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PAPER

Synthesis, structure and spectroscopic properties of calix[4]phloroglucinarene dodecamethyl ether and its trifluoroacetic acid complex

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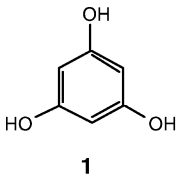
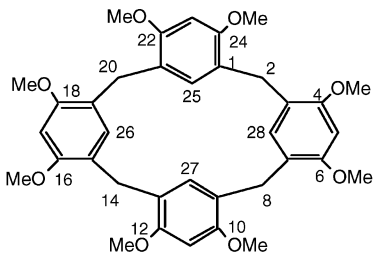
The action of trifluoroacetic acid (TFA) on 2,4,6-trimethoxybenzyl alcohol **3** affords the title tetrameric compound in high yield as a maroon TFA complex, **4**; trituration of which with acetone gives the free, colorless, calix[4]phloroglucinarene (**5**) that can also be directly isolated by treating the reaction mixture with base. The novelty of compounds **4** and **5** is that they possess four additional methoxy groups, which occupy the cavity of the known calix[4]resorcinarene octamethyl ether (**2**). Ultraviolet-visible spectroscopic analysis shows that TFA-complex **4** exhibits transannular charge-transfer interactions between the opposite aromatic rings. The ^{1}H-NMR spectrum of the TFA-complex **4** does not change over a wide temperature range, strongly suggesting that it adopts a saddle (1,3-alternate) structure. The conformation of the free phloroglucinarene **5** is temperature-dependent, as determined by variable temperature ^{1}H NMR spectroscopy. Tetramer **5** adopts a partial cone conformation at low temperatures, but at elevated temperatures is similar to that of the TFA complex **4** (saddle). Tetramer **5** is conformationally mobile at ambient temperature, but generally has a flattened cone (boat) conformation. The $\Delta G^{\neq}$ for inversion in **5** between partial cone and boat conformation is 12.5 Kcal mol^{-1}, while that between boat and saddle conformation is 14.3 Kcal mol^{-1}. Conformational changes are also dependant on pH.

Introduction

The effect of substituents at the bridging carbon atom of a calixarene on conformation is well-documented.[1] However, little is known about the conformational changes in resorcinarenes, possessing substituents on the inner aromatic carbon atoms. This can be attributed largely to the paucity of reaction routes to resorcinarenes or transformation of known resorcinarenes to compounds with a variety of intracavity substituents. Our recent studies[2] on the utility of TFA for cyclizing benzyl alcohols, has allowed us to prepare directly, in good yield, some unusual resorcinarenes with methoxy groups in the cavity, for which we adopt the generic name phloroglucinarene[3] on the basis of the parent phloroglucinol, **1**. This development affords an opportunity to study the effect of the inner-position groups on the conformation of calixarenes.



1
(Phloroglucinol)



2
(Calix[4]resorcinarene octamethyl ether)

Results and discussion

When 2,4,6-trimethoxybenzyl alcohol (**3**) was treated with TFA (10% in $CHCl_3$) for 2 h at ambient temperature and the resulting solution was diluted with carbon tetrachloride and evaporated, maroon-red crystals (**4**), which tested acidic to litmus paper, were isolated in 88% yield (mp 140–142 °C, Scheme 1).

The cyclic, tetrameric structure of the product was confirmed by mass spectrometry (M^+ 720). The spectrum also provided evidence for the presence of complexed TFA giving characteristic peaks at *m/z* 114, 69 and 45 for the CF_3COOH^+, CF_3^+ and $COOH^+$ ions, respectively. Elemental analysis was consistent with 2.5 molecules of TFA and one of water per molecule of the tetramer **4**.

The ^{1}H and ^{13}C NMR spectra of compound **4** were simple (Tables 1 and 3) and indicated a symmetric cyclic structure. Singlets were observed for the aromatic, methylene and two types of methoxyl protons (the latter in a ratio 2 : 1) in the ^{1}H NMR spectrum, while the ^{13}C NMR spectrum showed seven different carbon atoms, four aromatic, one methylene and two methoxyls. These data support a cyclic structure for compound **4** with a rigid saddle or very rapidly flipping conformation with an average saddle structure (see structure **5d** in Fig. 2, DUDU[4] and Fig. 1).

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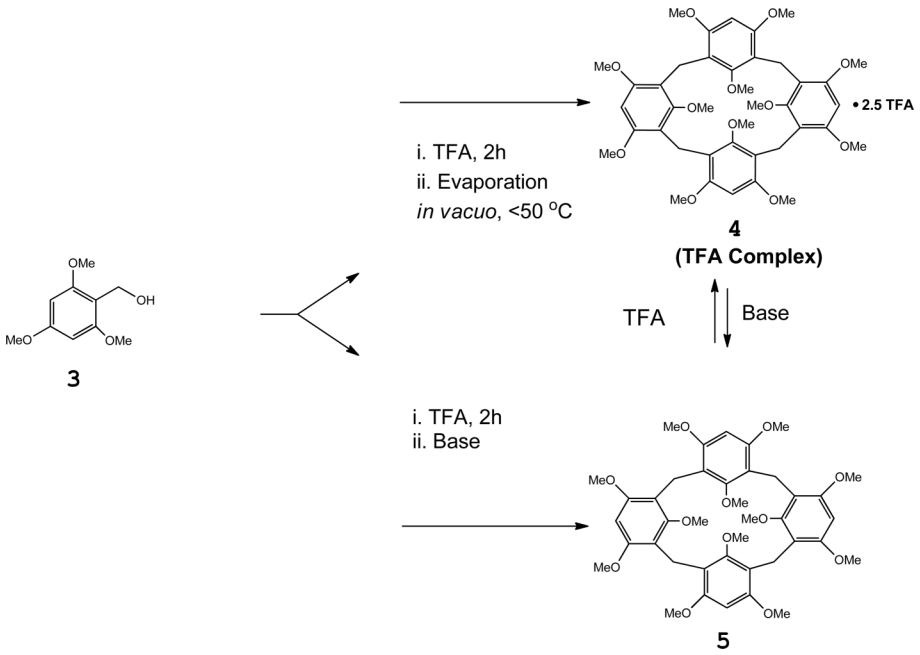

