ISSN 0022-4766, Journal of Structural Chemistry, 2020, Vol. 61, No. 2, pp. 225-231. © Pleiades Publishing, Ltd., 2020.
Russian Text © The Author(s), 2020, published in Zhurnal Strukturnoi Khimii, 2020, Vol. 61, No. 2, pp. 239-245.

IDENTIFICATION OF INTERMEDIATES AND PRODUCTS OF 2,4,6-TRIMETHYL-1,3,5-HEXAHYDROTRIAZINE TRIHYDRATE AND GLYOXAL REACTION IN AN AQUEOUS SOLUTION BY NMR SPECTROSCOPY

V. P. Tuguldurova[1]*, O. A. Kotelnikov[1], R. S. Cheltygmasheva[1], A. V. Kotov[1], A. V. Fateev[1,2], A. A. Bakibaev[1], and O. V. Vodyankina[1]

In situ formation of 2-methylimidazole as a result of 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate and glyoxal interaction in an aqueous solution is studied for the first time using NMR spectroscopy. In addition to the reactants and products, the reaction mixture is shown to contain stable intermediate products of the trimer decomposition as well as glycolic acid.

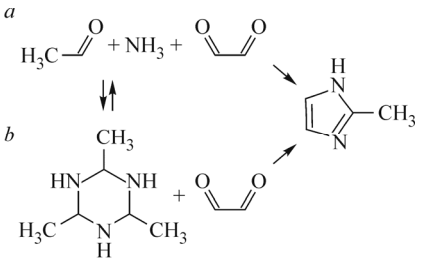
DOI: 10.1134/S0022476620020067

Keywords: 2-methylimidazole, glyoxal, 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate, NMR spectroscopy, in situ, glycolic acid.

INTRODUCTION

Imidazole and its derivatives are of great importance in human life activities [1]. Among them, 2-methylimidazole (2-MI) is of special interest. This compound is used in the synthesis of pharmaceutical substances [2], production of ionic liquids [3], it accelerates hardening of epoxy resins [4], and is used as an anti-icer component for aircraft [5].

There are various methods of imidazole synthesis [6-8]. This work considers the classical Debus–Radziszewski 2-MI synthesis by the reaction of glyoxal with ammonia and acetaldehyde (Scheme 1).



Scheme 1. Formation of 2-MI under acetaldehyde, ammonia, and glyoxal reaction (*a*) and 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate and glyoxal reaction (*b*).

[1]Tomsk State University, Tomsk, Russia; *tuguldurova91@mail.ru. [2]Tomsk State Pedagogical University, Tomsk, Russia. Original article submitted June 3, 2019; revised September 19, 2019; accepted September 26, 2019.

Recent theoretical and experimental data on the reactions and the mechanisms of imidazole formation under simultaneous interaction of mono- and dicarbonyl compounds with ammonia and amines in aqueous solutions were reported in [9, 10]. In [9], a mechanisms of imidazole formation through the interaction of glyoxal, formaldehyde, and methylamine through a key intermediate diimine was suggested. The authors of [10] considered two variants of imidazole formation: through the diimine intermediate attacking the aldehyde carbonyl group and through two monoimine intermediates that form a ring when interacting with each other. However, neither of works [9, 10] provides clear evidences that these intermediates and mechanisms actually exist.

The analysis of literature devoted to such processes reveals only scattered data on the reactions of imidazole formation; however, there are currently no confirmed data concerning specific mechanisms and the structures of possible intermediates and byproducts for these processes. Therefore, the aim of the present work is to study in details the mechanism of 2-methylimidazole formation through the reaction of acetaldehyde, glyoxal, and ammonia by identifying the structures of long-living (in experimental conditions) intermediates and byproducts using in situ NMR spectroscopy. Since acetaldehyde and aqueous ammonia are highly volatile, all these three reactants are difficult to be placed simultaneously into the NMR tube; therefore, we used an adduct of acetaldehyde and ammonia, 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate (acetaldehyde ammonia trimer, THT) [11], as a synthetic equivalent of acetaldehyde and ammonia for the reaction with glyoxal to form 2-MI (Scheme 1).

