Kinetic Study of the Condensation of Salicylaldehyde with Diethyl Malonate in a Nonpolar Solvent Catalyzed by Secondary Amines

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ABSTRACT: The kinetics of condensation between salicylaldehyde and diethylmalonate in a toluene solution in the presence of secondary amines (i.e., piperidine and 4-piperidinopiperidine) as catalysts was investigated. It was found that the reaction proceeds via the Knoevenagel mechanism, and the kinetic model was numerically verified. © 2009 Wiley Periodicals, Inc. Int J Chem Kinet 41: 589–598, 2009

INTRODUCTION

The Knoevenagel condensation is generally defined as the reaction between an aldehyde and compounds with "active methylene groups" in the presence of organic/inorganic bases, ammonia, or their salts. This wide definition includes a number of reactions with different reactivities of substrates, kind of catalyst, as well as polarity of solvents. Finally, two mechanisms depending on the kind of a catalyst were proposed [1]. The Hann and Lapworth mechanism assumes the formation of the β-hydroxy intermediate as a product of the addition of a carbanion, which is produced in the reaction of an "active methylene compound" and base, to an aldehyde [2]. In turn, the Knoevenagel mechanism is proposed to proceeds via an active amino compound (e.g., iminium ion, aminal) that is formed from an aldehyde and amine [3].

The Knoevenagel condensation is one of the important methods for the coumarins synthesis [4]. Recently, the influence of microwave irradiation on the kinetics of such reactions was investigated and an increase of the reaction rate under microwave conditions

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Figures 1–4 are available as supporting information in the online issue at www.interscience.wiley.com.

was observed [4,5]. To explain the origin of such an effect, the mechanism of these kinds of reactions was investigated.

EXPERIMENTAL

Materials

Piperidine was heated with solid potassium hydroxide for 5 h under reflux condenser. Then it was distilled and stored in a closed vessel. 4-Piperidinopiperidine (98%; Sigma-Aldrich, St. Louis, MO, USA) was recrystallized from hexane. Salicylaldehyde (>99%, Fluka, Steinheim, Germany), diethylmalonate (>99%; Fluka), morpholine (>98%; Fluka), diazabicyclo[2.2.2]octane—DABCO (98%; Sigma-Aldrich), Et_3N (>98%; POCH) and toluene (POCH) were used as received.

General Methods

Melting points, measured on an Electrothermal IA9200 microscope plate, are uncorrected. The progress of reactions was monitored by both a gas chromatograph (GC) HewlettPackard 5890 coupled with a mass detection (MS) HewlettPackard 5971 and a gas chromatograph Agilent 6850 with a flame ionization detector (FID). Both chromatographs were equipped with HP-1 columns. ^{1}H NMR spectra were recorded with a Bruker AVANCE-300 spectrometer. FT-Raman spectra were obtained using an EZRaman-M spectrometer, using 670-nm excitation and 200-mW power laser.

Kinetic Investigations

An appropriate amount of substrates, catalyst (piperidine or 4-piperidinopiperidine), and naphthalene (internal standard) were dissolved in a toluene and placed in a flask, closed and kept at room temperature until more than 90% substrate conversion was obtained (it took about 10 days). At appropriate time intervals, a sample of the mixture was withdrawn and diluted in acetone (it was found that aminals easily decompose to starting materials in the acetone solution). Reaction progress was monitored by means of GC-FID, using naphthalene as an internal standard.

Catalytic Tests

The mixture of 10 mL of toluene, 5 mmol of catalyst (DABCO, Et_3N, or morpholine), 0.2 mL (20 mmol) salicylaldehyde, 0.4 mL (25 mmol) diethylmalonate was kept at 70°C for a 4 h. The presence of reaction product by GC-MS was found.

