 0 to 14 and the absorption plotted *versus* pH (Fig. 1).

Table 1 Base-catalysed hydrolysis of phenyl benzoate esters[a]

Ester	$k_{obs}/10^{-3}$ s^{-1} [b]	[OH]/mol dm^{-3} [c]	N [d]	λ/nm [e]	k_{OH}/mol dm^{-3} s^{-1} [f]	M.p./°C [g]
Benzoate						
4-*tert*-butylphenyl-	0.49–20	1–50	7	300	0.41	80–82
2,6-dimethylphenyl-	0.056–0.71	10–150	6	285	0.49	41–42
2,4,6-trimethylphenyl-	0.22–1.1	10–80	6	295	0.012	58–60
4-Nitrophenyl substituted benzoate						
4-methoxy-	0.33–2.2	1–6	3	400	0.117	
4-methyl-	0.78–6.2	1–15	3	400	0.27	
4-chloro-	5.6–41	1–15	3	400	1.85	
3-chloro-	1.11–11	0.1–1	3	400	3.52	
4-trifluoro-	2.1–21	0.1–1	3	400	6.42	
4-nitro-	9.4–83	0.1–1	3	400	26.4	

[a] Conditions 25 °C, 50% (v/v) ethanol–water, ester concentrations ~0.2 μmol dm^{-3}. [b] Range of observed rate constants. [c] Range of hydroxide ion concentrations; pK_w = 14.14 and (pH = meter reading − 0.34). [d] Number of data points, not including duplicate runs. [e] Wavelength for the kinetic study. [f] Errors in k_{OH} are no greater than ± 10%. [g] M.p. of ester; the 4-nitrophenyl substituted benzoate esters are known compounds.

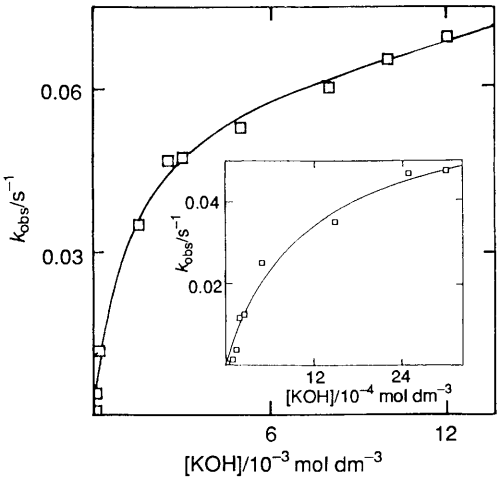


Fig. 2 Fit of eqn. (3) to the rate constants for hydrolysis of 4-chlorobenzoyl tetra-4-*tert*-butylcalix[4]arenes. The theoretical line is drawn from eqn. (1) employing parameters from Table 3.

Product analysis was carried out by reacting ester (0.15 g) in 50% (v/v) ethanol–water (100 cm^3) at pH 11.50 and 25 °C. The solution was acidified and evaporated to give a residue which was examined by IR spectroscopy.

Results

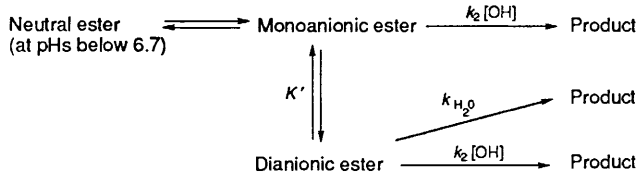
The hydrolysis of all the esters gave good pseudo-first-order kinetics in ester concentration up to > 90% of the total reaction. The rate constants for the model esters are proportional to hydroxide ion concentration. Second-order rate constants (k_{OH}, recorded in Table 1), were obtained for the model esters by division of the pseudo-first-order rate constants by hydroxide ion concentration. IR analysis of the products of the reaction of the esters in ethanol–water solvent gave no evidence for the ethyl ester product but indicated carboxylic acid. In the case of the 4-nitrobenzoate ester of the calixarene, 4-nitrobenzoic acid was isolated by recrystallisation in good yield.

The pseudo-first-order rate constants for the hydrolysis of the substituted benzoate esters of tetra-4-*tert*-butylcalixarene on the hydroxide ion concentration are given by eqn. (1). The fit

$$k_{obs} = (k_1K_w/K'_a + k_2[OH])[OH]/(K_w/K'_a + [OH]) \quad (1)$$

of the data to eqn. (1) is illustrated in Fig. 2 for the hydrolysis of the 4-chlorobenzoate ester.

