Conformations and Vibrational Spectra of Cyclosporine A in Solutions: Molecular Dynamics Simulation and DFT Study

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Abstract: Cyclosporine A is an important immunosuppressive undecapeptide drug, which shows interesting secondary structures and various conformations under different environmental conditions. A combined MD simulation and DFT study is performed to understand the main conformations and vibrational spectra of cyclosporine A in gas-phase and in chloroform and acetonitrile solutions. It is shown that in nonpolar environments the backbone β-sheet and loop structures as well as the side-chain ^{1}OH…OC^{1} H-bond of the residue MeBmt^{1} are mostly maintained during long-time MD simulations, with two main conformations observed dependent on the orientations of bulky side-chains. The "starting" conformation with the MeBmt^{1} and MeLeu^{6} side-chains staying close to the respective Abu^{2} and Ala^{7} residues shows a type II′ β-turn and an inverse γ-turn, with considerable inverse H-bonding bifurcations for both turn structures. The "final" conformation with the MeBmt^{1} and MeLeu^{6} side-chains staying close to the respective MeVal^{11} and Val^{5} residues instead shows a looser β-sheet structure and a β-turn interconvertible between type II′ and type I with less inverse H-bonding bifurcation. The "intermediate" conformation containing a tight ^{1}OH…OC^{3} H-bond is observed only during simulations in acetonitrile solution. DFT calculations are used to refine important CsA conformers and to predict their infrared and vibrational circular dichroism spectra. The characteristic absorption bands in the amide II, I and A regions are discussed for important secondary structures including the β-turn, β-sheet, γ-turn, side-chain H-bonds, and *N*-methyl substitution to peptide bonds. A detailed comparison with available experimental data suggests that in nonpolar solutions CsA mainly assumes the "starting" conformation.

Most relevant references:

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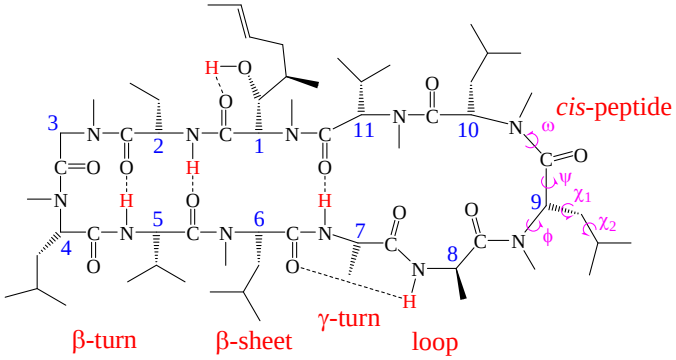

Schematic structure of cyclosporine A (CsA, 196 atoms)

cyclo(-MeBmt^{1}-Abu^{2}-Sar^{3}-MeLeu^{4}-Val^{5}-MeLeu^{6}-Ala^{7}-*D*-Ala^{8}-MeLeu^{9}-MeLeu^{10}-MeVal^{11})