Aminals Preparation

2.55 g pipridine (30 mmol) was dropped to 1.22 g salicylaldehyde (10 mmol) and vigorously mixed. Next, the mixture was kept in a refrigerator for 5 days. The crude solid product was purified by twice recrystalization from hexane, yielding a white solid, m.p. 87°C; H NMR 300 MHz, $CDCl_3$): 12,0 (s, 1H), 7.3–7.1 (m, 1H), 6.9–6.7 (m, 3H), 3.75 (s, 1H), 2.5 (s, 8H), 1.5 (d, 12H).

5.04 g 4-piperidinopiperidine (30 mmol) was dissolved in minimal amount of dichloromethane, and the solution was dropped to 1.22 g salicylaldehyde (10 mmol) and vigorously mixed. Next, the mixture was put in the refrigerator for 5 days. The crude solid product was purified by twice recrystallization from hexane, yielding a white solid, m.p. 140°C; H NMR (300 MHz, $CDCl_3$): 11.63 (s, 1H), 7.26–7.14 (m, 1H), 6.79–6.75 (m, 3H), 3.76 (s, 1H), 3,00 (d, $J = 12$ Hz, 2H), 2.56–2.18 (br, 14H), 1.74–1.57 (br, 22H).

Numerical Calculations

On the basis of the postulated reaction mechanism, a system of differential equations describing changes of concentration each chemical compounds was made. Rate constants were estimated by the least-square fitting method (based on the Levenberg–Marquardt algorithm) using computational program Dynafit [6]. Minimized function was as follows:

$$\sum_{j=1}^{M}\sum_{i=1}^{N_j}([C]_{j,i} - [\hat{C}]_{j,i})^2$$

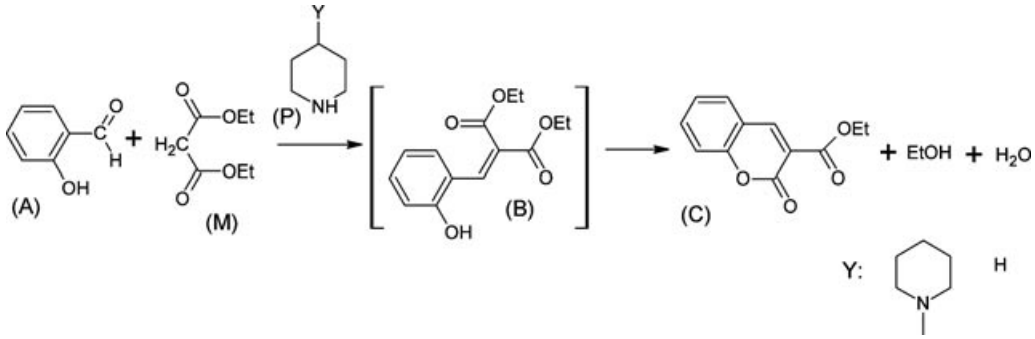
where M is the number of runs with different initial substrate concentrations $[A]_{j,1}$,$[M]_{j,1}$; N_j is the number of measurements in j run (thus $\sum_{j=1}^{R} N_j = N$ express the total number of data points); $[C]_{j,i}$ is the product concentration, expressed as a mean value based on the substrate consumption: $[C]_{j,i} = ([A]_{j,1} - [A]_{j,i} + [M]_{j,1} - [M]_{j,i})/2$; $[\hat{C}]_{j,i}$ is the estimated product concentration; $[A]_{j,i}$,$[M]_{j,i}$ are measured substrate concentrations.

The quality of fitting was expressed as sum of squares and a relative error of rate constants estimations. Both parameters were calculated by means of Dynafit.

