1991

Theoretical Study of (3, 6) Cyclohemiketal Form of L-Ascorbic Acid

M. Hodošček

G. Fodor

M. Eckert-Maksić

CROATICA CHEMICA ACTA CCACAA 64 (3) 529–537 (1991)

ISSN 0011-1643
UDC 451
CCA-2019

Original Scientific Paper

Theoretical Study of ⟨3,6⟩Cyclohemiketal Form of L-Ascorbic Acid

M. Eckert-Maksić[a], *M. Hodošček*[b] *and G. Fodor*[c]

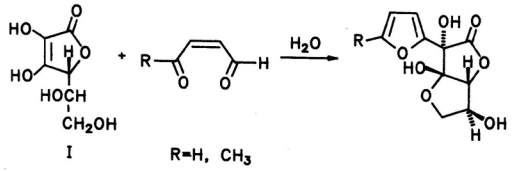
[a]*Ruđer Bošković Institute, Zagreb, Croatia,* [b]*Boris Kidrič Institute, Ljubljana, Slovenia,* [c]*Department of Chemistry, West Virginia University, Morgantown, WV 26506-6045, USA*

Received October 9, 1991

The question of the stability of the bicyclic form of AA is addressed by several theoretical methods varying in the level of sophistication. Both semi-empirical and *ab initio* approaches indicate that the bicyclic form is somewhat more stable than the 2,3-enediol tautomer (*I*). However, the tautomer *I* has a significantly higher dipole moment indicating that it gains additionally in stability if dissolved in polar solvents due to strong electrostatic solvent-solute interactions.

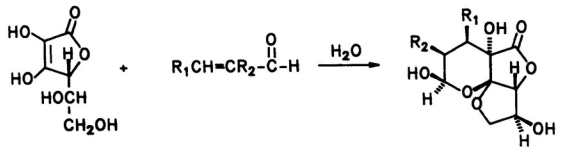
INTRODUCTION

Since its discovery in 1928,[1] L-ascorbic acid (AA) has attracted considerable interest of researchers. In particular, its structural features,[2] chemistry[3,4] and versatile biological properties[4] have been studied in detail. We just note in passing that L-ascorbic acid is one of the most important orthomolecular substances playing a crucial role in orthomolecular medicine.[5] However, it was not until a few years ago that the reaction of ascorbic acid with 4-keto-2-alkenals or with maleic aldehide was recognized by one of us (Scheme 1).[6] Later, the reaction of AA upon β-carbon of an α,β-unsaturated carbonyl compound, basically a Michael addition, was discovered (Scheme 2).[7] In both cases, the final product resulted from a synchronous (or subsequent) ring closure between C–3 and C–6 of the original ascorbic acid moiety, that is furano[3,2-*b*]furans were formed.[8,9] Both reactions showed to be widely expandable, leading to a variety of products with interesting pharmacological properties. For instance, most furylgulonolactones are immunopotentiating, while some of the ketocycloalkyl derivatives show virostatic effect.[11] Interestingly enough, the furano-furan moiety is also present in a number of natural products, such as ascorbigen, delesserine, rhodomellol, *etc.* It is worth mentioning that ascorbigen can be prepared by reacting AA with 3-hydroxymethyl indole.[11] Similarly, delesserine and rhodomellol are accessible by using the Michael reaction of ascorbic acid with 4-hydroxy-benzylalcohols.[12]



I R=H, CH_3

Scheme I



I R_1=R_2=H;
R_1=CH_3, R_2=H;
R_1=H, R_2=CH_3

Scheme II

A question arises whether ascorbic acid itself can undergo cyclization of the side chain to yield 3-ketogulonolactone⟨3,6⟩cyclohemiketal. Some evidence in favour of such a possibility is provided by methylation of AA with dimethylsulphate, which results in the formation of methylketal-⟨3,6⟩-cyclohemiketal of 3-ketogulonic acid lactone-2-methyl ether as a by-product.[13] The latter compound is very closely related to the frozen form (although blocked) of the bicyclic structure of ascorbic acid. Furthermore, the bicyclic form of AA seems to be involved in the degradation pathway of AA under non-oxydative conditions.[14]

As a part of our continuing interest in the properties of AA and related compounds,[15-19] we have undertaken a theoretical study of 2,3-enediol tautomer of AA (*I*) and its bicyclic counterpart (*II*). The former, as it is well known, corresponds to the AA tautomer detected in the solid state[2] as well as in solution.[20-22]

