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Conformational transitions of macromolecules in an eluent flow and their manifestation in the chromatography of polymers

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The behaviour of macromolecules in a free eluent flow, in a confined space, and in a flow passing through a pore system is considered. It is shown that the behaviour of macromolecules can be described by different theories such as the De Gennes theory and the theory of A DiMarzio and C M Guttman. Specific features of chromatographic fractionation and separation processes with the use of membranes formed from ultrahigh-molecular-mass polymers, which are widely used as constructional materials, are discussed. To account for these features, theoretical models considering conformational transitions of macromolecules in the eluent flow and taking into account possible degradation of macromolecules under the influence of the flow are applied. The current state of theoretical and experimental studies of the behaviour of macromolecules in a fluid flow is surveyed.
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I. Introduction

Two theories in the polymer chemistry which describe the unusual behaviour of macromolecules in solutions under a flow gradient were developed almost simultaneously in the 1970s. In the theory suggested by De Gennes,[1] internal transformations of a macromolecule under a shear strain emerging in a flow are considered, whereas the translational motion of the macromolecule under the influence of the liquid flow remains largely unattended. In the absence of any perturbation, a macromolecule takes the shape of a coil. According to De Gennes,[1] this shape gets distorted under the action of a shear strain: the molecule stretches along the shear direction. However, the Brownian motion interferes with this stretching. A certain (critical) value of shear stress is required to uncoil. If this value is reached, the transition occurs abruptly since the number of monomer units available for interaction with the solvent increases in the course of uncoiling. The De Gennes theory was recognized and used as a basis of numerous computer programmes for simulation of polymer behaviour in solutions (see, *e.g.*, Refs. 2 – 6).

The other theory, which was developed by DiMarzio and Guttman,[7] is focused on the movement of macromolecules due to a liquid flow. In contrast to the De Gennes model, which considers a separate molecule, the model of DiMarzio and Guttman examines behaviour of a large set of macromolecules differing by molecular masses and, hence, by the coil sizes. According to calculations performed in terms of this model, separation of macromolecules according to their coil sizes occurs if the molecules move, *e.g.*, in a laminar flow, with larger coils moving faster.† It is noteworthy that DiMarzio and Guttman considered the behaviour of macromolecules in a liquid flow, without taking into account their possible conformational transformations and effects of these transformations on the final separation, while De Gennes analyzed a purely theoretical case of the movement of a separate macromolecule, which automatically excluded any separation by masses or coil sizes.

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† The title of the article [7] is just 'Separation by Flow'.

The flow of solutions of polymers through porous media, *e.g.*, membranes and chromatographic columns, is additionally complicated by heterogeneity of the flow field both in radial and longitudinal directions. Nonetheless, the experimental confirmation of the De Gennes theory was obtained and several unusual effects observed in chromatography of polymers found their explanations in the studies of these systems. Surprisingly, hydrodynamic chromatography was developed almost without taking into consideration the De Gennes theory of conformational transitions of macromolecules in a liquid flow. One of the goals of the present review is to demonstrate the utility of the simultaneous application of these theories for understanding of the process of polymer separation using hydrodynamic chromatography.

II. Conformational transitions of macromolecules in a free eluent flow

Experimentally detectable stepwise changes of viscosity and birefringence of polymer solutions with the change in the velocity of fluid flow [8, 9] is usually attributed to transitions of macromolecules from the coil to stretch conformation (so called coil–stretch or CS transition).[1] This transition occurs when the shear force applied to a macromolecule starts to prevail over uncompensated influence of solvent molecules, which causes Brownian motion and determines the coil conformation of the macromolecule in a static solution. According to the theory,[1–3] this occurs if the macromolecule deformation rate ($\dot{\varepsilon}$) exceeds a certain critical value ($\dot{\varepsilon}_c$), which is inversely proportional to the maximum relaxation time of a polymer chain (τ),

$$\dot{\varepsilon}_c = \frac{A}{\tau} \qquad (1)$$

here A is a constant close to unity.

Therefore, the conditions required for CS transition emerge if

$$\dot{\varepsilon}_c \tau \approx 1$$

The relaxation time τ depends on several parameters such as solvent viscosity, polymer molecular mass, temperature, mobility of the polymer chain and so on and can be calculated by a reported formula [10–12]

$$\tau = \frac{\eta_s M^{\alpha}}{kT} \approx \frac{\eta_s R_{g0}^3}{kT} = \frac{6.22\,\Phi_0\,R_{g0}^3\,\eta_s}{RT} \qquad (2)$$

Here η_s is the solvent viscosity, M is the polymer molecular mass, α is a constant, which varies from 1.5 to 1.8 depending on the nature of the polymer; k is the Boltzmann constant, T is absolute temperature, R_{g0} is the gyration radius of the macromolecuar coil in the non-perturbed state, $\Phi_0 = 2.84 \times 10^{23}$ is the Fox–Flory parameter.

Substituting the expression for τ into Eqn (1) shows that the critical deformation rate is lower when the polymer molecular mass and solvent viscosity are higher. According to De Gennes,[1] the conformational transition can be a first-order or second-order transition depending on the type of the flow field profile (whether it is longitudinal, transverse or more complex gradients) in which the macromolecule resides. In the first case, the transition can be accompanied by emergence of hysteresis in the dependence of the molecular conformational state on the shear rate and the appearance of two equally stable conformations (double equilibrium). It is worthy of note, however, that it is difficult in practice to produce a uniform flow in which every molecule would be influenced by a constant flow gradient; therefore, flows in practice are characterized by heterogeneity and complexity of the flow field profile.[13]

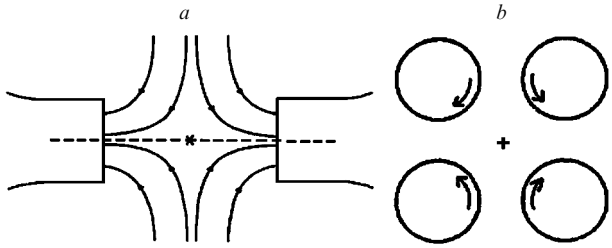


Figure 1. Diagrams of flows that can be obtained with the use of devices producing a longitudinal velocity gradient.[14]
(*a*) Device with four opposite nozzles; (*b*) device with four rotating cylinders; the point where macromolecule stretching is observed are marked with a cross.

Shortly after the development of the De Gennes theory, various devices were suggeste to create specified flow fields.[2, 13, 14] The devices that created so-called longitudinal flow gradient were especially popular since a sharp CS transition was predicted by the De Gennes theory for this type of flow field. The typical designs of such devices ensuring stretching of molecules by the flow virtually without their movement are shown in Fig. 1. The stretching of molecules was controlled by changes in birefringence with the use of a microscope. The use of these devices made it possible to confirm the De Gennes theory experimentally, on one hand, and to obtain data indicating the necessity of its further refinement, on the other hand. The following limitations of the De Gennes model were noted.[3, 15, 16]

First, the model of a finitely extensible non-linear spring (the dumb-bell model) was used in the theory. This simplified model does not make it possible to reproduce the movement of a polymer chain. For instance, the root-mean-square distance between the spring ends is always equal to its average contour length.

Second, De Gennes carried out his calculations of macromolecules on the assumption of time-independent stationary flow but he discussed the process of polymer chain stretching, which depends on time, and, in particular, hysteresis of the dependence of relative elongation on the strain rate (Fig. 2).

Third, the approximation of Peterlin was used,[17] in which the function of instantaneous spring stretching was replaced by the function of root-mean-square stretching. The Peterlin approximation gives correct results for non-linear springs at a constant friction coefficient. However, if the friction coefficient is a function of the distance between chain junctions, this approximation can give rise to S-shaped dependences of the root-mean-square distance between the chain ends on the stretching velocity, which have no physical meaning.

To remove these restrictions, Bird and co-workers [15, 16] considered the behaviour of a polymer chain in a uniaxial elongational flow using a more complex model, in which the

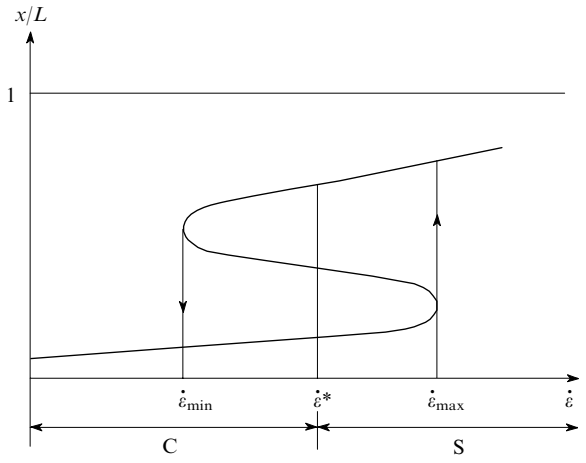


Figure 2. Appearance of hysteresis upon transition of a molecule from coil (C) to stretched (S) conformation in elongational flow according to De Gennes;[1]
x is the elongation of a macromolecule in the liquid flow, L is length of the macromolecule in the initial state, the hysteresis loop is indicated by arrows.

real chain was replaced by a chain of spheres connected by a finitely extensible spring with non-linear elasticity (so-called FENE model [18]). According to the results of this modelling, the polymer molecule transforms under the influence of an elongational flow from coil to stretch conformation gradually, but not stepwise as the De Gennes theory predicted. Four intermediate states were discerned: equilibrium coil, deformed coil, locally unravelled coil and stretched chain.

Another important consequence of this modelling consists in demonstration of the fact that local rearrangements of individual fragments of a chain occur earlier than transformation of the whole chain and that the overall transition is a much more complicated process than mere polymer chain unfolding.

It was also concluded [15, 16] that the S-shaped dependence of relative extension on the stretching velocity (see Fig. 2), which was described by De Gennes and considered in many cases as evidence for the CS transition, was a result of the inappropriate use of the Peterlin approximation. However, Bird and co-workers also used this approximation, but considered non-stationary flow, and, in their opinion, their results were in better agreement with the initial conditions. Nevertheless, it was pointed out that it would be advisable to carry out analogous modelling without use of Peterlin approximation to estimate the sensitivity of the obtained results to this approximation and test other models of CS transitions.[19–21] In any case, the authors agreed with the implication of Rabin [22] that the polymer molecule has to be modelled as a freely jointed chain, but not as a spring.

Henyey and Rabin [23] related the possibility of occurrence of a CS transition as a first-order or second-order transition to rotational isomerism of a polymer chain. They noted that the transition energy is different for *gauche* and *trans* conformations of a polymer molecule. According to calculations, if a *trans* conformation has lower transition energy, a second-order transition gradually occurs; if a *gauche* conformation has lower transition energy, a first-order transition occurs. This implies that a second-order transition should be observed for rigid-chain polymers such as polyelectrolytes, whereas a first-order transition should take place for conventional polymers existing in coil forms.

