Barium(II)-ion Assisted Monodeacetylation of Partial-cone Calix[4]arene-crown-5 Diacetate. A Convenient Preparation of Partial-cone Calix[4]arene-crown-5 Monoacetate

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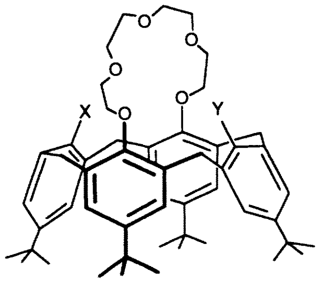
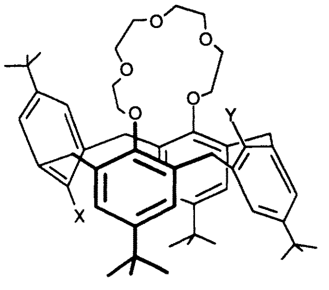
The barium(II)-ion assisted monodeacetylation of *p*-cone calix[4]arene-crown-5 diacetate **4** in MeO$^-$/MeOH is a fast and convenient method for the selective preparation of *p*-cone calix[4]arene-crown-5 monoacetate **5**, which is not readily accessible by direct acetylation of the parent bisphenolic compound.

Remarkable examples of metal-ion control of stereochemistry in the acetylation of calix[4]arene 1,3-diethers have been recently reported.[1] Thus, acetylation of the potassium or sodium salt of **1** with two mol equiv. of AcCl afforded the cone[2] diacetate **2**, whereas an analogous treatment of the thallium(I) salt gave the *p*-cone diacetate **4**. Both diacetates were obtained in virtually quantitative yield.



1 X,Y = OH
2 X,Y = OAc
3 X = OH, Y = OAc



4 X,Y = OAc
5 X = OAc, Y = OH
6 X = OH, Y = OAc

In connection with our studies on metal-ion catalysis in calixarene systems,[3] the preparation of the two conformationally rigid stereoisomeric calix[4]arene-crown-5 monoacetates* **3** and **5** was required. The cone isomer of the monoacetate **3** was readily obtained[1] in quantitative yield *via* acetylation of the sodium salt of **1** with 1 mol equiv. of AcCl. On the other hand, we now report that reaction of 1 mol equiv. of AcCl with the thallium(I) salt of **1** afforded a mixture of products that was shown by HPLC and NMR analysis to consist of a 1 : 1 : 1 mixture of the bisphenol reactant **1**, the *p*-cone diacetate **4**, and a third component that was subsequently identified as the desired *p*-cone monoacetate **5** [eqn. (1)]. No trace of **3** was detected in the mixture. Thus, acetylation of the thallium(I) salt of **1** exhibits the required stereoselectivity, but the two acetylation steps appear to proceed at comparable rates. Consequently, preparation of the *p*-cone monoacetate **5** by direct acetylation of **1** is inconvenient because of the difficulties of isolation of **5** from the complex mixture on a preparative scale. Therefore, an alternative route for the selective preparation of **5** was sought.

Table 1 Metal-ion catalysis in the basic methanolysis of compound 4 in MeOH at 25 °C[a]

Metal ion	k_{obs}/dm^3 mol^{-1} s^{-1} [b]	k_{obs}/k_0 [c]
Na$^+$	3.7×10^{-2}	39
K$^+$	7.1×10^{-2}	75
Rb$^+$	1.2×10^{-1}	125
Cs$^+$	1.9×10^{-2}	20
Sr^{2+}	6.5×10^{-3}	7
Ba^{2+}	2.3×10^{-1}	223

[a] All data refer to the reaction of the acetyl group adjacent to the polyether bridge. [b] Spectrophotometric rate measurements. [c] $k_0 = 9.4 \times 10^{-4}$ dm^3 mol^{-1} s^{-1}, is the rate constant of the reaction carried out in the absence of metal ions (from the HPLC experiment plotted in Fig. 2).

$$\mathbf{1} \xrightarrow[\text{iii, H}_3\text{O}^+]{\text{i, EtOTl, Et}_2\text{O; ii, AcCl, 1 mol equiv.}} \mathbf{1} + \mathbf{5} + \mathbf{4} \qquad (1)$$

Since our previous studies[4,5] had shown that basic methanolysis of aryl acetates bearing a polyether moiety in the proximity of the acetoxy group is significantly accelerated by alkali-, and even more so, by alkaline-earth metal ions, the prediction was made that a metal ion would selectively enhance the rate of cleavage of the acetyl group adjacent to the polyether bridge of the readily available diacetate **4**,[1] and that **5** could be selectively obtained upon acid quenching after the first deacylation step (Scheme 1).