CALCULATIONS

Calculations were done by using the MNDO semiempirical method[23] and several *ab initio* procedures differing in the choice of the basis set. The MNDO approach was found to reproduce satisfactorily most of the physico-chemical properties of AA and related molecules in our previous studies.[15-19] Its application in the present work allows a comparison of the electronic and structural parameters for the furano-furan form of AA with those of other AA tautomers at the same level of theory. Owing to the molecular complexity of compounds examined, optimization of their geometries at the *ab initio* level of theory was done by using STO-3G[24] and MINI-1[25] basis set only. Subsequently, one-point calculations for STO-3G (6-31G/STO-3G) and MINI-1 (6-31G/ /MINI-1) optimized structures employing 6-31G[25] basis set were performed. It should

be mentioned that STO-3G and MINI-1, calculations in tautomer *I* were done by considering only the side-chain conformation of the minimum energy as predicted by MNDO formalism ($\angle O_6C_6C_5O_5 = \sim 66^\circ$).

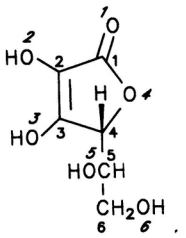
In the course of our work two other studies of AA have appeared.[27,28] One was concerned with the oxidation ability of AA,[27] whereas the other reported STO-3G calculations of various conformers of the 2,3-enediol tautomer of AA.[28]

Ab initio calculations in the present work were carried out with the GAUSSIAN-86[29] suit of programs, whilst MNDO calculations were performed with the MOPAC 5.0 package.[30]

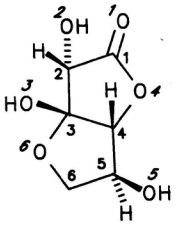
RESULTS AND DISCUSSION

Geometric Data

The calculated bond distances and bond angles of the fully optimized structures *I* and *II* are listed in Tables I and II, respectively. The MNDO calculated geometry of *I* has been discussed in detail by us previously[15-19] and it is included here only for the sake of comparison. It should be pointed out that all independent structural parameters are varied simultaneously in the optimization procedure for both STO-3G and MINI-1 basis sets. The geometry parameters for *I* resulting from STO-3G optimization are in full accordance with recently published *ab initio* results.[27,28]



I



II

Perusal of the data displayed in Table I reveals that each of the applied methodologies defines its own geometry scale, yielding structural data which are only in moderate agreement with experimental estimates (obtained however in crystals[2]). On the other hand, the main trends are correctly reproduced with all three procedures. This is related to salient features, like the planarity of the lactonic ring, the trend of changes of particular bonds, *etc.* For instance, the C_4O_4 bond is correctly predicted to be longer than its C_1O_4 counterpart irrespective of the method used, which is a consequence of a difference in hybridization at C_4 and C_1 sites.[16] Similarly, the C_1C_2 bond is predicted to be significantly shorter than the C_3C_4 bond compatible with the experimental[2] X-ray structure. This can be easily interpreted in terms of the higher average s-character involved in the C_1C_2 σ-bond and the π-electron delocalization. It is also apparent that MNDO and STO-3G estimates are closer to the experimental values than those calculated by using the MINI-1 procedure. This holds particularly for the bond

TABLE I

Comparison of the selected structural parameters for I, as calculated by STO-3G, MINI-1 and MNDO procedures and experimental data

Parameter	STO-3G	MINI-1	MNDO[a]	Exp.[b]
Bond distances (Å)				
C_1O_4	1.403	1.436	1.375	1.355
C_4O_4	1.443	1.483	1.423	1.444
C_3C_4	1.534	1.551	1.547	1.493
C_2C_3	1.322	1.347	1.375	1.338
C_1C_2	1.509	1.528	1.502	1.452
C_1O_1	1.215	1.258	1.220	1.216
C_3O_3	1.396	1.425	1.349	1.361
C_2O_2	1.383	1.410	1.341	1.326
C_4C_5	1.560	1.576	1.582	1.521
C_5C_6	1.556	1.576	1.575	1.521
C_5O_5	1.435	1.476	1.397	1.431
C_6O_6	1.433	1.468	1.398	1.427
Bond angles (deg)				
$C_1O_4C_4$	108.2	109.3	111.9	
$C_3C_4O_4$	105.5	104.2	103.9	
$C_5C_4C_3$	109.5	110.4	108.8	
$O_1C_1O_4$	123.0	123.6	119.3	
$O_3C_3C_2$	132.0	130.9	131.6	
$O_2C_2C_3$	128.0	128.2	126.3	
$C_5C_4C_3$	112.1	112.0	115.6	
$C_6C_5C_4$	112.2	111.0	112.2	
$O_5C_5C_4$	110.6	109.6	112.4	
$O_6C_6C_5$	105.7	104.8	108.8	

