Russian Chemical Bulletin, International Edition, Vol. 66, No. 1, pp. 70—75, January, 2017

Theoretical and experimental study of imine-enamine tautomerism of condensation products of propanal with 4-aminobenzoic acid in ethanol

P. A. Kalmykov,[a]* I. A. Khodov,[b,c] V. V. Klochkov,[c] and M. V. Klyuev[a]

[a]*Ivanovo State University,*
39 ul. Ermaka, 153025 Ivanovo, Russian Federation.
E-mail: k_p.a@mail.ru, klyuev@inbox.ru
[b]*G. A. Krestov Institute of Solution Chemistry, Russian Academy of Sciences,*
1 ul. Akademicheskaya, 153045 Ivanovo, Russian Federation.
E-mail: ilya.khodov@gmail.com
[c]*Kazan (Volga Region) Federal University,*
18 ul. Kremlevskaya, 420000 Kazan, Russian Federation.
E-mail: Vladimir.Klochkov@kpfu.ru

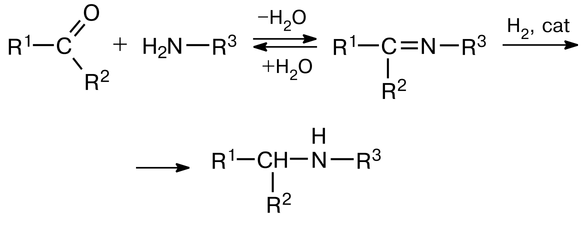
The tautomerism of the reaction products of propanal with 4-aminobenzoic acid in ethanol was studied by J-modulated spin-echo (JMOD) ^{13}C NMR spectroscopy and gradient-enhanced heteronuclear (ge-2D) ^{1}H—^{13}C HSQC spectroscopy. The existence of imine and enamine tautomeric forms of the reduced compounds in solution was established. The tautomeric equilibrium of the condensation product of propanal with 4-aminobenzoic acid in ethanol was found to be shifted toward the imine form. Quantum chemical calculations by the density functional theory (DFT) method demonstrated that the 4-(*N*-propylidene)aminobenzoic acid molecule forms a stronger hydrogen bond with an ethanol solvent molecule compared to the enamine molecule, resulting in a higher stability of the ethanol adduct of azomethine compared to the adduct of enamine.

Key words: hydrogenation amination, Schiff bases, imine-enamine tautomerism, density functional theory, NMR spectroscopy, ge-2D HSQC, JMOD.

Systems based on carbon nanomaterials (carbon nanotubes, carbon nanofibers, nanodiamonds (ND), graphene-like nanomaterials, *etc.*) containing transition metals are of interest for application in chemical and pharmaceutical industry. These systems exhibit high catalytic activity for hydrogenation of unsaturated organic compounds containing various functional groups.[1]

The liquid-phase reductive amination (Scheme 1) is a green chemistry method, which is applied as a one-pot procedure for the synthesis of structurally different secondary and tertiary amines.[2]

Scheme 1



cat is a catalyst.
R^1, R^2, R^3 are alkyl, aryl, or aryl heterocycles.

Previously, we have demonstrated that this reaction can proceed under mild conditions (ethanol or propan-2-ol as the solvent, $T = 318$ K, $P(H_2) = 0.1$ MPa) in the presence of different catalysts based on platinum- and palladium-containing carbon nanomaterials.[1] In the present work, the hydrogenation amination of aldehydes with primary amines was investigated. We studied the reductive amination of propanal with 4-aminobenzoic acid under mild conditions ($T = 318$ K, $P(H_2) = 0.1$ MPa, ethanol) in the presence of a palladium-containing carbon nanomaterial based on ethylenediamine-functionalized graphite oxide as a model reaction. Quantum chemical calculations were performed for the molecules of the reduced compounds. The correlations responsible for characteristic groups of atoms were studied by gradient-enhanced 2D heteronuclear correlation (ge-2D ^{1}H—^{13}C HSQC) NMR spectroscopy in order to prove the existence of imine-enamine tautomerism in solution and confirm the chemical structure of the compound produced by hydrogenation.

