A novel host molecule *p*-[1-(4-hydroxyphenyl)-1-methylethyl]-calix[8]arene. Synthesis and complexation properties in non-aqueous polar solution

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A novel deep-cavity calixarene, *p*-[1-(4-hydroxyphenyl)-1-methylethyl]calix[8]arene 1 was synthesized and its complexation with aromatic compounds was examined. Reaction of *p*-[1-(4-methoxyphenyl)-1-methylethyl]phenol 2 with paraformaldehyde under various conditions only resulted in *p*-[1-(4-methoxyphenyl)-1-methylethyl]calix[8]arene 3, and no corresponding calix[4]arene and calix[6]arene were detected. Removal of the methyl in the ether groups of 3 afforded 1 in 80% yield. Solubilization, fluorescence and photochemical probe studies demonstrated that 1 forms inclusion complexes with a variety of aromatic compounds in polar non-aqueous solutions.

Introduction

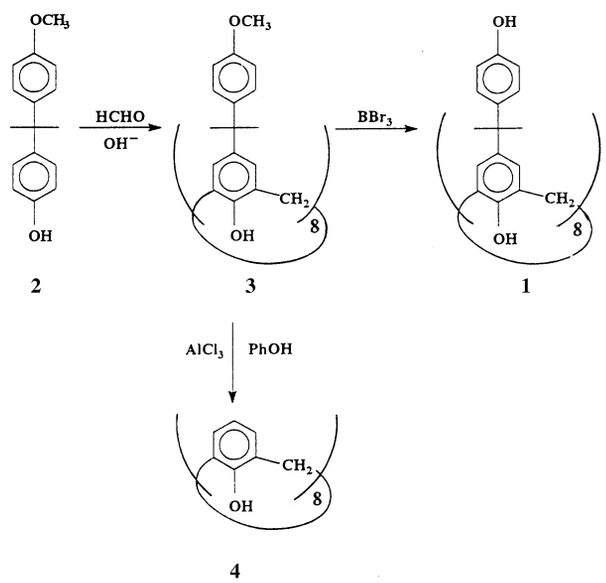
Calixarenes are basket-shaped compounds of potential interest for host–guest complexation and biomimics.[1–5] In order to make calixarenes capable of binding large organic guest molecules, considerable effort has been expended in extending the length of the calixarenes cavity, and several deep-cavity calixarenes have been synthesized by derivatisation at the 'upper rim'.[6–12] However, the chemistry of deep-cavity calixarenes has been slow to develop because of the lack of high-yield synthetic pathways to such compounds. Therefore the design of new calixarene derivatives and the exploration of new synthetic methods are of obvious interest.

The complexation and catalytic properties of calixarenes and their derivatives have been extensively studied.[13–18] It has been well established that calixarenes can include small molecules in the solid state.[13,14] Unambiguous evidence for inclusion complexes of calixarenes in solution has also been reported.[15,16] These studies mainly involved aqueous solutions and hydrophobic binding of nonpolar substrate groups into the relatively nonpolar calixarene cavity. There are only a few examples of the complexation of neutral molecules in non-aqueous solutions.[17,18] It seems to us that some calixarene derivatives should also be able to bind nonpolar substrates in a polar non-aqueous medium and in this case the driving force for the complexation is lipophobic interactions. In the present work we wish to report the synthesis of *p*-[1-(4-hydroxyphenyl)-1-methylethyl]calix-[8]arene **1** for the first time, and demonstrate that this calixarene can form inclusion complexes with a variety of aromatic compounds in polar non-aqueous solutions.

Results and discussion

Synthesis of *p*-[1-(4-hydroxyphenyl)-1-methylethyl]calix[8]arene 1

Since bisphenol A is a phenol with a highly branched *p*-substituent, we initially thought that this compound might undergo 'one-step' condensation with paraformaldehyde and base to produce calixarenes.[12] However, in our experiments both the Zinke–Cornforth and the Petrolite procedures failed to yield any trace of calixarenes. Thus, we converted one OH group in bisphenol A into a methoxy group to produce *p*-[1-(4-methoxyphenyl)-1-methylethyl]phenol **2** and used this compound as a starting material to synthesize *p*-[1-(4-methoxyphenyl)-1-methylethyl]calix[8]arene **3**. Then **3** undergoes demethylation to yield *p*-[1-(4-hydroxyphenyl)-1-methylethyl]-calix[8]arene **1** as shown in Scheme 1.