However, discrepancies in description of CS transitions are noted not only in the theory (*i.e.*, modelling), but also in the experiment. For example, Menasveta and Hoagland [12] analyzed reported data on the dependence of critical strain rate on molecular mass of polymers and noted that some authors [14, 24, 25] used the following correlation:

$$\dot{\varepsilon}_c \propto N^{\alpha} \qquad (2)$$

(here N is the degree of polymerization) with the exponent $\alpha = -1.5$ irrespective of the solvent quality, while the power law dependence was indeed affirmed when a good solvent was used,[26] but with a different exponent value of -1.8. A study [13] of polystyrene birefringence in toluene, which is a good solvent, gave the exponent of -1.49. For an impermeable coil,‡ the exponent should be -1.5 according to Eqn (2) at θ conditions; however, the same equation gives the value of -1.8 for a good solvent.[12] Therefore, the authors [12] concluded that it is necessary to find out the cause of the discrepancies obtained both in the theory and experiment before this correlation is used for molecular mass analysis as it has been done in some studies.[27, 28]

Kroll and Gompper [29] modelled CS transitions using the transformation matrix method, the algorithm of a growing polymer chain and the Monte Carlo method and concluded that the scaling correlation of the N^{α} type should be valid not only at low, but also at high strain rates and be applicable to both flexible and rigid macromolecules both in good solvents and at θ conditions. Qualitative observance of this correlation at large extension was explained by a model of so-called yo–yo conformation suggested by Ryskin,[19, 20] where the polymer chain is assumed to be fully stretched in its middle part and contains practically non-deformed coils at the ends, with the coil sizes decreasing with the increase in the strain rate.

Different behaviours of polymer chains in *trans* and *gauche* conformations (relative to the monomer units) under the action of shear strain was also noted.[29] The modelling showed that the CS transition is a first-order transition for the *gauche* conformation and a second-order transition for the *trans* conformation. It was found for a polymer chain in the *gauche* conformation that the probability distribution function of the mean-square distance between the chain ends $P(R^2)$ had two clear-cut maxima: the maximum at lower R^2 value corresponded to the coiled polymeric molecules, whereas the maximum at higher R^2 value corresponded to stretched molecules. This was an unexpected result. In the authors opinion, this bimodal distribution definitely indicated the occurrence of a first-order CS transition. Thus, according to the data of Kroll and Gompper, the CS the transition in polymers can be either first-order or second-order transition. Moreover, at certain conditions, co-existence of coiled and stretched conformations is possible.

Since the above results of theoretical modelling are contradictory, additional calculations or, better, an experimental check of obtained conclusions was insistently

‡ A polymer solution in a θ-solvent for which the energy of interaction with the polymer chain is equal to the energy of interaction of chains with one another.

required. However, until recently, the latter could be performed using only indirect methods such as measurements of viscosity or birefringence of solutions. However, observation of conformations of a single molecule turned out to be possible in studies of such high-molecular-mass objects as DNA. In these studies,[30–34] one end of a DNA molecule was attached to some spherical microparticle (usually, a latex particle), while the other remained free. This made it possible to keep the macromolecule from translational movement and to study hydrodynamic interaction of the polymer with the liquid flow. A typical picture observable using a microscope is shown in Fig. 3. As the experiments showed, the relative extension of a DNA molecule found as the ratio of gyration radii in the static and stretched states correlates with the function $\eta v L^{0.54}$, where η is the solution viscosity, v is the linear velocity of the liquid flow. This correlation indicates that DNA molecules participate in hydrodynamic interaction with solvents even at relative stretching of 80%. The power law dependence is valid in a wide range of relative extensions; however, at low relative extension ($x/L < 0.3$), it has the following form:

$$x \approx v^{0.7}$$

The data obtained on visual observation of DNA extension under the shear strain of the liquid flow forced to reconsider the models of molecular behaviour in liquid flows. Different models of polymer solution dynamics in an elongational flow were critically re-examined taking into account not only expansion of the macromolecular coils but also possible scission of the macromolecules.[35] It was confirmed that, first, the values of critical shear rate for the CS transition depend on whether the polymer molecule is located in a stagnant zone (see Fig. 1) or moves with the liquid flow and second, the hybrid models such as the yo–yo model mentioned above[19,20] are more adequate. These models are more preferable from the energetic point of view because they reproduce the decrease in the internal energy of a macromolecule upon natural deformation of its polymeric chain for several extension levels.

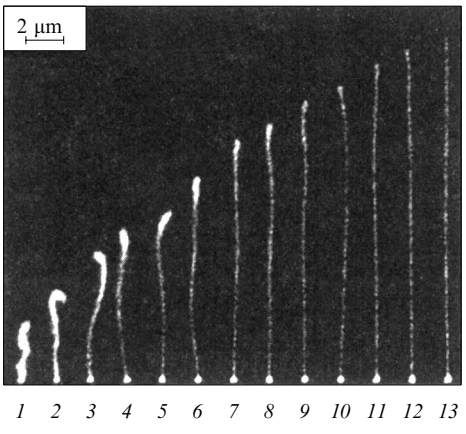


Figure 3. Image of a fluorescent-labelled DNA molecule (64.6 μm long) attached by one end to a latex particle of 0.3 μm in diameter and deformed by liquid flows of different velocities.[33]
The liquid phase viscosity is 0.95 cP.

Point	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
vs/μm s^{-1}	1	2	3	4	5	7	10	12	15	20	30	40	50
x/L (%)	15	22	31	38	42	49	60	63	67	72	78	81	83

At the same time, according to another study,[36] the main effect on the mechanism of the CS transition is rendered by the solvent type (whether it is good, bad or θ-solvent) and by the flow type (elongational flow, shear flow, homogenous flow, *etc.*). In a bad solvent, the macromolecule contracts to a globule, and depending on the above listed factors, the CS transition occurs as a first-order or second-order transition *via* several intermediate conformations determined by threshold values of the shear rate. The contracted chain was considered as containing some numbers of fragments of size ξ, each including g monomeric units. These fragments tend to coalesce with the formation of a single globule of the size

$$r_c = \left(\frac{N}{g}\right)^{1/3} \xi$$

where N is the total number of monomeric units. When the shear force reaches its critical value

$$f_c = \frac{kT}{\xi}$$

the first-order transition occurs, which transforms the coil conformation into a conformation simultaneously including weakly deformed globule and rod conformation. It is noteworthy that complete expansion of the polymer chain due to expansion of separate fragments but not single monomeric units was considered in this study.[36]

De Gennes shortly summarized the preceding modelling data and experimental results on conformational transitions in macromolecules.[37] He noted that it took over 20 years for chemists and physicists to admit flexibility of macromolecules and mobility of their chains, which can be directly observed for single macromolecules such as DNA. In the tensile strain field of a liquid flow, the macromolecules are extended along the flow direction. However significant extension can be observed only if the elongational flow acts for quite a long time. However, fulfilment of the latter condition can result in scission of the macromolecule, usually, in the middle of its chain. De Gennes likened this process to tug-of-war of two boy teams with a thin rope. Each of the boys is unable to break the rope, but the rope can be broken under the strain due to joint efforts.

In the opinion of De Gennes, the most unusual result of direct observation of conformational transitions is the discovery of the unusual form of molecular individualism of polymers consisting in that two DNA molecules being for the same time under the action of the same elongational flow may undergo different conformational transitions and take different shapes. Perkins *et al.*,[38] who observed this effect, also concluded that polymers are not susceptible to a cooperative spontaneous CS transition, as it was assumed in the De Gennes theory. Moreover, at the same strain rate, different conformers can exist (Fig. 4). This point of view caused sharp criticism from De Gennes,[37] who pointed out that the character of a CS transition strongly depends on the initial state of a particular macromolecule, which was not determined in the experimental study.

This contradictory interpretation of experimental observations initiated further studies of various model systems and modelling of conformational transitions in macromole-

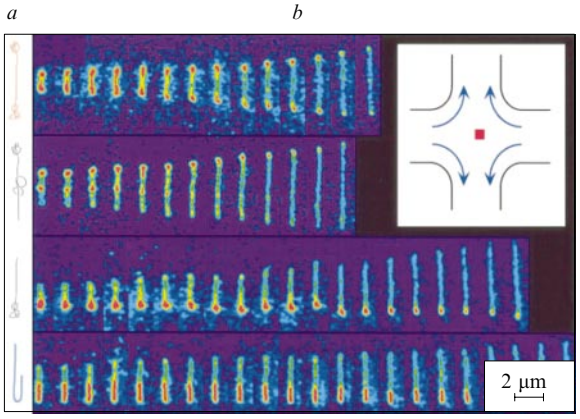


Figure 4. Conformations (*a*) and photomicrographs (*b*) of DNA molecules in different conformations depending on the shear velocity.[38]
The maximum shear velocity of 0.86 s^{-1} corresponds to the molecule shown on the right. Coexistence of different conformations (shown in the same column) was observed at each shear velocity.

cules. Agarwal *et al.*[39] modelled the dynamics of Brownian motion of macromolecules in a simple field of shear strain using the ball–rod model of polymer chains and found that near the CS transition point, the time required to extend a macromolecule can be much longer than the time which can be theoretically obtained from the formula

$$t = \left[1 + \ln(\sqrt{N})\right]\dot{\varepsilon}^{-1}$$

It was demonstrated that the conformation of a macromolecule strongly depends on its initial state. Furthermore, at $\dot{\varepsilon}$ values close to critical ones, macromolecules are subject to Brownian fluctuations between the coil and partly stretched conformations, *i.e.*, more than one equilibrium conformations are possible.

Cifre and de la Torre[40] modelled the dynamics of Brownian motion and studied CS transition kinetics. The transition kinetics was expressed in terms of fractions of molecules remaining in the coil conformation at certain shear strain. At the beginning, the process is slow, and all molecules remain in the coil conformation for a certain time. This time is longer for polymers with higher molecular mass. Then the concentration of molecules in the coil conformation decreases exponentially. In the authors opinion, the molecular individualism manifests itself in that the time necessary for the CS transition depends on the excess of the tensile strain applied to a molecule over its critical value. This excess strain determines not only the transition time, but also other features of the transition.

Smith *et al.*[41] extended the studies of conformational transformations of individual DNA macromolecules, which were considered as flexible polymeric chains because each chain contained roughly 440 persistence lengths, by considering effects of shear flow but not elongational flow (Fig. 5).

No sharp CS transition was observed for this type of flow field, but large aperiodic temporal conformational oscillations were noticed, which were consistent with end-

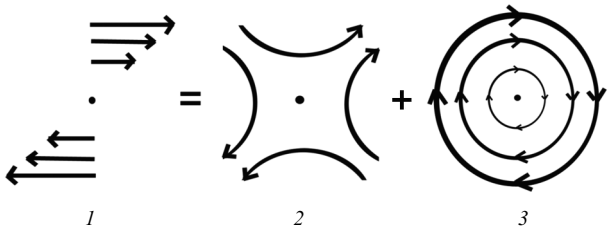


Figure 5. Shear flow profile (*1*), which can be represented as a superposition of elongational flow (*2*) and rotational flow (*3*).[41]

over-end tumbling of molecules and gave rise to U-shaped conformers of stretched macromolecules. Smith and Chu[42] made an attempt to find an answer to the comment of De Gennes[37] concerning uncertainty of the starting state of macromolecules in the experiments on visual observation of DNA conformational transitions. A four-nozzle device (see Fig. 1 *a*) was filled with a polymer solution, kept for a while to let macromolecules to take the random coil conformation, and only after that, an elongational flow was applied. It was shown that the critical shear rate strongly varies and depends on the initial random coil conformation of the macromolecule in the equilibrium state. In the authors opinion, the occurrence of U-shaped conformations (Fig. 6) at high stretching velocities reflects nonergodic dynamics, which takes place when a statistical mechanical system is subjected to a non-adiabatic or sudden external influence. As can be seen in Fig. 6, the occurrence of a certain conformation of a macromolecule in a strained state is related to the orientation of the initial coil relative to the direction of the elongational flow.

In a series of studies,[43–45] the occurrence of hysteresis upon CS transition in DNA molecules was experimentally demonstrated for the first time, whereby the possibility of the first-order CS transition was confirmed. It was observed for a narrow range of flow velocities that a DNA molecule could exist in a coiled or stretched conformation depending on its prehistory. The calculated diagram of the dependence of the conformer free energy on stretching velocity exhibited two minima in the region corresponding to the CS transition (a similar dependence was noted earlier[36]).

