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The reactivity of natural phenols

E T Denisov, T G Denisova

Contents

I.	Introduction	1047
II.	The structures of phenols	1050
III.	The dissociation energy of the O – H bond in phenols	1051
IV.	Reactions of phenols with peroxyl radicals	1055
V.	Reactions of radicals $R^{\bullet}$ and $RS^{\bullet}$ with phenols	1059
VI.	Oxidation of phenols with oxygen, ozone and peroxides	1061
VII.	Reactions of phenoxyl radicals	1062
VIII.	Conclusion	1070

Abstract. This review surveys physicochemical data of natural phenols published in recent years. The structures of some compounds of this class are given. A complete set of the dissociation energies of the O – H bonds for 71 natural phenols is presented. Kinetic characteristics of the reactions of peroxyl, alkyl and thiyl radicals with natural phenols, exchange reactions of phenoxyl radicals with phenols and reactions of phenoxyl radicals with lipids, hydroperoxides, cysteine and ascorbic acid are compiled and described systematically. The reactivity of phenols in radical reactions and the factors that determine the reactivity (the enthalpy of reaction, triplet repulsion, the electronegativities of atoms at the reaction centre, the presence of π-electrons adjacent to the reaction centre, the radii of atoms at the reaction centre, steric hindrance, the force constants of the reacting bonds) are discussed. An important role of hydrogen bonding between surrounding molecules and the OH groups of natural phenols in decreasing their reactivities is noted. The bibliography includes 151 references.

I. Introduction

Oxygen is indispensable for the vital activity of organisms on the Earth as a source of energy. However, generating free radicals, such as $RO_2^{\bullet}$, $HO_2^{\bullet}$, $O_2^{-\bullet}$ and $HO^{\bullet}$ in an organism, it initiates oxidation and destruction processes that are harmful for biomolecules. For the regulation of these dangerous consequences, the evolution has created a protecting mechanism in which bioantioxidants including natural phenols of various structures feature an important part. Central to natural phenols are α-tocopherol and its analogues that constitute vitamin E.

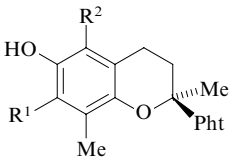
Over the last four decades, the role of tocopherols as antioxidants in model systems (*in vitro*) has been thoroughly studied; besides, numerous investigations address their biological roles in living organisms (*in vivo*). The results of these studies are surveyed in monographs, reference books and reviews (see, for example, Refs 1 – 12). It was established that α-tocopherol is highly reactive towards the peroxyl radicals. In this reaction, it is converted to tocopherol quinone, the reduced form of which, *i.e.*, tocopherol hydroquinone, is even more reactive. Although α-tocopherol intensively terminates reaction chains in lipoxidation and inhibits the oxidative process, under certain conditions it can also stimulate oxidation. Such a pro-oxidating effect of tocopherol is due to chain propagation reactions involving the tocopheroxyl radicals. Tocopherols exert a complex effect on an organism. As the lipoxidation retardants, they prevent the accumulation of toxic products such as aldehydes, ketones and acids. As the free radical acceptors, tocopherols inhibit *cis – trans*-isomerization of unsaturated acid residues in lipids, which is harmful to an organism, and thus retain the elasticity and permeability of lipid membranes. By reacting with free radicals emerging in proteins and DNA on treatment with oxygen and penetrating radiation, they restore their integrity and functional activity.

The reactions and behaviour of other natural phenols, such as flavonoids and ubiquinols, which are more than 300 in number, were studied to a considerably lesser degree. Along with tocopherols, they play an important role in the vital activity of human and animals as well as in the physiology of plants. Currently, intensive investigations of these compounds, *viz.*, their structures and oxidation pro-

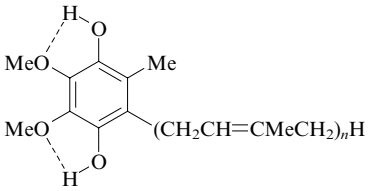
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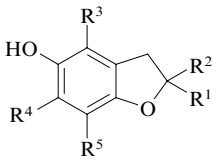
ducts, their reactions with radicals, *etc*., are being carried out. The present review covers the results of recent physicochemical studies of natural phenols obtained over the last years. Figure 1 depicts the names and structural formulae of phenols which are discussed below.



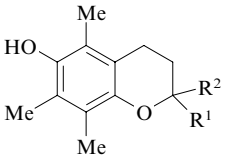
Tocopherols (**1**–**4**)
$R^1 = R^2 = Me$ (α, **1**);
$R^1 = H$, $R^2 = Me$ (β, **2**);
$R^1 = Me$, $R^2 = H$ (γ, **3**);
$R^1 = R^2 = H$ (δ, **4**);
Pht = $CH_2(CH_2CH_2CHMeCH_2)_3H$ (phytyl).



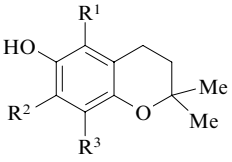
Ubiquinols (**5a**–**e**)
n = 0 (**a**), 2 (**b**), 6 (**c**), 9 (**d**), 10 (**e**).



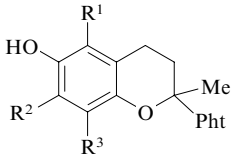
5-Hydroxy-2,3-dihydrobenzo[*b*]furans (**6a**–**g**)
$R^2 = R^3 = R^4 = Me$: $R^1 = Me$, $R^5 = H$ (**a**);
$R^1 = H$, $R^5 = Me$ (**b**); $R^1 = R^5 = Me$ (**c**);
$R^3 = R^4 = Bu^t$, $R^5 = H$: $R^1 = R^2 = Me$ (**d**),
n-C_5H_{11} (**e**), Ph (**f**); $R^1 = R^3 = R^4 = R^5 = Me$,
$R^2 = CO_2H$ (**g**).



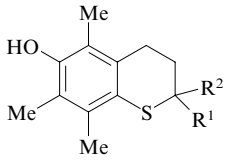
6-Hydroxy-5,7,8-trimethylchromanes (**7a**–**g**)
$R^1 = R^2 = H$ (**a**);
$R^1 = Me$: $R^2 = CH_2OH$ (**b**), OMe (**c**), CO_2H (**d**), CO_2Me (**e**), CH_2CO_2H (**f**), CH_2CO_2Me (**g**).



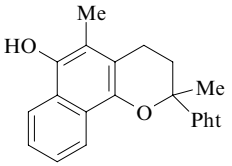
6-Hydroxy-2,2-dimethylchromanes (**8a**–**h**)
$R^1 = R^2 = Me$: $R^3 = H$ (**a**), Me (**b**);
$R^1 = R^2 = Et$: $R^3 = Me$ (**c**), H (**d**);
$R^1 = R^2 = Pr^i$: $R^3 = Me$ (**e**), H (**f**);
$R^2 = Bu^t$, $R^3 = H$: $R^1 = Me$ (**g**), Pr^i (**h**).



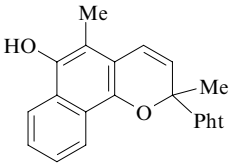
6-Hydroxytocols (**9a**–**h**)
$R^1 = R^2 = R^3 = H$ (**a**);
$R^1 = R^2 = Et$: $R^3 = H$ (**b**), Me (**c**);
$R^1 = R^2 = Pr^i$: $R^3 = H$ (**d**), Me (**e**);
$R^2 = Bu^t$, $R^3 = H$: $R^1 = Me$ (**f**), Pr^i (**g**);
$R^1 = R^2 = Me$, $R^3 = H$ (**h**).



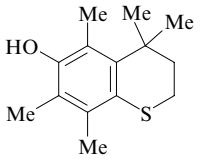
6-Hydroxy-5,7,8-trimethyl-3,4-dihydro-2*H*-1-benzothiopyrans (**10a**–**e**)
$R^1 = H$: $R^2 = H$ (**a**), Me (**b**);
$R^1 = Me$: $R^2 = Me$ (**c**), Pht (**d**), CO_2Me (**e**).



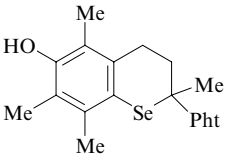
6-Hydroxy-2,5-dimethyl-2-phytyl-7,8-benzochromane (**11**)



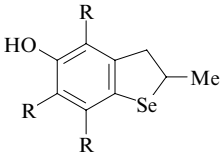
6-Hydroxy-2,5-dimethyl–2-phytyl-7,8-benzochromene (**12**)



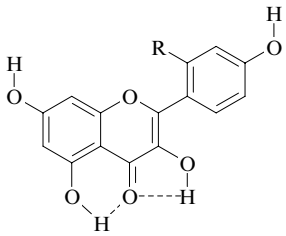
6-Hydroxy-4,4,5,7,8-pentamethyl-3,4-dihydro-2*H*-1-benzothiopyran (**13**)



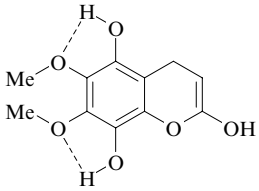
5,7,8-Trimethylselenotocol (**14**)



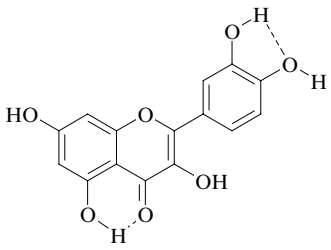
5-Hydroxy-2-methyl-2,3-dihydrobenzo[*b*]-selenophenes (**15**, **16**)
R = Me (**15**), H (**16**).



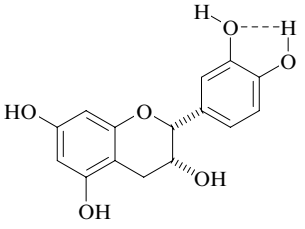
R = H (Kaempferol, **17**),
OH (morin, **18**)



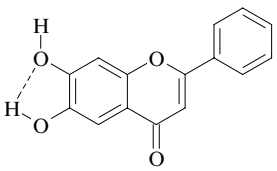
Ubichromenol (**19**)



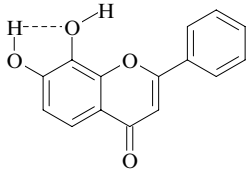
Quercetin (**20**)



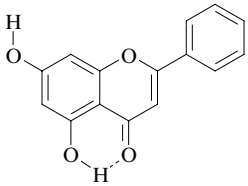
(−)-Epicatechin (**21**)



6,7-Dihydroxyflavone (**22**)

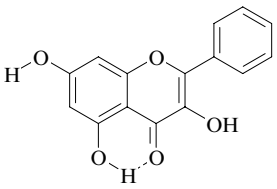


7,8-Dihydroxyflavone (**23**)

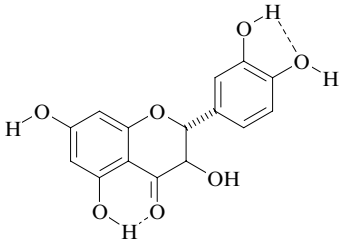


Chrysin (**24**)

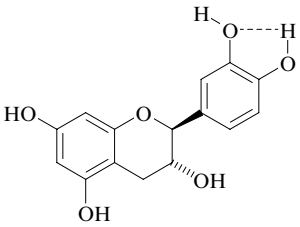
Figure 1. Names and structural formulae of natural phenols.



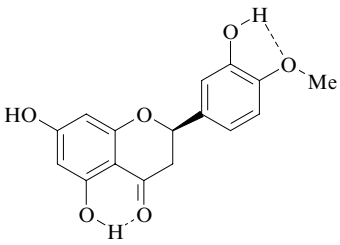
Galangin (**25**)



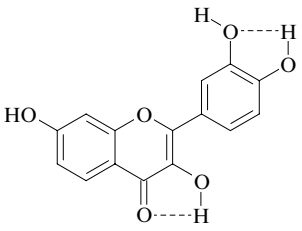
Dihydroquercetin (**26**)



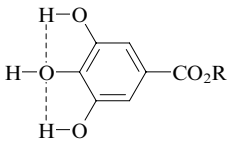
Catechin (**27**)



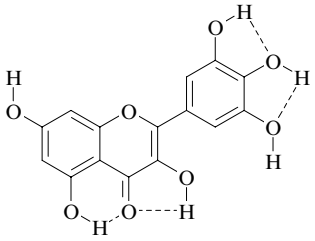
Hesperitin (**28**)



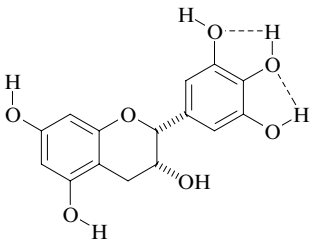
Fisetin (**29**)



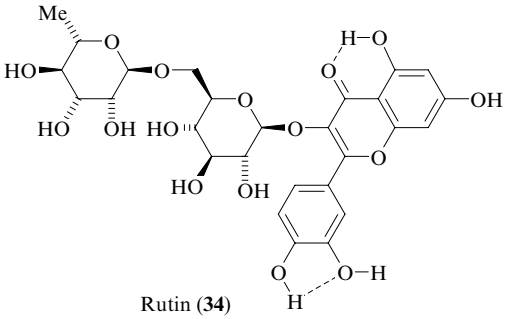
R = H (Gallic acid, **30**),
Pr (propyl gallate, **31**)



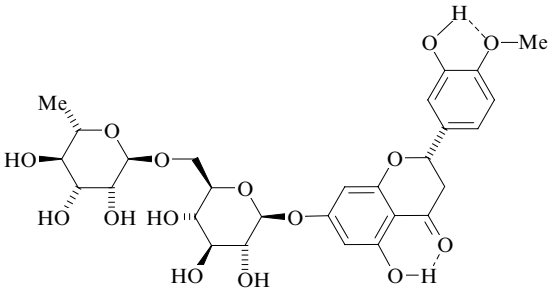
Myricetin (**32**)



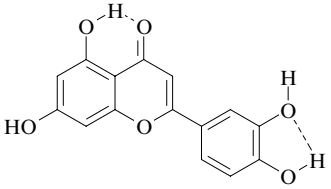
(−)-Epigallocatechin (**33**)



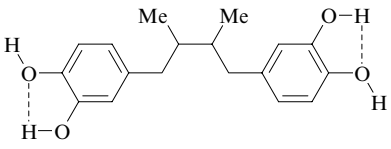
Rutin (**34**)



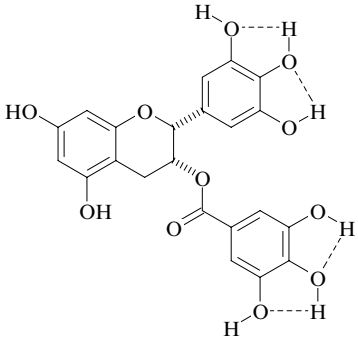
Hesperidin (**35**)



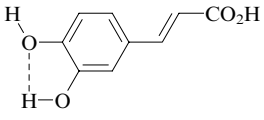
Luteolin (**36**)



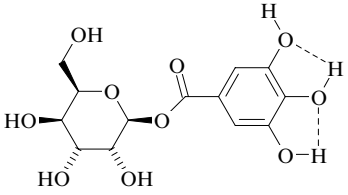
Nordihydroguaiaretic acid (**37**)



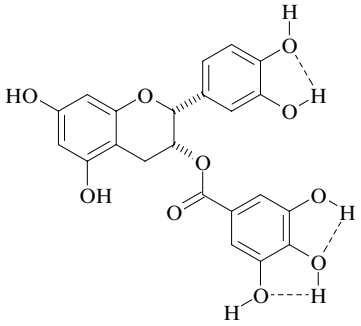
(−)-Epigallocatechin gallate (**39**)



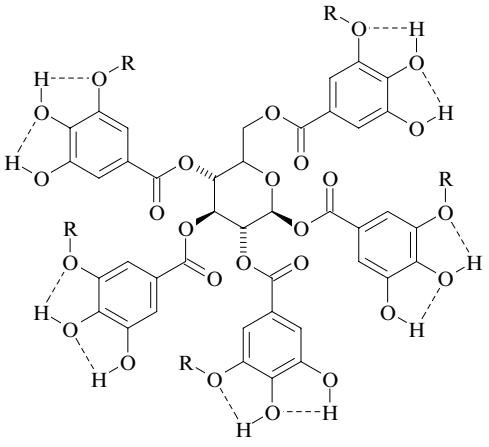
Caffeic acid (**38**)



β-Glucogallin (**40**)



(−)-Epicatechin gallate (**41**)



Tannic acid (**42**) (R is gallate)

Figure 1 (continued).

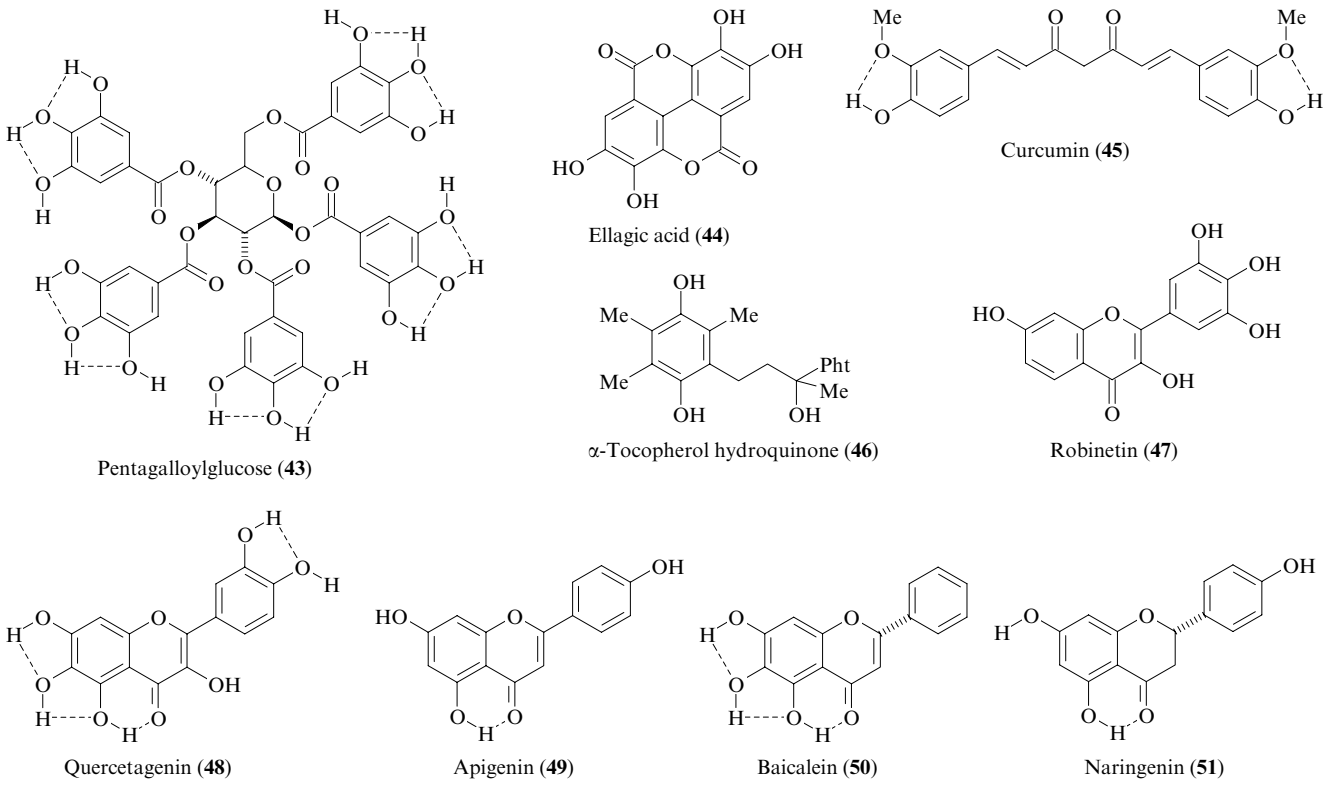


Figure 1 (continued).

