On the Relative Stability of Ascorbic Acid Tautomers

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The four possible tautomers of ascorbic acid were studied by the semiempirical MINDO/3 and MNDO methods. The most stable tautomer **1** corresponds to that identified in solution and solid state by the ^{13}C-NMR and X-ray techniques, respectively. Its estimated structural parameters are in reasonable agreement with data obtained by the combined use of X-ray and neutron diffraction methods. The MNDO bond angles exhibit a dramatic improvement over the MINDO/3 ones. The most acidic proton corresponds to the O-H bond attached to the ring in the immediate neighbourhood of the side chain.

Introduction

L-ascorbic acid (Vitamin C) was isolated first by Szent-Györgyi [1] in 1928 and soon it became apparent that this substance takes a part in a vast number of physiological processes [2]. It affects cholesterol synthesis [3], inhibits the formation of nitrosoamines which seem to have carcinogenic behaviour [4] and provides an efficient cure of scurvy [2, 5]. Not with standing the important role of ascorbic acid and its radical(s) in a wide variety of biochemical reactions, theoretical studies are rather sparse. Flood and Skancke [6] performed a π-type of calculation on ascorbic acid and the parent tetronic acid by using a modified PPP method [7]. The effect of the side chain on the π-system was considered by additional CNDO/2 computation. The agreement with available UV data was good but the predicted bond distances in the five membered ring were in rather poor accordance with experimental values. The STO-3G calculations were executed on ascorbic acid and its anion [8] but they were based on the X-ray structural parameters [9, 10] and only two dihedral angles determining the conformation of the side chain and its relative orientation to the ring have been optimized. It is therefore worth while to reexamine ascorbic acid and the closely related compounds employing methods which do optimize all geometric parameters. This is of some importance because there is some doubt and discussion in the literature concerning the most stable tautomer of vitamin C in solutions [11]. The semiempirical MINDO/3 and MNDO methods seem to be a suitable tool for this purpose since they give fairly good estimates of the molecular size, shape and energetics [12, 13]. The errors introduced by these approximate approaches will most likely cancel out in comparing relative enthalpies of various tautomers, and we can expect quite reliable ordering of their stability. In order to increase the credebility of the results we applied both methods mentioned above to four possible tautomers of ascorbic acid. The essential results are discussed in the following section.

Results and Discussion

The calculated interatomic distances and bond angles are displayed in Table 1 and compared with experimental data for the form **1** (Scheme) which occurs in the solid state as the most stable tautomer. The experimental values were obtained by the combined X-ray and neutron diffraction analyses [9, 10]. The latter elucidates distances involving hydrogen atoms. Theoretical estimates of bond distances are only in qualitative agreement with experiment. Discrepancies could be ascribed to differences between gas phase and solid state geometries and approximations inherent in MNDO/3 and MNDO methods. In this connection it should be pointed out that the crystal unit cell contains two molecules in the asymmetric unit and the data cited in Table 1 correspond to their average structure.

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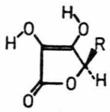
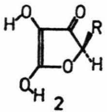
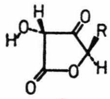
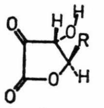
Table 1. Comparison of the estimated structural parameters with available experimental data for four ascorbic acid tautomers (bond distances and angles in Å and degrees, respectively).

