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## Interaction of Isonicotinic Acid Hydrazide with Carboxylic Acid Anhydrides

There has been presented data on the synthesis of monoamides and cyclic imides which are derivatives of isonicotinic acid hydrazide. Cyclic anhydrides of carboxylic acids (succinic, maleic and phthalic) easily react with the hydrazide of isonicotinic acid with cycle opening, forming isonicotinoylhydrazide of dicarboxylic acids, and under more severe conditions the latter are transformed into cyclic acid imides. The structures of the synthesized compounds were studied using <sup>1</sup>H- and <sup>13</sup>C-NMR spectroscopy, as well as data from two-dimensional COSY (<sup>1</sup>H-<sup>1</sup>H) and HMQC (<sup>1</sup>H-<sup>13</sup>C) spectra. The values of chemical shifts, multiplicity and integral intensity of <sup>1</sup>H and <sup>13</sup>C signals in one-dimensional NMR spectra were determined. Homo- and heteronuclear interactions confirming the structure of the studied compounds were established using spectra in the COSY (<sup>1</sup>H-<sup>1</sup>H) and HMQC (<sup>1</sup>H-<sup>13</sup>C) formats. In the approximation of the density functional B3LYP with a base set of 6-31G(d), the enthalpy of the reactions ΔH<sub>r</sub> in the absence and in the presence of a solvent — isopropanol (self-consistent reaction field method) were calculated quantum-chemically.

**Keywords:** isonicotinic acid hydrazide, anhydrides, 1,4-dicarboxylic acid monoamide, phthalic acid acylhydrazides, cyclic imides, quantum chemical calculation, heteronuclear interactions, NMR spectroscopy.

### Introduction

Over the past decade, tuberculosis has once again become one of the leading causes of death in the world; at least three million people die from tuberculosis in the world every year [1, 2]. The urgency of the problem of tuberculosis incidence is associated with the spread of drug-resistant strains of the causative agent of tuberculosis, therefore there is a constant need to find new means to combat diseases caused by resistant pathological strains to improve human life. One of the main ways to find and develop new antibacterial drugs is to modify the structure of known anti-tuberculosis drugs. Isonicotinic acid hydrazide occupies a leading place in the treatment of various forms of tuberculosis and it has many different derivatives with wide variation of antitubercular activity and toxicity of compounds [3]. The introduction of an amide fragment and a carboxyl group into a molecule of biologically active substances is of practical interest, since N-substituted amides of carboxylic acids have valuable and unique properties that determine their widespread use as biologically active substances [4, 5]. It should be noted that monoamides of 1,4-dicarboxylic acids, namely succinic, maleic and phthalic acids are readily available intermediates in the synthesis of cyclic acid imides. In comparison with their predecessors, they are widely used as herbicides, insecticides, fungicides, and are also physiologically active substances of a wide spectrum of action, possessing antimicrobial, anti-tuberculosis, antiviral, antitumor and other types of activity [6–8]. As an example, we can cite such successfully used anticonvulsant drugs as ethosuximide and pufemide which are derivatives of succinimide [9, 10]. Among phthalic acid acylhydrazides obtained by the interaction of salicylic, isonicotinic and *p*-toluylic acid hydrazides, substances with high hypoglycomic activity were found [10].

In the scientific literature, work continues on the search for new tuberculostatic derivatives of isonicotinylhydrazides and methods for their preparation. Previously published works of the authors [11, 12] contain interesting data on acyl derivatives of isonicotinic acid hydrazide. Treatment of isonicotinylhydrazine with phthalic anhydride did not directly lead to the production of cyclic phthaloyl. Instead, 1-isonicotinyl-2-(*o*-carboxybenzoyl) hydrazine was formed, which, when heated to 200–210 °C, was

