JOURNAL OF MATERIALS SCIENCE **39** (2004) 5435–5439

On the mechanism of mechanochemical synthesis of phthalylsulphathiazole

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The present study deals with the participation of fluid phases in the mechanochemical synthesis of phthalylsulphathiazole. Model experiments with optical microscope using crystalline samples revealed the possibility of the interaction between sulphathiazole and phthalic anhydride without their direct contact with each other at a temperature of about 100°C. The shift of the reaction temperature into lower-temperature region under mechanical activation of the reagents is demonstrated by means of scanning calorimetry. Assumption concerning the transport of phthalic anhydride through the gas phase as the most probable mechanism of synthesis in the mechanochemical reactor is put forward.

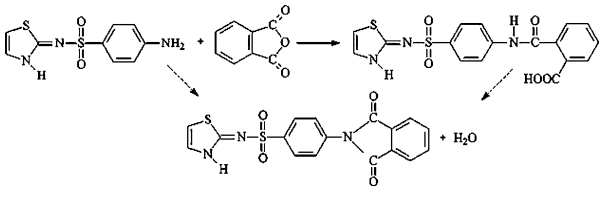
1. Introduction

One of the promising directions in the synthesis of organic compounds is mechanochemical synthesis as one of the versions of the so-called dry technologies which are likely to be economically effective (due to a decrease in the number of stages) and ecologically safer in comparison with traditional processes [1].

The acylation of sulphathiazole by phthalic anhydride is one of the most widely investigated solid states in organic chemistry; it serves as a model in investigating the mechanism of solid-phase reactions [2–5]. It turned out to be attractive from the viewpoint of technology to obtain phthalylsulphathiazole in mechanochemical reactor because higher yield and higher rate of obtaining the target product are provided [4, 5].

Traditional methods to synthesize phthalylsulphathiazole involve either heating of aqueous and alcoholic solutions of sulphathiazole and phthalic anhydride in the presence of acid catalysts or fusion of the components [6]. A shortcoming of both versions is the necessity to purify phthalylsulphathiazole from by-products, which are phthalazole imide or anil for the fusion method, and additionally diethyl esters of phthalic acid for the aqueous and alcoholic mixture.

Unlike these methods, mechanical treatment of a mixture of sulphathiazole and phthalic anhydride allows obtaining rather pure phthalylsulphathiazole free from by-products; the reaction accelerates in the presence of benzoic acid [5].



However, the mechanism of the process has been poorly investigated. In particular, it was unclear how reagents are transferred in the mechanochemical reaction, and how the substantial acceleration of the reaction performed in mechanochemical activator, in

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comparison with the classical solid-phase process, can be explained.

2. Experiment

Chemically pure (KhCh grade) phthalic anhydride was used. Suphathiazole was purified by recrystallization of the commercial substance (Kursk Pharmaceutical Plant, Russia) from water at a temperature not higher than 95°C; stable modification III was thus obtained [7, 8]. The metastable form I was obtained by heating the form III to 175°C for 45 min [7]. The crystals of modification III for optical microscopic experiments were obtained by slow evaporation from a solution composed of ethanol and 25% aqueous solution of ammonium; the crystals were hexahedral plates with the best developed (102) surface.

Mechanical activation was performed with AGO-2 planetary-centrifugal mill (ISSC&M SB RAS) with water-cooled drums and rotation frequency 630 and 890 rpm, providing 20 and 40 g ($g = 9.8$ m/s^2) acceleration of steel balls used as milling bodies; drum volume was 40 ml; SPEX-8000 vibrational mill (CertiPrep Inc., USA) was also used (acceleration of milling body: 8–10 g, drum volume: 60 ml). In order to carry out mechanical activation, an equimolar mixture of sulphathiazole (1.26 g) and phthalic anhydride (0.74 g) was loaded into the working drums. Benzoic acid (0.1, 0.2 g) was added into the reaction mixture. The mass of balls was 60 g, ball diameter was 0.3 cm.

Particle size analysis of the mixtures after mechanical activation was performed by processing the scanned image obtained with the Neophot-2 optical microscope (Carl-Zeiss Jena).

