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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Thermodynamic and Kinetic Aspects of a Single-Reactor Synthesis of 5-Amino-3-methyl-1,2,4-triazole Hydrochloride from Aminoguanidine and Acetic Acid

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Abstract—Fundamental thermodynamic and kinetic aspects of the reaction in which acetic acid guanyl hydrazide is formed from aminoguanidine and acetic acid in aqueous solutions at pH 0.6–1.5 and the kinetics of cyclization of acetic acid guanyl hydrazide hydrochloride to 5-amino-3-methyl-1,2,4-triazole hydrochloride in a melt were studied. Methods for synthesis of acetic acid guanyl hydrazide hydrochlorides and 5-amino-3-methyl-1,2,4-triazole hydrochloride were developed.

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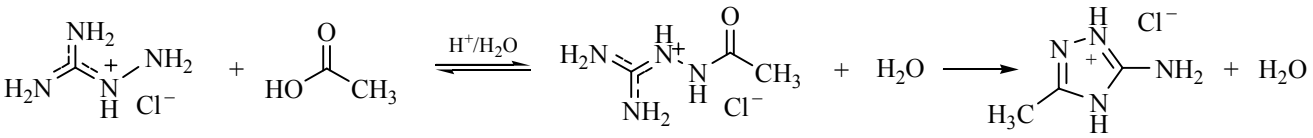
Carboxylic acid guanyl hydrazides are widely used for synthesis of 3-substituted 5-amino-1,2,4-triazoles [1–8]. One of the most important methods for synthesis of guanyl hydrazides and 3-substituted 5-amino-1,2,4-triazoles is the reaction of amino-guanidine with carboxylic acids [5–15]. It is believed that, depending on conditions, this reaction can yield both guanyl hydrazides [4–9] and 3-substituted 5-amino-1,2,4-triazoles [10–15]. In the latter case, it is assumed that the guanyl hydrazides being formed are cyclized into aminotriazoles in the course of the reaction. Despite the wide use of the reaction of aminoguanidine with carboxylic acids for synthesis of aminotriazoles, its fundamental kinetic and thermo-dynamic aspects and the effect of synthesis conditions on the reaction direction has long remained poorly understood.

Recently, the kinetic and thermodynamic aspects of the reaction of aminoguanidine with malonic acid in aqueous solutions have been studied and the synthesis conditions of 5-amino-3-carboxymethyl-1,2,4-triazole and bis-5-amino-1,2,4-triazol-3-ylmethane have been optimized [8]. In order to further analyze the reaction of aminoguanidine with carboxylic acids and optimize this method for synthesis of 3-substituted 5-amino-1,2,4-triazoles, we examined in the present study the fundamental kinetic and thermodynamic aspects of the reaction in which acetic acid guanyl hydrazide hydrochloride (GH) is formed from aminoguanidine (AG) and acetic acid (AcOH) in acid aqueous solutions and the kinetics of GH cyclization into 5-amino-3-methyl-1,2,4-triazole hydrochloride (AMT) in a melt:



AG AcOH GH AMT

The above sequence of reactions can yield 3-substituted 5-amino-1,2,4-triazoles (in the form of salts) in a single-reactor process, with bypassed stages of isolation of guanyl hydrazides and their cyclization in a free form [3] or under the action of alkalis [4–9]. In technological regard, this must diminish the amount of wastewater and waste inorganic salts.

EXPERIMENTAL

We used aminoguanidine hydrocarbonate (Merck) with the main substance content of no less than 98%; the rest of the reagents were of chemically pure grade. Twice distilled water was used to prepare aqueous solutions.

Experiments for analysis of the reaction of GH formation were performed as described in [7]. The reactor temperature was maintained to within ±0.5°. The solution acidity was determined with a Mettler Toledo S40-KS instrument equipped with an InLab®Expert Pro combined electrode. The AG concentration c_{AG} (M) in reaction mixtures was determined by iodatometric titration [7]. The GH concentration was calculated by the formula

$$c_{GH} = c_{AG,0} - c_{AG},$$

where $c_{AG,0}$ and c_{AG} are the initial and running concentrations of AG in the reaction mixture (M).

