Optical Rotation Calculation of a Highly Flexible Molecule: The Case of Paraconic Acid

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The absolute configuration of (*S*)-(−)-paraconic acid is correctly assigned on the basis of ab initio calculations of the specific optical rotation (OR) at the sodium D line, carried out both in vacuum and in methanol. Density functional theory (DFT) and Møller−Plesset second-order perturbation theory (MP2) are used to determine the most stable conformational structures, whose OR values are then calculated using DFT linear response theory and London atomic orbitals. The total OR is obtained by averaging these values using the population fractions determined from Boltzmann's statistics. The total OR of the MP2 structures has the correct sign both in vacuum and in solution, whereas only the solvent-relaxed DFT structures correctly reproduce the experimental sign. The strong solvent effect on the total OR is shown to arise primarily due to the variations in the relative energies of the various conformations.

Introduction

The determination of the absolute configuration (AC) of chiral molecules is a very important step in asymmetric synthesis. The AC of the synthesized product can be assigned by comparing the electronic circular dichroism (ECD) spectrum with structurally similar molecules having the same chiral centers, by using empirical rules to determine the sign of its optical rotation (OR), or finally by converting the product to a molecule of known AC (for a review on these techniques, see ref 1). If the molecule crystallizes, the AC can also be determined by using X-ray crystallography.[2,3]

In recent years, advances in the field of theoretical chemistry have led to the development of new computational approaches for calculating OR at different levels of accuracy, including methods such as the Hartree−Fock (HF),[4] density functional theory (DFT),[5] and coupled cluster (CC)[6] methods. Moreover, the large number of papers that have been published on theoretical studies of OR[1,7−12] are contributing to the elucidation of the factors that determine OR, thus allowing for both qualitatively and quantitatively accurate determinations of molecular OR, and hence the direct assignment of the AC of a molecule.

From these studies, the following conclusions can be drawn: of the currently available ab initio methodologies, DFT has emerged as the best choice in terms of balancing accuracy and computational cost;[7,8] the inclusion of diffuse functions in the basis set is mandatory; that is, basis sets of at least aug-cc-pVDZ quality must be used;[1,7,9] solvent effects appear to be important, but their magnitude depends on the particular solute−solvent system under study;[10] there is a dramatic dependence of the predicted specific rotation ($[\alpha]_D^{25}$) on the molecular geometry[9] and, in the case of floppy molecules, on the relative energies of the different molecular conformations;[7,11] the dependence of $[\alpha]_D^{25}$ on the vibrational motion may be relevant, but also in this case, the magnitude of the vibrational correction is found to depend on the molecule being investigated.[12]

In the present work, the results of OR ab initio calculations are presented for the paraconic acid molecule, the precursor of a family of highly substituted γ-butyrolactones. The possible use of these compounds in the medical field as antitumoral and antimicrobical agents has been studied (see ref 13 for a review); moreover, the esters of paraconic acid have wide industrial application in the production of perfumes and solvents.[14] The AC of paraconic acid was determined in 1983[15] by its conversion to a molecule of known chirality, making it the ideal candidate for testing the feasibility and reliability of OR calculations on this class of molecules as a way to determine their absolute configurations.

The paraconic acid conformational structures have been determined using both DFT and Møller−Plesset second-order perturbation theory (MP2), and the OR values have been calculated using a local version of the time-dependent DFT code in DALTON,[16] accounting for the solvent effect using the polarizable continuum model (PCM).[10,17] The effect of the solvent on the conformational populations and the OR is discussed, along with the reliability of MP2 and DFT in determining the correct conformational structures and relative energies of this nonrigid molecule. We will show that good agreement with the available experimental data can be achieved.

Definitions and Computational Details

In the framework of semiclassical theory, the specific OR at frequency (ω) of a *flexible* chiral molecule, that is, a molecule exhibiting more than one stable conformer can be written as the following:[7]

$$[\alpha]_\omega = \frac{\mathrm{ee}(E_1)}{100}\frac{28\,800\pi^2 N_A \nu^2}{c^2 M}\sum_{i=1}^{n} x_i\beta_i(E_1) \qquad (1)$$

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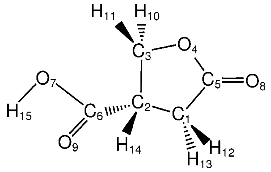

Figure 1. Structure labels of (*S*)-(−)-paraconic acid with the atom numbering used throughout the paper. The numbering does not refer to the standard IUPAC numbering.[39]

where ee(E_1) is the enantiomeric excess of enantiomer E_1, x_i is the population fraction of the *i*th conformer, M is the molar mass of the molecule, N_A is Avogadro's number, c is the speed of light in vacuum, and $\omega = 2\pi\nu$.

