Computational and Theoretical Chemistry 1013 (2013) 97–101

Contents lists available at SciVerse ScienceDirect

Computational and Theoretical Chemistry

journal homepage: www.elsevier.com/locate/comptc

On the mechanism of biological activity of hydroquinone derivatives that inhibit tumor cell respiration. A theoretical study

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ARTICLE INFO

Article history:
Received 12 February 2013
Received in revised form 8 March 2013
Accepted 9 March 2013
Available online 18 March 2013

Keywords:
Hydroquinone
Antitumoral mechanism
Antitumoral drugs
Tumor cell respiration
DFT calculation

ABSTRACT

A simple mechanism to understand the biological activity of a series of hydroquinone derivatives is proposed. To validate this proposition Gibbs free energies of formation of the different species involved were calculated. The calculations were performed using density functional theory (DFT) at B3LYP/6-31++G(2df,p) level of theory, including solvation effect. The results show that two important variables to examine are the equilibrium phenol-phenoxide and the solvation energy of neutral species, since the balance between both variables affects the capability of the molecules to cross membranes. Once the molecule crossed the membrane, the formation of radical species shows a qualitative correlation with the magnitude of IC_{50} values. This provides a reasonable criterion to search for more efficient anticancer drug.

1. Introduction

Anti-oxidant properties of polyphenols are well known. Despite this, on certain particular conditions they also present pro-oxidant activity [1–3]. The way by which these molecules react, as anti-oxidant or pro-oxidants, depends on several factors, such as the concentration of chemical species capable to drive the electron transfer processes, the capability of the molecule to form complexes with redox active metals, the pH of the medium and the molecular redox potential [4].

The full oxidation process of hydroquinones and chatecols to quinones, present a two electron mechanism initiated by a one electron transfer [5]; these redox properties have been associated to their pro-oxidant activity, which can accelerate oxidative damage to either DNA or proteins and carbohydrates. It has been reported that they also present antiproliferative and cytotoxic properties in several tumor cell lines [6–8], through the formation of the semiquinone radical [9]. In this context, our group has been working on the synthesis, mechanism of formation and tumor cell respiration inhibition of quinone and hydroquinone derivatives [10–12].

Mitochondria have been suspected to play a crucial role in cancer genesis and for this reason it has become an important target for cancer therapy [13–16]. Consequently, there is a high probability that the active site of these molecules is located inside the mitochondria [17]. Therefore, in order to reach their targets, these derivatives have to cross several membranes; however, the probability that non-protonated polyphenols cross membranes is low.

Furthermore, due to the existence of a proton concentration gradient, there is a difference in pH across the peripheral and internal mitochondrial membranes, generating a potential difference. Weak acids, possibly protonated in acid medium, diffuse inside more basic compartments of the system, become de-protonated and concentrate there [18]. This process is selective and may help to deliver anti-cancer molecules inside the mitochondria. In healthy tissue the interstitial pH is neutral, whereas in cancer tissue it is acidic, mainly because of the excessive glycolysis, used as a source of ATP [19–21]. Recently, weak acids have been successfully employed as anti cancer agents [22–25].

Thermodynamic and electronic properties of important biological processes are sometimes difficult to evaluate experimentally. Besides, quantum chemical methods have been widely used to predict many of these properties. For instance, few years ago a series of high level ab initio and semi-empirical calculations were performed to model four possible reaction pathways, between either 2-Butene-1,4-dione or p-benzoquinone with triplet state molecular oxygen [26]. More recently, a series of density functional theory (DFT) calculations, at different levels of sophistication, were performed to study the stability and reaction pathways of o-, m- and p-dihydroxybenzene derivatives, their semiquinone radicals

