Possibilities and peculiarities of spray technologies in organic synthesis

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Abstract

Size effects considerably change the state and physicochemical properties of dispersal systems. The peculiarities of chemical processes occurring in small (nano, pico, and femtolitre) volumes are of a great importance for the production technologies of unique materials. The aim of this work was the experimental confirmation of size effects during chemical processes in small volumes and their interpretation based on the concepts of chemical thermodynamics.

The object of the study consisted in reactions of organic synthesis conducted in ensembles of sessile drops formed by aqueous solutions of organic compounds with the participation of a gaseous medium. The methods of optical microscopy with digital image processing were used for observation. The experiments definitely demonstrate the influence of geometric parameters (radius, contact angle) on the kinetics of phase and chemical transformations in polydisperse ensembles of sessile drops of organic and aqueous-organic mixtures interacting with volatile reagents in a gaseous medium. These features are manifested in the kinetics of changes in the size of drops as well as in the morphology of products obtained by their evaporation.

The interpretation of size effects in the framework of equilibrium chemical thermodynamics explains the shifts in chemical equilibrium and changes in the reaction rate. The equilibrium conditions arising in drops of different volumes during mass transfer with the gas phase were described. It is stated that the most important factor in the processes of organic synthesis using spray technologies is the high surface activity of organic substances. Comprehension and practical application of these peculiarities allows adjusting the reaction rate, improving the mutual solubility of partially miscible reagents, and affecting the composition and properties of the final product.

Keywords: organic synthesis in spray, size effects, chemical equilibrium constants, liquid-vapour equilibrium, nanoreactor.

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1. Introduction

Chemical processes involving nanoreactors are a rapidly developing area of nanotechnologies [1]. Any system with the size of the reaction zone comparable with colloid sizes can be called a nanoreactor. Most commonly the following are studied: nanoreactors in micelles formed by surfactants, in liposomes, nanocapsules, pores of nanostructured materials, and in microemulsions [2–5]. Drops in spray technologies are sometimes also considered to be nanoreactors. In fact, spray pyrolysis has already been used as an energy-efficient way of obtaining nanoparticles of metals, oxides, and other compounds [8, 9] used for the creation of functional and construction materials with special properties [10, 11]. The voids of porous materials in the volumes of which the synthesis is conducted, for example, for the modification of the properties of the surface of pores [14] should also be considered as nanoreactors.

The total amount of inorganic materials manufactured using spray technology is so far significantly greater than the amount of organic ones. At the same time, in organic synthesis these technologies have been successfully implemented in the production of pharmaceutical drugs [15] and polymers [16, 17], in particular through photopolymerisation [18,19], during the synthesis of particles with special morphology [20]. The effectiveness of spray processes allows creating green technologies for organic synthesis based on them [21].

Any volatile reagents or monomers can be quickly introduced to the synthesis during the spray stage. However, the prospects of using micro and nanoreactors are mainly associated with the peculiarities of chemical and phase composition of dispersed phases which are formed differently from macroscopic systems in the process of evolution of dispersed particles. The comprehension and practical application of these peculiarities allows increasing the reaction rate, improving the mutual solubility of partially miscible reagents, and affecting the composition and the properties of the final product [20, 22], etc. The processes in spray drops with organic components are more complicated as compared to inorganic substances [23]. In this case, the knowledge of patterns and correlation between physicochemical properties of the components

with size effects allows engaging a greater number of control parameters, which means that there are more opportunities for obtaining a wider range of materials.

In works [24–27] it is shown that a decrease in the size of drops contributes to an increase of the solubility of partially soluble components to the point of thermodynamic instability of heterogeneous state of nonmiscible components, while high supersaturation is more thermodynamically stable in small drops than in large ones. An expected consequence for reversible chemical reactions is additional influence of the volume of such heterogeneous "reactor" on chemical equilibrium. In a trivial version, an increase of the solubility or concentration of a solution of one of the reagents shifts the equilibrium towards the formation of the products when the solvent evaporates.

