Efforts towards prediction of NH(D) and CH(D) isotopic exchange effects on ^{13}C NMR spectra of small, rigid lactams via computational chemistry

The effects of deuterium substitution at NH and CαH positions in cyclic lactams (CLs) on ^{13}C chemical shifts are being investigated, computationally and experimentally. A variation of a local mode computational method (Yang and Hudson (J. Phys. Chem. A2010, 114 12283-12290)) is being used. The H/D isotope effect is the difference in the zero-point average for H and D. The "local mode" method used for the averaging involves computation of stretch and bend distribution functions for the NH and CH bonds and NMR chemical shifts computed for each value of displacement with the assumption that the effects are additive. The test cases to date include CLs with ring size 5-10, diketopiperazine (DKP), and N-methylacetamide (NMA). These studies have demonstrated the effectiveness of using the local mode approach for calculation isotope effects where the peptide bond is in the *cis* conformation. Our objective is to establish all of the conformational factors that may contribute to predicting the shifts for *trans* peptide bond structures which can lead to more accurate modeling and predictions for larger peptides. More recently, additional efforts to increase agreement between experimental and predicted values include addition of explicit solvent molecules, hydrogen bond dimerization, thermal averaging of the low frequency NH out-of-plane mode, and deviations from the additivity approximation. Our methods were rooted in Density Functional Theory (DFT), but now we are looking at utilizing MP2, as well as Amsterdam Density Functional (ADF) for computations.