Experimental

Methods of investigation. The hydrogenation amination products were analyzed by NMR spectroscopy. The samples were

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 0070—0075, January, 2017.

prepared in standard 5 mm NMR tubes without additional purification. The spectra were recorded on an AVANCE III-500 multipurpose pulsed NMR spectrometer (Bruker, Germany) operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. The JMOD ^{13}C NMR spectra were acquired using 8192 scans; ge-2D ^{1}H—^{13}C HSQC spectra, with 16 full scans per increment. The number of increments n_i of the acquisition time *t*2 for the determination of the second frequency axis was chosen taking into account the condition $n_i \geq$ sw1/2, where sw1 is the spectral window width. The ge-2D ^{1}H—^{13}C HSQC spectra were optimized for the spin-spin coupling constant $J_{\rm C,H}$ = 145 Hz, which is the common compromise between the signals of aliphatic and aromatic atoms. This constant is suitable for most organic compounds. All NMR experiments were performed in non-deuterated solvents, and it was of particular interest to verify the results of the synthesis in the reaction media. Therefore, we employed broad-band decoupling both in 1D JMOD ^{13}C NMR and ge-2D ^{1}H—^{13}C HSQC spectra recorded with a pulse sequence. The Waltz-16 broad-band decoupling was used to eliminate satellite signals that appear in the ^{1}H NMR spectrum of a non-deuterated solvent due to direct ^{1}H—^{13}C spin-spin coupling. The temperature was controlled at 293 K using a BCU-05 temperature control system (Bruker).

A procedure for the preparation of the catalyst (palladium-containing (5 wt.%) carbon nanomaterial based on ethylenediamine-functionalized graphite oxide), its investigation, and selected catalytic characteristics were reported previously.[1,3,4]

The hydrogenation amination of propanal with 4-aminobenzoic acid was performed under mild conditions (T = 318 K, $P(\rm H_2)$ = 0.1 MPa, ethanol) as follows: in a glass reactor equipped with a heating/cooling jacket for temperature control and a magnetic stirrer, the catalyst (30 mg) was loaded under a layer of ethanol (5 mL) and $\rm NaBH_4$ (10 mg) in a hydrogen flow, and the activation with hydrogen was performed for 10 min. Then a mixture of amine (4-aminobenzoic acid, 2 mmol) and aldehyde (propanal, 2 mmol) dissolved in ethanol (20 mL) was added to the reactor under a hydrogen flow.

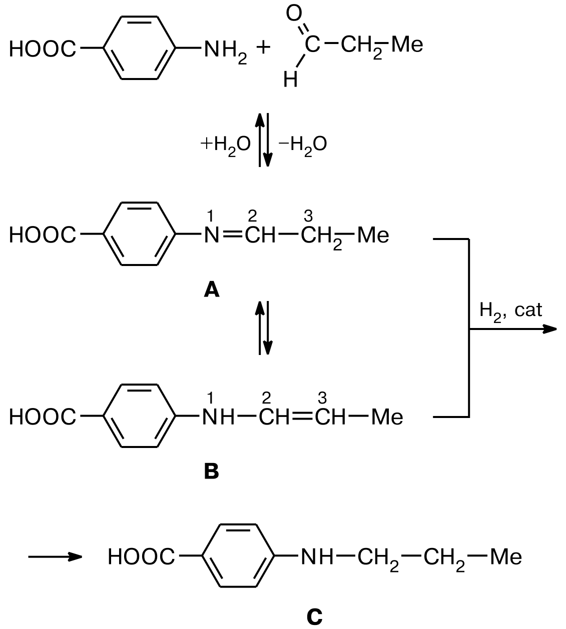
The hydrogenation amination products were analyzed on a series 3700 gas chromatograph, ICP-MS II model, equipped with a flame ionization detector. A TsvetKhrom-8 generator was used as a source of hydrogen, the hydrogen purity was 99.999%; a glass chromatography column 3 mm in diameter and 2000 mm in length packed with Lucoprene G-1000 (5%) on Chromaton N-AW-DMCS; nitrogen as a carrier gas, temperature of injection was 363—503 K, the column temperature was 333—453 K, the carrier gas flow rate was 1.8±0.02 L h^{-1}, the hydrogen flow rate was 40 mL min^{-1}, the injection volume of the sample was 0.1—2 μL. According to GLC, the yield of 4-(*N*-propyl)aminobenzoic acid was 98%.