cyclized to 1-isonicotinyl-2-phthaloyl hydrazine. However, the interaction of isonicotinylhydrazide with maleic anhydride under similar conditions did not lead to the production of a cyclic product, and the final product was 1-isonicotinyl-2-( $\beta$ -carboxyacrylyl)hydrazine [11]. In [12], the synthesis of only 4-(2-isonicotinoylhydrazino)-4-oxobutanoic acid obtained by the interaction of isoniazide with succinic anhydride was described and crystal structure data was given. We have previously published a number of papers on the study of hydrazine derivatives as synthons in the search for new anti-tuberculosis drugs [13–16]. Interesting results were obtained in the synthesis of  $\beta$ -N-(methacrylylcarbamothioyl)isonicotinohydrazide, which, when boiled in 2-propanol, underwent intramolecular cyclization to form  $\beta$ -N-(5-methyl-4-oxo-5,6-dihydro-4H-1,3-thiazine-2-yl)isonicotinohydrazide [17]. Previously, we also described the synthesis and study of the structure of N-(1,3-dioxoisindoline-2-yl)isonicotinamide by the X-ray diffraction method [18]. It follows from the data obtained that bond lengths and valence angles in compounds **6** are close to the usual ones [15, 16]. The phthalimide cycle is flat with an accuracy of  $\pm 0.013$  Å. The amide group is located almost perpendicular to it [19]. Thus, it follows from the analysis of the literature data that the direction of the reaction of the interaction of isonicotinic acid hydrazide with dicarboxylic acid cyclic anhydrides and the nature of the formation of final products depend on a number of factors that require further research.

### Experimental

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were taken on a JNM-ECA 400 spectrometer (399.78 and 100.53 MHz, respectively) using DMSO- $d_6$  solvent. The reaction progress and purity of the obtained compounds were monitored by thin-layer chromatography on Silufol UV-254 plates in isopropyl alcohol-benzene-ammonia systems (10:5:2). The plates were developed with iodine vapors. The reaction products were isolated by recrystallization or column chromatography on aluminum oxide. All solvents used in the work were purified and absolutized in accordance with known methods [13–17].

**The general method of obtaining isonicotinoylhydrazide of 1,4-dicarboxylic acids (1–3).** To 0.02 mol of isonicotinic acid hydrazide in 20 ml of ethanol or ethyl acetate, a solution of 0.02 mol of 1,4-dicarboxylic acid anhydride (succinic, maleic and phthalic) in 20 ml of ethanol or ethyl acetate was added with stirring. The reaction mixture was stirred at 40–50 °C for an hour. The precipitate was filtered out and recrystallized from ethanol.

**4-(2-Isonicotinoylhydrazinyl)-4-oxobutanoic acid (1).** The yield of product **1** is 86.1 %; melting point is 245–246 °C.  $^1\text{H}$  NMR spectrum (DMSO- $d_6$ ),  $\delta$ , ppm: (J, Hz): 2.42–2.43 m (4H, H-11, 11, 12, 12), 7.72 d (2H, H-3, 5,  $^3\text{J}$  6.0), 8.70 d (2H, H-2, 6,  $^3\text{J}$  6.0), 10.01 br.s. (1H, H-8), 10.61 br.s. (1H, H-9), 11.86 br.s. (1H, H-14).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , md: 28.64 (C-12), 29.26 (C-11), 121.83 (C-3, 5), 140.01 (C-4), 150.91 (C-2, 6), 164.43 (C-7), 171.00 (C-10), 174.06 (C-13).

**4-(2-Isonicotinoylhydrazinyl)-4-oxobut-2-enoic acid (2).** The yield of product **2** is 96 %; melting point is 183–184 °C.

