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Quantum Mechanical Calculations of Conformationally Relevant ^{1}H and ^{13}C NMR Chemical Shifts of N-, O-, and S-Substituted Calixarene Systems

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In memory of our dear friend Professor Luigi Gomez-Paloma

Abstract: QM GIAO calculations of ^{13}C and ^{1}H chemical shift values of the ArCH$_2$Ar group in N-, O-, and S-substituted calixarene systems were performed with a hybrid DFT functional MPW1PW91 and 6-31G(d,p) basis set. A good reproduction of experimental data was obtained for some representative calixarenes and for a series of simplified calixarene models. This allowed the derivation of chemical shift surfaces versus ϕ and χ dihedral angles. The applicability of chemical shift surfaces in the study of calixarene conformational features is illustrated.

Keywords: calixarenes • conformation analysis • density functional calculations • GIAO • NMR spectroscopy

Introduction

In recent years, interest for bowl-shaped calixarene macrocycles[1] has quickly grown making them ubiquitous in several areas of supramolecular chemistry, where they have found numerous interesting applications.[1,2] This interest is undoubtedly related to their ready accessibility from convenient starting materials, to their facile chemical transformation and to their conformational versatility. In fact, owing to the possible relative orientations of the *n* constitutive phenol rings, different molecular shapes can be assumed by each calix[*n*]arene macrocycle, which directly influence its supramolecular properties. Thus, the smallest term of the series, namely calix[4]arene, can adopt an all-*syn cone* conformation **1**, which possesses a hydrophobic cavity capable of hosting a variety of species,[1] and three other ones (partial cone **3**, 1,3-alternate **4** and 1,2-alternate) with one or two *anti*-oriented phenol rings.[1a] Interconversion among these four conformations can be definitively impeded by attaching sufficiently bulky substituents to the phenolic OH groups (the so-called lower or narrow rim), thus giving rise to discrete atropisomers.

The intriguing conformational features of calixarene macrocycles have long attracted much attention, and therefore empirical rules to recognise their conformations were devised since the early works. The first of these, Gutsche's "^{1}H NMR $\Delta\delta$" rule,[2] is based on the chemical shift difference of each pair of ArCH$_2$Ar protons, which can be diasterotopic or homotopic for symmetry reasons thus leading to AX (AB) or A$_2$ systems, respectively. In particular, a ^{1}H NMR $\Delta\delta$ value of 0.7–1.0, or greater, indicates a *syn* orientation of the two corresponding proximal phenol rings as in the *cone* conformation, whereas a $\Delta\delta$ value close to zero (0.3–0.0) identifies an *anti* orientation between them, as in the 1,3-alternate conformation. Intermediate values of 0.5–0.3 ppm are usually attributed to an *out* or flattened orientation or to an averaged fast-exchanging conformation.[2]

A second empirical criterion, de Mendoza's "^{13}C NMR single rule",[3] is based on the ^{13}C NMR chemical shift of the ArCH$_2$Ar carbon, which can assume a value of 30–33 ppm for a *syn* orientation, whereas a $\delta \approx 36$–39 is characteristic of an *anti* disposition. Again, intermediate δ values of 33–36 can be attributed to an *out* orientation or to an averaged situation.[3]

The conformational features of the larger calix[*n*]arenes become increasingly more complex by increasing the

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number *n* of aryl rings. In fact, an exponentially increasing number of conformations become possible through the increased number of possible combinations of *syn*/*anti* dispositions of aryl rings joined to their inward/outward possible orientations.[4] In addition, owing to the larger dimension of their annulus, increasingly bulkier groups at both rims or even intramolecular bridging are necessary to obtain discrete conformational isomers.[5] Furthermore, pictorial descriptions and iconographical representations become increasingly difficult and far less precise.[4] In this regard, a more accurate description of the calixarene conformation can be obtained by means of ϕ and χ torsion angle values of the Ar-CH_2-Ar bonds, as proposed by Ugozzoli and Andreetti.[6a] Thus, when two adjacent aryl rings have a *syn* orientation, the signs of the ϕ and χ are opposite, whereas they are the same for the *anti* orientation.[6b]

Because of their higher conformational complexity, it can be expected that unusual conformations become possible for larger calixarenes. In such cases, their spectral characteristics are unknown or whether Gutsche's and de Mendoza's rules could still be usefully applied. Furthermore, it is not always easy to attribute the correct conformational meaning to some uncommon experimental ^{1}H NMR $\Delta\delta$ values. For example, we observed a $\Delta\delta(^1H)$ value of 1.55 for a 1,4:2,3-calix[7]bis-crown-3 derivative,[7] and Arduini et al. found $\Delta\delta$ values of up to 1.86 for some bis-bridged calix[4]arenes.[8] Very recently, Abraham et al. observed $\Delta\delta(^1H)$ values of $\approx$1.70 for calix[4]arene derivatives bearing cyclohepta-2,4,6-trienyl substituents on the upper rim.[9] These higher values have often been interpreted as more flattened cone conformations, to which, in contrast, should be assigned intermediate values of 0.5–0.3 ppm on the basis of the aforementioned Gutsche's rule.[2] To investigate these aspects, we have very recently undertaken a quantum mechanical (QM) study[10] on the ^{13}C and ^{1}H chemical shift values of $ArCH_2Ar$ groups of some representative calixarene systems using GIAO (gauge-including atomic orbital)[11] calculations with the hybrid DFT functional MPW1PW91[12] and a 6-31G(d,p) basis set.[13] This study[10] showed that the OR groups on the lower rim influenced both the magnetic non-equivalence of the methylene protons and the shielding variations of the corresponding ^{13}C nucleus.[14] These observations prompted us to extend the QM GIAO studies to mercapto-[15] and aminocalixarene derivatives,[16] in which hydroxyl groups are replaced by mercapto and amino groups, to verify the influence of these groups on the conformationally relevant NMR data of $ArCH_2Ar$ groups. Following our preliminary communication, we report here a full account of these studies.

The replacement of OH groups on the lower rim of the calix[4]arene macrocycle by mercapto[15] or amino groups[16] is a very interesting way of modifying the lower rim. Mercapto- and aminocalixarenes present a different conformational behaviour with respect to their parent phenolic calixarenes. In fact, literature data[15c] show that adjacent ArSH groups are preferably *anti*-oriented in mercaptocalixarenes. Thus, *p*-*tert*-butyltetramercaptocalix[4]arene (**4d**) adopts a 1,3-alternate conformation in the solid state and in solution.[15c] Gutsche has shown that the ^{13}C NMR chemical shift of the $ArCH_2Ar$ groups of **4d** occurred at 45.71 ppm, displaced downfield ($\approx$9.7 ppm) with respect to the oxygen-bearing calixarenes (O-calixarenes) with *anti*-oriented rings. Instead, when ArSR groups in S-calixarenes are *syn*-oriented, a ^{13}C NMR chemical shift of 39.0 ppm was found.[15b,c] Analogous $ArCH_2Ar$ groups between *syn*-oriented phenol rings resonate at $\approx$31 ppm.[3a] On this basis, Gutsche has extended de Mendoza's "^{13}C NMR single rule" to establish the conformation of mercaptocalixarenes by means of the ^{13}C NMR chemical shift of their $ArCH_2Ar$ groups (Table 1).

