

Original article

UDC 547.057-312:615.012

DOI: 10.15372/CSD2025632

EDN: JAZODI

Behaviour of succinic anhydride and benzocaine in the solid-phase reaction

T. G. TYURINA¹, T. V. KRYUK¹ , T. A. KUDRYAVTSEVA¹, G. K. VOLKOVA², V. V. BURKHOVETSKII²¹Litvinenko Institute of Physical Organic and Coal Chemistry, Donetsk, Russia²Galkin Donetsk Institute for Physics and Engineering, Donetsk, RussiaE-mail: t_tjurina@mail.ru, ktvl2010@mail.ru , tkudryavceva19@gmail.com, volkova9586@mail.ru, val-bur_63@mail.ru

Abstract

The possibility of obtaining benzocaine succinamide under the conditions of mechanochemical reaction of succinic anhydride with benzocaine (a local anesthetic) is demonstrated. It has been established that mechanical treatment in a ball mill results in amorphisation of initial substances, promoting adsorption of succinic anhydride on the surface of drug crystals, which leads to the chemical interaction between initial components. An intensive development of solid-phase interaction was determined to proceed intensively during 10 days after the load was removed. The maximum transformation degree (~90 %) was detected for the mechanical treatment of an equimolar mixture of benzocaine and succinic anhydride, in the amount of 4 g, in a ball mill for ~2 h. With a decrease in the mixture mass or increase in the load applied, the maximum yield is achieved within a shorter time. The conversion degree was determined to decrease with an increase in the time of mechanical action in all cases. The detected feature can be related to the equilibrium amidation under the conditions of heating during the long-term action of the impact load.

Keywords: succinic anhydride, benzocaine, mechanical treatment, benzocaine succinimide synthesis

Funding: The work was carried out with support from the Ministry of Science and Higher Education of the Russian Federation within budgetary funding for the Project “Investigation of the reactions of mechanochemical synthesis employing natural, synthetic polymers and organic compounds (FRES-2023-0002)”.

For citation: Tyurina T. G., Kryuk T. V., Kudryavtseva T. A., Volkova G. K., Burkhovetskii V. V., Behaviour of succinic anhydride and benzocaine in the solid-phase reaction, *Chemistry for Sustainable Development*, 2025, Vol. 33, No. 1, P. 67–75. DOI: 10.15372/CSD2025632. EDN: JAZODI.

INTRODUCTION

Solid-phase mechanochemical synthesis is taking on greater and greater importance in organic chemistry and, in particular, in the pharmaceutical industry. The major advantages of solid-phase synthesis include elimination of toxic solvents from the process, reduction of the number of technological stages to a minimum, time shortening with an increase in the yield of target prod-

ucts, the possibility to obtain the substances that are formed only in trace amounts when obtained using other methods, cannot be isolated from a solution, or their synthesis cannot be performed in the liquid phase, as stressed in all reviews published to date [1–11], etc.

All the indicated characteristics of solid-phase reactions are relevant in the context of green chemistry, causing evergrowing attention to the application of mechanochemistry for obtaining pharma-

ceutical substances (PS): antiepileptic, anticonvulsant, antidiabetic [5, 7, 10], antibacterial [5, 10], gastroprotective, hypotensive, hormonal [10] preparations, polypeptides [3, 5, 7, 10, 11], biologically significant heterocycles [5, 8, 10] and so on.

A very broad range of methods emerged in the mechanochemical synthesis of pharmacologically active compounds: liquid-assisted grinding (LAG) [6–8, 10, 11], mechanoensymatic reactions [6, 7], photomechanochemistry [6] and so on, so it has become possible to propose the term Medicinal Mechanochemistry [5, 6]. This area of mechanochemistry includes not only the synthesis of products through the chemical interaction between solid reagents, but also the formation of pharmaceutical solid dispersed systems. Mechanically activated systems are either solid dispersions in which PS are in the amorphised state or in the molecular form, or the complexes of PS with natural or synthetic polymers [1, 2, 5, 7, 9, 10, 12–14]. As a consequence of activation, a substantial increase in the solubility of medicinal substances occurs, which involves an increase in the efficiency of their action (enhanced biological availability, decreased dosing).

Under the weak mechanical action (comminution in a mortar), eutectic mixtures with improved solubility were obtained also for compounds that can react with each other, for example, for a mixture of an organic acid (ketoprofen) and an amine causing anesthetic action (benzocaine (BC), novocaine, or tetracaine) [15].

One of reactions used most frequently to synthesise pharmaceutical substances is the formation of amides; according to different estimates, the reactions involving N-acylation with the formation of amide bonds during the synthesis of potential medicinal substances account for 25 to 66 % [8, 16]. The amide group is one of the most widespread structural fragments of bioactive molecules, in particular natural compounds (peptides, proteins) and synthetic PS (β -lactam antibiotics, sulphanilamide preparations anesthetics, etc.).

To this date, a number of mechanochemical approaches to obtaining amides have been developed through the interaction of an amine and an acid [17], amine and ester [18], esters with ethanol and calcium nitride [19]. These reactions proceed at high rates and in high yields, however, they require the addition of activating reagents: (1-cyano-2-ethoxy-2-oxoethyliden-aminoxy)-dimethylaminomorpholinocarbenium hexafluorophosphate (COMU) or tetramethylchloroformammonium N,N,N',N'-hexafluorophosphate (TCFH)

and K_2HPO_4 [17], potassium *tert*-butanolate (KOTBu) [18], $InCl_3$ [19]. These processes are carried out according to LAG technology [18, 19].