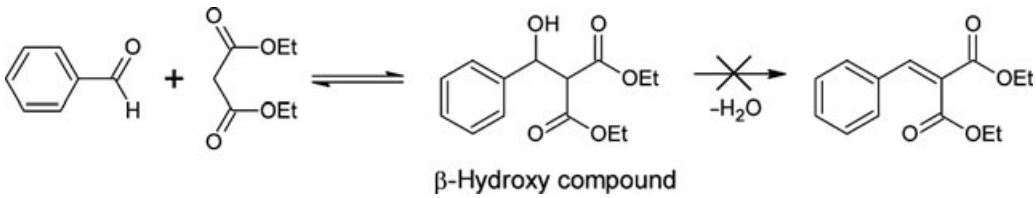
RESULTS AND DISCUSSION

Nonkinetic Consideration

The aim of the presented work was to determine the condensation mechanism of salicylaldehyde (**A**) and



Scheme 1 The reaction of salicylaldehyde (**A**) and diethylmalonate (**M**) in the presence of a secondary amine (**P**).



Scheme 2 Possible paths of 2,2-diethoxycarbonyl-1-phenyl-ethenol-1 decomposition.

diethylmalonate (**M**) catalyzed by a secondary amine (**P**) in a nonpolar solvent (Scheme 1).

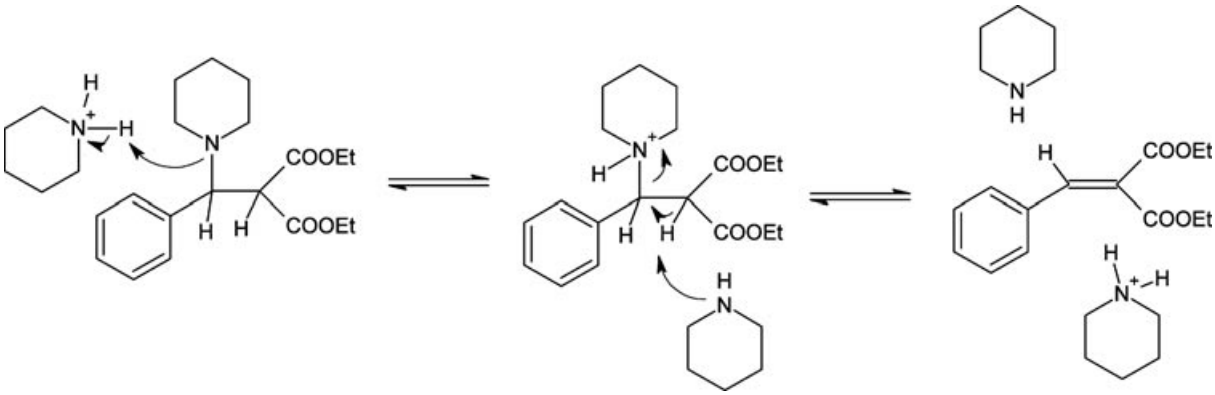
The investigated reaction occurs via two main steps, i.e., the Knoevenagel condensation that affords a benzylidene derivative (**B**) and then lactonization of the derivative **B** that yields the final product 3-ethoxycarbonylcoumarin (**C**). The second step seems to be irreversible since the analysis of a solution of the coumarin **C** in EtOH even after heating was not indicating a retroreaction toward **B** and then **A** and **M**. Moreover, the last step (lactonization) is a fast one and the traces of unsaturated derivative **B** was detected by means of chromatographic methods (GC/MS, HPLC). Therefore, it was possible to simplify the investigated reaction and consider only the first step, i.e., the Knoevenagel condensation.

The kinetics of the Knoevenagel condensation of benzaldehyde with malonic ester in the presence of secondary amines as a catalyst has already been investigated [7,8]. It was found that the β-hydroxy product was very resistant to dehydratation and easily decomposed to the starting materials (Scheme 2). Thus, the final product of the reaction is formed from the β-amino compounds, which supported the Knoevenagel mechanism. A similar mechanism for the condensation of methyl arylsulfinylacetate with various aldehydes was proposed by Tanikaga et al. [9]. A further study showed that the deamination of β-amino compound is the rate-limiting step (Scheme 3), which can be accelerated in the presence of H^+ (e.g., as the protonated amine) [7]. In turn, the condensation of aromatic aldehydes (e.g., benzaldehyde) with various compounds with active methylene groups of different acidities in the absence of any catalyst followed the Hann–Lapworth mechanism, and the ionization of a compound with an active methylene group was the rate-determining step [10a–10d].