Table 1. Empirical rules for ^{13}C NMR values of $ArCH_2Ar$ groups of S- or O-calixarenes as derived by Gutsche.[15c]

	ArSR/ArSR	ArSR/ArOR	ArOR/ArOR
syn	39.5 ± 0.5	36 ± 2	31
anti	46.8 ± 2.0	≈45 (extrapolated)	37

A ^{13}C chemical shift of $ArCH_2Ar$ groups at 39–40 ppm is indicative of a *syn* orientation of the two ArSR rings, while δ $\approx$46–47 is indicative of an *anti* orientation of the two pertinent groups (Table 1).[15c] When the methylene group is flanked by one ArOH and one ArSR ring, a ^{13}C chemical shift of 36 ppm is indicative of a *syn* orientation of the two rings.[15c] In the absence of experimental data relative to the *anti* orientation of ArOH and ArSR rings, Gutsche extrapolated a δ value of $\approx$45 ppm for the pertinent $ArCH_2Ar$ groups.[15c] As reported above, the ^{13}C NMR chemical shift of the $ArCH_2Ar$ groups in the S-calixarene derivatives was shifted downfield with respect to the corresponding O-calixarenes.

There have been fewer studies on aminocalixarenes compared to mercaptocalixarenes. Shinkai[16a,b] and Biali[16c,d] have shown that the substitution of a hydroxyl group with an amino group lowered the strength of the hydrogen bond at the lower rim. This involves a lowering of the energy barrier for the cone-to-cone inversion process with respect to that of the parent calixarene. In fact, the barrier estimated for monoamino-trihydroxy-*p*-*tert*-butylcalix[4]arene is 14.8 kcal mol^{-1},[16c] as opposed to 13.9 kcal mol^{-1}[16b] for diaminodihydroxy-*p*-*tert*-butylcalix[4]arene and 15.7 kcal mol^{-1} for the parent *p*-*tert*-butylcalix[4]arene. These values are in agreement with the presence of a broad signal relative to the $ArCH_2Ar$ groups in their ^{1}H NMR spectra at 298 K, indicating a conformational mobility comparable to the NMR time-scale. In contrast to S-calixarene and to the parent O-calixarene systems, no rules exist for the conformational assignment of N-calixarenes based on the ^{1}H and ^{13}C NMR chemical shifts of their $ArCH_2Ar$ groups

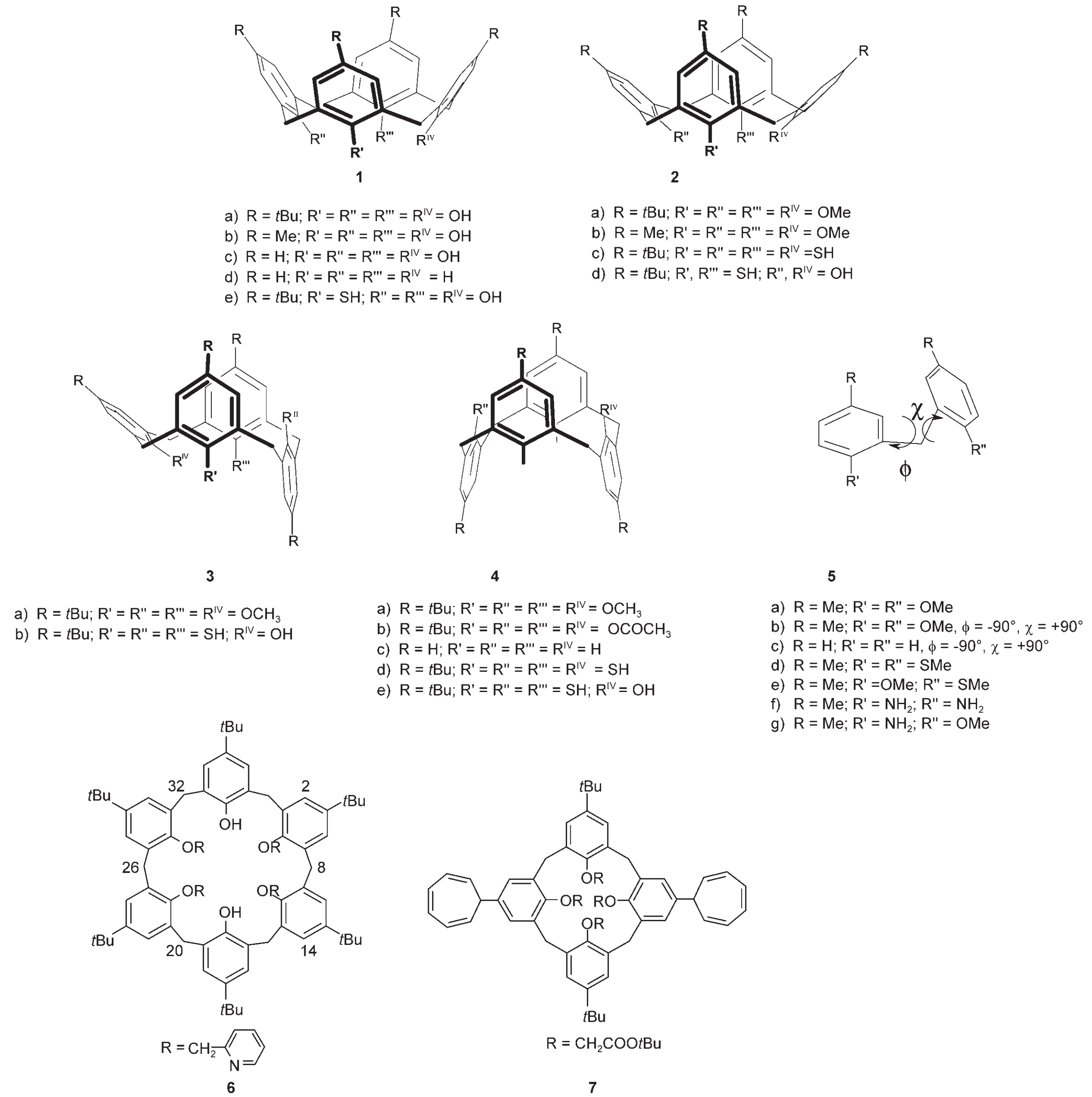
Results and Discussion

Reliability of the method and QM calculations of the ^{1}H and ^{13}C chemical shifts of significant calix[4]arenes: As groundwork to verify the reliability of our method for the QM calculations, we first investigated the ^{1}H and ^{13}C NMR shifts of some complete calixarene systems (compounds **1**–**4**). Subsequently, we explored the conformational diversity of oxygen-, mercapto- and amino-calixarenes by taking into consideration all the conformers derived by a systematic variation of 30° of the ϕ and χ angles of some simplified calixarene model structures (**5**, Scheme 1).

In general, we followed the strategy of a protocol recently reported by our research group[17] that suggests a preliminary geometry optimisation of the compound of interest at the hybrid DFT MPW91PW91 level[11] with the 6-31G(d) basis set followed by a calculation of the nuclear shielding with the GIAO (gauge-including atomic orbital)[11] approach with the same functional and the 6-31G(d,p) basis set (Gaussian03 software package).[18]

As is evident from Table 2, which gives the calculated vs. the experimental values of a number of hydroxy-, mercapto- and aminocalixarenes, a very good performance of the applied protocol is maintained for all the different conformations and all the different patterns of substitution of the analysed calixarenes.