[a] Ref. 16; [b] Ref. 2

distances within the lactonic fragment. Finally, it should be noted that, at all levels of theory, there is a notable discrepancy between the calculated length of the carbon-carbon bonds within the chain and the corresponding experimental values. They are found to be longer by either 0.4 Å (STO-3G) or 0.08 Å (MNDO, MINI-1) than the values experimentally assigned. Similarly, most of the bond angles change as the level of calculation varies in general, however, they agree within ~3° with experimentally determined values, with MINI-1 estimates being again the least accurate.

A striking feature of the predicted structure of *II* is the long C–C bond length as estimated by all theoretical procedures. Unfortunately, the experimental geometry is not available. Comparison with the X-ray data of the structurally related tricyclic molecule representing the Michael adduct of ascorbic acid and acrolein[8] indicates that the bond distances might be exaggerated indeed. It is believed, however, that relative differences between similar bonds in related molecules are much more accurately reproduced than their absolute values provided the same theoretical framework is used. It is interesting to point out that the lactonic ring is predicted to be essentially planar within MNDO formalism, whereas both *ab initio* procedures predict significant distortion from the planarity, as evidenced by the data presented in Table II. It goes without saying that the *ab initio* results should be considered between the semiempirical and *ab initio* predictions of the distribution of bond distances within the lactonic fragment.

TABLE II

Main structural parameters of II, as calculated by STO-3G, MINI-1 and MNDO procedures

Parameter	STO-3G	MINI-1	MNDO
Bond distances (Å)			
C_1–O_4	1.399	1.424	1.370
C_4–O_4	1.438	1.383	1.407
C_3–C_4	1.566	1.589	1.599
C_2–C_3	1.562	1.583	1.600
C_1–C_2	1.563	1.583	1.556
C_1–O_1	1.212	1.255	1.219
C_3–O_3	1.426	1.459	1.391
C_2–O_2	1.430	1.463	1.386
C_4–C_5	1.568	1.587	1.582
C_5–C_6	1.558	1.583	1.573
C_5–O_5	1.429	1.467	1.392
C_6–O_6	1.434	1.465	1.402
C_3–O_6	1.440	1.480	1.409
Bond angles (deg)			
$C_1O_4C_4$	110.2	110.6	113.5
$C_3C_4O_4$	109.2	107.0	107.9
$C_5C_4C_3$	104.3	104.0	104.1
$O_1C_1O_4$	121.8	123.1	118.2
$O_4C_3C_2$	114.1	114.1	111.6
$O_6C_3C_4$	107.3	105.7	111.9
$O_2C_2C_3$	113.2	112.5	110.1
$C_5C_4C_3$	104.2	104.9	104.3
$C_6C_5C_4$	102.7	103.8	104.3
Dihedral angles (deg)			
$C_3C_4O_4C_1$	−4.8	−7.4	−0.3
$C_2C_3C_4O_4$	12.5	19.3	0.7
$C_6C_5C_4C_3$	6.3	0.4	3.4
$O_6C_3C_4C_5$	15.3	20.1	−1.5
$C_5C_4C_3O_1$	119.6	116.5	119.3

Energies

Calculated total energies and relative stabilities of structures *I* and *II* are summarized in Table III. Their dipole moments are included too, since polarity is important for getting some idea of a possible solvent effect in solution.[31] A survey of the results reveals that all employed methods predict a higher stability of the furano-furan form of AA in the gas phase. We commence a discussion with MNDO results which indicate that bicyclic form is by 8.0 kcal/mol more stable than *I*. A question arises: Why? In order to shed some more light into this result we shall employ the MNDO energy partitioning analysis (Table IV).

