

Optical Rotation Angle of *S*-4-phenyl-2-oxazolidinone: Importance of the Hydrogen Bonded Dimer

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INTRODUCTION

The Chemical, biological and pharmaceutical properties of chiral molecules depend on their stereochemistry. Therefore, there is great interest in determining the absolute configuration of these compounds. However, even the determination of the absolute configuration of simple molecules might be challenging, involving spectroscopic procedures or crystallographic methods. Indeed, it may even require the partial or total synthesis of the molecule. In this work, we studied the *S*-4-phenyl-2-oxazolidinone (SPO) molecule (see Fig. 1) and its hydrogen bonded dimer. We performed full geometry optimizations followed by optical rotation (OR) angle calculations with several DFT methods looking for one of low computational cost, which can best provide the OR angle values that will be used to assist the determination of the absolute configuration of other chiral molecules.

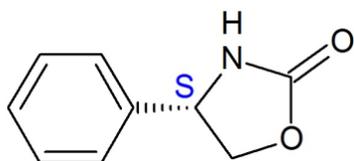


Figure 1. Chemical structure of *S*-4-phenyl-2-oxazolidinone (SPO).

METHODS

First, we employed molecular mechanics to generate the conformers of SPO. We took the two generated conformers, optimized their geometries and calculated the OR angle with four DFT methods (B3LYP, PBE, PBE0 and ω B97XD¹) with nineteen basis sets for the monomer. The dimer was calculated employing the B3LYP, PBE0 and ω B97XD methods with only six basis sets. All calculations were performed for the isolated molecule, and for the molecule in chloroform, using PCM. The OR angles were obtained performing a Boltzmann average over all conformations.

RESULTS AND DISCUSSION

The experimentally observed value of the OR angle for SPO is 48°. For all methods employed, the OR angles calculated for the isolated monomer give the correct sign but the wrong magnitude, yielding values between 120° and 200°. The results with the chloroform solvent are smaller but still considerably overshoot the experimental value, as in ω B97XD/cc-pVTZ with 115,56°. These results might originate from the formation of dimers between molecules of SPO in solution, which can affect the outcome of the value of the OR angle. Indeed, the OR angles calculated for the dimers are compatible with this possibility, since the calculated signs and magnitudes are closer to the experimental value, resulting in calculated OR angles between 35° and 70° for the ω B97XD method.

CONCLUSIONS

Our best results were for the ω B97XD method, where the dimer had OR angle values of 59,46° and 66,31° with the cc-pVDZ basis set and 38,73° and 69,43° with the def2-TZVP basis set for calculations performed for the isolated and solvated molecules, respectively. For the SPO molecule, calculating only the monomer is not enough to correctly assign its absolute configuration. Consequently, for the case of molecules with unknown absolute configuration, the possibility of dimer formation must be taken into consideration for the assignment of their absolute configuration.

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¹ J.-D. Chai and M. Head-Gordon, “Long-range corrected hybrid density functionals with damped atom-atom dispersion corrections,” *Phys. Chem. Chem. Phys.*, **10**(2008) 6615-20.