EXPERIMENTAL

The qualitative composition of the reaction mixture was studied in situ on a 400 MHz Bruker AVANCE III HD NMR spectrometer. Acetaldehyde ammonia trimer (Sigma Aldrich) was placed in a tube and dissolved in deuterated water. Then the tube was placed in the NMR spectrometer, the magnetic field was adjusted, then the tube was taken out and filled with a calculated amount of glyoxal (Sigma Aldrich 40% aqueous solution) according to the molar ratio THT:glyoxal = 1:1. The moment of glyoxal introduction was assumed to be the reaction starting point. The tube with the reaction mixture was first placed into an ultrasonic bath for 20 s and then into the NMR spectrometer to record the spectra. The ^{1}H, ^{13}C, DEPT-135, HSQC ^{1}H–^{13}C, HMBC ^{1}H–^{15}N NMR spectra were recorded after the reaction termination at a temperature of 294 K. Liquid ammonia was used as the external reference to determine the chemical shift of nitrogen. Initial and final pH values of the reaction mixture were 10.67 and 9.65, respectively.

RESULTS AND DISCUSSION

1D NMR spectroscopy. Fig. 1 shows the ^{1}H NMR spectrum of the reaction mixture at the final reaction moment; proton signals of the reagent (THT) and the reaction product (2-MI) are indicated. The chemical shifts of the protons of the trimer methyl group and that of the quartet of methine protons occur at 1.07 ppm and 3.55 ppm, respectively. The singlet of protons of the methyl substituent in 2-MI occurs at 2.18 ppm, and the signals of methine protons of the imidazole ring were recorded in the weak field (6.79 ppm). The overall spectrum of the reaction mixture (Fig. 1) contains the signals of both the reagent and the reaction product. However, there are additional signals that can be assigned to possible intermediate reaction products or byproducts. In the region of 1 ppm, there are proton doublets that can be assigned to the formation of structures close to the one of acetaldehyde ammonia trimer and are its decomposition products (linear trimers, dimers, and monomers). This assumption is confirmed by the appearance of quartet signals at 3.50-5.20 ppm assigned to the methine protons. Also, there is an unidentified singlet signal (3.49 ppm) next to the quartet of the CH group of the trimer ring.

Fig. 2 shows the ^{13}C NMR spectrum of the reaction mixture. As can be seen, the reaction mixture contains the signals of the reagent and the reaction product: the signals of methyl groups of 2-MI and THT occur at 12.3 ppm and 20.2 ppm, respectively, while the signals of methine carbons of THT were found at 64.4 ppm, and those of methine groups of the imidazole ring at 121.2 ppm. There is a signal of the quaternary carbon of 2-MI at 145.8 ppm. Also, the ^{13}C NMR