Another solution to the problem of uncertainty of the macromolecule initial state was suggested by Ren *et al.*[46] They took into account the fact that DNA is a charged macromolecule, and the extension induced by the flow can be compensated by applying an electrical field. Electrical field switching on and off brought a macromolecule to the equilibrium state or, on the contrary, to the state of a sudden stretching, in which it undergoes numerous conformational transformations, which were described earlier.[41–45]

Certainly, DNA molecules are unique objects, which allow one to observe conformational transitions. Such observations are impossible for the majority of synthetic polymers; therefore, a number of methods were proposed for indirect observation of macromolecule stretching process in a liquid flow. As noted above, the solution birefringence measurements are often used for this purpose. However, more information can be provided by light scattering measurements, since they can serve for direct estimation of the changes in macromolecule size in a flow. The first

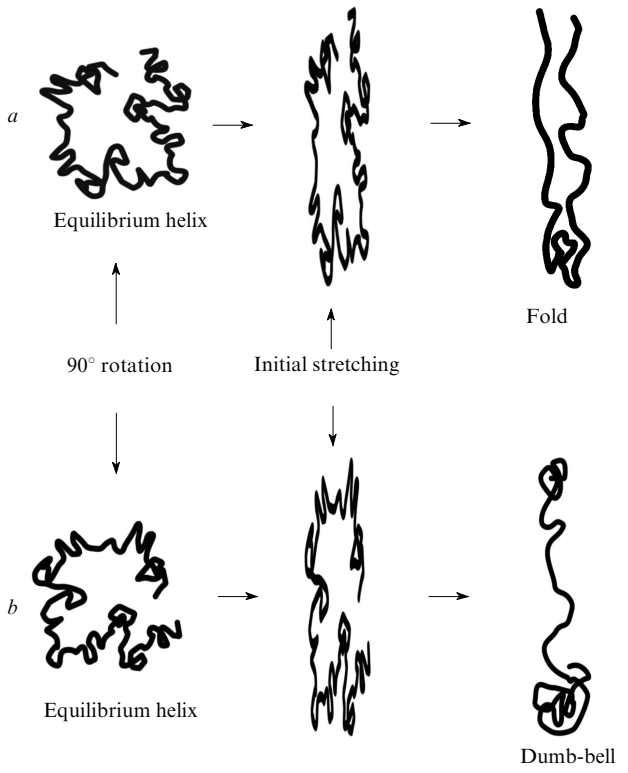


Figure 6. Schematic diagram of deformation of the macromolecular coil conformation under the influence of elongational flow when the coil is oriented along (*a*) and across (*b*) the flow.[42]

experiments along this line were carried out by Lumley[47] with the use of solutions of polyoxyethylene oxide. A maximum four-fold increase in the size of molecules oriented along the flow was revealed. A similar result was obtained by Smith *et al.*[48] for dilute solutions of polyisobutylene: the elongation factor (the ratio of the length of gyration radius projection on the elongation axis to the gyration radius in the unperturbed state) did not exceed 4. In addition, it was shown in the study of elongation of polyisobutylene molecules of different molecular mass (M) in a liquid flow that polymer molecules of lower molecular mass are elongated to a higher extent than molecules of higher molecular mass. However, Menasveta and Hoagland,[49] who studied solutions of polystyrene with $M = 2 \times 10^7$ Da, found only a two-fold increase in the gyration radius at an extremely high value of dimensionless stretching velocity (the Deborah parameter) equal to 20 (typically, the CS transition occurs when this parameter is equal to 0.5).

Lee and Muller[50] studied the CS transition in monodisperse polystyrene using methods of static and dynamic light scattering and confirmed that the polymer chain becomes fully stretched in the direction of elongational flow; however, its elongation turned out to be much smaller than it was predicted by the simple dumb-bell model. Solvent quality and polymer molecular mass significantly influence the macromolecule stretching: a polymer in a bad solvent and a polymer of lower molecular mass exhibit larger relative elongation at a fixed stretching velocity. The data obtained with the use of light scattering method were compared with the results of theoretical modelling.[51] Optical measurements made it possible to determine mean elongation $\langle x \rangle$ of DNA macromolecules and mean square gyration radius $\langle R_g^2 \rangle^{1/2}$ of polystyrene molecules as functions of the stretching velocity. The same parameters were obtained in dynamics simulations of Brownian motion (the input data were consistent with characteristics of DNA and polystyrene used in the experiments). A good agreement between experimental and simulation data was obtained for DNA, whereas for polystyrene, the observed deformation appeared much smaller than that predicted in the simulations. In the authors opinion, a possible reason of these discrepancies consists in misinterpretation of the results of light scattering measurements for polymer coils in a highly deformed state for yet unknown reasons.

The results of comparison of different algorithms of approximation of data obtained by different versions of multiangle light scattering support this suggestion.[52] Of the three used algorithms (the Berry, Zimm and Debye methods), the Zimm method was least reliable (the choice of a particular method was dictated by the shape of scattering particles). In the case of random coil polymers, the most precise method was that of Berry. However, the increase in accuracy of the light scattering method does not solve the problem of fundamental discrepancy in estimations of polymer behaviour in the elongational flow, which were obtained on the basis of theoretical models and visual observations. This fact initiated the study of a new series of model systems, while development of computer technology made it possible to perform simulations based on more complex models and describe interactions in polymer–solvent systems with higher precision.

Wang and Chatterjee performed calculations[53] taking into account finite extension of a polymer chain, and this improved agreement between theoretical and experimental data. At the same time, they pointed out that the improvement in the description of polymer chain extension occured at the expense of reduction in the precision of determination of its orientation. Liu *et al.*[54] carried out simulation of polymer behaviour under the action of both shear and elongational flows using a bead–rod chain model, incorporating intra-chain hydrodynamic interaction and excluded volume effects. The authors traced the influence of the polymer chain size and shape, as well as the capability of the chain to rotate on the critical shear rate. The slope of the tangent to the plot $\log(R_g^2)$ *vs.* $\log(\dot{\varepsilon})$ at the inflection point increases with increasing polymer molecular mass in agreement with theoretical data and experimental observations, In the authors opinion, this fact indicates a possibility of the first-order transition.

Neelov *et al.*[55, 56] used Brownian dynamics simulation to describe the behaviour of a freely jointed polymer chain with and without taking into account hydrodynamic interactions. Effects of the chain size and shape, and also of stretching intrinsic viscosity on the critical rate of the CS transition were considered. According to the calculations, a sharp change of the polymer chain conformation should occur if critical shear rate is exceeded; the critical rate increases if hydrodynamic interactions are taken into account. On the whole, these results are in accord with the previously reported data. The obtained exponents in the scaling expression for critical rate of the CS transition [see Eqn (2)] were $\alpha = -1.96$ if hydrodynamic interactions were taken into account and $\alpha = -1.55$ if not, *i.e.*, they were

found to be close to the values given, *e.g.*, in one of the previous studies.[12]

A substantial body of theoretical modelling is devoted to polymer behaviour in turbulent flows (see the work by Afonso and Vincenzi[57] and references cited therein). Because such flows are not typical of chromatography, these studies are not discussed here.

Morrison *et al.*[58] modelled the effect of the stretching force (f) on macromolecule stretching (x) in bad and good solvents. They found that $\langle x \rangle \propto f$ in a good solvent for small values of the force and $\langle x \rangle \propto f^{2/3}$ for larger values. However, these correlations are completely valid only for polymers with $> 10^5$ monomer units to satisfy all assumptions concerning the polymer structure. Properties of the polymer also affect the type of CS transition. For example, in the case of slightly hydrophobic polymers in a bad solvent, existence of different conformers such as perfect coil, globule, rods, *etc.*, is possible, whereas for a strongly hydrophobic polymer, its globular structure is preserved as long as the force f is lower than its critical value. When the critical value is reached, a fast transition into rod-like conformation occurs.

Somani *et al.*[59] used Brownian motion simulation for a polymer chain, which was approximated by the bead–spring model including hydrodynamic interactions and the polymer excluded volume effect, to study the influence of the solvent quality on the CS transition in macromolecules placed in an elongational flow. Unlike the data of simulation performed in earlier studies, it was found that the critical shear rate decreases more dramatically with enhancement of the solvent quality. In addition, the solvent quality significantly affects the exponent in the scaling correlation between the critical rate and the polymer molecular mass: the exponent increases with increasing solvent quality. At the same time, the Deborah parameter (the dimensionless shear rate)

$$\mathrm{De} = \dot{\varepsilon}\tau$$

does not depend on either the polymer molecular mass or the solvent quality.

The CS transition in polymers with globular structure was analyzed once again by Sing and Alexander-Katz[60] (for comparison, see, *e.g.*, Ref. 36). According to revised data,[60] the CS transition in this polymer has a smooth character if it is not complicated by any intramolecular interactions between the chain fragments or by any non-solvation effects, which retard the transition. If it is so, a fast irreversible transition into the stretched conformation occurs in the system when the critical shear rate is reached. In the authors opinion, their results correct and extend the available views about CS transitions in globular macromolecules.

Radhakrishnan and Underhill[61] used simulation of Brownian dynamics for the bead–spring model of a polymer chain, while studying the effect of solvent quality on the magnitude of hysteresis in the dependence of relative elongation on the stretching velocity at a CS transition. The solvent quality was taken into consideration in two different ways:

— by increasing the size of the Kuhn segment (N_K), while keeping the excluded volume parameter δ/l^3 constant (δ is the excluded volume quantity, l is the length of the Kuhn segment);

— by increasing the excluded volume, while keeping the size of the Kuhn segment constant.

In the former case, the hysteresis width increased with increasing N_K, whereas in the latter case, it decreased with the increase in the excluded volume parameter δ/l^3. On this basis, it was concluded that for molecules similar to single-stranded DNA, for which $\delta/l^3 \approx 1$, in a good solvent, the CS transition should be accompanied by less pronounced hysteresis than for molecules with the same N_K in a θ-solvent.

Radhakrishnan and Underhill[61] did not study the effect of the polymer concentration in a solution on the hysteresis width. This effect was considered by Prabhakar,[62] who found that the hysteresis width significantly increases if the polymer concentration exceeds the critical value of coil interpenetration (c^*). Large fluctuation displacements of macromolecules at stretching velocities corresponding to the hysteresis region result in stronger overlap of partly stretched macromolecules than it occurs in a static equilibrium solution. Due to hydrodynamic screening, the chain friction coefficient increases; therefore, the stretched conformation can exist even at very low stretching velocities. The hysteresis width decreases when the polymer concentration in the solution becomes lower than c^*. The dependence of the hysteresis width on the polymer concentration (c) is non-monotonic, but has a clear-cut maximum at $c/c^* = 1$.

In addition to theoretical modelling of the CS transitions in solutions of polymers, experimental studies were continued. Particularly, Pelletier *et al.*[63] measured viscosity characteristics of polyacrylamide solutions. They found that if the beginning of deviation of the solution behaviour from the Newtonian model is considered as the CS transition point, the critical value of $\dot{\varepsilon}_c$ is lower than the theoretically predicted value by an order of magnitude. In the author's opinion, this discrepancy indicates that the parameter $\dot{\varepsilon}_c$ corresponds to an average macromolecule deformation rate in a certain range of rates. It was shown that $\dot{\varepsilon}_c$ does not depend on the polymer concentration in a solution if the concentration is lower than the concentration of mutual penetration of polymer coils, but is dependent on the weight-average molecular mass of the polymer in accordance with a known relation

$$\dot{\varepsilon}_c \propto M_w^{-2}$$

With the purpose to find new objects whose transformations could be directly observed (like DNA the conformational transitions of which were observed by Chu and coworkers[45]), Stone *et al.*[64] studied the behaviour of micelles formed by polymers. Micelles are less mobile than polymer chains, but due to their size, they can be observed with a microscope. It was shown[64] that in an elongational liquid flow, micelles undergo a fast CS transition if the critical stretching velocity is reached, and the relationship between the micelle relaxation time and length is consistent with the hydrodynamic theory. At high values of the Deborah parameter, micelles are stretched at the velocity almost equal to the liquid flow velocity, but folded conformations are frequently formed. In contrast to DNA molecules, micelles exhibit fewer regimes of alignment along the flow.