The scalar quantity $\beta_i(E_1)$ (for the *i*th conformer of enantiomer E_1) is related to the trace of the frequency-dependent mixed electric dipole−magnetic dipole polarizability ($G'_{\alpha\beta}$)

$$\beta = -\frac{1}{3\omega}\sum_{\alpha=x,y,z} G'_{\alpha\alpha} \tag{2}$$

$$G'_{\alpha\beta} = -\mathrm{Im}\langle\langle \mu_\alpha; m_\beta \rangle\rangle_\omega \tag{3}$$

where μ_α is the α-component of the electric dipole moment operator and m_β is the β-component of the magnetic dipole moment operator. $\beta_i(E_1)$ is in this work calculated via linear response theory,[18] and gauge origin independence is obtained using London atomic orbitals.[19,20]

To determine the optical rotation of a floppy molecule, one has to, according to eq 1, determine the OR for the various (energetically relevant) conformers of the given molecular species.

The starting geometry of (*S*)-(−)-paraconic acid was obtained by optimization at the HF/6-311++G**[21] level of theory. From this geometry, a HF/6-311++G** relaxed potential energy surface (PES) scan was carried out by modifying the dihedral angles C1−C2−C3−O4 (see Figure 1 for atom numbering) and C3−C2−C6−O7 in the ranges ±40° and [0, 360]°, respectively. This leads to the identification of six minima which we will label **A**, **B**, **C**, **D**, **E**, and **F**. Attempts were also made at moving the hydrogen H15 by rotating around the C6−O7 bond in order to change the dihedral angle H15−O7−C6−O9 from ≈0° (as in all the conformers in Figure 2) to ≈180°, but even in the cases where intramolecular hydrogen bonding with the ring oxygen O4 could be achieved, the energies of these optimized conformations were significantly higher than those of conformations **A**−**F** due to increased strain in the five-membered ring. This is not too surprising, since the atom O4 is expected to have very small basicity due to electronic resonance with the carbonyl group in the five-membered ring.

The structures of the six conformers were finally optimized in vacuum at both the DFT (using the hybrid Becke three-parameter Lee−Yang−Parr B3LYP functional[22]) and MP2 levels of theory, using the aug-cc-pVDZ[23] and 6-311++G** basis sets, and then reoptimized in the methanol solvent, here modeled by the polarizable continuum model (PCM),[10,24] using the aug-cc-pVDZ basis set only. Only methanol was chosen as solvent for two reasons: (i) the solubility of paraconic acid in nonpolar solvents is extremely limited, making the experimental measurement of OR in such solvents too sensitive to experimental error, and (ii) the polarity of the solvent counteracts the possible dimerization of the acid itself.[25] For carboxylic acids, in fact, dimerization may occur both in the gas phase and in solution. Accounting for hypothetical dimeric conformational forms present during the experimental measurement[26] in the theoretical simulations would lead to a very large (if at all feasible) increase in the computational effort required for the calculation of the OR of paraconic acid.

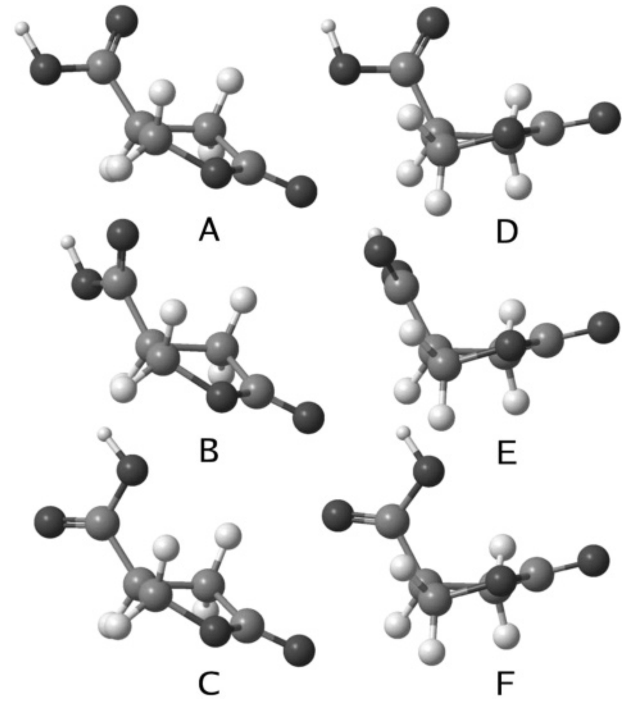

Figure 2. Conformations of minimum energy optimized in methanol solution using the polarizable continuum model at the DFT/B3LYP/aug-cc-pVDZ level of theory. The letters identify the various conformers whose properties are given in Tables 1−3.

