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SOURCE OF THE INTRAANNULAR HYDROGENS IN THE DEHYDROXYLATION OF CALIX[4]ARENE DIETHYL PHOSPHATE ESTER DERIVATIVES

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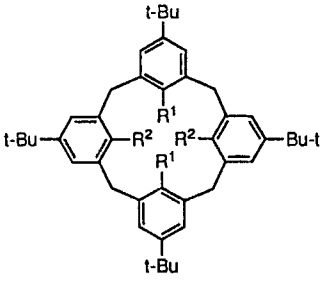
The different possible sources of the intraannular hydrogens in the dehydroxylated calixarenes obtained by reductive cleavage of the calix[4]arene diethyl phosphate esters 2 and 6 are analysed. Two calixarene diethyl phosphate esters (4 and 5) full deuterated in the ethyl groups were synthesized. Reductive cleavage of 4 and 5 (potassium–ammonia) resulted in the formation of the OH-depleted calixarenes 3 and 7, respectively, which did not incorporate any deuterium at the intraannular positions, as judged by integration of the NMR signals. Quenching with D_2O of the reaction mixture of either 2 or 6 and potassium–ammonia did not result in any deuterium incorporation in the products. The labelling experiments rule out the possibility that the source of the intraannular hydrogens is the diethyl phosphate ester groups or the quencher. It is concluded that the most probable sources of the hydrogen atoms in the OH-depleted calixarenes is the ammonia molecule.

INTRODUCTION

Calixarenes are macrocyclic compounds which can be easily prepared by condensation of phenol derivatives and formaldehyde.[1] The parent compound, *p-t*-Bu-calix[4]arene (**1**), exists in the solid state in a 'cone' conformation capable of including a small organic molecule in its cavity.[2] In addition to their 'host' properties, calixarenes can behave as ligands by coordination of metal ions with the OH groups.[3] The OH-ligating groups of some calixarenes have been chemically modified in order to alter or improve their binding capabilities.[4,5]

In their study of the reduction of phenols to aromatic hydrocarbons, Kenner and Williams[6] showed that phenolic OH groups can be replaced with hydrogen via a two-step process involving the conversion of the OH into a diethyl phosphate ester, and cleavage of the resulting ester by treatment with an alkali metal dissolved in liquid ammonia. This reaction was later reinvestigated[7a] and modified[7b] by Rossi and Bunnett, who showed that preparative aminodephosphatation (i.e. conversion of the diethyl phosphate ester into an amino group) can be achieved by adding KNH_2 to the reaction mixture.[7b] The method is relatively insensitive to steric effects. For example, 2,6-dimethylphenyl(diethyl phosphate) can be converted to the corresponding aniline in one step in 78% (isolated) yield.[7b] The proposed reaction mechanism of the aminodephosphatation reaction[8] involves a transfer of



1 $R^1 = R^2 = OH$
2 $R^1 = R^2 = OPO(OEt)_2$
3 $R^1 = R^2 = H$
4 $R^1 = R^2 = OPO(OCD_2CD_3)_2$
5 $R^1 = OPO(OCD_2CD_3)_2, R^2 = OH$
6 $R^1 = OPO(OEt)_2, R^2 = OH$
7 $R^1 = H, R^2 = OH$

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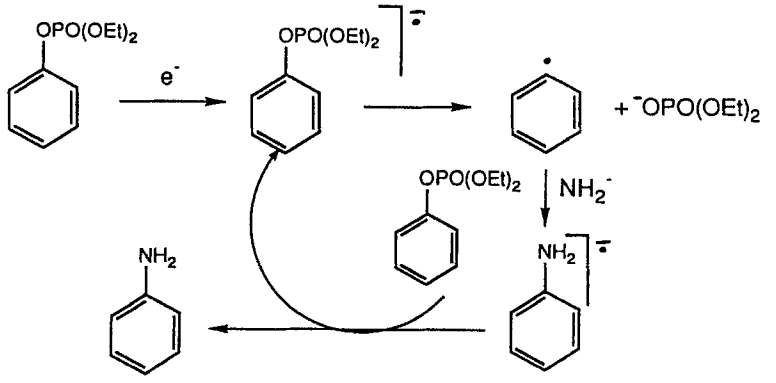