Concluding this section, one may say that the theory of CS transition in polymers in a liquid flow, which was proposed by De Gennes more than fifty years ago, has

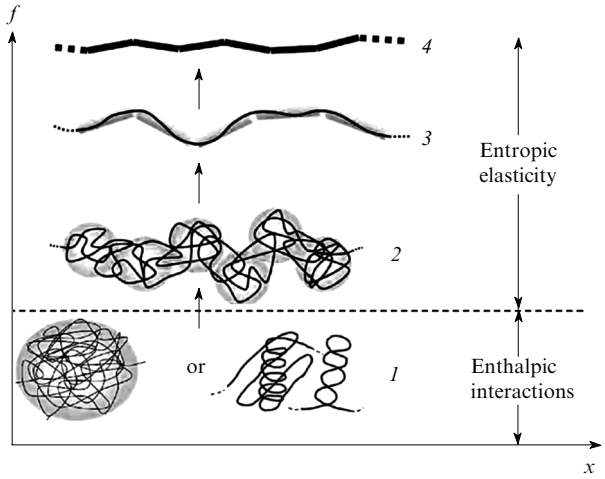


Figure 7. Extension and conformations of a macromolecule in a liquid flow depending on the tensile strain.[67]
(*1*) Linear region, $x \approx f$; (*2*) Pincus blobs, $x \approx f^{1/\nu-1}$; (*3*) worm-like conformation, $x \approx 1-f^{1/2}$; (*4*) freely jointed chain, $x \approx 1-f^{-1}$.

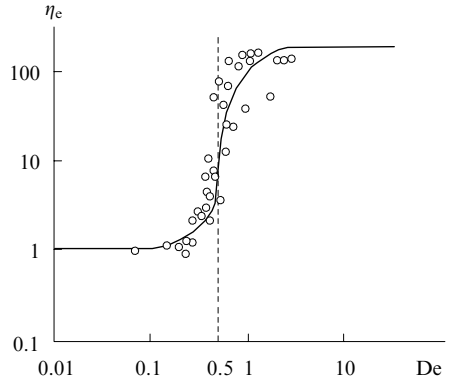


Figure 8. Variation in the experimental (dots) and calculated (curve) effective viscosity (η_e) of a polymer solution during its flow through a layer of spherical particles *vs*. Deborah parameter.[75] Solvent is ethylene glycol, $N = 120$, $\tau = 0.14$ s, $M = 18. \times 10^6$ g mol^{-1}, polymer concentration is 50 ppm, intrinsic viscosity is 1136 cm^3 g^{-1}.

been recognized and confirmed in numerous experiments and theoretical calculations.[2, 3, 65, 66] The development of experimental technique made it possible to carry out visual observation of the CS transitions in separate macromolecules. In numerous simulations based on Brownian dynamics, the effects of different factors such as hydrodynamic interaction, excluded volume, *etc*. on conformational transformations in macromolecules were considered. The results of these simulations are summarized in the diagram in Fig. 7. Elongation of a macromolecule is a function of applied shear strain. The results of simulation are very similar to experimental results in the case of DNA molecules. However, the agreement between theoretical and experimental data is worse for synthetic polymers, especially, for polymers with high molecular mass. A possible cause is higher mobility of synthetic polymers resulting in difficulty of simulating their behaviour in solutions. The problems of simulation manifested themselves most evidently in an attempt to predict distortion of the coil conformation on the basis of light scattering data.[65]

Thus, in spite of substantial progress in the description of dynamic behaviour of macromolecules in a liquid flow, a certain gap in the understanding of this process still remains.

III. Conformational transitions of macromolecules in a confined space

The conformational transformations of macromolecules caused by hydrodynamic interactions with a liquid flow, which were discussed above, may be considered as processes occurring in a non-confined uniform flow. This is an idealized situation. Movement of a polymer solution in channels with diameters considerably larger than the macromolecule size, where interactions with surfaces may be neglected, represents a situation close to this idealization. The behaviour of macromolecules in such flows is rather indistinguishable from their behaviour in flows of infinite volume. Similarly to the case of movement of non-confined polymer solution flow, the filtration of polymer solutions through a porous medium is accompanied by an increase in the viscosity as a certain flow velocity has been reached[68–80] (Fig. 8). Theoretical models explaining this effect[3, 72] are similar to the models of behaviour of macromolecules in an elongational flow (see above). The size of particles, which form the porous layer[71] and configuration of channels in this layer[73] were noted as additional factors affecting the point at which the viscosity starts to increase. Detailed investigation of these factors showed the following:[74]

— decrease in the particle size of the porous layer results in decreasing the Reynolds number at which viscosity increases;

— increase in the polymer concentration does not affect the starting point of the viscosity change, but results in higher final viscosity values;

— effects of the polymer molecular mass become apparent only if the molecular mass is high ($>10^6$ Da);

— increasing temperature and solvent viscosity decrease the Reynolds number at which polymer solution viscosity increases.

These conclusions[74] are quite simple, but they demonstrate satisfactory agreement between experiment and predictions made on the basis of bead–spring FENE model for dilute polymer solutions.[3]

Besides the classical systems, in which the size of macromolecules is smaller than the cross-section of channels through which the solution is filtered, the systems with macromolecules whose size is comparable with or even larger than the cross-section of the channels are often considered. For the first time, the latter systems were investigated in the late 1970s.[80–83] The conclusions obtained in these studies are uncommon and require detailed consideration here.

A static system including a solution with polymer concentration c_0 in contact with an open-ended conical pore of diameter D was considered by Daoudi and Brochard.[83] While analyzing the chemical potential of the polymer in the solution and in the pore, the authors concluded that concentrations of the polymer in the pore (c_D) and in the solution (c_0) are equal if the diameter of the polymer

molecules is smaller than the pore diameter; the c_D concentration decreases exponentially from c_0 to 0 when the macromolecule size exceeds the pore diameter. Thus, in a static dilute solution, a polymer penetrates into a pore only if the pore diameter is larger than the size of the polymer coils.

When a solution flow moves through a conical pore, two forces act on a polymer molecule: an entropic force, which tends to preserve the initial conformation of the molecule, and a friction force, which seeks to change the conformation of the molecule and pull it into the pore. The latter force is caused by the liquid flux (J_s) and is capable to counterbalance the entropic force if the flux reaches a critical value (J_c). If $J_s < J_c$, the friction force is too weak to draw the polymer molecule into the pore; if $J_s > J_c$, the macromolecule goes through the pore. It is interesting that contrary to intuitive expectations, the critical flux

$$J_c \propto \frac{\zeta T}{\eta_s}$$

(ζ is a measure of the pore conicity, T is absolute temperature, η_s is the solvent viscosity) is found to be independent of either macromolecule size (N) or minimum pore size since both acting forces are proportional to the N/D ratio. However, the absence of dependence of J_c on N and D is a result of a series of simplifications made by the authors in deriving the above relation. For instance, if one takes into account that terminal and central sectors of a macromolecule interact with a solvent in different ways, one gets another relation, which shows that J_c increases with increasing N and decreasing D. The dependence of J_c on N rapidly reaches saturation, and for large N, the value of J_c virtually does not depend on the macromolecule size. According to the authors' opinion, this fact is a distinctive characteristic of the systems in which a solution goes through channels (pores).

Similar dependences were established [83] when, instead of a separate molecule, a flux of the solution with polymer concentration $c_0 < c^*$ through a conical pore was considered. In this system, if $J_s < J_c$, pores are plugged, whereas if $J_s > J_c$, the solution freely goes through the pore; the transition between these regimes is very sharp. It is interesting to note that, according to the calculations, polymer molecules move faster than the solvent in a large region of the conical pore. Nonetheless, they remain in an equilibrium state because the macromolecule relaxation time is much shorter than the time of passage through the pore. In the authors' opinion, the conformational changes under the influence of a liquid flow, which were considered in the previous section, play an insignificant role in the case of conical pores since the critical flux of a solvent causing macromolecule stretching (J_c') substantially exceeds the critical solvent flux drawing the macromolecule through a pore (J_c),

$$J_c' \approx \frac{J_c}{\zeta^2}$$

An opposite situation is observed when the pore diameter is invariable (*e.g.*, a cylindrical capillary or a slit). In this case, the molecule should be stretched by the flow before it becomes capable to penetrate into the pore. As noted above, the required solvent flux

$$J_c' \approx \frac{kT}{\eta_s}$$

should considerably exceed the solvent flux drawing a macromolecule through a conical pore. Like J_c, in the first approximation, the quantity J_c' depends on neither the pore nor macromolecule size. However, more precise treatment shows that this dependence does exist; furthermore, J_c' depends on the pore geometry.

Flowing through pores of semidilute solutions, in which interpenetration of coils of macromolecules occurs, was also considered by Durst *et al.*[76] This revealed the same basic regularities as were found for dilute solutions, but should be corrected for other sizes and conformations of macromolecules.

The theoretical model developed by De Gennes was tested by Long and Anderson.[84,85] They filtered dilute solutions of polystyrene with narrow molecular mass distribution within $10^5 - 2 \times 10^7$ Da through a porous membrane. The dependences of the polymer fraction unable to penetrate the membrane (the reflection coefficient σ) on the membrane pore size (R_0), macromolecule size (R_s) and liquid flow velocity (q) were obtained. At $R_s < R_0$, the dependence of the coefficient σ on the ratio R_s/R_0 was in line with the predictions in terms of the rigid-sphere model. However, at $R_s > R_0$, the coefficient σ depended on the flow velocity: at low velocities, its value corresponded to practically complete retention of the polymer, whereas at high velocities it conformed to almost complete polymer penetration through the membrane. In agreement with the De Gennes theory, the dependence of σ on q was not affected by the macromolecule or pore sizes. At the same time, the changes in the coefficient σ with the increase in the flow rate q were smooth rather than stepwise. The authors also constructed an empirical relationship covering all σ values found by them using the following common variable

$$\theta \approx \left(\frac{R_s}{R_0}\right)^{1-3n} q^{-n}$$

The parameter n obtained from experimental data approximation using the same function was 0.33. According to the authors, this indicates the absence of dependence of σ on the polymer molecule size if the polymer has sufficiently high molecular mass.

The same conclusions were made by Adamski and Anderson [86] from experiments on filtration of polystyrene solutions through a mica membrane. Three types of polystyrene were studied: linear, comb-branched and star-branched. In the case of a linear polymer, the σ value decreased with increasing flow velocity, being independent of the polymer molecular mass; at low flow velocities, the amount of polymer retained by the membrane was described by the equation

$$1 - \sigma < q^{1.69}$$

For the studied types of polystyrene, the σ coefficient increased with the increase in chain branching at a fixed flow rate. The authors suggested using filtration through membranes with known pore structure as a method for estimating the polymer branching.