Eqn. (1) may be derived theoretically from a mechanism [eqn. (2)] in which hydroxide ion attacks monoanionic (see later) and



(2)

dianionic forms of the ester. The fit of the data to eqn. (1), employing K_w obtained here, gives parameters k_1, k_2 and pK'_a which are recorded in Table 2. The value of pK'_a determined kinetically is reasonably close to one of the values obtained by spectrophotometric titration in the case of the parent ester (6.84, 12.14 and > 14.02). The pK'_a corresponding to the first ionisation indicates that at the pHs employed in this work, the neutral ester is the minor form and the kinetically determined pK'_a corresponds to formation of the dianion. Hydrolysis of the parent calixarene ester was carried out in solutions containing Na^+ and K^+ ions; the parameters k_1, k_2 and pK'_a were shown to be identical within experimental error. Kinetic parameters from Tables 1 and 2 fit Hammett sigma eqns. (3)–(6) well. The

$$pK'_a = -2.90 \pm 0.06\sigma + 11.78 \pm 0.03 \quad (r = 0.9977) \quad (3)$$

$$\log k_1 = 1.86 \pm 0.09\sigma + 1.33 \pm 0.04 \quad (r = 0.9895) \quad (4)$$

$$\log k_2 = 2.21 \pm 0.05\sigma - 0.34 \pm 0.03 \quad (r = 0.9971) \quad (5)$$

$$\log k_{OH} = 2.23 \pm 0.11\sigma - 0.26 \pm 0.047 \quad (r = 0.9953) \quad (6)$$

data for the hydrolysis of the 4-nitrophenyl benzoate esters at 25 °C for 50% (v/v) ethanol–water are similar to those obtained Kirsch, Clewell and Simon[10] for 33% (v/v) acetonitrile–water at 25 °C; the ρ value obtained is also comparable with their value (2.01).[10]

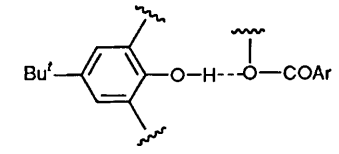
Discussion

Coupling Between Hydroxy Groups and Ester.—The very large substituent effect on the ionisation constant (pK'_a) [eqn. (3)] leaves no doubt that there is substantial coupling between the phenolic proton and the ester function. There would normally be very little substituent effect due to through-bond transmission because the phenolic hydroxy group closest to the substituents is separated from the carbonyl of the ester by six atoms and one of these is a carbon in its sp^3 hybridisation state. The phenolic hydroxy group of aryl salicylates, which has a closer connectivity than in **1**, shows little dependence of its pK'_a

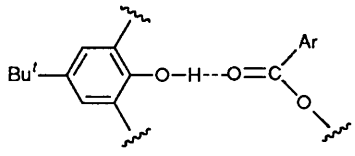
Table 2 Hydrolysis of substituted mono-benzoate esters of tetra-4-*tert*-butylcalix-4-arenes[a]

Ester	λ/nm[b]	[OH]/ 10^{-3} mol dm^{-3}[c]	$k_{obs}/10^{-4}$ s^{-1}[d]	N[e]	k_1/ dm^3 mol^{-1} s^{-1}[f]	k_2/ dm^3 mol^{-1} s^{-1}[f]	pK'_a[g]
Parent	295	1–12	22–610	12	20	0.5	11.70
4-Chloro	284	0.1–12	6.5–696	10	53	1.2	11.10
4-Nitro	322	0.005–1.25	1.6–509	9	502	26.0	9.50
3-Chloro	284	0.01–6	5.4–720	9	170	2.9	10.70
3-Nitro	285	0.015–1.25	5.1–370	9	483	16.2	9.69
4-Methyl	300	2.5–25	70–900	9	9.9	0.20	12.34
3-Cyano	283	0.01–5	3.6–700	11	265	10.47	10.07

[a] Conditions 25 °C, 50% (v/v) ethanol–water, ionic strength held at mol dm^{-3} with KCl. [b] Wavelength for kinetic study. [c] Range of hydroxide ion concentrations. [d] Range of observed rate constants. [e] Number of data points not including duplicates. [f] Error not greater than ±10%. [g] pK'_a determined from the kinetic results.



