Russian Chemical Reviews

October 1981

Translated from *Uspekhi Khimii*, 50, 1721-1809 (1981)

U.D.C. 547.172

Chemical and Biological Kinetics

N.M.Emanuel'

Examples of the application of the methods and ideas of chemical kinetics in various branches of chemistry and biology are considered and the results of studies on the kinetics and mechanisms of atuoxidation and inhibited and catalysed oxidation of organic substances in the liquid phase are surveyed. Problems of the kinetics of the ageing of polymers and the principles of their stabilisation are discussed and certain trends in biological kinetics (kinetics of tumour growth, kinetic criteria of the effectiveness of chemotherapy, problems of gerontology, etc.) are considered.
The bibliography includes 281 references.

CONTENTS

I.	Introduction	901
II.	Kinetics of the liquid-phase oxidation reactions of organic substances	902
III.	Kinetics of the ageing of polymers and their stabilisation	921
IV.	Kinetics of biological processes	928

I. INTRODUCTION

Approximately half a century ago a new branch of natural science began to be formulated in various countries, namely chemical physics, which deals with the physical principles of chemistry and includes the physics of the structure of matter and of chemical reactions (chemical kinetics).

In 1931 Academician N.N.Semenov founded in the USSR the Institute of Chemical Physics of the USSR Academy of Sciences which has since celebrated its 50th anniversary. In this Institute, which has a long tradition in the field of kinetic research, general kinetics have been developed in many directions. At the time of the organisation of the Institute the studies of a group of scientists working under Semenov's supervision at the Physicotechnical Institute in Leningrad led to the discovery of branched chain reactions and laid the foundations of the theory of chain inflammation and thermal explosion. These scientific advances rapidly received high recognition in world science. They have occupied an important place as the foundation of Soviet chemical physics, which is distinguished by specific research into the kinetics and mechanisms of chemical reactions and combustion and explosive processes.

A quantitatively rigorous general theory of chemical chain reactions was created. This theory deals with the quantitative aspects of unbranched chain processes which have become the object of studies in chemical kinetics at the beginning of this century as a result of the outstanding research of Bodenstein and Nernst. The theory of chain termination on walls and within the space of the reaction vessel has been developed in the Institute of Chemical Physics of the USSR Academy of Sciences for unbranched chain reactions and the general case of chain termination in space and on the surface has been considered theoretically. Differential equations and their integral forms, whereby chain propagation can be described as a function of time, i.e. the

kinetics of chain reactions can be described, have been obtained. A theory of branched chain processes has been particularly thoroughly developed for the case of chain branching as a result of the multiplication of active centres (atoms and radicals) in the chemical interaction of active centres with molecules as well as a theory of energetic chain branching due to the excess energy of the reaction products (in the 1960's). Many new phenomena characteristic of branched chain processes have received a clear physical interpretation and a theoretical foundation. These are in the first place a theory of the lower and upper inflammation limits and the discovery of an unusual form of the regions of the chain inflammation of combustible gases in the form of "peninsulas" in terms of pressure–temperature variables.

A theory of degenerate branched chain reactions has been created. This theory made it possible to understand and describe quantitatively many instances of the slow development of a chain avalanche which does not lead to the inflammation of the combustible gas mixture. Subsequently many slow oxidation reactions of organic substances, initially in the gas phase and then in a condensed phase (in the liquid state and in solid polymers) were examined from the standpoint of this theory.

Much attention has been devoted to the study of the detailed chemical mechanisms of chain reactions, the identification of free atoms and radicals, the determination of their concentrations, and the study of elementary processes involving them.

The Institute of Chemical Physics has made a fundamental contribution to the theory of combustion and explosive processes, the thermal explosion of gases and condensed explosives, the propagation of flame in connection with the kinetics of chemical combustion reactions, and the detonation theory.

The mathematical apparatus of general kinetics consist of systems of differential kinetic equations including time as an independent variable.

A system of the type

$$\frac{dF_i}{dt} = f_i(F_1, F_2, \ldots F_n; t; a_1, a_2, \ldots a_m)$$

taking into account, when necessary, also heat and mass transfer, makes it possible to describe the kinetics of a wide variety of processes in chemistry, physics, biology, and geology. In this equation F_i are quantities varying with time and characterising the properties of the system, t is the time, and a_1, a_2, ..., a_m is a set of constant parameters. If the equations can be integrated in terms of quadratures, a set of formulae is obtained for the description of the kinetic curves for the process under consideration:

$$F_i(t) = \int_{t_0}^{t} \frac{dF_i}{dt} dt \quad .$$

The laws governing the development of gas-phase reactions represent the most complete field of general kinetics. Despite their enormous theoretical and practical importance, the kinetics of chemical reactions in condensed systems (liquid and solid) have been less thoroughly developed. The kinetics of biological processes have been still less developed.

This review is devoted to the kinetics of liquid-phase reactions in relation to the oxidation of organic substances, the chemical physics of the ageing and stabilisation of polymers, and the kinetics of certain biological processes.

II. KINETICS OF THE LIQUID-PHASE OXIDATION REACTIONS OF ORGANIC SUBSTANCES

During the last quarter of the century, considerable progress has been achieved in the kinetics and mechanisms of the oxidation processes of organic substances in the liquid phase.

1. Chemical Oxidation Mechanism

As a result of numerous studies throughout the world, the fundamental oxidation mechanism has been established. It includes elementary stages involving chain initiation (the formation of primary free radicals), chain propagation—the so-called "degenerate" branching, which lags behind the time of propagation of the main chain, the molecular decomposition of the peroxide with formation of a wide variety of oxidation products, and chain termination, which consists as a rule in the recombination of the radicals $RO_2^{\cdot}$.

The oxidation reaction does not always occur in an "unperturbed" form of this kind. In many instances the oxidation takes place in the presence of various inhibitors and catalysts, so that the overall oxidation mechanism is significantly complicated. In the general case account must be taken of the reactions of the active radicals $RO_2^{\cdot}$ and $R^{\cdot}$ as well as hydroperoxides with inhibitors and their reaction products, the set of elementary processes occurring in the presence of more than one inhibitor in the system, the complex formation reactions of homogeneous and heterogeneous catalysts with virtually all the starting materials, intermediates, and final products, and the reactions of the resulting complexes.

Thus the oxidation mechanism can be represented by the following set of elementary reactions in the most general form[1–4].

Autoxidation

$$2RH + O_2 \xrightarrow{k_0} 2R^{\cdot} + H_2O \ , \qquad (0)$$

$$RH + O_2 \xrightarrow{k_0'} R^{\cdot} + HO_2^{\cdot} \ , \qquad (0')$$

$$R^{\cdot} + O_2 \xrightarrow{k_1} RO_2^{\cdot} \ , \qquad (1)$$

$$R^{\cdot} \xrightarrow{k_{1'}} R_1^{\cdot} + P_1 \ , \qquad (1')$$

$$RO_2^{\cdot} + RH \xrightarrow{k_2} ROOH + R^{\cdot} \ , \qquad (2)$$

$$RO_2^{\cdot} \xrightarrow{k_{2'}} R'COH + R''O^{\cdot} \ , \qquad (2')$$

$$RO_2^{\cdot} + ROOH\ (ROH,\ R'COR'') \xrightarrow{k_{2''}} R^{\cdot} + P_2 \ , \qquad (2'')$$

$$ROOH \rightarrow RO^{\cdot} + {}^{\cdot}OH \ , \qquad (3)$$

$$ROOH + RH\ (R_1COOH,\ R'COR'',\ \ldots) \xrightarrow{k_{3'}} 2R^{\cdot} + P_3 \ , \qquad (3')$$

$$ROOH + ROOH \xrightarrow{k_{3''}} RO^{\cdot} + RO_2^{\cdot} + H_2O \ , \qquad (3'')$$

$$R^{\cdot}\ (R^{\cdot},\ RO^{\cdot},\ {}^{\cdot}OH) + RH \rightarrow R_1^{\cdot} + R'H\ (R''H,\ ROH,\ H_2O) \ , \qquad (4)$$

$$ROOH \rightarrow P_4 \ , \qquad (5)$$

$$RO_2^{\cdot} + RO_2^{\cdot} \rightarrow P_5 \ , \qquad (6)$$

$$RO_2^{\cdot} \rightarrow \dot{\rho} \ . \qquad (6')$$

Inhibited oxidation

$$RO_2^{\cdot} + InH \rightarrow In^{\cdot} + ROOH \ , \qquad (7)$$

$$\dot{R} + InH \rightarrow In^{\cdot} + RH \ , \qquad (7')$$

$$\dot{R} + Q \rightarrow P_6 \ , \qquad (7'')$$

$$ROOH + \rangle SH\ (\rangle PH) \rightarrow P_7 \ , \qquad (7''')$$

$$R\dot{O}_2 + In^{\cdot} \rightarrow InOOR \ . \qquad (8)$$

Catalysed oxidation

$$Cat + O_2 \rightleftharpoons Cat \ldots O_2 \xrightarrow{+RH} \dot{R} \ , \qquad (9)$$

$$Cat + RH \rightleftharpoons Cat \ldots RH \xrightarrow{+O_2} \dot{R} \ , \qquad (10)$$

$$Cat + R\dot{O}_2 \rightarrow Cat \ldots R\dot{O}_2 \begin{cases} \xrightarrow{+RH} P_8 + \dot{R} \ , & (11) \\ \longrightarrow \text{chain termination.} & (12) \end{cases}$$

Here $\dot{p}$ is an inactive radical, InH a phenol or an amine, Q an inhibitor reacting with alkyl radicals, Cat a homogeneous or heterogeneous catalyst, $\rangle SH(\rangle PH)$ a sulphur-containing (or phosphorus-containing) inhibitor which reacts with hydroperoxides, and P_i are products.

For a long time, the detection and identification of the active centres of chain reactions (free radicals and atoms) were regarded as a kind of unique achievements. The wide-scale application of electron paramagnetic resonance (EPR) method altered the situation. The existence of free radicals has been detected by EPR in low-temperature oxidation reactions of various hydrocarbons. In many cases the spectra consist of a singlet with a g-factor of 2.015; the absorption line width depends on the structure of the peroxy-radicals and varies from 6 to 30 G (Fig.1, Table 1).[5-7]

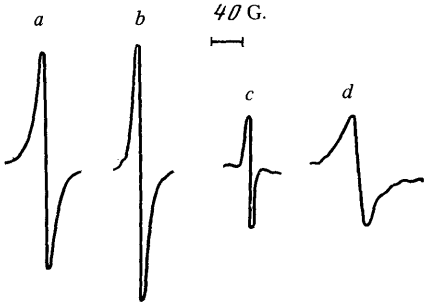


Figure 1. EPR spectra of peroxy-radicals in the oxidation of various substances: *a*) of cumene, catalysed by cobalt stearate, $[CoSt_2] = 1$ g litre^{-1}, 90 °C; *b*) of decalin, initiated by dicyclohexyl percarbonate, [PC] = 0.1 M, 85 °C; *c*) of 1,1'-diphenylethane, initiated by dicyclohexyl percarbonate, [PC] = 0.13 M, 69 °C; *d*) of iso-octane, initated by dicyclohexyl percarbonate, 78 °C.[5]

The formation of free radicals (chain initiation) in liquid-phase oxidation processes takes place as a rule in the bimolecular interaction of oxygen with the organic compound via reaction (0').[3] A termolecular chain initiation reaction [reaction (0)] was discovered in the 1960's in relation to the oxidation of cyclohexanol and cyclohexanone[8-10]. The possibility of this reaction was subsequently confirmed in relation to the oxidation of n-decane[11], tetralin[9,12], and indan[12] (Table 1).

The termolecular mechanism of chain initiation can involve an intermediate stage in which a complex is formed in accordance with the scheme

$$RH + O_2 \rightleftarrows RH \ldots O_2 \ ,$$
$$RH \ldots O_2 + RH \rightarrow 2\dot{R} + H_2O_2 \ .$$

The formation of such complexes has been demonstrated spectrophotometrically[12].

In a fully developed oxidation process radicals are formed via degenerate chain branching. The rate of degenerate branching can be determined from the consumption of the inhibitor introduced into the reaction mixture at various stages of the oxidation process. It has been shown by this method, for example, in the study of Knorre et al.,[16] that in oxidation of n-decane the hydroperoxide is the only branching product. The chain branching rate constant $k_3 = 6 \times 10^8 \exp(-24\,800/RT)$ (s^{-1}).[16]

Table 1. The rate constants for chain initiation in the oxidation of various organic compounds.

Substance	A_0', litre mol^{-1} s^{-1}	E_0', kcal mol^{-1}	A_0, litre^2 mol^{-2} s^{-1}	E_0, kcal mol^{-1}	Refs.
	Bimolecular reaction (0')		Termolecular reaction (0)		
Cyclohexane	$8.0 \cdot 10^{12}$	40.0			[15]
Isopropylbenzene	$3.5 \cdot 10^{9}$	27.4			[15]
o-Xylene	$2.0 \cdot 10^{8}$	31.0			[15]
Ethyl methyl ketone	$3.0 \cdot 10^{9}$	30.0			[13]
Ethanol	$6.0 \cdot 10^{7}$	30.0			[13]
Phenol	$7.0 \cdot 10^{12}$	35.0			[14]
p-Methoxyphenol	$7.5 \cdot 10^{9}$	27.0			[14]
p-Cresol	$3.0 \cdot 10^{11}$	32.0			[14]
α-Naphthol	$2.2 \cdot 10^{9}$	25.0			[14]
β-Naphthol	$4.5 \cdot 10^{10}$	29.0			[14]
α-Naphthylamine	$1.5 \cdot 10^{10}$	30.0			[14]
α-Naphthylphenylamine	$2.8 \cdot 10^{10}$	31.0			[14]
β-Naphthylphenylamine	$3.5 \cdot 10^{10}$	32.0			[14]
Tetralin			$4 \cdot 10^{3}$	20.7	[9]
Indan			$3.9 \cdot 10^{3}$	18.8	[12]
Cyclohexanol			8.3	16.0	[10]
Cyclohexanone			$2.1 \cdot 10^{2}$	17.5	[9]

Degenerate chain branching can occur not only as a result of the unimolecular decomposition of the hydroperoxide via reaction (3) but also via the bimolecular reaction (3') with participation of the hydrocarbon. According to reaction (3'), the rate of branching decreases linearly with increasing hydrocarbon concentration[3].

With the decrease of the C–H bond strength in the hydrocarbon molecule in the sequence decane > 2,7-dimethyloctane > ethylbenzene > methyl oleate, the rate of decomposition of n-decyl hydroperoxide into radicals increases, which constitutes yet another piece of evidence for the occurrence of the bimolecular chain branching reaction (3').[17]

At high hydroperoxide concentrations, which are particularly characteristic of the oxidation of α-olefins, the decomposition of the hydroperoxides and hence the degenerate chain branching take place via reaction (3''), the occurrence of which is promoted by the formation of hydrogen-bonded associated species:

$$ROOH + HOOR \rightleftharpoons [ROOH \ldots HOOR] \rightarrow R\dot{O} + R\dot{O}_2 + H_2O \ .$$

For high degrees of reaction, the products accumulating in the reaction mixture begin to participate in the chain branching. Organic acids, capable of forming a 2 : 1 complex with hydroperoxides, are important in this sense. Under the

influence of intermolecular hydrogen bonds, the dissociation of the O–O bond in the hydroperoxide molecule in such a complex is facilitated, which leads to the formation of free radicals[18,19]:

$$ROOH + 2RCOOH \overset{K}{\rightleftarrows} [ROOH \ldots 2RCOOH] \rightarrow R\dot{O} + \dot{O}H + 2RCOOH .$$

A study of the mechanism of chain propagation established that, as for gas-phase reactions, the liquid-phase oxidation reactions of organic compounds include in certain cases, together with the main chain propagation reaction

$$R\dot{O}_2 + RH \rightarrow ROOH + \dot{R} , \qquad (2)$$

also the isomerisation of peroxy-radicals accompanied by the decomposition of the radical with dissociation of the C–C bond and the formation of carbonyl compounds and radicals:

$$R\dot{O}_2 \rightarrow R'CHO + R''\dot{O} . \qquad (2')$$

The chain propagation in the oxidation of α-olefins constitutes two parallel reactions, in one of which the peroxy-radicals interact with the C–H bond [reaction (2)] with formation of hydroperoxides, while in the other peroxy-radicals add to the unsaturated bond [reaction (2‴)].[20] This reaction pathway leads to the formation of oxides, polyperoxides, and other products:

$$R\dot{O}_2 + \diagdown\!\!\diagup C\text{–}H\,(RH) \rightarrow ROOH + \dot{R} , \qquad (2)$$

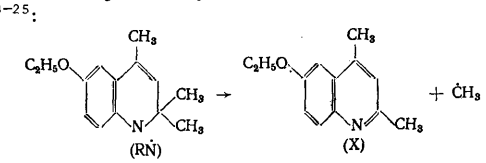
$$R\dot{O}_2 + \diagdown C{=}C\diagup\,(RH) \rightarrow R\dot{O}_2\text{–}\underset{|}{C}\text{–}\dot{C}\diagup \rightarrow \text{products.} \qquad (2''')$$

The rates of reactions (2) and (2‴) have been determined from the accumulation of hydroperoxides and the consumption of double bonds[21,22] in the oxidation of cyclohexene and phenylcyclohexene.

The rate constants k_2 and $k_{2'''}$ were calculated from the parameters $k_2/k_6^{1/2}$ and $k_{2'''}/k_6^{1/2}$ and the rate constant k_6 for the recombination of peroxy-radicals (determined by the method of interrupted illumination). The corresponding rate constants have the following values (in litre mol^{-1} s^{-1}): $k_2 = 5.7 \times 10^4 \exp[(-6300 \pm 300)/RT]$, $k_{2'''} = 1.4 \times 10^9 \exp[(-14\,000 \pm 600)/RT]$, and $k_6 = 1.5 \times 10^6$ for cyclohexene[21,22] and $k_2 = 2.2 \times 10^5 \exp[(-5000 \pm 300)/RT]$, $k_{2'''} = 1.4 \times 10^8 \exp[(-8400 \pm 300)/RT]$, and $k_6 = 2.5 \times 10^8$ for phenylcyclohexene[21,22].

The conjugation of the C=C bond with the phenyl group increases the reactivity of the α-olefin, which is manifested by a considerable decrease of the activation energy for the addition of the peroxy-radicals to the unsaturated bond in phenylcyclohexene relative to cyclohexene. It is also striking that there is a considerable increase of k_6 following the introduction of the phenyl substituent into the cyclohexene molecule, whereas by analogy with the corresponding alkanes, a lower value of k_6 for phenylcyclohexene relative to cyclohexene should have been expected in view of the steric effect of the substituent (the values of k_6 for cyclohexane and phenylcyclohexane are respectively 1.6×10^6 and 1.6×10^5 litre mol^{-1} s^{-1}).

In the oxidation of 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (ethoxyquin) the rate-limiting stage in the chain propagation reaction is the decomposition of the primary free radical accompanied by the elimination of the methyl radical[23–25]:



(13)

The rate constant for this reaction is $k_{13} = 1.3 \times 10^{13} \exp(-20\,800/RT)$ (litre mol^{-1} s^{-1}).

At elevated temperatures this reaction leads to the formation of 6-ethoxy-2,6-dimethylquinoline (X) (Fig. 2) with a a selectivity up to 90% in chlorobenzene and more than 60% in n-decane, cumene, styrene, and phenylacetylene. At $t > 100$ °C the oxidation of ethoxyquin is a chain process.

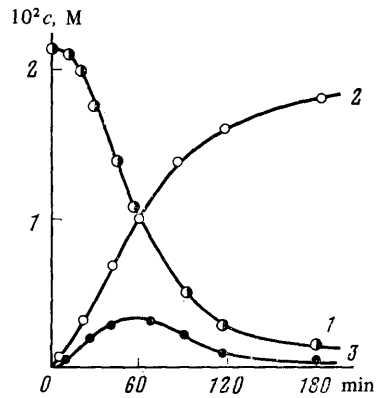
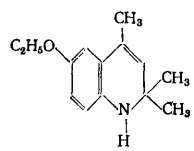


Figure 2. Kinetic curves for the consumption of ethoxyquin (curve *1*), the accumulation of the quinoline product (curve *2*), and the accumulation of methyl hydroperoxide (curve *3*) in the autoxidation of ethoxyquin in chlorobenzene (110 °C, oxygen flow rate 0.5 litre h^{-1}).[24]

The active centres for the chains are the free radicals RṄ, ĊH$_3$, and CH$_3$Ȯ$_2$ participating in the reactions

$$\dot{C}H_3 + O_2 \rightarrow CH_3\dot{O}_2 , \qquad (14)$$



$$+ CH_3\dot{O}_2\,(R\dot{O}_2,\ R\dot{O}) \rightarrow R\dot{N} + CH_3O_2H\,(RO_2H,\ ROH) , \qquad (15)$$

$$R\dot{N} + R\dot{N} \rightarrow RN\text{–}NR . \qquad (16)$$

The rate constant for the reaction of peroxy-radicals with the N–H bond of ethoxyquin is very high ($k_{15} \geq 10^6$ litre mol^{-1} s^{-1}) and does not limit the rate of oxidation. The rate constant for the recombination reaction (16), measured by flash photolysis, is $2k_6 = 9.8 \times 10^6$ litre mol^{-1} s^{-1} (20 °C, benzene).[26] Chain branching proceeds via a reaction of type (3′):

$$RNH + CH_3OOH\,(ROOH) \rightarrow R\dot{N} + CH_3\dot{O}(R\dot{O}) + H_2O .$$

In inert solvents this reaction proceeds with participation of methyl hydroperoxide.

At low temperatures, where the rate of decomposition of the radical RṄ via reaction (13) is low, ethoxyquin is one of the most effective antioxidants, since the rate constant for the interaction of peroxy-radicals with ethoxyquin [reaction (15)] is significantly greater than, for example, the corresponding constant for ionol ($k = 2 \times 10^4$ litre mol^{-1} s^{-1}, 60 °C [3]) and the RṄ radical formed is relatively inactive.

In hydrocarbons undergoing oxidation the RṄ radicals partly undergo a cross recombination reaction:

$$R\dot{N} + R\dot{O}_2 \rightarrow \text{products},$$

as a result of which the stoichiometric inhibition coefficient for ethoxyquin is greater than unity ($f \cong 1.3$ for the oxidation of phenylacetylene, styrene, ethylbenzene, and β-carotene; 50–60 °C).

Above 100 °C, the inhibiting efficiency of ethoxyquin falls in the oxidation of ethylbenzene, n-decane, and styrene, since the methylperoxy-radical formed in stage (15) is involved in the transfer of the hydrocarbon oxidation chain. The interaction of ethoxyquin with hydroperoxides plays a significant role in decreasing its efficiency as an inhibitor.

Ethoxyquin is an effective antioxidant for phenylacetylene even at a relatively high temperature. The inhibition is then due to the ethoxyquin reaction product—the corresponding quinoline.

The reactivity of the $R\dot{O}_2$ radicals with respect to the oxidation products [reaction (2″)] was determined by special kinetic procedures[27,28]; it was shown that, in the oxidation of n-decane, the ratios of the rate constant for reaction (2) (k_2) and the rate constants for the chain propagation as a result of the interaction of the radical $R\dot{O}_2$ with the alcohol ($k_{2''}$,ROH) and the hydroperoxide ($k_{2''}$,ROOH) are $k_2 : k_{2''},\mathrm{ROH} : k_{2''},\mathrm{ROOH} = 1 : 6 : 13$. The activation energies for the elementary stages[29,30] are $E_2 = 14.5$ kcal mol^{-1} and $E_{2''},\mathrm{ROH} = E_{2''},\mathrm{ROOH} = 10$ kcal mol^{-1}.

Thus the oxidation products are extremely reactive and have a significant influence on the oxidation mechanism.

The reactions of the $R\dot{O}_2$ radical with peroxides, alcohols, and ketones involve the interaction of two dipoles, which is significantly influenced by the dielectric constant of the medium.

The composition of the products of the oxidation of ethyl alcohol and ethyl methyl ketone at a pressure of 50 atm and a temperature of ~150 °C in a stainless steel reactor[32,33] is determined by the competition of two elementary chain propagation stages [reactions (2) and (2′)]. The principal oxidation products of ethyl methyl ketone are acetic acid, ethyl acetate, and diacetyl. In the oxidation of ethyl alcohol the products of the bimolecular reaction of the $R\dot{O}_2$ radical, namely acetic acid and ethyl acetate, constitute 80% of the total oxidation products. When ethyl methyl ketone and ethyl alcohol are diluted by a non-polar substance (benzene) the amount of the decomposition products of the $R\dot{O}_2$ radicals increases, because the addition of benzene diminishes the dielectric constant of the medium and the rate of reaction (2) falls.

The activation energy for reaction (2) in the oxidation of ethyl methyl ketone and ethyl alcohol increases with decrease of the dielectric constant of the medium[34]. The dipole moment of the activated complex $\mu_{\neq} = 8.4$ D, obtained from experimental data for the oxidation of ethyl methyl ketone, agrees well with the value calculated for one of the structures of the activated complex (8.1 D), i.e. in the case of ethyl methyl ketone the rate of reaction (2) is influenced solely by the dielectric constant of the medium. Not only the polarity of the medium but also the association of the alcohol via intermolecular hydrogen bonds plays an important role in the oxidation of the alcohol.

Chain termination in liquid-phase chain reactions takes place in the vast majority of cases via a quadratic recombination or disproportionation [reaction (6)] mechanism. The quadratic chain termination in the oxidation of hydrocarbons is apparently a complex process proceeding via a multistage mechanism[35–37]. According to Russell[38], the disproportionation of primary and secondary peroxy-radicals proceeds via an intermediate stage involving the formation of a cyclic complex, although it has been suggested that the process proceeds via a more complicated mechanism involving a zwitterion formation stage[37].

Tertiary peroxy-radicals probably interact via the mechanism

$$2R\dot{O}O \begin{cases} \rightarrow ROOR + O_2 , & (17a) \\ \rightarrow 2R\dot{O} + O_2 . & (17b) \end{cases}$$

The t-alkoxy radicals decompose with formation of a ketone and a low-molecular-weight primary radical, which is subsequently involved in disproportionation cross-reactions with the radicals $R\dot{O}O$.

For example, the radical $\dot{C}H_3$ is formed in the decomposition of the cumenyloxy-radical:

$$\begin{gathered} C_6H_5C(CH_3)_2\dot{O} \rightarrow C_6H_5(C{=}O)CH_3 + \dot{C}H_3 , \\ \dot{C}H_3 + O_2 \rightarrow CH_3\dot{O}_2 , \\ CH_3\dot{O}_2 + R\dot{O}_2 \rightarrow H_2CO + O_2 + ROH . \end{gathered} \qquad (18)$$

It is noteworthy that much attention has been devoted recently in the literature on the liquid-phase oxidation mechanism to the $R\dot{O}_2$ disproportionation reaction [reaction (17b)] as the chain propagation stage in the oxidation of hydrocarbons with tertiary[39] and secondary[40] C–H bonds.

A recent study[41] of the quadratic chain termination in the oxidation of cumene by the chemiluminescence method showed that the primary cumenylperoxy-radicals $C_6H_5CH(CH_3)CHO\dot{O}$, involved in the disproportionation cross-reactions

$$R\dot{O}O + C_6H_5CH(CH_3)CH_2O\dot{O} \rightarrow ROH + O_2 + C_6H_5CH(CH_3)CHO , \qquad (19)$$

play a major role in chain termination. Despite the low concentration of the primary peroxy-radicals, the contribution of reaction (19) to the overall rate of recombination is then comparable to the contribution of reaction (17) and greatly exceeds that of reaction (18) in the chain termination mechanism.

Various non-stationary methods are used to measure k_6, including rapid chemiluminescence (CL) methods[35,42]. A novel chemiluminescence method has been recently developed for the determination of the recombination and disproportionation constants of free peroxy-radicals in cases where the relevant processes are not accompanied by intense luminescence sufficient for its measurement under non-stationary conditions[43]. The method is based on the measurement of the non-stationary chemiluminescence in the coupled oxidation of the test substance RH with a small amount of an added "standard" compound R_1H characterised by fairly high chemiluminescence yields in chain termination processes. Non-stationary conditions are obtained as a result of the rapid introduction of an initiator into the system. The chemiluminescence arising in the coupled system is due to the reactions

$$\begin{gathered} R\dot{O}_2 + R_1\dot{O}_2 \rightarrow \text{products}, \\ R_1\dot{O}_2 + R_1\dot{O}_2 \rightarrow \text{products}. \end{gathered}$$

The ratio of the concentrations of the radicals $R\dot{O}_2$ and $R_1\dot{O}_2$ is determined by the rates of the chain propagation cross-reactions

$$R\dot{O}_2 + R_1H \rightarrow ROOH + \dot{R}_1 , \qquad (22)$$

$$R_1\dot{O}_2 + RH \rightarrow R_1OOH + \dot{R} . \qquad (23)$$

The effective rate constant for the recombination of radicals k_6^{eff} in mixtures of different composition is described by the formula

$$\ln \frac{1 + (I/I_\infty)^{1/2}}{1 - (I/I_\infty)^{1/2}} = 2(w_i k_6^{\mathrm{eff}})^{1/2} t$$

(I is the chemiluminescence intensity and I_∞ the limiting value of I for the given rate of chain initiation w_i), analogous to that used to decribe the non-stationary kinetics in the oxidation of pure hydrocarbons[42]. The constant k_6^{eff} varies

linearly with mixture composition and is given by an expression of the form

$$k_6^{\text{eff}} = k_6 + 2\frac{k_{22}}{k_{23}}(k_{20} - k_{21})\frac{[R_1H]}{[RH]},$$

which makes it possible to calculate the required constant k_6 from the dependence of k_6^{eff} on the ratio $[R_1H]/[RH]$. The method has been used[44] to determine k_6 for the oxidation of substituted 3-phenylindans.

In certain special cases there is apparently a possibility also of linear termination together with quadratic chain termination in liquid-phase oxidation reactions. A change of the chain termination reaction[45–47] from quadratic to linear with increase of temperature has been established in a study of the kinetics of the oxidation of unsaturated compounds: 4-(2,6,6-trimethyl-1-cyclohexenyl)but-3-en-1-one (β-ionone) and the acetoacetate ester of the corresponding alcohol (β-ionol acetate). At temperatures below 70 °C the rate of oxidation of these compounds w varies in proportion to $w_i^{1/2}$, which is a kinetic feature of quadratic chain termination; at 70–80 °C the variation of w is proportional to w_i, which indicates the predominance of linear termination in this case (Fig.3). Kinetic analysis has shown that the linear chain termination is due to the isomerisation of the free peroxy- or alkyl-radicals involved in the chain propagation[45]:

$$RO_2^{\cdot}(R^{\cdot}) \rightarrow \dot{\rho}\,. \qquad (6')$$

The change in the chain termination mechanism is accompanied by a relative decrease of the rate of reaction.

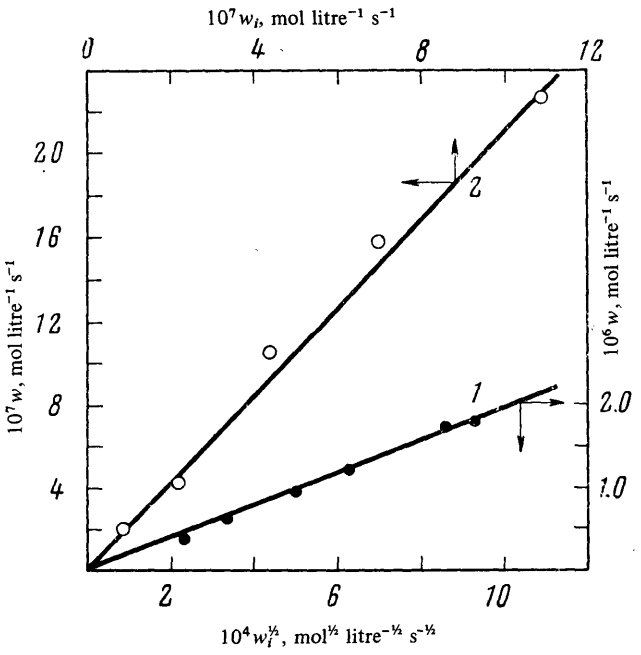


Figure 3. Dependence of the rate of absorption of oxygen in the initiated oxidation of β-ionone at 60 °C on $w_i^{1/2}$ (line 1) and at 85 °C on w_i (line 2); β-ionone concentration (M): 1) 0.09; 2) 0.1; initiators: 1) azobisisobutyronitrile; 2) benzoyl peroxide; solvent—chlorobenzene[46].

2. Oxidation Kinetics

In order to analyse the characteristics of the degenerate branched chain oxidation reactions of organic compounds occurring over a period of time, it is possible to examine a simplified mechanism reflecting the principal kinetic types of the elementary reactions of the initial compound (RH), the active centres—peroxy-radicals ($RO_2^{\cdot}$), and the intermediates (ROOH) involved in the formation of free radicals. In conformity with the detailed mechanism presented above, the following reactions are involved†:

$$\left.\begin{array}{l} RH + RO_2^{\cdot} \xrightarrow{k_2} RO_2^{\cdot} + ROOH, \\ \qquad\qquad \xrightarrow{k_2'''} RO_2^{\cdot} + \text{products}; \end{array}\right\} \text{(chain propagation)}$$

$$\left.\begin{array}{l} RO_2^{\cdot} + RO_2^{\cdot} \xrightarrow{k_6} P_6, \\ RO_2^{\cdot} \xrightarrow{k_{6'}} \rho\,; \end{array}\right\} \text{(chain termination)}$$

$$\left.\begin{array}{l} RH \xrightarrow{k_0} RO_2^{\cdot}, \\ ROOH \xrightarrow{k_3} RO_2^{\cdot}, \\ ROOH + ROOH \xrightarrow{k_{3''}} RO_2^{\cdot}. \end{array}\right\} \text{(chain initiation)}$$

The kinetic equations for the rate of a reaction proceeding via the above mechanism at quasi-stationary concentrations of free radicals are

$$w_i - k_6[RO_2^{\cdot}]^2 - k_{6'}[RO_2^{\cdot}] = 0\,, \qquad (24)$$

$$-\,d[RH]/dt = k_2[RO_2^{\cdot}][RH]\,, \qquad (25)$$

$$-\,d[ROOH]/dt = \alpha k_2[RO_2^{\cdot}][RH] - k_3[ROOH] - k_{3''}[ROOH]^2\,, \qquad (26)$$

$$w_i = k_0[RH] + \delta k_3[ROOH] + \delta k_{3''}[ROOH]\,, \qquad (27)$$

where δ is the number of free radicals per ROOH molecule decomposed and α is a parameter defining the fraction of ROOH in the sum of products formed in the chain propagation stages.

It follows from Eqns.(24) and (25) that in quadratic chain termination, where $k_6[RO_2^{\cdot}] \gg k_{6'}$, we have

$$[RO_2^{\cdot}] = (w_i/k_6)^{1/2},$$
$$-\,d[RH]/dt = k_2[RH](w_i/k_6)^{1/2}, \qquad (28)$$

while in linear termination, where $k_{6'} \gg k_6[RO_2^{\cdot}]$, we have

$$[RO_6^{\cdot}] = w_i/k_{6'},$$
$$-d[RH]/dt = k_2[RH](w_i/k_{6'}). \qquad (29)$$

The study of the kinetics of the oxidation of organic compounds of different classes led to the derivation of various functions $w_i = w_i\{[RH]\}$ and the corresponding overall kinetic equations. Up to a certain degree of conversion, particularly in the initial stages, the amount of compound consumed may be proportional to the ROOH concentration:

$$[ROOH] = \alpha([RH]_0 - [RH]). \qquad (30)$$

† The following assumptions have been made: all the radicals, including alkyl, alkoxy-, and hydroxy-radicals, are rapidly converted into peroxy-radicals: $\dot{R} + O_2 \rightarrow RO_2^{\cdot}$; $RO(OH)^{\cdot} + RH \rightarrow \dot{R}$ + products; the chain length is small, which makes it possible to neglect the consumption of RH associated with the formation of free radicals other than peroxy-radicals in the stage involving the decomposition of the intermediates (chain initiation). The product (ROOH) involved in chain branching is formed in one of the chain propagation reactions.