II. The structures of phenols

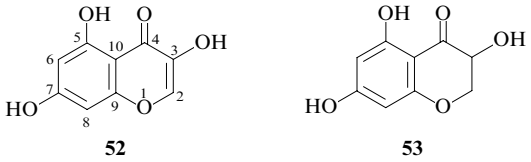
Interatomic distances in organic compounds can experimentally be measured by X-ray diffraction analysis and microwave spectroscopy and calculated by quantum mechanics methods. For phenols, all the methods give similar values that differ by not more than 10^{-12} m.[13] For instance, certain interatomic distances (experimental and theoretical) for an analogue of α-tocopherol, *viz.*, 6-hydroxy-5,7,8-trimethylchromane (**7a**),[14] 3,5,7-trihydroxychromen-4-one (**52**) and 3,5,7-trihydroxychroman-4-one (**53**) are given in Fig. 2.[15] It is evident that quantum chemical calculations are in good agreement with experimental data.

Bond lengths in the molecule of phenol (C_6H_5OH) have similar values:[13]

Bond	C–C	C–H	C–O	O–H
r/Å	1.393	1.083	1.374	0.957

Bond angles in phenol have the following values: θ(CCC) = 120.1 ± 0.7°, θ(CCO) = 122.1°, θ(COH) = 108.8°. For comparison, Table 1 lists the bond angles in compounds **52** and **53** calculated by quantum chemical methods.[15]

In hydroxychromanes, the dissociation energy (DE) of the O–H bond depends on the angle between the plane of the benzene ring and the C(9)–O bond. This angle affects the degree of overlap of the π-orbitals of the ring and the p-orbital of the electron pair of the oxygen atom (see Section III). In the molecule of 6-hydroxy-5,7,8-trimethylchromane (**7a**), this angle is equal to −15.9°.[14]



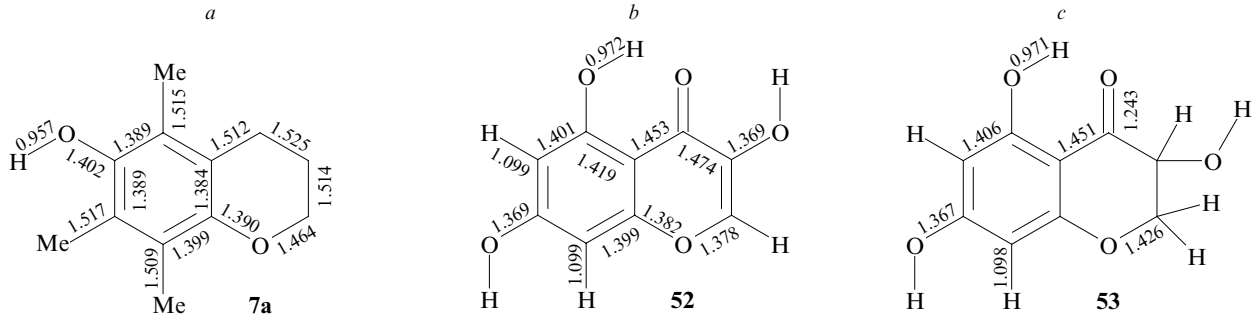


Figure 2. Interatomic distances (in Å) in the molecules of 6-hydroxy-5,7,8-trimethylchromane (*a*) (according to X-ray diffraction data),[14] 3,5,7-trihydroxychromen-4-one (*b*) and 3,5,7-trihydroxychroman-4-one (*c*) (according to quantum chemical calculations by the AM1 programme).[15]

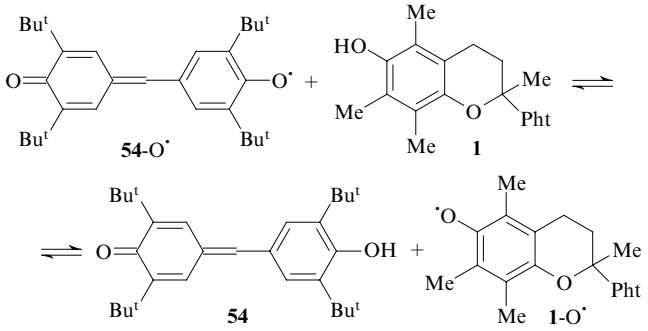
Table 1. Angle values (in degrees) in the molecules of chromenone **52** and chromanone **53** (quantum chemical calculations by the AM1 programme).[15]

Angle θ	Compound	
	52	**53**
∠OC(2)C(3)	118.0	118.0
∠C(2)C(3)C(4)	117.4	117.4
∠C(3)C(4)C(10)	114.4	116.6
∠C(10)C(5)C(6)	121.1	119.8
∠C(5)C(6)C(7)	119.5	119.3
∠C(6)C(7)C(8)	121.1	121.4
∠C(7)C(8)C(9)	118.4	116.7
∠C(8)C(9)C(10)	122.4	121.8
∠C(3)C(4)O	120.3	118.5
∠C(2)C(3)O	118.6	106.2
∠C(3)OH	107.0	107.2
∠C(5)OH	110.2	110.6
∠C(7)OH	108.3	108.4

III. The dissociation energy of the O—H bond in phenols

Among natural phenols, α-tocopherol (**1**) is the most popular subject for measuring the dissociation energy of the O—H (D_{O-H}) bond. The first of such estimates was obtained [16] by using the Polanyi — Semenov linear correlation (PSC) for the reactions of peroxyl radicals with phenols.[17]

For the estimation of the DE difference (ΔD_{O-H}), the equilibrium between the galvinoxyl stable radical (**54**-O$^{\bullet}$),† and α-tocopherol (**1**) was studied.[18, 19]



The concentrations of galvinoxyl (**54**-O$^{\bullet}$) and α-tocopheroxyl (**1**-O$^{\bullet}$) radicals were determined by EPR spectra. The equilibrium in this system is dynamic, since α-tocopheroxyl radicals disproportionate, which results in a decrease in the concentrations of both types of the radicals over time. The equilibrium is established quickly, while the disproportionation of radicals **1**-O$^{\bullet}$ occurs slowly [the rate constant for the disproportionation ($2k_{disp}$) is 1.3×10^3 litre mol^{-1} s^{-1}].[20] The equilibrium constant (K) could be calculated by mathematical processing of kinetic curves, it was found to be 0.80 at 298 K in benzene. On the assumption that the change in the Gibbs energy in this system is equal to the change in the reaction enthalpy ($\Delta G = \Delta H$), the difference ΔD_{O-H} was calculated:

$$\Delta D = D_{O-H}(\mathbf{54}) - D_{O-H}(\mathbf{1}) = -0.5 \text{ kJ mol}^{-1},$$

therefore

$$D_{O-H}(\mathbf{1}) = D_{O-H}(\mathbf{54}) - \Delta D = 329.7 + 0.5 = 330.2 \text{ kJ mol}^{-1}.$$

It should be borne in mind that in polar solvents hydrogen bonds between the solvent molecules and the phenolic OH groups are formed. This is necessary to take into account in calculating the DE of an O—H bond. In such a solvent, the following formula is true:

$$\Delta D = D_{O-H}(\mathbf{54}) - D_{O-H}(\mathbf{1}) + \Delta H_H(\mathbf{54}) - \Delta H_H(\mathbf{1}\text{-O}^{\bullet}), \quad (1)$$

where ΔH_H is the enthalpy of formation of a hydrogen bond between the solvent and the corresponding phenol. For example, the enthalpy of formation of a hydrogen bond between methanol and 2,6-dimethylphenol (an analogue of α-tocopherol) is equal to 13.7 kJ mol^{-1}, whereas between methanol and 2,6-di-*tert*-butylphenol (an analogue of galvinol) it is 8.9 kJ mol^{-1}. The difference between these values is 4.8 kJ mol^{-1} (calculated by the ΔH_H increments of the corresponding phenols).[21] It should be taken into consideration in a correct calculation of ΔD.

Similar values of $D_{O-H}(\mathbf{1})$ are provided by photoacoustic calorimetry (PAC) [22] and an electrochemical method of the assessment of D_{O-H} from the redox potential (ROP).[23] An average value of D_{O-H} for α-tocopherol (**1**) according to the data given in Table 2 is equal to 330.0 ± 4.7 kJ mol^{-1}.

For a large number of natural phenols, D_{O-H} were estimated by experimental kinetic studies with the use of the method of intersecting parabolas (MIP).[24] For α-tocopherol (**1**) as the reference phenol, $D_{O-H} = 330.0$ kJ mol^{-1} (this value was selected from numerous experiments). Based on the experimental data, the difference in the activation energies of reactions of the peroxyl radicals‡ ($RO_2^{\bullet}$) with compound **1** (the rate constant k_1 and the activation energy E_1) as well as with any other phenol Ar^{i}OH (k_i, E_i) was calculated:

$$\Delta E_i = E_i - E_1 = RT \ln\left(\frac{n_i k_1}{k_i}\right),$$

where n_i is the number of equireactive O—H groups in the molecule Ar^{i}OH. All reactions of the peroxyl radicals with phenols belong to one class. Each class of reactions is characterized by the following parameters in the MIP:[1, 2, 24]

1) coefficient b ($2b^2$ is the force constant of a reacting bond),

$$b_{O-H}(\text{PhOH}) = 4.665 \times 10^{11} \text{ (kJ mol}^{-1})^{1/2} \text{ m}^{-1};$$

2) elongation (r_e) of reacting bonds in the transition state;

3) parameter br_e [for the reaction $RO_2^{\bullet}$ + PhOH this parameter is equal to 13.16 (kJ mol^{-1})$^{1/2}$];

† Hereinafter, the symbol O$^{\bullet}$ at the number of a compound signifies the corresponding phenoxyl radical, and the symbol $O_2^{-\bullet}$ denotes the radical anion.

‡ In this review, R denotes, as a rule, any alkyl substituent including an oligomeric or polymeric chain.

Table 2. The dissociation energy of the weakest O−H bond and redox potentials of natural phenols.

Phenol	Position of the O−H bond	n_{O-H} (see [a])	D_{O-H} /kJ mol^{-1}	$E_{1/2}$/V (see [b])	Method	Ref.	Phenol	Position of the O−H bond	n_{O-H} (see [a])	D_{O-H} /kJ mol^{-1}	$E_{1/2}$/V (see [b])	Method	Ref.
1	6	1	336.4	–	PSC	16	**9c**	6	1	331.9	–	MIP	24
			326.4	–	PSC	28	**9d**	6	1	335.7	0.89	MIP	24
			328.9	–	ESR	29	**9e**	6	1	336.3	–	MIP	24
			330.1	–	ESR	18	**9f**	6	1	333.2	0.88	MIP	24
			330.0	0.86	MIP	25	**9g**	6	1	339.3	–	MIP	24
			327.3	–	ESR	19	**10a**	6	1	332.5	–	MIP	24
			323.4 ± 8.0	–	PAC	22	**10b**	6	1	333.9	–	MIP	24
			338.5	–	ROP	23	**10c**	6	1	333.4	–	MIP	24
2	6	1	335.2	–	MIP	16	**10d**	6	1	333.3	0.89	MIP	25
			335.6	0.92	MIP	25				334.7	–	MIP	24
			335.3 ± 2.0	–	MIP	24	**10e**	6	1	337.8	–	MIP	24
3	6	1	334.8	–	MIP	16	**11**	6	1	321.4	–	MIP	24
			335.1	0.93	MIP	25	**12**	6	1	322.1	–	MIP	24
			334.9 ± 2.0	–	MIP	24	**13**	6	1	329.8	–	MIP	24
4	6	1	341.4	–	MIP	16	**14**	6	1	335.7	–	MIP	24
			342.8	–	MIP	25	**15**	5	1	334.5	–	MIP	24
			335.6	0.99	PAC	22	**16**	5	1	342.3	–	MIP	24
			341.5 ± 2.0	–	MIP	24	**17**	7,4′	2	348.9	–	MIP	24
5a	1, 4	2	343.8	–	MIP	25	**18**	7,4′	2	363.6	–	MIP	24
			346.0	–	MIP	24	**19**	1,4	2	350.2	–	MIP	24
5b	1, 4	2	344.3	–	MIP	25	**20**	4′	1	343.0	–	MIP	24
			345.7	–	MIP	24	**21**	4′	1	346.2 ± 1.8	–	MIP	24
5c	1, 4	2	344.3	–	MIP	25				339.7	–	ESR	30
			345.7	–	MIP	24	**22**	6	1	332.3	–	MIP	24
5d	1, 4	2	344.8	–	MIP	24	**23**	8	1	333.0	–	MIP	24
5e	1, 4	2	345.6	–	MIP	24	**24**	7	1	357.1	–	MIP	24
6b	5	1	326.7	–	MIP	16	**25**	7	1	363.1	–	MIP	24
6c	5	1	326.4	–	MIP	16	**26**	4′	1	343.6	–	MIP	24
6g	6	1	334.0	–	MIP	16	**27**	4′	1	348.1 ± 1.3	–	MIP	24
7a	6	1	330.9	–	MIP	16	**28**	3′	1	353.8	–	MIP	24
7b	6	1	330.9	–	MIP	16	**29**	4′	1	348.0 ± 1.7	–	MIP	24
7c	6	1	334.4	–	MIP	16	**30**	4	1	347.4	–	MIP	24
7d	6	1	336.5	–	MIP	16	**31**	4	1	334.6	–	MIP	24
7e	6	1	333.3	–	MIP	16				339.7	–	ESR	30
7f	6	1	333.0	–	MIP	16	**32**	4′	1	340.9	–	MIP	24
7g	6	1	330.9	–	MIP	16	**33**	4′	1	344.6	–	MIP	24
8b	6	1	328.9	–	MIP	16	**34**	4′	1	343.2 ± 0.6	–	MIP	24
			328.4	0.87	MIP	24	**35**	3′	1	345.8	–	MIP	24
8c	6	1	331.9	–	MIP	24	**36**	4′	1	342.7	–	MIP	24
8d	6	1	333.6	–	MIP	24	**37**	4, 4′	2	351.3	–	MIP	24
8e	6	1	337.0	–	MIP	24	**38**	4	1	339.8	–	MIP	24
8f	6	1	335.7	–	MIP	24	**39**	4′, 4″	2	338.7 ± 0.3	–	MIP	24
8g	6	1	332.5	–	MIP	24	**40**	4	1	335.0	–	MIP	24
8h	6	1	340.7	–	MIP	24	**41**	4′, 4″,	2	339.6 ± 1.3	–	MIP	24
9a	6	1	340.1	1.05	MIP	24	**42**	4	5	341.6	–	MIP	24
9b	6	1	333.9	–	MIP	24	**43**	4	5	338.1	–	MIP	24

Note: The following abbreviations are used: PSC is the Polyanyi–Semenov correlation, ESR is the equilibrium with a stable radical, MIP is the method of intersecting parabolas, PAC is photoacoustic calorimetry, ROP is the redox potential. [a] The number of equireactive O−H bonds; [b] polarographic half-wave reduction potential.

4) coefficient α which is

$$\alpha = \frac{b_{O-H}(PhOH)}{b_{O-H}(ROOH)} = 1.014$$

for the reaction under consideration;

5) zero-point vibration energy of the phenolic O−H bond, which is 21.5 kJ mol^{-1} (Refs 1, 2 and 24).

The energy of the phenolic O−H bond (D_i) was calculated by equation:[25]

$$D_i = 330 + 2br_e\alpha^{-2}\left(\sqrt{E_{ei}} - \sqrt{E_{e1}}\right) - (\alpha^{-2} - 1)\Delta E_i, \qquad (2)$$

where $E_{ei} = E_i + 21.5 - 0.5RT$, and $E_{e1} = 27.6$ 5 kJ mol^{-1} (Ref. 24). The dissociation energies of the O−H bonds of

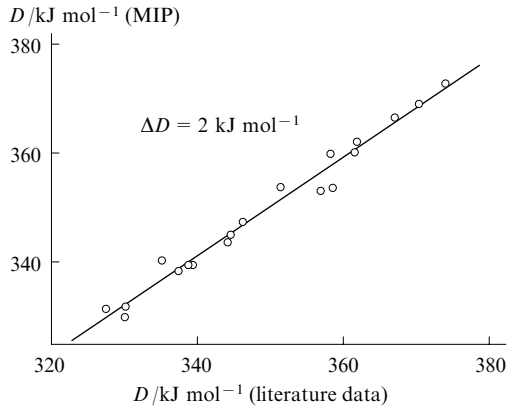


Figure 3. The correlation of D_{O-H} for synthetic phenols[25] derived from kinetic data by MIP with D_{O-H} of the same phenols obtained by other methods.[26]

synthetic phenols calculated using this equation agree well with the results obtained by other methods (Fig. 3),[26] the root-mean-square difference between them does not exceed 2 kJ mol^{-1}.

Table 2 presents the dissociation energies of the O—H bonds of natural phenols and their analogues, the position of the most reactive O—H bond and the number of this type of bonds. For a number of phenols, the redox potentials (half-wave reduction potentials $E_{1/2}$ in acetonitrile) obtained by cyclic voltammetry are documented.[27]

As seen from the data in Table 2, all ubiquinols (compounds **5a**–**e**) possess virtually the same dissociation energy of the O—H bond, which is independent of the length of a substituent (the number *n* in formulae **5a**–**e**). An average value of D_{O-H} is 345.2 ± 0.8 kJ mol^{-1} (8 measurements). It should be borne in mind that both O—H groups in ubiquinols are involved in hydrogen bonding with the *ortho*-methoxy groups (see Fig. 1). Phenolic groups form very strong intramolecular hydrogen bonds. For instance, in a phenolic crown ether (for the structure, see Ref. 31) the enthalpy of formation of such a bond is 21 kJ mol^{-1}, whereas the concentration of free O—H groups is only 0.1% at 323 K.