**2-(2-Isonicotinoylhydrazinocarbonyl)benzoic acid (3).** The yield of product **3** is 21 %; melting point is 219–220 °C.  $^1\text{H}$  NMR spectrum (DMSO- $d_6$ ),  $\delta$ , ppm: (J, Hz): 7.85 d (2H, H-3, 5,  $^3\text{J}$  6.0), 7.92–7.99 m (4H, H-12, 13, 14, 15), 8.82 d (2H, H-2, 6,  $^3\text{J}$  6.0), 11.70 br. s (1H, H-18), 11.70 s (2H, H-8, 9).  $^{13}\text{C}$  NMR spectrum,  $\delta_c$ , ppm: 121.99 (C-3, 5), 124.52 (C-12, 14), 129.95 (C-11, 16), 136.02 (C-13, 15), 138.21 (C-4), 151.31 (C-2, 6), 164.74 (C-7, 17) and 165.61 (C-10).

**General method of obtaining phthalimides (4-6).** A mixture of 0.01 mol of isonicotinic acid hydrazide and 0.01 mol of phthalic anhydride in 25 ml of dimethylformamide was mixed at a temperature of 120 °C in a flask with a Dean-Stark apparatus for 3.5 hours. After cooling to room temperature, the reaction mixture was diluted with 100 ml of distilled water with intensive stirring. One day later, the white precipitate was filtered out, washed with ethanol and dried at room temperature.

**N-(2,5-dioxopyrrolidine-1-yl)isonicotinamide (4).** The yield of product **4** is 28.7 %; melting point is 156–157 °C.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: (J, Hz): 2.49 s (4H, H-11ax, 11eq, 12ax, 12eq), 7.34 d (2H, H-3, 5,  $^3\text{J}$  4.8), 8.71 d (2H, H-2, 6,  $^3\text{J}$  4.8), 9.37 c (1H, H-9).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 28.77 (C-11, 12), 121.86 (C-3,5), 139.97 (C-4), 151.07 (C-2, 6), 164.53 (C-7), 171.30 (C-10, 13).

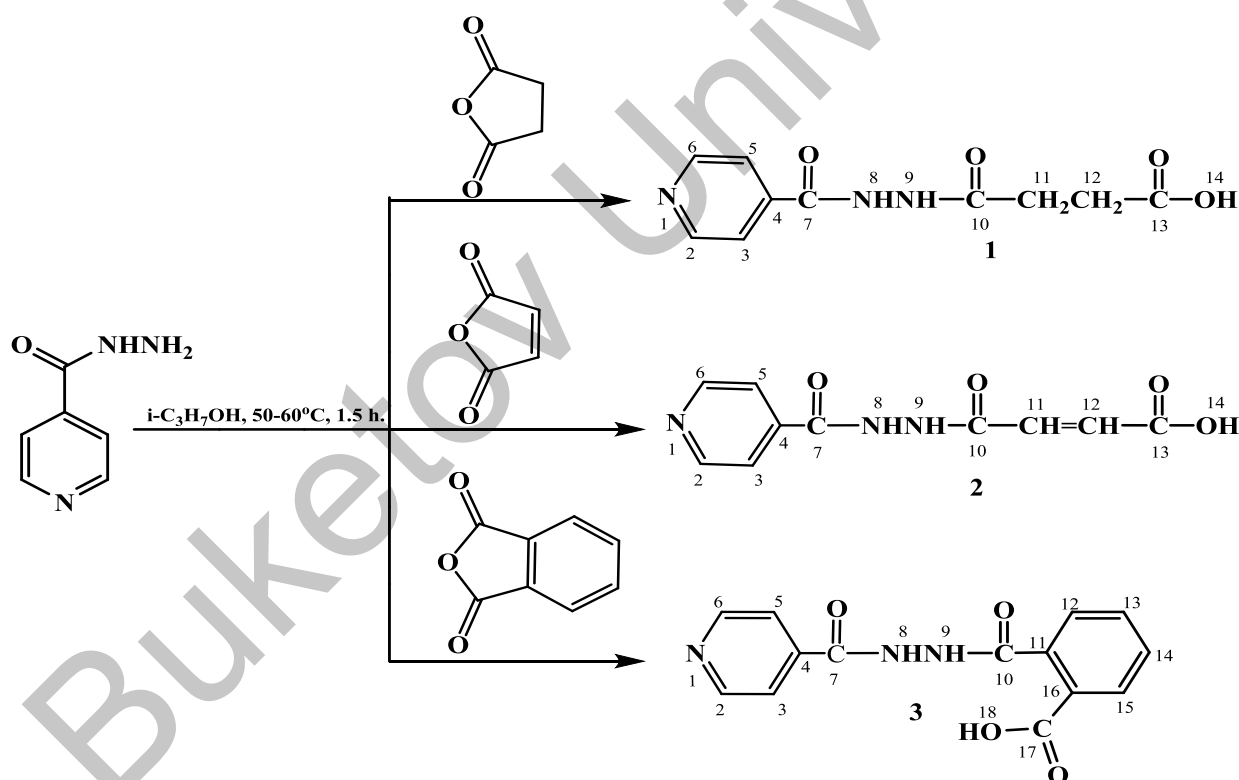
**N-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)isonicotinamide (5).** The yield of product **5** is 22.1 %; melting point is 288–290 °C.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: (J, Hz): 3.62 br. s (1H, H-8), 6.63 d (1H, H-11,  $^3\text{J}$  15.6), 6.99 d (1H, H-12,  $^3\text{J}$  15.6), 7.34 d (2H, H-3, 5,  $^3\text{J}$  4.0), 8.73 d (2H, H-2, 6,  $^3\text{J}$  4.0).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 132.01 (C-11), 134.53 (C-12), 162.85 (C-13), 164.39 (C-11), 121.88 (C-3, 5), 139.97 (C-4), 150.98 (C-2, 6), 166.65 (C-7).

