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Phenols as Sources of Radicals in Biochemical Systems

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The principal radical products of the initial stages of the autoxidation of phenols in polar media are examined. Attention is concentrated on the characteristics of superoxide radicals in connection with their toxic properties and important role in certain biochemical processes. The possible contribution of the radical products of the autoxidation of phenols to the mechanism of their antitumour activity is discussed.
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I. INTRODUCTION

In 1956–1957 Emanuel' put forward for the first time the hypothesis that, in principle, inhibitors of radical reactions might be used to treat certain diseases, the occurrence and the development of which may be attributed to either the appearance of free radicals which are not characteristic of the organism under normal conditions or to the breakdown of the regulation of the radical reactions occurring in the organism under the conditions of normal metabolism [1–4]. The limitations associated with toxicity led to the isolation of relatively non-toxic alkylphenols and certain polyphenols and hydroxypyridines from the large group of compounds known in chemistry as inhibitors. Comprehensive studies have been made on the carcinolytic and antitumour activities of these substances under Emanuel''s supervision.

Considerable experience has been gained in modern biochemistry concerning studies on the metabolism and physiological activities of natural and synthetic phenols in the living organism. The results of this research have been compiled mainly in a series of collected volumes and monographs [5–8]. Among the pharmacological preparations used at present, phenolic compounds are widely represented. However, it is by no means always possible to discover any relation between the pharmacological activity of a preparation and the presence of a phenolic hydroxyl in its molecule.

A significant fraction of the radicals arising in the organism under normal conditions appears to comprise radical intermediates formed from the cofactors of oxidation-reduction enzymes in the process of their functioning. In the majority of the enzymes such radicals are firmaly bound to the active centres, as a result of which they are incapable of participating in non-specific free-radical reactions. However, the formation of superoxide radicals—the products of one-electron reduction of oxygen capable of initiating chain reactions in solution—has been demonstrated in a number of enzyme systems [9]. Such systems are apparently of interest from the standpoint of the possibility of inhibiting their action with the aid of free-radical reaction inhibitors.

The ability of phenols and other compounds to inhibit free-radical reactions is known to be associated with the presence in their molecules of a relatively weak bond (60–70 kcal mole^{-1}) which enables the inhibitor to participate readily in exchange reactions with the system radicals to form inactive radicals [10,11]. Emanuel' and coworkers [12] showed that the radicals arising in proteins under the influence of radiation can react in a similar manner directly with an inhibitor molecule, forming an inhibitor radical.

On the other hand, owing to the presence of the weak bond, the inhibitor readily undergoes autoxidation. Free radicals, which can react with cell components, damaging them, and can be involved in metabolic processes, arise in the system under these conditions. The present review deals with this aspect of the action of phenolic inhibitors of free-radical reactions.

II. RADICAL PRODUCTS OF THE AUTOXIDATION OF PHENOLS IN POLAR MEDIA

The formation of relatively stable semiquinone radical-anions is characteristic of the oxidation of phenols in polar media. As in other radical reactions of phenols, the autoxidation process involves a rearrangement of the aromatic bond systems into a quinolid system with formation of cyclohexadienones (phenol–dienone rearrangements) and conversely dienone–phenol rearrangements also take place. The intermediate molecular autoxidation products (quinones) accelerate the oxidation process, the rate of which at advanced stages is determined by the characteristics of the reduction of the quinone [13–15]. The main radicals formed in the initial stages of the autoxidation of phenol are phenoxy-radicals PhO$^{\cdot}$, superoxide radical-anions $O_2^{\cdot-}$ and semiquinones $SQ^{\cdot-}$.

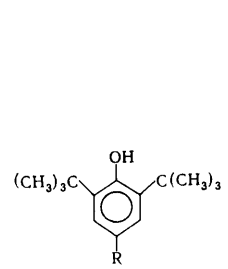
1. Phenoxy-radicals and Semiquinones in Autoxidation Processes

The autoxidation of phenols in alkaline media apparently begins with the fundamental reaction

$$PhO^- + O_2 \rightarrow Ph\dot{O} + O_2^{\cdot-} . \qquad (1)$$

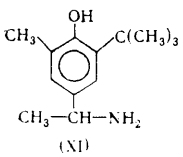
In view of the short lifetime of phenoxy-radicals in polar media [16,17], they cannot be detected by ESR under static conditions.

The kinetics of the autoxidation of sterically hindered phenols with electron-donating substituents in the *p*-position have been studied for phenols (I)–(XI).

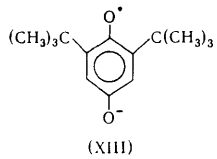


(I)–(X), (XII)

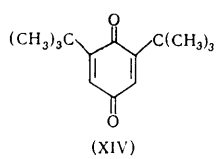
(I) R = H
(II) R = C_2H_5
(III) R = $CH_2CH(CH_3)_2$
(IV) R = CH_2Ph
(V) R = CH_3OCH_3
(VI) R = $CH_2OC_2H_5$
(VII) R = $CH_2N(CH_3)_2$
(VIII) R = $CH_2N(C_2H_4OH)_2$
(IX) R = CH_2NH_2
(X) R = CH_3CHNH_2
(XII) R = Ph



(XI)



(XIII)



(XIV)

In the oxidation of these phenols by molecular oxygen under static conditions in an aqueous alcoholic alkaline solution a radical having a triplet ESR spectrum with a splitting of 1.2–1.4 G and intensity ratios of 1 : 2 : 1 was detected. The structure of the spectrum persisted for a long time (tens of minutes) in the absence of oxygen. The kinetics of the accumulation of the radicals with the triplet spectrum were studied for phenols (VIII)–(XI).[18] The kinetic accumulation curve passes through a maximum and most of it can be described formally by the equation for first-order kinetics. Part of the curve beyond the maximum may be regarded as the kinetic curve for the consumption of the radicals. The temperature variation of the rate constant for the disappearance of the radicals was determined. For all four phenols, the activation energy obtained from this relation is 23.0 ± 0.5 kcal mole^{-1}.

