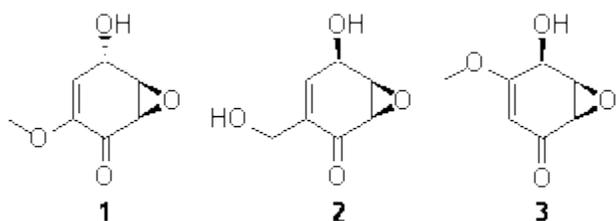


COMPUTING OPTICAL ACTIVITIES

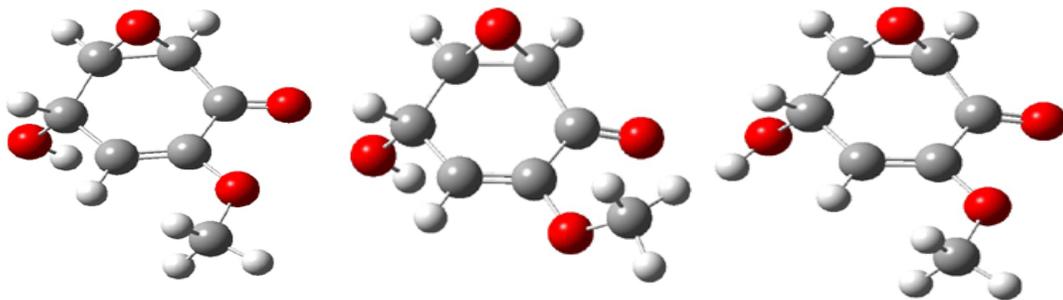
A growing area for the application of computational chemistry is in the structural identification of compounds. In the book, I discussed the use of computed IR spectra to identify intermediates in the photolysis of phenyl nitrene and carbene and the benzyne. In previous blogs, I have written posts ([here](#), [here](#) and [here](#)) about recent use of computed NMR spectra to discern the structure of new natural products. With this post I discuss the use of computed optical activity to determine the absolute configuration of molecules.

Rosini and co-workers have examined a number of oxygenated cyclohexene epoxides to explore the use of TDDFT computed optical activity as a means for determining absolute configuration.¹ In chapter 1.6.3, I discuss the work of the Gaussian team on benchmarking optical rotation and ORD. They find that B3LYP/aug-cc-pVDZ computed optical activities are in quite reasonable agreement with experiment.²⁻⁴ In this work, Rosini explores using a smaller basis set (6-31G(d)), the role of solvent, and also if computed spectra can be used to assess the absolute configuration of new molecules.

They first benchmark the B3LYP/6-31G(d) computed optical activities for a number of related cyclohexene epoxides against B3LYP/aug-cc-pVDZ and experimental values. I will begin by discussing two of their examples: (+)-chaloxone **1** (PubChem) and (+)-epoxydon **2** (PubChem).



Five conformations of **1** were optimized in the gas phase and then their optical activities for the sodium D line were computed using TDDFT with both the small and larger basis set. These computations were then repeated to model the effect of solvent using PCM; the solution (methanol) B3LYP/6-31G(d) structures are shown in Figure 1.