Theoretical studies on acetic acid[27,28] concluded that the ΔG of formation of the dimers is negative only in nonpolar solvents (i.e., heptane and $CHCl_3$), whereas more polar solvents (i.e., dimethyl sulfoxide (DMSO) and water) can counteract the dimerization process. Since methanol is both a quite polar solvent and capable of hydrogen bonding, the paraconic acid is considered to be present predominantly in the monomeric form in the experimental environment, and no further calculations have been carried out for the dimeric forms.

Note that, at the MP2 level, a **B**-like conformer does not exist in vacuum, and the DFT/B3LYP/PCM **B** conformer was then used as a starting point for the MP2/PCM optimization. All geometry optimizations were done using the Gaussian program.[29] Default values for the cavities were assumed in the case of the PCM, that is, cavities centered on the heavy atoms including the bonded hydrogens.[30]

The calculations of $\beta(\omega)$ were for all conformers carried out at the sodium D line ($\lambda = 589.3$ nm), both in vacuum and in the solvent, using the DFT/B3LYP implementation[6,31] of linear response theory present in the DALTON 2.0 package.[16] The solvent effect was accounted for by using PCM linear response theory as implemented in a local version of DALTON, using the same cavities as those in the geometry optimization.

Results and Discussion

To determine the total OR reliably, it is mandatory to have the best possible values for both the OR of the various conformers and their relative energies (and hence their population fractions). To compare the DFT/B3LYP and the MP2 relative energies, and thus determine the most suitable method for these kinds of calculations, we have used both of them and investigated which one leads to a total OR in the best agreement with experiment.

TABLE 1: Paraconic Acid. Values of the Dihedral Angles C1−C2−C3−O4 (Ring-Puckering Internal Coordinate) and C3−C2−C6−O7 (Carboxylic Group Torsional Internal Coordinate) of the Various Conformers Optimized at the DFT/B3LYP and MP2 Levels Both in Vacuum and in Methanol[a]

		DFT			MP2	
conformer	dihedral angle	6-311++G** vacuum	aug-cc-pVDZ vacuum	aug-cc-pVDZ PCM/CH_3OH	aug-cc-pVDZ vacuum	aug-cc-pVDZ PCM/CH_3OH
A	C1−C2−C3−O4	−27.7	−27.0	−25.8	−32.7	−31.3
	C1−C2−C6−O7	281.7	281.4	298.7	267.4	294.6
B	C1−C2−C3−O4	−30.0	−29.3	−27.2	[b]	−32.6
	C1−C2−C6−O7	209.3	209.5	206.2	[b]	215.0
C	C1−C2−C3−O4	−29.6	−28.8	−27.4	−33.4	−32.9
	C1−C2−C6−O7	59.7	60.3	57.8	62.8	62.7
D	C1−C2−C3−O4	24.5	22.8	23.5	32.5	33.1
	C1−C2−C6−O7	297.6	296.1	294.7	288.8	280.8
E	C1−C2−C3−O4	23.7	22.1	23.6	30.7	29.5
	C1−C2−C6−O7	172.2	173.8	177.2	172.3	193.5
F	C1−C2−C3−O4	23.0	21.9	23.5	30.4	29.6
	C1−C2−C6−O7	71.4	71.2	66.5	82.3	71.9

[a] The dihedral angles are in degrees. [b] An energy minimum corresponding to a **B**-like geometry could not be found.