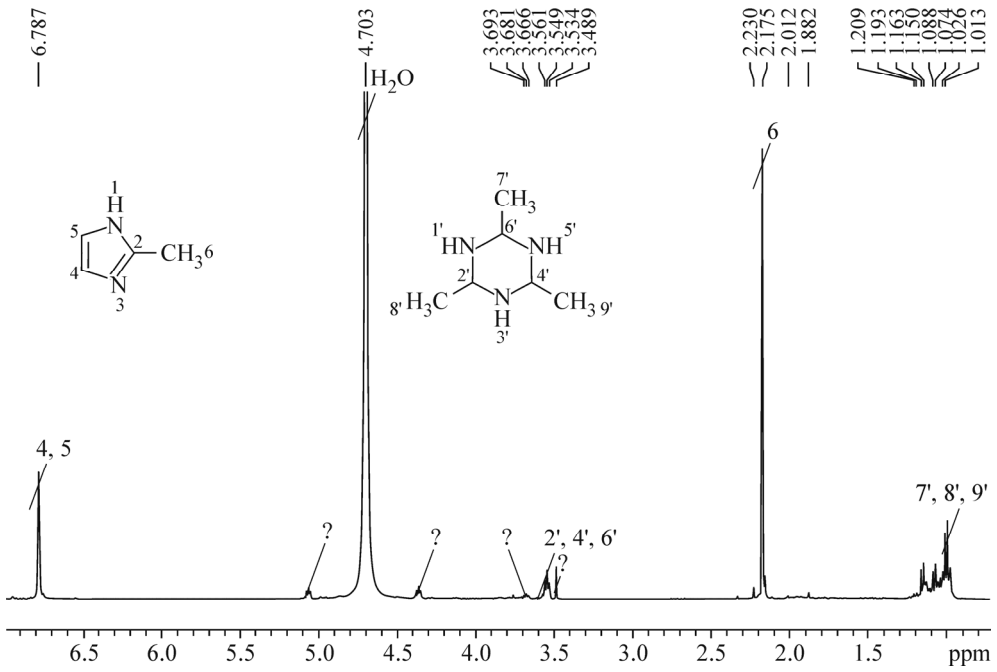


Fig. 1. ^{1}H NMR spectrum of the reaction mixture of 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate and glyoxal at the final reaction moment. The solvent is D_2O.

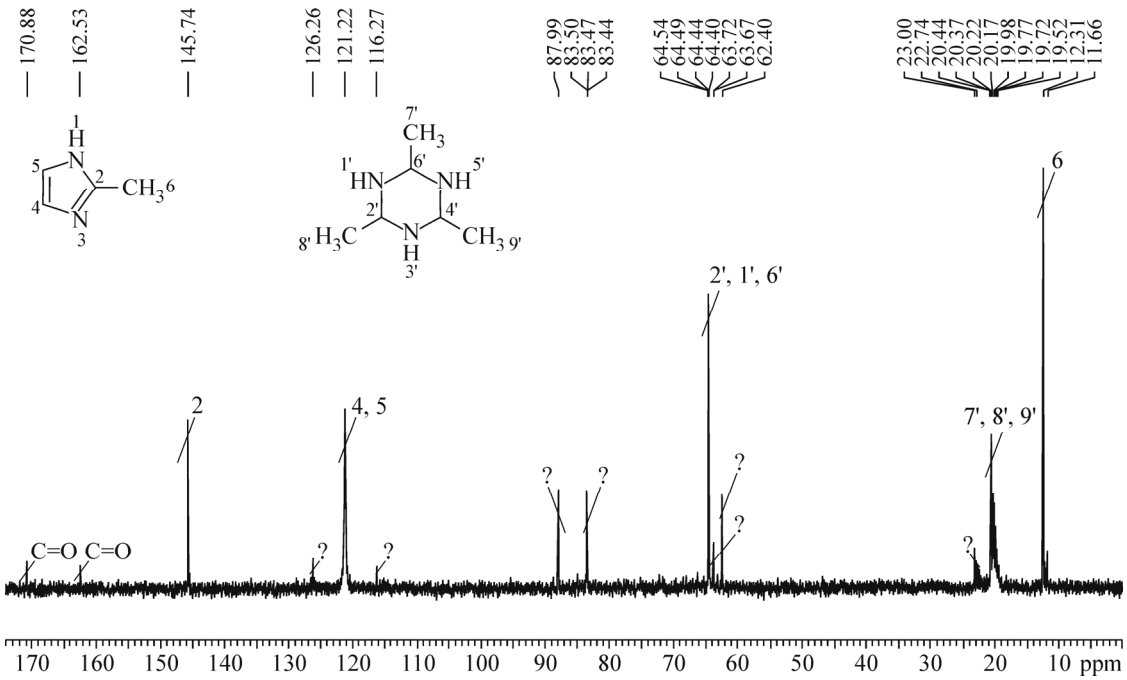


Fig. 2. ^{13}C NMR spectrum of the reaction mixture of 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate and glyoxal at the final reaction moment. The solvent is D_2O.

spectrum of the reaction mixture contains additional signals of the intermediate reaction products or byproducts: two signals (162.5 ppm and 170.9 ppm) in the weak field can be assigned to the carbons of the carbonyl group, the other seven signals were not identified (indicated by question marks in Fig. 2).

A DEPT-135 spectrum (Fig. 3) was recorded to determine the number of substituents on carbon atoms with unidentified signals.