In view of the toxicity of activating reagents, the direct interaction between initial substances in the absence of additives is of interest. This method was employed to synthesise phthalazol from phthalic anhydride and sulphathiazole [20, 21]. The reactions of phthalic anhydride and succinic anhydride (SA) with sulphacetamide [22], carboxylic acids with *p*-toluidine [23] and a broad range of aromatic mono- and diamines [24] were also carried out. The process was carried out in ball mills [20–22, 24], with subsequent pressurising and heating of the resulting tablets, as well as subjecting to shear strain in the equipment like Bridgman anvil [23]. It has been determined that in most cases, independently of the nature and molar ratio of initial reagents, the reaction proceeds according to the stoichiometry and is irreversible, leading to the formation of the corresponding monoamide, while reagent conversion is determined by the conditions of mechanical activation (the mass of initial load, the amount and mass of milling bodies, the value, type and duration of the imposed load, and temperature) [20–24]. For anhydride aminolysis in a ball mill, the high reaction rate is, according to [21], a consequence of several effects, the major ones being anhydride transport through the gas phase and the reaction of its vapour with the crystal surface, which is permanently renewed as a consequence of drug dispersion.

The goal of the present work was to study aminolysis of succinic anhydride by anesthetics (benzocaine) under the conditions of solid-phase synthesis.

EXPERIMENTAL

The reagents used in the work were: SA of analytically pure grade, BC (FS 001585-291216), $NaNO_2$ of chemically pure grade, HCl of specially pure grade, KBr of analytically pure grade, NaOH of pure grade, $CaCl_2$ of pure grade, deuterated dimethylsulphoxide ($DMSO-d_6$, 99.9 %, Sigma-Aldrich).

The treatment of BC, SA and their mixtures was carried out at the molar ratio anhydride/amine = 1 : 1 using two methods:

1) in the MLW KM-1 vibratory ball mill (GDR) under the following conditions: 3000 r.p.m., ball mass 0.2 kg; imposed load 20–30 N, mass of the material 1 or 4 g, treatment time 3 min, 1, 2, 3 or 4 h;

2) in the vibratory attrition grinder 75T-DrM (the Teplogorsk Plant of Hydraulic Equipment, Lugansk) under the conditions: the mass of the working body 1.13 kg; vibratory acceleration 300–490 m/s², vibration velocity 0.942–1.57 m/s, effective load 339–550 N, the mass of substance to be treated 4 g, treatment time 2 or 5 min. After treatment, the mixtures were kept in a desiccator over CaCl₂ at room temperature.

To study the characteristics of reaction product, a sample of the mixture after treatment for 3 h and exposure for 10 days was washed from residues of initial reagents using chloroform. The product yield was 70.9 %.

The content of carboxylic groups ($\omega(\text{COOH})$) in initial mixtures and in the samples after mill treatment was determined by acid-base titration, and primary amino groups were determined by nitritometry using an I-160MI ion meter (Izmeritel, Belarus) using a glass electrode ES-10603, silver chloride electrode ESr-10103 and a platinum electrode EPL-02. Titrant volume corresponding to the equivalence point was determined from the intersection of the second derivative ($\Delta^2\text{pH}/\Delta V^2$) with the abscissa axis.

¹H NMR spectra were recorded with a Bruker Avance II spectrometer (400 MHz) (Bruker, Germany) at 25 °C; the procedure was zg30 (standard); initial substances and their mixtures before and after treatment in the ball mill are completely soluble in DMSO-*d*₆. Infrared spectra were recorded at room temperature using a Specord 75IR spectrophotometer (Analytik Jena, Germany) within the region of 4000–400 cm⁻¹ (in tablets with KBr). The X-ray diffraction (XRD) data were obtained using a DRON-3 diffractometer (LNPO Burevestnik, Russia) with CuK_α-radiation, wavelength $\alpha = 1.54181 \text{ \AA}$ ($U = 30 \text{ kV}$, $I = 20 \text{ mA}$). The content of the crystalline phase of SA and BC after treatment in the ball mill was calculated similarly to the calculation of amorphous phase content [25] as a ratio of the integral intensity of crystalline peaks to the total integral intensity. Electron microscopic studies were carried out using a scanning electron microscope (SEM) JSM-

6490LV (JEOL, Japan) with the energy-dispersive attachment INCA Penta FETx3 (Oxford Instruments NanoAnalysis, UK). Before SEM studies, the samples were glued on a double-sided conductive carbon adhesive tape, and then carbon was sprayed onto the samples using a VUP-5 installation (SELMi, Ukraine).

RESULTS AND DISCUSSION

The previous publications described the synthesis of benzocaine succinamide (4-(ethoxycarbonyl)-phenyl-1-aminooxabutanoic acid, SA-BC) according to the following procedures: 1) in solution, by boiling a mixture of SA with a 12-fold excess of BC in dry toluene for 10 h [26] or 2) by the interaction of SA and BC (1 : 1.2) in a mixture of trimethylchlorosilane (ClSiMe₃) and dimethylformamide (DMFA) (20 °C, 10 h) [27], as well as in chloroform (60 °C, 2 h) [28].

The reaction proceeds according to the scheme presented in Fig. 1.

