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CsF-Promoted Acetyl Dance at the Narrow Rim of *p-tert*-Butyl[3.1.3.1]homooxacalixarene

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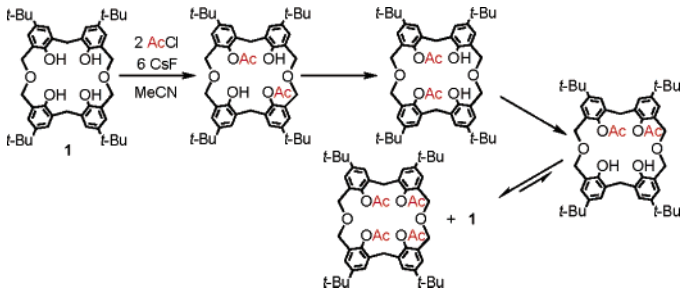
ABSTRACT



In the acetylation of an oxygenated calix[4]arene homologue in the presence of CsF as a base, relaxation of the reaction system to the equilibrium composition takes place through several intra- and intermolecular steps that can be easily controlled to obtain the various acetyl derivatives. The effect of different bases is also discussed.

In the chemistry of calixarenes[1] a few cases are known of aroyl[2] or phosphoryl[3] migration under basic conditions, its occurrence being mainly suggested by the formation of unexpected derivatives. 3,5-Dinitrobenzoyl migrations in derivatives of *p-tert*-butylcalix[4]arene have also been reported to occur in the presence of typical transacylation catalysts (pyridine and imidazoles).[4] To obtain an otherwise elusive dimethyl ether derivative of an oxygenated homologue of calix[4]arene, we have recently used protection of two vicinal phenol groups by esterification with a bifunctional bridging unit,[5] without any evidence of anomalous regiochemistry. With the aim of further evaluating the potential of ester formation as a protecting step in the chemistry of homooxacalixarenes,[6] we investigated the partial acetylation of *p-tert*-butyl[3.1.3.1]homooxacalixarene[7] **1** and now report on the peculiar dynamic picture observed in the presence of CsF and other bases.

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(1) For books on calixarenes, see: (a) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, England, 1989. (b) Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, England, 1997. (c) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, The Netherlands, 1991. (d) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, The Netherlands, 2001. (e) *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, 2000.

(2) (a) Kim, J. M.; Nam, K. C. *Bull. Korean Chem. Soc.* **1997**, *18*, 1327. (b) Lynch, J. A.; Mestayer, J. J.; Blanda, M. T. *J. Supramol. Chem.* **2001**, 139. (c) Kleij, A. W.; Souto, B.; Pastor, C. J.; Prados, P.; de Mendoza, J. *J. Org. Chem.* **2003**, *68*, 8711.

(3) (a) Vysotsky, M. O.; Tairov, M. O.; Pirozhenko, V. V.; Kalchenko, V. I. *Tetrahedron Lett.* **1988**, *39*, 6057. (b) Markovsky, L. N.; Visotsky, M. O.; Pirozhenko, V. V.; Kalchenko, V. I.; Lipkowski, J.; Simonov, Y. A. *Chem. Commun.* **1996**, 69.

(4) K. A.; Fronczek, F. R.; Watson, W. H.; Kashyap, R. P.; Gutsche, C. D. *J. Org. Chem.* **1995**, *60*, 8394.

(5) Masci, B.; Levi Mortera, S.; Persiani, D.; Thuéry, P. *J. Org. Chem.* **2006**, *71*, 504.

(6) For homooxacalixarenes, see, in particular: Masci, B. in ref 1d.

(7) The ambiguous name *p-tert*-butyltetrahomodioxacalix[4]arene is currently used for compound **1**. For nomenclature of homooxacalixarenes, see refs 5 and 6.

