Thermodynamic prediction of proton and hydrogen atom abstraction in dehydroascorbic acid and its bicyclic form

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Abstract: Conformation analysis of dehydroascorbic acid and its bicyclic form was performed using the density functional theory. For the energetically preferred conformations, ionization potentials (IP) and bond dissociation enthalpies (BDE) were calculated using the B3LYP functional and 6-311++G** basis set. The effects of aqueous solution were estimated using the solvation model based on density (SMD) and the polarizable continuum model (IEF-PCM). The obtained results were compared with available experimental data for reference L-ascorbic acid (vitamin C). Our calculations indicate that the investigated bicyclic metabolic product of vitamin C can also exhibit limited radical scavenging ability due to the thermodynamically preferred dissociation of tertiary —CH bonds.

Keywords: vitamin C, oxidation product, radical scavenger, pK_a values

Introduction

Chemistry of L-ascorbic acid (**AA**, vitamin C) has been widely studied due to its biological importance (Bendich and Langseth, 1995). This water-soluble organic acid is a well-known radical scavenger and an antioxidant in living systems. Although the molecule of vitamin C normally loses only one electron, two electron oxidations can be observed under *in vitro* electrochemical conditions (Deakin et al., 1986). Apart from being a distinguished reducing agent of reactive radical species, vitamin C is a cofactor in the enzymatic biosynthesis of collagen, catecholamine, carnitine, and peptide neurohormones. It is transported across the blood-brain barrier in its oxidized form, called dehydroascorbic acid (**A**). This molecule is also involved in the oxidation of low-density lipoprotein (Wilson, 2002). Furthermore, dehydroascorbic acid has found its purpose in pharmaceutical industry. It has been used as a biochemical marker of oxidative stress in clinical investigations, as vitamin C dietary supplement or as a mucolytic drug called Ascoxal (Fisher and Ten Pas, 1966).

Since the vitamin C structure determination in 1930s, its oxidation mechanism, which is complex and still not fully understood, has been studied (Tu et al., 2017). Thermodynamics and kinetics of reactions associated with the mechanism have been studied by numerous experimental and theoretical research groups. Vitamin C is in these reactions oxidated to one-electron form – short-lived ascorbate radical, or to fully oxidized two-electron **A** form. Dehydroascorbic acid can also

be formed by oxidation of the ascorbate radical or by the disproportionation reaction between two ascorbate radicals. Although the structure of **A** is generally presented as a molecule with one non-aromatic ring (Fig. 1), this structure is known to be energetically unstable in water. It is assumed that the structure of dehydroascorbic acid is an intermediate which immediately goes through ring closure, and along with hydration, forms a stable bicyclic form **B** (Fig. 1). To date, structures associated with the oxidation products of vitamin C have been studied extensively in many theoretical and experimental works (Bielski et al., 1981; Bielski et al., 1985; Kurata and Nishikawa, 2000). Recently, Tu and Njus (Tu et al., 2017; Njus et al., 2020) explored theoretically the oxidation mechanism of ascorbic acid and its reaction with superoxide determining the lowest energy conformations of oxidation products and deprotonated forms of ascorbic acid. In agreement with nuclear magnetic resonance measurements, the bicyclic hydrated isomer of dehydroascorbic acid was found to be the most stable structure of the fully oxidized form of ascorbic acid in aqueous solution. The suggested Pourbaix diagrams and calculated pK_a values were in good agreement with the available experimental values.

The mentioned experimental and theoretical works suggest that the antioxidant activity of the studied molecules is related to the dissociation of hydroxyl groups. On the other hand, thermodynamics of the deprotonation reaction from tertiary —CH bonds has not been discussed or analyzed. Therefore, we decided to theoretically investigate the thermo-

Fig. 1. Schematic structure and atom numbering of L-ascorbic acid (**AA**), dehydroascorbic acid (**A**) and its bicyclic form (**B**).

dynamics of hydrogen atom and proton abstraction from the tertiary methyl —CH groups of dehydroascorbic acid and its bicyclic hydrated isomer (Fig. 1). Partial aims of this study are: (1) perform conformational analysis for the gas-phase and water environment; (2) calculate the reaction enthalpies and Gibbs energies at the room temperature and (3) evaluate the corresponding pK_a values. The obtained results were compared with published theoretical and available experimental data.