TABLE 2: Relative Energies (in kcal/mol) and Relative Percentage Abundances of the Various Conformers of (*S*)-(−)-Paraconic Acid Obtained by Geometries Optimized at the DFT/B3LYP and MP2 Levels Both in Vacuum and in Methanol[a]

	DFT			MP2	
conformer	6-311++G** vacuum	aug-cc-pVDZ vacuum	aug-cc-pVDZ PCM/CH_3OH	aug-cc-pVDZ vacuum	aug-cc-pVDZ PCM/CH_3OH
A	0.00	0.00	0.00	0.00	0.37[b]
	38.54%	38.46%	37.87%	41.77%	19.03%
B	0.11	0.10	0.42	[c]	0.75[b]
	31.91%	32.51%	18.61%	[c]	10.14%
C	0.88	0.97	1.07	0.92	1.34[b]
	8.78%	7.49%	6.23%	8.84%	3.72%
D	0.78	0.76	0.47	0.25	0.00[b]
	10.26%	10.59%	17.15%	27.42%	35.71%
E	0.92	0.90	0.59	0.70	0.56[b]
	8.13%	8.46%	13.90%	12.88%	13.96%
F	1.65	1.62	1.07	0.90	0.42[b]
	2.38%	2.49%	6.24%	9.10%	17.43%

[a] The percentages are calculated using Boltzmann's statistics and refer to a temperature of 298.15 K. For each conformer, the energy is given in the first row and the percentage in the second row. [b] Note that the absolute minimum conformer is in this case **D**. [c] An energy minimum corresponding to a **B**-like geometry could not be found.

In Table 1, we have collected the values of the two internal coordinates that vary the most among the different conformations, namely, the dihedral angles C1−C2−C3−O4 (describing the ring-puckering motion) and C3−C2−C6−O7 (describing the COOH torsional motion). Positive values of the C1−C2−C3−O4 dihedral angle characterize the {**A**, **B**, **C**} conformers, which are called "bottom-of-plane" conformations in the rest of this paper, whereas negative values are exhibited by the {**D**, **E**, **F**} conformations, which will be referred to as "top-of-plane" conformations. The structures of the conformers, which are qualitatively the same independently of the basis set or theory used, are shown in Figure 2.

We first consider the geometry parameters reported in Table 1. In the case of DFT/B3LYP, changing the basis set from 6-311++G** to aug-cc-pVDZ reduces on average the absolute value of the C1−C2−C3−O4 angle by ≈5% and leaves the C3−C2−C6−O7 torsional angle almost unchanged. Larger C1−C2−C3−O4 variations are seen when including the solvent; the changes are then ≈ −6% for the bottom-of-plane conformers and ≈ +6% for the top-of-plane ones: in solution, more positive C1−C2−C3−O4 values are preferred compared to the vacuum case. For the C3−C2−C6−O7 angle, absolute variations up to 7% are observed, depending on the conformer. In the case of MP2, the most important solvent effect is the stabilization of the **B**-like conformer, which furthermore is not present in vacuum, and the reduction of the absolute value of the C1−C2−C3−O4 angle; that is, more planar ring structures are preferred. The variations in the torsional angle between vacuum and solution are larger for MP2 than for DFT/B3LYP, being as large as ≈14% for the **E** conformer. Both the vacuum- and solvent-relaxed DFT/B3LYP conformers are more planar than the MP2 ones, with all the MP2 optimized geometries having absolute values for C1−C2−C3−O4 larger than 29°.

In Table 2, we have collected the relative energies and percentage occurrences based on Boltzmann's statistics for the different conformations and methods investigated. We note that, in the case of DFT/B3LYP, the **A** conformer is always the absolute energy minimum, and changing the basis set does not significantly alter the population of the different conformations. The solvent destabilizes primarily the **B** conformer, reducing its weight by a factor of 2, and stabilizes at the same time the {**D**, **E**, **F**} structures, in particular conformation **D** which in the solvent has almost the same energy as the **B** conformer. For MP2, the solvent stabilization of the top-of-plane conformers is even more evident: the **D** conformation becomes the absolute minimum, and the total population fraction of the {**D**, **E**, **F**} top-of-plane conformations is larger than 50%. We note that, for both DFT/B3LYP and MP2, the solvent stabilizes the structures having all oxygen atoms on the same side of the ring.

