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Quantum-Chemical Studies on *Cis-Trans* Isomerization of Ac-Pro-NHMe and Its C^δ-Methylated Derivatives

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Calculations on conformational free energies of Ac-Pro-NHMe and its C^δ-methylated derivatives have been carried out with the higher levels of quantum-chemical methods to figure out the *cis-trans* isomerization of the imide bond of proline and C^δ-methylated prolines in the gas phase and in solution. *Trans*- and *cis*-conformers are found to have a similar degree of puckering of proline ring, whereas the transition state is more puckered, which can be attributed to the $sp^2 \rightarrow sp^3$ hybridization of the N atom of pyrrolidine ring. By comparing changes in activation free energy and activation enthalpy, it is known that the *cis-trans* isomerization is entirely enthalpy-driven in the gas phase and in solution. *Cis* populations and rotational barriers are increased as the solvent polarity is increased, to which electrostatic interactions appear to contribute considerably. The methylation at the C^δ (or C5) of pyrrolidine ring leads the dipeptides to exist predominantly in *cis* conformers. In particular, Ac-5,5-diMePro-NHMe is found to be >90% in the *cis* conformer, which is ascribed to the less steric interactions between two C^δ-methyl groups and acetyl group in the *cis* conformer than the *trans* conformer. *This work was supported by the STEPI (1998).*