ISSN 0018-1439, High Energy Chemistry, 2014, Vol. 48, No. 5, pp. 303–309. © Pleiades Publishing, Ltd., 2014.
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RADIATION CHEMISTRY

Reactions of Cyclopentanone, γ-Butyrolactone, and Their Derivatives with α-Hydroxyethyl Radicals

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Received February 21, 2014; in final form, March 27, 2014

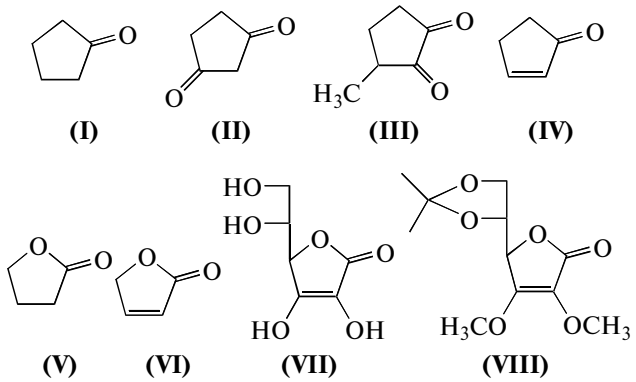
Abstract—The interaction of cyclopentanone, 2-cyclopentenone, 1,3-cyclopentanedione, 3-methyl-1,2-cyclopentanedione, γ-butyrolactone, 2(5H)-furanone, ascorbic acid, and 5,6-*O*-isopropylidenyl-2,3-*O*-dimethylascorbic acid with α-hydroxyethyl radicals (α-HER) generated during the radiolysis of deaerated ethanol has been studied in the continuous irradiation mode. The test compounds, except γ-butyrolactone, oxidize α-HER. 2(5H)-Furanone and 2-cyclopentenone give hydroxyethylation products via the free-radical chain mechanism. In contrast to 2(5H)-furanone and 2-cyclopentenone, ascorbic and 5,6-*O*-isopropylidenyl-2,3-*O*-dimethyl-L-ascorbic acids are weaker oxidants for α-HER and attach these radicals at the multiple carbon–carbon bonds.

DOI: 10.1134/S0018143914050051

Ascorbic acid is the major intracellular antioxidant, inhibiting free radical oxidation of biologically important compounds [1]. The acid reduces with high reaction rate constants various in vivo generated oxygen-centered radicals [2], such as tocopherol [3], carotenoid [4], and plant phenol [5] radicals. Along with homolytic oxidation reactions, ascorbic acid and some of its derivatives can control processes of free-radical fragmentation of hydroxylated organic compounds [6–10] that include the step of formation of α-hydroxylated carbon-centered radicals (**α-HCR**). These processes lead to the degradation and modification of carbohydrates [11], ribonucleotides [12], hydroxy amino acids, peptides [13], and lipids [14]. The reactivity of ascorbic acid toward α-HCR is largely determined by the >C=O group conjugated with the >C=C< double bond [9, 10]. This moiety is also present in the structure of quinones [15], flavonoids [16], B vitamins [17], hydroxyarylaldehydes [18], coumarinoids [19], and curcuminoids [20], which effectively inhibit free-radical fragmentation reactions. To reveal the mechanism of the reaction of α-HCR with the >C=O group of ascorbic acid, in this study we used a series of carbonyl-containing five-membered cyclic compounds that are widespread as a moiety of cardiac glycosides [21], aromatics [22], and other substances. Therefore, our study may also contribute to the investigation of the radical-controlling properties of these physiologically important compounds.

EXPERIMENTAL

Cyclopentanone (**I**), 1,3-cyclopentanedione (**II**), 3-methyl-1,2-cyclopentanedione (**III**), L-ascorbic acid (**VII**), acetaldehyde, and (+/–)-*meso*-2,3-butanediol available from Sigma-Aldrich and 2-cyclopentenone (**IV**) and 2(5H)-furanone (**VI**) from Alfa Aesar and Fluka, respectively, were used without further purification. γ-Butyrolactone (**V**) was distilled at 5 mm Hg prior to use. 5,6-*O*-Isopropylidenyl-2,3-*O*-dimethyl-L-ascorbic acid (**VIII**) was prepared as described in [6]. The structural formulas of the compounds are given in Scheme 1. The purity of the compounds used was monitored by gas chromatography–mass spectrometry; it was at a least 98%.



Scheme 1.

