Exploration of Coupled-Cluster Vibrational Raman Optical Activity for β-Lactone Structural Analogs

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β-lactones have been shown to be useful inhibitors of bacteria, cancer, and obesity. The characteristic, four-membered ring of β-lactones is susceptible to nucleophilic attack at the second and fourth carbons [Christenson et al, *Biochemistry* 2017]. Here, the β-lactone product of the *geobacter bemijiensis* enzyme was used as a model for the structural analogs computed. The *geobacter bemijiensis* β-lactone product has two long, *trans* carbon tails attached to C_3 and C_4, which are both in the S configuration.

Vibrational Raman optical activity (VROA) detects the scattering of polarized light, which has distinctive interactions with stereoisomers. Furthermore, enantiomers can be identified by their equal but opposite VROA signals. Computational VROA requires a geometry optimization, Hessian, and ROA tensor derivative computations.

Extensive basis set testing on S-methyloxirane revealed asp-cc-pvdz to be an effective, modestly-sized basis set for the β-lactone computations. Full spectra were first computed using 6-31G* as a smaller basis set to identify regions of high signal intensity. These regions were then computed with asp-cc-pvdz for comparison to the 6-31G* spectra. Transferable components in the VROA spectra were sought by comparing the signal intensity trends of similar vibrational mode regions amongst the β-lactone structural analogs. Signal intensity trends between (S)-3-methyl-2-oxetanone and (S)-3-methyl-2-azetidinone provided the greatest similarities as the only difference between these molecules was the oxygen replaced by an N-H in the ring. However, the spectra of the other structural analogs suggest only coincidental similarities. Two distinct groupings of vibrations were observed in the plot of intermediate tensor $\beta(A)^2$ versus the cosine of the abstract angle associated with this tensor, ψ. One grouping corresponded to vibrations above 3000 cm^{-1} and the other corresponded to all other vibrational modes. Vibrational modes above 3000 cm^{-1} had large VROA signal intensities in all β-lactone structural analogs computed. Abstract angle ϕ displayed similar behavior with intermediate tensor $\beta(G')^2$. In addition to comparing basis sets 6-31G* and asp-cc-pvdz at the CC2 wavefunction level of theory, CC2 and CCSD were also compared with asp-cc-pvdz basis sets for the largest β-lactone structural analog. Applications of this research include a baseline reference for experimentalists to identify the absolute configuration of the chiral centers in development of β-lactone medications.