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Absolute Configuration Assignment of Inherently Chiral Calix[4]arenes using DFT Calculations of Chiroptical Properties

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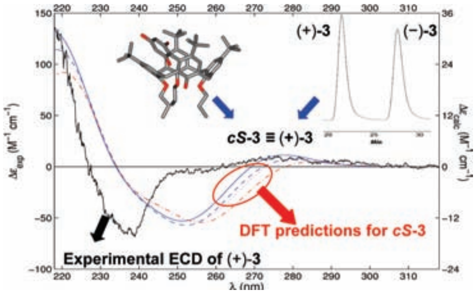
ABSTRACT



The racemate of an inherently chiral meta-substituted calix[4]arene derivative 3 has been resolved via enantioselective HPLC. Measured optical rotation dispersion and electronic circular dichroism have been compared with DFT theoretical predictions. The comparison indicates that the absolute configuration of the dextrorotatory enantiomer (+)-3 is *cS*. The procedure has been successfully tested against a literature precedent confirming the validity of the method.

Inherently chiral calixarenes,[1,2] whose fascinating chirality is due to an asymmetric substitution pattern coupled to their nonplanar molecular geometry, have attracted the attention of several research groups over the past two decades because of their potential applications in several enantiodiscrimination processes such as recognition,[3] catalysis,[3a,4] and sensing.[5]

Their practical exploitation has been somewhat delayed by a difficult optical resolution, which usually has been achieved by enantioselective HPLC methods.[6] However, as recently demonstrated by Huang and co-workers, appropriate procedures can be devised to obtain gram-scale quantities

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(1) For comprehensive reviews on calixarenes, see: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713. (c) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (d) *Calixarenes* 2001; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001.

(2) For reviews on inherently chiral calixarenes, see: (a) Böhmer, V.; Kraft, D.; Tabatabai, M. *J. Inclusion Phenom. Mol. Recognit.* **1994**, *19*, 17. (b) Otsuka, H.; Shinkai, S. *Supramol. Sci.* **1996**, *3*, 189. (c) Vysotsky, M.; Schmidt, C.; Böhmer, V. *Adv. Supramol. Chem.* **2000**, *7*, 139.

(3) For typical representative examples, see: (a) Araki, K.; Inada, K.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 72. (b) Narumi, F.; Hattori, T.; Matsumura, N.; Onodera, T.; Katagiri, H.; Kabuto, C.; Kameyama, H.; Miyano, S. *Tetrahedron* **2004**, *60*, 7827. (c) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2005**, *61*, 8517. (d) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Org. Lett.* **2007**, *9*, 3117. (e) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Eur. J. Org. Chem.* **2008**, 5957.

(4) (a) Dieleman, C.; Steyer, S.; Jeunesse, C.; Matt, D. *J. Chem. Soc., Dalton Trans.* **2001**, 2508. (b) Xu, Z.-X.; Li, G.-K.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2008**, *64*, 8668. (c) Shirakawa, S.; Kimura, T.; Murata, S.-I.; Shimizu, S. *J. Org. Chem.* **2009**, *74*, 1288. (d) Shirakawa, S.; Shimizu, S. *Eur. J. Org. Chem.* **2009**, 1916.

(5) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2005**, *61*, 8517.

(6) For typical examples of enantioselective HPLC resolution of inherently chiral calixarenes, see ref 2 in the Supporting Information.

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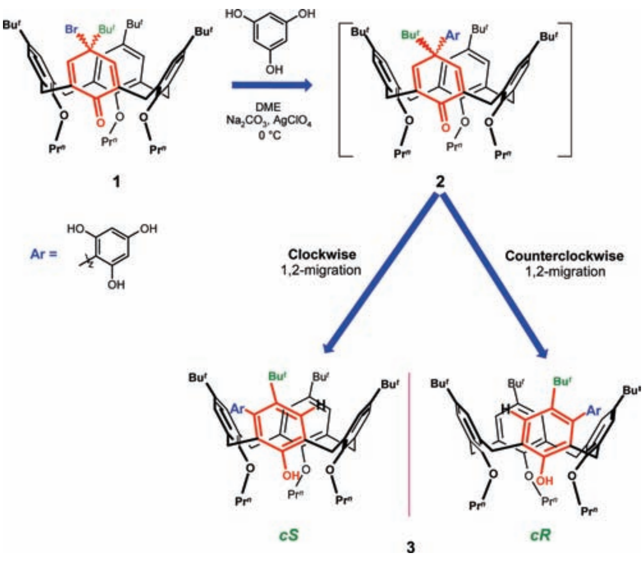
of enantiopure inherently chiral calix[4]arene derivatives to be used for subsequent applications.[7]