Computational Details

All quantum chemical calculations were carried out by the Gaussian 16 software package (Frisch et al., 2016). Visualizations of the parent molecules, their radicals and ions were designed in the Molekel program package (Flukiger et al., 2002). Geometries were optimized using the B3LYP (Lee et al., 1988; Becke, 1988) DFT hybrid functional with the 6-311++G** basis set (Binkley et al., 1980). Vibrational frequency calculations were included at the same level of theory to confirm that the optimised structures were real stationary points and no imaginary vibrations were present. As both dehydroascorbic acid structures have numerous conformers according to the alkyl chain and several rotatable hydroxyl groups, these were investigated first. The lowest-energy structures were used to obtain gas-phase enthalpies and Gibbs free energies of the radicals/ions at $p = 101325$ Pa and $T = 298.15$ K. Furthermore, these structures were used as starting points for re-optimization in aqueous solution to obtain more accurate pK_a values. Solvent contribution was applied using SMD (Marenich et al., 2009) and IEF-PCM (Tomasi et al., 2005) polarizable continuum models. The combination of B3LYP with implicit solvent models offers relevant prediction of thermodynamic quantities (Michalík and Lukeš, 2016).

Results and Discussion

The selected energetically preferred structures of L-ascorbic acid (**AA**), dehydroascorbic acid (**A**) and its bicyclic form (**B**) are depicted in Fig. 2. Orientation of the hydroxyl substituents allows the formation of intramolecular hydrogen bonds (see Tab. 1) which contribute to the relative stability of their geometry. For reference L-ascorbic acid, the selected conformation was taken from Tu and Schlegel (2017). The energetically preferred geometry is represented by a planar five-membered ring and a 1,2-dihydroxyethyl chain bent in the direction of the ring forming three stable hydrogen bonds between the groups. The dehydroascorbic acid **A** molecule contains a planar furan-2,3,4(5H)-trione moiety and an 1,2-dihydroxyethyl group. Multiple possible rotations of the 1,2-dihydroxyethyl group around C5—C6 and C6—C7 bonds with respect to the planar ring lead to eighteen possible conformers. For molecule **B**, the presence of bicyclic rings reduces the number of possible conformations. With respect to the orientation of hydroxyl groups, eight possible structures were identified. In case of vitamin C, the studied conformation contains three intramolecular hydrogen bonds. The shortest bond length is that of C4OH...OC7, e.g. 1.757 Å in the gas-phase. The most stable conformation **A** contains only two hydrogen bonds between C6OH...OC4 atoms, with the length of 2.285 Å, and between C6OH...OC7 atoms, with the length of 2.818 Å. The oxolane rings of bicyclic **B** molecule are not planar but bent to each other, leaving groups OH7 and OH3 behind their plane. Therefore, the most energetically preferred **B** conformer possesses eight internal hydrogen bonds. Compared with the gas-phase geometries, the inclusion of implicit solvent models affects the intramolecular bond lengths.

Chemical structure of the studied molecules has direct impact on the homolytic or heterolytic bond

Fig. 2. Optimal gas-phase B3LYP/6-311++G** geometries of energetically preferred conformations of studied molecules. Conformation **AA(7-OH)** with two intramolecular hydrogen bonds was used for the evaluation of PA and pK_a values. Values in parentheses represent the corresponding electronic energies in hartree.

dissociation. For further thermodynamic calculations of the most stable state and its derivatives, geometries of conformer **A** and **B** were selected (see Fig. 2). Thermodynamics of homolytic dissociation of chemical bonds can be estimated from the bond dissociation enthalpies (BDEs) which represent a one-step mechanism of hydrogen atom transfer (HAT). This quantity can be calculated as

$$BDE = H(A^\bullet) + H(H^\bullet) - H(A-H) \quad (1)$$

where $H(A^\bullet)$ stands for the total enthalpy of formed radical, $H(H^\bullet)$ for total enthalpy of hydrogen atom, and $H(A-H)$ is the total enthalpy of the molecule. The total gas-phase enthalpy of hydrogen atom is $-1306 \text{ kJ mol}^{-1}$ and the contribution of the solvation enthalpy in water is -4 kJ mol^{-1} (Rimarčík et al., 2010).