The similarity of the ESR spectra and of the kinetics of the consumption of the radicals suggests that the oxidation of all the phenols investigated results in the formation of the same radical—2,6-di-t-butyl-1,4-benzosemiquinone (XIII). Its formation is characteristic of the oxidation of sterically hindered phenols with an electron-donating substituent in the *p*-position and is accompanied by the elimination of the *p*-substituent[19]. The semiquinone (XIII) is a secondary radical product formed in the initial stages of the oxidation process, probably as a result of the decomposition of an intermediate hydroperoxide with a *p*-quinolid structure—the product of the oxidation reactions of the phenoxy-radical. A detailed mechanism of the initial stages of the autoxidation of phenols has been described in a review[14].

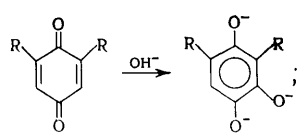
With increase of the conjugation chain and of the size of the substituent in the *p*-position, the stability of the phenoxy-radical increases. In the case of 2,6-di-t-butyl-, 4-phenyl-, and 4-naphthyl-phenols, the formation of phenoxy-radicals was observed by ESR in an aqueous alcoholic alkaline solution[20].

Direct evidence for the formation of phenoxy-radicals in the autoxidation of phenols in an aqueous alcoholic alkaline solution was obtained for phenols (VIII) and (XII)[21] by the stopped-flow method[22]. The spectra of the reaction mixture were recorded 2 s after the onset of oxidation. Absorption bands were observed for (XII) in the visible region with maxima at 428–430, 460, 480, 504, and 540 nm. Comparison of the spectrum of the reaction mixture in the oxidation of (XII) with the spectrum of (VIII) and with those of various phenoxy-radicals in polar media (results obtained by pulse photolysis and pulse radiolysis[17,23–25]) leads to the conclusion that the 428–430 nm band corresponds to the absorption of the phenoxy-radical.

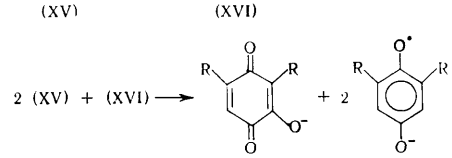
The spectrum of the reaction mixture of phenol (VIII) is more complex. In the range 430–450 nm there is a fairly broad asymmetric peak, which is probably the result of the superposition of the characteristic bands of the phenoxy-radical and the semiquinone (XIII), since it is known from the literature that different substituted semiquinones absorb mainly at 430–440 nm and less vigorously at 400 to 415 nm.[25–28] However, under certain conditions (0.005 M, 50°C) a spectrum with a narrow symmetric peak at 430 nm was also obtained for the reaction mixture of this phenol[21].

The formation of the phenoxy-radical is also supported by the detection in the reaction mixture obtained in the oxidation of phenols (V) and (VII) of disproportionation products of phenoxy-radicals—the corresponding methylenequinones [2,6-di-t-butyl-α-(*NN*-dimethylamino)-methylenequinone and 2,6-di-t-butyl-α-methoxymethyl-methylenequinone], which are stable in aqueous alcoholic alkaline solution. Under the influence of acid, these methylenequinones are converted into 3,5-di-t-butyl-4-hydroxybenzaldehyde, which has been found in the oxidation products of (VIII) following the addition of concentrated hydrochloric acid to the reaction mixture. 2,6-Di-t-butyl-1,4-benzoquinone (XIV)—the disproportionation product of the semiquinone (XIII)—was also found in the reaction mixture[19].

The study of the kinetics of the consumption of the semiquinone from phenol (VIII) by ESR showed that at advanced stages of the process an appreciable increase of the concentration of the radicals begins. When oxygen is supplied to the system after the attainment of the maximum concentration of radicals, the latter are initially almost instantaneously destroyed, after which their concentration increases sharply. This form of kinetic curve can be accounted for by the fact that the quinone (XIV), accumulating at advanced stages, is reduced and one of the reduction products is the semiquinone (XIII).[19] In the reaction of quinones with OH^- via a nucleophilic substitution mechanism the quinone is reduced to the semiquinone and *o*-hydroxyquinone should then accumulate in the system[29,30]. The principal reaction stages can be formulated as follows for alkyl-*p*-benzoquinones as an example:



(XV) (XVI)



The formation of 2,6-di-t-butyl-3-hydroxy-1,4-benzoquinone was demonstrated in the oxidation of 2,6-di-t-butyl-4-(β-hydroxyethyl)aminomethylphenol. The structure of the *o*-hydroxyquinone was demonstrated by infrared spectroscopy, ESR, and NMR. Its formation was also

demonstrated in the direct interaction of the corresponding quinone with alkali [19].

According to the ideas of Blyumenfel'd and coworkers [31,32], the primary step in the reduction of the quinone is direct electron transfer from OH^- to the quinone:

$$X + OH^- \rightleftarrows SQ^{\cdot-} + \dot{O}H , \quad (2)$$

after which the $\dot{O}H$ radicals interact with the initial quinone to form the hydroxyquinone.

The physicochemical properties and reactions of phenoxy-radicals and semiquinones have been described in detail in reviews and monographs (see Khudyakov and Kuz'min's review [25] with its bibliography).

2. Superoxide Radical-anions and an Enzymatic Method for the Investigation of Their Role in Autoxidation Processes

The formation of a phenoxy-radical as a result of the transfer of a single electron to an oxygen molecule leads to the formation of the superoxide radical-anion $O_2^{\cdot-}$, which is highly reactive. The absorption spectrum of the superoxide radical-anion, obtained by pulse radiolysis, has a maximum at 240–250 nm in aqueous solution, the extinction coefficients having widely different values according to different investigators [33,34]; $\epsilon_{O_2^{\cdot-}} = 1950 \pm 50$ litre $mole^{-1}$ cm^{-1} appears to be the most probable value [34]. The application of the "fast freezing technique" [35] made it possible to obtain the ESR spectrum of the $O_2^{\cdot-}$ radical-anions in frozen aqueous solution; the radical-anions were formed with the aid of various chemical and enzymatic systems for the reduction of molecular oxygen; $g_\perp = 2.0$ and $g_\parallel = 2.08-2.09$. [35,36] The ESR spectrum of $O_2^{\cdot-}$ in anhydrous acetonitrile is similar to its spectrum in a frozen aqueous solution, but differs significantly from the spectrum in anhydrous dimethylformamide [37].

