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Reactions in Frozen Multicomponent Systems

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Results of research on chemical reactions in frozen multicomponent systems are summarised. Transition of a system into a peculiar solid state leads to the appearance of several characteristic features, which can be explained on the basis of a structural - kinetic model. A list of 104 references is included.

CONTENTS

I. Introduction 391
II. Types of reactions and processes 392
III. Kinetic features 392
IV. Structural and phase inhomogeneity 395
V. Structural - kinetic model 398
VI. Some applications of the model 402

I. INTRODUCTION

Investigations on the kinetics and the mechanism of chemical reactions in ordered systems, in particular at low temperatures, constitute a new and rapidly developing branch of chemistry. The attention and interest of world science was directed to this field mainly by Soviet scientists, primarily Academician N. N. Semenov. In his contributions to the International Symposium on Macromolecular Chemistry at Moscow in 1960[1] and to the Eighteenth International Congress of Pure and Applied Chemistry at Montreal in 1961[2] he summarised experimental results, obtained by that time by several Soviet scientists, on low-temperature polymerisation, formation and destruction of free radicals, and rapid chain reactions in the photochemical hydrobromination of alkenes.

Semenov had studied chemical reactions in the solid phase at low temperatures as early as the 1920s. When sulphur and cadmium vapours produced deposits on a surface cooled in liquid air, explosive formation of cadmium sulphides was observed when the layer reached a certain thickness[3,4]. The method of molecular beams, proposed in these papers for the study of reactions at low temperatures, has since been successfully applied to the investigation of polymerisation[5-7] and the halogenation of alkenes[8].

At the end of the 1950s Semenov, with his ever present sense of the novel, gave active support to investigations, begun in the Department of Chemical Kinetics directed by him at Moscow State University, on the chemical reactions of halogens and hydrogen halides with various substances at temperatures close to the boiling point of nitrogen. This work revealed that in some cases lowering the temperature may favour a chemical process, and a reaction that does not take place at room temperature may be accomplished at low temperatures. It was discovered that certain chemical processes occurred spontaneously and rapidly at low temperatures, that chain reactions could take place in the solid phase, and that phase transitions and unstable molecular complexes of donor–acceptor type played a special role in effecting chemical changes at low temperatures. The results have been summarised in reviews[9-12]. These investigations, combined with studies of initiated and non-initiated polymerisation at low temperatures, and the formation and conversion of free atoms and radicals, established the foundations of a new branch of chemical physics—cryochemistry.

The accomplishment of chemical changes in the solid phase at low temperatures considerably extends our views on the elementary act in a chemical process. Transition of a reacting system from the gaseous to the liquid and solid states is accompanied by the intensification of intermolecular interactions, which begin to play an important part. Unstable reactive species can be investigated at low temperatures. Cryochemistry opens the way to obtaining and studying unstable intermediates involving radicals, ions, and reactive molecules, a path to the synthesis of new chemical compounds that are difficult or quite impossible to obtain in other ways.

The reaction having the lowest activation energy is most likely to occur at low temperatures. Hence a kind of energy selection may occur, leading to the formation of only one chemical product in a series of parallel processes. This will permit the establishment of a new chemical technology, characterised by the controlled synthesis of required products. At low temperatures substances can be obtained in a high degree of purity, uncontaminated by side-products and without poisoning the environment.

Until not long ago attention was paid mainly to photochemical and radiation-chemical processes in the study of chemical reactions at low temperatures. These aspects were analysed by Semenov[1,2] and in several other monographs and reviews[13-15].

Two periods—from the end of the nineteenth century to the middle of the 1950s and from the end of the 1950s to the present time—can be traced quite clearly in the investigation of chemical reactions at low temperatures. Mainly haphazard and qualitative work was undertaken during the first period; it has been surveyed in monographs[16,17]. Systematic investigation of different chemical reactions at low temperatures began during the 1950s, after it had been established that active atoms and radicals are stabilised at the temperature of liquid helium[16,17].

At the end of the 1950s research on low-temperature polymerisation was begun both here and abroad[1]. At the same time studies were begun in Moscow University on the addition of halogens to double bonds at temperatures close to 77 K.[18] It was discovered in the early 1960s that chemical and biochemical processes can occur in frozen solutions at temperatures below the melting point of the solvent[19]. The conversion of various monomers at low temperatures, the generation and transformation of radicals in solids, and low-temperature reactions of halogens

and halogen hydrides with alkenes and cyclic compounds are being investigated in many Soviet institutes and laboratories. A systematic study of such processes has been made in Moscow University.

Research during recent years has shown increasingly clearly that detailed knowledge of the phase condition of ordered systems is necessary for an understanding of the mechanism of chemical changes occurring in them. It is extremely important to examine the formation and the development of defects in solids and to establish the relation between these processes and change in the reactivity of the system. The effect of the heterogeneity of a specimen on the occurrence of chemical reactions in it should be most clearly evident in multicomponent systems.

Research at Moscow University during recent years has shown that many kinetic rules governing chemical processes occurring in frozen multicomponent systems can be understood if the liquid phase is considered to constitute the defects responsible for the chemical reactions. Conditions for the formation of such a phase may be produced in multicomponent systems during preparation of the specimens or at the instant of reaction.

The study of solid multicomponent systems, in particular frozen solutions, is of great practical interest. This is connected primarily with problems in the low-temperature preservation of food products and of biological and medical preparations.

The present Review surveys several chemical and biochemical reactions occurring in multicomponent systems, especially in frozen solutions. These belong to an important class of solid-phase processes possessing several specific features.

II. TYPES OF REACTIONS AND PROCESSES

Investigators working at low temperatures are faced with several difficulties. Analysis of the reaction products must usually be carried out after the system has warmed up to room temperature. This involves a phase transition, during which the mobility of the molecules increases and various processes can easily occur[1,2], which must be taken into account. Douzou et al. have shown[20,21] that fall in temperature is accompanied by abrupt changes in such macroscopic properties of the system as its dielectric constant, viscosity, and hydrogen-ion concentration.

The first investigations of reactions involving at least two substances were usually made in vacuum equipment with layer-by-layer freezing of the reactants. The progress of the reaction was followed thermographically, and various chemical and physicochemical methods of analysis were applied after warming to room temperatures[10,22]. However, reactions under such conditions yield insufficiently homogeneous mixtures, so that it is difficult to obtain quantitative results.

The method of molecular beams[8,23] enables homogeneous multicomponent mixtures to be obtained at low temperatures. Combining it with spectral or calorimetric measurements gives information on the composition of the products and on the effective activation energy[11,24]. Condensation in molecular beams and the method of matrix isolation are used also to investigate photochemical processes[25]. Special designs of cuvettes and cryostats together with spectral methods of analysis enable the composition of the products to be studied, and in several cases also the kinetics of their formation, directly at low temperatures[26]. Inert vitrifying solvents can conveniently be used here.

Experimental studies of reactions in frozen solutions are usually made[27] by running together solutions of the reactants and freezing rapidly in liquid nitrogen. The specimens are then placed in a cryostat at the experimental temperature, with allowance for the effect of establishment of the temperature in the specimen and occurrence of the reaction during warming up. In a kinetic study chemical or physicochemical analyses of a series of specimens are made at definite time intervals. Electron spin resonance can be employed for processes involving stable radicals, to give data on reaction kinetics directly at the experimental temperature, without heating of the specimen[28]. Fig. 1 shows as example the temperature dependence, obtained by the above technique, of the rate of reaction of 4-hydroxy-2,2,6,6-tetramethylpiperidinoxyl with hydrazobenzene.

Table 1 gives experimental results for various chemical and biochemical reactions occurring in multicomponent systems at low temperatures. Polymerisation, photochemical and radiation-chemical reactions, and processes involving stabilised radicals are not included, since they fall outside the scope of the present Review. It is evident that the most diverse types of processes can be accomplished at low temperatures in frozen solutions, with and without solvents.

III. KINETIC FEATURES

Analysis of experimental results obtained for various chemical processes at low temperatures will reveal several of their common and most characteristic features. The temperature dependence of reaction velocity illustrated in Fig. 1 is typical of the frozen multicomponent systems listed in Table 1. Reaction occurs below the freezing point of the solvent, and takes place formally in the solid phase. Several experiments have shown that a process is more rapid in frozen solutions than e.g. in supercooled liquid solutions at the same temperature[28]. Fig. 1 shows the extremal temperature dependence of reaction velocity in frozen solutions. The rate of reaction in a solid matrix at a lower temperature is greater than in the liquid phase. Thus transition of a system from the liquid phase to the frozen state is accompanied by increase in the rate of a process: i.e. the phenomenon of a negative temperature coefficient is observed.

The most characteristic feature of reactions in binary systems, which have been investigated at low temperatures mainly in the absence of a solvent, is the influence of phase transitions. Most of the mixture usually reacts when one of the starting materials melts. If the reactants undergo phase transitions below the melting point of the mixture, reaction may take place in the solid phase. In the cyclohexene–chlorine system, for example, reaction occurs at −170°C, at the instant of transition of cyclohexene from a vitreous to a crystalline state[8,23].

In the absence of solvents, chemical reactions occur readily at low temperatures, at high rates, and usually give a single product in nearly theoretical yield[10]. In order to elucidate the mechanism several reactions between halogens and alkenes have been studied in nonpolar solvents over a wide temperature range. The characteristic kinetic feature under such conditions is a negative temperature coefficient[12,29]. Increase in rate with fall in temperature has recently been observed for the reaction of nitrosyl chloride with α-oxides[30] and in those between halogens and phenylcyclopropanes[31].

Table 1. Chemical reactions in frozen solutions and at low temperatures.

