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Acylation of sulfathiazole with maleic anhydride under mechanochemical activation

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It was found that a product of the title reaction is maleanilic acid, which was obtained at a high rate and selectivity.

The solid-phase chemical synthesis is of interest, because of its advantages over conventional synthetic methods in terms of selectivity, the number of stages, the use of solvents, *etc.*[1] A promising method is the mechanical treatment of reagents in activator mills[2] to perform reactions in a solid phase.

Without transport *via* the vapour phase or a solution-mediated reaction, solid–solid reactions are initiated only when the reactants are in direct contact. As estimated, only ~10^{-6} of the total surface area is within the range of the influence of chemical forces due to neighbouring particles. This implies that the onset of product formation is restricted to a very small fraction of the surface. Since bulk diffusion through the contact points is very limited, low rates are characteristic of solid-phase reactions;[3] fast solid–solid reactions observed in some cases cannot be explained.[4]

At the same time, many processes with the participation of molecular crystals have a high rate under mechanochemical activation.[5] Estimation of local temperature at contacts between two particles[6,7] and experimental data[8] on the temperature of milling bodies during the mechanical activation of organic compounds suggest the formation of fluid states (liquid or gaseous) under mechanical treatment leading to an increase in the area of reagent contact and the reaction rate. Solid-state processes with the participation of liquid or gaseous states can include a topochemical stage.[3] The mixing and compaction of reagents may proceed during mechanical treatment to form mechanocomposites,[5] whose properties are different from those of physical mixtures.

The interaction of sulfathiazole with phthalic anhydride was found to occur at a high rate under mechanochemical activation[9,10,11] depending on the power and intensity of mechanical treatment. The reaction with sulfathiazole single crystals can proceed without direct contact between the solid reagents[11] through the formation and growth of the product nuclei. This suggests[11] that the process goes on through the interaction of the solid sulfathiazole with gaseous phthalic anhydride as a result of its sublimation. The topochemical character of the interaction leads to the selectivity of mechanochemical acylation of sulfathiazole with phthalic anhydride[11] by the formation of the amide.

Since maleic anhydride has a lower melting point than phthalic anhydride, one might expect that, in this case, the liquid or gaseous phases would participate in mechanochemical acylation. The purpose of this work was to study the interaction of sulfathiazole with maleic anhydride under mechanochemical activation.

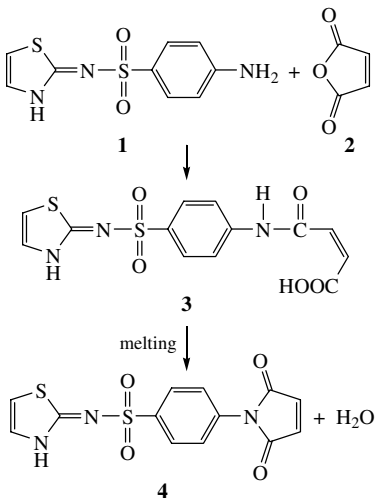
Sulfathiazole was purified by recrystallization from water to give stable modificaiton III of sulfathiazole.[12] Maleic anhydride of reagent grade was used.

The mechanochemical treatment of the reaction mixtures was carried out in a steel reactor using a SPEX-8000 vibratory mill (CertiPrep Inc., USA). The following mixtures were prepared for the synthesis: sulfathiazole (1.44 g) + maleic anhydride (0.56 g) (1:1 molar ratio) and sulfathiazole (1.44 g) + maleic anhydride (0.62 g) (1:1.1 molar ratio).

The conversion was monitored by IR spectroscopy comparing the relative intensities of the absorption bands of carbonyl group vibrations in the anhydride (1848 cm^{-1}) and the acid (1725 cm^{-1}).[10] The IR spectra were recorded on a Vector-22 spectrophotometer (Bruker) in tablets with KBr (1:150).

The occurrence of by-products was tested by comparing with melted reaction mixtures using gas chromatography–mass spectrometry (GC-MS): Agilent 5973N EI/PCI (Varian) column DB-1, 30 m×0.32 mm (0.50 μm, 100% dimethylpolysiloxane), T_{ev} = 280 °C, T_{col} = 260 °C.

The X-ray powder diffraction patterns were obtained using a D8 Discover GADDS diffractometer (Bruker) and CuKα radiation. Calorimetric measurements were performed using a DSC-204 differential scanning calorimeter (Netzsch) with a standard aluminium sealed crucible at a heating rate of 6 K min^{-1}; the sample weight was 5–10 mg. The electron-microscopic studies were carried out using a JEM2000-FX electron microscope (–196 °C).