The AcOH concentration c_{AcOH} (M) was calculated by the formula

$$c_{AcOH} = c_{AcOH,0} - c_{GH},$$

where $c_{AcOH,0}$ is the initial concentration of AcOH.

The equilibrium constants of the reaction of GH formation, KGH, were calculated by the formula

$$K_{GH} = \frac{[GH]}{[AcOH]\,[AG]}, \quad (1)$$

where [GH], [AcOH], and [AG] are the equilibrium concentrations of the reactants (M).

As it was done in [7], we assumed in our kinetic and thermodynamic calculations that aminoguanidine reacts in the form of an aminoguanidinium cation (AG). Under the conditions of our experiments, the concentration c_{AG} is almost equal to the analytical concentration of aminoguanidine because, in the pH range under study (0.6–1.5), the concentration of the unprotonated form of aminoguanidine is negligible (pK_a 11.5 [16]). The concentration c_{AcOH} was also taken to be equal to the analytical concentration of AcOH because the degree of dissociation of acetic acid is negligible (pK_a 4.6 [17]) under these conditions.

The concentrations [GH], [AcOH], and [AG] in Eq. (1) were determined by analyzing the composition of the reaction mixtures after equilibrium was attained. The equilibrium state was reached from the sides of both forward and reverse reactions until the concentrations being analyzed coincided within the experimental error. The reaction mixtures necessary for studying the reverse reaction were obtained by heating AG, AcOH, and HCl in the minimum amount of water at 60°C for 6 h. Under these conditions, the yield of guanyl hydrazides markedly exceeded the equilibrium yield in dilute solutions. Then the resulting mixture was diluted with water to a required volume and the hydrolysis of GH was studied.

Experiments devoted to a study of the fundamental kinetic aspects of the reaction of GH cyclization into AMT were performed in 15-ml test tubes, each charged with 0.1 g of GH. The temperature of the reaction mixtures was maintained constant within ±0.5° with a thermostat having the form of an oil bath placed on an IKA RCT basic magnetic rabble with a heater, equipped with an external thermocouple. The test tubes with the reaction mixture were kept in the thermostat for the required time, and then the reaction mixture was dissolved in 40 ml of a 0.025 M KH_2PO_4 solution and the AMT concentration was determined. The AMT concentration was analyzed by high-performance liquid chromatography (HPLC) on a Milikhrom-5.3 chromatograph with a UV detector (80×2 mm column packed with Separon C_{18} sorbent, 0.025 M aqueous solution of KH_2PO_4 as mobile phase, elution rate 80 μl min^{-1}, detection at a wavelength of 210 nm, sample volume 6 μl, chromatographic column temperature 35°C). The elution time of AMT was 5.1 min. The pK_a of acetic acid guanyl hydrazide was determined by potentiometric titration of GH with a 0.1 N solution of KOH by the method described in [17].

NMR spectra were recorded with a Bruker Avance 600 spectrometer (600 MHz for1H and 150 MHz for 13C, DMSO-d_6 as solvent and TMS as internal standard), and mass spectra, using a Finnigan MAT Incos 50 instrument (direct introduction of a sample into the ionic emission source with an ionization energy of 70 eV). An elemental analysis was made with a Perkin–Elmer analyzer. The melting points were determined in sealed capillaries with a PTP instrument.