The mixture was sampled during mechanical activation; the target product was isolated from the samples by washing with water heated to 75–80°C. The residual sulphathiazole content was determined in washing water based on the absorption of its diazotized derivative [9] with Shimadzu UV-240 instrument at $\lambda = 345$ nm. Transformation degree was calculated on the basis of the obtained data.

The presence of by-products in reaction mixtures was detected by means of thin layer chromatography using ethanol—chloroform system of solvents. Identification was performed in the presence of reference substances at $\lambda = 252$ nm.

The IR spectra were recorded with UR-20 spectrophotometer within the range 400–4000 cm^{-1} (4–4.5 mg of the substance per 540 mg of KBr).

X-ray phase analysis was performed with B8 Discover GADDS instrument (Bruker) using Cu K_α radiation.

Optical microscopic observations were carried out with NU-2E microscope (Carl-Zeiss Jena). Components of mixture were placed on the heating table in contact with each other or at a distance of 5 mm. Photographs of the surface of sulphathiazole III crystal were made with Neophot-2 microscope (Carl-Zeiss Jena) with the help of scanning attachment.

Thermal analysis curves were recorded with DSC-204 differential scanning calorimeter (Netzsch), heating rate: 6 K/min, aluminium crucibles; sample mass was 5–10 mg.

3. Results and discussion

The reaction product was identified by means of X-ray phase analysis, IR- and UV-spectroscopy; it was phthalylsulphathiazole. Chromatographic analysis of reaction mixtures after mechanical activation demonstrated the absence of by-products at all stages of the process.

The data on the accumulation of phthalylsulphathiazole in reaction mixtures are shown in Fig. 1. The synthesis was performed using both the modification III and metastable modification I of sulphathiazole as the initial reagent. One can see that the reactivity of modification I is higher than that of modification III. This difference is especially vividly expressed at the initial stages of the synthesis and gradually becomes

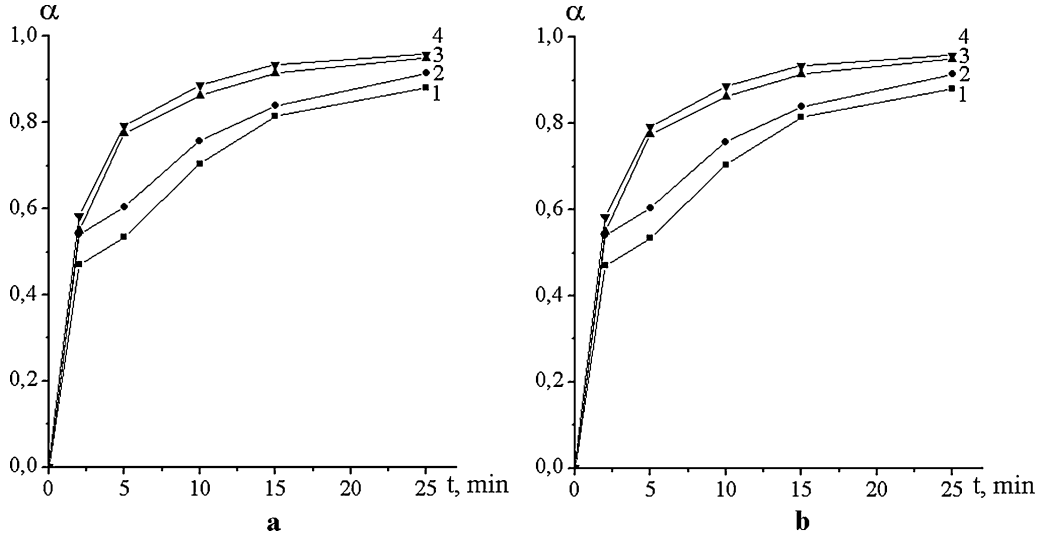

Figure 1 The dynamics of product accumulation in reaction mixtures in AGO-2 mill and in Spex-mill 8000: (a) 1—sulphathiazole III—phthalic anhydride (Spex-mill 8000), 2—sulphathiazole I—phthalic anhydride (Spex-mill 8000), 3—sulphathiazole III—phthalic anhydride (AGO-2, 20 g), 4—sulphathiazole I—phthalic anhydride (AGO-2, 20 g). (b) sulphathiazole I—phthalic anhydride with benzoic acid added to the reaction mixture: 1—0.1 g (Spex-mill 8000), 2—0.2 g (Spex-mill 8000); 4—0.2 g, 3—0.1 g (AGO-2, 40 g), 4—0.2 g (AGO-2, 40 g).