Scheme 1

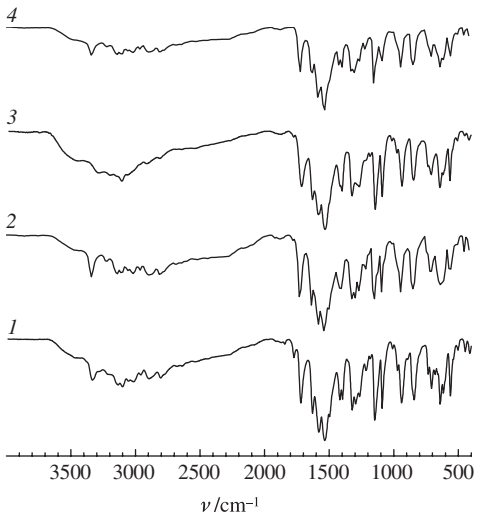


Figure 1 IR spectra of the reaction mixtures of sulfathiazole and maleic anhydride: (1) physical mixture; reaction mixture after mechanical treatment in a mill for (*2*) 5 or (*3*) 20 min, (*4*) reaction mixture after heating at 70 °C for 90 min.

The single crystals of sulfathiazole, modification III, as hexagonal plates were obtained by slow evaporation of a solution of sulfathiazole in a mixture of ethanol with ammonia solution. The interaction of sulfathiazole crystals with maleic anhydride vapour and melt was monitored using a NU-2E optical microscope (Karl Zeiss Jena) at 50–70 °C.

The GC-MS analysis of the reaction mixture after mechanical activation revealed only one reaction product (Scheme 1), which was isolated from the reaction mixture by washing with water. Its characteristics correspond to those of maleanilic acid **3**: τ = 25.59 min, *m*/*z* = 98, 100, 156, 253, 255, 355 (M + 2), mp 216–217 °C (EtOH). Its IR spectrum (Figure 1, curve *3*) contains the C=O vibration band at 1725 cm^{-1}. Under heating of **3** up to 230 °C, among other low-molecular products the GC-MS analysis revealed a small amount of imide **4** (τ = 23.98 min, *M* = 335), which is likely formed at the initial stage of thermal decomposition. The absence of this compound from the products of mechanical treatment allowed us to conclude that the reaction proceeds selectively, and temperature in the vial does not reach the melting point of the reaction product.

In the IR spectra of reaction mixtures after mechanochemical activation, a decrease in the intensity of the absorption band at 1780 cm^{-1} corresponding to maleic anhydride (Figure 1) was observed. The transformation degree reached ~80% after mechanochemical activation for 5 min. After mechanical treatment for 20 min, the transformation degree was close to 100%, maleic anhydride was not detected by IR spectroscopy. Note that, for sulfathiazole acylation with phthalic anhydride under similar conditions, the transformation degree did not exceed 40%.[11] Such a striking difference in acylation rates can be due to a lower melting point of maleic anhydride (54 °C), which provides its transformation into the liquid state, leading to better contact between reagents.

Under heating the mixture of sulfathiazole with maleic anhydride to 70–90 °C, maleic anhydride melts, whereas sulfathiazole remains in a solid state. A comparison of the IR spectra of reaction mixtures after heating and mechanochemical activation (Figure 1) showed that they were identical in the region 2000–400 cm^{-1}, including the region of vibrations of C=O groups. The differences in absorption bands in the region of the stretching vibrations of NH and OH groups that can participate in the formation of intermolecular bonds[13] are likely due to differences in the product disordering. The formation of the same product under thermal and mechanochemical action on reaction mixtures suggests that mechanochemical treatment involves the melting of maleic anhydride, and solid sulfathiazole reacts with liquid maleic anhydride.