Quantum chemical calculations were performed using the NWChem program package.[5] The geometry optimization and vibrational frequency calculations were performed by the density functional theory method using the B3LYP functional and the correlation-consistent valence triple-zeta cc-pVTZ basis set. All calculations were carried out taking into account nonspecific solvation in terms of the PCM model in an ethanol medium (dielectric constant is 24.852). Data on the electron density distribution on atoms were obtained in terms of the natural bond orbital (NBO) theory. The visualization of the molecules and their characteristics was made using the ChemCraft program.[6]

Results and Discussion

The condensation of amines with aldehydes is known to give azomethines (Scheme 2, compound **A**) in tautomeric equilibrium with the corresponding enamines (see Scheme 2, compound **B**). The quantitative ratio of these tautomers largely depends on many factors: the nature of the solvent, the structures of the reactants, the temperature, the possibility of the formation of H-complexes or complexes with metal cations.[7] The model hydrogenation amination reaction with 4-aminobenzoic acid affords 4-(*N*-propyl)aminobenzoic acid (**C**) as the hydrogenation product of compounds **A** and **B**.[8]

Scheme 2



In this work, reaction product **C** was obtained in 98% yield (GLC data) under mild conditions (T = 318 K, $P(\rm H_2)$ = 0.1 MPa, ethanol) in the presence of a palladium-containing carbon nanomaterial based on ethylenediamine-functionalized graphite oxide.

Stable tautomeric forms of the condensation products, *viz.*, the imine form (4-(*N*-propylidene)aminobenzoic acid (**A**)) and the enamine form (4-(*N*-propenyl)aminobenzoic acid (**B**)) (Fig. 1), were established by quantum chemical calculations taking into account nonspecific solvation (ethanol) in terms of the PCM method. All vibrational frequencies of the molecules were real. According to calculations, molecule **B** is planar; the pyramidal nitrogen inversion is absent. The molecule has lower values of both the total electron energy and the Gibbs free energy (298 K): $\Delta E(\mathbf{B} - \mathbf{A})$ = 1.58 kcal mol^{-1}, ΔG^0_{298} $(\mathbf{B} - \mathbf{A})$ = = 2.01 kcal mol^{-1}. This is explained by the conjugation of

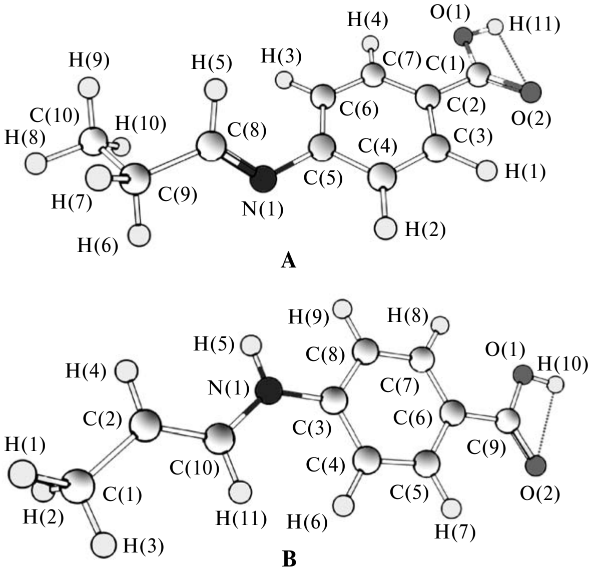


Fig. 1. Stable tautomers of azomethine (4-(*N*-propylidene)-aminobenzoic acid) (**A**) and enamine (4-(*N*-propenyl)amino-benzoic acid) (**B**) molecules.

the π system of the double bond with the atomic p_z orbital of nitrogen and the π system of the benzene ring. These data suggest that the enamine form is energetically more favorable than the imine form. Azomethine molecule **A** is nonplanar; the torsion angle is φ(C(6)—C(5)—N(1)—C(8)) = 50° (see Fig. 1, molecule **A**).