In order to test the above hypothesis and to make a proper choice of the metal-ion catalyst, an exploratory kinetic investigation involving a number of alkali- and alkaline-earth metal bromides was carried out in methanol solution at 25 °C. The diacetate **4** (0.7 mmol dm^{-3}) was reacted with an excess of Me$_4$NOMe (50 mmol dm^{-3}), either in the absence or presence of metal bromides (25 mmol dm^{-3}). The results reported in

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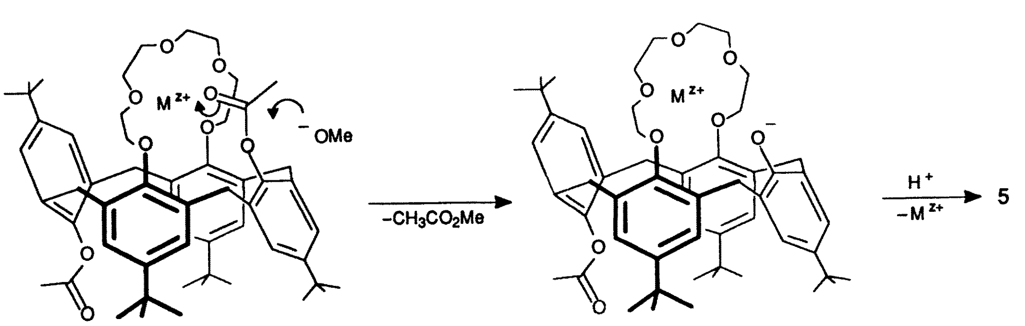
* Fast conversion of the *p*-cone isomer **6** into the more stable cone isomer **3** is expected to take place *via* rotation of the OH group through the calixarene annulus. Similarly, the 1,3-alternate isomer (not shown in the formulae) should convert rapidly into **5** *via* the same mechanism.



Scheme 1

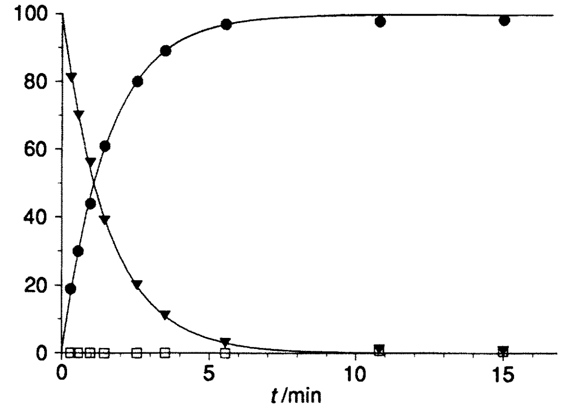


Fig. 1 Barium-ion assisted basic methanolysis of **4** at 25 °C, as monitored by HPLC. Mole fraction (× 100) of **1** (□), **4** (▼) and **5** (●), as a function of time. The curves are calculated from the integrated first-order equation, with $k = 1.1 \times 10^{-2}$ s^{-1}, which corresponds to a second-order rate constant $k_{obs} = 0.22$ dm^3 mol^{-1} s^{-1}.

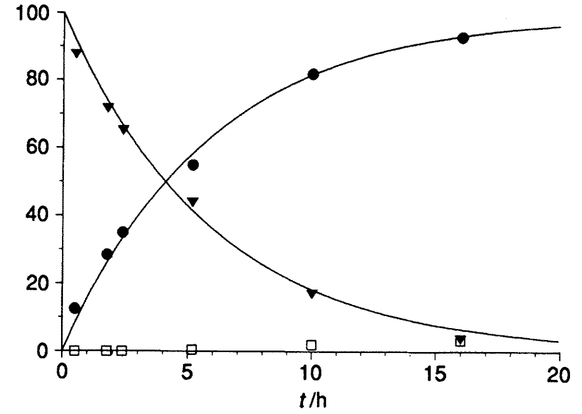


Fig. 2 Basic methanolysis of **4** in the absence of metal ions, at 25 °C, as monitored by HPLC. To avoid any interference from adventitious impurities of metal ions, 20 mmol dm^{-3} of [2.2.2] cryptand were added. Mole fraction (× 100) of **1** (□), **4** (▼) and **5** (●), as a function of time. The curves are calculated from the integrated first-order equation, with $k = 4.7 \times 10^{-5}$ s^{-1}, which corresponds to a second-order rate constant $k_o = 9.4 \times 10^{-4}$ dm^3 mol^{-1} s^{-1}.

Table 1 show that rate enhancements of methanolysis are significant in most cases. Incidentally we note that the relatively small rate enhancement brought about by Sr^{2+} is at variance with previous findings[4,5] that the catalytic efficiencies of Sr^{2+} and Ba^{2+} are comparable to each other and are usually much higher than those of the monovalent metal ions. At present we have no explanation for this unexpected behaviour, which deserves careful attention in future studies.

