Letter

Conformation of *syn*- and *anti*-phenylquinazoline calix[4]arene diethers†

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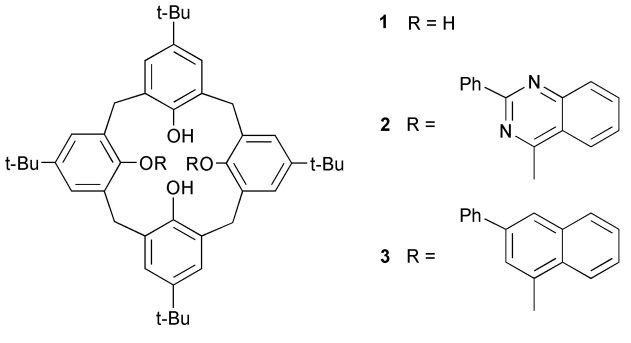
The disubstituted calixarene *syn*-2 adopts in the crystal the unusual 1,3-alternate conformation but this conformation is not the lowest in energy of the isolated molecule in the gas phase.

The calixarenes are molecular hosts capable of adopting a large number of conformations resulting from the different possible orientations of the aryl rings. The conformation of calix[4]arenes is commonly discussed in terms of four basic forms (cone, partial cone, 1,2-alternate and 1,3-alternate) derived from the possible up–down arrangements of the aryl rings. For the parent *p*-*tert*-butylcalixarene (**1**) the cone conformation is the lowest in energy.[1] The phenolic OH groups of **1** can pass through the calix annulus (the cone-to-cone inversion process of **1** has a barrier of 15.7 kcal mol^{-1})[2] but when four bulky residues are attached to the oxygen atoms (*e.g.*, *n*-propyl groups), this passage is effectively blocked under the laboratory timescale.[3] If two bulky groups are present at two intraannular positions, two atropisomeric forms can be isolated (*syn* and *anti*) arising from the two possible relative orientations of the substituted rings.[4] The *syn* form usually prefers a cone conformation. In this Letter we report a disubstituted calixarene derivative that adopts in the crystal the usually unfavorable 1,3-alternate conformation. Solution and computational studies were conducted to investigate if indeed this conformation corresponds to the lowest energy form.



4-Chloro-2-phenylquinazoline is a reagent utilized for the transformation of phenols to anilines.[5] Initially, a phenolate is reacted with the reagent yielding a quinazoline ether. This ether is pyrolized at high temperatures and the product is hydrolyzed to afford an aniline derivative.[5] With the long range goal to attempt a similar transformation on a disubstituted calixarene,[6] calixarene **1** was reacted with 2.5 equivalents of NaH and 4-chloro-2-phenylquinazoline, yielding a mixture of the *syn* and *anti* disubstituted calixarene ether derivatives[7] (*syn*-**2** and *anti*-**2**) that were separated by chromatography. Although the rotations of the substituted rings of **2** are frozen, the passage of the phenol rings through the ring annulus is unencumbered by the intraannular substituents. This latter process interconverts the cone, partial cone (*syn*) and 1,3-alternate conformations of *syn*-**2**, and the partial cone (*anti*) and 1,2-alternate conformations of *anti*-**2** (Fig. 1).[8]

Single crystals of *syn*-**2** and *anti*-**2** were grown from chloroform and their solid-state conformations determined by X-ray diffraction. Notably, *syn*-**2** adopts in the crystal a 1,3-alternate conformation (Fig. 2) lacking any intramolecular O–H···O hydrogen bond. Calixarene *anti*-**2** adopts a 1,2-alternate conformation (Fig. 3). In both compounds the phenylquinazoline substituents adopt a nearly planar conformation and orient the fused rings towards the calix cavity.[9]

If the passage of the unsubstituted rings *via* the macrocyclic annulus is fast on the NMR timescale, the observed NMR spectra should correspond to the weighted average of the spectra of the individual conformations depicted in Fig. 1.

