Russian Chemical Reviews **68** (8) 637 – 652 (1999) © 1999 Russian Academy of Sciences and Turpion Ltd

UDC 544.43 : 547

Transformations of organic compounds under the action of mechanical stress

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Abstract. Transformations of organic compounds (monomeric and polymeric) under the action of mechanical stress are considered. Two types of processes occur under these conditions. The first type involves disordering and amorphisation of crystal structure and conformational transformations as a result of rupture of intermolecular bonds. The second type includes mechanochemical reactions activated by deformation of valence bonds and angles under mechanical stress, namely, the rupture of bonds, oxidation and hydrolysis. Data on the organic mechanochemical synthesis of new compounds or molecular complexes are systematised and generalised. It is demonstrated that mechanical treatment ensures mass transfer and the contact of reacting species in these reactions. Proteins are especially sensitive to mechanical stress and undergo denaturation; enzymes are inactivated. The bibliography includes 115 references.

I. Introduction

Mechanical treatment of a substance can induce numerous transformations, which include, firstly, rupture and formation of valence bonds and deformation of bond angles, and, secondly, both destruction and generation of weaker intermolecular interactions (disordering, amorphisation of the crystal structure, conformational transitions and polymorphic transformations).

Mechanochemistry started to develop in the 1940 – 1950s, based on the results of applied studies dealing with polymer processing (plasticisation and rolling of elastomers, grinding of glassy polymers) (see, for example, Refs 1 – 5). Later, substantial progress has been attained in the mechanochemistry of inorganic compounds (metals, salts, oxides);[6 – 13] the influence of high pressure combined with shear strain on the rate of solid-state transformations of low-molecular-mass organic compounds has been studied;[14 – 17] the occurrence of mechanochemical reactions in high-energy mills has been discovered;[18 – 21] mechanochemical transformations of coals have been studied;[22] free radical reactions induced by mechanical stress have been considered;[23, 24] and experimental studies and theoretical calculations for mechanochemical reactions involving cleavage of C – C bonds[25 – 27] and oxidation and hydrolysis reactions have been performed.[28 – 30] (The vast majority of these studies were concerned with solid-phase processes.)

A new and fairly promising line of research representing technology of the future, nanotechnology, is closely related to mechanochemistry. A non-traditional application of atomic force and tunnelling microscopes has been reported;[31] it was proposed to use them for micro-manipulation, *i.e.*, for positioning atoms and molecules at distances required to initiate a chemical reaction between them (molecular design).

Despite the fact that mechanochemistry of organic compounds has been successfully developing in recent years (most of the studies in this field were carried out by Russian scientists), the results obtained have not been surveyed; the reasons and the mechanisms of the influence of mechanical stress on chemical processes have not been analysed. The purpose of this review is to fill this gap and to present mechanochemistry (in particular, mechanochemistry of organic compounds) as a field of science developing at the border between chemistry and physics.

II. Rupture of intra- and inter-molecular bonds upon mechanical treatment

Organic compounds, both polymeric and monomeric, contain bonds of two types, namely, strong interatomic (covalent) bonds within the molecules and relatively weak (van der Waals, hydrogen) intermolecular bonds. Naturally, the weaker intermolecular bonds should be the first to split under the action of mechanical stress; this results in disordering or loosening of the structure of substances. The degree of disordering depends on the type of mechanical treatment, the amount of energy supplied and the substance structure. Crystalline materials undergo amorphisation and polymorphic transformations under mechanical stress; polymers undergo conformational transitions. It should be noted that in the case of polymers, mechanical treatment induces rupture of both types of bonds, because intermolecular bonds are formed along the whole length of polymer chains and the total energy needed to cleave them becomes commensurable with the energy of valence bonds.

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Received 9 December 1998
Uspekhi Khimii **68** (8) 708 – 724 (1999); translated by Z P Bobkova

1. Rupture of intermolecular bonds

a. Amorphisation of molecular crystals and polymorphic transformations †

During fine disintegration of a substance, after the substance particles have reached a particular size, the new surface no longer forms and plastic flow of the substance starts. In some cases, further mechanical treatment results in the particle aggregation. As a rule, the specific surface area (S_{sp}) of the initial organic crystals falls in the range of $0.1-1$ $m^2\ g^{-1}$; after grinding, it increases several-fold depending on the dose of mechanical energy delivered, the structure of the substance, the presence of moisture, impurities, *etc*. In some cases, exceptionally high S_{sp} values have been attained. Thus the specific surface areas attained on grinding of cortisone acetate and saponic acid (based on gas adsorption data) were as high as 130 $m^2\ g^{-1}$ (see Ref. 32) and 400 $m^2\ g^{-1}$ (see Ref. 33), respectively. These unusually high S_{sp} values point to extensive disordering (loosening) of the structures of these materials.

As a rule, grinding causes a decrease in the degree of crystallinity and sometimes complete amorphisation, which was confirmed by X-ray diffraction patterns and IR spectra recorded for various crystals — ampicillin trihydrate, digoxin, sodium prasteron sulfate,[33] sulfanilamides,[34,35] phthalylsulfathiazole,[36] sulfathiazole,[37] *etc*. Analysis of the X-ray diffraction patterns of sulfamonomethoxine (Fig. 1 *a*) allowed the researchers cited [34] to conclude that the observed broadening of diffraction lines is due to both a decrease in the size of crystallites (to ~ 100 Å) and an increase in the lattice micro-distortions (2–2.5-fold).

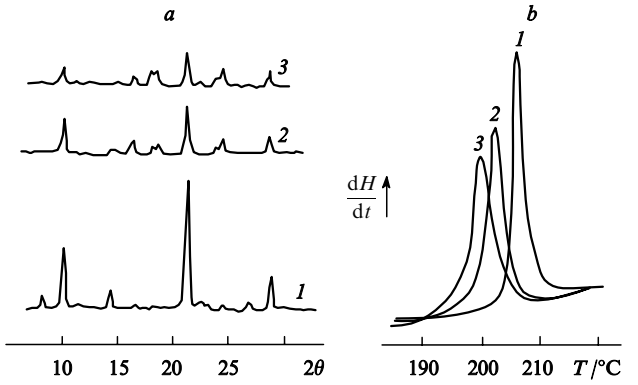


Figure 1. X-Ray diffraction patterns (CuK_α radiation) (*a*) and differential scanning calorimetry curves (*b*) of sulfamonomethoxine powders after grinding in a jet mill.[34]
The initial sample (*1*) and the samples having been passed four (*2*) and six (*3*) times through the jet mill.

Amorphisation increases the rates of dissolution and solubility of compounds;[33,34] it decreases the melting points and heats of melting of crystals and extends the temperature ranges of melting.[33]

Fig. 1 *b* presents the variation of the melting point and the heat of melting of sulfamonomethoxine powders as functions of the degree of disintegration found from the data of differential scanning calorimetry (DSC).[34] The values for the change in free energy (ΔG) calculated in two ways, namely, from the decrease in the melting point and the heat of melting and from the increase in the solubility of sulfamonomethoxine on grinding, agree with each other and reach $0.8-0.9$ kJ mol^{-1} (see Ref. 34).

† The data on the influence of mechanical treatment on the properties of low-molecular-mass organic crystals, presented in the review, have been mainly taken from publications devoted to the technology of drugs, which often includes various types of mechanical treatment, for example, grinding or pressing.

In some cases, for instance, for fullerene, the peak corresponding to a phase transition (~ 260 K) completely disappears from the thermograms.[38]

For most of the organic crystal studied, disordering of the crystal structure is associated with disturbance of the system of intermolecular hydrogen bonds, which is confirmed by IR spectra.[33,34,39]

Some organic crystals, for example, barbiturates, streptocid, sulfathiazole, theophylline, cortisone acetate, *etc*.[32,33,37] undergo polymorphic transformations on grinding, as indicated by X-ray diffraction, calorimetric and spectroscopic data. In the case of sulfathiazole, mechanically induced reversible transition of the form stable at room temperature into a metastable form occurs (the latter is usually produced by heating the stable form at ~ 174 °C).[37] In the case of cortisone acetate, a structure with $P2_1$ point group of symmetry passes into a structure with $P2_12_12_1$ group of symmetry.[32] It was found [31] that under the action of anisotropic compression forces, C_{60} fullerene is transformed into known carbon phases (diamond, graphite) and into some metastable crystalline and amorphous modifications.

During the polymorphic transformations induced by mechanical treatment, one form does not pass directly into another; this occurs *via* a disordered non-crystalline state. Upon prolonged mechanical treatment, the new phase arising also becomes amorphised.[32,37]

The changes in the physico-chemical properties of substances induced by pressing are similar to those occurring on grinding. Normally, pressing causes a decrease in the degree of crystallinity and polymorphic transformations.[33] This has been detected for streptocid, phenylbutazone, chloropropionamide, ephedrine hydrochloride, libexin, noxyron, *etc*. However, the rate of dissolution of some substances can decrease upon pressing due to the aggregation of powder particles.

b. Structure disordering and conformational transitions in polymers

As in the case of molecular crystals, the mechanical dispersion of polymers in mills at low temperatures (~ 80 K) results in substantial disordering (loosening) of their structure caused by loss of the intermolecular van der Waals contacts. This is indicated, for example, by the sharp increase in the adsorption of inert gases by polymers. The specific surface area of dispersed poly(methyl methacrylate) (PMMA) calculated from argon sorption isotherms is $600-800$ $m^2\ g^{-1}$ (see Ref. 11), and that of poly(methyl silsesqioxane) (PMSSO) is 400 $m^2\ g^{-1}$ (see Ref. 40) under the same conditions.

During unfreezing of a PMMA sample, the disordered structure relaxes even at 120 K and the specific surface area diminishes to a value of several square meters per gram. However, in the case of PMSSO, the disordered state is retained during heating of the samples to 500 K. This can be explained by the specific chemical structure of PMSSO; mechanical dispersion of this polymer is accompanied by free radical reactions giving valence cross-links, which stabilise the arising disordered state.[40]

Crystallisation of solutions (melts) of polymers and separation of liquid phases on exposure to an external mechanical field are phenomena long known in the physical chemistry of polymers.[41,42] This is due to the fact that under tensile or shear stress, macromolecular coils are untwisted, the number of contacts between macromolecules increases, and, as a consequence, the degrees of their aggregation and orientation increase.

A mechanical action (static compression under $75-100$ kbar combined with shear deformation) on crystalline polyoxymethylene (POM) induces conformational transitions of various types.[43,44] In particular, a broad range of rotational isomers of chains were found and a phase transition of the hexagonal modification into an orthorhombic one was detected in POM crystals with straightened chains which had been subjected to hydrostatic compression. Evidently, even under conditions of only hydrostatic compression, tangential stresses and micro-

shears may appear due to the anisotropy of the mechanical properties of the crystals.

During mechanical grinding and pressing of proteins, cleavage of hydrogen bonds and disturbance of hydrophobic and electrostatic interactions occur, resulting in changed conformations of protein molecules and their denaturation. Mechanically induced denaturation of proteins and inactivation of enzymes are considered in Section V.