The formation of SA-BC is confirmed by comparing the IR spectra of initial reagents and reaction product (Fig. 2). Some absorption bands (a. b.) in the spectra of BC and in the product coincide, which is a consequence of the inclusion of a whole BC molecule, with the exclusion of the amino group, which is exchanged for the amide group. The latter is evidenced by the fact that the a. b. at 1275 cm⁻¹ is absent from the spectrum of SA-BC, while it is present in the spectrum of BC and relates to the aromatic amino group, and by the presence of a. b. at 1535, 1290 cm⁻¹ ($\delta_{\text{NH}} + \nu_{\text{CN}}$, $\delta_{\text{NH}} + \nu_{\text{CN}}$, respectively). The appearance of the spectrum also changes within the region of ν_{NH} vibrations: instead of a. b. at 3410 and 3328 cm⁻¹ (ν_{as} and ν_{s} NH₂) for BC we see 3424 and 3324 cm⁻¹ (a free and associated -CO-NH- group). In addition, there is a. b. at 1700 cm⁻¹ in the spectrum of SA-BC, which is the evidence of the presence of COOH-group in the dimeric form.

The formation of SA-BC is confirmed with even higher confidence by the analysis of NMR spectroscopic results. It has been determined [29]

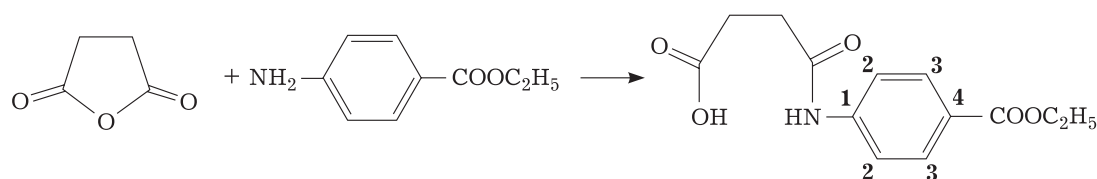


Fig. 1. Synthesis of benzocaine succinamide.

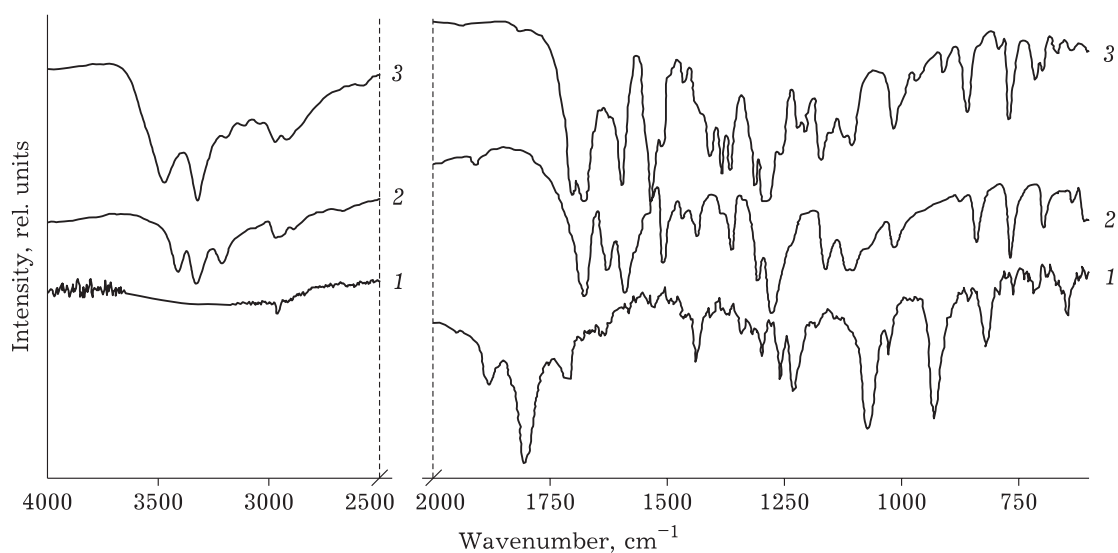


Fig. 2. IR spectra of succinic anhydride (1), benzocaine (2) and the product of their interaction, obtained after treatment for 2 h in the ball mill (20 N) and exposed for 10 days (3).

that the ^1H NMR spectrum of the product of SA reaction with BC in chloroform solution contains a triplet, a quadruplet and two doublets centred at 1.29, 4.26, 7.72 and 7.88 ppm, with the ratio of signal integral intensities 3 : 2 : 2 : 2, which allows their reliable assignment to the resonance of protons of methyl, methylene groups, aromatic protons **3** and **2** of the benzocaine fragment in SA-BC, respectively. The corresponding signals in the initial amine are observed at 1.255, 4.18, 6.57 and 7.62 ppm, with the same integral intensity ratio.

Because of inconsistencies in the values of chemical shifts in the ^1H NMR spectra of 4-(ethoxycarbonyl)-phenyl-1-amino-oxabutanoic acid and their assignments in literature sources [26, 27], while the ^{13}C NMR data for this compound have not been published previously, we present the results obtained by us.

^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 1.29 t (3H, CH_2CH_3 , $J = 7.1$ Hz); 4.27 q (2H, $\text{O}-\text{CH}_2-\text{CH}_3$, $J = 7.1$ Hz); 2.56 m (4H, $(\text{CH}_2)_2$); 7.71 d (2H, C^3H , $J = 8.8$ Hz); 7.89 d (2H, C^2H , $J = 8.8$ Hz); 10.316 s (1H, NH); 12.16 br. s (1H, COOH). ^{13}C NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 14.0 (CH_2CH_3); 28.4 ($\text{NH}(\text{CO})-\text{CH}_2\text{CH}_2\text{COOH}$); 30.0 ($\text{NH}(\text{CO})-\text{CH}_2\text{CH}_2\text{COOH}$); 60.2 (CH_2CH_3); 118.0 (C^2); 123.7 (C^4); 130.1 (C^3); 143.4 (C^1NH); 165.2 (COOC_2H_5); 170.6 ($\text{CO}-\text{NH}$); 173.6 (COOH).