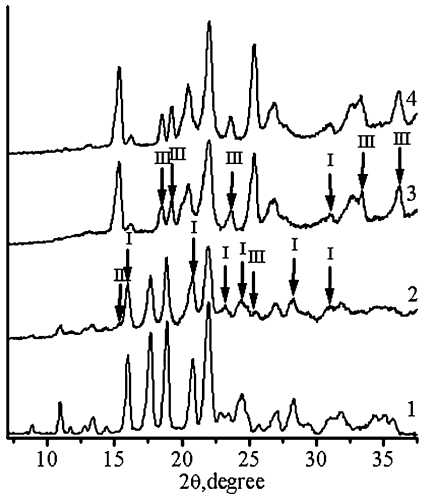

Figure 2 Polymorphous transition of sulphathiazole I → III under mechanical activation in AGO-2: 1—initial sulphathiazole I, 2—sulphathiazole after mechanical activation for 2 min, 3–10 min, 4–25 min.

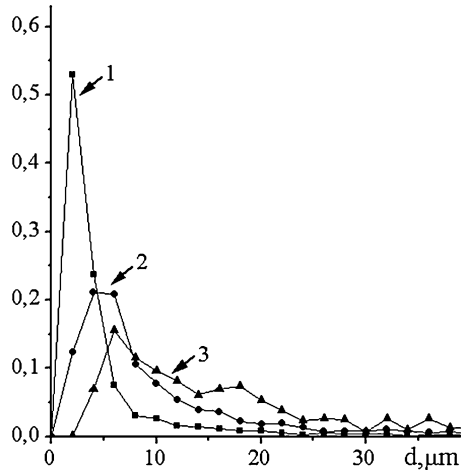

Figure 3 Numerical particle size distribution in reaction mixtures: sulphathiazole III—phthalic anhydride after activation in AGO-2 (20 g) for 0.5 min (1), 3.5 min (2), 7.5 min (3).

smoothed out during the process. The metastable form exhibits higher activity when activator with lower energy is used; in the case of AGO-2, the difference in the reactivity decreases. No substantial increase in synthesis rate and yield of product was observed when acceleration was increased up to 40 g.

The addition of benzoic acid caused acceleration of the process when activators with low energy were used; with increased content of benzoic acid, the effect was larger.

A decrease in the differences in product accumulation dynamics versus time for modification I is likely to occur as a result of the parallel mechanically induced phase transition I → III [10]. To confirm this assumption, we recorded diffraction patterns of sulphathiazole samples activated under the given conditions (Fig. 2). Phase transition was observed as early as after mechanical treatment for 2 min. No reverse transition was revealed under the given parameters of mechanical activation.

Results of particle size analysis of reaction mixtures (Fig. 3) show that particle size is conserved during mechanical treatment, which can be an evidence of the absence of melting under the given conditions of mechanical activation. The observed insignificant shift of the maximum of distribution after treatment for a long time is likely to be due to aggregation of the product.

Since calculations performed in [11] show that temperature at the contacts between two particles can reach substantial values during mechanical treatment, one may assume that fluid (liquid or gaseous) state can play a substantial role in the reaction. To clarify this question, we performed model experiments using crystalline samples of sulphathiazole and phthalic anhydride.

An important result of optical microscopic experiments is the discovery that the reaction proceeds even when sulphathiazole and phthalic anhydride crystals are separated from each other by a spatial gap. At a temperature as low as 105°C, the reaction of phthalic anhydride vapour with sulphathiazole proceeds at a noticeable rate through the formation and growth of phthalylsulphathiazole nuclei on the surface of sulphathiazole crystals (Fig. 4), which is typical for gas–solid topochemical reactions [12]. We may assume that this mechanism is also realized in the mechanochemical reactor.