According to a theoretical calculation performed by density functional theory,[32] the difference $\Delta\Delta G^{\neq}$(298 K) for two transition states for the abstraction of an H atom by the methoxyl radical from a hydrogen-bonded O—H group of ubiquinol **5a** and from a free OH group is 7.5 kJ mol^{-1}. Assuming that $\Delta E(RO_2^{\bullet} + \mathbf{5}) = \Delta\Delta G^{\neq}(MeO^{\bullet} + \mathbf{5})$ and using Eqn (2), we obtain the value of D_{O-H} = 329.0 kJ mol^{-1} for a free O—H group of ubiquinols, *i.e.*, almost the same as that for α-tocopherol (**1**).

In tocopherols **1**–**4**, the value D_{O-H} depends on the number and arrangement of methyl groups in the aromatic ring (see Table 2). At the same time, replacement of methyl groups by ethyl, isopropyl and *tert*-butyl ones in positions 5 and 7 affects slightly the DE values of tocols **9** (see Fig. 1):

Compound	R^1	R^2	D_{O-H} /kJ mol^{-1}
9a	H	H	340.1
9b	Et	Et	333.9
9d	Pr^i	Pr^i	335.7
9g	Pr^i	Bu^t	339.3

Substitution of phytyl (Pht) for the methyl substituent in position 2 exerts virtually no effect on the value of D_{O-H} of 6-hydroxychromanes: D_{O-H}(2-Me, 2-Me) − D_{O-H}(2-Me, 2-Pht) = 0.4 ± 0.7 kJ mol^{-1} (7 pairs of compounds from Table 2 were compared). In phenols **7**, the nature of substituents R^1 and R^2 in position 2 virtually has no impact on the DE of the O—H bond: for seven phenols, the average value is 332.8 ± 2.0 kJ mol^{-1}. However, the nature of substituents R^1—R^3 in hydroxychromane **8** appreciably influences the value of D_{O-H} altering it in the range 328 to 341 kJ mol^{-1}. Substitution of a naphthalene ring for the benzene ring on going from γ-tocopherol (**3**) to phenol **11** reduces D_{O-H} by 13 kJ mol^{-1} (see Table 2). Substitution of S and Se for O atoms in α-tocopherol results in a small decrease in DE: D_{O-H} are 330.0, 334.0 and 335.7 kJ mol^{-1} for compounds **1**, **10d** and **14**, respectively. The presence or the absence of methyl groups in position 2 in 6-hydroxy-5,7,8-trimethyl-3,4-dihydrobenzothiopyrans **10a**–**c** does not affect the DE of the O—H bond: D_{O-H} (in kJ mol^{-1}) = 332.5 (2-H, 2-H), 333.9 (2-H, 2-Me), 333.4 (2-Me, 2-Me) (see Table 2).

The molecules of chrysin (**24**) and galangin (**25**) contain two phenolic groups. One of them, *viz.*, the OH group in position 5 is linked to the adjacent carbonyl group by a hydrogen bond, hence it is the 7-OH group that is the most reactive. As a result, for compounds **24** and **25** the number of equireactive O—H bonds (n_{O-H}) is 1, and D_{O-H} differ little: 357.1 and 363.1 kJ mol^{-1}, respectively. For morin (**18**), D_{O-H} of the OH groups in positions 7 and 4′ are apparently roughly the same and equal to 363.6 kJ mol^{-1} (n_{O-H} = 2).

In catechol (1,2-dihydroxybenzene, **55**), one hydroxyl group weakens the adjacent O—H bond (thus, in pyrogallol D_{O-H} = 339.9 kJ mol^{-1}, while in phenol D_{O-H} = 369.0 kJ mol^{-1}) (Ref. 1). One of two O—H groups in compound **55** is bound by a hydrogen bond, which increases its effective strength roughly by 10 kJ mol^{-1} [for comparison, in quercetin (**20**) D_{O-H} = 343.0 kJ mol^{-1} and in hesperitin (**28**) 353.8 kJ mol^{-1}; in the latter compound, the peroxyl radical attacks the OH group linked to a methoxy group by a hydrogen bond]. Thus, in catechol (**55**) only one OH group reacts with $RO_2^{\bullet}$, the second is inactive due to the formation of a strong hydrogen bond.

An average value of D_{O-H} in flavanones and flavones is 344.7 ± 2.6 kJ mol^{-1}. In 1,2,3-trihydroxybenzenes only one O—H bond actively reacts with $RO_2^{\bullet}$, whereas the other two are involved in hydrogen bonding. For such phenols a fairly wide range of D_{O-H} values is observed (in parentheses, compound numbers are indicated): 347.4 (**30**), 337.2 ± 2.5 (**31**), 340.9 (**32**), 344.6 (**33**), 343.2 (**34**), 345.8 (**35**) and 338.7 kJ mol^{-1} (**39**).

Thus, DE of the O—H bond in natural antioxidants ranges from 330 [for α-tocopherol (**1**)] to ~364 kJ mol^{-1} [for morin (**18**)]. These compounds compose a group with very close values of of D_{O-H}; it includes tocopherol, ubiquinols, flavones, flavanones and gallates. The diversity of their structures seems to be associated with the pecularities of the media where they manifest their antioxidant activity. The redox potentials of these compounds increase with an increase in the DE of the phenolic O—H bond, which depends on a number of structural factors.

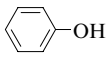
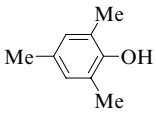
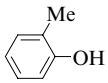
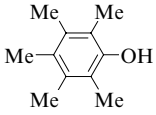
In recent years, quantum chemical methods, particularly density functional theory, are often used for the assessment of the DE of an O—H bond in phenols.[13–16,32–43] Let us

note that the results of calculations, as a rule, differ substantially from the experimental data. For example, for the simplest phenol (PhOH) the experimentally measured D_{O-H} are in the range 365 to 378 kJ mol^{-1} (Ref. 26), while the calculation results depend on the basis function sets employed:[16, 33, 36]

Basis set	D_{O-H}/kJ mol^{-1}	Ref.
6-31G	332.8	36
6-31G(d)	322.7	36
6-31G(d,p)	346.2	36
	341.7	33
6-31G(d,p′)	361.3	36
6-31 + G(d)	328.9	33
6-31 + G(d,p)	344.2	33
6-311 + G(d,p)	347.7	33
6-311 + G(2d,p)	348.0	33
6-311 + G(2d,2p)	350.7	33
6-311 + G(3d,2p)	350.1	33

The most important factor affecting the strength of the O—H bond is the stabilization of a phenoxyl radical due to the overlap of the unpaired electron orbital of the oxygen atom with the π-electrons of the benzene ring. The stabilization energy can be judged by a comparison of the DE of the O—H bond in phenol (PhOH) (D_{O-H} = 369 kJ mol^{-1}) (Ref. 1) and in an aliphatic alcohol ROH (D_{O-H} = 432 kJ mol^{-1}) (Ref. 42).The difference is 63 kJ mol^{-1}, therefore reactions of peroxyl radicals with natural phenols, which are essential for the inhibition of oxidation, are always exothermic.

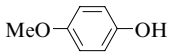
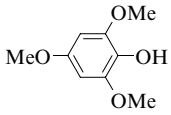
The second factor that influences the DE of the O—H bonds of natural phenols is the inductive effect of alkyl, in particular, methyl, groups. Below the data are given that illustrate the role of the inductive effect of methyl groups on the DE of the O—H bond in phenols:[1]

Phenol	D_{O-H}/kJ mol^{-1}	Phenol	D_{O-H}/kJ mol^{-1}
	369.0		347.5
	360.0		340.0

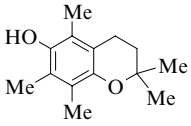
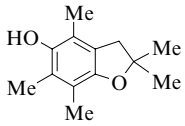
An analogous effect is also observed in tocopherols: the more methyl substituents are present in the benzene ring of a tocopherol the weaker is its O—H bond.

Tocopherol	The number of the Me groups	D_{O-H}/kJ mol^{-1}
1 (α)	3	330.0
2 (β)	2	335.5
3 (γ)	2	335.0
4 (δ)	1	341.5

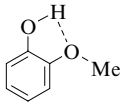
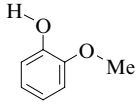
The third factor is the enhancement of the stabilization of a phenoxyl radical due to interaction of the p-electrons of the O atom of an alkoxyl substituent or a hydroxyl group with the π-electrons of the benzene ring. The magnitude of this effect is clearly seen from the following comparison:[1]

Phenol	D_{O-H}/kJ mol^{-1}
	369.0
	346.0
	335.0

The fourth factor is the stereoelectronic one, which has been discussed in detail.[16] The point is that for bicyclic phenols, such as hydroxychromanes and hydroxybenzofurans, an important parameter is the angle θ between the C—O bond of the annulated oxygen-containing ring and the plane of the benzene ring. The smaller this angle the larger the overlap of the p-electron orbitals of the O atom of the pyran or furan ring with the π-electrons of the benzene ring and the higher the stabilization energy of the phenoxyl radical. This is exemplified by the data given below:

Phenol	 (**8a**)	 (**6c**)
Angle θ/deg	17	6
D_{O-H}/kJ mol^{-1}	328.9	326.4

The fifth factor is the intramolecular hydrogen bonding. In 1,2-dihydroxybenzenes and 2-alkoxyphenols (for instance, in ubiquinols **5**), the OH groups are involved in the formation of intramolecular hydrogen bonds, which affects their reactivity. A quantum chemical calculation of the Gibbs energy of the transition state for the reaction of the methoxyl radical with *o*-methoxyphenol in two distinct states, *viz*., with a free O—H group and with that bound by a hydrogen bond, was carried out.[32] Below, the results of such a calculation performed by the density functional method in the B3LYP/6-31G(d,p) approximation are presented.

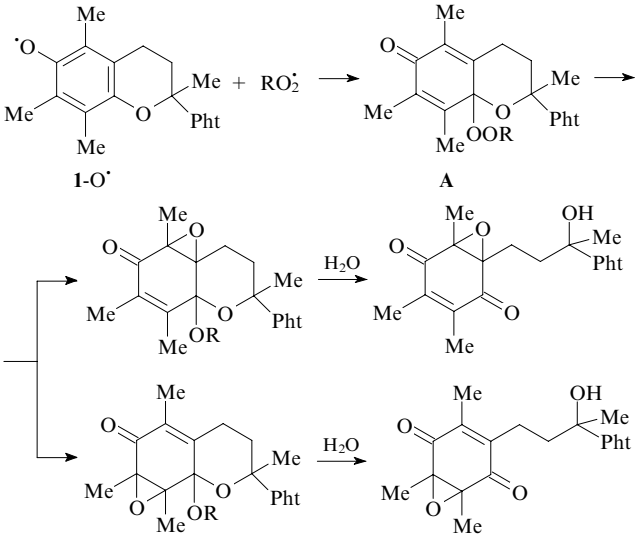
Configuration	ΔG/kJ mol^{-1}	$\Delta G^{\neq}$/kJ mol^{-1}
	−67.8	18.0
	−86.6	10.5

It is evident that the Gibbs energy (ΔG) of the reaction of MeO$^{\bullet}$ with the phenolic O—H group bound by a hydrogen bond is 18.8 kJ mol^{-1} higher, and the Gibbs energy of the transition state ($\Delta G^{\neq}$) is 7.5 kJ mol^{-1} higher than that with a free O—H group.

IV. Reactions of phenols with peroxyl radicals

Reaction products. As a result of a reaction of a peroxyl radical with a phenol, a phenoxyl radical is produced, its further transformations lead to one or other stable product. The peroxyl radicals react very rapidly with the phenoxyl radicals. This kind of reactions involving synthetic phenols and their products have been discussed.[1, 2, 44, 45]

The oxidation products of natural phenols by peroxyl radicals were studied by the example of the oxidation of α-tocopherol (**1**, or TcOH).[46–49] The peroxyl radicals were generated upon decomposition of an aza-initiator [$Me_2(CN)CN{=}NC(CN)Me_2$ or $Bu^iMe(CN)CN{=}NC.(CN)MeBu^i$] in the presence of oxygen or *tert*-butyl hydroperoxide (Bu^tOOH) at 310 or 323 K. It was demonstrated that the primary reaction product of $RO_2^{\bullet}$ with the α-tocopheroxyl radical (**1**-O$^{\bullet}$, or TcO$^{\bullet}$) is the quinolide peroxide **A**. Other compounds are formed as a result of its subsequent conversions. The oxidation products of α-tocopherol and probable reaction pathways of their formation are presented below.



The stoichiometry of the chain termination reactions in phenols. The issue of the stoichiometry of chain terminations in phenols upon oxidation is closely related to the reactions involving phenoxyl radicals. A phenoxyl radical generated by the reaction

$$RO_2^{\bullet} + ArOH \longrightarrow ROOH + ArO^{\bullet},$$

can further be converted to a quinolide peroxide or a quinone:[2, 44, 45]

$$ArO^{\bullet} + RO_2^{\bullet} \longrightarrow OArOOR,$$

or dimerize:

$$ArO^{\bullet} + ArO^{\bullet} \longrightarrow \text{products}.$$

If the formation of the quinone predominates, the stoichiometric coefficient of inhibition (f)§ is equal to 2, and if the dimerization reaction does, then $f = 1$. In the general case:[1, 2]

$$f = 1 + \left\{1 + \frac{k(ArO^{\bullet} + ArO^{\bullet})[ArO^{\bullet}]}{k(ArO^{\bullet} + RO_2^{\bullet})[RO_2^{\bullet}]}\right\}^{-1}. \qquad (3)$$

§ The coefficient f characterizes the inhibiting capacity of a phenol in given oxidation conditions.

In particular, $k(TcO^{\bullet} + TcO^{\bullet}) \approx 10^3$ litre mol^{-1} s^{-1}, while $k(TcO^{\bullet} + RO_2^{\bullet})$ is five orders of magnitude higher. Hence, for the α-tocopheroxyl radical the coefficient f must be close to 2, which is observed experimentally. In the general case, the stoichiometric coefficient varies from 1 to 2 (per phenolic group) depending on the conditions of the oxidation process.

This does not apply, however, to *o*- and *p*-hydroquinones (QH_2) from which semiquinone radicals are formed, which undergo the following reactions:

$$HQ^{\bullet} + RO_2^{\bullet} \longrightarrow Q + ROOH,$$

$$HQ^{\bullet} + HQ^{\bullet} \longrightarrow QH_2 + Q.$$

(The reactions of the *o*- and *p*-semiquinone radicals with $RO_2^{\bullet}$ yield *o*- and *p*-quinones, respectively.[1, 2])

For these phenols, $f = 2$ only in those instances where a semiquinone radical is not involved in other reactions, otherwise $f < 2$.

A semiquinone radical possesses a high reductive activity and reacts sufficiently fast with oxygen,[1, 2, 31, 50]

$$HQ^{\bullet} + O_2 \longrightarrow Q + HO_2^{\bullet},$$

and the hydroperoxyl radical formed propagates the oxidation chain. In this case, $f < 2$, and its dependence on the oxidation conditions is expressed by the formula

$$(2-f)(f-1)^{-1} = \frac{k(HQ^{\bullet} + O_2)[O_2]}{k(HQ^{\bullet} + RO_2^{\bullet})[RO_2^{\bullet}] + k(HQ^{\bullet} + HQ^{\bullet})[HQ^{\bullet}]}. \qquad (4)$$

The more intensive the reaction of oxygen with a semiquinone radical the smaller the stoichiometric coefficient. In experiments on the oxidation of *o*- and *p*-hydroquinones, $f < 2$ was observed indeed.[31, 50–52]

For the estimation of the stoichiometric coefficient of inhibition, two methods are used.[53]

According to one of them, a phenol and an initiator, which ensures a required constant initiation rate v_i, are introduced into a substrate. The experimental conditions are selected so that all the peroxyl radicals formed react with the phenol, *i.e.*,

$$k(ArOH + RO_2^{\bullet})[ArOH][RO_2^{\bullet}] \gg 2k_t[RO_2^{\bullet}]^2.$$

The initial rate of phenol consumption (v_{ArOH}) is measured. The coefficient f is calculated as the ratio v_i/v_{ArOH}.

In the second method, f is estimated from the induction period (τ) caused by phenol-induced chain termination in the substrate being oxidized in the presence of an initiator. The oxidation conditions are chosen in such a way that during the induction time the chain termination involves chiefly the phenol molecules (see the above-given inequality). Coefficient f is calculated as the ratio $v_i\tau/[ArOH]_0$. The values of f for a number of natural phenols are listed in Table 3.

The rate constant of the reaction of peroxyl radicals with a phenol. A peroxyl radical abstracts an H atom from the weakest phenolic group:

$$RO_2^{\bullet} + ArOH \longrightarrow ROOH + ArO^{\bullet}.$$

Table 3. Stoichiometric coefficients of inhibition.

Phenol	n_{O-H} (see [a])	f	Conditions	Ref.
1	1	2.0	styrene, 303 K	52
5a	2	1.9	the same	54
5e	2	1.0	"	54
7d	1	1.84	micelles, methyl linoleate, 310 K	55
8b	1	2.0	styrene, 303 K	52
9b	1	2.0	the same	54
9c	1	2.1	"	54
9d	1	1.9	"	54
9e	1	1.6	"	54
11	1	1.5	"	54
17	3	2.05	micelles, methyl linoleate, 310 K	55
20	4	1.9	styrene, 303 K	52
21	4	6.3	micelles, methyl linoleate, 310 K	55
26	4	1.4	styrene, 303 K	52
27	4	5.7	micelles, methyl linoleate, 310 K	55
29	3	1.5	styrene, 303 K	52
30	3	1.87	micelles, methyl linoleate, 310 K	55
31	3	1.55	the same	55
32	5	2.5	"	55
33	5	0.9	styrene, 303 K	52
34	4	4.6	micelles, methyl linoleate, 310 K	55
36	4	1.0	styrene, 303 K	52
37	4	4.1	the same	52
42	25	11.9	micelles, methyl linoleate, 310 K	55

[a] The total number of phenolic groups in a molecule.

