

Theoretical determination of the redox electrode potential of cyanidin

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Abstract: The redox electrode potential of cyanidin was determined both by experimental (cyclic voltammetry) and theoretical methods, at the HF/6-311G(d) level of theory. An isodesmic reaction scheme, involving 1,2-benzoquinone as reference molecules, was proposed for the computation of the electrode potential of cyanidin. The results of the *ab initio* computations were in reasonable agreement with the available experimental measurements; the differences between experiment and theory were within the range of 0.02–0.05 V. Geometric parameters of the six more stable conformers of cyanidin were computed, as well as the properties, such as atomic charges and contribution to the HOMO (highest occupied molecular orbital) energies, of each hydroxyl group of cyanidin.

Keywords: cyanidin; electrode potential; *ab initio* methods; atomic charges; antioxidant.

INTRODUCTION

During the last years, antioxidants have gained an increased importance due to their large number of applications in the pharmaceutical and medical field.¹ They were found to play a positive role as adjuvants in the treatment of diabetes² and cardiovascular diseases.³

Among the various type of antioxidants, anthocyanidins are one of the polyphenolic derivatives with highest antioxidant activity. Several studies were reported that outline the enhanced antioxidant activity of anthocyanidins by both experimental^{4–7} and theoretical^{8,9} methods.

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In this regard, the study of the redox properties of a compound is a good possibility for predicting its behavior in more complex biological systems.¹⁰ Moreover, calculation of the electrode potential with a high degree of accuracy may lead to valuable information regarding the nature of the redox reactions.¹⁰

A literature survey regarding the theoretical determination of redox properties revealed a number of studies within this field. Namazian *et al.*¹¹ reported the computation of electrode potential of a coumestan derivative, as well as a study regarding the electrode potential of quinines with an accuracy of 0.03 V.¹² Tsutsui and Sakamoto¹³ reported the correlation of experimental electrode potentials for a series of silyl-substituted 1,4-benzoquinones with theoretical calculations of LUMO energy levels. Namazian and Coote¹⁴ calculated the absolute redox potential of rutin both by experimental and computational methods. In addition, the oxidation potentials of dihydroxy-anthracene thioxanthene derivatives¹⁵ and the electrode potentials for substituted 1,2-dihydroxybenzenes in aqueous solution¹⁶ were theoretically and experimentally determined.

The combination of quantum-chemical and electrostatic solvation calculations also led to good results in computing the pK_a values and redox potentials in various complexes, organic molecules and enzymes. Thus, computations of redox potentials and pK_a values of hydrated transition metal cations by a combined density functional and continuum dielectric theory,¹⁷ the estimation of pK_a values of amines in water from quantum mechanical calculations using a polarized dielectric continuum representation of the solvent¹⁸ and DFT computations of pK_a values and redox potentials in the bovine Rieske iron-sulfur protein¹⁹ were reported. Solvent effects on the redox potential²⁰ and absolute acidities²¹ of various sulfur complexes were investigated. The redox-dependence of the pK_a values of the CuB His ligand of cytochrome c oxidase,²² as well as DFT/electrostatic calculations of the pK_a values in cytochrome c oxidase²³ were performed. The DFT theory has been employed for the calculation of redox potentials of [2Fe2S] clusters in ferredoxin and phthalate dioxygenase reductase²⁴ and for electrostatic calculations of manganese superoxide dismutase active site complexes in protein environments.²⁵ Furthermore, Popovic and Stuchebrukhov investigated the coupled electron and proton transfer reactions during the O → E transition in bovine cytochrome c oxidase.²⁶

The present study deals with an evaluation, by theoretical methods, of the redox electrode potential of cyanidin. A number of studies regarding the antioxidant activity of various vegetal extracts,²⁷ as well as a theoretical study regarding an evaluation of the antioxidant activity of each OH group (by computation of the bond dissociation enthalpy (BDE) index)²⁸ were previously reported. It is well known that the antioxidant properties of cyanidin are given by the presence of the five hydroxyl groups that are present on both the benzopyrylium and phenyl rings (Fig. 1).

