SOLID-PHASE REACTIONS OF AROMATIC AMINES WITH CARBOXYLIC ACIDS UNDER CONDITIONS OF SHEAR DEFORMATION AND HIGH PRESSURE

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Solid mixtures of carboxylic acids and aromatic amines react under shear deformation at high pressure (to 8 GPa) for form amides, in the case of ortho-phenylenediamine-substituted benzimidazoles are formed. Under these conditions the conversion rates are hundreds of thousands of times higher than when the same processes are carried out in liquid phase. The cyclization reaction is accelerated to a lesser degree than the reaction of formation of the corresponding amide. The increase of the length of the carboxylic acid radical prevents the cyclization reaction.

Keywords: shear deformation, high pressure, aromatic amines, carboxylic acids, amide, benzimidazole, amidization, cyclization.

Earlier studies [1-5] showed that organic compounds that contain amine and carboxyl groups are capable of reacting in solid state if they are subjected to shear deformation at high pressure (SD + HP). Thus, the ammonium salts of mono- and dibasic carboxylic acids convert under these conditions to amides [1, 2]; amino acids and their mixtures react to give peptides [3, 4]; the reaction of *ortho*-phenylidenediamine and phenylacetic acid is accompanied by the formation of dibazole [5].

We have investigated the conversions of mixtures of various solid aromatic amines with carboxylic acids under conditions of SD+HP.

The SD+HP experiments were conducted in an anvil apparatus [6] at pressures to 8 GPa, temperatures of 195 and 293 K, and anvil rotation angles to 720°.

After the experiments the materials were analyzed by gas-liquid and liquid chromatography. The LC analysis utilized S-18 and Silosorb-600 columns (L = 20 cm, 15,000 and 20,000 theoretical plates, respectively). The eluents used were mixtures of acetonitrile with water (S-18) and a mixture of hexane, chloroform, and isopropyl alcohol (Silosorb).

The PMR spectra were also acquired with the goal of identifying the reaction products and calibrating the chromatograph (Bruker WM-250 spectrometer).

A broad set of mixtures of various aromatic amines with carboxylic acids that contain both aliphatic and aromatic radicals was taken at the beginning of the study of the reaction of amines with acids under conditions of SD+HP.

The reaction mixtures, experiment conditions, and their results are given in Table 1. It can be seen from these data that all of the tested pairs of reagents react to form aromatic amines.

The yields of reaction products determined by two methods (GLC and LC) are the same within the limits of analysis error and therefore only the LC data are given in Table 1. The SD+HP conditions are favorable for synthesis of aromatic amides, the yields of which reach 50% and higher.

In the reactions with *ortho*-phenylenediamine (OPD), a reaction of cyclization with the formation of the corresponding benzimidazoles (BIs) was observed in addition to the formation of the amide (Table 1, experiments 15 and 16); this reaction was the subject of study in a series of experiments involving OPD and a number of monobasic acids. The results of these experiments are reported in Table 2.

As can be seen from Table 2, OPD reacts with acids to form the corresponding benzimidazoles. As in the preceding experiments (Table 1), other conversion products of the reaction mixtures were not detected, i.e., at the rotation angles indicated in Table 2 the reaction mixture reacts only partially.

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No.	Composition of s (1:1 (mole))	Yield of amide (henzimidazole).	
	amine	acid	%
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	Aniline * p-Toluidine * o-Aminophenol 2-Aminopyridine * * o-Phenylenedia- mine *	(HOOC) ₂ CH ₂ HOOC (CH ₂) ₂ COOH HOOCCH ₂ Ph HOOCCP _h HOOCCH ₂ Ph HOOCCH ₂ Ph HOOCCH ₂ Ph HOOCCH ₂ Ph HOOCCH ₂ Ph HOOC (CH ₂) ₂ COOH HOOC (CH ₂) ₈ COOH HOOCCH ₂ Ph HOOCAd	$\begin{array}{ c c c c c c c c c c c c c c c c c c c$

TABLE 1. Solid-Phase Reactions of Aromatic Amines with Carboxylic Acids under Conditions of SD+HP (6 GPa, 293 K, rotation angle 360°)

*Reaction conducted in adamantane (1:1, mole, 10% + 90% Ad).

[†]Rotation angle of anvils 720°.

Note. When dibasic acids were used the diamide was not detected in the reaction products and the figures given in the table relate to the yield of monoamide.