2. Rupture of valence bonds

a. Models of mechanical rupture

Rupture of a valence bond on stretching (the simplest mechanochemical reaction) can be represented as follows.[31] Two atoms forming a bond are spaced by distance r_0 and are connected by springs to the walls of the surrounding structure. The energy of bond breakage U_{br} can be represented as the sum of the potential energy of the bond U_{bond} and the elastic strain energy U_{el} of the structure to which the atoms belong. The latter parameter varies as a function of the displacement of atoms from the position where they form the bond towards the equilibrium position with respect to the structure to which they are linked (corresponds to a certain positive value of bond rigidity $k_{s,str}$)

$$U_{el} = \frac{1}{2}k_{s,str}(\Delta d - \Delta r)^2,$$

$$U_{br}(\Delta r, \Delta d) = U_{bond}(\Delta r) + U_{el}(\Delta r, \Delta d).$$

Here $\Delta r = r - r_0$ and $\Delta d = d - d_0$ are the differences between the atom coordinates in the stressed and unstressed states, respectively; d_0 is the distance between the ends of the spring in the nonstretched state.

Figure 2 shows the variation of the potential energy of a C–C bond as a function of Δr for various Δd values. The model parameters used in the calculation have been reported.[31] It can be seen from the Figure that as Δd increases, two potential wells appear instead of one well and subsequently they are again replaced by one potential well. As $k_{s,str}$ increases, the potential barrier decreases and finally it entirely vanishes.

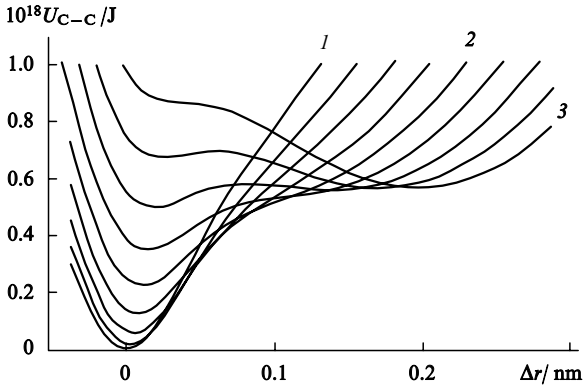


Figure 2. Potential energy of the C–C bond as a function of the distance.[31] Δd /nm: (*1*) 0, (*2*) 0.1, (*3*) 0.2.

Figure 3 presents plots for the height of the potential barrier $U^{\neq}$ *vs* the rigidity of bonds of various types for equal depths of the wells.[31] When $k_{s,str} > 90$ N m^{-1} and the characteristic times for bond rupture are $\geqslant 10^{-7}$ s, energy dissipation is small with respect to kT for all types of bonds. In the case of C–C bonds, the requirements to the rigidity are less stringent; it is sufficient that $k_{s,str} > 60$ N m^{-1}. In the case of weaker bonds, C–Si and Si–Si, the requirements are even lower.

The kinetic theory of the strength of solids, apart from the purely mechanical rupture of interatomic valence bonds induced by an external force, takes account of the destructive role of thermal motion, *i.e.* cleavage of interatomic bonds is caused by

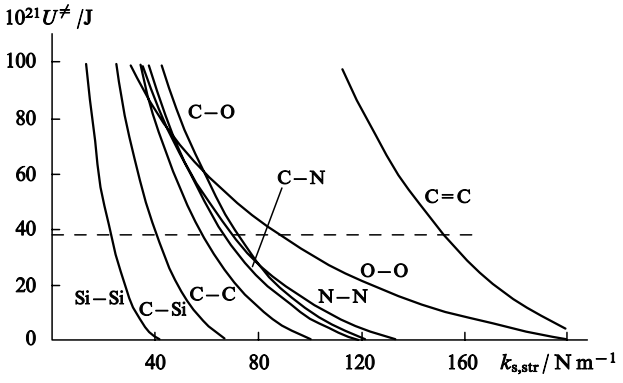


Figure 3. Height of the potential barrier for the stretching of bonds *vs* their rigidity.[31]

energy fluctuations arising due to the thermal motion of atoms rather than by the external force itself.[45] According to a concept developed in a publication [45] (thermofluctuation mechanism), two elementary stages should be distinguished in the bond rupture, namely, (1) force perturbation of interatomic bonds in a loaded body, which decreases the energy barrier to the bond cleavage and (2) splitting of stressed bonds upon thermal fluctuations.

The rate constant for the bond rupture k can be calculated from the equation

$$k = k_0 \exp\left(\frac{E_a - \sigma v_a}{RT}\right),$$

where k_0 and E_a are the preexponential factor and the activation energy for the thermal bond rupture, respectively, σ is the mechanical stress and v_a is the unit activation volume.

The rupture of valence C–C bonds in polymers has been studied most comprehensively (both theoretically and experimentally). The deformation of valence bonds in stretched samples of oriented linear polymers (polypropylene, polyamide, polytetrafluoroethylene, *etc.*) has been observed by IR spectroscopy.[45] The absorption bands corresponding to stretching vibrations of the C–C bonds in the polymer backbones shift to lower frequencies upon stretching. The band contours for stressed (stretched) samples also change. According to estimates,[45] the maximum loads of individual bonds in polymers attained on stretching are 10–20 GPa. The thermofluctuation elementary events of destruction occur within small activation volumes (commensurable with the volume of atoms) upon great overstress.

It has been assumed [46–48] that not only rupture of stretched bonds can be induced by thermofluctuations in a stressed polymer but also self-ionisation of macromolecules accompanied by ejection of electrons. A calculation of the electronic spectrum of a macromolecule with stretched C–C bonds showed [47] that the elongation of a bond gives rise to a local electron level; its energy for a factor of two elongation is ~4–5 eV, which is close to the energy of charge separation in a polymer.

The electrons having been liberated under the action of mechanical stress can be captured by traps (molecules with large electron affinity, structure defects) and are again released when the traps have been destroyed; this accounts for the mechanical emission of electrons, which has been found to accompany stretching of films and grinding of some polymers [polyethylene (PE), polyethylene terephthalate] and organic crystals.[46,48,49]

The decrease in the ionisation potential of molecules subjected to mechanical stresses has been described by quantum-chemical methods.[27,30] Figure 4 shows the calculated plot for the variation of the ionisation potential I as a function of bond angles in the propane molecule.[27] It can be seen that an increase in the deformation of the molecule results in lower I values.

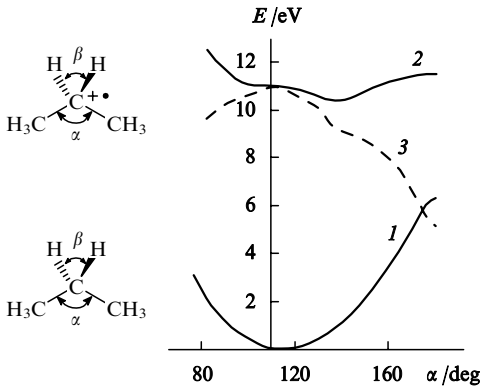


Figure 4. Quantum-chemical calculation for the change in the ionisation potential upon deformation of bond angles α and β ($\alpha = \beta$) in the propane molecule.[27]
Curves (*1*) and (*2*) show the potential energy (E) of propane and its radical cation, respectively; curve (*3*) is the difference between curves (*2*) and (*1*).

Apart from the mechanical emission of electrons, some other experimental results cannot either be interpreted in terms of the thermofluctuation mechanism. Firstly, the compositions of the molecular products of thermally and mechanically induced destructions are different.[25,26,45] The products of mechanical destruction contain no heavy fragments of polymer chains, which are typically present in the case of thermal degradation. The formation of light products on mechanical destruction indicates that the vibrational energy is distributed non-uniformly, being located in regions with a size of not more than 10 Å. Secondly, mechanical destruction of some polymers (PMMA, the three-dimensional epoxy polymer based on diglycidyl ether of resorcinol and *meta*-phenylenediamine, and ebonite) has been found to give high-energy molecular products.[25,26] The kinetic energy of these species was estimated using the time-of-flight mass spectrometer equipped by a device for high-speed detection of molecules. The velocity of the flight of the molecular products formed was used to calculate the translation temperature, which amounted to 2000 – 5400 K for the above-mentioned polymers.

The appearance of vibrationally excited states upon destruction of a PMMA sample was confirmed by thermal radiation spectra.[50] It can be seen from Fig. 5 that radiation consists of two components — Planck's radiation and a characteristic narrow emission band at 8.3 μm, which appears 10 – 60 μs after the sample fracture; this band is related to deactivation of the vibrationally excited centres, which arise during destruction of the sample and whose nature is unknown. Analysis of the spectra

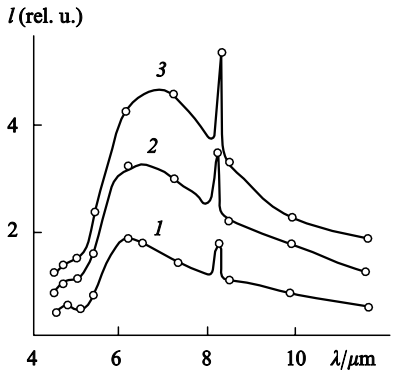


Figure 5. Heat radiation spectra recorded during fracture of a PMMA sample.[50]
Time elapsed after the onset of destruction 10 (*1*), 20 (*2*) and 30 μs (*3*).

obtained led to the conclusion that the average warming of the sample during the polymer fracture does not exceed 200 °C.

In a series of publications (see a review[25] and the studies cited therein), the destruction of a stretched chain of atoms has been studied by methods of molecular mechanics. Studies[25–27] on mechanodestruction of one-dimensional models of polymer chains consisting of 50 and 100 carbon atoms led the researchers to the conclusion that solitons play the crucial role in mechanodestruction. Over a long period (~10 ps) after the rupture of a stretched chain, the elastic energy stored in the chain is not thermalised and no thermal fluctuations (in the generally accepted sense[45]) occur. It was shown that movement of high-energy solitons may be accompanied by the formation of C – C double bonds and by discharge of the side-chain atoms. It was shown that rupture of one chain may yield several high-energy molecular products capable of inducing destruction of the adjacent polymer chains; thus, chain branching is possible.