According to literature data, the highest antioxidant character is attributed to the OH groups in the *o*-position on the phenyl ring (namely the 3'-OH and 4'-OH), followed by the 3-OH group and, finally the 5-OH and 7-OH groups.²⁹

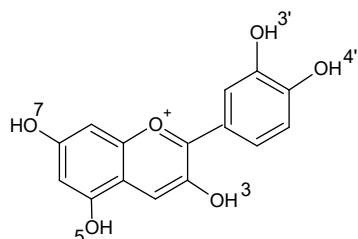
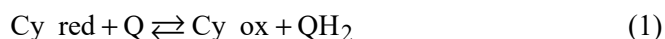
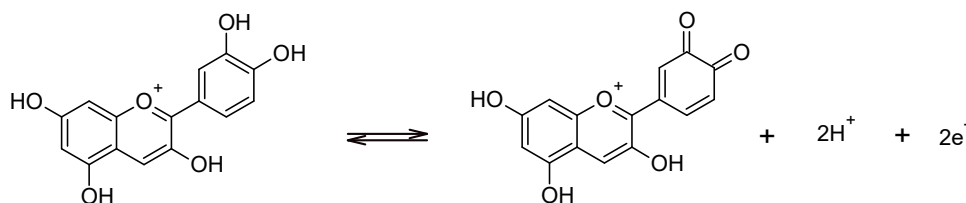


Fig. 1. The structure of cyanidin.

Within the present study, the calculation of the electrode potential by means of an isodesmic reaction scheme was performed and comparisons with the results of the experimental determination of electrode potential of cyanidin in methanolic solution were made. The hypothetical reaction is the following:



As the most reactive groups are 3'-OH and 4'-OH, the following *o*-quinone derivative is considered the oxidation product of cyanidin:



As reference molecules, the 1,2-benzoquinone/1,2-dihydroxybenzene couple ($E^\ominus = 0.795 \text{ V vs. SHE}$)³⁰ was chosen.

The investigated species are given in Fig. 2.

METHODOLOGY

Computational part

The conformational analysis of cyanidin was performed by means of Spartan'14 software,³¹ and the six most stable conformers were chosen. The geometries of the reduced and oxidized species were optimized with no imaginary frequencies being obtained. For the solvent-phase computations, the Polarizable Continuum model was chosen (namely the integral equation formalism polarizable continuum model (IEF-PCM), where the solute is characterized by the electron density).³² In order to perform the optimizations in a methanolic phase, the minima structures that had previously been obtained in vacuum were used as starting geometries.

For the calculation of the theoretical redox electrode potential of cyanidin, the thermodynamic cycle shown in Scheme 1 was employed.

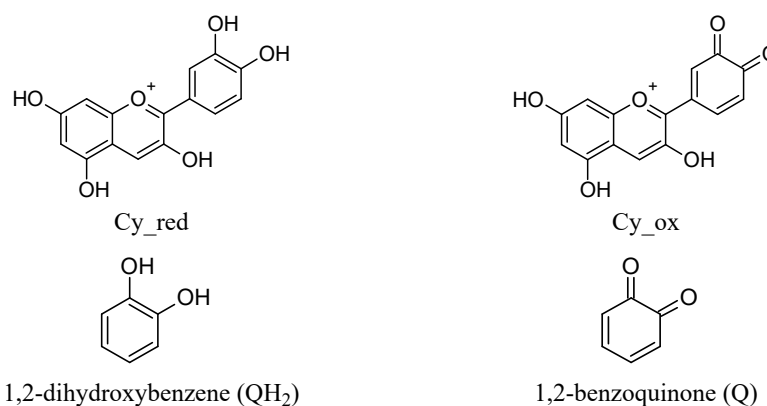
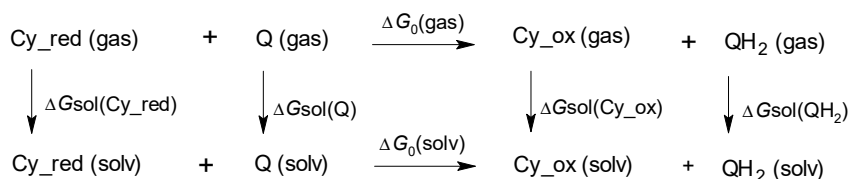


Fig. 2. Reactants and products of the isodesmic reaction employed for the computation of the electrode potential of cyanidin.