4a



4b

on the substituent in the aryl ring.[11] The negative Hammett ρ value for the pK'_a of the calixarenes indicates that electron donating substituents will decrease the acidity. A hydrogen bond acceptor interaction through either the ether or carbonyl oxygens (**4a**, **b**) is a possible explanation and the hydrogen bonded network of the calixarene[5,12] seems to support this. However, substituted monobenzoate esters of catechol have essentially constant pK_a values[13] and the phenolic hydroxy group of aryl salicylates, which has a closer connectivity than in **1**, shows little dependence of pK_a on substituents in the aryl ring.[11] A better explanation of the large Hammett ρ value for the pK'_a is that the second ionisation produces a phenoxide which is reactive enough to form an intramolecular adduct with the ester carbonyl function [eqn. (7)]. The observed pK'_a of the

$$\text{Ester H}^- \overset{K_a}{\rightleftharpoons} \text{Ester}^{2-} \overset{K_{eq}}{\rightleftharpoons} \text{Adduct} \qquad (7)$$

system would be due to a combination of the true ionisation (pK_a) and the subsequent equilibrium (pK_{eq}); thus $K'_a = K_a \times K_{eq}$. Since the true ionisation should be relatively insensitive to σ, then the Hammett ρ for K'_a will depend on the ρ value for K_{eq}. Formation of tetrahedral adducts from substituted benzoate esters and oxyanions has ρ values in the range observed here.[14] Evidence that phenolate ion character is suppressed in the dianion is that the extinction coefficient at 280 nm for the change in the parent ester in the titration is about tenfold less than the value found by Shinkai[12e] for a non-acylated calix[4]arene analogue where adduct formation could not occur. Simple model building indicates that an adduct could readily form as illustrated in Fig. 3; some of the low energy conformations of the calixarene ester involve close contact between ester carbonyl and phenoxide ion.

Resolution of Kinetic Ambiguity.—The rate constant, k_1, could be due to a mechanism involving bimolecular hydroxide ion attack on the ester monoanion or one involving attack of water on the oxydianion (k_{H_2O}). The values of the Hammett ρ parameter for k_1 and K'_a provide us with a clear distinction between the mechanisms. The rate constant for water attack on the dianion is given by $k_{H_2O} = k_1 \times K_w K'_a$; thus the Hammett ρ value for k_{H_2O} will be $\rho(k_1) + \rho(pK'_a) = -1.04$ [see eqns. (3) and (4)]. It is inconceivable that there would be an increase in positive charge in the nucleophilic attack as would be required by a negative ρ value. A negative ρ value could result from bond fission preceding bond formation, a situation only envisaged with exceptionally powerful leaving groups. We conclude that the Hammett ρ value provides unambiguous distinction in the kinetic ambiguity, in favour of hydroxide ion attack on monoanionic ester (k_1).

The parameter k_2 is also subject to kinetic ambiguity where the mechanism could be hydroxide ion attack on the calixarene ester dianion, or water on the trianion; distinction by use of Hammett ρ values is also clear-cut. The ρ value for the first-order decomposition of the trianion is -0.69 [$\rho = 2.21 - 2.90$, see eqns. (3) and (5)], assuming that the ρ value for the third ionisation of the calixarene esters is the same as that for the second ionisation. A negative ρ value would not result from a mechanism involving attack of water on the trianionic ester.

The question of kinetic ambiguity in reactions involving ionisable protons is very important, particularly in considering biological reactions which invariably involve acids and bases. The distinction between kinetically ambiguous mechanisms has been addressed in general by Jencks,[15] and specifically for many reactions of catechol esters and salicylates related to the present system.[16–20]

Enhanced hydrolytic Rates for Calixarene Esters.—Tables 1 and 2 reveal substantial rate enhancements for the hydrolysis of the calixarene parent ester **1a** (in both k_1 and k_2) over the second-order rate constants (k_{OH}) for hydroxide ion attack on the model esters 4-*tert*-butylphenyl benzoate (**2a**), 2,6-dimethylphenyl benzoate (**2b**) and 2,4,6-trimethylphenyl benzoate (**2c**) where no intramolecular hydrogen bond interactions are possible. The closest model in terms of steric requirements is probably the 2,4,6-species (**2c**) which has a rate constant respectively 1600- and 40-fold less than k_1 and k_2. The steric requirement of the models, determined by inspection of CPK space-filling models, is less than that in the calixarene ester; this and the additional factor that the chemical analogues are uncharged whereas **1a** has negative charge (above pH 6.7) indicates that there is a significant underestimation of the rate enhancement in the reaction of hydroxide ion with **1a**. We can rule out nucleophilic participation by the phenolic oxyanions in calixarene ester hydrolysis as the origin of the acceleration because the intermediate would have the identity of the reactant. Such a virtual reaction should indeed occur in the calixarene esters as a result of collapse of the tetrahedral adduct. It

