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## Molecular Receptors with the Calix[4]arene Substructure. Synthesis of Derivatives with Mixed Ligating Functional Groups

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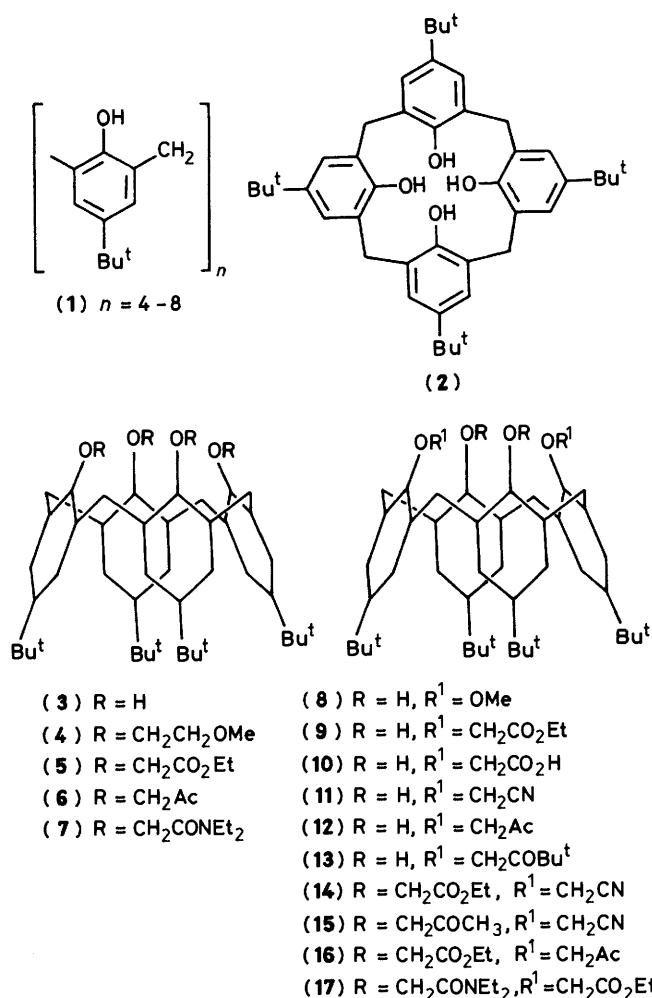
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*p*-t-Butylcalix[4]arene has been derivatised regioselectively at positions 1 and 3 of the four equivalent phenolic groups using electrophiles such as ethyl bromoacetate, chloroacetone, bromopinacolone, and chloroacetonitrile; the products are useful precursors for the synthesis of tetrasubstituted calixarenes with mixed ligating functional groups.

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Macrocyclic oligomeric phenols of the calixarene family, *e.g.* *p*-t-butylcalix[*n*]arenes (**1**) are useful molecular substructures or

platforms on which to assemble preorganised ligands capable of acting as ion or molecule receptors.<sup>1-12</sup> The relatively rigid



tetramer (2) in the cone conformation<sup>13</sup> appears more suited to this purpose than the larger, more flexible hexamer (1;  $n = 6$ ) or octamer (1;  $n = 8$ ). The cone conformation of (2), for which (3) is a useful idealised representation, preorganises potential ligating groups in a convergent arrangement favourable to ion or molecule reception.<sup>14</sup> Functional group modification of the tetramer has produced a new series of receptors particularly well adapted for phase transfer of alkali metal cations from water into non-polar solvents. Originally, Ungaro and his co-workers<sup>15</sup> converted (2) into ether (4), but observed only low levels of phase transfer with this derivative. Recently, however, several groups<sup>2,3,6,8</sup> have reported that attachment of ester and oxo groups to the tetramer, e.g. as in (5), produces a series of new derivatives with very high phase transfer ability towards  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Rb}^+$ , and  $\text{Cs}^+$  with, in some cases, a high selectivity for  $\text{Na}^+$ . Stable, crystalline complexes with  $\text{Na}^+$  and  $\text{K}^+$  have been isolated with tetraester (5),<sup>16</sup> tetraketone (6),<sup>16</sup> and tetraamide (7).<sup>9</sup> X-Ray analysis of the (7)-KSCN complex<sup>9</sup> shows that the cation is encapsulated within a symmetrical cavity defined by the four inward-pointing amide and ethereal oxygen atoms. Phase-transfer of calcium ion has also been observed with amide derivatives of (2).<sup>17</sup> Calixchorands<sup>18</sup> and calixpherands<sup>19</sup> (i.e. bridged calixarenes) have also been synthesized recently and found to have significant receptor activity.