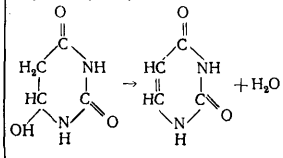
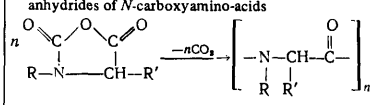
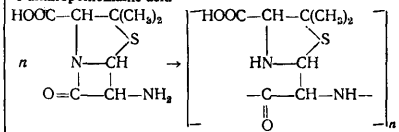
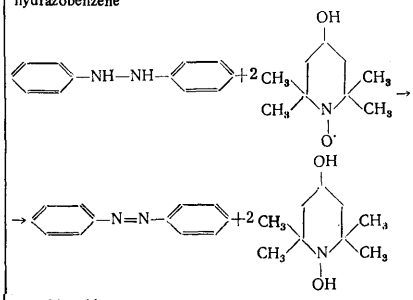
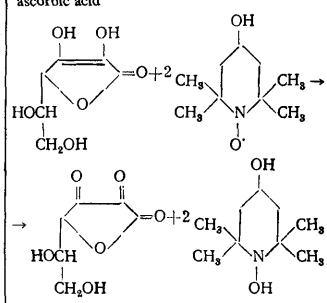
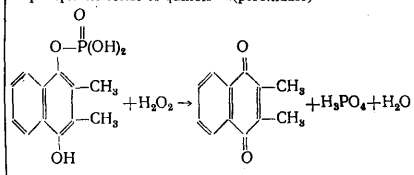
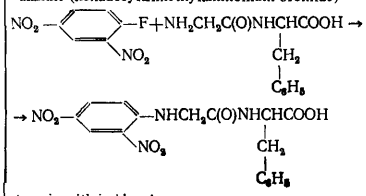
No.	Process	Reaction, substance (catalyst)	Solvent	*t*, °C	Ref.
1	Halogenation of alkenes and aromatic compounds	$>C=C< + Hal_2 \rightarrow >CHal-CHal<$	*none*	−45 — −196	9, 18, 84
		ethylene, propene, isobutene, cyclohexene, hex-1-ene halogens: chlorine, bromine			
		bromination of hex-1-ene	cyclohexane, benzene	0 — −110	42
		bromination of toluene	none	−70 — −142	9
		$C_6H_5-CH_3 + Br_2 \rightarrow C_6H_5-CH_2Br + HBr$			
2	Reaction of alkenes with NO_2	alkenes: propene, isobutene, but-1-ene, hex-1-ene, cyclohexene, cyclopentadiene, buta-1,3-diene; main products: dinitroalkanes, nitroalkyl nitrites and nitrates	none	0 — −90	9
3	Inorganic addition and exchange substitution	$2NO + Cl_2 \rightarrow 2NOCl$ $HBr + Cl_2 \rightarrow HCl + ClBr$ $2NO + O_2 \rightarrow 2NO_2$	none	−116 — −165 −105 — −182 −95	9
4	Hydrohalogenation of alkenes	$(CH_3)_2C=CH_2 + HHal \rightarrow (CH_3)_2CHal-CH_3$ Hal = Br, Cl, I	none	−100 — −190	9
5	Hydrolysis	acetic anhydride	water	−10	85
		$(CH_3CO)_2O + H_2O \rightarrow 2CH_3COOH$			
		p-nitrophenyl acetate			
		$NO_2-C_6H_4-O-COCH_3 + H_2O \rightarrow NO_2-C_6H_4-OH + CH_3COOH$			
		β-propiolactone (catalyst: imidazole)			
		$CH_2-CH_2-C(=O)-O + H_2O \rightarrow HO-CH_2-CH_2-COOH$			
		δ-thiovalerolactone and γ-thiobutyrolactone (morpholine)	water	−10 to 45	85, 86
		penicillins G and V, 6-aminopenicillanic acid (imidazole, histidine, histamine, carnosine, OH^-)	water	to −78	19
6	Hydroxylaminolysis	formamide, acetamide, propionamide, asparagine, glutamine, 2,5-diketopiperazine, cytosine, acetylcholine; esters of glycine, serine, tyrosine, phenylalanine, and glutamic acid	water	to −23	60, 65, 87, 88
		$R-C(=O)-NH_2 + NH_2OH \rightarrow R-C(=O)-NH-OH + NH_3$			
		ethyl ester of lysine, methyl esters of lysine and arginine (trypsin)	water	−18	89
7	Inhibition by structural analogues (in hydroxylaminolysis)	esters of phenylalanine, serine, lysine, tyrosine, and glutamic acid; other cpd.	water	−18	90
8	Decomposition	hydrogen peroxide ($CuCl_2$, $FeCl_3$)	water		91
		$H_2O_2 \rightarrow H_2O + \frac{1}{2}O_2$			
		t-butyl peroxyformate (2,6-lutidine, pyridine)	*p*-xylene	to −70	92, 93
		$HC(O)OOC(CH_3)_3 \rightarrow HOC(CH_3)_3 + CO_2$			
9	Menshutkin reaction	$CH_3I + (C_2H_5)_3N \rightarrow [(C_2H_5)_3NCH_3]I$	benzene, nitrobenzene, dioxan, CCl_4, water	to −196	42, 94 44, 61–64
10	Formation of epoxides	2-chloroethanol (reaction with NaOH)	water	to −15	95
11	Mutarotation	glucose (HCl)	water	−7	96
12	Dehydration	5-hydro-6-hydroxyuridine	water	−10	72
					
13	Electron transfer	$Fe^{3+} \rightleftarrows Fe^{2+}$	water	to −196	97
14	Polymerisation	anhydrides of *N*-carboxyamino-acids	dioxan	to −26	98
					
		6-aminopenicillanic acid	water	to −28	99
					
		adenosine cyclic 3′,5′-phosphate, oligo(2′-*O*-methylinosine 3′-phosphate) (on poly-C matrix)	water water	−15 −15	100 101

Table 1 (Cont'd.)

No.	Process	Reaction, substance (catalyst)	Solvent	t, °C	Ref.
15	Oxidation	hydrazobenzene 	dioxan	to −196	42, 44
		ascorbic acid 	water	−30 to 40	42
16	Enzymic oxidation	phosphoric esters of quinols (peroxidase) 	water	−30 to 50	65
17	Nucleophilic substitution	fluoro-2,4-dinitrobenzene with glycylphenylalanine (hexadecyltrimethylammonium bromide) 	water	−30 to 30	83
18	Chemical inactivation of enzymes	trypsin with imidazole	water	−18	102
		α-chymotrypsin with urea	water	to −70	103
19	Denaturation of DNA	in solutions buffered at various pH	water	−13 to 25	104

Reactions with halogens are characterised by the formation of unstable intermediate donor–acceptor complexes of diverse composition and structure. The role of such complexes has been discussed in great detail[12], as well as the participation of complexes in the formation of radicals[32]. A negative temperature coefficient can be regarded as kinetic evidence that molecular complexes are involved in the chemical reaction. The participation of unstable donor–acceptor complexes will explain the main features of chemical reactions occurring at low temperatures in the absence of a solvent or in a non-freezing solvent. This concept is also extremely useful for analysing the mechanism of reactions of many different organic compounds[33].

Various hypotheses, usually without adequate experimental support, have been adduced to explain the features of chemical reactions in frozen multicomponent systems. The acceleration of chemical processes in frozen solutions has been attributed to change in the reaction mechanism, catalysis by the surface of the solid phase, the occurrence of phase transitions, the presence of various defects, the concentrating of reactants in non-freezing regions of the solvent, the existence of molecular compounds, a favourable spatial arrangement of the reactants, and an increase in the mobility of protons in ice. In the Reviewers' opinion the decisive role belongs to structural inhomogeneity and the consequent high mobility of the reactant molecules.

IV. STRUCTURAL AND PHASE INHOMOGENEITY

The variety of chemical processes occurring at low temperatures and the similarity of their inherent features indicate that the course of chemical reactions in frozen solutions is influenced by quite general factors. The occurrence of a reaction requires a certain degree of mobility of the molecules; it is impossible to understand the reasons for the acceleration of chemical changes and to elucidate their mechanism without knowledge of the structure and the phase constitution of the frozen solutions. Unfortunately, the structure of frozen solutions has not been adequately studied, and hardly any data are available on the phase state and the molecular mobility in such systems under the reaction conditions.

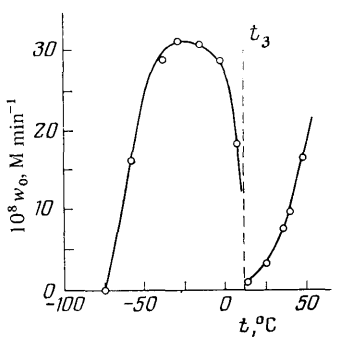


Figure 1. Temperature dependence of rate of reaction of 4-hydroxy-2,2,6,6-tetramethylpiperidino-oxyl (R) with hydrazobenzene (Hab) in liquid and frozen dioxan solutions, with $[R]_0 = [Hab]_0 = 10^{-4}$ M.

Structural heterogeneity of frozen aqueous solutions was detected in the investigation by electron spin resonance of the distribution of paramagnetic ions—VO^{2+}, Mn^{2+}, and Gd^{3+}—at the temperature of liquid nitrogen [34-38]. Analogous results were obtained in a study of solid solutions of organic compounds by the method of stable radicals [39,40]. In solid solutions of sulphuric acid of concentration > 3.5 M the distribution of vanadyl ions is almost uniform, whereas in specimens that freeze as polycrystals a non-uniform distribution of these ions is observed.