The absolute configuration of inherently chiral calixarenes has been rarely assigned, usually by single-crystal X-ray diffractometry.[8] Considering the intrinsic difficulties commonly associated with this method, we wish to apply here a more general and practical approach based on DFT calculations and solution measurements of chiroptical properties. We have found workable, within reasonable computational limits, the prediction of optical rotation at several experimental wavelengths, that is a portion of the optical rotation dispersion (ORD) curve,[9] as well as the calculation of the electronic circular dichroism (ECD) spectrum.[10]

Very recently, we have evidenced that inherently chiral meta-substituted calix[4]arenes[11] can be easily obtained by exploiting the so-called "*p*-bromodienone route"[12] with highly activated aromatic substrates.[13] In this case, the key event that leads to chiral meta substitution is a clockwise or counterclockwise dienone−phenol rearrangement of the *p*-aryldienone intermediate **2** (Scheme 1). In this way, among different other aromatic moieties, a phloroglucinol ring was introduced at the meta position of a calix[4]arene macrocycle leading to inherently chiral derivative **3** (Scheme 1).[13]

Scheme 1



The racemic nature of **3** was evidenced by the doubling of several resonances in its ^{1}H NMR spectrum upon addition of Pirkle's reagent [(*S*)-(+)-(9-antryl)-2,2,2-trifluoroethanol] (Figure 1).

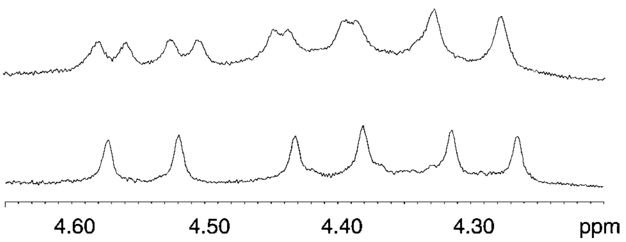


Figure 1. Methylene region of the ^{1}H NMR spectrum (CDCl$_3$, 400 MHz, 298 K) of **1** before (bottom) and after (top) addition of Pirkle's reagent.

A definitive proof was obtained by enantioselective HPLC on Chiralpak ADH stationary phase that, by using 2-propanol/*n*-hexane (2:98) as mobile phase, led to a good resolution (resolution factor $R_s = 3.47$) of the two enantiomeric peaks.[14] The two enantiomers were obtained after repeated injections and collection of the eluates corresponding to the two chromatographic peaks. Analytical HPLC reruns of these peaks gave values of enantiomeric excess (ee) > 99.9% and of 98.6% for the first and second one, respectively.[14] The ECD spectra of both eluates were measured and they were mirror images of each other indicating their enantiomeric nature (Figure 2).

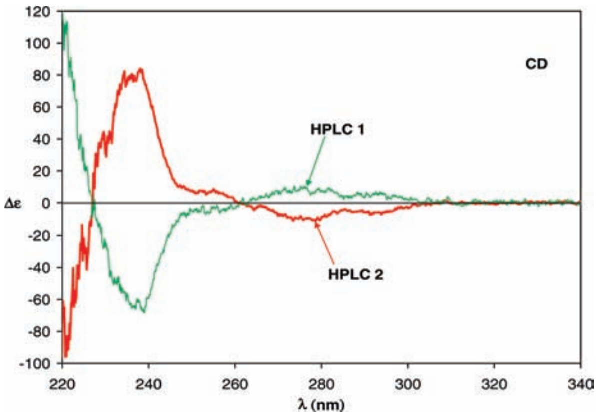


Figure 2. ECD spectra of first (green) and second (red) HPLC fractions, corresponding to (+)-**3** and (−)-**3**, respectively. Δε in M^{-1} cm^{-1}.

In accordance with this result, a specific rotation $[\alpha]^{25}_D$ of +108 (c 0.16, CH$_2$Cl$_2$) was measured for the first-eluted sample of compound **3** while the second one afforded an

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(7) Miao, R.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *J. Org. Chem.* **2005**, *70*, 7662.

(8) (a) Narumi, F.; Hattori, T.; Yamabuki, W.; Kabuto, C.; Kameyama, H. *Tetrahedron: Asymmetry* **2005**, *16*, 793. (b) Xu, Z.-X.; Zhang, C.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2007**, *9*, 4447. (c) h, M. A.; Yesypenko, O. A.; Pirozhenko, V. V.; Shishinka, S. V.; Shishkin, O. V.; Boyko, V. I.; Kalchenko, V. I. *Tetrahedron* **2009**, *65*, 7085.