Acid	Composition of reaction mixture, OPD:acid, mole	Yield, %		Conver- sion of	Method
		amide	benzimi- dazole	reaction mixture	analysis
HCOOH CH ₃ COOH C ₂ H ₅ COOH C ₄ H ₉ COOH C ₄ H ₉ COOH C ₆ H ₁₃ COOH C ₇ H ₁₅ COOH C ₁₄ H ₂ COOH C ₁₄ H ₂ COOH C ₁₄ H ₂₃ COOH C ₁₅ H ₂₇ COOH Ad-COOH	$ \begin{array}{c} 1:1 \\ 1:0.3* \\ 1:0.3* \\ 1:0.3* \\ 1:0.3* \\ 1:0.3* \\ 1:0.3* \\ 1:0.3* \\ 1:0.3* \\ 1:0.3* \\ 1:1 \\ 1:0.3 \\ 1:1 \\$	$ \begin{array}{c} 1.9\\ -\\ 0.4\\ 0.7\\ 0.7\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\$	$\begin{array}{c} 2.8\\ 0.1\\ 0.2\\ 0.4\\ 0.6\\ -\\ -\\ -\\ -\\ -\\ 11.6\\ 9.1\\ 10.3\\ 19.2\\ 20.5\\ 22.5\\ 16.0\\ 7.7\\ 9.9\end{array}$	4.7 0.1 0.7 1.1 1.2 3.0 5.0 6.0 7.5 18.1 13.1 16.4 25.6 27.2 29.0 20.0 9.7 11.4 ‡	IC I
Pn-CH ₂ COOH	1:1	7.2	5.3	12.5	LC
	Acid HCOOH CH_3COOH C_2H_5COOH C_2H_5COOH C_4H_5COOH $C_6H_{13}COOH$ $C_7H_{15}COOH$ $C_7H_{15}COOH$ $C_1H_{21}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$ $C_{13}H_{27}COOH$	$\begin{array}{c c} Acid & \begin{array}{c} Composition \\ of reaction \\ mixture, \\ OPD:acid, mole \\ \\ \\ HCOOH & 1:1 \\ CH_3COOH & 1:0.3 * \\ C_2H_3COOH & 1:0.3 * \\ C_3H_7COOH & 1:0.3 * \\ C_4H_3COOH & 1:0.3 * \\ C_6H_{13}COOH & 1:0.3 * \\ C_7H_{15}COOH & 1:0.3 * \\ C_7H_{15}COOH & 1:0.3 * \\ C_8H_{17}COOH & 1:0.3 * \\ C_9H_{19}COOH & 1:0.3 * \\ C_{14}H_{20}COH & 1:1 \\ C_{11}H_{23}COOH & 1:1 \\ C_{12}H_{23}COOH & 1:1 \\ C_{15}H_{27}COOH & 1:1 \\ C_{15}H_{21}COOH & 1:1 \\ Ad-COOH & 1:1 \\ \end{array}$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $

TABLE 2. Yield of Substituted Benzimidazoles during SD + HP for the Reaction of *ortho*-Phenylenediamine with Carboxylic Acids (6 GPa, rotation angle 360°)

*At 1:1 composition the starting components are a mixture of solid and liquid phases; at a 1:0.3 composition all the mixtures are solid.

[†]Because of the instability of the reaction products at the temperatures of GLC analysis the data obtained by this method should be viewed as tentative [‡]Rotation angle 720°.



Fig. 1. Dependences of logarithms of conversion of equimolar reaction mixtures (1, 2) and yield of benzimidazoles (1', 2') (log; Y, yield; conversion, %) on pressure (P): 1) o-phenylenediamine + phenylacetic acid; 2) o-phenylenediamine + lauric acid (293 K).

The following property can be followed (the series of 0.3:1 composition; experiments 2-9 and 11): the longer the aliphatic radical, the higher the conversion of the reaction mixture. The following trend is seen in experiments 10-15, conversion is higher in the case of acids with an odd number of carbon atoms in the molecule, i.e., an effect of alternation of reactivity of the acids is manifested. The explanation for this is probably the same as in [7, 8]: the reactivity of carboxylic acids in a homologous series has an alternating character that results from variations of shear stress that are observed as one moves through a series of these acids.

