Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 6383–6386
Bioorganic & Medicinal Chemistry Letters

Effects of quinones on free-radical processes of oxidation and fragmentation of hydroxyl-containing organic compounds

O. I. Shadyro,* A. A. Sosnovskaya, I. P. Edimecheva, N. I. Ostrovskaya, K. M. Kazem, I. B. Hryntsevich and A. V. Alekseev

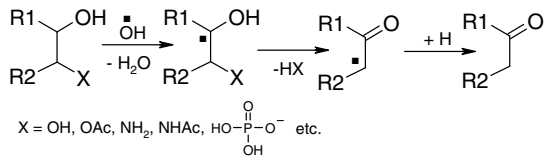
Department of Chemistry of the Belarusian State University, Nezavisimosty av., 4, 220030 Minsk, Belarus

Received 6 August 2007; accepted 22 August 2007
Available online 4 September 2007

Abstract—The coenzymes Q and Vitamin K_3, as well as their synthetic analogues, have been found to inhibit free-radical processes of fragmentation of hydroxyl-containing organic compounds and oxidation of the latter by molecular oxygen. It has been established that the observed effects are due to the ability of quinones to oxidize the α-hydroxyl-containing carbon-centered radicals formed from the starting compounds.

Ubiquinones and group K vitamins actively participate in the most essential biochemical oxidation-reduction processes.[1] Many of these reactions are accompanied by formation of reactive oxygen species (ROS), and that is why much attention was given to studying interactions of the latter with quinones.[2] High reactivity of quinones toward ROS accounts for the ability of the former to protect biologically important substances from free-radical injury. Quinones were also found to display antioxidant properties by inhibiting lipid peroxidation.[3] However, this can be realized effectively only in those cases when quinone reduction into the respective phenolic compounds is possible, the latter playing the role of antioxidants.[4,5] The effects produced by quinones on oxidation of hydroxyl-containing organic compounds have not been established as yet.

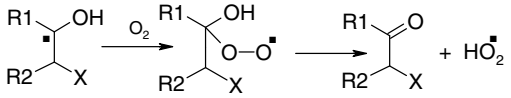
In our studies a concept is being developed, according to which ROS interaction with hydroxyl-containing organic substances can cause not only oxidation, but also fragmentation that can be depicted by the following general scheme[6]:



(1)

Realization of the process (1) accounts for deamination of amino alcohols and amino acids,[7] as well as for destruction of peptides,[7] di- and polysaccharides.[8,9] We were first to show that hydroxyl-containing glycerophospholipids, cerebrosides and sphingolipids [10,11] undergo fragmentation according to a mechanism similar to (1) to form substances of a lower molecular weight possessing properties of the signaling molecules. The key stage of the process (1) is decomposition of $R^1C^{\cdot}(OH)CH(X)R^2$ radicals, which has been shown to proceed according to a concerted mechanism via a cyclic transition state .[11,12]

The fragmentation processes (1) of hydroxyl-containing substances are inhibited by oxygen, because O_2 molecules actively interact with carbon-centered radicals to form oxidation products according to scheme[12]:



(2)

Being oxidants, quinones interact with $R^{\cdot}CHOH$ radicals by oxidizing them also, and this, as shown in,[13] may result in blocking the fragmentation reactions of type (1).

In this connection, the goal of the present study was to find out the effects of coenzymes Q_0 and Q_{10}, Vitamin K, as well as their synthetic analogues, on free-radical processes of oxidation and fragmentation for a number of hydroxyl-containing organic compounds. Structures of the starting compounds are shown in Figure 1.

