JOC Article

Absolute Configuration of Natural Cyclohexene Oxides by Time Dependent Density Functional Theory Calculation of the Optical Rotation: The Absolute Configuration of (−)-Sphaeropsidone and (−)-Episphaeropsidone Revised

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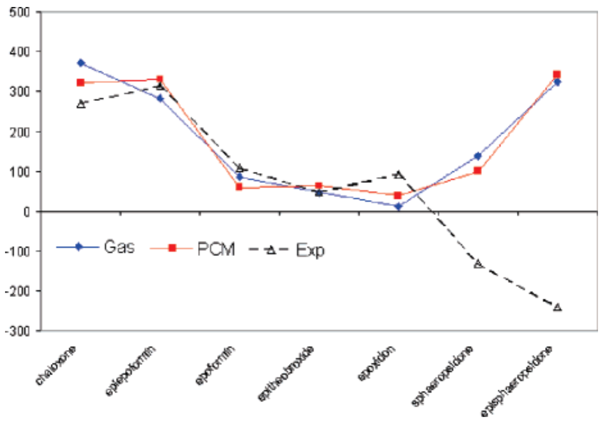

The optical rotatory power of some natural cyclohexene oxides, such as (+)-chaloxone, **1**, (+)-epiepoformine, **2**, (+)-epoformine, **3**, (+)-epoxidone, **5**, (−)-sphaeropsidone, **6**, (−)-episphaeropsidone, **7**, and the synthetic compound (+)-epitheobroxide, **4**, has been calculated by means of the TDDFT/B3LYP method using the 6-31G(d) and aug-cc-pVDZ basis sets, both in the gas phase and in solution by means of the polarizable continuum model. For compounds **1** and **2**, which possess high (about 300 units) optical rotations, gas-phase calculations with the smaller basis set are able to reproduce the experimental values both in sign and order of magnitude. By contrast, a larger basis set is required to satisfactorily simulate the OR values of **3** and **4**, which show smaller (about 100 units or less) rotations. The inclusion of the solvent effects is different for different compounds; for **1** and **2**, it leads to a better agreement between experiment and prediction, while for **3** and **4**, the presence of hydrogen bonding groups makes the application of continuum solvation models less satisfactory. For the flexible system **5**, the absolute configuration could not be determined using gas-phase calculations and the smaller basis set, but both inclusion of solvent and larger basis set effects are compulsory. It is noteworthy that calculations both in the gas phase and in the solvent lead to a positive rotatory power for the laevorotatory natural compounds **6** and **7** if the ACs reported in the literature are employed to do the theoretical prediction. This strongly indicates that the ACs previously assigned to these compounds in the literature are not correct and that the TDDFT prediction of OR values has become by now a practicable tool for AC assignments.

Introduction

The past few years have witnessed an increasing interest for the quantum-mechanical calculation of the optical rotatory power at the sodium D line,[1-4] $[\alpha]_D$, that is, the most common experimental parameter to label an optically active compound. The reason for such an interest is clear: these calculations could provide a practical solution to one of the most important problems of the structural organic chemistry, a reliable (and

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(1) The general theory of the optical rotatory power is given by: (a) Rosenfeld, L. Z. *Phys.* **1928**, *52*, 161−174. (b) Condon, E. U. *Rev. Mod. Phys.* **1937**, *9*, 432−457. (c) Buckingham, A. D. *Adv. Chem. Phys.* **1967**, *12*, 107−142.

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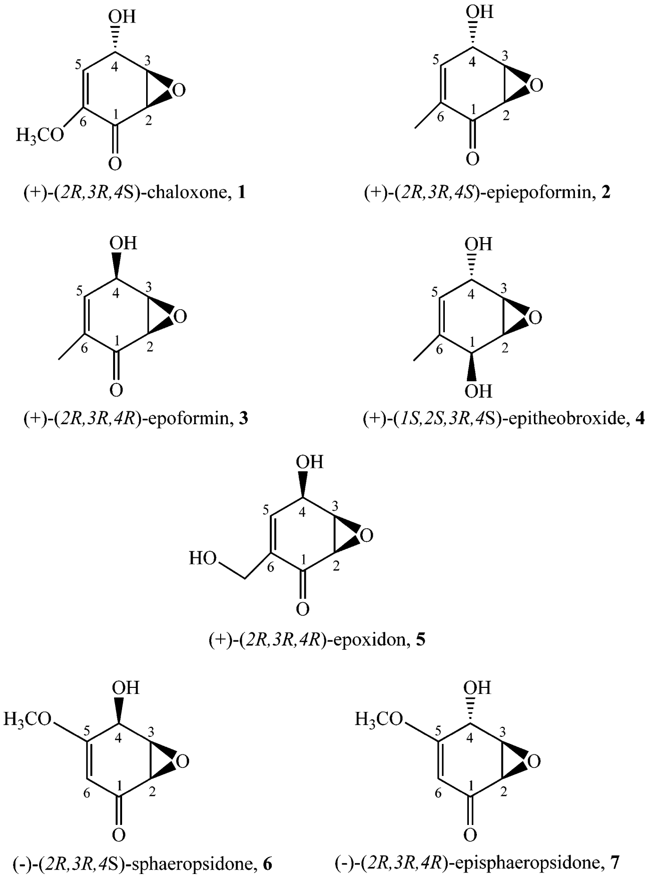
possibly easy) determination of the molecular absolute configuration. The determination of absolute configuration from a comparison of experimental data and theoretical predictions requires that the simulated values are fully reliable in sign and order of magnitude. Since the seminal papers,[2] where the very first OR calculations using the Hartree−Fock/small basis set approach were carried out, many studies have been done at different levels of theory to set up methods which couple reliability and accuracy to a reasonable computational effort (see ref 3 for recent reviews). From this point of view, the impressive and rigorous investigations of Stephens and co-workers[4] have demonstrated that TDDFT calculations with the B3LYP hybrid functional and extended basis sets (i.e., aug-cc-pVDZ or higher) give completely reliable results (with an acceptable computational effort) in reproducing experimental optical rotation of at least 100 deg [dm g/cm^3]$^{-1}$. However, considering that the computational complexity of the available methods rapidly increases with the dimension of the system, it is easy to see that a theoretical analysis of the chiroptical properties of large molecules such as some natural products, for instance, can become impossible using the common desktop computers. In addition, the computer time is not the only important parameter to be taken into account; at least in some instances, the memory requirement could be so high, even for a medium size organic molecule adopting a large basis set, to make the calculation not feasible at all. The only possible alternative when one wants to treat big systems and possesses only a desktop computer is using small basis sets (e.g., 6-31G(d)). For a few years, we have been engaged[5] in a research project aimed at showing that, at least under certain circumstances, small basis set calculations of chiroptical properties provide reliable results. With this paper, we intend to further verify the reliability of this computational approach in the determination of the absolute configuration. To this end, we studied the series of compounds reported in Chart 1. They belong to a family of highly oxygenated cyclohexane-based metabolites, mainly epoxides, that have been isolated from bacteria, fungi, higher plants, and molluscs. These compounds possess a variety of biological activities (which range from antifungal, antibacterial, antitumor, phytotoxic, and enzyme inhibition[6−13]), and for this reason, they have been the subject of several structural and synthetic studies.[10−13] So a study aimed at calculating their optical rotatory power to reliably assign the