As noted above, re-orientation and conformational transitions in a liquid flow are possible not only for macro-

molecules with flexible-chain structure, but also for polymers with rigid globular structure.[36] A study of such polymers also exhibited dependence of the filtration result on the liquid flow velocity.[87] Solutions of poly(1,4-diphenyl-2,6-benzothiazole) in methanesulfonic acid were used in this study; they were filtered through a mica membrane. The average length of the polymer molecules was either 118 or 180 nm, while the membrane pore size was of 60–90 nm. The reflection coefficient decreased if the flow velocity was larger than the value $0.1(kT/\eta_s)$. The σ value at the zero flow was ~ 0.8 in accordance with the theory based on steric interaction of a macromolecule having a rigid-rod conformation with a cylindrical pore. The dependence of σ on the dimensionless flow parameter $q\eta_s/kT$ for the studied polymer was similar to the dependences observed for solutions of linear polystyrene in good solvents, although the conformations of the polymers were different, and solvent viscosities differed by a factor of more than 20.

The qualitative agreement between the De Gennes theory and experimental results indicated that separation of polymers by filtration through a membrane was possible only if the flow velocity was lower than the critical velocity. Under these conditions, diffusion processes, which were not taken into account in previous studies,[80–83] could considerably affect the migration of a polymer through a membrane. This gap was filled by modelling macromolecule migration through a membrane in the absence of liquid flux ($J_s = 0$).[88–91] It was shown that the time required for linear polymer molecules to diffuse through a single membrane increases with the increase in the number of monomer units proportionally to $N^{5/2}$. If a membrane package is used, three filtration regimes can be realized depending on the distance between neighbouring membranes (d). If d is smaller than the gyration radius of a polymer molecule, the penetration mechanism is reptation[92] and diffusion coefficient is proportional to N^{-2} (Ref. 88). In an intermediate region, when d is larger than the gyration radius but smaller than the length of the macromolecule, the major direction of macromolecule movement yet remains a direction perpendicular to the membrane plane (*i.e.*, penetration). If d exceeds the macromolecule length, the diffusion regime shifts to Rouse-diffusion, and movement in the direction perpendicular to the membrane plane becomes slower.[88]

Sung and Park[89–91] carried out a series of simulations of diffusion of macromolecules through membranes and developed a physical statistical model of penetration of a macromolecule into a membrane pore. They considered the penetration process as diffusion of a macromolecule, which overcomes an energy barrier (Fig. 9). According to their calculations, larger mobility of the macromolecule chain impedes passage of the macromolecule through a membrane, whereas stepwise overcoming of an energy barrier, making its chain less mobile, accelerates the penetration.[89] Furthermore, the study of the dependence of the time required for passage through a membrane on the polymer chain length revealed that macromolecules with long chains pass through a membrane faster because they have more conformations with quite low free energy. Short polymer chains exhibit a dynamics of passage through pores typical of rigid particles at Brownian motion: the velocity of penetration into a membrane for globular polymers is lower than for coil polymers.[91] However, comparison of polymers of different chemical nature showed that weak

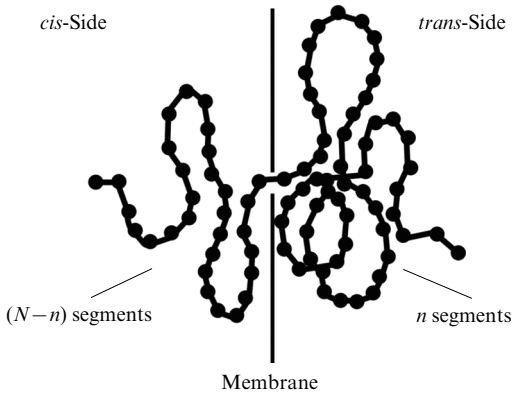


Figure 9. Schematic representation of macromolecule diffusion through a membrane.[89]

interactions between the molecules and pore walls, which are analogous to hydrogen bonding, can additionally assist the passage of polymer molecules through pores.[88] For instance, poly(isopropylacrylamide) goes through pores of a polycarbonate membrane more quickly than dextran, which has lower molecular mass, because entropy loss upon entering the pore is partly counterbalanced by the enthalpy of hydrogen bonding in the former case.[93]

Numerous simulation studies were performed to establish conformations assumed by macromolecules after their penetration into a pore. For instance, Milchev *et al.*[94] simulated conformations of macromolecules in a cylindrical pore, and Cifra and Bleha[95,96] carried out simulation for a slit-like pore. As expected, the set of possible conformations became restricted, and macromolecules assumed a conformation determined by the confinement. In subsequent simulations, the factors such as interactions with the pore walls[97] and mobility of macromolecule chains[98] were taken into consideration. The most interesting simulation was made by Hermsen *et al.*,[99] who considered the process of entering a macromolecule into a pore. The Monte Carlo method was used in this simulation, and asphericity of the chain was analyzed as a function of position of the centre of mass on the cylindrical pore axis. It was found that this function passes through a maximum long before all Kuhn segments of the chain get into a pore. In contrast to smooth entrance of a macromolecule into a pore in an intermediate position when the centre of mass is located at the distance approximately equal to one gyration radius from the pore, the chain segment inside the pore becomes substantially elongated, while the external chain segment preserves the coil shape (it is so-called flower conformation) (Fig. 10). When the centre of mass gets into the pore, the chain elongation inside the pore becomes slower, and the averaged conformation resembles a deformed coil.

It is noteworthy that the results of simulation strongly depend on the chosen model and not always agree with experimental data. In particular, Nieh and Kumar[100] studied conformations of polymer molecules with $N \approx 2000-7000$ in a good solvent in Vycor glass pores of 7 nm size using small-angle neutron scattering. It was unexpectedly found that the polymer chain had the same size as in the free solution. At the same time, the simulation results showed that the chain should be strongly elongated

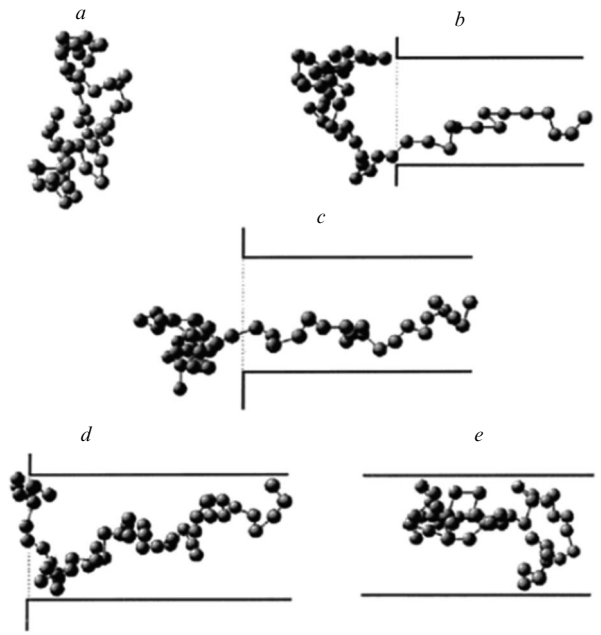


Figure 10. Chain conformations at different stages of penetration into a pore.[99]
Penetration degree (%): (*a*) 0 (free solution), (*b*) 28, (*c*) 42, (*d*) 89, (*e*) 100 (complete penetration).

in the pore. In the search for the reasons of this contradiction, the authors noticed that polymer chains are confined only by the walls of pores of arbitrary shape and that pores are interconnected, whereas analysis of small-angle neutron scattering data was based on the model of isolated cylindrical pore. A repeated analysis including a more realistic description of pores showed that the chains in pores were indeed elongated in comparison with the chains in the free solution and their sizes corresponded to those predicted in the simulation.

Other purposes were pursued in the experimental studies of polymer solution flow through a membrane performed by Wu and co-workers.[101–106] The authors intended to get an experimental proof for the prediction made by De Gennes that the conformational transition proceeds as a first-order transition. With this purpose, they chose a special double-layer membrane (Fig. 11 *a*) with conical pores in accordance with the theory requirements. The inlets of the pores were sufficiently large so as not to obstruct the passage of polymer coils; the outlet was 20 nm in diameter. Polystyrene molecules with $M = 3.5 \times 10^4$ Da and with the coil size of 9 nm could freely pass through the membrane, while polystyrene molecules with $M = 6.9 \times 10^6$ Da and with the coil size of 99 nm could not. The results are shown in Fig. 11 *b*.

As can be seen, the relative content of the polymer in the solution after filtration depends on the polymer molecular mass (which is accounted for *via* the ratio of macromolecular coil diameter to pore diameter) and on the velocity of liquid flow through the membrane.

Polystyrene with low molecular mass freely passed through the membrane at any flow velocity, whereas polystyrene with molecular mass of 6.9×10^6 Da was stopped by the membrane at low flow velocities and passed through at higher velocities. The transition between these regimes was quit sharp, indicating that this is a first-order transition. For comparison, the results obtained earlier by Anderson and co-workers[84–87] in experiments on filtration of polystyrene solutions through mica membranes are also shown in this figure (see data series *1–3* in Fig. 11 *b*). As can be seen, the CS transition in this case is smooth and rather corresponds to a second-order transition. The exact pore geometry in mica membranes is unknown, but clearly, it not only affects the type of conformational transition during filtration of polymer solution through the membrane, but also influences other transport characteristics of the flow.

This conclusion was confirmed by simulation of particle scattering dynamics for the FENE model of the polymer chain in channels of different geometry.[107] It was found that the circular-cross-section channels are more favourable for

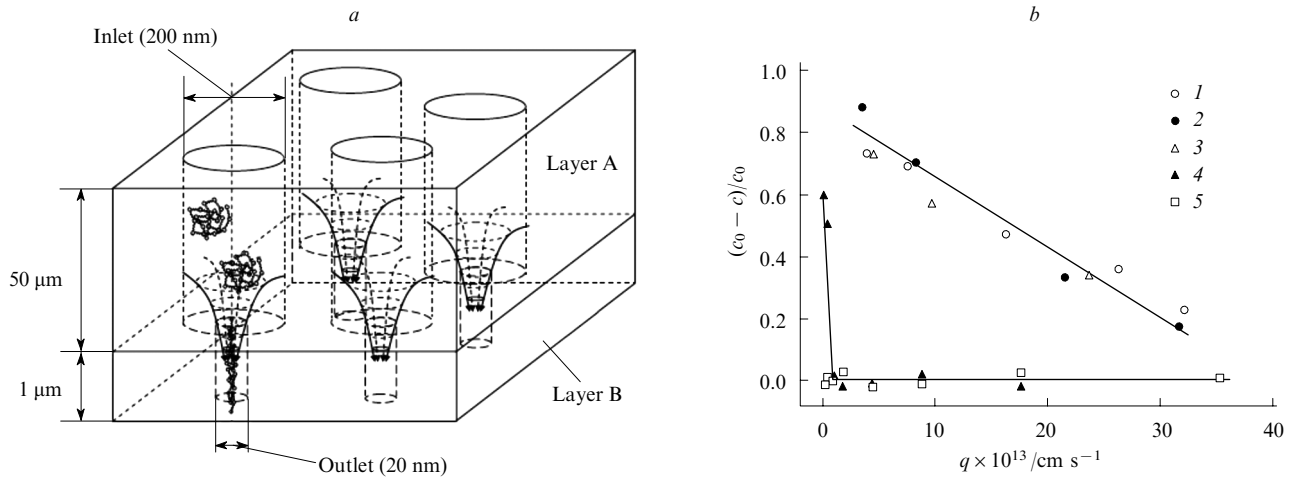


Figure 11. Schematic representation of a two-layer membrane (*a*) and dependence of filtration outcome on the flow velocity (*b*);[101]
c_0 and c are the starting and final (in the filtrate) polymer concentrations, respectively; λ: (*1*, *5*) 0.9, (*2*) 1.9, (*3*) 3.5, (*4*) 9.9; $\lambda = 2\,R_h/D$, where R_h is the radius of a macromolecular coil, D is the pore diameter.

macromolecule stretching than the square cross-section channels in the corners of which flow circulation is possible. Macromolecules are predominantly concentrated in the middle of a channel. Macromolecules located closer to the channel walls are elongated to a higher extent than macromolecules located at the channel centre and usually having a coil conformation. It was also noted that the presence of a polymer has no effect on the temperature profile of a flow, but strongly affects the density and velocity distributions in the flow. However, according to the data of Z Li *et al.*,[108] the effect from the polymer presence on the flow velocity profile is insignificant, but one should take into account the fact that because of hydrodynamic interaction of polymer molecules with channel walls, the molecules migrate towards the channel centre.