Keywords: Coenzymes Q; Vitamin K3; Quinones; Radicals; Oxidation; Fragmentation.
* Corresponding author. Tel.: +375 17 206 6146; fax: +375 17 209 5464; e-mail: shadyro@open.by

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.08.076

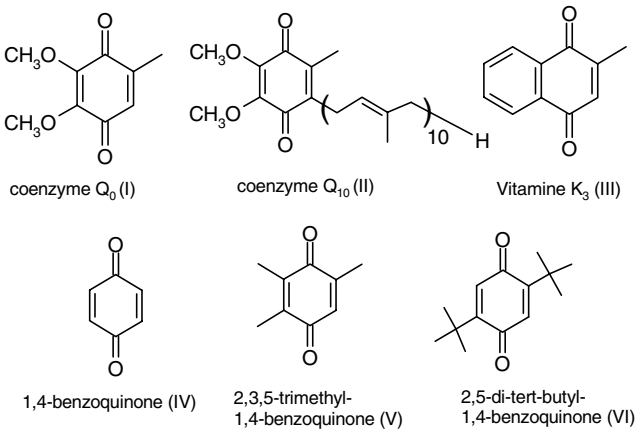


Figure 1. Structures of the starting compounds.

The most of the compounds used in the study were commercially available. 2,3,5-Trimethyl-1,4-benzoquinone (V) and 2,5-di-*tert*-butyl-1,4-benzoquinone (VI) were synthesized using the procedures described in.[13]

Ethanol (96% vol.) was purified by sorption on Wolfen Zeosorb LA ceolites followed by twice repeated distillation using a 3 m high rectification column.

Twice-distilled water was used for preparing solutions of all the hydroxyl-containing compounds listed above. Adjustment of 2-aminoethanol solution pH values to 6.8–6.9 was performed by adding appropriate amounts of perchloric acid. Into the solutions thus prepared, weighed amounts of quinones under study were introduced, to obtain concentrations 5×10^{-4} M for glycerol-1-phosphate solutions, 1×10^{-2} M for maltose solutions, and 1×10^{-3} M for solutions of the rest of compounds. Concentration of 2-methyl-1,4-naphtoquinone (Vitamin K_3) in aqueous solutions was 7.5×10^{-4} M due to its limited solubility in water.

γ-Radiation from a ^{137}Cs source was used for initiating free-radical processes. To prepare deaerated ethanol solutions of the compounds studied, the solvent was preliminarily bubbled through with high purity argon (99.9%) for 50 min. All the subsequent procedures, up to sealing of ampoules with solutions, were performed under argon atmosphere. To remove dissolved oxygen from aqueous solutions, the ampoules with solutions were blown through with argon for 45 min and then sealed. The dose rate of γ-radiation was (0.34 ± 0.03) Gy/s, and the absorbed dose range was 0.2–3.5 kGy. The absorbed dose range for maltose solutions was 1–20 kGy. Radiation-chemical yields of oxidation products were calculated from relationships reflecting the respective product accumulation as function of dose absorbed.

Analyses of radiolysis products (i.e. ethanal, methanol, 2-butanone, 2-hydroxyethanal, and 3-hydroxy-2-butanone) were performed using gas chromatographic techniques according to procedures described in.[13,14] Glucose concentration in maltose solutions was determined by HPLC as described in.[9] Concentration of phosphate ions in glycerophosphate solutions was measured spectrophotometrically according to.[13] Ammonia analysis in solutions of 2-aminoethanol was made using liquid chromatography technique described in.[7]

For determination of hydrogen peroxide formed during oxidation of ethanol and glucose, the spectrophotometric method, based on formation of a yellow complex of H_2O_2 with titanyl sulphate in sulphuric acid solutions, was used.[15]

Effects of quinones (I–VI) on oxidation processes taking place with hydroxyl-containing compounds were studied using ethanol and glucose as substrates. It is known that radiolysis of ethanol in the presence of O_2 results in free-radical oxidation of ethanol to form two main products, acetaldehyde and hydrogen peroxide[16]:

$$CH_3CH_2OH \xrightarrow{\gamma} CH_3\dot{C}HOH \xrightarrow{O_2} CH_3CH(O\dot{O})OH \longrightarrow CH_3CHO + H\dot{O}_2 \quad (3)$$

$$2H\dot{O}_2 \longrightarrow H_2O_2 + O_2 \quad (4)$$

In the absence of oxygen, radiolysis of ethanol leads to formation of acetaldehyde and 2,3-butanediol (2,3-BD):

$$CH_3CH_2OH \xrightarrow{\gamma} CH_3\dot{C}HOH \xrightarrow{CH_3\dot{C}HOH} CH_3CH(OH)CH(OH)CH_3 \ (5) \qquad CH_3CHO + CH_3CH_2OH \ (6)$$

The data obtained on product yields for radiolysis of air-saturated and deaerated ethanol in the presence and in the absence of the test compounds are presented in Table 1.

