Chemical Physics Letters 677 (2017) 35–40

Contents lists available at ScienceDirect

Chemical Physics Letters

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

Research paper

Electrochemical and theoretical characterization of the electro-oxidation of dimethoxycurcumin

Lily Arrue [a], Tomas Barra [a], María Belén Camarada [b,*], Ximena Zarate [c], Eduardo Schott [a,d,*]

[a] Departamento de Química Inorgánica, Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago-22, Chile
[b] Universidad Bernardo OHiggins, Centro Integrativo de Biología y Química Aplicada (CIBQA), General Gana 1702, Santiago, Chile
[c] Instituto de Ciencias Químicas Aplicadas, Facultad de Ingeniería, Universidad Autónoma de Chile, Av. Pedro de Valdivia 641, Santiago, Chile
[d] Centro de Nanotecnología y Materiales Avanzados, CIEN-UC, Pontificia Universidad Católica de Chile, Av. Vicuña Mackenna 4860, Macul, Santiago de Chile, Chile

ARTICLE INFO

Article history:
Received 31 January 2017
In final form 23 March 2017
Available online 29 March 2017

Keywords:
Electrochemical oxidation
Dimethoxycurcumin
DFT
Voltammetry

ABSTRACT

Dimethoxycurcumin (DMC) ((1E,6E)-1-(3,4-dimethoxycyclohexyl)-7-(3,4-dimethoxyphenyl) hepta-1,6-diene-3,5-dione) is a natural polyphenolic compound that appears together with curcumin in turmeric. Both molecules have wide range biological activities as antioxidant, anti-inflammatory and anti-carcinogenic agent. To evaluate the oxidation process and kinetics for DMC, the rate constant, electron transfer and diffusion coefficients for the electrochemical oxidation were determined. Therefore, its electrochemical behavior over a platinum electrode in anhydrous media was investigated. Furthermore, DFT calculations were performed to give a rational explanation to the obtained results. All the results support the fact that the central —CH_2— group is the most reactive against an oxidation process.

1. Introduction

Drug discovery and development has been directly related to plant and natural sources. Natural products have served as inspiration for a large part of the current pharmacopoeia [1]. Curcumin (Fig. 1), is an organic molecule present in turmeric (*Curcuma longa*), a yellow pigment and spice commonly used in India and surrounding countries [2]. Curcumin is characterized by its biological activity and medical properties such as anti-oxidant, anti-inflammatory, anti-angiogenic and anti-viral [3–6]. Despite the promising characteristics of curcumin, studies have demonstrated its unviable therapeutic application due to its instability, low water solubility and poor bioavailability [7]. In the search for new curcumin analogues with improved properties, different structures have been proposed [8]. Dimethoxycurcumin (DMC) is a symmetric structural derivative of curcumin where the —OH groups of the phenolic ring are replaced with methoxy functional groups (see Fig. 1). DMC has showed to be more potent than curcumin in inhibiting proliferation and inducing apoptosis of cancer cells, and has lower degradation rate in comparison to curcumin [9–12]. Sandur and coworkers have reported the strong anti-inflammatory activity of DMC, having superior bioavailability and comparable efficacy to curcumin [13] and recently have showed that DMC can enhance the cancer cell killing when combined with radiation [14].

Mechanisms for the action of DMC can be related to several biological targets. Although not fully established, it is proposed that the anti-tumor activity of DMC is mainly due to the stability, potent antioxidant and free-radical scavenger properties [15,16], which result in the interception and neutralization of chemical carcinogens, such as ROS (reactive oxygen species) and NOS (nitric oxide and peroxynitrite species). The remarkable antioxidant properties of DMC are assigned specifically to the —CH_2— methylene group of the β-diketone structure [17], which exhibit as its parent molecule, keto-enol tautomerism in solution [18]. The crystal structure determined by X-ray diffraction shows that the enol form is stabilized by strong intramolecular bonds between the hydroxyl group and the keto group [19].

The role of natural products, like curcumin and DMC, as scavengers of reactive species can be studied using electrochemistry. Electrochemical methods are generally based in the measurement of the charge transfer that occurs at the interface of an electrode and a solution [20]. These types of measurements have certain advantages for the determination of antioxidant activity [21] such as low cost, simplicity, and shorter analysis time compared to other techniques. Electrochemical measurements leading to the determination of kinetic and thermodynamic parameters for antioxidants (e.g., oxidation potential, number of electrons transferred, electrode reaction rate constant) are very relevant, not only for evaluating the antioxidative, but also for understanding their

* Corresponding authors.
E-mail address: maschotte@gmail.com (E. Schott).

http://dx.doi.org/10.1016/j.cplett.2017.03.067
0009-2614/

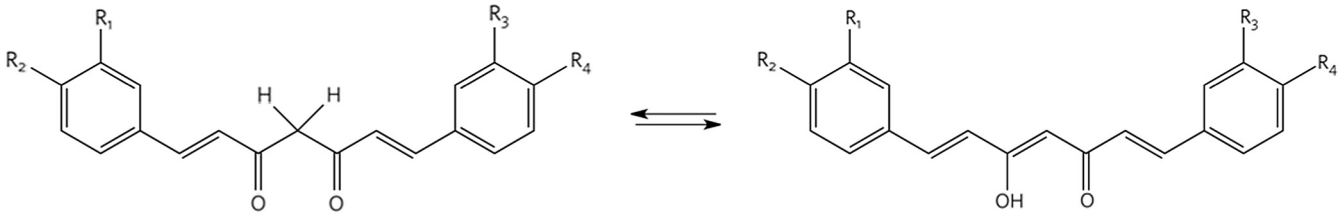

Fig. 1. Keto-enol tautomers of dimethoxycurcumin (R1 = R2 = R3 = R4 = —OCH_3) and curcumin (R1 = R3 = —OCH_3, R2 = R4 = —OH).

reaction mechanisms. The electrochemical technique cyclic voltammetry (CV) is one of the most common ways to characterize electroactive systems. Oxidation potential values measured trough CV have been used to compare the antioxidant strength of compounds such as phenolic acids, flavonoids, cinnamic acids among others [22]. Commonly, the half-wave oxidation potential ($E_{1/2}$) provides information about the antioxidant activity of the compound under study [23]. High values of $E_{1/2}$ are often associated with a lower capability or strength for the electrodonation and thus, to act as antioxidant. It has been reported that organic molecules with a lower value of oxidation potential, i.e. higher susceptibility to be oxidized, have higher radical scavenging activities [24].