In this case Eqn.(27) can be put in the form

$$w_i = k_0[RH] + \alpha\delta k_3([RH]_0 - [RH]) + \alpha^2\delta k_{3''}([RH]_0 - [RH])^2 \quad (31)$$

Eqn.(31) holds when the consumption of ROOH can be neglected in Eqn.(26) or when there are several compounds formed consecutively and decomposing into free radicals.

Integration of Eqn.(28) or (29) leads to different expressions, depending on the ratios of the rate constants for the chain initiation stages. We shall examine several cases.

1. The decomposition of ROOH is a first-order reaction and the chain termination is quadratic: $k_3 \gg k_{3''}[ROOH]$; $k_{6'} = 0$. In this case Eqn.(31) and the solution of Eqn.(28) are

$$w_i = k_0[RH] + \alpha\delta k_3([RH]_0 - [RH]) \quad (32)$$

$$\ln\frac{1 + (1 - [RH]/[RH]_0)^{1/2}}{1 - (1 - [RH]/[RH]_0)^{1/2}} = c_1 t, \quad (33)$$

where $c_1 = k_2\{\alpha\delta k_3[RH]_0/k_6\}^{1/2}$ is a parameter.

Eqn.(33) holds in the oxidation of β-carotene and phenylcyclohexene (at temperatures below 90 °C).[48,49] Eqn.(32) has been derived experimentally by determining w_i during the reaction by the method of inhibitors. In most cases Eqn.(32) holds in the initial stages of the reaction where its extent is low and one can assume that $[RH] \cong [RH]_0$; formula (33) can then be fitted by the equation of a parabola:

$$[ROOH] = c_1'' t^2 \quad (34)$$

where $c_1'' = 0.25\alpha^2 k_2^2 [RH]_0^2 \delta k_3/k_6$ is a parameter. Hydroperoxides accumulate in accordance with a parabolic law in the oxidation of aromatic alkyl-substituted hydrocarbons and paraffinic hydrocarbons in the initial stages of the reaction[50].

2. The decomposition of ROOH is a second-order reaction and the chain termination is quadratic: $k_{3''}[ROOH] \gg k_3$; $k_0 \ll k_{3''}[ROOH]$; $k_{6'} = 0$.

Function (31) and the solution of Eqn.(28) then become

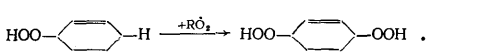
$$w_i = \alpha^2\delta k_{3''}([RH]_0 - [RH])^2$$
$$\ln\frac{([RH]_0 - [RH])}{[RH]} = \frac{\alpha k_2 (\delta k_{3''})^{1/2} [RH]_0}{k_6^{1/2}} t + \text{const} \quad (35)$$

Using Eqn.(30), it is possible to obtain from Eqn.(35) an expression for the accumulation of the hydroperoxide:

$$\ln\frac{[ROOH]}{\alpha[RH]_0 - [ROOH]} = \frac{\alpha k_2 (\delta k_{3''})^{1/2} [RH]_0}{k_6^{1/2}} t + \text{const} \quad (36)$$

Eqns.(35) and (36) have been obtained for the consumption of cyclohexene and the accumulation of cyclohexenyl hydroperoxide in the autoxidation of cyclohexene[49] up to a degree of conversion of ~20% (Fig.4).

The main pathway in the consumption of cyclohexenyl hydroperoxide involves its oxidation via a chain mechanism with participation of the C–H bonds, as in the initial cyclohexene:



(37)

This process determines the maximum concentration of the intermediate and the rate of formation of free radicals. The main product of the reaction of a monohydroperoxide is the dihydroperoxide (Fig.4, curve 3).

Cyclohexenyl hydroperoxide is more reactive in reactions with peroxy-radicals than is cyclohexene. Thus, for a degree of reaction in excess of 20% (at 70 °C), the cyclohexene undergoing oxidation is a multicomponent system in which the initial compound is consumed under the conditions of its joint oxidation with the primary reaction product.

3. The product ROOH and the initial compound have similar reactivities in the formation of free radicals and the chain termination is linear: $\delta k_3 \cong k_0$; $k_6 = 0$.

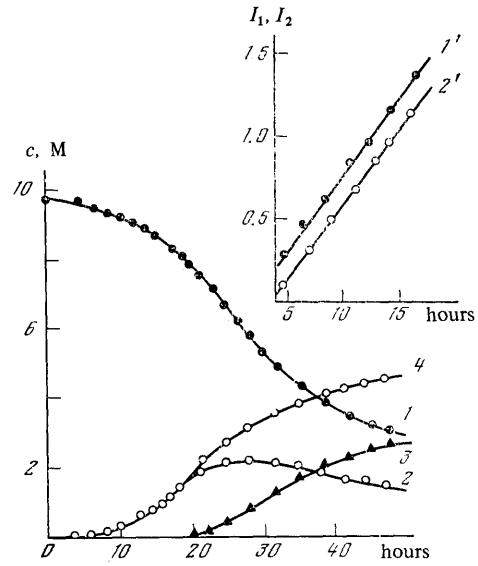


Figure 4. *a*) Kinetic curves for the consumption of cyclohexene (curve *1*), the accumulation of cyclohexenyl hydroperoxide (curve *2*), the accumulation of dihydroperoxide (curve *3*), and the sum of peroxides (curve *4*) in the oxidation of cyclohexene in a closed vessel under the conditions of the saturation of the liquid phase with oxygen; *b*) transformed kinetic curves for the consumption of cyclohexene (curve *1'*) and the accumulation of cyclohexenyl hydroperoxide (curve *2'*) in terms of the variables of Eqns.(35) and (36) up to a 20% degree of conversion of the hydrocarbon; 70 °C; $I_1 = 2 + \lg(\{[RH]_0 - [RH]\}/[RH])$; $I_2 = 2 + \lg([ROOH]/\{\alpha[RH]_0 - [ROOH]\})$ for $\alpha = 0.7$.[49]

In this case the decrease of w_0 as a consequence of the consumption of the compound is compensated by the increase of w_p and as a result the overall rate of formation of free radicals hardly changes in the course of the process. Eqn.(29) and the solution of Eqn.(28) have the form

$$w_i = k_3[RH]_0, \quad (38)$$

$$[RH] = [RH]_0 \exp(-c_3 t). \quad (39)$$

where $c_3 = k_2\delta k_3[RH]_0/k_{6'}$ is an effective first-order rate constant.

Eqn.(38) and the first-order kinetic equation (39) have been obtained[45] for the oxidation of the unsaturated compound 4-(2,6,6-trimethyl-1-cyclohexenyl)but-3-en-2-yl acetate (β-ionol acetate) (Fig.5). In this case the first-order equation merely simulates a complex chain mechanism. This is indicated, for example, by the dependence of the effective rate constant c_3 on the initial concentration of the compound (Fig.5).

Phenylacetylene is apparently oxidised in accordance with a first-order equation with linear chain termination. This process constitutes oxidative polymerisation with a very small contribution by stages of the oxidative-degrative type[51].

In the oxidation of ethyl methyl ketone the rate of formation of free radicals w_i remains constant up to the complete decomposition of the compound with quadratic chain termination[52]:

$$w_i = c = \text{const}. \quad (40)$$

This feature of the chain initiation is associated with the thermal decomposition in the course of the reaction of two consecutively formed intermediates—a ketohydroperoxide and diacetyl.

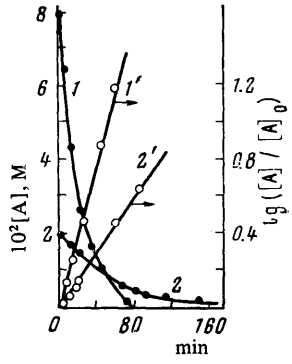


Figure 5. Kinetic curves for the consumption of β-ionol acetate (A) (curves *1* and *2*) and the semilogarithmic forms of the curves (curves *1'* and *2'*); solvent—chlorobenzene; 80 °C.[45]

Integration of Eqn.(28) leads to the expression

$$[RH] = [RH]_0 \exp(-c_3' t) \quad (41)$$

where $c_3' = k_2(w_i/k_6)^{1/2}$ is the effective rate constant. Thus we have a first-order equation, like Eqn.(39), but with another structure of the effective constant c_3'.

4. Free radicals are formed only with participation of the initial compound and the chain termination is quadratic: $k_0 \gg k_3$, $k_0 \gg k_{3''}[ROOH]$, $k_{6'} = 0$. According to Eqn.(31), the rate of chain initiation decreases in the course of the process:

$$w_0 = k_0[RH]\ . \quad (42)$$

Integration of Eqn.(28) leads to the expression

$$\frac{1}{[RH]_0^{1/2}} - \frac{1}{[RH]^{1/2}} = c_4 t\ , \quad (43)$$

where $c_4 = 0.5k^2(k_0/k_6)^{1/2}$ is a parameter.

Evidently Eqn.(43) is the kinetic equation of an unbranched chain reaction. Eqns.(42) and (43) have been obtained for the autoxidation of phenylcyclohexene above 90 °C.[49] For this cyclo-olefin, a change in the oxidation process conditions from degenerate branched (at t < 90 °C) to unbranched (at t > 90 °C) is observed due to the characteristics of the reactions of the intermediates.

The autocatalytic nature of the process at low temperatures is due to the formation in reaction (2) of unsaturated hydroperoxides, which readily decompose into free radicals. The main cause of the change in process conditions with increase of temperature is the oxidation of unsaturated hydroperoxides with participation of C=C bonds, leading to the formation of thermally stable compounds. At the same time the rate of reaction of phenylcyclohexene with oxygen (chain initiation) and the activity of the free radicals in chain propagation are sufficiently high for the reaction to develop at a high rate and without chain branching.

Thus the type of kinetic equation for the reaction is determined by the nature of the decomposition of the intermediates and the ratio of the reactivities of the initial compound and the intermediates in the formation of free radicals.

The overall kinetic equations contain the parameters c_1, c_2, etc., which can be determined from transformed kinetic curves. For autocatalytic reactions, the parameters of the equations contain the rate constants for chain propagation, termination, and degenerate branching: $c = k_2(\alpha\delta k_3/k_6)^{1/2}$. These parameters can serve as characteristics of the reactivity of organic compounds in oxidation processes.

3. Oxidation of Multicomponent Mixtures. Coupled Oxidation

In the coupled oxidation of binary mixtures of hydrocarbons R_1H and R_2H, two types of radicals, $R_1\dot{O}_2$ and $R_2\dot{O}_2$, which can interact with both hydrocarbons, are involved in chain propagation and termination[3]. As a result, together with the chain propagation and termination reactions occurring in the oxidation of the pure hydrocarbons R_1H and R_2H,[53–56] i.e.

$$\dot{R}_1 + O_2 \rightarrow R_1\dot{O}_2\ , \quad (1)$$

$$R_1\dot{O}_2 + R_1H \rightarrow R_1OOH + \dot{R}_1\ , \quad (2)$$

$$R_1\dot{O}_2 + R_1\dot{O}_2 \rightarrow \text{products}, \quad (6)$$

$$\dot{R}_2 + O_2 \rightarrow R_2\dot{O}_2\ , \quad (44)$$

$$R_2\dot{O}_2 + R_2H \rightarrow R_2OOH + \dot{R}_2\ , \quad (45)$$

$$R_2\dot{O}_2 + R_2\dot{O}_2 \rightarrow \text{products}, \quad (46)$$

chain propagation and termination cross-reactions also take place:

$$R_1\dot{O}_2 + R_2H \rightarrow R_1OOH + \dot{R}_2\ , \quad (47)$$

$$R_2\dot{O}_2 + R_1H \rightarrow R_2OOH + \dot{R}_1\ , \quad (48)$$

$$R_1\dot{O}_2 + R_2\dot{O}_2 \rightarrow \text{products}. \quad (49)$$

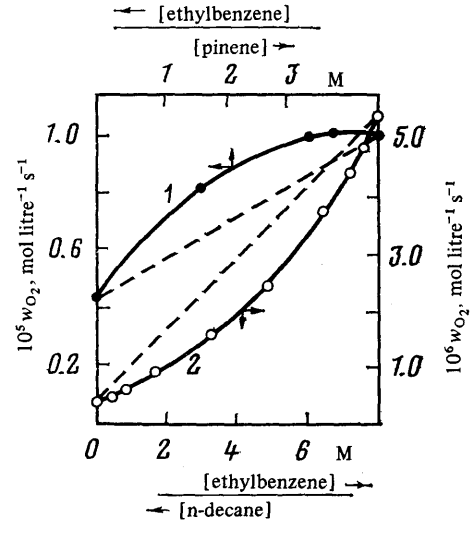


Figure 6. Dependence of the rate of oxidation on the composition of the mixtures of hydrocarbons: 1) pinene–ethylbenzene (70 °C); 2) n-decane–ethylbenzene (77 °C).

The occurrence of reactions (47)–(49) leads to the non-additive dependence of the rate of oxidation on the mixture composition (Fig.6).

Under the conditions of initiated oxidation, when the above joint oxidation mechanism is valid, the rate of absorption of oxygen is described by the formula

$$w_{O_2} = w_i^{1/2} \frac{r_1[R_1H]^2 + 2[R_1H][R_2H] + r_2[R_2H]^2}{((r_1^2/b_1^2)[R_1H]^2 + 2\Phi(r_1r_2/b_1b_2)[R_1H][R_2H] + (r_2^2/b_2^2)[R_2H]^2)^{1/2}}, \quad (50)$$

where $b_1 = k_2/k_6^{1/2}$, $b_2 = k_{45}/k_{46}^{1/2}$, $r_1 = k_2/k_{47}$, $r_2 = k_{45}/k_{48}$, and $\Phi = k_{49}/(k_6k_{46})^{1/2}$. This equation is used widely in the determination of the reactivity of peroxy-radicals with respect to a series of hydrocarbons (Table 2). Together with the chain propagation and termination "cross-reactions", reactions involving alkyl radicals can play a significant role in the oxidation of multicomponent mixtures[59–62]:

$$\dot{R}_1 + R_2H \rightarrow R_1H + \dot{R}_2, \quad (51)$$

$$\dot{R}_2 + R_1H \rightarrow R_2H + \dot{R}_1. \quad (52)$$

Table 2. The rate constants for the reactions $R_1\dot{O}_2 + R_2H \rightarrow R_1OOH + \dot{R}_2$ (75 °C).

R_2H	$R_1\dot{O}_2$	k_{47}, litre mol^{-1} s^{-1}	References
o-Xylene	allylbenzene	4.0	57
o-Xylene	tetralin	2.0	57
o-Xylene	α-methylstyrene	0.9	57
Cumene	allylbenzene	6.5	57
Cumene	tetralin	2.6	57
Cumene	α-methylstyrene	1.0	57
Ethylbenzene	allylbenzene	6.2	57
Ethylbenzene	tetralin	3.9	57
Ethylbenzene	α-methylstyrene	1.4	57
Ethylbenzene	2,7-dimethyloctane*	0.12	58
Allylbenzene	tetralin	19	57
Allylbenzene	α-methylstyrene	9.2	57
Tetralin	allylbenzene	44	57
Tetralin	α-methylstyrene	12	57
α-Methylstyrene	allylbenzene	400	57
α-Methylstyrene	tetralin	100	57
2,7-Dimethyloctane	ethylbenzene*	4.8	58
1-Methyl-3-phenylindan	ethylbenzene**	39.2	44
1,3-Dimethyl-3-phenylindan	ethylbenzene**	17.8	44
1,1-Dimethyl-3-phenylindan	ethylbenzene**	30.4	44

*At 77 °C.
**At 60 °C.

If account is taken of the possibility of competition between reactions (1) and (51) and between (44) and (52) in initiated oxidation, then Eqn.(50) is transformed into[63]

$$w_{O_2} = w_i^{1/2} \frac{k_2[R_1H] + k_{47}[R_2H] + c(k_{48}[R_1H] + k_{45}[R_2H])}{(2k_6 + 2k_{49}c + 2k_{46}c^2)^{1/2}}, \quad (53)$$

where

$$c = \frac{(k_{51}[R_2H]/k_1[O_2])(k_2[R_1H] + k_{47}[R_2H]) + k_{47}[R_2H]}{(k_{52}[R_1H]/k_{44}[O_2])(k_{48}[R_1H] + k_{45}[R_2H]) + k_{48}[R_1H]}.$$

Analysis of Eqn.(53) shows that reaction (51) influences most strongly the kinetics of the oxidation of nearly equimolar mixtures. The overall rate of oxidation is sensitive to reaction (51) with $k_{51} \geq 10^3$ litre mol^{-1} s^{-1}.

As a result of the large difference between the activation energies for the reactions of free radicals $\dot{R}_1$ with O_2 and R_2H, reaction (51) occurs to a large extent at high temperatures.

Degenerate chain branching reactions also play an important role in the non-initiated oxidation of multicomponent systems at 100–140 °C. The rate of degenerate branching is then determined by the rates of unimolecular and bimolecular decomposition of the hydroperoxides R_1OOH and R_2OOH:

$$\left.\begin{aligned} R_1OOH &\rightarrow R_1\dot{O} + \dot{O}H, \\ R_2OOH &\rightarrow R_2\dot{O} + \dot{O}H, \end{aligned}\right\} \quad (3)$$

$$\left.\begin{aligned} R_1OOH + R_1H &\rightarrow R_1\dot{O} + \dot{R}_1 + H_2O, \\ R_2OOH + R_2H &\rightarrow R_2\dot{O} + \dot{R}_2 + H_2O, \\ R_1OOH + R_2H &\rightarrow R_1\dot{O} + \dot{R}_2 + H_2O, \\ R_2OOH + R_1H &\rightarrow R_2\dot{O} + \dot{R}_1 + H_2O. \end{aligned}\right\} \quad (3')$$

The occurrence of the new chain transfer reaction (51) as well as the branching reactions results in a sharp difference between the characteristics of the oxidation of multicomponent mixtures under these conditions and those of initiated oxidation. Thus, in the degenerate branched chain oxidation reaction of mixtures of ethylbenzene with paraffins (n-decane, 2,7-dimethyloctane, 130 °C), one observes an acceleration of the oxidation of n-decane by small amounts of added ethylbenzene instead of its retardation (as in initiated oxidation) (Fig.7). On further increase of the content of ethylbenzene in the mixture to 7.5 vol.%, the consumption of n-decane begins to be inhibited strongly and virtually ceases in the presence of ~10 vol.% of ethylbenzene in the mixture[60]. Under these conditions, virtually only ethylbenzene is oxidised. The maximum rate of oxidation of ethylbenzene is observed in the range of ratios of mixture components in which the maximum rate of oxidation of n-decane is attained.

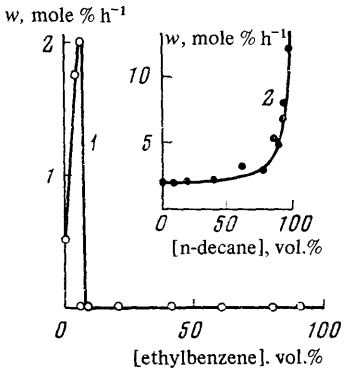


Figure 7. Dependence of the initial rate of oxidation of n-decane (curve *1*) and ethylbenzene (curve *2*) on the composition of the n-decane–ethylbenzene mixture; 130 °C.[60]

Mathematical analysis of the kinetic scheme of the coupled oxidation of two hydrocarbons (in relation to the oxidation of a mixture of n-decane and ethylbenzene at 130 °C), taking into account the chain transfer reaction (51) and the degenerate branching reactions (3)–(3'), showed[62] that the experimental dependence of the rates of oxidation of the mixture components on the mixture composition cannot be explained without taking into account reaction (51).

Thus, under the conditions of the high-temperature coupled oxidation of hydrocarbons, the set of elementary reactions making up the process mechanism greatly increases.

Reaction (51) must be taken into account particularly in the thermo-oxidative degradation of polymers, where the diffusion of O_2 into the polymer is difficult.

On the basis of coupled oxidation reactions, it is possible to devise technological processes in which the oxidising agents are highly reactive peroxy-radicals and not molecular oxygen. One of the substances being oxidised is then the source of peroxy-radicals, which interact with the second mixture component.

An example of such a reaction is the formation of epoxypropane and an organic acid by the joint (coupled) oxidation of aldehydes and olefins[64,65]. This process proceeds via the mechanism of a chain reaction and the main epoxidising agent is the acylperoxy-radical[66]:

$$RCOO\dot{O} + CH_2{=}CHCH_3 \rightarrow [RCOOO \cdot C_3H_6] \rightarrow -\overset{|}{C}-\overset{|}{C}- + RCO\dot{O} ,$$
$$\diagdown O \diagup$$

$$RCO\dot{O} + RH \rightarrow RCOOH + \dot{R} .$$

Together with the radical reaction, there is also a molecular pathway in the epoxidation of propene with peracetic acid (the Prilezhaev reaction[67]). However, the contribution of this reaction in the coupled acetaldehyde–propene process does not exceed 15 mole % of the overall rate of formation of epoxypropane. The concentration of dissolved oxygen has a significant influence on the rate of formation of epoxypropane[58].

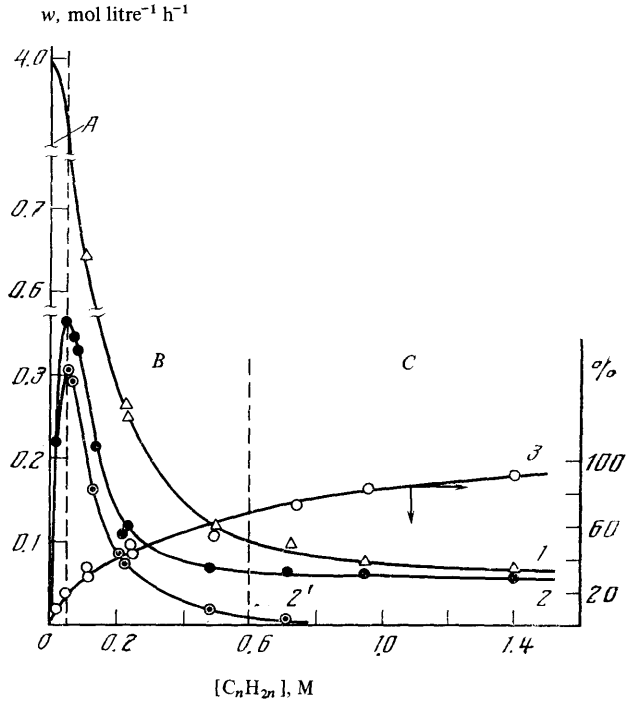


Figure 8. Dependence of the rate of consumption of benzaldehyde (curve *1*) and accumulation of epoxynonane (curve *2*) on the concentration of non-1-ene in chlorobenzene; *2'*) calculated curve for the rate of epoxidation of non-1-ene with perbenzoic acid; 3) variation of the yield of epoxynonane relative to the benzaldehyde which has reacted. Temperature 90 °C; rate of supply of oxygen 3 litres h^{-1}.[69]

The coupled oxidation of non-1-ene and benzaldehyde[69] is characterised by a nearly 100% selectivity in the formation of 1,2-epoxynonane relative to both initial reactants which have reacted—the olefin and the aldehyde. There is an extremum in the rate of formation of 1,2-epoxynonane as a function of the initial concentration of non-1-ene (Fig.8). The ratio of the rates in the two pathways leading to the formation of 1,2-epoxynonane (epoxidation by acylperoxy-radicals and the peracid) is determined by the composition of the initial mixture and the kinetic parameters of the system. At relatively low concentrations of the aldehyde the formation of epoxynonane has a radical mechanism, while at high values of [RCHO] the main epoxidising agent is the peracid.

In the coupled oxidation of olefins (C_nH_{2n}) and aldehydes (RCHO) an important role is played by the addition of acylperoxy-radicals to the double bond [reaction (60)], which is the main chain termination pathway, because the relatively inactive polyperoxy-radical $M\dot{O}_2$ formed under these conditions cannot enter into the exchange reaction (54) during the period of the propagation of the primary chain, i.e. the condition $1/k_{59}[C_nH_{2n}] < 1/k_{54}[RCHO]$ holds. The overall process mechanism can be formulated thus:

$$M\dot{O}_2 + RCHO \rightarrow RCOO\dot{O} + MOOH , \quad (54)$$

$$RCHO + O_2 \rightarrow R\dot{C}O + H\dot{O}_2 , \quad (55)$$

$$R\dot{C}O + O_2 \rightarrow RCOO\dot{O} , \quad (56)$$

$$RCOO\dot{O} + RCHO \rightarrow RCOOOH + R\dot{C}O , \quad (57)$$

$$RCOO\dot{O} + RCHO \rightarrow RCOOH + R\dot{C}O , \quad (58)$$

$$RCOO\dot{O} + C_nH_{2n} \rightarrow RCOO\dot{O} + \diagup C-C \diagdown O \diagup , \quad (59)$$

$$RCOO\dot{O} + C_nH_{2n} \rightarrow M\dot{O}_2 \xrightarrow{k'_{60}} \dot{M} \xrightarrow{k''_{60}} M\dot{O}_2 \rightarrow \text{molecular products}, \quad (60)$$

$$RCOOOH + RCHO \rightarrow 2RCOOH , \quad (61)$$

$$RCOOOH + C_nH_{2n} \overset{K_{63}}{\rightleftarrows} RCOOOH \ldots C_nH_{2n} \rightarrow \diagup C-C \diagdown O \diagup + RCOOH , \quad (62)$$

$$RCOOOH \ldots C_nH_{2n} \rightarrow RCOOH + {}^1/_2O_2 + C_nH_{2n} , \quad (63)$$

$$RCOO\dot{O} + RCOO\dot{O} \rightarrow \text{molecular products}. \quad (64)$$

When the proposed mechanism holds, the rate of formation of the epoxide (w_e) is described by the formula

$$w_e = \frac{k_{59}[C_nH_{2n}]w_i}{k + k_{60}[C_nH_{2n}]} + \frac{k_{57}k_{62}[RCHO]^2 w_i (1 + K_{63}[C_nH_{2n}])}{(k + k_{60}[C_nH_{2n}])\{k_{61}[RCHO] + (k_{62} + k_{63})K_{63}[C_nH_{2n}]\}} \quad (65)$$

where $k = k_{64}[RCOO\dot{O}]$. The first term in Eqn.(65) characterises the epoxidation of the olefin by the RCOOȮ radicals and the second characterises its epoxidation by the peracid (the Prilezhaev reaction).

The extremum in the relation between the rate of epoxidation and the olefin concentration is due to the molecular stage in the epoxidation of the olefin by the peracid, because in zone *B* (Fig.8) there is a sharp decrease of the steady-state concentration of the peracid in proportion to the square of the concentration of the olefin. The constancy of w_e as $[C_nH_{2n}]$ increases (zone *C*, Fig.8) is due to the radical component of the rate of oxidation; the role of the peracid becomes negligible. A 100% yield of 1,2-epoxynonane relative to the unconsumed benzaldehyde is characteristic of zone *C*. At low olefin concentrations (zones *A* and *B*, Fig.8) the incomplete utilisation of the active oxygen in epoxidation (Fig.8 curve *3*) is associated with reaction (61) and also with the molecular decomposition of the peracid induced by the olefin.

The rate constant for the epoxidation of the olefin by acylperoxy-radicals has been obtained for the joint oxidation of benzaldehyde and non-1-ene: $k_{54} = 1.8 \times 10^4$ litre mol^{-1} s^{-1}.

The mechanism of the coupled oxidation of olefins and aldehydes shows that the interaction of the RCOOȮ radical with an olefin leads to the formation of two new radicals—the active radicals RCȮ and the radicals $M\dot{O}_2$ which determine the

development of the polymerisation pathway in the system resulting in a decrease of the yield of the epoxide.

Analysis of the system showed that when the radicals $M\dot{O}_2$ are relatively inactive compared with $R\dot{C}O$ and do not participate in chain transfer to the aldehyde, the relative contributions of reactions (59) and (60) can be altered by a special procedure, which has come to be called selective inhibition[70] and thus the selectivity of the oxidation can be significantly increased by suppressing the undesirable reaction pathway as a result of the introduction of the appropriate inhibitor.

The selective inhibition method has been used to increase the yield of styrene oxide in the coupled oxidation of styrene and acetaldehyde[71] and to increase the yield of epichlorohydrin in the coupled oxidation of allyl chloride and acetaldehyde[72]. The inhibitor used was tanol (the 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yloxy-radical). In the presence of this inhibitor, which interacts with the radicals $\dot{M}$, the polymerisation reaction pathway [reaction (60)] is almost completely arrested (Fig. 9).

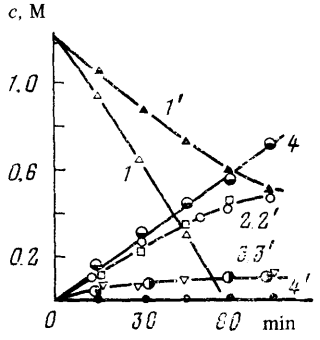


Figure 9. Kinetic curves for the consumption of styrene (curve *1*), the accumulation of benzaldehyde (curve *2*), styrene oxide (curve *3*), and the polymer (curve *4*) in the joint oxidation of styrene and acetaldehyde in benzene at 70 °C; the primed numerals denote the corresponding quantities in the presence of 2×10^{-5} M tanol. The end of the induction period was adopted as the starting point of the time readings[71].

A necessary condition for selective inhibition is the ability of the inhibitor to interact preferentially with one of the radicals of the chain. This can be achieved both by selecting an inhibitor and with markedly different constants for interaction with different types of radicals and by maintaining an optimum inhibitor concentration in the system. The calculation of the optimum inhibitor concentration range, based on the coupled oxidation mechanism given above and supplemented by elementary stages with participation of tanol ($\dot{I}m$), i.e.

$$R\dot{C}O + \dot{I}m \rightarrow RCOIm, \quad (66)$$

$$\dot{M} + \dot{I}m \rightarrow MIm, \quad (67)$$

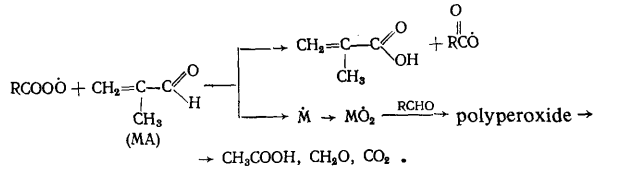
$$MIm\ (RCOIm) + M\dot{O}_2\ (RCOO\dot{O}) \rightarrow \begin{cases} MO_2M + \dot{I}m, \\ \text{molecular products,} \end{cases}$$

$$M\dot{O}_2 + M\dot{O}_2 \rightarrow \text{molecular products,} \quad (68)$$

leads to the following condition for selective inhibition in the system[70]:

$$\frac{k_{56}k_{60}[O_2]}{k_{66}(k_{59}+k_{60})} > \dot{I}m > \frac{k''_{60}(w_i k_{68})^{1/2}[O_2]}{k'_{60}k_{67}[C_nH_{2n}]}. \quad (69)$$

The selective inhibition method has also been used to develop a new procedure for the synthesis of methacrylic acid (MAA) [73] by the liquid-phase oxidation of methacroleine (MA), which can be regarded as a coupled reaction involving two reaction centres of the same molecule:



The use of tanol as the inhibitor and of a heterogeneous catalyst (TiB_2) made it possible to devise a process with a selectivity of 84 mole % (with respect to the aldehyde which has reacted) for a degree of conversion of 40 mole % (Table 3).

Table 3. The influence of tanol (T) on the composition and yields of methacroleine oxidation products (70 °C; air pressure 25 atm; solvent—benzene; TiB_2 catalyst).[73]

Starting materials		Reaction time, h	Degree of conversion, mole %	[MAA]/Δ[MA], %	CH_3COOH/Δ[MA], %
[MA], M	10^5[T], M				
0.50 *	—	7	10	—	—
0.46 **	0.29	7	3.5	82.0	13.5
1.00 ***	1.16	3	41	84.0	16.0
1.00 ***	—	3	62	32.0	27.0

*In the absence of the catalyst.
**Catalyst at a concentration of 1.0 g litre^{-1}.
***Catalyst at a concentration of 2.5 g litre^{-1}.

4. Kinetics of Oxidation Reactions in Open Systems

The study of the kinetics of chemical reactions in open systems as a theoretical basis for continuous processes in chemical engineering has made a definite contribution to the solution of problems of the optimisation of technological processes. The results of studies of the kinetics of liquid-phase oxidation reactions of hydrocarbons in open systems are considered below. The complex radical chain oxidation mechanism can be represented by the following sequence of transformations:

$$\underset{\text{hydrocarbon}}{RH} \xrightarrow{k_I} \underset{\text{hydroperoxide}}{ROOH} \xrightarrow{k_{II}} \underset{\text{ketone}}{R'COR''} \xrightarrow{k_{III}} \underset{\text{acid}}{R'COOH}. \quad (70)$$

Here k_I, k_{II}, and k_{III} are the overall reaction constants representing sets of rate constants for elementary stages.

In a continuous process the substance RH to be oxidised is introduced into the reactor at a constant rate and part of the reacting mixture is removed. The attainment of steady-state concentrations of products is characteristic of reactions in open systems. The steady-state concentration of the final product is then higher the lower the specific rate# of

The specific rate ν is the volume of the initial liquid component supplied per unit time per unit volume of the reactor and has the dimension of reciprocal time.

supply of the starting materials v.[75] For intermediates, for example, the hydroperoxide[75], this relation has an extremum (Fig.10) and, in conformity with the simplified mechanism (70), can be formulated thus:

$$\frac{d[ROOH]}{dv} = \frac{k_I[RH]_0(v^2 - k_I k_{II})}{(k_I + v)^2(k_{II} + v)^2} .$$

The rate of accumulation of all the oxidation products also passes through a maximum as a function of v and the maximum rate of accumulation of the more extensive oxidation product is attained at lower flow rates v. The maximum rate of accumulation of the final reaction product is attained at the same flow rate as the maximum steady-state concentration of the precursor. This property of an open system suggested a method for determining the pathways leading to the formation of the final reaction products[75]. It consists in comparing the positions of the maxima in the relations between the rates of accumulation of the final products and the steady-state concentrations of intermediates, on the one hand, and the flow rate, on the other. When these maxima are attained for the same flow rate, one can assume that the intermediate is a direct precursor of the given final product.

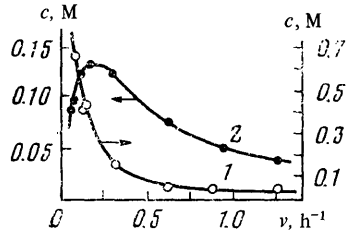


Figure 10. Dependence of the stationary concentrations of acids (curve *1*) and hydroperoxides (curve *2*) on the rate of supply of n-decane in the oxidation of the latter in an open system at 140 °C.[75]

A characteristic feature of reactions in open systems—the attainment of steady-state concentrations of the starting materials and reaction products—made it possible to develop a new kinetic method for the determination of the rate constants for the formation and consumption of intermediates in complex reactions involving free radicals. The method is based on the variation of the steady-state concentration of the intermediate, the rate of consumption of which is to be measured, keeping constant the steady-state concentration of free radicals. This is achieved by supplying into the reaction vessel initially the pure starting material and then its mixtures with the given product P at the same flow rate. Since v remains constant, the steady-state concentrations of free radicals are the same in both cases. The effective rate constant $k_{2''}[RO_2]$ for the consumption of the product P can be calculated from the difference between the steady-state concentrations established when these solutions are introduced into the vessel, namely $[\bar{P}]$ and $[\bar{P}]_1$ respectively:

$$[P]_0/([\bar{P}]_1 - [\bar{P}]) = (1 + k_2'' [\dot{RO}_2]/v) ,$$

where $[P]_0$ is the concentration of P in the mixture entering the vessel.

This method has been used to determine the reactivity of products with respect to the radicals $R\dot{O}_2$ in the oxidation reactions of ethylbenzene and n-decane[28]. As an example, Fig.11 presents the steady-state concentrations of methylphenylmethanol and acetophenone for different contents of methylphenylmethanol in the ethylbenzene supplied to the vessel. The effective rate constant for the consumption of methylphenylmethanol ($k_{2''}, ROH$) was determined from the slope of the relation between $[\overline{ROH}]_1 - [\overline{ROH}]$ and $[ROH]_0$ (Fig.11, curve *4*). The reactivity of the $R\dot{O}_2$ radical with respect to the n-decane oxidation products was determined by the same method.

