

Computational Prediction of Dobutamine Redox Potential: Theoretical and Experimental Investigation

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Abstract

Computational and experimental approach on standard redox potential of dobutamine was developed in aqueous media. A direct and indirect calibrated B3LYP/6-311++G (d, p) method predicted the aqueous phase redox potential of dobutamine as 0.850 V Respectively. The electronic densities of dobutamine calculation at oxidation and reduction state in HOMO and LUMO proved that energies of dobutamine LUMO in oxidation form are lower than dobutamine LUMO in reduction. Therefore, the electron transfer from HOMO to LUMO in dobutamine oxidation form is easier than in dobutamine reduction form. The experimental E° was obtained using cyclic voltammetry at activated glassy carbon electrode as 0.79V versus SHE. The results show that there is a satisfactory agreement between the experimental and computational standard potential value of dobutamine.

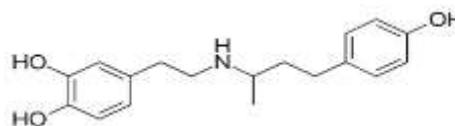
Keywords

Dobutamine; Density Functional Theory; Standard Electrode Potential; Cyclic Voltammetry.

1. INTRODUCTION

Catechol amines are biogenic amine with biological activity [1-2]. They are molecules which play pathological and physiological role in human body. Dobutamine (DB) is a synthetic catecholamine (scheme 1) used as therapeutic drug for cardiogenic shock and coronary, heart failure [3-4]. The chemical structure of catechol amines contains monoamine and adjacent hydroxyl groups, which are prone to oxidation [5-6]. Recently, computational determination of electrode potential of catecholamine's derivative has been in great attention [7-8]. In order to predict the redox potential value of these compound, some quantum mechanics methods such as Ab initio and density functional theory (DFT) have been used. Accurate calculation of electrode redox potential of catecholamine is beneficial for proper interpreting of their electron- transfer mechanism in many areas such as biochemistry and pharmacology. The propensity of an organic molecule for electron donation or acception is determined by standard redox potential. Based on comprehensive investigation, the oxidation of catecholamine group of DB includes loss of two electrons and two protons (in aqueous media) and formation of its corresponding quinone form [9-10]. In the case of its difficulty of experimental measurement, the cost-effective DFT simulation maybe performed to benchmark redox potential of

organic molecules contain hundreds of atoms [11-12]. In this works, the experimental and theoretical investigations have been adopted to predict E° of redox couple of DB. Firstly, formal electrode potential (E) of DB redox couple was measured at different pH by cyclic voltammetry. Then, Thermodynamic functions and E° was theoretically calculated and compared with experimental results to assess accuracy of the quantum computations of redox potential and structural characteristic of DB.



Scheme 1. Chemical structure of DB.

2. EXPERIMENTAL

Experimental analysis was performed using Autolab PGSTAT 101 equipped with NOVA software. Cyclic voltammetry measurement was made by three electrode system containing Pt counter electrode, SCE as reference electrode and activated glassy carbon as working electrode. Phosphate buffer was used as electrolyte and pH adjustment. GC was activated at NaHCO_3 (0.1M) from -1.1 V to +1.7 V using continual scans in CV (16 cycles) at scan rate of 100 mVs^{-1} . Theoretical calculation both direct and indirect method was applied for theoretical calculation of standard

electrode potential. All ab initio computations were performed using Gaussian 09 software. The Gibbs energy for each component (G_i°) used for calculation of standard energy of reaction (ΔG_{rxn}°):

$$\Delta G_{rxn}^\circ = \sum v_i G_i^\circ \quad (1)$$

Where v_i is the stoichiometric coefficient. All calculated Gibbs energy and energy values of LUMO and HOMO for both reduced and oxidized forms of DB in the gas and solution phase were performed using frequency calculations at DFT-B₃LYP level of theory as what is used in literatures for standard potential calculation of other catecholamines [28].