For reference L-ascorbic acid (see Tab. 2), the gas-phase BDEs for possible radical structures formed from the hydroxyl groups and tertiary methyl group are in the range of 332 kJ mol^{-1} to 450 kJ mol^{-1} . The values of C3—OH and C5—H are in the best agreement with the available experimental value of $326.4 \text{ kJ mol}^{-1}$ (Warren et al., 2010). The homolytic dissociation of hydroxyl groups located at the side 1,2-dihydroxyethyl substituent is less preferable. For **AA** and **A** molecules, the gas-phase

Tab. 1. Calculated B3LYP/6-311++G** gas-phase, SMD and IEF-PCM intramolecular hydrogen bond lengths of most stable conformers.

	Substituent	R(O...H)/Å		
		Gas-phase	SMD	IEF-PCM
AA	C3OH...OC4	2.599	2.688	2.649
	C4OH...OC7	1.757	1.661	1.689
	C6OH...O1	2.214	2.392	2.295
A	C6OH...OC4	2.285	2.270	2.470
	C6OH...OC7	2.818	2.724	2.715
B	C3OH...OC7	2.422	2.762	2.525
	C3OH...O1	2.977	3.111	3.036
	C7OH...O1	2.358	2.452	2.394
	C7OH...OC6B	3.113	3.093	3.157
	C6AOH...OC7	2.273	2.229	2.238
	C6AOH...OC6B	2.672	2.718	2.705
	C6BOH...OC5	2.572	2.718	2.695
	C6BOH...OC6A	2.623	2.531	2.545

BDEs are higher by about 100 kJ mol^{-1} . Interestingly, molecule **A** gas-phase BDEs for homolytic splitting of C5—H bond is 342 kJ mol^{-1} . The energetically preferred homolytic cleavage of C—H

bonds was predicted for various Δ 5- and Δ 7-sterols by Lengyel et al. (Lengyel et al., 2012) and Škorňa et al. (Škorňa et al., 2014). Considering the implicit solvent models, the BDE values slightly deviate (1 to 5 kJ mol⁻¹) in most calculations but there are more significant differences ($\sim$ 10 kJ mol⁻¹) in molecule **AA** hydroxyl groups C3—OH and C6—OH, molecule **A** C6—OH and molecule **B** C3—H and C7—OH groups.

Abstraction of hydrogen atom is also possible *via* a two-step mechanism denoted as single electron transfer followed by proton transfer (SET-PT). In the first step, the electron is abstracted from the molecule and the proton transfer reaction results in a cation radical. Thermodynamics of the first step of the SET-PT mechanism is described by ionization potential (IP),

$$IP = H(A-H^{+\bullet}) + H(e^-) - H(A-H) \quad (2)$$

where $H(A-H^{+\bullet})$ is total enthalpy of radical cation, and $H(e^-)$ is enthalpy of electron. The total gas-phase enthalpy of electron is 3.145 kJ mol⁻¹ and the contribution of the solvation enthalpy in water is -105 kJ mol⁻¹ (Rimarčík et al., 2010).

Predicted gas-phase ionization potential values for **AA** and **A** molecules are 794.3 kJ mol⁻¹ and 872.8 kJ mol⁻¹, respectively. The presence of two cyclic moieties in **B** molecule increases the IPs

by about 11 kJ mol⁻¹. Entering the solvent models, the values drop to 557.3 kJ mol⁻¹ (SMD) and 581.7 kJ mol⁻¹ (IEF-PCM). The minimum value appears to be the SMD one. In general, vitamins with higher *IP* values are more susceptible to ionization and they have stronger antioxidant potential (Pandithavidana and Jayawardana, 2019). Thermodynamics of heterolytic dissociation of chemical bonds can be described using through proton affinity (PA), which is for the anion formation defined as:

$$PA = H(A^-) + H(H^+) - H(A-H) \quad (3)$$

where $H(A^-)$ is enthalpy of anion and $H(H^+)$ is total enthalpy of proton. The total gas-phase enthalpy of proton is 6.197 kJ mol⁻¹ and the contribution of the solvation enthalpy is -1090 kJ mol⁻¹ (Rimarčík et al., 2010).