Acetic acid 2-guanyl hydrazide hydrochloride (GH). A mixture of 30 g (0.220 mol) of aminoguanidine hydrocarbonate, 26.77 g (0.242 mol) of a 33% solution of HCl, and 39.64 g (0.660 mol) of AcOH was boiled under agitation for 1 h and the excess amount of AcOH was evaporated in a vacuum. A 100-ml portion of 2-propanol was added to the residue and the mixture was boiled under agitation for 5 min and cooled to 0–5°C. The precipitate formed was filtered off, recrystallized from 2-propanol, and dried at 70°C. Yield 20.1–22.5 g (60–67%), mp 138–139°C. ^{1}H NMR spectrum, ^{1}H, δ, ppm: 1.87 s (3H, CH_3), 7.87 br.s (4H, $2NH_2$), 9.53 c (1H, NH), 10.10 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.77 q (CH_3, J = 128.8 Hz), 158.80 s (C=N), 169.73 m (CO). Mass spectrum, m/z (I_{rel}, %): 116 $[M - HCl]^+$ (13), 98 (29), 73 (14), 57 (21), 43 (100). Found (%): C 23.28, H 6.07, N 36.51; M 152.3 (potentiometric titration). $C_3H_9N_4OCl$. Calculated (%): C 23.61, H 5.95, N 36.72; M 152.58.

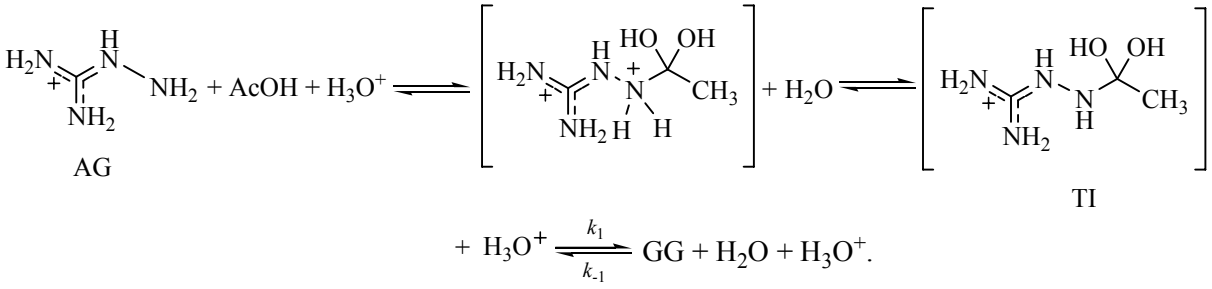
5-Amino-3-methyl-1,2,4-triazole hydrochloride (AMT). A mixture of 13.6 g (0.10 mol) of aminoguanidine hydrocarbonate, 12.17 g (0.11 mol) of a 33% solution of HCl, and 18.1 g (0.30 mol) of AcOH was heated to 115–120°C under agitation for 1 h, AcOH was evaporated, and the reaction mixture was heated to 180–190°C and kept at this temperature for 2 h. The resulting melt was cooled to 50–60°C and 20 ml of ethyl acetate was added. The mixture was boiled with reflux for 3–5 min and then was cooled. The crystalline precipitate was filtered off and dried at 70°C. We obtained 12.6–12.9 g of AMT, with a content of the main substance of 96–97% (yield 90–93%) according to HPLC data. After recrystallization from 30 ml of 2-propanol, the yield of the analytically pure product was 8.9–9.4 g (66–70%), mp 135–137°C. ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH_3), 8.01 br.s (2H, NH_2). ^{13}C NMR spectrum, δ, ppm: 10.87 q (CH_3, J = 131.0 Hz), 147.42 t (C-3 of triazole, J = 7.7 Hz), 151.11 s (C-5 of triazole). Mass spectrum (EI), m/z (I_{rel}, %): 98 $[M - HCl]^+$ (54), 57 (46), 42 (100). Found (%): C 27.01, H 5.18, N 41.39; M 134.7 (potentiometric titration). $C_3H_7N_4Cl$. Calculated (%): C 26.78, H 5.24, N 41.63; M 134.57.