The conformational analysis of molecule **A** was performed by quantum chemical calculations (B3LYP/cc-pVTZ) taking into account nonspecific solvation (ethanol) by the PCM method (Fig. 2). The torsion angle containing the reduced bond >C=N was analyzed as the soft coordinate. It was found that one stable conformer with φ(C(6)—C(5)—N(1)—C(8)) = 50° exists under the reaction conditions. The barrier to internal rotation about this torsional coordinate is 0.82 kcal mol^{-1}. The results of calculations demonstrated that the barrier to internal rotation is higher than the energy of thermal motion of the molecules at the temperature of the experiment (0.632 kcal mol^{-1}).

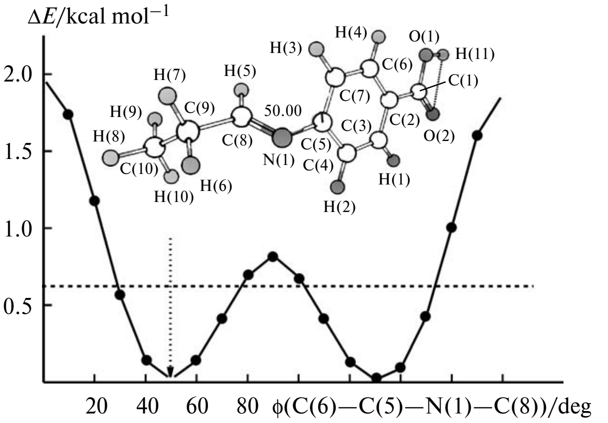


Fig. 2. Potential energy function of internal rotation of the *N*-propylidene moiety about the C—N bond; the dashed line indicates *RT* (at 318 K).

In a protic solvent, compounds containing the carboxyl group can form dimers or salts (if metal cations are present in the solution) and also form hydrogen bonds with the solvent molecules. Since molecules **A** and **B** are structurally similar and contain similar functional groups, it can be assumed that the dimerization and salt formation exert a similar effect on the reduction of unsaturated bonds. However, the hydrogen bonding between the solvent molecule and the lone pair of the nitrogen atom (a proton acceptor capable of forming a hydrogen bond only with one ethanol molecule) can have a considerable effect on stability of the adducts of molecules **A** and **B** with the solvent and on the rate of reduction of >C=N— and >C=C< bonds. The PCM method was used in quantum chemical calculations (B3LYP/cc-pVTZ) for the interaction of molecules **A** and **B** with an ethanol molecule taking into account nonspecific solvation (ethanol) (Fig. 3). The ethanol molecule was oriented so that its hydroxyl hydrogen atom points to the lone pair of the nitrogen atom. All

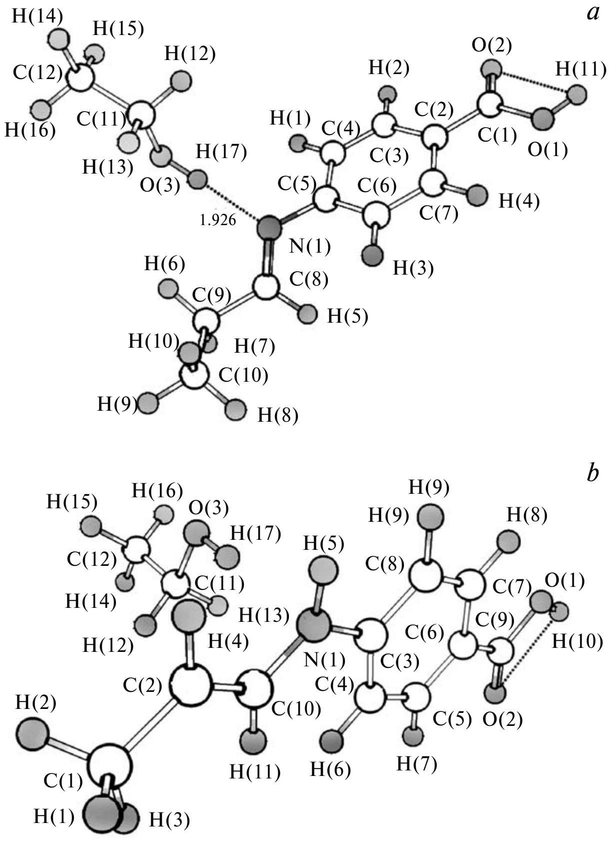


Fig. 3. Adducts of molecules **A** (*a*) and **B** (*b*) with an ethanol molecule; a hydrogen bond length is given (Å).