Scheme 1

We used a procedure resembling that in the literature[19] to synthesize **3**, which involved refluxing a mixture of **2**, paraformaldehyde, and potassium hydroxide in xylene. Recrystallization of the crude product from chloroform–methanol afforded 51% of **3** as a white powder. The structure of the product proposed for the cyclic octamer rests mainly on its ^{1}H NMR, ^{13}C NMR and mass spectra and the spectral data are given in the Experimental section. Furthermore, it has been well established that the *tert*-butyl groups in *p*-*tert*-butylcalixarenes can be removed to yield *p*-H-calixarenes.[20,21] Similarly, we treated calixarene **3** with anhydrous $AlCl_3$ and phenol in dry toluene and obtained the substituent-removed calixarene in 86% yield, which was proved to be identical to the specially synthesized *p*-H-calix[8]arene[21] **4** by ^{1}H NMR, elemental analyses and mass spectra. This observation confirms that the macrocyclic ring of calixarene **3** is built up from eight units.

The calixarene **3** is the unique product in the synthesis described above. We also investigated the possibility of preparing *p*-[1-(4-methoxyphenyl)-1-methylethyl]calix[4]arene and *p*-[1-(4-methoxyphenyl)-1-methylethyl]calix[6]arene. Gutsche reported[12] that the reaction of *p*-*tert*-butylphenol with 37% aqueous formaldehyde and sodium hydroxide and treatment with diphenyl ether gave the corresponding calix[4]arene. On

Table 1 I_1/I_3 values of pyrene (1.0×10^{-5} M) fluorescence in various polar solvents in the absence and presence of **1** (1.0×10^{-2} M)

	Solvent	Acetone	Ethanol	Methanol	Acetic anhydride	Tetrahydrofuran
I_1/I_3	In the absence of **1**	1.58	1.18	1.29	1.61	1.32
	In the presence of **1**	0.96	0.98	0.98	1.00	0.96

Table 2 The association constants of aromatic compounds with **1** in alcohol solutions

Compound	Pyrene	Anthracene	Acenaphthene
K/dm^3 mol^{-1}	15	56	15
Compound	Chrysene	Anthraquinone	Fluorene
K/dm^3 mol^{-1}	59	89	32

the other hand, refluxing a mixture of *p-tert*-butylphenol, paraformaldehyde and rubidium hydroxide in the ratio of 2.2:4:1 in xylene resulted in the corresponding calix[6]arene in good yield.[20] However, use of **2** as the starting material these procedures only yielded **3** in 42 and 34% yields respectively, and no trace of other cyclic oligomers was detected. Furthermore, heating of **3** under the *p-tert*-butylcalix[8]arene isomerization conditions[12] did not result in the formation of the corresponding calix[4]arene and calix[6]arene. These observations suggest that the bulky substituents in **2** cause severe steric hindrance and prevent it from forming smaller cyclic oligomers.

Removal of the methyl in the ether groups of **3** was effected with BBr_3 at room temperature affording *p*-[1-(4-hydroxyphenyl)-1-methylethyl]calix[8]arene **1** in 79% yield as a slightly brown powder. ^{1}H NMR and ^{13}C NMR spectra and the mass spectrum indicate that the calix[8]arene structure has been retained. The spectral details and assignments are given in the Experimental section. This compound is more soluble in polar solvents such as ethanol, acetone, dimethyl sulfoxide and diethyl ether than **3**. For instance, the solubilities in ethanol and acetone are as high as *ca*. 0.1 and 0.3 M respectively. However, the solubilities in non-polar solvents are very low. This fact might be attributed to the existence of more hydroxy groups in **1** than in **3**. The high solubility of **1** in polar solvents enables us to study its complexation with a variety of polycyclic aromatic hydrocarbons in polar non-aqueous solution.

Complexation of 1 with polycyclic aromatic hydrocarbons in polar solvents

The first evidence for the formation of inclusion complexes of **1** with apolar substrates in polar solvents was obtained by a fluorescence probe study. It is well established that the vibrational structure of pyrene monomer fluorescence depends on its environment.[22] The fluorescence intensity ratio of the first to third vibrational peaks, I_1/I_3, increases dramatically with an increase in solvent polarity. Thus, the variation of I_1/I_3 of pyrene has been widely used to investigate the microscopic environment in macromolecules,[23] molecular assemblies[24] and host–guest complexes.[25] In the present study, a 5×10^{-6} M solution of pyrene in acetone only shows monomer fluorescence and I_1/I_3 was 1.58. Addition of **1** to the solution results in the decrease in I_1/I_3 (0.96), suggesting that the complex of **1** with pyrene is formed and the microscopic polarity in the complex is smaller than that of acetone. In other polar solvents analogous results were obtained and are listed in Table 1. It is significant that in all solvents studied, the I_1/I_3 values in the presence of **1** are almost identical. This strongly suggests the formation of an inclusion complex of **1** with pyrene. Since the pyrene molecule is included in the cavity of **1**, the microscopic polarity around the molecule is independent of solvent. It is also significant that in the presence of **1** no pyrene excimer fluorescence was detected. This precludes the formation of a 1:2 host–guest complex.