In aqueous solution the $O_2^{\cdot-}$ radical-anion is in equilibrium with $H\dot{O}_2$:

$$O_2^{\cdot-} + H^+ \rightleftarrows H\dot{O}_2 , \quad (3)$$

whose $pK = 4.88 \pm 0.1$. [38,39] The rate constants for the recombination of $H\dot{O}_2$ and $O_2^{\cdot-}$ and for the cross-recombination are 7.6×10^5, $<10^2$, and 8.5×10^7 litre $mole^{-1}$ s^{-1} respectively [39]:

$$H\dot{O}_2 + H\dot{O}_2 \rightarrow H_2O_2 + O_2 , \quad (4)$$

$$O_2^{\cdot-} + O_2^{\cdot-} + 2H^+ \rightarrow H_2O_2 + O_2 , \quad (5)$$

$$H\dot{O}_2 + O_2^{\cdot-} + H^+ \rightarrow H_2O_2 + O_2 . \quad (6)$$

The $O_2^{\cdot-}$ radical-anion is an intermediate in the reduction of oxygen and can behave both as an oxidant and as a reductant depending on the composition of the reaction mixture. According to the latest data, the redox potential $E_0(O_2/O_2^{\cdot-}) = -0.33 \pm 0.01$ V, while $E_0' = 0.94 \pm 0.02$ V was obtained for the $O_2^{\cdot-}/H_2O_2$ system at pH 7. [40,41]

There are data showing that spontaneous dismutation of $O_2^{\cdot-}$ leads to the formation of $^1\Delta g$ singlet oxygen [42,43].

The formation of hydrogen peroxide is characteristic of the oxidation of phenols [44]. In the presence of H_2O_2 the reaction

$$O_2^{\cdot-} + H_2O_2 \rightarrow O_2 + OH^- + \dot{O}H \quad (7)$$

can take place [45] (by analogy with the reaction proposed for Fenton's reagent [46]). In this case hydroxy-radicals are generated together with the superoxide radical-anions in the system where phenol undergoes autoxidation.

Reaction (2) of the quinone with OH^- to form the semiquinone, discussed in Subsection 1, may be accompanied also by the reduction of quinones by the $O_2^{\cdot-}$ radical-anions with formation of the semiquinone:

$$X + O_2^{\cdot-} \rightleftarrows SQ^{\cdot-} + O_2 . \quad (8)$$

The rate constants for the forward reaction (8), obtained by pulse radiolysis for a number of quinones are listed in Table 1.

Table 1. The rate constants for the reactions $X + O_2^{\cdot-} \rightarrow SQ^{\cdot-} + O_2$ involving different quinones in aqueous solution containing 5 M isopropyl alcohol and 1 M acetone [27].

Quinone	$10^{-9}k_8$, litre $mole^{-1}$ s^{-1}
p-Benzoquinone	1.0
2-Methylbenzoquinone	0.76±0.1
2,3-Dimethylbenzoquinone	0.45±0.1
2,5-Dimethylbenzoquinone	0.36±0.1
2,6-Dimethylbenzoquinone	0.58±0.1
Duroquinone	0.005
Vitamin K	<0.0002
2,3-Dimethylnaphthoquinone	0.004
Cytochrome *c*	0.0001

The equilibrium constants K_C for duroquinone, vitamin K, and 2,3-dimethylnaphthoquinone are $(2.3 \pm 0.2) \times 10^{-2}$, $<10^{-3}$, and 2×10^{-2} respectively [27].

The use of the enzymes catalase and superoxide dismutase to investigate autoxidation in aqueous solutions established the important role of the $O_2^{\cdot-}$ radical-anions in the autoxidation of a wide variety of organic compounds: catecholamines [47–49], 6,7-dihydroxytryptamine and dialuric acid [49], pyrogallol [50], reduced flavins [51], tetrahydropteridines [52], reduced phenazine metasulphate [53], thiols [54], and inorganic sulphite [55].

Catalase catalyses the decomposition of hydrogen peroxide via the reaction

$$2H_2O_2 \rightarrow 2H_2O + O_2 \quad (9)$$

and superoxide dismutase catalyses the dismutation of the $O_2^{\cdot-}$ radical-anions via reaction (5). [56]

The conclusions reached concerning the role of H_2O_2 in the oxidation of catecholamines on the basis of the influence of catalase on this process are extremely contradictory [47–49,57]. The discrepancies between the results are probably due to the inadequate purity of the catalase preparations, which may contain an admixture of superoxide dismutase [58]. The problem of the contribution of reaction (7) and of the role of $\dot{O}H$ radicals in autoxidation process therefore remains open.

The leading role of the $O_2^{\cdot-}$ radical-anions in autoxidation processes can be demonstrated by the following examples. When superoxide dismutase is added to a system in which 6-hydroxydopamine undergoes autoxidation at pH 7.4–9.0, the rates of formation of the quinone and of absorption of oxygen decrease by 83 and 73% respectively [48]. In the oxidation of epinephrine to adrenochrome at pH 10.2, the inhibition reaches about 80% [47] and in the autoxidation of pyrogallol at pH 7.9–9.1 it ranges from 99 to 90%. [50]

The inhibition of autoxidation in the presence of superoxide dismutase can probably be accounted for by the suppression of reactions (8), (10), and (11):

$$PhO^- + O_2^{\cdot-} \xrightarrow{H^+} PhO^{\cdot} + H_2O_2 , \quad (10)$$

$$SQ^{\cdot-} + O_2^{\cdot-} \xrightarrow{H^+} X + H_2O_2 . \quad (11)$$

The dependence of the degree of inhibition on the pH of the medium, which is not related to the stability of superoxide dismutase, is noteworthy. For pyrogallol, the inhibition is more pronounced at pH < 10, while for epinephrine or tetrahydropteridines it is actually more marked at pH > 8.5, decreasing as the pH is reduced.

