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Quantum Mechanical Calculations of Conformationally Relevant ^{1}H and ^{13}C NMR Chemical Shifts of Calixarene Systems

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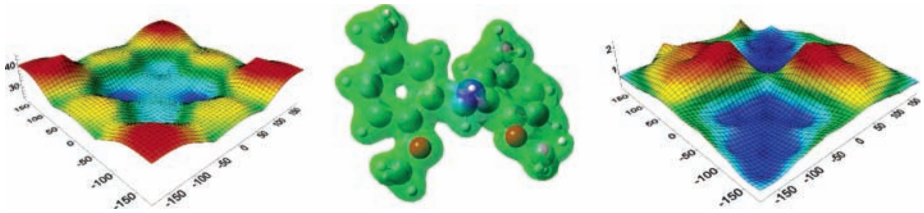
ABSTRACT



QM GIAO calculations of ^{13}C and ^{1}H chemical shift values of the $ArCH_2Ar$ group have been performed, using the hybrid DFT functional MPW1PW91 and the 6-31G(d,p) basis set, on some representative calixarenes and on a series of simplified calixarene models allowing derivation of chemical shift surfaces versus ϕ and χ dihedral angles. A good reproduction of experimental data was obtained. The applicability of chemical shift surfaces in the study of calixarene conformational features is illustrated.

Over the past two decades calix[*n*]arenes[1] have gained a prominent position in several fields of supramolecular chemistry thanks to their ready availability and easy chemical modification. In this respect, of particular relevance is their conformational isomerism that, in the case of calix[4]arenes, gives rise to four discrete conformational isomers (*cone*, *partial-cone*, *1,2-alternate*, and *1,3-alternate*) by attaching sufficiently bulky groups at the lower rim.[1]

The identification of these conformations is usually achieved by application of two simple rules: the Gutsche's "^{1}H NMR $\Delta\delta$" rule[2] and the de Mendoza's "single ^{13}C NMR" rule.[3] The first is based on the chemical shift separation of $ArCH_2Ar$ protons, which may give rise to an AX, AB, or A_2 system. In particular, it is now well established that a $\Delta\delta \approx 0.7-1.0$ is indicative of a *syn* orientation of the two pertinent aromatic rings, typical of the *cone* conformation. A $\Delta\delta \approx 0.3-0.0$ is characteristic of the *anti* orientation (i.e., *1,3-alternate* conformation), while intermediate values ($\Delta\delta \approx 0.3-0.7$) are assigned to intermediate *out* orientation or to the conformationally averaged system in the fast exchange regime. In a similar way, the "single ^{13}C NMR" rule is related to the ^{13}C NMR chemical shift of the $ArCH_2Ar$ group ($\delta \approx 30-33$, *syn*; $\delta \approx 33-36$, *out* or averaged; $\delta \approx 36-39$, *anti*).[3]

By increasing the number *n* of aryl rings, an exponentially increasing number of conformations of the calix[*n*]arene

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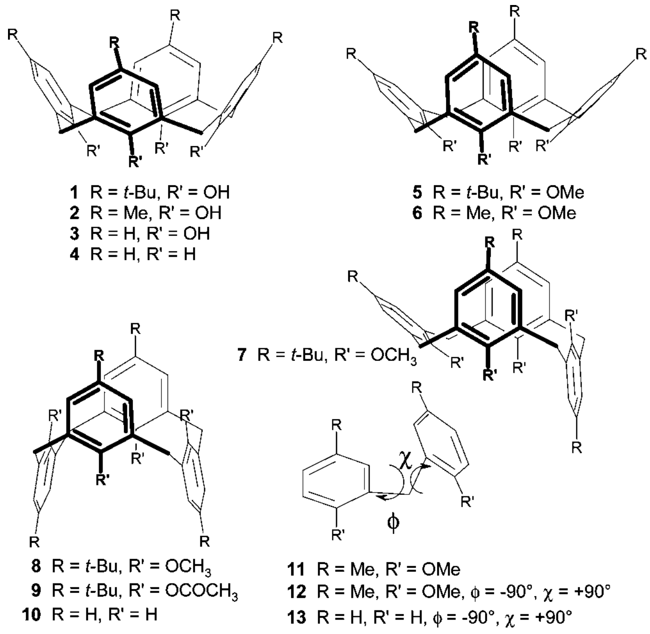
(1) For general reviews on calixarenes, see: (a) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, UK, 1998. (b) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens J., Eds.; Kluwer: Dordrecht, The Netherlands, 2001.

