On the Mechanism of Mechanochemical Synthesis of Phthalylsulphathiazole

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Abstract

This work deals with mechanochemical synthesis of phthalylsulphathiazole involving fluid phases. Model optical microscopy experiments with crystal samples have revealed that sulphathiazole can interact with phthalic anhydride without direct contact of these substances at temperatures of about 100 °C. Scanning calorimetry measurements showed that the synthesis temperature is lowered during mechanical activation of reagents. The reagents do not undergo fusion under the conditions of mechanical activation. Transport of phthalic anhydride through the gas phase was assumed to be the most likely mechanism of synthesis in a mechanochemical reactor.

INTRODUCTION

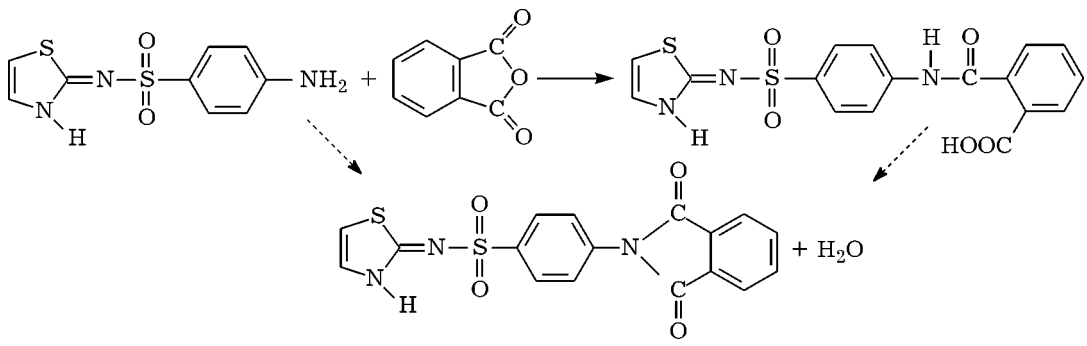
Mechanochemical synthesis is one of the promising directions in synthesis of organic compounds; this is one of the variants of so-called dry technologies, promising to become an economically profitable (due to reduced number of stages) and ecologically clean procedure compared to the traditional processes [1].

Acylation of sulphathiazole with phthalic anhydride is one of the widely studied solid-phase processes in organic chemistry, which serves as a model reaction in the mechanistic studies of solid-phase reactions [2–5]. Synthesis of phthalylsulphathiazole in a mechanochemical reactor is also attractive from the viewpoint of production technology, since it ensures higher yields and higher rate of process leading to the desired product [4, 5].

Traditional methods for the synthesis of phthalylsulphathiazole are either heating aqueous and alcoholic solutions of sulphathiazole and phthalic anhydride in the presence of acid catalysts, or fusion of the mixture components [6]. A limitation of both variants is the necessity of subsequent purification of phthalylsulphathiazole from by-products: phthalazolimide or anil in the fusion method, and additionally purification of diethyl phthalate in the case of an alcohol – water mixture.

In contrast to these methods, mechanical treatment of a mixture of sulphathiazole and phthalic anhydride can yield pure phthalylsulphathiazole that is free of by-products, with the reaction accelerated in the presence of benzoic acid [5].

However, the mechanism of the process has yet remained uninvestigated. In particular, the mechanism of reagent transport during the mechanochemical reaction was not clear, and the factors greatly accelerating the reaction conducted in a mechanical activator relative to the classical solid-phase process were unknown.



EXPERIMENTAL

For synthesis we used phthalic anhydride of chemically pure grade. Sulphathiazole was purified by recrystallization of the commercial product (Kursk Pharmaceutical Plant) from water at temperatures below 95 °C to obtain stable modification III [7, 8]. Metastable form I was obtained by heating form III at 175 °C for 45 min [7]. For optical microscopy experiments, the crystals of modification III were obtained by slowly evaporating them from an ethanol – 25 % aqueous ammonia solution; the crystals were hexahedral plates with a best developed (102) surface.