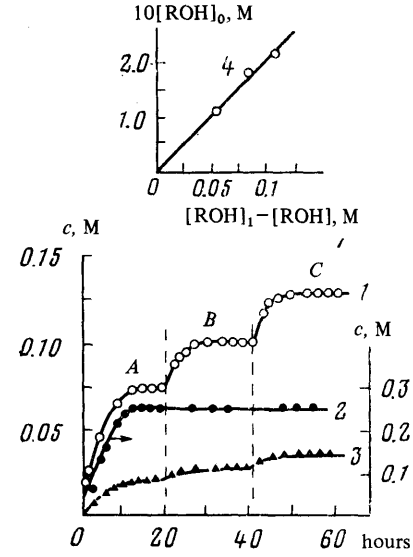


Figure 11. Kinetic curves for the accumulation of methylphenylmethanol (curve *1*), hydroperoxide (curve *2*), and acetophenone (curve *3*) in the oxidation of ethylbenzene in an open system with supply into the reaction vessel of ethylbenzene (*A*) and solutions of methylphenylmethanol in ethylbenzene containing 0.05 M (*B*) and 0.1 M (*C*) alcohol; v = 0.215 h^{-1}; 4) dependence of the difference between the stationary concentrations of methylphenylmethanol on its concentration in ethylbenzene $[ROH]_0$; v = 0.102 h^{-1}; 118 °C.[28]

If several isomers containing a functional group in different positions are formed in the reaction, the proposed method makes it possible to determine the rates of formation and consumption of each isomer separately without determining the concentrations of the individual isomers[77].

5. Catalysis of Oxidation

The most important method for increasing the rate and selectivity of oxidation involves the use of homogeneous and heterogeneous catalysts. Catalytic hydroperoxide oxidation and decomposition reactions as well as the problem of using catalysts to increase the selectivity of liquid-phase oxidation have been examined in detail recently in a number of reviews [78-81] and we shall therefore deal only very briefly with studies on catalysis.

The acceleration of liquid-phase oxidation processes by the addition of variable-valence metal compounds is associated with the participation of the catalysts in the chain branching

(radical decomposition of the hydroperoxide), chain initiation (activation of oxygen), and chain propagation stages. The decomposition of hydroperoxides, leading to the formation of free radicals, is the stage of the oxidation process involving the catalyst which has been studied in greatest detail. In most cases this reaction ensures the acceleration of the oxidation in the presence of both homogeneous[79] and heterogeneous[81] catalysts based on variable-valence metals.

The decomposition of hydroperoxides proceeds via an intermediate stage involving the formation of complexes between the catalyst and the hydroperoxide. To demonstrate this, a combination of kinetic and physicochemical (ultraviolet and infrared spectroscopy, NMR, EPR, etc.) methods for the quantitative investigation of catalyst–hydroperoxide systems under various conditions was used[82–84]. The simplest mechanism of the decomposition of a hydroperoxide, taking into account the formation of intermediate complexes between the catalyst and the hydroperoxide, is

$$n\,M^{n+} + m\,ROOH \rightleftarrows [n\,M^{n+} m\,ROOH] \rightarrow n\,M^{(n+1)+} + R\dot{O} + OH^- + (m-1)\,ROOH;$$

$$n_1 M^{(n+1)+} + m_1 ROOH \rightleftarrows [n_1 M^{(n+1)+} m_1 ROOH] \rightarrow$$

$$\rightarrow n_1 M^{n+} + R\dot{O}_2 + H^+ + (m_1 - 1)\,ROOH\ .$$

The quantities m, m_1, n, and n_1 depend on the nature of the catalyst and the hydroperoxide[83–85].

In the decomposition of the hydroperoxide in the presence of heterogeneous catalysts the process proceeds via a homogeneous-heterogeneous mechanism: the radicals formed in the decomposition of the hydroperoxide on the catalyst surface escape into space, where they can propagate the oxidation chain or recombine:

$$ROOH + S \begin{cases} \longrightarrow [ROOH \ldots S] \rightarrow R\dot{O} + [\dot{O}H \ldots S] \\ \longrightarrow [ROOH \ldots S] \rightarrow R\dot{O}_2 + [H \ldots S] \end{cases}.$$

This hydroperoxide decomposition mechanism has been demonstrated by the method of inhibitors[86] and by measuring the chemiluminescence of solutions[87] in the decomposition of cumenyl hydroperoxide in the presence of iron oxides.

The method proposed[89] for the investigation of the conductivities of transistor semiconducting structures has been used successfully to investigate complexes with partial charge transfer between the hydroperoxide and the heterogeneous catalyst. It makes it possible to identify the intermediate complexes and to determine their polarities and formation constants. The method is based on the change in the conductivity of the semiconducting triode structure of the type $p-n-p$ or $n-p-n$ following the adsorption of electron-donating and electron-accepting molecules. The adsorption of acceptors widens the base (the narrow middle band) in structures of the type $n-p-n$ and is accompanied by a decrease of conductivity. The adsorption of electron donors leads to an increase of n-type conductivity in the surface region of the base; for structures of the type $p-n-p$, donors and acceptors have the opposite effects.

The quantitative parameters of complex formation in the interaction of organic hydroperoxides with catalysts—copper and potassium hexacyanoferrates(III) and germanium oxide—have been obtained with the aid of this method[90]. The hexacyanoferrates(III) were deposited on the oxidised surface of a silicon structure of the $n-p-n$ type by adsorption from aqueous solutions. Fig.12 illustrates the variation of the conductivity $\Delta I/I_0$ of the structure with deposited hexacyanoferrates(III) (I_0 is the conductivity of the initial structure) under the influence of the adsorption of the hydroperoxide. It follows from the analysis of these curves that, in relation to both catalysts, α-phenylethyl hydroperoxide behaves as an electron donor. The limiting change in conductivity ΔI, observed when the catalyst surface is saturated with the hydroperoxide, is almost an order of magnitude higher for $Cu_3[Fe(CN)_6]_2$ than for $K_3[Fe(CN)_6]$. Thus the charge transferred from the hydroperoxide molecule to the first catalyst is much greater than for the second catalyst.

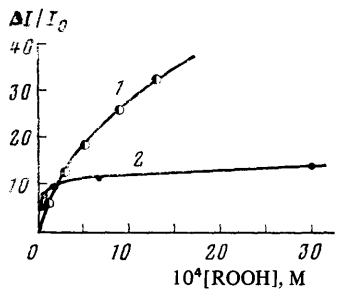


Figure 12. Variation of the conductivity of a transistor structure of the type $n-p-n$ with deposited metal hexacyanoferrates(III) as a function of the concentration of α-phenylethyl hydroperoxide in solution: 1) $Cu_3[Fe(CN)_6]_2$; 2) $K_3[Fe(CN)_6]$; solvent—heptane; 30 °C.[90]

The equilibrium constant for the formation of the complex of α-phenylethyl hydroperoxide with the catalyst, found from Fig.12 for $K_3[Fe(CN)_6]$, exceeds by a factor greater than 20 the equilibrium constant for $Cu_3[Fe(CN)_6]_2$ (Table 4).[90] It is significant that the equilibrium constant for the complex of the $Cu_3[Fe(CN)_6]_2$ catalyst with α-phenylethyl hydroperoxide, obtained by the method of transistor structures, virtually agrees with independent measurements of the same quantity by the kinetic method (5.5×10^2 litre mol^{-1}).[90] Table 4 also lists the parameters of the complex formation reactions of α-phenylethyl and t-butyl hydroperoxides with germanium oxide. In this case the activation of the hydroperoxide is associated with the transfer of an electron from the catalyst to the hydroperoxide.

Table 4. Physicochemical parameters of hydroperoxide–catalyst complexes (30 °C; solvent—heptane; gas phase—argon).[90]

Catalyst	α-Phenylethyl hydroperoxide		t-Butyl hydroperoxide		Cumenyl hydroperoxide	
	K, litre mol^{-1}	$\Delta I/I_0$	K, litre mol^{-1}	$\Delta I/I_0$	K, litre mol^{-1}	$\Delta I/I_0$
$Cu_3[Fe(CN)_6]_2$	$7.0 \cdot 10^2$	80.0	—	—	—	—
$K_3[Fe(CN)_6]$	$1.7 \cdot 10^4$	14.0	—	—	$1.4 \cdot 10^4$	3.0
Cu^{2+}/GeO_2	$7.7 \cdot 10^4$	10.0	—	—	—	—
Cu^{2+}/GeO_2 *	$6.1 \cdot 10^4$	18.5	$5.8 \cdot 10^3$	36.0	—	—
GeO_2	$3.0 \cdot 10^4$	4.5	—	—	—	—

*Gas phase—oxygen.

Comparison of the physicochemical characteristics of complexes of various hydroperoxides and heterogeneous catalysts with the activities of the catalysts in the hydroperoxide decomposition reaction shows that the highest rates of decomposition correspond to the formation of more polar and weaker reactant–catalyst bonds.

Together with the decomposition of the hydroperoxide, the formation of free radicals in the interaction of the catalyst with the starting materials—oxygen and the hydrocarbon (activation of oxygen and the hydrocarbon)—can play a major role in the presence of catalysts. The activation of oxygen apparently plays the main role in the initiation of the oxidation chain in the presence of catalysts. The possibility of the process via the mechanism

$$M^{n+} + O_2 \rightarrow M^{n+} \ldots O_2 ,$$
$$M^{n+} \ldots O_2 + RH \rightarrow M^{n+} + \dot{R} + H\dot{O}_2 ,$$

was first demonstrated by the method of inhibitors for the oxidation of ethylbenzene in the presence of nickel acetylacetonate[91] and was subsequently confirmed for a number of homogeneous and heterogeneous catalysts.

The activation of oxygen on the catalyst with subsequent increase of the rate of chain initiation apparently plays an important role in oxidation reactions in the presence of copper complexes of *o*-phenanthroline[92]. The study of the influence of oxygen on the rate of oxidation of cumene in the presence of copper complexes of *o*-phenanthroline at 30–40 °C demonstrated a strong dependence of the rate of oxidation on the oxygen pressure up to 760 mmHg [92] (Fig.13).

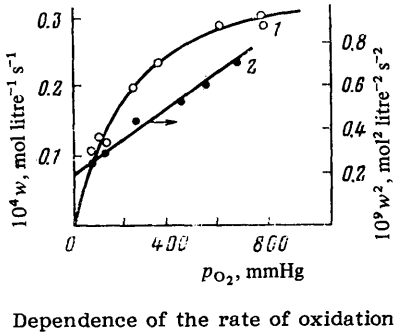


Figure 13. Dependence of the rate of oxidation of cumene in the presence of the complex $Cu(acac)_2$ with *o*-phenanthroline on the partial pressure of oxygen (curve *1*) and the transformed version of this relation (curve *2*); 30 °C.[92]

The relation obtained can be readily explained by the involvement of the catalyst in the chain initiation reaction. Indeed the rate of oxidation of cumene should be described by the following equation in this case:

$$w = \frac{k_2}{k_6^{1/2}} [RH] \sqrt{w_0 + k' [O_2]} ,$$

which holds satisfactorily in the experiment (Fig.13). Furthermore, the rate of oxidation of cumene is in this case three times higher than the rate of oxidation calculated by the formula $w = (k_2^2/k_6)[RH]^2$, which takes into account the involvement of the catalyst only in chain branching.

The formation of charge-transfer complexes between $Rh(PPh_3)_3Cl$ and oxygen has been detected by EPR. In the presence of oxygen the diamagnetic catalyst species are converted into the complex $Rh(II).O_2^-$, in the EPR spectrum of which it is possible to identify groups of lines due to Rh(II) and O_2^- (Fig.14).[21] The role of these complexes in the oxidation process has been established by introducing into the systems certain specific additivies, which make it possible to increase the concentration of the oxygen complexes, the rate of oxidation increasing in the presence of such additives (Fig.14).

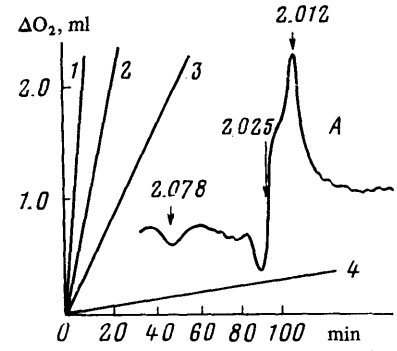


Figure 14. Kinetic curves for the absorption of O_2 in the oxidation of solutions of cyclohexene (line *1*), ethylbenzene (line *2*), and nonene (line *3*) in toluene in the presence of the modified complexes $Rh(PPh_3)_2COCl$ at 25 °C and kinetics of the absorption of O_2 by a solution of cyclohexane in the presence of the unmodified catalyst (line *4*). *A*) EPR spectrum of the modified catalyst at 77 K.

The activation of oxygen and the involvement of the catalyst in the chain initiation reaction are apparently largely responsible for the catalytic effect in the presence of variable valence metal oxides[93]. For a series of metal oxides, the initiating function in oxidation processes apparently reduces solely to their involvement in chain initiation. Thus the oxides ZnO, FeO, and NiO hardly decompose the hydroperoxide. In the presence of these catalysts virtually the only oxidation product is the hydroperoxide (Table 5).[93]

Table 5. The oxidation of cumene and the rate of decomposition of cumenyl hydroperoxide in the presence of metal oxides at 73 °C.[93]

Catalyst	Amount of catalyst, mg ml^{-1}	[ROOH], mole %	[DMPA], mole %	[AP], mole %	$10^2 w_{ROOH}$, mol litre^{-1} min^{-1}
MnO	0.10	54	17.0	2.0	100
Co_2O_3	2.50	52	16.0	1.6	55
Fe_2O_3	2.50	78	10.0	1.2	24
FeO	30.0	90	3.0	0.25	2
NiO	1.5	87	4.2	0.13	2
Cr_2O_3	2.5	89	2.0	0.1	0.5
ZnO	20.0	96	2.0	0.1	0
Bi_2O_3	10.0	90	2.0	0.1	0

[It is not clear from the context what DMPA and AP are (Ed. of Translation)].

To increase the rate and selectivity of the liquid-phase oxidation of organic compounds in the presence of homogeneous and heterogeneous catalysts, the principle of the donor–acceptor modification of these catalysts is used[94]. Thus the selectivity of the oxidation of isopropylbenzene to the hydroperoxide can be increased from 82 to 92% (relative to the absorbed oxygen) with the aid of the preliminary

adsorption of carbon dioxide or dicyanomethylene-2,4,7-trinitrofluorenone [DTF] on the surface of the heterogeneous catalyst (AgO).[94] Electron-donating modifying agents (CO, NH_3) increase in this process the rate of oxidation and the rate of accumulation of the product (alcohol), while electron-accepting modifying agents (CO_2, DTF) decrease the rate of oxidation and ensure a high process selectivity with respect to the hydroperoxide.

An example of the modifying effect of solid additives is provided by the oxidation of ethylbenzene on silver catalysts containing 0.02 at.% of various metals (Ca, Mo, Cl, Bi, and Co).[95] The catalyst may be modified in the course of the oxidation process itself as a result of the accumulation of certain reaction products. Thus, in the liquid-phase oxidation of tetralin in the presence of the Ag_2O catalyst deposited on SiO_2 (Fig.15),[96] the composition of the products initially agrees with the composition of the products of the non-catalysed oxidation: the three main reaction products (tetralyl hydroperoxide, 1-tetralol, and 1-tetralone) accumulate at comparable rates. As the process develops, the accumulation of the ketone and alcohol stops completely and the only reaction product becomes the hydroperoxide, i.e. the catalyst is modified with participation of oxygen-containing products. The modified catalyst ensures the inhibition of the chain reaction and can activate molecular oxygen.

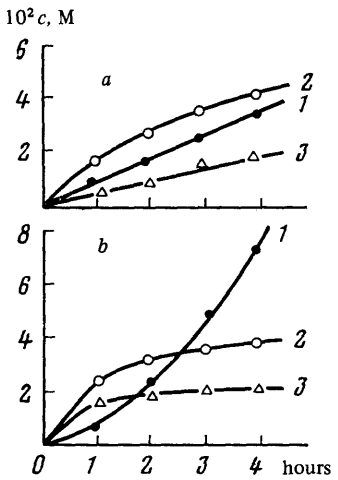


Figure 15. Kinetic curves for the accumulation of tetralyl hydroperoxide (curve *1*), 1-tetralone (curve *2*), and 1-tetralol (curve *3*) in the oxidation of tetralin: *a*) without catalyst; *b*) in the presence of 0.4 g litre^{-1} of deposited heterogeneous catalyst; 130 °C.[96]

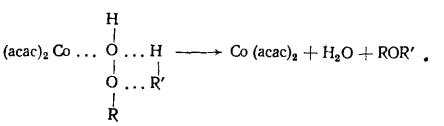
The efficiency of the donor–acceptor modification when homogeneous catalysts are used has been demonstrated in relation to the oxidation of ethylbenzene in the presence of nickel bis(acetylacetonate) [97] and the oxidation of cyclohexane catalysed by the rhodium complex $Rh(PPh_3)_3Cl$.[98]

The decomposition of the hydroperoxide without the formation of free radicals (molecular decomposition of the hydroperoxide) can play an important role in the mechanism of the catalytic oxidation of hydrocarbons and other organic compounds. Such decomposition can lead to the formation of new products uncharacteristic of the non-catalytic oxidation. On the other hand, the intense molecular decomposition of the hydroperoxide, which is an important source of free radicals, can lead to the inhibition of the oxidation process.

Direct evidence for the molecular pathway leading to the decomposition of the hydroperoxide in the presence of the catalyst has been obtained with the aid of the method of inhibitors in relation to the decomposition of n-decyl hydroperoxide in the presence of copper stearate[85]. The considerable (up to 90%) molecular decomposition of the hydroperoxide is characteristic of the decomposition of tetralinyl hydroperoxide in the presence of cobalt stearate[99].

The study of the dependence of the rate of decomposition of the hydroperoxide and of the consumption of the inhibitor (radical decomposition) on the catalyst and hydroperoxide concentrations established that both decomposition pathways proceed via the formation of the same complex[100,101]. The "cage effect" of the solvent plays an important role in the molecular mechanism of the decomposition of the hydroperoxide[102]. The radicals formed in the decomposition of the complex M^{n+}.ROOH can either recombine in the solvent cage (molecular decomposition of the hydroperoxide) or can diffuse from the cage (radical decomposition). The ratio of the radical and molecular hydroperoxide decomposition pathways depends greatly on the viscosity of the medium (η): with increase of η, the contribution of the molecular decomposition of ROOH increases. The molecular decomposition of the hydroperoxide in the presence of heterogeneous catalysts takes place via an analogous mechanism[98].

In the non-catalytic decomposition of the hydroperoxide, the involvement of solvent molecules [reaction (3′)] in the process leads to an increase of the rate of formation of free radicals. In the presence of the catalyst the addition of organic solvents with a mobile C–H bond acclerates the molecular decomposition[98,102]. Thus, in the decomposition of cumenyl hydroperoxide in the presence of $Co(acac)_2$, the rate of decomposition of the hydroperoxide is almost independent of the concentration and nature of the solvent. The contribution by the molecular decomposition increases greatly with increase of the hydrocarbon concentration in the solvent and to a greater extent the smaller the C–H bond strength in the hydrocarbon[102], which is apparently associated with the interaction of RH with the hydroperoxide activated by the partial electron transfer to the catalyst–ROOH complex:



The decomposition of t-butyl hydroperoxide in the presence of oxide catalysts is significantly inhibited by the addition of hydrocarbons with a mobile C–H bond. A change in the composition of the reaction products is then observed—the accumulation of a new product, namely an asymmetric hydroperoxide containing the t-butyl group and the alkyl group forming part of the composition of the solvent. The hydroperoxide decomposes in this case without the release of free radicals into space and is apparently a "concerted" process (simultaneously dissociated of the bonds in the starting materials and the formation of new bonds in the hydroperoxides).

The catalytic oxidation of organic compounds in alkaline media by molecular oxygen is apparently a promising reaction[103–105]. Copper complexes of *o*-phenanthroline and bipyridyl can serve as catalysts in such systems. Alcohol and ketones capable of forming ions in alkaline media are oxidised. The rate of oxidation of these substances is

independent of the nature of the base and increases with increase of the pH of the medium in the pH range from 10 to 12 (Fig.16). At pH > 12 the rate of oxidation falls owing to the deactivation of the catalyst.

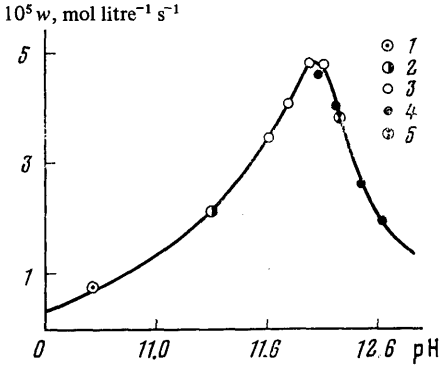


Figure 16. Dependence of the rate of oxidation of ethyl methyl ketone (EMK) on the pH of the medium in the presence of various bases: 1) $Mg(OH)_2$; 2) Na_2CO_3; 3) $(C_2H_5)_3N$; 4) NaOH; 5) $Ca(OH)_2$; 10 ml H_2O, 0.5 ml EMK; $[CuCl_2]_0 = 5 \times 10^{-3}$ M; $[o\text{-phen}]_0 = 1.5 \times 10^{-2}$ M; 50 °C.[92]

The alkali + $CuCl_2$ + *o*-phenanthroline catalytic system is capable of ensuring at pH > 9 rates of oxidation of alcohols and ketones up to 50–80 mole % per hour and more (at 30° to 50 °C), which are virtually unattainable in the catalytic oxidation of organic substrates in neutral media.

The main products of the oxidation of alcohols and ketones, i.e. acids, are the primary reaction products under the conditions of alkaline oxidation. The anions are the active form of the substrate. The strong influence of the medium on the electron-donating capacity of the anions makes it possible to alter the rate of the process and the selectivity of the oxidation by changing the solvent. Thus the rate of oxidation of a 40% solution of methanol in benzene is almost an order of magnitude higher than the rate of oxidation of methanol in bulk. The oxidation apparently develops via a non-chain mechanism without the release of free radicals into space and proceeds as a result of the interaction of O_2 with the anion A^- activated by its incorporation in the complex $Cat.A^-$ with the catalyst.

In the general form, the oxidation mechanism consists of a sequence of the following stages[106]:

$$Cu^{2+} + R'\overline{C}HC(O)R'' \rightleftarrows Cu^{2+} \cdot R'\overset{\ominus}{C}HC(O)R'',$$

$$Cu^{2+} \cdot R\overline{C}HC(O)R'' + O_2 \rightarrow Cu^{+} + R'C\overset{O}{\underset{OH}{\diagup\diagdown}} + R''C\overset{O}{\underset{OH}{\diagup\diagdown}},$$

$$Cu^{+} + R'\overline{C}HC(O)R'' \rightleftarrows Cu^{+} \cdot R'CHC(\dot{O})R''$$

$$Cu^{+} \cdot R'\overline{C}HC(O)R'' + O_2 \rightarrow Cu^{2+} + R'C\overset{O}{\underset{OH}{\diagup\diagdown}} + R''C\overset{O}{\underset{OH}{\diagup\diagdown}},$$

In the oxidation of ketones the interaction of the coordinated anion with O_2 proceeds at very high rates and does not limit the rate of oxidation. In the oxidation of alcohols oxygen participates in the rate-limiting stage of the process and in this case the rate of oxidation greatly depends on the oxygen pressure[104].

6. Metal Complex Inhibition

Approximately three decades ago, the phenomenon of the dual function[107] of variable-valence metal compounds in liquid-phase oxidation reactions was discovered. It consists in the fact that, with increase of the initial concentration of the metal complexes, there is a sharp (critical) change in the rate of reaction—a transition from the catalytic to inhibited oxidation conditions. Recently there has been a considerable growth of interest in the use of metal complexes as inhibitors of liquid-phase oxidation and in the study of the mechanism of the metal complex inhibition.

The inhibition of oxidation in the presence of metal compounds is due to two causes: the decomposition of the hydroperoxide into non-radical products and the interaction of free radicals with metal complexes. The latter type of inhibition is most common. The mechanisms of the reactions of $R\dot{O}_2$ radicals with metal compounds, leading to the termination of oxidation chains, are considered below.

The inhibition by the sulphur-containing metal complexes, namely bis(dialkyl phosphorodithioates) $[M(dtp)_n]$,[111–118] bis(*N*,*N*-dialkyldithiocarbamates) $[M(dtc)_2]$,[109–115] bis(8-mercaptoquinolinates) $[M(toq)_n]$,[119] and bis(α-thiopicolinanilides) $[M(tpa)_2]$ [108,109] takes place as a result of chain termination by the complexes. The stoichiometric inhibition coefficient *f* and the rate constant for the reaction of $R\dot{O}_2$ with the metal complexes depend greatly on the decomposition of the chelate unit, the nature of the metal, the coordinating atoms of the ligand, and the oxidation potential of the complex and its geometry (Table 6).

Table 6. Dependence of the effectiveness of inhibition (fk_7) by sulphur-containing complexes on the oxidation potentials ($E_{1/2}$) (oxidation of ethylbenzene; 75 °C; initiator—azobisisobutyronitrile; $w_i = 1 \times 10^{-6}$ mol litre^{-1} s^{-1}).[119]

Compound	$10^{-3}kf_7$, litre mol^{-1} s^{-1}	$+E_{1/2}$, V
	$M(toq)_n$	
$Zn(toq)_2$	2.3	1.10
$Ag(S\text{-}toq)$	1.3	0.93
$Co(S\text{-}toq)_3$	11	0.59
$Ni(S\text{-}toq)_2$	7.5	0.56
$Cu(toq)_2$	>60	0.48
	$M(dtc)_n$	
$Zn(dtc)_2$	1.6	1.01
$Bi(dtc)_3$	5.7	0.86
$Pb(dtc)_2$	6.3	0.80
$Ni(dtc)_2$	23	0.60
$Cu(dtc)_2$	60	0.43
	$M(tpa)_2$	
$Ni(tpa)_2$	2.6	0.88
$Cu(tpa)_2$	13	0.75

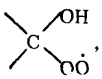
Table 6 shows that the inhibiting activity of the metal complexes is higher the greater the ease of oxidation of the complex[109,119]. An increase of the degree of covalence of the metal–ligand bond in the complex also promotes an increase of its inhibiting activity in the oxidation reaction[120]. The mechanism of the inhibition includes in this case the formation of a complex of $R\dot{O}_2$ with the chelate and subsequent electron transfer to the peroxy-radical[121]. The central metal ion plays the role of an agent transferring an electron to the peroxy-radical from the ligand, which is also split off in the

form of a radical incapable of participating in the chain propagation reaction. The degree of oxidation of the metal remains unchanged.

For $M(dtc)_2$, the reaction mechanism can be formulated as follows[109,110]:

$$M(dtc)_2 + R\dot{O}_2 \rightleftarrows \{M(dtc)_2 \ldots R\dot{O}_2\} \rightarrow \{[M(dtc)_2]^+ \ldots RO_2^-\},$$
$$\{[M(dtc)_2]^+ \ldots RO_2^-\} \rightarrow M(dtc)RO_2 + 2dt\dot{c},$$
$$2dt\dot{c} \rightarrow \text{disulphide}.$$

An analogous mechanism has been proposed for the inhibition of oxidation by the copper(I) complexes of triphenyl phosphite[122] as well as a number of phosphorodiothioates[115–118].

The electron transfer reaction between $R\dot{O}_2$ and the metal compounds can lead in some cases to a change in the oxidation state of the metal ion. Thus the oxidation of the Co^{2+} and Mn^{2+} ions has been observed in the interaction with radicals[123,124]. The phenomenon of repeated chain termination by metal ions has been observed in the oxidation of cyclohexanol and other secondary alcohols as well as amides in the presence of salts and certain complexes of copper, iron, cobalt, magnesium, and cerium[125]. This phenomenon is due to the fact that the hydroxyperoxy-radicals , formed in the oxidation of secondary alcohols, can interact with metal ions in both valence states:

$$\rangle C(OH)O\dot{O} + Cu^{2+} \rightarrow H^+ + Cu^+ + O_2 + \rangle C{=}O,$$
$$\rangle C(OH)O\dot{O} + Cu^+ \rightarrow \rangle C(OH)OO^- + Cu^{2+}.$$

In this system the quantity f may increase to 10^3.

The oxidation-reduction potential of the metal ion is very important for the operation of the mechanism presented above. At high oxidation-reduction potentials the degree of involvement of the metal in the decomposition of the hydroperoxide increases; at low oxidation-reduction potentials the rate of reaction of M^{n+} with $R\dot{O}_2$ falls.

For certain types of metal complex inhibitors, the interaction with peroxy-radicals takes place via a mechanism involving the abstraction of a hydrogen atom from the ligand. The inhibition of the oxidation of cumene and cyclohexa-1,3-diene by cobalt(III) complexes [as well as iron(II), nickel(II), and copper(II) complexes] with dimethylglyoxime and other dioximes[126,127] and also by nickel bis(α-phenylanthranilate) apparently involves this mechanism[128].

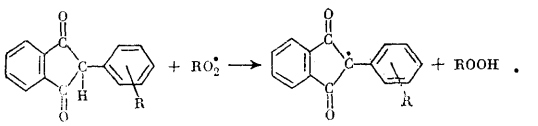
A hydrogen atom is abstracted from the ligand in the complex much more readily than from the free ligand, which indicates the activation of the ligand in the complex. Thus $k_{12} = 9 \times 10^2$ litre mol^{-1} s^{-1} (at 90 °C) for *N*-phenylanthranilic acid in ethylbenzene, while $k_{12} = 4.5 \times 10^3$ litre mol^{-1} s^{-1} for the nickel complex of *N*-phenylanthranilic acid[128].

7. The Mechanism of the Inhibited Oxidation

The study of the mechanism of the action of inhibitors and the establishment of theoretical principles for the selection of effective antioxidant additives is an important task in chemical kinetics. New classes of antioxidants have been investigated, rapid methods for the estimation of their efficiency have been proposed, and the details of the elementary stages of the inhibition process have been determined in recent years. Many fundamental results have been obtained with the aid of modern physical research methods—the chemiluminescence method, EPR, NMR, flash photolysis, and chemically induced nuclear polarisation (CINP).

The oxidation process is usually inhibited by adding to the system inhibitors which interact with free radicals and terminate oxidation chains[129]. The most common inhibitors of this type are phenols and aromatic amines. They cause chain termination via reaction (7).

Together with amines and phenols, 2-arylindan-1,3-diones, which have a reactive C–H bond, also serve as inhibitors[130]:



The constants k_7 for these inhibitors depend on the substituent in the benzene ring and amount to 1×10^2–6×10^4 litre mol^{-1} s^{-1} (Table 7). The substituents in the *p*-position, both electron-donating and electron-accepting, increase k_7, while those in the *o*-position decrease it. The influence of *p*-substituents is described by the Hammett equation in the form[131]

$$\lg(k_7/k_{7,\,st}) = 0.28\sigma + 1.01E_R.$$

Table 7. The rate constants, activation energies, and stoichiometric coefficients (f) for the reactions of cumenylperoxy-radicals with 2-arylindan-1,3-diones at 60 °C.[131]

R*	$10^{-4}k_7$, litre mol^{-1} s^{-1}	f	E_{act}, kcal mol^{-1}
	1.95	1.0	7.3
p-Br	2.9	1.7	5.0
p-Cl	2.8	1.2	6.0
p-N(CH$_3$)$_2$	2.25	2.0	5.0
p-OCH$_3$	2.0	1.8	5.5
o-OCH$_3$, *p*-OCH$_3$	0.12	—	—
o-OCH$_3$, *p*-OCH$_3$	0.01	—	—
p-CH$_3$	1.60	1.6	7.8
o-CH$_3$	0.09	—	—
β-Naphthyl	2.5	1.8	5.5
α-Naphthyl	0.88	1.0	9.5
Ionol	0.89	2.0	5.3

*Substituent in the 2-diphenyl[2-phenyl?] ring.

The subscript st refers to the unsubstituted 2-phenylindan-1,3-dione and σ and E_R are the polar and resonance constants of the substituents.

Together with reaction (7), there is also a possibility of recombination inhibition mechanisms. A new example of an inhibitor of this type is 1,2-bis(*p*-dimethylaminophenyl-1,2-diphthaloylethane)(PP). The inhibiting activity of PP is due to the equilbirium

$$PP \underset{k(-)}{\overset{k(+)}{\rightleftarrows}} 2\dot{P} \qquad (71)$$

and the irreversible reaction

$$R\dot{O}_2 + \dot{P} \rightarrow \text{products}. \qquad (72)$$

The radical P has been detected by EPR. The equilibrium constant is $k_{71} = 6.16 \times 10^2 \exp(-17\,300/RT)$ mol litre^{-1}, the rate constant for the recombination of $\dot{P}$ radicals at 20 °C is $k_{(a)} = 2 \times 10^8$ litre mol^{-1} s^{-1} and $k_{72} \geq 10^8$ litre mol^{-1} s^{-1}.[133]

The question of reactivity with respect to alkyl radicals is important for the mechanism of the action of inhibitors:

$$InH + \dot{R} \rightarrow In\dot{} + RH, \qquad (7')$$

$$\dot{R} + \dot{R} \rightarrow \text{products}. \qquad (73)$$

Estimates of the parameter $k_7'/k_{73}^{1/2}$ for the interaction of 16 inhibitors (amines and phenols) with alkyl radicals derived from ethhlbenzene showed[137] that its maximum possible value is $(0.4–3.5) \times 10^{-1}$ litre$^{1/2}$ mol$^{-1/2}$ s$^{-1/2}$. For $k_{73} = 2.8 \times 10^8$ litre mol^{-1} s^{-1}, we have $k_7' < (1–6) \times 10^3$ litre mol^{-1} s^{-1}. For *N*-phenyl-β-naphthylamine, $k_7'/k_{73}^{1/2} = (3.2 \pm 0.2) \times 10^{-2}$ litre$^{1/2}$ mol$^{-1/2}$ s$^{-1/2}$ and $k_7' = 6.7 \times 10^2$ litre mol^{-1} s^{-1}.

Thus phenols and aromatic amines interact with alkyl radicals much less vigorously than with peroxy-radicals, for which as a rule $k_7 \cong 10^4–10^5$ litre mol^{-1} s^{-1}.

The stable aliphatic nitroxy-radicals are effective acceptors of alkyl radicals[135]:

$$>\dot{N}O + \dot{R} \rightarrow NOR \quad . \qquad (74)$$

Aromatic nitroxy-radicals, which are capable of reacting with both the radicals $\dot{R}$ and $R\dot{O}_2$, act less selectively. Repeated chain termination in the oxidation of certain unsaturated hydrocarbons[137] and polypropylene[138] has been demonstrated for both types of nitroxy-radicals, apparently as a result of the regeneration of $>\dot{N}O$ when the ether derivatives of aliphatic nitroxy-radicals $>NOR$ interact with peroxy- and alkoxy-radicals and with oxygen[136]:

$$>NOR + R\dot{O}_2\ (R\dot{O},\ O_2) \rightarrow >N\dot{O} + \text{product}.$$

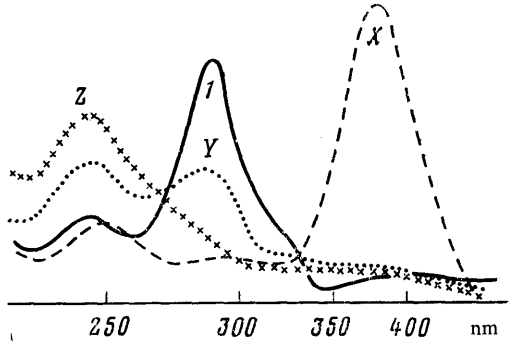
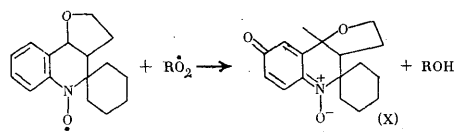


Figure 17. Ultraviolet absorption spectra of the 4-methyl-2-spiro-cyclohexyl-3,4,2',3'-tetrahydrofurano-1,2,3,4-tetraquinolin-1-yloxy-radical (curve *1*) and its reaction products (curves *X*, *Y*, and *Z*). Solvent—ethanol; [AIBN] = 4.9×10^{-2} M; $[\dot{NO}]_0 = 5.2 \times 10^{-4}$ M; 60 °C. Spectra *X* and *Z* were obtained in oxygen and spectrum *Y* was obtained in nitrogen[139].