The phase constitution of about ten binary systems has been studied by e.s.r. [28,41-43] with the stable 4-hydroxy-2,2,6,6-tetramethylpiperidino-oxyl radical as tracer, varying in concentration from 10^{-7} M to 2×10^{-4} M. Analysis of the structure was based on the difference between the spectra of the radical in solution and in the solid state. Binary and ternary solutions of various compositions were examined over a wide temperature range, from 40 to −196°C. Solutions consisted either of the solvent and the tracer radical or of solvent, additive, and radical. The solvents used were water, dioxan, benzene, nitrobenzene, hexane, cyclohexane, etc. Substances having freezing points both above and below that of each solvent were chosen as additives—other solvents and also iodomethane, triethylamine, hydrazobenzene, azobenzene, hex-1-ene, ascorbic acid, inorganic salts, and other substances.

In all the systems investigated the e.s.r. spectrum of the tracer radical at −18°C is a triplet. The correlation times τ suggest that the mobility of the radical in frozen solutions at this temperature is comparable with its mobility in the liquid phase. As example Fig. 2 shows the spectra in three systems. The combined results indicate that frozen multicomponent systems are heterogeneous with respect to structure and, what is especially important, phase. Such systems are characterised by the coexistence of two phases—solid and liquid—over a very wide temperature range. One of these phases has been termed [44] a liquid microphase, to emphasise the abnormally high molecular mobility in this phase.

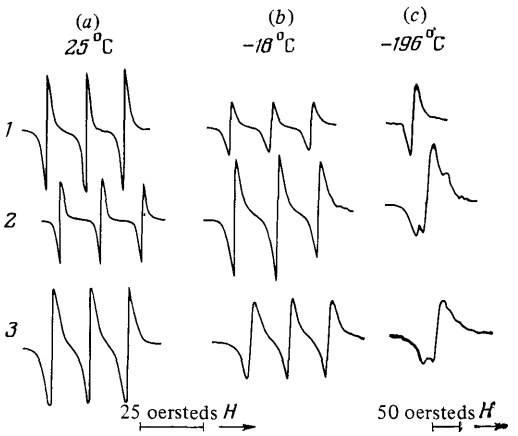


Figure 2. Spectra (e.s.r.) of 4-hydroxy-2,2,6,6-tetramethylpiperidino-oxyl in: *a*) liquid; *b*), *c*) frozen 10^{-5} M solutions in various solvents: 1) dioxan (m.p. 11.8°C); 2) water (0°C); 3) cyclohexane (6.5°C). Correlation times ($10^{12}\tau$, s): 1*a*) 3.3; 1*b*) 66; 2*a*) 23; 2*b*) 130; 3*a*) 5.0; 3*b*) 16.

The existence of regions of high mobility has since been detected in an investigation of electronic spin–lattice relaxation times T_1 and e.s.r. spectra of frozen aqueous solutions of paramagnetic ions [45]. In aqueous (0.5 M) manganese(II) nitrate solutions high mobility is preserved down to −50°C. In this system the relaxation time T_1 increased sharply when the temperature changed only slightly, from 4.1×10^{-9} to $\sim 3 \times 10^{-8}$ s between −50 and −57°C. [45] Cooling from one temperature to the other was obviously accompanied by freezing of the liquid microphase, when the whole specimen became in fact solid.

The e.s.r. spectrum of diphenylpicrylhydrazyl shows a sharp increase in line width near the setting temperatures of solutions in toluene [46]. This is due to displacement of the hydrazyl radicals into uncrystallised regions and increase in their local concentration. The bell-shaped temperature dependence of the intensity ratio of e.s.r. spectra due to radical-pairs having a transition $\Delta M_S = 2$ and to radicals having the transition $\Delta M_S = 1$ in frozen solutions (10^{-3} M) of the stable 2,2,6,6-tetramethylpiperidino-oxyl radical in cyclohexane is also caused by structural heterogeneity of the system and the formation of liquid microregions on freezing [47].

Recent results have indicated the existence, on the surface of ice below 0°C, of a quasi-liquid layer in which the coefficient of self-diffusion of water molecules is as much as 10% of the value in liquid water under normal conditions[48]. Abnormally high mobility of water molecules is observed in frozen solutions of biopolymers, and is usually attributed to a special state of water in the hydrate sheath[49,50].

Electron spin resonance enables only a paramagnetic component to be followed. More complete information on the composition of the liquid microphase is obtained by nuclear magnetic resonance[42,44], the theory of which indicates[51] that absorption lines in solids are broader than those in the liquid phase and are not recorded in high-resolution n.m.r. spectra. If a liquid microphase is formed in a frozen solution, in which reactants are concentrated, narrow resonance lines must be expected to appear in the high-resolution n.m.r. spectra of such solutions, corresponding to reactants that retain their mobility and to part of the solvent. Comparatively narrow resonance signals due to solutes and solvent are indeed observed in frozen solutions[28,52].

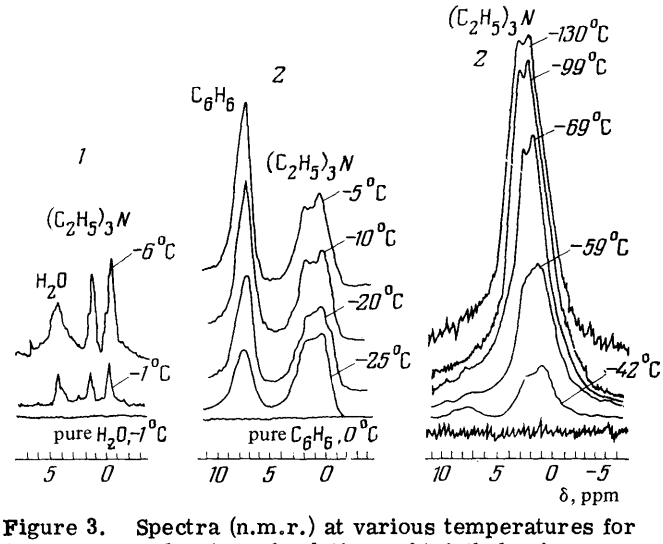


Figure 3. Spectra (n.m.r.) at various temperatures for frozen pure solvents and solutions of triethylamine: 1) 0.04 M; 2) 0.4 M.

Fig. 3 shows as example high-resolution n.m.r. spectra for frozen solutions of triethylamine in water and in benzene. It is evident that the pure solvents do not give such spectra when frozen. The spectra of the frozen solutions contain absorption bands corresponding to triethylamine and to the solvent. A frozen solution is found to contain highly mobile triethylamine molecules down to −130°C.

Integration of the n.m.r. spectra has enabled the temperature variation of the composition of the liquid microphase to be traced. The temperature dependence obtained for the ratio of the numbers of moles of iodomethane and benzene $P_{CH_3I}/P_{C_6H_6}$ in the liquid microphase of frozen benzene solutions and in the liquid solution (0.4 M CH_3I) is given in Table 2. The absolute numbers of moles of various substances in the liquid microphase have been calculated by comparing the results of integrating their spectra and those of a standard, a sealed capillary containing a concentrated solution of sulphuric acid. It is found (see also Fig. 3) that a liquid microphase, consisting of part of the solvent and solutes, is present in frozen solutions down to several tens of degrees below the melting point. Fall in temperature is accompanied by decrease in volume of the liquid microphase, as solvent freezes out and the concentration of the solutes increases.

Table 2.

t, °C	25	−29	−47	−59	−80
	liquid solution		frozen solutions		
$P_{CH_3I}/P_{C_6H_6}$	0.036	1.6	3.3	4.4	13.4

The composition of the microphase depends on the temperature, the proportion of solute increasing with fall in temperature. Table 2 shows that the ratio of the quantity of iodomethane to that of benzene in the liquid microphase of frozen solutions changes by factors of 8.5 and 370, relative to the liquid solution at 25°C, when the temperature falls to −29 and −80°C respectively. In this case we may consider that benzene is dissolved in iodomethane in the liquid microphase, since this contains far more of the latter than of the former.

The composition of the liquid microphase at a given temperature remains unchanged when a specimen is cooled from room temperature to −130°C and then allowed to warm up until the solution has completely thawed out. When the specimen is cooled to −196°C, the liquid microphase gradually disappears: i.e. molecules in the microheterogeneities lose their high mobility. The liquid microphase reappears when the specimen warms up. Comparison of specimens that have first been frozen in liquid nitrogen with those that have not been immersed in it but have been frozen in the resonator of the spectrometer at the specified temperature has shown that formation of the liquid microphase is independent of the method of freezing: it has the same composition in the two cases.

The temperature range of existence of the liquid microphase, the degree to which solutes are concentrated in it, and its volume at a given temperature are determined by the quantity of solutes and by the physicochemical properties of the system, of which the most important are the cryoscopic properties of the solvent and the ability to form eutectics.

The complete reversibility of the variation in the e.s.r. and n.m.r. spectra with temperature shows that the state of frozen multicomponent systems obtained with rates of cooling < 100 deg min^{-1} is close to thermodynamic equilibrium. Hence the volume V_L of microregions of high molecular mobility will be determined by the equation of state of the system. This volume decreases with fall in temperature: i.e. $\partial V_L/\partial T > 0$. To each temperature corresponds a microphase volume in which chemical reaction will occur (if its components are able to interact). When the drop in temperature is sufficient, reactions will cease owing to the increase in viscosity, the decrease in molecular mobility, and the Arrhenius law.

Fig. 4 shows as example the variation in the volume of the liquid microphase during the reaction of triethylamine with iodomethane in frozen benzene. The initial volume

of the specimen is $V_0 = 0.36$ ml. Increasing extent of reaction, with decrease in the number of moles, is evidently accompanied by a decrease in V_L. At the same time the total concentration of solutes in the liquid microphase c_L remains constant (Fig. 5). This concentration increases with fall in the temperature, and hardly changes on introduction of the additive. At a given temperature and with a given initial concentration of starting materials, the composition of the liquid microphase depends mainly on the cryoscopic properties of the solvent. The total concentration of solutes in the liquid microphase can be found from the formula

$$c_L = (T_0 - T)/\Delta,$$

where T_0 is the melting point of the solvent and Δ (in deg M^{-1}) is its cryoscopic constant. Table 3 shows quite good agreement between experimental values and those calculated by means of this constant. The result indicates that the state of a slowly frozen multicomponent system is close to thermodynamic equilibrium.