For mechanical activation we used an AGO-2 planetary-centrifugal mill with rotating rates of 630 and 890 rpm (acceleration of the working bodies (steel spheres) 20 and 40 *g*, roll capacity 40 ml) and a SPEX-8000 (CertiPrep Inc., USA) vibrating mill (acceleration of working bodies 8–10 *g*, roll capacity 60 ml). The spheres were 60 g in weight and 0.3 cm in diameter.

For synthesis, the working drums were charged with an equimolar mixture of sulphathiazole (1.26 g) and phthalic anhydride (0.74 g). Benzoic acid was added to the reaction mixture in amounts of 0.1 and 0.2 g. In the course of mechanical activation of the mixture, samples were taken, from which the main product was isolated by washing the reaction mixture with water heated to 75–80 °C. The residual content of sulphathiazole in the washing waters was determined from absorption of its diazotized derivative [9] on a Shimadzu UV-240 instrument at $\lambda = 345$ nm. Conversion was calculated from the obtained data.

The presence of by-products in the reaction mixtures was determined by thin-layer chromatography in an ethanol – chloroform system of solvents. The products were identified in the presence of witness substances at $\lambda = 252$ nm.

Particle-size analysis of the mixtures after mechanical activation was carried out by processing the scanned image obtained with a Neophot-2 optical microscope (Carl Zeiss Jena). IR spectra were recorded on a UR-20 spectrophotometer in the range 400–4000 cm^{-1} in KBr pellets. X-ray phase analysis was conducted on a V8 Discover GADDS (Bruker) instrument, CuK_α radiation.

An optical microscopy study was carried out with a NU-2E microscope (Carl Zeiss Jena). The components of the mixture were placed on a warm plate in contact with each other or at a distance of 5 mm.

Thermoanalytic curves were obtained with a DSC-204 (Netzsch) differential scanning calorimeter, heating rate 6 °C/min, sealed aluminum crucibles, 5–10 mg samples.

RESULTS AND DISCUSSION

The reaction product was identified as phthalylsulphathiazole by X-ray phase analysis and IR and UV spectroscopy. Chromatographic analysis of the reaction mixtures after mechanical activation showed that by-products were absent at all stages of synthesis.

Data on accumulation of phthalylsulphathiazole in the reaction mixtures are presented in Fig. 1. Synthesis was carried out using both sulphathiazole modification III and metastable modification I as the starting reagent. It can be seen that the reactivity of modification I is higher than that of modification III. This difference is most pronounced at the initial stages of synthesis and gradually vanishes in the course of the process. The metastable form exhibits higher activity when an activator with