CHART 1



(+)-(2*R*,3*R*,4*S*)-chaloxone, **1**

(+)-(2*R*,3*R*,4*S*)-epiepoformin, **2**

(+)-(2*R*,3*R*,4*R*)-epoformin, **3**

(+)-(1*S*,2*S*,3*R*,4*S*)-epitheobroxide, **4**

(+)-(2*R*,3*R*,4*R*)-epoxidon, **5**

(-)-(2*R*,3*R*,4*S*)-sphaeropsidone, **6**

(-)-(2*R*,3*R*,4*R*)-episphaeropsidone, **7**

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absolute configuration is certainly of interest. In addition, such compounds are the ideal candidates to further test the simplified protocol we have proposed for the quantum-mechanical calculation of the optical rotatory power. The absolute configuration of molecules **1**−**5** has been firmly established (vide infra) so they can work very well as test-case studies. Moreover, all of them present (with the only exception of **4**) quite high values of optical rotation; following the already cited analysis performed by Stephens,[4] this fact should guarantee a reliable reproduction of the experimental $[\alpha]_D$ values, at least with a B3LYP/aug-cc-pVDZ calculation. All of the compounds also possess an α,β-unsaturated ketone chromophore, that is, a chromophore with intense Cotton effects in the vis−UV region due to valence shell transitions;[14] it is thus reasonable to assume that the optical rotations at the sodium D line are dominated by these low-energy Cotton effects, so our simplified treatment[5] should be applied to **1**−**5**. However, in this paper, we will treat **1**−**5** with the small basis set approach and, thanks to their small size, we will also perform more sophisticated calculations, and thus we will able to compare the results obtained with the two approaches: a substantial equivalence of the results will constitute another probe of the correctness of the simplified treatment. Considering that all of the above molecules contain hydroxyl groups and the experimental $[\alpha]_D$ values have been measured in hydroxylated polar solvents as methanol and ethanol, the effects of the environment on the optical rotation could be relevant, and as a consequence, an analysis based on values calculated in the gas phase could be not correct, rendering the configurational assignment ambiguous. So another important issue of this paper will be a study of the solvent effects on both the geometry and the optical rotation. Such effects will be accounted for using a continuum solvation model, namely, the integral equation formalism version of the polarizable continuum model (IEFPCM).[15] In this framework, the solvent is represented as a polarizable continuum dielectric and the solute is assumed to be embedded in a molecular cavity of proper shape and dimension within such a dielectric. By introducing an apparent surface charge distribution on the cavity surface representing the response of the solvent to the presence of the solute, it will be possible to quantify solvent-induced changes both in the solute geometry and its optical rotatory power.[4e] In conclusion, this paper will be organized as follows: (i) Compounds **1**−**5**, which have safe absolute configuration will be first analyzed. Their optical rotation will be calculated in the gas phase, by the small and extended basis set approach. The calculations will be repeated in the presence of the solvent to study the role played by the environment. (ii) Once evaluated, the importance of all of the issues quoted above, molecules **6** and **7**, the configuration of which cannot be considered safe (vide infra), will be considered to verify the assignment reported in the literature.

Results and Discussion

The calculations in this investigation have been carried out following the protocol described below. The structures to be used as starting geometries in the QM optimizations have been created by means of a conformational analysis with the SPARTAN02 software,[16] using the methods of molecular mechanics (MMFF94s force field) and retaining only the structures differing by 2 kcal/mol in energy or less. All of the resulting geometries have been fully optimized at the DFT/B3LYP/6-31G(d) level both in gas phase and in the selected solvent; for selected molecules, B3LYP/aug-cc-pVDZ optimizations have been also done as benchmarks. In all cases, the free energy values at $T = 298$ K have been employed to calculate the population of each conformer, using the Boltzmann statistics. The calculations of the optical rotatory power have been carried out at the TDDFT/B3LYP/6-31G(d) or aug-cc-pVDZ level both in gas phase and in solution. The theoretical values of optical rotation (to be compared with the experimental ones) have been obtained as weighted averages on the Boltzmann populations calculated in the gas phase or in the selected solvent. Rotational strength calculations have been carried out at the TDDFT/B3LYP/6-31G(d) and TDDFT/B3LYP/aug-cc-pVDZ levels in the gas phase both in velocity and in length formalism for the first 30 states. The simulated ECD spectra have been obtained using overlapping Gaussian functions with a width, $\sigma = 0.15$ eV, according to ref 5e. All of the calculations for solvated systems have been obtained using the IEFPCM with molecular cavities built in terms of interlocking spheres centered on all the atoms constituting the solute ($R_C = 2.04$ Å, $R_O = 1.824$ Å, $R_H = 1.44$ Å). Only in the case of CH_3, CH_2, and CH groups we have used a single sphere centered on the carbon atom (with radii equal to 2.4 Å for CH_3 and 2.28 Å for CH_2 and CH).

All of the QM calculations have been carried out using the Gaussian03 package,[17] and the results obtained are reported in the following sections, one for each compound.

(+)-Chaloxone, 1. This compound has been first isolated from the fungus *Chalara microspora* and its absolute configuration assigned[18] by comparing the sign of the 330 nm Cotton effect with that of the same band in other, structurally related compounds having known configuration. It shows an optical rotation value of +271 in ethanol. Following the protocol described at the beginning of this section, five stable conformers have been found in the gas phase: the structure, relative free energies, and populations are reported in Figure 1.

The energy (and the structure) of these different conformers depends on the relative disposition of the −OMe and −OH groups. In the most populated conformer (67%), the hydrogen atoms of the −OH group and that linked to C(4) are in anti relationship, and the methyl group of −OMe is directed toward the vinyl hydrogen; this should reduce possible steric interactions. A change in the orientation of the methoxy group produces a significant reduction of the population: when the methyl group

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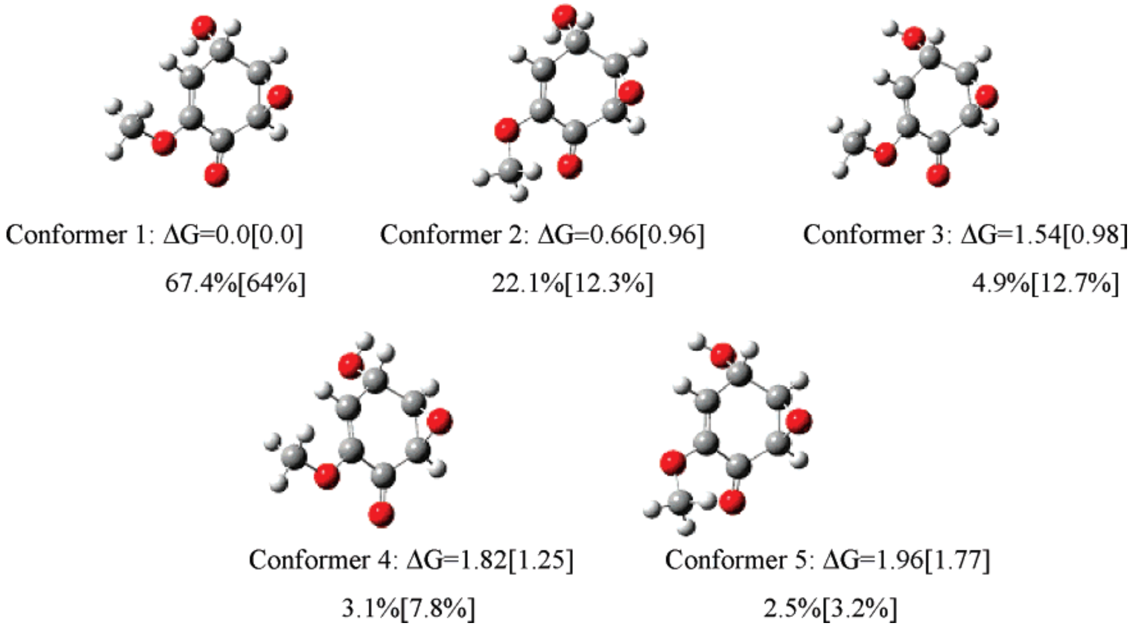

Conformer 1: ΔG=0.0[0.0] 67.4%[64%]

Conformer 2: ΔG=0.66[0.96] 22.1%[12.3%]

Conformer 3: ΔG=1.54[0.98] 4.9%[12.7%]

Conformer 4: ΔG=1.82[1.25] 3.1%[7.8%]

Conformer 5: ΔG=1.96[1.77] 2.5%[3.2%]

FIGURE 1. B3LYP/6-31G(d) structures, relative free energies (kcal/mol), and populations of the most stable conformers of (2*R*,3*R*,4*S*)-chaloxone in the gas phase. Values in brackets refer to B3LYP/aug-cc-pVDZ calculations.

TABLE 1. Values of $[\alpha]_D$ for Each Conformer of (2*R*,3*R*,4*S*)-Chaloxone in the Gas Phase and the Corresponding Averaged Values Obtained Using the Boltzmann Populations Reported in Figure 1[a]

conformer	6-31G(d)//6-31G(d)	aug-cc-pVDZ//6-31G(d)	aug-cc-pVDZ//aug-cc-pVDZ
1	+264	+243	+251
2	+722	+759	+750
3	+324	+305	+309
4	+187	+198	+201
5	+741	+797	+785
<average>	+378	+372	+333

[a] All values are in deg [dm g/cm^3]$^{-1}$ (X//Y means that the X level of calculation has been used for [α] using the geometries and populations obtained at the Y level).