We have now addressed the problem of designing calixarene derivatives with mixed functionality about the calix, the intention being to examine structure-receptor relationships on a broad front for a range of ligating heteroatomic groups. Gutsche<sup>13</sup> had already observed that tetramer (2) reacts with

diazomethane to produce the diagonally substituted diether (8), and a similar regioselectivity was also observed by Ungaro<sup>18</sup> for reaction of (2) with *t*-butyl bromoacetate; both products were believed to adopt the cone conformation. In our preparation of the tetraester (5), tetramer (2) was exposed to a large excess of ethyl bromoacetate for long periods. Reduction of the calixarene:bromoacetate ratio and the reaction time gave mixtures of products representing various stages of alkylation. It was thus possible to isolate the diester (9), m.p. 182–184 °C, in 78% yield by treating (2) with ethyl bromoacetate (mol ratio 1:2) for 15 h in acetone under reflux in the presence of potassium carbonate. The <sup>1</sup>H n.m.r. spectrum of (9) exhibited two *t*-butyl singlets at  $\delta$  0.96 and 1.24, a single AB system for the bridging methylene groups at  $\delta$  3.25 and 4.48 ( $J$  12 Hz), a singlet for the  $\text{OCH}_2\text{CO}$  groups, and two singlets for the aromatic protons. These data confirm that the substitution is of the alternate pattern shown in (9), but do not distinguish between a cone and a 1,3-alternative conformation. However, the fact that further alkylation of (9) with ethyl bromoacetate produced the tetraester (5) in the cone conformation suggests that the diester does indeed possess this conformation. Hydrolysis of (9) using sodium hydroxide in aqueous ethanol under reflux for 24 h furnished diacid (10). In a similar fashion tetramer (2) was alkylated with chloroacetonitrile-sodium iodide to afford the crystalline 1,3-dinitrile (11) (57%), m.p. 290 °C (decomp.). Chloroacetone was also used to effect partial alkylation. As in the dinitrile preparation, reaction was facilitated by halide exchange with sodium iodide and diketone (12), m.p. 135–136 °C, was obtained in 83% yield. Treatment of (2) with *ca.* 2 equiv. of bromopinacolone furnished the di-*t*-butyl ketone (13), m.p. 210–212 °C, in good yield. The dinitrile (11) and the diketones (12) and (13) exhibited n.m.r. features closely similar to those of the diester (9); we presume that these derivatives also possess the cone conformation, as does the tetraketone (6).

The availability of 1,3-difunctionalised calix[4]arenes in the conformation most appropriate to preorganisation of binding sites opens up the way to mixed ligand receptors. Thus treatment of the dinitrile (11) with ethyl bromoacetate furnished the dinitrile diester (14), m.p. 221–223 °C, whereas use of chloroacetone-sodium iodide produced the dinitrile diketone (15), m.p. 235–236 °C. The diester diketone (16) was obtained by alkylation of the diketone (12) with ethyl bromoacetate in acetone. Other mixed functionalities are also accessible. Thus treatment of diester (9) with 2-chloro-*N,N*-diethylacetamide in the presence of potassium bromide gave the diester diamide (17), m.p. 82–84 °C. The n.m.r. spectra of these fully alkylated calixarenes were completely consistent with the presence of the cone conformation in each. That this was indeed the case for diester diketone (16) was strongly indicated by its high phase-transfer activity in a standard two-phase test for alkali metal cations. Not only were all the alkali metal cations transported (as picrates) from water into dichloromethane, but there was peak selectivity for  $\text{Na}^+$  comparable to that found with the tetraester (5). The diester diamide (17) also showed a high affinity for  $\text{Na}^+$ , but unlike the tetraester (5) or the tetraketone (6), it had an even higher affinity (88% extraction) for  $\text{Ag}^+$ .

These preliminary studies should facilitate the design and construction of new ion and molecule receptors using a variety of oxygen and nitrogen-based functional groups attached to the calixarene substructure.

#### Acknowledgements

E. M. C. thanks Loctite (Ireland) Ltd. for a postgraduate studentship.

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Received 28th September 1988; Paper 8/03848A