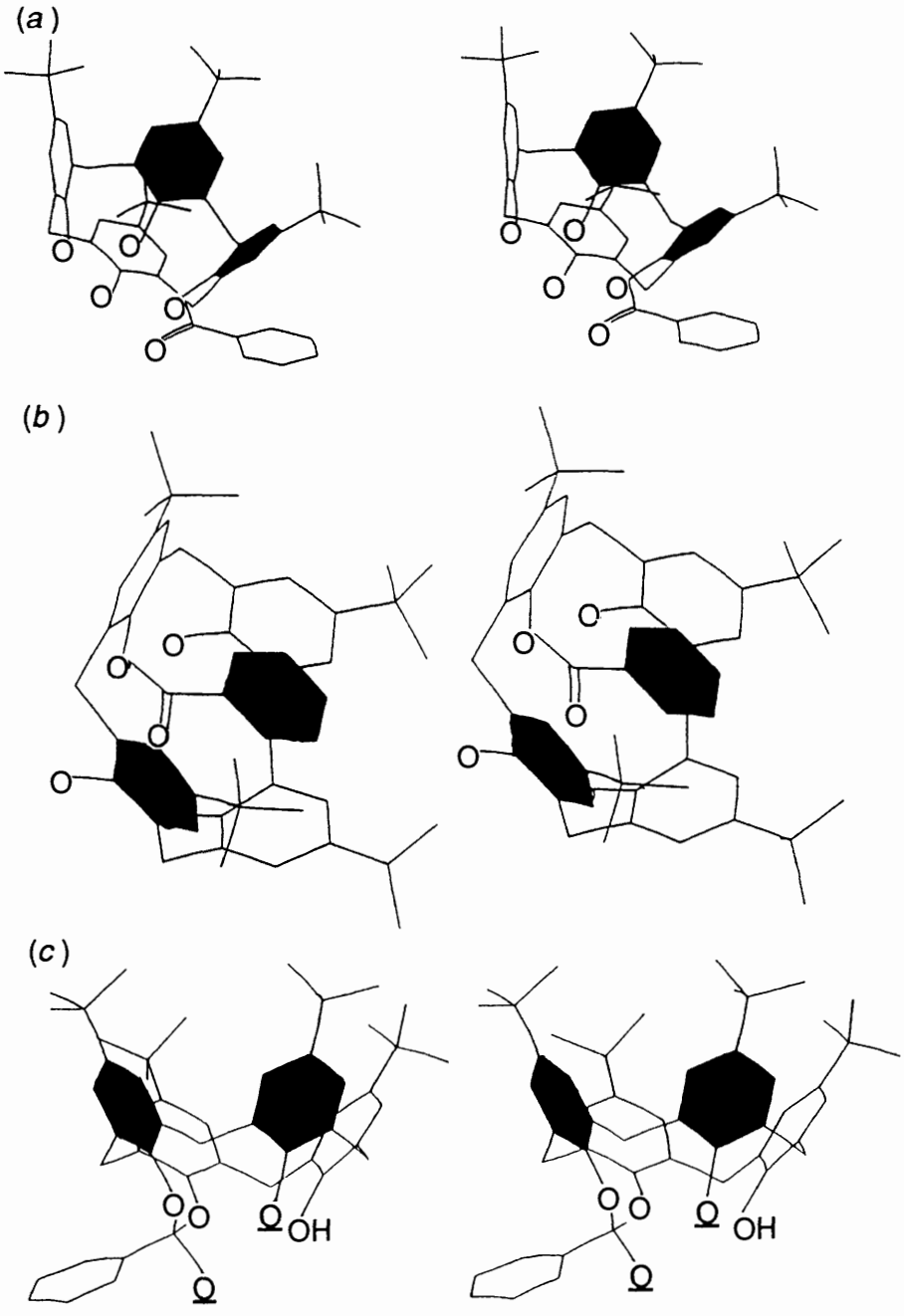


Fig. 3 Stereo-drawings of various conformations of the monobenzoate of tetra-4-*tert*-butylcalix[4]arene: (*a*) conformation with ester perching on the bottom rim of the 'cone'; (*b*) conformation with ester within the 'cone'; (*c*) a possible conformation for an internal adduct between oxyanion and ester with the phenyl group derived from the benzoyl function perching on the bottom rim of the 'cone'. Hydrogen atoms are generally omitted to assist clarity and the benzenoid rings are represented without their double bonds. The drawings were made with the assistance of the Alchemy III software of the Tripos Corporation and do not represent structures minimised by molecular orbital or molecular mechanics protocols.

is likely that the value of K_{eq} will be favourable for adduct formation, which will therefore suppress even further the rate constants k_1 and k_2 below their expected values; as we are not in a position to determine K_{eq}, we are not able to estimate its effect on the observed rate parameters. It is expected that the trianion will give a more favourable tetrahedral adduct relative to the dianion case due to its extra nucleophilicity; this could explain in part why the value of k_2 is not so enhanced over its analogue (only 40-fold) as is k_1. The ρ value for k_1 is slightly less than that for bimolecular reaction of hydroxide ion with 4-nitrophenyl benzoates under the same conditions. Kirsch, Clewell and Simon[10] showed that ρ is independent of leaving groups in simple hydroxide ion attack on the substituted benzoate ester; thus it is likely that bond formation for k_1 is less advanced in accord with its higher reactivity compared with the models. The ρ value for k_2 is more positive than that for k_1 reflecting greater bond formation with hydroxide ion in the transition state due to the negative charge already present in the dianion compared with that in the monoanion.