Scheme 1

Table 1 The ^{1}H NMR chemical shifts (δ_{ppm} from TMS) of compounds **4** and **5** at various temperatures in $CDCl_3$ (300 MHz)[4]

	ArH	CH_2	$OCH_{3(o)}$[a]	$OCH_{3(i)}$[a]
4	6.29 (s, 4H)	3.83 (s, 8H)	3.81 (s, 24H)	3.57 (s, 12H)
5[b]	6.27 (bs, 2H)	3.90–3.10 (bm)	3.90–3.10 (bm)	3.90–3.10 (bm)
	5.89 (bs, 2H)			
5[c]	6.14 (s, 4H)	3.58 (s, 8H)	3.62 (s, 24H)	3.33 (s, 12H)
5[d]	6.09 (bs)	3.88 (bs)	3.67 (bs)	3.47 (bs)
5[e]	6.36 (s, 1H)	3.82 (d, 2H)	3.96 (s, 6H)	3.76 (s, 3H)
	6.30 (s, 1H)	3.42 (d, 2H)	3.93 (s, 6H)	3.09 (s, 6H)
	5.91 (s, 2H)		3.75 (s, 6H)	2.93 (s, 3H)
			3.64 (s, 6H)	

[a] H_o = outer methoxyl protons; H_i = inner methoxyl protons. [b] Spectrum taken at 18 °C; all peaks broad. [c] Spectrum taken at 180 °C in DMSO. [d] Spectrum taken at 100 °C in $CDCl_3$. [e] Spectrum taken at −58 °C in $CDCl_3$.

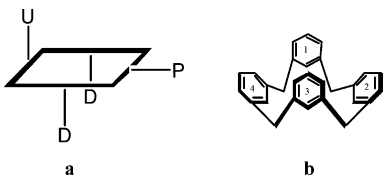

Fig. 1 (a) A schematic drawing showing the arene units above (U), below (D) and in the mean plane (P) of the molecule (a) (containing all the four bridging methylene units). (b) Cone conformation of a calix[4]arene, UUUU (DDDD).

The colorless, TFA-free calix[4]phloroglucinarene (**5**), could be obtained by triturating **4** with acetone (74%). A variety of other polar solvents could also be used to effect TFA removal.[5] Alternatively, tetramer **5** could be isolated directly by washing the reaction mixture of alcohol **3** and TFA with base (89%, Scheme 1). The crystalline material obtained from trituration, (**5**), was colorless and had a higher melting point (268–269 °C) than the TFA complex **4** (mp 140—142 °C). Except for the total absence of the ions associated with TFA, the mass spectrum of **5** was essentially identical to that of the TFA-complexed tetramer **4**.

Compound **5** could also be reconverted to **4**. The addition of six equivalents of TFA to an equivalent of **5**, gave **4** after a slow evaporation of the acid followed by crystallization of the red residue from hexane/chloroform at 0 °C. The ambient ^{1}H and ^{13}C NMR spectra of **5** (Tables 1 and 3) exhibited very broad absorptions indicative of coalescence for equilibrating conformations. The 1 : 1 ratio of the two broad aromatic absorptions indicates equivalent

Table 2 Predicted ^{1}H NMR multiplicity patterns for all of the protons in the six major conformations of **5** (number of singlets and multiplicity ratio[a] see Fig. 2)[4]

Number	Conformation	ArH	CH_2	$OCH_{3(o)}$[b]	$OCH_{3(i)}$[b]
5a	UUUU(DDDD)	1s	1 AB q	1s	1 s
5b	UUDU(DDUD)	3s (1 : 1 : 2)	2 AB q (1 : 1)	4s (1 : 1 : 1 : 1)	3s (1 : 2 : 1)
5c	UUDD(DDUU)	1s	1 AB q, 1 s (1 : 1)	2s (1 : 1)	1s (1)
5d	DUDU(UDUD)	1s	1s	1s	1s
5e	UPDP(DPUP)	3s (1 : 1 : 2)	1AB q	4s (1 : 1 : 1 : 1)	3s (1 : 2 : 1)
5f	UPUP(DPDP)	2s (1 : 1)	1 AB q	2s (1 : 1)	2s (1 : 1)

[a] Predicted ratios reflect the ratio of protons in each category. [b] H_i = inner OMe protons; H_o = outer OMe protons.