Scheme 1. Thermodynamic cycle employed for the computation of the electrode potential of cyanidin.

The redox electrode potential was computed by using the Eqs. (1)–(4); according to Scheme 1, the value of n is 2 (n is the number of exchanged electrons):

$$\Delta G_{\text{T}} = -nF(E^0 - E_{\text{Q/QH}_2}^0) \quad (1)$$

$$\Delta G_{\text{T}} = \Delta G_{\text{gas}} + \Delta \Delta G_{\text{sol}} \quad (2)$$

$$\Delta G_{\text{gas}} = G_{\text{gas}}(\text{products}) - G_{\text{gas}}(\text{reactants}) \quad (3)$$

$$\Delta \Delta G_{\text{sol}} = \Delta G_{\text{sol}}(\text{products}) - \Delta G_{\text{sol}}(\text{reactants}) \quad (4)$$

For the computations of the Gibbs free energies, the zero point energy (ZPE) and thermal corrections were taken into account. The computed values of G_{gas} and ΔG_{sol} for all species involved in the present study are given in the Supplementary material to this paper.

The value of Faraday constant employed throughout this study was $F = 96485 \text{ C mol}^{-1}$ and the electrode potential for the 1,2-benzoquinone/1,2-dihydroxybenzene couple is 0.565 V vs. Ag/AgCl/satd. KCl.

The computations of the electrode potential of cyanidin were performed at the HF/6-311G(d) level of theory. The basis set was chosen by taking into account the results of previous studies regarding the successful calculation of various electrode potentials at the HF/6-31G(d)¹⁰ and HF/6-31G(d,p)¹⁵ levels of theory with discrepancies (between theory and experiment) of 0.018 and 0.024 V, respectively.

Equations (5)–(7) were employed for the computations of the electronic properties of the six conformers of cyanidin, namely the chemical potential (μ), hardness (η) and electrophilicity index (ω).³³ The computations were performed for the gas-phase geometries of the species, optimized at the HF/6-311+G(d,p) level of theory:

$$\mu = \frac{(E_{\text{HOMO}} + E_{\text{LUMO}})}{2} \quad (5)$$

$$\eta = \frac{(E_{\text{LUMO}} - E_{\text{HOMO}})}{2} \quad (6)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (7)$$

As mentioned before, the conformational analysis was performed with the Spartan'14 software;³¹ for all the other computations, the Gaussian 09W program³⁴ was employed throughout the present study.

Experimental part

The oxidation peaks in cyclic voltammetry appear at 0.53, 0.68, 0.92 and 1.10 V vs. Ag/AgCl (see the Supplementary material to this paper).

The cyclic voltammogram was recorded on a Voltalab 80 PGZ 402 apparatus, equipped with VoltaMaster 4 software (version 7.0). The following operating conditions were chosen: working electrode, glassy carbon electrode; reference electrode, Ag/AgCl/satd. KCl; auxiliary electrode, Pt wire; supporting electrolyte, 0.1 M NaClO₄ in methanol (pH 2.35); scan rate: 500 mV s⁻¹.

RESULTS AND DISCUSSION

Geometry details

The structure of cyanidin comprises a planar construction of a benzopyrylium ring that has a phenyl moiety in position 2. All the compounds within the anthocyanidins class have a variable number of hydroxyl and methoxy groups; in the specific case of cyanidin, there are five hydroxyl groups positioned at 3, 5, 7, 3' and 4'. This leads to the possibility of a large number of conformers, as a function of the position of the O–H bonds towards the corresponding rings. As a result, after performing the conformational analysis of cyanidin, six more stable conformers were chosen for the present study. Along with the results for the most stable conformer, the same computations were performed for the other 5 structures, in order to evaluate the influence of the O–H bond orientation on the properties of each conformer.

The optimized geometries of the 6 investigated structures are depicted in Fig. 3 and given in Table I.

According to these results, the most stable structure is conformer **2**. The geometric parameters of the six conformers are given in Table II, and show that the two structures (namely **3** and **4**) where the 3-OH groups are non-coplanar with the phenyl chromenylium ring are the least stable ones.