The basis set of 6-311++G(d, p) was chosen to consider the size of studied molecules. The conductor like polarizable continuum model (CPCM) was used to calculate the solvation free energies at B3LYP/6-311++G(d, p), level of theory [26] the CPCM solvation calculations applied to evaluate condensed-phase free energies are slightly less accurate than the gas-phase models, and the best method has a mean assigned error and standard deviation of 0.4 and 0.5 Kcal/mol respectively [26]. The optimization of geometry is the most important step for the calculation of the formal potential. The optimized structures are true energy-minimums, as no imaginary frequency is predicted. The standard Gibbs energy of each species was calculated by summation of $G_{i,gas}^0$ (gas phase Gibbs energy) and $G_{i,solv}^0$ (solvation phase Gibbs energy) using following equation [15]:

$$G_i^\circ = G_{i,gas}^0 + G_{i,solv}^0 \quad (2)$$

Where $G_{i,gas}^0$ is the gas-phase energy of each component and $G_{i,solv}^0$ is the solvation energy of the component.

3. RESULT AND DISCUSSION

3.1. Experimental measurement of formal electrode potential

Cyclic voltammograms of DB display at Fig.1. DB showed reversible redox peaks from pH=3.0 to pH=6.0, which can be assigned to catechol group of DB. At pHs higher than 6.0 the reduction peak disappear gradually. These peaks have shifted to less positive potential by increasing pH. The plot of formal potential versus pH give the equation of with linear regression. The slope of 0.057 per unit of pH indicate the Nernstian behavior of DB and also participation of equal number of protons and electron in DB redox mechanism [16-17]. The formal electrode potential E° was regarded as the average of anodic peak potential and cathodic peak potential [18].

Based on the relation between formal potential of redox couple, E° , pH and:

$$E^\circ = E^\circ - 2.303 \frac{mRT}{nF} pH \quad (3)$$

It is found that there is linear relationship between formal potential of the redox couple of DB and pH with linear regression equation of $E^\circ = -0.057 pH + 0.553$ and the intercept of 0.553 which considered as standard potential of dobutamine versus SCE.

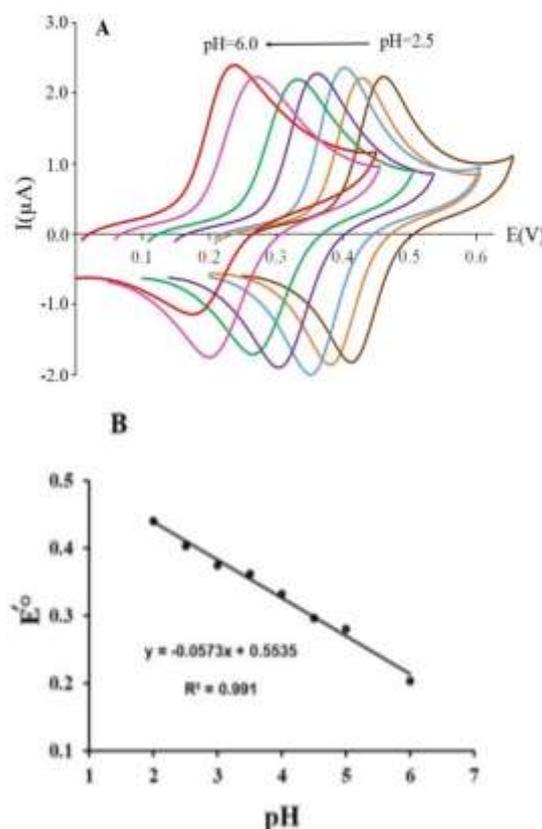
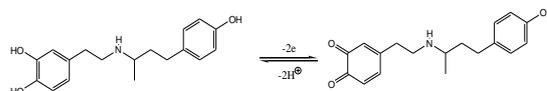


Fig. 1. (A) Cyclic voltammograms of DB at pHs of 2.5, 3.0, 3.5, 4.0, 4.5, 5.0 and 6.0 and (B) plot of formal potential versus pH.