All the models for bond rupture known to date are one-dimensional and are restricted to the views of classical mechanics. Only the first attempts to pass from one-dimensional to two-dimensional models have been undertaken.[51]

Nevertheless, the one-dimensional chains considered above can be accepted as a satisfactory approximation to real linear macromolecules. Description of the mechanically induced bond rupture in three-dimensional systems (cross-linked polymers and low-molecular-mass crystals) is a more complicated task, none of the models presented being suitable for this purpose.

b. Formation of free radicals

Free radicals resulting from the rupture of valence bonds during mechanically induced destruction of many polymers and some low-molecular-mass compounds have been detected by EPR.[23,24,52] The appearance of 'mechanical' macroradicals was observed on stretching of films and fibres and on grinding of linear and three-dimensional polymers in a mortar, in a mill, *etc.* The EPR spectra of 'mechanical' macroradicals have been thoroughly studied, which permitted identification of the type of bond being cleaved in each polymer; it was found that the covalent bonds in the polymer backbones and cross-links (or bridges) undergo homolytic cleavage. Thus vinyl polymers [PE, polypropylene, poly(methyl acrylate), PMMA, polystyrene (PS), *etc.*] and polypeptides [poly(amino acids), proteins] undergo cleavage of C – C bonds; in the case of carbon-and-oxygen polymers [polyformaldehyde, poly(ethylene oxide), polyesters and three-dimensional polyesteracrylate], C – C and/or C – O bonds are split; for ladder and three-dimensional network organosilicon polymers [PMSSO and polyphenylsilsesquioxane (PPSSO)], rupture of the Si – O bonds is observed, and in some polypeptides (trypsin, insulin, serum albumin), cleavage of C – C and C – S bonds occurs.

When polymers are subjected to mechanical treatment in a mill, the rate of accumulation of macroradicals (dR/dt) in the beginning of the process is constant and then it gradually decreases and approaches zero; thus, the concentration of macroradicals reaches a limiting value. The kinetics of radical accumulation are described by the equation[24]

$$\frac{dR}{dt} = W_d - W_r , \qquad (1)$$

where W_d is the rate of bond rupture, equal to $k_d[M]$; W_r is the rate of the decay of radicals upon interaction with one another, equal to $k_r[R]^2$; [M] is the concentration of bonds that can be cleaved; [R] is the concentration of macroradicals; k_d and k_r are effective rate constants for these reactions in the solid phase (see below).

At the beginning of the mechanical grinding when $W_d \gg W_r$, $(dR/dt)_0 \cong W_d$, *i.e.* when the intensity of the mechanical energy supply is constant, the rate of destruction depends only on the polymer nature. The rate of destruction in laboratory vibrational mills with energy input of 1 – 10 W g^{-1} at temperatures of 100 – 300 K amounts to 10^{14} – 10^{16} g^{-1} s^{-1}. The steady-state concentration of free radicals $[R]_{lim}$ (for $dR/dt = 0$) in linear

flexible-chain polymers is $(1-5)\times 10^{18}$ g^{-1} and that for rigid-chain (especially three-dimensional) polymers is $10^{19}-10^{20}$ g^{-1}.

The relative rates of destruction of various polymers during grinding under identical conditions are compared in Table 1. The rate of bond rupture is determined, first of all, by the rigidity of the structure. It increases on passing from flexible-chain PE to more rigid PS and then to polypeptides, the structures of which are noted for special rigidity owing to the presence of peptide bonds in the backbone and a dense network of hydrogen bonds. The maximum destruction rates were detected for three-dimensional polymers (glyceromaleate, α,ω-diethylene glycol phthalatedimethacrylate).

Table 1. Relative rates of mechanical destruction of polymers at $T\simeq 100$ K.[24]

Polymer	M_w	M_n	$(dR/dt)_{rel}$ (see [a])
PE	290 000	–	1
PS	300 000	–	17
PPSSO	450 000	–	20
PEM [b]	–	–	120
Collagen	–	290 000	30
Subtilisin	–	27 000	55
Serum albumin	–	67 000	45
Trypsin	–	24 000	40
Insulin	–	5 733	6
Gramicidin	–	1 140	1.5

[a] The rate of destruction of PE was taken to be unity.
[b] PEM is a cross-linked polymer of α,ω-diethylene glycol phthalatedimethacrylate.

The rate of mechanical destruction and, hence, of the formation of free radicals decreases with a decrease in the molecular mass of the polymer. Thus the rate of formation of radicals in insulin, which has the lowest molecular mass among the series of proteins studied, is 7–9 times lower than those in other proteins.

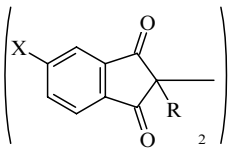
The question of the limiting molecular mass M_{lim} or the limiting degree of polymerisation n_{lim} below which the mechanical destruction of covalent bonds is terminated and only weak intermolecular bonds are broken has arisen repeatedly in the mechanochemistry of polymers.[1,24] The n_{lim} value depends on the chemical structure of the polymer and the relationship between the strengths of valence and intermolecular bonds and can be roughly estimated from the expression

$$U = n_{lim} U_{coh}, \qquad (2)$$

where U is the strength of a valence bond being cleaved and U_{coh} is the cohesion energy for a monomer unit. Expression (2) does not take into account the structural inhomogeneity of a real polymeric material and the stress gradient.

The cohesion energy is especially large for polymers which contain hydroxy, carboxy, amino and other groups which form intermolecular hydrogen bonds (for polypeptides U_{coh} reaches 40–50 kJ mol^{-1} per amino-acid residue). For these polymers, low n_{lim} and M_{lim} values should be expected. Indeed, for polyethylene $n_{lim}\simeq 100$, while in the case of polypeptides, $n_{lim}\simeq 6$. Therefore, free radicals have been detected after mechanical treatment of relatively low-molecular-mass cyclopeptides containing only ten (gramicidin) and twelve (bacitracin) amino-acid residues in the ring.[52]

Free radicals are formed when some low-molecular-mass organic compounds are subjected to high pressure together with shear deformation. To detect the radicals, a special resonator has been designed for an EPR spectrometer, which acts simultaneously as one of the anvils.[16,17,53] Thus in arylindandione dimers



X = H, Cl, NMe_2; R = *p*-$Me_2NC_6H_4$

destruction involves the $C_\alpha-C_\alpha$ bond, the strength of which ($U\simeq 70$ kJ mol^{-1}) is comparable with the U_{coh} value. It was found that hydrostatic pressure (up to 0.7 GPa) without shear strain does not induce the formation of radicals, *i.e.* it is the shearing component of the mechanical stress that causes the bond rupture.

Fig. 6 shows the dependence of the yield of free arylindandione radicals (in relative units) on the angle of rotation of the anvils at a constant pressure.[16] When the angles of rotation are small, the yield of radicals rapidly increases (curves *1*, *2*, the linear section), *i.e.* the radical generation process predominates. An increase in the angle decreases the yield of radicals and their recombination starts to predominate. Ultimately, as in the case of mechanodestruction of polymers (see above), the concentration of radicals reaches a limiting value.

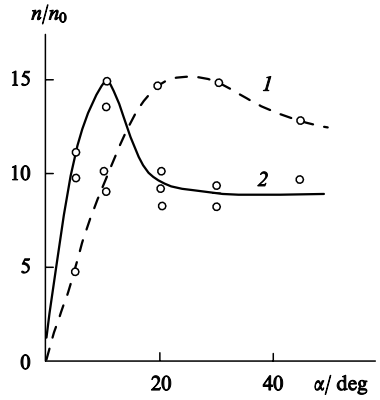


Figure 6. Yield of arylindandione radicals *vs* angle of rotation of the anvils α at a pressure of 7 (*1*) and 12 kbar (*2*);[16]
n_0 is the initial concentration and n is the current concentration of reacting species.

Under the same conditions, the EPR spectrum of C_{60} fullerene was found to exhibit a signal which was assigned to the carbon radicals formed upon destruction of the C_{60} molecules.[53] The rate of generation of these radicals is comparable with the rate of generation of arylindandione radicals ($\sim 10^{16}$ g^{-1} s^{-1}).

Indirect evidence pointing to the cleavage of valence bonds to give free radicals has been obtained under the action of an indenter, shock waves and vibratory grinding of the crystals of some nitro compounds.[49] For example, minor concentrations (10^{16} g^{-1}) of $\dot{N}O_2$ radicals were detected by EPR spectroscopy upon vibratory grinding of pentaerythritol tetranitrate or cyclotrimethylenetrinitramine. It was suggested [49] that in this case, the formation of paramagnetic centres is related to the effect of the radiation which arises upon the fraction of crystals. To elucidate the reasons for the appearance of paramagnetic species more precisely, further studies are required.

Mechanical destruction in the solid phase can be represented as a sequence of the following stages:[54,55]

$$R-R \xrightarrow{k_i} (R^{\bullet}\cdots R^{\bullet}) \xrightarrow{k_m} R^{\bullet} + R^{\bullet},$$

and the effective rate constant for the destruction, k_d, can be represented as follows:

$$k_d = \frac{k_m k_i v}{k_m + k_i}. \quad (3)$$

The first stage is a reaction characterised by the rate constant k_i and resulting in the formation of ($R^{\bullet}\cdots R^{\bullet}$) radicals, which occur in unit volume or in cage v. The k_m constant characterises departure of the radicals from the cage. The molecule in the pre-rupture state is stretched, and after bond cleavage, the radicals are removed from each other and leave the unit volume. The rupture of the bond rather than the emergence of the radicals from the cage is the limiting step in the destruction, *i.e.*, $k_i \ll k_m$.

III. Free-radical reactions

The free radicals having formed upon the mechanical destruction enter into ordinary free-radical reactions — recombination, decomposition, addition and substitution. The reactions occurring in the field of mechanical stress should be distinguished from those proceeding after the field has been removed (post-effect). The former type of reaction would involve most likely mechanically activated species. In addition, mechanical treatment causes plastic deformation of the material and migration of particles. In the latter type of reaction, the role of mechanical action reduces mostly to the generation of radicals, while the subsequent free-radical processes obey the rules inherent in them.

Virtually all of the mechanochemical free-radical reactions described to date occur in the solid phase; therefore, the specific features of the kinetics of solid-phase reactions should be taken into account.

1. Recombination

The elementary step of radical interaction (recombination) in the solid phase is preceded by the step in which they approach each other. This can occur either as chemical migration of a free valence or as physical migration of the reacting species.[23, 24] In the former case, recombination is a complex process consisting of separate elementary steps. (Some of these reactions are considered below.) In the latter case, recombination kinetics are determined by the mobility of radicals. The decay of macroradicals in a polymer matrix having been subjected to mechanical grinding occurs near the glass transition temperature T_g.[24] At this temperature, the segmental mobility of the polymer chains is unfrozen and the radicals become able to move large distances and meet one another.

The decay of radicals in the field of mechanical stress, *i.e.* under conditions of forced mobility of reacting species, is a specific case. The effective rate constants for recombination of free radicals during grinding in a mill can be estimated from the kinetics of accumulation of free radicals.[24, 54]

When $dR/dt = 0$, the rate constant for recombination k_r has the form [see Eqn (1), Section II.2.b]

$$k_r = \frac{W_d}{[R]^2_{lim}}.$$

Depending on the nature of the polymer and the energy input of the mill, the k_r values at 100–300 K range from 10^{-24} to 10^{-21} cm^3 s^{-1}.