According to the Hann and Lapworth mechanism, the catalytic activity of tertiary amines increases when the basicity of an amine rises and does not depend on its structure. On the other hand, the Knoevenagel mechanism requires only secondary or primary amines as a catalyst, and tertiary amines do not catalyze the condensation because they cannot form amino intermediates in the reaction with an aldehyde. To decide which of two presented mechanisms is more probable in the reaction of salicylaldehyde (**A**) and diethyl malonate (**M**), catalytic tests were performed in the presence of secondary as well as tertiary amines (Table I).

Based on the results shown in Table I, the condensation of salicylaldehyde (**A**) and diethyl malonate (**M**) in a toluene solution proceeds via the Knoevenagel mechanism rather than the Hann–Lapworth mechanism. Tertiary amines (i.e., diazabicyclo[2.2.2]octane (DABCO) and Et_3N) did not catalyze the reaction, but secondary amines (i.e., morpholine and piperidine) that posses similar basicity to the tertiary amines catalyzed the reaction.

Furthermore, in the case of the Knoevenagel condensation catalyzed by secondary amines, the reaction



Scheme 3 Acid-catalyzed deamination of β-amino compound.

Table I Correlation between Catalytic Activity of the Selected Secondary and Tertiary Amines and Their Basicity

Base	pK_b	Catalytic Activity Yield of Coumarin (%)
DABCO	5.8/9.8[a]	0
Et_3N	3.2	0
Morpholine	5.3	15
Piperidine	2.9	53

[a] pK_1 and pK_2 values are taken from [11].

proceeds via intermediates like an aminal (**AP2**) or an imminium salt ($\mathbf{AP}^+$), which is considerably more electrophilic than the aldehyde [1]. In accordance with that a mechanism is outlined in Scheme 4.

In addition to the main reactions, side reactions can occur, i.e., carbanion generation via deprotonation of the active methylene groups by a base (amine) and addition of the carbanion to the aldehyde to give the β-hydroxy compound as well as the acid–base reaction between salicylaldehyde and the amine catalyst.

Reaction Intermediates

On the basis of detailed kinetic investigations on the aldolic stage of the Knoevenagel condensation of benzaldehyde and diethyl malonate, Kinastowski and Mroczyk [7,8] suggested that the condensation via an intermediate β-amino compound is most probable. The β-amino compound was formed as the product of reactions of diethylmalonate with two key intermediates, i.e. aminal or/and iminium cation. The synthesis of aminals with similar structure to the aminal $\mathbf{AP}_2$ from benzaldehyde and piperidine was already described by Patai et al. [10e]. Later, Tanaka et al. proved the structure of these aminals using NMR spectroscopy [12]. On the other hand, it is well known that iminium cations like $\mathbf{AP}^+$ are intermediates in the Mannich condensation, in which the cations are generated from formaldehyde and an amine [13].