For adequate determination of the equilibrium constants of the reaction of GH formation from AG and AcOH by analysis of concentrations of the equilibrium mixtures, it was necessary to make sure that the reaction of GH cyclization into AMT does not occur in the conditions under study. An HPLC analysis of the reaction mixtures demonstrated the absence of AMT, i.e., the GH cyclization does not occur in acid aqueous solutions (pH 0.6–1.5) at temperatures of up to 100°C and does not hinder equilibration. The equilibrium constants K_{GH} obtained at temperatures of 40–80°C are presented below:

T, °C	K_{GH}, l mol^{-1}
40	10.7±0.3
50	6.3±0.18
60	4.6±0.12
70	3.5±0.14
80	2.6±0.10

Upon changes in acidity within the range under study, K_{GH} remained unchanged within the experimental error. The linear dependence of logarithms of K_{GH} on inverse temperature made it possible to apply van't Hoff's isobar equation to calculate the heat effect of the reaction of GH formation to be $\Delta H_{GH} = -31.5 \pm 2$ kJ mol^{-1}. This value is close to enthalpies of similar reactions in which malonic acid guanyl hydrazide is formed from aminoguanidine and malonic acid (–27.5 ± 2.0 kJ mol^{-1}) and malonic acid diguanyl hydrazide is formed from aminoguanidine and malonic acid guanyl hydrazide (–34.6 ± 5.3 kJ mol^{-1}) [7].

The kinetics of the reaction of GH formation was studied in the reagent concentration range 0.3–1.0 M and pH 0.6–1.5. When processing kinetic data, we



were based on the assumption that this reaction occurs by the mechanism that is characteristic of reactions between amines and carboxylic acids under acid catalysis conditions [18, 19] and is similar to that of the reaction of aminoguanidine with malonic acid [7].

With this mechanism, the reaction rate must be described, irrespective of which stage, formation of a tetrahedral intermediate (TI) or its hydrolysis [18], is rate determining, by the kinetic equation

$$(dc_{GH})/(d\tau) = k_1 c_{AG} c_{AcOH} c(H_3O^+) - k_{-1} c_{GH} c(H_2O) c(H_3O^+), \quad (2)$$

where k_1 and k_2 are the rate constants of the forward and reverse reactions, respectively.

Because the reaction is performed in dilute aqueous solutions, it has a pseudozeroth order with respect to H_2O. Therefore, the rate constant of the reverse reaction can be expressed in terms of $k'_{-1} = k_{-1}c(H_2O)$.

At a constant pH, Eq. (2) takes the form

$$(dc_{GH})/(d\tau) = k'_1 c_{AG} c_{AcOH} - k''_{-1} c_{GH},$$

where $k'_1 = k_1 c(H_3O^+)$ and $k''_{-1} = k'_{-1} c(H_3O^+)$ are the effective rate constants of the forward and reverse reactions, respectively.

The constant k'_1 was calculated by the linear least-squares method, with the integral form of the kinetic equation used for the reversible bimolecular reaction [20]

$$\tau = \frac{1}{k'_1}\left\{\frac{1}{X_1 - X_2}\ln\left[\frac{(c_{AG,0} - X_1)(c_{AG} - X_2)}{(c_{AG,0} - X_2)(c_{AG} - X_1)}\right]\right\},$$

$$X_{1,2} = \frac{[K_{GH}(c_{AcOH,0} - c_{AG,0}) + 2c_{AG,0}] \pm \sqrt{[K_{GH}(c_{AcOH,0} - c_{AG,0}) + 2c_{AG,0}]^2 + 4(K_{GH} - 1)c_{AG,0}^2}}{2(K_{GH} - 1)}.$$

The rate constant of the reverse reaction, k''_{-1}, was found from the relation $k''_{-1} = k'_1/K_{GH}$.

The adequacy of the chosen kinetic model to the experimental data was assessed by calculating Fisher's criterion. The calculated values of Fisher's criterion did not exceed the tabulated data for the 95% probability in the whole range of experimental data [20], which points to adequacy of the chosen kinetic model to the experimental data and does not contradict the suggested reaction mechanism.