Lux food-grade ethanol (96 vol %) was purified by distillation on a fractionating column before use. Because of the high volatility of the solvent, deaerated solutions of the test compounds with a concentration of 10^{-3} mol/L in ethanol were prepared according to the following procedure. The solutions were purged with high purity (99.9%) argon in pycnometers for 60 min, the evaporated solvent was replenished with deaerated ethanol, and the solutions were stirred.

Ampoules, preliminarily purged with argon, were filled with a solution and then sealed. Irradiation was carried out on an MRKh-γ-25M facility with a ^{60}Co source. The dose rate was 0.323 ± 0.008 Gy/s, and the dose range was 0.2–4.3 kGy.

The concentrations of acetaldehyde (AA) and 2,3-butanediol (2,3-BD), which are products of radiation-induced transformation of deaerated ethanol, and compounds **I–VI** were determined on a Shimadzu GC-17A gas chromatograph using an RTX-WAX fused-silica capillary column. An external standard was used for qualitative and quantitative analyzes. The analysis conditions were as follows: initial temperature, 40°C; temperature rise to 250°C with a gradient of 13°C/min; injector temperature, 240°C; detector temperature, 230°C; linear carrier gas (nitrogen) velocity, 30 cm/s; flame ionization detector; and sample size, 1 μL. Quantitative analysis for **VII** and **VIII** was carried out spectrophotometrically on a Specord S600 instrument.

The products of radiation-induced reactions of compounds **I–VI** were identified using the GC–MS technique on a Shimadzu GCMS-QP2010 instrument as in [18–20]. The structure of the radiolysis products of 2(5H)-furanone (**VI**) was confirmed by ^{1}H NMR using a Bruker Avance 400 spectrometer operating at a frequency of 400 MHz. The radiation-chemical yields were determined using the results of at least two independent runs; the error of determination was calculated by the least squares technique at a confidence level of 0.95.

RESULTS AND DISCUSSION

Radiation chemistry of ethanol is well documented [23], so it is a convenient model for studying the reactivity of substances toward α-hydroxyethyl radicals (α-HER) generated with a radiation-chemical yield of ~5.5 eV particle/100 eV under these conditions mainly as a result of ion–molecule reaction (2):

$$CH_3CH_2OH \xrightarrow{\gamma} CH_3CH_2O\overset{\oplus\cdot}{H} + e^{\ominus}_{solv}, \quad (1)$$

$$CH_3CH_2O\overset{\oplus\cdot}{H} + CH_3CH_2OH \longrightarrow CH_3CH_2O\overset{\oplus}{H}_2 + CH_3\dot{C}HOH. \quad (2)$$

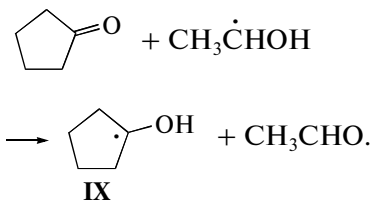
In the absence of additives, α-HER are consumed in bimolecular combination and disproportionation reactions (3) and (4) to give 2,3-DB and AA, respectively:

$$CH_3\dot{C}HOH + CH_3\dot{C}HOH \longrightarrow CH_3CH(OH)CH(OH)CH_3, \quad (3)$$

$$CH_3\dot{C}HOH + CH_3\dot{C}HOH \longrightarrow CH_3CHO + CH_3CH_2OH. \quad (4)$$

Therefore, the determination of radiation-chemical yields of the main products of ethanol radiolysis in the presence of additives in combination with data on the final molecular products of their radiolysis makes it possible to establish the mechanism of interaction of α-HER with the test substances.

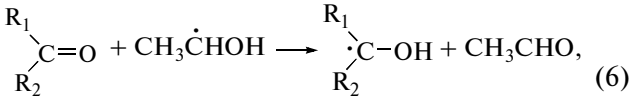
Irradiation of deaerated ethanol in the presence of cyclopentanone results in a lower radiation-chemical yield of 2,3-BD and a higher radiation-chemical yield of AA as compared with the solute-free system (table). According to the GC–MS data, the only molecular product of radiation-induced conversion of the solute in deaerated ethanol is cyclopentanol (Fig. 1a). The set of data obtained shows the ability of cyclopentanone to oxidize α-HER via the reaction:



(5)

IX

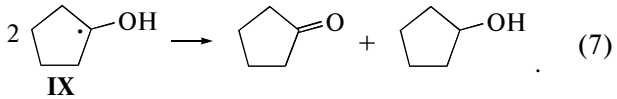
The oxidation reaction of hydroxyalkyl radicals, similar to reaction (5), is a characteristic feature of radiation chemistry many of carbonyl compounds. We have shown that aliphatic and aromatic aldehydes [24], quinones [15], flavonoids [16], ascorbic acid [9, 10], and some group B vitamins [17] react with α-HER in the same manner:



(6)

R_1, R_2 = H, Alkyl, Aryl.