Such a mechanism is confirmed by the following facts.[1,2,45] Phenoxyl radicals were detected by EPR as the primary reaction products. Replacement of the H atom by deuterium gives rise to a kinetic isotope effect. In natural phenols, the ratio of rate constants k_H/k_D is 5.4, 4.6 and 4.4 for compounds **1**, **6b** and **6c**, respectively,[16] which is fairly consistent with the abstraction of an H atom according to the above-given reaction, which proceeds in an adiabatic regime.[56] Solvents forming hydrogen bonds with a phenolic group retard this process by preventing an attack on the O–H bond (see below). The rate of a chain reaction inhibited by a phenol is inversely proportional to the concentration of the phenol terminating the chains. The rate constants for reactions of phenols with peroxyl radicals [$k(RO_2^{\bullet} + ArOH)$] can be found in reviews and reference books.[1–4,57,58] Table 4 provides values of the constants for a number of natural phenols.

By the example of reactions of $RO_2^{\bullet}$ with α-tocopherol (**1**), it can be seen that the rate constants measured for this reaction by different methods are similar. A somewhat overestimated value of the rate constant was given by the chemiluminescence method.[59] In a micellar system, $k(RO_2^{\bullet} + ArOH)$ is noticeably lower than in a homogeneous solution in a hydrocarbon, which, first of all, is due to hydrogen bonding between a phenolic OH group and a water molecule at the interface (see below). In recent years, studies on the measurements of the rate constants for these reactions in various solvents have been published (Table 5).

It is clear that there is a linear correlation between the values of $\log k$ and D_{O-H} of natural phenols (Fig. 4):

$$\log k\,(298\ \mathrm{K}) = (29.9 \pm 0.3) - (0.071 \pm 0.001) \times D_{O-H}\ (\mathrm{kJ\ mol^{-1}}). \quad (5)$$

It should be noted that this dependence is valid only for the reactions of phenols with $RO_2^{\bullet}$, where R is a secondary or primary alkyl group. For such radicals, the DE of the O–H bond in the hydroperoxides formed are the same: $D_{O-H}(ROOH) = 365.5$ kJ mol^{-1} (Refs 1, 2 and 42). In the general case, the rate constant for the reaction $RO_2^{\bullet}$ + ArOH depends on the enthalpy (ΔH), which for such processes is equal to the difference $D_{O-H}(ArOH) - D_{O-H}(ROOH)$. Consequently, the stronger the ROO–H bond the higher the reaction rate constant. In turn, the DE of an ROO–H bond depends on the structure of the hydroperoxide.[67] Table 6 provides the enthalpies (ΔH_e), activation energies (E), rate contants (k) and interatomic distances O–H in the transition state ($r^{\neq}_{ArO-H}$ and $r^{\neq}_{ROO-H}$) for the reactions of peroxyl radicals with α-tocopherol (**1**) calculated using the MIP.[67] It can be seen that, depending on the DE of the ROO–H bond, the enthalpies of these reactions range from −74 to −28 kJ mol^{-1}, and the activation energies vary from 1.3 to 9.5 kJ mol^{-1}.

The rate constant for a reaction of $RO_2^{\bullet}$ with a phenol that characterizes the reactivity of the phenol as an antioxidant is temperature-dependent. Hence, for estimation of phenol reactivities, it is expedient to make use of the Arrhenius activation energy [$E = \ln(n_{O-H}A/k)$, where n_{O-H} is the number of the O–H bonds, A is the preexponential factor]. It should be borne in mind that the rate of a reaction of $RO_2^{\bullet}$ with a phenol is affected by the nature of the solvent, first of all, by its ability to form a hydrogen bond with the hydroxyl group (see below).

The influence of a hydrogen bond. Upon an attack on non-polar C–H bonds of a hydrocarbon by an $RO_2^{\bullet}$ radical, the solvent does not virtually influences the rate constant for chain propagation (k_p) of this reaction.[2] This is also suggested by experiments on cumene oxidation in various solvents. The rate constant for the reaction $RO_2^{\bullet}$ + $PhPr^i$ is virtually fixed: $k_p = 0.82 \pm 0.09$ litre mol^{-1} s^{-1} at 323 K in five solvents (isooctane, benzene, acetonitrile, *tert*-butanol and pyridine).[68]

A different situation is observed when $RO_2^{\bullet}$ reacts with the phenolic O–H groups. A polar solvent Y forms a hydrogen bond with an O–H group

$$ArOH + Y \rightleftharpoons ArOH\cdots Y,$$

which prevents the O–H bond from an attack by radicals. For the first time it was demonstrated[69] by the example of a reaction of $RO_2^{\bullet}$ with α-naphthol in solvent mixtures: heptane–n-butanol and cyclohexane–cyclohexanol. In these cases, a decrease in the rate constant for the reaction $RO_2^{\bullet}$ + ArOH was observed as the content of the alcohol in a solution increased.

The inactivating effect of a polar solvent is characteristic of all radical reactions involving the O–H and N–H bonds. For the first time this circumstance was noticed by Beresin *et al.*[70] in investigations of reactions of methyl radicals with the O–H bond of *tert*-butanol. A tritium label was introduced into this bond and a kinetic study of the reaction of methyl radicals with the O–T bond of the alcohol was carried out.

$$^{\bullet}CH_3 + TOBu^t \longrightarrow CH_3T + Bu^tO^{\bullet}.$$

It was established that the increase in the concentration of the alcohol in heptane reduced the reaction rate constant

Table 4. Rate constants of peroxyl radical reactions with natural phenols.

Phenol	T/K	k /litre mol^{-1} s^{-1} (method)	Ref.	Phenol	T/K	k /litre mol^{-1} s^{-1} (method)	Ref.
1	303	3.20×10^6 (A), 2.9×10^6 (A)	16, 54	**10c**	303	1.80×10^6 (A)	54
	310	3.2×10^6 (A)	52	**10d**	303	1.44×10^6 (A)	54
	323	8.5×10^6 (B), 2.24×10^6 (C)	59, 60	**10e**	303	8.57×10^5 (A)	54
2	303	1.30×10^6 (A)	16	**11**	303	1.14×10^7 (A)	54
3	303	1.40×10^6 (A)	16	**12**	303	1.02×10^7 (A)	54
4	303	4.4×10^5 (A)	16	**13**	303	2.80×10^6 (A), 3.31×10^6 (A)	16, 54
5a	303	3.1×10^5 (A)	54	**17**	310	1.3×10^5 (A), 8.4×10^3 (D)	52, 55
	310	3.3×10^4 (D)	55		323	1.0×10^6 (B)	59
5e	303	3.5×10^5 (A)	54	**20**	310	1.9×10^6 (A), 1.2×10^4 (D)	52, 55
6b	303	5.40×10^6 (A)	16		323	2.1×10^7 (B), 2.02×10^6 (C)	59, 60
6c	303	5.70×10^6 (A)	16	**21**	310	6.4×10^3 (D)	55
6g	303	1.60×10^6 (A)	16	**22**	323	1.57×10^6 (C)	60
7a	303	2.70×10^6 (A)	16	**23**	323	1.41×10^6 (C)	60
7b	303	2.70×10^6 (A)	16	**24**	323	1.14×10^4 (C)	60
7c	303	1.50×10^6 (A)	16	**26**	310	9.0×10^5 (A)	52
7d	303	1.10×10^6 (A)	16		323	1.9×10^7 (B)	59
7e	303	1.80×10^6 (A)	16	**27**	310	1.6×10^6 (A), 6.5×10^3 (D)	52, 55
7f	303	1.90×10^6 (A)	16		323	6.6×10^6 (B), 4.93×10^5 (C)	59, 60
7g	303	2.70×10^6 (A)	16	**29**	310	2.0×10^6 (A)	52
8b	303	3.80×10^6 (A)	16		323	1.2×10^7 (B)	59
8c	303	2.1×10^6 (A)	54	**30**	310	1.2×10^6 (A), 5.6×10^3 (D)	52, 55
8d	303	1.6×10^6 (A)	54	**31**	310	5.0×10^4 (D)	55
8e	303	8.8×10^5 (A)	54	**32**	310	1.7×10^4 (D)	55
8f	303	1.1×10^6 (A)	54	**33**	310	3.2×10^6 (A), 9.2×10^3 (D)	52, 55
8g	303	1.9×10^6 (A)	54	**34**	310	1.1×10^4 (D)	55
8h	303	4.6×10^5 (A)	54	**35**	323	2.24×10^4 (C)	60
9b	303	1.5×10^6 (A)	54	**36**	310	1.5×10^6 (A)	52
9c	303	2.1×10^6 (A)	54		323	2.2×10^7 (B)	59
9d	303	1.1×10^6 (A)	54	**37**	310	1.6×10^6 (A)	52
9e	303	1.0×10^6 (A)	54		323	1.0×10^7 (B)	59
9f	303	1.7×10^6 (A)	54	**38**	310	1.5×10^6 (A), 2.1×10^4 (D)	52, 55
9g	303	5.9×10^5 (A)	54		323	1.5×10^7 (B)	59
9h	303	1.80×10^6 (A)	16	**39**	310	9.2×10^3 (D)	55
10a	303	2.10×10^6 (A)	54	**42**	310	1.4×10^4 (D)	55
10b	303	1.67×10^6 (A)	54				

Note. Method A, measured by the rate of styrene oxidation; B, measured by chemiluminescence in diphenylmethane; C, calculated using the literature data [60] from the ratio $fk(RO_2^{\bullet}+Ar^iOH)/2k(RO_2^{\bullet}+TcOH)$, the constants are measured in the oxidation of linoleic acid in micellar solution; D, measured by the rate of methyl linoleate oxidation in emulsion.

Table 5. Rate constants for the reactions of peroxyl radical with natural phenols in various solvents.

Phenol	Substrate, solvent	T/K	k /litre mol^{-1} s^{-1}	Ref.
1	styrene	303	3.20×10^6	61
	methyl linoleate, PhCl	323	3.55×10^6	62
5a	styrene	310	4.40×10^5	51
5e	"	310	7.00×10^5	54
20	methyl linoleate, PhCl	323	4.30×10^6	62
20	PhEt	331	2.90×10^4 (see [a])	63
21	methyl linoleate, PhCl	323	4.18×10^6	62
38	styrene	303	2.9×10^5	61
44	$CHCl_3$, H_2O (pH 4.5)	298	4.5×10^7	64
45	styrene	303	3.40×10^4	65
46	PhEt	323	2.4×10^6	66

[a] The product $fk(RO_2^{\bullet}+ArOH)$ was measured.

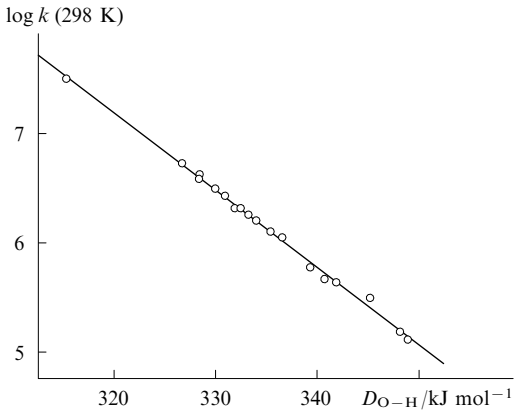
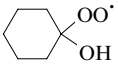
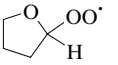


Figure 4. The dependence of $\log k(RO_2^{\bullet}+ArOH)$ on DE of the O–H bond for natural phenols in non-polar solvents, at 298 K (according to data from Tables 2 and 4).

Table 6. Thermodynamic and kinetic parameters of the reactions

$RO_2^{\bullet} + TcOH \longrightarrow ROOH + TcO^{\bullet}$,

calculated using MIP (D_{TcO-H} = 330.0 kJ mol^{-1}, $A_0 = 3.20 \times 10^7$ litre mol^{-1} s^{-1}).[67]

Radical	D_{ROO-H} /kJ mol^{-1}	$-\Delta H_e$ /kJ mol^{-1}	E/kJ mol^{-1}	k (310 K) /litre mol^{-1} s^{-1}	$r^{\neq}_{ArO-H} \times 10^{10}$ /m	$r^{\neq}_{ROO-H} \times 10^{10}$ /m
$HO_2^{\bullet}$	369.0	38.7	5.2	4.20×10^6	1.128	1.226
$R_2CHO_2^{\bullet}$	365.5	35.2	6.6	2.46×10^6	1.132	1.222
$R_3CO_2^{\bullet}$	358.6	28.3	9.4	8.22×10^5	1.141	1.214
	362.1	31.8	8.0	1.44×10^6	1.137	1.218
$RPhC(OH)O_2^{\bullet}$	359.8	29.5	8.9	9.99×10^5	1.139	1.215
$ROCH(R)O_2^{\bullet}$	367.3	37.0	5.9	3.24×10^6	1.130	1.224
$R_2CHOCR_2O_2^{\bullet}$	358.4	28.1	9.5	7.96×10^5	1.141	1.213
$ROCHPhO_2^{\bullet}$	374.8	44.5	3.0	9.87×10^6	1.121	1.234
	367.6	37.3	5.8	3.40×10^6	1.130	1.225
$RC(O)O_2^{\bullet}$	387.1	56.8	1.3	3.49×10^7	1.106	1.249
$R_3CC(O)O_2^{\bullet}$	376.9	46.6	2.3	1.33×10^7	1.118	1.236
$PhC(O)O_2^{\bullet}$	403.9	73.6	1.3	4.00×10^8	1.106	1.320
$RC(O)CRHO_2^{\bullet}$	369.8	39.5	4.9	4.74×10^6	1.127	1.227
$RC(O)OCPhHOO^{\bullet}$	376.4	46.1	2.4	1.24×10^7	1.119	1.236

due to the alcohol self-association. Experimental data on the influence of a hydrogen bond on the reactivity of phenols, alcohols, acids and aromatic amines in radical reactions were discussed in monographs[2, 32, 53, 71] as well as in recently published papers.[72–83] The inactivating action of polar solvents is also observed in the case of natural phenols. In Table 7, data on the reaction of α-tocopherol (**1**) with peroxyl, alkoxyl and diphenylpicrylhydrazyl radicals in various solvents are summarized.

Table 7. Rate constants (in litre mol^{-1} s^{-1}) for radical reactions with α-tocopherol (**1**) in various solvents.[72, 76]

Solvent	Radical			
	$Me_2PhCO_2^{\bullet}$	$RCH_2CHPhO_2^{\bullet}$	$Me_3CO^{\bullet}$	DPPH[a]
n-C_6H_{12}	2.0×10^7	–	9.9×10^9	7.4×10^3
CCl_4	1.4×10^7	–	4.2×10^9	3.6×10^3
PhH	–	3.4×10^6 (see [b])	3.1×10^9	1.8×10^3
PhMe	–	3.0×10^6 (see [b])	–	–
PhCl	2.7×10^6	–	3.6×10^9	2.7×10^3
PhOMe	1.5×10^6	–	2.0×10^9	1.4×10^3
AcOH	8.8×10^5	–	7.7×10^8	6.2×10^2
Bu^{t}OH	5.6×10^5	–	1.8×10^8	5.7×10^2
MeCN	3.8×10^5	–	9.4×10^8	4.9×10^2
AcOEt	2.3×10^5	–	2.9×10^8	1.6×10^2

[a] DPPH is diphenylpicrylhydrazyl; [b] measured at 303 K, other measured at 298 K.

As evident from the these data, in a polar solvent $k(RO_2^{\bullet} + \mathbf{1})$ is almost two orders of magnitude smaller and so are the rate constants for the reactions of other radicals with compound **1**. Figure 5 illustrates a correlation between $\log[k(RH)/k(Y)]$ and the β_H^2 parameter for the reactions of the peroxyl and *tert*-butoxyl radicals with phenol **1** in various solvents. The parameter β_H^2 characterizes the acceptor ability of solvent Y to form a hydrogen bond.[84, 85] The correlation shown in Fig. 5 is described by the following parametric equation (T = 296 K):[77]

$$\log k(RH) - \log k(Y) = 0.19 \pm 0.13 + (3.00 \pm 0.36)\, \beta_H^2 . \quad (6)$$

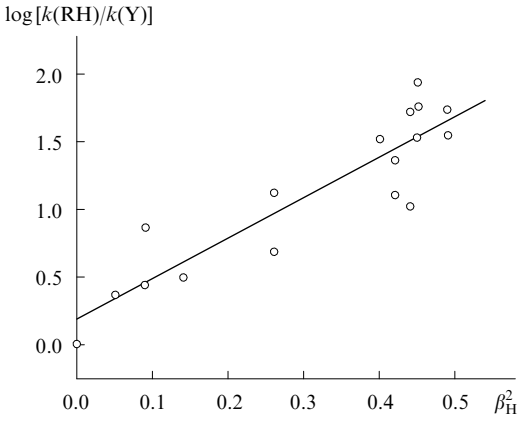


Figure 5. The correlation between $\log[k(RH)/k(Y)]$ and β_H^2 for the reactions of the peroxyl radicals of cumene and styrene and the *tert*-butoxyl radical with α-tocopherol in various solvents (see Table 7).

An analogous effect of a decrease in the empirical rate constant $k(RO_2^{\bullet} + ArOH)$ in a polar solvent was observed.[62] The kinetics of the inhibited oxidation of methyllinoleate at 323 K was traced by variation in the concentration of dissolved oxygen. The concentration of O_2 was measured from broadening of the EPR spectrum of the stable nitroxide radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), induced by exchange interaction with oxygen. Below are measurement results for the rate constant of the

reaction of $RO_2^{\bullet}$ (in litre mol^{-1} s^{-1}) with phenols at 323 K in two solvents.

Phenol	Solvent	
	PhCl	Bu^{t}OH
1	3.5×10^6	6.3×10^5
20	4.3×10^5	2.1×10^4
21	4.2×10^5	1.7×10^4

Thus, the reactivities of phenols in the alcohol that forms strong hydrogen bonds decrease roughly by an order of magnitude as compared to the reaction in chlorobenzene.

Since $RO_2^{\bullet}$, like other O-centred radicals, is a hydrogen bond acceptor, its reaction with a phenol proceeds apparently in two steps. First, a complex of the $RO_2^{\bullet}$ radical with a phenol forms, and then abstraction of a hydrogen atom occurs after activation:

$$RO_2^{\bullet} + HOAr \overset{K}{\rightleftharpoons} ROO^{\bullet}\cdots HOAr,$$

$$ROO^{\bullet}\cdots HOAr \xrightarrow{k} ROOH + ArO^{\bullet}.$$

The first stage proceeds rapidly, without activation energy. The equilibrium concentration of $ROO^{\bullet}\cdots HOAr$ complexes is determined by the Gibbs energy of the hydrogen bond formation:

$$[ROO^{\bullet}\cdots HOAr] = K_H[ArOH][RO_2^{\bullet}] =$$

$$= \exp\left(-\frac{\Delta G^{\neq}}{RT}\right)[ArOH][RO_2^{\bullet}].$$

The experimental rate constant (k_{exp}) is equal to kK_H, and the activation energy $E_{exp} = E + \Delta H_H$. The experimental data on the reactions of diphenylaminyl radicals with phenols[86,87] are in favour of such two-step reactions. For some of them, a negative temperature coefficient is observed in consequence of the validity of inequality: $E < |\Delta H_H|$.