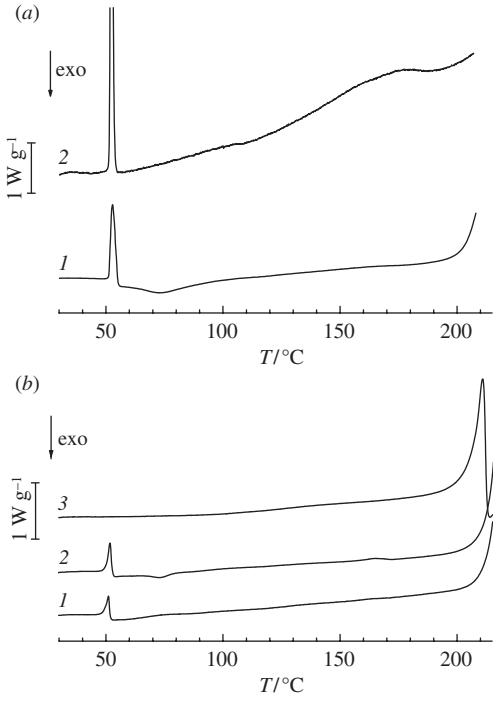


Figure 2 DSC curves: (*a*) (*1*) physical mixture of sulfathiazole and maleic anhydride (1:1), (*2*) maleic anhydride; (*b*) reaction mixtures with maleic anhydride taken in an excess after mechanochemical activation for (*1*) 1, (*2*) 2 or (*3*) 8 min.

Since the solid + liquid reactions can proceed as a topochemical process, through the formation and growth of product nuclei, we carried out model experiments with sulfathiazole single crystals. The formation of the product nuclei was observed in the interaction of sulfathiazole crystals with both the vapour and the melts of maleic anhydride. This suggests that in the mechanochemical activator, too, the interaction of sulfathiazole with the maleic anhydride melt can have a topochemical character, which is responsible for selectivity.

The DSC curve of a mixture of sulfathiazole with maleic anhydride [Figure 2(*a*), curve *1*] exhibits an endothermic peak due to maleic anhydride melting at 54 °C, followed by an exothermal effect, which is likely to be due to the interaction of sulfathiazole with maleic anhydride. The effects in the region 150–180 °C are caused by the decomposition of the residual maleic anhdyride and, possibly, by the III–I transition in sulfathiazole, which is evidence of incomplete reaction at increased temperature. The incomplete interaction under non-isothermal conditions can be explained by a relatively large size (0.1–0.3 mm) of sulfathiazole particles, which have no sufficient time to react as the reaction proceeds in the diffusion regime. Thus, the thermoanalytical investigation of the reagent mixture under heating showed that the interaction takes place above the melting point of maleic anhydride and corresponds to the solid + liquid process.

To examine the hypothesis of maleic anhydride melting in the mechanochemical activator, we carried out calorimetric, electron-microscopic and X-ray powder diffraction investigations of mixtures containing maleic anhydride in an excess with respect to an equimolar mixture.

After mechanical activation for 1 and 2 min, the mixtures containing maleic anhydride in excess behave during heating similarly to the physical mixtures of components [Figure 2(*b*),

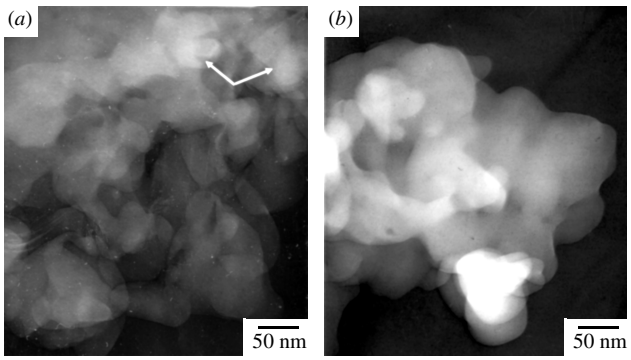


Figure 3 Microphotographs of the samples of the reaction mixture of sulfathiazole and maleic anhydride (1:1.1 molar ratio) after mechanochemical activation for (*a*) 1 and (*b*) 5 min.

curves *1* and *2*]. With an increase in the time of preliminary mechanochemical activation, no thermal effects of maleic anhydride melting and recrystallization were observed. This situation is characteristic of an amorphous state of a substance distributed over a matrix.[14,15] The electron-microscopic micrographs (Figure 3) show that, at the initial stage of mechanical activation, particles with uneven edges [indicated with arrows in Figure 3(*a*)], are present in the samples indicating to incomplete grinding and non-uniform mixing of the reaction mixture. As the time of mechanical activation increased [Figure 3(*b*)], we almost never observed particles with uneven edges, perhaps due to the rapid filling of cracks and irregularities with a melt of maleic anhydride. The X-ray diffraction patterns (not shown) of the reaction mixture containing maleic anhydride in excess after mechanical treatment for 5 min contain the reflections of sulfathiazole and the reaction product; no reflections of maleic anhydride were detected. The results suggest that mechanochemical activation involves the melting of maleic anhydride and its distribution over the surface of sulfathiazole and the reaction product. This results in the formation of a mechanocomposite in the reaction mixture; its properties differ from those of a physical mixture of the components.

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