The second bit of evidence for the formation of host–guest

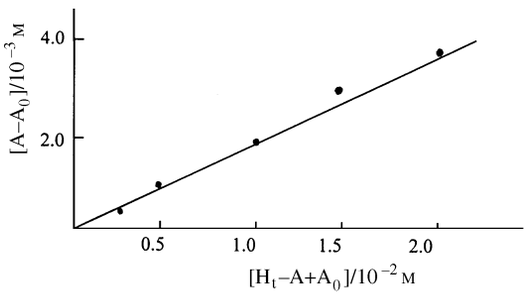
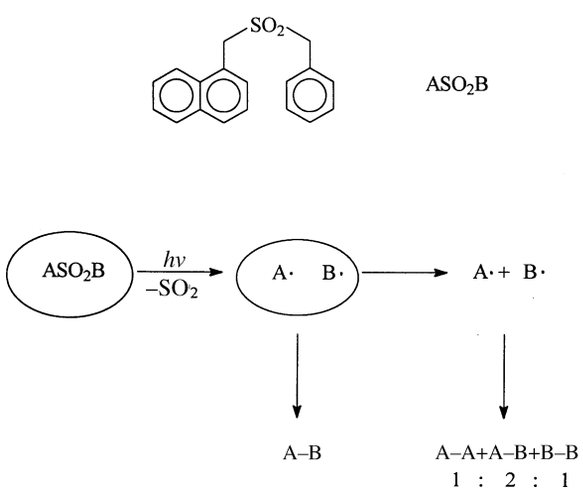


Fig. 1 Plot of $(A - A_0)$ as a function of $(H_t - A + A_0)$ for complexation of **1** with anthracene in alcohol. A and A_0 represent the concentration of anthracene in alcohol in the presence and absence of **1**. H_t is the total concentration of **1**.

complexes of **1** with polycyclic aromatic hydrocarbons was provided by a solubilization study. For example, excess solid anthracene was added to a solution of **1** in ethanol. The suspension solution was agitated vigorously at ambient temperature, and was then filtered. The concentration of anthracene solubilized in ethanol was determined by UV spectroscopy. The plot of the complex concentration *vs*. the total concentration of **1** subtracting the complex concentration (see Experimental section) is linear and shown in Fig. 1. This result strongly suggests that **1** and anthracene form complexes in a 1:1 host–guest manner. From the slope of the plot, the association constant (k) was found to be 56 dm^3 mol^{-1}. By a similar solubilization procedure the association constants for **1** with other aromatic molecules in alcohol were determined and are listed in Table 2. We believe that the driving force for the complex formation of **1** with aromatic molecules in polar solvents is lipophobic interactions.

The third piece of evidence for inclusion complex formation of **1** with aromatic compounds was provided by the photochemical reaction of aryl methyl sulfones in the presence of **1**. It is well established[26] that photolysis of aryl methyl sulfones such as 1-naphthyl benzyl sulfone (ASO_2B; A = 1-naphthyl; B = benzyl) results in the homolytic cleavage of the S–C bond to give two paired radicals which undergo further decomposition with loss of SO_2 to yield paired radicals A$^{\bullet}$ and B$^{\bullet}$. The resultant radical pair may undergo either recombination to give product A–B or escape to form free radicals A$^{\bullet}$ + B$^{\bullet}$, which eventually form couple products A–A, A–B, and B–B in the ratio of 1:2:1 (Scheme 2). The solvent molecules create a 'cage' surrounding



Scheme 2

the radical pair which slows down the diffusive separation of the two radicals (in Scheme 2 the cage is represented by a ring). A solvent 'cage effect' is defined simply as the ratio of the radical pairs which react directly in a geminate reaction to the total radical pairs generated, and can be calculated by eqn. (1) for the photochemical reaction of ASO_2B.

$$\text{Cage effect \%} = (A{-}B - A{-}A - B{-}B)/(A{-}B + A{-}A + B{-}B) \quad (1)$$

Photolysis of ASO_2B in acetone results in the products A–A, A–B and B–B. Analysis of these products according to eqn. (1) reveals that the cage effect is close to zero. However, photolysis of ASO_2B in acetone in the presence of **1** gives a cage effect of 43%. Obviously, this observation is attributable to the inclusion of ASO_2B in the cavity of **1**. Thus, the cavity of **1** plays the role of supercage to prevent the generated radical pair from diffusive separation.