In aqueous solutions, phenols undergo deprotonation. This gives rise to a new oxidation channel, namely, the reaction of electron transfer from the phenoxide ion to the peroxyl radical.

$$ArOH + H_2O \rightleftharpoons ArO^- + H_3O^+,$$

$$RO_2^{\bullet} + ArO^- \longrightarrow RO_2^- + ArO^{\bullet}.$$

The pH dependence of the experimental rate constant for the reactions of $CCl_3O_2^{\bullet}$ radicals with phenol **49** in aqueous solutions (298 K, pulse radiolysis) is shown below:[64]

pH	4.5	7.0	8.5	10.7
k_{exp}/litre mol^{-1} s^{-1}	4.5×10^7	1.4×10^8	3.2×10^8	4.2×10^8

As pH is increased, the concentration of the phenoxide ions is increased and, accordingly, the effective rate constant is elevated. The same is observed in solutions with high basicity (formamide, triethylamine, pyridine, *etc.*), where $RO_2^{\bullet}$ reacts with phenols much faster than it can be expected taking into account the retarding effect of the hydrogen bond.[73] The electron transfer is also characteristic of the reactions of phenols with the superoxide ion $O_2^{-\bullet}$.

$$O_2^{-\bullet} + ArO^- \longrightarrow O_2^{2-} + ArO^{\bullet}.$$

In aqueous solution, reactions with electron transfer occur rapidly. The rate constants for the reaction of $O_2^{-\bullet}$ with phenols (H_2O, 293 K, pH 7) are listed below:[88]

Phenol	**21**	**33**	**39**	**41**
k /litre mol^{-1} s^{-1}	6.8×10^4	4.1×10^5	7.3×10^5	4.3×10^5

V. Reactions of radicals R$^{\bullet}$ and RS$^{\bullet}$ with phenols

The parabolic model of a radical reaction. Unlike the reactions of peroxyl radicals, the reactions of other radicals with phenols, especially natural ones, are poorly studied.[57] The semi-empirical model MIP helps to fill this gap.[1,2,89,90] The model treats the transition state of the reaction of radical X$^{\bullet}$ with a phenol

$$X^{\bullet} + ArOH \longrightarrow XH + ArO^{\bullet}$$

as a point of intersection of two potential curves. One of them characterizes the stretching vibration of the O–H bond being broken, the other characterizes that of the X–H bond being formed. The stretching vibrations are regarded as harmonic ones. From this the main equation of MIP follows:

$$br_e = \alpha(E_e - \Delta H_e)^{1/2} + E_e^{1/2}. \quad (7)$$

This equation includes the following reaction characteristics: the classical enthalpy of reaction, which equals:

$$\Delta H_e = D(ArO-H) - D(X-H) + 0.5hN_A\Delta\nu, \quad (8)$$

where the last term is the difference in the energies of zero-point stretching vibrations of the atoms of reacting bonds (h is Planck s constant, N_A is Avogadro's number, $\Delta\nu$ is the frequency differences of the stretching vibrations of the O–H and X–H bonds); the classical potential barrier to a reaction (E_e), which is related to the the Arrhenius activation energy (E) by the correlation:

$$E_e = E + 0.5\,hN_A\nu_{ArO-H} - 0.5\,RT, \quad (9)$$

where ν_{ArO-H} is the frequency of the stretching vibration of the O–H bond; b and $\alpha = b_{O-H}/b_{X-H}$ are coefficients; (r_e) is the elongation of reacting bonds in the transition state.

For reactions with the coefficient α being equal to, or close to, 1, E_e is calculated by the equation:

$$\sqrt{E_e} = \frac{br_e}{1+\alpha} + \frac{\alpha\Delta H_e}{2br_e}, \quad (10)$$

and for the reactions with the coefficient α that substantially differs from unity, it is carried out using the expression:

$$\sqrt{E_e} = B\left\{1 - \alpha\sqrt{1 - \frac{\Delta H_e}{Bbr_e}}\right\}, \quad (11)$$

where $B = br_e/(1-\alpha^2)$. For phenols, the coefficient b is 46.65×10^{10} (kJ mol^{-1})$^{1/2}$ m^{-1}. The reaction activation energy is calculated by the equation:[89]

$$E = E_e - 0.5hN_A\nu_{ArO-H} + 0.5\,RT, \quad (12)$$

where $0.5hN_A\nu_{ArO-H}$ is the enegy of the zero-point vibration, which is equal to 21.5 kJ mol^{-1}.

The rate constant for a radical reaction was calculated by the Arrhenius equation:

$$k = n_{O-H}\, A \exp\left(-\frac{E}{RT}\right), \quad (13)$$

where A is the pre-exponential factor which is fixed for reactions of the same class. Eqns (10) and (11) are true, if ΔH_e of a reaction varies within the interval: $\Delta H_{e\,min} < \Delta H_e < \Delta H_{e\,max}$. Values of $\Delta H_{e\,min}$ and $\Delta H_{e\,max}$ are documented in the reference book [1].

Each class of radical reactions is characterized by one reaction site and constant values of ν_{O-H}, ν_{X-H}, br_e and A, as well as by a classical potential barrier of a thermally neutral reaction (for $\Delta H_e = 0$) E_{e0}, which is calculated by the formula:[89]

$$E_{e0} = \left(\frac{br_e}{1+\alpha}\right)^2. \quad (14)$$

By combining the results of quantum chemical calculations and those of the method of intersecting parabolas, a straightforward method for the calculation of interatomic distances in the reaction site of a transition state using the values of the reaction enthalpy and activation energy has been developed.[91,92] It allows obtaining interatomic distances in the transition state of a reaction, which coincide with those calculated by density functional theory. As applied to the reactions under consideration, the calculation of interatomic distances by this method was conducted according to the following formulae (for $\Delta H_{e\,min} < \Delta H_e < \Delta H_{e\,max}$):

$$r^{\neq}_{ArO-H} = r_{ArO-H} + \beta b^{-1}\sqrt{E_e}\,, \quad (15)$$

$$r^{\neq}_{X-H} = r_{X-H} + \alpha\beta b^{-1}\sqrt{E_e - \Delta H}\,. \quad (16)$$

The interatomic distances were taken equal to the following values:[93] $r_{O-H} = 0.967\times10^{-10}$ m, $r_{C-H} = 1.092\times10^{-10}$ m, $r_{S-H} = 1.340\times10^{-10}$ m, the normalization coefficients (β) were taken from Ref. 92 Kinetic parameters and coefficients for selected reaction classes are given in Table 8.

Reactions of alkyl radicals with phenols. Alkyl radicals react very rapidly (at diffusion-controlled rates) with oxygen,[2] therefore their reaction with phenols occurs only in anaerobic conditions. Experimental data on such reactions are scanty. In Table 9, data on the reactions of alkyl radicals (R$^{\bullet}$) with α-tocopherol (**1**) in various solvents are summarized.

Table 8. MIP kinetic parameters for the reactions of the R$^{\bullet}$, $RO_2^{\bullet}$, RS$^{\bullet}$ and ArO$^{\bullet}$ radicals with natural phenols.[89–92,94]

Reaction class	α	β	$0.5\,hN_A\Delta\nu$ /kJ mol^{-1}	br_e/(kJ mol^{-1})$^{1/2}$	A_0 /litre mol^{-1} s^{-1}	$-\Delta H_{e\,min}$ /kJ mol^{-1}	$\Delta H_{e\,max}$ /kJ mol^{-1}
$RO_2^{\bullet}$ + ArOH	1.014	1.49	0.3	13.16	3.20×10^7	49.1	53.6
$(R^1)^{\bullet}$ + ArOH	1.247	1.44	4.1	19.25	1.00×10^8	115.8	280.1
$(R^2)^{\bullet}$ + ArOH	1.247	1.44	4.1	21.00	1.00×10^8	150.7	341.4
RS$^{\bullet}$ + ArOH	1.405	1.39	6.4	17.00	1.00×10^8	55.9	210.9
ROOH + ArOH	0.958	–	−1.0	20.00	1.00×10^9	235.7	302.3
ArO$^{\bullet}$ + R^1H	0.802	1.44	−4.1	15.62	1.00×10^9	179.5	173.3
ArO$^{\bullet}$ + R^2H	0.802	1.44	−4.1	16.84	1.00×10^8	231.5	213.3
ArO$^{\bullet}$ + ROOH	0.986	1.49	−0.3	13.00	3.20×10^7	51.3	52.3
ArO$^{\bullet}$ + ArOH	1.000	1.49	0.0	12.61	1.00×10^9	42.1	42.1
ArO$^{\bullet}$ + RSH	0.712	1.39	−6.4	12.11	1.00×10^8	118.0	95.9
O_2 + ArOH	1.014	1.49	0.3	13.16	2.00×10^9	49.1	53.6

Note. The following notation is used: R^1H is an alkane, R^2H is an alkene.

Table 9. Rate constants of alkyl radical reactions with α-tocopherol (**1**).

Radical	Solvent	k /litre mol^{-1} s^{-1}	Method	Ref.
$CH_2{=}CH(CH_2)_3C^{\bullet}H_2$	2,2,4-trimethylpentane	1.15×10^6	MCR	95
	PhMe	6.0×10^5	MCR	95
	PhOMe – PhMe	4.4×10^5	MCR	95
	MeCN – PhMe	2.3×10^5	MCR	95
	Bu^{t}OH	3.2×10^4	MCR	95
	γ-valerolactone	2.0×10^4	MCR	95
	PhH	1.7×10^6 (see [a])	MCR	96
$Cl_3C^{\bullet}$	CCl_4	4.5×10^6 (see [b])	FP	97
$MeC^{\bullet}HOH$	EtOH	5×10^5	PR	98
$PhCMe_2C^{\bullet}H_2$	Bu^{t}OH	3.2×10^4	MCR	95
	γ-valerolactone	2.0×10^4	MCR	95

Note. MCR is the method of competing reactions, FP is flash photolysis, PR is pulse radiolysis. [a] At 343 K; [b] at 293 K, other at 298 K.

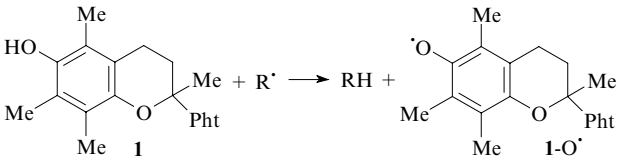


Table 10 lists ΔH_e as well as E and k values calculated by MIP for the reactions of secondary alkyl radicals with a number of phenols. It is clear that the reactions are exothermic for all the phenols. As the enthalpy of a reaction increases, its activation energy also increases (from 12 to 30 kJ mol^{-1}), and the rate constant decreases from 1.0×10^6 to 1.6×10^3 litre mol^{-1} s^{-1}.

Table 10. Thermodynamic and kinetic parameters of the reactions

ArOH + *sec*-R$^{\bullet}$ ⟶ RH + ArO$^{\bullet}$,

calculated using MIP (D_{R-H} = 412.0 kJ mol^{-1}, $A_0 = 1.00 \times 10^8$ litre mol^{-1} s^{-1}).[67]

Phenol	$-\Delta H_e$ (see [a])	E (see [b])	k (310 K) /litre mol^{-1} s^{-1}	$r^{\neq}_{ArO-H} \times 10^{10}$ /m	$r^{\neq}_{C-H} \times 10^{10}$ /m
1	77.9	15.3	2.63×10^5	1.151	1.502
2	72.6	17.5	1.12×10^5	1.157	1.496
3	73.0	17.4	1.19×10^5	1.156	1.497
4	66.4	20.2	3.99×10^4	1.163	1.490
8b	79.5	14.7	3.39×10^5	1.149	1.504
11	86.5	11.9	1.01×10^6	1.142	1.511
18	44.3	30.2	1.60×10^3	1.186	1.467
20	64.9	20.8	3.10×10^4	1.165	1.488
21	61.7	22.2	1.79×10^4	1.168	1.485
22	75.6	16.3	1.82×10^5	1.153	1.499
24	50.8	27.2	2.63×10^3	1.179	1.473
25	67.0	19.9	4.41×10^4	1.163	1.490
27	59.8	23.1	1.29×10^4	1.170	1.483
28	54.1	25.7	4.74×10^3	1.176	1.477
37	56.6	24.5	1.48×10^4	1.173	1.479

[a] ΔH values are given in kJ mol^{-1}; [b] E values are in kJ mol^{-1}.

Reactions of thiyl radicals. Thiyl radicals emerge in proteins as a result of interaction of various radicals with the thiol groups of L-cysteine. The reactions of thiyl radicals with phenols are not studied, yet they are important in the total balance of radical conversions involving natural phenols. The activation energies and rate constants for these reactions were calculated theoretically by using MIP.[67] The calculation results are listed in Table 11.

It can be seen that among these reactions there are both endothermic and exothermic ones; their activation energies vary from 13 to 36 kJ mol^{-1}, and the rate constants range from 86 to 7.6×10^5 litre mol^{-1} s^{-1}.

Reactions of phenols with diphenylpicrylhydrazyl. Reactions of a variety of stable radicals with phenols are often employed for the assessment of the effectiveness of the latter as antioxidants. A complete summary of such reactions is available.[99] The reaction of phenols with diphenylpicrylhydrazyl (diphenylpicrylhydrazyl is a stable radical with a high extinction coefficient: ε = 9660 litre mol^{-1} cm^{-1} at λ = 516 nm) can be mentioned as an example.

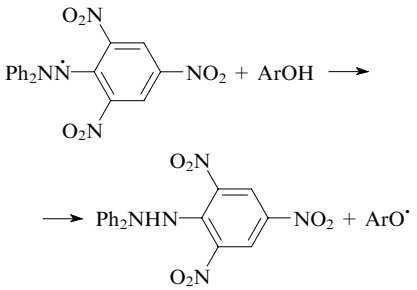
Table 11. Thermodynamic and kinetic parameters of the reactions

ArOH + RS$^{\bullet}$ ⟶ RSH + ArO$^{\bullet}$,

calculated using MIP (RS$^{\bullet}$ is the thiyl radical of L-cysteine, D_{RS-H} = 360 kJ mol^{-1}, $A_0 = 1.00 \times 10^8$ litre mol^{-1} s^{-1}).[67]

Phenol	ΔH_e (see [a])	E (see [b])	k (310 K) /litre mol^{-1} s^{-1}	$r^{\neq}_{ArO-H} \times 10^{10}$ /m	$r^{\neq}_{RS-H} \times 10^{10}$ /m
1	−23.6	17.0	1.38×10^5	1.148	1.666
2	−18.3	19.8	4.66×10^4	1.155	1.659
3	−18.7	19.6	5.06×10^4	1.154	1.660
4	−12.1	23.2	1.25×10^4	1.163	1.651
8b	−25.2	16.1	1.91×10^5	1.146	1.668
11	−32.2	12.6	7.62×10^5	1.137	1.677
18	10.0	36.0	8.59×10^1	1.190	1.624
20	−10.6	24.0	9.04×10^3	1.164	1.650
21	−7.4	25.8	4.50×10^3	1.168	1.646
22	−21.3	18.2	8.65×10^4	1.151	1.663
24	3.5	32.1	3.88×10^2	1.182	1.632
25	−12.7	22.8	1.42×10^4	1.162	1.652
27	−5.5	26.9	2.96×10^3	1.171	1.643
28	0.2	30.2	8.25×10^2	1.178	1.636
37	−2.3	28.7	1.45×10^3	1.175	1.639

[a] ΔH values are given in kJ mol^{-1}; [b] E values are in kJ mol^{-1}.



The weaker the O−H-bond of a phenol the faster the process. The rate constants (in litre mol^{-1} s^{-1}) of this reaction with a number of phenols (MeOH, 298 K) are listed below.[100]

Phenol	k	Phenol	k
17	2.35×10^3	**36**	2.29×10^3
20	4.76×10^2	**47**	1.14×10^2
21	4.89×10^2	**48**	4.40×10^3
26	2.20×10^2	**49**	0.1
27	5.30×10^2	**50**	6.30×10^2
32	7.55×10^1	**51**	4.0

VI. Oxidation of phenols with oxygen, ozone and peroxides

Reactions of phenols with oxygen. Phenols react with oxygen in the following way:

ArOH + O_2 ⟶ ArO$^{\bullet}$ + $HO_2^{\bullet}$,

to generate reactive radicals $HO_2^{\bullet}$ that initiate chain oxidation.[1,2] This reaction is very endothermic since the H−O_2

bond that is formed ($D = 220$ kJ mol^{-1}) is much weaker than the O–H bond in phenols (see Table 2). The activation energy of this reaction, according to MIP, is virtually equal to its enthalpy ($E = \Delta H + 0.5\,RT$), and the pre-exponential factor depends on ΔH.[101] The kinetic parameters for the reactions of tocopherols **1**–**4** with oxygen at 310 and 400 K as calculated by MIP are provided below.

Parameter	Phenol			
	1	**2**	**3**	**4**
ΔH /kJ mol^{-1}	110.0	115.3	114.9	121.5
A /litre mol^{-1} s^{-1}	7.36×10^{10}	8.36×10^{10}	8.29×10^{10}	9.58×10^{10}
k (310 K) /litre mol^{-1} s^{-1}	1.30×10^{-8}	1.89×10^{-9}	2.18×10^{-9}	1.95×10^{-10}
k (400 K), /litre mol^{-1} s^{-1}	1.9×10^{-4}	4.40×10^{-5}	4.92×10^{-5}	7.82×10^{-6}

It is evident that at 310 K the rate constants for the reactions involving tocopherols are very low. At [TcOH] = 1×10^{-3} mol litre^{-1} and [O_2] = 2×10^{-3} mol litre^{-1}, the rate (v_i) of radical generation in the case of α-tocopherol (**1**) is just 2.6×10^{-14} mol litre^{-1} s^{-1}. However, because of a high activation energy, with an increase in temperature the rate of such a reaction increases by a large factor, and $v_i = 3.8\times10^{-10}$ mol litre^{-1} s^{-1} at 400 K.