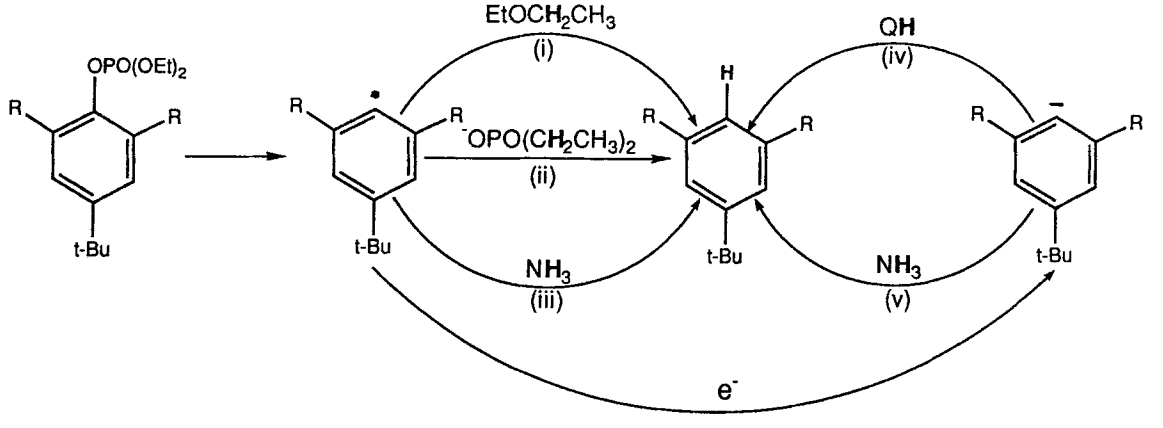
Scheme 1

the (solvated) electron to the phosphate ester molecule, and the rupture of the resulting radical anion into an aryl radical and diethyl phosphate ion. The aryl radical recombines with amide ion to form the radical anion of aniline, which subsequently transfers an electron to another phosphate ester molecule. [Scheme 1 (metal counter ions have been omitted for simplification)] The mechanism was dubbed by Bunnett[8] $S_{RN}1$. Evidence has been presented that two-electron pathways are operating in the solvent electron-mediated fragmentation of phenyl(diethyl phosphate) esters[9].

The $S_{RN}1$ mechanism seemed an attractive route for the preparation of the aminocalixarenes. However, treatment of the *p-t*-Bu-calix[4]arene diethyl phosphate ester **2** with KNH_2 in liquid ammonia at $-78\,^{\circ}C$ resulted exclusively in the replacement of the phosphate groups by hydrogen and yielded **3** quantitatively.[10] Similarly, treatment of the octa(diethyl phosphate ester) of *p-t*-Bu-calix[8]arene with KNH_2–K–NH_3 yielded a *p-t*-Bu-[1[8]]metacyclophane system.[10] Since both calixarene phosphate esters are solids, they were dissolved in a small amount of diethyl ether prior to their addition to the ammonia solution.

POSSIBLE SOURCES OF HYDROGEN IN THE DEHYDROXYLATED CALIXARENES

Several possibilities can be envisioned for explaining the absence of aniline products in the reaction of the calixarenes diethyl phosphate ester derivatives with KNH_2–K–NH_3. In all cases it must be assumed that the reaction of the intermediate phenyl radicals (cf. Scheme 1) with the amide ion is slower (probably owing to steric effects) than the reaction with the hydrogen atom donor or than its reduction to phenyl anion. Clearly, at some stage of the reaction a hydron or hydrogen atom must be abstracted by the radical or carbanionic intermediate. The most likely routes for this abstraction are (i) the phenyl radical abstracts a hydrogen from the diethyl ether molecule; (ii) the phenyl radical abstracts



Scheme 2

a hydrogen from a neighbouring diethyl phosphate group (either attached to the molecule or already cleaved); (iii) the phenyl radical abstracts a hydrogen from the ammonia; (iv) the radical is further reduced by the solvated electron to phenyl anion, which is subsequently hydronated with the quenching reagent (NH_4Cl); (v) the phenyl anion is hydronated by the ammonia before the quenching takes place. These routes are summarized in Scheme 2. Rossi and Bunnett,[7a] in their analysis of the mechanism of the dehydroxylation of phenols concluded that the hydrogen atom originates either from the ether molecules (i.e. H abstraction by the phenyl radical) or by abstraction of a hydron of the ammonia by the aryl anion.[7] On the other hand, Shono *et al.*[11] concluded from labelling studies that in the electrochemical dephosphatation of phenol diethyl phosphate esters about 40% of the hydrogen came from the substrate itself.