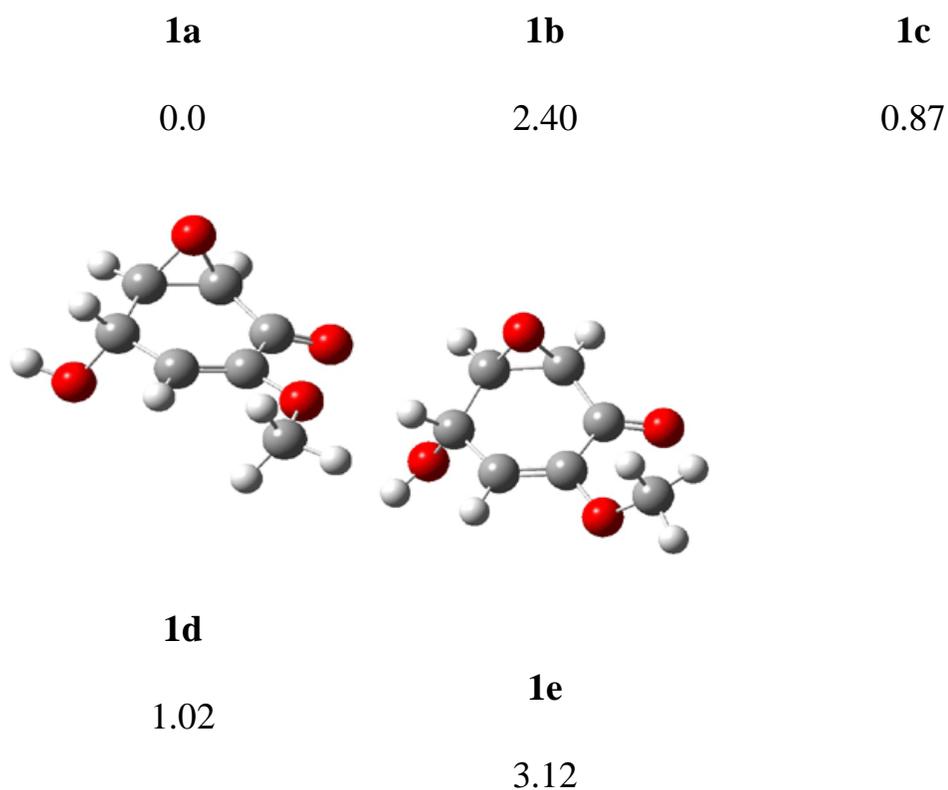


Figure 1. PCM(methanol)/B3LYP/6-31G(d) optimized structures of **1**. Relative free energies of each conformer in kcal/mol.¹

The optical rotation at the sodium D line was then computed with TDDFT in both gas and solution phase with the smaller and larger basis set. The values were then averaged based on a Boltzmann weighting using the computed free energies of each conformer. The optical rotation for each conformer and the average values are listed in Table 1. The experimental optical rotation is +271.

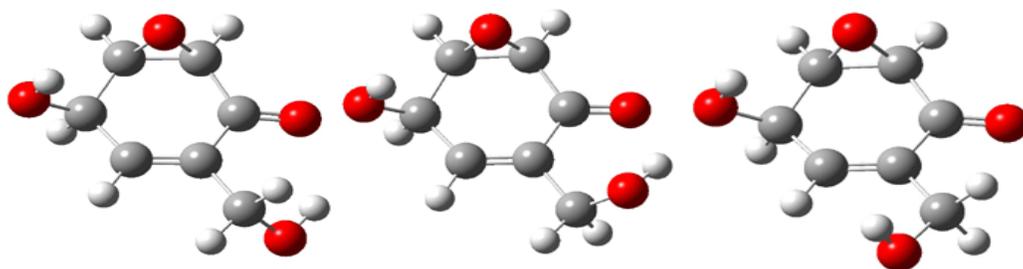
The authors note that while the gas phase B3LYP/6-31G(d) average value is far off the experimental value, it does predict the correct sign, and since all of the five conformers give rise to a positive rotation, any error in the energies will not affect the sign. The computed gas phase value with the larger basis set is in better agreement with experiment. However, it is still too large, but the solution values are much better. In fact, the PCM/B3LYP/aug-cc-pVDZ value is in excellent agreement with experiment.

Table 1. Computed optical activity of the conformers of **1** in gas and solution phase.

conformer	gas		solution	
	6-31G(d)	aug-cc-pvDZ	6-31G(d)	aug-cc-pvDZ
1a	+264	+251	+304	+308
1b	+723	+750	+690	+707
1c	+324	+309	+398	+385
1d	+187	+201	+246	+268
1e	+741	+785	+756	+769
Average ^a	+378	+333	+318	+322

“Based on a Boltzmann weighting of the population of each conformation.