If the components of the reaction show surface activity, even more complicated patterns are formed. For such reagents, the Gibbs energy of the formation is different in the subsurface layer and in the volume. Correspondingly, constants of the reaction's chemical equilibrium should also be different in the subsurface layer and in the volume, while the effective equilibrium constant becomes dependent on the volume fraction of the subsurface layer. Then, according to the Van 't Hoff equation associating Gibbs energy of the reaction with equilibrium constants, surface activity of the products contributes to the shift of equilibrium towards the products, while the surface activity of the reagents decreases the equilibrium concentration [23]. In the general case, volume, specific area, and radii of curvature of the surface of drops become the factors regulating the conditions of the course and kinetics of chemical processes in a drop or an ensemble of drops exchanging components through the disperse medium.

As a rule, it is almost impossible to control the course of chemical processes in a quickly flying drop of spray, separate drops of concentrated emulsion, or pores of the material. However, the description of chemical processes occurring in small volumes is definitely of interest for many areas of modern technologies. Therefore, one of the goals of this research was the experimental simulation of size effects for

chemical transformations in a small volume based on visual observation and interpretation of these effects based on concepts of chemical thermodynamics. Ensembles of sessile drops partly allow simulating such processes [23–27].

2. Experimental

Reactions were conducted both in open and in partially or completely closed systems. During the reaction, the conditions corresponding to an open system were implemented in the simplest way. A transparent slide with an ensemble of drops of the solution of one of the reagents obtained while spraying was placed on the object plate of the microscope. In close proximity to the ensemble of drops there was a reservoir with volatile reagents (or their solution) or blotting paper soaked in a corresponding solution. Closed and partially closed conditions were implemented in a more complicated way. The unit used in these experiments is presented on a scheme (Fig. 1). The ensemble of drops was placed on the lower surface of the object plate *2*, lying on supports *3*. The volatile reagent solution *4* was placed under the object plate *2* on a movable object plate *5*. The choice of the shape of support *3* allows partially or completely limiting the mass transfer with the environment. Such structure allowed adjusting the presence of volatile reagents and the solvent in the system as well as controlling the rate of their evaporation into the external environment or recondensation between the drops and the reservoir.

The solution of a substrate was applied to the slide using a push-button sprayer. Glass treated with a chromic mixture and washed with distilled water or Lavsan were used as slides. Some object plates were treated with chlorosilane to increase the hydrophobicity.

The described microscopic observations can be performed using any microscope with a digital interface. The following microscopes were used in this work: MBS-10 with a DEM-200 eyepiece camera, Dino-Lite AM451, and Levenhuk D670T. To eliminate the thermal effect of the lighting, LED lights and mirrors were used. The evolution of the ensemble of drops in the course of the reaction was recorded as video files or a series of images. Two methods of observation were used: 1) two directly interacting solutions were continuously
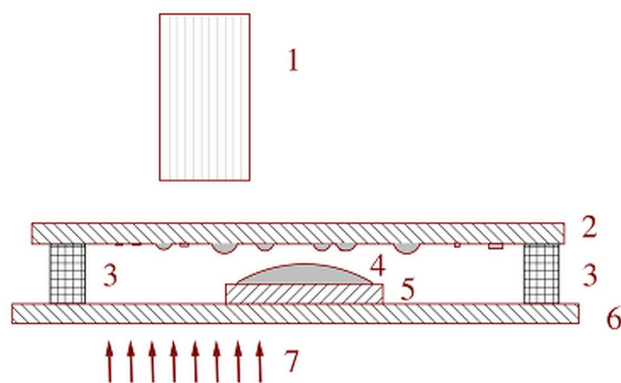

Fig. 1. Installation diagram. *1* – microscope objective, *2* – object plate with sprayed droplets, *3* – support, *4* – solvent, *5* – glass reservoir for volatile reagents, *6* – transparent base, moved by the microscope's target, *7* – lower illumination

recorded on video under the microscope; 2) the reaction was conducted in a chamber for a certain period of time, and after that the slide with drops was placed on the object plate of the microscope and the process of their evaporation from the open slide was recorded. In this case, the slide with the reagent was kept above distilled water for the same period of time as a blank experiment.