**N-(1,3-dioxisoindoline-2-yl)isonicotinamide (6)**. The yield of product **6** is 32 %, melting point is 220-221 °C. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: (J, Hz): 7.85 d (2H, H-3, 5, <sup>3</sup>J 5.0), 8.82 d (2H, H-2, 6, <sup>3</sup>J 6.0), 7.92–7.95 m (2H, H-13, 14), 7.97-8.00 m (2H, H-12, 15), 11.72 br. s (1H, H-8). <sup>13</sup>C NMR spectrum,  $\delta$ C, ppm: 121.96 (C-3, 5), 124.52 (C-12, 15), 129.94 (C-11, 16), 136.03 (C-13, 14), 138.20 (C-4), 151.32 (C-2, 6), 164.73 (C-7), 165.62 (C-10, 17).

**Quantum chemical calculations** were carried out using Gaussian and GaussView software packages [20, 21]. The equilibrium geometry and vibrational frequencies of the molecules were calculated in the approximation of the density functional B3LYP with a base set of 6-31G(d). The enthalpy of reactions in the presence of a solvent-isopropanol at a temperature of 50 °C was calculated by the method of a self-consistent reaction field. Similar calculations were performed for reactions in the gas phase in the absence of a solvent at a temperature of 25 °C.

### Results and Discussion

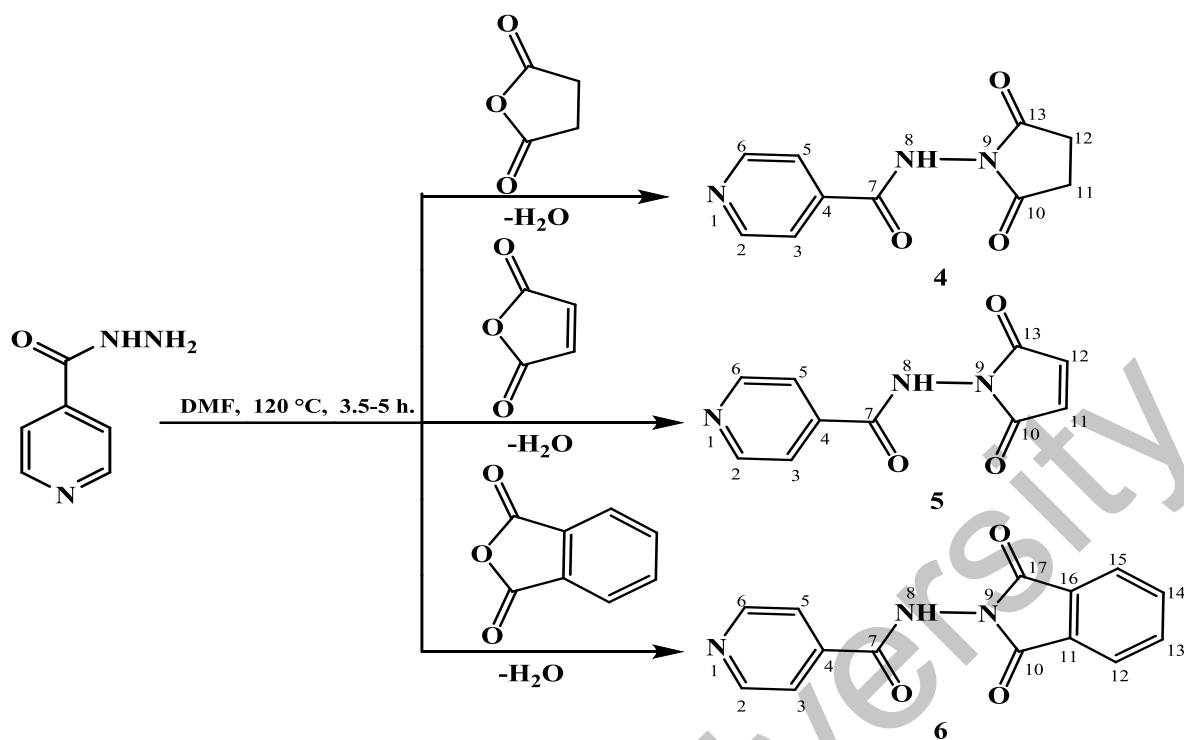