TABLE 2. B3LYP/6-31G(d) Relative Free Energies with Respect to the Most Stable Conformer (kcal/mol) and Corresponding Populations and $[\alpha]_D$ for (2*R*,3*R*,4*S*)-Chaloxone in Methanol[a]

conformer	Δ*G*	% pop	$[\alpha]_D$/6-31G(d)	$[\alpha]_D$/aug-cc-pVDZ
1	0.0	70.0	+304 (+15)	+308 (+27)
2	2.40	1.2	+690 (−4)	+707 (−7)
3	0.87	16.0	+398 (+23)	+385 (+26)
4	1.02	12.4	+246 (+31)	+268 (+41)
5	3.12	0.4	+756 (+2)	+769 (−4)
<average>	–	–	+318	+322

[a] The $[\alpha]_D$ values (deg [dm g/cm^3]$^{-1}$) are obtained at TDDFT/B3LYP/6-31G(d) and aug-cc-pVDZ levels (in parenthesis, the percent variations with respect to gas-phase values are reported).

is close to the carbonyl moiety, the population reduces to only 22% at B3LYP/6-31G(d) and to 12% with the larger basis set. It is also interesting to note that the disposition of the H−O−C(4)−H moiety is quite important, as it can be easily appreciated comparing the populations of conformers 1 and 3. We can now calculate the optical rotation; in Table 1, we report the OR calculated at the TDDFT/B3LYP/6-31G(d) and aug-cc-pVDZ levels for each conformer and the corresponding values weighted on the Boltzmann populations reported in Figure 1.

As it can be seen from the table, the total averaged value obtained at the 6-31G(d) level (+378) reproduces both the sign and the order of magnitude of the experimental value (+271 in methanol) even if the quantitative agreement is not good (the theoretical figure is by far larger, 100 units, than the experimental value). In the same table, the results obtained with the larger basis set are also reported. These lead to total averaged values of +372 using the 6-31G(d) geometry/populations and +333 using the aug-cc-pVDZ geometry/populations, showing that, for this system, the effect of the quality of the basis set is not important both on the values of the property and on the average. We can then conclude that, even if numerically speaking the agreement is not so good, for chaloxone the calculations confirm the literature assignment, namely, (+)/(2*R*,3*R*,4*S*). This conclusion is confirmed by the fact that each conformer is dextrorotatory so any possible inaccuracy in evaluating the population of each conformer does not affect the sign of the total rotation. In order to definitely check the reliability of these results with respect to the experiments, we have repeated the conformational analysis and the calculation of OR including the solvent effects through the IEFPCM approach briefly described in the Introduction. In Table 2, we report the results obtained for the same five conformers shown in Table 1 (due to the low sensitivity of the gas-phase populations on the basis set, only B3LYP/6-31G(d) geometries/populations have been used).

By comparing the results of Tables 1 and 2, we can see that the presence of the solvent induces significant changes in the relative stability of the conformers. In particular, conformer 2 is largely destabilized with respect to the gas phase in favor of conformers 3 and 4. This result can be explained looking at the differences among the conformers' electronic distributions: using the simplified but effective description represented by the dipole moments, we see that conformer 2 presents the smallest dipole moment (about 1.3 Debye), while conformers 3 and 4 present the largest ones (6.5 and 6.0 Debye, respectively). These values correlate well with the solvent-induced changes in the Boltzmann populations. By contrast, conformer 1 remains the most populated one exactly as in gas phase even if its dipole

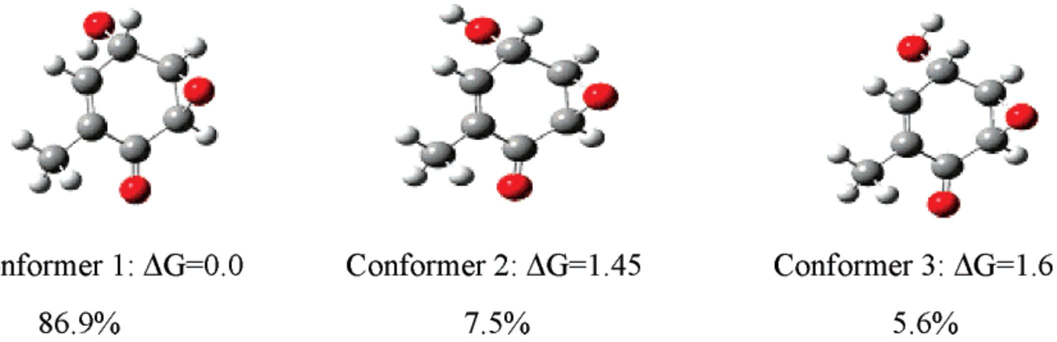

FIGURE 2. B3LYP/6-31G(d) relative free energies (kcal/mol) and populations of the three most stable conformers of (2*R*,3*R*,4*S*)-epiepoformin in the gas phase.

moment (3.9 Debye) is significantly smaller than those of conformers 3 and 4. This clearly shows that the minimization of the steric interactions in this conformer remains the leading force even in polar solvents. Analyzing the effects of the solvent on the optical rotatory power, we note that the largest percent variations with respect to gas-phase values are on the most polar conformers 3 and 4 and on the most stable conformer 1. These solvent effects on the relative stabilities of the various conformers together with the parallel effects on the optical rotation of each conformer finally lead to averaged values of +318 and +322 using the smaller or the larger basis set, respectively, or, in other words, to a 16 and 13% diminution of the OR with respect to gas-phase calculations toward a better agreement with the experiment.

TABLE 3. Values of $[\alpha]_D$ Obtained at TDDFT/B3LYP/6-31G(d) and aug-cc-pVDZ Levels for Each Conformer of (2*R*,3*R*,4*S*)-Epiepoformin in the Gas Phase and the Corresponding Averaged Values Obtained Using the Boltzmann Populations Reported in Figure 2 (values are in deg [dm g/cm^3]$^{-1}$)

conformer	6-31G(d)	aug-cc-pVDZ
1	+293	+282
2	+354	+349
3	+189	+211
<average>	+292	+283

TABLE 4. B3LYP/6-31G(d) Relative Free Energies with Respect to the Most Stable Conformer (kcal/mol) and Corresponding Populations and $[\alpha]_D$ for (2*R*,3*R*,4*S*)-Epiepoformin in Ethanol[a]

conformer	Δ*G*	% pop	$[\alpha]_D$/6-31G(d)	$[\alpha]_D$/aug-cc-pVDZ
1	0.00	62.3	+326 (+11)	+331 (+18)
2	0.78	16.8	+413 (17)	+103 (16)
3	0.65	20.9	+232 (+23)	+269 (+28)
<average>	−	−	+321	+330

[a] The $[\alpha]_D$ values (deg [dm g/cm^3]$^{-1}$) are obtained at TDDFT/B3LYP/6-31G(d) and aug-cc-pVDZ levels (in parenthesis, the percent variations with respect to gas-phase values are reported).

(+)-Epiepoformine, 2. (+)-Epiepoformin, **2**, was purified by Nagasawa and co-workers in 1978[8] from the culture filtrate of an unidentified fungus isolated from a diseased leaf and showed marked inhibition activity against the germination of lettuce seeds, and it has been the subject of several synthetic attempts.[11,19] It shows an optical rotation value of +315 in ethanol.[19c,d] Following the protocol described at the beginning of this section, three stable conformers have been found in the gas phase: the structure, relative free energies, and populations are reported in Figure 2 (from now, if not explicitly said, only B3LYP/6-31G(d) geometries/populations will be considered).

In conformer 1, the hydrogen atom of the −OH group is in anti relationship with the hydrogen atom linked to C(4). In conformers 2 and 3, the same hydrogen atoms are in a similar gauche situation; therefore, they possess similar structure and energy. The calculation of the OR with the DFT/B3LYP method and the 6-31G(d) or aug-cc-pVDZ basis set level affords the results collected in Table 3.

The final averaged value obtained using the 6-31G(d) basis set is in very good agreement with the experimental one, +315. This agreement confirms the literature assignment for (+)-epiepoformin: (+)/(2*R*,3*R*,4*S*). The calculations repeated using the higher quality aug-cc-pVDZ basis set lead to very similar results (+283). As in the case of (+)-chaloxone, also for epiepoformin, the effect of the quality of the basis set on the calculated OR of each conformer (and the final one) is negligible. A last comment, here, as for (+)-chaloxone, all of the conformers are dextrorotatory, which guarantees an average value which is dextrorotatory. As done before for chaloxone, also for epiepoformine, we have repeated the conformational and the OR analysis by including IEFPCM solvent effects. The results obtained are reported in Table 4.