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Table 3 The ^{13}C NMR chemical shifts (δ_{ppm} from TMS) of calix[4]phloroglucinarenes **4** and **5** at 18 °C in $CDCl_3$ (75 MHz)

	Ar**C**OMe$_{(i)}$	Ar**C**OMe$_{(o)}$	Ar**C**CH$_2$	Ar**C**H	O**C**H$_{3(i)}$[a]	O**C**H$_{3(o)}$[a]	**C**H$_2$
4	156.46	156.13	116.04	92.45	59.75	55.22	15.76
5[b]	159.98	156.34	117.05	92.03	60.53	56.06	16.76
5[c]	160.25	156.84	117.36	92.25	60.61	56.17	17.16
5[d]	159.60 (1)	156.31 (2)	116.55 (4)	91.63 (2)	61.12 (2)	56.30 (2)	16.80 (2)
	159.50 (1)	155.86 (6)	116.44 (2)	90.09 (1)	60.32 (1)	56.08 (4)	16.21 (2)
	159.14 (2)		115.52 (2)	90.00 (1)	60.14 (1)	55.29 (2)	

[a] C_i = inner carbon; C_o = outer carbon. [b] All peaks broad. [c] Spectrum taken at 64.7 °C. [d] Spectrum taken at −52 °C; the parenthesized numbers represent number(s) of carbon atoms.

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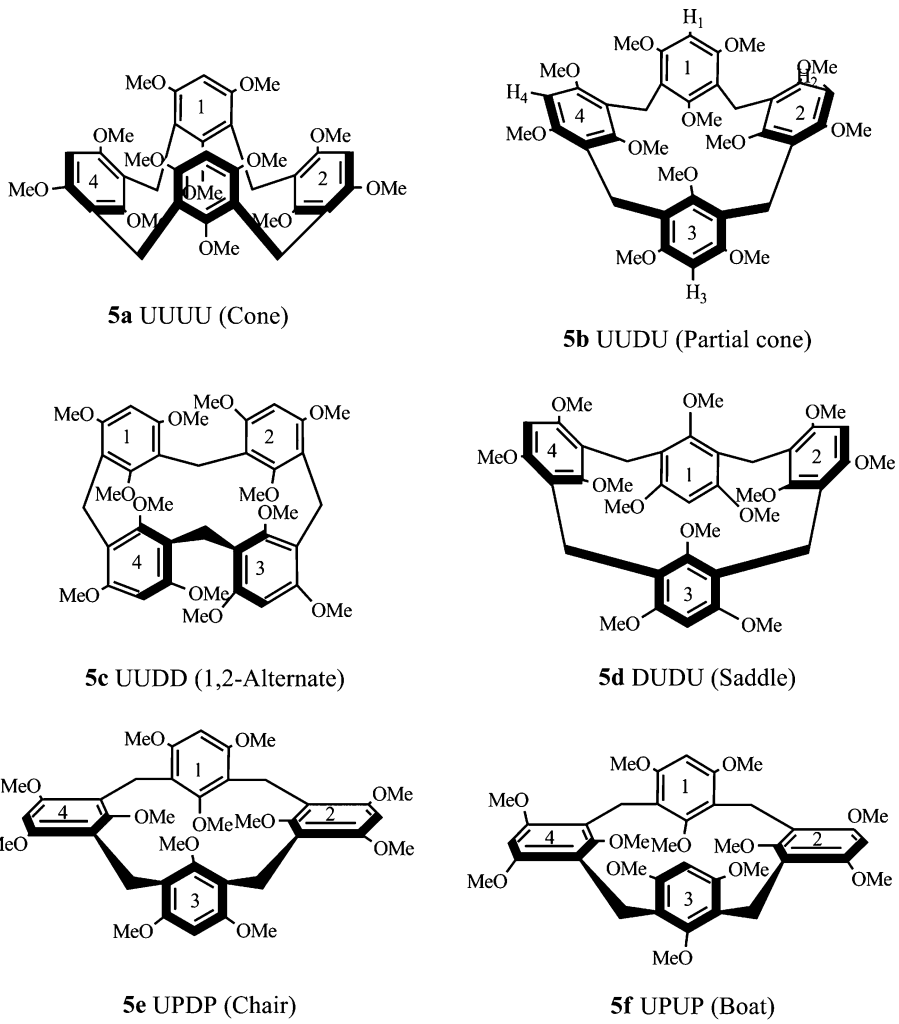

Fig. 2 Six major conformations of calix[4]phloroglucinarene **5**.[4]

pairs of aromatic protons, while the two broad absorptions in the methoxyl region (with a ratio of 5 : 1) implies that two high field methoxyl groups are positioned in the shielding region of opposite aromatic rings. (The NMR data at the different temperatures are also given in Tables 1 and 3.)

In order to make a reasonable conformational assignment for **5** with ^1H NMR data (see later VT NMR studies), a comparison of the multiplicity patterns of the different protons predicted for six major conformations of calix[4]phloroglucinarene **5a–f** (Fig. 2) are shown in Table 2. Although the absorption peaks are broad, on average, the NMR data of **5** match an UPUP (boat) conformation (Tables 1, 3 and Fig. 2, **5f**).