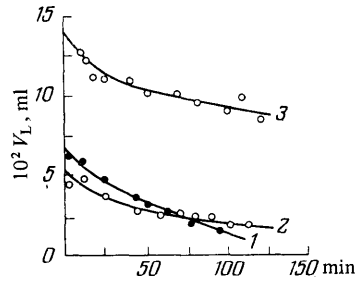


Figure 4. Variation in volume of liquid microphase in reaction of iodomethane with triethylamine (initially 0.2 M) in frozen benzene solutions: 1) at −5°C; 2) at −10°C; 3) with 0.4 M cyclohexane at −5°C; $V_0 = 0.36$ ml.

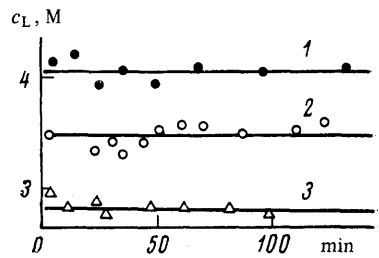


Figure 5. Variation in total solutes concentration c_L in liquid microphase during reaction of triethylamine with iodomethane (both initially 0.2 M) in frozen benzene at: 1) −10°C; 2) −5°C with 0.4 M nitrobenzene; 3) −5°C.

The reason for the formation of a liquid microphase in frozen solutions is that the inclusion of solutes in the crystal lattice of a solid solvent requires a greater quantity of energy than that consumed in the rise in chemical potentials accompanying increase in the concentration of components in the liquid microphase. The origin of microheterogeneities is clear also when eutectics are formed: the concentrating effect accompanying freezing may lead to a composition corresponding to a eutectic mixture. Data on the composition of the liquid microphase obtained by the n.m.r. method show that solutes constitute ~ 20–30% of the total volume of the liquid microphase at temperatures 10–15 deg below the freezing point of the solution.

Table 3. Total concentration of solutes in liquid microphase c_L and observed rate constants k_{exp} in reaction of triethylamine with iodomethane in frozen solutions in benzene, with initial reactant concentrations of 0.2 M.

Additive, 0.4 M	t, °C	$10^4 k_{exp}$, s^{-1}		c_L, M	
		n.m.r.	titration	n.m.r.	calc.
Benzene	−5	1.3±0.7	2.8±0.3	3±1.5	1.8
Nitrobenzene	−5	23±12	13±3	3.5±1.7	1.8
None	−5	4.6±2.3	3.2±0.3	3±1.5	1.8
None	−10	2.7±1.4	2.9±0.3	4±2	2.7

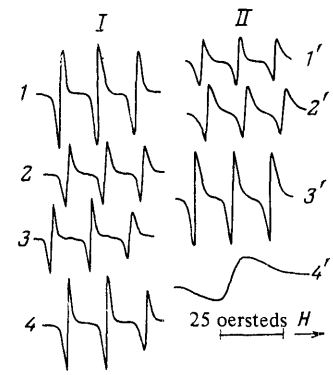


Figure 6. Spectra (e.s.r.) of 10^{-5} M 4-hydroxy-2,2,6,6-tetramethylpiperidino-oxyl in: I) dioxan (m.p. 11.8°C) at −18°C; II) naphthalene (m.p. 80.1°C) at 25°C in the presence of 0.5 M additions of (correlation time $10^{11}\tau$, s): 1) t-butyl alcohol (13); 2) tetrachloromethane (4.4); 3) water (21); 4) azobenzene (29); 1′) dioxan (4); 2′) t-butyl alcohol (15); 3′) nitrobenzene (26); 4′) no addition.

Structural heterogeneity and phase non-uniformity are typical not only of frozen solutions but also of many other multicomponent systems. Fig. 6 shows as example e.s.r. results indicating the existence of a liquid microphase (at 25°C) in solid naphthalene (m.p. 80.1°C) when various additives are introduced[42]. In the absence of an additive the spectrum of the iminoxyl radical in naphthalene is a singlet, which is typical of frozen solutions in other solvents at the temperature of liquid nitrogen. This is converted into a triplet on addition of dioxan, t-butyl alcohol, or nitrobenzene. Thus additive concentrations of 0.5 M or less increase the mobility of the radical by several powers of ten, while the correlation time τ

changes from $< 10^{-5}$–10^{-6} to 4×10^{-11} s. Such a change in mobility is due to the formation, in the matrix of solid naphthalene, of regions of high molecular mobility, which is preserved at a temperature 55 deg below the melting point.

More and more results have appeared recently on molecular mobility in polymers. They indicate that polymer matrices with fillers behave as two-phase systems. The polystyrene–benzene system is characterised over the range −100 to 100°C by two nuclear magnetic spin–spin relaxation times T_2. Protons of benzene are responsible for the "phase" with the longer relaxation time T_{2a}, and protons of the macromolecules for the "phase" with the shorter time T_{2b}.[52] With fall in temperature the population density of the former "phase" diminishes. A sharp decrease in T_{2a} relaxation times is observed in the region of the melting point of benzene. This is evidence of partial crystallisation of benzene and that it in considerable measure determines the composition of this phase. Strictly speaking, the molecular motion of benzene in polystyrene is described by a spectrum of correlation times, and estimates show that the relaxation of benzene molecules in a polystyrene matrix is due mainly to rotational motions[52].

The plasticisation of a polymer by compounds of low molecular weight leads to an increase in molecular mobility. This conclusion is based on the variation in the e.s.r. spectra of radicals and the increase in their rate of conversion[53–55].

Interesting results have been obtained on the behaviour of liquid inclusions in potassium chloride crystals in the field of a temperature gradient[56]. The rate of movement depends on the size of the inclusions and on the applied temperature gradient.

The structure of solid multicomponent systems obtained from the liquid state depends significantly on the setting conditions, primarily on the rate of cooling. Such experiments have been made mainly on alloys. Rates of $\sim 10^3$–10^7 deg s^{-1} lead to extension of the range of solid solutions and a considerable decrease in the liquation of impurity elements, ultimately yielding a homogeneous alloy. Metastable phases and amorphous structures can be obtained with the above rates of cooling[57].

Little if any study has been made of the influence of rate of cooling on the structure of frozen organic-solvent solutions. The thermodynamic disequilibrium of the resulting systems can reasonably be expected to increase with the rate of freezing, which would influence significantly the kinetics of reactions occurring in them. The composition of supersaturated solid solutions formed in the *p*-chloronitrobenzene–*p*-bromonitrobenzene system depends on the rate of crystal growth[58].

It has recently been established that structural inhomogeneity is characteristic not only of crystallising but also of vitrifying systems, e.g. inorganic glasses[59].

Thus available experimental results indicate that multicomponent systems formed from the liquid state with fall in temperature possess both structural and phase heterogeneity. Such systems contain phases differing in composition, physicochemical properties, and degree of molecular mobility.

V. STRUCTURAL–KINETIC MODEL

The phase constitution of multicomponent systems has been examined, and kinetic data on chemical reactions have been obtained for the first time, directly in frozen solutions by application of the e.s.r. and n.m.r. methods. The former has been used to study a reaction involving a stable iminoxyl radical, 4-hydroxy-2,2,6,6-tetramethylpiperidino-oxyl, and the latter to investigate the Menshutkin reaction[44]. Microwave spectrometry has permitted simultaneous observation of the phase state of the system and the kinetics of the reaction, as well as elimination of the possible effect of thawing, which occurs when specimens are analysed by other methods. Comparison of results obtained by different methods has in turn yielded necessary information on the role of freezing–unfreezing processes. Values obtained by different methods showed good mutual agreement (Table 3). Thus the phase transition connected with thawing out and the method of freezing have hardly any effect on kinetic results for spontaneous chemical reactions.

Let us consider the requirements that should be taken into account in any model intended to describe reactions in frozen solutions. The fundamental kinetic laws discussed in Section III are observed with chemical processes of the most diverse types. Hence the proposed model should be generally applicable and be based on principles taking into account the physicochemical properties common to all frozen systems. On the other hand, the chemical specificity of each individual process should appear in the model.

No-one has hitherto attempted to consider together reactions involving active species (e.g. radicals stabilised in matrices at low temperatures by the action of various types of radiation) and spontaneous chemical reactions occurring in solid matrices. In the Reviewers' opinion these kinetically dissimilar processes are actually most closely interconnected, and form the basis for the same general rules.

Our results on the kinetics of chemical reactions in frozen solutions and their phase condition suggest a structural–kinetic model for chemical reactions in solid matrices[44]. Frozen multicomponent systems have been shown to be heterogeneous with respect to phase. To a first approximation they can be imagined to consist of regions differing in composition and hence with different physicochemical properties. Solutes are preferentially concentrated in some regions, and the solvent is concentrated in others.

Phase heterogeneity may arise also by the action of various types of radiation and other physical agents. Even monocrystalline specimens become inhomogeneous under the influence of γ-rays, with maximum heterogeneity in the vicinity of active species stabilised at low temperatures. We can thus speak of the amorphisation of structure around stabilised radicals.

The actual occurrence of chemical reactions in solid matrices is made possible by the emerging phase heterogeneity (under the influence of freezing, radiation, or some other factor). This brings together the reactants, and thereby satisfies an important condition for reaction to occur. Thus chemical reaction takes place in certain regions of a frozen system. Molecular mobility varies significantly within a region, and shows differences in temperature variation in regions differing in composition. Study by e.s.r. and n.m.r. of the phase condition of frozen binary and ternary systems has shown that the freezing of solutions (in the usual solvents) of substances differing in chemical nature concentrates the latter in regions of enhanced molecular mobility. Over a wide temperature range, extending several tens of degrees below the freezing point, this is closely similar to the mobility in the liquid phase. To a first approximation these regions can be regarded as a liquid microphase located in a solid matrix.