Five conformers of epoxydon **2** were also located, and the computed solution structures are shown in Figure 2. The computed optical rotations for both the gas and solution phase for these structures (and the Boltzmann weighted averages) are listed in Table 2. The experimental value for the optical rotation of **2** is +93.



2a

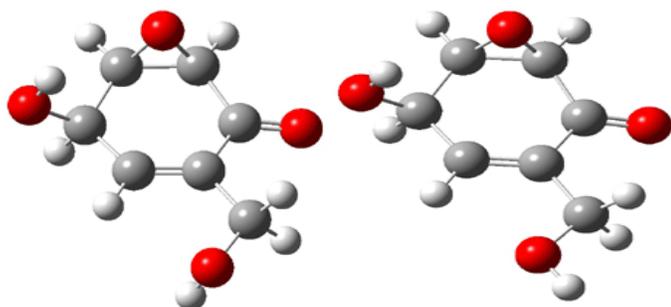
0.0

2b

0.32

2c

0.23



2d

2e

0.22

0.66

Figure 2. PCM(methanol)/B3LYP/6-31G(d) optimized structures of **2**. Relative free energies of each conformer in kcal/mol.¹

In this case, the small basis set performs very poorly. The gas phase B3LYP/6-31G(d) value

of $[\alpha]_D$ is -16, predicting the wrong sign, let alone the wrong magnitude. Things improve with the larger basis set, which predicts a value of +57. Since conformer **2a** is levorotatory and the other four are dextrorotatory, the computed relative energies are key to getting the correct prediction. This is made even more poignant with the solution results, where the PCM/B3LYP/aug-cc-pVDZ prediction is quite acceptable.

Table 2. Computed optical activity of the conformers of **2** in gas and solution phase.

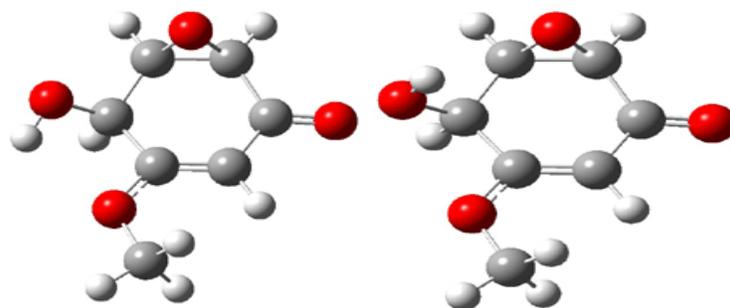
	gas		solution	
	6-31G(d)	aug-cc-pvDZ	6-31G(d)	aug-cc-pvDZ
2a	-97	-43	-85	-36
2b	+130	+210	+113	+166

2c	+14	+63	+8	+58
2d	+113	+119	+37	+71
2e	+29	+86	+19	+67
Average ^a	-16	+57	+4	+61

^aBased on a Boltzmann weighting of the population of each conformation.

They conclude with two examples of application of computation to assignment of structure. I discuss here the absolute configuration of (-)-sphaeropsidone **3** (PubChem).

Rosini located two conformations of **3**, shown in Figure 3. The computed optical rotations are listed in Table 3. The experimental value for **3** is -130. Both conformers are computed to be dextrorotatory with *all* computational methods. The magnitude of the computed values using the larger basis set is in nice agreement with experiment, but the sign is wrong. Rosini concludes that the absolute configuration of **3** has been misassigned.



3a

0.06

3b

0.0

Figure 3. PCM(methanol)/B3LYP/6-31G(d) optimized structures of **3**. Relative free energies of each conformer in kcal/mol.¹

Table 3. Computed optical activity of the conformers of **3** in gas and solution phase.

	gas		solution	
conformer	6-31G(d)	aug-cc-pvDZ	6-31G(d)	aug-cc-pvDZ
3a	+99	+172	+67	+135
3b	+54	+109	+20	+69
Average ^a	+85	+146	+43	+101

^aBased on a Boltzmann weighting of the population of each conformation.

Source: <http://comporgchem.com/blog/?p=36>