Ultraviolet studies

The electronic spectra of the complexed calix[4]phloroglucinarene (**4**) and free analog **5** are of interest because of the possibility for a variety of intramolecular interactions due to conformational change. The ultraviolet (UV) spectrum of **5** in chloroform exhibits maxima at λ_{max} 284 nm (ε = 7,300) and 248 nm (ε = 10,200), with a

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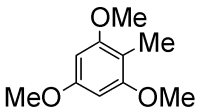
shoulder at 276 nm (ε = 7,000). No absorption is observed above 320 nm in **5** (*i.e.* no charge transfer band is present). The ultraviolet spectrum of **5** is similar to that of 2,4,6-trimethoxytoluene (**6**, $CHCl_3$, λ_{max} 274 nm (ε = 2,300) and 248 nm (ε = 4,200)), with the exception that the longer wavelength absorption is bathochromically shifted in **5** by 10 nm. Using the UV spectral shifts of cyclophanes as a model,[6–8] the shift in **5** is indicative of transannular interaction between the aromatic rings.



6

(2,4,6-Trimethoxytoluene)

The UV spectrum of the TFA complex **4** in chloroform exhibits similar maxima at λ_{max} 284 nm (ε = 2,900) and 248 nm (ε = 5,100), with a shoulder at 276 nm (ε = 2,600). In addition, there are weak charge transfer (CT) bands at 568, 444 and 328 nm (ε = 76, 63 and 81, respectively).

The TFA complex **4** and TFA-free phloroglucinarene **5** undergo interconversion in solution controlled by the TFA concentration. The sensitivity could be spectroscopically monitored by UV and/or NMR spectroscopy. Thus, when *ca.* 2/3 of an equivalent of TFA was added to **5** in chloroform, a pink (light maroon red) color develops. Three broad CT bands at *ca.* 550, 440 and 350 nm (similar to those in **4** and suggesting its presence) were observed in the visible spectrum. These bands were spectrophotometrically detected (before the color in the cuvette became visible to the eye) when as little as 1/3 of an equivalent of TFA was present. The bands increased in intensity when 2.5 equivalents of TFA were added, forming what we believe to be the (rigid) tri-protonated species, in which each proton bridges one intracavity and two extracavity methoxy oxygen atoms (see Fig. 3). Continued addition of TFA (up to a total of 10.7 equivalents) intensified the color (now maroon red) and the visible absorptions were identical to those in **4**. Tetramer **5** was thus converted to **4** in the presence of TFA.

When *ca.* 14 equivalents of TFA had been added, continuing the above addition, the solution turned yellow. A new band appeared at 370 nm, but one weak CT band remained at 550 nm. The 370 nm band became increasingly more intense (the yellow color deepening), even when as much as 362 equivalents of TFA had been added. It is suggested that this form is the multi-protonated calix[4]phloroglucinarene **4′** (Fig. 3), which, like **4**, is rigid in a saddle-type structure, but somewhat splayed to minimize like-charge interactions.

For spectral comparison, the trimethoxytoluene **6** showed no color change upon treatment with a few equivalents of TFA in chloroform. However, upon the addition of *ca.* 70 equivalents of TFA, the solution turned yellow and a band appeared at 384 nm. The solution did not turn red and no charge transfer bands appeared near or above 500 nm. The 384 nm band is likely due to a protonated form of **6**.

The reverse of the above conversion (complex **4** to **5**) could also be followed by UV spectroscopy. When triethylamine (0.5, then 1.0 equivalent) was added to the TFA complex **4**, the intensity of the bands at 568 and 444 reduced. The addition of *ca.* 2.4 equivalents of the amine gave rise to a spectrum that no longer exhibits these

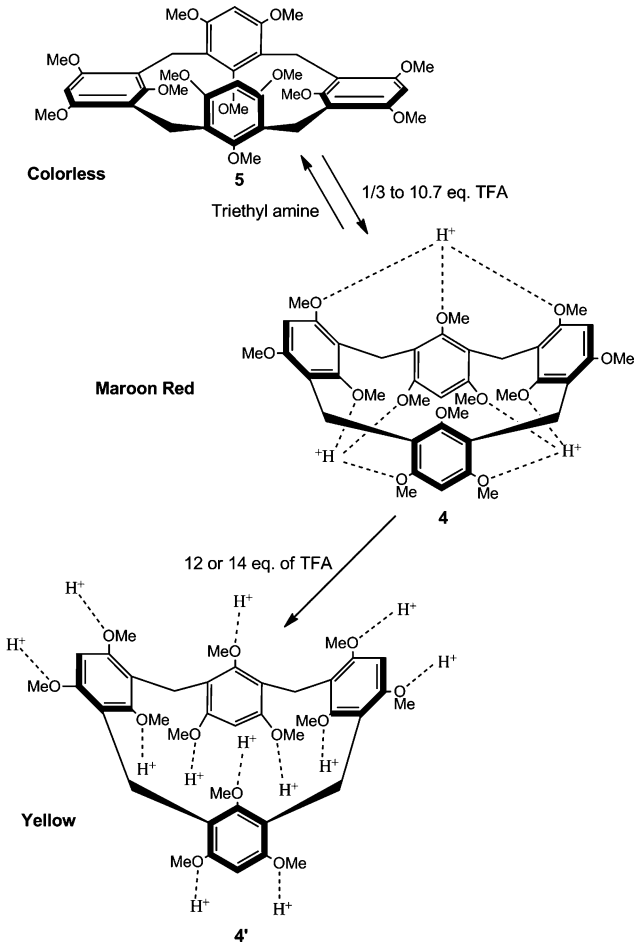


Fig. 3 The interconversion of **5** and **4** with TFA or triethyl amine. Proton-bridge-locked and polyprotonated forms of **4**.