This apparently indicates the occurrence of two oxidation mechanisms, only one of which is associated with a significant role of the $O_2^{\cdot-}$ radical-anion. The predominance of one of these mechanisms depends on specific conditions.

After a new method is discovered, a period of its intensive application usually begins, in which the limitations of the method are not always taken into account. In view of this, some data concerning the characteristics of autoxidation in the presence of superoxide dismutase are given below.

Autoxidation reactions are extremely sensitive to traces of variable-valence metals, which have a significant influence on the rate and mechanism of the process. In the presence of Cu^{2+}, Mn^{2+}, and Fe^{2+} ions superoxide dismutase does not inhibit the oxidation of pyrogallol. The influence of metal ions is eliminated in the presence of diethylenetriaminetetraacetic acid, while ethylenediaminetetraacetic acid (0.001 M) does not suppress the action of Fe^{2+} at micromolar concentrations. The $O_2^{\cdot-}$ radical-anions probably form with metal ions intermediate complexes which do not react with superoxide dismutase[50].

The absence (under certain conditions) of inhibition by superoxide dismutase of the oxidation of low-molecular-weight thiols in the presence of heavy metals is probably associated with a similar phenomenon; on this basis, the stage involving the interaction of the thiol with the $O_2^{\cdot-}$ radical-anion has been apparently erroneously excluded[54] from the mechanism of the oxidation of thiols.

Recent data have shown[59] that phenols, particularly catechols, can combine reversibly with superoxide dismutase and can interact with the metal forming part of the active centre of the enzyme via a process of the type

$$Cu^{2+} + PhO^- \rightarrow Cu^+ + SQ^{\cdot-}. \quad (12)$$

(Superoxide dismutase contains copper, zinc, manganese, or iron depending on its biological source.)[9]

It can be shown for *p*-benzosemiquinone as an example that Cu^{2+} readily forms complexes with semiquinones and the lifetime of such complexes is significantly longer than the lifetime of the semiquinones themselves (owing to the delocalisation of the electron over the electron shell of copper and the electrostatic repulsion of the complexes from one another[28]). Apparently in consequence of the elimination of reaction (11) in the presence of superoxide dismutase and of the stabilisation of the semiquinone as a result of complex formation, the steady-state concentration of semiquinones increases and in many cases, for example in the autoxidation of 1,2-dihydroxybenzene-3,5-disulphonic acid (Tiron) can exceed by two powers of ten the steady-state concentration in the absence of superoxide dismutase. The ESR spectrum of the autoxidising Tiron–superoxide dismutase system then shows a new signal, which has been attributed to a complex formed by the copper bound in the enzyme with catechol, and the intensity of the initial copper signal falls[59]. Apart from complex formation with the metal, semiquinones can also be stabilised by their non-specific sorption on the protein molecule[60-63].

Thus not only the elimination of the $O_2^{\cdot-}$ radical-anion from the system but also the stabilisation of the semiquinones can contribute to the inhibition of the phenol autoxidation process observed in the presence of superoxide dismutase. Therefore, in elucidating the role of superoxide radical-anions in autoxidation processes with the aid of superoxide dismutase, account must be taken of both the consumption of the substance being oxidised and of the accumulation of semiquinones in the system.

The study of the influence of various organic solvents on the superoxide dismutase activity showed that the highest activity (about 90% of that in aqueous solution) is observed in *N*-methylformamide. The results obtained[64] extend the scope of the application of superoxide dismutase in the study of the mechanisms of the oxidation of organic compounds.

III. OXIDATIVE INACTIVATION OF SH-CONTAINING ENZYMES

It has been shown that propyl gallate (PG), a polyphenol inhibitor of free-radical reactions, does not inhibit the reaction catalysed by lactate dehydrogenase (LDH) (approximately 10^{-4} M) following its direct addition to the reaction system. Nor is the enzyme inactivated as a result of its prolonged preliminary incubation with PG under conditions excluding the autoxidation of phenol, nor in incubation with stable phenol autoxidation products. Enzyme activity is lost only when LDH is incubated with PG under the conditions of its autoxidation. These data led to the conclusion that the inactivation is caused by the free radicals formed from PG during its autoxidation[65,66].

This conclusion was confirmed[67] in a study of the effect of PG on other enzymes acting via various mechanisms: glyceraldehydephosphate dehydrogenase (GAPD) (also an autoxidation-reduction enzyme in glycolysis)[68], aldolase (a glycolytic lyase)[69], and RNA polymerase—the enzyme involved in the synthesis of RNA on a DNA matrix[70].

The conclusion that the radical products of the autoxidation of the inhibitor exhibit inactivating activity has been confirmed by kinetic data. The activation energy for the inactivation of LDH is 8300 ± 500 cal mole^{-1} and is equal to the activation energy for the autoxidation of PG under the same conditions[71]. The agreement between the activation energies for the oxidation of PG and the inactivation of the protein shows that the rate-limiting stage in the activation of the enzyme by the inhibitor is the stage involving the formation of the semiquinone and the $O_2^{\cdot-}$ radical-anion via the overall reaction

$$PG^- + O_2 + OH^- \rightarrow SQ^{\cdot-} + O_2^{\cdot-} + H_2O,$$

where PG^- is the anion derived from propyl gallate.

SH is the most reactive group in proteins. The extensive factual data on the reactivity and role of mercapto-groups in the structure and functions of proteins are contained in Torchinskii's monograph[72].