In particular, with respect to the oxygen-bearing calixarenes (O-calixarenes), the cone structure of *p-tert*-butylcalix[4]arene (**1a**) shows calculated $\delta(^{13}C)$ and $\Delta\delta(^{1}H)$ values of 34.5 and 0.87, respectively, that are close to experimental ones (32.7 and 0.75 ppm).[19] Similarly, for the 1,3-alternate conformation **4b**, both the calculated ^{13}C value of 40.0 ppm



1

a) R = *t*Bu; R' = R'' = R''' = R^{IV} = OH
b) R = Me; R' = R'' = R''' = R^{IV} = OH
c) R = H; R' = R'' = R''' = R^{IV} = OH
d) R = H; R' = R'' = R''' = R^{IV} = H
e) R = *t*Bu; R' = SH; R'' = R''' = R^{IV} = OH

2

a) R = *t*Bu; R' = R'' = R''' = R^{IV} = OMe
b) R = Me; R' = R'' = R''' = R^{IV} = OMe
c) R = *t*Bu; R' = R'' = R''' = R^{IV} =SH
d) R = *t*Bu; R', R''' = SH; R'', R^{IV} = OH

3

a) R = *t*Bu; R' = R'' = R''' = R^{IV} = OCH_3
b) R = *t*Bu; R' = R'' = R''' = SH; R^{IV} = OH

4

a) R = *t*Bu; R' = R'' = R''' = R^{IV} = OCH_3
b) R = *t*Bu; R' = R'' = R''' = R^{IV} = $OCOCH_3$
c) R = H; R' = R'' = R''' = R^{IV} = H
d) R = *t*Bu; R' = R'' = R''' = R^{IV} = SH
e) R = *t*Bu; R' = R'' = R''' = SH; R^{IV} = OH

5

a) R = Me; R' = R'' = OMe
b) R = Me; R' = R'' = OMe, ϕ = -90°, χ = +90°
c) R = H; R' = R'' = H, ϕ = -90°, χ = +90°
d) R = Me; R' = R'' = SMe
e) R = Me; R' =OMe; R'' = SMe
f) R = Me; R' = NH_2; R'' = NH_2
g) R = Me; R' = NH_2; R'' = OMe

R = CH_2–(pyridyl)
6

R = $CH_2COOtBu$
7

Scheme 1. Structures of model compounds **1**–**7**.

Table 2. Experimental and calculated $\delta(^{13}C)$ and $\Delta\delta(^{1}H)$ values for the methylene groups of compounds **1**–**4** and **5b**–**c**.

	$\delta(^{13}C)_{exp}$	$\Delta\delta(^{1}H)_{exp}$	$\delta(^{13}C)_{calcd}$	$\Delta\delta(^{1}H)_{calcd}$
1a[19]	32.7	0.75	34.5	0.87
1b[21]	31.2	1.11	34.1	0.90
1c[22]	31.7	0.71	34.1	0.87
1d	–	–	44.7	0.08
1e[15c]	32.7, 37.6	0.67, 0.80	34.4, 39.0	0.87, 0.88
2a[20]	29.7	1.07	33.5	1.47
2b	–	–	32.9	1.51
2c	–	–	42.1	
2d[15c]	37.8	0.78	39.0	0.91
3a[20]	37.7, 30.8	0.06, 1.02	40.0, 33.6	0.03, 1.37
3b[15c] [a]	38.7, 45.5	–	38.3, 47.1	0.13, 0.98
4a	–	–	40.0	0.00
4b[3a]	38.2	0.00	40.8	0.00
4c	–	–	43.6	0.01
4d[15c]	45.7	0.00	46.8	0.00
4e	–	–	43.9, 46.8	0.01, 0.27
5b	–	–	34.5	1.52
5c	–	–	45.1	0.07

[a] This compound exhibited an equilibrium between 1,3-alternate and partial-cone conformation at room temperature.[15c]

and $\Delta\delta(^{1}H)$ of 0.0 ppm agreeably reproduce the experimental data (38.2 and 0.0 ppm, respectively).[3a] Predicted ^{13}C chemical shifts of 40.0 and 33.6 ppm for partial cone **3a** very closely mimic the experimental ones (37.7 and 30.8 ppm),[20] while $\Delta\delta(^{1}H)$ values of 1.37 and 0.03 ppm are in less agreement with the observed data (1.02 and 0.06 ppm), which is probably attributable to the high conformational mobility of this compound. The same rationalisation can be invoked to explain the higher $\Delta\delta(^{1}H)$ values (Table 2) predicted for tetramethoxycalix[4]arenes **2a**–**b** (whose minimum energy structures have a C_{2v} cone conformation).

An analogous good performance was found for the reproduction of the NMR properties of some significant calix[4]-arenethiol compounds, namely **2c**, representing a flattened cone structure, and **4d**, representing a 1,3-alternate conformation. The experimental ^{13}C value of 45.7 ppm observed for **4d** is nicely reproduced by the calculated counterpart 46.8, in accordance with the rule proposed by Gutsche.[15c] On the other hand, the experimental ^{13}C NMR value of 39.0 ppm found for the *syn*-oriented ArSR groups of a 1,2-alternate tetrakis((dimethylcarbamoyl)thio)calix[4]arene[15b,c] derivative is reproduced well by the theoretical value of 42.1 ppm calculated for the *syn*-oriented ArSH groups of **2c**.

At this point, the calculation of the NMR shielding properties was extended to mixed S,O-substituted calixarenes. Thus, calculations were carried out on the cone structure of calix[4]arenemonothiol **1e**, on the flattened-cone conformation of the calix[4]arenedithiol **2d**, on the partial-cone **3b**, and on the 1,3-alternate **4e** conformations of calix[4]arenetrithiol. Briefly, in monothiol **1e**, calculated ^{13}C values of 39.0 and 34.4 were in good agreement with the observed values of 37.6 and 32.7, and the $\Delta\delta(^{1}H)$ of 0.88 and 0.87 fitted well with their experimental counterpart (see Table 2). The flattened cone **2d** showed a calculated ^{13}C value of 39.0 and $\Delta\delta(^{1}H)$ of 0.91 versus 37.8 and 0.78 (experimental), respectively. Finally, the predicted values for the **3b** and **4e** conformations of the trithiol compound clearly confirm the assessment of Gutsche, who suggested a preponderance of the partial-cone conformation **3b** in solution. In fact, as shown in Table 2, a better agreement between experimental and theoretical data can be obtained in this case.

In accordance with literature data, our calculations on calix[4]arenes in which the *para* substituent is a methyl group (**1b**)[21] or a proton (**1c**),[22] compared with those of **1a**, showed that the different *para* substitution does not significantly affect the ^{13}C chemical shift values or the $\Delta\delta(^{1}H)$ (see Table 2).

On the basis of this evidence, our exploration of the conformational diversity was carried out taking into consideration all the conformers derived by a systematic variation of 30° of the ϕ and χ angles of model structures **5a**, **5d**–**g**, consisting of two toluene moieties connected at C3 by a single methylene and displaying all the significant different patterns of O-, S-, and N-substitution at the lower rim. In particular, model **5a** has two *p*-methoxy substituents and represents the most common calix[*n*]arene systems,[23] while model **5d** and **5f** represent thio- and aminocalix[*n*]arenes, respectively. Finally, to investigate the conformational diversity of calix[*n*]arenes endowed with mixed substitution patterns, model **5e**, containing O,S-substituents and model **5f**, containing O,N-substituents, were also taken into consideration.