CT bands and the maroon red color was no longer visible. Further addition of the amine did not change the spectrum, which was now superimposable on that of **5**.

In a separate experiment, with a rapid addition of TFA (39 equivalents) to **5**, the maroon red color was instantly generated and the appropriate bands associated with **4** were observed. These bands reached a maximum intensity after standing for 17.5 h. The intensity of the 566 and 444 nm bands then began to decrease after this time and continued to do so, even after 37 h. After 12 days, the solution was still a deep maroon red, but a short wavelength band at ε_{max} 326 nm could be observed. This experiment suggests that **5** is a precursor of **4** in its preparation from **3** and TFA. The sequential protonation (described above) seems to permit continual conformational changes, which ultimately give rise to the multi-protonated form (yellow color), while maintaining a weak CT band. Rapid generation of **4** from **5**, however, generates a saddle conformation, which is slowly transformed to the multi-protonated form (yellow color).

In order to understand the contribution of the intracavity methoxyl-groups of the TFA complex **4** to its charge transfer property, the UV spectrum of a model calix[4]resorcinarene octamethyl ether (**2**), (free of intracavity methoxyl groups), was examined in the same manner described above for TFA-free phloroglucinarene **5** (slow addition of TFA). Thus, a chloroform solution of ether

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2 ultimately turned deep purple upon the addition of TFA and a 566 nm CT band was observed in the visible spectrum. However, this charge transfer band was generated only when over a hundred equivalents of TFA was added (with emergence of a faint pink color). The intensity of the band (and color) only increased with addition of TFA beyond 100 equivalents. Thus, the greater amount of the acid required for the model compound (**2**) to generate and maintain a CT interaction is not required in **4** because of the presence of the intracavity methoxyl groups, allowing for greater ease in bridging the methoxyl groups and hence fixing the proper intramolecular distances between the rings for maximum CT interaction.

The presence of charge transfer bands in **4** (and when **5** was treated with less than *ca.* 14 equivalents of TFA to generate **4**), suggests that TFA plays a role in restricting the conformational mobility. The rigid saddle conformation of **4** (corroborated by its NMR spectrum, see later) possesses alternate aromatic rings that align in a nearly parallel arrangement, allowing for transannular interactions. This conformation would be generated when a proton bridges two or more methoxyl groups on adjacent and/or opposite rings (Fig. 3). In this situation, a saddle conformation would almost certainly be adopted, allowing for maximum CT interactions. While a single bridging proton (properly positioned to interact with three methoxyl groups; two outer and one inner), would be minimal to restrict mobility in the tetramer and allow for some CT interactions to occur, two protons would bridge two sets of methoxy units and would cause further conformational restrictions. Three protons thus positioned would remove all of the conformational mobility in the tetramer. The saddle conformation would thus be fixed with these proton-bridge-locks positioning alternate aromatic rings parallel to one another so that maximum CT can occur.

This is supported by the elemental analysis of **4**, where 2.5 TFAs/tetramer unit is found, along with water. Thus, one equivalent of **4** possesses twelve methoxyl equivalents (groups). If one TFA is required per three methoxyl groups, the minimum required to maintain a fixed conformation for CT interaction is more than two but less than three, or 2.5.[9]

The saddle conformation is maintained until *ca.* 14 equivalents are added. At this point, protonation of each methoxyl site is realized (12 equivalents is the minimum required) and a yellow entity (370 nm band) is produced, where all of the methoxyl groups are individually protonated and the proton-bridge-locks are lost. A new conformation is generated, in which the rings repel one another due to the excess charge on each ring. The CT interactions (bands above 500 nm) are substantially reduced in the multi-protonated form **4′** and the tetramer becomes conformationally mobile again, limiting CT interactions. These conclusions are substantiated by the ^{1}H NMR studies of **5** in the presence of TFA.

NMR studies

(a) Effect of TFA on ^{1}H NMR spectrum of TFA-free calix[4]phloroglucinarene (5). As described above, at ambient temperature the ^{1}H NMR spectrum of **5** exhibited very broad absorptions in the aromatic, methoxyl and methylene regions, indicating a mixture of conformers. TFA-complex **4**, on the other hand, exhibits sharp and distinct absorptions, suggesting the presence of a rigid or very rapidly flipping conformations, which average to a saddle structure (first and second entries in Table 1). When 1/2 equivalent of TFA was added to **5** at ambient temperature, the very broad nature of the peaks was removed and replaced by more distinct and sharper absorptions, the chemical shifts of which were close to that of compound **4**. These peaks did not sharpen with time, but did sharpen with a further addition of 1/2 equivalent of TFA. Although further sharpening occurred with the addition of more acid, an identical spectrum to that of **4** was not obtained until a total of four equivalents of TFA were added, at which point the solution turned red. However, when three equivalents of TFA were added and the solution was allowed to stand for 2.5 h, the spectrum was identical to that of pure **4**.

These results support the ultraviolet studies *vide supra*, indicating that a threshold of <3 equivalents of TFA causes complex formation and demonstrate that the conformation of the tetramer is acid-dependent.