Repeated chain termination in the inhibition by the aromatic 4-methyl-2-spirocyclohexyl-3,4,2',3'-tetrahydrofurano-1,2,3,4-tetrahydroquinolin-1-yloxy-radical of the oxidation of β-carotene[139] is due to a relay of radical reactions of the nitroxy-radical and its conversion products (Fig.17), which interact alternately with peroxy- and alkyl-radicals. The first stage involves the reaction of $>\dot{N}O$ with the radicals $R\dot{O}_2$:



The resulting quinone-nitrone (X) is an acceptor of the radicals $\dot{R}$:

$$X + 2\dot{R} \rightarrow Y; \quad Y + R\dot{O}_2 \rightarrow Z \quad .$$

The product Y then reacts with $R\dot{O}_2$.

As a result of the sequence of these reactions, five chains are terminated by the $>N\dot{O}$ fragment.

The radicals $In\dot{}$ formed in the interaction of InH with $R\dot{O}_2$ via reaction (7) interact with peroxy-radicals to form recombination products—quinolide peroxides (QP) [reaction (8)].

The values of k_8 for phenoxy-radicals depend little on the structure of $In\dot{}$ and $R\dot{O}_2$ and are in the range $(1.7–7.2) \times 10^8$ litre mol^{-1} s^{-1} (at 60 °C).[140–142] The probability α of the formation of QP depends on the concentration of the phenol, the rate of initiation, the rate constants k_7 and k_8, and the rate constant for the reaction

$$In^{\cdot} + In^{\cdot} \rightarrow \text{products}, \qquad (75)$$

and is defined by the equation[143]

$$\alpha^2(1+\alpha) - \frac{A}{k_9}(1-\alpha) = 0;$$

$$A = \frac{k_8^2 w_i}{k_7^2 [InH]^2} \quad .$$

Quinolide peroxides are formed with the highest probability ($\alpha = 1$) in inhibition by sterically hindered phenols whose phenoxy-radicals are stable and whose constants k_{75} are low. In the oxidation of low-molecular-weight hydrocarbons[144] in the presence of 2,4,6-tri-t-butylphenyl the yield of quinolide peroxide reaches 100%. Under the conditions of the inhibited oxidation, quinolide peroxides are capable of decomposing into radicals[143].

The initiating capacity of quinolide peroxides is comparable to that of azobisisobutyronitrile and benzoyl peroxide and is greatly superior to that of t-butyl hydroperoxide (Table 8).[143,144] The probability of the emergence of radicals from the cage in the decomposition of quinolide peroxides is close to unity. Their decomposition leads to a decrease of the antioxidant effectiveness of sterically hindered phenols in the autoxidation of hydrocarbons and polymers[143].

Table 8. Kinetic parameters of the thermal decomposition of quinolide peroxides (QP) [In = 2,4,6-tri-t-butylperoxy-radical, R = $C(CH_3)_3$] and certain initiators[143].

Compound	Decomposition rate constant, s^{-1}	$10^5 k$, s^{-1}
o-QP	$1.1 \cdot 10^{14} \exp[(-30500 \pm 1000)/RT]$	6.6
p-QP	$9.8 \cdot 10^{13} \exp[(-33000 \pm 2000)/RT]$	0.18
Azobisisobutyronitrile	$1.6 \cdot 10^{15} \exp(-30800/RT)$	57
Benzoyl peroxide	$3.0 \cdot 10^{14} \exp(-30800/RT)$	11
$(CH_3)_3COOH$	$3.6 \cdot 10^{12} \exp(-33000/RT)$	0.006

*At 93 °C.

Extensive information about the kinetics of reaction (75) for phenoxy-radicals has been obtained by flash photolysis[145–148]. The process mechanism can be represented by the following set of stages:

$$Ph\dot{O} + Ph\dot{O} \rightarrow D \quad , \qquad (76)$$

$$D \rightarrow Ph\dot{O} + Ph\dot{O} \quad , \qquad (77)$$

$$D \rightarrow \text{products}. \qquad (78)$$

The stage involving the irreversible transformation of the dimer [Eqn.(78)] is characteristic of radicals having at least one unoccupied *o*- or *p*-position. In this stage there is a possibility of the regeneration of the inhibitor. For the majority of phenoxy-radicals, $k_{76} \approx 10^9$–10^7 litre mol^{-1} s^{-1}.[148] The introduction of bulky substituents into the *p*-position relative to the O–H group causes a decrease of k_{76}. For example, the rate constant for the recombination of "galvinoxyl" radicals at 90 °C is 4.8×10^4 litre mol^{-1} s^{-1}.[149] The comparatively slow recombination of sterically hindered phenoxy-radicals is limited by molecular mobility. The cause of this effect consists in the low value of the steric factor for the interaction of these radicals[145].

The kinetic characteristics of the side processes involving inhibitors, i.e. the reactions of the inhibitor and its radicals with the hydrocarbon, the hydroperoxide, and oxygen, have been obtained. The kinetic parameters k_{79}/k_8, characterising the participation of the radical of *N*-phenyl-β-naphthylamine in the chain propagation reaction with a hydrocarbon (ethylbenzene), i.e.

$$\dot{\text{In}} + \text{RH} \rightarrow \text{InH} + \dot{\text{R}}, \qquad (79)$$

measured by the chemiluminescence method, is 3×10^{-9}.[150]

The rate constants for the reaction

$$\dot{\text{In}} + \text{ROOH} \rightarrow \text{InH} + \text{R}\dot{\text{O}}_2, \qquad (80)$$

involving t-butyl hydroperoxide and 2,6-di-t-butyl-4-R-phenols increase with increasing strength of the O–H bond in the phenol (the activation energy then falls). Thus, on passing from R = OCH_3 (D_{OH} = 73.9 kcal mol^{-1}) to R′ = CN (D_{OH} = 81.9 kcal mol^{-1}), the values of k_{80} at 60 °C increase from 0.07 to 170 litre mol^{-1} s^{-1} and the activation energy falls from 18 to 8.8 kcal mol^{-1}.

The formation of phenoxy-radicals in the reaction of a hydroperoxide with phenols[151],

$$\text{InH} + \text{ROOH} \rightarrow \begin{cases} \rightarrow \text{molecular products}, \\ \rightarrow \text{R}\dot{\text{O}} + \text{Ph}\dot{\text{O}} + \text{H}_2\text{O}, \end{cases} \qquad (81)$$

has been demonstrated by EPR for 2,4,6-tri-t-butylphenol. The constant k_{81} depends strongly on the structure of the phenol. For the interaction of cumenyl hydroperoxide with 2,6-dimethoxyphenol at 140, $k_{81} = 6.5 \times 10^{-3}$ litre mol^{-1} s^{-1} has been found, while the constant for the reaction with the sterically hindered 2,4,6-tri-t-butylphenol is $k_{81} = 7.5 \times 10^{-5}$ litre mol^{-1} s^{-1}.

It has been shown[152] that the reaction of aromatic amines, phenols, and naphthols with molecular oxygen,

$$\text{InH} + \text{O}_2 \rightarrow \dot{\text{In}} + \text{H}\dot{\text{O}}_2,$$

requires an activation energy of 25–35 kcal mol^{-1}. The contribution of this reaction to the initiation of the oxidation must be taken into account only above 180 °C and at high oxygen pressures.

For a long time, the question of the mechanism of the interaction of phosphites with a hydroperoxide [reaction (7‴)] remained controversial. The yield of radicals in this reaction is very low[154]. It was suggested that the reaction is either limited via a cryptoradical mechanism, with a low degree of liberation of radicals into space, or that two reactions take place in the system, involving radical and non-radical decomposition. Since the reaction products are the same in both cases, it was not possible to determine which of the two alternative mechanisms operates. It has been demonstrated unambiguously with the aid of CINP [153] that the reaction proceeds via two competing channels—radical and non-radical. The radical pathway, induced by the polarisation of the ^{31}P nuclei, makes an extremely small contribution (10^{-2} to 10^{-4} of the overall decomposition).

A special method using computers—an automatic system for testing inhibitors (ASTI), which takes into account the set of elementary stages in the action of inhibitors in the oxidation process—has been recently developed and introduced (Fig.18). Tests are performed simultaneously on four highly sensitive differential manometric sets of apparatus, with automatic recording of the rate of oxidation, located in the experimental section. The experimental data are transmitted to the intermediate memory of the computer—an autonomous accumulator on a magnetic drum (section B). Sections A and B are linked by a communication line. On command of the experimentor, the data are introduced into the computer for treatment; the results of the computation are transmitted to the laboratory and are reproduced in the form of tables and graphs with the aid of a graph plotting apparatus.

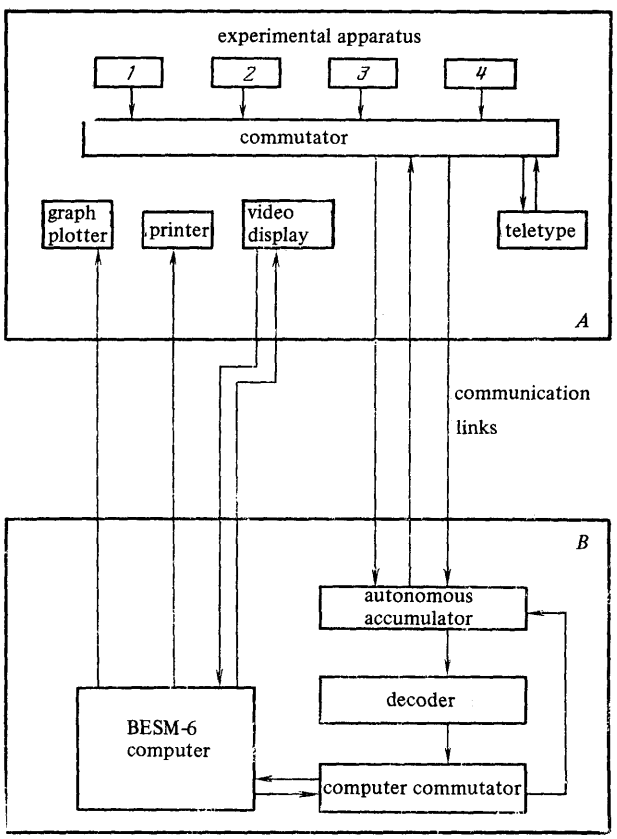


Figure 18. Schematic illustration of the automated system for testing the efficiency of stabilisers (ASTI): *A*) experimental section; *B*) section for the interpretation of data.

8. Synergism

The effects of synergism, which is manifested by the fact that the inhibiting effect of a mixture of two inhibitors exceeds the sum of the effects of each separately, is of practical importance. The mechanism of the synergism in the inhibition of oxidation by a mixture of inhibitors, each of which reacts with the radicals $\text{R}\dot{\text{O}}_2$, has been most thoroughly

investigated. The mechanism of the action of a mixture of inhibitors includes, together with the main elementary stages of the inhibited oxidation process [reactions (0), (2), (3), and (6)–(8)], also the following reactions[155–157]

$$In_1^{\cdot} + RH \rightarrow In_1H + \dot{R}\,(R\dot{O}_2)\,, \qquad (82)$$

$$In_1^{\cdot} + In_2H \rightarrow In_1H + In_2^{\cdot}\,, \qquad (83)$$

$$In_2^{\cdot} + In_1H \rightarrow In_2H + In_1^{\cdot}\,. \qquad (84)$$

The synergism is based on the phenomenon of the radical interaction of the inhibitors[155–158] consisting in the reduction of the more active inhibitor In_1H as a result of the transfer of a hydrogen atom to the radical $In_1^{\cdot}$ from the molecule of the less active inhibitor In_2H [reaction (83)]. The inhibitors In_1H can be primary and secondary aromatic amines, substituted *p*phenylenediamines, hydroxylamine ethers, and sterically unhindered alkylphenols[159]. The reducing inhibitors can be phenols and bisphenols containing bulky substituents in the 2,6-positions. The effective reduction of In_1H occurs only when the radical $In_2^{\cdot}$ formed is inactive and does not enter into the reversible reaction (84).

The influence of reaction (83) on inhibition by mixtures is enhanced due to the suppression, as a result of its occurrence, of reaction (79), which lowers the inhibiting activity of aromatic amines and unshielded phenols.

It has been shown by computer calculations that this mechanism describes satisfactorily the dependence of the synergistic effect on the overall concentration of inhibitors[160], the kinetic characteristics of the substrate being oxidised[156], the efficiency of the action of each inhibitor in the mixture[156,157], and the mixture composition[161]. For mixtures of the same inhibitor In_2H with inhibitors In_1H having the different antiradical activities, the synergistic effect increases with increase of the rate constant for the reaction of $R\dot{O}_2$ with In_1H and the maximum on the plot of the dependence of τ on the mixture composition shifts in the direction of mixtures containing a higher percentage of In_2H.[161]

A similar mechanism of the regeneration of the inhibitor explains in many instances the synergistic effect of a mixture of aromatic amines and sulphur-containing compounds, for example, mixtures of *N*-phenyl-β-naphthylamine and bis(2-hydroxy-5-methyl-3-t-butyl) sulphoxide[162]. The product of the thermal transformation of the sulphoxide (P) behaves as the reductant for the amine. The same mechanism is possible in inhibition by mixtures containing sulphides, where the product P can be obtained by the reaction of the sulphides with the hydroperoxide and subsequent decomposition of the resulting sulphoxide. The synergistic effect of a mixture of copper and nickel bis(*N*,*N*'-diethyldithiocarbamates) with thiuram disulphide—the product of the reaction of these complexes in liquid-phase oxidation—is due to the regeneration of the initial form of the metal-complex inhibitor $M(dtc)_2$.[163]

Together with the mechanism of the synergism discussed above, which is due to the regeneration of the active inhibitor, cases are possible where the synergism is due to the formation of a new active inhibitor in the system. This apparently happens in the inhibition of oxidation by mixtures of aromatic amines and copper compounds[164]. The formation of a new copper complex of the amine is responsible in this instant for the inhibiting effect[165]. The mechanism of the action of the synergistic mixture of an amine (AmH) with copper salts includes, together with the reactions known for each component, new stages[165] involving the complexes:

$$AmH + Cu(II) \rightleftarrows Cu(II)\cdot AmH\,,$$

$$Cu(II)\cdot AmH + R\dot{O}_2 \rightarrow Cu(II)\cdot Am^{\cdot} + ROOH\,, \qquad (85)$$

$$Cu(II)\cdot Am^{\cdot} + R\dot{O}_2 \rightarrow Cu(II) + \text{product}, \qquad (86)$$

$$Cu(II)\cdot AmH + ROOH \rightarrow Cu(II)\cdot AmH + \text{product}. \qquad (87)$$

The mechanism describes quantitatively the characteristics of the initiated oxidation of ethylbenzene in the presence of a mixture of $CuSt_2$ and *p*-toluidine. An interesting feature of the action of such mixtures is the marked increase of their activity with increase of temperature[166]. The enhancement of the inhibition is caused by the formation of a new product of the thermal transformation of the primary complex, which has a higher inhibiting activity. It has been shown in recent years that the synergistic effect can be exhibited by mixtures of inhibitors reacting with the radicals $R\dot{O}_2$ (aromatic amines and phenols) and with acceptors of the radicals $\dot{R}$ (quinones and nitroxy-radicals),[167] as well as mixtures of u.v. absorbers and antioxidants[168]. As a consequence of the diffusion of the inhibitors from the bulk of the specimen to the surface layer, the synergistic effect greatly increases in the solid phase (diffusion synergism)[169].

9. Critical Phenomena in Liquid-Phase Oxidation

Analysis of kinetic equations for degenerate branched chain reactions with linear chain termination (for example, by an inhibitor) has demonstrated the possibility of the existence of limiting phenomena[170] of the kind observed in fully branched chain processes.

At a constant rate of initiation of the free radicals, the inhibitor is consumed linearly at a rate

$$-d[InH]/dt = w_i/f\,. \qquad (88)$$

In a degenerate branched chain reaction the inhibitor is consumed during the period of inhibition with self acceleration [in contrast to reaction (88)] as a consequence of the increase of the rate of initiation of chains during the reaction. For certain values and ratios of the rate constants for the elementary stages, there is a possibility of a progressive increase of the inhibition periods up to a sharp arrest of the reaction at a certain inhibitor concentration $[InH]_{cr}$.

For branched chain processes, the concentrations of the hydroperoxide and free radicals under the conditions of chain termination by the inhibitor are given by the equations

$$[R\dot{O}_2] = \frac{w_0 + \delta k_p [ROOH]}{f k_7 [InH]}\,, \qquad (89)$$

$$\frac{d[ROOH]}{dt} = \nu w_0 + \varphi [ROOH]\,, \qquad (90)$$

where $\nu = k_2[RH]/fk_7[InH]$ is the chain length, $w_i = w_0 + \delta k_p[ROOH]$ the rate of chain initiation, and $\phi = \delta k_p(\nu - 1/\delta)$ the reaction self-acceleration factor.

It follows from Eqn.(90) that, for $\phi > 0$, i.e. when $\nu > 1/\delta$, the hydroperoxide accumulates with self acceleration: $d[ROOH]/dt > 0$. For $\phi > 0$, i.e. when $\nu < 1/\delta$, conditions in which the hydroperoxide concentration may be assumed to be quasi-stationary, i.e. $d[ROOH]/dt = 0$, are established after a time interval. The change in conditions occurs at $\phi = 0$ ($\nu = 1/\delta$), which determines the critical inhibitor concentration:

$$[InH]_{cr} = \frac{\delta k_2 [RH]}{f k_7}\,. \qquad (91)$$

The limiting phenomena were first observed in the oxidation of n-decane catalysed by copper stearate[107].

The characteristic features of the critical phenomena for metal complexes can be seen in relation to the kinetics of the oxidation of n-decane in the presence of bis{3-hydroxo-2-benzo[*b*]thenylideneanilinato}copper (CuL_2) (Fig.19). At low concentrations the copper chelate greatly accelerates the reaction. At high concentrations inhibition periods appear and increase sharply at a critical concentration $[CuL_2]_{cr}$.[172]

However, at the end of the inhibition periods the process takes place under catalytic conditions, owing to the consumption of the chelate down to low concentrations[172]. Since the rate constants for chain termination by metal complex inhibitors depend on the structure of the chelate unit, the critical inhibitor concentration depends on the nature of the chelate [according to Eqn.(91)].

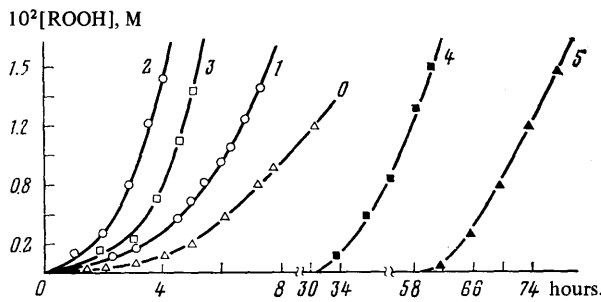


Figure 19. Kinetic curves for the accumulation of hydroperoxides in the oxidation of n-decane (120 °C) without a catalyst (0) and in the presence of bis{3-hydroxy-2-benzo[*b*]-thenylideneanilinato}copper(II) at different concentrations (M): 1) 1.5×10^{-6}; 2) 9.0×10^{-5}; 3) 1.1×10^{-4}; 4) 1.2×10^{-4}; 5) 1.5×10^{-4}.[171]

The existence of critical concentrations of transition metals has been established for simple and complex compounds of manganese, cobalt, and other metals[170]. Critical phenomena are also observed for phenols and aromatic amines[1,173].

Limiting phenomena occur in the oxidation of n-butane under pressure when the hydrocarbon is diluted with benzene. The reaction proceeds at a high rate only when the mole fraction of butane is ≥0.28, the process undergoing a sharp arrest when butane is consumed to give this dilution[174]. By taking into account the limiting phenomena, it is possible to explain the arrest of the oxidation of n-decane in the presence of potassium permanganate[175].

Limiting phenomena should be observed for a fairly high rate constant for the decomposition of hydroperoxides into free radicals and a low chain initiation rate constant[171]. In this case there are short inhibition periods τ in the region of inhibitor concentrations below the critical value and there is a sharp increase of τ following the attainment of limiting conditions where the rate of the process is determined mainly by the rate of chain initiation. The critical phenomena for organic inhibitors and metal complexes are therefore observed in most cases when the hydroperoxides decompose with participation of metal-containing catalysts.

Distinct limiting phenomena are observed in the continuous inhibited oxidation of hydrocarbons (open systems).[176] The critical inhibitor concentration is in this case given by[177]

$$[\mathrm{InH}]_{cr} = i_{cr} = \left(\sqrt{i_{\varphi=0}} + \sqrt{w_0/fv}\right)^2,$$

where $i_{\phi=0}$ is the inhibitor concentration defined by Eqn.(91) and w_0 is the rate of chain initiation.

Fig. 20 illustrates the accumulation of hydroperoxides in the oxidation of n-decane under conditions where the hydrocarbon with different concentrations of α-naphthol is continuously supplied into the reaction vessel and the oxidised product is removed from it, also continuously, at the same rate. Evidently a sharp change in the process conditions occurs for a slight alteration of the InH concentration in the entering solution—from 9.0×10^{-6} to 9.05×10^{-6} M.[176]

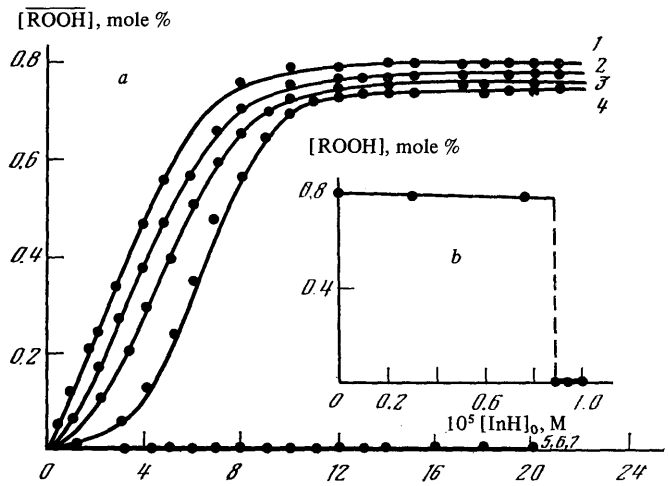


Figure 20. *a*) Kinetic curves for the accumulation of the hydroperoxide in the oxidation of n-decane in an open system in the presence of α-naphthol. Inhibitor concentration in the solution entering the vessel (M): 1) 0.0; 2) 3×10^{-6}; 3) 7.5×10^{-6}; 4) 9.0×10^{-6}; 5) 9.05×10^{-6}; 6) 1.2×10^{-5}; 7) 1.4×10^{-5}; *b*) dependence of the stationary concentration of the hydroperoxide on the inhibitor concentration[176].

III. KINETICS OF THE AGEING OF POLYMERS AND THEIR STABILISATION

Much attention has been devoted to the chemical kinetics of the ageing of polymers and to problems of their stabilisation as one of the branches of the modern science of macromolecular compounds. The knowledge of the kinetics and principal parameters of ageing makes it possible to predict the useful life and the optimum utilisation of polymeric materials. The results of kinetic studies of the ageing of polymers also make it possible to put forward the fundamental principles of the selection of effective stabilisers, increasing the quality of polymeric materials and their useful life.

During two decades, this field has greatly developed. It has become a special branch of the chemistry of the solid state in which studies are made of complex coupled radical-chain, ionic, and molecular reactions under the conditions of solid polymeric matrices with participation in the chemical process of the polymeric molecules of the matrix[178,179].

Specific types of the ageing of polymeric materials—thermal and thermo-oxidative ageing, ageing under the influence of light, penetrating radiation, and mechanical degradation, ageing under the influence of corrosive chemicals, biochemical and microbiological ageing, etc.—have been examined in a large number of monographs[180–190]. The experimental results obtained in recent years at the Institute of Chemical Physics of the USSR Academy of Sciences have been published recently[178,179]. In the present section we shall therefore briefly summarise the principal ideas of the chemical

physics of the ageing of polymers and the principles and problems of the stabilisation of polymers and polymeric materials.

1. The Ageing of Polymers as a Multifactorial Problem

The ageing of polymers can be defined as a set of chemical and physical transformations occurring in the polymer during its use, processing, or storage and leading to its losing a set of useful properties. Here one must bear in mind that the polymer is acted upon by numerous factors: heat, light, penetrating radiation, oxygen moisture, corrosive chemical compounds, and mechanical loads; therefore the ageing of the polymers must be considered as a multifactorial problem.

From the point of view, a system of equations for a multidimensional space can be proposed for the description of the time variation of the properties Y_i of a polymeric material under conditions X_i:[178]

$$Y=f(X, t)\,. \qquad (92)$$

The material is suitable for use in the course of a certain period τ, after which, under conditions X, the point Y leaves the region of operational suitability ε_0 in this space (Fig.21). The solution of Eqns.(92) would make it possible to determine the useful life of the polymer τ. In principle, this problem is susceptible to solution in a general form by modern computer techniques. The following processes are usually considered: thermal degradation, photodegradation, mechanodegradation, oxidation, hydrolytic degradation, etc.—these are limiting cases of the ageing process in which the changes in the properties of the material are determined by one factor only.

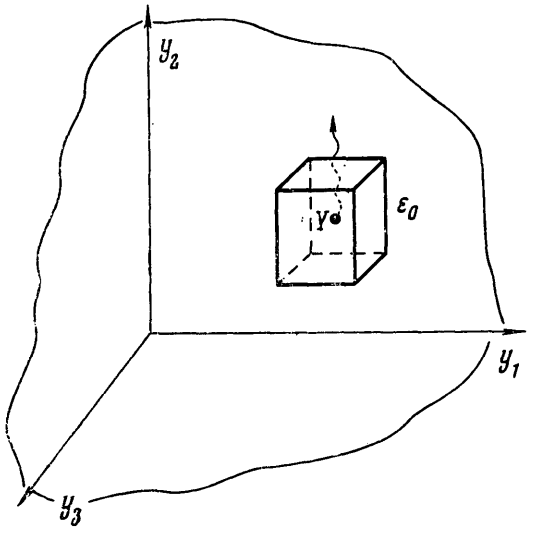


Figure 21. A qualitative picture of the time variation of the set of properties of a polymer Y (special case—point in a three-dimensional space); ε_0—the region of the operational suitability of the polymer[178].

In the general case ageing involves three stages: initiation—the stage in which active ageing centres are formed; development of ageing—the principal stage determining the changes in the properties of the polymeric material; the stage in which the active ageing centres are destroyed.

The physicochemical nature of the initiation of ageing can be various. For example, in photoageing this involves the formation of free radicals or ions under the influence of light, the appearance of ions, electrons, and radicals under the influence of radiation, and in mechanodegradation the initiation consists in the dissociation of molecules by mechanical forces with formation of free radicals.

External factors determine in the first place the initiation stage. Certain influences act also on the development of ageing. For example, the presence of oxygen converts the entire process into an oxidative reaction (thermal degradation becomes thermal oxidation, photolysis becomes photooxidation, and mechanodegradation becomes oxidation in the field of mechanical forces). Temperature influences all the elementary stages with the exception of processes whose activation energy is close to zero.

2. The Nature of the Active Centres

One of the principal problems of the chemical physics of ageing and the stabilisation of polymeric materials is the determination of the nature of the active centres responsible for the ageing of polymers and the mechanisms of their migration. It can now be regarded as to a large extent solved: the principal types and chemical nature of the active centres and their electronic structure have been determined, methods have been developed for the identification and measurement of the number of active centres, and the principal reactions and in many instances also their quantitative characteristics (rate constants on activation energies) are known[191,192].

The chemical reactions in the ageing of polymers proceed in most instances with participation of three types of active species: free radicals, excited species, and, to a lesser extent, ions. It has been shown in many studies that free radicals play the main role in the ageing of polymeric materials, which is due to the fact that reactions involving either the homolytic dissociation of the main molecular chain or the homolytic abstraction of atoms or radicals from side groups are characteristic of the majority of polymers. The structure and properties of the free radicals participating in the ageing of polymers and polymeric materials have been thoroughly investigated by EPR.[193] The central and terminal macroradicals and polymer radical-ions have been identified, the formation of low-molecular-weight radicals in the decomposition of macroradicals and the formation of radicals from stabiliser molecules have been demonstrated, and the formation of radical pairs has been observed.

Ions are formed in polymers usually only at the stage involving the initiation of the radiation processes associated with the degradation of polymers in corrosive media. Unfortunately, owing to the lack of special methods resembling EPR, it is much more difficult to identify the active centres in degradation by an ionic mechanism. In this field there have been virtually no systematic studies, with the exception of those concerning the degradation of certain natural polymers in solution[189].

Electronically excited molecules in the lowest excited singlet or lowest triplet states can play the most important role in the photochemical ageing of polymers. Two-quantum photochemical processes with participation of the highest triplet states as well as certain labile species in an excited state, for example, "hot" free radicals, are important[186,187].

3. Kinetics of the Polymer Ageing Processes

The thermal oxidation and photo-oxidation of polymers have been most thoroughly investigated, apparently because these processes are very close to the liquid-phase oxidation reactions of organic substances, which have been thoroughly studied.

The rate constants for the elementary reactions in polymers have been usually measured by modifications of methods developed previously for liquid-phase processes[178]. The rate of initiation w_i has been measured by the method of inhibitors in various versions and also by determining the induction period of the inhibited oxidation. The chain termination rate constant has been determined from the equation $k_t = w_i/[R\dot{O}_2]^2_{st}$, if the stationary concentration of peroxy-radicals is known, or by a non-stationary method based on the kinetics of the destruction of the radicals $R\dot{O}_2$ formed in the polymer, for example, after brief exposure to ultraviolet light. The parameter $k_p/k_t^{1/2}$, characterising the susceptibility of the polymer to oxidation, has been determined from the rates of the initiated chain oxidation (w_i = const.).

The kinetic parameters obtained showed that, compared with the liquid phase, the absolute values of the rate constants for the elementary processes in the solid polymer are usually smaller and the activation energies are higher. In addition, the differences between the relative reactivities of substances of different chemical types involved in isotypical chemical processes diminish ("level off"), which is due to the difficulty of the transport of reactants and the stability of the walls of the cage surrounding the reaction centres, which are characteristic of the solid phase[178].

The kinetics of the thermo-oxidative and photo-oxidative ageing processes for polymers in a highly elastic state and many semicrystalline polymers above their glass points qualitatively differ little from the kinetics of the oxidation of melts and low-molecular-weight organic substances. As an example, one may quote the oxidation of a polypropylene powder at low temperatures using a highly sensitive manometric apparatus which permits the measurement of the amount of absorbed oxygen from the very earliest oxidation stages (Fig. 22).[194]

The oxidation of films of isotactic polypropylene at 130 °C, investigated up to more advanced reaction stages, proceeds similarly (Fig. 22b). The process takes place with self-acceleration: its rate increases from the very beginning and at a degree of oxidation of ~15% reaches a maximum, after which it gradually falls. The variation of the rate of oxidation parallels the accumulation of hydroperoxides (Fig. 22b, curve 3), which indicates the decisive role of hydroperoxides in the propagation of polymer oxidation processes[195].

Thus the oxidative ageing of polymers is a degenerate branched chain reaction. It has been shown at a quantitative level that the photo-oxidation of polyolefins (PH) is described by the following kinetic scheme[196]:

$$PH \rightarrow P\dot{O}_2,$$
$$P\dot{O}_2 + PH \xrightarrow{O_2,\, k_p} POOH + P\dot{O}_2 \text{ (propagation)},$$
$$POOH \xrightarrow{h\nu} P\dot{O} + \dot{O}H \rightarrow 2P\dot{O}_2 + S \text{ (branching)},$$
$$[C{=}O] \xrightarrow{h\nu} P\dot{O}_2 + S,$$
$$P\dot{O}_2 + P\dot{O}_2 \xrightarrow{k_t} [C{=}O] \text{ (termination)},$$

where [C=O] are carbonyl compounds and S represents the step involving the dissociation of macromolecules. The rate constants for all the elementary reactions in the above scheme, which are required for the description of the kinetics of the accumulation of products, were determined by independent methods. The agreement between calculations and experiment confirmed the reliability of the proposed scheme.

In the course of their ageing, processes characteristic only of high-molecular-weight compounds take place in the polymers: degradation and cross-linking, the formation of cross-linked three-dimensional structures, and the propagation of reactions along the polymer chain.

The specific features of the structure of macromolecules are manifested, for example, in the kinetics of thermal degradation. The presence of two macroscopic thermal degradation stages is characteristic of the majority of polymers[197]. In the initial stage the process proceeds at a relatively high rate and with a low activation energy. At advanced stages the

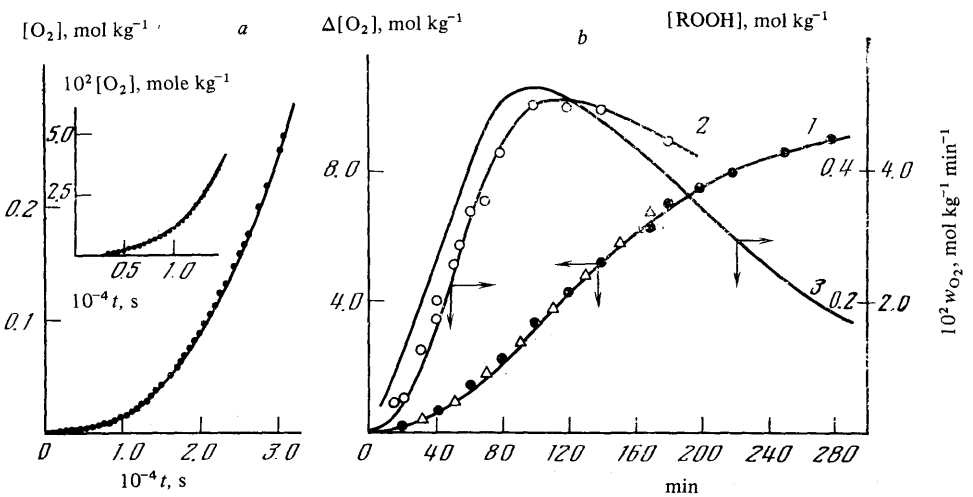


Figure 22. a) Kinetic curves for the absorption of oxygen in the autoxidation of polypropylene powder at 92 °C (the inset shows the initial stages of the process)[194]; b) kinetic curves for the autoxidation of polypropylene films at 130 °C: 1) absorption of O_2; 2) variation of the rate of oxidation; 3) accumulation of hydroperoxides[195].

rate of degradation falls and the activation energy increases. The fraction of the substance decomposing in the first stage depends on the method of synthesis of the polymer (Fig. 23).

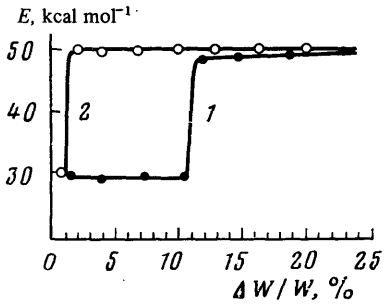


Figure 23. Dependence of the activation energy for the thermal degradation of polyvinyltoluene obtained by radical (curve *1*) and anionic (curve *2*) polymerisation on the degree of conversion (weight loss) $\Delta W/W$.[197]

The low activation energy for the initial stage is evidently associated with the fact that at this stage weak bonds or defective sites in macromolecules are ruptured. Only after they have been used up does the degradation of the normal strong bonds in the polymer begin. The artificial creation of defects in the polymer by its photolysis or preliminary oxidation can lead to the complete disappearance of the second, slower stage of the process. On the other hand, the formation of a defect-free structure makes the concentration of weak bonds insignificant, which has been achieved in polycaproamide.

4. Characteristics of the Chemical Reaction in the Polymer Matrix

The non-equivalence of the local properties of the environment of the reactive centres and correspondingly their spatially different chemical reactivities are characteristics of polymers as structurally inhomogeneous systems. Chemical reactions therefore occur in the first place in those regions where the conditions are most favourable. As a result, at a certain degree of conversion, the reactions are strongly retarded—the so-called "kinetic arrest of the reaction" is observed. A change of conditions, for example of temperature, leads to the renewal of the reaction. As an example, Fig. 24 illustrates the kinetics of the destruction of macroradicals in polymethacrylic acid under the conditions of a stepwise variation of temperature. The phenomenon of the "kinetic arrest" of the reaction has been observed in a wide variety of processes in solid polymers[178]. Methods have now been developed for the description of processes of this kind with the aid of the so-called polychromatic kinetics[198,199,200]. The variation of the macroscopic concentrations of the reactants is described by an integro-differential equation, which assumes the following form in the case of the simplest unimolecular reaction:

$$\frac{d[A]}{dt} = -\int_0^\infty kA(k)\,dk\,, \qquad (93)$$

where $A(k)$ is the density of the distribution of the concentration of substance A with respect to its reactivity, characterised by the chemical reaction rate constant k. The distribution $A(k)$ varies with time both due to the chemical transformation of substance A, described by Eqn. (93), and due to relaxation and diffusion processes, which alter the local properties of the medium around the reaction centre.