The merits of this type of energy decomposition, its physical meaning and application within various semiempirical schemes were considered in detail first by Pople[32] and subsequently by several other researchers.[33-35] We found it useful in discussing the relative stability of other AA tautomers,[15,16] AA anions,[16,18] and AA radicals.[17-19] To

TABLE III

Total energies (a.u.) relative energies (kcal/mol) and dipole moments (debye) of I and II as calculated by ab initio and MNDO procedures

Calculational Method	E_t (a.u.)		ΔE_t[a]	μ/debye	
	I	*II*	kcal/mol	*I*	*II*
STO–3G	–672.11120	–672.17640	41.0	2.01	0.77
6-31G/STO-3G	–680.67637	–680.67711	1.0	3.71	1.55
MINI-1	–676.37567	–676.40132	16.1	2.99	1.48
6-31G/MINI-1	–680.66218	–680.66412	1.2	3.93	2.04
MNDO	–2814.78[b]	–2814.44[b]	8.0	3.07	1.35

[a] $E_t = E_t(I) - E_t(II)$. [b] in eV.

TABLE IV

Decomposition of the SCF energies of I and II, as obtained by the MNDO method

E/eV	*I*[a]	*II*
E_1	–2515.8	–2519.2
E_2	–313.5	–312.3
E_3	14.9	16.7
E_t	–2814.8	–2814.4

[a] Ref. 17.

put it briefly, the total SCF energy (E_t) is partitioned into mono- (E_A) and bicentric (E_{AB}) contributions:

$$E_t = \sum_A E_A + \sum_{A<B} E_{AB} \tag{1}$$

In discussing the relative stabilities of AA tautomers, we found it convenient to decouple the two-center term into bonding and nonbonding interactions. Hence, formula (1) takes the form:

$$E_t = E_1 + E_2 + E_3 \tag{2}$$

where $E_1 = \sum_A E_A$ is a one-centre energy, $E_2 = \sum_{A-B} E_{AB}$ is a sum of stabilizing interactions of directly bonded atoms and $E_3 = 1/2 \sum_A E_{Anb}$ is a total molecular nonbonded repulsion term expressed as a sum over all atoms.

Detailed analysis of the results displayed in Table IV indicates that (at least within the MNDO formalism) the enhanced stability of the bicyclic structure is primarily due to a difference in monocentric terms. A low value of the single-center energies in *II* overcompensates the increased non-bonded repulsions and somewhat weaker bonding interactions. The largest changes in the single-center terms are found at the O_3 position (–306.4 in *I vs.* –307.7 in *II*), at the C_1 (–99.5 in *I vs.* –100.6 in *II*) and C_4 (–101.0 in *I vs.* –101.9 in *II*) atoms. Furthermore, the $E_1(C_3)$ and $E_1(C_2)$ terms indicate a sta-

bilization of 0.6 and 0.4 eV, respectively. Finally, the contribution of the side-chain atoms to the observed difference is small ($|0.1| - |0.31|$ eV) compared to the atoms forming the lactonic ring and the atoms attached to it. It is noteworthy that the aforementioned trends correlate well with the changes of electron densities at the corresponding atoms. For instance, O_3 and C_1 atoms in *II* gain in electron densities by 0.08 and 0.20 units. Similarly, C_3 and C_2 atoms have diminished electron densities by 0.20 and 0.18 units, respectively.

Contrary to the monocentric terms, the sum of E_2 and E_3 energies appear to be higher in bicyclic structure as indicated earlier (Table IV). The largest change in the E_2 terms is observed for the atoms participating in the lactonic ring. In *I*, they contribute –85.9 eV to the total bonding interactions, whilst in *II* their sum equals –74.2 eV. Larger fraction of the difference between these two values is, however, compensated by forming the new bond between the C_3 and O_6 atoms in structure *II*.

Finally, it should be pointed out, that the results of the energy partitioning technique should be taken with due caution in view of the approximate notion of the MNDO method and small difference between the corresponding terms.

Let us now turn our attention to the *ab initio* results. We observe that ΔE_t, as calculated by minimal basis sets, varies from 26.1 kcal/mol (MINI-1) to as much as 41.0 kcal/mol (STO-3G) in favour of structure *II*. In sharp contrast to this, the 6-31G basis set calculations on STO-3G and MINI-1 geometries yield the ΔE_t value of only 1 kcal/mol (Table III), with structure *II* again being favoured.