(b) Variable temperature ^{1}H and ^{13}C NMR studies. The ^{1}H and ^{13}C NMR spectra of complexed calix[4]phloroglucinarene **4** are not temperature-dependent from −58 to +100 °C. In contrast, the conformation of **5** exhibits a marked dependence on temperature. When **5** was dissolved in chloroform and cooled to −58 °C, the ^{1}H NMR spectrum shows (see fifth entry in Table 1) three sharp singlets in the aromatic region (1 : 1 : 2), seven sharp singlets for the twelve methoxyl groups (three intracavity methoxyls 3 : 6 : 3; four equivalent extracavity methoxyls, 6 : 6 : 6 : 6) and an AB quartet for one methylene unit. A second methylene unit is masked by the methoxyl peaks (see the additional evidence for the presence of a second methylene unit in the ^{13}C NMR data, Table 3). On the basis of the aromatic and methoxyl absorptions alone, the conformation of **5** (which is "frozen out" at this temperature) must be either the chair form (UPDP, Fig. 2, **5e**) or the partial cone form (UUDU, Fig. 2, **5b**). This conclusion is drawn from the predicted patterns for a chair or partial cone conformation (Table 2).

The ^{13}C NMR spectrum of **5** at −58 °C, however, supports the partial cone (UUDU) conformation (Table 3). Although seven broad carbon peaks were observed at ambient temperature in the ^{13}C NMR spectrum of **5**, at −58 °C its ^{13}C NMR spectrum showed a total of 18 peaks corresponding to ten aromatic and six methoxyl carbons, the latter in an approximate ratio of 2 : 1 : 1 : 2 : 4 : 2 (two of the seven different methoxyl groups being coincident). More diagnostically, two distinct peaks were observed for the methylene carbon atoms, which confirmed the existence of two non-equivalent bridging methylene groups (one of which was directly observed as an AB quartet in the ^{1}H NMR spectrum).

As the temperature was raised, all the absorptions broadened in the ^{1}H and ^{13}C NMR spectra. The two lower field aromatic absorptions in the ^{1}H NMR spectrum coalesce into a single broad peak just above −8 °C. At this temperature, the H_1 and H_3 protons[10] (Fig. 2, **5b**) equilibrate with the higher field aromatic protons (H_2 and H_4), which are now also observed as a broad singlet.

At 40 °C, coalescence of the aromatic protons, the methylene protons and the methoxyl protons is observed (the latter in two groups), suggesting structure **5f**. The single broad absorption for each proton group sharpens as the temperature is further raised.

At 100 °C, (the maximum temperature obtained in $CDCl_3$), four somewhat broadened single lines suggest the spectrum for the symmetrical saddle conformation (Fig. 2, 5d). Correspondingly,

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the seven broad peaks observed in the ^{13}C NMR spectrum of **5** are replaced by seven sharper absorptions at 64.7 °C, akin to those observed for **4**.

Using the equation suggested by Akabori *et al.*,[11] the free energy ($\Delta G^{\neq}$) for inversion between the partial cone and boat conformation (the first coalescence) is 12.5 Kcal mol^{-1}, while that between the boat and the saddle (1,3-alternate) structure is 14.3 Kcal mol^{-1}. These values are similar to those reported for the related *p-tert*-butyl-calix[4]arenes.[1,12,13]

In the ^{1}H NMR spectrum of **5** in DMSO at 180 °C, these lines are observed as sharp singlets. The chemical shifts of these lines differ slightly from those observed for **4** in $CDCl_3$ due to the anisotropic effects of the solvent. Except for the upfield shift of the peaks, the spectrum is almost identical to that of the TFA complex **4**. This strongly suggests that, on average, the conformation of **5** at elevated temperatures is the same as that of **4** (DUDU).

(c) Variable temperature ^{1}H NMR studies of 5 with added TFA. Since the saddle conformation of **4** is temperature-independent and **5** is rapidly equilibrating through an average saddle conformation at elevated temperatures, is it possible to trap **5** as **4** by the addition of TFA at a high temperature? Thus, when **5** was heated in the NMR probe from 18 to 100 °C in the presence of TFA, the broad spectral lines observed for **5** at temperatures between 40–100 °C sharpened whenever TFA (3, 6, 12, 16 and 24 equivalents) was added at a specific temperature (40°, 60°, 80° and 100 °C, respectively), but there was little indication of complete conversion to **4** on the NMR timescale. This suggests that there is no cooperativity between the temperature and TFA in effecting the conformational conversion of **5** to **4**.

Conclusion

The effect of substitution of the inner aromatic carbon atoms of resorcinarene on its conformation has been demonstrated for the first time. Calix[4]phloroglucinarene **5**, like C-alkylated calix[4]resorcinarenes[1] and calix[4]arenes,[1] exhibits structural, conformational and complexing properties, which are of interest for molecular recognition. In contrast to many calixarenes, **5** (and its TFA complex **4**) are easily prepared in high yield and are interconvertible under the proper pH conditions. Although the complexed form (**4**) maintains a conformationally rigid saddle structure that is temperature independent, the uncomplexed form (**5**) exists at ambient temperature as a mixture of conformers including, but not necessarily limited to the chair (UPDP), boat (UPUP) and 1,2-alternate (UUDD) structures. The mixture gives rise to a single partial cone conformation below ambient temperature (−58 °C) and a rapidly equilibrating conformational mixture at about +180 °C, which averages to a saddle structure. The uncomplexed material (**5**), which is colorless, turns maroon red in the presence of acid (TFA gives **4**) and the addition of excess acid generates a yellow solution. The color change is related to transannular charge-transfer interactions between adjacent and/or opposite rings. The complexing TFA, which seems to bridge methoxyl groups on adjacent and opposite rings in the macrocycle fixes a saddle conformation. The structure becomes more conformationally mobile as the methoxyl groups become separately protonated upon the addition of excess acid. The thermal and pH sensitivity and associated physical properties of phloroglucinarene **5** may be of importance in electro-optics and other suitable display devices. In addition, the presence of methoxyl groups and the potential to actualize functional group transformations make **5** a good macrocycle for complexation and related studies. Reports on the facile generation of halide and other derivatives of **5** are in preparation.