Simulation of the dynamics of particle scattering for the FENE model of the polymer chain in order to study the dendrimer (star-shaped polymer) movement in a tube with a diameter at least twice as large as the radius of the polymer coil was reported.[103–106] It was predicted and experimentally confirmed that star-shaped polymers with many arms tend to migrate to the centre of the tube where the flow velocity is larger; therefore, these polymers are faster eluted from the centre of a tube. The critical flow velocity for dendrimers depends on the degree of polymerization of both the whole chain (N) and its separate fragments (N_b)

$$q_c \approx N^{\omega} N_b^{\varphi}$$

In contrast to previously reported values of $\omega = 1/3$ and $1/4$, as well as of $\varphi = 1/15$ and $-1/4$ for weakly and strongly confined macromolecules, respectively, it was found that $\omega = 1.0$ and $\varphi = -0.4$. In the authors' opinion, these values better describe the behaviour of dendrimers. The dependence of the q_c quantity on the pore diameter was given in the form

$$q_c \approx D^{-0.8}$$

Other corollaries of the theoretical model suggested by De Gennes were also verified in experiment.[103, 104] Measurements of the critical flow rate at which macromolecules with high molecular mass start to pass through a membrane, confirmed that it is independent of M. However, the experimentally obtained linear critical flow rate of 5.56×10^{-15} ml s^{-1} turned out to be 10–200 times lower than the theoretically predicted value. This discrepancy was attributed to the wrong assumption of solvent impermeability of some elongating chain fragments, which was made in the De Gennes theory. Acceptance of full hydrodynamic permeability of these fragments and determination of their virtual length made it possible to reconcile theory with experiment and explain the decrease in the critical flow rate with increasing pore size. Using a new mathematical apparatus, Freed and Wu [105] confirmed that hydrodynamic friction forces are underestimated in the classical De Gennes theory, because of which the classical theory predicts critical flow rate values that are 10^2–10^3 times larger than the experimentally obtained values. This discrepancy is eliminated by taking account of hydrodynamic interactions of fragments of elongated chains, and the results obtained in this way are in good agreement with the experimental data.

Thus, the restriction of free migration of macromolecules in channels and pores of different configurations and sizes was the subject of numerous theoretical and experimental studies. As can be expected, confinement of the space where molecule is placed results in that the macromolecule assumes a shape determined by the shape of the channel in which it is placed (Fig. 12). However, the authors of many of the developed models did not even raise the question of how a macromolecule whose size in a static solution is considerably larger than the diameter of the channel falls into these confined conditions. The answer to this question was given by the De Gennes theory.[80, 81] An important point of this theory (especially, for studies of polymers by chromatography) is introduction of the concept of critical flow rate of a liquid flux, above which macromolecules, due to their deformation, are capable to penetrate into channels with diameters smaller than the polymer coil diameter. In the classical theory, this flow rate depends on neither the polymer molecular mass nor the channel diameter. However, this was at variance with experimental observations. Therefore, a certain correction of the theory was carried out that made it possible to bring experimental data and theoretical results into agreement.[101–106]

It is noteworthy, however, that some discrepancy between theoretical models (see above) and the practice of polymer separation (especially, of biopolymers) still remains. The ultrafiltration method has been successfully used in biochemistry for separation of biopolymers for a long time, and special membranes necessary for separation of polymers according to their masses are commercially available.[110] In recent years, asymmetrical flow field-flow fractionation technique has found wide application.[111] In this method, membranes with a specified level of mass

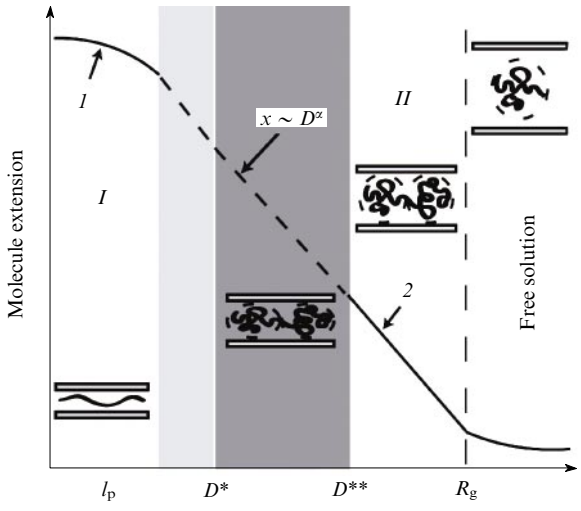


Figure 12. Schematic representation of different regimes of macromolecule extension depending on the channel size.[109]
(*I*) Regime of almost complete chain extension (Odijk regime); *II* regime of the dumb-bell conformation (De Gennes regime); (*1*) the curve segment corresponds to the relationship:
$\langle x \rangle = (L/\lambda)(\lambda \cos\theta) = L[1 - 2\alpha(D/l_p)^{2/3}]$,
(*2*) the curve segment corresponds to the relationship
$\langle x \rangle \approx L(wl_p)^{1/3}(D)^{-2/3}$. The following designations are used: L is the contour length of the chain, θ is the angle of segment deflection, D is the channel diameter, l_p is the persistence length of the polymer chain, w is the effective width of the polymer chain, D^* and D^{**} are transition regime parameters.

selectivity are used. Having accepted the validity of the above theoretical and experimental data, one concludes that the efficiency of application of the listed separation techniques is largely determined by proper choice of the liquid flow velocity, which has to be lower than the critical velocity.

IV. Flowing of polymer solutions through a sorbent layer (chromatographic column)

The above regularities in behaviour of macromolecules in a liquid flow were obtained for idealized cases, *viz*., a real polymer chain was replaced by some ideal model [the dumb-bell model, a bead–spring chain without (Rouse model) or with taking account (Zimm model) of hydrodynamic interactions, *etc*.], the flows had strictly defined profiles (elongational flow, shear flow, *etc*.), the consideration was typically carried out for a single channel of strictly specified shape. In real systems, a porous structure is usually produced by packing grained particles into a layer or by synthesis of the porous layer, and idealized conditions can hardly be achieved in these systems. The channel geometry in real structures is often unknown (for instance, in monolithic sorbents or polymer membranes) and, additionally, channels are spread in the shape and size. Naturally, the liquid flow going through the pores cannot be homogeneous or definite.

The study of macromolecule conformations in a flow even in a simple porous medium is additionally complicated by the Lagrange instability, which results from shear stress (polymer molecules during their movement are affected by different forces because of numerous narrower and wider sections in the porous structure).[112] Measurements of viscosity, birefringence and light scattering for a polymer solution are used most often for the study of conformational changes in macromolecules. Several chromatography techniques can be applied to investigation of the passage of polymer solutions through a porous medium. Hoagland and Prud'homme[112] were the first to pay attention to this opportunity and suggested using hydrodynamic chromatography technique to study the changes of macromolecule sizes in a liquid flow. This method was theoretically substantiated by DiMarzio and Guttman[7] in 1970. Then it was proposed for separation of polymers according to coil size. An analytical form of the dependence of the retention time on the coil size was obtained. Subsequently, it was repeatedly adjusted, and at present, it is expressed by the following equation:[113]

$$\varphi = (1 + 2\lambda - C\lambda^2)^{-1} \qquad (3)$$

Here φ is a relative elution time, which is the ratio of the polymer elution time to the elution time of a low-molecular-mass standard, λ is the ratio of the macromolecule radius to the channel radius, C is a coefficient.

Equation (3) was obtained for a laminar liquid flow with a parabolic velocity profile. With the lapse of time, the effects of other factors such as permeability of a polymer coil for a solvent, macromolecule rotations, *etc*. were included in the equation. All of these effects are described by the quadratic term, and the coefficient C in Eqn (3) varies by more than an order of magnitude depending on the chosen model.[113] At the same time, it turned out that the relative retention of a polymer in the chromatographic column is independent of the liquid flow velocity as it was pointed out by DiMarzio and Guttman.[7] The model of hydrodynamic chromatographic separation does not assume penetration of a polymer coil into a capillary channel if the coil size is larger than the channel diameter; therefore, the φ value goes to infinity at $\lambda \to 1$, *i.e*., the channel becomes blocked. This aspect of the model is in obvious contradiction with the behaviour of macromolecules in a liquid flow (see above). Therefore, experimental verification of the hydrodynamic chromatography technique (HDC) acquired special relevance.

DiMarzio and Guttman[7] suggested a device construction, which, according to their opinion, could ensure a continuous process of particle separation by the HDC method. However, this device turned out too complicated. In practice, this method was implemented to separate polymers, colloidal particles, latexes and other similar substances using unfilled capillaries[114,115] and columns packed with non-porous (or impermeable for the separated substances) sorbents. The first studies devoted to HDC of polymers[116–118] merely demonstrated the possibility of their separation, but did not consider any regularities of this approach, and even the separation mechanism was not always interpreted correctly because there was a view that it is just a kind of size exclusion chromatography.[116]

In the studies devoted to the HDC behaviour of polymers,[112,119,120] a dependence of the relative retention time on the eluent flow velocity was experimentally established. It was valid for polymers with ultrahigh molecular mass (of about 15×10^6 Da) but inoperative for polymers with molecular mass of $< 2 \times 10^6$ Da. In one of these publications,[112] this dependence was directly attributed to deformation of macromolecules in a liquid flow in accordance with the De Gennes theory. The authors analyzed the dependence of the relative size of a polymer coil on the Deborah parameter and showed that changes start at De > 0.5 as it was predicted by the CS transition theory. Moreover, the dependence of the macromolecule sizes measured by HDC was constructed for rigid and very large objects such as tobacco mosaic virus and polysaccharide xanthan. The behaviour of these objects agreed with the predictions of the simple dumb-bell model. At the same time, as in the previous studies, no effect of flow velocity on the HDC data was revealed for polymers with low molecular mass. Analogous results were also obtained by other authors for columns of different types: the flow velocity had no effect on the relative retention time of polymers with molecular mass of $\leqslant 10^6$ Da; however, for polymers with higher molecular mass, the increase in the flow velocity resulted in the increase in the relative retention time.[121,122] Some factors which could potentially lead to a dependence of the relative retention time on an eluent flow rate were considered by Stegeman *et al*.[123] Those were the factors listed below.

1. Diffusion caused by heterogeneity of the flow velocity profile. In a laminar flow, the regions located near the channel walls are the regions of enhanced shear strain as the flow velocity gradient in the radial direction is maximal there; the region of low strain is located at the centre of the channel. As a result, molecules that are situated near the walls and have entropy lower than the entropy of molecules at the centre of the channel diffuse from the walls to the centre. This process is intensified with increase in the flow velocity and molecular mass of particles, *i.e*., with their size,

and with decrease in the channel diameter. Under the HDC conditions, this results in reduction in the relative retention time with increasing flow velocity. Some authors [103–108] who observed this effect noted that the diffusion direction can be reversed and macromolecules can predominantly diffuse to walls if the coils are permeable for a solvent.

