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Experimental and theoretical elucidation of structural and antioxidant properties of vanillylmandelic acid and its carboxylate anion

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ABSTRACT

Vanillylmandelic acid (VMA), an important metabolite of catecholamines that is routinely screened as tumor marker, was investigated by the various spectroscopic techniques (IR, Raman, UV–Vis, antioxidant decolorization assay and NMR). Structures optimized by the employment of five common functionals (M05-2X, M06-2X, B3LYP, CAM-B3LYP, B3LYP-D3) were compared with the crystallographic data. The M05-2X functional reproduced the most reliable experimental bond lengths and angles (correlation coefficient >0.999). The importance of intramolecular hydrogen bonds for structural stability was discussed and quantified by the NBO analysis. The most prominent bands in vibrational spectrum were analyzed and compared to the experimental data. The positions of the carbon and hydrogen atoms in NMR spectra were well reproduced. The differences in UV–Vis spectrum were investigated by adding the explicit solvent and by performing NBO and QTAIM analyses. The discrepancy in the two spectra of about 50 nm could be explained by the solvent effect on carboxyl group. The most probable antioxidant activity mechanism was discussed for VMA and its carboxylate anion. The Molecular Docking study with the C - reactive protein additionally proved that variety of functional groups present in VMA and its anion allowed strong hydrogen and hydrophobic interactions.

1. Introduction

Catecholamines are usually tested from patients with neural crest tumors, particularly neuroblastoma. Their relative amounts, as well as of their metabolites, are important for the tumor screening, but homovanillic and vanillylmandelic acids are among those that are regularly addressed and the most effective [1–5]. Vanillylmandelic acid (VMA) is produced as the metabolite of epinephrine and norepinephrine [6].

The proper determination and quantification of VMA are important because an increased amount can be an indication of the disorder in neurotransmitter metabolism as well. The excess amount can be a consequence of an alternative reaction pathway if some of the enzymes do not function properly [7]. This further leads to organic aciduria and belongs to the group of inborn errors of metabolism (IEM) [8,9]. The elevated concentrations are also reported for patients with ganglioneuroblastoma [10], chemodectoma [6], chronic diarrhea [11], hypoxia, cystic fibrosis of the pancreas [12] and glycogen storage disease [11]. The investigation of the concentration of this metabolite in real urine sample by various techniques such as gas chromatography/mass spectrometry [13], fluorimetry [14], capillary electrophoresis [7], attenuated total reflectance FTIR [15], voltammetry [16] and high performance liquid chromatography [1] has been reported. There are also tests that include coupling of diazotized aromatic amines with VMA and production of characteristically colored dyes [17,18], although there are results that suggest their non-specificity and reaction with other naturally occurring molecules in the body [18,19]. But, to the best of our knowledge, there hasn't been any quantum chemical description of this important molecule, its structure, inter- and intramolecular interactions, assignment of bands in electronic and vibrational spectra, as well as interactions with proteins. Proper explanation of these properties would allow better assessment in concentration measurement and experiment outcomes. Therefore, the aim of this work is to evaluate theoretically determined features by Density Functional Theory (DFT), Natural Bond Orbital (NBO) and Quantum Atoms in Molecules (QTAIM) analyses and compare them to experimentally available data.

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