(2) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, UK, 1989; pp. 110−111. Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160.

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

10.1021/ol052166g CCC: $30.25



1 R = *t*-Bu, R' = OH
2 R = Me, R' = OH
3 R = H, R' = OH
4 R = H, R' = H

5 R = *t*-Bu, R' = OMe
6 R = Me, R' = OMe

7 R = *t*-Bu, R' = OCH_3

8 R = *t*-Bu, R' = OCH_3
9 R = *t*-Bu, R' = $OCOCH_3$
10 R = H, R' = H

11 R = Me, R' = OMe
12 R = Me, R' = OMe, ϕ = -90°, χ = +90°
13 R = H, R' = H, ϕ = -90°, χ = +90°

macrocycle become possible, whose pictorial descriptions are increasingly difficult to achieve. For instance, this problem led Gutsche to propose the additional terms of "inward" and "outward" orientation for calix[5]arene macrocycle.[4] However, a more accurate description is obtained by using the ϕ and χ torsion angle values of the Ar$-$CH$_2-$Ar bonds, as proposed by Ugozzoli and Andreetti.[5]

The higher conformational diversity of the larger calixarenes implies the possibility of an unusual orientation of two proximal Ar rings through an appropriate combination of ϕ and χ values. In these instances, it is yet unclear if the Gutsche's and the de Mendoza's rules could still be applied. On the other hand, it is also unclear what conformational significance should be attributed to experimental values beyond the above limits observed in some instances.[6]

To clarify these aspects we decided to undertake a quantum mechanical (QM) study to evaluate conformationally relevant ^{1}H and ^{13}C chemical shifts of representative calixarene systems. In fact, QM calculations have successfully been used in the characterization of natural and synthetic compounds[7] and in the determination of the conformation of flexible molecules.[8] In addition, they have also been successfully applied in structural determination of peptides,[9] proteins,[10] oligosaccharides, and glycopeptides.[11]

At the beginning of our work, we calculated the ^{1}H and ^{13}C chemical shifts of three significant calix[4]arenes in the cone (**1**), partial-cone (**7**), and 1,3-alternate conformation (**9**), following the main lines of a protocol recently reported by our group.[12] In particular, the initial geometries were optimized at the hybrid DFT MPW91PW91 level,[13] using the 6-31G(d) basis set, while the nuclear shielding properties were calculated with the GIAO (gauge-including atomic orbital)[14] approach, using the same functional and the 6-31G-(d,p) basis set (Gaussian 03 Software Package).[15]

As can be clearly seen in Table 1, theoretical ^{1}H and ^{13}C chemical shifts (c.s.) of calixarene bridging methylenes agreeably reproduce experimental values.

Table 1. Experimental and Calculated ^{13}C δ and ^{1}H $\Delta\delta$ Values for the Methylene Groups of Compounds **1**$-$**13**

	^{13}C δ exp	^{1}H $\Delta\delta$ exp	^{13}C δ calctd	^{1}H $\Delta\delta$ calctd
1[16]	32.7	0.75	34.5	0.87
5[17]	29.7	1.07	33.5	1.47
7[17]	37.7	0.06	40.0	0.03
	30.8	1.02	33.6	1.37
8			40.0	0.00
9[3a]	38.2	0.00	40.8	0.00
6			32.9	1.51
2[18]	31.2	1.11	34.1	0.90
3[19]	31.7	0.71	34.1	0.87
4			44.7	0.08
10			43.6	0.01
12			34.5	1.52
13			45.1	0.07

In detail, for the cone structure of *p-tert*-butylcalix[4]arene (**1**), the calculated ^{13}C c.s. and ^{1}H $\Delta\delta$ values are 34.5 and 0.87 ppm, respectively, close to the experimental ones (32.7 and 0.75 ppm).[16] As concerns the 1,3-alternate conformation **9**, both the calculated ^{13}C value of 40.0 ppm and the ^{1}H $\Delta\delta$ of 0.0 ppm are in very good agreement with the experimental data (38.2 and 0.0 ppm, respectively).[3a] Calculated ^{13}C c.s. values of 40.0 and 33.6 ppm for partial-cone **7** are also in very good agreement with the observed ones (37.7 and 30.8 ppm),[17] while ^{1}H $\Delta\delta$ values of 1.37 and 0.03 ppm show a little discrepancy with the experimental data (1.02 and 0.06 ppm) probably due to the high conformational mobility of this compound. The same argument also can be used to

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(4) Stewart, D. R.; Krawiec, M.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 586.