Since all the enzymes enumerated above contain SH groups, which form part of the active centre or are important for the maintenance of the native structure, it was natural to suppose that the proteins are inactivated as a result of the interaction of their SH groups with the radicals formed in the autoxidation of the inhibitor. Indeed, direct experiments showed[68,69,73] that the radical

products of the autoxidation of PG oxidise the SH groups of the proteins with formation of S–S groups. Throughout the joint oxidation of PG and the protein, the total amount of SH and S–S groups remains constant. This implies that neither radical nor molecular intermediates in the oxidation of PG add to the protein molecule via the sulphur atoms. The inability of *o*-hydroxyquinone, formed in the oxidation of PG,[74-76] to add to the SH group is probably due to the presence of a powerful electron-donating substituent (OH group) in the ring next to the unsubstituted hydrogen[77]. One cannot rule out the possibility that the inhibitors of radical processes, whose oxidation leads to the formation quinones capable of adding to the SH-groups, inactivate the SH-containing enzymes not only as a result of the oxidation of SH groups but also by the addition of the quinone to the latter.

SH-containing compounds, including proteins are known to be capable of reducing antioxidant radicals. Their synergistic activity in relation to inhibitors is in fact associated with this factor. The enhanced rate of the consumption of SH groups in the presence of an inhibitor undergoing oxidation and the appearance of an induction period on the kinetic curve for the oxidation of the inhibitor in the presence of the protein (in the absence of the protein, PG is oxidised under these conditions at a constant rate) suggest that, during the induction period in the oxidation of PG, the following reactions take place[73]:

$$PG^- + O_2 + OH^- \rightarrow SQ^{\cdot-} + O_2^{\cdot-} + H_2O;$$
$$PG^- + O_2^{\cdot-} + H^+ \rightarrow SQ^{\cdot-} + H_2O_2;$$
$$RS^- + SQ^{\cdot-} + H^+ \rightarrow PG^- + RS^{\cdot};$$
$$RS^- + O_2^{\cdot-} + 2H^+ \rightarrow RS^{\cdot} + H_2O_2;$$
$$2\,RS^{\cdot} \rightarrow RS - SR;$$
$$2\,O_2^{\cdot-} + 2\,H^+ \rightarrow H_2O_2 + O_2.$$

It has been shown for LDH[78] that the oxidation of the SH groups alters the kinetic characteristics of the enzyme: the stability of the LDH complex with the coenzyme—reduced nicotinamide-adenine dinucleotide (NADH)—is significantly reduced (the dissociation constant increases by a factor of 4–5).

Thus the decrease of the activity of enzymes as a result of their interaction with radicals proceeds not only owing to the decrease of the number of active centres but also owing to a change in the affinity of the coenzyme for the enzyme. The latter may be caused by structural changes resulting from the oxidation of SH groups to S–S, which are not characteristic of the enzyme in the intact state.

The influence of radical autoxidation products on the structure of SH-containing proteins has been demonstrated in experiments on GAPD and aldolase by the change in specific rotation. A decrease in laevorotation and, after prolonged incubation corresponding to the decrease of the enzyme activity by about 80% and the oxidation of SH groups to the extent of 50–80%, the appearance of dextrorotation are characteristic of both enzymes (Table 2).

The inactivation of the enzyme by radicals can be prevented by allowing the inhibitor to react with the enzyme in the presence of a reducing agent: NADH for LDH[71] or β-mercaptoethanol for RNA polymerase[70]. The protection of the protein from inactivation is accompanied by the oxidation of NADH to NAD^+. It is known from the literature that NADH forms a stable complex with the SH groups of LDH. The presence of this complex stabilises the protein and protects it from thermal denaturation, denaturation by urea, and the action of various agents on the SH groups.[79-83] Since in the system with PG undergoing autoxidation the protective effect of NADH is accompanied by its oxidation, the stabilisation of LDH is temporary and its duration depends on the NADH concentration. The oxidation of LDH and NADH present together in a medium containing PG undergoing oxidation obeys the general rule governing the behaviour of a mixture of two inhibitors of different strengths in autoxidation reactions[84].

Table 2. The change in the specific rotation α_{541}^{25} (degrees) of aldolase and GAPD on oxidation[68,69].

System	Duration of oxidation, min				
	0	15	30	45	60
Aldolase*	−63.0	−58.8	−48.0	—	−19.5
Aldolase*–0.001 M PG	−63.0	−26.0	—	—	+2.2
GAPD*	−37.6	−23.6	−23.6	−23.6	−23.6
GAPD*–0.001 M PG	−37.6	−17.6	−8.8	+3.1	—

*In universal buffer at pH 9.7.

The conclusion that radicals formed in the autoxidation of PG oxidise the LDH–NADH complex has been confirmed by data for the oxidation of NADH in the complex by $O_2^{\cdot-}$ radical-anions obtained by pulse radiolysis[85]. It was shown that the oxidation of NADH is a chain process. The chain length is a function of the ratio [NADH]:[LDH], the concentration $[O_2]$, the dose rate, and the pH of the medium. The maximum chain length is 9.6.

The incubation with glutathione of LDH inactivated by the autoxidation radicals does not reactivate the enzyme[73]; cysteine reactivates GAPD only under certain conditions[68]. The profound changes in the structure of the protein caused by the oxidation of the SH groups can be explained by the thiol–disulphide exchange reaction[68,73]. By analogy with the reduction of simple disulphides by mercaptans, this reaction can be treated as a result of nucleophilic attack on the disulphide linkage by the mercaptide anion:

$$R'S^- + R - S - S - R \rightarrow R'-S-S-R' + RS^-.$$

According to some investigators, this reaction can proceed via a chain mechanism and can lead to the aggregation and denaturation of proteins[86,87].

The changes in the quaternary structure of proteins as a result of the oxidation of SH groups are also indicated by data showing an increase of the bond strengths between the GAPD and aldolase subunits after incubation of these enzymes in the presence of PG undergoing oxidation[88-90]. The sorption of semiquinones[60-63] and of the phenols themselves on inactive centres of the proteins can make a definite contribution to the change in the enzyme structure. This can probably explain the influence of PG on the equilibrium between the oligomer and its subunits in the case of LDH and GAPD.[90]

The reaction of the autoxidation radicals with the SH groups of proteins is fairly selective. Thus ribonuclease and trypsin, which are proteins without SH groups, are not inactivated in the presence of PG undergoing autoxidation[68]. According to Tanksley et al.[91], the inhibition of the conversion of pepsinogen into pepsin in the presence of gossypol a naturally occurring phenol, is enhanced at

alkaline pH of the medium and with increase of temperature, which should promote the oxidation of gossypol. It was shown that, under these conditions, gossypol combines with the ϵ-amino-groups of lysine via covalent linkages.