As the antioxidant character is strongly correlated with the ability to donate electrons, higher HOMO energies outline an increased antioxidant character. The total HOMO energies are depicted in Table I and show only insignificant differences among the six compounds; instead, computations of the contribution to the HOMO energy of each group suggest that 4'-OH, 3'-OH and 3-OH have a more pronounced antioxidant character. Significantly lower values were obtained for the contributions of the 3-OH and 5-OH groups in the non-planar conformers **3** and **4**.

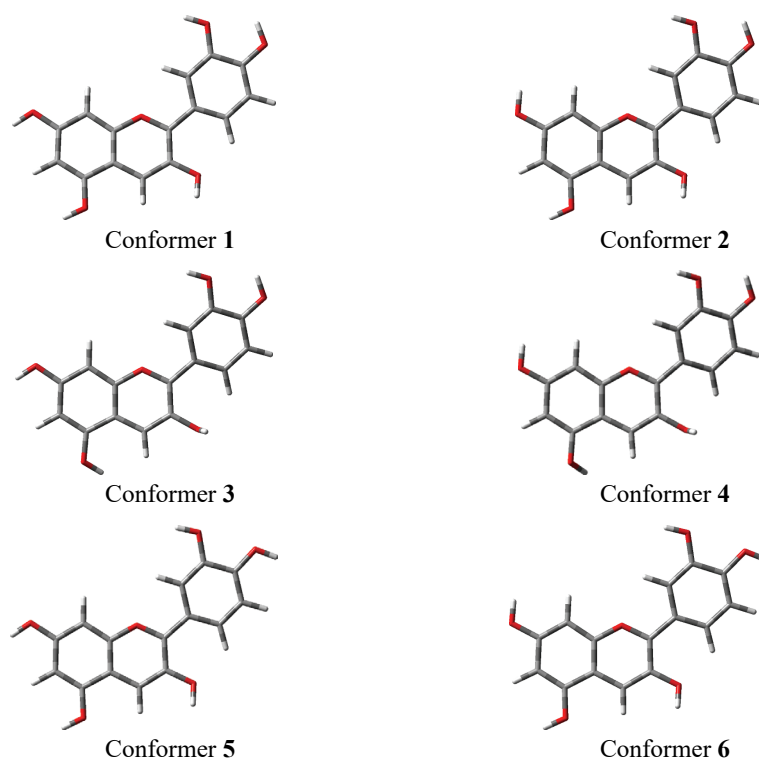


Fig. 3. Structures investigated within the present study.

TABLE I. Total energy, dipole moment and HOMO energy of the investigated structures; vacuum computations at the HF/6-311+G(d,p) level

Conformer	Energy, a.u.	Dipole moment, D ^a	E_{HOMO} / a.u.
1	-1023.645985	6.846	-0.412464
2	-1023.646411	4.640	-0.413827
3	-1023.637457	4.160	-0.421845
4	-1023.636135	2.217	-0.422812
5	-1023.638734	7.170	-0.411516
6	-1023.639350	4.497	-0.412631

^a1 C m = 3×10²⁹ D

TABLE II. Geometric parameters of the O–H groups, dihedral angle, ° (for the gas phase optimized geometries)

Conformer	C3'–C4'–O4'–H	C4'–C3'–O3'–H	C4–C3–O3–H	C6–C5–O5–H	C6–C7–O7–H
1	–0.054	–178.360	–15.470	0.211	–0.170
2	0.190	–175.388	–20.576	0.240	–179.730
3	–0.216	178.673	–95.912	158.185	0.502
4	0.059	–176.179	–95.110	–23.566	–178.909
5	179.968	–179.891	–17.256	0.193	–0.135
6	179.984	–179.680	–18.625	0.187	–179.898

An experimental study reported by de Lima²⁹ showed that the OH groups of the phenyl ring are the first that undergo oxidation, followed by the 3-OH group. The least reactive are the 5-OH and 7-OH groups. This appears to be in good agreement with the results presented in Table III. The same study reported a value of 564 mV for the first oxidation peak (corresponding to the oxidation mechanism, Eq. (1)).