It can be seen in Fig. 1 that, in the pH range under study, is directly proportional to the concentration $c(H_3O^+)$. A similar dependence of k'_1 and k'_{-1} on $c(H_3O^+)$ is observed at other temperatures. This serves as evidence in favor of the suggested mechanism and makes it possible to calculate the rate constants k_1 and k'_{-1} (Table 1).

The linear dependence of the logarithms of the constants k_1 and k'_{-1} on inverse temperature (Fig. 2) made it possible to calculate parameters of the Arrhenius equation $k = A\exp(-E_a/RT)$ to be $\ln A = 6.02 \pm 0.06$ and $E_a = 24.3 \pm 0.2$ kJ mol^{-1} for the forward reaction and $\ln A = 15.8 \pm 0.1$ and $E_a = 55.8 \pm 0.4$ kJ mol^{-1} for the reverse reaction. It is significant that the activation energy of the reaction between aminoguanidine and acetic acid is substantially lower than that of a similar reaction of aminoguanidine with malonic acid (42.1 ± 3 kJ mol^{-1}) [7]. Explaining the influence exerted by the structure of carboxylic acid on the activation energy requires an additional study of the reaction under discussion for the example of other carboxylic acids.

When processing the kinetic data for the reaction of GH cyclization into 5-amino-3-methyl-1,2,4-triazole hydrochloride, we assumed that the volume of the

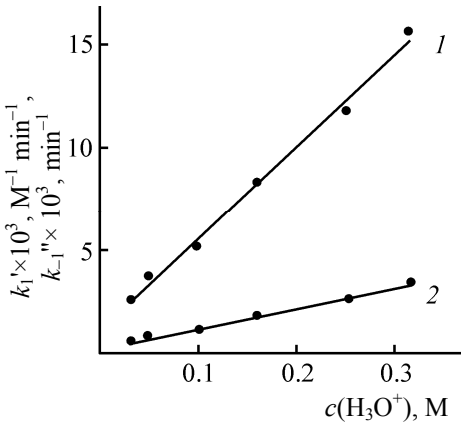


Fig. 1. Dependence of (*1*) k_1' and (*2*) k_{-1}' on $c(H_3O^+)$ at 60°C. (k_1') Effective rate constant of the forward reaction and (k_{-1}'') effective rate constant of the reverse reaction.

reaction mixture remains unchanged in the course of the reaction. The experimental data are best described by a first-order kinetic equation of the reaction:

$$(dn_{AMT})/(d\tau) = kn_{GH},$$

where k is the rate constant (s^{-1}), and n_{AMT} and n_{GH}, molar amounts of AMT and GH in the reaction mixture.

n_{AMT} was found using HPLC, and n_{GH} was calculated by the formula

$$n_{GH} = n_{GH,0} - n_{AMT},$$

where $n_{GH,0}$ is the initial molar amount of GH.

We calculated the rate constants k by the least-squares method, using the integral form of a first-order kinetic equation [20]. The values of k, found at various temperatures, are presented below:

T, °C	k, min^{-1}
150	0.0016±0.0001
160	0.0053±0.0003
180	0.024±0.003
200	0.099±0.006

A calculation of Fisher's criterion demonstrated the adequacy of the chosen kinetic model to the experimental data.

The linear dependence of ln k on inverse temperature makes it possible to calculate the parameters of the Arrhenius equation: $\ln A = 31.9 \pm 0.2$ and $E_a = 134.3 \pm 0.8$ kJ mol^{-1}.