Continuing our search in this direction [13–18], we carried out our own research and studied the reaction of the interaction of succinic, maleic and phthalic anhydrides with isonicotinic acid hydrazide. We conducted the research in two stages. At the first stage, under the conditions we studied, cyclic anhydrides of dicarboxylic acids in mild conditions easily reacted with isonicotinic acid hydrazide with the opening of the oxolan cycle. The reaction of cyclic dicarboxylic acid anhydrides with isonicotinic acid hydrazide was carried out at a reagent ratio of 1:1 in an isopropanol medium at a temperature of 50–60 °C for 1.5 hours. It was established that under the conditions studied, the reactions under consideration can proceed with the formation of the corresponding monoamides of dicarboxylic acids **1-3** (Scheme 1).



Scheme 1. Modification of isonicotinic acid hydrazide with anhydrides under mild conditions

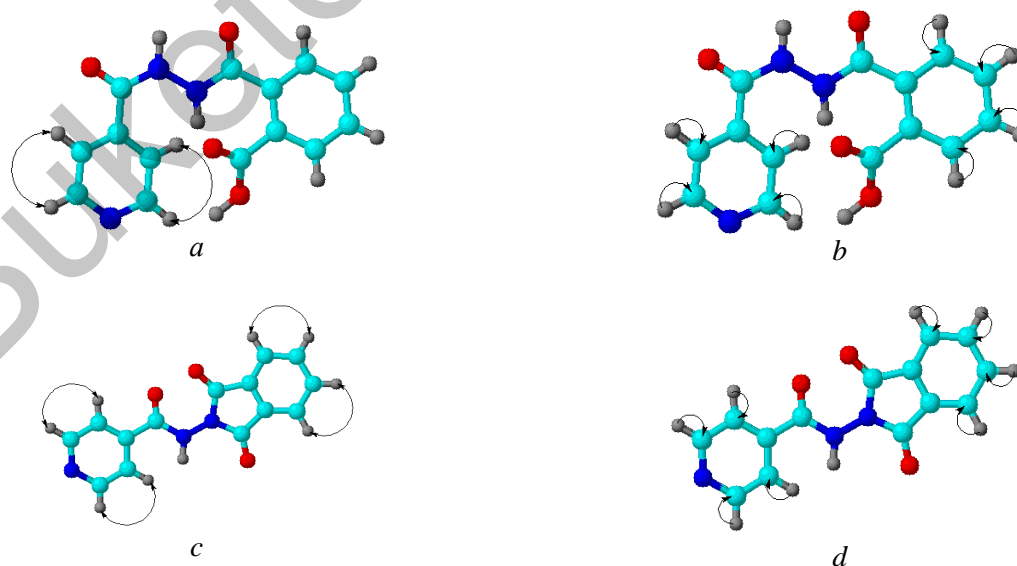
The resulting compounds **1-3** after recrystallization are white crystalline substances that are soluble in most organic solvents, except for saturated hydrocarbons.