The experiments were conducted under room conditions (humidity: 25–45 %; temperature: 20–24 °C). To improve observability, medium and low-concentrated solutions were used, which allowed increasing the time of maturation of the ensemble of drops before the start of crystallisation.

All the reagents used were chemically pure.

3. Results and discussion

The description of phase transformations in a small volume [24] has demonstrated that microscopy is a convenient tool for experimental verification of the results of thermodynamic simulation. The developed methodology allowed discovering and observing for the first time two unusual effects in the solutions drops being evaporated: oscillating crystal–solution phase transformations as well as non-Ostwald behaviour of the ensemble of the drops of the solution where the lifetime of large drops in homogeneous state is shorter than the lifetime of small drops [24, 25].

Using ensembles of drops of different sizes, it is also possible to prove the influence of size effects on the dynamics of the course of reaction predicted in the framework of formal kinetics

and chemical thermodynamics. The search for these patterns was one of the main tasks of experimental observations.

Simple well-known reactions with volatile components were chosen for the observations. This allowed spatially separating the interacting components so that one or both reagents could be absorbed by a drop of the solution from the vapour phase. In this case, the dissolution rate of the reagent and its concentration in drops of different sizes as well as the reaction rate must depend on the curvature of the surface of the drop. In most cases, such criteria of the process as the morphology of the phase being formed and the evaporation rate of the drops were mostly sensitive to size effects.

Let us consider some of the options.

An example of the interaction between two volatile reagents is the reaction of formation of hexamethylenetetramine (urotropin) when formaldehyde is interacting with ammonia $6CH_2O + 4NH_3 \rightarrow C_6H_{12}N_4 + 6H_2O$. When a solution of any of the reagents is sprayed, drops evaporate from the open surface completely and rather quickly. If a slide with a solution of formaldehyde is sprayed on it remains for a short time (for 1 minute or longer) above the reservoir with the ammonia solution, a crystallization (Fig. 2) is observed during the evaporation of drops, which is definitely indicative of the formation of urotropin. It should be noted that the experiment reproduced the size effect described in [23] where formation of a multitude of secondary drops was observed on the surface free from evaporating drops. Fig. 2c shows that the reaction occurs both in the original and the newly formed drops. Fig. 2b shows that crystallisation takes place in large drops first. This is the manifestation of another size effect, non-Ostwald behaviour, that we previously described in [24, 28]. It is associated with the fact that significantly greater supersaturation of the solution can be achieved in small drops.

A similar example is the formation of crystals during the interaction between the ensemble of drops of the hydrogen peroxide solution and acetone vapour.

The interaction between the aqueous solution of urotropin and iodine is an example of reaction of low-volatile substrate with the vapour of a volatile reagent. Complex compounds (clathrates) are formed in the reaction of urotropin with iodine. An ensemble of drops of the aqueous solution of urotropin on a glass slide was kept above the alcohol solution of iodine, after which the structures formed during the evaporation of the drops were recorded. In this case, significant differences were observed in the morphology and the colour of urotropin crystals growing from the solution before and after the interaction with iodine vapour. It should be noted that there are also significant differences in morphology of crystals growing from the drops of aqueous and alcohol solution, which was taken into account during the observation.