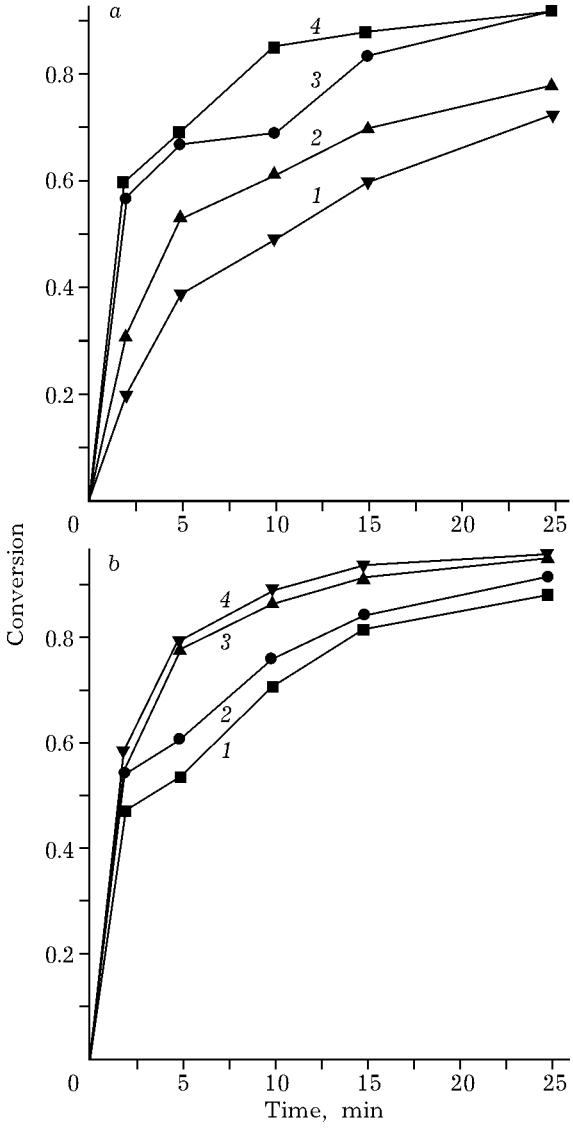


Fig. 1. Dynamics of product accumulation in the reaction mixtures in AGO-2 and SPEX-8000 mills: *a* – sulphathiazole III – phthalic anhydride, SPEX-8000 (*1*); sulphathiazole I – phthalic anhydride, SPEX-8000 (*2*); sulphathiazole III – phthalic anhydride, AGO-2, 20 *g* (*3*); sulphathiazole I-phthalic anhydride, AGO-2, 20 *g* (*4*); *b* – sulphathiazole I – phthalic anhydride with benzoic acid added in the reaction mixture: 0.1 g, SPEX-8000 (*1*); 0.2 g, SPEX-8000 (*2*); 0.1 g, AGO-2, 40 *g* (*3*); 0.2 g, AGO-2, 40 *g* (*4*).

low energy intensity is used; in the case of AGO-2, the difference in reactivity decreases. For energy intensity 40 *g*, no significant increase in the reaction rate and product yield has been observed.

Addition of benzoic acid accelerated the process when activators with low energy intensity were used, the effect increasing with the content of benzoic acid.

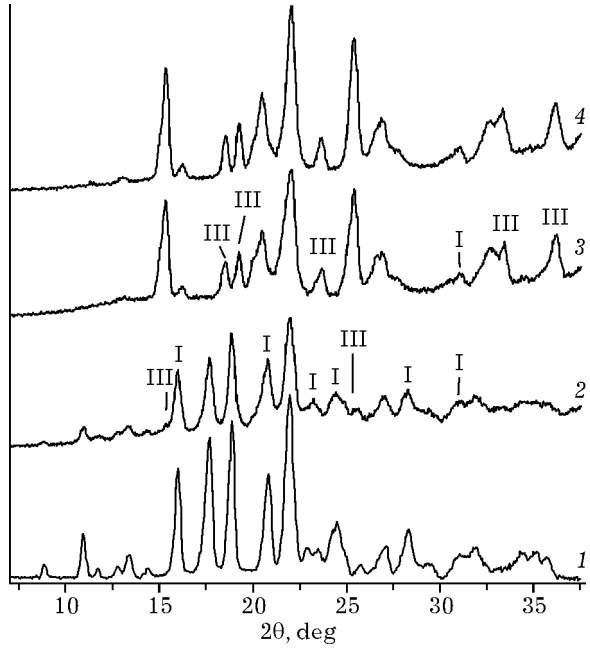


Fig. 2. Polymorphic transition I → III of sulphathiazole during mechanical activation in AGO-2: *1* – initial sulphathiazole I, *2–4* – sulphathiazole after mechanical activation for 2 (*2*), 10 (*3*), and 25 min (*4*).

In the case of modification I, the decreased differences in the time dynamics of product accumulation may be explained by the occurrence of a mechanically induced parallel phase transition I → III [10]. To support this assumption, we obtained the diffractograms of the sulphathiazole samples mechanically activated under these conditions (Fig. 2). Phase transformation was evidenced even after 2 min of mechanical treatment. Reverse transformation was not revealed under these conditions of mechanical activation.

