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Propanal Hydroamination with *p*-Aminobenzoic Acid

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Abstract—The propanal hydroamination was studied. It was found that the reaction in ethanol proceeded faster than in 2-propanol. By ^{1}H and ^{13}C NMR method the existence was proved of a tautomeric equilibrium in ethanol solution between 4-(propylideneamino)benzoic acid and its enamine form, 4-(prop-1-en-1-ylamino)benzoic acid.

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Among versatile amines unsymmetrical secondary amines that exhibit uncommon chemical and biological properties are especially interesting [1, 2]. One of the general methods of the synthesis of these amines is the catalytic hydrogenating amination of aldehydes. The absence of harmful side products in this process compared, for instance, with the synthesis of these products using halo derivatives, permits regarding this reaction as a "green" method [3]. In this connection the continuation of the study of the hydrogenating amination of a series of aliphatic and heterocyclic aldehydes with aromatic, alicyclic, or heterocyclic amines or their precursors leading to the formation of unsymmetrical secondary amines is urgent.

The target of this study was the investigation of propanal hydroamination with *p*-aminobenzoic acid including the kinetics of the process.

The hydrogenating amination of propanal with 4-amino-benzoic acid was carried out under mild conditions at 25–45°C and the atmospheric pressure of hydrogen in two solvents (2-propanol and ethanol) in the presence of a catalyst (1% Pd/C). The kinetic and activation parameters are presented in the table. The hydroamination proceeded in the kinetic range as shows the Thiele criterion (0.01–0.06 depending on conditions) and was of the zero order with respect to the reagents and of the first order in hydrogen and catalyst according to the data of [4]. It turned out that the hydroamination was faster in ethanol and possessed a lower activation energy, but more negative entropy. The rate constants of the reaction were nearly twice larger in ethanol than in 2-propanol, and we attribute it to the higher polarity of the ethanol as well as the structural features of 2-propanol molecules.

The azomethine formed as an intermediate product can be involved in the solution into a prototropic triade tautomerism (the proton migration between the extremes of the triade, the system of three atoms among which two are connected by a double bond, occurs with the shift of the double bond) [5]. In order to study this tautomerism the azomethine, 4-(propylideneamino)benzoic acid, was synthesized by the propanal condensation with the *p*-aminobenzoic acid at heating in ethanol solution. The azomethine structure was confirmed by IR, ^{1}H, and ^{13}C NMR spectra in DMSO-d_6. In the solution of 4-(propylideneamino)benzoic acid in DMSO-d_6–C_2D_5OD, 1 : 0.2, a tautomeric equilibrium azomethine A ⇆ enamine B was observed. In the ^{1}H NMR spectrum two separate proton signals were observed: of azomethine group N=CH (s, 7.66 ppm) and of enamine group NCH=CH (d, 6.62 ppm). These hydrogen atoms are specific for each tautomer, therefore the ratio of their intensity characterizes the ratio of the imine and enamine forms in the solution. The ratio of the integral intensity of the said signals was 1 : 1. The stabilization of the enamine form was favored by ethanol as a polar protic solvent [6, 7].

The analysis of IR, ^{1}H and ^{13}C NMR spectra of the hydroamination product showed that the formed compound was a secondary aliphatic-aromatic amine. In the ^{1}H NMR spectrum of the reduced product of reaction **I** compared with the initial compounds A and B was found the lack of

a singlet at 7.66 (N=CH) and a doublet at 6.62ppm (NCH=CH). Also a displacement was observed of the aromatic protons signals belonging to tautomers A and B to the strong field in the region 6.10–8.20 ppm and an appearance of a multiplet at 2.96 ppm from the reduced CH_2 group indicating the increase in the number of protons by two in the final compound.

The presence in solution of an equilibrium between the sufficiently stable tautomeric forms suggests that the final product, the secondary amine, may form by reduction of both azomethine and enamine. The problem, whether the hydrogenation proceeds concurrently with both tautomers or the reduction suffers mainly the more reactive one (with a shift of the equilibrium) requires additional investigation.

EXPERIMENTAL

IR spectra were registered on a spectrophotometer IR-Vertex 80 Bruker in the range 4000–400 cm^{-1} from pellets with KBr. ^1H and ^{13}C NMR spectra were recorded on spectrometers Bruker AC-200 (200.13 and 50.32 MHz respectively) and Bruker Avance-500 (500.13 and 400.32 MHz respectively), internal reference TMS.

4-(Propylideneamino)benzoic acid. To a solution of 0.232 g (4 mmol) of propanal in 10 ml of ethanol was added 0.548 g (4 mmol) of *p*-aminobenzoic acid dissolved in 10 ml of ethanol. The mixture was heated at 45°C for 30 min, cooled to 22°C, and maintained at this temperature for 3 h. The separated precipitate was filtered off, washed with ethanol, and dried in air. Yield 0.65 g (92%). Colorless crystals, mp 208–210°C. IR spectrum, ν, cm^{-1}: 3065 (CH_{Ar}), 2968, 2933, 2876 (CH_{Alk}), 1918 (Ar–N), 1672 (C=O), 1619 (C=N), 1527, 1488, 1461, 1416, 1383 (Ar), 1338, 1317, 1284, 1244, 1226 (CH_{Alk}), 1178, 1148, 1088, 1034, 1004, 958, 925 (CO), 868, 835, 775, 700, 673, 652, 637, 604 (CH_{Ar}). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.95 t (3H, CH_3), 1.72 m (2H, CH_2), 6.60–7.80 m (4H, C_6H_4), 7.64 s (1H, HC=N). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 18.75 (CH_3), 22.67 (CH_2), 121.30 (2C, CH_{Ar}), 130.67 (C_{Ar}), 132.37 (2C, CH_{Ar}), 150.25 ($C_{Ar}N$), 158.07 (HC=N), 168.85 (COOH). ^1H NMR spectrum (DMSO-d_6–C_2D_5OD), δ, ppm: 0.96 t (3H, CH_3, A), 1.11 t (3H, CH_3, B), 1.72 m (2H, CH_2, A), 3.44 m (1H, $CHCH_3$, B), 6.60–7.80 m (4H, C_6H_4, A, B), 6.62 d (1H, CH=C, B) 9.72 s (1H, NHC, B). ^{13}C NMR spectrum (DMSO-d_6–C_2D_5OD), δ, ppm: 18.65 (CH_3, A, B), 22.60 (CH_2, A), 98.44 ($CHCH_3$, B), 111.77 (2C, CH_{Ar}, B), 118.02 (C_{Ar}, B), 121.24 (2C, CH_{Ar}, A), 129.99 (2C, CH_{Ar}, B), 130.45 (2C, CH_{Ar}, A), 149.63 (CHN, B), 151.55 ($C_{Ar}N$, A), 158.13 (HC=N, A), 168.89 (COOH, A, B).