(9) Giorgio, E.; Viglione, R. G.; Zanasi, R.; Rosini, C. *J. Am. Chem. Soc.* **2004**, *126*, 12968, and references therein.

(10) For comprehensive articles on ECD, see: (a) *Circular Dichroism, Principles and Applications*; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000.

(11) Notwithstanding the special interest for the inherent chirality of meta-substituted calix[4]arenes, functionalizations at the meta position of calixarene aromatic rings are relatively uncommon. For some representative examples, see: (a) Reddy, P. A.; Gutsche, C. D. *J. Org. Chem.* **1993**, *58*, 3245. (b) Verboom, W.; Bodewes, P. J.; Essen, G. V.; Timmerman, P.; Hummer, G. J. V.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron* **1995**, *51*, 499. (c) Mascal, M.; Warmuth, R.; Naven, R. T.; Edwards, R. A.; Hursthouse, M. B.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3435. (d) Barton, O. G.; Neumann, B.; Stammler, H.-G.; Mattay, J. *Org. Biomol. Chem.* **2008**, *6*, 104.

experimental $[\alpha]^{25}_{D}$ of −106.5 (*c* 0.12, CH_2Cl_2), in agreement with its 98.6% ee.

In order to assign the absolute configuration of each eluted sample we considered the *cS* configuration[15] of **3** for the DFT calculations.[14] A MMFF94/Monte Carlo conformational search was performed using Spartan 02[16] with default parameters and by fixing the propyloxy tails to a zigzag shape. The resulting conformations were subjected to geometry optimization using Gaussian 03[17] at the B3LYP/6-31G* level. OR and ECD calculations were performed at TDDFT/B3LYP level, as implemented in Gaussian 03, using a number of basis sets of different composition (see later for a description).

Owing to the rigid calix[4]arene structure and the fixed propyloxy tails, only four conformations were detected by MMFF94/Monte Carlo search, which differ mainly for the different orientation of the three OH groups of the phloroglucinol moiety. The ring of the latter was found almost perpendicular to the linked calixarene aryl ring.[14]

The orientation of the OH group at the para position of this ring is of very low importance, conversely the two OH groups at the meta positions show a markedly preferred orientation pointing toward the center of the linked calixarene aryl ring, most likely due to OH−π interactions.[18] Considering the noninfluential orientation of the phloroglucinol OH group in the para position and discharging all MMFF94 conformations with a relative energy exceeding 3.5 kcal/mol, that is with vanishing populations, only one conformation remains (very similar to conformer **a** in Figure 3) in which the OH group at the lower rim establishes a single H-bond with the OPr group on the left. Any attempt to reorient the H-bond at the lower rim toward the other OPr group on the right was unsuccessful after MMFF94 energy minimization. We interpreted this as a failure of the MMFF94 force field, and we decided to perform a B3LYP/6-31G* geometry optimization of both structures with the H-bond directed either on the left or on the right, using the starting geometry of the lowest energy MMFF94 conformer. We end up with the two conformations **a** and **b** shown in Figure 3. The B3LYP/6-31G* relative energy of **b** with respect to **a** was 1.12 kcal/mol, corresponding to a mixture of 87% of **a** and 13% of **b** of Boltzmann populations at 298 K.[14]

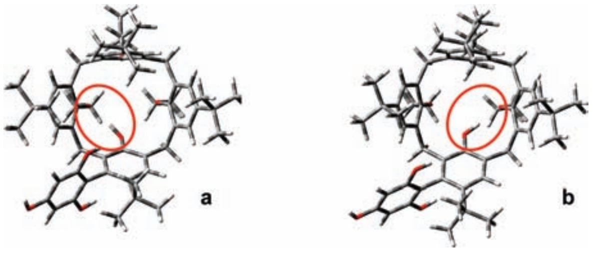

Figure 3. Top view of conformers **a** and **b** of *cS*-**3** optimized at the B3LYP/6-31G* level, showing the different orientation of the H-bond at the lower rim.

The specific rotation of the optical isomer contained in the first-eluted HPLC fraction (+)-**3** was measured for a number of wavelengths at room temperature (*c* 0.16, CH_2Cl_2) to obtain a portion of its optical rotation dispersion (ORD) curve (see Figure 4, black line). The OR's of conformers **a** and **b** of *cS*-**3** were computed using the TDDFT/B3LYP method.[19] Solvent was not included.