The results of particle-size analysis of the reaction mixtures (Fig. 3) show that particle dispersity does not change with treatment time. This may be indicative of the absence of reagent melting under these conditions of mechanical activation. The insignificant shift of the distribution maximum observed after prolonged treatment presumably results from product aggregation.

The calculations reported in [11] show that mechanical treatment can drastically increase the temperature at points of contact between two particles; therefore, it can be inferred that the fluid (liquid or gaseous) states play a significant role in the reaction. To elucidate this question, model experiments were carried out

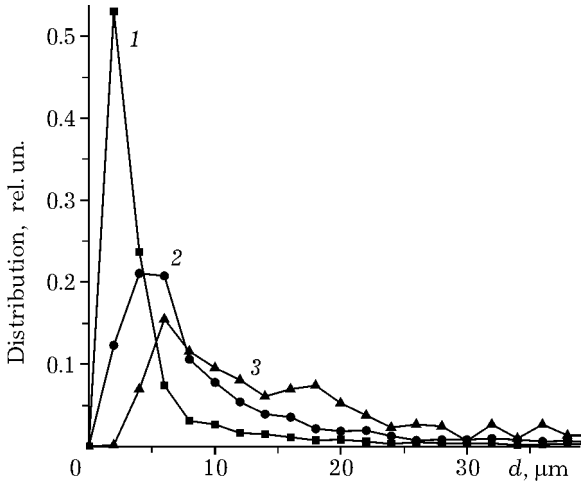


Fig. 3. Numerical distribution of particle size in sulphathiazole III – phthalic anhydride reaction mixtures after activation in AGO-2 (20 *g*) for 0.5 (*1*), 3.5 (*2*), and 7.5 min (*3*).

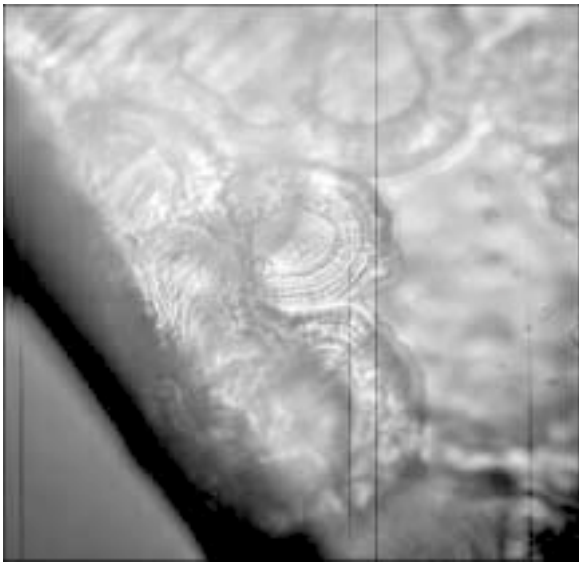


Fig. 4. Micrograph of a sulphathiazole crystal after exposure to phthalic anhydride vapours at 105 °C for 60 min.

using crystal samples of sulphathiazole and phthalic anhydride.

As a result of optical microscopic experiments it was found that the reaction also takes place when sulphathiazole and phthalic anhydride crystals are separated in space. The reaction of phthalic anhydride vapours with sulphathiazole occurs at an appreciable rate even at 105 °C through formation and growth of phthalylsulphathiazole nuclei on the surface of sulphathiazole crystals (Fig. 4), which are typical for gas – solid topochemical reactions [12]. This mechanism is also assumed for the reaction in a mechanochemical reactor.

The results of experiments on heating the mixtures of sulphathiazole and phthalic anhydride are given in Fig. 5. An exothermal effect is observed at 115–135 °C on curve *1*; this effect is apparently a superposition of the endothermal effects of sublimation and melting of phthalic anhydride and the exothermal effect of the reaction of sulphathiazole with phthalic anhydride. The endothermal effects observed at higher temperatures probably reflect side reactions, liberating liquid or gaseous products (135–155 °C), as well as phase transition (160–170 °C) and melting (195–199 °C) of sulphathiazole, and decomposition of residual phthalic anhydride (175–195 °C). After 0.5 min of mechanical activation, the thermoanalytical curve shows an exothermal effect in the range 90–105 °C, which is probably associated with recrystallization, the exothermal effect shifts to the region of low temperatures, and a weak endothermic effect shows at 128–130 °C due to the melting of the residual phthalic anhydride.