Radical recombination can be represented by the following scheme:

$$R^{\bullet} + R^{\bullet} \xrightarrow{k_m} (R^{\bullet}\cdots R^{\bullet}) \xrightarrow{k_i} \text{molecular products.}$$

In the step characterised by the constant k_m, the radicals approach each other under the action of plastic deformation caused by mechanical stress. Using Eqn (3) provided that $k_m \ll k_i$, we obtain $k_r = k_m v$. The volume of a cage v is approximately 5×10^{-22} cm^3, and the frequency of the translation of radicals during mechanical treatment of the material in the mill (80–100 K) is 10^{-3} to 1 s^{-1}.

Recombination of radicals in the solid phase is characterised by a distribution of rate constants with the boundary values k_{max} and k_{min}. This may be due to the fact that the local reaction conditions — the size of the cage, mutual orientation of the reacting species, the closest environment, *etc.*— are different.[16, 53, 56–58] Species interacting in any system can be characterised at any instant by the distribution function $n(k,t)dk$, which determines the number of species that react in unit volume at instant t with a rate constant k ($k_{min} \leqslant k \leqslant k_{max}$). Since species can migrate between various fractions of the distribution function (*i.e.*, between states with different k), it becomes 'intermixed'. The form of 'intermixing' of the distribution function is determined by the processes that induce the changes in the kinetic properties of the reacting species. In particular, mechanical dispersion brings about 'mechanical intermixing' of the distribution function.[58]

If mechanical intermixing results in the reaction rate constant k becoming equal to k_{max}, this means that the reaction occurs under kinetically controlled conditions. However, a different regime when $k_{min} \ll k \ll k_{max}$ and the reaction is controlled by diffusion is more frequently encountered in practice.

The post-effect recombination can be described satisfactorily by equations of polychronous kinetics.[16, 53]

$$\frac{n}{n_0} = \left(\ln\frac{k_{max}}{k_{min}}\right)^{-1}(-\ln k_{min} - \ln n_0 t).$$

The difference between k_{max} and k_{min} for arylindandione radicals reaches five orders of magnitude. The k_{max} value depends only slightly on the pressure applied and on the angle of shear and is approximately 5×10^{-20} cm^3 s^{-1}. Thus, shear strain and pressure scarcely influence the rates of the fastest reactions but do influence the rates of the slowest ones.

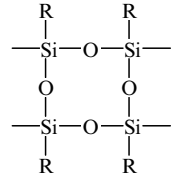
Obviously, the formation of free space and creation of a favourable arrangement of radicals are the limiting steps for radical recombination.

2. Radical decay

It is known[24, 59] that mechanical treatment of polymers is accompanied by decay of macroradicals. In macroradicals, the bond located in the β-position to the unpaired electron is weakened; the activation energy for the rupture of this bond in hydrocarbon radicals in the gas phase is about 100–120 kJ mol^{-1} and in some cases [*e.g.* in the $-CH_2\dot{C}MeX$ radicals in PMMA (X = CO_2Me) and polyisobutylene (X = Me)], it decreases to 50–70 kJ mol^{-1}.

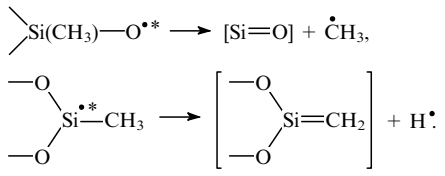
Mechanodestruction of polyformaldehyde, polyisobutylene and polyorganylsiloxanes at low temperatures, *i.e.* under conditions when the thermal decay of macroradicals occurs at an extremely low rate, has been found to give light volatile products.[24, 60]

Thus the light products of mechanodestruction obtained by grinding of PMSSO in a mill at temperatures of $\leqslant$200 K include mostly hydrogen, methane and ethane; those in PPSSO consist of hydrogen and benzene.[60]



R = Me (PMSSO), Ph (PPSSO).

The compositions and the conditions of formation of products imply that hydrogen atoms and $\dot{C}H_3$ and $\dot{C}_6H_5$ radicals are formed during the mechanodestruction. Presumably, the mechanical destruction of polymers gives rise to vibrationally excited macroradicals, which then decompose to yield low-molecular-mass radicals. Thus destruction of PMSSO involves the following processes:



The formation of hydrogen atoms was proved experimentally.

Figure 7 *a* shows the kinetic curves for the formation of H_2 and CH_4 and for the accumulation of free radicals ($R^{\bullet}$) during destruction of PMSSO. The diffusion of light species ($H^{\bullet}$ and $\dot{C}H_3$) results in migration and decay of the free valence; therefore, the amount of macroradicals observed in the destruction of PMSSO is always lower than the amount of monomeric products (per g of the polymer). The evolution of hydrogen and the formation of CH_4, C_2H_6 and $R^{\bullet}$ are compared in Fig. 7 *b*; the plot was constructed using the results of a large number of experiments, in which the intensity of destruction of PMSSO varied by a factor of up to 50 (various conditions of mechanical treatment — duration of grinding, design of the working vessel, *etc*., were used). Irrespective of the destruction intensity and dispersion conditions, the total amount of the volatile products evolved in the PMSSO destruction exceeds ~4.5-fold the number of free radicals observed. The overall rate of formation of low-molecular-mass radicals ($H^{\bullet}$ and $\dot{C}H_3$) is higher than the rate of formation of macroradicals by a factor of 8–9. These data attest to a very high (~0.9) probability of decomposition of 'hot' macroradicals.

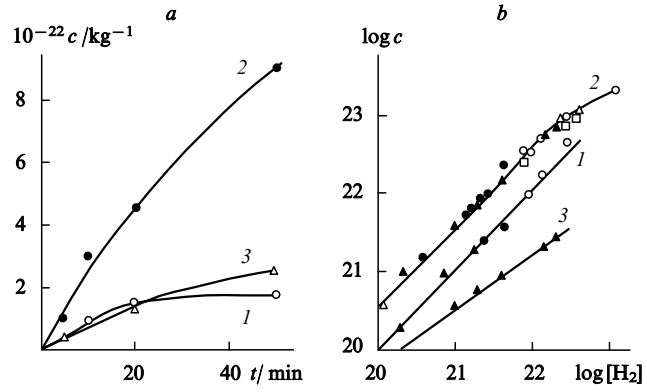


Figure 7. Kinetics of accumulation of radical and molecular products (*a*) of the mechanical destruction of PMSSO and comparison of their concentrations (*b*);[60]
(*a*) (*1*) [$R^{\bullet}$], (*2*) [CH_4], (*3*) [H_2]; (*b*) (*1*) [$R^{\bullet}$], (*2*) [CH_4], (*3*) [C_2H_6] (different designations refer to different rates of formation of hydrogen and different conditions of mechanical destruction).

In the case of PPSSO, the rates of formation of volatile products and free radicals are commensurable and the total rate of formation of low-molecular-mass radicals ($H^{\bullet}$ and $\dot{C}_6H_5$) is twice as high as the rate of formation of macroradicals; the probability of decomposition of 'hot' radicals for PPSSO is about 0.6–0.7.

The mechanical treatment of polymers yields internal macroradicals, *i.e*. radical products of interaction of the primary terminal macroradicals with surrounding macromolecules (see Section III.3). It has been assumed that the internal macroradicals decompose during mechanodestruction to give terminal radicals and unsaturated compounds; after that, the terminal radicals interact with macromolecules to give internal macroradicals, *i.e*. a chain reaction occurs.[61] However, experiments with polyethylene samples containing high concentrations of internal radicals, prepared by exposure of the samples to radiation, demonstrated that the role of mechanically induced destruction of internal radicals is relatively insignificant, recombination being the main pathway for the decay of these radicals.[62] This may be due to the non-uniform distribution of elastic energy among individual bonds in an amorphous solid; as a consequence, the ratio between the rates of rupture of weakened bonds (in the internal radicals) and normal bonds in macromolecules is determined by the probability of energy localisation on these bonds rather than by the ratio of their strengths.

3. Hydrogen atom transfer

The influence of mechanical stress on the free-radical transfer of a hydrogen atom has been considered theoretically using the model of the symmetrical process

$$H_3C^{\bullet} + HCH_3 \longrightarrow H_3CH + {}^{\bullet}CH_3, \qquad (4)$$

which occurs under normal conditions with a high activation energy ($\simeq$60 kJ mol^{-1}).[31] The calculation of the influence of methane compression on the height of the barrier to reaction (4) showed that within the framework of this model (extended LEPS potential and *ab initio* calculation methods), at a compression force of 3.6 nN, $U^{\neq} = 0$. However, at room temperature, there is no need to diminish the barrier to zero. Thus at a compression force of 1 nN, $U^{\neq} \simeq 18$ kJ mol^{-1} and the reaction proceeds at room temperature at a plausible rate.

The influence of tensile stress on the rate of hydrogen atom transfer is considered in Section IV in relation to the reaction of ozone with polyolefins.

The following method proved to be fruitful for studies of low-temperature free-radical reactions:[24] solutions of polymers frozen at 80–100 K were subjected to mechanical dispersion in a vibratory mill; the role of mechanical treatment reduced mainly to the generation of free radicals and ensuring the mass transfer and the contact between the reacting particles. It was found that reactions proceed both during treatment of mixtures in the mill and after the mill has been switched off and the temperature has increased. A series of reactions involving carbon-centred and peroxyl radicals (which are readily formed when carbon-centred radicals contact with atmospheric oxygen) have been found.

For instance,[24] it was shown that at low temperatures (~100 K), macroradicals abstract hydrogen atoms from various types of bonds, O–H (phenol), N–H (primary and secondary amines), S–H (benzenethiol and phenylmethanethiol) and C–H (alkylbenzenes, acetonitrile, malonic acid). The C–H bonds are especially strong and reactions involving these bonds are characterised by high activation energies (>30 kJ mol^{-1}). The rate constants were found to be 4–6 orders of magnitude greater than those calculated from the data obtained for the liquid phase at elevated temperatures.

The kinetics of the reaction of the macroradicals formed upon destruction of PS, polyvinyl acetate, *etc*., with malonic acid

$$R^{\bullet} + CH_2(COOH)_2 \longrightarrow RH + {}^{\bullet}CH(COOH)_2 \qquad (5)$$

was studied[24] over a broad temperature range (100 to 200 K) (Fig. 8). It can be seen from the Figure that at 100–150 K, the reaction rate scarcely depends on the temperature; at T > 150 K, it sharply increases and at T > 200 K the reaction rate cannot be measured because it is too high.[24]

The experimental rate constants for hydrogen atom transfer are in good agreement with those calculated with allowance for the tunnelling of hydrogen through the potential barrier.

The hydrogen atom transfer determines the migration and stabilisation of radical states in polymers. Thus it is known[23,24] that the radical products of mechanical destruction of polymers contain, even at low temperatures (~80 K), internal macroradicals, resulting from abstraction of hydrogen atoms from polymer chain units.