In Eq (3) m and n are the number of protons, and electrons in redox reaction respectively [19]. Since the standard electrode potential of the SCE is 0.24 V relative to the Standard Hydrogen Electrode, the standard reduction potential of dobutamine obtained as 0.79 V versus SHE. As proved in literature, the oxidation mechanism of DB containing formation of o-benzoquinone derivative by losing two electrons and two protons as following [17]:



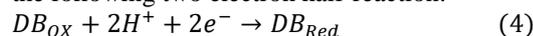
When GC activated with NaHCO₃ (0.1M) a couple of reversible redox peak was emerged at ($E_a=0.43V$ and $E_c=0.38 V$; pH=3). Dobutamine molecule structure contain pH sensitive groups with $pK_{a1}= 8.71$, $pK_{a2}= 10.90$, $pK_{a3}= 13.68$ [20-

21]. The reversible redox behavior was assigned to the catechol functional group. However, phenol moiety of DB can undergo reversible redox reaction at more positive potential. Fig 1 shows the effect of pH on the peak potential of DB at activated glassy carbon in 0.1M phosphate buffer (pH from 2.5 to 6) containing 0.1 mM DB using CV.

3.2. Calculation of electrode potential of DB: Theoretical prediction

3.2.1. Direct method

Standard redox potential of DB is calculated using the following two electron half-reaction:



The Gibbs energy change, $\Delta G^*(t)$, is related to the absolute potential through the following equation:

$$E^\circ = \frac{\Delta G^*(t)}{nF} \quad (5)$$

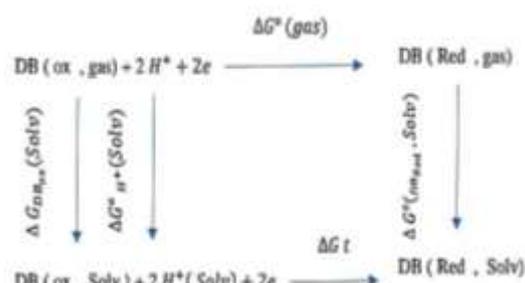
Where n is the number of electrons transferred (in this case n=2), F (96185 Cmol⁻¹) is the Faraday constant and $\Delta G^*(t)$ is the Gibbs energy change half reaction.

As scheme (2) shows, $\Delta G^*(t)$ can be calculated from its component by introducing a thermodynamic cycle,

$$\Delta G^*(t) = \Delta G^0(g) + \Delta G^*(solv, DB_{Red}) - \Delta G^*(solv, DB_{OX}) - 2\Delta G^*(solv, H^+) + \Delta n\Delta G^{0 \rightarrow *}(6)$$

The parameters defined as: change of Gibbs free energy of Scheme 2 in the gas-phase: $\Delta G^*(t)$; $\Delta G^*(solv., DB_{Red})$ and $\Delta G^*(solv., DB_{OX})$ are solvation energies of DB_{Red} and DB_{OX} in water, respectively. $\Delta G^{0 \rightarrow *}$ is the correction for the change in standard state from 1 atom for gas-phase calculations "°" to 1 molL⁻¹ for solution phase "°*" which is 7.9 kJmol⁻¹ for each component (RTln24.46) [23]; Δn is the change of moles of Scheme 1 and has a value of -2 in the present system. We have used the literature value of -1104.6 kJ mol⁻¹ (-264.0 kcal mol⁻¹) for aqueous $\Delta G^*(solv, H^+)$ which has been recently reported by Truhlar and Cramer.