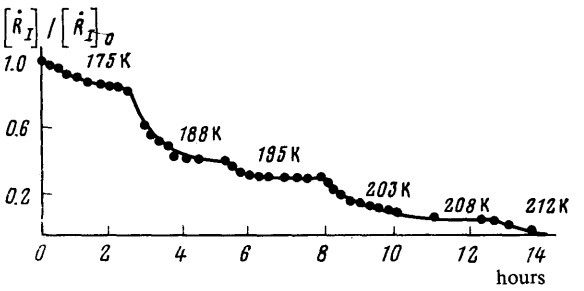


Figure 24. Kinetic curves for the thermal decomposition of central macroradicals in polymethacrylic acid in the temperature range 175–212 K.[221]

At temperatures considerably below the glass point of the polymer the process proceeds, as it were, in microreactors with unaltered local properties. Solution (93) then has the form of an integral Fredholm equation of the first kind:

$$[A] = \int_0^\infty e^{-kt}A(k)\,dk\,. \qquad (94)$$

Thus the kinetic curve for the variation of the concentration of A is a representation (in the sense of a Laplace transformation) of the initial distribution function $A(k)$. The form of the function $A(k)$ can be obtained from the kinetic curve $[A](t)$ by the reverse Laplace transformation.

The principles of polychromatic kinetics made it possible to calculate the distributions of species with respect to rate constants, activation energy, and activation entropy and to establish the fundamental mechanisms of the averaging out of the kinetic non-equivalence of the species and the conditions for the transition from polychromatic to monochromatic kinetics[191].

The kinetics and direction of chemical reactions in solid polymers are influenced significantly by the molecular dynamics and physical structure of the polymer, which occurs as a consequence of a change in the translational diffusion coefficients of the low-molecular-weight reactants or a change in the frequencies and amplitues of the segmental movements of the macromolecules and macroradicals, which influence directly the chemical reaction step itself.

It is well known that mobility influences the kinetics of the destruction of macroradicals in solid polymers—the rate of destruction decreases on transition from the amorphous to the crystalline phase, the rate constant for the destruction in oriented specimens is lower than in non-oriented specimens, the stability of macroradicals increases when the polymer is cross-linked, the rate of destruction of macroradicals in three-dimensional polymers increases with increase in the length of the oligomeric block, etc.

The molecular mobility has been varied[201,202] by altering the external pressure and by introducing into the polymer chemically inert solvents, which induced plasticisation. Under

these conditions, the rate constants for the recombination of radicals in amorphous polymers decreased with increase of pressure at temperatures above T_g. The destruction of peroxy-radicals in polystyrene[203] and polypropylene[204] was accelerated by the addition of small amounts of benzene.

The influence of molecular mobility on the rates of reaction of phenoxy-radicals with polyolefin hydroperoxides[205,206] and of nitroxy-radicals with phenols[207] in solid polyolefins has also been studied. It was found that the rates of these reactions are independent of the nature of the polymer and increase following the addition of aromatic solvents, whose role reduces to increasing molecular mobility. The increase of the rate constants for the above reactions is correlated with the increase of the frequency of rotation of the paramagnetic probe[205,207].

In mechanodegradation the change in the lifetime of the polymers cannot be described by taking into account only the changes in the rate constant for the elementary chemical processes in accordance with the Zhurkov equation

$$k = k_0 e^{-\frac{E-\gamma\sigma}{RT}}, \qquad (95)$$

where E is the activation energy, σ the mechanical stress, and γ a proportionality coefficient. A radical chain mechanism agrees only qualitatively with the experimental results. It has been shown[208,209] (Fig. 25) that mechanical stresses do not exert an appreciable influence on the rate of formation of radicals in chemical or radiation-chemical initiation and hence on the rate of degradation of macromolecules initiated by these radicals. At the same time the lifetime of polymers

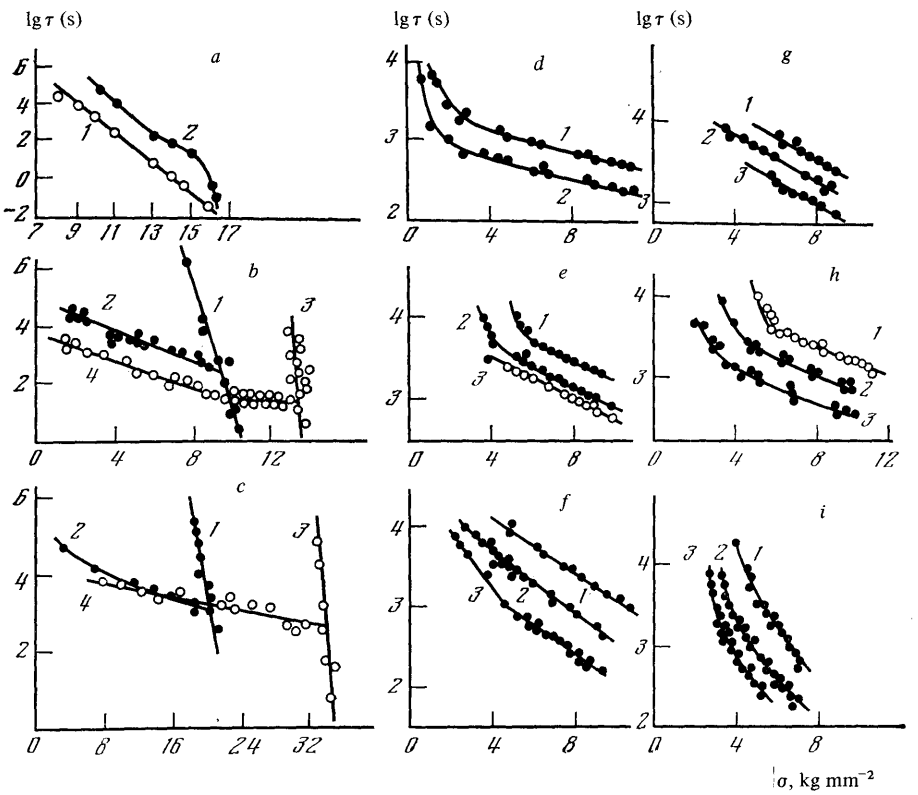


Figure 25. Variation of the lifespan of the polymer (τ) under a mechanical stress (σ) due to the introduction of an inhibitor (*a*) [222] and initiators (*b*–*i*) [209] of radical reactions: *a*: 1) pure nitrocellulose; 2) nitrocellulose with added 0.3% of the 4-ethyl-4-hydroxy-2,2,6,6-tetramethylpiperdin-1-yloxy-radical; *b*) 1,2-polycarbonate and 3,4[sic]-triacetylcellulose containing added $FeCl_3$, without (curves *1* and *3*) and with (curve *2*) photolysis of the additive; *c*) 1,2-poly(ethylene terephthalate) and 3,4-polycaproamide containing added $FeCl_3$, without (curves *1* and *2*) and with (curve *3*) photolysis of the additive; *d*) photodecomposition of triacetylcellulose without additives [1) 314 K; 2) 360 K; unfiltered light of DRSh-500 lamp; $I = 1.6 \times 10^{21}$ m^{-2} s^{-1}]; *e*) photodecomposition of triacetylcellulose with 0.6 wt.% of naphthalene [1) 286 K; 2) 301 K; 3) 323 K; nitrogen; $I = 2.6 \times 10^{21}$ m^{-2} s^{-1}; $\lambda > 300$ nm]; *f*) photodecomposition of triacetylcellulose with 9.1 wt.% of benzoyl peroxide [1) 303 K; 2) 325 K; 3) 348 K; air; $I = 0.4 \times 10^{21}$ m^{-2} s^{-1}; $\lambda > 300$ nm]; *g*) photodecomposition of triacetylcellulose with 0.16 wt.% of $HFeCl_4$ [1) 293 K, air depleted in oxygen; 2) 293 K; 3) 308 K; air; $I = 0.6 \times 10^{20}$ m^{-2} s^{-1}; $\lambda > 340$ nm]; *h*) photodecomposition of triacetylcellulose with 1.1 wt.% of naphthalene [1) 304 K; 2) 329 K; 3) 360 K; air; $I = 1.6 \times 10^{21}$ m^{-2} s^{-1}; $\lambda > 300$ nm]; *i*) thermal decomposition of triacetylcellulose with 9.1 wt.% of benzoyl peroxide [1) 378 K; 2) 388 K; 3) 393 K; air].

diminishes with increasing stress, i.e. a smaller number of breaks in macromolecules becomes sufficient for their decomposition. The breakdown of the specimen is not therefore related to the occurrence of a critical number of breaks, as suggested previously. The decomposition of the polymer is determined not only by the kinetics of its chemical degradation but also by the kinetics of the physical relaxation processes as a result of which the structure of the polymer changes after the breaks in the molecules.

5. Relation Between Practically Important Properties of the Polymers and the Kinetics of Ageing

Knowledge of the kinetics of the changes in their physicomechanical characteristics, for example, the relative elongation on rupture, the ultimate tensile strength, etc., is important in the practical utilisation of polymeric materials. The determination of the detailed ageing mechanism made it possible to relate the changes in these properties under various operating conditions for the polymers to the kinetic characteristics of their ageing. In particular, this relation has been established for the photo-oxidation of polypropylene[210].

Fig. 26 presents kinetic curves for the variation of the relative elongation in the photo-oxidation of various specimens of polypropylene (PP) under the influence of light of different intensity and spectral composition. Despite the fact that the curves have different shapes, they can be made to coincide when the number of breaks in the macromolecular chain Ω during the process time is plotted along the abscissa axis.

The number of breaks is defined as the sum of steps involving the photodecomposition of branching products—hydroperoxides and carbonyl compounds:

$$\Omega = \int_0^t (\alpha [\text{ПООН}] + \alpha' [\text{C=O}])\, dt \ . \qquad (96)$$

Thus the dynamics of the variation of the physicomechanical properties of the polymer is related to the kinetics of the chemical ageing process and calculations can be made on the latter using measurements of its kinetic characteristics.

6. Fundamental Principles of the Stabilisation of Polymeric Materials

The known methods of stabilising polymeric materials can be classified in terms of the stage of the ageing process on which they act. A large group of stabilisers comprises substances which decrease the probability of the formation of active centres at the initiation stage. They include agents quenching excited states ("quenchers")—substances which react with admixtures catalysing the decomposition of polymers. Stabilisers which deactivate chemically active reaction products, for example, substances which decompose hydroperoxides, are particularly important.

The stabiliser influencing the propagation stage of the ageing process, for example, the oxidation chain propagation stage, include substances which prevent the penetration of oxygen into the polymeric material or lower its concentration in the material.

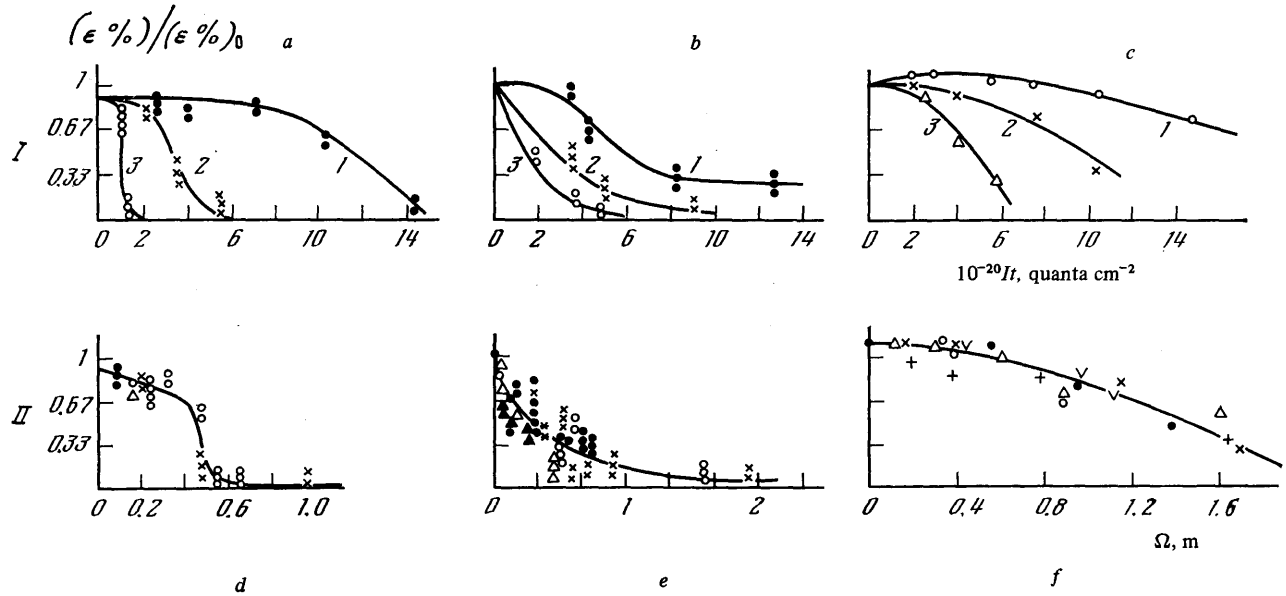


Figure 26. Variation of the relative elongation on rupture in the course of the photo-oxidation of polypropylene: *a*)–*c*) dependence on the amount of light with λ = 254 nm incident on the specimen [light intensity (10^{-15} *I*, quanta cm^{-2} s^{-1}): 1) 4; 2) 0.7; 3) 0.24]; *d*)–*f*) dependence on the number of breaks in the macromolecules of the specimen in a given time; *a*) and *d*) isotropic specimen; *b*) and *e*) oriented annealed specimen; *c*) and *f*) oriented specimen (950%).[178]

The class of stabilisers accelerating the stage involving the destruction of active centres, for example, the acceptors of free radicals or the inhibitors of free radical processes InH, is most widely used in practice and has been most thoroughly investigated. The mechanism of the action of such substances and the criteria used to estimate their efficiency were examined in detail above (Section II, 7). As in the liquid-phase oxidation of hydrocarbons, critical inhibitor concentrations have been observed in the oxidation of polymers, above which the inhibition period of the oxidative degradation increases sharply. A synergistic effect, arising when various stabilising compositions are used, has also been observed[211-213].

The kinetic characteristics are usually determined at comparatively low stabiliser concentrations. The region of extensive inhibition of autoxidation at sufficiently high concentrations (much higher than the critical concentration), usually employed under technological conditions, is of practical interest. Kinetic analysis is significantly simplified under these conditions by the fact that the quasi-stationary principle becomes applicable not only to free radicals but also to the branching product—the hydroperoxide. For example, the mechanism of the inhibited oxidation by sterically hindered phenols can be described as follows[214]:

$$\text{initiation} \xrightarrow{+O_2,\ w_0} R\dot{O}_2\ ,$$
$$R\dot{O}_2 + RH \xrightarrow{+O_2;\ k_2} ROOH + \dot{R}\ ,$$
$$ROOH \xrightarrow{+O_2;\ k_3} 2f R\dot{O}_2 + \text{product},$$
$$R\dot{O}_2 + PhOH \xrightarrow{k_7} ROOH + Ph\dot{O}\ ,$$
$$R\dot{O}_2 + Ph\dot{O} \xrightarrow{k_8} QP\ (\text{quinolide peroxides}),$$
$$Ph\dot{O} + Ph\dot{O} \xrightarrow{k_9} PhOH + \text{products},$$
$$QP \xrightarrow{+O_2,\ k_{11}} 2\delta R\dot{O}_2 + \text{products}.$$

In the presence of the effective antioxidant used in practice, the contribution of the remaining reactions is usually small.

Table 9 presents analytical expressions for the induction period τ, the critical concentration $[PhOH]_{cr}$, and the rate of consumption w_{PhOH} of the inhibitors—phenols of two types: (I) k_9 is small and the radicals $Ph\dot{O}$ are destroyed only via reaction (8); (II) k_9 is large and the radicals $Ph\dot{O}$ are destroyed only via reaction (9). Evidently the characteristics of the antioxidant activity (τ and w_{PhOH}) under the conditions used depend little on the antiradical activity of the inhibitors (on the constant k_7) and are largely determined by the constant for the interaction of the inhibitor radicals k_9 and the probability of the emergence of radicals from the cage in the decomposition of hydroperoxides (f) and quinolide peroxides (δ). In solid polymers f and δ are relatively low, which is consistent with the high antioxidant activity of the inhibitor. On passing to a melt, the antioxidant activity diminishes owing to the increase of f and δ, which is sometimes formally interpreted as a result of the additional formation of free radicals by inhibitor molecules.

In practice it is important to obtain from standard tests on stabilisers information necessary for predicting their effectiveness under the operating conditions. As mentioned above, on passing from the liquid phase to a solid polymer, the reactivity of stabilisers levels off. The relative reactivities of the species in the solid polymer (k_S) and in the liquid phase (k_L) are linked by the relation[215]

$$\frac{(k_1)_S}{(k_2)_S} = \left[\frac{(k_1)_L}{(k_2)_L}\right]^{1/2}. \qquad (97)$$

Eqn.(97) makes it possible to select stabilisers for polymeric materials (antioxidants, quenchers) on the basis of much less laborious experiments, carried out in model liquid-phase systems.

The influence of molecular physics on the chemical reactions in polymers leads to the discovery of new physical principles of the stabilisation of polymeric materials by specific structural-physical modification of the material (deformation, stress, orientation, isotropic compression, regulation of the supermolecular structure and morphology, etc.). For example, the rate of formation of the branching product (the hydroperoxide) diminishes in oriented polyolefins, which leads to an increase of the thermal stability of the oriented filaments compared with isotropic films[216]. There are many factors governing the stabilisation and the increase of the strength and lifetime of polymeric materials as a result of their structural-physical modification[191].

Table 9. Characteristics of the antioxidant activity of stabilisers under the conditions of extensive inhibition of oxidation[214]*.

Parameter	Type of phenol	
	I	II
$[PhOH]_{cr}$	$\frac{fk_2[RH]}{(1-f-\delta)k_7}$	$\frac{2fk_2[RH]}{(1-2f)k_7}$
τ	$\frac{2(1-f-\delta)(\gamma-1)^2[PhOH]}{\gamma^2 w_0}$	$\frac{2(1-2f)(\gamma-1)^2[PhOH]}{\gamma^{*2} w_0}$
w_{PhOH}	$\frac{w_0}{2(1-bf-\delta)}$	$\frac{w_0}{2(1-2bf)}$

*Here $b = 1 + \frac{k_2[RH]}{k_7[PhOH]}$; $\gamma = [PhOH]/[PhOH]_{cr}$.

7. Special Procedures for the Stabilisation of Polymers

Many stabilisers cannot be used at sufficiently high concentrations for a variety of reasons. In particular, some of them impart an undesirable colour to the polymeric material. Thermal stabilisers can be effective photosensitisers. The free radicals formed from stabiliser molecules in some cases enter into reactions promoting the decomposition of the polymer. Furthermore, the stabiliser can be consumed in useless side processes.

It is therefore desirable to produce stabilising compositions in such a way that the effective inhibitor acts in accordance with the *in statu nascendi* principle, i.e. in such a way that its main bulk is in a bound state, in a kind of "depot", and the active form of the stabiliser is released by it gradually or when necessary.

A quantitative criterion of the efficiency of the action of the inhibitor is *in statu nascendi* can be formed by analysing a simplified kinetic mechanism of the action of such an inhibitor on an initiated chain process.

$\xrightarrow{w_i} \dot{r}$—initiation of the formation of the active radical;

$Z \xrightarrow{k} \dot{R}$—the formation from the "depot" of the active form of the inhibitor $\dot{R}$, which behaves as a stabiliser (for simplicity, the stabiliser in a radical form is considered);

$\dot{R} + \dot{r} \xrightarrow{k_7}$—inhibition reaction;

$\dot{R} \xrightarrow{k_{10}} \dot{r}$—the generation of the active centre by a reaction involving the inhibitor.

The effectiveness of the stabilisation is characterised by the ratio of the rate of initiation to the rate of consumption of the active form of the inhibitor (for $k_{10} \gg k$):

$$\Psi = \frac{w_i}{\mathrm{d}[\dot{R}]/\mathrm{d}t} \cong \frac{w_i}{k[Z]} \quad (98)$$

If the inhibitor is introduced into the system at the initial instant at a concentration $[Z]_0$, the efficiency of its action is determined by the expression

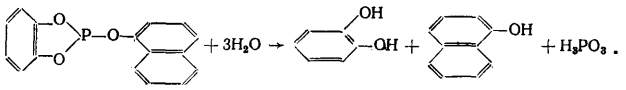
$$\Psi_0 = \frac{w_i}{w_i + 2k_{10}[Z]_0} \quad (99)$$

Since $k_{10} \gg k$ by hypothesis, it follows that $\Psi > \Psi_0$. The ratio $\Psi/\Psi_0 = Q$ can serve as a criterion of the efficiency of the action of the inhibitor *in statu nascendi*:

$$Q = \frac{\Psi}{\Psi_0} = \frac{w_i + 2k_{10}[Z]_0}{k[Z]_0} \simeq \frac{2k_{10}}{k} \quad (100)$$

Sterically hindered piperidines protect polymers from the action of light by the "depot" mechanism[217]. The mechanism of the light stabilisation of polymers by sterically hindered piperidines is more complex than that considered above. The piperidines themselves are not stabilisers but are converted under the influence of radiation into a mixture of nitroxy-radicals and other compounds which act as inhibitors.

Phosphorus acid esters, whose hydrolysis gives rise to the corresponding phenols or catechols, also function as a "depot":[218]



Clathrate compounds, from which the stabiliser is liberated on thermal decomposition and photodecomposition, can apparently also act via the "depot" mechanism.

Not only compounds from which the stabiliser is synthesised in the course of ageing but also the diffusion of the stabiliser to the degradation zone from another, undecomposed part of the polymer can be used as a stabiliser "depot". The diffusion phenomenon has been recently observed in the study of the photo-oxidation of polybutadiene films[219,220]. In the presence of an ultraviolet absorber light does not penetrate into the bulk of the polymer specimen. Photo-oxidation takes place only in the surface layer, which results in the consumption of the antioxidant (A). A concentration gradient of A is produced and the antioxidant diffuses from the bulk of the polymer to the surface layer. Since the deep layers serve as a source of inhibitor, thick specimens are oxidised more slowly than thin ones. It has recently been shown that this phenomenon is the main cause of the synergism observed in the stabilisation of polymers by mixtures of u.v. absorbers (UVA) and antioxidants, which interact with free radicals[219] or decompose hydroperoxides[220].

In the diffusion mechanism the synergistic effect depends on the ratio of the rates of reaction (w_r) and diffusion (w_d). For $w_r \gg w_d$, there is insufficient time for the diffusion of antioxidants to affect the process and synergism is not observed. The maximum effect can be obtained for the opposite condition: $w_d \gg w_r$. Here the entire oxidant is consumed in the inhibition of the photo-oxidation process in the photoreaction zone and the oxidation induction period is $\tau = \tau_0(L/l)$, where τ_0 is the induction period for $w_r \gg w_d$ and l and L are the thicknesses of the photoreaction zone and of the polymer films respectively.

The ideas developed concerning the mechanism of the synergism have created a scientific basis for the selection of effective synergistic mixtures which protect polymers from light-induced ageing, taking into account the properties of the polymer and the stabilisers, as well as the operating conditions. Within the framework of the mechanism examined, the requirements for the thickness of the specimens and for conditions under which accelerated tests of the light stability of polymers stabilised by synergistic mixtures must be performed also become understandable.

IV. KINETICS OF THE BIOLOGICAL PROCESSES

The living organisn is regarded as the most complex system of coupled chemical reactions under the influence and with participation of a multiplicity of chemical and physical factors, which initiate, catalyse, inhibit, and regulate these processes. This is responsible for the possibility of employing in biological and medical research methods and ideas characteristic of chemistry, physics, and mathematics.

Kinetic studies in biology permit quantitative estimates of the rate of propagation of the most important biological processes and of the influence on the latter by various factors as well as the establishment of quantitative criteria for the estimation of the efficiency of such influences. The mathematical description of the kinetics then involves a series of parameters which can be used to model the processes investigated and to analyse them using modern computer techniques.

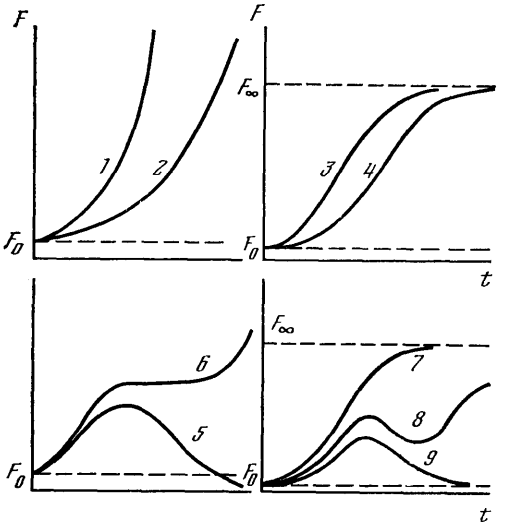


Figure 27. Plots of the functions used to described the kinetics of tumour growth. The analytical forms of the curves are presented in Table 10.[226]

Extensive kinetic studies on many pathological processes and phenomena—carcinogenesis, malignant growth, radiation damage, as well as the ageing of the living organisms—are being prosecuted at the present time[223–226]. The broad principles of the kinetic approach to the study of biological objects can be examined in relation to experimental tumour processes[226].

1. Kinetics of Tumour Growth

The differential equation for the growth of a tumour can be formulated as follows:

$$\frac{1}{F}\frac{dF}{dt} = \varphi(t) \quad , \qquad (101)$$

where $\phi(t) = \phi_1(t) - \phi_2(t)$ and F is the volume, diameter, or weight of the tumour, the number of tumour cells, or any other quantity characterising the growth of the tumour. The quantity $(1/F)(dF/dt)$ is the specific rate of growth, $\phi_1(t) \geq 0$ characterises the overall rate of multiplication of the cells, and $\phi_2(t) \geq 0$ characterises the overall rate of their destruction. The function $\phi(t)$ can be both positive and negative.

The overall form of the solution of the differential equation (101) is given by the expression

$$F = F_0 e^{\int \varphi(t)dt} \quad . \qquad (102)$$

Different deterministic models of the growth of a tumour can be reduced to the selection of the corresponding functions $\phi(t)$. Fig. 27 illustrates schematically the types of kinetic curves corresponding to the model functions frequently employed. Table 10 presents the corresponding kinetic equations. After the selection of the most suitable functions approximating the experimental data, regression analysis is carried out by standard methods. A linearising transformation is usually performed for the function F, which simplifies the calculation of the kinetic parameters.

Table 10. Functions used to describe the kinetics of tumour growth.

Name of function	Type of $\varphi(t)$	Differential equation*	No. of curve in Fig. 27
Exponential	$\varphi = \text{const}$	$F = F_0 e^{\varphi t}$	1
Exponential with a constant term	$\varphi = \frac{1}{1/a + c \cdot e^{-at}}$	$F = F_0 e^{at} + F_1$	—
Power	$\varphi = \frac{b}{t+a}$	$F = F_0 \left(1 + \frac{t}{a}\right)^b$	2
" "	$\varphi = \frac{b}{t+a} - c$	$F = F_0 \left(1 - \frac{t}{a}\right)^b e^{-ct}$	—
Gompertz function	$\varphi = ae^{-bt}$	$F = F_\infty \exp\left\{-\frac{a}{b} e^{-bt}\right\}$	3
Logistic function	$\varphi = \frac{b}{1 + e^{bt/a}}$	$F = \frac{F_\infty}{1 + ae^{-bt}}$	4
Bertalanphi function	$\varphi = \frac{be^{-bt}}{1/a - e^{-bt}}$	$F = F_\infty (1 - ae^{-bt})$	—
Polynomial function	$\varphi = \varphi_0 + \varphi_1 t + \cdots + \varphi_s t^s$	$F = F_0 \exp\left\{\varphi_0 t + \frac{1}{2}\varphi_1 t_2 + \cdots + \frac{1}{s+1}\varphi_s t^{s+1}\right\}$	5, 6
Asymmetric polynomial exponential function	$\varphi = (a_0 + a_1 t + \cdots + a_s t^s) e^{-bt}$	$F = a \exp\{[c_0 + c_1 t + \cdots + c_s t^s] e^{-bt}\}$	7, 8, 9

*Here a, b, and c are constants.

Extensive experimental data on the kinetics of the growth of tumours have now accumulated [226]. More than 60 experimental strains of solid and ascites transplantable and spontaneous animal tumours and leukaemias have been investigated. The equations presented above are used for a formal kinetic description of the development of these malignant processes.

An exponential relation is fairly frequently used both in experimental studies and for the analysis of the growth of human tumours. Fig. 28*A* presents generalised kinetic curves for exponentially growing animal tumours in terms of the dimensionless coordinates $\eta = e^{\theta}$, where $\eta = F/F_0$ and $\theta = \phi t$.

In principle, the most general type of kinetic curve is an S-shaped curve, because it is natural to expect that F tends to a limiting value in the course of the growth of the tumour by virtue of the characteristics of the development of tumours in the organism. In those cases where a logistic function of the type $F = F_\infty/(1 + ae^{-bt})$ is applicable to the description of the kinetics of the growth of such tumours, it is possible to construct a generalised plot in terms of the variables of the equation $\eta = 1/(1 + e^{\theta})$, where $\eta = F/F_\infty$ and $\theta = \ln a = bt$ (Fig. 28*B*).

For a comparative analysis of the rates of growth of different experimental tumours, one can use the maximum specific rate of growth ϕmax. [226] For tumours growing exponentially, $\phi\text{max} = \phi$.

Analysis of the distribution of 62 experimental tumours with respect to ϕmax showed that the cumulan of the distribution in the range from $\phi\text{max} = 0$ to $0.7\ \text{day}^{-1}$ is linear, i.e. that the distribution of ϕmax in this range is virtually uniform. From this it follows that tumours can apparently exist with arbitrarily small specific rates of growth. Approximately 80% of the tumours examined in terms of their values of ϕmax fall within this linear range. There are many fewer tumours for which $\phi\text{max} > 0.8\ \text{day}^{-1}$.

2. Kinetic Criteria for the Estimation of the Effictiveness of Antitumour Preparations

The study of the kinetics of the development of tumour processes has made it possible to develop a series of criteria of the effectiveness of a particular therapeutic agent. For this purpose, it is necessary to compare control and experimental kinetic curves.

In the simplest case where tumour growth takes place exponentially both in the control,

$$F_c = F_0 e^{\varphi_c t} \qquad (103)$$

and in the experiment,

$$F_e = F_0 e^{\varphi_e t} \quad , \qquad (104)$$

the ratio

$$\varkappa = \varphi_e/\varphi_c \quad , \qquad (105)$$

showing by what factor the rate of development of the experimental process is reduced compared with the control, can be used as a measure of the effectiveness. For exponentially growing tumours, this criterion was introduced in 1962 [227] and was subsequently used in many investigations.

A series of criteria, used independently of the type of kinetic curves for the tumour growth in the control and in the experiment, have also been proposed [226]. In particular the criterion

$$\varkappa_9' = 1 - (\bar{F}_{te}/\bar{F}_{tc})\,100 \quad , \qquad (106)$$

which is called the percentage inhibition, is frequently used in the USSR. Here $\bar{F}_{te}$ is the average experimental value of F and $\bar{F}_{tc}$ is the value for the control.

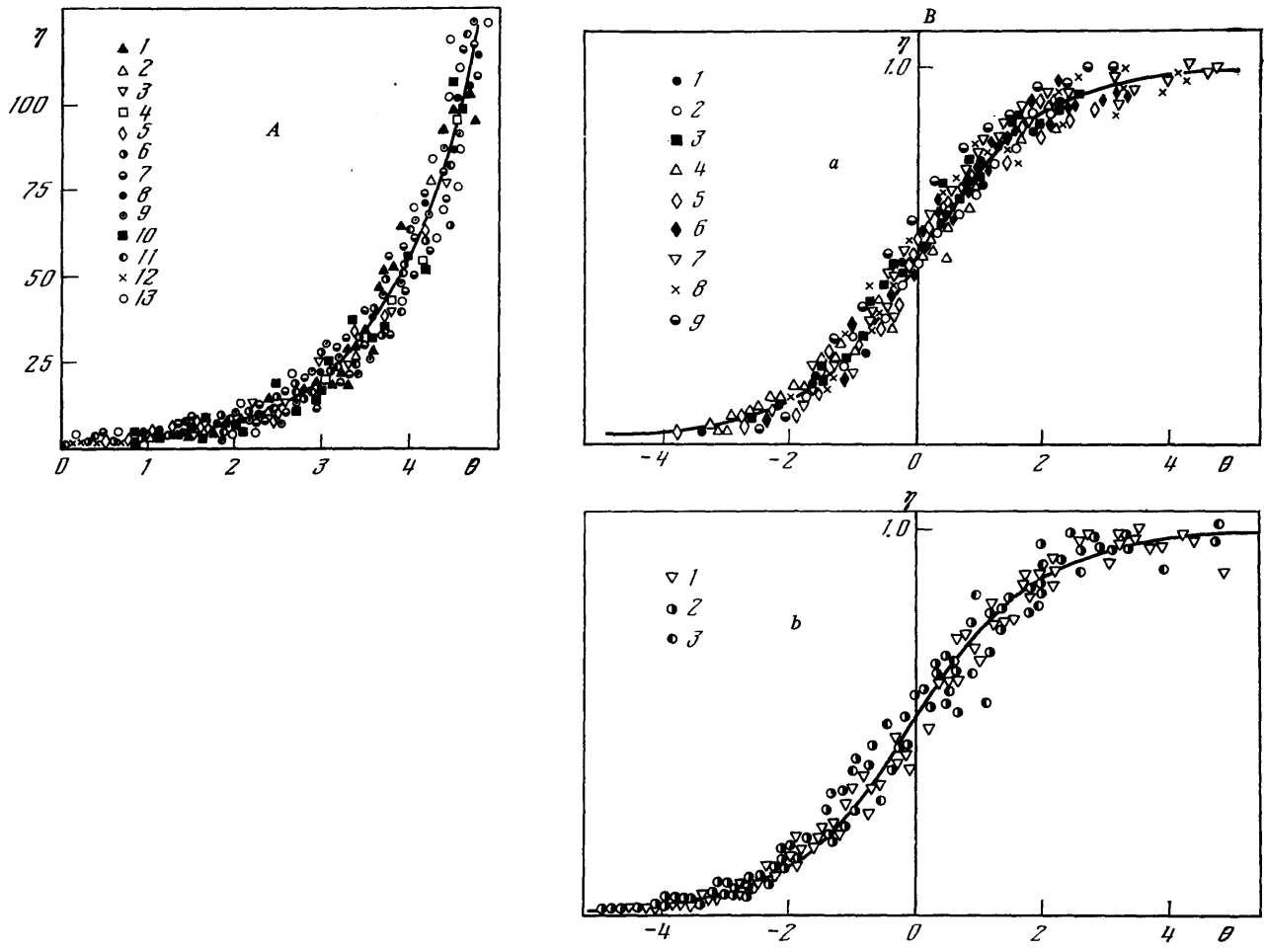


Figure 28. *A*) Generalised kinetic curve for the exponential growth of tumours $\eta = e^{\theta}$ for various types of transplanted tumour processes: 1) tumours in rat skin induced by radiation; 2) adenocarcinoma 755; 3) sarcoma 180; 4) sarcoma CCK; 5) haepatomas; 6) Ehrlich ascites carcinoma; 7) Svec erythromyelosis; 8) Waler carcinosarcoma; 9) reticulosarcomatosis; 10) leukaemia La; 11) leukaemia L-1210; 12) spontaneous leukaemia in mice of AKR strain; 13) leukaemia La; B) generalised S-shaped kinetic curves for the growth of solid (*a*) and ascites (*b*) experimental tumours; *a*: 1) Walker carcinosarcoma; 2) Geren carcinoma; 3) sarcoma 45; 4) adenocarcinoma 755; 5) haepatomas; 6) melanomas; 7) sarcoma 180; 8) other models (osteogenic Ridgeway sarcoma, sarcoma T241, adenocarcinoma EO-771, and carcinoma C1025); 9) Svec erythromyelosis; *b*): 1) sarcoma 180; 2) Ehrlich ascites carcinoma; 3) leukaemia L-1210.[226]

It should be noted that the kinetic criterion κ [Eqn.(105)] for exponentially growing tumours characterises the tumour process much more satisfactorily than the percentage inhibition criterion κ'_9, since κ is the independent of the time of completion of the experiment. The relation between κ and κ'_9 is given by§

$$\varkappa_0' = \{1 - \exp[(1-\varkappa)\varphi e^{t}]\}1^{\circ}0 \quad . \qquad (107)$$

The advantage of the kinetic criterion consists in its high "sensitivity" in the assessment of the most effective preparations. The criterion κ therefore makes it possible to solve one of the main problems of experimental chemotherapy—to establish a relation between the chemical structure and the antitumour activity of the most effective preparations.