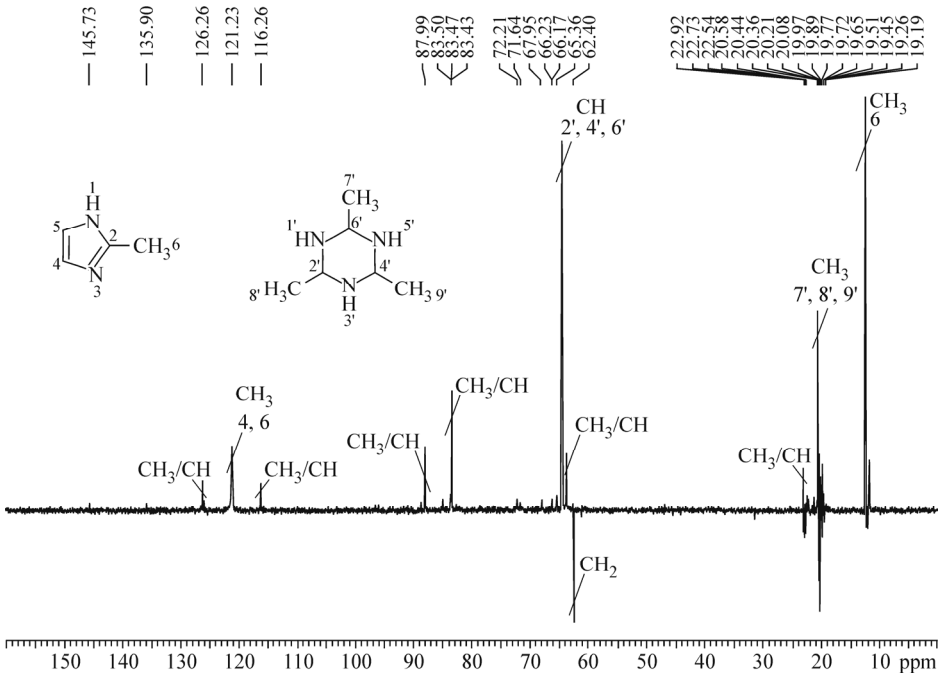


Fig. 3. DEPT-135 ^{13}C NMR spectrum of the reaction mixture of 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate and glyoxal at the final reaction moment. The solvent is D_2O.