(5) Ugozzoli, F.; Andreetti, G. D. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *15*, 337.

(6) For example, for a 1,4:2,3-calix[7]bis-crown-3 derivative we have observed a ^{1}H $\Delta\delta$ value of 1.55 (Martino, M.; Gaeta, C.; Neri, P. *Tetrahedron Lett.* **2004**, *45*, 3387). In a similar way some bis-bridged calix[4]arenes showed a ^{1}H $\Delta\delta$ value up to 1.86 (Arduini, A.; Pochini, A.; Secchi, A. *Eur. J. Org. Chem.* **2000**, 2325).

(7) Barone, G.; Gomez-Paloma, L.; Duca, D.; Silvestri, A.; Riccio, R.; Bifulco, G. *Chem. Eur. J.* **2002**, *8*, 3233. Della Monica, C.; Randazzo, A.; Bifulco, G.; Cimino, P.; Aquino, M.; Izzo, I.; De Riccardis, F.; Gomez-Paloma, L. *Tetrahedron Lett.* **2002**, *43*, 5707. Wipf, P.; Kerekes, D. *J. Nat. Prod.* **2003**, *66*, 716.

(8) Stahl, M.; Schopfer, U.; Frenking, G.; Hoffmann, R. W. *J. Org. Chem.* **1996**, *61*, 8083. Barone, G.; Duca, D.; Silvestri, A.; Gomez-Paloma, L.; Riccio, R.; Bifulco, G. *Chem. Eur. J.* **2002**, *8*, 3240.

(9) de Dios, A. C. *Prog. NMR Spectrosc.* **1996**, *29*, 229. de Dios, A. C.; Oldfield, E. *J. Am. Chem. Soc.* **1994**, *116*, 5307. Oldfield, E. *J. Biomol. NMR* **1995**, *5*, 217.

(10) Pearson, J. G.; Le, H.; Sanders, L. K.; Godbout, N.; Havlin, R. H.; Oldfield, E. *J. Am. Chem. Soc.* **1997**, *119*, 11941.

(11) Swalina, C. W.; Zauhar, R. J.; DeGrazia, M. J.; Moyna, G. *J. Biomol. NMR* **2001**, *21*, 49.

(12) Cimino P.; Gomez-Paloma, L.; Duca, D.; Riccio, R.; Bifulco, G. *Magn. Reson. Chem.* **2004**, *42*, S26.

(13) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664.

(14) Ditchfield, R. *J. Chem. Phys.* **1972**, *56*, 5688. Wolinski, K.; Hinton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.

(15) See the Supporting Information for additional details.

(16) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.

(17) ^{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 (Groenen, L. C.; van Loon, J.-D.; Verboom, W.; Harkema, S.; Casnati, A.; Ungaro, R.; Pochini, A.; Ugozzoli, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2385). See the Supporting Information for further details.

explain the higher ^{1}H $\Delta\delta$ values (Table 1) predicted for tetramethoxycalix[4]arenes **5** and **6** (whose minimum energy structures have a C_{2v}-cone conformation).

In addition, comparison of the analogous parameters calculated for calix[4]arenes in which the para substituent is a methyl (**2**)[18] or a proton (**3**)[19] with those for **1** showed, besides a good agreement, that the different para substitution does not significantly affect the ^{13}C chemical shift values or the ^{1}H $\Delta\delta$ (see Table 1), in accordance with what is known in the literature.[1-3]

On this basis, in the second stage of our work, we explored the conformational diversity taking into consideration all the conformers derived by a systematic variation of 30° of the ϕ and χ angles of a simplified calixarene model structure (**11**) consisting of two *p*-methoxytoluene moieties connected at C-3 by a single methylene.[20]

As for **1−3**, **5−7**, and **9** we optimized the initial geometries at the MPW1PW91/6-31G(d) level, and we used the obtained geometries as input for the single-point calculation relative to the nuclear magnetic shielding at the MPW1PW91/6-31G(d,p) level. The results are reported in Figure 1 (top), which shows the three-dimensional surface of Ar−CH$_2$−Ar ^{13}C c.s. as a function of the ϕ and χ angles. Figure 1 (bottom) illustrates a contour plot derived from the same data. In addition, similar representations are reported in Figure 2 for the ^{1}H $\Delta\delta$ values of ArCH$_2$Ar protons versus the ϕ and χ angles.