An example of interaction between a non-volatile reagent with a volatile one is also presented by the reaction of glycine with formaldehyde. In this case, the interaction between the solution of glycine and the formaldehyde vapour shows only in the significant decrease in the evaporation rate. After being sprayed, the drops of the aqueous solution of glycine on an open glass slide evaporate and crystallise (at $t = 22\pm1$ °C, humidity 40–53 %) for several minutes (Fig. 3a) in a sequence reproducing non-Ostwald behaviour. Under the same conditions, crystallisation does
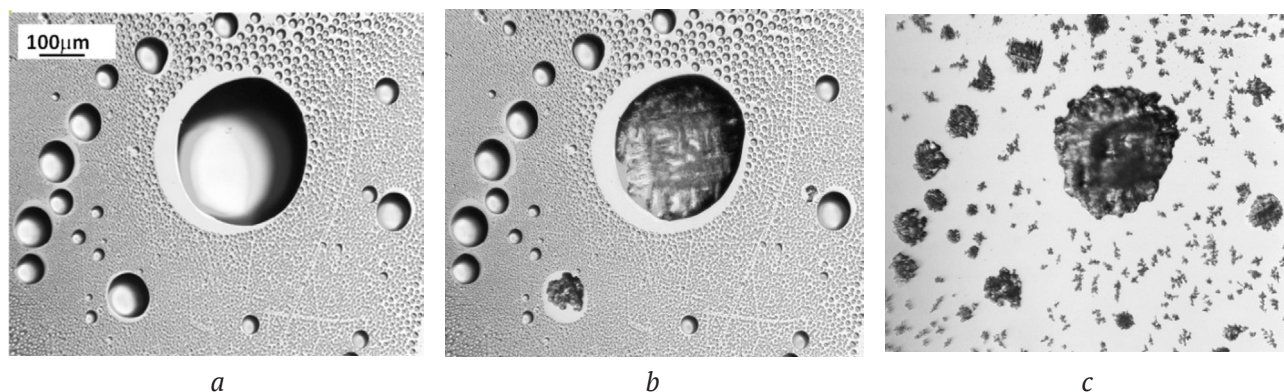

| a | b | c |

Fig. 2. The sequence of states of drops of formaldehyde solution kept in ammonia vapour during its evaporation (hydrophobised slide)
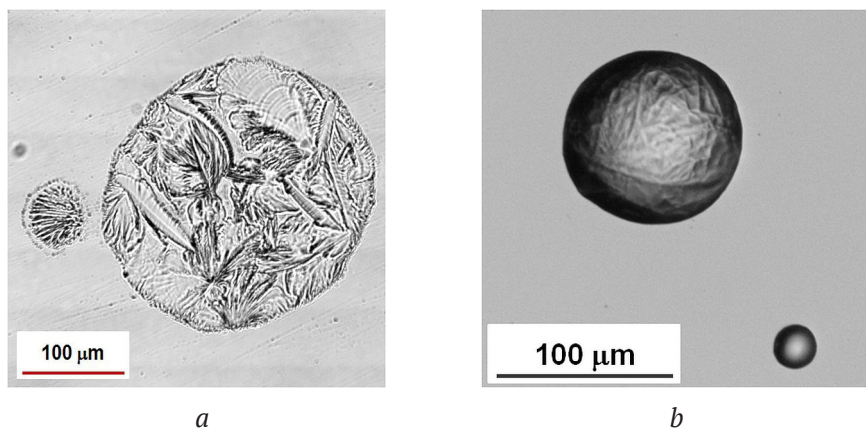
a

b

Fig. 3. Glycine crystals (a), droplet surface after reaction with formaldehyde (b)

not occur after the contact with formaldehyde vapour, and a film is formed on the surface of the largest drops (Fig. 3b). It can be assumed that the result of the interaction was the trimerisation or polymerisation of N-methylene glycine [29, p. 334].

The experiments with aqueous solutions of resorcinol interacting with formaldehyde turned out to be the most demonstrative, and the interpretation of the obtained images was definitive (Fig. 4). The criteria of the process were the morphology of the structures formed on the slide after the evaporation of the drops and the evaporation rate. Crystallisation with the formation of clusters of needle crystals subject to weathering occurs in the drops of the original resorcinol solution on the slide only in case of forced drying with a warm airflow (Fig. 4a). The product of the reaction is an amorphous polymer, resorcinol formaldehyde resin.