Reactions of phenols with ozone. Ozone is a very active oxidant. With phenols it reacts as follows:[1,2]

$$ArOH + O_3 \longrightarrow ArO^{\bullet} + HO_3^{\bullet}.$$

The O–H bond in the radical $HO_3^{\bullet}$ formed is sufficiently strong (D_{O-H} = 350.4 kJ mol^{-1}),[1,2] hence such reactions are as a rule exothermic and proceed rather rapidly. For a number of phenols the activation energies and rate constants were calculated by MIP.[102] The primary reaction product is a phenoxyl radical, which was proved by EPR, particularly, by the example of α-tocopherol oxidation.[103] Table 12 shows the results of a kinetic study of the reaction of compound **1** with ozone by the stopped-flow method.

As follows from the data listed in Table 12, α-tocopherol (**1**) reacts with ozone in acetonitrile more slowly than in CCl_4 due to the formation of a hydrogen bond between the O–H group of the phenol and a molecule of the solvent (see above). The concentration of protons in H_2O affects the reaction rate: the higher pH the higher the oxidation rate of compound **1**. Obviously, this is related to the acidic dissociation of phenol **1** and the emergence of a new route of its oxidation by electron transfer from the α-tocopherol anion to the molecule of ozone.

$$TcOH + H_2O \rightleftharpoons TcO^- + H_3O^+,$$

$$TcO^- + O_3 \longrightarrow TcO^{\bullet} + O_3^{-\bullet},$$

$$O_3^{-\bullet} + H_2O \longrightarrow O_2 + HO^{\bullet} + HO^-.$$

Reactions of phenols with peroxides. Phenols react with peroxides resulting in free radicals:[1,2]

$$ArOH + ROOH \longrightarrow ArO^{\bullet} + H_2O + RO^{\bullet}.$$

The reaction of α-tocopherol (**1**) with dibenzoyl peroxide was studied[105] and an analogous mechanism was suggested:

Table 12. Reaction rate constants for the oxidation of α-tocopherol (**1**) and its derivatives with ozone measured by the stopped-flow method.[103,104]

Phenol	Solvent	pH	$k\times10^{-3}$ /litre mol^{-1} s^{-1}
α-Tocopherol (**1**)	CCl_4	–	5.48 ± 0.43
	MeCN	–	1.45 ± 0.08
	MeCN + 5% H_2O	–	33.5 ± 0.5
	SDS	2.3	13
	SDS	2.9	22
	SDS	4.8	110
	SDS	6.3	320
	SDS	6.8	660
	SDS	7.0	750
	SDS	2.3	31[a]
	SDS	4.7	140[a]
	SDS	5.8	320[a]
α-Tocopherol-quinone	CCl_4	–	11.5 ± 0.2
α-Tocopheryl acetate	CCl_4	–	0.14 ± 0.01

Note. SDS is a micellar aqueous solution of sodium dodecyl sulfate.
[a] At 310 K, other at 298 K.

$$TcOH + PhC(O)OOC(O)Ph \longrightarrow TcO^{\bullet} + PhC(O)OH + PhCO_2^{\bullet}.$$

This reaction is endothermic, its enthalpy is:[106]

$$\Delta H = D_{TcO-H} + D_{O-O} - D_{PhCOO-H} =$$
$$= 330.0 + 128.5 - 438.0 = 20.5 \text{ kJ mol}^{-1}.$$

The radical $TcO^{\bullet}$ being formed was detected by EPR. The rate constant for this reaction measured using EPR in n-heptanol in the range 313–353 K, is:[105]

$$k = 4.0\times10^7 \exp\left(-\frac{52\,700}{RT}\right) \text{ litre mol}^{-1}\text{ s}^{-1}.$$

Table 13. Thermodynamic and kinetic parameters of the reaction

$$ArOH + ROOH \longrightarrow ArO^{\bullet} + H_2O + RO^{\bullet},$$

computed by using MIP.[1]

Phenol	ΔH /kJ mol^{-1}	E /kJ mol^{-1}	k /litre mol^{-1} s^{-1}	
			310 K	400 K
1	12.0	89.5	8.28×10^{-7}	2.06×10^{-3}
2	17.3	92.2	2.93×10^{-7}	9.23×10^{-4}
3	16.9	92.0	3.17×10^{-7}	9.81×10^{-4}
4	23.5	95.3	8.56×10^{-8}	3.56×10^{-4}
8b	10.4	88.7	1.13×10^{-6}	2.62×10^{-3}
11	3.4	85.2	4.34×10^{-6}	7.45×10^{-3}
18	45.6	107.0	9.28×10^{-10}	1.07×10^{-5}
20	25.0	96.1	6.34×10^{-8}	2.82×10^{-4}
21	25.2	96.2	6.09×10^{-8}	3.27×10^{-4}
22	14.3	90.6	5.28×10^{-7}	1.46×10^{-3}
24	39.1	103.9	3.59×10^{-9}	3.05×10^{-5}
25	22.9	95.0	9.65×10^{-8}	3.90×10^{-4}
27	30.1	98.8	2.27×10^{-8}	1.27×10^{-4}
28	35.8	101.8	7.09×10^{-9}	5.16×10^{-5}
37	33.3	100.4	1.18×10^{-8}	7.67×10^{-5}

MIP permits the calculation of E and k for the reactions of phenols with peroxides and hydroperoxides.[107,108] Table 13 lists the results of such calculations for a number of natural phenols.

VII. Reactions of phenoxyl radicals

Tocopherols and other bioantioxidants exert not only inhibitory, but also pro-oxidant effect on the oxidation of organic compounds favouring oxidation under certain conditions. This is manifested in an experiment as a maximum on the dependence of the induction period of inhibited oxidation on the concentration of the inhibitor.[2–4,109,110] The effect of dual action of an inhibitor has found theoretical rationale in kinetic schemes of the oxidation of a substrate inhibited by compound **1** in which the involvement of tocopheroxyl radicals in the chain propagation steps is considered.[111,112]

Reactions of phenoxyl radicals with hydroperoxides. The reaction

$$ArO^{\bullet} + ROOH \longrightarrow ArH + RO_2^{\bullet}$$

is reverse to the reaction of chain termination (see Tables 4–6). Since D_{O-H} for hydroperoxides *sec*-ROOH, which equals 365.5 kJ mol^{-1} (Ref. 106), is higher than D_{O-H} of natural phenols (see Table 2), these reactions are endothermic. However, as we can see from the data in Tables 14 and 15, they proceed sufficiently fast (k varies from 1 to 0.01 litre mol^{-1} s^{-1} at room temperature) and can well affect the rate of oxidation. Table 15 lists the results of MIP calculations for kinetic parameters of the reactions of phenoxyl radicals with the hydroperoxide groups of lipids.

Reactions of phenoxyl radicals with the C–H groups of lipids. Another phenoxyl radical-induced reaction of chain propagation that has been investigated is the attack on the C–H bonds of lipids in the α-position with respect to the double bond. Table 16 summarizes experimental data for the reactions of the phenoxyl radicals with the C–H-groups of several unsaturated acids (ethylbenzene and stearic acid are given for comparison), and Table 17 presents enthalpies, activation energies and rate constants for the reaction with the C–H groups of linoleic acid calculated with the use of MIP. These bonds are weak (D_{C-H} = 318 kJ mol^{-1}),[106] their reactions with the phenoxyl radicals are exothermic and nevertheless they proceed with high activation energies.

Reactions of phenoxyl radicals with the S–H group of L-cysteine. The activation energies of the biochemically essential reactions of phenoxyl radicals with the thiol group of L-cysteine, a protein constituent, were estimated for the first time by the present authors.[117] The calculation results are presented in Table 18. These reactions are endothermic although occur quite rapidly. This is facilitated by a low classical potential barrier to this thermoneutral reaction (E_{e0} = 50.0 kJ mol^{-1}). The low value of the potential barrier is due to a combination of two factors. This is the triplet repulsion, which is significant due to the strong O–S bond and increases the activation energy. The other factor is a great difference in electronegativity between the O and S atoms of the reaction site, which conversely reduces the activation energy (see below).

Table 14. Experimental rate constants for the reactions of phenoxyl radicals with hydroperoxides (the stopped-flow method).

Phenoxyl radical	ROOH	ΔH/kJ mol^{-1}	k (298 K)/litre mol^{-1} s^{-1}	E/kJ mol^{-1}	Ref.
1-O$^{\bullet}$	MLHP[a]	35.5	5.0×10^{-1}	44.5	113
	Bu^{t}OOH	28.6	4.1×10^{-1} (see[b])	45.0	114
6c-O$^{\bullet}$	Bu^{t}OOH	32.2	2.6×10^{-1} (see[b])	46.2	114
6d-O$^{\bullet}$	Bu^{t}OOH	–	1.1×10^{-1} (see[b])	48.3	114
6e-O$^{\bullet}$	Bu^{t}OOH	–	1.4×10^{-1} (see[b])	47.7	114
8b-O$^{\bullet}$	Bu^{t}OOH	30.2	3.7×10^{-1}	45.3	113
8e-O$^{\bullet}$	MLHP[a]	28.5	1.3×10^{-1}	47.9	115
9c-O$^{\bullet}$	Pr^{n}OOH	33.6	2.0×10^{-1}	46.8	113
	Pr^{i}OOH	33.6	3.7×10^{-1}	45.3	113
	Bu^{n}OOH	33.6	2.2×10^{-1}	46.6	113
	Bu^{s}OOH	33.6	3.5×10^{-1}	45.4	113
	Bu^{t}OOH	26.7	6.5×10^{-1}	43.9	113
	MLHP[a]	33.6	1.3×10^{-1}	47.9	115
9b-O$^{\bullet}$	Pr^{n}OOH	31.6	2.7×10^{-2}	51.8	113
	Pr^{i}OOH	31.6	6.8×10^{-1}	43.8	113
	Bu^{n}OOH	31.6	3.9×10^{-1}	45.2	113
	Bu^{s}OOH	31.6	6.4×10^{-1}	43.9	113
	Bu^{t}OOH	24.7	1.1	42.6	113
	MLHP[a]	31.6	2.5×10^{-1}	46.3	115
9e-O$^{\bullet}$	Pr^{n}OOH	29.2	2.5×10^{-2}	52.0	113
9d-O$^{\bullet}$	Pr^{n}OOH	29.8	1.3×10^{-1}	47.9	113
	Bu^{n}OOH	29.8	1.34×10^{-1}	47.8	116
	Bu^{s}OOH	29.8	2.42×10^{-1}	46.3	116
	Bu^{t}OOH	22.9	3.65×10^{-1}	45.3	116
9f-O$^{\bullet}$	Pr^{n}OOH	32.3	9.3×10^{-2}	48.7	113
9g-O$^{\bullet}$	Pr^{n}OOH	26.2	8.0×10^{-3}	54.8	113

[a] MLHP is methyl linoleate hydroperoxide. [b] The solvent is EtOH, in the other instances it is benzene.

Table 15. Thermodynamic and kinetic parameters of the reactions

$ArO^{\bullet} + sec\text{-}RO_2H \longrightarrow ArOH + sec\text{-}RO_2^{\bullet}$,

calculated with the use of MIP (D_{ROO-H} = 365.5 kJ mol^{-1}).[117]

Phenoxyl radical	ΔH_e /kJ mol^{-1}	E /kJ mol^{-1}	k (310 K) /litre mol^{-1} s^{-1}	$r^{\neq}_{ArO-H} \times 10^{10}$ /m	$r^{\neq}_{ROO-H} \times 10^{10}$ /m
1-O$^{\bullet}$	35.2	42.4	2.24	1.223	1.132
2-O$^{\bullet}$	29.9	39.3	7.57	1.216	1.139
3-O$^{\bullet}$	30.3	39.5	6.91	1.217	1.138
4-O$^{\bullet}$	23.7	35.8	30.2	1.209	1.146
8b-O$^{\bullet}$	36.8	43.4	1.54	1.225	1.130
11-O$^{\bullet}$	43.8	47.7	2.92×10^{-1}	1.233	1.122
18-O$^{\bullet}$	1.6	23.9	$2.94 \cdot 10^{3}$	1.181	1.174
20-O$^{\bullet}$	22.2	34.9	41.9	1.207	1.148
22-O$^{\bullet}$	32.9	41.1	3.82	1.220	1.135
24-O$^{\bullet}$	8.1	27.3	8.09×10^{2}	1.189	1.166
27-O$^{\bullet}$	17.1	32.1	1.25×10^{2}	1.201	1.155
32-O$^{\bullet}$	24.3	36.1	26.4	1.209	1.148
37-O$^{\bullet}$	13.9	30.3	2.46×10^{2}	1.197	1.158
38-O$^{\bullet}$	11.4	29.0	4.13×10^{2}	1.194	1.162

Table 16. Experimental rate constants of phenoxyl radical reactions with unsaturated acids and their esters.

Phenoxyl radical	Reactant	Solvent	T /K	k /litre mol^{-1} s^{-1}	Ref.
1-O$^{\bullet}$	methyl linoleate	PhH	323	7.5×10^{-2}	118
	"	EtOH	310	2.7×10^{-2}	114
	ethylbenzene	n-C_7H_{16}	293	5.0×10^{-3}	119
	stearic acid	n-C_7H_{16}	293	2.8×10^{-2}	119
	methyl oleate	n-C_7H_{16}	293	2.5×10^{-1}	119
	linoleic acid	n-C_7H_{16}	293	1.00×10^{2}	119
	2,6-dimethylocta-2,4,6-triene	n-C_7H_{16}	293	1.94×10^{2}	119
	arachidonic acid	n-C_7H_{16}	293	1.0×10^{4}	119
6d-O$^{\bullet}$	methyl linoleate	EtOH	310	2.5×10^{-3}	114
6e-O$^{\bullet}$	"	EtOH	310	2.8×10^{-3}	114
7g-O$^{\bullet}$	"	PhH	298	2.0×10^{-2}	115
8b-O$^{\bullet}$	"	EtOH	310	2.3×10^{-2}	114
8f-O$^{\bullet}$	"	PhH	298	1.8×10^{-2}	115
9b-O$^{\bullet}$	"	PhH	298	5.0×10^{-2}	120
9c-O$^{\bullet}$	"	PhH	298	2.3×10^{-2}	115
9e-O$^{\bullet}$	"	PhH	298	3.3×10^{-3}	115
9d-O$^{\bullet}$	ethyl oleate	PhH	298	1.0×10^{-5}	120
	methyl linoleate	PhH	298	1.9×10^{-2}	120
	ethyl linoleate	PhH	298	1.8×10^{-2}	120
	ethyl linoleate	PhH	298	3.8×10^{-2}	120
	ethyl arachidonate	PhH	298	4.8×10^{-2}	120
	cis-docosa-4,7,10,13,16,19-hexaenoic acid	PhH	298	9.1×10^{-2}	120
9f-O$^{\bullet}$	methyl linoleate	PhH	298	1.6×10^{-2}	120
9g-O$^{\bullet}$	"	PhH	298	1.1×10^{-3}	120
18-O$^{\bullet}$	"	EtOH	310	2.4×10^{-1}	114

Reactions of semiquinone radicals with oxygen. Among bioantioxidants, the derivatives of 1,2-di- and 1,2,3-trihydroxybenzenes are rather abundant (see Fig. 1). These compounds produce semiquinone radicals that possess high reducing abilities. Such radicals, in particular, react with oxygen to generate the reactive radicals $HO_2^{\bullet}$ (Ref. 1), which, naturally, decreases the inhibitory activity of a phenol. For instance, for *p*-hydroquinone the rate constant for the reaction



is 4.7×10^{2} litre mol^{-1} s^{-1} (experimental data, styrene, 323 K).[31] For *o*-hydroquinone, the rate constant for such a reaction was calculated using MIP:

$$k = 6.4 \times 10^{7} \exp\left(-\frac{47600}{RT}\right) = 0.6 \text{ litre mol}^{-1} \text{ s}^{-1} \text{ (310 K)},^{31}$$

Table 17. Thermodynamic and kinetic parameters of the reactions

$ArO^{\bullet}$ + n-$C_5H_{11}CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H \longrightarrow ArOH$ + n-$C_5H_{11}CH{=}CHC^{\bullet}HCH{=}CH(CH_2)_7CO_2H$,

calculated using MIP (D_{R-H} = 318.0 kJ mol^{-}).[117]

Phenoxyl radical	$-\Delta H_e$/kJ mol^{-1}	E/kJ mol^{-1}	k (310 K)/litre mol^{-1} s^{-1}	$r^{\neq}_{ArO-H} \times 10^{10}$/m	$r^{\neq}_{C-H} \times 10^{10}$/m
1-O$^{\bullet}$	16.1	64.3	1.48×10^{-3}	1.437	1.270
2-O$^{\bullet}$	21.4	62.0	3.51×10^{-3}	1.432	1.275
3-O$^{\bullet}$	21.0	62.2	3.29×10^{-3}	1.433	1.274
4-O$^{\bullet}$	27.6	59.5	9.43×10^{-3}	1.398	1.309
8b-O$^{\bullet}$	14.5	64.9	1.14×10^{-3}	1.439	1.268
11-O$^{\bullet}$	7.5	67.9	3.55×10^{-4}	1.445	1.262
18-O$^{\bullet}$	49.7	50.8	2.73×10^{-1}	1.377	1.330
20-O$^{\bullet}$	29.1	58.9	1.19×10^{-2}	1.397	1.310
22-O$^{\bullet}$	18.4	63.3	2.16×10^{-3}	1.435	1.272
24-O$^{\bullet}$	43.2	53.3	1.04×10^{-1}	1.384	1.323
27-O$^{\bullet}$	34.2	56.8	2.64×10^{-2}	1.392	1.318
32-O$^{\bullet}$	27.0	59.7	8.58×10^{-3}	1.399	1.308
37-O$^{\bullet}$	37.4	55.6	4.33×10^{-2}	1.389	1.318
38-O$^{\bullet}$	39.9	54.6	6.33×10^{-2}	1.387	1.320

Table 18 Thermodynamic and kinetic parameters of the reactions

$ArO^{\bullet}$ + RSH $\longrightarrow$ ArOH + $RS^{\bullet}$,

computed by using MIP ($RS^{\bullet}$ is the thiyl radical of L-cysteine, D_{RS-H} = 360 kJ mol^{-1}).[117]

Phenoxyl radical	ΔH_e/kJ mol^{-1}	E/kJ mol^{-1}	k (310 K)/litre mol^{-1} s^{-1}	$r^{\neq}_{ArO-H} \times 10^{10}$/m	$r^{\neq}_{RS-H} \times 10^{10}$/m
1-O$^{\bullet}$	23.6	46.7	1.32	1.665	1.148
2-O$^{\bullet}$	18.3	44.3	3.47	1.658	1.155
3-O$^{\bullet}$	18.7	44.4	3.23	1.659	1.154
4-O$^{\bullet}$	12.1	41.4	1.05×10^{1}	1.650	1.163
8b-O$^{\bullet}$	25.2	47.5	9.82×10^{-1}	1.667	1.146
11-O$^{\bullet}$	32.2	51.0	2.59×10^{-1}	1.676	1.137
18-O$^{\bullet}$	−10.0	32.2	3.76×10^{2}	1.623	1.190
20-O$^{\bullet}$	10.6	40.8	1.34×10^{1}	1.649	1.644
22-O$^{\bullet}$	21.3	45.7	2.02	1.662	1.151
24-O$^{\bullet}$	−3.5	34.8	1.37×10^{2}	1.631	1.182
27-O$^{\bullet}$	5.5	38.6	3.18×10^{1}	1.642	1.171
32-O$^{\bullet}$	12.7	41.7	9.34	1.651	1.162
37-O$^{\bullet}$	2.3	37.2	5.39×10^{1}	1.638	1.175
38-O$^{\bullet}$	−0.2	36.1	8.09×10^{1}	1.635	1.178

and for α-tocopherolhydroquinone (**46**) $k = 9.5 \times 10^{2}$ litre mol^{-1} s^{-1} (298 K).[120] This reaction does occur with natural phenols containing hydroxy groups in positions 1 and 2, as indicated by cases with $f < 2$ (see Table 3).