Thus, the results of thermoanalytical studies indicate that the interaction of reagents starts below the melting point of phthalic anhydride, and the process temperature decreases as a result of mechanical activation.

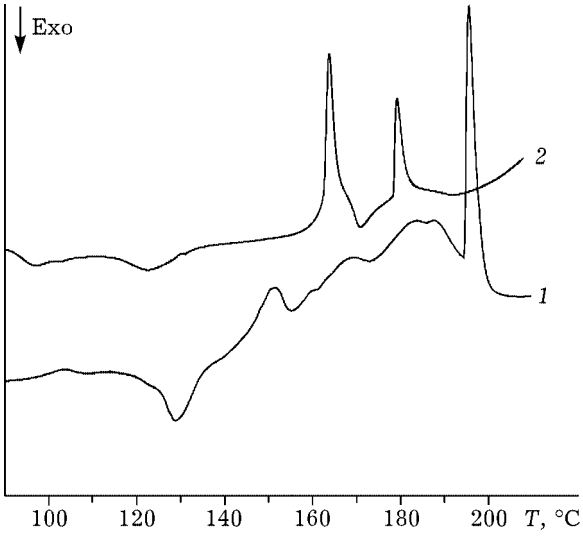


Fig. 5. Thermoanalytical curves of sulphathiazole III – phthalic anhydride mixtures: *1* – physical mixture, *2* – mechanically activated mixture (AGO-2, 20 *g*, 0.5 min).

The arguments above suggest that the basic processes determining the synthesis are transport of phthalic anhydride through the gas phase and the reaction of its vapours with the surface of sulphathiazole crystals.

Strictly speaking, the interaction involving the liquid phase formed as a result of contact melting cannot be ruled out completely. As is known, synthesis of phthalylsulphathiazole through melting of the starting components is accompanied by the formation of by-products, but these compounds were not found in the reaction mixtures; therefore, it is believed that contact melting is of minor importance in mechanochemical synthesis. Moreover, the influence of the crystalline state of sulphathiazole on the reaction indicates that this component is most likely to be in the solid state in the course of synthesis.

The mechanism of the process involving the gas phase suggests that an essential role is played by diffusion processes which should ensure reagent supply to the reaction surface through the product layer. Mechanical treatment leads to uninterrupted renewal of the surface of sulphathiazole crystals as a result of grinding, thus removing the diffusion-induced retardation of the process. It is quite possible that the role of benzoic acid, whose accelerating action manifested itself to a greater extent in a less energy-intensive activator, lies not so much in its catalytic properties, but in its ability to modify the rheological behavior of the mixture, promoting the crushing of sulphathiazole particles.

The gas + solid mechanism was also presumably realized in the solid-phase synthesis of phthalylsulphathiazole (in pressed pellets) reported in [2, 3], while the authors believed that they dealt with a reaction between solids. The strange increase in the reaction rate for sulphathiazole pellets with increased porosity observed in [3] is readily explicable from the viewpoint of the mechanism suggested here.

CONCLUSIONS

The high reaction rate achieved in a mechanochemical activator in comparison to classical solid-phase synthesis is apparently a consequence of three main effects:

1. Local evolution of heat at points of contact, which ensures sublimation of phthalic anhydride and its transfer to the surface of sulphathiazole crystals.

2. Continuous renewal of the surface of sulphathiazole crystals as a consequence of their crushing in the course of mechanical treatment.

3. Continuous removal of phthalylsulphathiazole from the reaction zone, which ensures the removal of possible diffusion-induced difficulties for the reaction.

Acknowledgements

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