In a series of experiments, the aqueous solution of resorcinol sprayed on the object plate was in contact with formaldehyde vapour over the time from 15 seconds to 30 minutes. In case of a short duration of interaction, the smallest drops produced an amorphous film when evaporating (Fig. 4b), while typical needle crystals were formed in the drops of medium and large size. With the increased time of reaction, thin structures remained even when larger drops were evaporating. After a ten-minute exposure, needle crystals were not found. It should be noted that resorcinol crystals were completely sublimated from the glass after several days, while the structures formed as a result of the reaction remained unchanged during long-term observation.

A relevant example of a reversible reaction is polycondensation of lactic acid. Elimination of one of the products of the reaction from the reaction mixture shifts the equilibrium towards the
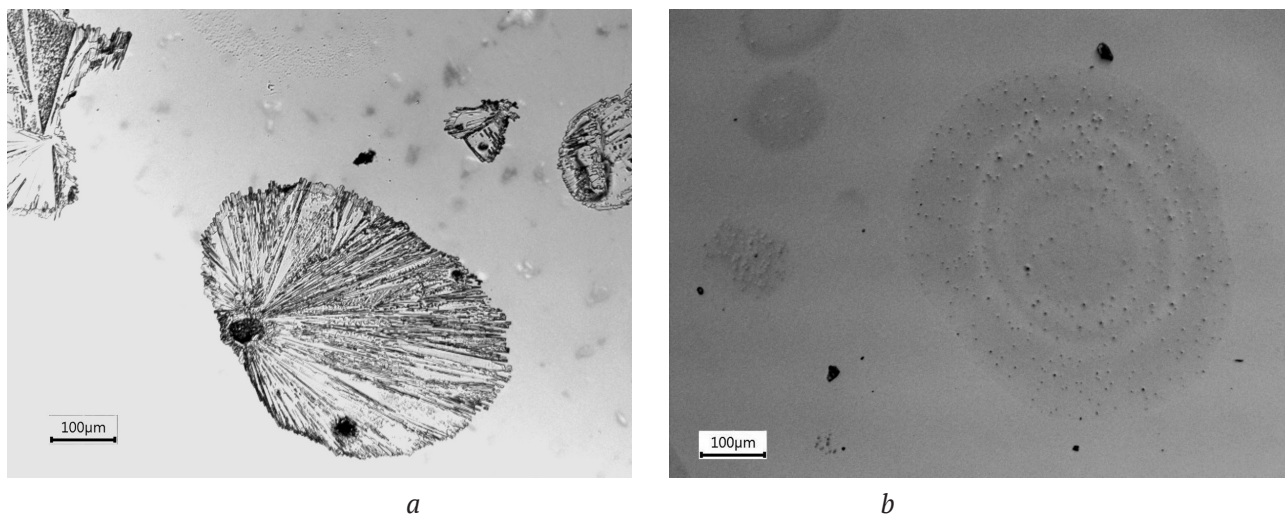

a

b

Fig. 4. Crystals formed from drops of an aqueous solution of resorcinol upon forced drying (a); film obtained from this solution after treatment with formaldehyde vapour (10% CH_2O) (b)

formation of a polymer. Therefore, the elimination of water is the key process in the production of polylactide from lactic acid. The task is complicated by the increased viscosity of the reaction mixture hindering heat and mass transfer, which causes local overheating that leads to reactions of gumming and other undesirable transformations. Conditions of heat and mass transfer in the spray allow effectively maintaining the concentration and temperature of the reaction mixture during the whole process. Observations showed that a solid product, which is insoluble when water is applied to the object plate, was formed in the sprayed drops of the aqueous solution of lactic acid at room temperature. Thus, it can be stated that lactide or oligolactide are formed in the spray without any additional influence (heating, vacuuming) and accessory reagents (solvents, catalysts) that are used in existing technologies.

The described experiments allow observing the differences in the reaction occurring in "microreactors" of different volumes. The interpretation presented below explains the thermodynamic nature of these size effects.

3.1. Thermodynamic interpretation

The thermodynamic approach to the study of peculiarities of the course of chemical processes in nanoscale systems is sufficiently widespread and effective [30].