2. Deformation of macromolecules under the influence of an eluent flow. Stegeman *et al.* [123] considered this process as a macromolecule deformation caused by a free liquid flow and concluded that its contribution should be insignificant under the HDC conditions. However, the data analyzed above (see Section II) and, especially, the data on polymer solution filtration [84–87, 101, 102] indicate the opposite.

3. Radial migration of particles due to solvent inertia. A force arising because of solvent inertia, which is directed perpendicularly to the flow axis, acts on spherical particles driven along the channel by a viscous flow. This force causes migration of particles towards the channel walls into a ring-shaped region located at a distance of $0.6\,r$ (r is the channel radius) from the flow axis. The effect of the force of inertia increases with increasing flow velocity, increasing particle size and decreasing channel radius.

4. Hydrodynamic diffusion of macromolecules in a non-uniform flow. According to model calculations,[124–128] molecules which cannot be oriented along the flow because of its profile curvature (for example, because of parabolic profile of the laminar flow) diffuse towards the profile concavity. Therefore, in a laminar flow in a hollow tube, molecules diffuse to its centre, while in a tube filled with a sorbent whose channels are formed by grain surfaces, molecules diffuse to the sorbent surface.

5. The effect of a flow splitting. This effect was predicted back by Giddings.[129] It consists in that large molecules are forced to move to the sorbent surface when the flow is split at a sorbent particle. This results in that the polymer concentration at the sorbent surface is higher than the equilibrium concentration. Giddings also thought that macromolecules could get stuck in narrow channels. However, as it has been shown in the previous Section, this can occur only if the flow velocity is lower than the critical one. According to Giddings, the effect of flow splitting increases with the increase in the polymer molecular mass and in the solvent flow velocity.

Thus, a large number of factors can potentially give rise to a dependence of the relative retention time of a polymer on the flow velocity. The effects of these factors are uncorrelated and often differently directed. Many of these factors have no sufficient experimental justification or theoretical substantiation, which restricts their utility for explanation of mechanisms of macromolecule separation by HDC. Accumulation of experimental data still remains an important task in the field of HDC, and it really gives unexpected results.

The dependence of relative retention of high-molecular-mass polymers on the eluent flow velocity was confirmed once again by Stegeman *et al.*,[130] while the study of Venema *et al.*[131] showed that, besides this dependence, peak splitting was observed in chromatograms at high flow velocities in the case of very high-molecular-mass polymers (9.8×10^6 Da). According to the data obtained,[131] this splitting was not related to destruction of the polymer molecules; the nature of this phenomenon remained unknown. Liu *et al.*[132, 133] studied this effect more exten-

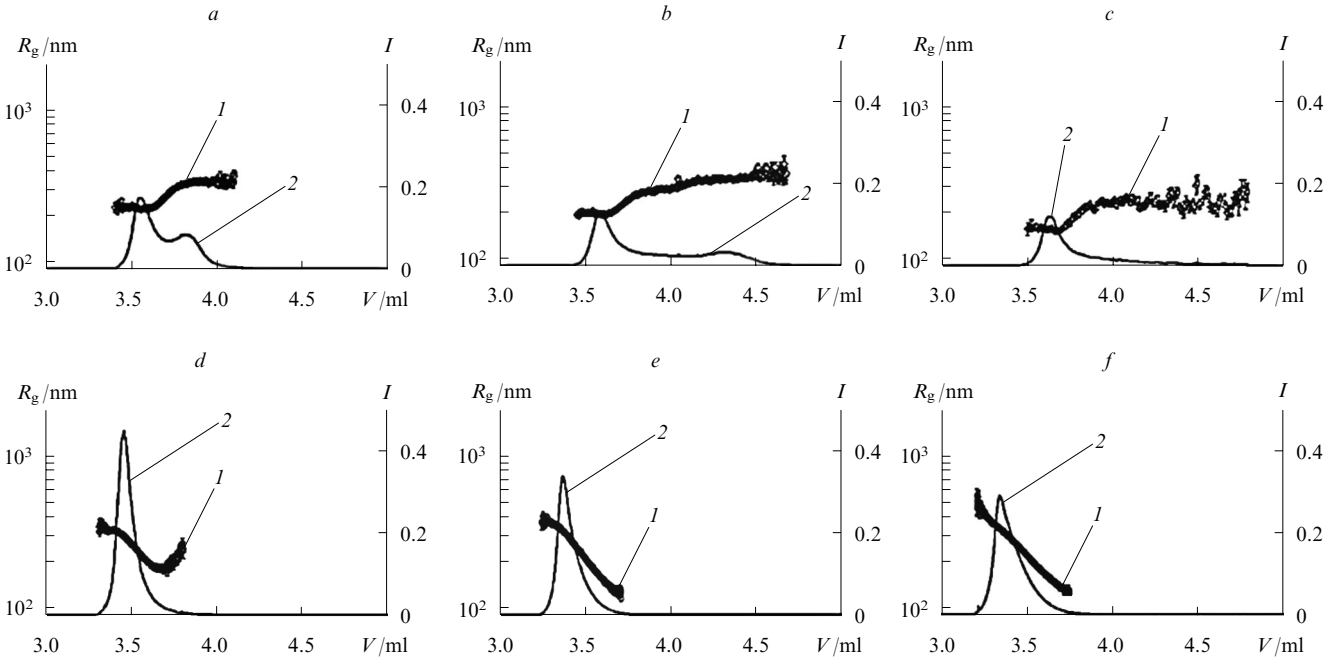


Figure 13. Gyration radius R_g (*1*) and concentration profile (*2*) for elution of polystyrene with molecular mass of 14.37×10^6 Da using a column packed with non-porous particles 15 μm in size *vs.* eluent flow velocity.[132]
Flow velocity /ml min^{-1}: (*a*) 0.3, (*b*) 0.5, (*c*) 1.0, (*d*) 0.1, (*e*) 0.05, (*f*) 0.025. The concentration profile of the elution was measured with the use of a refractometric detector, the macromolecule sizes were determined using a light scattering detector. I is the refractive index, V is the eluent volume.

sively. When HDC of polystyrene standards was carried out using a column packed with non-porous spherical particles and a light scattering detector (MALS), it was found that if two peaks appeared in the chromatogram, macromolecule size distribution within each peak became monodisperse (Fig. 13 *a*). The authors attributed the observed very unusual effect to simultaneous occurrence of two independent processes: the CS transition in macromolecules under the influence of flow and switching of the retention mechanism from HDS to slalom chromatography.

The slalom chromatography mechanism was discovered in the separation of large fragments of nucleic acids,[134, 135] molecules of which do not penetrate into pores and, as in HDC, they move in the intergrain space. However, the sequence of elution of polymers in the slalom chromatography is opposite to that in HDC, *viz*., low-molecular-mass polymers are eluted faster than high-molecular-mass polymers. This inversion of the elution sequence is usually attributed to retardation of long macromolecules on the sorbent grains[136, 137] during their movement along the column (Fig. 14).

It is noteworthy that before the study of Liu *et al*.,[132] slalom chromatography separation mechanism was noted only for biopolymers (mainly DNA) but not for synthetic polymers. According to the authors opinion, all macromolecules in the sample were in the coil conformation at low flow velocities (0.025–0.10 ml min^{-1}) and only one peak emerged in the chromatogram that was indicative of a rather broad dispersion of coil sizes (from 425 to 125 nm), although the sample polydispersity (M_w/M_n) was equal to 1.3 according to the manufacturer. For every eluent flow velocity, there is a certain critical coil size (R_{gc}) such that macromolecular coils of this size undergo the CS transition at this flow rate. Molecules with $R_g > R_{gc}$ have already been unfolded at a particular flow velocity and are eluted according to the mechanism of slalom chromatography, *i.e*., after molecules with coil size of R_{gc}. Conversely, molecules with $R_g < R_{gc}$ remain in the coil conformation and are eluted according to the HDC mechanism, *i.e*., also after molecules with coil size of R_{gc}. Thus, the first peak in the chromatogram corresponded to a mixture of large and small molecules. Since the light scattering detector gave an average size of molecules, the mutual compensation of the sizes gives rise to the first plateau in the chromatogram (see Fig. 13 *a*–*c*) with the average size close to R_{gc}. The polymer molecules that are eluted to form the second peak and, respectively, the second plateau, represented, in the authors' opinion, a mixture of macromolecules with $R_g \gg R_{gc}$ and $R_g \ll R_{gc}$; the former macromolecules are highly extended, while the latter are almost not extended and exist in the coil conformation. Mixing of these types of macromolecules resulted in the increase in the average coil size determined by the light scattering detector and the appearance of the second plateau. According to this model, polymer molecules with a coil size corresponding to the critical coil size at the given flow velocity are always eluted first.

The model of Liu *et al*.[132, 133] postulated for the first time a close relationship between chromatographic separation and conformational transitions of polymers. This model also demonstrated the potential of chromatography for the study of fine conformational transition processes in polymers that are difficult to detect by other methods. Naturally, the proposed theory could not explain all features in the behaviour of ultrahigh-molecular-mass polymers in chromatographic processes; however, it triggered further studies along this line.

In the study of polymer behaviour in columns filled with a monolithic sorbent[138] and with a sorbent with particles of 1.7 μm size (ultrahigh pressure liquid chromatography, UHPLC),[139] dependence of separation of high-molecular-mass polymers on the eluent flow velocity and the appearance of two peaks in the chromatogram upon reaching the critical eluent flow velocity were observed. The effect of the eluent flow velocity in experiments with monolithic columns was evaluated on the basis of the Deborah parameter. It was concluded that the observed effects are beyond the scope of the classical theory of polymer deformation in the liquid flow since the shear strain is not constant throughout the flow cross-section (the largest shear is at the periphery of the polymer coil). This may be responsible for the depend-

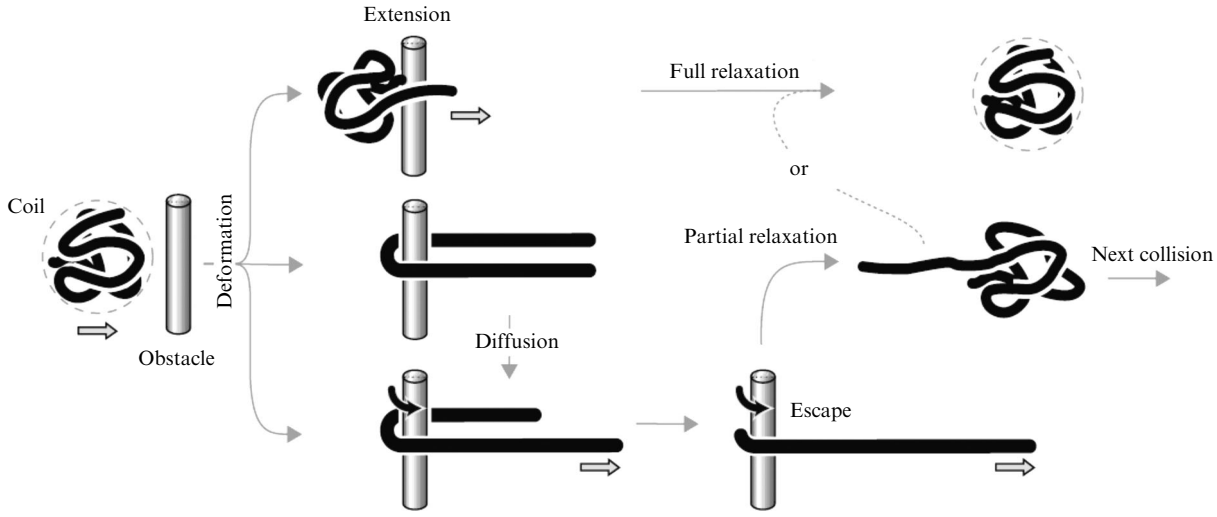


Figure 14. Schematic representation of different conformations of a polymer molecule, which arise when macromolecules collide with obstacles.[137]

ence of separation on the flow rate. This conclusion was based on the fact that even molecules whose coil size is close to the channel diameter move through a monolithic column faster than the eluent flow. This fact contradicts the classical theory of HDC and, according to the authors' opinion, this is related to the macromolecule movement according to the reptation mechanism.[92] At the same time, it was pointed out that macromolecules could be destroyed by the eluent flow in the course of separation with the use of UHPLC.[139] This problem was considered in detail in another study,[140] and it was shown that under the UHPLC conditions, polystyrene macromolecules with $M > 4 \times 10^6$ Da can undergo degradation, which can be avoided if low eluent flow rates are used.