§ The numbering of the criteria is based on that in a monograph[226].

Other kinetic criteria, based on the estimation of the average specific rates of tumour growth $\bar{\phi}(t)$, can also be proposed for the estimation of the effectiveness of the antitumour treatment. The average specific rate of growth in the time interval (t_1, t_2) is

$$\bar{\varphi}(t_1, t_2) = \frac{1}{t_2 - t_1}\int_{t_1}^{t_2} \frac{d(\ln F)}{dt}\, dt = \frac{\ln F(t_2) - \ln F(t_1)}{t_2 - t_1} \qquad (108)$$

and, as can be seen from the above equation, depends only on the values of F at the ends of the interval. Thus the quantity $\bar{\phi}(t_1, t_2)$ is equal to the exponent of the "equivalent exponential function", which passes through the ends of the kinetic curve $F(t)$ in the time interval considered.

The ratio of the average specific rates of tumour growth in the control and in the experiment can be adopted as a measure of the effect:

$$\bar{\varkappa} = \frac{\bar{\varphi}_c(t_{1c}, t_{2c})}{\bar{\varphi}_e(t_{1e}, t_{2e})} = \frac{t_{2e} - t_{1e}}{t_{2c} - t_{1c}} \cdot \frac{\ln F_c(t_{2c}) - \ln F_c(t_{1c})}{\ln F_e(t_{2e}) - \ln F_e(t_{1e})} \; . \qquad (109)$$

It is natural to adopt the instant t_1 when the therapeutic action begins as the common starting point for reckoning the time intervals (t_{1c}, t_{2c}) and (t_{1e}, t_{2e}) for the averaging. The ends of the time intervals can be chosen in different ways: (a) the ends of the average kinetic curves for tumour growth t_f are adopted as the ends of the time intervals for the averaging, whereupon

$$\bar{\varkappa}_{10} = \frac{\bar{\varphi}_c(t_1, t_{fc})}{\bar{\varphi}_e(t_1, t_{fe})} = \frac{t_{fe} - t_1}{t_{fc} - t_1} \cdot \frac{\ln F_c(t_{fc}) - \ln F_c(t_1)}{\ln F_e(t_{fe}) - \ln F_e(t_1)}; \quad (110)$$

(b) any instant t_2 at which both kinetic curves to be compared exist can be selected as the common end of the time intervals for the averaging. In this case

$$\bar{\varkappa}_{11} = \frac{\bar{\varphi}_c(t_1, t_2)}{\bar{\varphi}_e(t_1, t_2)} = \frac{\ln F_c(t_2) - \ln F_c(t_1)}{\ln F_e(t_2) - \ln F_e(t_1)}. \quad (111)$$

If the development of the tumour processes in the experiment and in the control proceeds in accordance with exponential laws, then

$$\bar{\varphi}_c(t_1, t_{2c}) = \varphi_c;\ \bar{\varphi}_e(t_1, t_{2e}) = \varphi_e \text{ and}$$
$$\bar{\varkappa}_{10} = \bar{\varkappa}_{11} = \frac{\varphi_c}{\varphi_e} = \varkappa,$$

i.e. the criterion derived previously is obtained.

The fact that the quantities κ_{10} and κ_{11} become infinite following the complete inhibition of tumour growth (at $\bar{\phi} = 0$) constitutes a definite disadvantage (Fig. 29*a*). It is therefore more convenient to employ modified criteria κ^*_{10} and κ^*_{11} which are free from this disadvantage:

$$\varkappa^*_{10} = 1 - \frac{1}{\varkappa_{10}}, \quad (112)$$

$$\varkappa^*_{11} = 1 - \frac{1}{\varkappa_{11}}. \quad (113)$$

Since both modified criteria are linear functions of the average specific rate of tumour growth in the experiment, i.e.

$$\varkappa^*_{10(11)} = 1 - \frac{1}{\varphi_c}\varphi_e, \quad (114)$$

the value $\kappa_{10} = \kappa_{11} = 0$ corresponds to the absence of an effect, positive values of κ_{10} and κ_{11} correspond to effective treatment (inhibition of tumour growth), and negative values correspond to treatment stimulating tumour growth (Fig. 29*b*).

The kinetic criterion κ proposed at the Institute of Chemical Physics of the USSR Academy of Sciences in 1962 has been used to investigate the antitumour effectiveness of a large number of chemical compounds of different classes, which made it possible to discover four new highly active preparations: 2,6-di-t-butyl-4-methylphenol (ionol or dibunol), nitrosomethylurea (NMU),[230,231] 1,2-bisdiazoacetylethane (diazan),[232] and PAT-1, a paramagnetic analogue of Thio TEPA.[233] Fig. 30 illustrates the antitumour effectiveness of a series of preparations in relation to the experimental leukaemia La in mice. Under the same "dibunol", ionol is nowadays used in clinical practice in the treatment of the cancer of the bladder and radiation cystitis in man[234] and NMU is used in the treatment of the undifferentiated cancer of the lung, lymphogranulomatosis, and melanoma[231–235].

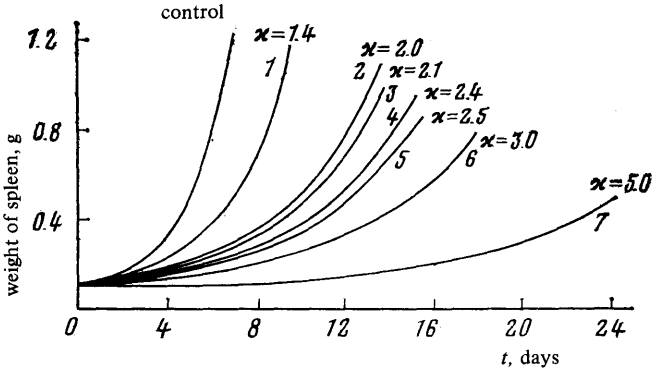


Figure 30. Inhibition of the growth of leukaemia La in mice under the influence of various chemotherapeutic preparations: 1) thiophosphamide, carminomicin; 6) mercapturopurine; 2) sarcolysine; rubomycin; 3) HMM; 4) dibunol, cyclophosphane; 6) PCNU [1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidinyl)-1-nitrosylurea]; 7) diazan.

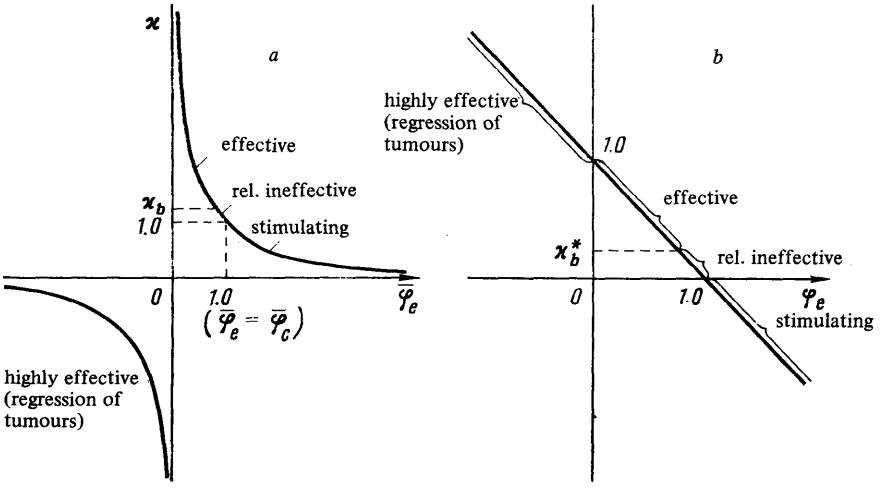


Figure 29. The regions in which therapeutic treatments are effective; $\kappa_b = 1.25$ and $\kappa^*_b = 0.2$ are conventional quantities separating relatively ineffective and effective treatments[226].

The development of kinetic approaches to the description of tumour growth processes in chemotherapeutic treatment is closely related to the problem of the pharmacokinetics of antitumour agents. The parameters of the pharmacokinetic equations are quantitative characteristics of processes involving the entry, distribution, transformation in the organism, and secretion of substances and their estimation makes it possible to relate the intensity of the therapeutic effects to the active concentration of the active forms of the preparation and not to the dose. This permits rational planning of chemotherapeutic regimes[236,237].

3. Kinetics of the Survival of Patients and the Effectiveness of Chemotherapy

The most important and most evident index of the effectiveness of the treatment of malignant tumours is the survival time of the patients. The survival time is a random quantity the statistical characteristics of which are determined by the type and stage of the development of the tumour, the theropeutic regime, and other factors.

Survival can be regarded as the kinetics of the change in the number of living patients determined by the distribution of the survival time in the initial group. The view that survival is a kinetic process makes it possible to apply to it standard mathematical methods adopted in kinetic studies and to obtain a complete quantitative description of survival with the aid of a small number of parameters having a definite physical significance. This is an advantage of the kinetic method over the traditional statistical method in which the percentage survival of patients is estimated solely in relation to a single specific time (for example, the five year survival)[238].

As a result of systematic studies on the kinetics of the survival of patients subjected to radical operations and untreated patients with malignant tumours in different locations, based on observations on several tens of thousands of patients, it has been established that the entire wide variety of forms of kinetic survival curves can be satisfactorily fitted by a small number of simple analytical relations.

If the factual data permit a detailed analysis of the survival curve, it is found that it is as a rule S-shaped. This is due to the unimodality of the corresponding distribution density $f(x)$ of the survival time, since the kinetics of the change in the fraction of surviving patients $P(t)$ are determined by integrating this density:

$$P(t) = \int_t^\infty f(x)\,dt \ . \qquad (115)$$

It has been shown that in many cases this distribution is of the lognormal type[238]:

$$f(x) = \frac{1}{x\sigma\sqrt{2\pi}} \exp\left[-\frac{(\ln x - m)^2}{2\sigma}\right], \quad x > 0 \ , \qquad (116)$$

so that the survival function is

$$P(t) = \frac{1}{\sqrt{2\pi}} \int_{\frac{1}{\sigma}\ln\frac{t}{T}}^\infty e^{-x^2/2}\,dx \ , \qquad (117)$$

where T is the median of the survival and σ^2 is the variance. The survival of patients suffering from cancer of the stomach, the mammary gland, the neck of the uterus, the lung, the mouth and the pharynx, and the tongue, as well as bone tumours can be described in terms of this relation.

In cases where clinical data are insufficiently detailed, it is useful to use a simpler one-parameter family of functions. Families of exponential and hyperbolic functions have been used for this purpose. In the first case the survival function is of the form $P(t) = e^{-kt}$ and describes, for example, the survival of patients with cancer of the stomach. In the second case the survival function is of the form $P(t) = 1/(a + kt)$; this case refers to cancer of the lung, the mammary gland, the rectum, the kidney, and the bladder.

It was shown that each location of the tumour is characterised by its own type of kinetic survival curve, which is the same for different hospitals and different times and is determined solely by the type of tumour[238]. This makes it possible to compare the effectiveness of different methods of treatment by comparing the different kinetic parameters.

Analysis of the influence of various clinical-morphological factors on the parameters of kinetic survival curves established that, for each type of tumour, the spread (stage) of the tumour process at the instant of diagnosis or the beginning of treatment plays the main role. The remaining factors such as sex, age, histological structure of the tumour, etc. are secondary.

The parameters of the functional relations for survival can be estimated along a comparatively short section of the kinetic curve, for example from data for the first 2–3 years of observation on patients subjected to a radical treatment or the first 3–6 months for non-operable patients. Knowing these survival constants, it is possible in its turn to extrapolate the kinetic curve to longer times and thus obtain a prognosis of survival at any time. Such prognosis is extremely important for practical medicine, since it makes it possible to accelerate the assessment of the effectiveness of new methods of treatment of malignant tumours. The observed 5–10 year survival of patients subjected to radical operations for cancer of the stomach, the lung, the mammary gland, the rectum and the large intestine, the kidney, and the bladder hardly differs from the calculated values obtained from data for 2–3 year survival.

The availability of stable kinetics relations for each type of tumour makes it possible to apply standard statistical procedures and to obtain estimates of the parameters for the general set of survival data for patients with tumours of a particular type. The analytical relations used to describe the factual data can be linearised in terms of appropriate coordinates and their parameters can be estimated by the method of linear regression. Such estimates have been obtained for patients who have undergone a radical operation for cancer of the stomach, the lung, the mammary gland, the bladder, and the rectum and for non-operable patients with cancer of the stomach and the lung[238].

These results have served as a theoretical and methodological basis for the development of a kinetic method for comparative estimates of the effectiveness of treatment in which the enormous amount of information accumulated in various clinics in the world is used as the "historical" control. The method makes it possible to abandon the simultaneous establishment of special control groups of patients and significantly accelerates the study of new medicinal compounds and the practical application of the most effective preparations.

As an example of the practical application of this method, Fig. 31 presents survival data from 33 clinics, generalised with the aid of the kinetic method, for patients with inoperable cancer of the lung who had not been subjected to a special treatment ("historical control") and survival data for 168 similar patients receiving chemotherapy. Fig. 31 shows that data for the 3 and 6 months survival of patients for whom a direct improvement was observed after chemotherapy (the majority of the patients were treated with nitrosomethyl-

urea) lie outside the 95% confidence zone of the "control". On the other hand, the survival of patients in which there was no improvement after treatment did not differ from the control. Thus kinetic analysis made it possible to observe that the use of prepations leading to a direct improvement of patients with cancer of the lung reliably increases their survival time, but the improvement is so far restricted to only 6 months.

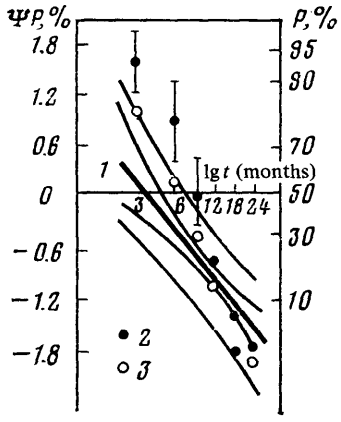


Figure 31. 1) Generalised survival curve for patients with inoperable lung cancer who have not been receiving chemotherapy, calculated from data from 33 clinics by the method of linear equation and transformed into a plot in terms of logarithmic statistical coordinates. The circles denote data for patients receiving chemotherapy: 2) cases involving improvement; 3) remaining cases[240].

The survival of patients is evidently closely related to the nature of the growth of the corresponding type of tumour, so that the study of this relation makes it possible to estimate from survival data parameters of tumour growth which cannot be derived by direct measurements[239].

A mathematical model relating to the survival of patients to the rate of growth of the mass of the tumour has been developed. The following expression has been obtained for the survival time:

$$t_m = \tau\gamma(V_0, V_m) \ , \qquad (118)$$

where τ is the time required for the doubling of the volume of the tumour and γ the coefficient of growth which depends on the nature of the growth of the tumour and on the rate of the initial (V_0) and final (V_m) masses.

The model makes it possible to estimate the mass of the tumour in the organism for different extents of the tumour process. It has been shown, for example, that the organisms of patients subjected to radical operations for cancer of the stomach without regional metastases, who subsequently died from the tumour, contained after the operation on average 10^7–10^8 residual tumour cells, while in non-operable patients there are 10^{11} tumour cells, etc. Such data can probably be used in the planning of the therapy of patients with different extents of the process.

Subject to the condition that the increase in survival as a result of treatment of the tumour (irradiation or chemotherapy) is due to the destruction of a specific proportion of tumour cells, the model makes it possible to estimate this fraction from survival data, i.e. to estimate the factor by which the treatment reduces the mass of the tumour. As an example, Fig. 32 presents kinetic curves for the survival of patients subjected to radical operations for cancer of the lung. For some patients, the treatment was confined to the operation, while others were given an additional chemotherapy with cyclophosphane [data from the Gertsen Moscow Institute of Oncology (MNIOI)]. Evidently the combined treatment led to an improvement of survival.

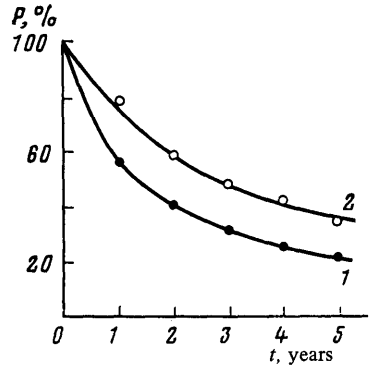


Figure 32. Kinetic survival curves for patients after radical operations for lung cancer; 1) surgical treatment alone; 2) chemotherapeutic treatment after operation [240].

According to the model, the decrease of the mass of the tumour as a result of the additional treatment is defined by the expression

$$\ln \frac{V'}{V} = \gamma\left(1 - \frac{T'}{T}\right) , \qquad (119)$$

where V and V' are the average masses of the tumours in patients belonging to the groups being compared and T and T' are the medians of the survival times of the patients in these groups.

The calculations showed that in the example presented in Fig. 32, the increase of survival was a result of the decrease of the mass of the tumour by a factor of 400 (the average for the group considered). This can be regarded as a quantitative index of the effectiveness of cyclophosphane in the combined treatment of cancer of the lung.

Similar parameters can be used also for comparative estimates of the effectiveness of different preparations.

4. Application of Factorial Analysis in the Quantitative Estimation of the Joint Action of Combined Preparations

The greatest effect in the chemotherapy of cancer is usually attained when two and more antitumour preparations are used. In practice optimum chemotherapeutic regimes are chosen empirically at the present time. The number of possible combinations is then extremely large and it is difficult to count on finding the objectively optimum regime. The possibility of a rigorous determination of the mutual influence of the preparations as a basis for the optimisation of combined chemotherapy then becomes particularly important.

The method of factorial analysis was used for the first time to assess quantitatively the joint action of diazan and cyclophosphamide in the treatment of leukaemia R-388.[232] This made it possible to determine the contribution of each preparation (factor) to the overall final result of the therapy and also to find a quantity characterising the interaction of the factors (λ).

The effectiveness and interaction of the factors can be expressed in an analytical form by the equation

$$\lambda_{k_1 k_2} = \sum_{l=1}^{m} \left\{ (-1)^q \sum_{i=1}^{m} \tau_{ij} \right\}, \qquad (120)$$

where $k_1 = 1, 2, \ldots, l$, $k_2 = 1, 2, \ldots, l$, $q = 1$ or 2, and τ_{ij} is the lifetime of the animal.

The application of factorial analysis led to the discovery of different degrees of therapeutic synergism for identical activity indices of the preparation. In Fig. 33 the experimental results are presented in the form of equieffective curves. A point in the plane represents the results of the combined action of two preparations taken in specific doses. The numerals in the graph represent the activity coefficients. By interpolating the values of the effectiveness on the basis of the experimental points, it is possible to calculate the values for other points and then to plot curves on which each point corresponds to the same effectiveness. Fig. 33 presents equieffective curves of κ ranging from 2 to 6.

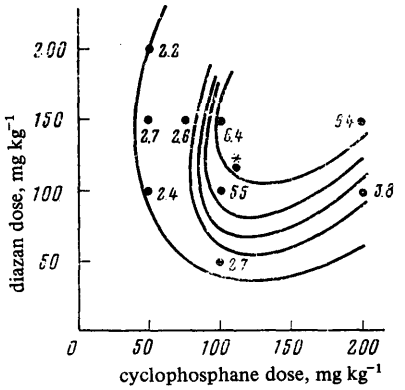


Figure 33. Equieffective curves for the combined treatment with diazan and cyclophosphane calculated for κ ranging from 2 to 6.[240]

The equieffective curves make it possible to determine the region of the maximum effectivness and to estimate the optimum treatment, i.e. to determine the minimum doses of the preparation sufficient to achieve the maximum effect. Evidently the point (represented by an asterisk) at which the diazan dose is 120 mg kg^{-1} and the cyclophosphane dose is 110 mg kg^{-1} corresponds to these conditions. Indeed subsequent experiments showed that the maximum effectiveness of the treatment is then observed.

This approach to the analysis of the results of polychemotherapy leads to the possibility of rigorously justified clinical recommendations and permits the solution of the problem of optimising combined therapy.

5. Classification of Antitumour Preparations in Terms of the Principle of Chemical Reactivity

The synthesis of substances with antitumour properties specified beforehand constitutes an insignificant fraction of the enormous amount of research throughout the world into the synthesis of new chemical compounds. To some extent, this is a consequence of traditional self-limitations, as a result of which the search for new effective antitumour preparations is usually prosecuted within the limits of a few empirically discovered classes of chemical compounds such as alkylating agents, antimetabolites, antibiotics, and hormonal preparations.

In terms of the mechanism of their action, these substances can be divided into two main groups—compounds characteristic of the metabolic processes in normal or tumour cells or derivatives similar to such compounds (biochemically functionally active compounds) and substances for which a purely chemical interaction with the cell molecules plays the main role (chemically functionally active substances).

A condition for the most effective application of the antitumour preparations of both groups is in most cases a natural or artificially created enhanced sensitivity of tumour cells to the action of preparations relative to normal cells.

Biochemically functionally active preparations. Enzymes (L-aspartase and ribonuclease), hormones (cortisone, prednisolone, testosterone, and diethylstilboestrol), certain metabolites from a series of membrane-active regulators of metabolic processes and structural analogues of metabolites—the antimetabolites of nucleic acid exchange (mercaptopurine, thioguanine, 5-fluorouracil, ftorafur, 5-azacytidine, etc.), and antimetabolites of folic acid metabolism (methotrexate and aminopterin) should be included among biochemically functionally active antitumour compounds.

It is possible to discover new effective preparations among biochemically functionally active substances. This is indicated particularly by the unexpectedly successful application in tumour chemotherapy of synthetic analogues of bioantioxidants—ionol, ambunol, etc.

Chemically functionally active compounds. It is known that the total number of specific substances with which chemists have dealt for one reason or another is almost ten million in the field of organic chemistry alone and there are no fundamental difficulties in multiplying this number by a large factor.

The classification of antitumour preparations generally adopted at the present time is based on several different principles: the mechanism of biological action (antimetabolites and hormones), the source (antiobiotics, alkaloids, and enzymes), and chemical properties (alkylating agents). Synthetic preparations the mechanism of whose action has not yet been established constitute a large group, which is not in fact included in the above classification. Such classification of the antitumour preparations is inadequate as a basis for the rational planning of the synthesis of new preparations or for the selection of potential antitumour agents from the enormous number of chemical compounds known at the present time. Furthermore, from a purely chemical standpoint, it is possible to put forward a more systematic classification based on the types of structures and the types of chemical reactivities of these compounds[240]. Indeed they can all be divided into five main groups in terms of their characteristic reactions:

(1) electrophilic reactions;
(2) free-radical reactions;
(3) complex formation reactions;

(4) nucleophilic reaction;
(5) cycloaddition.

In this section the chemical structures and mechanisms of the action of antitumour agents will be considered from the standpoint of the classification based on this principle.

(1) Electrophilic reactions. In the modern arsenal of effective antitumour agents the greatest proportion consists of chemical compounds reacting via the mechanism of electrophilic interactions, which include the formation of electrophilic species (carbonium ions which alkylate or acylate the nucleophilic centres of principal chemical components of the cell).

β-Chloroethylamines, β-chloroethyl sulphides, epoxides, aziridines, sulphonate and phosphate esters, halogenomethyl ketones, chloromethyl ethers, ammonium and sulphonium compounds, β-lactones, diazoketones, and nitrosocarbamides behave as alkylating agents *in vivo*.

Table 11. Alkylating agents.

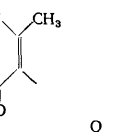
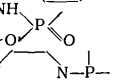
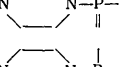
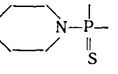
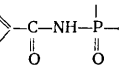
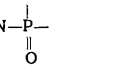
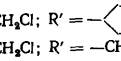
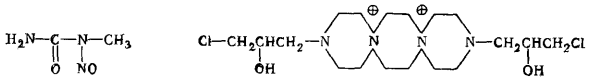
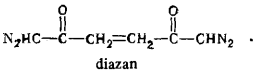
Overall formula	Carbonium ions	Name of preparation	R
		embichin	CH_3-
		chlorobutin	$HO-C(=O)-(CH_2)_3-C_6H_4-$
		sarcolysine	$HO-C(=O)-CH(NH_2)-CH_2-C_6H_4-$
$R-N(CH_2CH_2Cl)(CH_2CH_2Cl) \rightarrow [R-N(CH_2\overset{\oplus}{C}H_2)(CH_2CH_2Cl)]$		dopan	
		lofenal	$HO-C(=O)-CH(CH_2-C_6H_4-)-NH-C(=O)-CH_2-$
		cyclophosphane	
		dipin	
		thiodipin	
$R-N(CH_2)(CH_2) \rightarrow [R-NH-\overset{\oplus}{C}H_2CH_2]$		thiophosphamide	$-P(=S)-$
		benzotef	
		imiphos	
$R-S(=O)(=O)-OCH_2R' \rightarrow [R'-\overset{\oplus}{C}H_2]$		myelosan	$-(CH_2)_4-$; $R'=CH_3$
$R-C(=O)-CHN_2 \rightarrow [R-C(=O)-\overset{\oplus}{C}H_2]$		azaserine	$HOOC-CH(NH_2)-CH_2-O-$
		DON	$HOOC-CH(NH_2)-CH_2-CH_2-$
		diazan	$-CH_2-CH_2-$
		nitroso-methylurea	$-CH_3$
$R'HN-C(=O)-N(NO)-$		CCNU	$-CH_2CH_2Cl$; $R' =$ 
$-R-[\rightarrow N-\overset{\oplus}{C}\cdots O] \rightarrow [R^{\oplus}]$		BCNU	$-CH_2CH_2Cl$; $R' = -CH_2CH_2Cl$

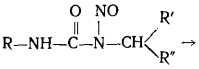
Table 11 presents the structures of the compounds encountered most frequently in practice and of the carbonium ions formed from them. Further progress in the synthesis of antitumour preparations with an alkylating activity is associated with the finding of new types of cytotoxic groups and also with the modification of transport fragments ensuring the selectivity of the action of the preparations. New effective antitumour preparations have been synthesised recently: nitrosomethylurea containing the functionally active nitrosocarbamide group[231], prospidin in which a spiro-heterocycle with quaternary nitrogen atoms serves as the carrier of the bis-β-chloroalkylamino-group[241], and 1,2-bisdiazoacetylethane (diazan) containing two diazoacetyl fragments[226]:

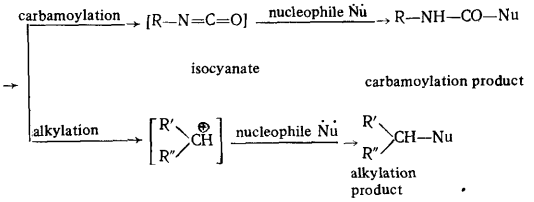

nitrosomethylurea

prospidin

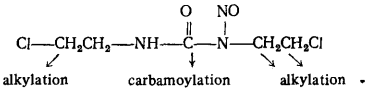

diazan

Nitrosomethylurea, proposed in 1964 as an antitumour preparation, and its homologues and analogues exhibit a dual electrophilic reactivity, in contrast to other alkylating agents, involving not only an alkylating activity but also a carbamoylating activity, which is responsible for the characteristics of the mechanism of the biological activity of compounds of this class:


nitrosocarbamide



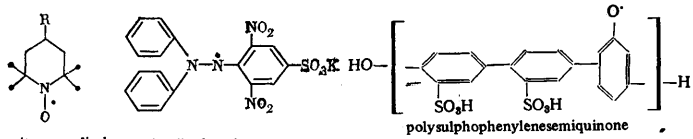
Chloroethylamino-derivatives of nitrosocarbamides contain several reaction centres, in particular the familiar preparation BCNU has a single carbamoylating centre and three different alkylating centres:



Prospidin also contains two types of alkylating centres—the ammonium and chloroalkyl groups. The ionic centres of spiro-heterocycles ensure the specific binding of the preparation to the chemical components of the cell. Prospidin is used in the treatment of cancer of the larynx, retinoblastomas, papillomatesis of the upper respiratory tract, and Kaposi's angiosarcoma[242].

(2) Free-radical reactions. Free-radical reactions constitute an appreciable proportion of the chemical processes occurring in living systems. It is therefore to be expected that compounds capable of being involved in these processes—stable radicals and antiradical agents (inhibitors)—should exhibit a physiological activity.

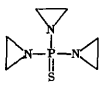
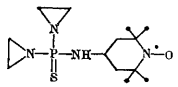
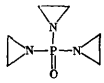
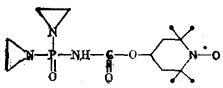
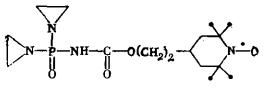
The antitumour effect of stable free radicals was first observed by ourselves in 1964 for nitroxy-radicals and triarylhydrazyls[243] and then for polysulphophenylenesemiquinone[244]:



The radiosensitising effect of nitroxy-radicals has also been demonstrated[225].

The use of stable radicals for the structural modification of certain known antitumour preparations is extremely promising. The paramagnetic derivatives of thiophosphamide, phosphamide, and triethylenemelamine synthesised and investigated at the present time are characterised by a toxicity lower by more than an order of magnitude than that of the initial compounds, while retaining the same or even higher antitumour activity (Table 12).

Table 12. The antitumour activities of paramagnetic analogues of antitumour agents[240].

Formula	LD_{50}^{a}, mg kg^{-1}	b, Δ^{b}, % (leukaemia La)	c, x^{c} (leukaemia La)	Inhibition of tumour growth^{b}, % WCS	SEM	EAC	S-180
 Thiophosphamide	18	20	0.3	100	100	45	—
	187	80	0.5	100	100	70	50
 Phosphamide	15	—	—	65	—	50	—
	150	170	1.0	100% inhibition of tumour growth			
	280	80	0.4	100% inhibition of tumour growth			

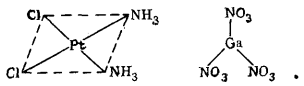
Notation: *a*) dose of the preparation for which 50% of the animals die due to its toxicity; *b*) increase of the average lifespan of the animals; *c*) WCS = Walker carcinosarcoma 256; SEM = Svec erythromyelosis; EAC = Ehrlich ascites carcinoma; S-180 = sarcoma 180.

The synthesis of chemically polyfunctional antitumour preparations, incorporating a stable nitroxy-radical as the carrier of the alkylating group, leads to a fundamentally new type of preparations with a combined mechanism of action, which combine the properties of substances with electrophilic reactivity and substances undergoing free-radical reactions.

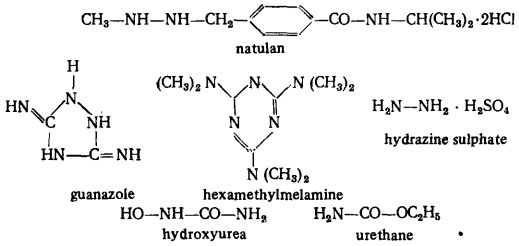
(3) Complex formation. Complex-forming agents capable of donor–acceptor interactions of various types (the formation of charge-transfer complexes, hydrogen bonding, hydrophobic interactions, and the formation of metal complexes) constitute a large and structurally varied group of antitumour preparations. Many antibiotics, which combine with the nitrogen-containing DNA bases as intercalating agents (antibiotics of the anthracycline [anthramycin? (Ed.of Translation)] series—adriamycin, rubomycin and carminomicin, antibiotics belonging to the aureolic acid group—olivomycin and mithramicin, as well as actinomycins) should be assigned to this group. The intercalation mechanism can be proposed for many polycyclic compounds and ionic forms of polyheterocycles (phenothiazines, phenoxazines, and acridines).

Metal salts and complexes (gallium nitrate and platinum group metal complexes) constitute a special group of antitumour preparations. The mechanism of their biological action is due to their ability to combine with information biomacromolecules. This field of tumour chemotherapy has in essence only begun to develop.

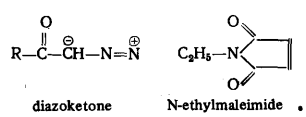
In the future one may expect the synthesis of new antitumour preparations consisting of a series of mononuclear and dinuclear complexes of various metals:



(4) Nucleophilic reactions. Nucleophilic reactions have not been considered at all in the literature as reactions of importance from the standpoint of the antitumour effect. Nevertheless the electrophilic centres of metalloenzymes (carbonyl and azomethine groups) can serve as targets for preparations with nucleophilic reactivity. Indeed, among antitumour preparations classified as substances with different (or even unelucidated) mechanisms of action, it is possible to distinguish derivatives of hydrazine, carbamide, and nitrogen-containing bases which are strong nucleophiles:



(5) Cycloaddition. Direct data indicating the possibility of cycloaddition reactions in the organism involving antitumour preparations are not at present available. However, the presence of activated double bonds in many metabolites does not rule out the Huisgen or Diels–Alder reactions. *N*-Ethylmaleimide and diazoketones can be included among antitumour agents capable of participating in these reactions:



The new classification of preparations in terms of types of reactivity, which the present author proposed, is more general than the traditional classification, permits a more

detailed treatment of the chemical and biochemical mechanisms of the action of antitumour preparations, and provides a basis for the rational planning of their synthesis. Preparations with hybrid structures and correspondingly with hybrid reactivities fit satisfactorily within the framework of this classification.

6. Correlation between the Chemical Structure and the Antitumour Activity of Compounds

Quantum-chemical calculations can be used to predict the biological activity and to select the optimum structures of antitumour preparations. Among the many methods for the determination of quantitative relations between the structures of compounds and their biological activities, those of Free and Wilson[245] and Hansch and Deutsch[246] are most widely used. The Hansch equation makes it possible to establish a correlation between the biological activity A and the physicochemical characteristics of the substance:

$$\lg A = \rho\sigma + \alpha\pi + \gamma E_s + B \,, \qquad (121)$$

where σ characterises the polar effects in the molecule (in particular it can be Hammett constants or quantum-chemical characteristics of the electronic structure), E_S are steric factors (for example Taft constants), and π represents the distribution of the preparation in the lipid–water system ($\pi = \lg P$, where P is the partition coefficient in the 1-octanol–water system). The polar factors σ depend on the distribution of electron density in the molecule and on the free valence indices of the reactive atoms, which determines in its turn the chemical reactivity of the molecule as a whole.

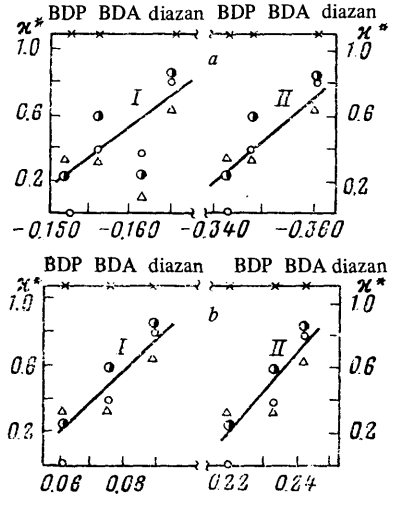


Figure 34. Correlation between the negative charges (*a*) and free valence indices (*b*) of the oxygen atoms (I) and carbon of the methine group (II) and the antitumour activity κ^* in a series of bisdiazoketones; BDD = bisdiazoacetyl; BDP = bisdiazoacetylpropane; ○—Ehrlich ascites carcinoma; ◑—leukaemia La; △—sarcoma 180.[240]

Quantum-chemical calculations of the structure of bisdiazoketones by the semiempirical CNDO/2 method[247] showed that a change in the electron-donating properties of the substituents influences significantly the distribution of electron density in the diazoketone fragment. It was found that the antitumour effect is correlated with the charges on the C and O atoms and the Wiberg indices and also with the Hammett constants σ and the energies of the highest occupied molecular orbitals E_{HOMO} and the lowest unoccupied molecular orbitals [E_{LUMO} (Fig.34)].