As seen from the data in Table 1, quinones (I–VI) inhibit the process of ethanol oxidation. This inhibition is manifested in a more effective suppression of hydrogen peroxide formation as compared to acetaldehyde.

It has been shown earlier[2,17] that quinones are able to oxidize α-hydroxyalkyl radicals effectively according to reaction:

$$R\dot{C}HOH + Q \longrightarrow RCHO + \dot{Q}H \quad (7)$$

Q - compounds I-VI

Consequently, realization of the process (7) in the course of radiolysis of aerated ethanol with quinones (I–VI) as additives will result in inhibition of ethanol oxidation according to reactions (3) and (4). This should lead to a significant decrease in the yields of H_2O_2, and this was indeed observed experimentally (see Table 1).

The conclusion that quinones effectively oxidize the $CH_3{\cdot}CHOH$ radicals follows from the data obtained for radiolysis of deaerated ethanol in the presence of quinones (see Table 1). The addition of quinones leads to suppression of formation of 2,3-butanediol and increase in yield of acetaldehyde, which is possible due to realization of reaction (7).

Table 1. Effects of quinones on yields (G) of products formed during radiolysis of ethanol in the presence and in the absence of oxygen

Test compounds, $C = 1 \cdot 10^{-3}$ M	$G \times 10^7$, mol/J			
	O_2		Ar	
	H_2O_2	CH_3CHO	2,3-BD	CH_3CHO
No additive	4.82 ± 0.29	5.40 ± 0.38	1.38 ± 0.02	1.61 ± 0.10
I	1.50 ± 0.14	3.10 ± 0.15	0.03 ± 0.005	4.35 ± 0.30
II*	2.12 ± 0.27	3.50 ± 0.38	0.05 ± 0.001	5.24 ± 0.18
III	1.75 ± 0.18	3.62 ± 0.38	0.04 ± 0.006	4.94 ± 0.16
IV	0.98 ± 0.05	3.45 ± 0.26	0.04 ± 0.001	5.15 ± 0.44
V	1.52 ± 0.17	3.10 ± 0.30	0.03 ± 0.01	3.64 ± 0.41
VI	1.30 ± 0.11	3.40 ± 0.18	0.06 ± 0.02	3.14 ± 0.32

* $C = 2.1 \times 10^{-4}$ M.

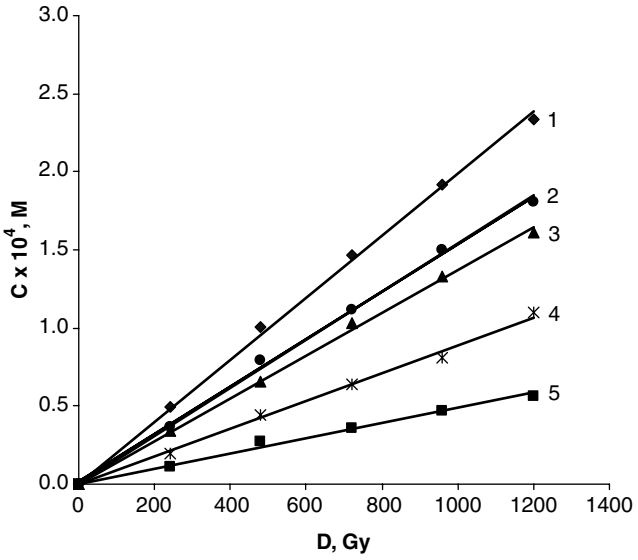


Figure 2. Effects of quinones ($C = 1 \cdot 10^{-3}$ M) on accumulation of H_2O_2 during radiolysis of air-saturated aqueous 0.1 M glucose solution. 1—without additives; 2, 3, 4, and 5—in the presence of additives: compounds III, V, I, and IV, respectively.