The kinetics of chemical reactions in frozen systems can be explained on the basis of certain fundamental principles. (i) Multicomponent systems are characterised by structural and phase inhomogeneity. The components are non-uniformly distributed in a matrix of the main substance. (ii) Phases having different degrees of molecular mobility coexist over a wide range of conditions. The molecular mobility of reactants in frozen systems over a wide temperature range is closely similar to the mobility in a liquid phase. (iii) Freezing is accompanied by a change in the physicochemical properties of the system, which differ significantly for different phases and cannot be obtained simply by extrapolating data for a homogeneous system. It must especially be noted that, even if the totality of microregions in which reaction mainly occurs are regarded as a liquid microphase, this differs markedly in physicochemical properties from the initial liquid solution and even from its supercooled state if the latter could be obtained.

The frozen system may not in general be necessarily in thermodynamic equilibrium. The function describing its true phase condition can then be found only experimentally. Yet solution of the main kinetic problem—to find the law governing the variation of reactant concentrations with time—is impossible in analytical form without knowledge of this function. Two limiting régimes, corresponding to two possible structural states of the system, can be distinguished for chemical reactions.

Firstly, reaction cannot occur to an appreciable extent during transition of the system from liquid to frozen states with a rate of cooling not exceeding 100 deg min^{-1}, which is frequently the case according to the experimental results. The phase condition of the system is then at or close to thermodynamic equilibrium. Such a régime may be termed *kinetic*. The condition $v < w_{12}$ then holds, where v is the rate of chemical reaction, e.g. in the liquid phase at the melting point, and w_{12} the rate of transition of the system from the phase state at temperature t_1 (at or above the melting point) to the state at temperature t_2 (below the melting point).

The second group of conditions, which we may term a *relaxation régime*, will apply to rapid reactions, when $v > w_{12}$, with rapid quenching of the system, e.g. rates of cooling of $\sim 10^3$–10^7 deg s^{-1}. The process will then be governed by the rate of the phase transition. It is especially significant that, with high rates of cooling, the state will not correspond to thermodynamic equilibrium. Transition to a non-equilibrium state may be produced also by other factors, e.g. radiation. The great majority of reactions involving stabilised radicals and other active species in solids occur under a relaxation régime, which, in the Reviewers' opinion, is responsible for the appearance of several unusual features, in particular stepwise recombination.

Formulae for reaction kinetics in frozen systems can be obtained from a combined examination of the equation of state of the system, the equation of material balance describing the distribution of components in individual phases, and kinetic equations defining specific reaction rates in each phase.

Examining the origin of equations for describing reactions occurring under a kinetic régime[44,60-64], we note that experiment shows that the system is then almost in thermodynamic equilibrium, and the unknown equation of state for the frozen system can be replaced by two principles soundly based on experiment. Freezing may be supposed to involve formation of a two-phase system, in which the reaction velocity is $v = v_L + v_S$, where v_L and v_S are the rates in the liquid microphase and in the solid phase respectively. With complete transfer of solutes to the liquid microphase we can ignore v_S, while the great molecular mobility of the reactants allows us to use for v_L the kinetic formula for the rate of a reaction in an ordinary liquid phase, taking into account the changes in temperature and in physicochemical properties accompanying freezing.

The Reviewers and their coworkers have obtained kinetic equations for reactions taking place under a kinetic régime[28,44,61,65]. For the rate of reaction in the liquid microphase of a frozen solution we can write

$$v_L = k^0 \cdot \exp(-E/RT) \cdot \prod_j c_{jL}^{n_j} \qquad (1)$$

where E is the activation energy of the reaction determined in the liquid phase, k^0 the pre-exponential factor, T the temperature of the experiment, c_{jL} the concentration of the jth reactant in the liquid microphase, in contrast to its concentration c_j in the unfrozen solution, and n_j the order of the reaction with respect to this reactant. We suppose that a specimen of volume V is frozen, in which the total concentration of all solutes (reactants, catalyst, additives, etc.) is $\sum_i c_i$. We suppose also that the frozen solution at temperature T contains a liquid microphase of volume V_L with a total concentration of solutes of $\sum_i c_{iL}$. Provided that the solutes become entirely concentrated in the liquid microphase on freezing, the material-balance equation is

$$V \cdot \sum_i c_i = V_L \cdot \sum_i c_{iL}. \qquad (2)$$

Since the experimental reaction velocity v_{exp} is determined for the whole unfrozen specimen of volume V, the material-balance equation with respect to rates becomes

$$v_{exp} V = v_L V_L. \qquad (3)$$

We introduce the concept of a concentrating factor β_i, the ratio of the concentration of the ith component in the liquid microphase of the frozen solution to its concentration in the unfrozen solution. When such concentrating is complete, β_i is the ratio of the volumes of the unfrozen solution and of the liquid microphase. From (2) and (3) we have

$$\beta_i = \sum_i c_{iL} \Big/ \sum_i c_i = V/V_L = v_L/v_{exp} \qquad (4)$$

or

$$\sum_i c_{iL} = \beta_i \cdot \sum_i c_i \quad \text{and} \quad v_{exp} = v_L/\beta_i. \qquad (5)$$

If the equation of state of the system is not known, experimental results show that $\sum_i c_{iL}$ can be determined by means of the relation

$$T_0 - T = \Delta \cdot \sum_i c_{iL}, \qquad (6)$$

where T_0 is the melting point of the solvent and Δ its cryoscopic constant. Combining (5) and (6), we obtain

$$\beta_i = \frac{T_0 - T}{\Delta \cdot \sum_i c_i} \quad \text{and} \quad v_{exp} = v_L \frac{\Delta \cdot \sum_i c_i}{T_0 - T}. \qquad (7)$$

From (1) and (7) we find that the experimental reaction velocity in the frozen solution is given by

$$v_{exp} = k^0 \cdot \exp(-E/RT) \cdot \left[\frac{T_0 - T}{\Delta \cdot \sum_i c_i}\right]^{\left(\sum_j n_j - 1\right)} \cdot \prod_j c_j^{n_j}. \quad (8)$$

The formula for the rate of a reaction in a frozen solution can be written as the product of the reactant concentrations and a factor that behaves formally as a rate constant:

$$v_{exp} = k_{exp} \cdot \prod_j c_j^{n_j}, \quad (9)$$

where

$$k_{exp} = k^0 \cdot \exp(-E/RT) \cdot \left[(T_0 - T)/\Delta \cdot \sum_i c_i\right]^{\left(\sum_j n_j - 1\right)}, \quad (10)$$

i.e. k_{exp} is the product of the usual reaction rate constant at temperature T and the concentrating factor β_i raised to a power depending on the total reaction order $\sum_j n_j$. The concentrating factor depends on the properties of the solvent (its melting point and cryoscopic constant), the experimental temperature, and the total concentration of all the solutes $\sum_i c_i$. The concentrating factor and temperature T will be larger the greater is the difference $T_0 - T$ and the smaller are Δ and $\sum_i c_i$. The inverse proportion relating β_i with Δ and $\sum_i c_i$ has a clear physical explanation. The equilibrium state between the liquid solution and the frozen solvent at temperature T corresponds to a definite concentration of solutes, which is inversely proportional to the cryoscopic constant of the solvent. Thus the lower had been the concentration of solutes in the liquid solution $\sum_i c_i$ the more strongly should they be concentrated for the freezing point of the solvent to be depressed by $T_0 - T$.

The reactants, reaction products, catalysts, and other additives contribute to $\sum_i c_i$. In the simplest case the concentration of an inert additive in the reaction mixture c_a far exceeds the sum of the concentrations of the remaining components (other than the solvent):

$$c_a \gg \sum_i c_i. \quad (11)$$

We can then write

$$\sum_i c_i \approx c_a, \qquad \sum_i c_{iL} \approx c_{aL} \quad (12)$$

$$\beta_i = \beta_a = \frac{T_0 - T}{\Delta \cdot c_a}, \quad (13)$$

i.e. the ratio of the volumes of unfrozen solution and liquid microphase, and hence the degree to which the reactants become concentrated, depend on the concentration of the inert additive.

Table 4 lists formulae for the rate constants k_{exp} of various types of reactions occurring in frozen solutions in the presence and in the absence of an additive. The experimental rate constants determined in frozen solutions containing an additive are seen to be independent of the reactant concentrations and to differ from the constants for the same reaction in the liquid phase by the $(\sum_j n_j - 1)$th power of the factor $\beta = (T_0 - T)/\Delta c_a$. In the absence of an additive, however, values of k_{exp} for reactions involving either a decrease of an increase in the number of moles depend on the instantaneous concentration of the reactants and are a function of the extent of reaction. The explanation is that, with reactions involving a change in the number of moles, the volume of the liquid microphase will change during the reaction in order to satisfy the condition of phase equilibrium. This requirement is equivalent to the condition

$$\sum_i c_{iL} = \text{const} \quad (14)$$

in the given solvent at temperature T.

Table 4. Values of factor γ in the formula

$$k_{exp} = k^0 \cdot \exp(-E/RT) \cdot \frac{T_0 \cdot T}{\Delta} \cdot \gamma$$

for the experimental rate constants of various types of reactions*.

Type of reaction	Factor
A+B⟶C	$([A]+[B]_0)^{-1}$
A+B⟶C+D	$([A]_0+[B]_0)^{-1}$
A+B⟶C+D+E	$(2[A]_0+[B]_0-[A])^{-1}$
A+B+K⟶C+K	$\frac{T_0-T}{\Delta\cdot([A]+[B]_0+[K])^2}$
A+B+K⟶C+D+K	$\frac{T_0-T}{\Delta\cdot([A]_0+[B]_0+[K])^2}$
A+B+K⟶C+D+E+K	$\frac{T_0-T}{\Delta\cdot(2[A]_0+[B]_0+[K]-[A])^2}$

* With $\sum_i c_i \simeq c_a$ we have $k_{exp} = k^0 \cdot \exp(-E/RT) \cdot \left(\frac{T_0-T}{\Delta \cdot c_a}\right)^n$, where $n = 2$ for bimolecular reactions in the presence of a catalyst (K), and $n = 1$ for uncatalysed reactions.