In the case of a spray, the existence of drops of a multi-component solution in the vapour of volatile components is determined by the equilibrium of chemical potentials of the components in the gaseous and condensed phases. As for perfect solutions, this condition is converted using the Kelvin equation, the Ostwald–Freundlich equation, and Raoult's law. Generally, they can be presented in the following way:

$$P_k\left(r, x_k\right) = P_{0,k} x_k \exp\left(\frac{2\sigma V_k}{rRT}\right) = P_{ex,k}, \qquad (1)$$

$$P_k\left(r, L_k\right) =$$
$$= P_{0,k} x_{k,sat} \exp\left(\frac{4\sigma_{SL}}{L}\frac{V_1}{RT}\right)\exp\left(\frac{2\sigma V_k}{rRT}\right) = P_{ex,k}, \qquad (2)$$

where σ is surface tension, V_k is the molar volume of a component, k, R is the universal gas constant, T is temperature, $P_{0,k}$ is the saturated vapour pressure above the flat surface of a pure component k, $x_{k,sat}$ is the concentration of a saturated

solution of the component forming the crystal, L is the size of the crystal, σ_{SL} is the surface energy of the solution–crystal interphase. Imperfection of the solution can be accounted for by supplementing ratios (1) and (2) with the activity coefficients $\gamma_k\left(x_i\right)$ using the corresponding models of an actual solution and the dependence of surface tension on the composition $\sigma(x_i)$ [25].

The equation (1) describes the equilibrium partial pressure of the components that are not present in the crystal. The equation (2) describes the equilibrium partial pressure of the component forming the crystal. If all the components of a drop are volatile, the following identity is established

$$\sum x_k = \sum \frac{P_{ex,k}}{P_{0,k}} \exp\left(-\frac{2\sigma}{r}\frac{V_k}{RT}\right) = 1 \qquad (3)$$

which definitively [27] determines the radius of a drop. The presence of non-volatile components (marked with index c) changes the identity:

$$\sum \frac{P_{ex,k}}{P_{0,k}} \exp\left(-\frac{2\sigma}{r}\frac{V_k}{RT}\right) + \sum x_c\left(r\right) = 1. \qquad (4)$$

In case of reversible chemical transformations, the ratios (1)–(4) are supplemented by constants of chemical equilibrium and describe the connection between equilibrium composition, partial pressures of the components in the external environment, radius of a drop, and the size of the crystal. In case of irreversible reactions, the radius of a drop changes over time becoming a function of the transformation degree.

Let us consider the size effect through the reaction

$$A + B \rightleftarrows C, \qquad (5)$$

occurring in a volatile solvent.

Let us describe some variants of the equilibrium state for this reaction:

1. All components are volatile, but their pressure in the external environment $P_{ex,k}$ is determined by external sources. The equilibrium constant K_x of the reaction (5) for a drop is presented as the expression

$$K_x = \frac{x_C}{x_A x_B} =$$
$$= \frac{P_{0,A} P_{0,B}}{P_{0,C}} \frac{P_{ex,C}}{P_{ex,A} P_{ex,B}} \exp\left(-\frac{2\sigma\left(V_C - V_B - V_A\right)}{rRT}\right). \qquad (6)$$

This assessment neglects the dependence of surface tension on the composition of $\sigma(x_i)$. The condition $\frac{4}{3}\pi r^3 = n_0 V_0 + n_A V_A + n_B V_B + n_C V_C$ associates the radius of a drop with the amount of the solvent n_0, reagents n_A, n_B and the product n_C in the drop. The radius of a drop and the equilibrium constant are definitely determined by the identity (3), while partial pressure of the solvent influences the equilibrium composition. According to (6), in case of small volume the equilibrium shifts toward the formation of a product if the reaction occurs with the decrease of the volume ($V_C - V_B - V_A < 0$).