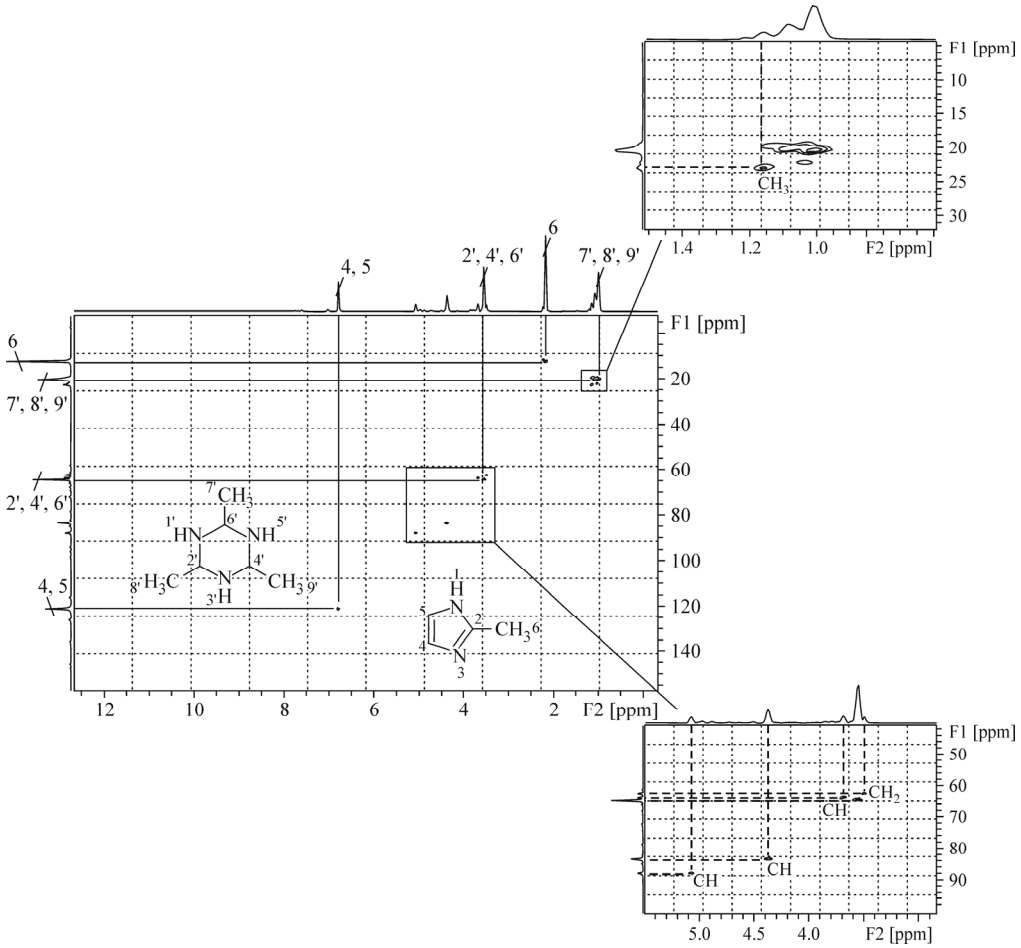
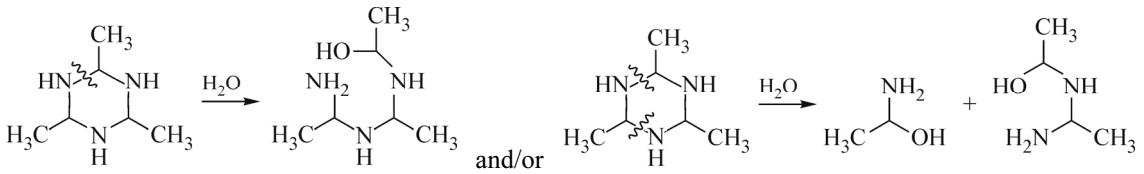


Fig. 4. $^{1}H–^{13}C$ HSQC spectrum of the reaction mixture of 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate and glyoxal at the final reaction moment. The solvent is D_2O.

As can be seen from Fig. 3, the DEPT-135 ^{13}C NMR spectrum expectedly contains no signals in the weak field region of carbonyl carbons (162.5 ppm, 170.9 ppm) and quaternary carbon of 2-MI (145.7 ppm). The signals of all carbons with odd numbers of substituents CH and CH_3 have positive intensities, while one unidentified signal with a chemical shift of 62.4 ppm has a negative intensity to indicate the methylene carbon signal.

2D NMR spectroscopy. Fig. 4 shows a HSQC $^{1}H–^{13}C$ NMR spectrum to confirm the above assignment of identified signals of ^{1}H and ^{13}C NMR spectra of the reagents and reaction products. Two regions of the spectrum are of interest. The first of them is the region of correlations between methyl protons and carbon atoms of THT. The comparative analysis of the spectral characteristics testifies that the neighboring proton signals (1.00-1.20 ppm) directly correlate with carbon signals (22.00-23.00 ppm) to indicate that the reaction is accompanied by the formation of the structures close to the one of THT (the products of its dissociation via the C–N bond), namely, linear trimers, dimers, and monomers (Scheme 2). The second region also evidences the formation of these structures, since there is a direct correlation between the quartets of methine proton (3.68 ppm, 4.35 ppm, 5.10 ppm) and the signals of methine carbons (63.7 ppm, 83.5 ppm, 88.0 ppm) similar to the methine group of THT.



Scheme 2. Possible decomposition pathways of 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate under the reaction conditions.

