Conformational preference and mechanism of decarboxylation of levodopa. A quantum dynamics/quantum mechanics study

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Abstract

The present study addresses the conformational preferences and the mechanism of decarboxylation of levodopa (LD). LD is used to increase dopamine concentrations in the treatment of Parkinson's disease. LD crosses the protective blood-brain barrier, where it is converted into dopamine by the process of decarboxylation. Molecular dynamics simulation has been carried out at the DFT/6-31++G level of theory to identify the global minimum structure of LD. Conformational preferences of the amino acid side chain of LD has been investigated at the B3LYP/6-311++G** level of theory. Fourier transform analysis has been performed to identify the origin of the rotational barriers. Electrostatic dipole moment and bond interactions underlie the observed potential energy barriers for rotation of the amino acid side chain of LD. The vital biological process of decarboxylation of LD has been examined in the gas phase and in aqueous solution. Without the presence of water, there is only one possible route for the decarboxylation of LD. In this concerted mechanism, a proton transfer and breakage of the C10C18 bond, take place simultaneously (E# = 73.2 kcal/mol). In solution, however, two possible decarboxylation routes are available for LD. The first involve the formation of a zwitterionic intermediate (E# = 72.4 kcal/mol). The zwitterionic form of LD have been localized using explicitly bound water molecules to model short-range solvent effects and self-consistent reaction field polarized continuum model to estimate long-range solvent interactions. The second route involve the formation of a cyclic structure in which a water molecule acts as a bridge linking the anticarboxylic hydrogen and -position carbon atom (E# = 59.8 kcal/mol). Natural bond orbital (NBO) analysis reveals that the conformational and overall stability of the amino acid side chain is facilitated by the antiperiplanar interactions between the phenyl moiety CH and CC bonds and CX bonds of the amino acid side chain. However, much of the major donor-acceptor interactions is of the lone pair type and is localized within the amino acid side chain itself. Results of the present work reveal that NBO data reflect nicely and identify clearly reaction coordinates at the transition species. (c) 2013 Wiley Periodicals, Inc.

Keywords

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