Compound	Bond	MINDO/3	MNDO	EXP.	Angle	MINDO/3	MNDO	EXP.
 1	$d(C_1-O_2)$	= 1.361	1.375	1.355	$C_1O_2C_3$	= 118.3	112.0	109.1
	$d(O_2-C_3)$	= 1.384	1.421	1.444	$O_2C_3C_4$	= 100.6	103.8	104.0
	$d(C_3-C_4)$	= 1.532	1.547	1.493	$C_3C_4C_5$	= 109.3	108.9	109.5
	$d(C_4=C_5)$	= 1.374	1.374	1.338	$O_2C_1O_6$	= 125.0	119.9	121.4
	$d(C_1-C_5)$	= 1.495	1.503	1.452	$C_5C_4O_7$	= 134.4	131.5	133.5
	$d(C_1=O_6)$	= 1.209	1.219	1.216	$C_4O_7H_8$	= 113.8	113.2	113.7
	$d(C_4-O_7)$	= 1.322	1.342	1.326	$C_4C_5O_9$	= 123.8	125.8	127.5
	$d(C_5-O_9)$	= 1.338	1.349	1.361	$C_5O_9H_{10}$	= 111.8	112.6	113.7
	$d(O_7-H_8)$	= 0.952	0.950		$C_4C_3C_{11}$	= 123.6	115.7	114.8
	$d(O_9-H_{10})$	= 0.952	0.949		$C_4C_3H_{12}$	= 107.0	109.1	111.0
 2	$d(C_1-O_2)$	= 1.354	1.372		$C_1O_2C_3$	= 113.3	110.0	
	$d(O_2-C_3)$	= 1.396	1.423		$O_2C_3C_4$	= 103.6	105.0	
	$d(C_3-C_4)$	= 1.551	1.571		$C_3C_4C_5$	= 104.5	104.2	
	$d(C_4-C_5)$	= 1.482	1.490		$O_2C_1O_6$	= 121.5	116.7	
	$d(C_1=C_5)$	= 1.380	1.381		$C_1O_6H_8$	= 116.1	114.3	
	$d(C_1-O_6)$	= 1.318	1.340		$C_3C_4O_7$	= 124.0	125.9	
	$d(C_4-O_7)$	= 1.208	1.217		$C_4C_5O_9$	= 119.9	121.4	
	$d(O_6-H_8)$	= 0.952	0.951		$C_5O_9H_{10}$	= 112.0	112.1	
	$d(C_5-O_9)$	= 1.341	1.351		$C_4C_3H_{12}$	= 105.9	108.0	
	$d(O_9-H_{10})$	= 0.952	0.949					
	$d(C_3-H_{12})$	= 1.139	1.123					
 3	$d(C_1-O_2)$	= 1.352	1.372		$C_1O_2C_3$	= 121.3	114.0	
	$d(O_2-C_3)$	= 1.382	1.411		$O_2C_3C_4$	= 102.6	105.8	
	$d(C_3-C_4)$	= 1.539	1.555		$C_3C_4C_5$	= 106.6	107.6	
	$d(C_4-C_5)$	= 1.546	1.557		$O_2C_1O_6$	= 125.0	118.9	
	$d(C_1-C_5)$	= 1.539	1.553		$O_7C_4C_3$	= 126.2	126.3	
	$d(C_1=O_6)$	= 1.205	1.217		$C_4C_5O_8$	= 116.0	113.1	
	$d(C_4=O_7)$	= 1.203	1.217		$C_5O_8H_9$	= 111.6	111.7	
	$d(C_5-O_8)$	= 1.359	1.388		$C_4C_5H_{10}$	= 106.5	109.7	
	$d(O_8-H_9)$	= 0.953	0.948		$C_4C_3H_{12}$	= 105.1	108.0	
	$d(C_5-H_{10})$	= 1.136	1.122					
	$d(C_3-H_{12})$	= 1.140	1.124					
 4	$d(C_1-O_2)$	= 1.348	1.367		$C_1O_2C_3$	= 121.6	114.0	
	$d(O_2-C_3)$	= 1.382	1.415		$O_2C_3C_4$	= 103.3	107.0	
	$d(C_3-C_4)$	= 1.559	1.592		$C_3C_4C_5$	= 104.4	103.0	
	$d(C_4-C_5)$	= 1.543	1.554		$O_2C_1O_6$	= 126.0	119.5	
	$d(C_1-C_5)$	= 1.536	1.529		$C_4C_5O_7$	= 127.7	127.6	
	$d(C_1=O_6)$	= 1.204	1.217		$C_3C_4O_8$	= 108.4	109.8	
	$d(C_5=O_7)$	= 1.201	1.213		$C_4O_8H_9$	= 112.2	111.9	
	$d(C_4-O_8)$	= 1.358	1.389		$C_3C_4H_{10}$	= 110.9	111.1	
	$d(O_8-H_9)$	= 0.952	0.948		$C_4C_3H_{12}$	= 108.5	108.8	
	$d(C_4-H_{10})$	= 1.137	1.123					
	$d(C_3-H_{12})$	= 1.139	1.124					