ELIMINATION OF ROUTE (i)

In our original procedure for the preparation of the dehydroxylated calixarenes, we used a small amount of dry diethyl ether in order to solubilize the calixarene diethyl phosphate ester before its addition to the liquid ammonia.[10] In order to rule out the possibility that diethyl ether molecules are the source of the hydrogen, the diethyl phosphate ester **2** was dissolved in a minimum amount in *tert*-butylamine (a solvent which is not a good hydrogen donor) and the reaction was carried out under the usual conditions (−78 °C, KNH_2–K–NH_3). The product was the metacyclophane **3**, i.e. identical with the product obtained in the presence of diethyl ether. It can therefore be concluded that even in the absence of diethyl ether the abstraction of hydrogen atoms or the reduction of intermediate phenyl radicals to phenyl anions is faster than the reaction of the phenyl radical with the amide ion. However, one cannot rule out the possibility that when present, the diethyl ether molecules are the source of the intraannular hydrogens. In order to rule out this possibility unequivocally, all the following reactions were carried out in the absence of diethyl ether using *tert*-butylamine for dissolving the calixarene phosphate esters.

ELIMINATION OF ROUTE (ii)

Pathway (ii) was ruled out by labelling experiments. We synthesized the two labelled calixarene diethyl phosphate esters (**4** and **5**) by analogy with the preparation of (unlabelled) diethyl phosphate esters **2** and **6**.

Reaction of PCl_3 with CD_3CD_2OD afforded $DPO(OCD_2CD_3)_2$.[12] Reaction of the labelled phosphite with CCl_4 in the presence of triethylamine resulted, according to the literature procedure for the unlabelled compound,[13] in the formation of $ClPO(OCD_2CD_3)_2$.

Reaction of calixarene **1** with $DPO(OCD_2CD_3)_2$–CCl_4–Et_3N under the conditions described previously for the formation of the unlabelled disphosphate **6**[14] resulted in the formation of the calixarene-d_{20} **5**. Treatment of **5** with $ClPO(OCD_2CD_3)_2$ and base in the presence of a phase-transfer catalyst resulted in the formation of tetraphosphate **4**. The ^1H NMR spectrum (methylene region) of the labelled **4** and unlabelled **2** are shown in Figure 1. The diethyl phosphate ester groups are enriched by >93% D, as judged by integration of the ^1H NMR spectrum. Reductive cleavage of the deuterated phosphates **4** and **5** (K–NH_3) resulted in the formation of calaxiarenes **3** and **7**, respectively, which did not incorporate any D at the intraannular positions as judged by integration of the NMR signals.

These labelling experiments rule out the possibility that the intraannular hydrogens in the dehydroxylated

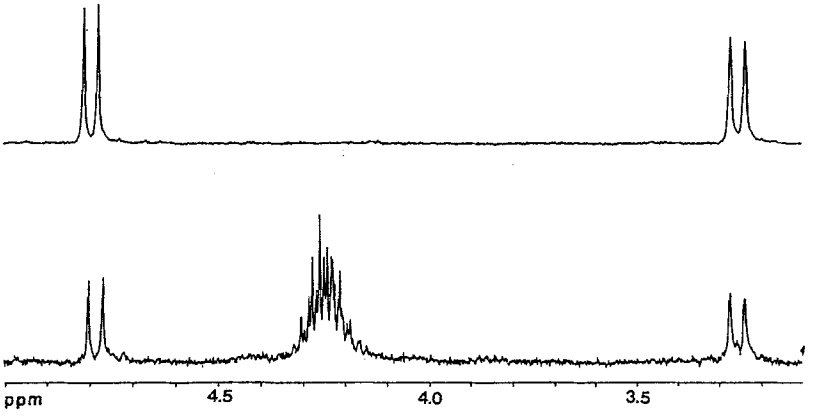


Figure 1. 400 MHz ^1H NMR spectra ($CDCl_3$, room temperature, methylene region) of tetrakis(diethyl phosphate)-*p*-*t*-Bucalix[4]arene. Top: d_{40} ester (**4**). Bottom: unlabelled compound (**2**)

calixarenes originate from the diethyl phosphate ester groups.

