

Solvent Effect on the Rate of the Mannich Reaction of Butyraldehyde with Formaldehyde

G. A. Marshalok^a, N. M. Karpyak^a, R. G. Makitra^b, and I. P. Polyuzhin^a

^a L'vovskaya politekhnik National University, ul. S. Bandery 12, L'viv, 79013 Ukraine
e-mail: natakarpia@mail.ru

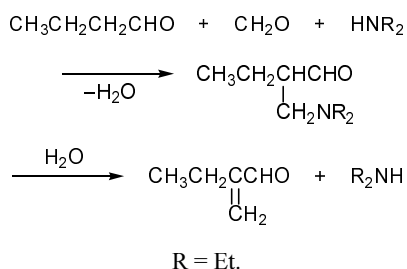
^b Institute of Geology and Geochemistry of Fossil Fuels, National Academy of Sciences of Ukraine, L'viv, Ukraine

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Abstract—The Mannich reaction of formaldehyde with butyraldehyde and diethylamine in hydrophilic solvents ensuring homogeneity of the medium follows the kinetic relations typical of an irreversible second-order reaction. The rate constants are determined by the ability of solvents to undergo self-association and their electrophilic solvation power; additional inclusion of the solvent polarity via multiparameter Koppel'–Pal'm equation is necessary to obtain a satisfactory quantitative correlation.

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Variation of the length and structure of the alkyl substituents in α -alkylacrylic acid esters makes it possible to change over a wide range technical properties of polymers derived therefrom (such as vitrification temperature, elasticity, etc.) [1]. Therefore, development of procedures for the synthesis of initial compounds for the preparation of such acids, namely α -alkylacroleins, attracts a certain interest. At present, a convenient method for the synthesis of α -alkylacroleins is Mannich condensation of formaldehyde with aliphatic aldehydes having no substituent in the α -position in the presence of secondary amines. This reaction was used most widely for the preparation of α -aminomethyl derivatives of ketones [2]. The kinetics and mechanism of the Mannich condensation were studied in [3–9]. In the reactions with aldehydes, dialkylamine molecule is eventually lost, and the final product is the corresponding α -alkylacrolein.



Acidity of the medium is crucial in the Mannich condensation. The reactions with ketones are generally

performed in acidic medium [5], whereas acids do not catalyze Mannich condensation with aldehydes; moreover, the latter almost do not react at $\text{pH} < 4$. By contrast, the condensation with aldehydes is accelerated in basic medium. Therefore, diethylamine is used preferably as free base rather than as hydrochloride. The same applies to the condensation of formaldehyde with ethyl cyanoacetate [10]. According to [4, 5], the reasons are differences in the mobility of the α -hydrogen atom in the carbonyl components and in the amine basicity.

Most authors who studied the kinetics of the Mannich reaction with ketones [5–7] reported that a satisfactory linear relation between $1/c^2$ (where c is the current concentration of formaldehyde [11]) and reaction time is observed in both acidic ($\text{pH} < 5$) and basic media ($\text{pH} > 9$), i.e., the reaction follows third-order kinetics. However, at pH values close to 7, the above dependence is not linear. An analogous pattern was also reported for the synthesis of methacrolein from propionaldehyde [3, 4].

According to [2, 3], preparative syntheses of unsaturated aldehydes, including α -ethylacrolein, were performed by mixing appropriate aldehyde with aqueous solutions of diethylamine hydrochloride and sodium carbonate, i.e., in a heterogeneous system. It was proposed in [12] to prepare β,β -dimethylaminopropiophenone by the Mannich reaction in the presence of a homogenizing solvent, e.g., ethanol. On the other

hand, Mannich reactions with ketones were carried out in solvents that are immiscible with water [9].

Taking into account the above published data, we presumed that properties of the solvent, primarily its nucleophilicity and polarity, should strongly affect the reaction rate. Therefore, we believed it to be reasonable to study in detail the synthesis of α -ethylacrolein under the Mannich reaction conditions. For this purpose, we examined the reaction of butyraldehyde with formaldehyde and diethylamine in 12 solvents miscible with water.

We have found that the reaction between equimolar amounts of formaldehyde, butyraldehyde, and diethylamine at various temperatures is formally described by the general second-order kinetic equation. Due to the presence of diethylamine, the pH value of the reaction mixture ranges from 10 to 11. Figure 1 shows that in this case a satisfactory linear relation exists in the coordinates $(1/c - 1/c_0)$ —time. Therefore, we used the second-order kinetic model which fits well the experimental data up to a conversion of 70–80% and determined the rate constants k by the integral method. We previously [13] studied the Mannich condensation of butyraldehyde with formaldehyde in aqueous phase in the presence of bis(2-hydroxyethyl)amine; the reaction mixture was homogeneous, and the process also followed second-order kinetics. It is doubtful that the observed disagreement with the data of [3, 4] concerning the overall order of the reaction would result from change of the substrate from propionaldehyde to butyraldehyde. A more probable reason is that in our case the reaction occurs in a homogeneous medium (in excess solvents miscible with water).