Experimental

General information

Melting points were determined on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Ultraviolet-visible (UV) spectra were recorded on Hewlett Packard Diode Array Spectrometer (model number 8452A). Nuclear magnetic resonance measurements were recorded on a Varian XL-300 Spectrometer operating at 300 MHz for ^{1}H (TMS internal standard) and 75 MHz for ^{13}C ($CDCl_3$, $\delta = 77.00$, DMSO-d_6, $\delta = 39.50$ and C_6D_6, δ 128 ppm internal standards). Spectra were obtained at ambient temperature after all variable temperature (VT) NMR studies were carried out to ascertain that no permanent conformational change or decomposition occurred. Elemental analyses were determined by Galbraith Laboratories Inc., Knoxville, Tennessee. Solutions were dried with anhydrous $MgSO_4$ before evaporation *in vacuo*.

Calix[4]phloroglucinarene dodecamethyl ether TFA-complex (4)

(a) Direct method. 2,4,6-Trimethoxybenzyl alcohol **3** (3.26 g, 16.5 mmol) was treated with TFA (10% in $CHCl_3$, 30 mL) for two hours at ambient temperature. A wine color was observed within three minutes and became more intense as the reaction progressed. CCl_4 was added and the resultant solution evaporated (cold) leaving the complex **4**, as a crystalline, maroon solid that tested acidic (pH < 3.0) to pH paper (3.70 g, 3.6 mmol, 87.8%), mp 140–142 °C. MS (*m/z*): 720 ($C_{40}H_{48}O_{12}$, M^+), 181 (100%, $C_{10}H_{13}O_3$, $M^+/4$), 114 (CF_3COOH^+), 69 (CF_3^+), 45 ($COOH^+$). UV/visible λ_{max}, ($CHCl_3$): 568 nm (76), 444 nm (63), 328 nm (81), 284 nm (2,900), 3h 276 nm (2600), 248 nm (5,100). ^{1}H and ^{13}C NMR (see Tables 1 and 3). Anal. calcd for $C_{40}H_{48}O_{12}\cdot(H_2O).(2.5\ CF_3COOH)$: C 52.76, H 5.22; found: C 52.70, H 5.47.

(b) Indirect method. TFA-free phloroglucinarene **5** (170 mg, 2.4 mmol) was dissolved in $CHCl_3$ (< 2 mL) and TFA (6 equivalents, 120 mL) was added. TFA and $CHCl_3$ were allowed to slowly evaporate after thorough mixing to give red crystals (mp 140–142 °C). Recrystallization from hexane at 0 °C gave pink crystals (mp 148–150 °C). All of the spectroscopic properties for complex **4** prepared in this manner were the same as those obtained under the direct method (a) above. Anal. calcd for $C_{40}H_{48}O_{12}\cdot(H_2O).(2.5\ CF_3COOH)$: C 52.76, H 5.22; found: C 52.76, H 5.50.

The reaction was also monitored by ^{1}H NMR spectroscopy. Phloroglucinarene **5** (24 mg) was dissolved in $CDCl_3$ and the ^{1}H NMR spectrum taken ($T = 18$ °C). TFA (1.9 mg, 0.5 equivalents) was added and the solution thoroughly mixed. The spectrum was taken again. This procedure was repeated until a total of 11 equivalents of TFA had been added (in the sequence 0.5, 0.5, 1.0, 1.0, ... equivalents).[14]

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Calix[4]phloroglucinarene dodecamethyl ether (5)

(a) Direct method. 2,4,6-Trimethoxybenzyl alcohol **3** (467 mg, 2.36 mmol) was treated with TFA (10% in $CHCl_3$, 10 mL) for 2 h at room temperature. The resultant deep wine solution was transferred to a separatory funnel and washed with aqueous K_2CO_3 (2 × 30 mL, 0.2 M). The light brown organic layer was dried and filtered and the solvent was evaporated under reduced pressure to give the free tetramer **5** as a tannish white crystalline solid (435.9 mg), mp 266–269 °C. Further purification by trituration with acetone or recrystallization from benzene gave a brilliant white crystalline solid (378.9 mg, 0.53 mmol, 89.2%), mp 268–269 °C. MS (*m*/*z*): 720 ($C_{40}H_{48}O_{12}$, M^+), 181 (100%, $C_{10}H_{13}O_3$); UV λ_{max} ($CHCl_3$): 284 nm (7,300), 250 nm (10,200), λ_{max} 276 nm (7,000). ^{1}H and ^{13}C NMR (see Tables 1 and 3). Anal. calcd for $C_{40}H_{48}O_{12}$: C 66.65, H 6.71; found: C 66.49, H 6.74.