2. All components, except for the solvent, are non-volatile, and the pressure of the solvent $P_{ex,0}$ in the system is constant. The equilibrium constant is presented as follows

$$K_x = \frac{x_C}{x_A x_B} = \frac{n_C\left(n_{0A} + n_{0B} - 2n_C + n_0\right)}{\left(n_{0A} - n_C\right)\left(n_{0B} - n_C\right)}, \quad (7)$$

here n_k is the amount of moles of the components. For non-volatile components in the reaction (5), the conditions of preserving the substance are $n_A + n_C = n_{0A}$, $n_B + n_C = n_{0B}$, here n_{0A} and n_{0B} are the original amount of moles of reagents A and B in the drop.

Substitution (1) gives the following result:

$$K(r) = \frac{n_C n_0}{\left(n_{0A} - n_C\right)\left(n_{0B} - n_C\right)} \frac{P_{ex,0}}{P_0} \exp\left(\frac{2\sigma V_0}{rRT}\right). \quad (8)$$

The condition associates the radius of a drop and the amount of the solvent. Taking into account the identity (4), the equilibrium constant and the radius are a function of the solvent pressure and the original composition of the drop. In this case, the radius of the drop in the process of achieving chemical equilibrium will decrease (the decrease in the number of moles of non-volatile components is accompanied by the evaporation of the solvent and volatile components). Another kinetic effect is associated with the fact that when highly diluted reaction mixtures are sprayed, the solvent quickly evaporates, which increases the concentration of reagents and accelerates the reaction. As for reversible reactions, the increased concentration of reagents shifts the equilibrium towards the product yield.

Through a variation in the volatility and non-volatility of products, reagents, or solvent, different types of reaction (5) can be analysed. Notably, in the general case, the equilibrium composition and the radius of drops are determined by partial pressures of volatile components.

A thermodynamic model (1)–(8) explains the size effects associated with chemical transformations in disperse systems with a gaseous disperse medium. It involves a number of significant approximations, the rejection of which allows considering more complicated patterns of behaviour of reaction mixtures in a small volume. The introduction of activity coefficients into (1)–(4) allows using different equations for the state of actual solutions. A comparison of the results obtained using the concepts of ideal and real solutions, is described in the work [23]. Dependence of surface tension on the composition of the solution ($\sigma = \sigma(x_i)$ has an additional effect on the state of the dispersal phase. The interaction with the interphase surface changes chemical potentials of the components and, correspondingly, the Gibbs energy of the reaction in the subsurface layer. At the same time, the effective equilibrium constant becomes a function of the volume fraction of the subsurface layer and the specific surface, complicating the correlation (8) between the composition of vapour, radius of spray drops, and the product content. High surface activity typical for most organic compounds allows significantly affecting the transformation degree in the disperse phase [23], which allows expecting a high level of effectiveness of spray technologies during organic synthesis.

Size effects during phase transformations are equally important for chemical processes [26]. Such influence was simulated in the work [31]. In this case, the course of chemical processes is determined by redistribution of components between co-existing condensed phases. The growth of solubility and the increase of homogeneity region create such conditions for the synthesis of substances that are almost impossible to implement in macroscopic systems with low-soluble reagents and can influence the kinetics of chemical processes, thus significantly increasing the rate of processes.

4. Conclusions

The experiments demonstrating chemical interactions in disperse systems with gaseous disperse medium confirm the existence of size effects that are mostly pronounced when observing the kinetics of evaporation of polydispersed ensembles of drops and morphology or solid products formed as a result of this. Thermodynamic interpretation of these effects for reversible chemical processes describes the correlation between equilibrium chemical composition of the disperse phase and the composition of gaseous medium. Size dependence of the chemical equilibrium constants (6)–(8) shows that the transition to micro and nanosized reactors allows significantly changing the product yield and the kinetics of its formation. Large specific surface with a small reaction volume ensures quick interphase mass and heat transfer stabilising the concentrations of reagents and the temperature of processes. Taking into account the effect of the form [32,33] with the same thermodynamic basis can considerably supplement size patterns during chemical processes. The described patterns allow using additional factors expanding the opportunities of spray and sol-gel technologies in the chemical synthesis of new materials.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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