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Determination of the absolute redox potential of Methyldopa: experimental and simulation methods

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Abstract

The standard redox potential of Methyldopa, in aqueous solutions is calculated experimentally by cyclic voltammetry on the surface of the activated glassy carbon electrode and also obtained theoretically by using accurate ab initio calculations along with the available salvation model of a polarizable continuum model. Innovative application of both direct and indirect methods resulted in the theoretical standard electrode potential of the methyldopa in order of 0.68 and 0.74 mV, respectively. The experimental standard redox potential of Methyldopa was obtained to be 0.72 mV versus standard Hydrogen Electrode-which is in good agreement with theoretical values.

Keywords: Methyldopa; standard redox potential; cyclic voltammetry; polarizable continuum model; abintio calculations.

Introduction

Catecholamines are the group of sympathominic compounds having the special structure of benzene ring with two hydroxyl groups, an intermediate ethyl chin, and a terminal amine group.

Phenylethanolamines such as norepinephrine have a hydroxyl group on the

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ethylchain. Catecholamines cause several general physiological changes preparing the body for physical activities.

Increases in heart rate, blood pressure, blood, blood glucose levels and the general reaction of the sympathetic nervous system are some of these typical changes or effects [1,2].

Methyldopa (L-α-Methyl -3, 4-dihydroxy phenylalanine as a catecholamine, is an alpha-adrenergic agonist (selective for α2-adrenergic receptors) physchoactive drug used as a sympathetic or antipertensive compound. Its use has been recently deprecated following the introduction of alternative safer classes of agents. However, it continues to have a role in curing other disorders like heart and gestational hypertension
[2-6].

Electron-transfer reactions are considered as a group of main or vital biological reactions occurring in all of creatures' body. Because of this matter, it is so important for chemists to measure the standard redox potential of the biological compounds which play a basic role in making identified how different species can get or emit electrons in biological processes.

Nowadays, there are various theoretical techniques used extremely for this kind of potential to be evaluated [7-15]. The computational electrode potentials were obtained with different simulation methods, such as density functional theory [16,18] and Hartree–Fock ab initio calculations [17]. In the present work, we apply simulation and experimental methods to the calculation of the standard redox potential of Methyldopa figure 1, as a very important drug.

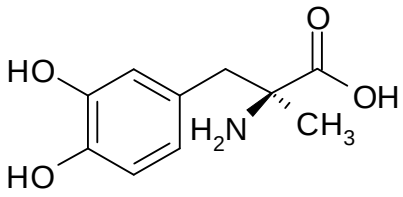


Figure 1. Structure of Methyldopa

Experimental and theoretical methods

Experimental

Materials and Methyldopa (l-α-methyl-3,4-dihydrophenylalanine) was obtained from Fluka and used as received. For preparation of buffer solution, we used H_3PO_4+$N_aH_2PO_4$ and N_aOH. A Metrohm model 691 pH/mV meters were used for measuring the pH.

Cyclic voltammograms were drawn using an Autolab, potentiostat/galvanostat PGSTAT 101 (ECO Chemic Utrecht The Netherlands), a personal computer for data storage processing and NOVA 1.8 software. A glassy carbon disk (2 mm diameter) as working electrode, and a graphite electrode as an auxiliary electrode with an Ag/AgCl as

reference electrode were used for all experiments. Prior to experiment, the glassy carbon electrode was hand-polished to a mirror-like finish with 0.0005 mm alumina in slurry using a polishing cloth and rinsed with doubly distilled water. The polished electrode was placed in 0.1 M sodium bicarbonate solution and preparation of the activated GCE performed by 16 continuous potential cycles over a wide potential range from -1.1 to 1.8 V versus Ag/AgCl at a scan rate of 100 mVs^{-1}.