Exchange reactions of phenoxyl radicals with phenols. Hydrogen exchange reaction between a phenol and a phenoxyl radical

$$Ar^1O^{\bullet} + Ar^iOH \longrightarrow Ar^1OH + Ar^iO^{\bullet}$$

occurs exceptionally fast. It is evident from a comparison of rate constants for the reactions of the $PhO^{\bullet}$ and $RO_2^{\bullet}$ radicals with tocopherols (in parentheses, the reaction temperature in K is indicated):[121]

Tocopherol	k/litre mol^{-1} s^{-1}	
	$PhO^{\bullet}$ (293)	$RO_2^{\bullet}$ (303)
1	1.10×10^{9}	1.20×10^{6}
2	9.4×10^{8}	5.9×10^{5}
3	2.5×10^{8}	1.4×10^{6}
4	5.6×10^{7}	4.4×10^{5}

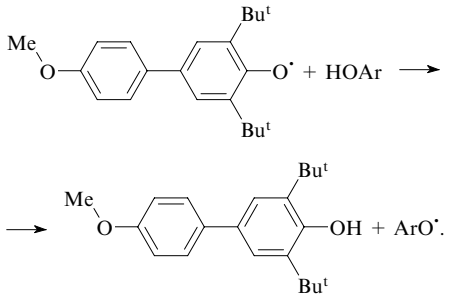
Although the above-mentioned reactions are similar as regards their enthalpies (D_{PhO-H} = 369 kJ mol^{-1}, D_{ROO-H} = 365.5 kJ mol^{-1}), and their transition state has

the same reaction site O···H···O, the abstraction reaction of the H atom by a phenol is two orders of magnitude faster. The exchange reactions between a phenol and a phenoxyl are characterized by a lower activation energy (see below) and a higher pre-exponential factor ($A = 1.0 \times 10^9$ litre mol^{-1} s^{-1} *vs.* 3.2×10^7 litre mol^{-1} s^{-1} for the reactions of phenols with $RO_2^{\bullet}$). Presumably, the exchange reaction like the reaction of $RO_2^{\bullet}$ with a phenol proceeds through preliminary formation of a hydrogen bond between reactants

$$Ar^1O^{\bullet} + Ar^iOH \overset{K_H}{\rightleftharpoons} Ar^1O^{\bullet}\cdots HOAr^i,$$

$$Ar^1O^{\bullet}\cdots HOAr^i \longrightarrow Ar^1OH + Ar^iO^{\bullet},$$

and the rate constant for the formation of a hydrogen bond between a phenol and a phenoxyl is much higher than that between $RO_2^{\bullet}$ and a phenol. A greater isotope effect for the exchange reaction (EtOH/EtOD, $T = 298$ K) is also concordant with such a mechanism.[122]



For this reaction, the ratios k_H/k_D are 22.9 (for compound **1**), 15.0 (for **2**), 15.0 (for **3**), 15.6 (for **4**) and 18.4 (for **12**). In aqueous solution, the exchange occurs through phenol ionization and electron transfer from a phenoxide ion to a phenoxyl radical. Table 19 lists rate constants for the exhange reactions between the phenoxyl radicals and natural phenols. More comprehensive data on such reactions can be found in the database [57] and a review.[123]

Table 20 shows the activation energies and rate contants for the exchange reactions between the phenoxyl radicals of natural phenols and α-tocopherol that were calculated by MIP.

Disproportionation of phenoxyl radicals. Phenoxyl radicals produced by reactions of phenols with the peroxyl radicals undergo a variety of disproportionation reactions with each other. The reaction mechanism depends on the structure of phenoxyl radicals; this issue is addressed in monographs [1, 2, 45] and reviews.[44, 130] In the case of phenoxyl radicals generated from natural phenols, two mechanisms predominate.

1. For 2- and 4-hydroxyphenoxyl radicals, the disproportionation with the formation of the corresponding quinone and the original phenol is typical. For example, for the ubiquinol radicals **5a**:

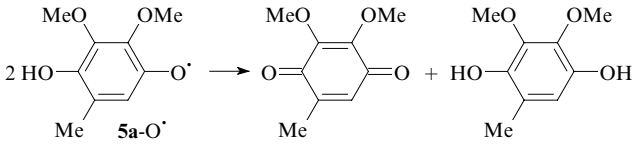


Table 19. Rate constants for the reactions of phenoxyl radicals with phenols.

Phenoxyl radical	Phenol	Solvent (pH)	T/K	k/litre mol^{-1} s^{-1}	Method	Ref.
PhO$^{\bullet}$	**1**	$Bu^t_2O_2$ – PhH, 3 : 1	298	1.1×10^9	FP	121
	1	$Bu^t_2O_2$ – MeCN, 2 : 1	298	3.1×10^8	FP	121
	3	$Bu^t_2O_2$ – PhH, 3 : 1	298	2.5×10^8	FP	121
	3	$Bu^t_2O_2$ – MeCN, 2 : 1	298	8.9×10^7	FP	121
	4	$Bu^t_2O_2$ – MeCN, 2 : 1	298	2×10^7	FP	121
	5a	$Bu^t_2O_2$ – PhH, 3 : 1	298	9.1×10^7	FP	121
	5e	$Bu^t_2O_2$ – PhH, 3 : 1	298	8.4×10^7	FP	121
	7d	H_2O (7)	298	4.1×10^8	PR	125
1-O$^{\bullet}$	**5e**	PhH	298	3.7×10^5	FP	124
	5e	EtOH	298	2.2×10^5	FP	124
7d-O$^{\bullet}$	**33**	H_2O (7)	293	3.3×10^4	PR	88
	39	H_2O (7)	293	3.3×10^4	PR	88
8a-O$^{\bullet}$	**5e**	PhH	298	4.4×10^5	FP	124
	5e	EtOH	298	2.7×10^5	FP	124
9c-O$^{\bullet}$	**5e**	PhH	298	2.9×10^5	FP	124
	5e	EtOH	298	1.4×10^5	FP	124
9d-O$^{\bullet}$	**5e**	PhH	298	8.5×10^4	FP	124
	5e	EtOH	298	3.6×10^4	FP	124
	24	EtOH	298	10^{-1}	FP	126
	24	$Pr^iOH - H_2O$, 5 : 1	298	10^{-2}	FP	126
	34	EtOH	298	1.03×10^1	FP	126
	34	$Pr^iOH - H_2O$, 5 : 1	298	7.40	FP	126
	20	EtOH	298	2.98×10^4	FP	126
	20	$Pr^iOH - H_2O$, 5 : 1	298	2.93×10^4	FP	126
	5e	EtOH	298	3.64×10^4	FP	126
	5e	$Pr^iOH - H_2O$, 5 : 1	298	5.33×10^4	FP	126
9e-O$^{\bullet}$	**5e**	PhH	298	1.6×10^4	FP	124
	5e	EtOH	298	8.6×10^3	FP	124
9f-O$^{\bullet}$	**5e**	PhH	298	7.7×10^4	FP	124
	5e	EtOH	298	3.5×10^4	FP	124

Table 19 (continued).

Phenoxyl radical	Phenol	Solvent (pH)	T/K	k /litre mol^{-1} s^{-1}	Method	Ref.
9g-O$^{\bullet}$	**5e**	PhH	298	7.1×10^3	FP	124
	5e	EtOH	298	3.7×10^3	FP	124
	1	Pr^{i}OH – H_2O, 5 : 1	298	1.65×10^4	SF	127
	2	Pr^{i}OH – H_2O, 5 : 1	298	1.09×10^4	SF	127
	3	Pr^{i}OH – H_2O, 5 : 1	298	1.47×10^4	SF	127
	5a	Pr^{i}OH – H_2O, 5 : 1	298	1.88×10^3	SF	127
	5e	Pr^{i}OH – H_2O, 5 : 1	298	7.54×10^3	SF	127
14-$O_2^{-\bullet}$	**21**	H_2O (7, 10)	293	1.1×10^7	PR	88
24-$O_2^{-\bullet}$	**41**	H_2O (3)	293	1.3×10^8	PR	88
	41	H_2O (7)	293	3.5×10^8	PR	88
33-$O_2^{-\bullet}$	**33**	H_2O (7)	293	2.2×10^7	PR	88
	33	H_2O (7)	293	3.8×10^7	PR	88
	33	H_2O (10)	293	1.6×10^8	PR	88
35-$O_2^{-\bullet}$	**7d**	H_2O (7)	293	1.9×10^8	PR	128
54-O$^{\bullet}$	**1**	EtOH	298	5.24×10^2	ESR	129
	17	EtOH	298	1.24×10^3	ESR	129
	18	EtOH	298	1.01×10^4	ESR	129
	20	EtOH	298	1.38×10^3	ESR	129
	25	EtOH	298	1.8×10^1	ESR	129
54-O$^{\bullet}$	**27**	EtOH	298	1.57×10^3	ESR	129
	28	EtOH	298	6	ESR	129
	29	EtOH	298	1.62×10^3	ESR	129
	32	EtOH	298	1.45×10^4	ESR	129
	34	EtOH	298	6.70×10^2	ESR	129
	36	EtOH	298	1.21×10^3	ESR	129
	49	EtOH	298	5	ESR	129

Note. SF is the stopped-flow method.

Table 20. Thermodynamic and kinetic parameters of the exchange reactions

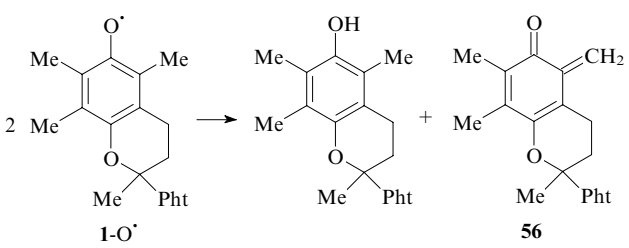
$ArO^{\bullet} + TcOH \longrightarrow ArOH + TcO^{\bullet}$,

calculated with the aid of MIP (D_{TcO-H} = 330 kJ mol^{-1}).[117]

Phenoxyl radical	ΔH_e/kJ mol^{-1}	E/kJ mol^{-1}	k (310 K) /litre mol^{-1} s^{-1}	$r^{\neq}_{TcO-H} \times 10^{10}$ /m	$r^{\neq}_{ArO-H} \times 10^{10}$ /m
1-O$^{\bullet}$	0.0	19.5	5.19×10^5	1.168	1.168
2-O$^{\bullet}$	−5.3	16.9	1.43×10^6	1.161	1.175
3-O$^{\bullet}$	−4.9	17.1	1.32×10^6	1.162	1.174
4-O$^{\bullet}$	−11.5	14.0	4.38×10^6	1.154	1.182
8b-O$^{\bullet}$	1.6	20.3	3.80×10^5	1.170	1.166
11-O$^{\bullet}$	8.6	23.9	9.37×10^4	1.179	1.157
18-O$^{\bullet}$	−33.6	4.5	1.76×10^8	1.125	1.210
20-O$^{\bullet}$	−13.0	13.3	5.82×10^6	1.151	1.184
22-O$^{\bullet}$	−2.3	18.3	8.08×10^5	1.165	1.171
24-O$^{\bullet}$	−27.1	7.1	6.35×10^7	1.134	1.202
27-O$^{\bullet}$	−18.1	11.0	1.42×10^7	1.145	1.191
32-O$^{\bullet}$	−10.9	14.2	3.40×10^6	1.154	1.182
37-O$^{\bullet}$	−21.3	9.6	2.45×10^7	1.141	1.195
38-O$^{\bullet}$	−23.8	8.5	3.71×10^7	1.138	1.198

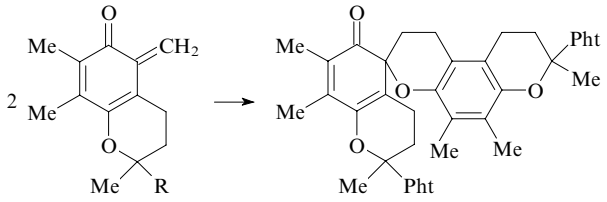
The phenoxyl radicals produced from compounds **5b**–**e**, **19**, **22**, **23**, **26**, **27**, **29**–**34**, **36**–**48** react likewise.

2. For the radicals generated from α-tocopherol and its analogues, a mechanism involving the formation of a labile methylenequinone of the type **56** is valid.[20]



1-O$^{\bullet}$ **56**

The methylenequinone **56** formed is unstable and undergoes rapid dimerization to a more stable quinone **57**.



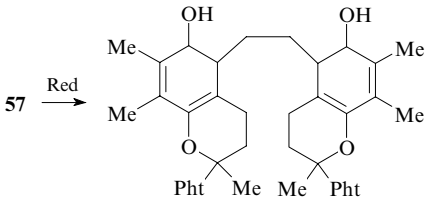
56 **57**

Table 21 provides rate constants for the disproportionation of phenoxyl radicals derived from natural phenols. The majority of measurements was carried out for the α-tocopheroxyl radical. It can be seen that the rate constant for its disproportionation varies within a range of one order of magnitude. Such a data scatter became the subject of special investigation.[20] Using various kinetic approaches and carrying out experiment with the α-tocopheroxyl radical deuterated at the methyl groups in positions 5 and 7, the authors came to the following conclusion:[20] in compound **1**, there is an impurity of (0.5 mol % – 1.5 mol %) of a highly reactive phenol (XH_2), which rapidly reacts with the α-tocopheroxyl radical thus accelerating its dissappearance through cross-recombination.

$$TcO^{\bullet} + XH_2 \rightleftharpoons TcOH + HX^{\bullet},$$

$$TcO^{\bullet} + {}^{\bullet}XH \longrightarrow TcOH + X.$$

The reduction of quinone **57**, which is a disproportionation product of α-tocopheroxyl radicals, may produce dibasic phenol **58**, which is regarded as the most probable impurity.



58

Red is reducing agent.

The rate constant for a 'pure' disproportionation process of α-tocopheroxyl radicals (chlorobenzene, 288 – 328 K) were calculated with account of the introduced corrections:

$$k = 2.5 \times 10^7 \exp\left(-\frac{25.5}{RT}\right) =$$

$$= 1.26 \times 10^3 \text{ litre mol}^{-1} \text{ s}^{-1} \text{ (310 K)}.^{20}$$

Reactions of phenoxyl radicals with $RO_2^{\bullet}$. The mechanism of the reaction of the radical $RO_2^{\bullet}$ with a phenoxyl radical depends on the structure of the latter; the reaction mechanism is discussed in detail in monographs.[2,45] If positions 2, 4, 6 in a phenoxyl radical are occupied with substituents, then the peroxyl radical adds to one of these positions to yield a quinolide peroxide. The reaction of $RO_2^{\bullet}$ with the α-tocopheroxyl radical and the products formed are considered above.

The reaction of $RO_2^{\bullet}$ with semiquinone radicals leads to quinones, for instance:

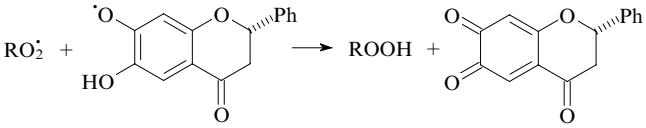


Table 21. Rate constants of the disproportionation of phenoxyl radicals and radical anions, measured by EPR and flash photolysis.

Phenoxyl radical	Solvent (pH)	T /K	$2k$ /litre mol^{-1} s^{-1}	Ref.	Phenoxyl radical	Solvent (pH)	T /K	$2k$ /litre mol^{-1} s^{-1}	Ref.
1-O$^{\bullet}$	$CHCl_3$	298	1.9×10^2	20	**8b**-O$^{\bullet}$	PhH	323	$1.32 \times 10^8 \exp(-29.7/RT)$	135
	$CHCl_3$	298	1.8×10^2	20		PhCl	310	8.9×10^2	20
	cyclo-C_6H_{12}	298	3.5×10^2	20	**17**-$O_2^{-\bullet}$	H_2O (8.5)	298	1.1×10^8	136
	PhH	298	8.8×10^2	20	**20**-O$^{\bullet}$	H_2O (8.5)	298	6.0×10^7	136
	PhH	298	6.0×10^3	20	**21**-O$^{\bullet}$	H_2O	298	1.35×10^7	137
	PhCl	310	5.0×10^3	20	**21**-$O_2^{-\bullet}$	H_2O (11.5)	298	5.3×10^5	138
	PhH	296	3.0×10^3	16	**26**-$O_2^{-\bullet}$	H_2O (8.5)	298	1.3×10^6	136
	PhH	299	$5.37 \times 10^7 \exp(-21.0/RT)$	131	**27**-O$^{\bullet}$	H_2O	298	7.85×10^6	137
	EtOH	293	$1.58 \times 10^8 \exp(-27.6/RT)$	132	**27**-$O_2^{-\bullet}$	H_2O (11.5)	298	5.9×10^5	138
	n-$C_7H_{15}OH$	293	$1.26 \times 10^6 \exp(-18.0/RT)$	132	**29**-$O_2^{-\bullet}$	H_2O (8.5)	298	1.2×10^7	136
	Bu^nOH	298	3.0×10^3	133	**31**-O$^{\bullet}$	H_2O	298	9.6×10^6	137
2-O$^{\bullet}$	PhH	296	4.0×10^4	16		H_2O (6.7)	298	8.0×10^8	139
3-O$^{\bullet}$	PhH	296	4.5×10^4	16	**34**-$O_2^{-\bullet}$	H_2O (8.5)	298	1.0×10^7	136
4-O$^{\bullet}$	PhH	296	1.5×10^5	16	**39**-O$^{\bullet}$	H_2O	298	4.5×10^7	137
6b-O$^{\bullet}$	PhH	296	4.0×10^3	16	**40**-O$^{\bullet}$	H_2O	298	3.15×10^7	137
6f-O$^{\bullet}$	EtOH	310	1.1	114	**41**-O$^{\bullet}$	H_2O	298	2.15×10^7	137
7d-O$^{\bullet}$	H_2O (4.5)	298	1.6×10^7	134	**42**-O$^{\bullet}$	H_2O	298	1.85×10^6	137
	H_2O (5.7)	298	3.6×10^5	134	**43**-O$^{\bullet}$	H_2O	298	7.4×10^5	137
7g-O$^{\bullet}$	EtOH	310	1.1	114	**43**-O$^{\bullet}$	EtOH	310	7.0×10^2	114
8a-O$^{\bullet}$	PhH	296	4.5×10^3	16					

In aqueous solution, $RO_2^{\bullet}$ reacts with a semiquinone radical ion ($Q^{-\bullet}$) with electron transfer, also resulting in a quinone.

$$HQ^{\bullet} + H_2O \rightleftharpoons Q^{-\bullet} + H_3O^+,$$

$$RO_2^{\bullet} + Q^{-\bullet} \longrightarrow RO_2^- + Q.$$

Reactions of $RO_2^{\bullet}$ and $O_2^{-\bullet}$ with phenoxyl radicals occur with high rate constants $\sim(1-5)\times10^8$ litre mol^{-1} s^{-1} (298 K, Table 22).