In order to obtain analytical expressions for the time variation of the concentrations of reactants or reaction products, the corresponding differential kinetic equations must be integrated. Considering as example the reaction A + B → C + D + E occurring in a frozen solution in the presence of an additive of concentration c_a, which does not appear in the stoichiometric equation, we write for the experimental rate constant

$$v_{exp} = \frac{d[C]}{dt} = k_{exp}[A] \cdot [B], \quad (15)$$

where (Table 4)

$$k_{exp} = k_0 \cdot \exp(-E/RT) \cdot \frac{T_0 - T}{\Delta \cdot c_a}. \quad (16)$$

The instantaneous concentrations [A], [B], and [C] during the reaction are related to the initial concentrations $[A]_0$ and $[B]_0$ by the formulae

$$[A] = [A]_0 - [C] \text{ and } [B] = [B]_0 - [C]. \quad (17)$$

Substituting (17) in (15), we obtain

$$\frac{d[C]}{dt} = k_{exp}([A]_0 - [C])([B]_0 - [C]). \quad (18)$$

The variables in this differential equation are separated:

$$\frac{d[C]}{([A]_0-[C])([B]_0-[C])} = k_{exp} \cdot dt. \quad (19)$$

Rearrangement of the left-hand side yields

$$\frac{1}{[A]_0-[B]_0} \cdot \left(\frac{d[C]}{[B]_0-[C]} - \frac{d[C]}{[A]_0-[C]}\right) = k_{exp} \cdot dt \quad (20)$$

integration of which, with the initial condition $[C] = 0$ at $t = 0$, gives

$$[C] = \frac{[A]_0[B]_0\{1-\exp[k_{exp} \cdot t([A]_0-[B]_0)]\}}{[B]_0-[A]_0 \cdot \exp[k_{exp} \cdot t([A]_0-[B]_0)]}, \quad (21)$$

It is evident that Eqn. (21), describing the rate curve representing accumulation of the reaction product C, is identical in form with the equation for the liquid phase, but with the usual rate constant $k = k_0 \exp(-E/RT)$ replaced by k_{exp} (Eqn. 16).

For the same reaction taking place in a frozen solution containing no additive the rate is given by Eqn. (15) but with k_{exp} dependent on the instantaneous concentration of one of the starting materials (Table 4):

$$k_{exp} = k_0 \cdot \exp(-E/RT) \cdot \frac{T_0-T}{\Delta \cdot (2[A]_0+[B]_0-[A])}. \quad (22)$$

Since formulae (17) still hold, we can write for the reaction velocity the differential equation

$$\frac{d[C]}{dt} = k_0 \cdot \exp(-E/RT) \cdot \frac{T_0-T}{\Delta} \cdot \frac{([A]_0-[C])([B]_0-[C])}{[A]_0+[B]_0+[C]}, \quad (23)$$

or

$$\frac{d[C]}{dt} = k \frac{([A]_0-[C])([B]_0-[C])}{[A]_0+[B]_0+[C]}, \quad (24)$$

where

$$k = k_0 \cdot \exp(-E/RT) \cdot \frac{T_0-T}{\Delta}.$$

After separation of variables Eqn. (24) becomes

$$d[C] \frac{[A]_0+[B]_0+[C]}{([A]_0-[C])([B]_0-[C])} = k \cdot dt. \quad (25)$$

Integration of this equation, after the requisite rearrangements and with the initial condition $[C] = 0$ at $t = 0$ will give

$$\frac{1}{[A]_0-[B]_0} \cdot \left[(2[A]_0+[B]_0) \cdot \ln\left(1-\frac{[C]}{[A]_0}\right) - [A]_0 \cdot \ln\left(1-\frac{[C]}{[B]_0}\right) - 2[C]\right] = kt. \quad (26)$$

Analytical expressions can similarly be obtained for the time dependence of the concentration [C] of the product of other types of bimolecular reactions in frozen solutions. Table 5 shows that it is only when the solution contains an additive or the number of moles remains unchanged that the rate curves of reactions in frozen solutions are described by the same equations as in the liquid phase but with different constants. The experimental rate constants are then proportional to the concentrating factor, and therefore depend either on the sum of the initial concentrations of the starting materials or on the concentration of the additive.

In the absence of an additive an explicit equation for the rate of accumulation of a product can in general ($[A]_0 \neq [B]_0$) be obtained only for reactions in which the number of moles is maintained. For reactions involving a change in the number of moles formal kinetic equations cannot be used to describe the rate curves in frozen systems. In particular, processing experimental data on the basis of formal equations may lead to errors in determining the order of a reaction.

The model also provides a qualitative explanation and a quantitative description of the observed bell-shaped temperature dependence of reaction velocity (Fig. 1). The physical meaning of such variation is that freezing the solutions and cooling them below the freezing point tends to slow down the reaction in conformity with the Arrhenius law and to accelerate it because of the increase in concentration of the reactants and the change in physicochemical conditions in the liquid microphase: competition between these three effects is responsible for the appearance of a maximum.

Table 5. Analytical formulae for the time dependence of the concentration of a product C of various types of bimolecular reactions (Table 4) occurring in frozen solutions in the absence of an additive*.

Reaction	Formula for [C], where $k_{exp} = k_0 \cdot \exp(-E/RT) \cdot \frac{T_0-T}{\Delta} \cdot \gamma$	γ
$A + B \rightarrow C$	$\frac{1}{[A]_0-[B]_0}\left[[B]_0 \cdot \ln\left(1-\frac{[C]}{[A]_0}\right) - [A]_0 \cdot \ln\left(1-\frac{[C]}{[B]_0}\right)\right] = k_{exp} t$	1
$A + B \rightarrow C + D$	$[C] = \frac{[A]_0[B]_0\{1-\exp[k_{exp} \cdot t([A]_0-[B]_0)]\}}{[B]_0-[A]_0 \cdot \exp[k_{exp} t([A]_0-[B]_0)]}$	$([A]_0+[B]_0)^{-1}$
$A + B \rightarrow C + D + E$	$\frac{1}{[A]_0-[B]_0}\left[(2[A]_0+[B]_0) \cdot \ln\left(1-\frac{[C]}{[A]_0}\right) - (2[B]_0+[A]) \cdot \ln\left(1-\frac{[C]}{[B]_0}\right)\right] = k_{exp} t$	1

*In the presence of an additive ($\sum_i c_i \simeq c_a$) the concentration [C] is given for all reactions by the formula for the reaction $A + B \rightarrow C + D$, with $\gamma = 1/c_a$.

In order to find the extrema in the general temperature dependence of reaction velocity in a frozen solution we differentiate Eqn. (8) with respect to temperature:

$$\frac{\partial v_{exp}}{\partial T} = k^0 \cdot \exp(-E/RT) \cdot \left(\prod_j c_j^{n_j}\right) \cdot \left(\frac{1}{\Delta \cdot \sum_i c_i}\right)^{\left(\sum_j n_j - 1\right)} \cdot (T_0-T)^{\left(\sum_j n_j - 1\right)} \cdot \left[\frac{E}{RT^2} - \frac{\sum_j n_j - 1}{T_0-T}\right] \quad (27)$$

and equate this $\partial v_{exp}/\partial T$ to zero. Formula (27) shows that this is possible only if

$$(T_0-T)^{\left(\sum_j n_j - 1\right)} \cdot \left[\frac{E}{RT^2} - \frac{\sum_j n_j - 1}{T_0-T}\right] = 0. \quad (28)$$

This can occur in several cases:

(a) $(T_0-T)^{\left(\sum_j n_j - 1\right)} = 0$,

i.e. the extremal point T^* corresponds to the melting point of the solvent, a case which is of no special interest and therefore will not be examined;

(b) $$\frac{E}{RT^2} - \frac{\sum_j n_j - 1}{T_0-T} = 0 \quad (29)$$

in which there are several possibilities. When the aggregate order of the reaction is unity (i.e. $\sum_j n_j = 1$), it follows from (29) that the presence of an extremum requires that $E/RT^2 = 0$. If $E \neq 0$, this condition is not realised at any temperature: i.e. the temperature dependence of v_{exp} for first-order reactions is devoid of extrema. With $\sum_j n_j = 1$ we have

$$\frac{\partial v_{exp}}{\partial T} \approx \frac{E}{RT^2} \cdot \exp(-E/RT) > 0. \quad (30)$$

Hence v_{exp} decreases as the temperature falls, and no acceleration of the reaction should be observed when solutions are frozen. Nor is condition (29) realised at any temperature if $\sum_j n_j < 1$. This means that the temperature dependence of v_{exp} does not pass through extrema, and the reaction velocity decreases with fall in temperature.

The total reaction order must exceed unity, i.e. $\sum_j n_j - 1 > 0$, for extrema to be present. The extremal point is then found by solving Eqn. (29) for temperature:

$$T^* = \left\{ \frac{E^2}{4R^2\left[\left(\sum_f n_f\right) - 1\right]^2} + \frac{E \cdot T_0}{R\left[\left(\sum_f n_f\right) - 1\right]} \right\}^{1/2} - \frac{E}{2\left[\left(\sum_f n_f\right) - 1\right]}. \quad (31)$$

This formula shows that the temperature T^* depends on the aggregate order of the reaction, and falls as the order increases. It depends also on the freezing point of the solvent and the activation energy in the liquid phase. Thus if several parallel reactions, having different orders or differing markedly in activation energy, take place in a system, each will occur at a maximum rate at a particular temperature of the frozen solution. This implies that, by conducting the process in the frozen solution at a chosen temperature, we are able to accelerate selectively one or more reactions occurring in parallel in the system.