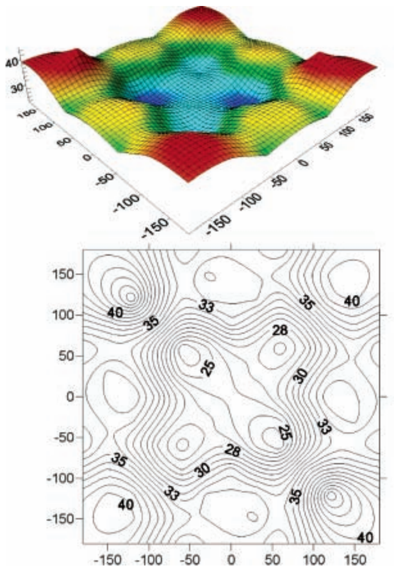

Figure 1. Surface (top) and contour plot (bottom) representation of the ^{13}C chemical shift values (ppm) of the ArCH$_2$Ar group of **11** versus the ϕ and χ angles (°), calculated at the MPW1PW91/6-31G(d,p) level.

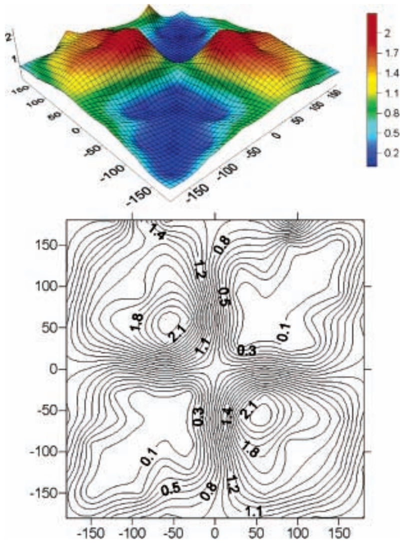

Figure 2. Surface (top) and contour plot (bottom) representation of the ^{1}H $\Delta\delta$ values (ppm) of the ArCH$_2$Ar group of **11** versus the ϕ and χ angles (°), calculated at the MPW1PW91/6-31G(d,p) level.

The obtained theoretical ^{1}H and ^{13}C chemical shift surfaces of the simplified calixarene model may be of great interest to clarify some of the above-discussed comformational aspects. In particular, the experimental ^{13}C δ and ^{1}H $\Delta\delta$ values for any given calix[*n*]arene can be straightforwardly fitted to the ^{13}C and ^{1}H c.s. contour plots here proposed to deduce its conformational properties through the facile derivation of the ϕ and χ torsion angle values. The comparison of several experimental data (including those reported in Table 1) reveals that ^{13}C c.s. are always well reproduced indicating the suitability of the simplified model to mimic a complete calixarene system.

The same conclusion holds true for ^{1}H $\Delta\delta$ values of conformationally blocked systems (for some examples see the Supporting Information). However, the simplified model leads to inaccurate results for conformationally mobile compounds (e.g. **1**), often well reproduced when the calculation is performed on the complete system.

An interesting application of the theoretical data depicted in Figures 1 and 2 concerns the relationship between the canting angle[21] of a calixarene aromatic ring and the corresponding ^{1}H and ^{13}C NMR data. By inspection of the above maps and with the aid of molecular models, it can be deduced that the higher ^{1}H $\Delta\delta$ values are predicted for a canting angle θ ranging from +50 to +100° corresponding to a cone conformation. On the other hand, the highest ^{13}C δ values are obtained for $\theta \approx -50$ to $-60°$ characteristic of a 1,3-alternate orientation.

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(18) Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* **1988**, *110*, 6153.

(19) Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2652.

(20) It should be noted here that linear oligomeric calixarene analogues, like **11**, are conformationally mobile and therefore they usually give rise to conformationally averaged ^{1}H NMR singlets for ArCH$_2$Ar groups. See, for example: Appiah, W. O.; DeGreeff, A. D.; Razidlo, G. L.; Spessard, S. J.; Pink, M.; Young, V. G., Jr.; Hofmeister, G. E. *Inorg. Chem.* **2002**, *41*, 3656. Gordon, B. W. F.; Scott, M. J. *Inorg. Chim. Acta* **1999**, *297*, 206. Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.

(21) Lipkowitz, K. B.; Pearl, G. *J. Org. Chem.* **1993**, *58*, 6729.