frequencies of the calculated adducts were real. In both cases, a hydrogen bond formed, this bond in molecule **A** being stronger than that in **B** (see Fig. 3). In azomethine **A**, the torsion angle containing the reduced bond >C=N— (φ(C(6)—C(5)—N(1)—C(8))) changed and became equal to 46.3°. The planarity of molecule **B** was distorted. The torsion angle φ(C(3)—C(10)—H(5)—N(1)) was 10.5°. A change in the geometric structure and the formation of a hydrogen bond were reflected in the values of the total electron energy and the Gibbs free energy. The **A** + EtOH adduct proved to be energetically more favorable compared to the **B** + EtOH adduct: ΔE((**A** + EtOH) – –(**B** + EtOH)) = 2.73 kcal mol^{-1}, $\Delta G°_{298}$((**A** + EtOH) – –(**B** + EtOH)) = 1.53 kcal mol^{-1}. The results of calculations suggest that in a protic solvent, azomethine molecules easily form hydrogen bonds with solvent molecules, thus influencing the imine-enamine tautomeric equilibrium and the type of the bond reduced in the course of the liquid-phase hydrogenation amination.

Data on the electron density and charge distribution in the molecules were obtained in terms of the NBO theory. In molecule **A** , the charge on the nitrogen atom of the >C=N— bond is –0.459 e (fractional elementary charge); on the carbon atom, 0.192 e. In molecule **B**, the charge on atom 2 of the >C=C< bond (see Scheme 2) is –0.022 e; on atom 3, –0.227 e. The following values were determined for the adducts. In the **A** + EtOH adduct, the charge on the nitrogen atom is –0.493 e; on the carbon atom, 0.212 e. In the **B** + EtOH adduct, the charge on atom 2 of the >C=C< bond (see Scheme 2) is –0.029 e; on atom 3, –0.218 e. The interaction of a hydrogen molecule with a noble metal surface can give rise to different forms of hydrogen, such as atomic hydrogen, hydrogen dissolved in a metal crystal lattice, a partially positively charged form of hydrogen, a partially negatively charged form of hydrogen, and adsorbed molecular hydrogen.[9] Taking into account the fact that hydrogen on the palladium surface bears a partial positive charge, it can be suggested that the reduction of >C=N— and >C=C< bonds starts with the interaction of the atomic p_z orbital of nitrogen or of the π system of >C=C< atoms of molecules **A** and **B** with activated hydrogen depending on the type of the unsaturated bond.

In order to establish the structures of the reduced compound and the reaction product and to clearly describe the hydrogenation, we used modern 1D and 2D NMR spectroscopy techniques. This approach is the major and often the only method of investigation of the structures of small organic molecules.[10—14] In the present study, we employed the combined analysis of the results of 1D J-modulated spin-echo (JMOD) ^{13}C NMR spectroscopy and ge-2D heteronuclear ^{1}H—^{13}C HSQC experiments. The JMOD ^{13}C NMR and ^{13}C APT NMR experiments, as well as the improved ^{13}C DEPT technique, allow the identification of the signals of methyl groups and atoms of CH groups, which have positive chemical shifts, while the chemical shifts of the signals of methylene groups are negative. The ge-2D ^{1}H—^{13}C HSQC experiments can be used to record cross-peaks of the signals from groups of ^{1}H and ^{13}C atoms linked by one chemical bond.