In order to calculate $\Delta G^0(g)$, the Gibbs free energy of DB_{OX} and DB_{Red} have been calculated in gas phase using DFT(B,LYP) level of theory and 6-311++G(d,p) basis set (Table 1). The Gibbs energy of H⁺(g) has been reported to be -26.3 kJmol⁻¹ [26]. Using Eq. (5-6), reduction potential of DB has been calculated as 5.25 V. In order to be able to compare the obtained value with the experimental value, it is necessary to calculate the standard potential of DB compared to the SHE. Therefore the absolute value of reduction potential of SHE is required. In this work we have selected the value 4.44 for the SHE as found in the electrochemical textbook [18]. Therefore, the E° of DB_{OX} relative to SHE calculated as 0.85 V.



Scheme 2. Thermodynamic diagram for calculation of ΔG_t .

Table 1. Internal energies, thermal corrections containing zero - point energy and Gibbs Free Energies

	DB OX	DB Red	Scheme 2
ΔG_{gas}^a	-2569593.59	-2572817.29	-3223.69
$\Delta nRT \ln(24.46)^a$	7.90	7.90	-15.80
$\Delta \Delta G^*(solv)^a$	-58.55	-49.46	2218.29 ^b
$\Delta G^*(t)^a$	-	-	1021.40 ^b

a: These energies are in kJ mol⁻¹.

b: the free energy of salvation of proton has been considered as -1092.0 kJmol⁻¹.

From comparison of experimental and theoretical E° , it can be concluded that standard electrode potentials of DB are in good agreement with discrepancy of 0.06 V.

Fig. 3 displays the electronic densities of DB_{ox} and DB_{red} in HOMO and LUMO stated which is chiefly located on benzene ring and hydroxyl groups.

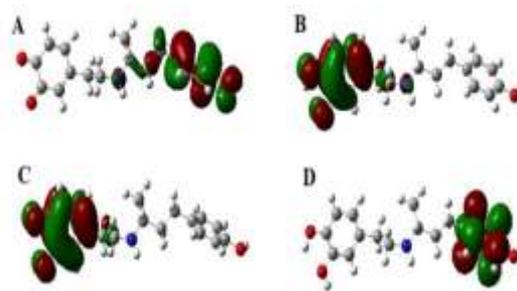


Fig. 3. The electronic density in the HOMO and LUMO states of DB_{ox} and DB_{red} computed by B3LYP/6-311++G(d,p) method. (A) HOMO orbital for DB_{ox}; (B) HOMO orbital for DB_{red}; (C) LUMO orbital for DB_{ox}; (D) LUMO orbital for DB_{red}.

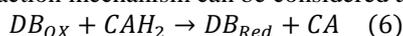
The energy values for HOMO and LUMO of DB_{ox} and DB_{red} calculated at B3LYP/6-311++G(d,p) level in solution and gas phase are presented in Table 2. The energies of DB_{ox} LUMO are lower than DB_{red} and the energy gap of DB_{ox} is less than those of DB_{red}. Therefore, the electron transfers from HOMO to LUMO in DB_{ox} is easier than in DB_{red}.

Table 2. Calculated eigen values of HOMO and LOMO, together with their energy gap.

Basis set	6-311++(d,p)			
Espectes	DBH ₂		DB	
Phase state	Gas	Solution	Gas	Solution
E _{HOMO} (eV)	-278.27	-278.32	-279.36	-279.63
E _{LUMO} (eV)	-0.63	-0.60	-5.07	-5.37
E _{HOMO-LUMO} (eV)	277.64	277.72	274.29	274.26

3.2.2. Indirect method:

This method calculates redox potential of reference molecule that is structurally related to DB category using an isodesmic reaction [24]. Considering catechol as reference molecule, the reaction mechanism can be considered as:

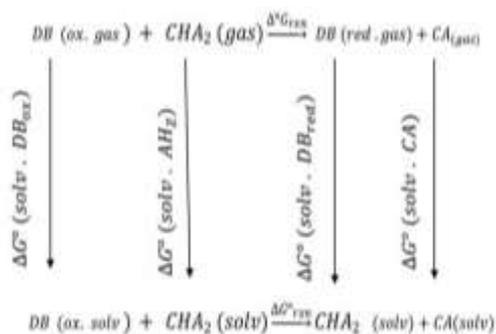


Where CAH₂ is reduction of catechol which converted to O- benzoquinone (CA) by reduction of DB_{ox}. The standard electrode potential E° of DB_{red} can be estimated using below equation:

$$E^\circ = E_{CAH_2}^\circ + \frac{\Delta G_{rxn}^\circ}{nF} \quad (7)$$

Where n is number of transferred electrons, E_{CAH₂}[°] is the experimental standard potential for CAH₂ and F is Faraday constant. In order to obtain standard electrode potential of DB the change of Gibbs free energy of reaction (5), is required (ΔG_{rxn}[°]). It is necessary to calculate the Gibbs free energy of each component to obtain the standard Gibbs energy of reaction. The standard Gibbs energy of reaction can be estimate using Eq.(1) and the standard Gibbs energy of each component is obtained using Eq.(2)

Table 3 shows the calculated Gibbs energy of molecules for both reduced and oxidized form in gas and solution phase using frequency calculation at DFT(B3LYP) level of theory and 6-311++G(d,p) basis set. By choosing 0.79 V [28] for the experimental value of the electrode potential of reference molecule using value that present in table 3 the standard electrode potential of DB is obtained to be 0.85 V versus SHE, which is an agreement with the experimental value.

**Scheme 3.** thermochemical cycle for indirect method.**Table 3.** The Gibbs free energy of the DB for both reduced (red.) and oxidized (ox.) forms in the gas and solution phases, accompanied by the change of Gibbs free energy of reaction, ΔG₁, in both gas and solution phases.

Mol ^a	G _{gas} ^b		G _{solu} ^b		ΔG ₁ ^b	
	Red	OX	Red	OX	Gas	Solution
1	-	-	-	-	0	0
	382.643	381.410	382.651	381.424		
2	-	-	-	-	-	-
	979.934	978.706	979.953	978.729	0.0045	0.0003

a: 1: Red=CAH₂, OX=CA, 2: Red=DBH₂, OX=DB

b: These energies are in atomic units, Hartree (1Hartree=2625.5 KJmol⁻¹)

4. CONCLUSION

Experimental standard potentials of DB_{ox}/DB_{red} using CV was found to be equal to V versus SHE which is in good agreement with theoretical model calculated by DFT method. The results show that formal potential of DB_{ox} / DB_{red} is mainly depend on pH value electronic densities in HOMO and LUMO state of DB_{ox} / DB_{red} in water at B3LYP/6-311 ++G** indicate that electron transfer from HOMO and LUMO in DB_{ox} is easier than in DB_{red}.

REFERENCES

- [1] H. Vasconcelos, L.C. Coelho, A. Matias, C. Saraiva, P.A. Jorge, J. M. de Almeida. Biosensors for Biogenic Amines: A Review. *Biosensors*, 11 (2021) 82.
- [2] C. Capitain, W. Sebastian, H. Joana, T. Nils, Investigation of C–N formation between catechols and chitosan for the formation of a strong, novel adhesive mimicking mussel adhesion. *Waste and Biomass Valorization*, 12 (2021) 1761.
- [3] M. Heringlake, A. Julian, B. Dominique, B. Stefaan, F. Sonja, G. Massimo, G. Elena, G. Fbio, H. Antoine, T. Wolfgang, T. Luigi, P. Piero, An update on levosimendan in acute cardiac care: applications and recommendations for optimal efficacy and safety. *Expert Rev. Cardiovasc. Ther.* 19 (2021) 325.
- [4] M.J. Jaguszewski, G. Aleksandra. T. Radoslaw, J.F. Krzysztof, S. Lukasz, Efficacy and safety of levosimendan and dobutamine in heart failure: A systematic review and meta-analysis. *Cardiol. J.* 28(2021)492..
- [5] T.V. Astaf'eva, M.V. Arsenyev, R.V. Rummyantsev, G.K. Fukin. V.K. Cherkasov, A.I. Poddel'sky, Imine-Based Catechols and o-Benzoquinones: Synthesis, Structure, and Features of Redox Behavior. *ACS omega*, 5 (2020) 22179.
- [6] B. Sun, D. Feng, M.L.H. Chu, I. Fish, S. Lovera, Z.A. Sands, S. Kelm, A. Valade, M. Wood, T. Ceska, T.S. Kobilka, F. Lebon, B.A.