Phenols, which behave as electron donors, readily form complexes with various acceptors, charge-transfer forces making a significant contribution to the stabilisation of the complexes. In this sense interaction with molecular oxygen can be regarded as a special case—total charge transfer via reaction (1) with formation of two free radicals. The energy of the highest occupied molecular orbital E_{HOMO} is used as a criterion of the susceptibility of phenols to oxidation[14]. In the case of charge-transfer complexes (CTC) the values of E_{HOMO} for different donors should be correlated with the stability constants of the complexes formed by the donors with the same acceptor.

The biochemically important complexes of phenols, catechols, and naphthalenediols with flavins and flavoproteins are well known[92-102]. The charge-transfer complex of naphthalene-2,3-diol and lumiflavin was isolated in a crystalline state. It was shown by X-ray diffraction that the complex has a "sandwich" structure in which the flavin molecule is located between two naphthalenediol molecules[101].

Table 3. The stability constants of the PG–FMN complexes.

Flavin	K_{st}, litre mole^{-1}	
	pH 6.3	pH 8.1
Oxidised	119	70
Reduced	$\leqslant$17	—
Half-reduced	1550	$\leqslant$20

The stability constants K_{st} of the complexes formed by PG with flavin mononucleotide (FMN) reduced to different extents have been obtained[98]. Table 3 shows that at pH 6.3 (where all the components are unionised) the most stable complex is formed with the half-reduced form of the flavin. The dependence of the stability constants of the complexes on the state of ionisation of the components and on the degree of reduction of the acceptor and also the linear relation between $\lg K_{st}$ and E_{HOMO} for FMN and various donors (Table 4) indicate a significant contribution of charge-transfer forces to the stabilisation of such complexes. It has been shown for xanthine oxidase[99,104] that the formation of complexes by phenols with flavin enzymes can lead to a significant inhibition of the enzymatic reaction.

Different aspects of the mechanism of the action of phenols on enzymes have been discussed[105]. Many phenols (mainly those with electron-accepting substituents) have been tested as uncoupling agents for oxidative phosphorylation and respiration. However, it was not possible to observe correlations between any physicochemical properties of the phenols and their uncoupling capacity. For comparison with the inhibiting activity of phenols in relation to LDH and hexokinase, the authors used, for example, the hydrophobic binding constant π and the Hammett constant σ. Of the 17 phenols investigated, 10 obey the correlation equation linear in π and σ, but the inhibition effect proved to be unrelated to the activity of the phenols as uncoupling agents. It is suggested that the uncoupling agents act directly on ATPase, forming a complex at the site of addition to the enzyme of the adenine component of the substrate[106].

It has been shown that PG also inhibits respiration and uncouples oxidative phosphorylation and respiration[107]. For phenols as inhibitors of malate dehydrogenase (an SH-containing enzyme), the correlation equation takes into account the same characteristics of the phenols (π and σ), but the equations are respectively linear and quadratic in these constants[108].

Table 4. The stability of the complexes formed by FMN with various donors and the values of E_{HOMO} for the donors (phosphate buffer, pH ~ 6).[100]

Compound	K_{st}, litre mole^{-1}	E_{HOMO} (in units of β)	References
FMNH	3.352	—0.105	103
FMN	2.000 (1.778)	0.496	103 (98)
Naphthalene-2,3-diol	2.384	0.338	96
β-Naphthol	2	0.436	93
Phenol	1.494	0.515	94
n-Propyl gallate	2.076	0.255	98

The inhibiting effect of dicumarol on respiration and phosphorylation and on the uncoupling of these processes has been attributed[109] to the direct inhibition of succinate dehydrogenase. Pyrogallol, sodium gallate, and other substituted phenols inhibit catechol methyltransferase[110-113]. The inhibition of the enzyme increases as a result of its preliminary incubation with pyrogallol[112]. It is suggested[50] that the $O_2^{\cdot}$ radical-anions and possibly OH radicals, formed by reaction (7), contribute to the inhibiting effect, particularly if one remembers that catechol methyltransferase contains "essential" SH groups.

IV. BIOCHEMICAL CHANGES UNDER THE INFLUENCE OF SUPEROXIDE RADICAL-ANIONS AND THE POSSIBLE ROLE OF THE LATTER IN THE ANTITUMOUR ACTIVITY OF PHENOLS (IN ENZYME SYSTEMS AND AT THE CELLULAR LEVEL)

A few years ago the biological role of $O_2^{\cdot}$ radical-anions was considered mainly in connection with the effect of radiation. After the discovery of superoxide dismutase[56], vigorous research was begun on the role of $O_2^{\cdot}$ in the metabolism of living organisms. It was found that the products of the one-electron reduction of oxygen ($O_2^{\cdot}$ radical-anions) are invariably present as metabolites in all plant and animal organisms and microorganisms employing molecular oxygen in their metabolic processes which have been investigated hitherto. All these organisms (no exceptions have so far been found) also contain enzymes from the family of superoxide dismutases, which catalyse selectively the dismutation of $O_2^{\cdot}$ radical-anions. The hypothesis that $^1\Delta g$ singlet oxygen is also a substrate of superoxide dismutase has been frequently discussed in the literature[43,114-116]. However, the latest data[117-120] have shown that $^1\Delta g$ oxygen is formed only on spontaneous dismutation of $O_2^{\cdot}$ and in the presence of superoxide dismutase the latter precedes the formation singlet oxygen.

Superoxide dismutase is one of the "fastest" enzymes. The rate constants for the overall second-order reaction, obtained by different investigators using various methods, agree satisfactorily [121-123]. According to the latest, improved data, $k = (2.37 \pm 0.18) \times 10^9$ litre mole^{-1} s^{-1} at 25°C, [123] which is close to the rate constants for diffusion-controlled reactions.