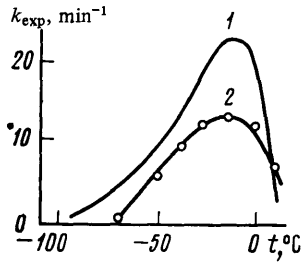


Figure 7. Temperature dependence of rate constant for the oxidation of hydrazobenzene by 4-hydroxy-2,2,6,6-tetramethylpiperidino-oxyl in frozen dioxan: 1) calculated curve; 2) experimental curve.

The occurrence in frozen solutions of the maximum reaction velocity predicted by the model indicates that these reactions have a negative temperature coefficient, i.e. an effective activation energy less than zero, over the temperature range $T_0 - T^*$. A formula can be obtained for the effective activation energy of a reaction in a frozen solution by differentiating with respect to the reciprocal of the temperature the logarithm of the experimental rate constant (Eqn. 10):

$$E_{eff} = -R\frac{d\ln k_{exp}}{d(1/T)} = E - \left[\left(\sum_f n_f\right) - 1\right]\frac{RT^2}{T_0 - T}. \quad (32)$$

This expression (32) indicates that, when the solution freezes, the activation energy of the reaction changes sign, and remains negative down to the temperature T^*, when it vanishes; after this E_{eff} again becomes positive.

VI. SOME APPLICATIONS OF THE MODEL

Experimental results are well reproduced by the equations obtained[42-44,60-66]. As example Fig. 7 compares the experimental temperature dependence with the calculated relation for the rate constant in the oxidation of hydrazobenzene by 4-hydroxy-2,2,6,6-tetramethylpiperidino-oxyl. Good qualitative agreement is evident, and at several temperatures nearly identical calculated and experimental values.

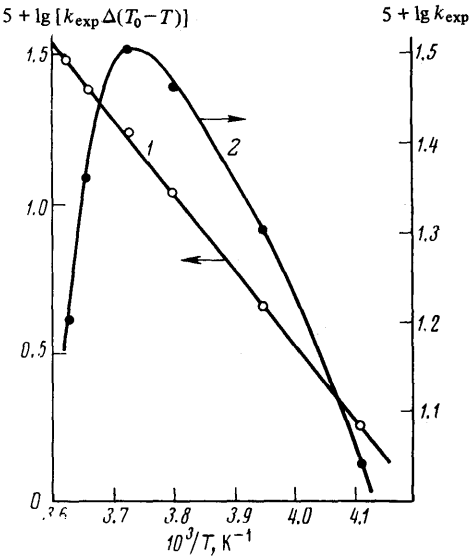


Figure 8. Influence of the reciprocal of the temperature in the Menshutkin reaction in frozen benzene on: 1) lg [$k_{exp}\Delta(T_0 - T)$]; 2) lg k_{exp}.

Results plotted in conformity with the Arrhenius equation do not lie on a straight line (Fig. 8). Linearisation can be effected by the use of coordinates allowing for transition of the system into the frozen state. Table 6 shows good agreement between the values thus obtained for the activation energies of reactions in frozen solutions and the corresponding activation energies in the liquid phase. Good agreement is evident also between calculated and experimental temperatures for maximum reaction velocity.

Let us consider briefly the possibilities of the structural-kinetic model for describing the kinetics of reactions occurring under a relaxation régime[67]. Stepwise recombination in the destruction of radicals stabilised in solids is especially interesting from this point of view. It is observed in systems of the most diverse chemical nature, including polymers[68-79]. The recombination of peroxy-radicals obtained by the photolysis of frozen aqueous hydrogen peroxide was one of the first examples of the stepwise recombination of radicals and the special role of phase transitions in effecting chemical reactions at low temperatures[9,71]. Fundamental kinetic laws were formulated[73] for the stepwise recombination of radicals.

Table 6. Calculated and experimental temperatures of maximum reaction velocity t_{max}^{calc*} and t_{max}^{exp}, with activation energies in the liquid phase and in frozen solutions E and E_{fr} (R = 4-hydroxy-2,2,6,6-tetramethylpiperidino-oxyl).

Solvent	E, kcal mole^{-1}	E_{fr}, kcal mole^{-1}	t_{max}^{calc}, °C	t_{max}^{exp}, °C
		$CH_3I + (C_2H_5)_3N$		
Benzene	9.4±1.0	11.4	−9±2	−5
Nitrobenzene	9.7±1.0	11.8	−8±2	−5
Dioxan	6.8±1.0	9.6	−9±2	−6
Water	20.3±1.0	23.2	−8±2	−8
		$R + C_{12}H_{12}N_2$		
Dioxan	6±1.0	6.5	−14±2	−20
		$R + C_6H_8O_6$		
Water	12±2	17	−10.5±3	−10

*Deviations calculated on the basis of the error adopted for E in ±1.0 kcal mole^{-1}.

The temperature dependence of the fraction of stabilised radicals (the "annealing" curve) is not in general linear. It probably represents the temperature dependence of the molecular mobility necessary for the destruction of radicals. The curve for radicals in adipic acid is almost linear under normal pressure, but at high pressures it becomes a more complicated function of temperature[74]. The thermal stability of radicals increases with increase in pressure, which is consistent with a decrease in molecular mobility with rise in pressure. It depends on the method of preparing the specimen and the mode of generation of the radicals (e.g. the type of radiation).

Various ideas and hypotheses have been put forward on the mechanism of the destruction of radicals in solids[68,70,73,75-78]. A polychromatic kinetic model of radical reactions in solids has been proposed[69] for the quantitative explanation of recombination. It has recently been suggested[79,80] that the free volume plays a part in the kinetics of radical destruction. Existing models do not explain all the observed regularities, and many concepts based on them are formally kinetic in character.

The concepts underlying the structural-kinetic model[44] also provide a qualitative description of the main kinetic features of the reactions of active species in solids[67]. They lead to a kinetic equation for the stepwise recombination of radicals, including the initial rapid destruction[67]. Such an approach will explain many aspects of solid-phase polymerisation and reactions in polymer systems. The laws governing photochemical reactions in solids can be explained by the same ideas. Solid-phase processes are characterised by a disproportionately large effect of small additions. Yields of products in photochemical and radiation-chemical reactions in multicomponent systems are usually non-additive and have abnormal values, while the rates of the processes are high. Tunnelling and the transfer of excitation and the free valency are often postulated to explain these features.

The concepts underlying the structural-kinetic model show, in the Reviewers' opinion, the absolute necessity of taking into account the fact[67] that, in regions surrounding already formed stabilised radicals, the medium possesses significantly different properties from those of the original matrix before exposure (this possibility had been pointed out by Semenov[2]). The yield of radicals and other species in this new structure will differ from their yield in regions of the solid not yet damaged by radiation. Thus differences in the mechanism and the efficiency of processes occurring in these regions of the solid must be taken into account. In particular, it must be expected that the yield of radicals will increase (because of the diminished cage effect) in radiation-damaged regions, i.e. where stabilised radicals are already present. Such an approach provides an explanation of the enhanced probability of formation of radicals near already existing radicals, and hence the increase in their rate of destruction with increase in dosage. The suggested mechanism may explain the high energy yield of the destruction of radicals, the low apparent activation energies, and the close similarity of radical-destruction rate constants in different substances[68]. The same mechanism should lead to a change in the type of dependence of the rate of accumulation of active particles on the dose. The formation of considerable quantities of radical-recombination products becomes understandable.

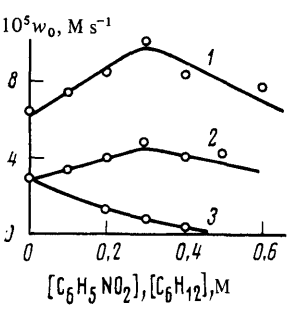


Figure 9. Effect of additives on rate w_0 of reaction of triethylamine with iodomethane in frozen solutions in: 1) dioxan at −8°C with additions of nitrobenzene (initial reactant concentration 0.11 M); 2) benzene at −5°C with additions of nitrobenzene (initial reactant concentrations 0.15 M); 3) as (2) but with added cyclohexane.

The existence in frozen solid matrices of regions of phase heterogeneity with a high mobility of interacting species would permit a physically clear interpretation of many kinetic features of chemical reactions in frozen solutions. These concepts have permitted a comparison of experimental and calculated values, as well as the prediction and detection of several new phenomena.

The rates of chemical reactions in frozen solutions are controlled by adding to the reaction mixture substances that are not involved in the process described by the stoichiometric equation. According to the model described in Section V, additions of inert substances should increase the volume of the liquid microphase and diminish the reactant concentrations. Non-polar additives behave in this way. Fig. 9 shows that polar additives have a dual effect: with low concentrations of the polar nitrobenzene reaction rates in the frozen solution are higher than in the solution without additive, because of the increase in polarity; with increase in the nitrobenzene concentration the dilution of the reactants in the liquid microphase increases because of the change in volume of this phase. The combined action of these two opposite effects leads to the appearance of maxima in the dependence of the initial reaction velocity on the additive concentration. The influence of the dielectric constant on reactions in frozen solutions has been discussed in detail [61,62].