It follows that each of the methodologies used in the present study predicts that the bicyclic structure is more stable than the form *I*, as intuitively expected on the basis of the increased number of chemical bonds. However, a word of caution is in place. In view of a minute difference in ΔE_t obtained by the 6-31G calculations, it is possible that the use of better basis sets may reverse the stabilities. In particular, better estimates of structural parameters would be highly desirable. This is probably more important in *ab initio* procedures than an explicit treatment of the electron correlation effect, although the latter is not neglibile either. It should be mentioned in this connection that the semiempirical studies predict also similar stabilities of 2,3-enediol and 3-ketoidonolactone AA tautomers,[16] indicating that a question of the most stable form in the gas phase has not been unequivocally resolved as yet. As a matter of fact, the experimental NMR measurements provide quite conclusive evidence that only form *I* is present in polar solvents.[20-22] A large dipole moment of this form as compared to all other tautomers indicates that solvent-solute interactions may well be responsible for the appearance of the former in polar solutions, offering additional stabilization to form *I*. A recent semiempirical work shows that solvent effects are indeed very important in determining the relative stabilities of AA tautomers in liquid phase.[36]

CONCLUSION REMARKS

The results presented here suggest that the furano-furan form of AA is of comparable stability with that of the 2,3-enediol tautomer. More specifically, MNDO and *ab initio* procedures indicate that the former is of a somewhat lower total energy in the gas phase but some caution has to be exercised in view of the highly approximate nature of the MNDO method and very modest minimal basis sets employed in the *ab initio* calculations of molecular structures. Hence, studies employing more refined basis sets are needed. Unfortunately, they are presently precluded by economical reasons.

As to the behaviour in solutions, tautomer *I* is exclusively detected in polar solvent, as revealed by the NMR technique.[17-19] Here, the solvent effect seems to play a crucial role. It remains, however, to be proven that AA is indeed able to exist in the bicyclic form. It is conceivable that new experimental techniques will be developed, able to detect much smaller amounts of tautomer forms other than *I*.

Acknowledgement. – The financial support of Ministry of the Republic of Croatia and the International Office of Kernforschungsanlage Jülich, Germany (M. E. M.) is gratefully acknowledged.

REFERENCES

1. A. Szent-Györgyi, *Biochem. J.* **22** (1929) 1387.
2. J. Hvoslef, *Acta Chem. Scand.* **18** (1964) 841; *Acta Crystallogr.* **B24** (1968) 23.
3. G. C. Andrews and Th. Crawford in: *Ascorbic Acid, Chemistry, Metabolism and Uses*, P. A. Seib and B. M. Tolbert, Eds., *Adv. Chem. Ber. Ser.* **200** (1982) pp. 59-79.
4. W. Friedrich, *Handbuch der Vitamine,* Urban & Schwarzenberg, 1987; O. Isler, G. Brubacher, and J. Kiss in: *Vitamine II, Wasserlösliche Vitamine,* O. Isler, Ed., and references cited therein.
5. L. Pauling, *How to Live Longer and Feel Better,* W. H. Freeman and Co., New York, 1986.
6. G. Fodor, R. Sussangkarn, R. Arnold, I. Karle, and C. George, *Paper, ORGN 75, 186th ACS National Meeting,* Washington, D. C. August 29, 1983; G. Fodor, K. Sussangkarn, H. Mathelier, I. Karle, and C. George, *J. Org. Chem.* **49** (1984) 5064.
7. G. Fodor, R. Arnold, T. Mohacsi, I. Karle, and J. Flippen-Anderson, *Tetrahedron* **39** (1983) 2137.
8. K. Sussangkarn, G. Fodor, I. Karle, and C. George, *Tetrahedron* **44** (1988) 7047.
9. K. Eger, G. Folkers, W. Zimmermann, R. Schmidt, and W. Hiller, *J. Chem. Res. (M)* (1987) 2352.
10. R. Arnold, G. Fodor, H. Mathelier, T. Monacsi, A. Szent-Györgyi, and R. W. Vetri in: *Protective Agents in Cancer,* D. C. H. McBrien and T. F. Slater, Eds., Acad. Press, 1983.
11. E. Pironen and A. I. Virtanen, *Acta Chem. Scand.* **16** (1962) 1286.
12. A. J. Poss and R. K. Belter, *J. Org. Chem.* **53** (1988) 1535.
13. P. V. Lu, D. V. Lillard, P. A. Seib, K. J. Kramer, and Y. T. Liang, *J. Agric. Food Chem.* **32** (1984) 21.
14. K. Goshina, N. Maezono, and K. Tokuyma, *Bull. Chem. Soc. Jpn* **46** (1973) 902.
15. P. Bischof, M. Eckert-Maksić, and Z. B. Maksić, *Z. Natruforsch.* **36a** (1981) 502.
16. M. Eckert-Maksić, P. Bischof, and Z. B. Maksić, *Croat. Chem. Acta* **58** (1985) 407.
17. M. Eckert-Maksić, P. Bischof, and Z. B. Maksić, *J. Mol. Struct. (Theochem)* **139** (1985) 407; *Z. Natruforsch.* **41a** (1986) 1315.
18. M. Eckert-Maksić, Z. B. Maksić, and P. Bischof in: *Modelling of Structure and Properties of Molecules*, Z. B. Maksić, Ed., Ellis Horwood, Chichester, 1987.
19. M. Eckert-Maksić and Lj. Maksimović, *Croat. Chem. Acta* **59** (1986) 757; *J. Mol. Struct. (Theochem)* **153** (1987) 121.
20. S. Berger, *Tetrahedron* **33** (1977) 1587.
21. J. V. Paukstelis, D. D. Mueller, P. A. Seib, and D. W. Lillard Jr. in: *Ascorbic Acid, Chemistry, Metabolism and Uses, Adv. Chem. Ser.* **200** (1982) pp. 125-149.
22. J. Lauterwein and A. Ruchman, private communication.
23. M. J. S. Dewar and W. Thiel, *J. Amer. Chem. Soc.* **99** (1977) 4907.
24. W. J. Hehre, R,. Stewart, and J. Pople, *J. Chem. Phys.* **51** (1969) 2657.
25. S. Huzinaga and Y. Sakai, *J. Chem. Phys.* **50** (1969) 1371; H. Tatewaki and S. Huzinaga, *J. Comp. Chem.* **3** (1980) 205.
26. R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.* **56** (1972) 2257; M. M. Francel, W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees, and J. A. Pople, *J. Chem. Phys.* **77** (1982) 3654.