The methylene protons of *syn*-**2** displayed in the ^{1}H NMR spectrum a pair of doublets at 3.53 and 4.01 ppm. This separation is smaller than the one observed for the cone conformation of **1**. Disregarding the anisotropic effects of the substituents, the smaller peak separation could be taken as indicating the presence of a flattened cone conformation, or the presence of a fast equilibrium between a cone form and the 1,3-alternate and/or partial cone conformations. Support for the presence of a cone and an additional conformation

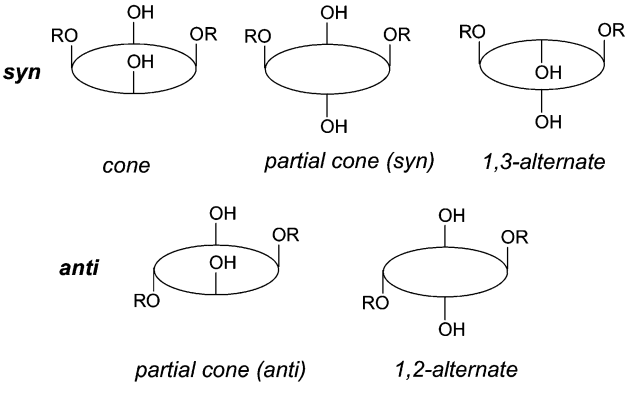


Fig. 1 Conformations of *syn*-**2** and *anti*-**2** that interconvert by rotation of the unsubstituted aryl rings.

† Dedicated to Volker Böhmer on the occasion of his 60th birthday.

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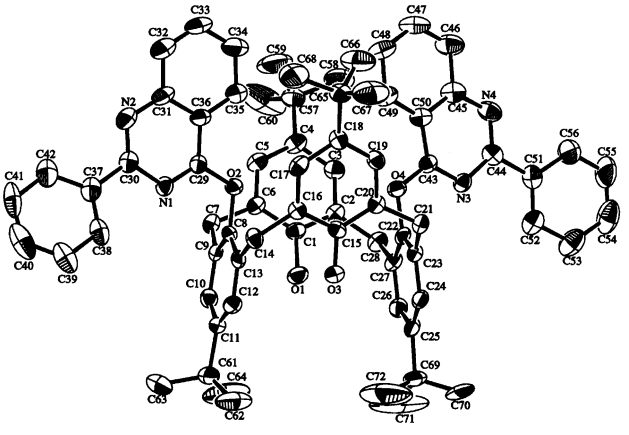

Fig. 2 Crystal structure of *syn*-**2**.

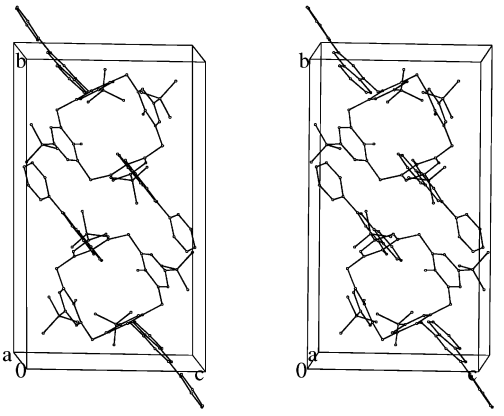

Fig. 4 Stereoview of the crystal packing of *syn*-**2**. Chloroform molecules were omitted for clarity.

was obtained from NOESY spectra. NOE cross peaks between the two aromatic proton signals of the central macrocyclic ring were observed, in agreement with the presence of a cone or cone-like conformation. In addition, NOE cross peaks were observed between the axial (*i.e.*, lower field) and equatorial (higher field) methylene signals with *different* aromatic protons. This suggests that an additional conformation with a pair of neighboring rings oriented *anti* is also present in the equilibrium.

Lowering the temperature of a CD_2Cl_2 sample of *syn*-**2** down to 190 K resulted in an initial broadening and then resharpening of some ^{1}H NMR signals, particularly the highest field *t*-Bu and lowest field phenylquinazoline signals (both achieving maximum broadening at 220 K). These spectral changes are characteristic of a dynamic process (exchange with a "hidden partner")[10] which interconverts two species in a strongly biased equilibrium (in the present case the major cone form with the 1,3-alternate and/or partial cone conformations). At 190 K the ^{1}H NMR spectrum indicated the presence of essentially a single form, ascribed to the cone conformation. The spectral changes associated with the exchange with a "hidden partner" were more marked in $CDCl_3$ (significant broadening of some *t*-Bu, methylene and phenylquinazoline signals were observed at 220 K) suggesting a larger relative concentration of the higher energy form(s). However, due to the higher melting point of the solvent further cooling to reach the slow exchange regime was not possible.