When comparing the energies both in vacuum and in solvent, the MP2 top-of-plane conformers are much more stable than

TABLE 3: (*S*)-(−)-Paraconic Acid. In the First Row for Each Conformer Is Reported the Specific Optical Rotation (deg cm^3 dm^{-1} g^{-1}) (α) Calculated at the DFT/B3LYP Level, Using London Atomic Orbitals and the Geometries Optimized at the Level Specified in the Top Lines (Unless Otherwise Stated), in the Second Row the Optical Rotation Weighted (α_w) by the Percentage Abundances in Table 1 Is Given, and at the Bottom Line of the Table, the Total Specific Optical Rotations ($[\alpha]_D^{25}$) Are Given, by the Sum of All the α_w[a]

	DFT geometries				MP2 geometries		
conformer	6-311++G** vacuum	aug-cc-pVDZ vacuum	aug-cc-pVDZ vacuum	aug-cc-pVDZ PCM/CH$_3$OH	aug-cc-pVDZ vacuum	aug-cc-pVDZ PCM/CH$_3$OH	aug-cc-pVDZ PCM/CH$_3$OH
A	−31.27	−42.35^b	−47.91	−27.50	−10.58	−17.29^c	−18.40
	−12.05	−16.32^b	−18.43	−10.41	−4.42	−7.22^c	−3.50
B	152.79	144.53^b	145.76	105.10	^{d}	^{d}	119.72
	48.76	46.12^b	47.39	19.56	^{d}	^{d}	12.14
C	112.01	95.73^b	91.47	72.77	109.74	90.41^c	84.32
	9.83	8.40^b	6.85	4.53	9.70	7.99^c	3.13
D	−250.61	−245.03^b	−253.88	−248.90	−251.71	−246.76^c	−222.36
	−25.72	−25.14^b	−26.90	−42.69	−69.01	−67.65^c	−79.40
E	−19.21	−10.78^b	0.36	−12.03	−13.49	−29.55^c	14.65
	−1.56	−0.88^b	0.03	−1.67	−1.74	−3.81^c	2.05
F	−188.13	−182.86^b	−182.67	−155.76	−217.33	−216.40^c	−176.02
	−4.47	−4.35^b	−4.55	−9.72	−19.77	−19.69^c	−30.69
$[\alpha]_D^{25}$	+14.78	+6.72	+4.40	−40.40	−85.23	−90.37	−96.27

[a] The experimental values of $[\alpha]_D^{25}$, measured in methanol solvent, are +47.1 (*c* 0.14, CH$_3$OH, ee 80%; for the *R*-enantiomer)[35] and −60 (*c* 2.08, CH$_3$OH).[34] [b] The α and α_w values were calculated for the DFT/B3LYP/6-311++G** geometries. [c] The α and α_w values were calculated for the MP2/vacuum geometries. [d] An energy minimum corresponding to a **B**-like geometry could not be found.

the B3LYP structures and simultaneously the bottom-of-plane structures are higher in energy.

In Table 3, we have collected our calculated ORs of the different conformations. We note from this table that the ORs of the various conformers are very different, both in sign and in absolute values, as has also been observed in previous investigations of the OR of conformationally flexible molecules.[7,11,32,33] Moreover, there is a wide range of percentage variation in the OR of the given conformers when changing the basis set or the theory or the environment used. Nevertheless, the only conformer that changes the OR sign is the **E** conformer, with the **B** and **C** ones always having positive values and the others always negative. Comparing the results in the first and second column of Table 3, we note that changing the basis set in the OR calculation only changes the OR values by an absolute average percentage of ≈12% (excluding the **E** conformer). Comparing the second and third columns, we note that the basis set effect on the geometries is only ≈4%. The solvent effect, when included both in the geometries and in the OR calculations, is much larger, with average variations in the OR between the values in the third and fourth column of ≈21% (also excluding the **E** conformer here). The same solvent effect of ≈20% can be seen in the case of MP2 when comparing the results in the fifth and sixth columns, even though the solvent effect in this case is only taken into account in the OR calculations; that is, the geometry is not allowed to relax in the solvent. Taking the solvent into account in the geometry optimizations leads to an average absolute difference among the numbers in columns five and seven of ≈30% (ignoring in this case the **B** conformer in addition to the **E** one).