27. Y. Abe, S. Okada, H. Harrii, S. Taniguchi, and S. Yamabe, *J. Chem. Soc. Perkin Trans. II* (1987) 715.
28. M. A. Al-Laham, G. A. Petersson, and P. Haake, *J. Comp. Chem.* **12** (1991) 113.
29. M. J. Frisch, J. S. Binkley, H. B. Schlegel, K. Roghavachari, C. F. Melius, R. L. Martin, J. J. P. Stewart, F. B. Bobrowicz, C. M. Rohlfing, L. R. Kahn, D. J. DeFrees, R. Seeger, R. A. Whiteside, D. J. Fox, E. M. Fleuder, and J. A. Pople, *GAUSSIAN 86*, Carnegie-Mellon Quantum Chemistry Publishing Unit, Pittsburgh PA, 1984.
30. J. J. P. Stewart, *OCPE Bull.* **9** (1989) 10.
31. T. J. Zielinski, *J. Comp. Chem,*. **4** (1983) 345 and references cited therein.
32. J. A. Pople, D. P. Santry, and G. A. Segal, *J. Chem. Phys.* **435** (1965) 125.
33. H. Fischer and H. Kollmar, *Theor. Chim. Acta* **16** (1970) 163.
34. M. J. S. Dewar and D. H. Lo, *J. Amer. Chem. Soc.* **93** (1971) 7201; M. J. S. Dewar, D. H. Lo, and Z. B. Maksić, *Croat. Chem. Acta* **46** (1974) 7.
35. J. B. Moffat in: *Conceptual Quantum Chemistry. Models and Applications*, Z. B. Maksić, Ed., *Croat. Chem. Acta* **57** (1984) 1475.
36. U. Höweler, Th. Bäcker, M. Klessinger, M. Eckert-Maksić, and Z. B. Maksić, *Croat. Chem. Acta* **64** (1991) 539.

SAŽETAK

Teorijski studij ⟨3,6⟩ciklohemiketalnog oblika L-askorbinske kiseline

M. Eckert-Maksić, M. Hodošček i G. Fodor

Opisani su rezultati proračuna molekulske strukture i stabilnosti 2,3-enediolnog (I) i ⟨3,6⟩ciklohemiketalnog (II) oblika L-askorbinske kiseline. Računi su provedeni primjenom semiempirijske MNDO metode i *ab initio* postupka, uz korištenje baznih skupova 3-21G i MINI-1. Sve primijenjene metode predviđaju veću stabilnost za bicilički tautomer (II). Tautomer I, međutim, posjeduje veći dipolni moment što upućuje na mogućnost jače stabilizacije tog tautomera u otopinama uslijed elektrostatskih interakcija s otapalom.