7. Free Radicals and Tumour Growth. Inhibitor-antioxidants as Anticarcinogenic and Antitumour Preparations

A little more than two decades ago, the author put forward ideas concerning the possibility of biophysical shifts associated with changes in the content of free radicals in tissues in various pathological states (malignant growth, radiation damage, and the effect of toxic substances).

Paramagnetic centres—free radicals (FR) and transition metal complexes (Mn, Fe, Mo, etc. complexes)—have now been detected in many tissues of animal and plant organisms functioning normally and their nature has been determined. Fig.35 illustrates the characteristic EPR spectrum of liver cells. The narrow EPR singlet with a g-factor of 2.003¶ corresponds to free radicals of the semiquinone type, observed in many other organs and tissues. Mainly flavins in the semioxidised state and the semiquinone form of ubiquinones, functioning as electron transferring agents in the respiratory and energy chains of mitochondria, are responsible for this signal.

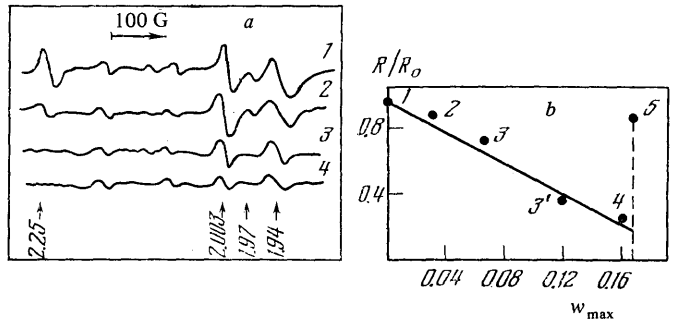


Figure 35. Paramagnetic centres in tissues of normal liver and in transplanted haepatomas: *a*) EPR spectra of frozen specimens of normal liver tissue (*1*), haepatoma 46 showing a minimal deviation (*2*), rapidly growing haepatomas 60 and 22a (*3* and *4*); *b*) relative content of free radicals in normal ($R/R_0 = 1.0$) and regenerating livers (*5*) and also in haepatomas with different rates of growth[226].

The EPR signal of flavin radicals in tissues has a half-width of 14–15 G,[248,249] and for ubiquinone radicals $\Delta H = 10$–11 G.[250] Depending on the ratio of the amounts of flavin, ubiquinone, and other free radicals, the EPR signal half-width for the tissue can vary from 10 to 16 G.

The signal with $g = 1.94$ is due to iron sulphur complexes in mitochondria. The haem iron of cytochrome P-450 in microsomes in a low-spin state gives rise to an anisotropic signal with $g = 1.91$, 2.25, and 2.42; the component with

¶ In certain studies a different value of the g-factor of the free radical signal has been reported (up to 2.005).

g = 2.25 is most intense. A signal with g = 1.97, due to molybdenum compounds of xanthine oxidase and sulphate redutase, can also be observed.

It is natural to expect that, in the development of pathological processes in the organism, the content of free radicals and other paramagnetic centres can differ from the norm and that EPR signals not characteristic of the organism under normal conditions may appear. Indeed, in many pathological processes such as radiation damage, cancer, virus diseases, and various stresses on the organism (hypoxia, hyperoxia, etc.), the content of free radicals (g = 2.003) and other paramagnetic centres in the tissues changes and new signals appear, for example, a signal with g = 2.03 [251–253] and a triplet signal with the centre at g = 2.007.[254,255]

A quantitative relation has been observed between the intensities of individual signals in the EPR spectra and the level of metabolic activity of the tissues[256]. This served as a basis for the study of the kinetics of the change in the paramagnetic properties of organs and tissues in carcinogenesis and tumour growth. The change in the content of paramagnetic centres in the tumour is one of the physicochemical characteristics of tumour growth.

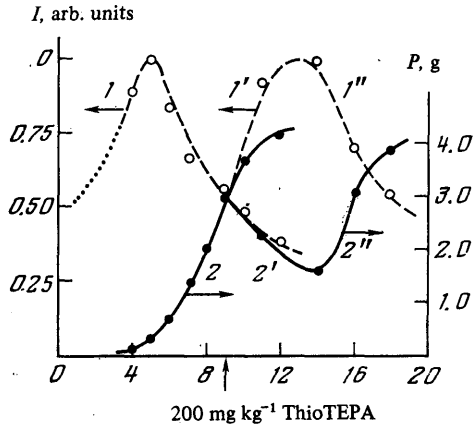


Figure 36. Variation of the content of free radicals (curves *1*, *1'*, and *1''*) in tumour tissue and of the weight of the tumour (curves *2*, *2'*, and *2''*) in the course of growth (curves *1* and *2*), regression (curves *1'* and *2'*), on treatment with ThioTEPA (200 mg kg^{-1}), and relapse (curves *1''* and *2''*) of adenocarcinoma 755 in mice. The arrow indicates the instant of administration of ThioTEPA (I = amplitude of signal with g = 2.00 in EPR spectrum).

In all cases (approximately 25 experimental tumours) the kinetic curves for the variation of the content of free radicals in the tumour passed through a maximum near the point of the maximum tumour growth[257]. As an example, one may consider curve *1* in Fig.36, which reflects the characteristics of the variation of the number of radicals in an experimental tumour (adenocarcinoma 755) on the 4th–12th day of its development (the EPR spectra were measured at 77 K). Taking into account the concentration of radicals in the tumour tissue on the 9th day, when the tumour was transplanted, one may postulate that in the first three days after transplantation the content of free radicals increases (shown by circles) up to the maximum values observed on the 4th–5th day. Evidently the maximum in the kinetic curves for the variation of the content of radicals is determined by consistent biophysical changes in malignant growth. The content of free radicals in developing tumours is appreciably below the norm (sometimes by a factor of 2–3).

The process of the development and growth of a malignant tumours induces specific biochemical changes in various organs and tissues of the animal tumour carrier. In particular, the decrease of the functional activity of the liver in the course of the growth of transplanted tumours is reflected in a decrease of the concentration of paramagnetic metal complex and free radical centres relative to the norm. It has been shown for six types of experimental transplanted leukaemias that the content of radicals in the livers of mice remains at the normal level in the course of the latent period of the development of the leukaemic process and then falls[258].

In the chemotherapy of tumours the EPR spectra of tumour cells and the organs of tumour carriers shown an increase of the intensity of EPR signals corresponding to the magnitude of the antitumour effect. Such data have been obtained, for example, when leukaemia La was treated with diazan, haepatoma 46 was treated with dibutyryl-cAMP, and melanoma B-16 was treated with thiophenosphamide. The observed increase of signal intensity in the EPR spectra under these conditions is probably associated with the growth of the metabolic activity of the tissues.

In the chemotherapy of adenocarcinoma 755 with cyclophosphane an increase of intensity (by 30–40%) and of the half-width of the free radical signal (from ΔH = 10 G to ΔH = 12–13 G) was observed in the tumour regression stage, while in the subsequent recovery of the tumour the opposite effect was noted (see Fig.36). This can be accounted for by changes in the ratio of the paramagnetic forms of flavin and ubiquinone and their different contributions to the measured EPR signal of the tumour tissue[259]. An analogous result was obtained also under clinical conditions: in the therapy of cancer of the rectum the decrease in the size of the tumour was accompanied by an increase of the intensity of the EPR signal of the free radicals in the specimens.

Thus the study of the kinetics of the changes in the paramagnetic properties of tissues can be used to investigate the development of tumours and to assess the effectiveness of the therapy.

Free-radical shifts have also been observed in kinetic studies of the paramagnetic properties of animal tissues in the course of chemical carcinogenesis. Fig.37 shows that complex multistage changes in the content of free radicals take place in rat livers in the course of the malignant degeneracy under the influence of diethylnitrosamine (DENA).[251] Analogous curves have been obtained in the carcinogenesis under the influence of other carcinogens: dimethylaminoazobenzene (DAB),[260] 3,4-benzopyrene[261], and Teflon[262].

The study of the kinetics of the variation of the concentration of radicals in tissues and cells in the course of viral, chemical, and spontaneous carcinogenesis made it possible to observe many common features, despite the different nature of the agents inducing this process, and to put forward hypotheses concerning the nature of these shifts. The most characteristic feature is a maximum on the curves for the content of free radicals in tissues in the initial period of carcinogenesis regardless of the species, sex, and age of the animals, the type of cells undergoing malignant degeneracy, and the experimental conditions.

An analogous maximum in the content of radicals in liver tissues has been observed when animals were treated with non-carcinogenic toxic substances—benzene, DDT, and oxidised sunflower oil (Fig.37*b*). Evidently the observed maximum is associated with a non-specific response of the organism to the introduction of the toxic compound.

The free-radical shifts observed in animal livers and also brains under the influence of toxic substances can serve as a measure of the influence on the organism of particular agents in the environment.

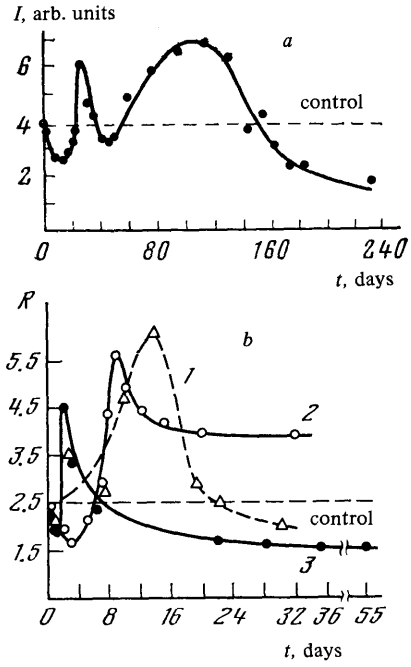


Figure 37. Variation of the content of free radicals (g = 2.003) in rat liver in carcinogenesis induced by diethylnitrosamine (a) and under the influence of toxic agents (b):[226] 1) oxidised sunflower oil; 2) benzene; 3) DDT.

The ideal of a significant role of free-radical shifts in tumour growth and carcinogenesis served as a basis for the hypothesis that inhibitors with a low toxicity which suppress the development of radical processes can prove to be effective anticarcinogenic agents. Numerous experiments have shown that the familiar inhibitor of radical processes and antitumour preparation 2,6-di-t-butyl-4-methylphenol (dibunol) does indeed exhibit an effective anticarcinogenic activity. Rat liver tumours have been induced by including dimethylaminobenzene (DAB) in the diet[263]. Under the influence of DAB, tumours arose in 90% of the animals after 90 days. When 0.3 wt.% of ionol was added to the food together with the carcinogen, tumours did not develop even after treatment with DAB for 150 days. Pre-tumour changes in the animal livers were completely absent.

The anticarcinogenic activity of radical process inhibitors which we established was confirmed by other workers[264,265].

We have investigated the molecular aspects of this extremely important problem[260]. We observed that the introduction of ionol together with the carcinogen prevents an increase of the concentration of free radicals in the initial stage of the action of the carcinogen, maintaining it at a level close to that in the normal liver tissue (Fig.38). Tumours did not arise in the course of twelve months of observation in animals receiving 2,6-di-t-butyl-4-methylphenol.

The experimental data obtained give rise to the problem of the development of methods for the prophylaxis of malignant diseases.

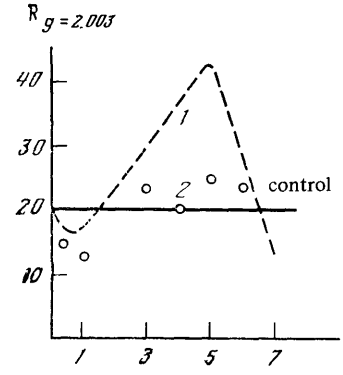


Figure 38. Variation of the concentration of free radicals in rat liver under the influence of DAB (*1*) and under the joint influence of DAB and ionol (*2*).[226]

8. The Antioxidant Activity of Lipids in Normal and Tumour Tissues and Chemotherapy

Approximately two decades ago, the concept of the antioxidant activity (AOA) of tissue lipids, characterising the involvement of bioantioxidants in metabolic processes, was introduced into biochemistry[266].

The value of AOA (in ml h g^{-1}) is determined from the ability of lipid fractions to inhibit the oxidation of a standard substrate, for example, methyl oleate, which is oxidised at a rate suitable for measurement even at physiological temperatures:

$$(\mathrm{AOA}) = \frac{\tau - \tau_{\mathrm{stand}}}{P} \quad , \qquad (122)$$

where τ and τ_{stand} is the time of attainment of the same degree of oxidation of the substrate with the lipid fraction and of a standard substrate and P is a sample of the lipid fraction. The quantity AOA is extremely sensitive to various normal physiological and pathological states of the organism and also to the action of physical and chemical factors.

The growth of transplanted tumours is accompanied by a change in the AOA of the lipid fractions of the tissues and organs of animal tumour carriers and in the tumour tissues formed compared with the norm (for organs) and with the initial value of AOA for the transplanted material[267,268]. This change passes through an extremum as a function of the time of development of the tumour process. In successful chemotherapy the retardation of tumour growth is accompanied also by the retardation of the increase of AOA. This can be used for monitoring the course of the therapy.

The study of the changes in AOA in animal tissues under the influence of chemical and physical factors leads to important conclusions. All the effective antitumour preparations reduce AOA compared with the normal level after administration to healthy animals[269] (Fig.39).

This effect is observed for all alkylating compounds and synthetic antioxidants when they are administered in doses ensuring the antitumour activity of hormones and antimetabolites. In the case of hormones the suppression of AOA after a certain time is replaced by an increase of AOA to which corresponds an acceleration of tumour growth in chemotherapeutic experiments. However, repeated administration of these preparations, ensuring the maintenance of the AOA level below the norm, results in the retention of the antitumour activity. These observations are fully consistent with clinical data concerning the application of hormones and antimetabolites as antitumour agents. Non-specific influences such as irradiation with X-rays and stress also cause a decrease of AOA and the corresponding antitumour effect.

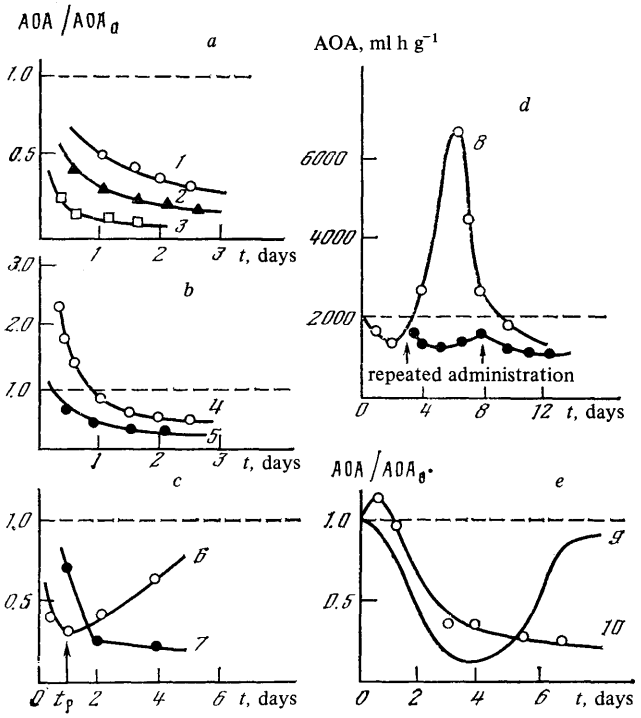


Figure 39. The influence of various preparations [*a*) alkylating agents; *c*) antimetabolites; *d*) hormones; *e*) physical factors] on the AOA of the lipids in the livers of healthy animals: 1) ThioTEPA; 2) phenylacetic acid; 3) myelosan, sarcolysine, spirazidine; 4) antioxidant; 5) nitrosomethylurea; 6) 6-mercaptopurine; 7) 5-fluorouracil; 8) adrenaline; 9) irradiation with a dose of 450 r; 10) cold; the horizontal dashed line indicates the normal value of AOA; t_r = the recommended instant for repeated administration[240].

An inverse correlation between antitumour activity and $(AOA)_{min}$—the minimum value of AOA which can be attained by a given antitumour treatment (Fig.40)—has been established for the model of the transplantable leukaemia La. On the basis of this correlation, it is possible to develop a new principle of the screening of antitumour preparations in which healthy animals are used to determine their effectiveness.

The study of the antioxidant properties of tissues can be used also for a rational selection of preparations with anticarcinogenic properties. The changes in the AOA of tissues in carcinogenesis correspond to the morphological stages of the latter (Fig.41).[271] It has been shown that, in the stage involving a decrease of AOA, anticarcinogenic activity is shown by preparations which increase AOA to values close to the norm; at later stages of carcinogenesis it is necessary to decrease AOA.[271,272] Thus at a given stage of carcinogenesis the AOA test makes it possible to establish the dose in which the antioxidant will exhibit an effect retarding carcinogenesis.

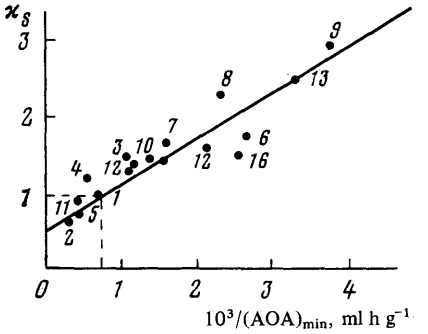


Figure 40. Dependence of the inhibition coefficient $\varkappa_S$ for transplanted leukaemia La on the reciprocal of the minimum AOA of lipids under the influence of antitumour preparations and other types of treatment[268].

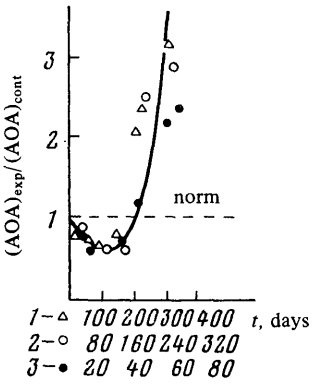


Figure 41. Variation of the AOA of mouse liver lipids in carcinogenesis; 1) o-aminoazotoluene; 2) γ-radiation; 3) 3,4-benzpyrene.[268]

9. Kinetic Aspects of the Ageing of Living Organisms. Physicochemical Principles of Increasing the Life Span

The ageing of man is one of the most dramatic laws of nature. A wide variety of processes in the living organism take place in open heterophase chemical systems under the influence of numerous chemical and physical factors. Many of the undesirable and "harmful" phenomena in chemistry are

also referred to as ageing processes. These are, for example, the ageing processes in polymers and articles made from them, examined above, the spoiling of food products and medicinal preparations, etc. Many processes with analogous elementary process mechanisms (molecular, ionic, and free-radical) take place both in the ageing of "non-living" chemical systems and in the ageing of living organisms. The entire experience concerning the control of chemical reactions gained in the study of chemical kinetics should be reasonably employed for the inhibition and suppression of ageing processes in living organisms.

There is as yet no single accepted method for the measurement of the rates of ageing of individual organisms in gerontology, although various procedures have been proposed for the determination of "biological age". Instead, statistical ageing indices, referring to a group of similar individuals, are usually employed. The main effect of ageing is that the probability of death in the forthcoming period of time (year, month, etc.) increases with age. The principal statistical ageing indices are therefore derivable from the survival curve. The survival curve $P(t)$ represents a function describing the dependence of the fraction of surviving organisms P on their age t. The principal mortality indices such as the mortality rate dP/dt and the quantity $R_m = (1/P) \cdot (dP/dt)$, which has come to be referred to as the strength, intensity, or index of mortality, can be derived from the survival curve. In the absence of ageing R_m = const., i.e. is independent of the age; ageing processes are manifested by the fact that R_m increases with age. The survival curve also yields other indices, such as the average and maximum lifespans, the average remaining lifespan, etc.[239]

Survival curves have the usual complex S-shape. For humans and certain laboratory animals, they can be fitted, for example, by the empirical Gompertz–Makeham formula:

$$R_m = A + R_0 e^{\alpha t}, \qquad (123)$$

where A, R_0, and α are constant parameters. Other empirical formulae are also used for laboratory animals.

The application of the probit method[273] in the treatment of these data makes it possible to represent the survival curve by a straight line making an intercept on the time axis equal to the age of the animals corresponding to 50% mortality ("median"); the average rate of mortality as a percentage can be determined from the slope of the straight line[274]. This method of representing data is particularly clear in those cases where the rate of the ageing process is altered by means of some kind of influence in the course of the experiment, as will be shown below (see also Fig.43).

In the case of effective influences leading to an increase of the lifespan of animals and to a change of particular parameters, the survival curves for the experimental group can differ in shape from the curves from the control group. The group of animals used to determine the survival curve can be divided to a first approximation into two subgroups: "short-lived" and "long-lived". Geroprotectors can have different effects on these subgroups and the nature of the changes in the overall survival curves is accordingly also different[275].

I. If the lifespan of all the members of the group increases by the same amount, the average and maximum lifespans also increase and the survival curve shifts to the right parallel to itself (Fig.42*a*). The mortality rate may not then change.

II. The influence may decrease the mortality rate in the group of "long-lived individuals". In this case the average and maximum lifespans also increase and the survival curve has the form shown in Fig.42*b*.

III. If the lifespan of the subgroup of short-lived individuals increases and the maximum lifespan remains unaltered, the curves have the form shown in Fig.42*c*. The mortality rate then increases but the average lifespan nevertheless also increases.

The proposed subdivision of the experimental group into two subgroups can serve as a basis for the classification of effective influences increasing the lifespan of animals.

Numerous data indicating the involvement of free radicals in ageing processes suggested that inhibitor-antioxidants should exhibit a prophylactic and therapeutic effect and should increase the lifespan of organisms. By preventing the development of different kinds of pathological processes, antioxidants can reduce the amount of damage in organisms and hence can prevent ageing.

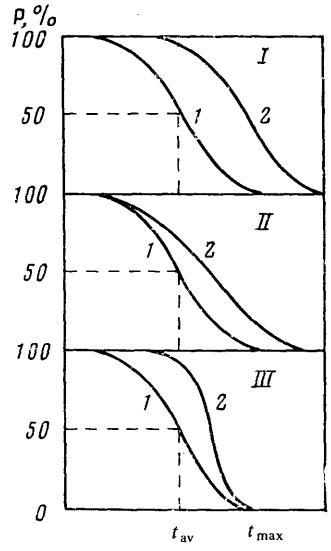
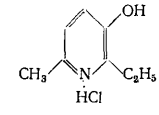


Figure 42. Various types of changes in the survival curve observed experimentally when the organism is treated with agents decreasing the rate of ageing: 1) control; 2) treatment with geroprotector[275].

Harman[276] observed that the addition to food of ionol (2,6-di-t-butyl-4-methylphenol), a well known radical process inhibitor, increases the lifespans of mice on average by 40%. 2-Mercaptoethanolamine, butylhydroxyanisole, and cysteine cause a somewhat smaller increase, the result depending on the breed of the animals. It has been shown[277] that the introduction of the antioxidant santoquin into food also increases the lifespan of mice. The lifespan of animals does not then exceed the maximum known for mice of the given strain under optimum conditions.

The lifespan of laboratory animals is also increased by the relatively non-toxic water-soluble antioxidant 2-ethyl-3-hydroxy-6-methylpyridine hydrochloride, a structural analogue of vitamin B_6:[278–280]



SHK and C3HA mice were given the geroprotector starting from the age of two months. In experiments with two month old SHK animals (Fig.43*a*) an increase of the latent period on the survival curve (the time of attainment of 10% mortality)

and an increase of the maximum lifespan from 25.4 months in the control to 29 months under the influence of the geroprotector were observed. The entire survival curve then underwent a parallel shift to the right. The average lifespan increased to 17.8 ± 6 months compared with 13.7 ± 0.5 months in the control. As a result of the probit transformation for the control and experimental groups, parallel straight lines were obtained. The mortality rate determined from them was 6.2% month^{-1}.

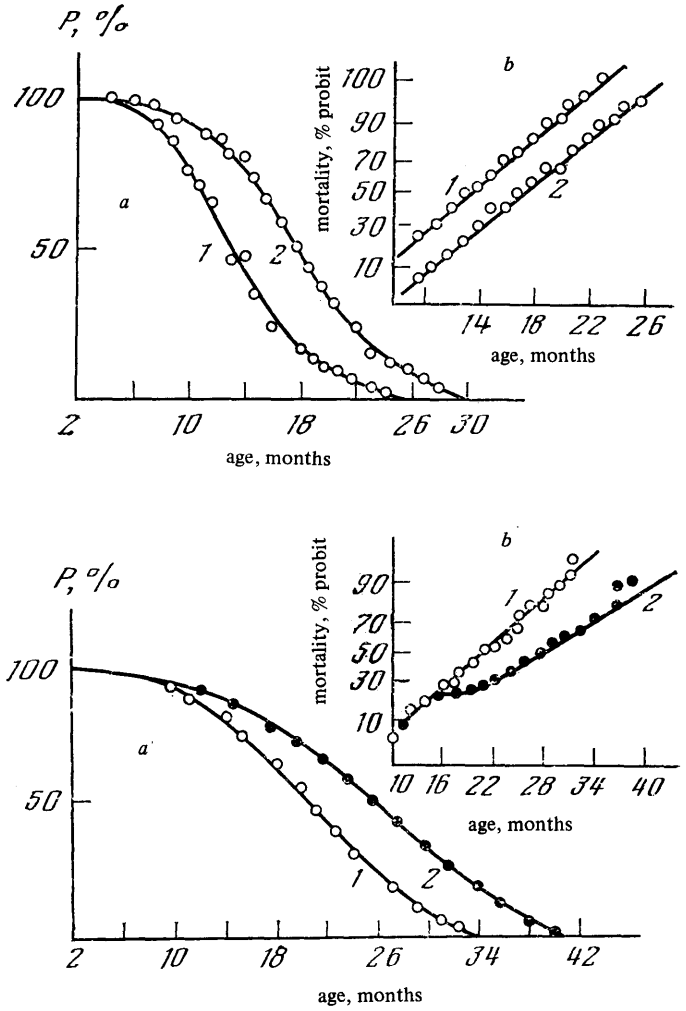


Figure 43. The influence of 2-ethyl-8-hydroxy-6-methylpyridine on the lifespan of SHK (*A*) and C3HA (*B*) mice. Treatment begun at the age of 2 months: *a*) survival curves; *b*) probit transformation; 1) and 2) control and experimental groups respectively[279,280].

Other results were obtained for two month old mice of the C3HA strain (Fig.43*b*). The average experimental lifespan reaches 27.05 ± 0.80 months and the maximum lifespan is 41.2 months compared with 21.90 ± 0.75 and 32 months respectively in the control. Line 2, observed by the probit transformation, has a break in the region of 16 months. The mortality rate decreases to 3.7% month^{-1} compared with 4.7% month^{-1} for the control group.

Comparison of the experimental data with the above analysis of the form of survival curves (Fig.42) shows that the nature of the action of 2-ethyl-3-hydroxy-6-methylpyridine hydrochloride depends on the strain of the animals. The effect of the geroprotector in experiments with two month old SHK mice can be assigned to type 1, since it exerts the same influence on all members of the population. In the case of 2 month old mice of the C3HA strain an effect of type 2 is observed, whereupon the mortality rate of the long-lived section of the population diminishes.

The influence of 2-ethyl-3-hydroxy-6-methylpyridine hydrochloride on the ageing of the Drosophila fly has also been observed reliably. The effectiveness of the geroprotector depends on its concentration, the stage of development of the Drosophila, and the age of the flies at the beginning of the experiment[281].

Experiments on the application of the geroprotector in the larval stage only are of particular interest. It was found that an increase of the lifespan of the adult fly is then observed. It has been suggested that defects leading subsequently to ageing accumulate in the tissues of the larva from which the organs of the adult fly are produced (the nervous tissue and the imaginal buds). The rate of ageing of adult individuals can be retarded by decreasing with the aid of the geroprotector the rate of accumulation of these defects during the larval period. It may be that the DNA molecules retain a "memory" of the geroprotecting effect.

The data obtained show that the kinetic approaches to the study of ageing are promising and that wide possibilities arise in gerontology from the application of antioxidants as geroprotectors.

---o0o---

This review has dealt with only a few examples of successful application of the methods and ideas of chemical kinetics to various branches of chemistry and biology. There is no doubt that chemical kinetics will make an increasing contribution to the solution of theoretical and practical problems of modern chemistry, chemical engineering, biology, and medicine.

REFERENCES

1. N.N.Semenov, "Tsepnye Reaktsii" (Chain Reactions), Goskhimtekhizdat, Leningrad, 1934, 555 pp.
2. N.N.Semenov, "O Nekotorykh Problemakh Khimicheskoi Kinetiki i Reaktsionnoi Sposobnosti" (Some Problems of Chemical Kinetics and Reactivity), Izd.Akad.Nauk SSSR, Moscow, 1958, 686 pp.
3. N.M.Emanuel', E.T.Denisov, and Z.K.Maizus, "Tsepnye Reaktsii Okisleniya Uglevodorodov v Zhidkoi Faze" (Liquid-Phase Chain Oxidation Reactions of Hydrocarbons), Izd.Nauka, Mosocw, 1965, 375 pp.
4. N.M.Emanuel', Vestnik Akad.Nauk SSSR, 1964(5)m 65.
5. V.F.Shuvalov, Ya.S.Lebedev, V.E.Tsepalov, and V.Ya.Shlyapintokh, Zhur.Fiz.Khim., 1964, **38**, 1297 [Russ.J.Phys.Chem., 1964(5)].
6. Ya.S.Lebedev, V.F.Tsepalov, and V.Ya.Shlyapintokh, Dokl.Akad.Nauk SSSR, 1961, **139**, 1409.
7. J.R.Thomas, J.Amer.Chem.Soc., 1963, **85**, 591.
8. E.T.Denisov, Dokl.Akad.Nauk SSSR, 1960, **130**, 1055.
9. E.T.Denisov, Kinetika i Kataliz, 1963(4), 53.
10. E.T.Denisov, Dokl.Akad.Nauk SSSR, 1961, **141**, 131.
11. Z.K.Maizus, N.M.Emanuel', and V.N.Yakovleva, Dokl.Akad.Nauk SSSR, 1962, **143**, 366.

12. D.J.Carlson and J.C.Robb, Trans.Faraday Soc., 1966, **62**, 3403.
13. G.E.Zaikov, Z.K.Maizus, and N.M.Emanuel', Neftekhimiya, 1964, **14**, 91.
14. L.N.Denisova, E.T.Denisov, and D.I.Metelitsa, Izv. Akad.Nauk SSSR, Ser.Khim., 1969, 1657.
15. L.N.Denisova and E.T.Denisov, Kinetika i Kataliz, 1969, **10**, 1244.
16. D.G.Knorre, Z.K.Maizus, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1958, **123**, 123.
17. Z.K.Maizus, I.P.Skibida, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1960, **131**, 880.
18. L.G.Privalova, Z.K.Maizus, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1965, **161**, 1135.
19. N.M.Emanuel', Izv.Akad.Nauk SSSR, Ser.Khim., 1974, 1056.
20. F.R.Mayo, A.A.Miller, and G.A.Russel, J.Amer.Chem. Soc., 1958, **50**, 2500.
21. V.L.Rubailo, A.B.Gagarina, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1975, **224**, 642; **224**, 883,
22. V.L.Rubailo, Candidate's Thesis in Chemical Sciences, Institute of Chemical Physics of the USSR Academy of Sciences, 1978.
23. T.D.Nekipelova and A.B.Gagarina, Dokl.Akad.Nauk SSSR, 1976, **226**, 626; **231**, 392.
24. T.D.Nekipelova, A.B.Gagarina, and N.M.Emanuel', Izv.Akad.Nauk SSSR, Ser.Khim., 1979, 734.
25. T.D.Nekipelova, A.B.Gagarina, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1978, **238**, 392, 630.
26. T.D.Nekipelova, Ya.N.Malkin, and V.A.Kuz'min, Izv. Akad.Nauk SSSR, Ser.Khim., 1980, 80.
27. Z.K.Maizus, N.M.Emanuel', and V.N.Yakovleva, Dokl. Akad.Nauk SSSR, 1960, **131**, 351.
28. I.P.Skibida, Z.K.Maizus, and N.M.Emanuel', Neftekhimiya, 1964, **4**, 82.
29. D.G.Knorre, Z.K.Maizus, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1957, **112**, 457.
30. I.P.Skibida, Z.K.Maizus, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1963, **149**, 1111.
31. G.E.Zaikov and Z.K.Maizus, Izv.Akad.Nauk SSSR, Ser.Khim., 1962, 1175.
32. E.A.Blyumberg, G.E.Zaikov, Z.K.Maizus, and N.M.Emanuel', Kinetika i Kataliz, 1960, 1, 510.
33. G.E.Zaikov and Z.K.Maizus, Kinetika i Kataliz, 1962, **3**, 846.
34. G.E.Zaikov and Z.K.Maizus, Dokl.Akad.Nauk SSSR, 1965, **150**, 116.
35. N.M.Emanuel', G.E.Zaikov, and Z.K.Maizus, "Rol' Sredy v Radikal'no-Tsepnykh Reaktsiyakh Okisleniya Organicheskikh Soedinenii" (The Role of the Medium in Radical Chain Oxidation Reactions of Organic Compounds), Izd.Nauka, Moscow, 1973.
36. I.A.Howard, in "Advances in Free Radical Chemistry", Acad.Press, London–Colchester, 1972, Vol.4, p.49.
37. P.S.Nangia and S.W.Benson, Int.J.Chem.Kinet., 1980, **12**, 29, 43.
38. G.A.Russel, Chem.Ind.(London), 1956, **49**, 1483.
39. G.A.Russell, J.Amer.Chem.Soc., 1957, **79**, 3871.
40. T.Mill, F.Mayo, H.Richardson, K.Irwin, and D.L.Allara, J.Amer.Chem.Soc., 1972, **94**, 6802.
41. V.A.Belyakov, R.F.Vasil'ev, and F.G.Fedorova, Dokl. Akad.Nauk SSSR, 1978, **239**, 344,
42. V.Ya.Shlyapintokh, O.N.Karpukhin, L.M.Postnikov, I.V.Zakharov, A.A.Vichutinskii, and V.F.Tsepalov, "Khemilyuminestsentnye Metody Issledovaniya Medlennykh Khimicheskikh Protsessov" (Chemiluminescence Methods for the Investigation of Slow Chemical Processes), Izd.Nauka, Moscow, 1966, p.299.
43. V.A.Belyakov and V.S.Rafikova, Izv.Akad.Nauk SSSR, Ser.Khim., 1974, 2445.
44. V.S.Rafikova, Z.K.Maizus, I.P.Skibida, and R.N.Volkov, Int.J.Chem.Kinet., 1981, **13**, 111.
45. N.M.Evteeva, A.B.Gagarina, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1975, **224**, 365.
46. N.M.Evteeva and A.B.Gagarina, Dokl.Akad.Nauk SSSR, 1979, **249**, 637.
47. N.M.Evteeva and A.B.Gagarina, Izv.Akad.Nauk SSSR, Ser.Khim., 1980, 2715.
48. A.B.Gagarina, O.T.Kasaikina, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1970, **195**, 387.
49. V.L.Rubailo, A.B.Gagarina, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1973, **213**, 151; 1975, **225**, 875, 617, 1111.
50. A.B.Gagarina, E.Danóczy, N.M.Emanuel, and D.Gal, Magyar kém Fol., 1971, **85**, 529.
51. T.D.Nekipelova, A.B.Gagarina, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1971, **197**, 865.
52. G.E.Zaikov, Z.K.Maizus, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1962, **140**, 405.
53. G.A.Russell, J.Amer.Chem.Soc., 1955, **77**, 4583.
54. I.A.Ingles and H.W.Melville, Proc.Roy.Soc.A, 1953, **218**, 163.
55. V.F.Tsepalov, V.Ya.Shlyapintokh, and P'ei-Huang Chu, Zhur.Fiz.Khim., 1964, **38**, 52 [Russ.J.Phys. Chem., 1964(1)].
56. J.Rouchaud, Bull.Soc.Chim.belges, 1966, **75**, 744.
57. B.S.Middleton and K.U.Ingold, Canad.J.Chem., 1967, **45**, 191.
58. V.S.Rafikova, E.F.Brin, and I.P.Skibida, Kinetika i Kataliz, 1971, **12**, 1374.
59. V.S.Rafikova, I.P.Skibida, and Z.K.Maizus, Izv. Akad.Nauk SSSR, Ser.Khim., 1972, 2368.
60. V.S.Rafikova, I.P.Skibida, Z.K.Maizus, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1968, **182**, 357.
61. V.S.Rafikova, I.P.Skibida, and Z.K.Maizus, Izv.Akad. Nauk SSSR, Ser.Khim., 1969, 1360.
62. V.S.Rafikova, Z.K.Maizus, and I.P.Skibida, Dokl. Akad.Nauk SSSR, 1971, **191**, 1137.
63. I.A.Opeida and I.P.Skibida, Teor.Eksper.Khim., 1975, **11**, 2368.
64. N.M.Emanuel', E.A.Blyumberg, P.I.Valov, D.V.Ivanyukov, and Yu.D.Norikov, USSR P.172 296, 26.3.1962; Byul.Izobret., 1965, No.13.
65. E.A.Blyumberg, P.I.Valov, Yu.D.Norikov, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1966, **167**, 579.
66. P.I.Valov, E.A.Blyumberg, and N.M.Emanuel', Izv. Akad.Nauk SSSR, Ser.Khim., 1966, 1334.
67. N.A.Prilezhaev, Zhur.Russ.Fiz.Khim.Obshch., 1910, **42**, 1397.
68. P.I.Valov, E.A.Blyumberg, and N.M.Emanuel', Izv. Akad.Nauk SSSR, Ser.Khim., 1969, 791.
69. L.A.Tavadyan, S.A.Maslov, and E.A.Blyumberg, Dokl.Akad.Nauk SSSR, 1977, **237**, 637.
70. L.A.Tavadyan, S.A.Maslov, E.A.Blyumberg, and N.M.Emanuel', Zhur.Fiz.Khim., 1977, **51**, 1301 [Russ. J.Phys.Chem., 1977(6)],
71. S.A.Maslov, E.A.Blyumberg, and N.M.Emanuel', Izv. Akad.Nauk SSSR, Ser.Khim., 1974, 2188.
72. E.A.Blyumberg, E.G.Rozantsev, and S.A.Maslov, USSR P.429 055, 7.04.72; Byul.Izobret., 1974, No.19.
73. L.A.Tavadyan, S.A.Maslov, and E.A.Blyumberg, Neftekhimiya, 1978, **18**, 668.
74. E.T.Denisov, Z.K.Maizus, I.P.Skibida, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1959, **128**, 755.
75. Z.K.Maizus, I.P.Skibida, and N.M.Emanuel', Kinetika i Kataliz, 1961, **2**, 538.