Conformational dependence of calculated ^{1}H and ^{13}C chemical shifts of O-substituted calixarenes: In analogy with the protocol followed for the complete systems **1**–**4**, all the conformers of **5a** obtained by a systematic variation of 30° of the ϕ and χ angles were optimised at the MPW1PW91/6-31G(d) level, and the resulting geometries were used as input data for the single-point calculation relative to the nuclear magnetic shielding at the MPW1PW91/6-31G(d,p) level. Figure 1 (top) shows the dependence of the calculated ^{13}C methylene chemical shift on the conformational variations. In particular, Figure 1 (top) represents the contour plot of Ar-CH_2-Ar ^{13}C chemical shifts as a function of the ϕ and χ angles; another parameter that is crucial for the conformational assessment of calix[*n*]arenes is the $\Delta\delta(^{1}H)$ values of $ArCH_2Ar$ protons. Such values are reported as a function of the ϕ and χ angles in Figure 1 (bottom) as contour plot (larger and coloured figures are available in the Supporting Information).

In this paper, we suggest the use of the obtained theoretical ^{1}H and ^{13}C chemical shift surfaces of the simplified calixarene model **5a** and of the following models **5d**–**g** to derive structural information about calix[n]arenes of unknown conformation whose experimental ^{1}H and ^{13}C spectra are available. Indeed, the experimental $\delta(^{13}C)$ and $\Delta\delta(^{1}H)$ values for any given calix[*n*]arene can be straightforwardly fitted to the contour plots of the ^{13}C and ^{1}H chemical shifts proposed here to determine its conformational properties through the clear-cut derivation of the ϕ and χ torsion angle values (see the Supporting Information). Of course, the fitting of the ex-

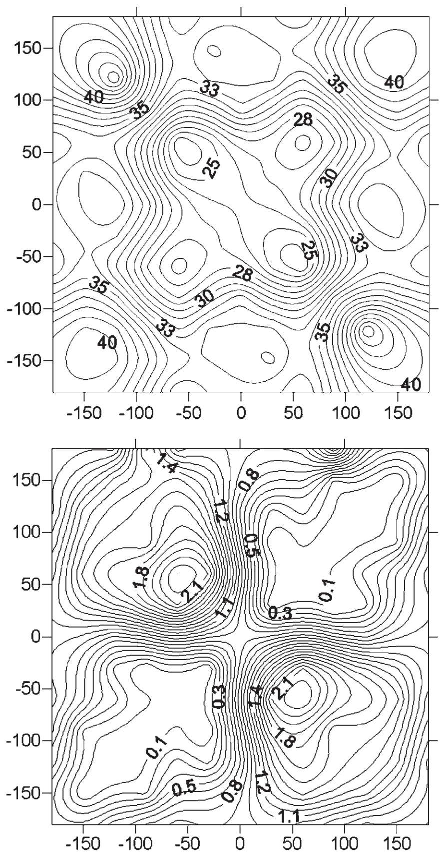


Figure 1. Contour plot representations of the $\delta(^{13}C)$(top) and $\Delta\delta(^{1}H)$ (bottom) values of the $ArCH_2Ar$ group of O-calixarene model **5a** versus the ϕ and χ angles [°], calculated at the MPW1PW91/6-31G(d,p) level.

perimental data will be accurate provided that the investigated product exhibits a substitution pattern compatible with model **5a** or models **5d**–**g**, that is, will be O-, S-, N-, S,O-, or N,O-substituted. In the case of standard methoxy-substituted calixarenes, the comparison of several sets of experimental data (including those reported in Table 2) reveals that ^{13}C chemical shifts are always well reproduced by our calculations, indicating the suitability of the simplified model to locally reproduce the features of a complete calixarene system.

Origin of the modulation of the ^{1}H and ^{13}C chemical shifts of O-calixarenes upon variation of the ϕ and χ angles: Our investigation of the origin of the modulation of ^{1}H and ^{13}C chemical shifts upon variation of the ϕ and χ angles showed that the -OR groups present on the aryl moieties are crucial factors for both the occurrence of magnetic non-equivalence of the methylene protons and the shielding variations of the corresponding ^{13}C nucleus.[10] These observations were derived from the analysis of calculated ^{13}C and ^{1}H shifts for compounds **1d**, **4c** and **5c**, which correspond to compounds **1a**, **4b** and **5b** without the non-influential *p*-substituent and -OR moiety. The results summarised in Table 2 suggest in fact that the $\Delta\delta(^{1}H)$ parameter decreases and is flattened to zero when the -OR groups are not present.[10] Similar considerations apply to the ^{13}C values, which in the absence of -OR groups are predicted to resonate in a very narrow range for compounds **1c**, **4c** and **5c** (44.7, 43.6 and 45.1 ppm, respectively, see Table 2) with respect to what is observed for compounds **1a**, **4b** and **5b** (34.5, 40.0 and 34.5 ppm, respectively, see Table 2).

Considering the above assessments, it has to be pointed out that the empirical rules described by Gutsche and de Mendoza may only be applied when -OR groups are present on the single calixarene aryl units. To extend the applicability of our results to O-, S-, N-, S,O- or N,O-substituted calixarenes, we investigated the conformational variations of models **5d**–**g**.

Conformational dependence of calculated ^{1}H and ^{13}C chemical shifts of S-substituted calixarenes: Calixarene thiols are a class of compounds that have attracted research interest for the moderate complexity of their synthesis;[15] however, the low number of available examples has hampered a deep understanding of their conformational behaviour.

For this reason, in analogy to model **5a**, we propose contour plots of $Ar\text{-}CH_2\text{-}Ar$ ^{13}C chemical shifts and of the $ArCH_2Ar$ proton $\Delta\delta(^{1}H)$ values as a function of the ϕ and χ angles obtained by systematic variation of 30° of the ϕ and χ angles of **5d** (Figure 2). A comparison of the $Ar\text{-}CH_2\text{-}Ar$ ^{13}C shifts of O-substituted with the S-substituted calixarenes gives an overall average difference of 6.8 ppm. This fairly large value not only suggests a stronger influence of the sulfur atom in deshielding the methylene groups, but it also confirms the prevalent role of the lower-rim substituent in the modulation of the ^{1}H and ^{13}C chemical shifts of calix[*n*]arenes upon variation of the ϕ and χ angles, as described above. In order to quantitatively represent the influence of the sulfur vs. the oxygen atom in the modulation of the methylene ^{13}C chemical shifts, we also propose the $\Delta\delta(^{13}C)$ values of the S- versus the O-substituted calixarenes as a function of ϕ and χ angles (Figure 3). This surface is not flat and the maximum differences in $\delta(^{13}C)$ are predicted for $\phi \approx -50°$, $\chi \approx +50°$ ($\Delta\delta \approx 9.5$) and for $\phi \approx +50°$, $\chi \approx +50°$ ($\Delta\delta \approx 8.5$), corresponding to cone and 1,3-alternate conformation, respectively, in fair agreement with Gutsche's observations (Table 1). It has to be recalled that the heteroatomic steric compression effect has been considered responsible for the modulation of the $ArCH_2Ar$ ^{13}C chemical shifts upon variation of the ϕ and χ angles of O-substituted calixarenes.[3a] Such modulation is represented in Figure 1 (top) and may be also singled out in Figure 2 (top) for what concerns the S-substituted calixarenes. A careful examination of Figure 3 reveals an opposite pattern with respect to Figures 1 and 2. Therefore, this suggests, as expected, a minor steric compression effect of the sulfur atom with respect to the oxygen.