Values collected in Tab. 2 indicate show significant differences in *PA*s between gas-phase and solvent calculations, as expected for the deprotonation mechanism. In case of the **AA** anion with starting geometry including a deprotonated 7-OH group, the resulting calculated geometry belongs to the anion with deprotonated 4-OH group. This proton transfer from 4-OH group to the negatively charged 7-O atom results in the presence of a hydrogen bond in the parent **AA** conformation (see Tab. 1). The stable geometry of **AA(7-O⁻)** anion was reached

Tab. 2. Ionization potentials (*IP*), bond dissociation enthalpies (*BDE*) and proton affinities (*PA*) calculated for the energetically preferred conformations.

	<i>IP</i> /kJ mol ⁻¹			<i>BDE</i> /kJ mol ⁻¹			<i>PA</i> /kJ mol ⁻¹		
	Gas	Water		Gas	Water		Gas	Water	
		SMD	IEF-PCM		SMD	IEF-PCM		SMD	IEF-PCM
AA	794	462	498						
A	873	557	582						
B	889	538	580						
AA(3-OH)				332	319	316	1421	109	120
AA(4-OH)				335	333	334	1305	67	61
AA(6-OH)				450	436	435	1472	159	178
AA(7-OH)*				426	432	430	1459	169	179
AA(5-H)				334	341	336	1476	196	200
A(6-OH)				440	432	430	1452	150	164
A(7-OH)				430	430	430	1351	84	89
A(5-H)				342	343	341	1334	80	80
B(3-OH)				429	431	427	1414	150	148
B(6-OH^A)				394	391	385	1406	109	117
B(6-OH^B)				391	390	382	1383	99	105
B(7-OH)				328	316	309	1377	106	108
B(3-H)				387	378	376	1390	121	119
B(8-H)				429	427	425	1533	269	264

*Starting geometry does not include hydrogen bond between C4OH...OC7 atomic pair.

for the conformation with one intramolecular hydrogen bond (see Fig. 1). The calculated gas-phase values for deprotonated hydroxyl groups range from 1305 kJ mol⁻¹ to 1472 kJ mol⁻¹. Similarly, as in the case of homolytic dissociation of the hydroxyl group, the energetically preferred dissociation is in the vicinity of the double carbon-carbon bond. The inclusion of solvent leads to rapid decrease of proton affinities; B3LYP values change from 67 kJ mol⁻¹ to 169 kJ mol⁻¹ (SMD) and 61 kJ mol⁻¹ to 179 kJ mol⁻¹ (IEF-PCM). Theoretical calculations for the **AA** molecule predict deprotonation as more energetically preferable for the 4-OH than for the 3-OH group. A possible explanation is related to the effect of π -electron conjugation occurring along the *trans*-oriented bonds O=C2—C3=C4—OH. In general, such conjugated groups are more likely to deprotonate (Wyman, 1955).

Formation of molecule **A** anion is most convenient through tertiary **A(5-H)** group (80 kJ mol⁻¹ in solvent). Hydrogen atom at the C5 atom (5-H) is more acidic than the other hydroxyl groups due to the classic withdrawing effect of three neighboring keto groups present in the molecule. Also, *PA* values of chain **A(6-OH)** and **A(7-OH)** groups show differences; the latter one is energetically preferred due to steric effects. In case of molecule **B**, both **B(6-OH)** groups show the lowest values of *PA*. Comparing tertiary **B(3-H)** and **B(8-H)** groups, the first exhibits lower *PA* value due to the presence of a hydroxyl group at the *sp*³ C3 atom.