It is apparent from the data listed in Table 1 that Ba^{2+} ion is the most effective promoter of the methanolysis. As shown by the time–concentration curves obtained by HPLC monitoring of samples of the reaction mixture (Fig. 1), the process is highly selective and the desired *p*-cone monoacetate **5** was obtained in quantitative yield upon acid quenching of the reaction mixture after 15 min. The product was *ca.* 99% pure, the only detectable impurities being **1** and **4**. Structure assignment was based on FAB-MS, ^1H and ^{13}C NMR spectral data and elemental analyses. Particularly significant in the confirmation of the *p*-cone structure are the signals at 38.6 and 31.1 ppm in the ^{13}C NMR spectrum, which, according to de Mendoza-Prados' single rule[6] should be assigned to the $ArCH_2Ar$ methylene carbons having the two aromatic rings in the *anti* and *syn* orientation, respectively.

For comparison purposes, the reaction carried out in the absence of metal ions was also monitored by HPLC (Fig. 2). Somewhat surprisingly, a rather selective cleavage of the acetoxy group adjacent to the polyether bridge is observed, although not as selective as in the Ba^{2+}-assisted reaction. This high selectivity is probably due to the exceedingly low reactivity of the other acetyl group which is apparently embedded in the calixarene cavity, as suggested by the finding[1] that the signal assigned to the methyl group is found upfield at −0.15 ppm in the ^1H NMR spectrum. It is apparent that use of Ba^{2+} ion as a promoter significantly increases the efficiency of the process in terms of rate and selectivity.

Experimental

NMR spectra were recorded in $CDCl_3$ on a Varian XL-300 spectrometer (*J* values in Hz).

HPLC analyses were carried out on a 25 cm × 4.6 mm Supelcosil LC-318 column with 0.5% CF_3CO_2H–MeOH as eluent, at a flow rate of 1 cm^3 min^{-1}. The instrument was fitted with a UV–VIS detector, operating at 230 nm. The *p*-cone diacetate **4**, the *p*-cone monoacetate **5**, and the bisphenolic compound **1** had retention times of 5.1, 6.1 and 7.3 min, respectively. Under the same conditions, the cone monoacetate **3** had retention time of 7.6 min.

Rate measurements were carried out either spectrophotometrically[4] by monitoring the increase of the aryloxide absorption at 290 nm, or by sampling the reaction mixture at time intervals, followed by HPLC analysis of the samples after work-up with dilute acid–chloroform.

Direct Acetylation of **1**.—To a stirred suspension of 0.6 mmol of the thallium(I) salt of **1** in dry CH_2Cl_2 (5 cm^3) was added dropwise acetyl chloride (0.6 mmol) dissolved in CH_2Cl_2 (5 cm^3) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for an additional 40 min and then diluted with water and extracted twice with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated to give a mixture of products that was analysed by HPLC.

Partial Methanolysis of **4**.—To a stirred solution of 0.04 mmol of **4** and 1.8 mmol of $BaBr_2$ in anhydrous MeOH (70 cm^3), were added dropwise 3.6 mmol of tetramethylammonium methoxide in MeOH (1.8 cm^3) at 25 °C. After 15 min the reaction mixture was quenched with dilute hydrochloric acid and extracted twice with chloroform. The combined organic extracts were dried ($MgSO_4$) and evaporated to give a quantitative recovery of **5**. Crystallisation from MeOH afforded the analytically pure compound in 77% yield, m.p. 235–6 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3390 (O–H) and 1737 (C=O); δ_H 7.20 (2 H, s, ArH), 7.07 (4 H, m, ArH), 6.76 (2 H, s, ArH), 4.42 (2 H, d, *J* 13, $ArCH_2Ar$), 4.04–3.53 (20 H, m, OCH_2CH_2O and $ArCH_2Ar$), 3.23 (2 H, d, *J* 13, $ArCH_2Ar$), 1.43 (9 H, s, Bu^t), 1.28 (9 H, s, Bu^t), 1.12 (18 H, s, Bu^t) and 0.90 (3 H, s, $COCH_3$); δ_C 168.8 ($COCH_3$), 152.1, 150.2, 147.0, 145.8, 141.4, 134.2, 132.1, 131.5, 128.5 (Ar, C–Z), 126.8, 125.9, 125.0, 124.4 (Ar, C–H), 73.4, 71.4, 70.8, 70.2 (OCH_2CH_2O), 38.6 ($ArCH_2Ar$), 34.3, 34.0, 33.9 [$C(CH_3)_3$], 31.8, 31.7, 31.4 [$C(CH_3)_3$], 31.1 ($ArCH_2Ar$) and 19.9 ($COCH_3$); *m/z* (FAB) 872 (M Na^+) and 888 (M K^+) (Found: C, 76.0; H, 8.55. $C_{54}H_{72}O_8$ requires C, 76.37; H, 8.55%).

Acknowledgements

This work was carried out as part of an EEC joint project, contract No. SC1*-0359. Thanks are due to MURST for financial support. We are grateful to Dr. L. Petrilli and Mr. F. Dianetti of the *Servizio Microanalisi del CNR, Area della Ricerca di Roma*, for providing elemental analytical data, as well as to Mr. G. D'Arcangelo, *Università di Tor Vergata, Roma*, for technical assistance in the FAB–MS experiments.

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Paper 2/06230E
Received 23rd *November* 1992
Accepted 4th *January* 1993