Figure 4 presents a fragment of the NMR spectrum of azomethine before the hydrogenation. This spectrum shows a heteronuclear cross-correlation signal at δ_C 149 and δ_H 5.45, which is indicative of a chemical bond between the nuclei of the —N=CH— group. The same approach was used to confirm the hypothesis of the existence of enamine in tautomeric equilibrium with azomethine. The concentration of enamine in the solution was much lower, and the characteristic peaks of the —NH—CH= group at δ_C 135 were not manifested (JMOD ^{13}C NMR). The characteristic heteronuclear cross-correlation signal at δ_C 135 and δ_H 7.53 was recorded by ge-2D ^{1}H—^{13}C HSQC, which is an order of magnitude more sensitive technique (Fig. 5). This signal ultimately confirms the chemical structure of enamine. Therefore, it was demonstrated that in ethanol the tautomeric equilibrium of the condensation product of propanal with 4-aminobenzoic acid is shifted toward the imine form, which is in agreement with the data published in the literature.[15] However, as mentioned above, the imine-enamine equilibrium depends on many factors. The data on different ratios of these forms were reported previously.[16,17] The hydrogenation produced a new compound, which is structurally similar to the starting compound and which contains a —CH_2—NH— group instead of —N=CH— and —NH—CH= groups. This is confirmed by the analysis of the ge-2D ^{1}H—^{13}C HSQC spectrum (Fig. 6). It can be seen that the signal of the carbon atom of the adduct of molecule **A** with a characteristic chemical shift (δ_C 51) correlates with the signal of hydrogen atoms (δ_H 3.22). This cross-peak is characteristic of the CH_2 group. Hence, the structure of 4-(*N*-propyl)aminobenzoic acid was unambiguously confirmed.

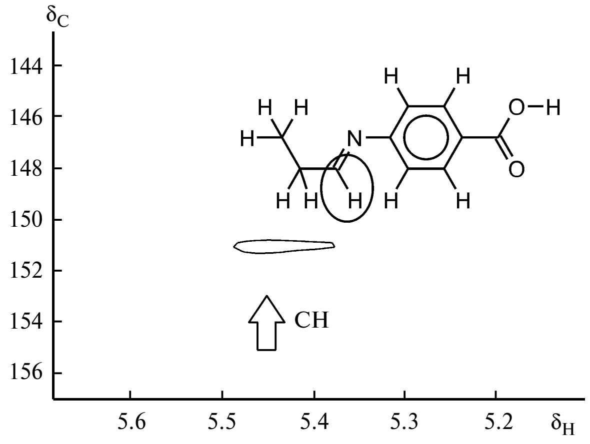


Fig. 4. Fragment of the ge-2D ^{1}H—^{13}C HSQC NMR spectrum of azomethine in ethanol.

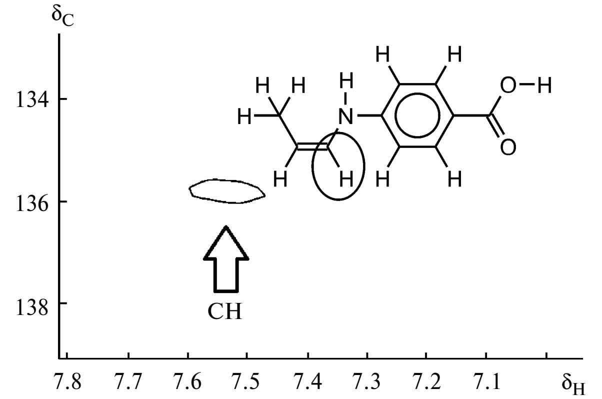


Fig. 5. Fragment of the ge-2D ^{1}H—^{13}C HSQC NMR spectrum of enamine in ethanol.