Yet another example of hydrogen atom transfer in polymers is provided by the reaction of peroxyl radicals with macromolecules, which is the rate-determining step in the low-temperature oxidation of polymers.[58]

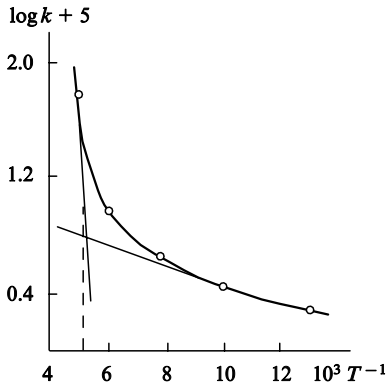


Figure 8. Temperature dependence of the rate constant for reaction (5).[24] The circles show the experimental results and the curve is based on calculations with application of the tunnelling correction.

$$ROO^{\bullet} + R'H \longrightarrow ROOH + {}^{\bullet}R'$$

This reaction was studied for PMMA and PS over a wide temperature range *in vacuo* after termination of mechanical treatment. As for other reactions occurring in the solid phase, in this case, too, kinetic non-equivalence of the reacting species was discovered; the distribution function of the 'mechanical' peroxyl radicals in PMMA and PS over rate constants at 210 – 300 K has a hyperbolic shape[58] (see also Section III.1). For instance, in polystyrene, the rate constants for individual fractions of the distribution function can differ by ten orders of magnitude:

$$k_{max} = 3.8 \times 10^8 \exp\left(-\frac{43}{RT}\right) \text{ and } k_{min} = 1.3 \times 10^{12} \exp\left(-\frac{88}{RT}\right)$$

(the activation energy is expressed in kJ mol^{-1}).

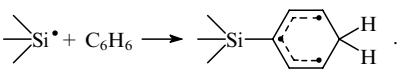
Thus, study of mechanochemical reactions of hydrogen atom transfer resulted in the elucidation of interesting specific features of the reaction kinetics, namely, tunnelling of a hydrogen atom at low temperatures, non-equivalence of the reacting species in the solid phase and 'mechanical intermixing' of the distribution function. However, no influence of mechanical stress on the activation energy for the hydrogen atom transfer was found.

4. Addition

A study of mechanical treatment of mixtures of polymers with monomers in a vibratory mill provided experimental data on the addition of free radicals to C=C bonds.[24] It was found that at 80 – 100 K, the $-CXX'\dot{C}H_2$ and $-CH_2\dot{C}XX'$ macroradicals (X = H, Me; X′ = Ph, CO_2Me, OCOMe) readily enter into the reaction

$$R^{\bullet} + CH_2 = CXX' \longrightarrow RCH_2\dot{C}XX'.$$

Under the same conditions, carbon-centred and silyl macroradicals add to benzene and its derivatives to give radicals of the cyclohexadienyl type,[63,64] for example,



The kinetics of the reaction

$$-CH_2\dot{C}(Me)CO_2Me + CH_2{=}CHPh \longrightarrow$$
$$\longrightarrow -CH_2C(Me)(CO_2Me)CH_2\dot{C}HPh,$$

which occurs on mechanical treatment of the initial compounds in a vibrational mill, has been studied in the 80 – 143 K temperature range.[24] At 80 K, the reaction does not proceed, and at 113 – 143 K the dependence of the rate constant on the temperature obeys the Arrhenius equation. The activation energy for the reaction (21 kJ mol^{-1}) is close to the activation energy for the same reaction in the liquid phase at 280 – 330 K.

Thus, no mechanochemical effects were found in the studies of addition reactions with relatively low activation energies. Apparently, these effects could be found for reactions with higher activation energies.

The role of mechanical stress in free-radical reactions studied to date is to initiate the formation of macroradicals and to ensure mass transfer (to let the reagents meet each other). No influence of mechanical treatment on the activation energy of these reactions was found.

IV. Oxidation and hydrolysis

The influence of mechanical stress on the potential barriers can be clearly followed for some reactions (oxidation, hydrolysis). Acceleration of oxidation under tensile stress was discovered by Kuz'minskii *et al.* back in 1953 (oxidation of elastomers by atmospheric oxygen).[65]

Krisyuk *et al.*[28,30] carried out oxidation of polyolefins by ozone.

$$RH + O_3 \longrightarrow [R^{\bullet} + HO^{\bullet} + O_2] \longrightarrow ROH + O_2$$

The oxidation (sorption of ozone and formation of free radicals) of oriented polypropylene films is accelerated 2 – 5-fold when a tensile stress σ ranging from 33 to 145 GPa is applied.

Mechanical stress accelerates hydrolysis of polyamides; this was first observed by Bershtein[66] and then studied by Krisyuk *et al.*[29,30] Both the oxidation of polyolefins with ozone and the hydrolysis of polyamides are accelerated on stretching of these polymers according to an exponential pattern (in the temperature range of 328 to 369 K)

$$\ln\frac{k}{k_0} = \frac{\alpha\sigma}{RT}, \tag{6}$$

where k_0 is the rate constant for the reaction (k) in the absence of tensile stress σ. The constant α characterises the sensitivity of the reaction to stress and depends on the polymer structure. This constant is defined by the equation

$$\alpha = \phi(l^{\neq} - l_0)s, \tag{7}$$

where ϕ is the overstress coefficient, which depends on the structure of the polymer material, $l^{\neq}$ and l_0 are the lengths of the reaction fragment in the transition and initial states, respectively, and s is the cross-section of the molecule.

Experimental data on the acceleration of oxidation of polypropylene by ozone are presented in Fig. 9 *a*, and the data for the hydrolysis of polycaproamide are shown in Fig. 9 *b*; these results confirm the validity of Eqn (6).

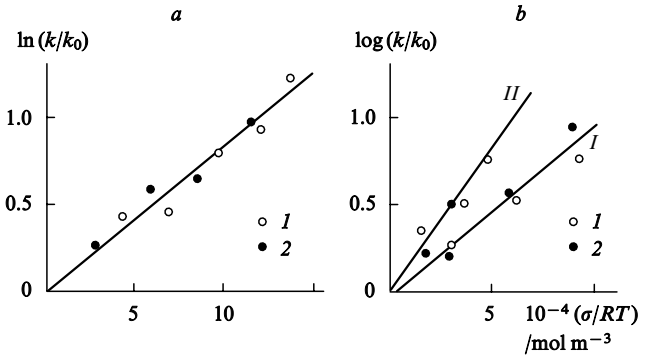


Figure 9. Rate constants for ozonisation of polypropylene (*a*) at 291 (*1*) and 313 K (*2*) and for hydrolysis of polycaproamide (*b*) at 393 (*1*) and 113 K (*2*) *vs* mechanical stress.[30] The stretching ratio of the samples is 6 (*I*) and 3 times (*II*).

It has been shown [28] that an increase in the rate of polyolefin oxidation cannot be explained either by the change in the diffusion and sorption parameters, or by the change in the molecular mobility, or by destruction of polymer chains. The change in the reactivity of the C–H bonds in polymer chains is caused by stretching and is similar to the situation with the abstraction of hydrogen atoms from strained rings.[67]

When a hydrogen atom is eliminated, the sp^3 hybridisation of the carbon atom changes to sp^2, resulting in a greater bond angle. This brings the structure closer to a transition state and, as a consequence, accelerates the reaction.

The acceleration of hydrolysis of polyamides can be interpreted at a qualitative level in a similar way. The C–N bonds in polyamide are strengthened due to delocalisation of the π electrons of the carbonyl groups, which interact with the nitrogen *p* orbitals. On stretching, the interacting orbitals move apart, the conjugation is violated and hydrolysis occurs faster. The effect of stretching resembles the influence of substituents in conformity with the Hammett–Taft equation.

Quantum-chemical calculation [30] for the cross-section of the potential energy surface for some monomers modelling polymer chains (methane, propane, butane) has shown that stretching of molecules weakens the C–H bonds. When the molecule is stretched, the energy of the initial state increases to a greater extent than the energy of the transition state, resulting in a lower activation energy for the reaction. Thus, the calculation showed that the C–H bond is actually activated and that the sensitivity of a reaction to deformation increases with an increase in the strength of this bond and with a decrease in the activity of the hydrogen acceptor.

The change in the activation energy of a reaction under the influence of a force *f* is described by the equation

$$\Delta E_a = f(l^{\neq} - l_0). \quad (8)$$

It follows from Eqns (6)–(8) that stretching of molecules would accelerate those reactions in which the formation of the transition complex is accompanied by elongation of the reactive fragment. Conversely, processes accompanied by a decrease in the length of this fragment should be retarded on stretching.

V. Mechanochemistry of proteins and polypeptides

The necessity of developing the mechanochemistry of proteins and polypeptides can hardly be overstated; indeed, study of the mechanochemical transformations provides a key for the understanding of some phenomena occurring in living cells and organisms. During preparation of food, medicines, *etc*., proteins undergo various types of mechanical treatment (grinding, pressing); this can change their structures and properties.

The main mechanochemical processes occurring in proteins include rupture of covalent bonds in polypeptide chains, mechanically activated hydrolysis of peptide bonds and destruction of weak intermolecular bonds. Mechanical treatment can also change the catalytic activity of protein enzymes.

1. Mechanical destruction of covalent bonds

Mechanical treatment (grinding, stretching) of samples of poly(amino acids) (polyalanine, polyleucine, polyvaline), fibrillar proteins (collagen, silk), globular proteins (trypsin, subtilisin, serum albumin), oligopeptides (gramicidin, bacitracin) has been found (EPR data) to yield free radicals,[24, 52, 68–70] the EPR spectra in gelatin, collagen, silk, serum albumin, *etc*. having much in common despite the different amino-acid composition of the proteins. The experimental data accumulated by now permitted determination of the structure of the resulting free radicals and the type of bond being cleaved.

Based on the analysis of spectral characteristics of the radicals resulting from mechanical treatment of polypeptides at ~80–100 K and their transformations on heating to 200–250 K [52] and on exposure to light, [69] one can conclude that the C–C bonds are cleaved predominantly.

$$-C(O)NHC_{\alpha}HRC(O)NHC_{\alpha}HR- \longrightarrow$$
$$\longrightarrow -C(O)NH\dot{C}_{\alpha}HR + \dot{C}(O)NHC_{\alpha}HR- .$$

Initially, this affords reactive terminal radicals, which then react with polypeptide chains to give internal radicals.[52]

$$\dot{R} + -C(O)NHC_{\alpha}HR'C(O)NHC_{\alpha}HR'- \longrightarrow$$
$$\longrightarrow RH + -C(O)NH\dot{C}_{\alpha}R'C(O)NHC_{\alpha}HR'-$$

The abstraction of hydrogen from the carbon atom in the α-position with respect to the CO group is accompanied in some cases (*e.g*. in polyleucine) by its transfer from side substituents to give $-NHCH(CH_2\dot{C}Me_2)C(O)-$.[52]

In the case of trypsin, albumin and insulin, the mechanically induced cleavage of the polypeptide backbones is accompanied by rupture of the C–S bonds. [52] The C–S bonds are weaker than the C–C bonds and are destroyed more rapidly. The proportion of sulfur-centred radicals, $\dot{R}_S$, ranges from 14% to 20% of the total number of radicals formed.