Conclusions

The base-induced condensation of *p*-[1-(4-methoxyphenyl)-1-methylethyl]phenol **2** and paraformaldehyde under various conditions is shown to yield *p*-[1-(4-methoxyphenyl)-1-methylethyl]calix[8]arene **3** as the unique product but no detectable amount of the corresponding calix[4]arene and calix[6]arene. Demethylation of 3 affords *p*-[1-(4-hydroxyphenyl)-1-methylethyl]calix[8]arene **1** in good yield. In the presence of **1**, the ratio of fluorescence intensities of the first to third peaks in pyrene fluorescence spectrum in all solvents studied were identical, suggesting formation of inclusion complexes of **1** with pyrene. Solubilization experiments showed that the association constants between **1** and aromatic compounds were 10–100 $dm^3\ mol^{-1}$. Photochemical reaction of aryl methyl sulfones in the presence of **1** exhibited a large cage effect, also providing evidence for inclusion complex formation.

Experimental

Instrumentation

^{1}H NMR spectra were measured with a Varian XL-300 (400 MHz) instrument in $CDCl_3$ or $(CD_3)_2SO$ using $SiMe_4$ as the internal standard. Field Desorption (FD) mass spectra were run on a Finnigan MAT-90 mass spectrometer. UV spectra were recorded on an Hitachi UV-340 spectrometer. Fluorescence spectra were recorded on a Hitachi MPF-4 spectrofluorimeter.

Materials

Preparation of *p*-[1-(4-methoxyphenyl)-1-methylethyl]phenol 2. To 200 ml of 10% aqueous sodium hydroxide solution cooled in an ice–water bath was added 45 g (0.2 mol) of bisphenol A with vigorous stirring. After bisphenol A had dissolved, 25 g (0.2 mol) of dimethyl sulfate was added over a period of 1 h and the solution was kept at room temp. for 1 h with vigorous stirring. The resultant precipitate was separated by filtration with a sintered glass filter and 200 ml of 10% aqueous NaOH added again and the mixture filtered to remove the unreacted material, then the precipitate was heated to 60 °C in another 200 ml of 10% of NaOH. The resultant solution was filtered while in 60 °C. To the filtrate 20% aqueous hydrochloric acid was added until the solution became acidic. The solution was extracted with diethyl ether and the organic layer was evaporated to give 25.8 g (54% yield) of **2** as a transparent liquid. $\delta_H(CDCl_3)$ 7.15 (4 H, *meta* to the OH and OCH_3 on the phenyl ring, q), 6.81 (4 H, the *ortho* site, q), 3.81 (3 H, OCH_3, s) and 1.67 (6 H, CH_3–C–CH_3, s).

Preparation of *p*-[1-(4-methoxyphenyl)-1-methylethyl]calix[8]arene 3. *p*-[1-(4-Methoxyphenyl)-1-methylethyl]calix[8]arene **3** was prepared as follows: a slurry of 17.0 g (0.070 mol) of **2**, 4.0 g of paraformaldehyde and 0.6 ml of 1 M KOH in 80 ml of xylene was refluxed under a N_2 atmosphere with vigorous stirring in a 250 ml of flask equipped with a water collector. After 1 h a white precipitate began to appear. The reaction mixture was refluxed for 4 h, then was cooled, and filtered. The precipitate was washed successively with toluene, diethyl ether and water and was then dried and recrystallized from $CHCl_3$–CH_3OH to afford 9.1 g (51% yield) of **3** as a white powder. Mp > 300 °C. Anal: calcd. for $C_{136}H_{144}O_{16}$: C, 80.31; H, 7.09. Found: C, 79.92; H, 7.17%; $\delta_H(CDCl_3)$ 9.55 (1 H, OH, s), 7.06 (2 H, ArH, d), 6.84 (2 H, ArH, s), 6.74 (2 H, ArH, d), 3.72 (OCH_3, 3 H, s), 4.27, 3.34 (2 H, 2 × d, CH_2), 1.48 (3 H, CH_3, s) and 1.43 (3 H, CH_3, s); $\delta_C(CDCl_3)$ 157.45, 146.67, 144.70, 142.7, 128.63, 127.69, 128.88, 113.35 (ArC), 32.22 (CH_2), 55.07 (OCH_3), 41.64 (–C–), 30.82 and 31.28 (CH_3); FD-MS: *m/z* 2032 (M^+).