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The expected acetyl derivatives **2**−**7** could be isolated as pure compounds, and their structure could be established by NMR and single-crystal X-ray diffraction.[8]

Mono- and diacetyl derivatives were actually obtained as the main reaction products when 1.0−1.5 or 2.0−2.5 mol of AcCl, respectively, was used in the presence of CsF in MeCN,[9] but in both cases, quite complicated reaction paths were apparent on monitoring the composition of the reaction mixture by either ^{1}H NMR or HPLC. Namely, as reported in Figure 1 for an experiment carried out at 50 °C with 1.5

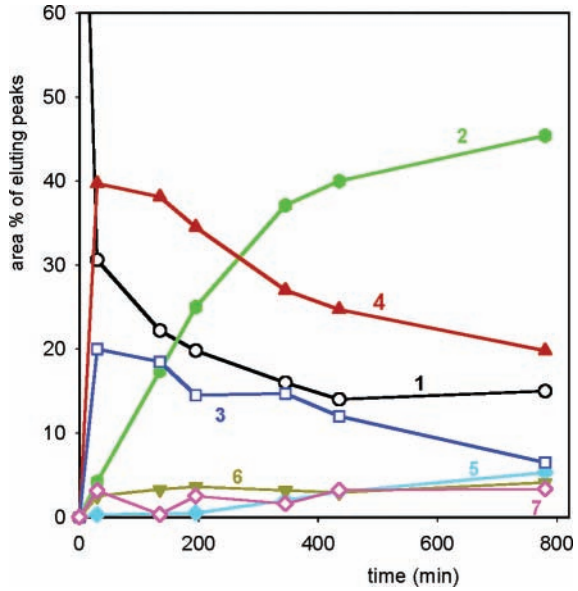
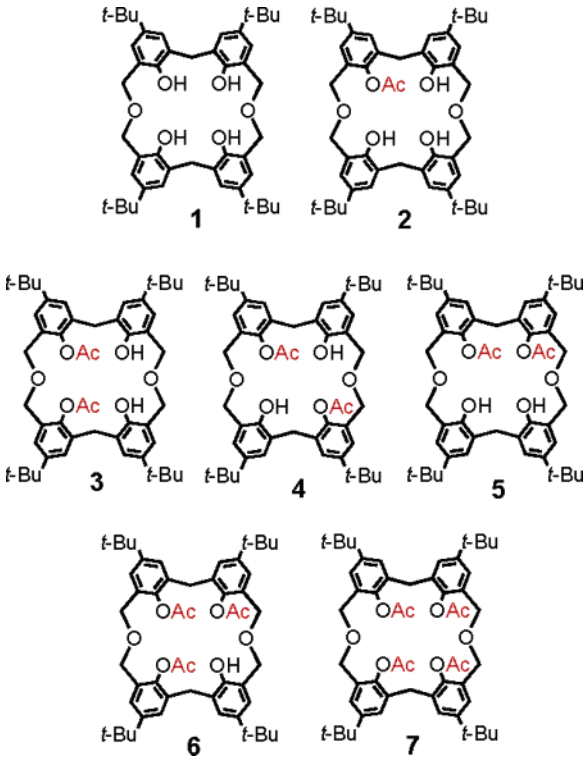


Figure 1. Time-dependent composition (HPLC) of the reaction mixture obtained from **1**, acetyl chloride, and CsF (1.0, 1.5, and 3.5 molar equiv, respectively) in MeCN at 50 °C.

molar equiv of AcCl and 3.5 molar equiv of CsF, extensive formation of **3** and **4** is observed after a few minutes. The monoacetyl derivative **2** appears to react with AcCl much more rapidly than the parent tetraphenol **1**,[11] and the first acetylation step is followed by a faster one, with the preferential formation of the distal diacetyl derivative **4**. The accumulation of the eventually observed **2** in the reaction medium only occurs later on, largely at the expense of **3** and **4**, as the result of an equilibration process that must involve intermolecular acetyl transfer.

The complicated reaction pattern observed when slightly more than 2 molar equiv of AcCl and 6 molar equiv of CsF were used could be more easily monitored on lowering the temperature, as shown in Figure 2.[12] Even at 0 °C, **1**



completely disappeared at once, but the monoacetyl derivative **2** could barely be detected, with the diacetyl derivatives **4** and **3** being formed along with a small amount of the triacetyl derivative **6**. On extrapolating the observed profiles for **3** and **4** to the very early reaction times, **4** seems to be the kinetically most favored product that rapidly isomerizes to give **3**, in up to 70% yield after 20 min. This has been checked to be a plateau value for **3** for an overall time of more than 2 h, with minor changes being observed for the other components. The composition of the reaction mixture dramatically changed upon raising the temperature to 50 °C, with the formation of the third diacetyl derivative **5** that gradually became the main product, although it was apparently involved in a further equilibration with the formation of significant amounts of the starting tetraphenol **1** and the tetraacetyl derivative **7**.