If we consider the total population-weighted ORs reported at the bottom of Table 3 and recall that the experimental OR values are −60 (*c* 2.08, CH$_3$OH)[34] and +47.1 (*c* 0.14, CH$_3$OH, ee 80%; for the *R*-enantiomer),[35] implicitly defined in units of deg cm^3 dm^{-1} g^{-1} throughout the rest of the paper, it can be seen that the DFT/B3LYP geometries and energies are unable to predict the correct sign without the inclusion of the solvent, whereas the MP2 energies and geometries give the correct sign of the total OR in all cases. It is not clear whether the DFT/B3LYP method is indeed capable of providing sufficiently accurate geometries and energetics for the different conformations, since it gives rise to an incorrect sign for the gas-phase OR and a somewhat exaggerated solvent effect. A possible improvement to the DFT/B3LYP/vacuum energetics could be expected using the Δ*G* values instead of the Δ*E* values in the calculation of the population fractions.[36] Calculating the Gibb's free energies in the case of DFT/B3LYP/aug-cc-pVDZ—using the thermal analysis based on vibrational frequency calculations[37]—leads, as the largest effects, to a small stabilization of the **B** conformer and a destabilization of the **C** one of ≈0.1 kcal/mol. These energy shifts change the total OR value from 4.40 (as reported in Table 3) to 7.13. Thus, the DFT/B3LYP approach remains unable to reproduce the experimental data obtained in a solvated environment using only the vacuum calculated OR values. The maximum deviation from the experimental value of the population-weighted $[\alpha]_D^{25}$ is +75 in the case of the DFT/B3LYP vacuum and −36 in the case of the MP2 solvent. The best value is only 20 units larger in the case of the DFT/B3LYP solvent (though this may appear to be slightly fortuitous) and 25 units smaller for MP2 in the vacuum phase. The difference in the behavior of these two theories derives from the larger stability of the top-of-plane conformers (all having negative OR) in the MP2 case: the inclusion of the solvent leads to a stabilization of the top-of-plane structures in the case of the DFT/B3LYP, greatly improving the final result, but apparently giving worse agreement with experiment for the MP2 prediction due to an "overstabilization" of these conformers.

When studying the optical activity of a molecule exhibiting different conformational forms, the reliability of the population-weighted OR values is a difficult issue. In two previous studies on the optical activity of flexible molecules,[7,32] the DFT/B3LYP/vacuum optimized conformers were able to correctly reproduce the experimental OR signs in six out of seven cases. In five of these cases[7] (the conformer geometries were optimized using the 6-31G* basis set), the experimental measures of $[\alpha]_D^{25}$ were carried out in CHCl$_3$, not capable of hydrogen bonding with the solute molecule, hence reducing the magnitude of solute−solvent interaction. In the remaining two cases[32] (namely, the L-alanine and L-proline amino acids, optimized in vacuum with the aug-cc-pVDZ basis set), all conformers with significant abundance exhibited the same sign of the OR, ruling out the effect of the conformational energy errors on the total OR sign. In the present work, it can be easily shown that even small errors in the DFT/B3LYP/vacuum/aug-cc-pVDZ energies are capable of reversing the sign of the total OR: a destabilization of 0.1 kcal/mol of the **B** and **C** conformers with a simultaneous stabilization of 0.1 kcal/mol of the **D** conformer would lead to a total OR of ≈ -10 units. Such a strong dependence of the total OR sign on small errors in the relative energies is not present in the other aug-cc-pVDZ cases. The lack of accuracy in the DFT/B3LYP/vacuum cases is ascribed to the quasi-cancellation of the contributions to the total OR of the **A**, **B**, and **D** conformers, making the total OR very sensitive to errors in the energetics. From preliminary results on the γ-methyl paraconic acid and methyl γ-methyl paraconate and ethyl γ-methyl paraconate, the DFT/B3LYP/vacuum/aug-cc-pVDZ optimized conformers lead to the correct sign in all cases, since in this case all the relevant conformers exhibit the same sign of the OR.[38]

Summary

As a preliminary study on the large family of molecules derived from paraconic acid, we have carried out a computational investigation of the optical rotation of this molecule. The ultimate purpose is to use the computed results to assign the AC of a series of α-methyl paraconic acid and ethyl α-methyl paraconates, whose ACs have not yet been experimentally determined.

In vacuum, the global OR is negative for the MP2 optimized conformations and positive for the DFT ones. The inclusion of methanol as a solvent as described by the PCM during the geometry optimization step leads to a sign change in the global OR obtained from the DFT structures, with the final numerical value in good agreement with experimental data. A more negative global OR value is obtained from the MP2 structures. The sign reversal in the DFT case going from vacuum to solvent is due mainly to a change in the relative energies of the various conformers. In the case of the DFT/B3LYP/vacuum calculations, the global OR value is very dependent on small errors in the determination of the relative energies, making the predicted global OR sign unreliable. In such cases, MP2 seems to perform better than DFT in assigning the energies for the various conformers, leading to a global OR sign less dependent on small errors in the energies.

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