By looking first at the solvent-induced changes on the Boltzmann populations, we observe a net increase for both conformers 2 and 3. Once again, these changes correlate well with the dipole moments (5.2 and 4.9 Debye with respect to 2.7 Debye of conformer 1). Regarding the solvent effect on the OR, for all conformers, we observe an increase ranging from 11 to 28%. This increase is reflected in the final average values of +321 and +330 with the smaller and the larger basis sets, respectively. These values if compared with the parallel ones calculated for the isolated compounds show once more that the inclusion of solvent effect, even if not large (around 10 and 17%, respectively), does not change the qualitative analysis (confirming the dextrorotatory character), but it increases the quantitative agreement with experiment. A further confirmation of the reliability of this assignment has been obtained by the analysis of the effects of OH rotation. We have performed a relaxed scan of the OH rotation (starting from conformer 1 and using a 20 step in the dihedral angle), and for each value of the angle, we have calculated the OR (using the 6-31G(d) basis set); the results obtained (reported in Figure 1 of the Supporting Information) show that such a rotation does not change the sign of $[\alpha]_D$, which remains positive for all angles, and it does not

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(19) (a) Tachihara, T.; Kitahara, T. *Tetrahedron* **2003**, *59*, 1773−1780. (b) Okamura, H.; Shimizu, H.; Yamashita, N.; Iwagawa.; T.; Nakatani, M. *Tetrahedron* **2003**, *59*, 10159−10164. (c) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Chem.—Eur. J.* **2000**, *6*, 3991−3996. (d) Carreno, M. C.; Merino, E.; Ribagorda, M.; Somoza, A.; Urbano, A. *Org. Lett.* **2005**, *7*, 1419−1422.

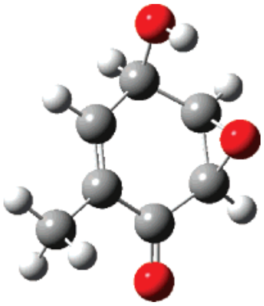

FIGURE 3. Structure of the most stable conformer of (2*R*,3*R*,4*R*)-epoformine in the gas phase.

affect the value (+321) obtained by considering the three minima only.

(+)-Epoformine, 3. This compound is a natural product isolated from the culture broth of *Penicillum claviforme*, which possesses antibiotic and cytotoxic properties (see ref 20). Its absolute configuration has been established by chemical synthesis[20] and therefore its $[\alpha]_D$ value is +109 in ethanol.[20] For this compound, only one conformer has been found in the gas phase (Figure 3).

(2*R*,3*R*,4*R*)-Epoformine presents only one conformer because in this structure it is possible to have the H−C(4)−O−H fragment in an anti relationship, which, as we noted above, represents a particularly favorable disposition and, at the same time, to have an intramolecular hydrogen bond between the OH on C(4) and the oxygen atom of the epoxide moiety. Using this structure, the OR calculation (TDDFT/B3LYP/6-31G(d) level) gives +50, that is, a value which corresponds in sign and order of magnitude to the experimental $[\alpha]_D$. This result can be assumed as a further confirmation of the configurational assignment (i.e., (+)/(2*R*,3*R*,4*R*)), even if the numerical agreement with experiments is not particularly satisfactory. The use the extended basis set (aug-cc-pVDZ) gives an OR of +86, a value which is in very good agreement with the experiment. We can thus conclude the analysis saying that if the experimental OR is not at least of the order of 100 units the use of an extended basis set is imperative, as indicated by Stephens and co-workers.[4] In order to improve the quality of the computational results with experimental data, another aspect to analyze, besides the basis set, is the presence of the solvent. In the previous analyses on chaloxone and epiepoformine, we have found that including solvent effects through the IEFPCM approach does not change the qualitative analysis obtained for the isolated systems but it leads to a better quantitative agreement with experiment. By repeating the same strategy also for epoformine, we observe that the value of $[\alpha]_D$ is reduced to +38 and +60 using the small or the extended basis set, respectively. These values are obtained considering only one stable conformer (the same found for the isolated system). In this case, the IEFPCM results lead to a worse agreement with the experiment (+109). To try to explain such a deviation, we can consider the nature of the conformer characterized by an intramolecular hydrogen bond between the −OH on C(4) and the oxygen atom of the epoxide moiety. The presence of a polar and protic solvent such as ethanol in fact can significantly affect such an intramolecular interaction in favor of an intermolecular one. An indirect evidence of this possible effect can be obtained by considering a relaxed scan of the OH rotation in the solvated system. The results obtained for the relative energy and the OR (both calculated using the 6-31G(d) basis set) are reported in Figure 2 of the Supporting Information. Here we only note that the OR values dramatically change not only in the magnitude but also in the sign by rotating the OH group. This is not unexpected as here, contrary to epiepoformine, there is a direct interaction of the OH with the epoxydic group. However, by repeating the average on the complete rotation, we obtain a final value of +45 which is quite close to that obtained considering only the most stable conformer (+38, at the same level of calculation). This analysis seems to show that, when in the presence of intramolecular H-bonds which could be largely affected by the presence of protic solvents, the description obtained using a continuum model cannot be complete, but specific solute−solvent effects should be explicitly included to get an accurate agreement with experiments.

(+)-Epitheobroxide, 4. This compound is not a natural product; it is an epimer of the natural (−)-theobroxide, which however presents a very small rotation, $[\alpha]_D$ −6 in ethanol.[13c] Of course, this fact makes our simplified approach to the calculation of the optical rotation impossible, so in order to have another case study, we shifted our interest toward **4**, and we named it (+)-epitheobroxide. This compound has been synthesized by Barros and co-workers and shows an OR value higher than that of (+)-theobroxide, $[\alpha]_D$ +48 in ethanol.[20] We found three possible conformers in the gas phase, and the structures, relative energies, and populations are reported in Figure 4.

Conformer 1 is the most stable because, in this structure, it is possible to have the hydrogen atom of the −OH group and that linked to C(4) in an anti relationship and, simultaneously, to form an intramolecular hydrogen bond between the −OH group on C(1) and the oxirane oxygen. Conformer 2 possesses higher energy because, even if the intramolecular hydrogen bond is maintained, the fragment H−O−C(4)−H is in a gauche relationship. The energy of conformer 3 is even higher because now the H−O−C(4)−H fragment is in an eclipsed relationship. Using the above described geometries, the OR calculation (TDDFT/B3LYP/6-31G(d) and aug-cc-pVDZ level) gives the results reported in Table 5.

The comparison of the final averaged value (+80 using the 6-31G(d) basis set) with the experimental one (+48) shows that calculations reproduce both sign and order of magnitude of $[\alpha]_D$, even if overestimating the experimental value. This result, however, can still be considered as convincing proof that, for **4**, holds the relationship (+)/(1*S*,2*R*,3*S*,4*R*). In fact, as in the case of (+)-chaloxone, each conformer is dextrorotatory and thus the average value will remain of the same sign even if there are errors in the populations of each conformer. More accurate calculations, using the aug-cc-pVDZ basis set, are reported in the same table. It is interesting to note that for this compound an important effect of the quality of the basis set is found: there is a significant reduction of the OR of the most populated conformers and thus a significant reduction of the final average value which now becomes +47, in excellent (and perhaps fortuitous!) agreement with the experiment. To check the reliability of this result, we have repeated the conformational and the OR analysis by including IEFPCM solvent effects. The results obtained are reported in Table 6.

By comparing the results reported in Tables 5 and 6, we note that the solvent-induced variations on $[\alpha]_D$ of the three conformers are larger than those observed for the previous compounds

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[20] Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 3233−3244.

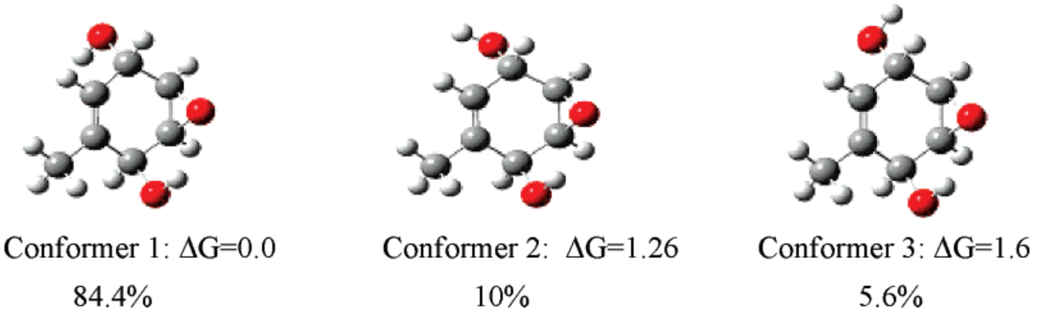

FIGURE 4. B3LYP/6-31G(d) relative free energies (kcal/mol) and populations of the most stable conformers of (1*S*,2*R*,3*S*,4*R*)-epitheobroxide in the gas phase.