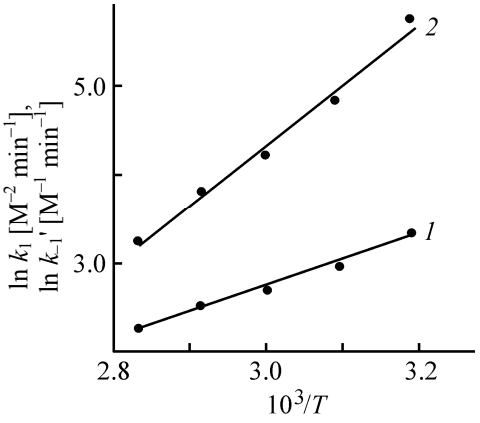


Fig. 2. Logarithms of the rate constants of (*1*) forward and (*2*) reverse reactions vs. the inverse temperature T^{-1} (K^{-1}). (k_1) Rate constant of the forward reaction and (k'_{-1}) rate constant of the reverse reaction.

The revealed fundamental thermodynamic and kinetic aspects of the reactions make it possible to formulate basic approaches to optimization of the GH synthesis and single-reactor synthesis of AMT from AG and AcOH. It is advisable to synthesize GH under acid catalysis conditions at pH ≤ 1. To raise the equilibrium yield of GH, it is appropriate to use an excess amount of acetic acid and to perform the synthesis with the minimum amount of water in the reaction mixture (similarly to the conditions suggested in [8]). The high activation energy of the reaction of AMT cyclization results in that the rate of GH cyclization is very low at temperatures of up to 140°C. Therefore, a selective synthesis of GH can be performed at the boiling point of the reaction mixture (~120°C). However, synthesis of AMT requires that GH should be cyclized at temperatures $T \geq 140$°C. Thus, to obtain AMT, it is advisable to perform the first stage of synthesis at the boiling point of the reaction mixture and, to pass to the second state, it is advisable to evaporate acetic acid and water released in the course of the reaction and to heat GH formed to a temperature exceeding 140°C.

Because hydrocarbonate (AGH) is the best available salt of aminoguanidine, we used this substance as a raw material when developing a single-reactor synthesis of GH and AMT. The required acidity of the reaction mixture was created with concentrated hydrochloric acid (HCl content 33%).

Let us consider the effect of technological parameters on the yield of GH and AMT.

Mixing the reagents gives a mixture of AG, AcOH, and H_2O. The subsequent boiling of the resulting mixture (temperature 118–120°C) gradually yields GH. It is inappropriate to use a >10% molar excess of HCl with respect to the stoichiometric amount of AGH, because this fails to cause a noticeable increase in the reaction rate (Fig. 3). Raising the AcOH : AGH molar ratio to more than 3 : 1 does not lead to any significant rise in the equilibrium conversion of AG (Table 2). Therefore, to obtain GH, it is appropriate to use the molar ratio AGH : HCl : AcOH = 1 : 1.1 : 3 at a synthesis duration of 2 h. On evaporating the excess amount of acetic acid in a vacuum and crystallization from 2-propanol, we obtained an analytically pure GH in 60–67% yield.

In a single-reactor synthesis of AMT, it is worthwhile to evaporate acetic acid under atmospheric pressure and heat GH to 180–190°C. It is inappropriate

Table 1. Rate constants k_1 and k'_{-1} at various temperatures

T, °C	k_1, M^{-2} min^{-1}	k'_{-1}, M^{-1} min^{-1}
40	0.034±0.003	0.0032±0.0004
50	0.051±0.004	0.0081±0.0009
60	0.068±0.002	0.0148±0.0008
70	0.079±0.005	0.0227±0.0023
80	0.102±0.005	0.0394±0.0034

Table 2. Effect of the initial AGH : AcOH ratio on the AG conversion α at 120°C. Molar ratio AGH : HCl = 1 : 1.1

AGH:AcOH, mol : mol	α, %, at indicated synthesis duration, min					
	5	10	20	40	60	120
1:1.2	41	62	70	78	83	83
1:1.7	78	85	89	90	91	91
1:2.0	83	88	94	94	95	95
1:3.0	89	92	96	97	97	97
1:4.0	91	95	97	98	98	98

to raise the temperature to above 190°C because of the partial decomposition of the product and its more difficult purification. At temperatures below 180°C, the cyclization reaction is too slow. The suggested variant of single-reactor synthesis can produce AMT in 90–93% yield and main substance content of no less than 96%.