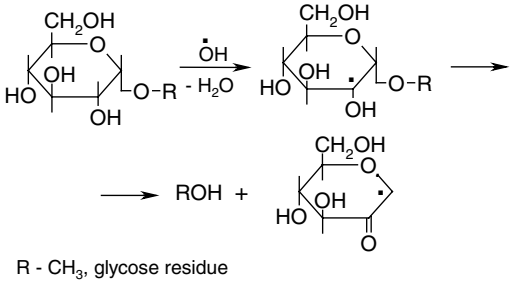
During radiolysis of aqueous glucose solutions in the presence of oxygen, accumulation of hydrogen peroxide takes place due to oxidation of carbon-centered α-hydroxyl-containing radicals formed from glucose according to reactions analogous to (2–4). As seen from Figure 2, the formation yields of H_2O_2 decrease significantly in the presence of quinone derivatives.

The data shown in Table 1 and in Figure 2 indicate that biologically relevant quinones inhibit oxidation processes of hydroxyl-containing organic compounds, mostly by blocking the formation of hydrogen peroxide. This may determine protective properties of quinones, because H_2O_2 hyperproduction is known to cause significant damage to biosystems.[3]

Effects of quinones on the fragmentation process (1) were assessed from the yields of products formed during radiolysis of aqueous solutions of α-diols, 2-aminoethanol, glycero-1-phosphate, α-methyl-D-glucopyranoside, and maltose. The obtained data are shown in Table 2.

It has been shown earlier that both γ-radiation and the action of Fenton's reagent induce processes of type (1), which lead to dehydration of α-diols, deamination of amino alcohols,[12] or dephosphorylation of glycerides.[6] As follows from the data presented in Table 2, quinones inhibit the processes of homolytic fragmentation of the above named compounds. This occurs in parallel with increasing yields of oxidation products of the starting compounds, as exemplified by radiolysis of aqueous solutions of ethylene glycol and 2,3-butanediol (see Table 2). This indicates that quinones inhibit the fragmentation process (1) due to oxidation of $R_1{\cdot}CH(OH)CH(X)R_2$ radicals.

It has been established[9] that radiolysis of aqueous solutions of α-methyl-D-glucopyranoside, di- and polysaccharides is accompanied by an OH-induced reaction leading to rupture of the O-glycoside bond according to the following scheme:



(8)

It follows from the data presented in Table 2 that quinones block this process effectively.

Table 2. Effects of quinones on yields of products formed during radiolysis of deaerated aqueous solutions of α-diols, 2-aminoethanol, glycero-1-phosphate, α-methyl-D-glucopyranoside, and maltose

Initial solutions	Products	$G \cdot 10^7$, mol/J				
		Without additives	I	III	IV	V
Ethylene glycol 0.1 M	CH_3CHO	1.64 ± 0.34	0.04 ± 0.01	0.06 ± 0.02	0.09 ± 0.03	0.04 ± 0.02
	$HOCH_2CHO$	0.25 ± 0.04	3.80 ± 1.1	3.09 ± 0.43	1.51 ± 0.11	1.67 ± 0.21
Ethylene glycol 3 M	CH_3CHO	17.00 ± 0.90	0.06 ± 0.01	0.16 ± 0.02	0.08 ± 0.01	0.27 ± 0.09
	$HOCH_2CHO$	0.76 ± 0.01	4.36 ± 0.51	2.13 ± 0.05	3.82 ± 0.21	3.6 ± 0.64
2,3-Butanediol 0.1 M	$CH_3OC_2H_5$	1.19 ± 0.10	0.04 ± 0.01	0.26 ± 0.01	0	0.37 ± 0.16
	$CH_3COCH(OH)CH_3$	0.20 ± 0.02	3.30 ± 0.14	3.61 ± 0.45	2.82 ± 0.13	3.12 ± 0.22
2-Aminoethanol 0.1 M	NH_3	3.44 ± 0.05	0.83 ± 0.07	1.05 ± 0.10	0.96 ± 0.03	1.08 ± 0.08
Glycero-1-phosphate 0.1 M	$H_2PO_4^-$	3.53 ± 0.20	1.97 ± 0.81	2.20 ± 0.30	1.87 ± 0.19	2.00 ± 0.20
Methyl-α-D-glucopyranoside 0.1 M	CH_3OH	1.71 ± 0.11	0.69 ± 0.09	1.15 ± 0.11	0.45 ± 0.05	—
Maltose 0.1 M	Glucose	1.20 ± 0.10	0.11 ± 0.06	—	0.37 ± 0.12	0.39 ± 0.07

