

# Water-soluble calixarenes as new inverse phase-transfer catalysts. Nucleophilic substitution of alkyl and arylalkyl halides in aqueous media

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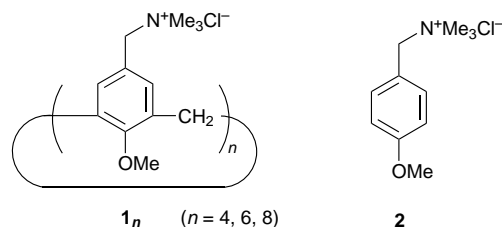
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The water-soluble calix[*n*]arenes **1<sub>n</sub>** (*n* = 4, 6 and 8) containing trimethylammoniomethyl groups act as efficient inverse phase-transfer catalysts in the nucleophilic substitution reaction of alkyl and arylalkyl halides with nucleophiles in water.

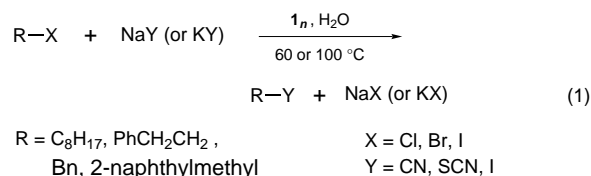
Inverse phase-transfer catalysts facilitate reactions between two immiscible reactants *via* the transport of an organic substrate into an aqueous solution of a second reactant where reactions take place.<sup>1,2</sup> The use of inverse phase-transfer catalysis (IPTC) has two major advantages over that of normal phase-transfer catalysis (PTC): (i) the aqueous catalyst solution is easily separated and recycled, and (ii) no other organic solvent is necessary if organic reactants are liquid at the reaction temperature. However, in sharp contrast to the case of normal PTC, the understanding, development and applications of this method for conducting organic reactions have not expanded yet to the extent that it deserves. This is mainly due to the fact that only a limited number of inverse phase-transfer agents are known, *e.g.* cyclodextrins (CDs) and their derivatives, water-soluble metal complexes and pyridine *N*-oxides.<sup>2</sup>

We now report that water-soluble calix[*n*]arenes **1<sub>n</sub>** (*n* = 4, 6 and 8) containing trimethylammoniomethyl groups can catalyse the nucleophilic substitution of alkyl and arylalkyl halides with simple nucleophiles in water, demonstrating the first example of the application of water-soluble calixarenes to organic reactions as efficient inverse phase-transfer catalysts.

During the past fifteen years, calixarenes have received increasing attention due to their utilization in supramolecular



chemistry.<sup>3</sup> Some functionalized calixarenes have been developed as new phase-transfer agents for normal PTC reactions.<sup>4</sup> We thought that water-soluble calixarenes would serve as a new class of inverse phase-transfer catalysts *via* their ability to form inclusion complexes. In this work we have prepared the water-soluble calixarenes **1<sub>n</sub>** (*n* = 4, 6 and 8)<sup>†</sup> and examined their catalytic ability using nucleophilic substitution reactions in water [eqn. (1)].<sup>‡</sup> The results are summarized in Table 1.



**Table 1** Nucleophilic substitution of alkyl and arylalkyl halides with simple nucleophiles<sup>a</sup>

| Entry | Catalyst                         | Substrate                            | Nucleophile | <i>T</i> /°C | <i>t</i> /h | Yield <sup>b</sup> (%) |
|-------|----------------------------------|--------------------------------------|-------------|--------------|-------------|------------------------|
| 1     | none                             | C <sub>8</sub> H <sub>17</sub> Br    | NaCN        | 100          | 6           | 6                      |
| 2     | <b>2<sup>c</sup></b>             | C <sub>8</sub> H <sub>17</sub> Br    | NaCN        | 100          | 6           | 3                      |
| 3     | β-CD                             | C <sub>8</sub> H <sub>17</sub> Br    | NaCN        | 100          | 6           | 20                     |
| 4     | <b>1<sub>4</sub></b>             | C <sub>8</sub> H <sub>17</sub> Br    | NaCN        | 100          | 6           | 61                     |
| 5     | <b>1<sub>6</sub></b>             | C <sub>8</sub> H <sub>17</sub> Br    | NaCN        | 100          | 6           | 83                     |
| 6     | <b>1<sub>8</sub></b>             | C <sub>8</sub> H <sub>17</sub> Br    | NaCN        | 100          | 6           | 85                     |
| 7     | <b>1<sub>6</sub></b>             | C <sub>8</sub> H <sub>17</sub> I     | NaCN        | 100          | 6           | 91                     |
| 8     | none                             | PhCH <sub>2</sub> CH <sub>2</sub> Br | NaCN        | 100          | 6           | 24                     |
| 9     | β-CD                             | PhCH <sub>2</sub> CH <sub>2</sub> Br | NaCN        | 100          | 6           | 45                     |
| 10    | <b>1<sub>4</sub></b>             | PhCH <sub>2</sub> CH <sub>2</sub> Br | NaCN        | 100          | 6           | 83                     |
| 11    | none                             | BnBr                                 | NaCN        | 60           | 2           | 31                     |
| 12    | β-CD                             | BnBr                                 | NaCN        | 60           | 2           | 55                     |
| 13    | <b>1<sub>6</sub></b>             | BnBr                                 | NaCN        | 60           | 2           | 85                     |
| 14    | <b>1<sub>6</sub><sup>d</sup></b> | BnBr                                 | NaCN        | 60           | 2           | 72                     |
| 15    | <b>1<sub>6</sub></b>             | BnBr                                 | KSCN        | 60           | 2           | 88                     |
| 16    | <b>1<sub>6</sub></b>             | BnBr                                 | KI          | 60           | 2           | 78                     |
| 17    | <b>1<sub>4</sub></b>             | BnCl                                 | NaCN        | 60           | 12          | 67 <sup>e</sup>        |
| 18    | none                             | 2-NaphthylCH <sub>2</sub> Br         | NaCN        | 60           | 2           | 0                      |
| 19    | β-CD                             | 2-NaphthylCH <sub>2</sub> Br         | NaCN        | 60           | 2           | 8                      |
| 20    | <b>1<sub>4</sub></b>             | 2-NaphthylCH <sub>2</sub> Br         | NaCN        | 60           | 2           | 47                     |
| 21    | <b>1<sub>6</sub></b>             | 2-NaphthylCH <sub>2</sub> Br         | NaCN        | 60           | 2           | 55                     |
| 22    | <b>1<sub>8</sub></b>             | 2-NaphthylCH <sub>2</sub> Br         | NaCN        | 60           | 2           | 82                     |

