Calculation of the CD spectrum of a peptide from its conformational phase space

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Met-enkephalin (Tyr-Gly-Gly-Phe-Met) and its unnatural analogue Ada-enkephalin are opioid peptides which act as inhibitors of tumor cells in a receptor-mediated fashion. We have investigated the structural preferences of these peptides in 2,2,2-trifluoroethanol in an attempt to calculate their respective CD spectra. To this end, we have characterized the conformational preferences of the zwitterionic and neutral forms of Met-enkephalin and of both the *R*- and the *S*-epimers of Ada-enkephalin, as obtained by replica exchange molecular dynamics. The CD spectrum for each peptide was subsequently obtained with a procedure of successive averaging, which accounts for the sidechains and the backbone variations of the peptides and the effect of the solvent on the CD spectra. To make a proper comparison with the experiment, we have produced composite spectra that account for the appropriate contributions of the zwitterionic and neutral forms of the peptides as well as the expected epimeric ratio. Such a procedure results in theoretically obtained CD spectra that successfully reproduce the most important features of the experimentally measured spectra. Consequently, the link between the CD spectra and the conformational phase space of flexible peptides can be established.