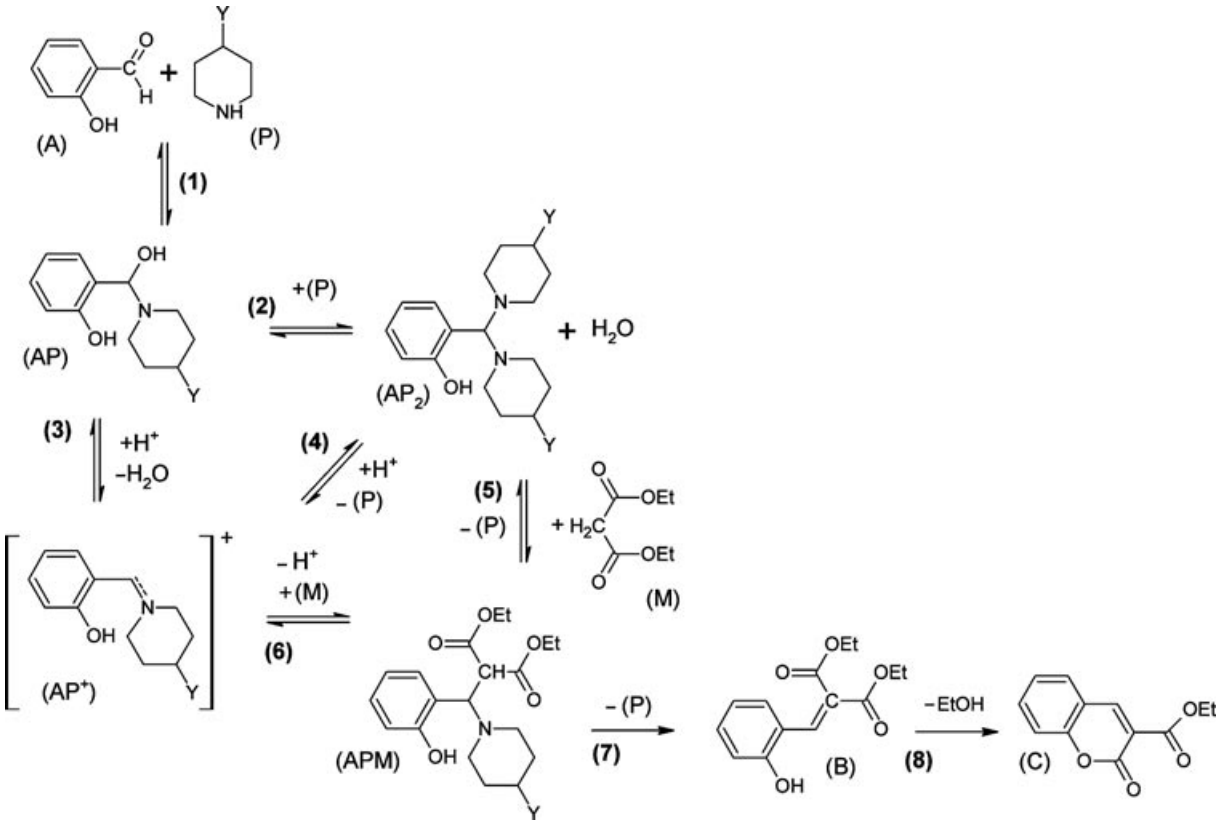
In our study, ^{1}H NMR analysis of the equimolar mixture of salicylaldehyde and piperidine showed that the aminal $\mathbf{AP}_2$ was readily formed (Scheme 5) and the reaction reached the equilibrium stage quickly (see Supporting Information Fig. 1). Aminals from salicylaldehyde and other secondary amines can also be easily prepared (see the Experimental section).

In addition, ^{1}H NMR analysis does not give information about formation of other compounds such as the hemaminal **AP** or iminium ion $\mathbf{AP}^+$. Recently, the kinetics of the Knoevenagel condensation of salicylaldehyde with benzyl acetoacetate in the presence of piperidine by means of Raman spectroscopy was investigated [14], and the formation of benzylidene-like product was observed. However, in the case of condensation of salicylaldehyde and diethylmalonate, the aminal **AP2** was the only intermediate detected by means of the method.

Eventually, only the aminal **AP2** as intermediate was detected and prepared in our investigation. The remaining compounds (intermediates) were not detected by means of chromatographic methods (HPLC, GC/MS) and Raman spectroscopy. It indicates that most of preliminary reactions, i.e., (1), (2), (3), (6), and (7) (Scheme 4) are equilibrium reactions, fast in both directions, and, for this reason, the concentration of intermediates is under the detection limit of analytical methods used.