- Kobilka, Crystal structure of dopamine D1 receptor in complex with G protein and a non-catechol agonist. *Nature communications*, 12 (2021) 1.
- [7] S. Riahi, M.R. Ganjali, H. Khajehsharifi, P. Norouzi, S. Taghipoor. Theoretical and experimental studies on some anticancer derivatives: Electrochemical investigation. *Int. J. Electrochem. Sci*, 4 (2009)122.
- [8] A.R.L. Da Silva, A.J. Dos Santos, C.A. Martinez-Huitle. Electrochemical measurements and theoretical studies for understanding the behavior of catechol, resorcinol and hydroquinone on the boron doped diamond surface. *RSC Adv.*, 8 (2018) 3483.
- [9] F. Hasanpour, M. Nekoeinia, A. Semnani, R. Shirazinia. Synthesis of semicarbazide catechol derivative as a potential electrode modifier: application in electrocatalysis of catechol amine drugs. *Chem. Pap*, 73 (2019) 2081.
- [10] Y. Zhang, M. Zhaomin, Electrochemical Behavior of Hydroquinone at Poly (Acridine Orange)-Modified Electrode and Its Separate Detection in the Presence of o-Hydroquinone and m-Hydroquinone. *Anal. Lett*, 39 (2006) 1289.
- [11] A. P. Davis, A. J. Fry, Experimental and computed absolute redox potentials of polycyclic aromatic hydrocarbons are highly linearly correlated over a wide range of structures and potentials. *J. Phys. Chem A*, 114 (2010) 12299.
- [12] T. Matsui, S. Jong-Won. A Density Functional Theory-Based Scheme to Compute the Redox Potential of a Transition Metal Complex: Applications to Heme Compound. *Molecules*, 24 (2019) 819.
- [13] M.M. Liu, Sh.M. Han, X.W. Zheng, L.L. Han, T. Liu, Zh.Y. Yu. Experimental and theoretical prediction of the redox potential of dopamine and its supramolecular complex with glycine. *Int. J. Electrochem. Sci*, 10 (2015) 235.
- [14] S. Miertus, E. Scrocco, J. Tomasi, Electrostatic interaction of a solute with a continuum. A direct utilization of ab initio molecular potentials for the prevision of solvent effects, *Chem. Phys.* 55 (1981) 117.
- [15] M. Namazian, H.R. Zare, M.L. Coote. Determination of the absolute redox potential of Rutin: Experimental and theoretical studies. *Biophysical chemistry*, 132 (2008) 64.
- [16] X. Yan, U. J. Charlotte, F. Diao, K. Qvortrup, D. Tanner, J. Ulstrup, X. Xiao. Surface-confined redox-active monolayers of a multifunctional anthraquinone derivative on nanoporous and single-crystal gold electrodes. *Electrochem. commun.*, 124 (2021) 106962.
- [17] F. Hasanpour, M. Nekoeinia, A. Semnani, S. Shojaei. NiMnO₃ nanoparticles anchored on graphene quantum dot: Application in sensitive electroanalysis of dobutamine. *Microchem. J.*, 142 (2018) 17.
- [18] A.J. Bard, L.R. Faulkner, *Electrochemical Methods: Fundamentals and Applications*, Wiley, New York, 2001.
- [19] A.J. Bard, R. Parsons, J. Jordan, *Standard Potentials in Aqueous Solution*, IUPAC: Marcel Dekker, Inc., New York, 1985.
- [20] S. Shahrokhian, M. Ghalkhani, R. Kohansal, R. Mohammadi, Biomimetic sensor for dobutamine employing nano-TiO₂/nafion/carbon nanoparticles modified electrode, *Electroanalysis* 28 (2016) 970.
- [21] S. Palanisamy, S.K. Ramaraj, S.M. Chen, V. Velusamy, T.C.K. Yang, T.W. Chen, Voltammetric determination of catechol based on a glassy carbon electrode modified with a composite consisting of graphene oxide and polymelamine, *Microchim. Acta* 184 (2017) 1051.
- [22] M. Namazian, H.A. Almodarresieh, M.R. Noorbala, H.R. Zare, DFT calculation of electrode potentials for substituted quinones in aqueous solution, *Chem. Phys. Lett.* 396 (2004) 424
- [23] M.D. Liptak, K.G. Gross, P.G. Seybold, S. Feldgus, G.C. Shields, Absolute pKa determinations for substituted phenols, *J. Am. Chem. Soc.* 124 (2002) 6421.
- [24] D. Chaparro, J. Alí-Torres. Assessment of the isodesmic method in the calculation of standard reduction potential of copper complexes. *Journal of molecular modeling*, 23 (2017): 1-8.
- [25] N.Regá, M.Cossi, V. Barone. Improving performance of polarizable continuum model for study of large molecules in solution. *J. Comput. Chem.* 20 (1999) 1186.
- [26] M. D. Liptak, G. C. Shields. Experimentation with different thermodynamic cycles used for pKa calculations on carboxylic acids using complete basis set and Gaussian-n models combined with CPCM continuum solvation methods. *Iran. Chem. Commun.* 85 (2001) 727.
- [27] M.M. Liu, S.M. Han, X.W. Zheng, L. L. Han, T. Liu, Z.Y. Yu, Experimental and Theoretical Prediction of The Redox Potential of Dopamine and Its Supramolecular Complex With Glycine. *Int. J. Electrochem. Sci.*, 10(2015) 235.
- [28] R.SamimiShalamzari, S.Mansouri, A.Eghbali. Determination of the absolute redox potential of methyl dopa: experimental and simulation methods. *Iran. Chem. Commun*, 3 (2015) 348.