Preparation of *p*-[1-(4-hydroxyphenyl)-1-methylethyl]calix[8]arene 1. A solution (20 ml) of BBr_3 (1.5 g) in CH_2Cl_2 was added dropwise under N_2 to a solution of 1.0 g of **3** in 20 ml of dry CH_2Cl_2 cooled in an ice–water bath and the mixture was stirred at room temp. overnight. The reaction mixture was poured into 250 ml of water and stirred for 30 min. Filtration gave a white solid. Recrystallization from ethanol–H_2O yielded 0.75 g (79% yield) of **1** as a slightly brown powder. Mp > 300 °C. Anal: calcd. for $C_{128}H_{128}O_{16}$: C, 80.00; H, 6.67. Found: C, 79.71; H, 6.89%; $\delta_C[(CD_3)_2SO]$ 6.89 (2 H, ArH, d), 6.70 (2 H, ArH, s), 6.58 (2 H, ArH, d), 3.71 (2 H, CH_2, s), 1.51 (6 H, CH_3, s); $\delta_C[(CD_3)_2SO]$ 154.84, 148.28, 142.65, 140.76, 127.14, 127.06, 126.23, 114.54 (ArC), 31.06 (CH_2), 40.87 (–C–), 30.76 (CH_3); FD-MS: *m/z* 1920 (M^+).

Removal of substituents from 3 and preparation of *p*-H-calix[8]arene 4. Compound **4** was prepared as described in the literature:[21] a slurry of 5.0 g of **3**, 2.2 g of phenol and 6.2 g of $AlCl_3$ in 80 ml of toluene was stirred at room temp. for 4 h in an N_2 atmosphere. The mixture was poured into 120 ml of 0.2 M HCl. The organic phase was separated, and toluene was evaporated resulting in the crude product. This product was washed successively with acetone–HCl, CH_3OH, $CHCl_3$, and diethyl ether to afford 1.8 g (86% yield) of **4** as a slightly grey powder: $\delta_H([^2H_5]$pyridine) 6.0–6.9 (3 H, ArH, m) and 3.6 (2 H, $ArCH_2Ar$, s); FD-MS: *m/z* 848 (M^+).

Fluorescence measurements

Fluorescence measurements were performed for solutions containing 1.0×10^{-5} M of pyrene and 1.0×10^{-2} M of **1** in various polar solvents. The samples were purged with nitrogen for at least 30 min before measurements were taken. The excitation wavelength for pyrene was 335 nm. The spectra were fully corrected for instrument response. The fluorescence intensity ratio of the first to third vibrational peaks, I_1/I_3, was calculated from the peak heights.

Solubilization of polycyclic aromatic compound

Compound **1** was dissolved in 10 ml of ethanol in a stoppered ampoule resulting in a clear solution, and to this solution excess of anthracene was added. The sealed ampoule was agitated for 20 min. After 1 d, the suspension was filtered by suction. The concentration of anthracene solubilized in the filtrate solution was determined by UV spectroscopy. Assuming the formation of 1:1 host–guest complex of **1** with anthracene, H + G = HG where H, G and HG represent the host **1**, the guest (anthracene) and the complex respectively, the association constant (k) can be calculated from eqn. (2) where [G] is the concentration of

$$k = [HG]/([H][G]) \quad (2)$$

uncomplexed anthracene and equal to the solubility of anthracene in the absence of **1** (A_0), [HG] is the concentration of the

complex and equal to the solubilized anthracene (A) subtracting A_0, and [H] is the concentration of uncomplexed **1** and can be calculated by subtracting [HG] from the total concentration of **1** (H_t). Thus, eqn. (2) can be rewritten as eqn. (3).

$$k = \frac{A - A_0}{(H_t - A + A_0)\,A_0} \qquad (3)$$

The plot of $(A - A_0)$ *vs.* $(H_t - A + A_0)$ should be linear if the 1:1 host–guest complex is indeed formed. The association constant was obtained from the slope of the plot.

Photolysis of naphthyl benzyl sulfone

1-Naphthyl (A) benzyl (B) sulfone was synthesized according to literature,[26] and a 5×10^{-6} M solution of it in 100 ml of acetone containing 500 mg of **1** was prepared by stirring overnight in a Pyrex reactor. The solution was purged with nitrogen and irradiated using a 450 W Hanovia high-pressure mercury lamp. After irradiation the solvent was evaporated, and the products were extracted with cyclohexane. The product distribution was analysed using GC on a 3% OV-17/Chrom Q column. The product distribution was determined to be AA:AB:BB = *ca*. 25:50:25 and *ca*. 14:72:14 in the absence and presence of **1** respectively.

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