In an independent experiment, a sample of pure **5** was reacted with excess CsF in MeCN at 50 °C and the rapid formation of **1** and **7** was observed as well, providing further evidence for the strict relation among the three compounds.

(8) In particular, a single-crystal X-ray analysis of **4** allowed to distinguish between **4** and **3** that feature the same signal pattern in the NMR spectra. In several cases, simple NMR spectra were only observed at high temperature, with an intermediate rate on the NMR time scale being observed for conformational interconversion at room temperature. The sharp signals generally observed even at room temperature for *tert*-butyl groups were used to analyze the mixture composition by ^{1}H NMR spectra.

(9) CsF in MeCN is a currently used base−solvent system in the alkylation at the narrow rim of calixarenes; see ref 10. For an early review on the use of the fluoride ion in organic synthesis, see: Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.

(10) See, for instance: (a) Neri, P.; Battocolo, E.; Cunsolo, F.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1994**, *59*, 3880. (b) Neri, P.; Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Piattelli, M., in ref 1d.

(11) The low solubility of the caesium salt of **1** in the reaction conditions should be taken into account.

(12) In a typical experiment, a mixture of **1**[13] (709 mg, 1.00 mmol) and CsF (930 mg, 6.11 mmol) in MeCN (45 mL) was refluxed for 1 h under a nitrogen atmosphere. Then the temperature was lowered to 0 °C and a cold solution of acetyl chloride (147 μL, 2.06 mmol) in MeCN (4 mL) was added. Aliquots (ca. 0.2 mL) of the reacting mixtures were taken at varying times through a syringe, quenched in cold water, and, after $CHCl_3$−H_2O workup, analyzed by HPLC or by ^{1}H NMR. The temperature was set at 50 °C after 130 min, and further aliquots were taken and analyzed. Preparative runs were carried out using either CsF or K_2CO_3 as a base. Column chromatography allowed pure samples of **2**, **4**, **5**, and **7** to be obtained, whereas analytically pure samples of **3** and **6** were obtained through HPLC chromatography.

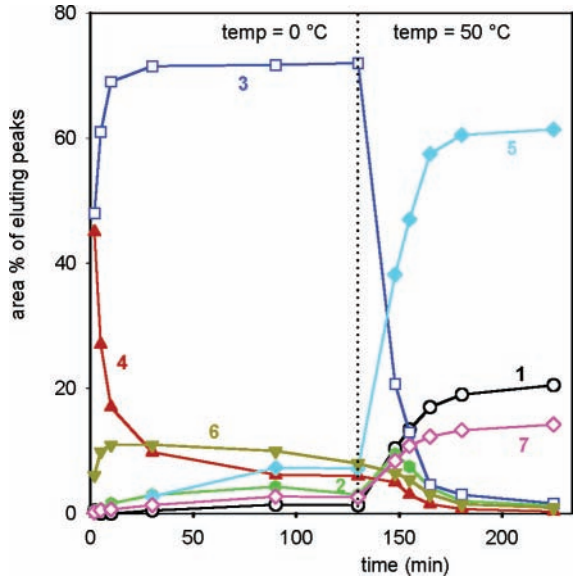
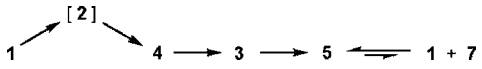


Figure 2. Time-dependent composition (HPLC) of the reaction mixture obtained from **1**, acetyl chloride, and CsF (1.0, 2.1, and 6.0 molar equiv, respectively) in MeCN. The temperature was raised from 0 to 50 °C after 130 min.

The transesterification process was also investigated on reacting purified acetylated products directly in NMR tubes. When pure **4** was reacted at 25 °C with excess CsF in CD_3CN, the isomerization to **3** took place, whereas further isomerization to **5**, accompanied by the formation of **1** and **7**, was observed upon heating at 50 °C. In a further experiment, **5** was formed on adding **1** to **7** and an excess of CsF. Thus, in the presence of excess CsF, a consistent picture is observed when 2 mol of acetyl chloride or ester groups are available for 1 mol of macrocyclic compounds. This can be sketchily summarized by the simplified sequence reported in Scheme 1.