Cyclopentanol as a molecular product of radiation-induced transformation of cyclopentanone (**I**) in deaerated ethanol is probably formed as a result of disproportionation of two radicals **IX**:



(7)

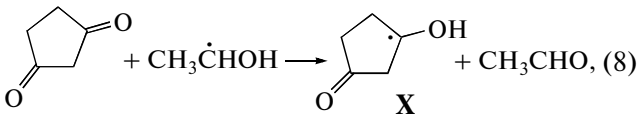
IX

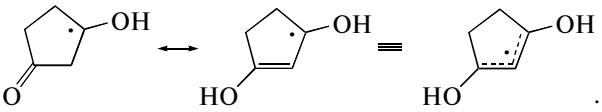
Introducing another carbonyl group into the cyclopentane ring; i.e., passing to 1,3-cyclopentanone, significantly enhances the reactivity of the additive toward α-HER, as indicated by a lower yield of 2,3-BD in the radiolysis of deaerated alcohol in the presence of **II** than in the case of **I**. As a result of oxidation of α-HER by 1,3-cyclopentandione, stable radical **X**

Effect of carbonyl derivatives of furan and cyclopentane on radiation-chemical yields of radiolysis products of deaerated ethanol

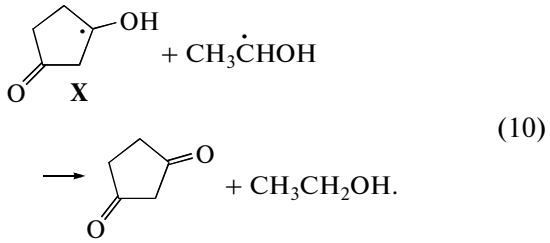
Test compound	Radiation-chemical yield (G), molecule/100 eV		
	acetaldehyde	2,3-butanediol	solute degradation
Additive-free	1.92 ± 0.06	2.11 ± 0.09	–
Cyclopentanone (**I**)	2.50 ± 0.10	1.74 ± 0.07	−0.99 ± 0.07
1,3-Cyclopentanedione (**II**)	2.36 ± 0.11	1.28 ± 0.05	−0.20 ± 0.04
3-Methyl-1,2-cyclopentanedione (**III**)	4.46 ± 0.25	0.21 ± 0.02	−1.77 ± 0.17
2-Cyclopentenone (**IV**)	1.70 ± 0.09	0	−8.65 ± 0.21
γ-Butyrolactone (**V**)	2.38 ± 0.11	2.12 ± 0.10	−0.62 ± 0.18
2(5H)-Furanone (**VI**)	2.07 ± 0.55	0	−62.77 ± 2.62
Ascorbic acid (**VII**)	2.37 ± 0.14	0.55 ± 0.15	−0.48 ± 0.11
5,6-*O*-isopropylidenyl-2,3-*O*-dimethyl-L-ascorbic acid (**VIII**)	2.65 ± 0.20	0.88 ± 0.11	−0.99 ± 0.13

of the allyl type due to keto–enol tautomerism can form:

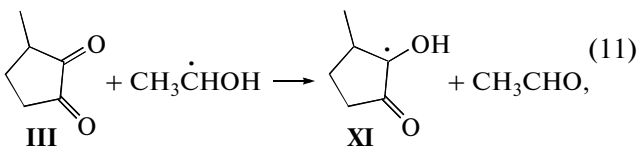


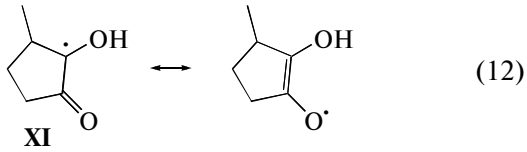


Judging by the low radiation-chemical yield of decomposition of 1,3-cyclopentanedione and by the ratios between the main products of ethanol radiolysis in its presence, radicals **X** exhibit reducing properties in reactions with α-HER and enter reactions that lead to regeneration of the additive:



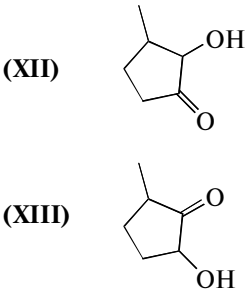
In the case of the 1,2-dicarbonyl compound **III**, the reaction with α-HER must lead to the formation of two more active carbon-centered radicals containing the carbonyl group in the α-position, e.g., **XI**:





The presence of a resonance structure with the unpaired electron on the oxygen atom should impart pronounced oxidative properties to radical **XI**; thus, the final product of its radiolytic transformations in ethanol should be 2-hydroxy-3-methylcyclopentanone (**XII**).

Compound **XII** and its isomer 2-hydroxy-5-methylcyclopentanone (**XIII**)



were identified by gas chromatography–mass spectrometry as products of radiolytic transformation of **III** in deaerated ethanol (Fig. 1b). In the presence of **III**, the formation of 2,3-DB is almost completely inhibited, thereby indicating its higher reactivity toward α-HER. Since the yield of acetaldehyde increases by more than two times compared with the additive-frees system, the majority of α-HER generated in the system are oxidized according to reactions (11) and

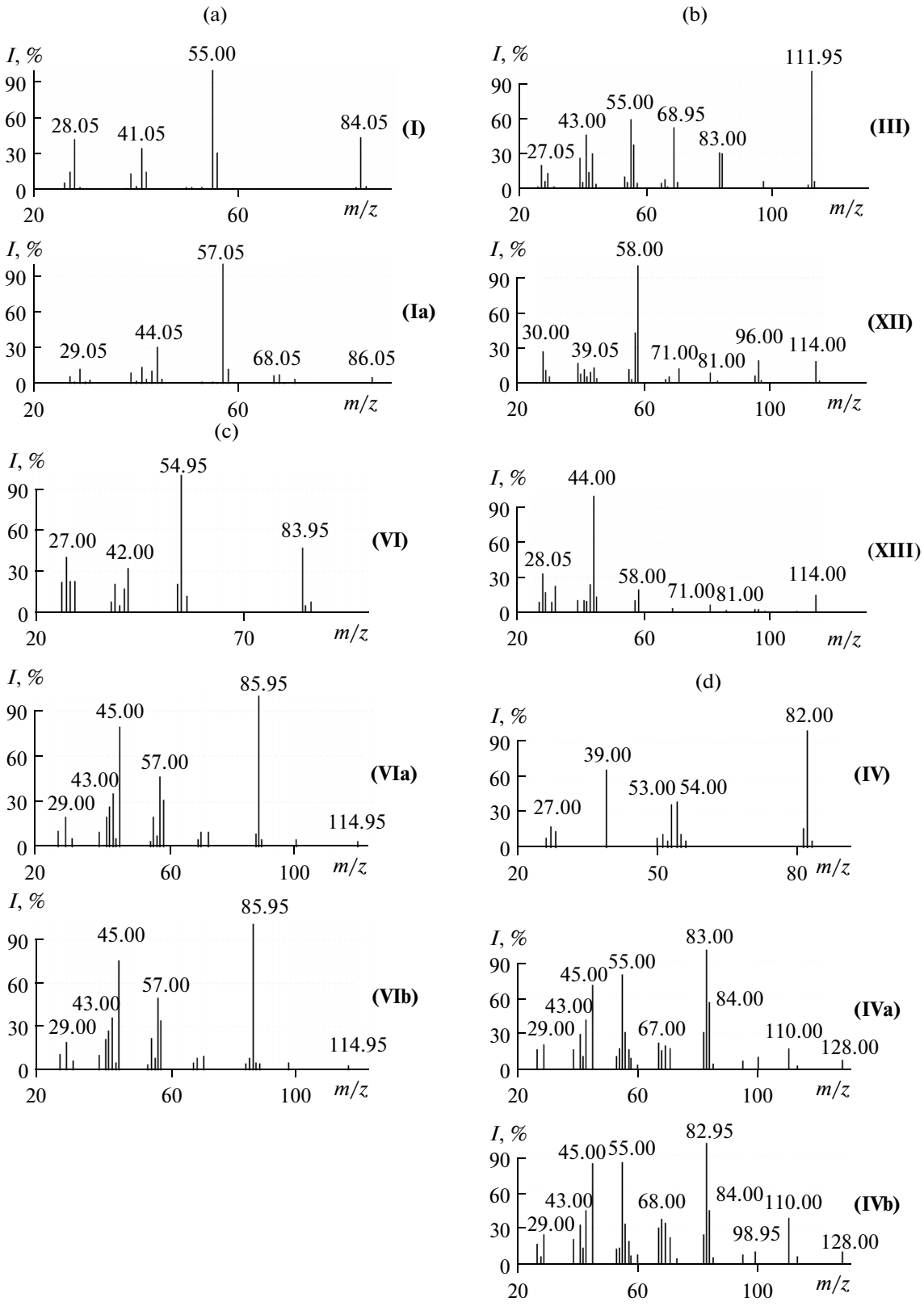
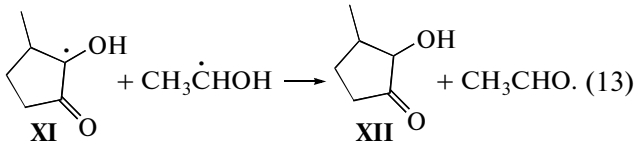
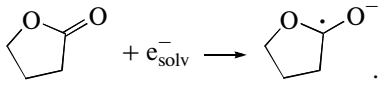