In the presence of atmospheric oxygen, carbon-centred radicals (both terminal and internal) are oxidised, being thus converted into peroxyl radicals. Sulfur-centred radicals are stable and are retained unchanged up to 340–360 K, when they become sufficiently mobile to recombine.

The rate of formation of free radicals in proteins is higher than that in linear synthetic polymers (see Section II.2.b and Table 1). The rate of mechanical destruction of collagen was calculated from the rate of accumulation of free radicals and compared with the rate of decrease in the molecular mass of this protein calculated from electrophoresis data.[70] The rates of rupture of the covalent C–C bonds in collagen dispersed in a micromill (80–90 K) or in a vibratory mill (100–150 K) amount to 1.5×10^{15} and 8.0×10^{15} bonds g^{-1} s^{-1}, respectively (EPR data) or 1.8×10^{15} and 9.6×10^{15} bonds g^{-1} s^{-1}, respectively (electrophoresis data); *i.e*. the values found by two independent methods are in satisfactory agreement with each other.[70]

The above data confirm the assumption that homolytic cleavage of the polypeptide chain is the main source of free radicals during the mechanical grinding of proteins.

2. Mechanically activated hydrolysis

As shown above (see Section IV), polyamides readily undergo mechanically activated hydrolysis. The possibility of this type of hydrolysis in proteins was demonstrated in relation to trypsin;[71] the sample obtained by mechanical dispersion of this compound at 295 K was found to contain hydrolysis products, namely, *N*-terminal amino acids (glycine, tyrosine, serine and glutamic and aspartic acid). When trypsin was dispersed at a low temperature (~80 K), amino acids were not formed.

3. Breaking of weak intermolecular contacts

The breaking of weak intermolecular contacts (hydrogen bonds and hydrophobic and electrostatic interactions) brings about conformational transitions and disordering of the protein structure; in our opinion, this is the main reason for mechanical denaturation (both reversible and irreversible). The conformational transitions have also been studied for globular proteins (trypsin, subtilisin)[71, 72] and for fibrillar proteins with rod-like molecules (collagen).[73]

Curves *1* and *2* of Fig. 10 show the decrease in the intrinsic viscosity [η] of collagen upon mechanical destruction.[73] Curve *1* was constructed using experimental data and curve *2* was calculated from the equation

$$[\eta] = 1.23 \times 10^{-9} M^{1.8},$$

where *M* is the molecular mass of the polymer after mechanical destruction. It was assumed that the change in the viscosity of a

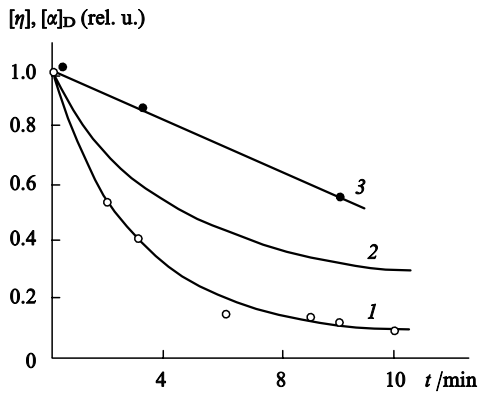


Figure 10. Variation of some properties of collagen during mechancal grinding;[73]
(*1*) and (*2*) decrease in the intrinsic viscosity [η] (*1* is experimental curve, *2* is calculated curve); (*3*) decrease in the specific optical rotation $[\alpha]_D$.

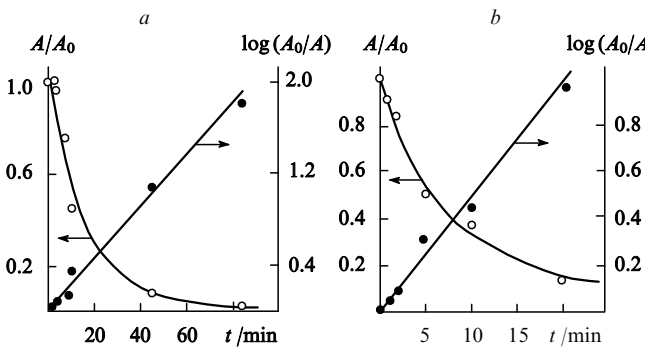


Figure 11. Kinetics of the decrease in the activity (A) of subtilisin (*a*) and trypsin (*b*) during mechanical treatment in a mill at 80 K; A_0 is the activity of the enzymes before the treatment.[72]

solution of collagen is entirely due to the decrease in the size of macromolecules caused by the rupture of covalent bonds during grinding, while the shape of the molecules remains unchanged. However, the experimental values are much smaller than the calculated ones, which might imply that the rod-like shape of macromolecules has changed.

One more piece of evidence for the change in the shape of collagen macromolecules is the substantial decrease in the specific optical rotation $[\alpha]_D$ for large degrees of grinding (see Fig. 10, curve *3*).[73, 74]

A clear representation of the change in the rod-like shape of collagen molecules (the appearance of concave molecules, spherical particles and associates of various shapes and sizes) is provided by electron photomicrographs[73] of dilute solutions of collagen samples subjected to mechanical treatment.

Thus, experimental data obtained for collagen indicate that the rupture of covalent bonds in the macromolecule to give free radicals is accompanied by the rupture of weak intermolecular contacts. This results in disordering (loosening) of the protein structure, the change in the macromolecule conformation and in 'mechanical' denaturation. At extensive stages of the process, collagen acquires the properties of flexible-chain gelatin;[73] in dilute solutions, it forms molecular coils and associates composed of several macromolecules held together by new intermolecular bonds, which arise randomly.

A water-insoluble fraction has been found in the samples of globular proteins, trypsin and subtilisin subjected to mechanical dispersion, the proportion of this fraction increasing with an increase in the duration of grinding.[71] However, its appearance is not related to covalent cross-linking, because this fraction dissolves on heating. Apparently, dispersion leads to a change in the conformation of the protein molecules, resulting in their association, referred to as 'mechanical' denaturation.

The conformational changes in trypsin molecules have also been observed by circular dichroism.[71] The decrease in the amplitude of the Cotton effect in the 250–310 nm range points to appreciable changes in the tertiary structure of the protein, which affect the local environment of chromophore groups, in particular, tryptophan.

4. The change in the catalytic and biological activity of proteins

It has been found[75–77] that on stretching a polyamide thread, the enzyme activity of trypsin or chymotrypsin immobilised on it decreases 3–6-fold. However, after termination of stretching and subsequent relaxation, the enzyme activity is restored, *i.e.* in this case, reversible deactivation of the enzyme occurs. Thus, by subjecting immobilised enzymes to mechanical treatment, one can change their conformations and control the catalytic properties.

Irreversible inactivation of enzymes was observed upon pressing (pressure $\leqslant 550$ MPa)[78] and mechanical grinding of some proteases.[71, 72] Experimental data for trypsin and subtilisin are presented in Fig. 11. Apparently, mechanical strain leads to the change in the enzyme conformation and in the microenvironment of the active site. It was found that some of the enzyme molecules completely lose their catalytic activity, and some molecules start to 'operate' at a lower rate than the molecules of the native enzyme.[72]

The influence of mechanical treatment on the thymalin — a polypeptide complex with immunomodulating properties — has been studied.[79, 80] After mild mechanical treatment in a mill, the biological activity of the preparation increases in both *in vitro* and *in vivo* experiments, which is highly important regarding the increase in its efficiency. The reasons for this phenomenon have not been elucidated yet.

VI. Mechanochemical synthesis

1. Solid-phase mechanochemical synthesis

The importance of mechanochemical synthesis among other methods of synthesis is constantly increasing. In particular, in recent years, substantial progress has been attained in the solid-phase mechanosynthesis using planetary activator mills and Bridgeman anvils.

The first studies along this line were concerned with reactions in polymer–monomer and polymer–polymer systems, resulting in modification of the initial macromolecules and formation of block and graft copolymers, which are used successfully for practical purposes. Mechanical treatment of these systems was carried out in masticators, extruders, mills, bending rolls, *etc.* More detailed description can be found in monographs.[1, 3, 4]

In this Section, we summarise the examples of solid-phase mechanochemical synthesis based on low-molecular-mass compounds carried out over the last decade.[14, 15, 18–20, 36, 81–87] The syntheses were carried out using various equipment ranging from simple mortars to planetary activator mills[8] and the Bridgeman anvils.[14] Planetary mills operate in pulse mode; the pressure created by these devices is normally about several Gigapascals. The Bridgeman anvils create a constant stress field with a pressure of up to ~ 10 GPa, and the pressure in specially designed diamond anvils can reach 550 GPa.[31]

The role of mechanical treatment is mainly to provide forced transfer of the reacting particles and to ensure their contact, although other mechanisms also contribute to the reactions.

It was found[14] that the degree of transformation of monomers into polymers in the Bridgeman anvils depends on the angle of rotation of the anvils (Fig. 12). Plastic deformation ensures mass

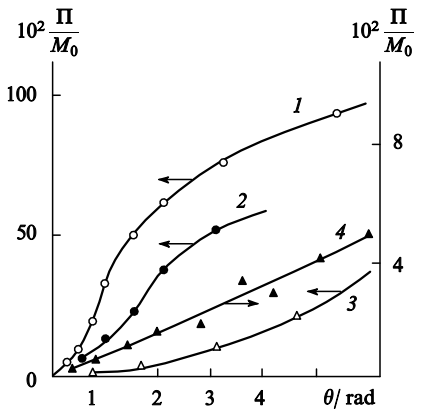


Figure 12. Yield of the polymer (Π/M_0) *vs* angle of rotation of the anvils (θ) (2000 MPa, 293 K);[14]
(*1*) acrylamide, (*2*) methacrylamide, (*3*) maleic anhydride, (*4*) trioxane (1000 MPa).

transfer and mixing of reactants and removes the reaction products from the reaction area.

Solid-phase mechanochemical reactions occurring under conditions of explosion induced by strong uniaxial compression have been found;[81] the characteristic times of these reactions are only $10^{-5}-10^{-7}$ s.

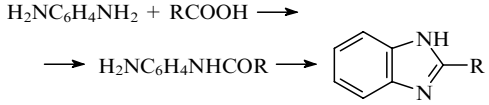
Two mechanisms of mechanochemical reactions are most likely: (1) under the action of mechanical stress, intermixing at the molecular level occurs and (2) the product is formed on the surface of macroscopic reacting species. However, in the case of explosion reactions, the high rates cannot be explained in terms of either of these mechanisms. It has been suggested[82] that an explosive chemical reaction is initiated by a shock wave, which loosens the lattice of reacting particles for the period of the relief of elastic stress and thus makes the system quasi-homogeneous.

Several examples of mechanochemical syntheses carried out under various conditions are presented below.