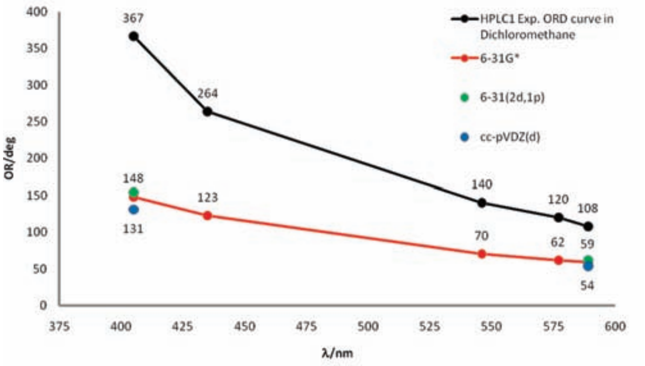

Figure 4. Portion of the ORD curve experimentally measured for (+)-**3** (black line) (*c* 0.16, CH_2Cl_2, 298 K) and theoretically calculated for *cS*-**3** at the TDDFT/B3LYP level using 6-31G* (red), 6-31G(2d,1p) (green), and cc-pVDZ(d) (blue).

The choice of the basis set(s) was based on the following arguments. It is generally agreed that diffuse functions are necessary for the calculation of chiroptical properties.[20] However, according to some preliminary tests,[14] diffuse functions have to be included on a well balanced basis set. In the present case, this implies a rather big basis set requiring prohibitively large computational resources. On the other hand, the inclusion of polarization functions improves the description of excited states at higher energy, which could be important for the OR predictions. Therefore, considering the large size of **3**, we decided to adopt the 6-31G* basis set to compute the OR for all the wavelengths considered in the experimental measure and two larger basis sets containing polarization functions, i.e., 6-31G(2d,1p) and cc-pVDZ(d)[21] to compute the OR at 589.3 and 405 nm. The predicted ORD obtained as weighted sum over the conformations is compared with the experimental data in Figure 4. As can be observed the agreement, in terms of OR sign and ORD trend, is fairly good with all the three basis sets and in particular with the smaller 6-31G* one.

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(12) Troisi, F.; Pierro, T.; Gaeta, C.; Neri, P. *Org. Lett.* **2009**, *11*, 697.

(13) Troisi, F.; Pierro, T.; Gaeta, C.; Carratù, M.; Neri, P. *Tetrahedron Lett.* **2009**, *50*, 4416.

(14) See the Supporting Information for further details.

(15) Dalla Cort, A.; Mandolini, L.; Pasquini, C.; Schiaffino, L. *New J. Chem.* **2004**, *28*, 1198.

(16) *Spartan 02*; Wavefunction, Inc., Irvine, CA.

(17) Frisch et al. *Gaussian 03*, Gaussian, Inc., Pittsburgh, PA, 2003.

(18) Atwood, J. L.; Hamada, F.; Robinson, K. D.; Orr, G. W.; Vincent, R. L. *Nature* **1991**, *349*, 683.

(19) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. *J. Phys. Chem. A* **2001**, *105*, 5356.

(20) Autcshbach, J. *Chirality* **2009**, *21*, E116.

(21) The cc-PVDZ(d) basis set has been obtained from the smaller cc-PVDZ basis set by adding a single set of d functions to heavy atoms. The exponents of these diffuse functions are those of the most diffuse d functions of the standard aug-cc-PVDZ basis set.

The ECD spectra of conformers **a** and **b** of *cS*-**3** were computed using the TDDFT/B3LYP method, adopting a number of different basis sets, i.e., 6-31G*, 6-31G(2d,1p), cc-pVDZ, and cc-pVDZ(d), using the first 50 rotational strengths.[14] Also in this case the solvent was not included. The weighted sum of the two conformers is compared with the experimental ECD spectrum of the first-eluted HPLC fraction in Figure 5.

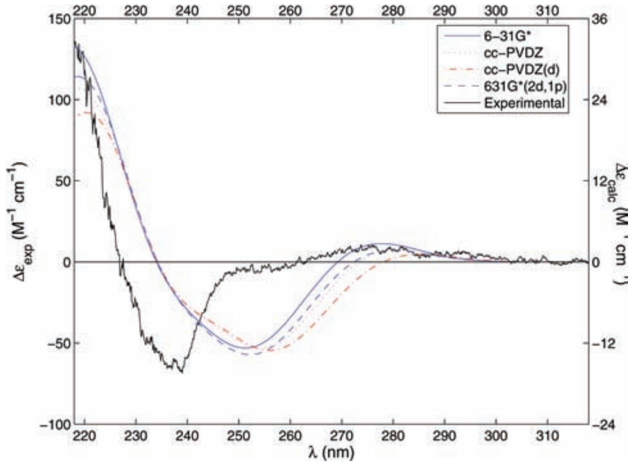

Figure 5. Comparison of the experimental (black) and TDDFT/B3LYP predicted ECD spectra.