Electrochemical studies of curcumin using different techniques and conditions have been performed to fully understand its oxidation mechanism [25–28]. Consequently, the goal of this study is to understand the oxidative mechanism of DMC using CV and computational techniques to understand its oxidation process at a platinum electrode in anhydrous media.

2. Experimental and computational methods

2.1. Chemicals

Chemicals used for the electrochemical measurements were provided by Sigma-Aldrich: dichloromethane (CH_2Cl_2), tetrabutylammonium tetrafluoroborate (TBATFB) and potassium chloride (KCl). All reagents were of analytical grade.

2.2. Synthesis of 1,7-bis(3,4-dimethoxyphenyl)heptane-3,5-dione or 3,4-dimethoxycurcumin (DMC)

The synthesis was performed using the methodology published by Khan et al. [29], as follows. In a round bottom flask 10 mL of ethyl acetate, 1 g (10 mmol) of acetylacetone and 0.52 g (7 mmol) of boric anhydride were added and the reaction mixture was stirred for 2 h at 70 °C. Then 3,4-dimethoxybenzaldehyde (20 mmol) and 10.8 mL (40 mmol) of tributyl borate were added and stirred for 1 h. While stirring, 0.4 mL of butylamine (4 mmol) dissolved in 10 mL of ethyl acetate was added dropwise every 60 min. Stirring was continued overnight. The following day, 40 mL of 4 M hydrochloric acid were added and the mixture was stirred for 60 min. The organic layers were separated and the aqueous fraction was extracted three times with 100 mL of ethyl acetate. The combined organic layers were washed with water and evaporated to dryness. The obtained solid was dissolved in boiling ethanol. Over the obtained solution the same amount of boiling water was added and allowed to stand overnight. DMC was filtered off, washed with cold ethanol and dried. On TLC DMC gave one spot with $CH_3CH_2OH/CHCl_3$ (1:1) as eluent. ^{1}H NMR(DMSO-d_6): 3.80 s, 6H; 3.83 s, 6H; 6.09 s, 1H; 6.79–6.83 d, 2H; 6.98–7.00 d, 2H; 7.24–7.26 d, 2H; 7.34 s, 2H; 7.57–7.61 d, 2H; 9.64 s, 2H; 16.29–16.48 s, 1H. ^{13}C-NMR(DMSO-d_6): 56.05, 101.50, 110.95, 112.13, 122.51, 123.38, 128.04, 140.89, 149.50, 151.44, 183.68. Mass spectra: 396 [M^+]. Yield: 58%.

2.3. Electrochemical methods

Cyclic voltammetry (CV) measurements were accomplished on a CH Instruments 760E potenciostat-galvanostat. A conventional three-compartment, three-electrode cell was employed throughout the work. A polycrystalline platinum disk (0.07 cm^2 geometric area) was used as working electrode. The counter electrode was a coiled Pt wire of large area, separated from the electrolytic solution by a sintered glass. Prior to each experiment the working electrode was polished to a mirror finishing with alumina slurry (particle size 0.3 mm), rinsed with water, and anhydrous dichloromethane. An Ag/AgCl electrode in N,N,N-trimethylmethanaminium chloride solution that matches the potential of a Ag/AgCl, KCl (1 M) electrode was used as reference electrode. Anhydrous dichloromethane was selected as solvent and the supporting electrolyte, tetrabutylammonium tetrafluoroborate, was dried at 110 °C and kept into a dryer. Dry syringes were employed for the manipulation of anhydrous dichloromethane maintained under inert atmosphere. Glassware was kept into an oven at 60 °C. High purity argon was flushed through the solution for 15 min prior to each experiment to remove any dissolved oxygen and an argon blanket was maintained over the solution during the measurements. All measurements were performed at room temperature.

2.4. Computational details

Density functional theory (DFT) as implemented in Gaussian 09 [31] software was employed to perform the computations of the studied systems. The hybrid Becke-3-parameter-Lee-Yang-Parr functional (CAM-B3LYP) [30,32,33] was employed, which provides additional long-range corrections. The Gaussian basis sets 6-31G (d) was used [34]. The molecular structures were fully optimized without symmetry constriction and the vibrational frequencies calculations were performed at the same level of theory as the geometry optimizations to confirm that all the optimized systems are stationary minima points. The implicit solvent–systems interactions were modeled using the polarizable continuum model for dichloromethane (PCM, $\varepsilon = 8.93$) [35].

To determine the free energies of the complexes, both geometry optimizations and frequency calculations were performed in the gas and condensed phase, as shown in Fig. 2, with the same solvent parameters used in the experiments.

For the open-shell compounds, the unrestricted DFT approach was employed. The standard Gibbs free energies in solution were obtained from calculations performed in the gas phase and in dichloromethane solution for the oxidized specie, all based on the Born−Haber cycle shown in Fig. 2. The gas-phase free energies were obtained from single-point energy calculations followed by frequency calculations. As shown in Fig. 2, the redox change of Gibbs free energy in solution has three components, which represent three different redox processes: (1) the redox free energy