Diels–Alder reaction. The action of shear stress on solid cyclopentadiene and cyclobutadiene (2–5 GPa, ~150 K) gives rise to dicyclopentadiene and vinylcyclohexene, respectively.[83]

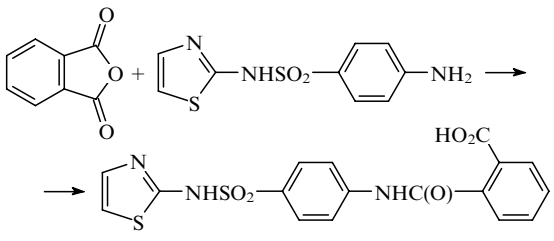
Synthesis of amides (acylation). Solid mixtures of aromatic amines with carboxylic acids react (pressure up to 8 GPa, rotation angle of anvils up to 720°, temperature 200–300 K) to give amides.[84] The yields reach 50% or even more; the rates of the transformations are greater than the rates of the same processes in the liquid phase by factors of hundreds of thousands.

In the case of *ortho*-phenylenediamine, cyclisation of the resulting amides yields the corresponding benzoimidazoles.



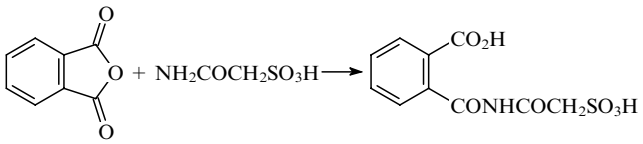
The cyclisation is accelerated by mechanical stress to a lesser extent than acylation.

Mechanochemical synthesis of phthalylsulfathiazole has been accomplished[18] by combined mechanical treatment of phthalic anhydride and sulfathiazole.



The product (formed in a nearly quantitative yield) is not contaminated by phthalazoleimide or phthalates, which are normally produced in the liquid-phase synthesis.

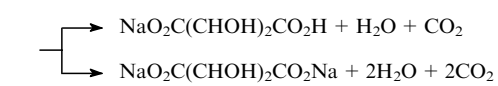
Generally, phthalic anhydride readily enters into solid-phase mechanochemical reactions. Thus its pressure-initiated reaction with sulfacetamide gives rise to *N*-phthalylsulfacetamide.[85]



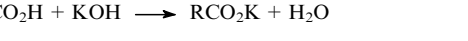
It should be noted that reactions with phthalic anhydride do not stop after termination of mechanical treatment.

Synthesis of polypeptides. The action of high shearing pressure on amino acids gives peptides. As in the case of amides, the reaction affords predominantly linear products rather than cyclic compounds (dioxopiperazines), which are usually formed in these reactions carried out in solutions and melts.[87]

Synthesis of metal carboxylates. A mixture of sodium hydrogen carbonate with tartaric acid has been found[88] to react under elevated pressures (1–15 kPa) yielding sodium tartrates



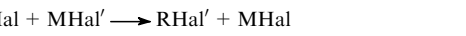
The action of high pressure in combination with shear strain under conditions of explosion induces the reactions



giving salts of organic acids in 70%–80% yields.

The reaction of sodium carbonate with benzoic or salicylic acids was carried out in a planetary activator mill.[89] The process has obvious advantages over the conventional liquid-phase synthesis — it occurs over one technological stage instead of standard six or seven stages, does not require the use of water, *etc*.

Halogen exchange



Hal = Br, I; Hal′ = F, Cl, I; M = Li, Na, K, Cs

occurs both with aromatic[20,21] and aliphatic (R = Me, Et, Pr^n) compounds.[90]

Synthesis of organometallic compounds. It has been shown that mechanochemical synthesis of organometallic and coordination compounds is, in principle, possible.[91–93] Cyclopentadienyl, dicarbollyl, β-diketonate and other organometallic derivatives were synthesised.

2. Mechanosynthesis and nanotechnology

One task of molecular nanotechnology, which has been developing successfully over the last 10–15 years, is the assembling of complex chemical structures. It has been shown[31] that a chemical reaction can, in principle, be carried out under conditions when it is controlled by forced mechanical migration of individual reacting species (atoms, molecules, free radicals). The work on the transfer of species is done by molecular mills and manipulators such as an atomic force microscope (AFM), scanning tunnelling microscope (STM) and some other devices. Using these instruments, atoms or molecules can be placed (positioned) into a definite position with respect to each other (with allowance for the distance between them and orientation needed for the reaction to be initiated). For example, AFM permits the surfaces to be positioned in relation to one another with an accuracy of ~0.01 nm with a compression force of up to 0.01 nN. STM was used to position xenon atoms (4 K) on the surface of a nickel single crystal, which resulted in the formation of a linear heptamer.[94] The capacities and prospects for the development of the 'posi-

tional' mechanosynthesis have been described in detail by Drexler.[31]

The positional mechanosynthesis is carried out *in vacuo* and differs substantially from the conventional gas- and liquid-phase syntheses. As for solid-phase reactions, the notion of concentration (the number of molecules of a given type in unit volume) is absolutely inapplicable to this type of mechanosynthesis. A certain role in the positional mechanosynthesis is played by local steric and electronic effects; however, mechanical positioning has the crucial influence on the reaction rate.

The force F acting on the particles and the 'activation' length $\Delta l^{\neq}$ are related by the expression [31]

$$\Delta l^{\neq} = -kT\left(\frac{d}{dF}\ln k_{\text{react}}\right)_T ,$$

where k_{react} is the rate constant for the reaction. Normally $\Delta l^{\neq} \simeq -0.1$ nm and possible compression forces reach 5 nN, which corresponds to $E_a \sim 300$ kJ mol^{-1}. More realistic estimates of the decrease in the activation energy due to the action of mechanical force are presented in the discussion dealing with the rupture of valence bonds (II.2.a) and free-radical substitution (III.3).

Within the one-dimensional model and the theory of transition state, the condition for the occurrence of a reaction is given by the expression

$$\Delta U^{\neq} \leqslant kT\left(\frac{t_{\text{react}} f_{\text{TST}}}{-\ln P_{\text{err}}}\right) ,$$

where $\Delta U^{\neq}$ is the height of the potential barrier, t_{react} is the time of the reaction, f_{TST} is the frequency factor (for a mechanochemical reaction with a relatively rigidly fixed arrangement of the reacting species, $f_{\text{TST}} \geqslant 10^{12}$ s^{-1}) and P_{err} is the probability of an error in a mechanochemical operation. At 300 K, assuming that $t_{\text{react}} = 10^{-7}$ s and $P_{\text{err}} = 10^{-15}$, $\Delta U^{\neq} \leqslant 20$ kJ mol^{-1}.

The positional mechanosynthesis has several advantages. Thus, unlike the conventional (diffusion mechanosynthesis), in this case, side reactions can be avoided, which is especially desirable for the synthesis of complex molecules containing a large number of functional groups. In the positional mechanosynthesis, non-planned collisions of molecules cannot occur and, hence, undesirable reactions are excluded.

However, among other factors, the applicability of this method is restricted by the fact that such mechanosynthetic systems are usually sensitive to thermal destruction; therefore, only reactions proceeding at room temperature, *i.e.* those having relatively low activation energy, can be carried out by positional mechanosynthesis.

Mechanical positioning ensures the transformation of the mechanical energy into chemical energy. It allows one to choose between alternative reaction pathways, to diminish the activation energy and to increase the effective concentration of the reactants because they are placed in the most favourable positions with respect to each other.

Presumably,[31] positional mechanosynthesis would be used for the construction of complex molecules, for example, diamond-like structures. A number of properties of diamond-like materials (strength, hardness, relatively low specific weight, *etc.*) permit them to be used in nanomechanical systems in order to perform positional mechanosynthesis of other complex molecules.

Diamond-like structures consist of polycyclic organic molecules composed of sp^3-hybridised carbon atoms.[95] Some planes, (110) and (100), contain strained reactive alkene groups, which provide for the ability of diamond-like structures to participate in synthetic transformations. The (111) plane in diamond is usually hydrogenated, which opens up the way for its chemical modification.

One modification route is based on the abstraction of a hydrogen atom, which plays an important role in the synthesis of diamonds.[95] The hydrogen abstraction can be achieved by virtue of free radicals of various structures. However, to enable positional mechanosynthesis, they should comply with definite requirements, namely, they should (a) have a very high hydrogen affinity, (b) contain no bulky groups in the structure, (c) represent a fragment of a structure that can be attached to the AFM or STM tip and used as the holder during positioning; (d) possess mechanical and chemical stability during positioning and (e) be readily generated and regenerated.[31,95]

Under the action of anisotropic compression forces ($\sim$20 GPa) at room temperature, fullerene can be converted into diamonds (see II.1.a); therefore, it might be a suitable substance for positional mechanosynthesis of diamond-like materials.

3. Polymerisation

The mechanochemical polymerisation was first discovered on grinding of acrylic and methacrylic acid derivatives (acrylamide, methacrylamide and sodium and potassium salts of these acids) in the presence of some salts, metals and oxides, which serve as initiators.[1]

High pressures ($\sim 10^3$ MPa) combined with shear stress induce polymerisation of compounds containing C=C bonds (ethylene, styrene, methylstyrene, *etc.*), C$\equiv$C bonds (acetylene derivatives), conjugated double bonds (butadiene, cyclopentadiene, *etc.*), aromatic rings (benzene, naphthalene, anthracene, *etc.*) and heterocycles (pyridine, thiophene, *etc.*) even at the temperature of liquid nitrogen.[14]

In principle, high pressures in combination with shear strain can cause reactions that do not occur under ambient conditions. For example, the activation energy for ethylene dimerisation is about 200 kJ mol^{-1}; however, under the action of pressure and shear strain, the π bond in the ethylene molecule can be cleaved. The resulting biradical [31] can either dimerise to give cyclobutane or initiate polymerisation.

It can also be claimed that the aromatic rings in benzene, pyridine, polynuclear compounds, *etc.*, can be cleaved in a similar way, although real mechanisms of these transformations are rather complex.[14]

In some cases, mechanical stress sharply accelerates polymerisation. Thus the rate constants for the mechanically initiated polymerisation of styrene, acrylamide and other monomers are 2–5 orders of magnitude greater than the corresponding constants found for these reactions in the liquid phase.[14]

Several groups of researchers [96–99] have discovered polymerisation of frozen monomers, which occurred at very high rates at low temperatures ($\leqslant$ 77 K). The influence of mechanical stress was found to be the main driving force of these processes. It has been shown [96] that local mechanical treatment (a needle prick) of frozen cyclopentadiene (77 K), prepared by the method of molecular beams, causes its chain polymerisation; similarly, a local treatment with a pin of γ-irradiated solid acetaldehyde initiates its cryopolymerisation even at 4.2 K.[99]

It was shown [99] that the local mechanical action on a frozen sample induces the formation of a primary crack, which initiates spontaneous propagation over the sample of a narrow area densely covered by an extensive network of freshly formed cracks. The chemical reaction occurs on the surface of cracks (or near them) and, in turn, create conditions for further destruction in the neighbouring area of the matrix. The solidity of the sample can be violated, for example, due to the temperature or density gradients, arising during the reaction and creating stresses, which destroy the sample. Thus, the matrix undergoes layer-by-layer dispersion under the influence of the running field of mechanical stress, and the reaction wave propagates spontaneously over the sample.