Kinetics Models

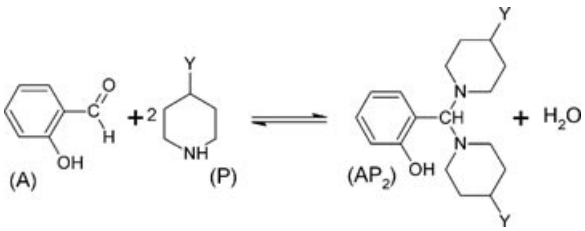
As can be seen in Scheme 4, the investigated reaction is complex. Moreover, there is a lack of strict information on both formation and concentration of each



Scheme 4 Proposed course of the Knoevenagel condensation of salicylaldehyde with diethylmalonate, catalyzed by secondary amine in a nonpolar solvent.

intermediate (i.e., **AP**, $\mathbf{AP}^+$, **B**). Nevertheless, kinetic modeling was chosen to prove the reaction mechanism.

It was found that the contact of piperidine with H_2O and CO_2 from the air causes generation of piperidine cation, which influences the kinetics of the Knoevenagel condensation [15]. However, in the investigated system there is a phenolic derivative, salicylaldehyde, which can act as a proton donor and protonates the amine catalyst, thus the influence of air may be neglected. Moreover, we also chose to use as a catalyst 4-piperidinopiperidine, which is a secondary amine that is more stable, less hygroscopic, easier to purify, and simultaneously soluble in nonpolar solvents. This catalyst has also another interesting feature—it possesses an additional tertiary amine group.



Scheme 5 Aminal formation from salicylaldehyde and piperidine.

According to the above considerations, it is possible to define three reaction paths (Scheme 4), i.e. 1-2-5-7-8,* 1-2-4-6-7-8, and 1-3-6-7-8, and for each path a numeric model (a system of differential equations) was created: K-1, K-2, K-3, respectively (Tables II and III). Then, the rate constants were numerically estimated for each kinetic model for the reactions catalyzed by both 4-piperidinopiperidine and piperidine. Next, the complex equation system was simplified by accepting reducing assumptions and model parameters for each approximation (A, B, C, D, and E) were determined (Tables III–VI).

Approximation A (K1A, K2A, K3A)

1. Hydronium ion concentration is constant and thus $k_4' = [H^+]k_4$, $k_3' = [H^+]k_3$; however, it is difficult to control the pH in such nonaqueous systems.

*For reaction numbers see Scheme 4. Rate constants are numbered in the same manner.