Synergism. Apart from phenols, such a powerful reductant as ascorbic acid ($AscH_2$) is present in the human organism. It plays an important role in the regeneration of the phenoxyl radicals reducing them by the reactions:[2–4]

$$PhO^{\bullet} + AscH_2 \longrightarrow PhOH + AscH^{\bullet},$$

$$AscH_2 + H_2O \rightleftharpoons AscH^- + H_3O^+,$$

$$PhO^{\bullet} + AscH^- \longrightarrow PhO^- + AscH^{\bullet}.$$

This kind of regeneration of phenols as oxidation inhibitors allows them to exert a continuous retardation effect in optimal concentrations. Table 23 lists rate constants for phenol regeneration reactions.

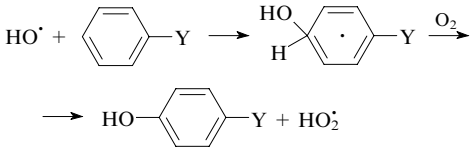
Another pathway of the regeneration of inhibitors is the reaction of hydroperoxyl radicals and the superoxide ion with quinones as the phenol oxidation products.[149] The $HO_2^{\bullet}$ radicals are formed in an organism by several channels. First, upon the oxidation of sugars (*via* the hydroxyperoxyl radicals).

$$R^1R^2C^{\bullet}OH + O_2 \longrightarrow R^1R^2C(OH)O_2^{\bullet} \longrightarrow R^1R^2C(O) + HO_2^{\bullet}.$$

Second, upon the oxidation of proteins as a result of an attack of radicals on the C–H bond in the α-position with respect to the amino group followed by rapid decomposition of the α-aminoperoxyl radical formed.

$$RC^{\bullet}(NH_2)CO_2H + O_2 \longrightarrow RC(O_2^{\bullet})(NH_2)CO_2H \longrightarrow$$
$$\longrightarrow RC{=}NHCO_2H + HO_2^{\bullet}$$

Third, upon the reaction of oxygen with hexadienyl radicals formed upon the addition of the hydroxyl radical to a benzene or heterocyclic ring, for example:



The cyclic mechanism of chain termination involves the following reactions:[149]

$$HO_2^{\bullet} + Q \longrightarrow O_2 + HQ^{\bullet},$$

$$HO_2^{\bullet} + {}^{\bullet}QH \longrightarrow H_2O_2 + Q.$$

Table 22. Rate constants of the reactions $R^{\bullet}$, $RO_2^{\bullet}$ and $O_2^{-\bullet}$ with phenoxyl radicals.

Phenoxyl radical	Reactant	Solvent (pH)	T/K	k/litre mol^{-1} s^{-1}	Method	Ref.
1-O$^{\bullet}$	Bu^{t}CMe(CN)O$_2^{\bullet}$	PhCl	318	$\sim4\times10^8$	ESR	20
	Bu^{t}CMe(CN)O$_2^{\bullet}$	PhCl	318	4.3×10^8	ESR	20
	$O_2^{-\bullet}$	MeOH	298	$\sim1\times10^9$	FP	140
7d-O$^{\bullet}$	HOCMe$_2$CH$_2$O$_2^{\bullet}$	H_2O (9.2)	298	1.6×10^8	PR	141
	$O_2^{-\bullet}$	H_2O (12)	298	5.5×10^8	PR	141
	HOCMe$_2$C$^{\bullet}$H$_2$	H_2O, Bu^{t}OH	298	1.5×108	PR	141
	$O_2^{-\bullet}$	MeOH (7)	298	4.5×10^8	PR	142
	$O_2^{-\bullet}$	H_2O (9.2)	298	5.5×10^8	PR	142
41-$O_2^{-\bullet}$	$O_2^{-\bullet}$	H_2O (6.7)	298	1.6×10^8	PR	139

Table 23. Rate constants of the reduction of phenoxyl radicals with ascorbic acid ($AscH_2$) and the ascorbate ion ($AscH^-$).

Phenoxyl radical	Reactant	Solvent (pH)	T/K	k/litre mol^{-1} s^{-1}	Method	Ref.
1-O$^{\bullet}$	$AscH_2$	PhH–EtOH, 2:1	298	4.9×10	PR	143
	$AscH_2$	PhH–EtOH, 2:1	298	5.49×10^2	SP	144
	$AscH^-$	H_2O/micelles (7.2)	293	9.0×10^5	SP	145
	$AscH^-$	H_2O/micelles (6.8)	298	7.2×10^7	FP	140
	$AscH^-$	H_2O/micelles (7.2)	298	3.8×10^4	FP	140
	$AscH_2$	EtOH	310	1.1×10^5	ESR	114
6a-O$^{\bullet}$	$AscH_2$	EtOH	310	8.3×10^4	ESR	114
6d-O$^{\bullet}$	$AscH_2$	EtOH	310	2.9×10^1	ESR	114
6e-O$^{\bullet}$	$AscH_2$	EtOH	310	3.3×10^1	ESR	114
7d-O$^{\bullet}$	$AscH^-$	H_2O (7.4)	295	1.3×10^7	PR	146
8b-O$^{\bullet}$	$AscH_2$	EtOH	310	9.5×10^4	ESR	114
9b-O$^{\bullet}$	$AscH_2$	PhH–EtOH–H_2O, 2:1:0.1	298	1.7×10^4	SP	147
9d-O$^{\bullet}$	$AscH_2$	PhH–EtOH–H_2O, 2:1:0.1	298	2.3×10^2	SP	147
	$AscH_2$	PhH–EtOH, 2:1	298	5.5×10^2	SP	148
9f-O$^{\bullet}$	$AscH_2$	PhH–EtOH–H_2O, 2:1:0.1	298	3.3×10^2	SP	147
9g-O$^{\bullet}$	$AscH_2$	PhH–EtOH–H_2O, 2:1:0.1	298	7.6×10^1	SP	147
	$AscH_2$	PhH–EtOH, 2:1	298	4.9×10^1	SP	149
	$AscH^-$	H_2O/micelles	298	3.2×10^2	SP	127

Note. SP is stationary photolysis.

VIII. Conclusion

In conclusion, let us summarize the factors that govern the reactivity of phenols in radical reactions.

1. *The enthalpy of reaction*. Low DE of the O−H bond of phenols is often regarded as the primary reason of their high reactivities. However, this is only one of the reasons. The decisive role in the formation of the activation energy is the enthalpy of a process, which depends on both the strength of the O−H bond in a phenol that is attacked and the X−H bond that is formed in the reactions

$$X^{\bullet} + Ar^{i}OH \longrightarrow XH + Ar^{i}O^{\bullet}.$$

Particularly, the DE of the O−H-bond in hydroperoxides depends on the nature of the constituent functional group, which is reflected in the reaction enthalpy and activation energy (see Table 6).

The enthalpy contribution to the activation energy can be estimated within the MIP approach. The classes of reactions of natural phenols that are discussed in the present review can be arranged in order of increasing magnitude of the classical potential barrier to the thermally neutral reaction (E_{e0}, in kJ mol^{-1}) as follows: 39.7 ($ArO^{\bullet}$ + $Ar^{i}OH$) < 42.7 ($RO_2^{\bullet}$ + $Ar^{i}OH$) < 50.0 ($RS^{\bullet}$ + $Ar^{i}OH$) < 73.4 ($R^{\bullet}$ + $Ar^{i}OH$).[1,2] Comparing E and E_{e0}, one can assess the contribution of the enthalpy to the activation energy (ΔE_H). From Eqns (12) and (14), it follows that

$$\Delta E_H = E - E_{e0} + 0.5\,hN_A\nu_{O-H} - 0.5\,RT. \qquad (17)$$

Figure 6 exemplifies a spectrum of the activation energies (E, E_{e0} and ΔE_H) for five reactions involving α-tocopherol (**1**).

In addition to the enthalpy of reaction as an important factor, there are other factors affecting the reaction activation barrier. The existence of such factors follows from a comparison of classical potential barries E_{e0} [see Eqn (14) and the above-given values of E_{e0} for various reaction classes]. It can be seen that reactions of different radicals with phenols substantially differ in their activation energies and at $\Delta H_e = 0$, where the enthalpy of the reaction does not influence its activation energy. The differences in E_{e0} values of the reaction classes considered above are determined by several reasons.[1,2,39,90]

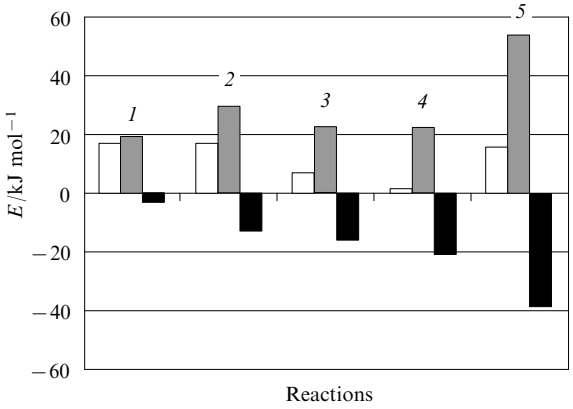


Figure 6. The activation energy spectrum for the reactions of compound **1** with the following radicals: β-tocopheroxyl (*1*), thiyl radical of L-cysteine (*2*), *sec*-$RO_2^{\bullet}$ (*3*), $RC(O)O_2^{\bullet}$ (*4*) and *sec*-$R^{\bullet}$ (*5*). White bars represent the activation energy of a reaction, grey bars represent the activation energy of a thermally neutral analogue of this class of reactions, black bars represent the contribution of the enthalpy of reaction to the activation energy; the corresponding activation energies were calculated by Eqns (10)–(12), (14); the parameters were taken from Table 8.

2. *Triplet repulsion*. One of three electrons of the reaction site ArO···H···X occupies a non-bonding orbital. Hence, the stronger the ArO−X bond the higher the energy of the non-bonding orbital and the greater the classical potential barrier of a thermally neutral reaction (E_{e0}).[1,2,89,90,150] This is well illustrated by comparison of E_{e0} for reaction classes: $ArO^{\bullet}$ + $Ar^{i}OH$ (E_{e0} = 39.7 kJ mol^{-1}) and $RO_2^{\bullet}$ + $Ar^{i}OH$ (E_{e0} = 42.7 kJ mol^{-1}), from one hand, and $R^{\bullet}$ + $Ar^{i}OH$ (E_{e0} = 73.4 kJ mol^{-1}), from the other. As in the hypothetical compounds ArOOAr and ROOAr the dissociation energy of the O−O bond is close to zero, in the transition states of reactions with a reaction site of the O···H···O type the triplet repulsion is also close to zero, and E_{e0} for these classes of reactions has a minimal value (40 and 43 kJ mol^{-1}).[1] At the same time, the strength of the PhO−CH_3 bond is 270 kJ mol^{-1}, which ensures a considerable triplet repulsion in the transition state C···H···O and elevates E_{e0} from 43 kJ mol^{-1} in the reactions $RO_2^{\bullet}$ + $Ar^{i}OH$ to 73.4 kJ mol^{-1} in the reactions $R^{\bullet}$ + $Ar^{i}OH$. The increase in E_{e0} due to triplet repulsion is the greater the stronger is the ArO−X bond. The contribution of triplet repulsion to the activation energy $\Delta E_{e0}(T)$ (kJ mol^{-1}) depends on DE of the ArO−X bond and is described by the empirical equation:[1,89]

$$\Delta E_{e0}(T)\,(\text{kJ mol}^{-1}) = (13.7\times10^{-22})\,b^2(1+\alpha)^{-2}\left(\frac{D_{ArO-X}}{D_{H-H}}\right). \qquad (18)$$

3. *The radii of atoms at the reaction site*. The increase in E_{e0} from 43 kJ mol^{-1} (for the reaction $RO_2^{\bullet}$ + $Ar^{i}OH$) to 51 kJ mol^{-1} (for the reaction $RS^{\bullet}$ + $Ar^{i}OH$) arises from an extra repulsion owing to an increase in the radius of the atom bearing a free valence and attacking a phenol (for comparison, $r_{S-H} = 1.34\times10^{-10}$ m, whereas $r_{O-H} = 0.97\times10^{-10}$ m).[1,2,89] This factor influences the total elongation of reacting bonds in a transition state. For each class of radical reactions, the elongation r_e is a fixed value.[89,90,151] A comparison of r_e(ArO···X) for different classes of reactions involving phenols and phenoxyl radicals demonstrates that this value is minimum for the reactions with the reaction site O···H···O where the triplet repulsion is minimum, the elongation of bonds in the transition state r_e(ArO···OOR) = 0.420×10^{-10} m. For the reactions of the thyil radical with phenols this distance is appreciably longer due to the influence of the bulk of the sulfur atom: r_e(ArO···S) = 0.518×10^{-10} m.

4. *The electronegativities of atoms at the reaction site*. This factor appears in the reactions with reaction sites of the X···H···Y type.[1,2,89] If the X and Y atoms possess different electron affinities, then in the transition state an additional Coulomb attraction develops between them. It is this attraction that lowers the classical potential barrier to the thermally neutral reaction E_{e0}. This is clear from compar-

ison of E_{e0} of reaction classes with the reaction sites X···H···X and X···H···Y, for instance:[1, 89, 90]

Reaction	Reaction site	E_{e0} /kJ mol^{-1}
R$^{\bullet}$ + RH	C···H···C	74.8
$RO_2^{\bullet}$ + RH	O···H···C	56.4
$N^{\bullet}H_2$ + HNR_2	N···H···N	98.6
$Ar_2N^{\bullet}$ + ArOH	N···H···O	29.5
$RO_2^{\bullet}$ + ArOH	O···H···O	43.3
$RO_2^{\bullet}$ + Ar_2NH	O···H···N	39.0

In all the above-cited examples, E_{e0}(X···H···Y) < E_{e0}(X···H···X). The decrease in E_{e0} is the stronger the greater is the difference in the electronegativies of atoms at the reaction site (ΔEA). The dependence of E_{e0} (kJ mol^{-1}) on ΔEA is described by the equation:[89]

$$\Delta E_{e0}(EA)\ (\text{kJ mol}^{-1}) = \\ = -(22.4\times10^{-22})\,b^2(1+\alpha)^{-2}\left(\frac{\Delta EA}{D_{H-H}}\right). \quad (19)$$

5. *π-Bond ajacent to the reaction site*. When a π-bond is near a reaction site, the electron density on it increases as a result of a shift of π-electrons.[89, 90] This augments the transition state energy and, consequently, the activation energy.[151] The contribution of such interaction to the activation energy can be judged by comparing E_{e0} for reaction classes: ArO$^{\bullet}$(RO$^{\bullet}$, $RO_2^{\bullet}$) + R^1H and ArO$^{\bullet}$(RO$^{\bullet}$, $RO_2^{\bullet}$) + R^2H, where R^1H are alkanes, and R^2H are alkenes with alkyl substituents.[1, 89]

Reaction	E_{e0} /kJ mol^{-1}		ΔE_{e0} /kJ mol^{-1}
	R^1H	R^2H	
ArO$^{\bullet}$ + RH	73.4	87.3	13.9
RO$^{\bullet}$ + RH	51.2	64.1	12.9
$RO_2^{\bullet}$ + RH	61.5	74.7	13.2

It is evident that π-interaction increases E_{e0} by 13.3 ± 0.4 kJ mol^{-1}.

6. *Steric factor*. This factor arises in those cases where bulky substituents are near the reaction site in a reactant. Among phenols, 2,6-di-*tert*-alkylphenols and the corresponding phenoxyl radicals belong to such reagents.[1, 2, 89] The E_{e0} values for the classes of the reactions involving unhindered (Ar^1OH) and sterically hindered (Ar^2OH) phenols are listed below.

Radical	E_{e0} /kJ mol^{-1}		ΔE_{e0} /kJ mol^{-1}
	X$^{\bullet}$ + Ar^1OH	X$^{\bullet}$ + Ar^2OH	
R$^{\bullet}$	62.9	85.4	12.5
ROO$^{\bullet}$	43.3	51.1	7.8
$Ar^1O^{\bullet}$	39.7	43.6	3.9
$Ar^2O^{\bullet}$	43.6	51.6	8.0

It is evident that in every case E_{e0}(X$^{\bullet}$ + Ar^2OH) > E_{e0}(X$^{\bullet}$ + Ar^1OH), and the difference between them, *i.e.*, the contribution of the steric factor to the activation energy, varies from 4 to 12 kJ mol^{-1}.

Thus, the reactivity of phenols in radical reactions depends on a whole set of factors, among which not only DE of the O−H bond, but also characteristics of the X−H and ArO−X bonds, the presence of substituents adjacent to the reaction site as well as the capability of molecules surrounding a phenol to form hydrogen bonds, from one hand, and to induce the phenol ionization, from the other, are essential.

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