The relationship between the reactivity and mechanical stresses arising in the reaction has been studied by EPR for the unfreezing of organic crystals of diacyl peroxides having been subjected to photolysis at $\sim$15 K.[100] Radical pairs and CO_2 molecules are formed in the system and create a high local pressure. The mechanical stress thus arising relaxes as a result of movement of these molecules towards the surface.

4. Formation of molecular complexes

Mechanical treatment of two-component systems gives rise to various types of molecular complexes — charge transfer complexes, inclusion compounds and complexes formed due to acid–base interactions, hydrogen bonds or simply van der Waals forces.

Complexation of the acid–base type between phenols and amines has been found for a mixture of hexamethylenetetramine (urotropin) and resorcinol.[101,102] The reaction proceeds both during explosion initiated by compression[101] and under relatively mild conditions, namely, in a disintegrator;[102] the yields are nearly quantitative in both cases.

It has been shown that interpolymer complexes (polymeric compounds stabilised by bonds of the ionic type) can be prepared by mechanochemical synthesis under high pressure combined with shear stress.[103] Polymethacrylic acid (polymeric acid) and PMMA or polymethylvinyltetrazole (polymeric base) were used as the initial compounds.

Combined mechanical grinding of polyvinylpyrrolidone (PVP) with some additives (Ad) (chloranil, phenothiazine, hydroquinone, acridine, *etc.*) gives charge transfer complexes of the $n-\pi$ and $\pi-\pi$ types, for example, $PVP^{+}Ad^{-}$ (with chloranil) or $PVP^{-}Ad^{+}$ (with phenothiazine).[104]

The samples obtained upon trituration in a mortar of two substances able to form stable radicals, one of which being an electron donor (D) (phenols, catechols, porphyrins, *etc.*) and the other being an electron acceptor (A) (*e.g.*, quinones) have been studied by EPR spectroscopy.[105] The researchers were able to record the EPR spectra of the primary reaction products, biradical triplet complexes or radical pairs, and secondary products — free radicals.

$$DA \longrightarrow D^{+\cdot}A^{-\cdot} \text{ (or } D^{\cdot}A^{\cdot}) \longrightarrow D^{\cdot} + A^{\cdot}.$$

The triplet molecular complexes or radical pairs generated by mechanical treatment are much more stable than those prepared by photolysis of the same donor–acceptor solid mixtures. Apparently, once formed, they are quickly incorporated into the new crystal lattice arising upon mechanical treatment.

Electron transfer has also been detected on exposure of mixtures of organic compounds, electron donors and acceptors, to elastic acoustic waves.[106]

Yet another example of electron transfer is represented by mechanochemical reactions of peroxyl macroradicals with compounds containing a tertiary amino group (phenothiazine and pyrazolone derivatives), which have been studied by EPR.[63]

$$ROO^{\cdot} + MeNXY \longrightarrow ROO^{-} + MeN^{+\cdot}XY.$$

The reaction occurs during mechanical grinding of a mixture of a polymer (PS, polyvinyl acetate, *etc.*) and a substance with electron-donating properties.

Combined mechanical grinding of α- and β-cyclodextrins with acetylsalicylic, benzoic or *p*-hydroxybenzoic acid yields inclusion compounds.[107] Their formation proceeds *via* a stage of amorphisation of polymers and low-molecular-mass crystals followed by dissolution of crystals in the amorphous medium. Hungarian researchers[38] prepared inclusion compounds by grinding γ-cyclodextrin with fullerene and thus attained solubilisation of the latter substance.

The vast majority of studies dealing with the synthesis of molecular complexes are associated with new methods for the development of drugs aimed at increasing their therapeutic activity, which depends on bioavailability. It is known[33,108] that bioavailability of drugs poorly soluble in water is determined by the rate of dissolution. It was found that combined grinding of drugs with polymers of various structures leads to distribution (to a molecular level) of the drug in the polymer matrix to give molecular complexes (in the literature devoted to the technology of drugs, these systems are normally referred to as solid dispersions[33]). As a rule, this combined grinding makes it possible to increase the solubility and the rate of dissolution of hydrophobic compounds in aqueous media.[33,108,109] Meanwhile, by appropriate selection of the initial pair consisting of a polymeric carrier and a drug, the liberation of the drug from the molecular complex can also be retarded (prolonged-action preparations). Preparations of this type have been obtained, for example, by joint grinding of some substance of the benzimidazole series with microcrystalline cellulose.[110]

The polymeric matrices used for this purpose are usually natural polymers, namely, cellulose and its derivatives, starch, cyclodextrins, proteins, chitin, chitosan and pectin and some synthetic polymers [poly(ethylene oxide) or polyvinylpyrrolidone].

The majority of drugs are low-molecular-mass organic compounds containing functional groups capable of forming intermolecular hydrogen bonds (C=O, OH, NH, *etc.*). During mechanical grinding of mixtures of drugs with polymers, the intermolecular hydrogen bonds are destroyed and new hydrogen bonds with macromolecules are formed (IR-spectroscopy data[108]). Thus the molecules of benzoic, salicylic and acetylsalicylic acids, hexobarbital, *etc.* form hydrogen bonds of the $>C=O\cdots HOR$ type with cellulose and oligosaccharide molecules. Derivatives of barbituric acid form in addition $NH\cdots O(H)R$ bonds with hydroxy groups of polymers. In the inclusion compounds described above, obtained by grinding of cyclodextrins with acetylsalicylic, benzoic and *p*-hydroxybenzoic acids, hydrogen bonds link the OH groups of cyclodextrin to the C=O groups of acids.

The redistribution of hydrogen bonds during grinding of acetylsalicylic acid (Aspirin) with some fillers (cellulose, alumina) has been studied fairly comprehensively by IR spectroscopy.[39] Aspirin is responsible for an absorption band with a maximum at 1695 cm^{-1}, due to the stretching vibrations of the C=O group in the dimer. Grinding of the sample results in broadening of this band and displacement of the ν_{CO} vibration frequency of the dimer to 1700–1710 cm^{-1}, indicating the appearance of a monomeric species with an intramolecular hydrogen bond. The conversion of the dimer into the monomer is also confirmed by optical diffuse refection spectra.[39] The formation of molecular complexes of Aspirin with fillers (vibration frequency ν_{CO} = 1749 cm^{-1}) was not detected in the study cited,[39] although it had been observed previously.[111]

Upon grinding of isobutylphenylpropionic acid (iboprufen) with poly(ethylene glycol), hydrogen bonds between the carboxy groups of the acid and the hydroxy groups of the polymer (IR-spectroscopy data) and van der Waals interactions between the polymer molecules and the aromatic rings of iboprufen (electronic absorption and luminescence spectra) were detected.[111]

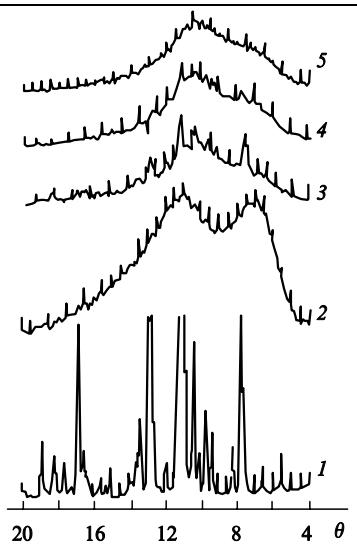


Figure 13. X-Ray diffraction patterns of sulfathiazole (*1*), polyvinylpyrrolidone (*2*) and their mixtures (*3*–*5*) after mechanical treatment for 3 (*3*), 6 (*4*) and 12 min (*5*).[112]

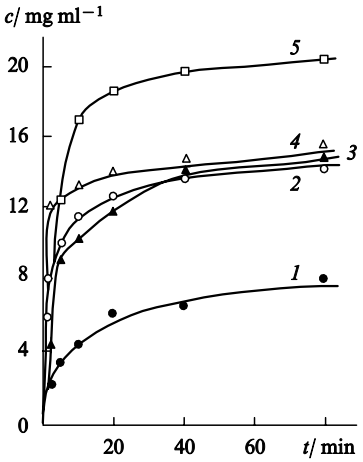


Figure 14. Change in the rate of dissolution of griseofulvin after mechanical treatment of its mixtures with polymers;[109]
(*1*) a mixture of griseofulvin with gelatin without mechanical treatment, (*2*) gelatin, (*3*) chitin, (*4*) polyethylene glycol, (*5*) chitosan.

After grinding of a drug–polymer mixture, peaks characteristic of the drug usually disappear from the X-ray diffraction patterns (an example is shown in Fig. 13).

The initial rate of dissolution of a drug after its combined grinding with polymers can increase by a factor of tens (an example is shown in Fig. 14). The increase in the solubility is especially pronounced when the mechanical treatment yields a new polymorphic modification with a higher solubility. For instance, in the case of grinding of sulfathiazole with polyvinylpyrrolidone in a planetary mill, the solubility of the drug increases almost 10-fold.[112]

Thus, the whole set of data described above, both direct (optical spectra) and indirect (the decrease in the melting point and heat of melting, the increase in the solubility and in the rate of dissolution), point to the formation of molecular complexes stabilised mostly by hydrogen bonds.

The practical importance of the molecular complexes with drugs (in particular, for increasing the bioavailability of the drug) becomes obvious from the results of bioassays, which are few in number but convincing.[33, 108, 113, 114]

VII. Conclusion

The review shows that mechanical stress induces numerous physical transformations and chemical reactions in organic compounds. They are based on the rupture of bonds, generation of free radicals, decrease in the activation energies of reactions, provision for the transport of reacting species, *etc*.; in some cases, some of the above-listed processes predominate, while in other cases, they occur and act simultaneously.

The practical potential of the mechanochemistry has been appreciated and adopted by investigators engaged in diverse branches of science. Solid-phase mechanochemical syntheses of various compounds have been performed by now. The yields in mechanochemical reactions are sometimes higher than those in similar reactions conducted in the liquid phase.

The advantages of mechanochemical synthesis include the possibility of performing it at low or room temperatures, environmental cleanness (no solvents are involved) and the simplicity of the process technology.

A mechanochemical process carried out in a reactor mill includes three main stages (a) grinding of the material in order to attain the optimum size of particles; (b) mixing of the reactants in order to attain the maximum contact between the particles (c) the reaction itself. At present, all the three stages occur simultaneously in the same device, although they require different levels of delivered energy. Apparently, for industrial implementation of mechanochemical synthesis, it would be expedient to separate the stages, *i.e*. to carry out each stage of the process in a separate specially designed reactor.[115]

Mechanochemical methods have been recognised in the technology of drug manufacture and are used to control the rate of drug dissolution and to increase their therapeutic activity.

The new promising line in mechanochemistry, positional mechanosynthesis, is closely related to the molecular nanotechnology and is regarded as technology of the XXIst century. Although the development of this line of research is only at its beginning and is now held up due to the absence of necessary equipment, there seems to be no conceptual obstacles to the design of mechanosynthetic machines.

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