Finally, from the above data, the interested reader may extrapolate conformational information about unknown calixarenethiols in two ways: a) straightforward fitting of ^{1}H and ^{13}C experimental chemical shifts to the plots reported in

Figure 2; b) comparison of the ^{13}C experimental chemical shifts of an unknown S-substituted calixarene with the ^{13}C data of a known O-substituted calixarene, and fitting of the resulting $\Delta\delta$(^{13}C) values in the plot reported in Figure 3. We should note that, provided experimental data is available for an O-substituted calixarene homologous compound, the method b) offers the possibility of cancelling out all the systematic errors that may be caused by the use of our current level of theory in the modelling of calixarene structures.

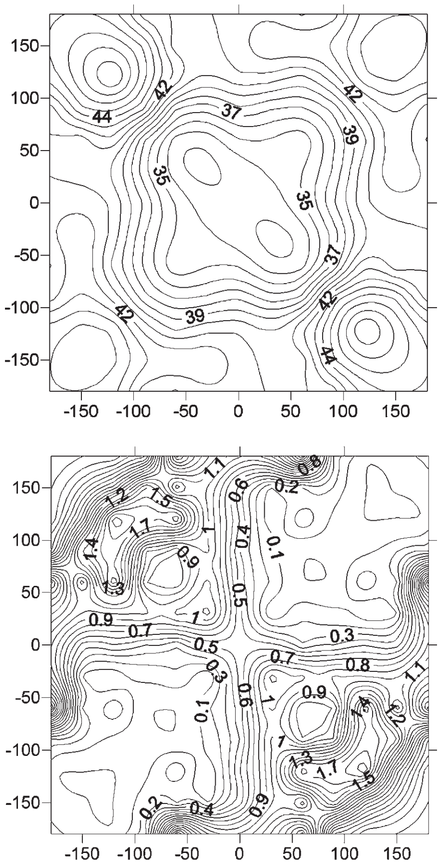


Figure 2. Contour plot representations of the δ(^{13}C) (top) and $\Delta\delta$(^{1}H) (bottom) values of the ArCH$_2$Ar group of S-calixarene model **5d** versus the ϕ and χ angles [°], calculated at the MPW1PW91/6-31G(d,p) level.

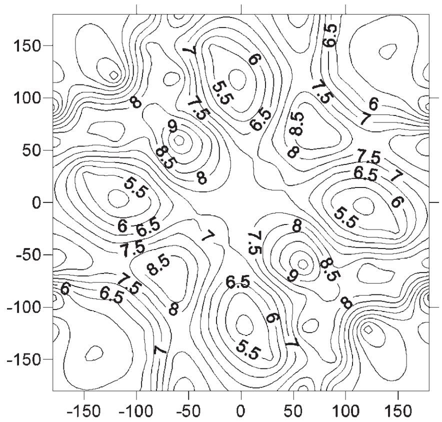


Figure 3. Contour plot representation of the ^{13}C chemical shift differences ($\Delta\delta$) between the ArCH$_2$Ar group of S/O-models **5d** and **5a** versus the ϕ and χ angles [°], calculated at the MPW1PW91/6-31G(d,p) level.

Conformational dependence of calculated ^{1}H and ^{13}C chemical shifts of N-substituted calixarenes: Together with calixarenethiols, aminocalixarenes constitute an important class of *n*-meric metacyclophanes bearing -NH$_2$ groups that substitute the -OH or OR. There is little information on the relationship between their conformation and the main features of their NMR spectra. Again, we have obtained both contour plots of Ar-CH$_2$-Ar ^{13}C shifts and of the ArCH$_2$Ar proton $\Delta\delta$(^{1}H) values as a function of the ϕ and χ angles by systematically varying by 30° the ϕ and χ angles of **5f** (Figure 4). A comparison of the Ar-CH$_2$-Ar ^{13}C shifts of O- with N-substituted calixarenes reveals an overall average difference of 2.2 ppm, suggesting a moderately stronger influence of the nitrogen atom in deshielding the methylene groups with respect to that exerted by oxygen. For a more detailed representation of the influence of the nitrogen vs. the oxygen atom in modulating the ^{13}C methylene shifts, we have reported in Figure 5 the $\Delta\delta$(^{13}C) values of the N- versus the O-substituted calixarenes upon variation of the ϕ and χ angles. It is interesting that a comparison of Figure 5 with 3, which, besides a general weaker influence of the nitrogen with respect to the sulfur, indicates that the trend in the modification of the ^{13}C chemical shifts with respect to the oxygen is again not flat. Moreover, it is evident in Figure 5 that only a single pair of maxima in the differences in δ(^{13}C) are predicted for the nitrogen pattern substitution ($\phi \approx -75°$, $\chi \approx -75°$ ($\Delta\delta \approx 4$), which may be attributable to the presence of a single lone pair on the nitrogen atom.

As seen in Figure 3 and for the calixarenethiols, the calculated $\Delta\delta$(^{13}C) values should be free from systematic errors and may be used for all cases in which the experimental data for an O-substituted calixarene homologous compound are available.

Conformational dependence of calculated ^{1}H and ^{13}C chemical shifts of mixed S,O- and N,O-substituted calixarenes: The syntheses of **1d**, **2a**, **3b** and **4e**[15c] demonstrate the interest of researchers toward the preparation of calixarenes containing mixed S,O- and possibly N,O-substituted calixarenes. It is for this reason that, in order to complete our work, we considered the systematic variation of the ϕ and χ of model **5e** and model **5g** to verify the influence of such substitution patterns on the conformationally relevant NMR data of ArCH$_2$Ar groups. In particular, Figure 6 shows the S,O-substitution pattern while Figure 7 shows the N,O-calixarenes. Qualitative comparisons of the Ar-CH$_2$-Ar ^{13}C shifts of O-substituted calixarenes with the S,O- and N,O-substituted analogues revealed average differences of 3.5 and 1.5 ppm, respectively.

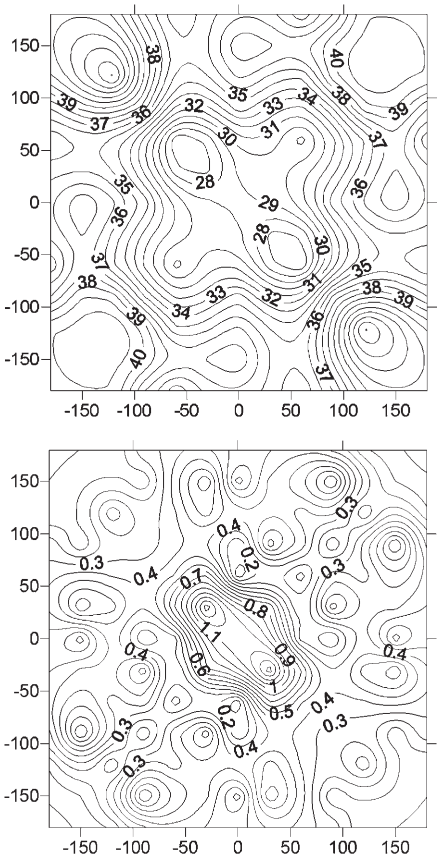


Figure 4. Contour plot representations of the $\delta(^{13}C)$ (top) and $\Delta\delta(^{1}H)$ (bottom) values of the ArCH$_2$Ar group of N-calixarene model **5f** versus the ϕ and χ angles [°], calculated at the MPW1PW91/6-31G(d,p) level.