76. I.P.Skibida, Z.K.Maizus, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1962, **144**, 170.
77. I.P.Skibida, Z.I.Kulitskii, and Z.K.Maizus, Dokl.Akad. Nauk SSSR, 1963, **148**, 1358.
78. D.I.Metelitsa, Uspekhi Khim., 1971, **40**, 1175 [Russ. Chem.Rev., 1971(7)].
79. I.P.Skibida, Uspekhi Khim., 1975, **44**, 1729 [Russ. Chem.Rev., 1975(10)].
80. N.M.Emanuel', Uspekhi Khim., 1978, **47**, 1329 [Russ. Chem.Rev., 1978(8)].
81. E.A.Blyumberg and Yu.D.Norikov, Symposium, "Problemy Kinetiki i Kataliza" (Problems of Kinetics and Catalysis), Izd.Nauka, Moscow, 1975, No.16, p.150.
82. G.M.Bulgakova, A.N.Shchupik, I.P.Skibida, K.I.Zamaraev, and Z.K.Maizus, Dokl.Akad.Nauk SSSR, 1971, 199, 376.
83. G.M.Bulgakova, I.P.Skibida, and Z.K.Maizus, Kinetika i Kataliz, 1966, 7, 332.
84. L.I.Matienko and Z.K.Maizus, Izv.Akad.Nauk SSSR, Ser.Khim., 1972, 1524.
85. I.P.Skibida, Z.K.Maizus, and N.M.Emanuel', Symposium, "Uspekhi Khimii Perekisnykh Soedinenii i Avtookisleniya" (Advances in the Chemistry of Peroxy-Compounds and Autoxidation), Izd.Khimiya, Moscow, 1969, p.156.
86. A.Ya.Valendo, Yu.D.Norikov, and E.A.Blyumberg, Izv.Akad.Nauk SSSR, Ser.Khim., 1971, 1320.
87. A.Ya.Valendo and Yu.D.Norikov, Izv.Akad.Nauk SSSR, Ser.Khim., 1972, 1002.
88. E.T.Denisov, Handbook, "Konstanty Skorosti Gomoliticheskikh Reaktsii v Zhidkoi Faze" (The Rate Constants for Homolytic Reactions in the Liquid Phase), Izd.Nauka, Moscow, 1975.
89. V.A.Burov, Yu.D.Norikov, L.V.Salukvadze, and B.N.Egorov, Dokl.Akad.Nauk SSSR, 1977, **237**, 1384.
90. L.V.Salukvadze, Yu.D.Norikov, and N.T.Silakhtaryan, Symposium, "Katalizatory Soderzhashchie Nanesennye Kompleksy" (Catalysts Containing Deposited Complexes), Izd.Sibir.Otd.Akad.Nauk SSSR, Novosibirsk, 1980, Part 1, p.85.
91. L.I.Matienko and Z.K.Maizus, Kinetika i Kataliz, 1974, **15**, 317.
92. O.N.Emanuel', A.M.Sakharov, and I.P.Skibida, Izv. Akad.Nauk SSSR, Ser.Khim., 1975, 2692.
93. E.A.Blyumberg, Z.K.Maizus, Yu.D.Norikov, I.P.Skibida, and N.M.Emanuel', Neftekhimiya, Kinetika i Kataliz, 1978, **18**, 590.
94. Yu.D.Norikov and L.V.Salukvadze, Dokl.Akad.Nauk SSSR, 1972, **203**, 632.
95. Sh.K.Bochorishvili, Yu.D.Norikov, E.A.Blyumberg, and V.I.Kokochashvili, Soobshch.Akad.Nauk Gruz.SSR, 1973, **70**, 353.
96. M.Ya.Gervits, M.S.Brodskii, L.D.Trusova, Yu.D.Norikov, E.A.Blyumberg, and V.I.Trofimov, Neftekhimiya, 1977, **17**, 428.
97. L.A.Mosolova, L.I.Matienko, and Z.K.Maizus, Izv. Akad.Nauk SSSR, Ser.Khim., 1980, 278.
98. L.D.Tyutchenkova, V.G.Vinogradova, and Z.K.Maizus, Izv.Akad.Nauk SSSR, Ser.Khim., 1978, 773.
99. I.P.Skibida, M.S.Brodskii, M.Ya.Gervits, L.A.Goldina, and Z.K.Maizus, Kinetika i Kataliz, 1973, **14**, 885.
100. B.G.Balkov, I.P.Skibida, and Z.K.Maizus, Izv.Akad. Nauk SSSR, Ser.Khim., 1970, 1780.
101. L.I.Matienko, L.A.Goldina, I.P.Skibida, and Z.K.Maizus, Izv.Akad.Nauk SSSR, Ser.Khim., 1975, 287.
102. L.I.Matienko, I.P.Skibida, and Z.K.Maizus, Izv.Akad. Nauk SSSR, Ser.Khim., 1975, 1322.
103. W.Brackmann and C.L.Gaasbeek, Rec.Trav.chim., 1966, **85**, 242.
104. O.N.Emanuel', A.M.Sakharov, and I.P.Skibida, Izv. Akad.Nauk SSSR, Ser.Khim., 1975, 2692.
105. A.M.Sakharov and I.P.Skibida, Oxidation Comm., 1979, 1(1), 113.
106. A.M.Sakharov and I.P.Skibida, Dokl.Akad.Nauk SSSR, 1980, **251**, 155.
107. D.G.Knorre, L.G.Chuchukina, and N.M.Emanuel', Zhur.Fiz.Khim., 1959, **33**, 877 [see Russ.J.Phys. Chem., Abs., Vol.33, Nos.1–6].
108. V.G.Vinogradova, Z.K.Maizus, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1969, **188**, 616.
109. N.M.Emanuel, Z.K.Maizus, and V.G.Vinogradova, React.Kinet.Catal.Letters, 1977, **6**, 119.
110. A.N.Zverev, V.G.Vinogradova, and Z.K.Maizus, Izv. Akad.Nauk SSSR, Ser.Khim., 1979, 1995.
111. I.V.Shkhiyants, N.A.Dzyubina, V.V.Sher, and P.I.Sanin, Neftekhimiya, 1973, **13**, 571.
112. J.A.Howard, Y.Ohkatsu, J.H.B.Chenier, and K.U.Ingold, Canad.J.Chem., 1973, **51**, 1543.
113. J.A.Howard and J.H.B.Chenier, Canad.J.Chem., 1978, **54**, 382.
114. J.H.B.Chenier, J.A.Howard, and J.C.Tait, Canad. J.Chem., 1978, **56**, 157.
115. S.Ivanov and I.Kateva, Dokl.Bolg.Akad.Nauk, 1968, **21**, 681.
116. S.K.Ivanov and S.Karshalykov, Erdöl und Kohle, 1971, 516.
117. D.Shopov and Sl.K.Ivanov, Izv.Otd.Khim.Nauk Bolg. Akad.Nauk 1969, II, Book 3, 637,
118. S.Ivanov and V.Yurittsin, Dokl.Bolg.Akad.Nauk 1972, **25**, 975.
119. A..Mazaletskii, V.G.Vinogradova, and Z.K.Maizus, Dokl.Akad.Nauk SSSR, 1980, **253**, 153.
120. V.G.Vinogradova, N.K.Kul'kova, Z.K.Maizus, and N.M.Emanuel', Izv.Akad.Nauk SSSR, Ser.Khim., 1972, 2118.
121. N.M.Emanuel, Z.K.Maizus, and V.G.Vinogradova, React.Kinet.Catal.Letters (in the press).
122. V.I.Kurashev, D.G.Pobedimskii, and L.G.Krivoshseeva, Zhur.Fiz.Khim., 1979, **53**, 501 [Russ.J.Phys.Chem., 1979(2)].
123. E.T.Denisov and N.M.Emanuel', Zhur.Fiz.Khim., 1956, **30**, 2499.
124. E.T.Denisov and N.M.Emanuel', Uspekhi Khim., 1958, **27**, 365.
125. A.L.Aleksandrov and E.T.Denisov, Izv.Akad.Nauk SSSR, Ser.Khim., 1969, 1652.
126. E.T.Denisov and N.G.Zubareva, Izv.Akad.Nauk SSSR, Ser.Khim., 1970, 575.
127. N.G.Zubareva, E.T.Denisov, and A.V.Ablov, Neftekhimiya, 1970, **11**, 108.
128. G.A.Kovtun, D.L.Lysenko, A.S.Berenblyum, and I.I.Moiseev, Izv.Akad.Nauk SSSR, Ser.Khim., 1981, 101.
129. N.M.Emanuel', E.T.Denisov, and Z.K.Maizus, "Tsepnye Reaktsii Okisleniya Uglevodorodov v Zhidkoi Faze" (Liquid-Phase Chain Oxidation Reactions of Hydrocarbons), Izd.Nauka, Moscow, 1965.
130. A.B.Gagarina, L.M.Pisarenko, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1973, **212**, 653.
131. A.B.Gagarina, L.M.Pisarenko, V.V.Moiseev, and N.M.Emanuel', Izv.Akad.Nauk SSSR, Ser.Khim., 1975, 1041.
132. A.B.Gagarina, L.M.Pisarenko, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1975, **221**, 640.

133. I.V.Khudyakov, L.M.Pisarenko, A.B.Gagarina, V.A.Kuz'min, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1975, **222**, 1390.
134. L.I.Belova and G.V.Karpukhina, Izv.Akad.Nauk SSSR, Ser.Khim., 1977, 1740.
135. M.S.Khloplyankina, A.L.Buchachenko, M.B.Neiman, and A.G.Vasil'eva, Kinetika i Kataliz, 1965, **6**, 394.
136. G.A.Kovtun, A.L.Aleksandrov, and V.A.Golubev, Izv.Akad.Nauk SSSR, Ser.Khim., 1974, 2197.
137. L.A.Tavadyan, S.A.Maslov, E.A.Blyumberg, and N.M.Emanuel', Zhur.Fiz.Khim., 1977, **51**, 1301 [Russ. J.Phys.Chem., 1977(6)].
138. Yu.B.Shilov, R.M.Batalova, and E.T.Denisov, Dokl. Akad.Nauk SSSR, 1972, **207**, 388.
139. O.T.Kasaikina, T.B.Lobanova, A.B.Gagarina, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1981 (in the press).
140. A.P.Griva and E.T.Denisov, Int.J.Chem.Kinetics, 1973, No.5, 868.
141. L.K.Mahoney and M.A.Da Rooge, J.Amer.Chem.Soc., 1975, **97**, 4722.
142. V.I.Rubtsov, V.A.Roginskii, V.B.Miller, and G.E.Zaikov, Kinetika i Kataliz, 1980, **21**, 612.
143. V.A.Roginskii, V.Z.Dubinskii, I.A.Schlyapnikova, and V.B.Miller, Europ.Polymer J., 1977, **13**, 1043.
144. V.A.Dubinskii, V.A.Roginskii, and V.B.Miller, Dokl. Akad.Nauk SSSR, 1975, **220**, 1390.
145. I.V.Khudyakov, P.P.Levin, and V.A.Kuz'min Uspekhi Khim., 1980, **49**, 1990 [Russ.Chem.Rev., 1980(10)].
146. I.V.Khudyakov, P.P.Levin, V.A.Kuzmin, and C.R.H.J.de Jonge, Int.J.Chem.Kinetics, 1979, **11**, 357.
147. V.A.Kuzmin, I.V.Khudyakov, P.P.Levin, N.M.Emanuel, C.R.H.J.de Jonge, H.J.Hageman, M.E.F.Biemord, and F.P.B.van der Maeden, J.Chem.Soc., Perkin Trans.II, 1979, 1540.
148. P.P.Levin, I.V.Khudyakov, and V.A.Kuz'min, Izv. Akad.Nauk SSSR, Ser.Khim., 1980, 255.
149. V.Z.Dubinskii, V.A.Belyakov, V.A.Roginskii, and V.B.Miller, 1975, 57.
150. G.V.Karpukhina, Z.K.Maizus, M.Ya.Meskina, and N.M.Emanuel', Zhur.Fiz.Khim., 1970, **44**, 1377 [Russ. J.Phys.Chem., 1970(6)].
151. V.S.Martem'yanov, E.T.Denisov, and L.A.Samoilova, Izv.Akad.Nauk SSSR, Ser.Khim., 1972, 1049.
152. L.N.Denisova, E.T.Denisov, and D.I.Metelitsa, Zhur. Fiz.Khim., 1970, **44**, 1670 [Russ.J.Phys.Chem., 1970(7)].
153. A.D.Pershin, D.G.Pobedimskii, V.A.Kubatov, and A.L.Buchachenko, Izv.Akad.Nauk SSSR, Ser.Khim., 1975, 581.
154. D.G.Pobedimskii and A.L.Buchachenko, Izv.Akad. Nauk SSSR, Ser.Khim., 1968, 1181.
155. G.V.Karpukhina, Z.K.Maizus, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1968, **182**, 870.
156. M.Ya.Meskina, G.V.Karpukhina, Z.K.Maizus, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1973, **213**, 1124.
157. E.A.Arakelyan, N.A.Azatyan, G.V.Karpukhina, and Z.K.Maizus, Neftekhimiya, 1980, **20**, 1058.
158. G.V.Karpukhina, Z.K.Maizus, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1963, **152**, 110.
159. G.V.Karpukhina, Z.K.Maizus, T.V.Zolotova, L.I.Mazaletskaya, and N.Ya.Meskina, Neftekhimiya, 1978, **18**, 708.
160. M.Ya.Meskina, G.V.Karpukhina, and Z.K.Maizus, Izv.Akad.Nauk SSSR, Ser.Khim., 1976, 2183.
161. M.Ya.Meskina, G.V.Karpukhina, and Z.K.Maizus, Izv.Akad.Nauk SSSR, Ser.Khim., 1977, 313.
162. T.V.Zolotova, G.V.Karpukhina, Z.K.Maizus, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1975, **223**, 120.
163. A.N.Zverev, V.G.Vinogradova, and Z.K.Maizus, Izv. Akad.Nauk SSSR, Ser.Khim., 1980, 2479.
164. V.N.Vetchinkina, Z.K.Maizus, I.P.Skibida, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1967, **177**, 625.
165. E.F.Brin, V.N.Vetchinkina, Z.K.Maizus, and I.P.Skibida, Izv.Akad.Nauk SSSR, Ser.Khim., 1979, 947.
166. V.N.Vetchinkina, I.P.Skibida, and Z.K.Maizus, Izv. Akad.Nauk SSSR, Ser.Khim., 1977, 1008.
167. L.I.Belova, G.V.Karpukhina, Z.K.Maizus, E.G.Rozantsev, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1976, **231**, 369.
168. O.N.Karpukhin, Mater Plast.Elast., 1975, **3**, 116.
169. V.B.Ivanov, S.F.Burlatsky, N.A.Rosenboym, and V.Ya.Shlyapintokh, Europ.Polymer J., 1980, **16**, 65.
170. N.M.Emanuel' and A.B.Gagarina, Uspekhi Khim., 1966, **35**, 619 [Russ.Chem.Rev., 1966(4)].
171. L.A.Smurova, T.V.Sirota, A.B.Gagarina, V.P.Litvinov, Z.G.Ostapenko, Ya.L.Gol'dfarb, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1971, **198**, 1378.
172. N.M.Emanuel, Z.K.Maizus, and I.P.Skibida, Angew. Chem., Int.Ed., 1967, **8**, 93.
173. Z.G.Kozlova, V.F.Tsepalov, and V.Ya.Shlyapintokh, Trudy Khim.i Khim.Tekhnol.(Gor'kii), 1961, **1**, 95.
174. E.A.Blyumberg, A.T.Malievskii, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1961, **136**, 1130.
175. E.M.Gol'dberg, L.K.Obukhova, and N.M.Emanuel', Neftekhimiya, 1962, **2**, 229.
176. A.B.Gagarina, Z.K.Maizus, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1961, **140**, 153,
177. V.M.Andreev, Zhur.Fiz.Khim., 1962, **36**, 42 [Russ.J. Phys.Chem., 1962(1)].
178. N.M.Emanuel', Uspekhi Khim., 1979, **43**, 2114 [Russ. Chem.Rev., 1979(12)].
179. N.M.Emanuel', Vysokomol.Soed., 1979, **A21**, 2624.
180. M.E.Neiman (Editor), "Starenie i Stabilizatsiya Polimerov" (The Ageing and Stabilisation of Polymers), Izd.Nauka, Moscow, 1964, p.362.
181. G.Ya.Gordon, "Stabilisatsiya Sinteticheskikh Polimerov" (Stabilisation of Synthetic Polymers), Izd.Nauka, Moscow, 1963, p.420.
182. J.Voigt, "Stabilisation of Plastics Light and Heat" (Translated into Russian), Izd.Khimiya, Moscow, p.640.
183. G.P.Gladyshev, Yu.A.Ershov, and O.A.Shustova, "Stabilizatsiya Termostoikikh Polimerov" (Stabilisation of Thermostable Polymers), Izd.Khimiya, Moscow, 1979, p.272.
184. B.M.Kovarskaya, A.B.Blyumenfel'd, and I.G.Levantovskaya, "Termicheskaya Stabilizatsiya Geterotsepnykh Polimerov" (Thermal Stabilisation of Heterochain Polymers), Izd.Khimiya, Moscow, 1977, p.264.
185. H.H.G.Jellinek (Editor), "Aspects of Degradation and Stabilisation of Polymers", Elsevier, New York, 1978, p.350.
186. B.Ranby and J.F.Rabek, "Photodegradation, Photooxidation and Photo-stabilisation of Polymers: Principles and Applications" (Translated into Russian), Izd.Mir, Moscow, 1978, p.674.
187. V.Ya.Shlyapintokh, "Fotokhimicheskie Prevrashcheniya i Stabilizatsiya Polimerov" (Photochemical Reactions and Stabilisation of Polymers), Izd.Khimiya, Moscow, 1979, p.344.

188. A.N.Machyulis and E.E.Tornau, "Diffuzionnaya Stabilizatsiya Polimerov" (Diffusional Stabilisation of Polymers), Izd.Mantis, Vilna, 1974, p.255.
189. Yu.V.Moiseev and G.E.Zaikov, "Khimicheskaya Stoikost' Polimerov v Agressivnykh Sredakh" (Chemical Stability of Polymers in Corrosive Media), Izd.Khimiya, Moscow, 1979, p.285.
190. V.R.Regel', A.I.Slutsker, and E.E.Tomashevskii, "Kineticheskaya Priroda Prochnosti Tverdykh Tel" (The Kinetic Nature of the Strength of Solids), Izd. Nauka, Moscow, 1974, p.650.
191. N.M.Emanuel' and A.A.Buchachenko, "Khimicheskaya Fizika Stareniya i Stabilizatsii Polimerov" (The Chemical Physics of the Ageing and Stabilisation of Polymers), Izd.Nauka, Moscow (in the press).
192. N.M.Emanuel', "Zadachi Fundamental'nykh Issledovanii v Oblasti Stareniya i Stabilizatsii Polimerov" (The Tasks of Fundamental Research into the Ageing and Stabilisation of Polymers), Lecture in the IVth Polymer School, Tallin, 1970.
193. V.K.Milinchuk, E.R.Klinshpot, and S.Ya.Pshezhetskii, "Makroradikaly" (Macroradicals), Izd.Khimiya, Moscow, 1980.
194. E.L.Shanina, V.A.Roginskii, and V.B.Miller, Vysokomol.Soed., 1979, **B21**, 892.
195. V.S.Pudov and M.B.Neiman, Symposium, "Starenie i Stabilizatsiya Polimerov" (The Ageing and Stabilisation of Polymers), Izd.Khimiya, Moscow, 1966, pp.5–26.
196. O.N.Karpukhin and E.M.Slobodetskaya, Vysokomol. Soed., 1976, **A18**, 2700.
197. V.R.Regel', O.F.Pozdnyakov, and A.V.Amelin, Mekhanika Polimerov, 1975, **1**, 90.
198. Ya.S.Lebedev, Yu.D.Tsvetkov, and V.V.Voevodskii, Kinetika i Kataliz, 1960, **1**, 496.
199. V.A.Radtsig, Vysokomol.Soed., 1976, **A18**, 1899.
200. O.N.Karpukhin, Uspekhi Khim., 1978, **47**, 1119 [Russ. Chem.Rev., 1978(6)].
201. F.Szocz and J.Placek, J.Polymer Sci., Polymer Phys. Ed., 1975, **13**, 1789.
202. L.A.Davis, J.Polymer Sci., Polymer Phys.Ed., 1974, **12**, 75.
203. G.P.Vaskerchan and Ya.S.Lebedev, Izv.Akad.Nauk SSSR, Ser.Khim., 1976, 1378.
204. E.L.Shanina, V.A.Roginskii, and V.B.Miller, Vysokomol.Soed., 1977, **B19**, 447.
205. A.P.Griva and E.T.Denisov, J.Polymer Sci., Polymer Chem.Ed., 1976, **14**, 1051.
206. V.A.Roginskii and V.B.Miller, Dokl.Akad.Nauk SSSR, 1973, **213**, 642.
207. A.P.Griva, A.N.Denisova, and E.T.Denisov, Dokl. Akad.Nauk SSSR, 1977, **232**, 1343.
208. L.N.Guseva, Ya.A.Mikheev, L.S.Rogova, and D.Ya.Toptygin, Dokl.Akad.Nauk SSSR, 1976, **226**, 863.
209. Yu.A.Mikheev, L.N.Guseva, L.S.Rogova, and D.Ya.Toptygin, Vysokomol.Soed., 1981, **A23**, 386.
210. E.M.Slobodetskaya, Uspekhi Khim., 1980, **49**, 1594 [Russ.Chem.Rev., 1980(8)].
211. M.B.Neiman, V.B.Miller, Yu.A.Shlyapnikov, and E.S.Torsueva, Dokl.Akad.Nauk SSSR, 1961, **136**, 647.
212. Yu.A.Shlyapnikov, Pure and Appl.Chem., 1980, **52**, 337.
213. Yu.A.Shlyapnikov, Uspekhi Khim., 1981, **50**, 1112 [Russ.Chem.Rev., 1981(6)].
214. V.Ya.Shlyapintokh, V.B.Ivanov, O.M.Khovstach, A.B.Shapiro, and E.G.Rozantsev, Dokl.Akad.Nauk SSSR, 1975, **225**, 1132.
215. E.V.Bystritskaya, T.S.Karpovich, and O.N.Karpukhin, Dokl.Akad.Nauk SSSR, 1977, **235**, 607.
216. N.Ya.Rapoport, N.M.Livanova, and V.B.Miller, Vysokomol.Soed., 1976, **A18**, 2045.
217. V.Ya.Shlyapintokh and V.B.Ivanov, in "Developments in Polymer Stabilisation" (Edited by G.Scott), Appl. Sci.Publ., London, Vol.5, Chapter 3 (in the press).
218. M.S.Khloplyankina, O.N.Karpukhin, A.L.Buchachenko, and P.I.Levin, Neftekhimiya, 1963, **5**, 1152.
219. V.B.Ivanov, S.F.Burlatsky, N.A.Rosenboym, and V.Ya.Schlyapintokh, Europ.Polymer J., 1980, **16**, 65.
220. V.B.Ivanov and E.L.Lozovskaya, Trudy MFTI, 1980, Ser.Obshch.i Mol.Fiz., 77.
221. E.Ya.Davydov, G..Pariiskii, and D.Ya.Toptygin, Vysokomol.Soed., 1977, **A19**, 977.
222. V.A.Mal'chevskii and V.A.Zakrevskii, Mekhanika Polimerov, 1978, 342.
223. N.M.Emanuel', in "Khimicheskaya Kinetika i Tsepnye Reaktsii" (Chemical Kinetics and Chain Reactions), Izd. Nauka, Moscow, 1966, p.531.
224. N.M.Emanuel', in "Pervichnye Mekhanizmy Biologicheskogo Deistviya Ioniziruyushchikh Isluchenii" (The Primary Mechanisms of the Biological Action of Ionising Radiation), Izd.Akad.Nauk SSSR, Moscow, 1963, p.73.
225. N.M.Emanuel, "Free Radicals in Chemical Chain Reactions and Biological Processes", XXIII Int.Congr. on Pure and Applied Chemistry, Boston (USA), 1971, p.325.
226. N.M.Emanuel', "Kinetika Eksperimental'nykh Opukholevykh Protsessov" (Kinetics of Experimental Tumour Processes), Izd.Nauka, Moscow, 1977.
227. N.M.Emanuel', N.P.Konovalova, and L.M.Dronova, Dokl.Akad.Nauk SSSR, 1962, **143**, 737.
228. N.M.Emanuel' and L.P.Lipchina, Dokl.Akad.Nauk SSSR, 1958, **121**, 141.
229. N.M.Emanuel', L.M.Dronova, N.P.Konovalova, Z.K.Maizus, and I.P.Skibida, Dokl.Akad.Nauk SSSR, 1963, **152**, 481.
230. N.M.Emanuel', E.M.Vermel', I.A.Rapoport, S.A.Kruglyak, L.M.Dronova, and L.A.Ostrovskaya, Dokl.Akad.Nauk SSSR, 1965, 163.
231. N.M.Emanuel', D.B.Korman, L.A.Ostrovskaya, L.B.Gorbacheva, and N.P.Dement'eva, "Nitrozoaokilmocheviny—Novyi Klass Protivoopukholevykh Preparatov" (Nitrosoalkylureas—A New Class of Anti-Tumour Preparations), Izd.Nauka, Moscow, 1978, 285 pp.
232. N.M.Emanuel', N.P.Konovalova, L.M.Volkova, and V.V.Rusanov, Vop.Onkol., 1979, **25**, 96.
233. N P.Konovalova, R.F.D'yachkovskaya, and E.T.Kiseleva, Vop.Onkol., 1973, **19**, 58.
234. V.A.Barsel', L.M.Dul'kin, and A.T.Demidov, Vop. Onkol., 1977, **23**, 50.
235. E.M.Vermel', N.P.Korman, B.V.Milonov, L.S.Evseenko, and R.S.Orlova, Vop.Onkol., 1970, **16**, 31.
236. V.A.Gor'kov, "Itogi Nauki i Tekhniki. Onkologiya" (Advances in Science and Engineering. Oncology), Izd.VINITI, Moscow, 1973, Vol.6, p.114.
237. D.S.Zaharko and R.L.Dedrick, "Pharmacology and Future Man", Basel, 1973, Vol.3.
238. N.M.Emanuel' and L.S.Evseenko, "Kolichestvennye Osnovy Klinicheskoi Onkologii" (Quantitative Foundations of Clinicial Oncology), Izd.Meditsina, Moscow, 1970.
239. N.M.Emanuel', L.N.Bulaevskii, and D.B.Korman, Izv.Akad.Nauk SSSR, Ser.Biol., 1970, 660.
240. N.M.Emanuel, Pure and Appl.Chem., 1979, **52**, 11.
241. V.A.Chernov, "Tsitostaticheskie Soedineniya v Khimioterapii Zlokachestvennyky Novoobrazovanii" (Cytostatic Compounds in the Chemotherapy of Malignant Neoplasms), Izd.Meditsina, Moscow, 1964, p.318.

242. L.F.Larionov, "Khimioterapiya Zlokachestvennykh Opukholei" (Chemotherapy of Malignant Tumours), Fizmatgiz, Moscow, 1962.
243. N.P.Konovalova, G.N.Bogdanov, V.B.Miller, M.B.Neiman, E.G.Rozantsev, and N.M.Emanuel', Dokl. Akad.Nauk SSSR, 1964, **157**, 707.
244. A.A.Berlin, G.N.Bogdanov, N.P.Konovalova, and B.I.Liogon'kii, Izv.Akad.Nauk SSSR, Ser.Biol., 1971, 294.
245. S.M.Free and J.W.Wilson, J.Medicin.Chem., 1964, **7**, 395.
246. C.Hansch and E.W.Deutsch, Biochim.et Biophys.Acta, 1966, **126**, 117.
247. V.G.Kartsev, V.V.Rusanov, and F.A.Medvedev, "Tezisy Mezhdunarodnoi Konferentsii po Kvantovoi Khimii, Biologii i Farmakologii" (Abstracts of Reports at the International Conference on Quantum Chemistry, Biology, and Pharmacology), Kiev, 1978, Vol.4, p.55.
248. A.A.Konstantinov and E.K.Ruuge, Bioorg.Khim., 1977, **3**, 787.
249. G.Palmer, F.Müller, and V.Massey, in "Flavins and Flavoproteins" (Edited by H.Kamin), Baltimore, University Park Press, 1971, pp.123–140.
250. E.K.Ruuge and A.A.Konstantinov, Biofizika, 1976, **21**, 586.
251. T.S.Shulyakovskaya, S.A.Vlasova, A.N.Saprin, K.E.Kruglyakova, and N.M.Emanuel', "Materialy Simpoziuma: Sostoyanie Svobodnykh Radikalov i Ikh Rol' pri Vozdeistvii Radiatsii i Zlokachestvennom Roste" (Symposium Proceedings: The State of Free Radicals and Their Role in the Action of Radiation and in Malignant Growth), Moscow, 1971, p.95.
252. A.J.Vithayathil, J.L.Ternberg, and B.L.Commoner, Nature, 1965, **207**, 1246.
253. A.N.Saprin and T.S.Shulyakovskaya, Dokl.Akad.Nauk SSSR, 1968, **189**, 889.
254. A.N.Saprin, V.A.Shabalkin, L.E.Kozlova, K.E.Kruglyakova, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1968, **181**, 1520.
255. N.M.Emanuel, A.N.Saprin, V.A.Shabalkin, L.E.Kozlova, and K.E.Kruglyakova, Nature, 1969, **222**, 165.
256. Yu.P.Kozlov, "Svobodnye Radikaly i Ikh Rol' v Normal'nikh i Patologicheskikh Protsessakh" (Free Radicals and Their Role in Normal and Pathological Processes), Izd.Nauka, Moscow, 1973.
257. N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1974, **217**, 245.
258. D.S.Khristianovich, L.M.Dronova, V.N.Varfolomeev, G.N.Bogdanov, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1977, **236**, 1011.
259. G.N.Bogdanov and N.M.Emanuel', Tezisy Simposiuma; Magnitnyi Rezonans v Biologii i Meditsine" (Symposium Proceedings: Magnetic Resonance in Biology and Medicine), Moscow, 1981, p.192.
260. N.M.Emanuel', A.N.Saprin, T.S.Shulyakovskaya, L.E.Kozlova, and T.V.Bunto, Dokl.Akad.Nauk SSSR, 1973, **209**, 1449.
261. A.Ya.Kogan, A.S.Sizikh, and A.N.Saprin, "Referaty IV Mezhdunarodnogo Biofizicheskogo Kongressa" (Abstracts of Reports at the IVth International Biophysical Congress), Moscow, 1972, Vol.4, p.207.
262. A.Ya.Kogan, A.N.Saprin, and A.S.Sizikh, "Materialy Simpoziuma: Sostoyanie Svobodnykh Radikalov i Ikh Rol' pri Vozdeistvii Radiatsii i Zlokachestvennom Roste" (Symposium Proceedings: The State of Free Radicals and Their Role in the Action of Radiation and in Malignant Growth), Moscow, 1971, p.90.
263. O.S.Frankfurt, L.P.Lipchina, T.V.Bunto, and N.M.Emanuel', Byul.Eksper.Biol.Med., 1967, **64**, 86.
264. L.W.Wattenberg, J.Nat.Cancer Inst., 1972, **48**, 4125.
265. L.W.Wattenberg, J.Nat.Cancer Inst., 1973, **50**, 1541.
266. E.B.Burlakova, N.M.Dzyuba, N.P.Pal'mina, and N.M.Emanuel', Dokl.Akad.Nauk SSSR, 1965, **163**, 1278.
267. N.P.Pal'mina and E.B.Burlakova, Symposium, "Aktual'nye Problemy Sovremennoi Onkologii" (Urgent Problems in Modern Oncology), Izd.Moskov.Gos.Univ., Moscow, 1973, Vol.3, p.86.
268. E.B.Burlakova, E.M.Alesenko, E.M.Molochkina, N.P.Pal'mina, and N.G.Khrapova, "Bioantioksidanty pri Luchevom Proazhenii i Opukholevom Roste" (Bioantioxidants in Radiation Damage and Tumour Growth), Izd.Nauka, Moscow, 1975.
269. N.P.Palmina, E.B.Burlakova, V.D.Gaintzeva, and N.P.Serina, Cancer Chemotherapy, 1976, **8**, 185.
270. N.P.Pal'mina and E.B.Burlakova, Symposium, "Aktual'nye Problemy Sovremennoi Onkologii" (Urgent Problems in Modern Oncology), Izd.Moskov.Gos.Univ., Moscow, 1973, Vol.3, p.86.
271. E.B.Burlakova and E.M.Molochkina, Vop.Onkol., 1974, **20**, 62.
272. O.S.Franfurt, L.P.Lipchina, T.V.Bunto, and N.M.Emanuel', Byul.Eksper.Biol.Med., 1967, **64**, 86.
273. V.Yu.Urbakh, "Biolmetricheskie Metody" (Biometric Methods), Izd.Nauka, Moscow, 1964.
274. N.M.Emanuel', Izv.Akad.Nauk SSSR, Ser.Biol., 1975, 785.
275. N.M.Emanuel and L.K.Obukhova, Exp.Geront., 1978, **13**, 25.
276. D.Harman, J.Gerontol, 1968, **23**, 476.
277. A.Comfort, J.Youhotsky-Gore, and K.Pathmanathan, Nature, 1971, **229**, 254.
278. L.K.Obukhova, Uspekhi Khim., 1975, **44**, 1914 [Russ. Chem.Rev., 1975(10)].
279. N.M.Emanuel', L.K.Obukhova, L.D.Smirnov, and T.V.Bunto, Dokl.Akad.Nauk SSSR, 1976, **226**, 961.
280. N.M.Emanuel', L.K.Obukhova, and L.D.Smirnov, Izv. Akad.Nauk SSSR, Ser.Biol., 1977, 32.
281. L.K.Obukhova, N.Sh.Nakaidze, A.M.Serebryany, L.D.Smirnov, and A.P.Akifiev, Exp.Gerontol., 1979, **14**, 335.

Institute of Chemical Physics,
USSR Academy of Sciences,
Moscow