Scheme 1



Interesting differences were observed on changing the nature and the amount of the added base. In particular, in the reaction with 2.4 equiv of AcCl and excess K_2CO_3 or Cs_2CO_3, the final product composition was analogous to that reported in Figure 2, but the reaction was much more sluggish; moreover, the isomerization step from **4** to **3** was not observed (see Supporting Information). On the other hand, in a series of experiments in CD_3CN, pure **3** was found to be largely converted into **4**, after only 1 min in the presence of excess K_2CO_3 or Cs_2CO_3 and after 20 min in the presence of excess KF. No further reaction was apparent at room temperature for several hours, the molar ratio between **3** and **4** in the apparent equilibrium mixtures being close to 0.35. The very fast reversal to **3** was observed on adding CsF to the mixture obtained with K_2CO_3, and further transformations, similar to those observed for CsF alone, were observed for longer reaction times. Interestingly, the marked preference for **3** with respect to **4** is only observed in the presence of excess CsF. In the presence of 3.0−3.5 mol of CsF for 1 mol of reacting **1** (see, for instance, the experiment reported in Figure 1), no clear indication of such a shift of the equilibrium is obtained.

NMe_4F proved to be another effective promoter of acetylation and transacetylation of **1**,[14] the most interesting difference with respect to CsF being that the pair **1**, **7** is definitely favored with respect to **5** in runs involving ca. 2 molar equiv of AcCl and excess base, as reported in Figure 3 for an experiment carried out at 50 °C. A similar effect

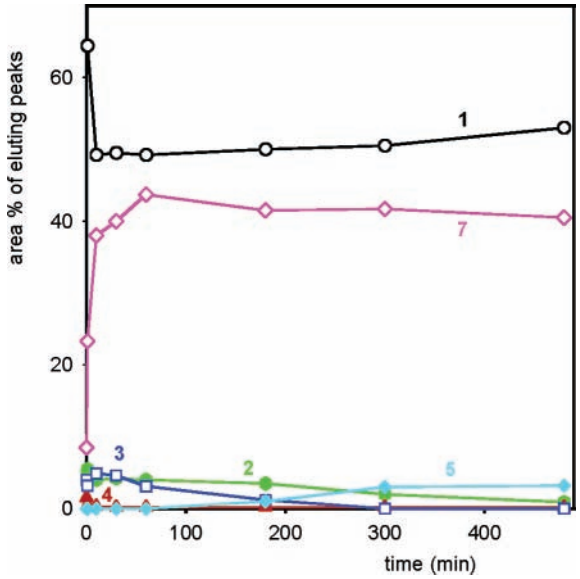


Figure 3. Time-dependent composition (HPLC) of the reaction mixture obtained from **1** (1 mol), acetyl chloride (2.4 mol), and Me_4NF (6 mol) in MeCN at 50 °C.

was observed on adding NMe_4Br to the final mixture obtained in the presence of CsF. The complexation of a NMe_4^+ ion by **7** cannot explain the above effects because the latter proved to be a very poor ligand.[15] On the other hand, an active role in the observed thermodynamic template effect of the NMe_4^+ ion could tentatively involve the conjugated base of **1** generated by the F^- ion because this anionic homooxacalixarene can bind strongly the quaternary ammonium ion and alter the equilibrium between **5** and the pair **1**, **7**.[16]

The strength of the possible intramolecular hydrogen bonds in anionic intermediates and products is expected to play an

(13) (a) Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48*, 1536. (b) Masci, B. *Tetrahedron* **2001**, *57*, 2841.

(14) Both CsF and Me_4NF are commercially available, but the latter is a more expensive and more hygroscopic reactant.