The kinetic properties of the reactions in which benzimidazoles formed were studied on mixtures of OPD with phenylacetic acid (PA) and lauric acid (LA). The effect of temperature, pressure, and magnitude of deformation on the yield of composition of reaction products was studied. In addition, kinetic dependences of the yield of reaction products in the melt at atmospheric pressure and various temperatures were recorded. The reaction of OPD with acids, as is well-known, is a two-stage process described by the following reaction equation:

$$H_2NC_{\theta}H_4NH_2 + RCOOH \xrightarrow{k_1}_{-H_1O} H_2NC_{\theta}H_4NHCOR \xrightarrow{k_2}_{-H_2O} \bigvee_{N}^{NH} C_{-R},$$

where k_1 and k_2 are the rate constants of the formation of the amide and benzimidazole, respectively.

In the case of lauric and phenylacetic acids a reaction between the amine and acid with the formation of a salt occurs at the moment of preparation of the starting mixture as the components are mixed in the mortar. Taking this into account, the differential equations of the reaction rates will be written in the following way:

$$-dC/dx = k_1 C$$
 (1)

$$dM/dx = k_1 C - k_2 M \tag{2}$$

$$\mathrm{d}B/\mathrm{d}x = k_2 M,\tag{3}$$

where C, M, and B are the concentrations of the salt, amide, and benzimidazole, respectively, and x is the shear deformation, $x = \theta r/h$ (θ is the rotation angle of the anvils, r is the radius of the differential zone of a sample, and h is the height of the sample pellet).

The effect of temperature was studied on mixtures of OPD with PA. The experiments were conducted at 195 and 293 K (8 GPa, anvil rotation 330°). Conversion of the starting mixture and the yield of benzimidazole (BI) were 13 and 7.4% at 195 K and 20.7 and 13.6% at 193 K.



Fig. 2. Dependences of conversion of an equimolar reaction mixture and yields of the products of the reaction of *o*-phenylenediamine + phenylacetic acid (a): 1) conversion of mixtures; 2) concentration of amide. Reaction of *o*-phenylenediamine + lauric acid (b) (6 GPa, 293 K): 1') conversion of mixture; 2') concentration of amide; 3) concentration of benzimidazole.

Evaluation of the activation energy of conversion of the reaction mixture gave a figure of 2.05 kJ/mole, and a value of 2.9 kJ/mole for the reaction of formation of BI. The activation energies are very low, which is characteristic for chemical processes occurring under conditions of SD+HP.

The effect of pressure was investigated on mixtures of OPD with both acids. The results are given in Fig. 1.

The dependences of the product yields on pressure were analyzed according to the equation $\ln W_{p_1}/W_{p_2} = -\Delta V^{\neq}(p_2 - p_1)/RT$ (where ΔV^{\neq} is the difference of activation volumes, W_{p_1} and W_{p_2} are the conversion and yield of BI at pressures p_1 and p_2 , respectively). The following results were obtained: for the PA + OPD system, $\Delta V_1^{\neq} = -0.52 \text{ cm}^3/\text{mole}$ and $\Delta V_2^{\neq} = -0.905 \text{ cm}^3/\text{mole}$; for LA + OPD, $\Delta V_1^{\neq} = -1.15 \text{ cm}^3/\text{mole}$ and $\Delta V_2^{\neq} = -1.315 \text{ cm}^3/\text{mole}$. Subscripts 1 and 2 relate to the conversion of the reaction mixture and to the formation of BI, respectively.

As can be seen from these data, the yield of BI increases with pressure and temperature faster than does conversion (consumption of reaction mixture to all of the amide formed in the reaction process), i.e., both pressure and temperature contribute to the cyclization reaction.

Figure 2 shows dependences of the yields of reaction products on magnitude of deformation (on rotation angle of anvils). From these dependences one can evaluate the conversions of the reaction mixtures per rotation (18 and 20% for mixtures with PA and LA, respectively) and also the initial values $(dC/dx)_0$, which characterize the intensity of the SD+HP process at the beginning of deformation of the sample $[(dC/dx)_0 = 6-7\%/rad (PA + OPD)]$ and 9-11%/rad (LA + OPD)].

One may note that the concentration of amide, both in the case of PA and LA, reaches a maximum of 7 and 6%, which is many times greater than the figures that characterize the same reactions accomplished in liquid phase (see below).

The following figures were obtained and calculated as a result of the investigation of the reaction of the reagents in the melt (1 atm).

PA + OPD system (1:1): rate 0.5%/min (384 K) and 0.8%/min (394 K); activation energy 57.8 kJ/mole; $E_1 - E_2 = -18.8$ kJ/mole; rate at 293 K, 0.0017%/min; $k_1/k_2 = 0.001$ (293 K). The starting mixture OPD + LA (1:1): rate 0.1%/min (378 K) and 0.55%/min (418 K); activation energy 55.7 kJ/mole; $E_1 - E_2 = -19.65$ kJ/mole; rate at 293 K, 0.00057%/min; $k_1/k_2 = 0.000097$ (293 K).