At the second stage, we conducted direct reactions of the interaction of the above initial reagents under harsh conditions. The reaction of succinic, maleic and phthalic acid anhydrides with isonicotinoyl hydrazide was carried out at a reagent ratio of 1:1 in a dimethylformamide solvent at a temperature of 120 °C for 3.5–5 hours (Scheme 2). The reactions proceeded in one stage, the yields of the obtained cyclic imides **4-6** ranged from 20 to 45 %.

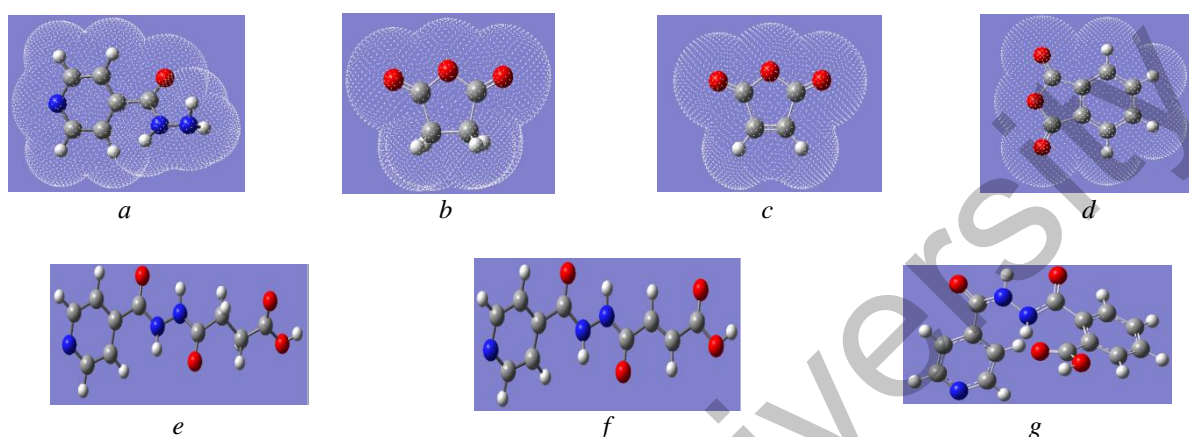


Scheme 2. Modification of isonicotinic acid hydrazide with anhydrides under severe conditions

The structures of synthesized compounds **1-6** were confirmed by <sup>1</sup>H- and <sup>13</sup>C-NMR spectroscopy, as well as by data of two-dimensional NMR, namely COSY (<sup>1</sup>H-<sup>1</sup>H) and HMQC (<sup>1</sup>H-<sup>13</sup>C) spectroscopy which allow establishing spin-spin interactions of homo- and heteronuclear nature (Fig. 1). The observed correlations in molecules **3** and **6** are shown in the diagrams. In the <sup>1</sup>H-<sup>1</sup>H COSY spectra of compounds **3** and **6**, spin-spin correlations are observed through three bonds of aromatic protons of the pyridine cycle H<sup>3,5</sup>-H<sup>2,6</sup> cross-peaks with coordinates at 7.84, 8.82 and 8.81, 7.85. Heteronuclear interactions of protons with carbon atoms through a single bond were established using <sup>1</sup>H-<sup>13</sup>C HMQC spectroscopy for the pairs present in the compound: H<sup>3,5</sup>-C<sup>3,5</sup> (7.84, 121.95), H<sup>13,14</sup>-C<sup>13,14</sup> (7.93, 124.50), H<sup>12,15</sup>-C<sup>12<</sup> (7.93, 136.05) and H<sup>2,6</sup>-C<sup>2,6</sup> (8.82, 151.31).