Theoretical calculations

The standard electrode potentials can be obtained theoretically by employing both indirect and direct methods [19]. In this work, we calculated the standard formal potential of Methyldopa with the applicationn of both direct and indirect methods. Standard ab initio molecular orbital theory calculations were carried out using Gaussian09 [20] software. For the calculations, we have used a very similar molecule to Methyldopa, RH_2, as shown in Figure 1. The Gibbs free energy of each species was calculated using the high-level composite method, DFT-B3LYP, level using a 6-31G basis set [20]. The zero-point energies and thermal corrections together with entropies have been used to convert the internal energies to the Gibbs energies at 298.15 K. Solvation energies, G_{isolv}, have been calculated using Conductor- like Polarisable Continuum Model (CPCM) [21]. Gaussian09 [20] has been employed for all DFT calculations.

Results and discussion

Experimental calculation of electrode potential

The effect of pH on the response of the activated glassy carbon electrode in 0.1M phosphate buffer containing 0.2Mm Methyldopa at different PH values ranging from 1.5 to 6 was investigated by cyclic voltammetry. Figures 2 and 3 show a linear relationship between formal potential, $E^{0\prime}$V, of the M- $Dopa_{ox}$/$Mdopa_{red}$ redox couple and pH, with a slope of 52 mV per unit of pH which is close to the anticipated Nernstian value of 59 mV for a two-electron two-proton process. The formal potential of the redox couple was obtained as the average of anodic and cathodic peak potentials [22]. Based on the relation between formal potential of the redox couple, $E^{\circ\prime}$ V, and pH, Eq.(1) [22], the standard formal potential of Methyldopa was obtained from the intercept of Figure 3 and was equal to 554 mV. Where m and n are the number of H^+ and electrons in the redox reaction, respectively, and all other symbols have their conventional meanings.

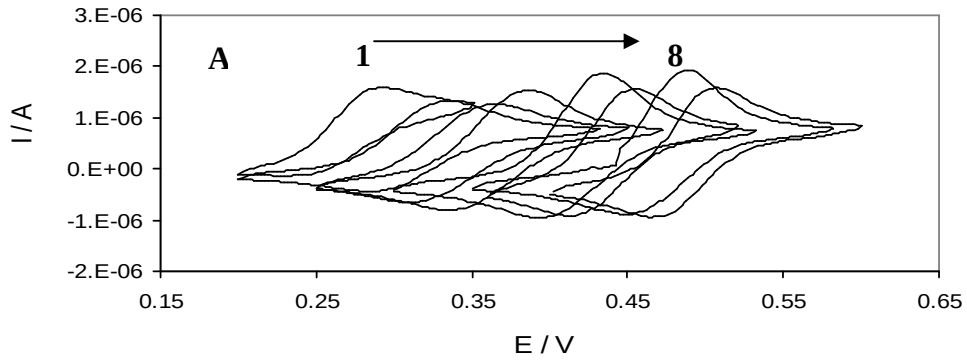


Figure 2. Cyclic voltammograms of activated glassy carbon electrode (AGCE) in 0.1 M phosphate buffer containing 0.2 mM Methyldopa in different pH values. The number of 8 to 1 correspond to 5.5, 5, 4.5, 4, 3, 2.5, 2, 1.5 pH. Scan rate was 25 mv / s.

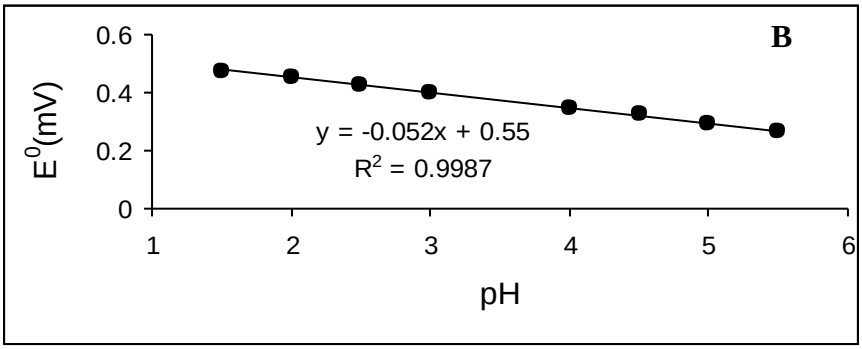


Figure 3. Variation of conditional formal potential versus solution pH

In the studied range of pH, both m and n are two [22,23]. Considering the standard electrode potential of the Ag/AgCl reference electrode as 0.20V relative to the Standard Hydrogen Electrode (SHE) [22]، the standard reduction potential of Methyldopa is 0.75V versus SHE.