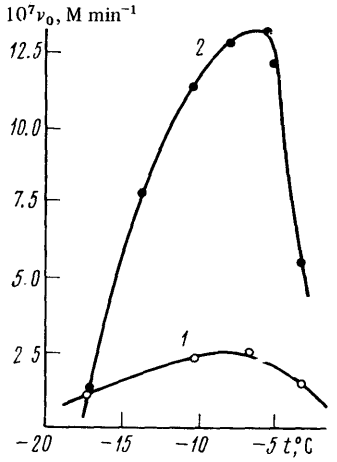


Figure 10. Temperature dependence of rate of oxidation of 4-hydroxy-2,3-dimethyl-1-naphthyl dihydrogen phosphate (2.5×10^{-5} M) by hydrogen peroxide (3.5×10^{-5} M) at pH 7.0 (0.1 M phosphate buffer) in ice in the presence of peroxidase (1.5×10^{-9} M): 1) individual oxidation; 2) in the presence of *p*-hydroxyphenyl dimethyl phosphate (1.4×10^{-5} M) as activator.

To describe the effect of additives we can formulate the general rule that the reaction is retarded in the frozen solution if the rate of the process in the liquid additive as solvent is lower than its rate in the solvent used in the experiment; an additive may either lower or raise the rate in a frozen solution if the rate in the liquid additive as solvent is greater than in the solvent to be frozen. Thus the rate of a process in a frozen solution can be regulated by additions of substances that are not involved in the stoichiometric equation and do not influence the kinetics of the reaction in the liquid phase. It is important to stress that the quantities of additives do not exceed 5% by volume, and are comparable with the concentrations of the reactants.

The structural-kinetic model suggests special effects produced by freezing for reactions having a complicated mechanism and involving a large number of species. Such processes include many biochemical and especially enzymic reactions. The spatially close approach of the reactants should lead to marked acceleration of such reactions, but diffusion hindrance would lead to sharp retardation.

The above suggestions have found some confirmation in the investigation of the two-substrate oxidation of quinol phosphates by hydrogen peroxide in the presence of peroxidase in frozen solutions [81]. Substrate–substrate activation is observed for this reaction in the liquid phase [82]: when two different compounds are oxidised together, the presence of one substrate activates the oxidation of the other. Only one of the substrates is oxidised, while the activator is not consumed until considerable degrees of conversion have been reached. Activation is a result of the concerted oxidation of substrates differing in reactivity at the stages of formation and interaction of radicals.

Fig. 10 illustrates the temperature dependence of the rate of two-substrate oxidation in ice. The presence of the activator is seen to increase the rate of oxidation of 4-hydroxy-1-naphthyl phosphate. The phenomenon of substrate–substrate activation in ice confirms the main assumptions of the structural-kinetic model, and shows that both freezing and the introduction of an additive—the other substrate—enable the rate of the process to be controlled and the efficiency of the enzyme to be enhanced.

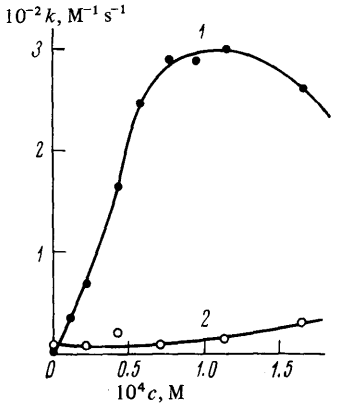


Figure 11. Dependence of rate constant of reaction of glycylphenylalanine (3.3×10^{-4} M) with fluoro-2,4-dinitrobenzene (3.3×10^{-4} M) on concentration of hexadecyltrimethylammonium bromide *c* at pH 7.25 (0.1 M phosphate buffer) in: 1) ice at −10°C; liquid phase at 20°C.

The concepts of the phase heterogeneity and the special properties of frozen solutions have enabled additional structure formation in ice to be predicted and detected. The example of nucleophilic substitution between glycylphenylalanine and fluoro-2,4-dinitrobenzene in ice has revealed a phenomenon resembling micellar catalysis in the liquid phase [83]. Comparison of the results plotted in Fig. 11 show that hexadecyltrimethylammonium bromide

becomes active in ice at concentrations that do not influence the reaction in the liquid phase. It is interesting that in the latter the main reaction is accompanied by hydrolysis of fluoro-2,4-dinitrobenzene, whereas transition of the system to the frozen state changes the direction of reaction: freezing accelerates selectively the condensation and suppresses the hydrolysis.

The above examples lead to the important conclusion that the freezing of a system is an effective new method for controlling the rate and the mechanism of a chemical reaction.

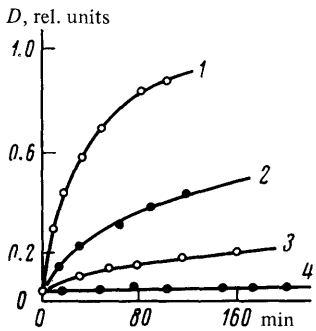


Figure 12. Rate curves for the accumulation of azobenzene in the oxidation of hydrazobenzene (initially 1.1×10^{-4} M) in the presence of 0.01 M ethanol in dioxan solution by: 1) iminoxyl radical in frozen solution at −5°C; 2) iminoxyl radical in liquid solution at 20°C; 3) air in liquid solution at 20°C; 4) air in frozen solution at −5°C.

The structural-kinetic model of reactions in multicomponent systems has led to the prediction and the detection of kinetic selection[28], the essence of which is that, among several parallel reactions in a liquid phase, only one is accelerated preferentially when the system passes into the frozen state. We consider as example two parallel bimolecular reactions

$$A + B \xrightarrow{k_1} E + F \qquad (I)$$

$$C + D \xrightarrow{k_2} K + H \quad . \qquad (II)$$

If D is present in excess, reaction (II) can be regarded as unimolecular and written

$$C \xrightarrow{k_3} K + H, \qquad (III)$$

where $k_3 = k_2[D]$. From Eqn. (8) the rates of reactions (I) and (III) in the frozen solution are

$$v_1 = k_{1\exp}[A][B] = \frac{T_0 - T}{\Delta \cdot ([A]_0 + [B]_0)} \cdot k_{01} \cdot \exp(-E_1/RT) \qquad (33)$$

$$v_3 = k_{3\exp}[C] = k_{02} \cdot \exp(-E_2/RT) \cdot [D][C] \quad . \qquad (34)$$

The ratio of the rates at temperature T is

$$\frac{v_1}{v_3} = \frac{T_0 - T}{\Delta \cdot ([A]_0 + [B]_0)} \cdot \frac{k_{01} \cdot \exp(-E_1/RT) \cdot [A][B]}{k_{02} \cdot \exp(-E_2/RT) \cdot [C][D]} \quad . \qquad (35)$$

The corresponding ratio in the supercooled liquid phase at the same temperature is

$$\frac{v_{1L}}{v_{3L}} = \frac{k_{01} \cdot \exp(-E_1/RT)}{k_{02} \cdot \exp(-E_2/RT)} \cdot \frac{[A][B]}{[C][D]} \quad . \qquad (36)$$

Comparison of (35) and (36) shows that the rate ratio varies differently in liquid and frozen solutions. Transition of the system from one phase to the other leads to a difference in rates defined by the relation

$$\frac{v_1/v_3}{v_{1L}/v_{3L}} \simeq \frac{T_0 - T}{\Delta \cdot ([A]_0 + [B]_0)} \quad . \qquad (37)$$

Fig. 12 illustrates the effect of freezing on the oxidation of hydrazobenzene by atmospheric oxygen and by the 4-hydroxy-2,2,6,6-tetramethylpiperidino-oxyl radical in dioxan. Calculation for 253 K gives the value 3.6×10^4, so that the rate of oxidation by dissolved oxygen has decreased by a factor exceeding 35000. Yet the rate of oxidation by the radical has accelerated in frozen solutions relative to the liquid phase. A similar pattern is observed in the oxidation of ascorbic acid[28].

One factor affecting the activation of chemical reactions on transition to the frozen state is the concentrating of the reactants. Such effects should be most strongly developed, of course, in reactions involving molecular complexes. Data on the halogenation of alkenes indicates that the phenomenon of a negative temperature coefficient is intensified when the system passes into the solid phase[66]. The combined activation of chemical processes by low temperatures and complex formation is clearly evident in the example of halogenations. Low-temperature reactions in the absence of a solvent (Table 1) have usually been investigated at temperatures at which the reactants exist in the solid phase. The preparation of such specimens may involve the formation of structural and phase discontinuities. Such a possibility is indicated by n.m.r. investigations on chlorine–alkene systems[84]. Thus at low temperatures some common features are exhibited by reactions in binary systems in the absence of a solvent and in multicomponent systems containing a solvent.

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Research on frozen multicomponent systems has shown that the structural and phase inhomogeneity of the specimens has a decisive influence on the kinetics of chemical reactions occurring in such systems. Experimental results indicate that transition of a system from one phase to another is accompanied by a considerable change in physicochemical properties. Even in cases in which structural inclusions can be regarded as a liquid phase, its density, viscosity, dielectric constant, and other physicochemical characteristics cannot be obtained by extrapolating values for the truly liquid systems. These parameters are determined by the properties of the frozen specimen as a single whole.

The situation is further complicated by the absence of a strict definition for most physicochemical parameters at low temperatures and in the solid phase. Hitherto we have known really very little about the true phase condition of multicomponent systems at low temperatures, especially when subject to various radiations and with change in temperature. In the Reviewers' opinion the most fertile approach to the solution of many problems of low-temperature chemistry is to consider not only the specific chemistry of the process but also the effect of the actual phase condition of the whole system.

Only macrokinetic rules based on the structural-kinetic model have yet been obtained for frozen multicomponent systems. Further investigations are necessary to establish the dependence of the rate constant on the structure and the phase condition of the system, and to determine the quantitative influence of various factors,

such as the movement of inclusions, methods of obtaining them, and the role of thermodynamic and kinetic factors in effecting chemical changes in frozen solid matrices. Solution of these problems is of great theoretical and practical interest. Research on chemical and biochemical reactions at low temperatures will enlarge our views on the mechanism of chemical change under extreme conditions, permit new approaches to the control of chemical synthesis, and enable optimum conditions to be predicted for the preservation of medical and biochemical preparations, as well as foodstuffs.

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