To estimate the relative energies of the *syn* and *anti* forms of **2** and the conformational preferences of the two atropisomers (in particular, the relative energy of the 1,3-alternate form of *syn*-**2**), we conducted molecular mechanics calculations using the MM3 force field.[11–13] To avoid parameterization problems, the calculations were performed on a model compound obtained by replacing the two 2-phenylquinazoline rings by 2-phenylnaphthalene groups (*e.g.*, **3**). According to the MM3 calculations, the *anti* form of **3** is 3.1 kcal mol^{-1} more stable than the corresponding *syn* form. The lowest energy conformation of *anti*-**2** is the 1,2-alternate (the conformer found in the crystal). For *syn*-**3** the lowest energy conformation is the *cone* with the partial cone (*syn*) and the 1,3-alternate forms lying 1.0 and 4.1 kcal mol^{-1} above it. This energetic order can be rationalized by the number of hydrogen bonds present in the cone (two), partial cone (one) and 1,3-alternate (none) conformers. On the basis of the calculations the solution NMR data of *syn*-**2** can be interpreted as indicating a fast equilibrium (on the NMR timescale) between the *cone* and the partial cone (*syn*) forms of the molecule. The presence in the crystal of the unusual 1,3-alternate conformation is most likely due to packing forces and not due to its intrinsic lower energy. Inspection of the packing of the molecules of *syn*-**2** in the crystal shows that the phenyl rings of the quinazoline moieties are located nearly above the macrocyclic aryl rings of a neighboring molecule (Fig. 4). On this basis it seems likely that intermolecular π–π stacking interactions contribute to the relative stabilization of the 1,3-alternate conformation in the crystal.

In summary, the reaction of *p-tert*-butylcalix[4]arene with 4-chloro-2-phenylquinazoline gives a mixture of the *syn*- and *anti*-1,3-diether derivatives. The *syn* form adopts in solution predominantly the cone conformation while in the crystal the energetically unfavourable 1,3-alternate conformation is present.

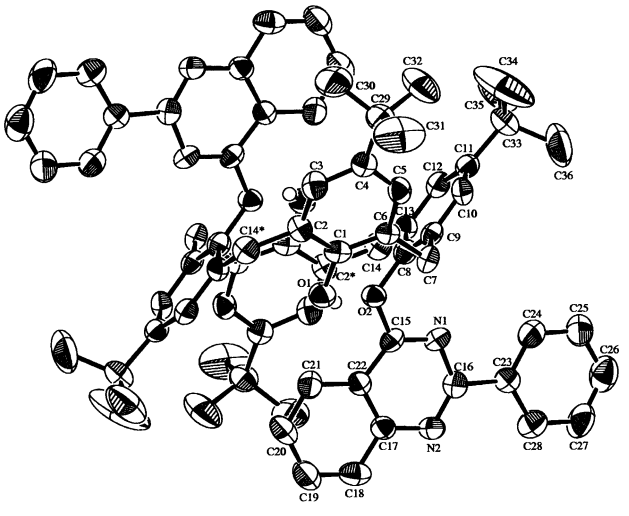

Fig. 3 Crystal structure of *anti*-**2**.

Experimental

Preparation of *syn*-2 and *anti*-2

p-tert-Butylcalix[4]arene (3 g, 4.63 mmol) was dissolved in 200 mL dry 2-methoxyethyl ether and to the mixture was added 0.46 g NaH (60% in mineral oil, 11.5 mmol) and the mixture was stirred under an inert atmosphere at 70 °C for 30 min. 4-Chloro-2-phenylquinazoline (2.8 g, 11.5 mmol) was added and the mixture was refluxed for 4 hours. After pouring the mixture over iced water, the precipitate was filtered and the two isomers separated by chromatography (silica, eluent: 3:1 CH_2Cl_2/hexane) yielding 1.25 g (26%) of *syn*-**2** and 0.55 g (11%) *anti*-**2**. ***Syn*-2**: mp: 292 °C, CI MS *m*/*z* 1057.3 (MH^+). ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 8.58 (d, $J = 7.6$ Hz, 2H), 8.39 (m, 4H), 8.16 (d, $J = 8.4$ Hz, 2H), 8.00 (dt, $J = 7.1$, 1.3 Hz, 2H), 7.70 (dt, $J = 7.5$, 1.0 Hz, 2H), 7.46 (m,