TABLE 5. Values of $[\alpha]_D$ Obtained at TDDFT/B3LYP/6-31G(d) and aug-cc-pVDZ Levels for Each Conformer of (1*S*,2*R*,3*S*,4*R*)-Epitheobroxide in the Gas Phase and the Corresponding Averaged Values Obtained Using the Boltzmann Populations Reported in Figure 4 (values are in deg [dm g/cm^3]$^{-1}$)

conformer	6-31G(d)	aug-cc-pVDZ
1	+79	+44
2	+124	+100
3	+17	+4
<average>	+80	+47

TABLE 6. B3LYP/6-31G(d) Relative Free Energies with Respect to the Most Stable Conformer (kcal/mol) and the Corresponding Boltzmann Populations for (1*S*,2*R*,3*S*,4*R*)-Epitheobroxide in Ethanol[a]

conformer	Δ*G*	% pop	$[\alpha]_D$/6-31G(d)	$[\alpha]_D$/aug-cc-pVDZ
1	0.00	71.9	+91 (+15)	+60 (+36)
2	1.03	12.6	+160 (+29)	+132 (+32)
3	0.91	15.5	+34 (+100)	+33 (+719)
<average>	–	–	+91	+65

[a] The $[\alpha]_D$ values (deg [dm g/cm^3]$^{-1}$) obtained at TDDFT/B3LYP/6-31G(d) and aug-cc-pVDZ levels (in parenthesis, the percent variations with respect to the gas-phase values are reported).

(for conformer 3, we observe values that are 2 and 8 times larger). We note that these effects are mainly due to solvent-induced geometry changes, in fact by recomputing $[\alpha]_D$ in the gas phase, but using the geometries optimized in solution, we obtain +91, +152, and +23 (using the small basis set) for conformers 1, 2, and 3, respectively, which are very close to the values reported in Table 6. When we pass from the single conformers to averaged values, the OR in solution becomes +91 and +65 using the small and extended basis set, respectively. These values, when compared with the corresponding ones for the isolated system, give a final +14 and +38% increase, but they do not change the configurational assignment. We note that this compound, exactly as (2*R*,3*R*,4*R*)-epoformine, presents an intramolecular H-bond which could be significantly perturbed by the presence of a protic solvent such as ethanol. As commented before, this specific solute–solvent interaction cannot be completely taken into account by a continuum model, and thus it is not unexpected that IEFPCM calculations do not improve the agreement with experiments.

(+)-Epoxidone, 5. (+)-Epoxydon was first isolated by Closse and co-workers in 1966[21] as a compound showing antimitotic activity. Its absolute configuration was assigned by the same authors by means of an empirical analysis of the CD spectrum and later confirmed by synthesis.[22] It shows $[\alpha]_D$ +93 in methanol. Our protocol for conformational analysis provides five stable conformers in the gas phase: the structure, relative energies, and populations are reported in Figure 5.

In all of the conformers, an intramolecular hydrogen bonding between the –OH group at C(4) and the oxirane O atom is present. However, in the two most stable structures, it is accompanied by another intramolecular hydrogen bonding between the $-CH_2OH$ moiety and the carbonyl group. This second stabilizing interaction is completely lacking in conformers 3, 4, and 5, which are much less populated. We can now calculate the optical rotation. In Table 7, we report the values of OR obtained (at TDDFT/B3LYP/6-31G(d) and aug-cc-pVDZ level) for each conformer and the OR values weighted on the Boltzmann populations. Due to the change of sign of $[\alpha]_D$ passing from one conformer to the other, for this compound, the effects of geometry and population can become quite important; we have thus preferred to check the validity of the B3LYP/6-31G(d) description with the larger basis set. The results are reported in Table 8 in brackets.

The data reported in Table 7 show that, for this compound, the most stable conformer is laevorotatory, while the remaining ones are dextrorotatory. The final averaged value (6-31G(d) basis set) is then −16, a number which represents only 20% of the experimental value and is opposite in sign to it. Clearly, one cannot draw conclusions about a configurational assignment in these conditions. The calculations have been then repeated at TDDFT/B3LYP/aug-cc-pVDZ levels, and the results are reported in the same table. The quality of the basis set has a significant effect not only on the properties but also on the geometries/populations. Keeping fixed the geometries of the conformers (and their populations), the OR of the most stable conformer, still negative, is slightly reduced and that of the other conformers is increased, so the final result (+11) is a positive rotation (as the experimental one), but it still represents a small fraction (12%) of the experimental value. By allowing geometry relaxation, we observe an increase of the OR in all conformers (less negative for conformer 1 and more positive for the others). This effect when combined with the new populations (see Figure 5) leads to an average value of +57, that is, in the direction of a better agreement with experiments both in sign and in magnitude.

The sensitivity of the (+)-epoxidone gas-phase calculations (Table 7) suggests that, in the case of a flexible molecule like the present one, neglecting the solvent effect is a too drastic approximation. To check this, we have repeated the analysis using IEFPCM. The results obtained both for the populations

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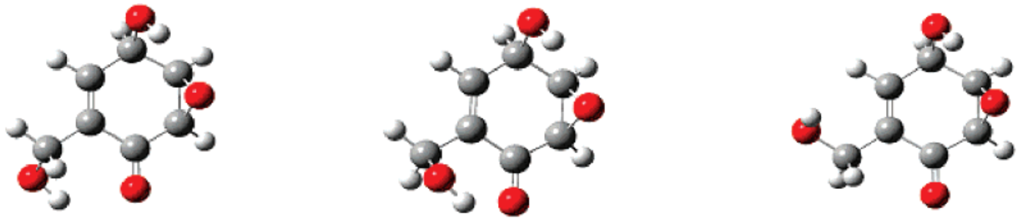
(21) Closse, A.; Mauli, R.; Sigg, H. P. *Helv. Chim. Acta* **1966**, *49*, 204–213.

(22) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2004**, *45*, 7683–7687.



Conformer 1: ΔG=0.0[0.0]
54.5%[40.6%]

Conformer 2: ΔG=0.67[0.42]
17.6%[20.1%]

Conformer 3: ΔG=0.96[0.81]
10.8%[10.3%]

Conformer 4 : ΔG= 1.03[0.93]
9.5%[8.5%]

Conformer 5: ΔG=1.17[0.40]
7.6%[20.6%]

FIGURE 5. B3LYP/6-31G(d) relative free energies (kcal/mol) and populations of the most stable conformers of (2*R*,3*R*,4*R*)-epoxydon in the gas phase. Values in brackets refer to B3LYP/aug-cc-pVDZ calculations.

TABLE 7. Values of [α]$_D$ for Each Conformer of (2*R*,3*R*,4R)-Epoxidon in the Gas Phase and the Corresponding Averaged Values Obtained Using the Boltzmann Populations Reported in Figure 5[a]

conformer	6-31G(d)// 6-31G(d)	aug-cc-pVDZ// 6-31G(d)	aug-cc-pVDZ// aug-cc-pVDZ
1	−97	−89	−43
2	+130	+219	+210
3	+14	+59	+63
4	+113	+107	+119
5	+29	+71	+86
<average>	−16	+11	+57

[a] Values are in deg [dm g/cm^3]$^{-1}$ (X//Y means that the X level of calculation has been used for [α] using the geometries and populations obtained at the Y level).

and the OR of the five conformers are reported in Table 8. As before, the geometries of all of the conformers have been reoptimized in solution.

As it can be seen, the final averaged values are significantly different from the corresponding ones obtained for the isolated system. Now positive [α]$_D$ values are obtained also using the small basis set, and with the larger basis set a better quantitative agreement with experiments is found. Such an improvement is determined by the combination of two effects, namely, the solvent effect on the relative stability of the various conformers (and thus on their weight in the average), and the solvent effect on the [α]$_D$ of each conformer. Let us first analyze the effect of the solvent on the relative stability of the conformers. Conformer 1 remains the most stable, but all of the others become closer to it. We note that only conformer 1 has a negative [α]$_D$, and thus the final positive average value can be correlated to the larger contribution of the other conformers. Indeed, this is the dominant effect as the percent variations of the [α]$_D$ values of all the conformers are negative; that is, the direct effect of the solvent on the OR, if not combined with a proper population analysis, would have led in the opposite direction, for example, to a worse agreement with experiments. As done before for other compounds, also here it is important to check the reliability of these results by analyzing the effects of possible internal rotations. Here are the two groups which should be analyzed, OH and CH_2OH. Assuming a similar behavior with the analogous system without the CH_2OH (i.e., epoformine), the effects of the (C4)OH rotation should not lead to any significant change in the average value. What is different here, however, is the possibility for the CH_2OH to rotate. In Figure 6, we report the results obtained for the relative energy and the OR (both calculated using the 6-31G(d) basis set) in a relaxed scan. We note that such a scan has been obtained starting from conformer 1 and using a 20 step in the dihedral angle (HO)CCC6C5.