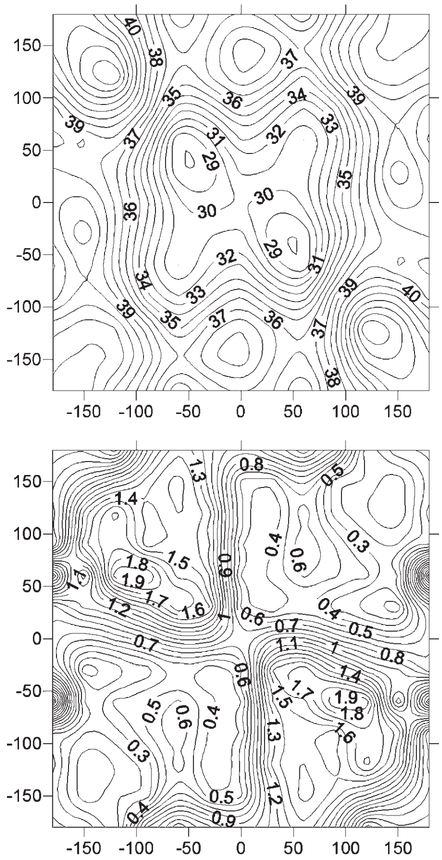


Figure 6. Contour plot representations of the $\delta(^{13}C)$ (top) and $\Delta\delta(^{1}H)$ (bottom) values of the ArCH$_2$Ar group of S,O-calixarene model **5e** versus the ϕ and χ angles [°], calculated at the MPW1PW91/6-31G(d,p) level.

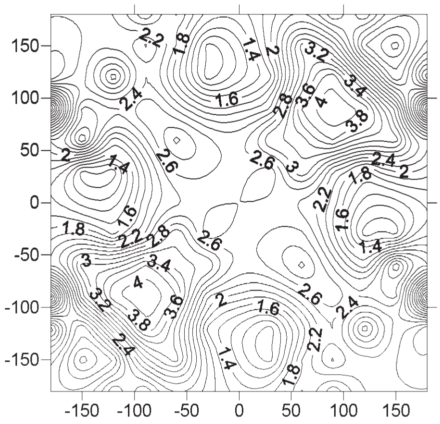


Figure 5. Contour plot representation of the ^{13}C chemical shift differences ($\Delta\delta$) between the ArCH$_2$Ar group of N/O-models **5f** and **5a** versus the ϕ and χ angles [°], calculated at the MPW1PW91/6-31G(d,p) level.

Applications of ^{1}H and ^{13}C chemical shift surfaces in the determination of calixarene conformations: The ^{1}H and ^{13}C chemical shift surfaces obtained in this work can be considered to be a useful tool in the conformational analysis of new calixarenes with an unknown three-dimensional structure. In particular, we propose two different strategies for the definition of the calixarene conformation based on the comparison between the experimental and the calculated ^{1}H and ^{13}C chemical shifts. In the first strategy, the experimental ^{1}H and ^{13}C chemical shifts of the calixarene under examination need to be fitted to the theoretical ^{1}H and ^{13}C chemical shift surfaces. For each methylene group, the simultaneous analysis of ^{1}H and ^{13}C values will allow us to obtain a limited number—usually a couple—of possible combinations of ϕ and χ angles.[24] On the basis of the so-obtained ϕ and χ angles, associated to all the methylenes belonging to the calixarene, it will be possible to build only a restricted number of conformers. The first and obvious criterion to follow in choosing the conformers is to discard arrangements that lack closure of the calixarene macrocycle. Secondarily, if more than a single conformation subsists, a force-field or higher level evaluation of the energies may be used to discriminate between the remaining candidate structures.

Thus, following this strategy, we used ^{1}H and ^{13}C chemical shift surfaces to predict the theoretical structure of the known compound 1,2,4,5-tetrapicolyl-*p-tert*-butylcalix[6]arene (**6**).[25] This macrocycle is conformationally flexible in solution and VT NMR studies indicated that the molecule is frozen at 183 K in the 1,2,4,5-alternate conformation. Such a conformation was determined in the solid state by means of

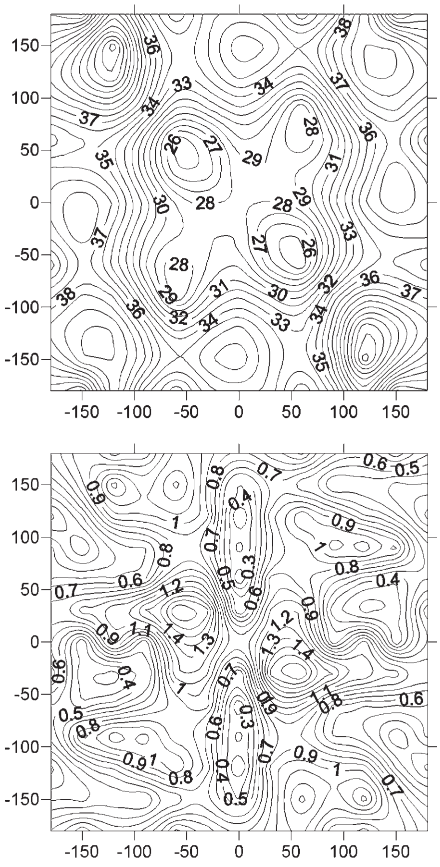


Figure 7. Contour plot representations of the $\delta(^{13}C)$ (top) and $\Delta\delta(^{1}H)$ (bottom) values of the $ArCH_2Ar$ group of N,O-calixarene model **5g** versus the ϕ and χ angles [°], calculated at the MPW1PW91/6-31G(d,p) level.

X-ray analysis and in solution by means of a detailed 2D NMR and molecular mechanics study. Thus, the presence of both *syn* and *anti* orientations of the aromatic rings makes **6** a very interesting candidate for testing the ability of our strategy based on ^{1}H and ^{13}C chemical shift surfaces to predict the conformation of calixarenes. Complete assignment for both proton and carbon spectra of **6** was obtained at low temperature.[25] Consequently, for each methylene group, the fitting of the corresponding couple of $\Delta\delta(^{1}H)$ and ^{13}C values in the contour plots allows us to obtain a couple of possible combinations of ϕ and χ angles (Table 3, and Figure S1 in Supporting Information).

Table 3. ϕ and χ torsion angles of **6** derived by fitting the experimental $\delta(^{13}C)$ and $\Delta\delta(^{1}H)$ values for the methylene groups on the corresponding chemical shift surface.