The system for the catalytic dismutation of $H\dot{O}_2$ radicals and $O_2^{\cdot-}$ radical-anions in the presence of Cu^{2+} in acid media can serve as a chemical model of the action of superoxide dismutase. The rate constants are about 10^8 and 8×10^9 litre mole^{-1} s^{-1} respectively [124], i.e. we have here the unique case where the reaction in the model chemical system is 3–4 times faster than in the presence of the enzyme.

The rate of reactions catalysed by superoxide dismutase is independent of the pH over a wide range of the latter (5.3–9.5). [9] The enzyme is reduced and inactivated by the final reaction product (H_2O_2). [125-128] The inactivation is a second-order reaction with a rate constant of 3.1 litre mole^{-1} s^{-1} at 20–25°C and is probably associated with the decomposition by the peroxide of one histidine residue, which is essential for activity, for each of the two polypeptide chains of the enzyme [128].

Evidently, together with catalase and peroxidase, superoxide dismutase constitutes a system for the protection of organisms from the toxic effect of oxygen and its reduction products. The system of bioantioxidants can be regarded as a second line of defence operating under conditions where enzyme systems do not work [9].

Several biological sources of $O_2^{\cdot-}$ radical-anions have now been discovered. Apart from the autoxidation reactions and the reoxidation of low-molecular-weight metabolites, mentioned in Section II, the $O_2^{\cdot-}$ radical-anions arise in the autoxidation of the oxygen adducts with haem-containing proteins: haemoglobin, myoglobin, and cytochrome R-450. [120,129,130] (For the formation of the autoxidation product of haemoglobin—methaemoglobin, an alternative mechanism of electron transfer, using external donors, particularly phenols, with intermediate formation of semiquinones from the latter, has also been suggested [131].) The electron transfer chains in plant chloroplasts [123,133], in mitochondria [116,134,135], and in microsomes [136-142] in animal organisms also function as sources of $O_2^{\cdot-}$ radical-anions. Their formation in electron transfer chains is attributed primarily to the functioning of flavin dehydrogenases [143,144].

The system in which xanthine is oxidised to uric acid, catalysed by xanthine oxidase, is the most thoroughly investigated enzymatic source of $O_2^{\cdot-}$ radical-anions [35,36,145]. During this reaction, oxygen is reduced in two stages to hydrogen peroxide. Experiments on the quenching of the chemiluminescence in the xanthine oxidase system in the presence of luminol showed that inhibitors of free-radical reactions belonging to the class of sterically hindered phenols and hydroxypyridines can behave as effective quenching agents [100], probably as a result of the capture of $O_2^{\cdot-}$ radical-anions. The binding of $O_2^{\cdot-}$ can probably also make an important contribution to the mechanism of the antitumour activity of inhibitors of free-radical reactions.

The $O_2^{\cdot-}$ radical-anions formed in electron transfer chains are involved in the peroxide oxidation of lipids and the hydroxylation of extraneous substances entering the organism (including medicinal compounds) [146-148], which are called xenobiotics. The enzyme system for the hydroxylation of xenobiotics is located in microsomes.

The detoxification of xenobiotics is attributed specifically to their hydroxylation, which leads to a decrease of their solubility in the lipid phase, hinders their passage through membranes, and facilitates their elimination from the organism. The mechanism of the functioning of the hydroxylating system has been discussed in a number of reviews [149-153].

The inhibition of the metabolism of xenobiotics by PG and other antioxidants has been demonstrated [154]; the authors explain it by the combination of the inhibitors with the flavoprotein. However, one cannot rule out the possibility that the inhibition is caused by the capture of the radicals involved in the hydroxylation processes. These radical species may be both $O_2^{\cdot-}$ and $\dot{O}H$. [140,155,156] Both types of radicals are formed also in model hydroxylation reactions [157,158]. A relation has been demonstrated between the xanthine oxidase system and the xenobiotic hydroxylation system, which includes cytochrome P-450, nicotinamide adenine dinucleotide phosphate, cytochrome *c* reductase, and the lipid component of phosphatidylcholine [159]. Xanthine oxidase is exceptionally widely distributed in living organisms. It has been recently suggested that one of the important and possibly the main function of this enzyme is catalysis by the latter of the formation of H_2O_2 and $O_2^{\cdot-}$ in the cell [160].

Studies by a number of workers have shown the existence of a direct relation between enzyme systems for the peroxide oxidation of lipids and for the hydroxylation of xenobiotics. These two systems apparently use the same electron-transport chain, as a result of which the induction of peroxide oxidation leads to a decrease of the rate of hydroxylation and conversely [161-164]. There are data concerning the existence of a factor which regulates the level of activity of these enzyme systems [142].

The radicals formed in the microsomal electron transfer chain can cause the haemolysis of erythrocytes [136,137,165], which can be averted, for example, by an increase of the level of the natural antioxidant (tocopherol) in the animals from which the erythrocytes have been taken and in the presence of superoxide dismutase and catalase. Both enzymes exhibit a similar effect, protecting mitochondrial membranes from lysis associated with the peroxide oxidation of lipids [135].

The involvement of $O_2^{\cdot-}$ radical-anions in the mechanism of the action of peroxidases has been noted in a number of studies [166,167]; the bactericidal action of the enzymes, which becomes more pronounced in the presence of phenols and epinephrine, has been attributed to these radicals [168,169] (possibly in consequence of their capacity for autoxidation with formation of $O_2^{\cdot-}$ radical-anions).