As it can be seen from the graph, conformers 2 and 3 are at the minimum of quite flat wells, while the corresponding well for the most stable conformer 1 is steeper. This means that an average on a range of dihedral angles centered on the value corresponding to the minima is required. By doing this, we determine that the resulting OR becomes +14, but by considering only the values of the three minima, we get −8. By taking into account this variation in the total average (including also conformers 4 and 5), we get a final OR of +20. Due to the significant effects that the basis set has on the OR value of this compound, we have repeated the scan of [α]$_D$ using the large basis set, and we have obtained a final value of +73 (the results of the scan are reported in Figure 3 of the Supporting Information). This result when compared to the experimental value of +93 shows that anytime conformational changes lead to important variations in the absolute value and in the sign of [α]$_D$ it is compulsory to perform a detailed analysis of these effects combined with those due to the solvent.

The results of the calculations described above clearly demonstrate that, for this class of compounds, the theoretical prediction of [α]$_D$ can be a practical method for a reliable configurational assignment. So we decided to approach the problem of the configurational assignment of (−)-sphaeropsidone, **6**, and (−)-episphaeropsidone, **7**. As a preliminary comment, we note that their structural determination was

TABLE 8. **Relative Free Energies with Respect to the Most Stable Conformer (kcal/mol) and Corresponding Populations and $[\alpha]_D$ for (2*R*,3*R*,4*R*)-Epoxidon in Methanol**[a]

conformer	Δ*G*	% pop	6-31G(d)// 6-31G(d)	aug-cc-pVDZ// 6-31G(d)	aug-cc-pVDZ// aug-cc-pVDZ
1	0.00 [0.00]	31.1 [26.5]	−85 (−13)	−88 (−2)	−36 (−16)
2	0.37 [0.11]	16.5 [22.0]	+113 (−13)	+193 (−12)	+166 (−18)
3	0.23 [0.22]	21.1 [18.2]	+8 (−46)	+54 (−9)	+58 (−8)
4	0.22 [0.30]	21.4 [16.0]	+37 (−67)	+51 (−52)	+71 (−40)
5	0.68 [0.25]	9.9 [17.3]	+19 (−36)	+50 (−29)	+67 (−22)
<average>	−	−	+4	+32	+61

[a] In brackets we report the aug-cc-pVDZ values and in parentheses, the percent variations with respect to gas-phase. X//Y means that the X level of calculation has been used for [α] whereas geometries and populations obtained at Y level.

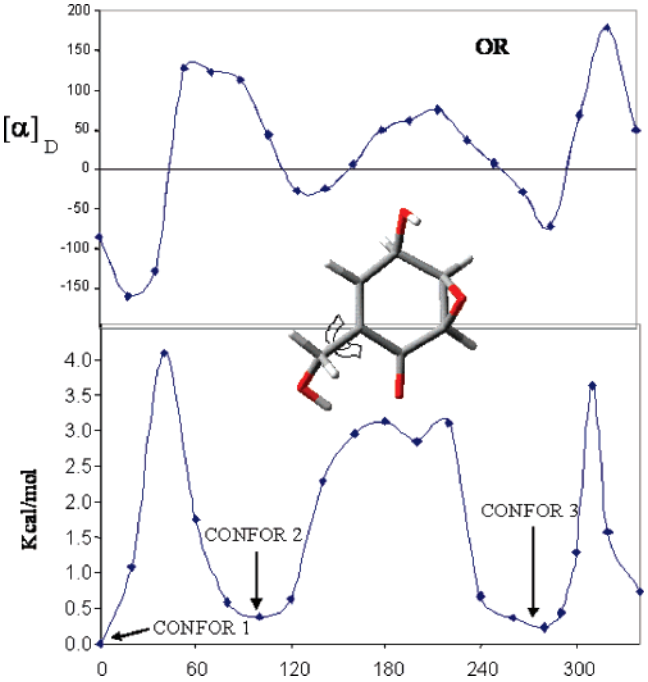


FIGURE 6. Relative free energies (kcal/mol) and $[\alpha]_D$ values (deg [dm g/cm^3]$^{-1}$) of (2*R*,3*R*,4*R*)-epoxidon in methanol with respect to rotation of the $-CH_2OH$ group. All quantities have been obtained performing a relaxed scan at the B3LYP/6-31G(d) level of the OH rotation using a 20 step in the angle.

obtained[23] only by an empirical analysis of the CD spectrum; that is, the CD spectra of these two compounds were simply compared to those of other similar compounds having known absolute configuration. In other words, these data were neither analyzed nor simulated by safe theoretical methods: as such, the results of this investigation are arguable. In addition, looking at the structures of Chart 1, one immediately observe that *(+)-**1** and (−)-**7** show very similar OR values but with opposite signs, even if they possess the same absolute stereochemistry*. This fact looks quite surprising, so we decided to reinvestigate the OR of these two compounds.

(−)-Sphaeropsidone, 6. (−)-**6** has been isolated[23] from *Sphaeropsis sapinea*, a fungal pathogen which causes stem and branch canker of the Italian cypress (*Cupressus sempervirens* L.). It possesses $[\alpha]_D = -130$ in methanol. Two different conformers have been found in the gas phase for (−)-**6** which are reported in Figure 7, together with the relative Boltzmann populations: both 6-31G(d) and aug-cc-pVDZ results are shown.

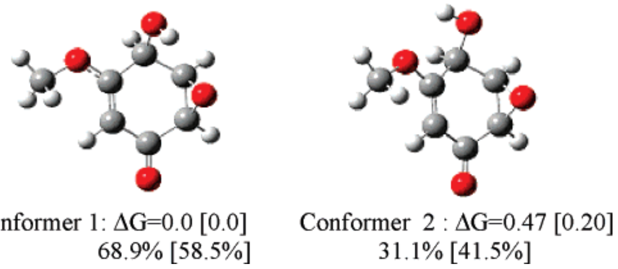


FIGURE 7. B3LY/6-31G(d) relative free energies (kcal/mol) and populations of the most stable conformers of (2*R*,3*R*,4*S*)-sphaeropsidone in the gas phase. Values in brackets refer to aug-cc-pVDZ calculations.

In the most stable conformer, there is an intramolecular hydrogen bond between the −OH on C(4) and the oxirane oxygen, with the H−O−C(4)−H fragment in an anti disposition and the methyl group of the methoxy substituent toward the vinyl hydrogen. This orientation of the two groups is maintained in conformer 2, but there is a different intramolecular hydrogen bonding between the −OH at C(4) and the methoxy oxygen, and this causes a gauche disposition of the H−O−C(4)−H fragment determining higher energy for this structure.

Looking at the Table 9, one can note that, using the small basis set, a theoretical value of +85 is obtained, a number which is of the same order of magnitude as the experimental one (−130) but with opposite sign. It is important to observe that both the conformers possess positive ORs, so the final result can only be a positive optical rotatory power, independent of the conformer distribution, in contrast to the experiment. By repeating the calculation to a higher level of the theory, we obtain again that the conformers are both dextrorotatory, and the theoretical value is now +140 (or +146 if the scaling is done using the aug-cc-pVDZ geometries/populations), that is, almost the same as the experimental one, but with the opposite sign. These results indicate then that the absolute configuration assigned in the literature and used in the calculation of $[\alpha]_D$ is not correct. However, to confirm this conclusion, we decided to repeat these OR calculations taking into account the solvent effect. Exactly as in gas phase, also in solution there are two stable conformers, namely, those previously indicated as conformers 1 and 2 and characterized by internal H-bonds. The OR results obtained for such structures are reported in Table 10 (due to the small effect of the basis set on the geometries/population shown in gas phase, here only the 6-31G(d) description has been used).

As it can be seen, the two conformers become almost isoenergetic (with conformer 2 only slightly more stable). A scan analysis on the OH rotation (see Figure 4 in the Supporting Information), however, has shown that these two minima are separated by a relatively high barrier which prevents a free OH

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(23) Evidente, A.; Sparapano, L.; Fierro, O.; Bruno, G.; Giordano, F.; Motta, A. *Phytochemistry* **1998**, *48*, 1139−1143.