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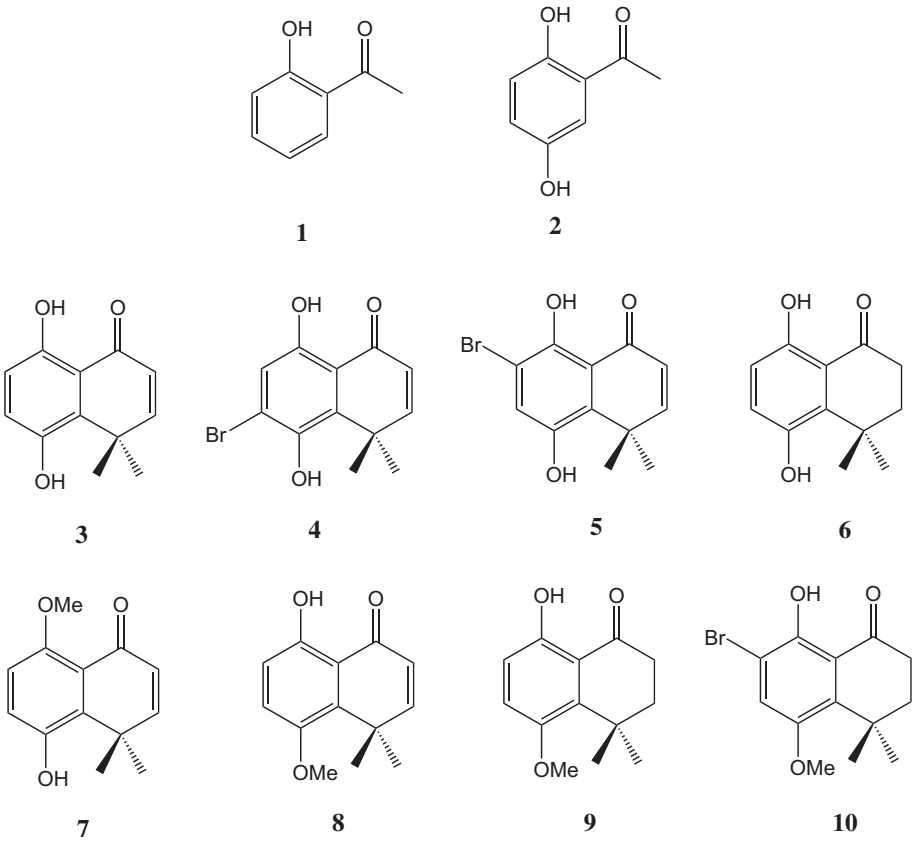
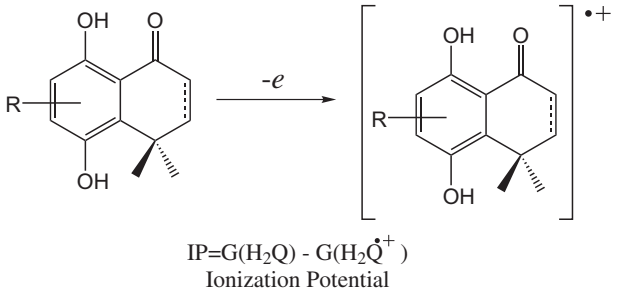
http://dx.doi.org/10.1016/j.comptc.2013.03.007



Scheme 1. Structures of the studied molecules.



Scheme 2. First ionization potential reaction. Structure 3 is employed throughout to represent the proposed mechanism.

and the corresponding benzoquinones; these calculations predict different decomposition pathways for o- and p-semiquinone radicals [27].

In this work we present a theoretical study to understand the biological activity of a series of phenols **1**, **7–10** and hydroquinones **2**–**6** (see Scheme 1) that present important inhibition of internal tumor cells respiration [10]. The activity has been studied measuring IC_{50} values ($<10^{-4}$ M) against tumor cell respiration of TA3 cell line and TA3-MTX-R multidrug resistant variety.

The first process that the molecules have to experience is to become de-solvated and cross the membranes. Then, to have a better understanding on the mechanism of action of these hydroquinone derivatives inside the mitochondria, we propose that the compounds experience the sequence of chemical reactions that appear in Scheme 3. Gibbs free energy of formation and free energy of solvation of all species involved were calculated at high level DFT theory. These results provide useful information about details of the mechanism of action of these molecules, as well as a criterion to search for new structures with improved biological activity.

2. Computational methods

All the hydroquinone geometries, including neutral anionic and cationic radical forms, were fully optimized at B3LYP/6-31++G(2df,p) level of theory. Solvent effects were evaluated by performing single-point calculations at the gas-phase stationary points involved in the reaction using the polarizable continuum model (PCM) with an integral equation formalism variant (IEFPCM) with UFF radii [28]. In order to adequately represent the biological media the modeled solvent was water. Gibbs free energies of solvation have been obtained with the SCFVAC method. All calculations were carried out using the Gaussian 03 suite of programs [29].

Adiabatic ionization potentials of the closed shell neutral molecules were obtained from differences in Gibbs free energies of formation, according to Scheme 2. In this and all subsequent schemes, we have used molecule **3** to represent the chemical processes involved.

Here $\Delta G°(H_2Q)$ and $\Delta G°(H_2Q^{\bullet+})$ are the standard Gibbs free energy of formation of the neutral molecule and the cationic radical, respectively.

Homolytic and heterolytic hydroxyl proton dissociation energies of the hydroquinone derivatives were also calculated from differences in Gibbs free energies of formation, as indicated in Scheme 3 [30].

The first step in the proposed mechanism is a rupture of one O-H bond, which can take place in two ways, heterolytic (Scheme 3I) and homolytic (Scheme 3II). Heterolytic dissociation reaction, with a Gibbs free energy ΔG_1°, corresponds to the formation of the solvated phenoxide ion, and can take place by two routes, a and b