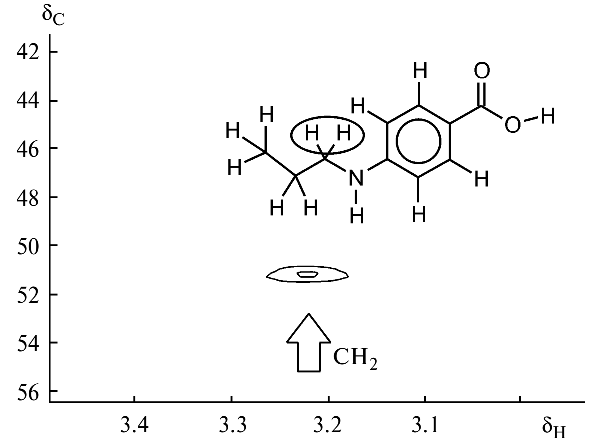


Fig. 6. Fragment of the ge-2D ^{1}H—^{13}C HSQC NMR spectrum of 4-(*N*-propyl)aminobenzoic acid in ethanol.

A fragment of the JMOD ^{13}C NMR spectrum of azomethine before the hydrogenation shows a positive signal of the CH group at the resonance frequency δ_C 149, which corresponds to the N=CH group. The hydrogenation of the —N=C< and —NH—CH=C< double bonds gives the reaction product of 4-(*N*-propyl)aminobenzoic acid, which is confirmed by both a downfield shift of the signal of the carbon atom in the JMOD ^{13}C NMR spectrum (at δ_C 51) and the negative chemical shift of the carbon atom. This, in turn, provides evidence of the formation of the methylene group.

To conclude, the palladium-containing catalyst based on ethylenediamine-functionalized graphite oxide is of considerable interest for liquid-phase one-pot hydroamination. It was demonstrated that the model hydrogenation amination reaction of propanal with 4-aminobenzoic acid under mild conditions (T = 318 K, $P(H_2)$ = = 0.1 MPa, ethanol) produces 4-(*N*-propyl)aminobenzoic acid in 98% yield (GLC data). The imine-enamine tautomerism of the condensation products of propanal with 4-aminobenzoic acid in solution was established and the structure of the reduction product of 4-(*N*-propyl)aminobenzoic acid was confirmed by ge-2D ^{1}H—^{13}C HSQC experiments. According to the results of JMOD ^{13}C NMR and ge-2D ^{1}H—^{13}C HSQC experiments, the concentration of 4-(*N*-propylidene)aminobenzoic acid in an ethanol solution is an order of magnitude higher compared to 4-(*N*-propenyl)aminobenzoic acid. Quantum chemical calculations by the density functional theory (DFT) method demonstrated that the 4-(*N*-propylidene)aminobenzoic acid molecule forms a stronger hydrogen bond with an ethanol solvent molecule compared to the enamine molecule, resulting in a higher stability of the ethanol adduct of azomethine compared to the adduct of enamine. The results of the NMR experiments combined with the quantum chemical calculations suggest that the tautomeric equilibrium of the condensation product of propanal with 4-aminobenzoic acid is shifted in ethanol toward azomethine (4-(*N*-propylidene)aminobenzoic acid). Apparently, both compounds are involved in the hydrogenation, but the solvated form of azomethine is the first to be reduced, because the concentration of azomethine in ethanol is an order of magnitude higher than that of enamine, as evidenced by the JMOD ^{13}C NMR spectra. It was suggested that the reduction of bonds in the condensation products of propanal with 4-aminobenzoic acid begins with the interaction of the atomic p_z-orbital of nitrogen or the π system of the >C=N— and >C=C< bonds of molecules **A** and **B** with activated hydrogen.

We would like to thank E. A. Lapykina and M. S. Fedorov for valuable advice and helpful discussion of quantum chemical calculations. We also thank M. G. Kiselev, G. A. Al´per, and S. V. Efimov for help in performing NMR experiments and discussion of the results.

This work was financially supported by the Ministry of Education and Science of the Russian Federation (Government Task No. 114121750070). The NMR spectroscopic studies were financially supported by the Russian Foundation for Basic Research (Projects Nos 16-03-00640, 16-53-150007, and 17-03-00459), the Council on Grants at the President of the Russian Federation (Program for State Support of Young Russian Scientists-PhD, Grant MK-9048.2016.3), and the Grant within the framework of the State support of the Kazan (Volga Region) Federal University aimed at improving its international competitiveness among the world´s leading research and educational centers.