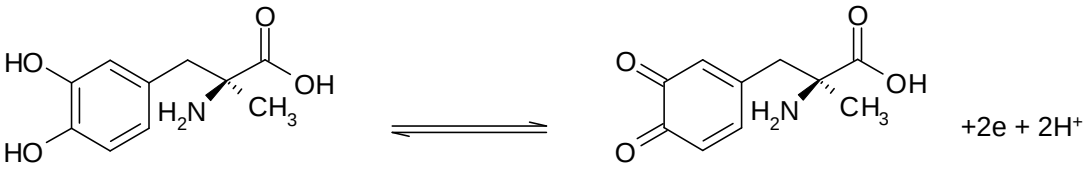
$$E^{o'} = E^0 - 2.303 \frac{mRT}{nF} pH \quad (1)$$

Theoretical computation of electrode potential

Direct method

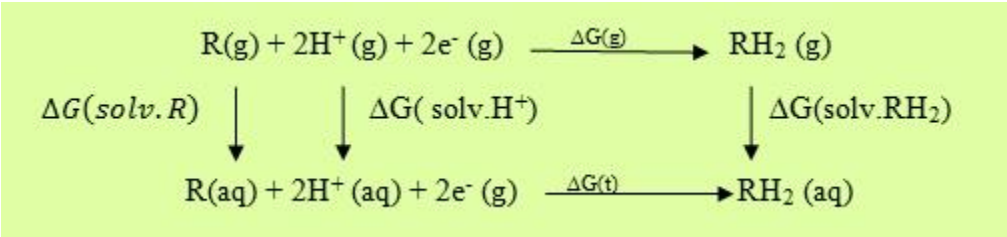
The standard redox potential of Methyldopa was calculated using two-electron half reaction show in Scheme 1, which will refer to as RH_2 can be reduced from its oxidized form, R.

$$R\ aq. + 2H^+\ aq. + 2\bar{e} \rightarrow RH_2\ aq. \quad (2)$$



Scheme 1. The two-electron, two-proton redox reaction of Methyldopa and the model compound used in the ab intio calculation and half reaction of Standard Hydrogen Electrode (SHE)

The standard Gibbs free energy change of this reaction, ΔG(t) is related to the absolute reduction potential *via* Eq(3) [22], Where n is the number of electrons transferred (n=2 in this case) and F is the Faraday, constant (96485 C mol−1). As Scheme 2 shows, ΔG° (t) can be calculated from its components by introducing a thermodynamic cycle.



Scheme 2. Thermodynamic cycle used to calculate total free energy of reaction (2) from its components

The G_3DFT level of theory as described in-Table 1. The Gibbs free energy of H^+ (g) has been reported to be −26.3 kJ mol^{-1} [29]. Using Eqs (3) and (4), the absolute reduction potential of R has been calculated as 5.06 V. To allow comparison with experiment, and assess the validity of this theoretical value as well, it is necessary to calculate the reduction potential of R relative to SHE. Therefore, the absolute value of reduction potential of Standard Hydrogen Electrode (SHE) is required. In the present work, we have selected the value of 4.44 V for SHE, which can be found in electrochemistry textbooks [20,27,28]. Therefore, E° has been calculated as 0.62 V versus SHE. The experimental redox potential for Methyldopa was measured above as 0.72 V using cyclic voltammetry. There is thus a discrepancy of only 0.05V between theory and experiment, which is typical of the expected error in the theoretical calculations at this level of theory. This good agreement between the experimental and theoretical values for the reduction potential verifies that the model used for the high-level ab initio calculations

was close enough to the structure of the real Methyldopa molecule to include the major of electronic and stereo interactions.