Fig. 1. Mass spectra of (a) cyclopentanone (**I**) and cyclopentanol (**Ia**), a product of its radiolysis in deaerated ethanol; (b) 3-methylcyclopentanedione-1,2 (**III**) and the products 2-hydroxy-5-methylcyclopentanone (**XIII**) and 2-hydroxy-3-methylcyclopentanone (**XII**) generated by its radiolysis in deaerated ethanol; (c) 2(5H)-furanone (**VI**) and the products 3-(1-hydroxyethyl)-γ-butyrolactone (**VIa**) and 2-(1-hydroxyethyl)-γ-butyrolactone (**VIb**) of its radiolysis in deaerated ethanol; and (d) cyclopentene-2-one-1 (**IV**) and the products 3-(1-hydroxyethyl)-cyclopentanone (**IVa**) and 2-(1-hydroxyethyl)-cyclopentanone (**IVb**) of its radiolysis in deaerated ethanol.



High degradation yields of the solute suggest that reactions analogous to reaction (10) are untypical of radical **XI**.

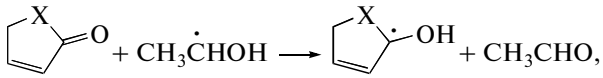
In contrast to the compounds considered above, the radiation-chemical yield of 2,3-DB during the radiolysis of **V** in deaerated ethanol is the same as in the solute-free ethanol, indicating that the solute is unable to interact with α-HER. The observed increase in the radiation-chemical yield of AA can be due to interaction of **V** with the solvated electron by reaction (14), since solvated electrons in the absence of acetaldehyde scavengers are reduced.



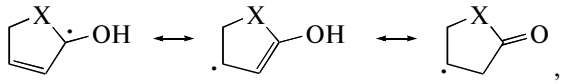
(14)

Introduction of the double carbon–carbon bond conjugated with the carbonyl group into the structure of **I** or **V** drastically alters the observed radiolytic behavior of the solutes. Irradiation of α,β-unsaturated carbonyl compound **VI** or **IV** in deaerated ethanol does not result in the formation of 2,3-DB (table), thereby indicating the complete inhibition of the α-HER combination reaction. This implies that **VI** and **IV** quantitatively react with radical intermediates.

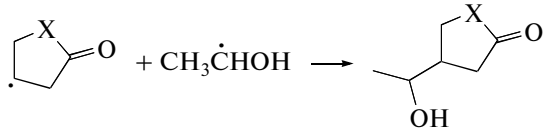
As the only molecular products of conversion of **VI** and **IV** in deaerated ethanol, adducts with a molecular mass of $M = M(\text{solute}) + M(\alpha\text{-HER}) + 1$ were identified by the GC–MS technique (Figs. 1c, 1d). Against the background of lacking 2,3-DB, the radiation-chemical yield of AA corresponds to that in the solute-free system, suggesting the manifestation of the oxidizing properties by the test α,β-unsaturated carbonyl compounds or the products of their radiolytic reactions. The identified products of free radical transformations of **VI** and **IV** can result from the following reactions:



(15)



(16)



(17)

X = –O–, –CH_2–.