(15) An association constant in the order of 5 L mol^{-1} was estimated by ^1H NMR for complexation of tetramethylammonium picrate by **7** in $CDCl_3$ solution at 298 K.

important role in the observed complicated picture. On extending arguments currently used in calixarene chemistry,[10] **5** should be disfavored with respect to **3** and **4** in the direct formation of diacetyl derivatives from **2** because it is formed from the least abundant monoanion, with the strength of the intramolecular hydrogen bond being expected to decrease on increasing the distance (Figure 4). By the same token, **5**

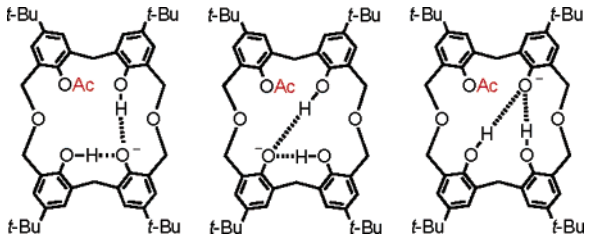


Figure 4. Decreasing strength, from left to right, of the intramolecular hydrogen bonding in the isomeric monoanions of **2**.

should be preferred with respect to **3** and **4** at equilibrium, as shown in Figure 5. In the present case, the above reversal

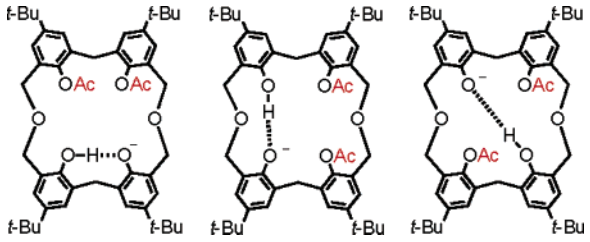


Figure 5. Decreasing strength, from left to right, of the intramolecular hydrogen bonding in the monoanion of the isomeric diacetylated products.

of selectivity due to either kinetic or thermodynamic control occurs with all the investigated bases, whereas other features, such as, in particular, the change in the relative stability of **3** and **4**, appear to be dramatically dependent on the specific salt used as a base and cannot be easily rationalized.

All the tested carbonates and fluorides, apart from Cs_2CO_3, are commonly considered to be weak bases that monodeprotonate calixarene polyphenols,[10] but several rate and equilibrium features indicate that specific roles are played by both the basic anion and the counterion. In particular, a fluoride ion can possibly somehow polarize the OH bonds besides monodeprotonating calixarenes, and counterions can act as both kinetic and thermodynamic templates.

Although a few instances of phosphoryl and aroyl ester migration in basic media can already be found in the literature on calix[4]arenes,[2−4] the present system allows an unprecedented direct insight into complex rearrangement patterns not involving nucleophilic catalysts. Namely, several esters are formed as a consequence of a cascade of acetyl transfer steps between two phenoxide ions, the different rate of the observed interconversions being an important clue. An easy intramolecular acyl transfer to the vicinal phenoxide ion appears to take place in the equilibration between **4** and **3** that is highly responsive to the nature of the salt used as a base, whereas cyclic transition states involving a larger number of bonds and higher temperatures are required to obtain **5**. The latter actually appears to form through intermolecular acetyl transfer steps because **5**, **1**, and **7** occur simultaneously in the tested conditions (Figure 2). Some catalytic contribution by the acid HF can also be postulated for acetyl transfer promoted by a fluoride ion as a base.

Although other bases have also been found to promote acetylation and transacetylation in the present system, CsF, along with NMe_4F, proved to be powerful agents in driving the acetyl dance[17] at the lower rim of **1**. Because of the observed easy occurrence of both intra- and intermolecular acyl transfer, interesting results are expected in the equilibration between polyphenols and acyl derivatives in mixed calixarene or calixarene-like systems, and dynamic combinatorial libraries of acyl derivatives, responsive to template effects, seem to be easily accessible thanks to CsF, NMe_4F, and other catalysts.

Supporting Information Available: General methods for the experimental procedures, synthesis of compounds **2**−**7**, ^1H and ^{13}C NMR spectra of compounds **2**−**7**, figures with representative HPLC and ^1H NMR analyses, crystal data, and displacement ellipsoid plots for compounds **4** and **5**. Tables of crystal and refinement data, atomic positions, displacement parameters, anisotropic displacement parameters, bond lengths, and bond angles in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Even neutral **1** binds the Me_4N^+ ion (see: Masci, B. *Tetrahedron* **1995**, *51*, 5459), but significantly larger values can be expected for the conjugated base as a ligand.

(17) Reference is made to the classic work of J. Bunnett on "halogen dance" in nucleophilic aromatic substitution. See: Bunnett, J. *Acc. Chem. Res.* **1972**, *5*, 139.