Namely, these two molecules have different environments and hence different packing conditions. The main difference lies in the conformation of the side chain. Geometry of the latter will be discussed in detail for all tautomers in a separate paper as well as the structures of ascorbic acid anions [14]. We mention only in passing by that the hydrogen H_8 is found to be the protolitic one in full agreement with the structure of sodium ascorbate [15]. The changes introduced by deprotonation are qualitatively well described. The five-membered rings in tautomers **1**−**4** are predicted to be essentially planar and the estimated nonplanarity is within the error of the employed methods for dihedral angles. This is in accordance with rough planarity of the five-membered ring moiety observed by experiments [13, 14].

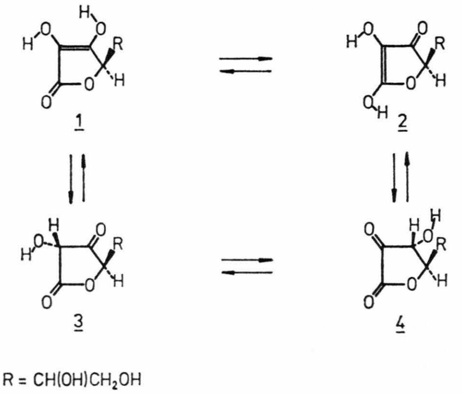
The calculated enthalpies, MINDO/3 entropies and the corresponding free-energies are given in Table 1. One observes that each method has its own enthalpy scale but both methods yield a consistent picture of the relative stabilities. Consequently, we

Table 2. Semiempirical estimates of heats of formations, entropies and Gibbs free energies for ascorbic acid tautomers[a].

Compound Method	**1**	**2**	**3**	**4**
MINDO/3	$\Delta H_f = -1169.5$	-1132.2	-1141.5	-1113.8
	$S^\circ_{298} = 447.5$	459.6	442.6	445.2
	$\Delta G_{298} = -1302.8$	-1269.2	-1273.4	-1246.5
MNDO	$\Delta H_f = -1039.7$	-1022.6	-1038.5	-1015.5

[a] Enthalpies in kJ mol^{-1}, entropies in $\text{JK}^{-1}\ \text{mol}^{-1}$ and free energies in kJ mol^{-1}.

can state with some degree of confidence that the tautomer **1** is the most stable one in the gas phase. The second most stable tautomer is **3**, while the most unstable is the tautomer **4**. The influence of entropy on the relative free energies is small as evidenced by the MINDO/3 results. The main effect is a slight shift in ΔG of the tautomer **2** toward the value of the tautomer **3**. The equilibrium constants for the cycle depicted in the Scheme are as follows: $K_{12} = 1.3 \times 10^{-6}$; $K_{24} = 1.1 \times 10^{-4}$; $K_{13} = 7.0 \times 10^{-6}$ and $K_{34} = 1.9 \times 10^{-5}$, where the first index corresponds to the initial tautomer. They clearly illustrate a shift of the equilibrium concentration(s) toward the most stable tautomer **1**. The rest of the constants are easily obtained by using data given in Table 2.



Scheme

To summarize, the present calculations and some earlier experimental evidence indicate that the tautomer **1** exhibits the largest stability in all three phases (vapour, liquid and solid states). The most acidic proton belongs to the O – H group attached to the ring in the nearest neighbourhood of the side chain.

Acknowledgement

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