Benchmarking TDDFT functionals in calculations of CD spectra of flexible peptides

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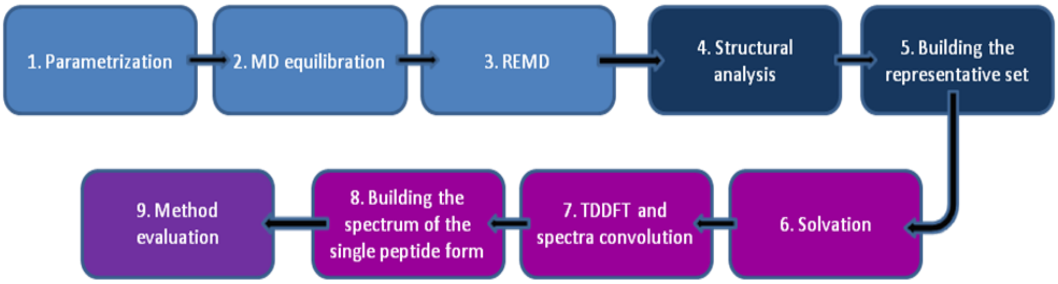
Circular dichroism (CD) spectroscopy is a standard experimental method for structural characterization of optically active chiral molecules, such as proteins and peptides. CD spectrum emerges as an ensemble average over the entire conformational phase space of the molecule. For highly flexible peptides with no dominant secondary structure, the interpretation of the experimental data becomes particularly challenging. Hence, theoretical modelling needs to be evoked to understand the measurements. Yet, until recently, no reliable method for calculating the CD spectrum was available. We combine a number of state-of-the-art theoretical approaches to provide a procedure for calculating CD spectra, as shown in the scheme below. [1] More specifically, conformational phase space is generated with replica exchange molecular dynamics. A set of representative structures is built by applying clustering methods. Finally, the CD spectrum of each representative structure is calculated using TDDFT. The final spectrum emerges as a weighted average of individual spectra.



Many studies in recent years pointed to a problem with modelling charge transfer excitations with TDDFT, which may affect the accuracy of calculated CD spectra. [2] Peptide systems prove to be especially interesting in this respect, as they were one of the first highlighted cases where conventional functionals exhibited relatively large charge transfer errors. [3] Motivated by these problems, we benchmarked the performances of B3LYP, CAM-B3LYP and M06-2X against high level *ab-initio* RI-CC2 calculations for selected peptide structures. Furthermore, we compared the performance of the functionals with the experimentally available data. Our results show that both CAM-B3LYP and M06-2X functionals correlate well with *ab-initio* calculations, while B3LYP exhibits aforementioned charge transfer errors. On the other hand B3LYP and M06-2X agree better with the experimental data compared to CAM-B3LYP. We clarify this apparent discrepancy by finding average excitation energies for charge transfers over many individual structures. In the case of B3LYP the surplus transitions, which are usually small in rotary strength, seem to become negligible upon finding a mean over many structures.

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