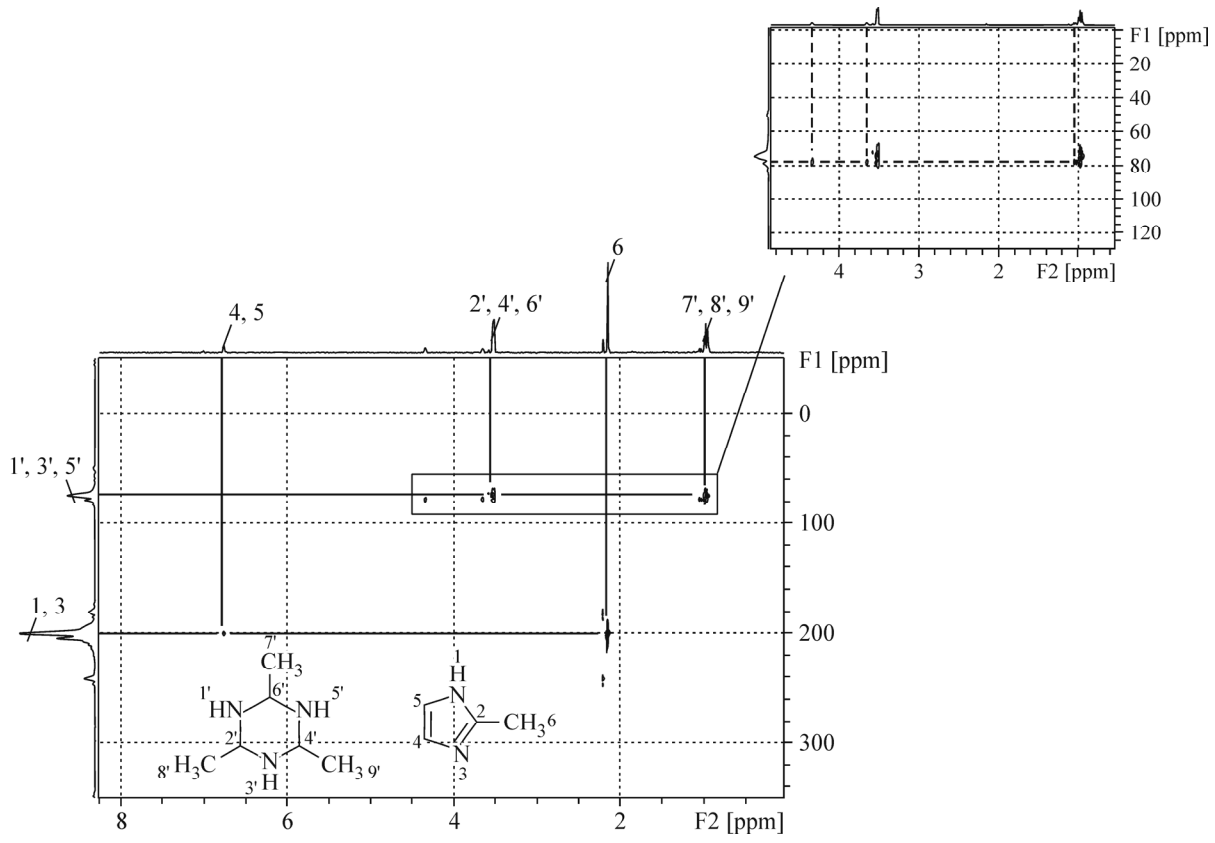


Fig. 5. $^{1}H–^{15}N$ HMBC spectrum of the reaction mixture of 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate and glyoxal at the final reaction moment. The solvent is D_2O.

It is noteworthy that the unidentified singlet signal in the region of 3.49 ppm of the proton spectrum directly correlates with the methylene carbon atom (62.4 ppm) to unequivocally indicate that the signal corresponds to the protons of the CH_2 group. Taking into account the presence of carbonyl carbons at 162.5 ppm and 170.9 ppm, we conclude that glycolic acid [12] is formed under the studied conditions in the reaction mixture from glyoxal during the Cannizzaro reaction [13, 14]. While the signal at 170.9 ppm is assigned to the atom of the carboxyl group of glycolic acid, the nature of the signal at 162.5 ppm was not identified in this work.

Fig. 5 shows long-range correlations between nitrogen and hydrogen atoms indicating that the protons of the trimer and 2-MI are assigned to the corresponding signals of nitrogen atoms. Detailed consideration of the spectrum in this region allows revealing more delicate correlations between the signals of methine and methyl protons similar to those of the trimer with the neighboring signal of the amine nitrogen.