However, the observed radiation-chemical yields of degradation of **IV** and **VI** are a few times higher than the yield of α-HER in deaerated ethanol (table), suggesting the chain character of the free-radical processes in the system. Therefore, reactions (15)–(17) are not dominant during the irradiation of **VI** and **IV** in deaerated ethanol. The GC–MS study of the conversion products of **VI** in deaerated ethanol showed the presence of two peaks with peak areas in the ratio of 1 : 1.3 corresponding to the products of α-HER addition to the multiple bonds of the solutes. However, this method does not allow the structure of these adducts to be unambiguously established because of its inability to distinguish structural isomers and diastereoisomers of a substance.

To determine the mechanism of addition of α-HER at the multiple bonds of the α,β-unsaturated carbonyl compounds in question, we performed the radiation-chemical synthesis of the adduct of this radical with **VI**. The choice of the compound is due to its high yields of radiation-induced conversion. The irradiation time was calculated as that required for the complete consumption of the reactant. The mixture of two isomeric products obtained after evaporation of the solvent, which did not contain other substances according to GC–MS data, was used for NMR measurements.

The NMR spectrum of the products of radiation-induced conversion of **VI** displays four groups of low-field signals (4.15–4.45 ppm): two doublets of doublets due to enantiotopic hydrogens K and L and two unresolved multiplets of enantiotopic hydrogen atoms A and B (Fig. 2). If the α-HER adducts with **VI** were diastereomers, signals of hydrogen atoms A and K, B and L would have the same chemical shifts and be displayed as two multiplets in the spectrum. In the spectrum measured, each hydrogen atom gives an individual multiplet; consequently, the adducts of α-HER with **VI** are structural isomers.

The upfield (1.15–1.25 ppm) signals of methyl groups P and E appear as two doublets due to splitting on hydrogen atoms O and G, respectively. According to simulation using the MestReNova 6.0.2 program, the signals of groups E and P are to appear at $\delta = 1.18$

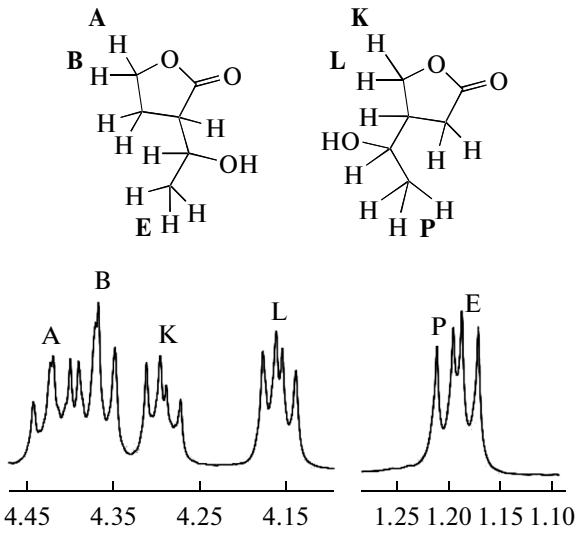
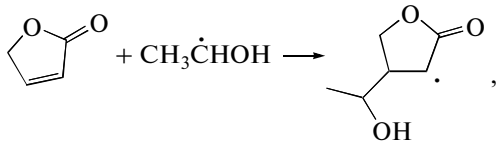


Fig. 2. Low- and upfield portions of the ^{1}H NMR spectrum of a mixture of products of radiation-chemical transformations of 2(5H)-furanone and assignment of signals of hydrogen atoms.

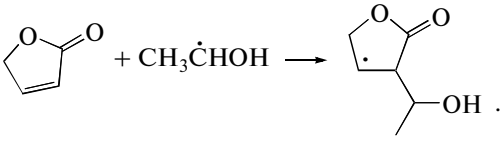
and 1.21 ppm, respectively. The integral signal intensity of the signal of group E is higher than that for group P; hence, the isomer mixture contains a greater amount of the C_2-addition product.

Thus, the NMR and GC–MS data show the formation of the products of C_2- and C_3-hydroxyethylation of 2(5H)-furanone in a ratio of 1.3 : 1 during its irradiation in deaerated ethanol.