6H), 7.08 (s, 4H), 6.92 (s, 4H), 5.54 (s, 2H, OH), 4.01 (d, $J = 14.2$ Hz, 4H), 3.53 (d, $J = 14.3$ Hz, 4H), 1.15 (s, 18H, *t*-Bu), 1.12 (s, 18H, *t*-Bu). ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 166.16, 160.17, 152.93, 150.62, 148.73, 145.24, 142.31, 137.70, 134.01, 132.50, 130.63, 128.52, 128.42, 128.39, 127.68, 127.30, 126.06, 125.47, 123.91, 114.84, 34.19, 33.89, 33.76, 31.59, 31.47, 31.15 ppm. ***Anti*-2**. mp: 358 °C, CI MS m/z 1057.4 (MH^+). ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 8.30 (dd, $J = 7.7$, 1.7 Hz, 4H), 7.91 (d, $J = 8.4$ Hz, 2H), 7.68 (dt, $J = 7.7$, 1.0 Hz, 2H), 7.52 (s, 4H), 7.43 (m, 6H), 6.96 (t, $J = 7.5$ Hz, 2H), 6.59 (s, 4H), 6.50 (d, $J = 8.0$ Hz, 2H), 5.82 (s, 2H, OH), 3.83 (d, $J = 15.4$ Hz, 4H), 3.76 (d, $J = 15.4$ Hz, 4H), 1.58 (s, 18H, *t*-Bu), 0.72 (s, 18H, *t*-Bu). ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 165.16, 159.44, 152.44, 149.61, 149.28, 145.91, 142.57, 137.68, 133.48, 133.37, 130.56, 128.43, 128.38, 127.69, 126.79, 126.03, 125.89, 125.09, 122.97, 114.18, 34.99, 34.73, 33.32, 31.80, 30.98, 29.71 ppm.

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8 Partial cone forms of **2** in which the unique ring (oriented in the opposite direction to the rest) is either an unsubstituted or substituted ring will be denoted partial cone (*syn*) and partial cone (*anti*), respectively.

9 *syn*-**2**: $C_{72}H_{72}N_4O_4{\cdot}CHCl_3$, $M_r = 1175.76$, triclinic, $P\bar{1}$, $a = 14.806(3)$, $b = 19.827$ (4), $c = 12.186(3)$ Å, $\alpha = 92.49(1)$, $\beta = 113.65(2)$, $\gamma = 81.35(1)°$, $V = 3239(1)$ Å^3, $T = 293$ K, $Z = 2$, $\mu = 0.193$ mm^{-1}, total reflections = 9024, reflections observed = 5157, $R_{int} = 0.88$, $R_1 = 0.0950$ (obs. data), $wR_2 = 0.1080$. *anti*-**2**: $C_{72}H_{72}N_4O_4{\cdot}CHCl_3$, $M_r = 1175.76$, triclinic, $P\bar{1}$, $a = 13.031(5)$, $b = 13.368(5)$, $c = 11.333(4)$ Å, $\alpha = 108.68(2)$, $\beta = 111.11(2)$, $\gamma = 61.57(2)°$, $V = 1592(1)$ Å^3, $T = 293.2$ K, $Z = 2$, $\mu = 0.196$ mm^{-1}, total reflections = 4436, reflections observed = 2545, $R_{int} = 0.30$, $R_1 = 0.0890$ (obs. data), $wR_2 = 0.1160$. CCDC reference numbers 187174 and 187175. See http://www.rsc.org/suppdata/nj/b2/b207533d/ for crystallographic data in CIF or other electronic format.

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12 MM3(96) is included in the SYBYL 6.5 program package (Tripos Ass., Inc., St. Louis, MO 63144).

13 A conformational search was performed for **3** with the stochastic search routine of the standard MM3(96) force field using the default parameters except for the number of pushes which was set to 10000.