Atom number	$\delta(^{13}C)_{exp}$	$\Delta\delta(^{1}H)_{exp}$	ϕ_{calcd}, χ_{calcd}
2 and 14	30.5	0.45	−15 and −85 +15 and +85
8 and 26	38.9	0.00	−125 and −125 +125 and +125
20 and 32	30.5	1.17	+15 and −85 −15 and +85

The theoretical torsion angles reported in Table 3 were then used to build a calix[6]arene model by means of a molecular modelling program (MacroModel version 9.0)[26] (see Supporting Information for a detailed explanation of the steps followed in building the model). Thus, a theoretical 1,2,4,5-conformation was obtained for **6** that shows a high degree of similarity with respect to the crystal structure (Figure 8). This is witnessed by an rmsd value of 1.3 Å obtained by superimposing the theoretical model on the X-ray structure, and by an rmsd value of 49° for the corresponding torsion angles.

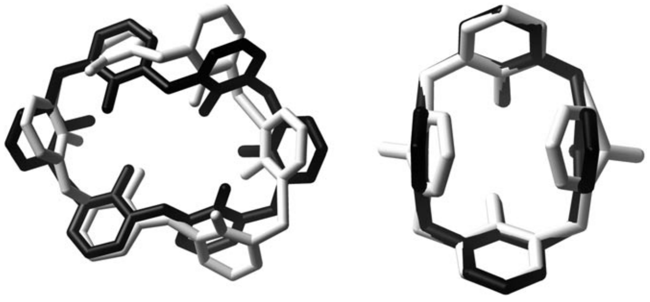


Figure 8. Superimposition of the theoretical model (white) and the X-ray structure (black) of calixarene derivatives **6** (left; rmsd = 1.3 Å, and rmsd = 49° for ϕ and χ angles) and **7** (right; rmsd = 0.6 Å, and rmsd = 23° for ϕ and χ angles).

As reported in our previous communication,[10] our method leads to accurate results for conformationally blocked calixarene systems. Thus, we also examined the conformationally blocked calix[4]arene **7** containing cycloheptatrienyl groups on the upper rim.[9] This derivative adopts a pinched cone conformation in the solid state and in solution with an unusual $\Delta\delta(^{1}H)$ $ArCH_2Ar$ proton value of 1.65 ppm. The combined fitting of the experimental ^{13}C (30 ppm) and $\Delta\delta(^{1}H)$ (1.65 ppm) values leads to only two possible pairs for the ϕ and χ angles: 90 and −25° and −90 and +25°, respectively (see Supporting Information). By imposing these theoretical torsion angles, we obtained the pinched cone structure shown in Figure 8 (white structure), which is good agreement with the X-ray structure (black in Figure 8). The efficiency of the fit can be demonstrated by both an rmsd of 0.6 Å between the theoretical and the crystal structure and by an rmsd value of 23° for the torsion angles.

In cases in which the above-proposed strategy could not be applied, owing to the complexity of the calixarene system or to the lack of one of the experimental ^{1}H or ^{13}C data sets, thus preventing a straightforward determination of the ϕ and χ angles, an alternative approach can be taken into account. In particular, the second strategy is based on a conformational search of the calixarene and the subsequent evaluation and validation of the resulting conformations. This can be achieved by comparing the experimental ^{1}H and ^{13}C chemical shifts with those derived from the contour plots by means of the ϕ and χ angles of each conformation. Such an approach is based on the reliable performance exhibited by Monte Carlo and/or Molecular Dynamics methods, with the use of appropriate force fields, in conformational searches and structural investigations of calixarenes. Moreover, to simplify the problem, a set of predominant conformations in the range of 10–20 kJ mol^{-1} can be selected that will reasonably include the actual arrangement of the molecule in solution. Finally, among all the best fitting structures, the most probable conformation should be the lowest energy one. This should be even more probable if this particular conformation is a global energy minimum

Conclusion

QM GIAO calculations of ^{13}C and ^{1}H chemical shifts of the ArCH$_2$Ar group in N-, O- and S-substituted calixarene systems, performed with a hybrid DFT functional MPW1PW91 and 6-31G(d,p) basis set, showed a good reproduction of experimental data for a group of representative calixarenes. Calculations for a series of simplified N-, O- and S-substituted calixarene models allowed the derivation of chemical shift surfaces versus ϕ and χ dihedral angles. On the basis of the presented data, a straightforward method that relies on the comparison of the experimental and the calculated NMR ^{1}H and ^{13}C chemical shifts is suggested for the assessment of the main conformational features of new calixarenes.

Experimental Section

Quantum mechanical calculations: Input structure files for the quantum mechanical calculations were obtained from X-ray data or by molecular modelling with the MacroModel 9.0 program (MM3 energy minimisation, CHCl$_3$ GB/SA implicit model solvent).[26] QM GIAO calculations of ^{1}H and ^{13}C chemical shifts were performed following the main lines of a protocol recently reported by our group.[17] In particular, the initial geometries were optimised at the hybrid DFT MPW91PW91 level[12] with the 6-31G(d) basis set, while the nuclear shielding properties were calculated with the same functional and the 6-31G(d,p) basis set (Gaussian 03 software package).[18] Average calculation times on a 3 GB Pentium IV processor (workstation running on Linux Redhat 9.0) are 1–2 weeks for a complete calix[4]arene structure and 1–2 days for the simplified (two aryl units) systems.

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[1] For comprehensive reviews, see: a) V. Böhmer, *Angew. Chem.* **1995**, *107*, 785–818; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713–745; b) A. Pochini, R. Ungaro, in *Comprehensive Supramolecular Chemistry, Vol. 2*, Pergamon, Oxford, **1996**, pp. 103–149; c) A. Ikeda, S. Shinkai, *Chem. Rev.* **1997**, *97*, 1713–1734; d) C. D. Gutsche, *Calixarenes Revisited*, Royal Society of Chemistry, Cambridge, **1998**; e) *Calixarenes 2001* (Eds.: Z. Asfari, V. Böhmer, J. Harrowfield, J. Vicens), Kluwer, Dordrecht, **2001**; f) *Calixarenes in the Nanoworld* (Eds.: J. Vicens, J. Harrowfield), Springer, Dordrecht, **2006**.

[2] a) C. D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge, **1989**, pp. 110–111; b) S. Kanamathareddy, C. D. Gutsche, *J. Org. Chem.* **1992**, *57*, 3160–3166.

[3] a) C. Jaime, J. de Mendoza, P. Prados, P. M. Nieto, C. Sanchez, *J. Org. Chem.* **1991**, *56*, 3372–3376; b) J. O. Magrans, J. de Mendoza, M. Pons, P. Prados, *J. Org. Chem.* **1997**, *62*, 4518–4520.

[4] D. R. Stewart, M. Krawiec, R. P. Kashyap, W. H. Watson, C. D. Gutsche, *J. Am. Chem. Soc.* **1995**, *117*, 586–601.

[5] For examples of calix[6]arene conformational isomers, see: a) P. Neri, C. Rocco, G. M. L. Consoli, M. Piattelli, *J. Org. Chem.* **1993**, *58*, 6535–6537; b) T. Saiki, K. Goto, R. Okazaki, *Chem. Lett.* **1996**, 993–994; c) S. Akine, K. Goto, T. Kawashima, *J. Inclusion Phenom. Macrocyclic Chem.* **2000**, *36*, 119–124; For examples of calix[8]arene conformational isomers, see: d) G. M. L. Consoli, F. Cunsolo, C. Geraci, E. Gavuzzo, P. Neri, *Org. Lett.* **2002**, *4*, 2649–2652.