Indirect method

The studied Methyldopa (M-d) can be oxidised by a two-electron oxidation reaction as shown in Scheme 1. The oxidised form of M-d (Md_{ox}) can also be converted to its reduced form (Md_{red}) using pyrocatechol (Q_{red}) as a reference molecule according to the following isodesmic reaction (1), [11-12]:

$$Q_{red} + C_{Md(ox)} \rightarrow Q_{ox} + C_{Md(red)} \quad (5)$$

Where Q_{ox} is o-benzoquinone, the oxidized form of pyrocatechol. The difference between the electrode potential of the two species can be obtained from the change in Gibbs free energy of reaction (5), [11,12,17]:

$$G^{\circ} = -nF(E^{\circ}_{m} - E^{\circ}_{Q}) \quad (6)$$

Where n is the number of electrons transferred (n=2 in this case) and F is the Faraday constant. In order to obtain standard electrode potential of Methyldopa, the change of Gibbs free energy of reaction (5), G°, is required along with the experimental value of electrode potential of the reference molecule, pyrocatechol [11and12]. In order to calculate the standard Gibbs energy of reaction (7), G°, one should calculate the standard Gibbs energy of each component, G° in reaction(8).

$$G = \quad {}_{i}G^{\circ}_{i} \quad (7)$$

Where G° is the standard Gibbs energy of each component and ϑ_i is the stoichiometric coefficient. The standard Gibbs energy of each component is obtained using the following expression [12 and13].

$$G^{\circ}_{i} = G^{\circ}_{i,gass} + G^{\circ}_{i,solv} \quad (8)$$

Where G_i, gas is the gas-phase energy of each component and $G^{\circ}_{i,solv}$ is the solvation energy of the component. As described earlier, Gibbs energy of each molecule in the gas and solution phase is necessary for the calculation of electrode potentials. Table (1) shows the calculated Gibbs energy of molecules for both reduced and oxidised forms in the gas and solution phase using frequency calculations at the DFT level of theory. The basis set of 6-31G was chosen for this calculation. By using values that present in Table 1 and choosing 0.792 V [6] for the experimental value of the electrode potentia of reference molecule, pyrocatechol, the standard electrode potential of Methyldopa is obtained to be 0.74 V, versus SHE. The theoretical value for Methyldopa is in an excellent agreement with the experimental electrode potential.

Table 1. Internal energies, thermal corrections including zero-point energy and Gibbs free energies for oxidized and reduced forms of methyldopa and also o-benzoquinone and pyrocatechol

	U^{0a}	TC^{b}	G^{0c}	G^{0c}
	Gas phase	**Gas phase**	**Gas phase**	**Aqueous phase**
$Q^{\bar{d}}$	-381.33056	0.055320	-381.275240	-381.288051
$QH_2^{\bar{e}}$	-382.58027	0.078148	-382.501328	-382.511375
$R^{\bar{f}}$	-743.073814	0.159984	-742.913825	-742.935760
$RH_2^{\bar{g}}$	-744.319324	0.183628	-744.135696	-744.155288

[a]Gas-phase internal energy.

[b]thermal corrections to the Gibbs free energies at 298.15 K.

[c]Gibbs free energies in the gas phase and aqueous solution

[d,e]The o-benzoquinone and pyrocatechol, reference redox coupl respectively

[f,g]The oxidized and reduced forms of methyldopa, respectively. All energies are in atomic units, Hartree (1 Har-tree = 2623.61722 kJ/mol).

Conclusion

According to the results reported here, it is true to be said that the oxidation of activated glassy carbon electrode is the reversible procedure whose conditional formal potential depends on the amount of PH strongly.

Moreover, being calculated through simulating or modeling method during this research, the quantitative values for the standard redox potential of the activated glassy carbon electrode are in agreement with (corresponding to) the values measured by empirical way.

Acknowledgments

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