CONCLUSIONS

The present work reports for the first time the formation of 2-methylimidazole as a result of the interaction of THT and glyoxal in aqueous solution. Long-living intermediates and byproducts in the studied conditions are identified using NMR data.

It was shown by the methods of 1D ^{1}H, ^{13}C NMR, and DEPT spectroscopy and 2D heteronuclear correlation HSQC (^{1}H–^{13}C) and HMBC (^{1}H–^{15}N) spectroscopy that the reaction mixture contains the structures with –CH and $–CH_3$ fragments connected to each other and to the amine nitrogen atom. Thus, we conclude that the main byproducts of this reaction are the products of THT decomposition due to the splitting of the C–N bond (linear trimers, dimers, and monomers). Intermediate imine-type compounds, which are widely discussed in literature (e.g. in [9, 10]), were not found, supposedly, due to their absence in the reaction mixture or due to their short lifetime.

The proton singlet signal at 3.49 ppm strongly correlates with the methylene carbon atom (δ = 62.4 ppm). Taking into account the signal at 170.9 ppm, the above data clearly indicate the formation of glycolic acid under the studied conditions. In the present work, the only unidentified signal is the peak at 162.5 ppm of the carbon spectrum. Determining its nature is a subject of our further research.

As a result of the conducted comprehensive NMR study of 2-methylimidazole formation by the reaction of acetaldehyde ammonia trimer and glyoxal, all proton and carbon signals were reliably identified. The obtained data showed that 2-methylimidazole is the main reaction product; also, there are minor amounts of stable intermediates that are the products of trimer decomposition required for the reaction and glycolic acid.

FUNDING

The work was supported by the Competitiveness Improvement Program of Tomsk State University (project No. 8.2.03.2018) and was performed within the State Assignment of the Ministry of Education and Science of Russia (project No. 4.4590.2017.6.7).

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

REFERENCES

1. L. Zhang, X. Peng, G. Damu, R. Geng, and C. Zhou. *Med. Res. Rev.*, **2014**, *34*, 340–437.
2. S. Kumari, K. S. Pramod, and K. Nitin. *Chem. Sin.*, **2010**, *1*, 36–47.
3. H. Olivier-Bourbigou, L. Magna, and D. Morvan. *Appl. Catal. A: General.*, **2010**, *373*, 1–56.

4. Yu. Ya. Meshcheryakov et al. Epoxy Oligomer for a Binding Composition, a Method for its Preparation and a Method for Producing a Binder Composition Based on it [in Russian]. Patent RF, no. 2221816, **2003**.
5. A. Shtankoviak et al. Aircraft Anti-Icing Agent and Anti-Icer for Aircraft [in Russian]. Patent RF, no. 2141990, **1999**.
6. A. Bhatnagar, P. K. Sharma, and N. Kumar. *Int*. *J*. *Pharmtech*. *Res*., **2011**, *3*, 268–282.
7. P. Manocha, S. Wakode, A. Kaur, K. Anand, and H. Kumar. *Int*. *J*. *Pharm*. *Sci*. *Res*., **2016**, *1*, 12–16.
8. S. Atanasova-Stamova, S. Georgieva, and M. Georgieva. *Scr. Sci. Pharm.*, **2018**, *5*, 7–13.
9. J. Kua, H. E. Krizner, and D. O. De Haan. *J*. *Phys*. *Chem*. *A*, **2011**, *115*, 1667–1675.
10. X. Wu, M. Huang, F. Kong, and S. Yu. *J*. *Dairy Sci*., **2015**, *98*, 8565–8571.
11. V. P. Tuguldurova, A. V. Fateev, V. S. Malkov, O. Kh. Poleshchuk, and O. V. Vodyankina. *J*. *Phys*. *Chem*. *A*, **2017**, *121*, 3136–3141.
12. A. J. Coggins and M. W. Powner. *Nat*. *Chem*., **2017**, *9*, 310–317.
13. P. Salomaa. *Acta Chem. Scand*., **1956**, *10*, 311–319.
14. A. Fratzke and P. Reilly. *Int*. *J*. *Chem*. *Kinet*., **1986**, *18*, 757–773.