The ^1H NMR spectra of products obtained in chloroform solution and by mechanical synthesis completely coincide with each other in signal positions and their intensity ratios, which confirms the identity of products synthesised using both

methods. At the same time, according to NMR and IR spectroscopic data, initial reagents do not undergo chemical transformations during mechanical treatment in the ball mill (1 h, 20 N) (the data are not shown).

After mechanical treatment under different conditions (the imposed load, treatment time, mass of the mixture were varied keeping the equimolar reagents ratio in the mixture), the samples of mixtures were analysed by nitritometry, pH measuring, NMR spectroscopy, SEM and XRD.

It has been established that immediately after load removal the formation of SA-BC is not detected (Fig. 3, curve 1), while 10 days later we observed a decrease in the content of free BC in all the studied compositions, which is evidence in favour of its interaction with the anhydride cycle. So, the reaction propagates intensively after the removal of mechanical action. In general, accumulation of the products of amidation goes on within a month after mechanical treatment. No changes in SA-BC content were revealed in the product of co-milling after 60 days in comparison with the 30 days long time interval (see Fig. 3, curves 3 and 4).

Relying on the results obtained, in the subsequent studies, we analysed the samples kept for not less than 10 days after co-milling.

Results of studies by SEM show that initial substances are characterised by a non-uniform structure. Benzocaine crystals are simple plate-like polyhedra with layered structure, with the longitudinal size 40–500 μm (Fig. 4, a). Succinic anhydride is composed of aggregated globular

particles 20–30 μm in size, with the inclusion of larger (up to 3 mm) particles of column-like structure (see Fig. 4, b). In the mixture that has not been subjected to mechanical treatment, BC and SA particles conserve their initial shapes and sizes (see Fig. 4, c). During co-milling, SA aggregates are decomposed into separate particles of irregular shapes and adsorbed on the surface of the drug crystals (see Fig. 4, d–f), which provides chemical interaction with the formation of amide. The size of agglomerates increases with an increase in the time of mechanical treatment: from 12–20 μm (0.5 h) to ~ 40 μm (4 h).

The diffraction patterns of BC and SA under investigation are completely identical to those available in the Match! database; the diffraction pattern is conserved after mechanical treatment, but a substantial decrease in the intensities of reflections is observed (Fig. 5, a, b). This provides evidence of the partial amorphisation of initial reagents without any changes in their chemical structure, and the absence of destruction. According to the estimation, the amount of the crystal phase in mechanically treated samples decreases down to ~ 20 % of the initial value.

In the physical two-component mixture, BC structure turned out to be more stable than SA structure: no one peak related to BC has disappeared, and the positions of peaks did not change (see Fig. 5). At the same time, some reflections related to SA shifted to smaller angles, some to larger

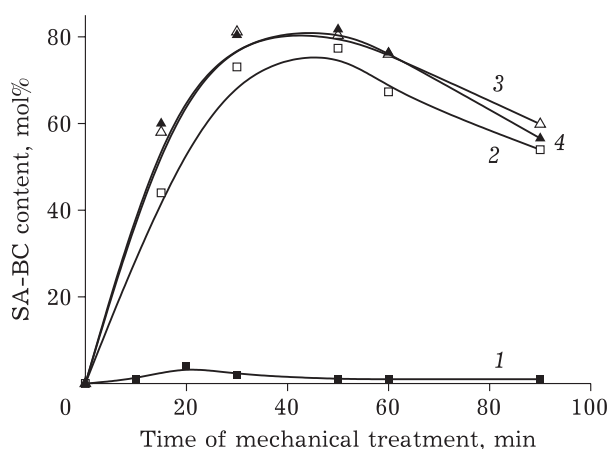


Fig. 3. Dependence of the amount of reaction product, benzocaine succinamide (SA-BC), on the time of mechanical treatment of the mixture in the ball mill and exposure after load removal: 0.5 h (1), 10 days (2), 30 days (3), 60 days (4) (the mass of the mixture is 1 g).

angles, which means that the interplanar spacing has changed. This allows us to state that BC is most likely the matrix of the resulting mixture.

After mechanical treatment of a mixture of SA and BC powders in the ball mill, substantial changes are observed in the diffraction patterns (Fig. 6). One can see that in comparison with the untreated physical mixture of the components the peaks over 2θ at 15, 18, 22, 27, 29, 31, 34° , related to SA crystals, disappear as early as after grinding for 0.5 h, while the peaks over 2θ at 16 – 18° , 20 – 24° , related to the amine, gradually