TABLE III. Contributions to E_{HOMO} (in a.u.); vacuum computations at the HF/6-311+G(d,p) level

Conformer	3'-OH	4'-OH	3-OH	5-OH	7-OH
1	0.267	0.348	0.325	0.168	0.243
2	0.237	0.339	0.295	0.149	0.210
3	0.273	0.345	0.191	0.114	0.221
4	0.275	0.335	0.184	0.077	0.215
5	0.298	0.350	0.296	0.159	0.230
6	0.292	0.347	0.285	0.137	0.224

The results of the global electronic parameters of the investigated structures are listed in Table IV and they show no significant differences among the six conformers.

TABLE IV. Chemical potential (μ), hardness (η) and electrophilicity (ω) of cyanidin (gas-phase computations at the HF/6-311+G(d,p) level of theory)

Conformer	μ / eV	η / eV	ω / eV
1	–7.31	3.91	6.83
2	–7.33	3.92	6.86
3	–7.50	3.97	7.09
4	–7.52	3.98	7.11
5	–7.29	3.90	6.82
6	–7.32	3.91	6.85

Electrode potential computations

In order to estimate the theoretical potential electrode of cyanidin, the thermodynamic cycle depicted in Scheme 1 was employed. The Gibbs free ener-

gies for the oxidized and reduced forms of cyanidin, as well as for quinone/hydroquinone couple are given in the Supplementary material.

According to Eqs. (1)–(4), the redox electrode potential (E^0) of cyanidin is:

$$E^0 = E_{Q/QH_2}^0 - \frac{\Delta G_T}{2F}$$

As mentioned earlier, the experimental determination of the oxidation potential of cyanidin was performed in 0.1 M NaClO₄ in methanol (pH 2.35); the pH influence was taken into account through a simplified form of the Nernst equation:

$$E^{0'} = E^0 - 0.059\text{pH}$$

The obtained results for the electrode potential of all the six conformers are listed in Table V.

TABLE V. Electrode potential of the conformers of cyanidin (HF/6-311G(d))

Conformer	Electrode potential, V
1	0.593
2	0.584
3	0.614
4	0.494
5	0.535
6	0.532

A value of 0.584 V was calculated for the redox electrode potential of the most stable cyanidin conformer. The values of the electrode potential for the other structures are within the range 0.494–0.614 V; the differences are believed to be due to the values of solvation energies of the oxidized and reduced forms of cyanidin. The results are in reasonable agreement with the experimental measurements, where values of 0.564²⁹ and 0.530 V (see Supplementary material) were obtained. Larger discrepancies with the experimental results were obtained for the conformers **3** and **4**, which are the least stable among the investigated structures.

CONCLUSIONS

The electrode potential of six conformers of cyanidin in aqueous solution were calculated at the HF/6-311G(d) level of theory by means of an isodesmic reaction scheme. The data range was 0.494–0.614 V, with an electrode potential of 0.584 V being obtained for the most stable conformer. Comparison with experimental results evidenced a calculation error of 0.05 V, which is attributed to an underestimation of the free energies computed within the PCM model.

Regarding the electronic properties of the six conformers, global parameters, such as electrophilicity, chemical potential and hardness were sparingly influ-

enced by the geometry of the molecules. On the contrary, local parameters, such as their contribution to the E_{HOMO} or atomic charges, were dependent according to the planarity of the OH groups with respect to the phenylbenzopyrylium skeleton.

SUPPLEMENTARY MATERIAL

Cyclic voltammogram and computational details related to the investigations presented in the paper are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding authors on request.

ИЗВОД

ТЕОРИЈСКО ОДРЕЂИВАЊЕ РЕДОКС ЕЛЕКТРОДНОГ ПОТЕНЦИЈАЛА ЦИЈАНИДИНА

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Редокс електродни потенцијал цијанидина одређен је и експерименталним (циклична волтаметрија) и теоријским методама на HF/6-311G(d) нивоу теорије. За израчунавање електродног потенцијала цијанидина предложена је изодезмична реакција са 1,2-бензохиноном као референтним молекулом. Резултати *ab initio* израчунавања су у доброј сагласности са доступним експерименталним мерењима; разлике између експеримента и теорије су у оквиру 0,02–0,05 V. Израчунати су геометријски параметри још шест стабилних конформера цијанидина, као и својства попут атомских наелектрисања и допринос HOMO (највиша заузета молекулска орбитала) енергија за сваку хидроксилну групу цијанидина.

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