Quantum Chemical Calculations of Warfarin Sodium, Warfarin and Its Metabolites

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Abstract. The structural, vibrational and electronic properties of warfarin sodium, warfarin and its metabolites have been investigated theoretically by performing the molecular mechanics (MM+ force field), the semi-empirical self-consistent-field molecular-orbital (AM1), and density functional theory calculations. The geometry of the molecules have been optimized, the vibrational dynamics and the electronic properties of the molecules have been calculated in their ground state in gas phase.

1 Introduction

Warfarin is a widespread anticoagulant used as medicine to prevent strokes. Racemic warfarin [3-α-(acetonylbenzyl)-4-hydroxycoumarin], a synthetic 4-hydroxycoumarin derivative and vitamin K antagonist [1], has been utilized for more than two decades as an oral anticoagulant (OA) and as a rodenticide. Its two enantiomers (chiral center at C-9) do not exhibit equivalent anticoagulant activity due to complex factors, including different intrinsic activities as well as differences in pharmacokinetics, pharmacodynamics and metabolism. A detailed information about the importance of warfarin from medical and biological relevance point of view is given in the Appendix.

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Dolmella et al. (1999) performed ab initio (Hartree-Fock (HF)), semiempirical molecular orbital (PM3), molecular mechanics and molecular dynamics/simulated annealing calculations on thirteen anticoagulant rodenticides. The results were also used in the assessment of toxicity and interaction with the target enzyme vitamin K 2,3-epoxide reductase (KO-reductase) in liver microsomes [2]. Synthesis and structure-activity relationships of some warfarin metabolites were also studied [3]. Warfarin is a substrate for CYP2C9 isozymes of P450s in vivo and recently, CYP2C9 and CYP2C19 inhibitors with 1 to 2 orders of magnitude lower K_i values than previously characterized compounds such as warfarin have been reported using three-dimensional quantitative structure activity relationship (3D-QSAR) analysis [4].

Current interest in ligand-based molecular modeling, together with knowledge accumulated from experimentation are used to build and test potential models for predicting ligand-protein interactions and hence drug-drug interactions, the sites of drug metabolism, toxicity, and other parameters. High affinity ligands for each P450 enzyme can help define the enzyme in the form of a pharmacophore, improving the identification of drug leads with the highest potential for drug-drug interactions based on their structure. In practice, this is a lofty goal because determining drug interaction potential in any quantitative manner requires an accurate, universal binding model that can predict any compound's affinity for a given enzyme. Warfarin is one of the most widely used model compounds in this field of research, besides its clinical importance and such risks as ICH and narrow therapeutic range.

The aim of the present theoretical study is to investigate the structural, electronic and vibrational properties of warfarin sodium, warfarin and its five metabolites due to their biological and medical importance. There are limited studies in the literature about the molecules considered in this work. The results of such theoretical work will aid in the elucidation of structure activity relationships of compounds in drugs before they can be safely evaluated and commercially developed as beneficial pharmaceuticals.

2　Computational methods

The geometries of warfarin sodium (**WS**), warfarin (**W**) and its metabolites (any derivative of the parent compound formed by enzymes of various tissues acting on it); 7-hydroxywarfarin (**7**), 8-hydroxywarfarin (**8**), 4'-hydroxywarfarin (**4'**), 6-hydroxywarfarin (**6**), 2,3-dihydro-2-methyl-4-phenyl-5-oxo-γ-pyrano(3,2-c)(1)benzopyran (**bp**) have been optimized using different level of quantum chemical calculations. Preoptimization has been performed by applying the molecular-mechanics (MM) method [5] using MM+ force field [6]. The high computational speed of molecular mechanics makes easier to perform better optimization using higher level of computation methods. This optimized structure was taken and the semi-empirical self-consistent-field molecular-orbital (SCF-MO) method [7] at AM1 [8] level within the restricted Hartree-Fock (RHF) formalism [9] has been applied. These calculations have been carried out with HyperChem 7.5 pro-