In keeping with the data given in Table 1, there is no clear relation between the rate constant ($\log k$) and any solvent parameter, in particular nucleophilicity which is defined as the basicity according to Pal'm (B) [14]. The rate constant tend to somewhat increase as the solvent basicity rises (Fig. 2), the experimental points are strongly scattered, and the points for acetonitrile (run no. 9), N,N -dimethylformamide (run no. 10), and N,N -dimethylacetamide (run no. 11) considerably deviate from the straight line plotted for the other solvents. Presumably, the rate of the process is affected by various mutually independent solvation factors. In such cases, multiparameter correlation equations are successfully applied to generalize experimental data. We used the Koppel'–Pal'm equation [15], supplemented by the squared Hildebrand solubility parameter [Eq. (1)].

$$\log k = a_0 + a_1 \frac{n^2 - 1}{n^2 + 2} + a_2 \frac{\epsilon - 1}{2\epsilon + 1} + a_3 B + a_4 E_T + a_5 \delta^2. \quad (1)$$

Here, n is the refractive index and ϵ is the dielectric constant, which determine, respectively, the solvent polarizability and polarity (i.e., factors responsible for nonspecific solvation); B – is the basicity according to Pal'm [14] and E_T is the Reichardt electrophilicity parameter (which determine the ability of a solvent to participate in acid–base interactions, i.e., its specific solvation power); and δ is the Hildebrand solubility parameter whose square is proportional to the cohesion energy density of a solvent [16]. The corresponding values are also given in Table 1. The calculations were performed according to the CAC IUPAC recommendations [17]; and the solvent parameters were taken from reviews [18, 19].

Treatment of the data for all 12 solvents (Table 1) gave no satisfactory results, the multiple correlation

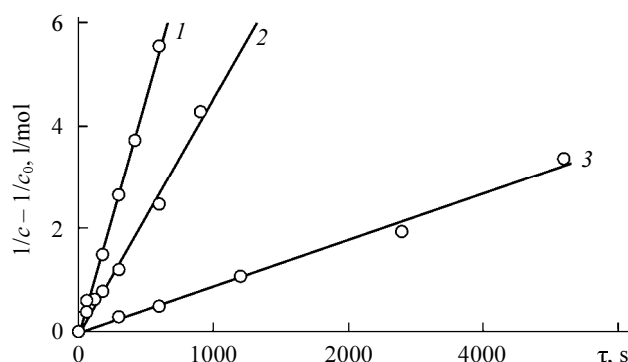


Fig. 1. Kinetic curves for the reactions of butyraldehyde with formaldehyde and diethylamine at 30°C in (1) 1,4-dioxane, (2) methanol, and (3) butyl acetate.

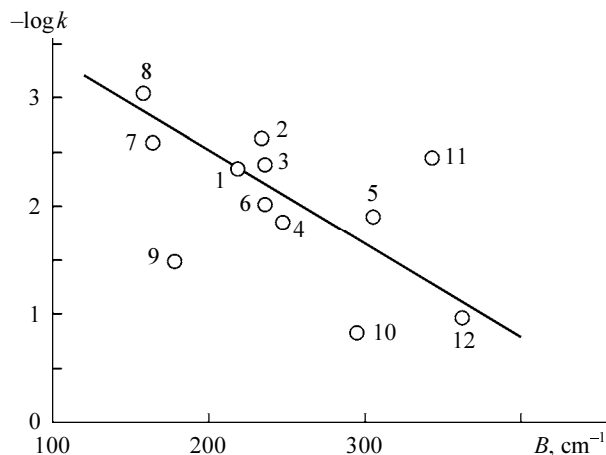


Fig. 2. Correlation between the rate constants of the Mannich reaction of butyraldehyde with formaldehyde and diethylamine and solvent basicity B . For solvent numbering, see Table 1.