ELIMINATION OF ROUTE (iv)

In order to find out whether this route is operating, the unlabelled phosphate esters **2** and **6** were reductively cleaved ($K-NH_3$) and the reaction mixture quenched with D_2O. According to the ^1H NMR the products (**3** and **7**, respectively) did not contain intraannular deuterons. These results rule out the quenching reagent as the source of the hydrogens.

By exclusion of the routes (i), (ii) and (iv), it can be concluded that the more probable source of the hydrogen atoms in the product is the ammonia. Our experiments do not allow us to discern between routes (iii) and (v) and therefore ancillary information must be used. Rossi and Bunnett[15] had presented evidence that the rate of abstraction of hydrogen by the phenyl radical is relatively slow. Since the presence of the solvated electron should reduce the phenyl radical into phenyl anion, we believe that the latter is the intermediate which abstracts the hydron from the ammonia.

CONCLUSIONS

The source of the intraannular hydrogens in the OH-depleted calixarenes is the ammonia. The rate of reaction of the intermediate phenyl radical with the amide ion is probably reduced owing to steric effects.

EXPERIMENTAL

NMR spectra were recorded on a Bruker WP 200 SY and AMX-400 pulsed Fourier transform spectrometers. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. *p-t*-Bu-calix[4]arene was prepared by the literature procedure.[16] Ethanol-d_6 (99% D incorporation) was purchased from Aldrich.

Diethyl-d_{10} *deuteriumphosphite.* The compound was prepared according to the literature procedure for the unlabelled compound.[12] A solution of phosphorus trichloride (2·5 ml) dissolved in diethyl ether (10 ml) was added slowly with stirring to 5 ml of ethanol-d_6 (99% D) at 0 °C. During the addition argon was bubbled into the mixture in order to remove the DCl formed. After 30 min, ammonia was introduced, and the precipitated ammonium chloride was filtered. Evaporation of the ether and low-pressure bulb-to-bulb distillation of the residue yielded 1·5 ml of diethyl-d_{10} hydrogenphosphite.

Diethyl-d_{10} *chlorophosphate.* The compound was prepared according to the literature procedure for the unlabelled compound.[13] Triethylamine (0·08 ml) was added dropwise under argon to a stirred solution of diethyl-d_{10} hydrogenphosphite and carbon tetrachloride (0·89 ml) cooled at 0 °C. The mixture was kept at 0 °C for 2 h and then overnight at room temperature. The solid triethylammonium chloride was removed by filtration and the light-brown liquid was bulb-to-bulb distilled under reduced pressure to yield 0·5 ml of diethyl-d_{10} chlorophosphate.

*5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(diethyl-*d_{10} *phosphoric acid ester)calix[4]arene (5).* The compound was prepared according to the procedure in Ref. 14. Reaction of *p-t*-Bu-calix[4]arene (0·4 g), diethyl-d_{10} hydrogenphosphite (0·33 ml), triethylamine (0·36 ml) and CCl_4 (0·8 ml) in 50 ml of toluene afforded 140 mg of **5** (24%). Chemical ionization mass spectrum: m/z 941·7 (MH^+).

*5,11,17,23-Tetra-*tert*-butyl-25,26-27,28-tetrakis (diethyl-*d_{10} *phosphoric acid ester)calix[4]arene (4).* A solution of 50% NaOH was added dropwise to a stirred solution of **5** (90 mg), diethyl-d_{10} chlorophosphate (0·45 l) and tetrabutylammonium bromide (10 mg) in 15 ml of dichloromethane. After 6 h of refluxing the solution was cooled to room temperature, the organic phase was separated, washed several times with brine, dried ($MgSO_4$) and evaporated. The oily residue was dissolved in methanol and water was added. The solid formed was filtered, yielded 40 mg (34%) of pure **4**, m.p. 207 °C. Chemical ionization mass spectrum: m/z 1234 (MH^+).

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