Selective Monohydrolysis of a Calix[4]arene Tetraethyl Ester with Trifluoroacetic Acid and its Inhibition by Na^+ Ion: Evidence for Hydronium Ion Complexation

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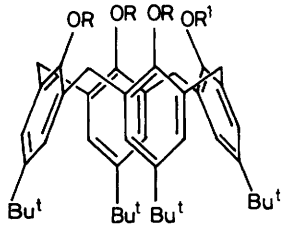
Calix[4]arene tetraethyl ester (**1a**) is hydrolysed by trifluoroacetic acid with the loss of one, and only one, ester group to form a monoacid triester; the process, which is inhibited by Na^+ ion, is believed to involve specific hydronium ion complexation within the calixarene receptor.

Several calix[4]arene derivatives, notably esters,[1] ketones,[2] and amides[3] of the general formula (**1**) exhibit ionophoric activity towards alkali cations. Phase-transfer, stability constant (in methanol), and transport studies with tetraethyl ester (**1a**) reveal a high selectivity for Na^+ over the other alkali cations.[4,5] Ion complexation has been interpreted in terms of a model in which Na^+ is encapsulated within the hydrophilic cavity defined by the four phenoxy oxygen atoms and the four ester carbonyl groups.[4] X-Ray diffraction studies of the K^+ SCN^- complex of the tetra-amide (**1b**) support this interpretation.[3a]

In the course of related studied with the tetraester (**1a**) we have observed an unexpectedly rapid reaction with trifluoroacetic acid (TFA) in chloroform at room temperature which could be followed conveniently by NMR spectroscopy. The following ^1H spectral changes in the aromatic region were observed when (**1a**) in $CDCl_3$ was treated with TFA. Immediately after mixing, the spectrum revealed the appearance of a new compound (20% conversion after 2–3 min) in which the four-fold symmetry of (**1a**) had been replaced by an approximate symmetry plane resulting in two singlets and one AB system. After *ca.* 1 h the conversion was completed to >90%; no additional new signals appeared within 24 h. From preparative-scale experiments we isolated a crystalline substance, m.p. 166–169 °C (88% yield), which was shown by HPLC analysis to be homogeneous. NMR analysis † established that the product was the triester monoacid (**2**),‡ and that the reaction was therefore one of hydrolysis.

The question arose as to whether this unusually easy hydrolysis of the tetraester (**1a**) is connected with its receptor properties towards monovalent cationic guests. In the first place, we established that a simple model ethyl ester, ethyl *p*-t-butyl phenoxyacetate (**3**), shows no measurable hydrolysis with TFA under similar conditions. Secondly, when a $CDCl_3$

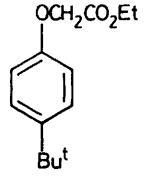


(**1**) R = R¹

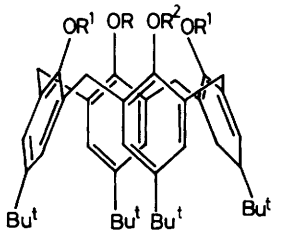
(**1a**) R = R¹ = CH_2CO_2Et

(**1b**) R = R¹ = CH_2CONEt_2

(**2**) R = CH_2CO_2Et, R¹ = CH_2CO_2H



(**3**)



(**4**) R = R² = CH_2CO_2Et, R¹ = CH_2COCH_3

(**5**) R = CH_2CO_2H, R² = CH_2CO_2Et, R¹ = CH_2COCH

† ^1H NMR data (400 MHz, $CDCl_3$) for (**2**) (δ values): ArH: 7.143 (s, 2 H), 7.133 (s, 2 H), 6.621 (d, 2 H, J_{AB} 2.36 Hz), and 6.526 (d, 2 H, J_{AB} 2.36 Hz); OCH_2CO: 4.939 (s, 2 H), 4.859 (d, 2 H, J_{AB} 15.7 Hz), 4.574 (s, 2 H), and 4.350 (d, 2 H, J_{AB} 15.7 Hz); $ArCH_2Ar$: 4.963 (d, 2 H, J_{AB} 12.8 Hz), 4.589 (d, 2 H, J_{AB} 12.4 Hz), 3.248 (d, 2 H, J_{AB} 12 Hz), 3.187 (d, 2 H, J_{AB} 12.9 Hz); OCH_2CH_3: 4.251 (q, 4 H, J_{AB} 7.2 Hz) and 4.208 (q, 2 H, J_{AB} 7.2 Hz); OCH_2CH_3: 1.300 (t, 6 H, J_{AB} 6.5–7.2 Hz) and 1.285 (t, 3 H, J_{AB} 7.2–7.9 Hz); $C(CH_3)_3$: 1.316 (s, 9 H), 1.305 (s, 9 H), and 0.815 (s, 18 H).

‡ Experimental procedure for hydrolysis of (**1a**) to (**2**). A solution of the tetraester (**1a**) (5.01 g, 5.05 mmol) in chloroform (100 ml) was treated with trifluoroacetic acid (0.2 ml). The solution was stirred at room temperature for 24 h and then washed with water. The dried solution was concentrated to leave a white solid which on recrystallisation from ethanol–water furnished (**2**) (4.8 g, 88%) as white crystals, m.p. 166–169 °C (Found: C, 72.3; H, 7.7. $C_{58}H_{76}O_{12}$ requires C, 72.2; H, 7.8%).

solution of (**1a**) was saturated with sodium thiocyanate prior to the addition of TFA, no detectable amounts of hydrolysis were observed over a 10-day period. Clearly, the sodium thiocyanate complex of (**1a**), which independently[4] is known to form, and whose presence in the $CDCl_3$ solution was confirmed prior to the addition of TFA, does not react with the acid. Thirdly, ethanol was produced in the reaction, though with time it was transformed into its trifluoroacetate, thus establishing that the process was one of hydrolysis by adventitious water and not transesterification.

We propose that hydrolysis is initiated by reversible hydronium ion complexation within the hydrophilic cavity of (**1a**) in much the same way that Na^+ is encapsulated. This is supported by the minor ^1H NMR spectral changes which occur in the tetraester immediately after the addition of TFA, the most distinctive being the shift to higher field of the A component of the AB system associated with the bridging methylene protons, a shift which also occurs, though to a much greater extent, on Na^+ complexation. All shifts induced by TFA are more pronounced at higher TFA concentrations, indicating a rapid equilibrium. All the signals, with the exception of the OCH_2CO singlet, are shifted in the direction of the Na^+ complex. The rate of hydrolysis, however, falls off with higher TFA concentrations, which is also consistent with attack by water on the complexed hydronium ion, the concentration of 'free water' decreasing with increasing complex concentration. Sodium ion forms a kinetically stable complex with the tetraester in $CDCl_3$ and when the calixarene cavity is thus occupied, hydronium ion complexation is precluded and hydrolysis is not observed. Interestingly, potassium thiocyanate also forms a complex with the tetraester, but K^+ does *not* inhibit hydrolysis by TFA. ^1H NMR data show that the K^+ complex is exchanging rapidly with the free ligand in $CDCl_3$, that there is now competition with hydronium ion complexation, and hydrolysis ensues.

This selective monohydrolysis is not limited to calix[4]arene tetraesters. We have found, for example, that the diester diketone (**4**) also undergoes mono-hydrolysis with TFA to produce the monoacid (**5**). The mixed derivative (**4**) is a good Na^+ ion receptor. Apart from intrinsic interest in the mechanism of hydrolysis, this reaction opens new routes to more elaborate calixarenes including double calixarenes.[6]

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