TABLE 9. Values of $[\alpha]_D$ for Each Conformer of (2*R*,3*R*,4*S*)-Sphaeropsidone in the Gas Phase and the Corresponding Averaged Values Obtained Using the Boltzmann Populations Reported in Figure 7[a]

conformer	6-31G(d)// 6-31G(d)	aug-cc-pVDZ// 6-31G(d)	aug-cc-pVDZ// aug-cc-pVDZ
1	+99	+159	+172
2	+54	+95	+109
<average>	+85	+140	+146

[a] Values are in deg [dm g/cm^3]$^{-1}$ (X//Y means that the X level of calculation has been used for [α] using the geometries and populations obtained at the Y level).

TABLE 10. Relative Free Energies with Respect to the Most Stable Conformer (kcal/mol) and Corresponding Populations and $[\alpha]_D$ for Each Conformer of (2*R*,3*R*,4*S*)-Sphaeropsidone in Methanol[a]

conformer	ΔG	% pop	$[\alpha]_D$/6-31G(d)	$[\alpha]_D$/aug-cc-pVDZ
1	0.06	47.4	+67 (−32)	+135 (−15)
2	0.00	52.6	+20 (−63)	+69 (−27)
<average>	−	−	+43	+101

[a] Values of $[\alpha]_D$ (deg [dm g/cm^3]$^{-1}$) are obtained at TDDFT/B3LYP/6-31G(d) and aug-cc-pVDZ levels (in parentheses, the percent variations with respect to gas-phase values are reported).

rotation. In addition, the two wells are quite steep (in fact, even small changes in the OH−O distances can significantly weaken the stabilizing H-bond interaction). For all of these reasons, we can safely limit the average to the two minima obtaining a final OR value of +43 and +101 with the small and the larger basis set, respectively. Here, as in the case of (+)-epoformine, intramolecular H-bonds are present and thus we expect that IEFPCM results could not account for the complete solvent effects: the agreement with the experimental figures is in fact not improved with respect to the values calculated in the gas phase. However, what it is important to stress here is that the conclusion that the absolute configuration found in the literature is not correct is still valid. Actually, this conclusion is based on the OR calculation at a single wavelength, 589 nm. As it has been recently pointed out,[24] often the calculated electronic transition wavelengths do not match those observed experimentally. Then the observed OR at 589 nm should not be compared to that calculated at 589 nm, but such a comparison should be done at a wavelength that is shifted according to the difference between calculated and observed electronic transition wavelength (i.e., the wavelength correction). The wavelength correction is difficult to determine, so to avoid this problem, the OR can be calculated at different wavelengths in the nonresonant region (ORD data). If the calculated ORD is a monosignate curve, the wavelength correction becomes irrelevant for comparing the sign of OR at 589 nm. As can be seen clearly from Figure 8, the predicted ORD curve for (−)-**6** is actually always positive between 700 and 365 (i.e., monosignate). Therefore, we can conclude that we do not need any wavelength correction for the comparison between predicted and experimental OR values. This means that the sign of OR calculated assuming the literature AC of (−)-**6** is really positive. This fact clearly supports our conclusion on the incorrectness of the literature AC assignment.

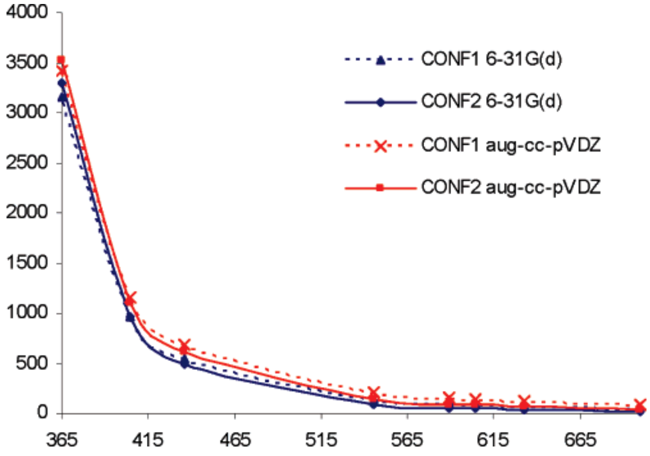

FIGURE 8. ORD of the two conformers of (−)-**6** in the 360−700 nm wavelength range.

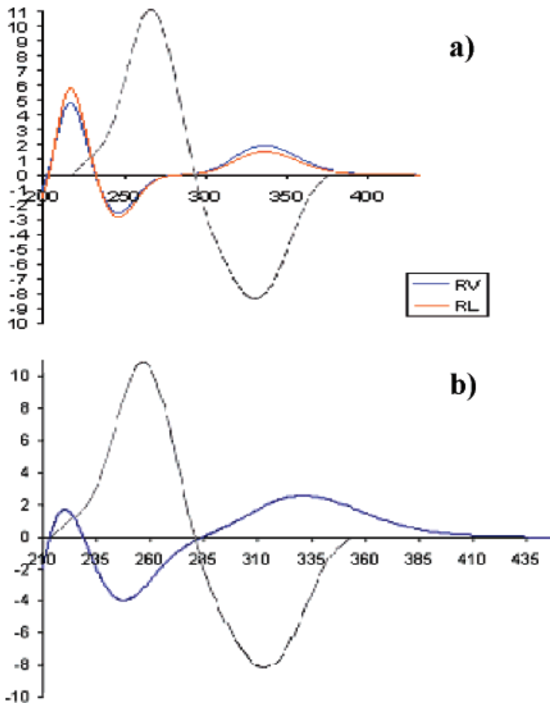

FIGURE 9. (a) Comparison of the predicted ECD spectrum at the TDDFT/B3LYP/6-31G(d) level in the length (red line) and velocity (blue line) formalism with the experimental ECD spectrum of (−)-**6**. (b) Comparison of the predicted ECD spectrum at the TDDFT/B3LYP/aug-cc-pVDZ level in the length (blue line) formalism with the experimental ECD spectrum of (−)-**6**.

Further support of the above conclusion comes from the analysis of the experimental ECD spectrum of (−)-**6**, which is reported in Figure 9; it shows a strong negative Cotton effect ($\Delta\epsilon$ ca. −9) centered at about 320 nm followed by an even stronger ($\Delta\epsilon$ ca. +11) positive Cotton effect centered at about 260 nm.

These two bands are related to the n−π^* (R band) and π−π^* (K band) of the α,β-unsaturated carbonyl chromophore, respectively, the chiroptical properties of which have been discussed in detail by Gawronski.[14] The signs of the Cotton effects related to these two transitions have been correlated to the sense of the helicity of the inherently dissymmetric enone chromophore; for a *trans*-enone chromophore having a negative twist, the R band is positive while the K band is negative.[14] It is important to note that both of the conformers of (−)-**6** reported in Figure 7 show a negative torsional angle of the *trans*-enone chromophore,

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(24) Polavarapu, P. L. *J. Phys. Chem. A* **2005**, *109*, 7013−7023; *Chirality* **2006**, *18*, 348−356.

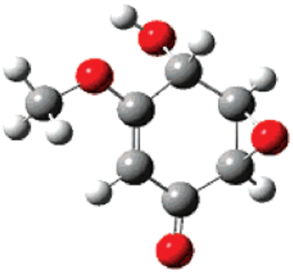

FIGURE 10. The most stable conformer of (2*R*,3*R*,4*S*)-episphaeropsidone in the gas phase.

and therefore, they should give rise, following the above rule, to a sequence of positive R band followed by a negative K band while the experimental ECD spectrum of (−)-**6** is in a mirror image relationship. This clearly means that the helicity of the enone chromophore of (−)-**6** is opposite to that of the structures reported in Figure 7; this is a consequence of the fact that the ACs of the stereocenters of the above structures are opposite to the experimental one. In Figure 9 is also a comparison between the experimental ECD spectrum and those calculated at both TDDFT/B3LYP/6-31G(d) and TDDFT/aug-cc-pVDZ levels. The calculated curves are both opposite in sign to the experimental one; that is, between 350 and 300 nm, a negative Cotton effect is observed followed by a second one between 300 and 220 nm, while the calculated spectra present a sequence of positive−negative bands in the same two regions. These results represent an independent validation of the conclusion that the AC reported in the literature for (−)-**6** is incorrect.

(−)-Episphaeropsidone, 7. The last compound studied in this investigation is an epimer of (−)-**6**, (−)-episphaeropsidone, (−)-**7**, which has been isolated and characterized together with (−)-**6** in ref 23 and presents both higher phythotoxic and antimicrobial activities than (−)-**6**. The optical rotation of (−)-episphaeropsidone is −240 in methanol. At both 6-31G(d) and aug-cc-pVDZ levels of calculations, only one conformer has been found for (2*R*,3*R*,4*R*)-episphaeropsidone in the gas phase, and this is reported in Figure 10.