The compounds GH and AMT can exist in several tautomeric forms. As indicated by ^{1}H NMR and ^{13}C proton-coupled NMR spectra and in accordance with the acid-base properties (pK_{BH^+} 8.68 ± 0.05 at 22°C), the structure of GH is presumably similar to that of other salts of carboxylic acid 2-guanyl hydrazides [21. The predominant AMT tautomer in a solution in dimethylsulfoxide is 5-amino-3-methyl-1,2,4-triazolium chloride. This is indicated by the chemical shifts of carbon atoms of the triazole ring in the ^{13}C NMR spectrum, whose signals are characteristic of 5-amino-1,2,4-triazolium salts [22].

CONCLUSIONS

(1) The reaction in which acetic acid guanyl hydrazide is formed from aminoguanidine and acetic acid in acid aqueous solutions is acid-catalyzed, reversible and exothermic and is first-order with respect to CH_3COOH, aminoguanidinium cation, and H_3O^+. The suggested mechanism of this reaction is similar to that of the reaction of amines with carboxylic acids under acid-catalysis conditions, but a monoprotonated form of aminoguanidine serving as a nucleophile.

(2) The reaction of thermal cyclization of acetic acid guanyl hydrazide hydrochloride is described by a first-order kinetic equation and has a high activation energy (134.3 ± 0.8 kJ mol^{-1}). Thus, the cyclization of salt forms of guanyl hydrazides of aliphatic carboxylic acids with an acceptable rate is only possible at comparatively high temperatures (≥140°C). This enables selective synthesis of salt forms of carboxylic acid 2-guanyl hydrazides from aminoguanidine and carboxylic acids in acid aqueous solutions at temperatures of 100–120°C.

(3) To provide a high yield, it is preferable to perform the first stage of the single-reactor synthesis of 5-amino-3-methyl-1,2,4-triazole at a molar ratio aminoguanidine hydrocarbonate : acetic acid : hydrochloric acid = 1 : 1.1 : 3 at 118–120°C; it is advisable to cyclize acetic acid 2-guanyl hydrazide after evapora-

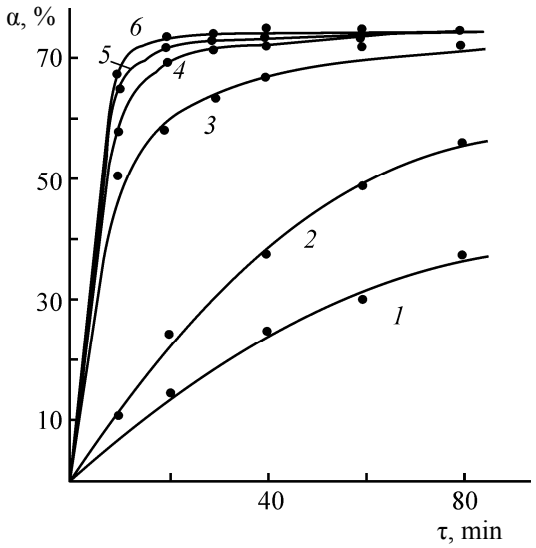


Fig. 3. AG conversion α vs. time τ at a temperature of 120°C. Molar ratio AGH : HCl : AcOH: (*1*) 1 : 1 : 1, (*2*) 1 : 1.03 : 1, (*3*) 1 : 1.05 : 1, (*4*) 1 : 1.08 : 1, (*5*) 1 : 1.1 : 1, and (*6*) 1 : 1.2 : 1.

tion of the excess amount of acetic acid at temperatures of 180–190°C.

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