The reaction systems reported in Tables 1 and 2 interact during a time of deformation reckoned in tens of seconds or even seconds. The data on the dependence of the yields of reaction products on pressure, temperature, and shear deformation, and also the results of the study of kinetics under conditions of SD+HP and under liquid-phase conditions make it possible to compare the rates and ratios of reaction rate constants in the synthesis of BI for SD+HP and in the melt.

For the evaluation we will take an anvil rotation time of 1 sec, which is easily achieved in experiments. Based on this and the conversion obtained by extrapolation to atmospheric pressure (see Fig. 1), the calculated rate of reaction of OPD with PA is 4%/sec. Since the rate in the melt at 293 K is 0.0017%/min, the reaction rate for SD+HP as a minimum is 140,000 times the rate of conversion in the liquid phase.

Analogously, the rate of synthesis with LA is 0.65%/sec and 0.00057%/min and, therefore, the reaction is at least 70,000 times faster for SD+HP.

We will use Eq. (2) for the evaluation of the ratio of the rate constants of amidization and of formation of BI. At the maximum point of the kinetic curve $dM/dx = k_1C - k_2M = 0$; hence $k_1/k_2 = M/C$ or $k_1/k_2 = 0.07$ for PA and 0.06 for LA.

For the liquid-phase reaction at 293 K this figure is 0.001 for the reaction of OPD + PA, while for LA + OPD $k_1/k_2 = 0.0001$. Thus, the ratio of constants varies 70- and 600-fold, respectively. Correction for pressure (extrapolation to atmospheric pressure) is capable only of increasing this figure (see Fig. 1).

Therefore, in cases of SD+HP there is a significant change of the selectivity of the process, with the size of the effect being highly dependent on the nature of the acid radical.

These calculations of the rates of conversion indicate that the reaction rates of amidization and synthesis of benzimidazoles are tens and even hundreds of thousands of times higher in cases of SD+HP than in the melt. The reactions at SD+HP differ further in that, by comparison with liquid-phase reactions, the reaction mixtures are richer in the intermediate product (the amide). The calculated ratios k_1/k_2 are tens and even hundreds of times higher than in the liquid-phase process. These facts are evidence that the rate of cyclization when a change is made to conditions of SD+HP increases to a lesser degree than the reaction of formation of the monoamide is accelerated.

The phenomenon of a relative deceleration of the cyclization reaction by comparison with the reaction of linear type can also be detected in other reactions. For example, amino acids in solutions or melts react to give cyclic products (diketopiperazines) with high yields, while under SD+HP conditions amino acids form primarily peptides (linear products), with the share of diketopiperazines being negligible [4].

It can be expected that the larger the geometric dimensions of the molecules, the more strongly inhibition on the part of the solid matrix in the ring-formation reaction should develop. The example with lauric and phenylacetic acids confirms this hypothesis: when one switches from liquid-phase conditions to SD+HP conditions in the case of lauric acid, the radical of which consists of a chain containing 11 carbons, ratio k_1/k_2 increases ten times more than in the same reaction with phenylacetic acid.

REFERENCES

- 1. A. A. Zharov and N. P. Chistotina, Dokl. Akad. Nauk SSSR, 306, No. 3, 650 (1989).
- 2. N. P. Chistotina and A. A. Zharov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 10, 2289 (1989).
- A. A. Zharov, I. I. Yakovleva, G. A. Adadurov, N. P. Chistotina, and A. G. Kazakevich, in: Summaries of Reports of the 11th All-Union Symposium on Mechanochemistry and Mechanoemission of Solids, September 11-14, 1990, Chernigov, Vol. 1, p. 22.
- 4. I. I. Yakovleva, Candidate's Dissertation, Chemical Sciences, Moscow (1990).
- 5. N. P. Chistotina, A. A. Zharov, N. E. Agafonov, and V. S. Bogdanov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1452 (1989).
- 6. N. P. Chistotina and A. A. Zharov, Prib. Tekh. Eksp., No. 2, 229 (1974).
- M. G. Matveev, A. A. Zharov, V. M. Zhulin, and E. B. Zhuravleva, Dokl. Akad. Nauk SSSR, 270, No. 5, 1156 (1983).