<sup>a</sup> Conditions: catalyst (0.5 mol%), substrate (4.6 mmol), nucleophile (10 mmol), water (5 ml), stirring speed 1300 rpm. In the reaction of 2-(bromomethyl)naphthalene, dipropyl ether (1 ml) was used (entries 18–22). <sup>b</sup> Based on substrate. Refers to GC yield (entries 1–7 and 11–17) or isolated yield (entries 8–10 and 18–22). <sup>c</sup> Catalyst: 3.0 mol% used. <sup>d</sup> Catalyst: 0.05 mol% used. <sup>e</sup> By-product: benzyl alcohol (8%).

Treatment of 1-bromooctane with NaCN in water for 6 h at 100 °C afforded 1-cyanooctane in 6% yield with 86% recovery of the starting material (entry 1). However, when we carried out the same reaction in the presence of the calixarene **1<sub>6</sub>** (0.5 mol%), the yield of 1-cyanooctane increased to 83% (entry 5). To evaluate the ability of **1<sub>6</sub>**, we examined the reactions with a conventional inverse phase-transfer catalyst, β-CD, and found that the calixarene **1<sub>6</sub>** is more efficient than β-CD by a factor of 5.5 for cyanide substitution on 1-bromooctane, and 2.3 and 6.9 for benzyl bromide and 2-(bromomethyl)naphthalene, respectively (entries 13 and 21). Noteworthy, the use of as little as 0.05 mol% of **1<sub>6</sub>** is sufficient, showing its remarkable catalytic activity (entry 14).

CDs function as inverse phase-transfer catalysts in aqueous–organic two-phase reactions of alkyl halides with nucleophiles owing to their ability to form host–guest complexes.<sup>5–7</sup> The water-soluble calixarenes may behave similarly to CDs, since they also have the ability to include organic guest molecules in their cavity. No acceleration effect is observed when (*p*-methoxybenzyl)trimethylammonium chloride **2** is added to the reaction mixture as a monomeric counterpart of **1<sub>6</sub>** (entry 2). The distribution of **1<sub>6</sub>** into the organic phase was negligible,§ indicating that the reaction catalysed by **1<sub>6</sub>** takes place predominantly in the aqueous phase.

The efficiency of the calixarenes **1<sub>n</sub>** varied depending on the size and/or shape of the substrate molecules. For example, no difference in the catalytic activities of **1<sub>n</sub>** is detected in the reaction of benzyl bromide (**1<sub>4</sub>** ≈ **1<sub>6</sub>** ≈ **1<sub>8</sub>**). On the other hand, their activities increase in the order of **1<sub>4</sub>** < **1<sub>6</sub>** ≈ **1<sub>8</sub>** for 1-bromooctane and in the order of **1<sub>4</sub>** ≤ **1<sub>6</sub>** < **1<sub>8</sub>** for 2-(bromomethyl)naphthalene. The size of the cavity of **1<sub>4</sub>** is large enough for benzyl bromide, but **1<sub>8</sub>** is required for bulkier 2-(bromomethyl)naphthalene. This result is consistently supported by the fact that *p*-sulfonatocalixarenes are capable of molecular recognition on the basis of the hole-size selectivity in an aqueous system.<sup>8</sup>

In conclusion, we have shown here that IPTC by water-soluble calixarenes **1<sub>n</sub>** provides a simple and effective means for conducting nucleophilic substitution reactions of activated and unactivated organic halides, in which they exhibit much higher activity than CDs. This is the first example of the use of water-soluble calixarenes in organic reactions as inverse phase-transfer catalysts.

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## Footnotes and References

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† The water-soluble calix[*n*]arenes **1<sub>n</sub>**·*n*H<sub>2</sub>O (*n* = 4, 6 and 8) were prepared following literature methods (ref. 9) and identified by IR and NMR spectroscopy as well as elemental analysis.

‡ General procedure for the nucleophilic substitution reactions is as follows. A mixture of substrate (4.6 mmol), nucleophilic reagent (10 mmol), a catalytic amount (0.5 mol%) of **1<sub>n</sub>**·*n*H<sub>2</sub>O and water (5 ml) was heated to 60 or 100 °C and stirred with a magnetic stirring bar. The resulting mixture was extracted with CHCl<sub>3</sub>. After the usual work-up, the crude product was purified by preparative GPC and its isolated yield was determined. For the reactions of 1-bromooctane and benzyl bromide with NaCN, the yield of product was determined by GC analysis of a mixture of Et<sub>2</sub>O extracts and an internal standard.

§ A mixture of **1<sub>6</sub>**·6H<sub>2</sub>O (0.157 g, 0.106 mmol) and water (25 ml) was extracted with Et<sub>2</sub>O (5 × 50 ml). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. No extract was detected by measurement of weight.

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