پیش بینی پتانسیل ردوکس دوبوتامین: بررسی محاسباتی و تجربی

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چکیده

روش تجربی و محاسباتی برای تعیین پتانسیل ردوکس دوبوتامین ارائه شد. روش مستقیم و غیر مستقیم با استفاده از تکنیک $B_3LYP/6-311++G(d,p)$ کالیبره شده در محیط آبی پتانسیل ردوکس دوبوتامین را 0.85 ولت پیش بینی کرد. محاسبات دانسیته الکترونی دوبوتامین در حالت اکسیداسیون و احیاء داخل اوربیتال های HOMO و LUMO ثابت کرد که انرژی اوربیتال LUMO دوبوتامین در حالت اکسیداسیون کمتر از حالت کاهش یافته آن می باشد. بنابراین انتقال الکترون از اوربیتال HOMO به LUMO فرم کاهش یافته دوبوتامین ساده تر از فرم کاهش یافته آن می باشد. مقدار تجربی E° دوبوتامین با استفاده از ولتامتری چرخه ای بر روی الکتروود کربن شیشه ای فعال شده 0.79 ولت نسبت به SHE بدست آمد. نتایج نشان داد که یک توافق رضایت بخشی بین مقدار تجربی و محاسباتی پتانسیل استاندارد دوبوتامین وجود دارد.

واژه های کلیدی

دوبوتامین؛ تئوری تابعی چگالی؛ پتانسیل استاندارد الکتروود؛ ولتامتری چرخه ای.