(b) Indirect method. TFA complex **4** (1.69 g, 1.65 mmol) was triturated with and dissolved in acetone (20 mL). A white crystalline material precipitated from the purple solution over a 30 min period. The precipitate was filtered, washed with acetone and dried under reduced pressure to give **5** (408.6 mg), mp 268–9 °C. Additional crops were collected (total 878.1 mg, 1.22 mmol, 73.9%). The color of the mother liquor gradually turned from purple to brown over the collection period. Crystals suitable for crystallographic analysis were obtained by recrystallization from chloroform/hexane. Other solvents that were found to effect the conversion of **4** to **5** are MeOH, EtOH, EtOAc, MeCN, benzene, acetic acid and DMSO. When EtOH was used as triturant, the color changed from red to blue and then to brown. All spectroscopic properties for the free phloroglucinarene **5** prepared in this manner were the same as those obtained under the direct method (a) above.

UV Studies of phloroglucinarenes 4 and 5

(a) The TFA complex 4. The spectrum of **4** (10.2 mg, in 10 mL $CHCl_3$) was recorded with successive additions of triethylamine (0.5, 1, up to a total of 2.4 equivalents). The visible bands at 568, 444 nm (and the red color) of **4** gradually disappeared with increasing additions of the amine and neither was observed after a total of 2.4 equivalents of the amine had been added. No changes were observed for the absorption at 328.

(b) i. The TFA-free 5. In the same manner described in (a) above TFA (0.3, 0.5, 0.7, up to a maximum of 362 equivalents) was added to a solution of **5** (7.2 mg in 10 mL $CHCl_3$). Both color and absorption changes were recorded over the period of addition and some days afterwards. **ii**. Similarly, the spectrum of **5** (18 mg in 10 mL $CHCl_3$) and TFA (39 equivalents) was taken upon mixing. There was no change observed when the spectrum was taken after 1, 2, 5, 24, and 72 h.

Variable temperature ^{1}H and ^{13}C NMR of the calix[4]phloroglucinarenes 4 and 5

(a) TFA complex 4. The ^{1}H and ^{13}C NMR spectra of **4** were recorded at ambient temperature (18 °C) and then at 90 °C ≥ T ≥ –33 °C; there was no change observed in the spectrum of **4**. (b) TFA-free **5**. The variable temperature ^{1}H NMR spectra of **5** were recorded in the same manner described for the analog **4** above, except for the following solvent and/or temperature changes: in DMSO, 18 °C ≤ T ≤ 180 °C. The following was recorded for the temperature range 90 °C ≤ T ≤ 180 °C: d; 6.14(s, 4H, Ar**H**), 3.62(s, 24H, OC**H**$_3$), 3.58 (s, 4H, C**H**$_2$), 3.33(12H, OC**H**$_3$). At 18 °C ≤ T ≤ 80 °C, broad peaks were observed for all protons. Refer to Tables 1 and 3.

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3 (*a*) 4,6,10,12,16,18,22,24,25,26,27,28-Dodecamethoxycalix[4]arene or 3,5,7,10,12, 14,17,19,21,24,26,28-dodecamethoxy[1.1.1.1]metacyclophane.[3b]; (*b*) D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, 1957, **73**, 5691–5701.
4 Calixarenes are known to exist in a number of conformations.[1] Four major conformations are the cone, partial cone, saddle (or 1,3-alternate) and 1,2-alternate. In this work, these four conformations and two additional conformations for compounds **4** and **5** are defined as given in Fig. 1. Thus, when an arene unit is below the mean plane of the macrocyclic ring (defined as the plane containing all bridging methylene carbon atoms Fig. 1a), it is denoted **D** (down). When up, it is denoted **U** (up). When the arene unit is in the mean plane, it is denoted **P**. In the cone conformation (Fig. 1b) all of the arene units are above (or below) the mean plane of the macrocyclic ring. This conformation is also referred to as UUUU (DDDD). (See **5a** in Fig. 2). Another conformation is where one of the aromatic rings is on the opposite side of the mean plane to the other three. This is referred to as the UUDU (moving clockwise from ring 1 to ring 4) or partial cone conformation (**5b**, Fig. 2). Two adjacent rings above the mean plane and two below defines the 1,2-alternate conformation, referred to as UUDD (**5c**, Fig. 2 (DDUU)). Two opposite rings above the mean plane and two below gives the saddle or DUDU (UDUD) conformation (**5d**, Fig. 2), frequently referred to as the 1,3-alternate conformation. The partial cone and the saddle conformations (**5b** and **5d** respectively in Fig. 2) are structurally related to two other conformations, which are of importance when considering motional properties of the calixarenes. From the cone conformation, the movement of one ring to the opposite side of the mean plane generates the partial cone. If before or after this ring flips, its two adjacent rings move into the mean plane, a chair or UPDP conformation is generated (**5c**, Fig. 2). In a similar manner, if two alternate rings are positioned in the mean plane from the saddle conformation, a sixth, the boat conformation (UPUP) is obtained (**5f**, Fig. 2).
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14 The spectra recorded (when from 0.5 to a total of 3 equivalents were added), appeared similar to that of **4** prepared either by the direct or indirect methods described above, but the peaks were slightly broadened in the corresponding regions. An identical spectrum to that of **4** was obtained, however, when a total of 4 equivalents of the acid were added the spectrum remained unchanged throughout with further addition of acid.

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