Table 1. Experimental rate constants for the Mannich reaction of butyraldehyde with formaldehyde and diethylamine at 30°C in different solvents and solvent parameters

Run no.	Solvent	$(k \pm \Delta k) \times 10^3, \text{ l mol}^{-1} \text{ s}^{-1}$	$\frac{n^2 - 1}{n^2 + 2}$	$\frac{\epsilon - 1}{2\epsilon + 1}$	$B, \text{ cm}^{-1}$	E_T	$\delta^2, \text{ kJ/mol}$
1	Methanol	4.53±0.33	0.2021	0.4780	218	55.4	876.2
2	Ethanol	2.45±0.24	0.2215	0.4707	235	51.9	676.0
3	Propan-2-ol	4.17±0.23	0.2303	0.4625	236	48.4	563.5
4	<i>tert</i> -Butyl alcohol	14.1±0.6	0.2359	0.4422	247	43.3	461.8
5	Tetrahydrofuran	12.4±0.5	0.2465	0.4072	305	37.4	363.8
6	1,4-Dioxane	9.68±0.37	0.2543	0.2316	236	36.0	408.0
7	Ethyl acetate	2.62±0.09	0.2275	0.3855	164	38.1	342.1
8	Butyl acetate	0.899±0.03	0.2393	0.3639	158	38.5	302.8
9	Acetonitrile	33.2±1.2	0.2120	0.4803	178	45.6	590.5
10	<i>N,N</i> -Dimethylformamide	148±12	0.2586	0.4803	294	43.8	613.6
11	<i>N,N</i> -Dimethylacetamide	3.58±0.18	0.2621	0.4810	343	43.7	479.1
12	Dimethyl sulfoxide	108±8	0.2826	0.4848	362	45.1	634.9

coefficient R for the five-parameter equation was equal to 0.908; this value is considerably lower than that recommended in [17] ($R \geq 0.95$). However, exclusion of the most deviating data for only one solvent, methanol, gave five-parameter Eq. (2) with an acceptable value of R .

$$\log k = 3.1618 - (2.742 \pm 7.568)f(n^2) + (5.021 \pm 1.533)f(\epsilon) + (0.118 \pm 2.283) \times 10^{-3} B - (0.269 \pm 0.040)E_T + (9.811 \pm 1.286) \times 10^{-3} \delta^2; \quad (2)$$

$$R = 0.9497, s = \pm 0.219, F = 14.04 > F_{\text{ref}} = 4.74 \\ (v_1 = 10, v_2 = 5).$$

On the other hand, the pair correlation coefficients for $\log k$ and particular parameters r are 0.55 and lower; this confirms our assumption that the reaction rate depends on different factors and that the dependence cannot be expressed using a single solvent parameter.

Equation (2), as well as those given below, were checked for validity by the Fisher consistency ($F > F_{\text{ref}}$) for the corresponding number of points with a confidence probability α of 0.95. The significance of particular solvation factors was determined according to the recommendations given in [17] by successive exclusion of the corresponding parameters and calculating R for the resulting equation with a lesser number of terms. It turned out that the basicity and polarizability factors are insignificant; after exclusion of the corresponding terms, the R value almost did not change. This result is consistent with the standard deviations of the coefficients at the respective terms,

which exceed the absolute values of the regression coefficients, as well as with the conclusion drawn from the data shown in Fig. 2. The absence of the effect of solvent basicity (i.e., nucleophilic solvation power) can readily be understood taking into account that the system contains a much stronger nucleophile, diethylamine. Thus the relation between the solvent properties and the rate constant of the reaction under study may be described by three-parameter Eq. (3):

$$\log k = 2.2020 + (4.838 \pm 1.393)f(\epsilon) - (0.255 \pm 0.033)E_T + (9.429 \pm 1.101) \times 10^{-3} \delta^2; \quad (3)$$

$$R = 0.948, s = \pm 0.223, F = 14.11 > F_{\text{ref}} = 3.64 \\ (v_1 = 10, v_2 = 7).$$

According to Eq. (3), the rate constant increases in parallel with the polarity and cohesion energy density of solvents, and it decreases as solvent electrophilicity rises. We can conclude that the determining factor in the process is the ability of the medium to undergo self-association: exclusion of the δ^2 term reduces R to 0.39, while exclusion of E_T reduces R to 0.53. The polarity factor is less significant but nevertheless important: exclusion of the $f(\epsilon)$ term gives a two-parameter equation with $R = 0.88$. Presumably, increase of the cohesion energy density favors formation of reaction complex from aldehyde and amine in the first stage. The reaction becomes faster as the solvent polarity rises, since polar solvents enhance charge distribution in the reaction complex thus reducing the energy barrier. On the other hand, more electrophilic solvents are capable of partially binding diethylamine via

formation of hydrogen bonds, so that the effective concentration of diethylamine decreases. Table 2 contains the experimental values of $\log k$ and those calculated by Eq. (3); the corresponding differences $\Delta \log k$ are also given. Figure 3 shows the correlation between the calculated and experimental $\log k$ values; it is seen that $\Delta \log k$ is either smaller or only slightly larger than the mean-square deviation $s = \pm 0.223$.