Here, owing to the absolute configuration at C(4), the intramolecular hydrogen bonding between the C(4) hydroxy group and the oxirane oxygen is not possible, while there is hydrogen bonding between the same hydroxy group and the methoxy oxygen. The TDDFT/B3LYP/6-31G(d) calculation of the OR of this structure affords +311, a value which is of the same order of magnitude, but opposite in sign, with respect to the experimental one. Repetition of the calculation with the aug-cc-pVDZ basis set gives +325 and +343 using the 6-31G(d) and aug-cc-pVDZ geometry, respectively, again values which are of the same order of magnitude, but opposite in sign, with respect to the experimental one. The addition of the solvent effect does not modify these results, but it only changes the OR value which passes to +328 and +343 with the small and the larger basis sets, respectively. These data confirm the previous conclusion that the configuration reported in the literature is not correct, as for sphaeropsidone. Also in this case, the importance of the wavelength correction has been evaluated. Here as well the calculated ORD curve (between 700 and 365 nm) (Figure 11) is always positive (i.e., monosignate). This ensures that the calculated OR at 589 nm is really positive for the AC reported in the literature, supporting our conclusion that this assignment was incorrect.

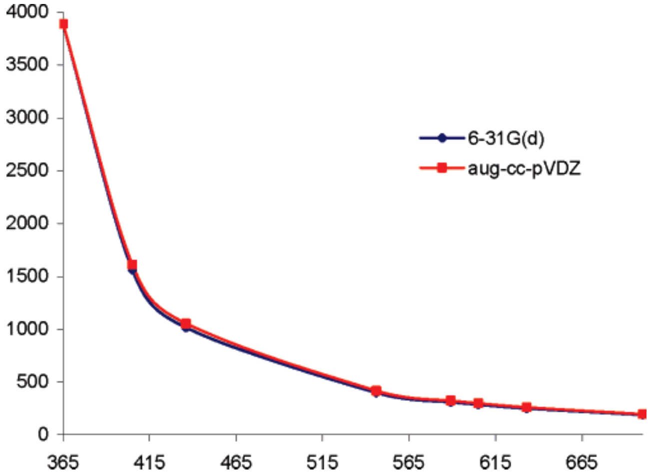

FIGURE 11. ORD of (−)-**7** in the 360−700 nm wavelength range.

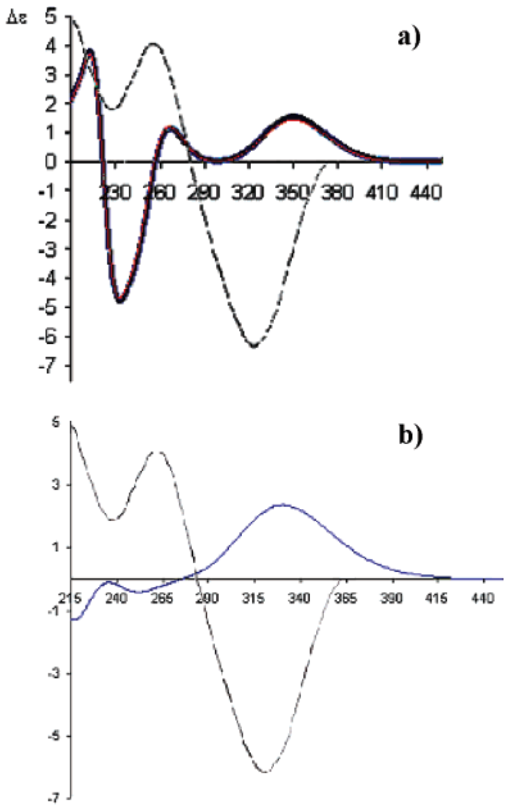

FIGURE 12. (a) Comparison of the predicted ECD spectrum at the TDDFT/B3LYP/6-31G(d) level in the length (red line) and velocity (blue line) formalism with the experimental ECD spectrum of (−)-**7**. (b) Comparison of the predicted ECD spectrum at the TDDFT/B3LYP/aug-cc-pVDZ level in the length (blue line) formalism with the experimental ECD spectrum of (−)-**7**.

Also in this case, the simulation of the analysis of the ECD spectrum has been attempted. This spectrum is reported in Figure 12.

It shows a strong negative CD band at about 330 nm ($\Delta\epsilon$ ca. −9) followed by a stronger positive ($\Delta\epsilon$ ca. +11) Cotton effect at 260 nm. Following the previous analysis done for (−)-**6**, the above two bands are related to the R and K bands of the inherently dissymmetric enone chromophore.[14] In this case as well, the *trans*-enone chromophore CD chirality rule predicts[14] a positive torsion of the chromophore itself, while our calculations, using the AC of (−)-**7** reported in the literature, provides an opposite (negative) twist of the same chromophore, therefore indicating that the ACs of the stereogenic centers of (−)-**7** should be reversed. In the same Figure 12 is a comparison between the experimental ECD spectrum and those calculated at both TDDFT/B3LYP/6-31G(d) and TDDFT/aug-cc-pVDZ levels; the two calculated curves are both opposite in sign with respect to the experimental one; that is, between 360 and 280 nm, a negative Cotton effect is observed followed by a second, really intense one between 360 and 220 nm, while the calculated spectra present a sequence of positive−negative bands in the same two regions. This result is an independent support to the conclusion that the AC reported for (−)-**7** is incorrect.

Concluding Remarks

This investigation has demonstrated that the absolute configuration of some important natural cyclohexene oxides such as **1**−**4** can be safely assigned by TDDFT/B3LYP calculations of the optical rotatory power at the sodium D line. For compounds **1** and **2**, which show high (ca. 300 units) rotatory powers determined in sign and magnitude by the lowest-energy Cotton effects, a simplified approach which uses a small basis set seems to be able to correctly reproduce the sign and the order of magnitude of the observed rotatory power. It is interesting to note that, in the case of **1**, the solvent effect *decreases* the gas-phase OR value, while for **2**, it *increases* the same figure, leading, in both the cases, to a better agreement with experiment. However, the absolute effect is rather limited (±15%), and therefore, it does not change the assignment obtained with gas-phase calculations. By contrast, in the case of smaller rotations (100 units or less), as for compounds **3** and **4**, the use of an extended basis set is needed in order to have good experiment/simulation agreement. In addition, the presence of conformers with intramolecular hydrogen bonding makes the use of a continuum model less satisfactory when in the presence of protic solvents. In these cases, in fact, perturbations due to competitive solute−solvent H-bonds should explicitly be included to get an accurate agreement with experiments. The case of (+)-epoxidone, **5**, is particularly complex; while experiments show a positive rotation (+93, ethanol), the gas-phase calculations predict that the most stable conformer is laevorotatory while the others are dextrorotatory. This leads to negative average rotation with the small basis set. These results are obviously not useful for a safe assignment of the absolute configuration; the only way to solve the problem is to use a large basis set and to take into account solvent effects and internal −OH rotations. The second lesson we can thus learn is that, when different conformers are present with opposite optical rotations, the solvent effect cannot be neglected, and a very sophisticated analysis is absolutely required. However, from the experimental organic chemist's point of view, the most important result concerns compounds **6** and **7**. Here, any kind of prediction (small or extended basis set, gas phase, or solvent calculation) leads to an optical rotation which is of the right order of magnitude, but opposite in sign, to the experimental one, assuming the absolute configuration reported in the literature. A parallel conclusion is obtained by considering calculated and experimental ECD spectra. All of these evidences show that the literature assignment is not correct. We would like to conclude this paper with a last consideration. Since the first quantum-mechanical calculations of optical rotation, important developments have been achieved both in the reliability and in the accuracy of the results, so, by now, these methods can even help in correcting previous AC assignments.

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Supporting Information Available: Relative free energies (kcal/mol) and OR values (deg [dm g/cm^3]$^{-1}$) of (2*R*,3*R*,4*S*)-epiepoformine in ethanol with respect to rotation of the OH group. Relative energies (kcal/mol) and OR values (deg [dm g/cm^3]$^{-1}$) of (2*R*,3*R*,4*R*)-epoformine in ethanol with respect to rotation of the OH group. Aug-cc-pVDZ $[\alpha]_D$ values (deg [dm g/cm^3]$^{-1}$) of (2*R*,3*R*,4*R*)-epoxidon in methanol with respect to rotation of the $-CH_2OH$ group. Relative energies (kcal/mol) and OR values (deg [dm g/cm^3]$^{-1}$) of (2*R*,3*R*,4*S*)-sphaeropsidone in methanol with respect to rotation of the OH group. B3LYP/6-31G(d) optimized geometries of all the conformers of all the compounds in the gas phase and in solution. This material is available free of charge via the Internet at http://pubs.acs.org.

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