Interestingly, the maximum ^{1}H $\Delta\delta$ value of 2.3 ppm is predicted for $\phi = -60°$ and $\chi = +60°$ corresponding to a "standing-up" situation (with a canting angle of 79°) for the calixarene aromatic ring, as depicted in Figure 3. This orientation is impossible in a calix[4]arene system because of geometrical restriction, but becomes possible in larger calix[n]arenes.[22]

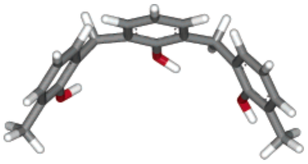

Figure 3. Geometry corresponding to the maximum ^{1}H $\Delta\delta$ value of 2.3 ppm predicted for a calixarene moiety.

In addition to the above chemical shift surfaces, we have investigated the origin of the modulation of ^{1}H and ^{13}C chemical shifts owing to variation of the ϕ and χ angles. A careful screening of all the different conformers of **11** shows that the $-$OR groups present on the aryl moieties may be crucial factors for both the occurrence of magnetic nonequivalence of the methylene protons and the shielding variations of the corresponding ^{13}C nucleus.

To have a deeper insight on this issue, we have run ^{13}C and ^{1}H calculation on compounds **4**, **10**, and **13**, which correspond to compounds **1**, **9**, and **12** depleted of the uninfluential para substituent and $-$OR moiety. For the sake of simplicity, Figure 4 displayes the structures **12** and **13**, both having a ϕ angle of $-90°$ and a χ angle of $+90°$, corresponding to a typical syn orientation. It can be noticed that the methylene protons are chemically and magnetically nonequivalent in **12**, as also demonstrated by a large ^{1}H $\Delta\delta$ value (1.52 ppm, see Table 1). On the other hand, methylene protons in **13** are chemically and magnetically equivalent, showing a calculated ^{1}H $\Delta\delta$ value of 0.07 ppm. The same observations apply to complete calixarene couples **1**/**4** (cone) and **9**/**10** (1,3-alternate). In particular, the nonequivalence of methylene protons in the cone conformation **1** (^{1}H $\Delta\delta$ value of 0.87 ppm, see Table 1) turns in a virtual magnetic equivalence in **4** (^{1}H $\Delta\delta$ value of 0.08 ppm, see Table 1) due to the removal of the $-OCH_3$ groups.

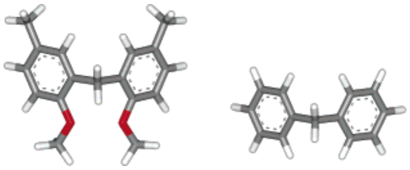

Figure 4. Geometrical comparison between structures **12** (left) and **13** (right).

Not surprisingly, the equivalence of methylene protons in **9** is respected upon removal of the $-OCH_3$ groups in **10**. All in all, the results summarized in Table 1 primarily suggest that the ^{1}H $\Delta\delta$ parameter decreases and it is flattened to zero when the $-$OR groups are not present. Similar considerations apply for the ^{13}C values, which in the absence of $-$OR groups are predicted to resonate in a very narrow range for compounds **4**, **10**, and **13** (44.7, 43.6, and 45.1 ppm, respectively, see Table 1) with respect to what is observed for compounds **1**, **9**, and **12** (34.5, 40.0, and 34.5 ppm, respectively, see Table 1).

From the above observations, it seems that the influence of the ϕ and χ angles on the ^{1}H and ^{13}C chemical shift values of the $Ar-CH_2-Ar$ units is predominantly dependent on the presence of the $-$OR groups characteristic of the majority of the calix[n]arenes reported in the literature and considered in our study.[23] Very briefly, the present study suggests a minor role for the anisotropic effects induced by the aromatic ring currents in determining the magnetic properties of the methylene (both ^{1}H and ^{13}C nuclei).

Therefore, it is important to remark that the results and the indications of this paper, as well as the empirical rules described by Gutsche and de Mendoza, may only be applied when $-$OR groups are present on the single calixarene aryl units.

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Supporting Information Available: Assignment of ^{13}C NMR resonances for **5** and **7** (Figures S1 and S2), details of QM calculations, enlarged contour plots (Figures S3 and S4), examples of applications of the maps on compounds **S1**−**S3** (Figures S5−S13), and QM outputs for **1**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] A consequence of this observation is that the increase of ^{1}H $\Delta\delta$ value (up to 1.70 ppm) observed for some calix[4]arenes blocked in a C_{2v} conformation has to be attributed to the vertical and parallel orientation of a couple of distal rings. See, for comparison: Orda-Zgadzaj, M.; Wendel, V.; Fehlinger, M.; Ziemer, B.; Abraham, W. *Eur. J. Org. Chem.* **2001**, 1549 (for additional details, see the Supporting Information).

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