The results of our study show that such homogenizing solvents as *N,N*-dimethylformamide and dimethyl sulfoxide accelerate the process by an order of magnitude, as compared to the other examined solvents. The polarity and cohesion energy density of these solvents are responsible for their accelerating effect. From the practical viewpoint, the use of DMSO or DMF should not complicate the procedure for isolation of the product (by distillation): the boiling points of DMSO, DMF, and α -ethylacrolein are 189, 153, and 95°C, respectively. Here, the still residue containing the solvent and secondary amine (which boils at a higher temperature) may be recycled.

EXPERIMENTAL

Reagent-grade butyraldehyde and diethylamine were purified by rectification prior to use; their physical constants were consistent with reference data. Formaldehyde of chemically pure grade was used as a 36% aqueous solution. The solvents were purified by standard methods [20].

Kinetic experiments were performed in a 50-cm³ glass reactor equipped with a magnetic stirrer and maintained at a constant temperature (30±0.2°C). The reactor was charged with 3.1 ml (0.03 mol) of diethylamine, 2.25 ml (0.03 mol) of 36% aqueous formaldehyde, and 35 ml of the corresponding solvent. The temperature of the mixture was adjusted to 30°C, and 2.7 ml (0.03 mol) of butyraldehyde was quickly added. This moment was taken as reaction start. Samples were withdrawn using a pipette through the reflux condenser. The progress of the reaction was monitored by the modified hydroxylamine technique for determination of overall concentration of aldehyde group according to [21]. The rate constants were calculated by the second-order equation $k\tau = 1/c - 1/c_0$, where $c_0 = 0.67$ M is the initial concentration of formaldehyde; c is the current concentration of formaldehyde (M), and τ is the reaction time (s). The process was monitored up to 80% conversion of formaldehyde. The rate constants given in Table 1 were calculated by the least-squares procedure.

Table 2. Experimental and calculated [by Eq. (3)] logarithms of the rate constants for the Mannich reaction of butyraldehyde with formaldehyde and diethylamine at 30°C in different solvents

Solvent	$\log k_{\text{exp}}$	$\log k_{\text{calc}}$	$\Delta \log k$
Methanol ^a	-2.3439	-1.3507	-0.9932
Ethanol	-2.6108	-2.3813	-0.2295
Propan-2-ol	-2.3799	-2.5890	0.2091
<i>tert</i> -Butyl alcohol	-1.8508	-2.3459	0.4952
Tetrahydrofuran	-1.9066	-1.9348	0.0282
1,4-Dioxane	-2.0141	-2.0106	-0.0035
Ethyl acetate	-2.5817	-2.4226	-0.1591
Butyl acetate	-3.0462	-2.9999	-0.0463
Acetonitrile	-1.4789	-1.5347	0.0558
<i>N,N</i> -Dimethylformamide	-0.8297	-0.8575	0.0278
<i>N,N</i> -Dimethylacetamide	-2.4461	-2.0971	-0.3490
Dimethyl sulfoxide	-0.9666	-0.9665	-0.0001

^a The data for this solvent were not included in further calculations.

In preparative experiments, α -ethylacrolein was isolated by simple distillation. The subsequent fractional distillation under reduced pressure gave a substance whose physical constants coincided with those reported in [22] for α -ethylacrolein. The purity of the product (determined by the hydroxylamine technique with respect to the aldehyde group [21]) was 98–99%; the same result was obtained by gas–liquid chromatography [23].

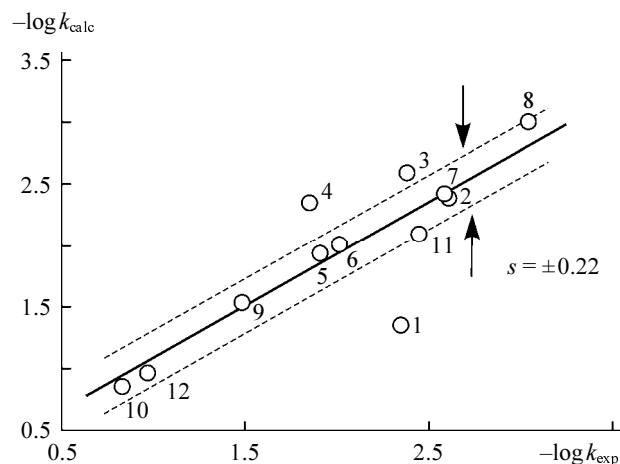


Fig. 3. Correlation between the calculated and experimental rate constants of the Mannich reaction of butyraldehyde with formaldehyde and diethylamine at 30°C in different solvents. For solvent numbering, see Table 1; the data for methanol (no. 1) were excluded from the calculations.

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