ZABOL UNIVERSITY

Faculty of Basic Science

Department of Chemistry

Subject

Theoretical study of various conformations of antidiabetic gliclazide drug and the investigation of solvent effect on its conformational stability

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Abstract

Gliclazide is an oral hypoglycemic drug from the second-generation sulfonylurea family, which effectively treats blood sugar level of the diabetes mellitus type 2 patients. Gliclazide chemical structure comprises of an aromatic ring, sulfonylyrea moiety and an azabicyclooctyl ring. In the present research work, possible conformers of Gliclazide were found through a conformational search around four central bonds in sulfonylurea moiety using B_3LYP/6-31g++G** level of theory by changing the dihedral angles and subsequent optimizations (conformational scan protocol) in Gaussian 16 software program. Each of the local minimum conformers found through changing around one of the bonds then was subjected to additional scans through other bonds. This way, 49 local minimum conformers were found in gaseous phase for Gliclazide. These conformers were then optimized in the presence of three different solvents including water, dimethyl sulfoxide and chloroform with B_3LYP/6-31g++G** level of theory using Polarizable Continuum Model (PCM) in order to investigating the solvent effects. Results showed that all confomers are more stable in the solvent phase relative to gaseous phase. The stabilities were increased by increasing the dielectric constant of solvent. The conformers were found most stable in water as solvent. Critical point calculations were done on the most stable conformer using Atoms in Molecules theory through AIM2000 software program. These calculations showed a strong intramolecular hydrogen bond as the key factor in conformer stability for Gliclazide. The NBO analyses of the most stable conformer in B_3LYP/6-31g++G** level of theory also proves the existence of the intramolecular hydrogen bond in this conformer and its amplification with the solvent dielectric constant.

Keywords: Gliclazide, Conformers, Quantum Chemical calculatons, Solvent Effects,