From the experimental point of view, the acid dissociation constant, or its logarithmic expression (*pK_a*), represents a quantitative measure of heterolytic dissociation in solution. The value of *pK_a* for water can be calculated from the Gibbs energies:

$$pK_a = [\Delta G_{aq}]/(2.303 RT) = [G_{aq}(A^-) + G_{aq}(H^+) - G_{aq}(HA)]/(2.303 RT) \quad (4)$$

where *G_{aq}*(A⁻) represents Gibbs free energy of anion, *G_{aq}*(H⁺) is total Gibbs free energy of proton (-1104.62 kJ mol⁻¹) (Alongi et al., 2010), and *G_{aq}*(HA) is total Gibbs free energy of the molecule. Symbol *R* stands for the gas constant and *T* is temperature. The calculated reaction Gibbs free energies (ΔG_{aq}) and evaluated *pK_a* values in water are collected in Table 3.

The lowest predicted *pK_a* value of reference vitamin C is 6.1 (IEF-PCM) and 7.3 (SMD) and it is related to the deprotonation of the 4-OH group. The reported experimental *pK_a* values of this weak dibasic acid are 4.25 and 11.79 (Combs, 2008). Probably the lower experimental acidity of deproteinized ascorbic acid is related to the occurrence of resonance structures of the ascorbate anion and the natural limitations of the implicit cavity solvent model. In case of dehydro-

ascorbic acid (**A**), the lowest *pK_a* values of 8.7 (SMD) and 9.3 (IEF-PCM) are due to the proton abstraction from the C5 atom. The reported experimental value measured in water is ~9 (Gutierrez, 1988). Unfortunately, their used experimental technique was not able to identify the abstracted bond. Consequently, compared with the available experimental data, proton abstraction from C5—H is the most probable. Influence of keto groups present in the molecule was assumed. It seems that the SMD model overtakes IEF-PCM model by giving the results in better compliance with literature. For molecule **B**, the lowest *pK_a* values are 13.1 (SMD) and 13.7 (IEF-PCM) corresponding with general *pK_a* values of aliphatic alcohols (Takahashi et al., 1971). The lowest value is related to the proton abstraction from the **6-OH^B** hydroxyl group, but the differences between the theoretical *pK_a* values for C3—H and 6O—H^A are minimal. Therefore, in sufficiently basic environment, the possibility of heterolytic dissociation from the mentioned tertiary hydrogen occurs. On the other hand, C8—H group does not share a carbon atom with a hydroxyl group and thus higher *pK_a* of 42.4 was measured (SMD). The value is regular for tertiary bonds in cyclic organic compounds (Shen et al., 2007).

Tab. 3. Reaction Gibbs energies and *pK_a* values calculated for water environment.

	$\Delta G/\text{kJ mol}^{-1}$		<i>pK_a</i>	
	SMD	IEF-PCM	SMD	IEF-PCM
AA(3-OH)	85.1	94.8	14.9	16.6
AA(4-OH)	41.8	35.0	7.3	6.1
AA(6-OH)	136.0	152.7	23.8	26.7
AA(7-OH)*	163.7	187.0	28.7	32.8
AA(5-H)	168.4	168.9	29.5	29.6
A(6-OH)	123.9	139.4	21.7	24.4
A(7-OH)	63.3	70.5	11.1	12.4
A(5-H)	49.6	52.7	8.7	9.3
B(3-OH)	129.9	127.3	22.8	22.3
B(6-OH^A)	84.9	92.0	14.9	16.1
B(6-OH^B)	74.9	78.5	13.1	13.7
B(7-OH)	83.6	85.2	14.7	14.9
B(3-H)	93.8	90.3	16.4	15.8
B(8-H)	242.3	236.8	42.4	41.5

*Starting geometry does not include hydrogen bond between C4OH...OC7 atomic pair.

Conclusion

Conformation analysis of dehydroascorbic acid and its bicyclic form was performed using the B3LYP DFT functional for the gas-phase and two implicit

solvent models, i.e., IEF-PCM and SMD. For the energetically preferred conformations, the bond dissociation enthalpies, ionization potentials and proton affinities were calculated; values of pK_a were predicted for water environment. Theoretical results indicate that the investigated bicyclic metabolic products of vitamin C can possess small radical scavenging ability. Furthermore, our calculations for vitamin C and dehydroascorbic acid indicate that, from the thermodynamic point of view, the preferable way of homolytic and heterolytic dissociation includes the C—H bond. Therefore, the antioxidant activity mechanism of L-ascorbic acid and its oxidated form should be possible through bonds of tertiary hydrogen groups.

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