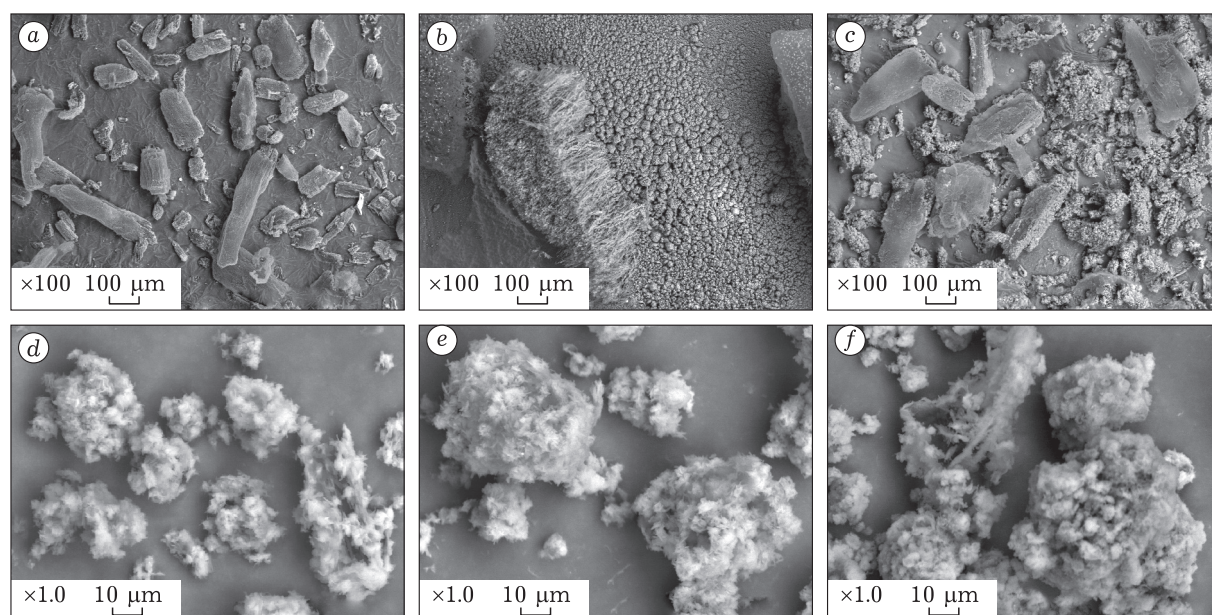


Fig. 4. Electron micrographs of benzocaine (a), succinic anhydride (b) and their equimolar mixture before (c) and after grinding in the ball mill (20 N) for 0.5 (d), 1 (e) and 4 h (f).

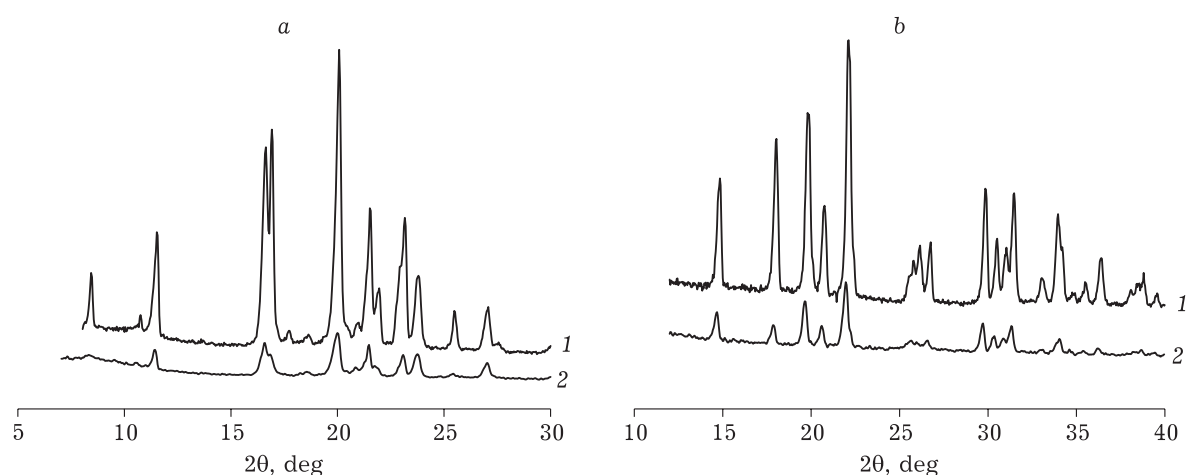


Fig. 5. Diffraction patterns of benzocaine (a) and succinic anhydride (b) before (1) and after (2) mechanical treatment in the ball mill for 1 h at 20 N.

broaden with an increase in the time of mechanical synthesis, which is evidence of BC amorphisation. New reflections over 2θ at 25.7° and 21.4° (an intense and a weaker one, respectively), obviously related to SA-BC, also appear in the diffraction patterns of the mechanically treated mixture. The XRD data show that mechanical treatment of a mixture of SA with BC results in their chemical interaction, and transformation degree depends on co-milling time. One may also state that PS is the matrix for anhydride during their interaction. However, in general, the close positions of reflections in the diffraction patterns before and after mechanical treatment do not allow us to make an unambiguous conclusion concerning the products of the solid-phase interaction of SA with BC.

According to the data of NMR spectroscopy (Table 1), recorded after 10 days long exposure of mechanically treated mixtures ~4 g in mass, the SA-BC/BC ratio after co-milling for 3 min is 73 : 17, that is, amidation reaches high transformation degree even at the initial time interval. Further treatment leads to an increase in conversion, and after reaction for 2 h only insignificant amount of benzocaine remains in the system (~1 mol%). Since there are no additional signals in ^1H NMR spectra, so another possible product, namely the cyclic amide, is not formed under these conditions.

An increase in the load from 20 N to 340–550 N does not have any noticeable effect on the degree of reagent transformation, though it allows a substantial decrease in reaction time: after the treatment of initial physical mixture for 2 min in the vibratory machine, SA-BC is formed in the amount

of 80 mol%, 5 min – 74 mol% SA-BC (according to the data obtained by acid group titration).