Results of experiments on heating the mixtures of sulphathiazole and phthalic anhydride are shown in Fig. 5. The curve describing physical mixture exhibits exothermal effect at 115–135°C, which is likely to be a combination of endothermic effects of sublimation and melting of phthalic anhydride and exothermal effect of the interaction of sulphathiazole with phthalic anhydride. Endothermic effects observed at higher temperature are likely to be related to a side reaction with the formation of liquid or gaseous products (135–155°C), phase transition (160–170°C) and melting (195–199°C) of sulphathiazole, decomposition of residual phthalic anhydride (175–195°C). After mechanical activation for 0.5 min, the thermal analysis curve exhibits exothermal effect in the region 90–105°C, which is likely to be connected with recrystallization of the mixture. Exothermal effect shifts to lower temperature, and a weak endothermic effect is observed at 128–130°C, which is due to melting of the residual phthalic anhydride.

Thus, results of thermal analysis studies show that the interaction between reagents starts below the melting point of phthalic anhydride; temperature of the process decreases as a result of mechanical activation.

The above considerations allow us to assume that the main processes determining the synthesis progress are the transport of phthalic anhydride through the gas phase and reaction of its vapour with the surface of sulphathiazole crystals.

Strictly speaking, one cannot completely exclude the interaction between reagents with the participation of the liquid phase formed as a result of contact melting. However, since the synthesis of phthalylsulphathiazole from initial components by means of melting is known to be accompanied by the formation of by-products,