Kinetic and energy characteristics of hydroamination

Solvent	Temperature, K	k_{app},[a] s^{-1} g-at Pd^{-1}	$E^{\neq}$, kJ mol^{-1}	$\Delta S^{\neq}$, J mol^{-1} K^{-1}
2-Propanol	298	0.37	53+6	–83+20
	308	0.48		
	318	0.69		
Ethanol	298	0.64	44+4	–109+13
	308	0.81		
	318	1.15		

[a] The error in the determination of the rate constant amounted on the average to 4–5%.

4-(Propylamino)benzoic acid (I). To a solution of 0.232 g (4 mmol) of propanal in 10 ml of ethanol was added 0.548 g (4 mmol) of *p*-aminobenzoic acid dissolved in 10 ml of ethanol. The mixture was heated at 45°C for 30 min and cooled to 22°C. In a flow of hydrogen 0.2 g (1% Pd) of catalyst Pd/C was charged into the reactor under a cover with a layer of 5 ml of ethanol, the catalyst was activated with hydrogen for 10 min, then the freshly prepared reaction mixture was introduced into the reactor, and the hydrogenation was carried out for 8 h. The formed precipitate was dissolved in ethanol at heating, and the reaction mixture was filtered from the catalyst. On cooling the filtrate the separated precipitate was filtered off on a glass frit, washed with ethanol, and dried in air. Yield 0.645 g (90%). Colorless crystals, mp 166–168°C [8]. IR spectrum, ν, cm^{-1}: 3402 (NH), 3065 (CH_{Ar}), 2968, 2932, 2876 (CH_{Alk}), 1918 (Ar–N), 1668 (C=O), 1602 (C–N), 1527, 1482, 1458, 1422, 1383 (Ar), 1347, 1335, 1317, 1301, 1283, 1244 (CH_{Alk}), 1178, 1148, 1088, 1031, 1003, 962, 929 (CO), 868, 832, 772, 700, 676, 637, 607 (CH_{Ar}). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.95 t (3H, CH_3), 2.02 m (2H, CH_2), 2.96 m (2H, CH_2N), 6.75–7.78 m (4H, C_6H_4), 9.72 s (1H, HN–C). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 16.03 (CH_3), 22.17 (CH_2), 60.20 (CH_2N), 118.71 (2C, CH_{Ar}), 121.98 (C_{Ar}), 132.91 (2C, CH_{Ar}), 154.62 ($C_{Ar}N$), 169.67 (COOH).

Procedure of kinetic measurements and calculations. The hydrogenating amination was carried out by procedure [4] in a glass reactor equipped with a magnetic stirrer under temperature control at 298, 308, 318 K and hydrogen pressure of 1 at. In a flow of hydrogen 0.2 g (1% Pd) of catalyst Pd/C was charged into the reactor under a cover with a layer of 5 ml of

solvent (2-propanol, ethanol), the catalyst was activated with hydrogen for 10 min, then in a flow of hydrogen the previously prepared reaction mixture (2 mmol of *p*-aminobenzoic acid and 2 mmol of propanal dissolved in 20 ml of the solvent) was introduced into the reactor and the hydrogenation was performed at constant vigorous stirring. The apparent reaction rate was measured by the volume of consumed hydrogen every 5 min:

$$w_a = \frac{V_{H_2}/\tau}{V_{mol}\ 60\ V_s},$$

where w_a is the apparent reaction rate, mol l^{-1} s^{-1}; V_{H_2} is the consumed volume of hydrogen (ml) over time interval ϕ, min; V_{mol} is the molar volume, ml/mol; V_s is the solvent volume, l.

The apparent rate constant was calculated by the equation:

$$k_{app} = \frac{w_a p}{[H_2]\ [cat]},$$

where $[H_2]$ is the hydrogen concentration, mol l^{-1}, [cat] is the catalyst concentration, g-at Pd l^{-1}; p is the correction factor accounting for the internal partial pressure of the solvent vapor:

$$p = \frac{p_{at} - p_s}{760},$$

where p_{at} is the atmospheric pressure at the time of the experiment, mm Hg; p_s is the pressure of the solvent vapor at the temperature of the experiment, mm Hg, calculated by Antoin equation [9]:

$$\ln p_s = A + B/(T + C);$$

where *A, B, C* are coefficient from the Handbook [9], *T* is the temperature of the experiment, K.

The hydrogen concentration was calculated from the hydrogen solubility in the solvent with accounting for Henry constant H, Pa m^{-3} mol^{-1} [10].

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