Specific alkali metal ion catalysis could occur in the calixarene system due to the favourable location of the oxygen atoms. Such catalysis observed in other ester fission reactions in ethanol[21] by, for example, the K^+ ion is ruled out in the present case by the observation that solutions containing only Na^+ as the counterion give similar rate parameters to those containing K^+. The alkali metal catalysis refers to reactions carried out in almost dry alcohols[21] and it is probable that the high water content of the present experiments suppresses such catalysis.

Conformation of the Calixarene Giving Rise to Acceleration.—Chemical shift and NOE studies[6,21,22] indicate that the mono-substituted calix[4]arenes have either 'cone' or 'flattened cone' structures. Due to the many conformations that calix[4]arenes can assume, it is impossible with the available data to draw any detailed conclusions as to the reactive state. We favour the 'cone' conformation [Fig. 3(*a*)] as the major contributor in which the benzoyl group perches on the lower rim of the 'cone'. There is excellent opportunity for hydrogen-bonding to occur between the hydroxy functions and the ether oxygen of the ester. Strong hydrogen bonding should occur between the phenolic hydroxy groups and the carbonyl oxygen when the benzoyl group resides within the 'cone' [Fig. 3(*b*)]. This conformation would enhance intramolecular nucleophilic attack by the phenolic hydroxy groups to form the adduct and would significantly depress any reaction trajectory for water or hydroxide ion attack.

Conclusion

The hydrolysis of the title esters in alkali is unambiguously attributed to attack of hydroxy ion on monoanion and dianion species; the rates are enhanced over those of analogues due to intramolecular hydrogen bonding from un-ionised phenolic hydroxy groups. The enhancement observed is a lower limit because of favourable tetrahedral adduct formation between oxyanion and ester carbonyl function, steric hindrance and electrostatic repulsion.