The entire set of results obtained by NMR, analysis of carboxylic group content, nitritometry under different treatment conditions shows that after the same load the product yield depends on grinding time and on the mass of the mixture. For instance, for a mixture with total mass 1 g, the yield of SA-BC reaches its maximum after treatment for ~50 min (see Fig. 3). In the case if the mass of mixture loaded for treatment is 4 g, the maximal amount of the product is formed after treatment for 2–3 h, while an increase in the time of co-milling to 4 h causes an increase in the amount of unreacted initial substances to ~14 mol% and to the corresponding decrease in the amount of SA-BC (see Table 1).

So, an increase in the time of mechanical treatment above the optimal value causes a decrease in amidation efficiency, independent of the load imposed.

An increase in the amount of unreacted compounds with an increase in the time of treatment in the mill was also observed by us for the mixtures of sulphanilamide with succinic anhydride [29], sulphanilamide with the copolymer of maleic anhydride or oxidised starch [30]. It can be assumed that this dependence may be related to the decomposition of the product under the action of long-term mechanical load, during which the product under treatment can be substantially heated.

The data published in [31] provide evidence in favour of this assumption. It has been noted that the reversibility of anhydride aminolysis by amines has not been described yet, and it has been shown

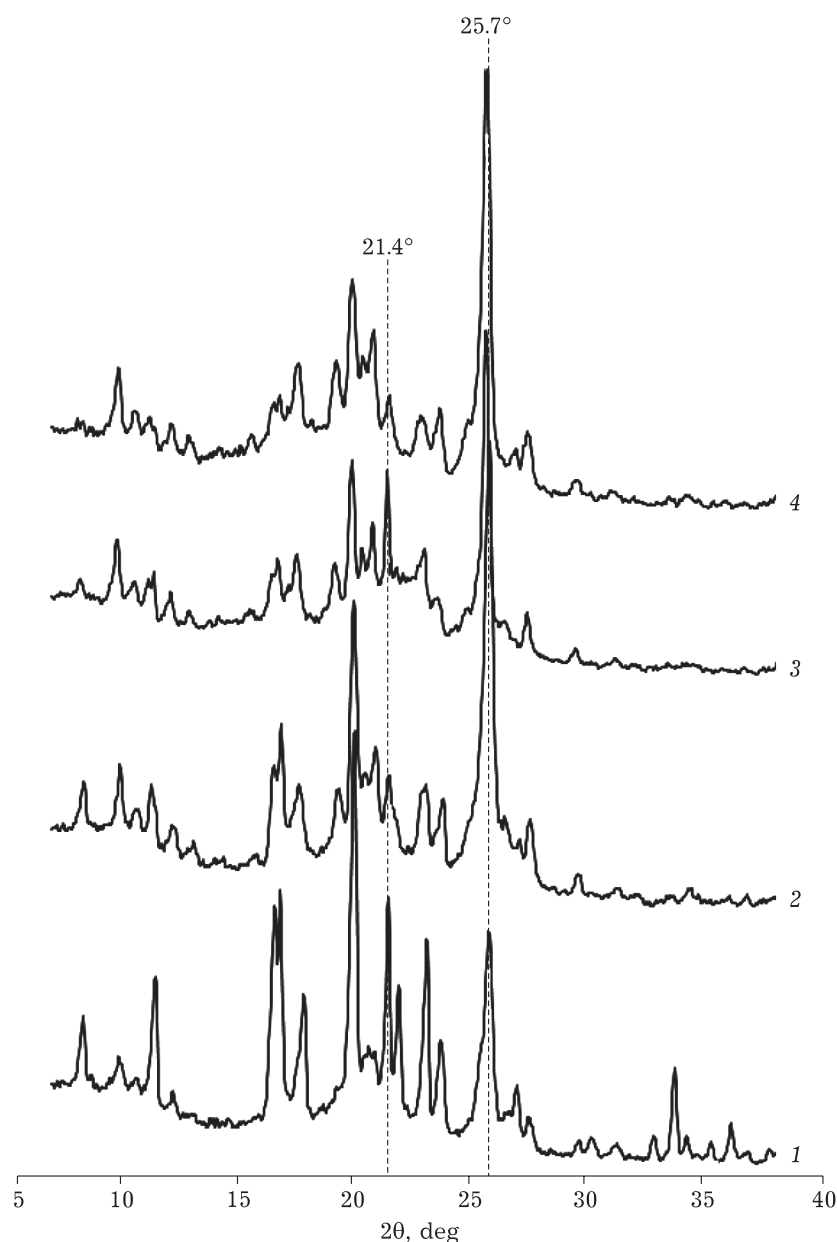


Fig. 6. Diffraction patterns of the equimolar mixture of benzocaine with succinic anhydride before (1) and after mechanical treatment in the ball mill (20 N) for 0.5 (2), 1 (3), 4 h (4).

on the basis of IR spectroscopic data that amide groups disappear in the product of maleic anhydride copolymer modification by octylamine under thermal treatment, but anhydride groups are again detected.