Although the computed molar circular dichroism ($\Delta\varepsilon$) is significantly underestimated, the agreement between theoretical and experimental ECD spectra, in terms of form and sign of the bands with respect to wavelengths, can be considered satisfactorily. Remarkably, the 6-31G* simulation is very similar to those obtained with the much more expensive 6-31G(2d,1p) and cc-pVDZ(d) basis sets. Deviations in $\Delta\varepsilon$ can be mainly attributed to the lack of diffuse functions and solvent effect.

In summary, we remark that (i) the OR magnitude at 589.3 nm is large enough to be considered for a reliable ab initio assignment,[22] (ii) the trend of the theoretical ORD curves match the experimental one,[9] and (iii) the sequence of bands in the ECD spectrum, even if not to scale, is well reproduced. Recalling that the application of more than one chiroptical spectroscopic method is recommended to obtain reliable molecular structural information,[23] we feel confident to conclude that the absolute configuration of (+)-**3** is *cS*-**3**.

To provide additional support of the validity of the above conclusion, we decided to perform an additional test of our method on an inherently chiral calixarene with known absolute configuration. The case reported by Xu et al.[8b] appeared to be appropriate for our purposes. In particular, we focused our attention on compound **4a** of that reference, which is a *m*-Br-substituted inherently chiral calix[4]arene, whose absolute configuration was determined by a single-crystal X-ray diffraction study as *cS*.[8b] A $[\alpha]^{25}_{D}$ of −15.9 and the ECD spectrum have been also reported.[8b] Considering its unreliable low value, we neglected OR calculations.[22] We then focused on the ECD and started our analysis, adopting the *cS* configuration of **4a** and performing the calculation as in the case of **3**. Fixing the propyloxy tails, the procedure provided one conformer corresponding to the X-ray structure reported by Xu et al.[8b] A second conformer, which could be described as the opposite pinched-cone, with a higher relative energy of 2.02 kcal/mol, was also taken into account. The weighted TDDFT/B3LYP ECD spectra calculated using 6-31G* and cc-pVDZ basis sets are reported in Figure 6.

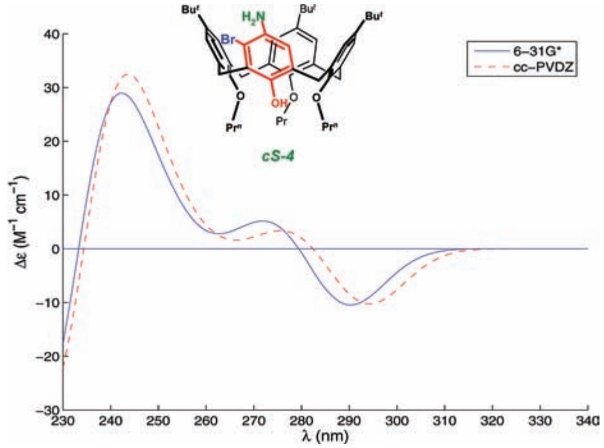

Figure 6. TDDFT/B3LYP ECD spectra of compound **4a**.[8b]

Although the molar circular dichroism ($\Delta\varepsilon$) is not directly comparable with the mdeg of ellipticity used in Figure 2 of ref 8b, the agreement with the experimental spectrum (form and sign of the bands with respect to wavelengths) is reasonably good. On this basis, the DFT-predicted absolute configuration is the same as that experimentally determined by X-ray diffractometry. This result provides further support for the validity of our approach.

In conclusion, the absolute configuration of the two enantiomers of inherently chiral, meta-substituted calix[4]arene **3**, resolved via enantioselective HPLC, has been determined using DFT calculations of chiroptical properties measured in solution. Considering the current reasonable computational limits, this approach can be easily extended to other inherently chiral calixarene derivatives, providing a practicable method to assign their absolute configuration.

Acknowledgment. We are grateful for financial support from the Italian MIUR. We also thank Dr. Amedeo Capobianco for useful discussions.

Supporting Information Available: Details of HPLC enantioresolution, Cartesian coordinates of conformers (*cS*)-**3a** and (*cS*)-**3b**, table of optical rotations, and details of DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Usually, ab initio assignments are considered to be reliable if the OR magnitude is higher than 28.9: Stephens, P. J.; McCann, D. M.; Cheeseman, J. R.; Frisch, M. J. *Chirality* **2005**, *17*, S52.

(23) Polavarapu, P. L. *Chirality* **2008**, *20*, 664.