The formation of the C_2- and C_3 adducts with close radiation-chemical yields indicates the ability of α-HER to add directly to multiple carbon–carbon bonds in **VI**:

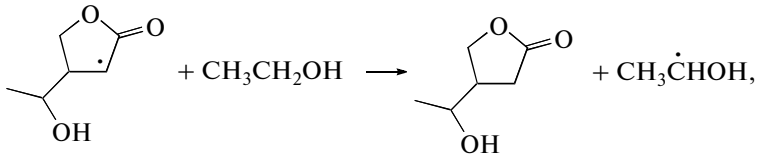


(18)

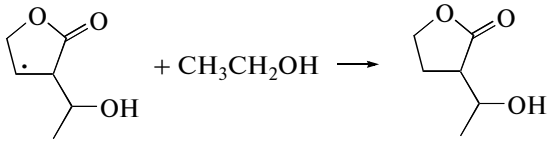


(19)

Judging by the high radiation-chemical yields of decomposition of **VI**, which are more than 10 times greater than the yields of α-HER in deaerated ethanol (table), the radicals generated in reactions (18) and (19) can abstract an H atom from ethanol, resulting in the hydroxyalkylation products identified and the regeneration of α-HER:



(20)



(21)

It is known that α,β-unsaturated carbonyl compounds are good substrates in nucleophilic and electrophilic addition reactions [25]. The addition of carbon-centered radicals to activated carbon–carbon bonds has been reported [18, 19, 26, 27]. A characteristic feature of homolytic addition reactions compared with heterolytic reactions is the lack of selectivity. The higher yield of the C_2-addition product of the radiolysis 2(5H)-furanone in deaerated ethanol can be associated with the formation of intermolecular hydrogen bond between the α-HER hydroxyl group and the carboxyl group of the solute by the attachment of the radical.

As in the case of 2(5H)-furanone, two hydroxyethylation products were detected by gas chromatography–mass spectrometry among the products of radiolytic transformation of cyclopentenone in deaerated ethanol. Moreover, identical changes in the radiation-chemical yields of AA and 2,3-DB were observed in the presence of carbonyl compounds compared with the solute-free system. We believe that the mechanism of the radiolytic transformation of cyclopentenone in deaerated ethanol is the same at that for 2(5H)-furanone. A decrease in the radiation-chemical yield of degradation relative to that in the presence of 2(5H)-furanone may be associated with either stronger oxidizing properties of **IV** or an increase in the probability of reactions (15)–(17).

Since radiation-induced transformations of ascorbic acid and 5,6-*O*-isopropylidenyl-2,3-*O*-dimethyl-L-ascorbic acid in deaerated ethanol have been discussed in [6–10], we will consider only the key differences in the mechanism of interaction with α-HER

between these carbonyl compounds and their carbonylated analogues **I–VI**.

Compounds **VII** and **VIII** alter the ratio of radiation-chemical yields of ethanol in favor of AA, acting as an oxidant in reactions with α-HER, like most carbonyl compounds. However, despite the presence of the carbon–carbon double bond conjugated with the carbonyl group, **VII** and **VIII** are mild oxidants, a fact that is probably due to the increase of electron density on the carbonyl group by electron-donating substituents at C_2 and C_3. No products of α-HER addition to **VI** and **VIII** have been detected by gas chromatography–mass spectrometry; hence, the presence of hydroxy or methoxy groups as substituents at the double carbon–carbon bond imposes steric constraints on the addition of α-HER.

CONCLUSIONS

The interaction of ascorbic acid and its carbonylated cyclic analogues with α-HER generated during radiation-induced transformations of deaerated ethanol have been studied in the continuous radiolysis mode. The test compounds, except γ-butyrolactone, oxidize α-HER as indicated by a change in the ratio between the yields of the main radiolysis products of deaerated ethanol in favor of acetaldehyde. It has been shown that the principal mechanism of radiolytic transformations of α,β-unsaturated carbonyl compounds **VI** and **IV** is the addition of α-HER to the carbon–carbon double bond. The process follows the short-chain mechanism in the case of **IV** and has a greater chain length for **VI**. The ^{1}H NMR and GC–MS studies showed that the products of C_2- and C_3-addition of α-HER in the case of 2(5H)-furanone are formed in a ratio of 1.3 : 1. Unlike α,β-unsaturated carbonyl compounds **IV** and **VI**, ascorbic and 5,6-*O*-isopropylidenyl-2,3-*O*-dimethyl-L-ascorbic acid are weaker oxidants of α-HER and do not form hydroxyethylation products by radiolysis in deaerated ethanol.

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Translated by S. Zatonsky