In the development of the tumour process significant changes occur in the enzyme systems for the protection of the organism from the toxic effects of the products of the peroxide oxidation of lipids (with the aid of glutathione peroxidase and glutathione reductase—enzymes governing the utilisation of lipid peroxides—and superoxide dismutase). With increase of tumour growth in the organs of the tumour-carrying animal, the activities of glutathione reductase and peroxidase pass through extrema, exceeding for a time by factors of 2.5 and 6 the corresponding levels of their activity under normal conditions, while the activity of superoxide dismutase hardly changes [170]. At the same time sharp changes are observed in the activity of the enzyme system for the peroxide oxidation of lipids [171] and peroxides accumulate [172]. The results indicate a disturbance of the balance in the processes involving the formation and utilisation of lipid peroxides, which is a characteristic link in the pathogenesis of malignant growth [170]. In the tumour itself the activities of glutathione peroxidase and superoxide dismutase, cal-

culated in terms of arachidonate (one of the principal sources of peroxides) are higher by factors of 2.5 and 12 than in the livers of intact animals. Thus the rate of formation of peroxides decreases in the tumour tissue probably in consequence of the capture of $O_2^{\cdot-}$ radical-anions by superoxide dismutase and their accelerated utilisation owing to the increased activity of glutathione peroxidase. This leads to an extremely low steady-state concentration of peroxide, which cannot be determined[170]. In chemical carcinogenesis and malignant growth the activity of the system for the hydroxylation of xenobiotics varies in opposition to the activity of the system for the peroxide oxidation of lipids[173].

The problems associated with the action of inhibitors as possible regulators of the processes occurring with participation of free radicals are outside the scope of the present review and are considered elsewhere[174].

The $O_2^{\cdot-}$ radical-anions play a significant role in phagocytotic processes. It has been shown that phagocytosis is accompanied by an increase in the rate of formation of $O_2^{\cdot-}$.[175] The bacteria *E.coli*, grown on a medium deficient in iron and with a deficiency of the iron-containing superoxide dismutase, are much more sensitive to the bactericidal action of the formed elements of blood[176]. In lymphogranulomatosis (a malignant tumour of lymphoid tissue) there is no increase of the oxidative metabolism of human leucocytes in phagocytosis[175].

The $O_2^{\cdot-}$ radical-anions can cause the degradation of the synovial (interarticular) fluid and the depolymerisation of a highly polymeric acid mucopolysaccharide contained in it—hyaluronic acid[177]. The inhibition of both processes by superoxide dismutase, catalase, and substances capable of binding $\dot{O}H$ radicals shows that the latter are also evidently involved in the depolymerisation and degradation processes. In inflammatory processes such as arthritis there is a distinct correlation between the number of leukocytes and the degree of degradation of the synovial fluid. These data are consistent with the finding that the synovial fluid contains superoxide dismutase and catalase at concentrations smaller by 2–3 orders of magnitude than the intracellular concentrations of these enzymes.

Since the lifetime of superoxide radical-anions is relatively long (compared, for example, with $\dot{O}H$ radicals), they can diffuse, in principle, within the bacterial cell and can have a lethal effect on DNA. The degradation of biomacromolecules (ribonuclease and lysine:RNA ligase) has been observed[178]. The experiments on the influence of PG undergoing oxidation on DNA have shown that the decrease of the viscosity of the DNA solutions observed in the course of incubation and the appearance of single and double breaks are due to the effect of radical and molecular inhibitor oxidation products[179]. Streptonigrin, an antibiotic with a *p*-quinonoid structure, has a similar effect on DNA when it is reduced in the presence of the latter[180] and the formation of $O_2^{\cdot-}$ radical-anions was demonstrated in this process[181]. The radiation-chemical yield of the deamination products (G) in the radiolysis of aqueous DNA solutions due to $O_2^{\cdot-}$ radical-anions is close to the value of G due to $\dot{O}H$ radicals[182].

The possible contribution of the radical products of the autoxidation of inhibitors to the mechanism of the antitumour action of these compounds at the cellular level can be inferred from certain indirect biochemical and cytological data quoted below. *In vivo* and *in vitro* experiments showed that inhibitors of radical reactions inhibit the synthesis of protein and nucleic acids in tumour cells[183–187], possibly as a result of the interaction of the radicals, formed in the autoxidation of the inhibitors with the SH groups of the enzymes[70]. The degree of suppression of biosynthesis increases with increase of pH in the incubation medium[186] and decreases when the aeration is inadequate[67].

PG suppresses glycolysis in tumour cells[188], which is caused, according to the data of Schön and Venker[189], by the denaturing effect of the inhibitor on the proteins. A number of inhibitors (nordihydroguaiaretic acid, butoxytoluene, ascorbyl palmitate, and octyl gallate) have been shown to block the dehydrogenase processes in the liver, which the authors explain by the oxidation of the antioxidants[190].

According to Emanuel' et al.[191], inhibitors suppress the activity of the oxidation-reduction enzymes in tumour cells. Succinate oxidase [succinate dehydrogenase?] and cytochrome oxidase are suppressed in the succinate oxidase chain of the system, the latter enzyme being more sensitive to the action of inhibitors. The degree of suppression of enzyme activity falls with increase of the overall concentration of the protein in the system (including inert protein), which indicates non-specific binding of the inhibitors to the proteins. The decrease of the degree of inhibition by an order of magnitude in the presence of a deficiency of oxygen[192] shows that the species sorbed are in all probability not the inhibitors themselves but radical or molecular products formed from them in the course of autoxidation.

Treatment with inhibitors leads to the suppression of the multiplication of tumour cells under the conditions of their growth and increases greatly the number of chromosomal aberrations, giving rise to an effect analogous to that of radiomimetic substances and free radicals[193,194]. This factor suggested[193] that the observed effects are associated with the action of the radicals formed from the inhibitors in the course of their oxidation in the cell substrate.

Substituted phenols, natural phenolic compounds, and stable radicals present at certain concentrations sensitise tumour cells to irradiation[195–200].

A separate study of the influence of inhibitors on the life cycle of cells demonstrated the blocking of phases in the cycle and the consequent disturbance of the dynamics of the cell population and a change in the distribution of the population among the different phases of the life cycle[201,202]. According to Terasinia[203] and Harris[204], certain stages in the cell cycle (the second half of the phase involving the synthesis of DNA and the end of the premitotic phase) are characterised by an increased content of SH groups. The cytotoxic action of a number of catecholamines and their polyhydroxy-analogues is attributed to the ability of these compounds to generate $O_2^{\cdot-}$ and $\dot{O}H$ during autoxidation. As a result of treatment with PG, tumour cells lose their capacity for transplantation and explantation[205–209].

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