It has been determined in [21] that three main effects are implemented in the mechanochemical synthesis of phthalyl sulphathiazole: 1) local heat release in contact points, providing sublimation of phthalic anhydride and its transfer to the surface of sulphathiazole crystals; 2) permanent renewal

of sulphathiazole crystal surface as a consequence of crushing during mechanical treatment; 3) continuous removal of the product from the reaction zone, which provides elimination of possible diffusion-caused limitations for the reaction to proceed. Bearing in mind the experimental results obtained by us, in the absence of BC melting and in the case of close melting points of phthalic and succinic anhydrides (130 and 120 °C, respectively), we may suppose that SA amidation by benzocaine under the conditions of mechanical treat-

TABLE 1

Intensities of signals in ^1H NMR spectra ($\text{DMSO}-d_6$, 400 MHz, 25 °C) of the equimolar mixture (4 g) of succinic anhydride with benzocaine and the products of its treatment in the ball mill (20 N) after exposure for 10 days

Group	Range of δ , ppm	Integral intensity of the signal for treatment time			
		0	3 min	2 h	4 h
Benzocaine (BC)					
2 H ($=\underline{\text{CH}}-\text{C}-\text{COO}$)	7.750–7.536	1.000	0.366	0.014	0.157
2 H ($=\underline{\text{CH}}-\text{C}-\text{NH}$)	6.653–6.457	1.010	0.365	0.010	0.154
NH ₂	6.073–5.823	0.970	0.347	0.010	0.139
CH ₂ (CH ₃)	4.289–4.067	1.010	0.395	0.021	0.187
CH ₃	1.364–1.142	1.530	–	–	–
1 H BC		0.502	0.184	0.007	0.080
Benzocaine succinamide (SA-BC)					
2 H ($=\underline{\text{CH}}-\text{C}-\text{COO}$)	7.927–7.725	0	1.000	1.000	1.000
2 H ($=\underline{\text{CH}}-\text{C}-\text{NH}$)	7.725–7.583	0	1.010	1.010	1.010
CH ₂ (CH ₃)	4.285–4.142	0	0.990	1.010	1.010
NH	10.326–10.124	0	0.525	0.490	0.490
COOH	12.319–11.832	0	0.479	0.480	0.324
1 H SA-BC		0	0.500	0.503	0.504
Conversion, %		0	73.0	98.7	86.4

Note. Dash – overlapping of the signals from CH_3 -groups of BC and SA-BC.

ment follows the regularities determined in [21]. The high reaction rate is provided by PS amorphisation. Mechanical action and the formation of chemical bonds between SA and BC are time-separated, which is characteristic of mechanochemical processes [20]. It is evident that the effect of treatment time on the solid-phase reaction of SA with BC is an extreme dependence.

CONCLUSION

The studies have shown that under external mechanical load on the mixture of benzocaine with succinic anhydride their solid-phase interaction proceeds, developing intensively within 10 days after load removal. It has been established based on X-ray powder diffraction and electron microscopy that mechanical treatment causes amorphisation of initial reagents. The solid-phase interaction at the interface proceeds due to the mass transfer of anhydride to the free benzocaine surface. The dependence of the yield of product (benzocaine succinamide) on the time of mechanical treatment passes through an extreme point (80–90 wt%) for different values of imposed load, and an increase in the load can shorten reaction time. The maximal transformation degree is affected by such factors as the load, treatment time, and the mass of the mixture.

REFERENCES

1. Lyakhov N. Z., Grigorieva T. F., Barinova A. P., Vorsina I. A., Mechanochemical synthesis of organic compounds and composites with their participation, *Russ. Chem. Rev.*, 2010, Vol. 79, No. 3, P. 189–203.
2. Dushkin A. V., Mechanochemical synthesis of organic compounds and rapidly soluble materials, in: *High-Energy Ball Milling: Mechanochemical Processing of Nanopowders*, M. Sopicka-Lizer (Ed.), Woodhead Publishing, Oxford, 2010, P. 224–247.
3. Wang G.-W., Mechanochemical organic synthesis, *Chem. Soc. Rev.*, 2013, Vol. 42, No. 18, P. 7668–7700.
4. Achar T. K., Bose A., Mal P., Mechanochemical synthesis of small organic molecules, *Beilstein J. Org. Chem.*, 2017, Vol. 13, P. 1907–1931.
5. Tan D., Friščić T., Mechanochemistry for organic chemists: an update, *Eur. J. Org. Chem.*, 2018, Vol. 2018, No. 1, P. 18–33.
6. Friščić T., Mottillo C., Titi H. M., Mechanochemistry for synthesis, *Angew. Chem. Int. Ed.*, 2020, Vol. 59, No. 3, P. 1018–1029.
7. Pérez-Venegas M., Juaristi E., Mechanochemical and mechanoenzymatic synthesis of pharmacologically active compounds: a green perspective, *ACS Sustainable Chem. Eng.*, 2020, Vol. 8, No. 24, P. 8881–8893.
8. Fantozzi N., Volle J.-N., Porcheddu A., Virieux D., García F., Colacino E., Green metrics in mechanochemistry, *Chem. Soc. Rev.*, 2023, Vol. 52, No. 19, P. 6680–6714.
9. Demet O., Mechanochemistry: a power tool for green synthesis, in: *Advances in Green Synthesis: Avenues and Sustainability*, Inamuddin, R. Boddula, M. I. Ahamed, A. Khan (Eds.), Springer, Cham, 2021, P. 23–39.
10. Bento O., Luttringer F., El Dine T. M., Pătry N., Bantreil X., Lamaty F., Sustainable mechanosynthesis of biologically active molecules, *Eur. J. Org. Chem.*, 2022, Vol. 2022, No. 21, Art. e202101516.