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References

1 (*a*) A. Warshel, G. Naray-Szabo, F. Sussman and J.-K. Hwang, *Biochemistry*, 1989, **28**, 3629; (*b*) A. Fink, in *Enzyme Mechanisms*, eds. M. I. Page and A. Williams, Royal Society of Chemistry, London, 1987 p. 159.
2 (*a*) R. Henderson, *J. Mol. Biol.*, 1970, **54**, 341; (*b*) T. A. Steitz and R. G. Schulman, *Ann. Rev. Biophys. Bioeng.*, 1982, **11**, 419; (*c*) M. N. G. James, *Can. J. Biochem.*, 1985, **5**, 251; (*d*) J. Kraut, *Annu. Rev. Biochem.*, 1977, **46**, 331; (*e*) M. Marquart, J. Walter, J. Diesenhofer, W. Bode and R. Huber, *Acta Crystallogr., Sect. B*, 1983, **39**, 480.
3 A. Williams, *Biochemistry*, 1970, **9**, 3383.
4 (*a*) A. Williams and G. Salvadori, *J. Chem. Soc. B*, 1971, 2401; (*b*) B. Asboth and L. Polgar, *Biochemistry*, 1983, **22**, 117; (*c*) P. Campbell, N. T. Nashed, B. A. Lapinskas and J. Gurrieri, *J. Biol. Chem.*, 1983, **258**, 59; (*d*) J. A. Wells, B. C. Cunningham, T. P. Graycar and D. A. Estelle, *Philos. Trans. R. Soc. London, A*, 1986, **317**, 415.
5 (*a*) C. D. Gutsche, *Calixarenes, Monographs in Supramolecular Chemistry*, vol. 1, ed. J. F. Stoddart, Royal Society of Chemistry, Cambridge, 1991. (*b*) *Calixarenes, a Versatile Class of Macrocyclic Compounds*, eds. J. Vicens and V. Bohmer, Kluwer Press, Dordrecht, 1991.
6 K. A. See, F. R. Fronczek, W. H. Watson, R. P. H. Kashyap and C. D. Gutsche, *J. Org. Chem.*, 1991, **56**, 7256.
7 A. Hassner and V. Alexanian, *Tetrahedron Lett.*, 1978, **46**, 4475.
8 C. D. Gutsche and M. Iqbal, *Org. Synth.*, 1990, **68**, 234.
9 D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 3rd edn., 1988.
10 J. F. Kirsch, W. Clewell and A. Simon, *J. Org. Chem.*, 1968, **33**, 127.
11 B. Capon and B. C. Ghosh, *J. Chem. Soc. B*, 1966, 472.
12 (*a*) C. D. Gutsche, *Acc. Chem. Res.*, 1983, **16**, 161; (*b*) S. Shinkai, *Topics Inclusion Sci.*, 1991, **2**, 173; (*c*) K. Araki, S. Shinkai and T. Matsuda, *Chem. Lett.*, 1989, 581; (*d*) P. D. J. Grootenhuis, P. A. Kollman, L. C. Groenen, D. N. Reinhoudt, G. J. van Hummel, F. Ugozzoli and G. D. Andreetti, *J. Am. Chem. Soc.*, 1990, **112**, 4165; (*e*) S. Shinkai, K. Araki, P. D. J. Grootenhuis and D. N. Reinhoudt, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1883; (*f*) V. Bohmer, E. Schode and W. Vogt, *Makromol. Chem.*, 1984, **5**, 221; (*g*) S. Shinkai, K. Araki, H. Koreishi, T. Tsubaki and O. Manabe, *Chem. Lett.*, 1986, 1351; (*h*) S. Shinkai, K. Araki, J. Shibata, D. Tsugawa and O. Manabe, *Chem. Lett.*, 1989, 931.
13 A. J. S. Kanagasooriam, unpublished observations, University of Kent, 1993.
14 S. L. Shames and L. D. Byers, *J. Am. Chem. Soc.*, 1981, **103**, 6170.
15 W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969, pp. 603–605.
16 E. J. Fuller, *J. Am. Chem. Soc.*, 1963, **85**, 1777.
17 B. Hansen, *Acta Chem. Scand.*, 1963, **17**, 1375.
18 T. C. Bruice and T. Oka, *J. Am. Chem. Soc.*, 1974, **96**, 4500.
19 M. L. Bender, F. J. Kezdy and B. Zerner, *J. Am. Chem. Soc.*, 1963, **85**, 3017.
20 A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, 1967, **89**, 4853; *J. Am. Chem. Soc.*, 1967, **89**, 4857.
21 (*a*) M. J. Pregel, E. J. Dunn and E. Buncel, *J. Am. Chem. Soc.*, 1991, **113**, 3545; (*b*) R. Cacciapaglia, A. R. van Doorn, L. Mandolini, D. N. Reinhoudt and W. Verboom, *J. Am. Chem. Soc.*, 1992, **114**, 2611.
22 C. Alfieri, D. Emanuele, A. Pochini and R. Ungaro, *Gazz. Chim. Ital.*, 1989, **119**, 335.

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