The data obtained in this study indicate that biologically active quinones inhibit free-radical fragmentation processes of type (1) and decrease the yields of H_2O_2 formed on oxidation of hydroxyl-containing organic compounds by molecular oxygen.

The facts established in our experiments point to some new properties of quinones, manifestation of which in biosystems may enhance stability of the latter towards the destructive action of reactive oxygen species.

References and notes

1. Lehninger, A. L. In *Principles of biochemistry*; Worth Publishers, Inc., 1985.
2. Mukherjee, T. In *Radiation Chemistry. Present Status and Future Trends*; Jonah, C. D., Rao, B. S. M., Eds.; Elsevier: Amsterdam, 2001; p 287.
3. Halliwell, B.; Gutteridge, J. M. C. In *Free Radicals in Biology and Medicine*, third ed.; Clarendon Press: Oxford, 1999.
4. Espinosa-Garcia, J. *J. Am. Chem. Soc.* **2003**, *126*, 920.
5. Ingold, K. U.; Bowry, V. W.; Stocker, R.; Walling, C. *Proc. Nat. Acad. Sci. U.S.A.* **1993**, *90*, 45.
6. Shadyro, O. I. In *Free Radicals in Biology and Environment*; Minisci, F., Ed.; Kluwer Academic Publishers: Netherlands, 1997; p 317.
7. Shadyro, O. I.; Sosnovskaya, A. A.; Vrublevskaya, O. N. *Int. J. Radiat. Biol.* **2003**, *79*, 269.
8. Gilbert, B. C.; King, D. M.; Thomas, C. B. *Carbohydrate Res.* **1984**, *125*, 217.
9. Edimecheva, I. P.; Kisel, R. M.; Shadyro, O. I.; Kazem, K.; Murase, H.; Kagiya, T. *J. Radiat. Res.* **2005**, *46*, 1765.
10. Shadyro, O. I.; Yurkova, I. L.; Kisel, M. A.; Brede, O.; Arnhold, J. *Free Radic. Biol. & Med.* **2004**, *36*, 1612.
11. Muller, S. N.; Batra, R.; Senn, M.; Giese, B.; Kisel, M.; Shadyro, O. I. *J. Am. Chem. Soc.* **1997**, *119*, 2795.
12. Petryaev, E. P.; Shadyro, O. I. In *Radiation Chemistry of Bifunctional Organic Compounds*; University Publ.: Minsk, 1986.
13. Shadyro, O. I.; Glushonok, G. K.; Glushonok, T. G.; Edimecheva, I. P.; Moroz, A. G.; Sosnovskaya, A. A.; Yurkova, I. L.; Polozov, G. I. *Free Rad. Res.* **2002**, *36*, 859.
14. Shadyro, O. I.; Edimecheva, I. P.; Glushonok, G. K.; Ostrovskaya, N. I.; Polozov, G. I.; Murase, H.; Kagiya, T. *Free Rad. Res.* **2003**, *37*, 1087.
15. Egerton, Sir A.; Everett, A. J.; Minkoff, G. J.; Rudrakanhana, S.; Salooja, K. C. *Anal. Chem. Acta* **1965**, *10*, 422.
16. von Sonntag, C. In *The Chemical Bases of Radiation Biology*; Taylor and Francis: London, 1987.
17. Simic, M.; Hayon, E. *Biochem. Biophys. Res. Com.* **1973**, *50*, 364.