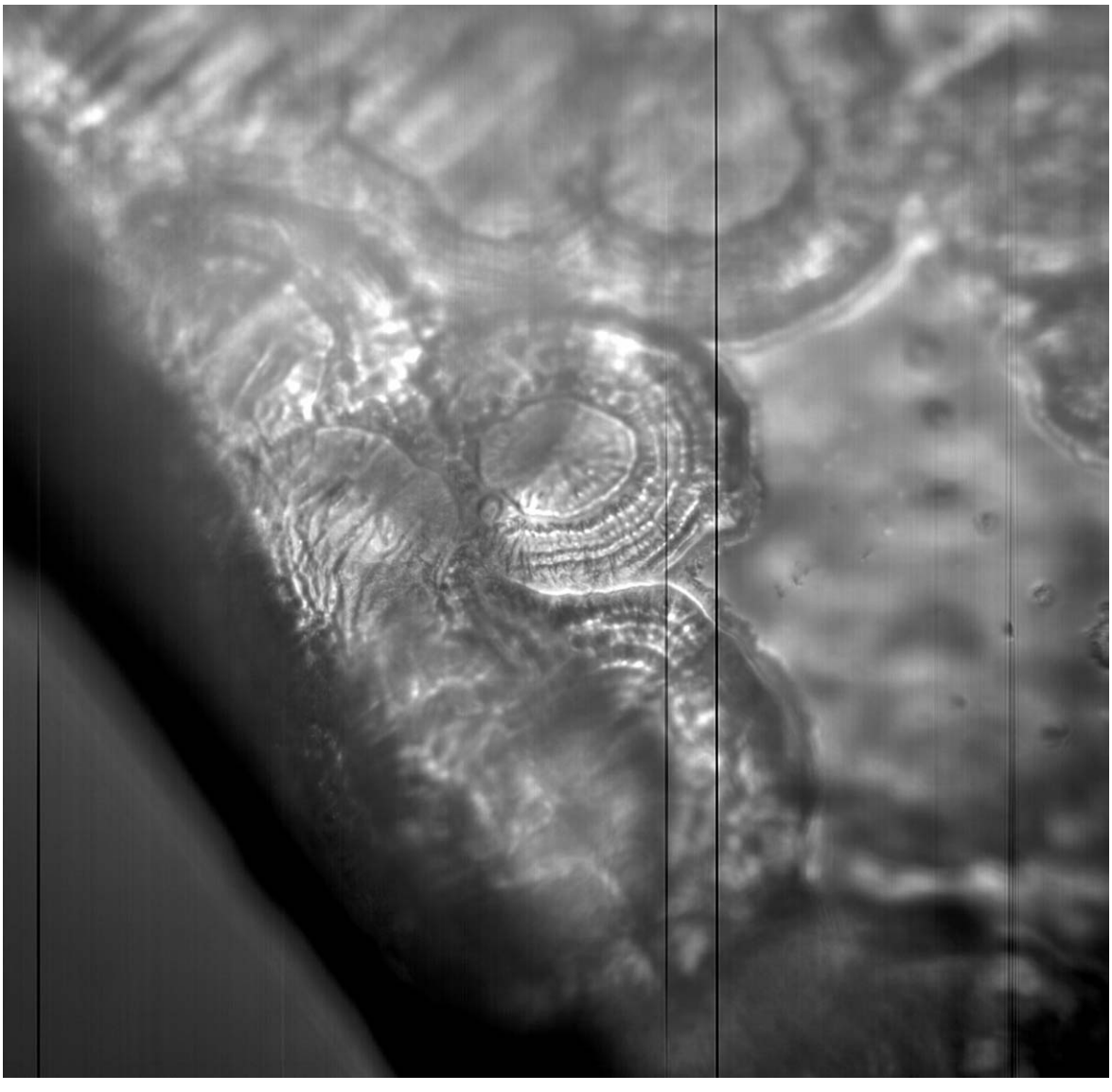

Figure 4 Microphotograph of sulphathiazole crystal after the action of phthalic anhydride vapour at 105°C for 60 min.

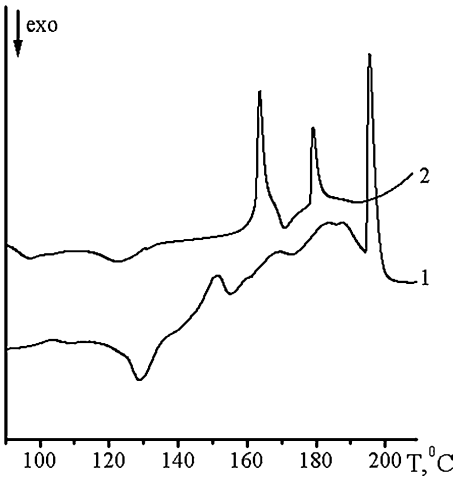

Figure 5 Thermoanalytic curves of mixtures of sulphathiazole III with phthalic anhydride: 1—physical mixture, 2—mechanically activated mixture (AGO-2, 20 g, 0.5 min).

whereas these compounds were not detected in reaction mixtures, it may be assumed that contact melting does not play any significant role in mechanochemical synthesis. In addition, the effect of crystal state of sulphathiazole on reaction progress is an evidence that the process most likely occurs not in the melt of components.

The mechanism of process with the participation of the gas phase involves the essential role of diffusion processes, which are to provide the admission of reagent to the reaction surface through the layer of product. Mechanical treatment helps to renew the surface of sulphathiazole crystals continuously as a result of grinding, thus eliminating diffusion deceleration of the process. It is quite possible that the role of benzoic acid, with its accelerating action better exhibited in activator with low energy, is not only reduced to its catalytic properties but is due to its ability to change the rheological properties of the mixture thus helping to grind sulphathiazole particles.

The gas + solid mechanism was likely to be realized also in the systems investigated by authors [2, 3], for the solid-phase synthesis of phthalylsulphathiazole in pressed tablets; those authors believed that they dealt with the reaction between solids. At least, the increase in rate process with increased porosity of sulphathiazole tablet, as observed by the authors of [3], is strange at first

glance but it can be easily explained from the viewpoint of the mechanism proposed by us.

High reaction rate, which is achieved in mechanochemical reactor in comparison with the classical solid-phase synthesis, is likely to be a consequence of three main reasons:

1. Local evolution of heat at the contacts, due to which the sublimation of phthalic anhydride is provided, along with its transport to the surface of sulphathiazole crystals.
2. Continuous renewal of sulphathiazole crystal surface, due to grinding during the treatment.
3. Continuous removal of phthalylsulphathiazole from the reaction region, which eliminates possible diffusion hindrance for the reaction.

Acknowledgments

The research has been supported by Award NO-008-X1 of the CRDF (USA), by the grants of RFBR (Russia) No. 02-03-33299, 03-03-06092 and grants of Russian Ministry of Education.

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Received 11 September 2003
and accepted 27 February 2004