

Structural Changes and Control on Conjugation of Glutathione with Chalcones and their Quinolinone Analogues

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Abstract:

The nucleophilic addition of cellular thiols onto polarized carbon-carbon double bond (Michael-reaction) toward reduced glutathione (GSH) is frequently associated with the biologic effects of chalcones and other α,β -unsaturated carbonyl compounds[1]. Such reaction can change intracellular redox status (redox signaling), which can modulate events such as DNA synthesis, enzyme activation, selective gene expression, and regulation of the cell cycle. In sulfonamide chalcones and their quinolinones derivatives the nucleophilic sulfur of the GSH is added onto the β -carbon atom of the enone moiety. Hence, knowing the relationship between molecular structure and GSH reactivity, especially on β -carbon, is important to further studies on the action mechanism[2]. In this sense, we evaluated the GSH reaction kinetic of a novel sulfonamide chalcone $C_{21}H_{15}N_2O_5S$ (**I**) and its quinolinone derivative $C_{28}H_{19}ClN_2O_5S$ (**II**) from their molecular structures. To provide explanations on how the molecular structure affects this non-enzyme catalyzed nucleophilic addition, the crystal structures of the compounds **I** and **II** were obtained from X Ray Diffraction and were conformationally investigated. Also, theoretical calculations using DFT were performed to support the structural features responsible for GSH reactivity. Single crystal X-ray diffraction of **I** and **II** were collected on Bruker APEX II CCD diffractometer and refinement of the structures ($R_1 = 5.27\%$ and $Goof = 1.045$ for **I** and $R_1 = 6.21\%$ and $Goof = 1.054$ for **II**) was made by SHELX[3] suit program and indicates the centrosymmetric monoclinic space group $P2_1/c$ for both **I** and **II** (Figure 1). It was observed GSH addition on **I** faster than **II** ($k_1 = 127.5$ for **I** and $k_2 = 26.1$ for **II**, where k_1 and k_2 are the kinetic constants for **I** and **II**, respectively). Experimental data suggest that the molecular planarity influences on the reactivity regarding on hyperconjugation effect. Compound **I** is supposed to be more reactive since before cyclization the chalcone moiety is planar ($\angle C8-C7-C2-N1 = 176.51^\circ$). Also, the α -proton present only in **I** contributes to positive charge over β -carbon, which increases k_1 . On the other hand, the decrease of the velocity on **II** is explained from the steric hindrance caused by the cyclization. Theoretical calculations performed at B3LYP/6-311++G(d,p) theory level showed a slight difference on the E_{GAP} of **I** and **II** ($E_{GAP} = 3.69$ and 3.97 eV for **I** and **II**, respectively), which explains the k values. Finally, it is also explained due the positive charge over β -carbon of **I**, theoretically found from the Molecular Electrostatic Potential maps.

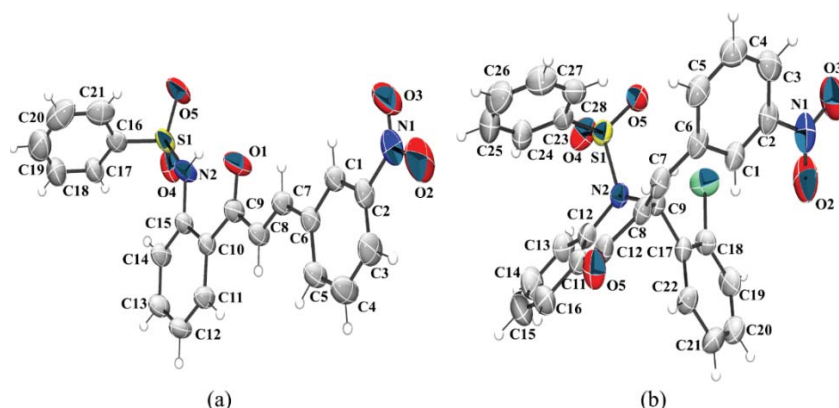


Figure 1: Ortep representation showing the thermal displacement of **I** (a) and **II** (b) with 50% probability. Hydrogens are present as spheres with arbitrary radii.

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