A more detailed study of the behaviour of ultrahigh-molecular-mass polymers during filtration of their solutions through capillary monolithic columns was carried out by Kurganov and co-workers.[141, 142] In the case of polystyrene with $M = 2.11 \times 10^7$, 8.91×10^6 and 4.41×10^6 Da, the authors observed a change in the elution profile with increasing flow rate, which was similar to the change shown in Fig. 15 for the sample with $M = 2.11 \times 10^7$ Da. At low flow rates, the single peak present in the chromatogram corresponds to polystyrene. Peak splitting appeared upon an increase in the rate. The higher the eluent velocity, the more distant the two peaks from the initial single peak. However, complete separation of these two peaks was not achieved even at the largest eluent flow rates reached in this study. The peak with lower relative retention (peak *I*) approached quite rapidly the limiting relative retention, which was not changed with further increase in the flow rate. The relative retention of the other peak (peak *II*) was infinitely increased with the increase in the flow rate. At fairly high eluent flow rates, the relative retention of peak *II* was even larger than that of the low-molecular-mass marker (benzene). Variations in the eluent flow rate resulted in similar changes in the elution profiles of polystyrene standards with $M = 8.91 \times 10^6$ and 4.41×10^6 Da; however, the extent of changes in the relative retention of these polymers was smaller than for polystyrene with $M = 2.11 \times 10^7$ Da.[141, 142] In the case of polystyrene standards with $M < 4 \times 10^6$ Da, no change in the elution profile was observed throughout the whole range of flow rates used, and the relative retention of these polymers was independent of the flow rate within the accuracy of measurements.

The authors [141, 142] also found that relative intensities of peaks *I* and *II* changed with the change in the eluent flow velocity. Indeed, peak *I* of polystyrene with $M = 2.11 \times 10^7$ Da was much more intense than peak *II* at low flow velocities, whereas both peaks had the same intensity at linear velocities of > 0.125 mm s^{-1}. On the contrary, the intensity of peak *II* for polystyrenes with $M = 8.91 \times 10^6$ and 4.41×10^6 Da was higher than that of peak *I* in the whole range of the used flow velocities.

The described changes in polymer elution profiles upon varying the eluent flow rates are quite similar to the known changes in the elution profiles of samples that are involved in some dynamic processes such as isomerization or enantiomerization in the chromatographic column.[143] A typical elution profile in so-called reactive chromatography is shown in Fig. 16 (additional examples can also be found in another study [144]). A mathematical tool suitable for calculating the rate constants for forward and reverse reactions from the elution profile was proposed. On the assumption that the transition from the coil conformation to the stretched conformation can be considered as a first-order reaction, Kurganov and co-workers [141, 142] used this mathematical tool to calculate the rate constants for the forward and reverse reactions and the equilibrium constant for this transition. As one would expect, it turned out that these constants were dependent on the eluent flow velocity, the rate constant of the forward reaction linearly increasing with the increase in the flow velocity. Self-acceleration of the coil–stretch transition process was predicted by the De Gennes theory, and the experimental observation of this effect can be considered as indirect evidence for the conformational nature of the phenomena that are observed in the chromatography of polymers. An alternative mechanism connecting the phenomena observed in chromatography of polymers to their destruction is considered briefly below.

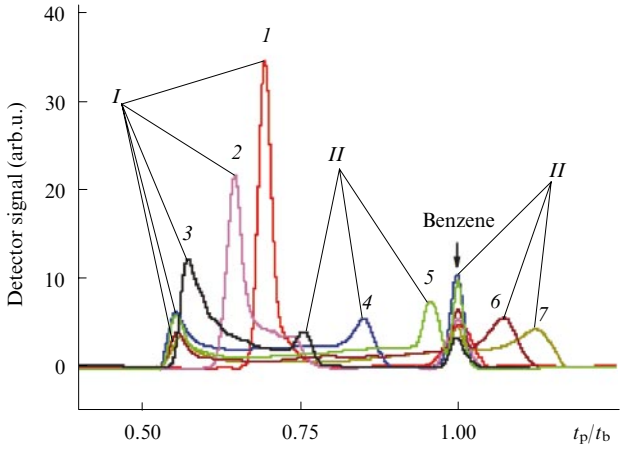


Figure 15. Changes in the elution profile for polystyrene standard with $M = 2.11 \times 10^7$ Da depending on the linear velocity of the eluent flow.[141]
Flow velocity /mm s^{-1} : (*1*) 0.0177, (*2*) 0.0291, (*3*) 0.0618, (*4*) 0.114, (*5*) 0.155, (*6*) 0.280, (*7*) 0.303; t_p and t_b are the retention times of the polymer and benzene, respectively. Peaks *I* and *II* are defined in the text.

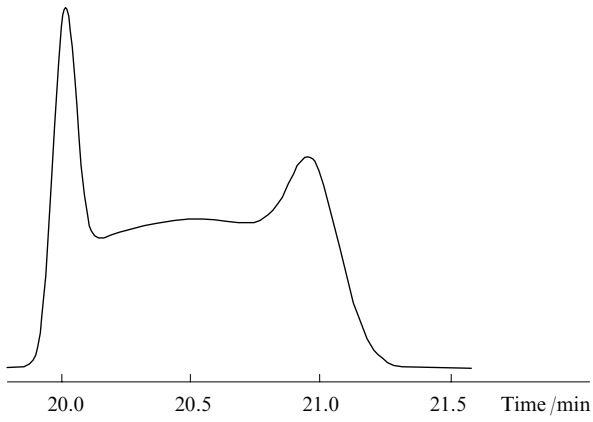


Figure 16. Typical elution profile of a sorbate involved in the chromatographic column in an isomerization reaction with an equilibrium constant of > 1.[143]

V. Degradation and destruction of macromolecules in an eluent flow

The possibility of degradation of polymer chains in a liquid flow was indicated back in 1970s;[145] the data on such degradation published before 1984 are summarized in a review.[146] The mechanism of the degradation process is quite complicated, and some details of this mechanism have not been clarified as yet. Two types of forces potentially capable of giving rise to macromolecule degradation are usually discerned in chromatographic systems: shear forces and extensional forces.[140] It is easy to notice that these forces coincide with the forces which were considered when stretching of macromolecules in a liquid flow was discussed (see Section II) and which are determined by the flow velocity profile (see Fig. 5). As noted above, the laminar flow typical of chromatography is not a purely shear or elongational flow; domination of a particular force depends on the arrangement of a macromolecule relative to the flow axis. The rate of destruction in a flow ($\dot{\gamma}$) moving through a layer of a grained sorbent can be found from the equation [146, 147]

$$\dot{\gamma} = \frac{4\bar{v}}{r_h} = \frac{4q}{\epsilon A r_h} \quad (4)$$

where $\bar{v}$ is the mean linear flow velocity, r_h is the mean hydraulic radius of channels in the sorbent layer, q is the volume flow rate, ϵ is the intergrain porosity, A is the layer cross-section. The r_h value is usually defined as the radius of the channel which has the same wettable surface area to volume ratio as the sorbent layer. It can be obtained from the equation

$$r_h = \frac{d_p \epsilon}{3(1-\epsilon)} \quad (5)$$

here d_p is the average size of sorbent particles.

It is noteworthy, however, that this definition of r_h is not the only one. For instance, Bird *et al.*[3] defined r_h as the radius of a capillary having the same hydrodynamic resistance as the sorbent layer; the value of r_h in this case is half that obtained from Eqn (5).

Besides the shear strain along the flow direction, a macromolecule moving through a porous layer is affected by a number of other forces arising due to both difference in flow velocities in different channels and occurrence of various hindrances on the path of the polymer molecule (see Fig. 14). These forces substantially exceed the shear force and, as it is assumed, are responsible for macromolecule degradation.[148]

For these strains (as in the case of elongation), a critical parameter $\dot{\gamma}_c$ was introduced; if this critical value is exceeded destruction of macromolecules occurs. Extension of macromolecules usually precedes the destruction since $\dot{\gamma}_c > \dot{\varepsilon}_c$ (Refs 149 and 150). In the case of ultrahigh-molecular-mass polymers, these parameters are approximately equal and a macromolecule may be destroyed in the coil conformation.[9, 14] According to the calculations of Keller and Odell,[14] this destruction can be observed for polymers with $M > 3 \times 10^7$ Da. According to simulations,[37, 147] if a macromolecule moves in a free flow ($r_h \gg R_g$), the scission point is located in the middle of the chain. However, it can be shifted if the macromolecule experiences some external impacts, for instance, from the sorbent particles (see Fig. 14). In particular, Hsieh *et al.*[151] simulated the destruction of macromolecules in a planar cross flow and found that polymer molecules can be cut in the middle of their chains and then they can undergo subsequent destruction (quartering). In contrast to the common view that the scission mainly occurs in the stagnation region of an elongational flow, the simulation showed a significant contribution of the shear flow existing near the channel walls, which is responsible for the scission of macromolecules at a flow intersection.

On the whole, polymer degradation depends on a very large number of factors, particularly, on the factors such as the nature and structure of the polymer, solvent viscosity, concentration, temperature, *etc.*[146, 152] Apparently, it explains a large scatter in the data obtained by different authors, although the number of publications devoted to scission of macromolecules is much smaller than, *e.g.*, the number of publications on conformational transitions of macromolecules in liquid flows. As a result of such uncertainty, experimental results obtained in a laboratory can hardly be reproduced in other laboratories, and, as suggested by Uliyanchenko *et al.*,[139, 140] the use of the Deborah parameter is the best way to obtain comparable and reproducible results.

* * *

Over the past few decades, polymer chemistry has made large progress in understanding and description of processes of conformational transformations of macromolecules. The developed theoretical concepts, which were analysed in the present review, formed the basis of many models used in rheology, chemistry of solutions of polymers, *etc.* At the same time, they are almost not used in chromatography of polymers, even in the areas such as size exclusion or hydrodynamic chromatography, which are directly related to the size and, hence, conformations of macromolecules. Until polymers with relatively low molecular mass (up to $\sim 10^6$Da) were studied with the use of chromatography, the flow velocity was not considered as a parameter influencing the results of the molecular mass analysis. The situation was sharply changed when ultrahigh-molecular-mass polymers became the objects of chromatographic study. In this case, the eluent flow velocity affects not only the column efficiency, but also the character of its calibration curve and, therefore, the results of the molecular mass analysis. Furthermore, in chromatographic studies of such polymers, a number of effects were revealed, which cannot yet be explained in the framework of the existing theories of conformational transitions or destruction of macromolecules. Further experimental and theoretical studies are required to elucidate the nature of these unusual effects.

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