[6] a) F. Ugozzoli, G. D. Andreetti, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *13*, 337–348; b) In particular, typical ranges of ϕ and χ values for the four basic calix[4]arene conformations are as follows (see ref. [1d] p. 46): symmetrical cone: $\phi=+88.9$, $\chi=-89.4$. Distorted cone: $\phi=+74$, $\chi=-124$; $\phi=+102$, $\chi=-63$; $\phi=+64$, $\chi=-107$; $\phi=+116$, $\chi=-58$. Partial-cone: $\phi=+91$, $\chi=-67$; $\phi=+75$, $\chi=-101$; $\phi=+156$, $\chi=+115$; $\phi=-130$, $\chi=-137$. 1,3-Alternate: $\phi=+161$, $\chi=+110$; $\phi=-131$, $\chi=-126$; $\phi=+131$, $\chi=+128$; $\phi=-130$, $\chi=-149$. 1,2-Alternate: $\phi=+81$, $\chi=-63$; $\phi=+116$, $\chi=+140$; $\phi=-81$, $\chi=+63$; $\phi=-116$, $\chi=-140$.

[7] M. Martino, C. Gaeta, P. Neri, *Tetrahedron Lett.* **2004**, *45*, 3387–3391.

[8] A. Arduini, M. Fabbi, M. Mantovani, L. Mirone, A. Pochini, A. Secchi, R. Ungaro, *J. Org. Chem.* **1995**, *60*, 1454–1457.

[9] M. Orda-Zgadzaj, V. Wendel, M. Fehlinger, B. Ziemer, W. Abraham, *Eur. J. Org. Chem.* **2001**, 1549–1561.

[10] G. Bifulco, L. Gomez-Paloma, R. Riccio, C. Gaeta, F. Troisi, P. Neri, *Org. Lett.* **2005**, *7*, 5757–5760.

[11] a) R. Ditchfield, *J. Chem. Phys.* **1972**, *56*, 5688–5691; b) K. Wolinski, J. F. Hinton, P. Pulay, *J. Am. Chem. Soc.* **1990**, *112*, 8251–8260.

[12] C. Adamo, V. Barone, *J. Chem. Phys.* **1998**, *108*, 664–675.

[13] For similar studies concerning other classes of compounds, see for peptides: a) A. C. de Dios, E. Oldfield, *J. Am. Chem. Soc.* **1994**, *116*, 5307–5314; b) E. Oldfield, *J. Biomol. NMR* **1995**, *5*, 217–225; c) A. C. de Dios, *Prog. Nucl. Magn. Reson. Spectrosc.* **1996**, *29*, 229–278; for proteins: d) J. G. Pearson, H. Le, L. K. Sanders, N. Godbout, R. H. Havlin, E. Oldfield, *J. Am. Chem. Soc.* **1997**, *119*, 11941–11950; for oligosaccharides, and glycopeptides: e) C. W. Swalina, R. J. Zauhar, M. J. DeGrazia, G. Moyna, *J. Biomol. NMR* **2001**, *21*, 49–61.

[14] The downfield shift induced by the oxygen atoms has also been experimentally proven for *exo*-calix[4]arenes (S. E. Biali, V. Böhmer, J. Brenn, M. Frings, I. Thondorf, W. Vogt, J. Wöhnert, *J. Org. Chem.* **1997**, *62*, 8350–8360).

[15] a) Y. Ting, W. Verboom, L. C. Groenen, J.-D. van Loon, D. N. Reinhoudt, *J. Chem. Soc. Chem. Commun.* **1990**, 1432–1433; b) C. G. Gibbs, C. D. Gutsche, *J. Am. Chem. Soc.* **1993**, *115*, 5338–5339; c) C. G. Gibbs, P. K. Sujeeth, J. S. Rogers, G. G. Stanley, M. Krawiec, W. H. Watson, C. D. Gutsche, *J. Org. Chem.* **1995**, *60*, 8394–8402; d) M. W. Hosseini in *Calixarenes 2001* (Eds.: Z. Asfari, V. Böhmer, J. Harrowfield, J. Vicens), Kluwer, Dordrecht, **2001**, chap. 6, pp. 110–129.

[16] a) F. Ohseto, H. Murakami, K. Araki, S. Shinkai, *Tetrahedron Lett.* **1992**, *33*, 1217–1220; b) K. Araki, H. Murakami, F. Ohseto, S. Shinkai, *Chem. Lett.* **1992**, 539–542; c) O. Aleksiuk, F. Grynszpan, S. E. Biali, *J. Org. Chem.* **1993**, *58*, 1994–1996; d) O. Aleksiuk, S. Cohen, S. E. Biali, *J. Am. Chem. Soc.* **1995**, *117*, 9645–9652.

[17] P. Cimino, L. Gomez-Paloma, D. Duca, R. Riccio, G. Bifulco, *Magn. Reson. Chem.* **2004**, *42*, S26–S33.

[18] Gaussian 03, Revision B.05, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C.

Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.

[19] C. D. Gutsche, B. Dhawan, K. H. No, R. Muthukrishnan, *J. Am. Chem. Soc.* **1981**, *103*, 3782–3792.

[20] ^{13}C NMR data for mobile tetramethoxycalix[4]arene conformers were obtained by means of an HMQC spectrum (−30 °C) on the basis of ^{1}H NMR assignments (L. C. Groenen, J.-D. van Loon, W. Verboom, S. Harkema, A. Casnati, R. Ungaro, A. Pochini, F. Ugozzoli, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1991**, *113*, 2385–2392).

[21] C. D. Gutsche, K. C. Nam, *J. Am. Chem. Soc.* **1988**, *110*, 6153–6162.

[22] C. D. Gutsche, J. A. Levine, *J. Am. Chem. Soc.* **1982**, *104*, 2652–2653.

[23] It should be noted here that linear oligomeric calixarene analogues, such as **5**, are conformationally mobile and therefore they usually give rise to conformationally averaged ^{1}H NMR singlets for $ArCH_2Ar$ groups. See, for example: a) V. Böhmer, F. Marschollek, L. Zetta, *J. Org. Chem.* **1987**, *52*, 3200–3205; b) W. O. Appiah, A. D. DeGreeff, G. L. Razidlo, S. J. Spessard, M. Pink, V. G. Young, Jr., G. E. Hofmeister, *Inorg. Chem.* **2002**, *41*, 3656–3667.

[24] An alternative approach to limit the number of possible combinations of ϕ and χ angles compatible with the experimental ^{1}H and ^{13}C values could be given by the Oldfield's Z-surface approach (H. Le, J. G. Pearson, A. C. de Dios, E. Oldfield, *J. Am. Chem. Soc.* **1995**, *117*, 3800–3807).

[25] P. Neri, M. Foti, G. Ferguson, J. F. Gallagher, B. Kaitner, M. Pons, M. A. Molins, L. Giunta, S. Pappalardo, *J. Am. Chem. Soc.* **1992**, *114*, 7814–7821.

[26] Molecular modelling was performed with MacroModel 9.0: F. Mohamadi, N. G. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440–467.

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