References

1. M. V. Klyuev, N. A. Magdalinova, P. A. Kalmykov, *Katalizatory gidrogenizatsii na osnove uglerodnykh nanomaterialov* [*Hydrogenation Catalysts Based on Carbon Materials*], Ivan. Gos. Un-t, Ivanovo, 2015, 224 pp. (in Russian).
2. M. Wills, *Topics Curr. Chem.*, 2016, **374:14**, 1.

3. *Byul. Izobret.* [*Inventor Bull.*], 2015, 15; http://www1.fips.ru/Archive/PAT/2015FULL/2015.05.27/Index_ru.htm (in Russian).
4. P. A. Kalmykov, A. A. Arbuzov, N. A. Magdalinova, B. P. Tarasov, M. V. Klyuev, *Petrol. Chem.* (*Engl. Transl.*), 2016, **56**, 503 [*Nanogeterogen. Katal.*, 2016, **1**, 43].
5. M. Valiev, E. J. Bylaska, N. Govind, K. Kowalski, T. P. Straatsma, H. J. J. van Dam, D. J. Wang, E. Nieplocha, T. L. Apra, W. A. de Jong Windus, *Comput. Phys. Commun.*, 2010, **181**, 1477.
6. G. A. Zhurko, D. A. Zhurko, *ChemCraft version 1.6 (build 312)*, 2015; http://www.chemcraftprog.com/download.html.
7. K. Z. Tilyabaev, F. G. Kamaev, A. M. Yuldashev, B. T. Ibragimov, *Russ. J. Gen. Chem.* (*Engl. Transl.*), 2012, **83**, 1967 [*Zh. Obshch. Khim.*, 2012, **48**, 948].
8. N. A. Magdalinova, T. G. Volkova, M. V. Klyuev, M. S. Gruzdev, *Russ. J. Gen. Chem.* (*Engl. Transl.*), 2010, **46**, 634 [*Zh. Obshch. Khim.*, 2010, **46**, 646].
9. D. V. Filippov, A. V. Kravchenko, M. V. Ulitin, A. A. Merkin, M. A. Ryazanov, *Izv. Vuzov, Ser. Khim. i Khim. Tekhn.* [*Proceedings of Educational Institutes: Chemistry and Chemical Technology*], 2011, **54**, 60 (in Russian).
10. I. A. Khodov, S. V. Efimov, V. V. Klochkov, G. A. Alper, L. A. E. Batista de Carvalho, *Eur. J. Pharm. Sci.*, 2014, **65C**, 65.
11. I. A. Khodov, S. V. Efimov, V. V. Klochkov, G. A. Alper, L. A. E. Batista de Carvalho, M. G. Kiselev, *J. Mol. Struct.*, 2016, **1106**, 373.
12. I. A. Khodov, M. G. Kiselev, S. V. Efimov, V. V. Klochkov, *J. Magn. Reson.*, 2016, **266**, 67.
13. I. A. Khodov, S. V. Efimov, M. Y. Nikiforov, V. V. Klochkov, N. Georgi, *J. Pharm. Sci.*, 2014, **103**, 392.
14. S. V. Efimov, I. A. Khodov, E. L. Ratkova, M. G. Kiselev, S. Berger, V. V. Klochkov, *J. Mol. Struct.*, 2016, **1104**. 63.
15. G. V. Varnakova, E. I. Karpeiskaya, E. I. Klabunovskii, *Bull. Acad. Sci. USSR*, *Div. Chem. Sci.* (*Engl. Transl.*), 1978, **27**, 34 [*Izv. Akad. Nauk SSSR, Ser. Khim.*, 1978, 43].
16. L. M. Kostochka, V. P. Lezina, *Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1994, **34**, 335 [*Khim. Geterotsikl. Soedin.*, 1994, **34**, 381].
17. V. F. Traven, I. V. Ivanov, V. S. Lebedev, T. A. Chibisova, B. G. Milevskii, N. P. Solov´eva, V. I. Polshakov, G. G. Alexandrov, O. N. Kazheva, O. A. Dyachenko, *Russ. Chem. Bull.* (*Int. Ed.*), 2010, **59**, 1605 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2010, 1565].

Received August 12, 2016;
in revised form November 3, 2016