Figure 1. Correlation schemes in the COSY (a) and HMQC (b) spectra of compounds **3** and **6**

In order to theoretically substantiate the influence of the medium (solvent) on the reaction nature, quantum chemical calculations were carried out to determine the enthalpy of reactions  $\Delta H_r$ . The change in the enthalpy of the system during the reaction is known to be calculated as the difference between the enthalpy of the products and the initial components. Quantum-chemically determined thermodynamic properties of molecules take into account the contribution of vibrations and rotations of the molecule. In the approximation of the density functional B3LYP with a base set of 6-31G(d) [20, 21], the enthalpy of the reactions  $\Delta H_r$  in the absence and in the presence of a solvent — isopropanol (self-consistent reaction field method) were calculated quantum-chemically. Figure 3 shows 3D configurations of reagent molecules and reaction products, their thermochemical data are given in Table 1.



*a* — isonicotinic acid hydrazide; *b* — succinic anhydride; *c* — maleic anhydride; *d* — phthalic anhydride; *e* — product 1; *f* — product 2; *g* — product 3 (B3LYP/6-31G(d) method)

Figure 3. 3D configurations of reagent molecules and reaction products (the most stable conformations)

Table 1

Theoretical values of the enthalpy of formation ( $\Delta_f H$ , A.U.) of compounds (B3LYP/6-31G(d) method,  $t = 25^\circ\text{C}$ )

Reaction Condition	Reagent 1	Reagent 2	Product	$\Delta H$ , kJ/mol
Reaction 1				
	isonicotinic acid hydrazide	succinic anhydride	Product 1	
In the absence of a solvent	-472.159598	-380.436910	-852.613950	-45.80
In the presence of isopropanol	-472.169012	-380.447614	-852.628478	-31.12
Reaction 2				
	isonicotinic acid hydrazide	succinic anhydride	Product 2	
In the absence of a solvent	-472.159598	-379.227522	-851.408555	-56.29
In the presence of isopropanol	-472.169012	-379.236069	-851.420723	-41.08
Reaction 3				
	isonicotinic acid hydrazide	succinic anhydride	Product 3	
In the absence of a solvent	-472.159598	-532.839917	-1005.004921	-7.62
In the presence of isopropanol	-472.169012	-532.848465	-1005.021645	-10.95

As follows from the calculated data, the solvent lowers the enthalpy of the reaction (by the absolute value) which is explained by the limited mobility of molecules in the condensed phase. The consequence of this is a decrease in the activation energy, and since the reactions are exothermic, the transition states in structure should be closer to the initial reagents.

### Conclusions

The results showed that the direction of the reaction of the interaction of isonicotinic acid hydrazide with cyclic dicarboxylic acids anhydrides depends on the reaction conditions. Under mild reaction condi-

tions, the corresponding isonicotinoylhydrazides of dicarboxylic acids are formed in high yield, while under harsher conditions the latter are transformed into imides of cyclic acids. In the approximation of the density functional B3LYP with a base set of 6-31G(d), the enthalpies of the reactions  $\Delta H_r$  in the absence and in the presence of a solvent were calculated quantum-chemically. According to the calculated data, the solvent lowers the enthalpy of the reaction (by the absolute value), which is explained by the limited mobility of molecules in the condensed phase. The consequence of this is a decrease in the activation energy, and since the reactions are exothermic, the transition states in structure will be closer to the initial reagents.

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