11. Cuccu F., De Luca L., Delogu F., Colacino E., Solin N., Mocchi R., Porcheddu A., Mechanochemistry: new tools to navigate the uncharted territory of “impossible” reactions, *ChemSusChem*, 2022, Vol. 15, No. 17, Art. e202200362.
12. Dushkin A. V., Possibilities of mechanochemical technology of organic synthesis and production of rapidly dissolving materials, Thesis for Dr. Sci. in Chemistry, Novosibirsk, 2005, 336 p. (In Russ.).
13. Lu M., Wei W., Xu W., Polyakov N. E., Dushkin A. V., Su W., Preparation of DNC solid dispersion by a mechanochemical method with glycyrrhizic acid and polyvinylpyrrolidone to enhance bioavailability and activity, *Polymers*, 2022, Vol. 14, No. 10, Art. 2037.
14. Myz S. A., Mikhailenko M. A., Mikhailovskaya A. V., Politov A. A., Kuznetsova S. A., Shakhtshneider T. P., Mechanochemical synthesis of cocrystals of betulin with adipic acid, *J. Sib. Fed. Univ. Chem.*, 2020, Vol. 13, No. 4, P. 511–524. (In Russ.).
15. Umerska A., Zotova J., Tajber L., Formation of low melting point binary systems comprising ketoprofen and an amide local anaesthetic, *Int. J. Pharm.*, 2021, Vol. 607, No. 9, Art. 120969.
16. Brown D. G., Boström J., Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? Miniperspective, *J. Med. Chem.*, 2016, Vol. 59, No. 10, P. 4443–4458.
17. Dalidovich T., Mishra K. A., Shalima T., Kudrjašova M., Kananovich D. G., Aav R., Mechanochemical synthesis of amides with uronium-based coupling reagents: a method for hexa-amidation of biotin[6]juril, *ACS Sustainable Chem. Eng.*, 2020, Vol. 8, No. 41, P. 15703–15715.
18. Nicholson W. I., Barreteau F., Leitch J. A., Payne R., Priestley I., Godineau E., Battilocchio C., Browne D. L., Direct amidation of esters by ball milling, *Angew. Chem. Int. Ed.*, 2021, Vol. 60, No. 40, P. 21868–21874.
19. Gómez-Carpintero J., Sánchez J. D., González J. F., Menéndez J. C., Mechanochemical synthesis of primary amides, *J. Org. Chem.*, 2021, Vol. 86, No. 20, P. 14232–14237.
20. Chuyev V. P., Lyagina L. A., Boldyrev V. V., Mechanochemical acylation of primary aromatic amines, *Dokl. Akad. Nauk SSSR*, 1990, Vol. 315, No. 4, P. 916–920. (In Russ.).
21. Mikhailenko M. A., Shakhtshneider T. P., Boldyrev V. V., On the mechanism of mechanochemical synthesis of phthalylsulphathiazole, *Chem. Sustain. Dev.*, 2004, Vol. 12, No. 3, P. 367–371.
22. Fukuoka E., Makita M., Yamamura S., Yoshihashi Y., Solid-state reaction between sulfacetamide and phthalic anhydride by grinding, *Chem. Pharm. Bull.*, 1994, Vol. 42, No. 6, P. 1342–1344.
23. Leont'ev A. I., Zharov A. A., Chistotina N. P., Solid state reactions of aromatic amines with carbonic acids under shear deformations at high pressures, *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, 1992, No. 9, P. 2147–2153. (In Russ.).
24. Khalikov S. S., Avdeeva A. V., Aripov Kh. N., Mechanochemical reactions of *N*-acylation of *p*-toluidine with carboxylic acids. II. Influence of the nature of the acid on the acylation process, *Uzbek. Khim. Zhurn.*, 1995, No. 3, P. 56–58. (In Russ.).
25. OFS.1.2.1.1.0011.15 X-ray Powder Diffractometry, in: State Pharmacopoeia of the Russian Federation, Vol. 1, Scientific Centre for Expert Evaluation of Medicinal Products, Moscow, P. 831. (In Russ.).
26. Srivastava R., Tiwari D. K., Dutta P. K., 4-(Ethoxycarbonyl) phenyl-1-amino-oxobutanoic acid–chitosan complex as a new matrix for silver nanocomposite film: preparation, characterization and antibacterial activity, *Int. J. Biol. Macromol.*, 2011, Vol. 49, No. 5, P. 863–870.
27. Zavyalov S. I., Zavozin A. G., Ezhova G. I., Kulikova L. B., Kravchenko N. E., Synthesis of *N*-aminobenzoic acids and esters, *Khim.-Farmatsevt. Zhurn.*, 1995, Vol. 29, No. 5, P. 45–47. (In Russ.).
28. Tyurina T. G., Kryuk T. V., Lavrova A. I., Synthesis of succinamides of *p*-aminobenzoic acid derivatives, *Bulletin of Donetsk National University. Series A: Natural Sciences*, 2019, No. 3–4, P. 127–133. (In Russ.).
29. Tyurina T. G., Kryuk T. V., Modification of maleic anhydride copolymers with aliphatic alkylamines and sulfanilamide, *Russ. J. Appl. Chem.*, 2019, Vol. 92, No. 3, P. 351–359.
30. Kryuk T. V., Tyurina T. G., Kudryavtseva T. A., Mechano-synthesis of sulfanilamide matrix forms, *Pharm. Chem. J.*, 2022, Vol. 56, No. 4, P. 493–496.
31. Hu G. H., Lindt J. T., Amidification of poly(styrene-co-maleic anhydride) with amines in tetrahydrofuran solution: a kinetic study, *Polym. Bull.*, 1992, Vol. 29, P. 357–363.

Submitted 03.05.2023

Approved 27.04.2024

Accepted 20.05.2024