Table II Kinetic Models. Approximations A and B

Model Name	Scheme	System of Differential Equations
		$\frac{d[A]}{dt} = -k_1[A][P] + k_{-1}[AP]$
		$\frac{d[P]}{dt} = -k_1[A][P] + k_{-1}[AP] - k_2[P][AP] + k_{-2}[AP_2][W] + 2k_5[AP_2][M]$
K-1A	$A + P \underset{k_{-1}}{\overset{k_1}{\rightarrow}} AP$	$\frac{d[AP]}{dt} = k_1[A][P] - k_{-1}[AP] - k_2[P][AP] + k_{-2}[AP_2][W]$
K-1B	$AP + P \underset{k_{-2}}{\overset{k_2}{\rightarrow}} AP_2 + W$	$\frac{d[AP_2]}{dt} = k_2[P][AP] - k_{-2}[AP_2][W] - k_5[AP_2][M]$
	$AP_2 + M \overset{k_5}{\rightarrow} 2P + C + E$	$\frac{d[W]}{dt} = k_2[P][AP] - k_{-2}[AP_2][W]$
		$\frac{d[M]}{dt} = -k_5[AP_2][M]$
		$\frac{d[C]}{dt} = \frac{d[E]}{dt} = k_5[AP_2][M]$
		$\frac{d[A]}{dt} = -k_1[A][P] + k_{-1}[AP]$
		$\frac{d[P]}{dt} = -k_1[A][P] + k_{-1}[AP] - k_2[P][AP] + k_{-2}[AP_2][W] + k'_4[AP_2] - k'_{-4}[P][AP^+] + k_5[AP^+][M]$
	$A + P \underset{k_{-1}}{\overset{k_1}{\leftrightarrow}} AP$	$\frac{d[AP]}{dt} = k_1[A][P] - k_{-1}[AP] - k_2[AP][P] + k_{-2}[AP_2][W]$
K-2A	$AP + P \underset{k_{-2}}{\overset{k_2}{\leftrightarrow}} AP_2 + W$	$\frac{d[AP_2]}{dt} = k_2[P][AP] - k_{-2}[AP_2][W] - k'_4[AP_2] + k'_{-4}[P][AP^+]$
K-2B	$AP_2 \underset{k'_{-4}}{\overset{k'_4}{\leftrightarrow}} AP^+ + P$	$\frac{d[W]}{dt} = k_2[P][AP] - k_{-2}[AP_2][W]$
	$AP^+ + M \overset{k_6}{\rightarrow} 2P + C + E$	$\frac{d[AP^+]}{dt} = k'_4[AP_2] - k'_{-4}[P][AP^+] - k_6[AP^+][M]$
		$\frac{d[M]}{dt} = -k_6[AP^+][M]$
		$\frac{d[C]}{dt} = \frac{d[E]}{dt} = k_6[AP^+][M]$
		$\frac{d[A]}{dt} = -k_1[A][P] + k_{-1}[AP]$
K-3A	$A + P \underset{k_{-1}}{\overset{k_1}{\leftrightarrow}} AP$	$\frac{d[P]}{dt} = -k_1[A][P] + k_{-1}[AP] + k_6[AP^+][M]$
K-3A	$AP \underset{k'_{-3}}{\overset{k'_3}{\leftrightarrow}} AP^+ + W$	$\frac{d[AP]}{dt} = k_1[A][P] - k_{-1}[AP] - k'_3[AP] + k'_5[AP^+][W]$
		$\frac{d[AP^+]}{dt} = k'_3[AP] - k'_{-3}[AP^+][W]$
	$AP^+ + M \overset{k_6}{\leftrightarrow} P + C + E$	$\frac{d[M]}{dt} = -k_6[AP^+][M]$
		$\frac{d[C]}{dt} = \frac{d[E]}{dt} = k_6[AP^+][M]$

2. β-Amino intermediate (APM) formation (5) and (6) is an irreversible step and thus $k_5 \gg k_{-5}$, $k_6 \gg k_{-6}$.
3. Amine elimination (7) and lactonization (8) are fast steps.

As can be seen (Table IV), this model does not fit to experimental data and next reductions should be applied.

Approximation B (K1B, K2B, K3B).

1. On the basis of additional numerical simulations, we found that adjusting values of $k_1/k_{-1} \approx 1$ and $k_1 \approx k_{-1} \approx 1000$ model fitting is the best. However, both the ratio and the absolute rate constant values can vary and they do not influence both model fitting and values of the other estimated

Table III Kinetic Models: Approximations C, D, and E

Model Name	Scheme	System of Differential Equations
K-1C	$A + 2P \underset{k_{-r}}{\overset{k_r}{\leftrightarrow}} AP_2 + W$	$\frac{d[A]}{dt} = -k_r[A][P]^2 + k_{-r}[AP_2][W]$
	$AP_2 + M \overset{k_5}{\rightarrow} C + 2P + E$	$\frac{d[P]}{dt} = -2k_r[A][P]^2 + 2k_{-r}[AP_2][W] + 2k_5[AP_2][M]$
		$\frac{d[W]}{dt} = k_r[A][P]^2 - k_{-r}[AP_2][W]$
		$\frac{d[M]}{dt} = -k_5[AP_2][M]$
		$\frac{d[C]}{dt} = \frac{d[E]}{dt} = k_5[AP_2][M]$
K-1D	$A + 2P \underset{k_{-r}}{\overset{k_r}{\leftrightarrow}} AP_2 + W$	$\frac{d[A]}{dt} = -k_r[A][P]^2 + k_{-r}[AP_2][W]$
	$AP_2 + M \overset{k_5}{\leftrightarrow} APM + P$	$\frac{d[P]}{dt} = -2k_r[A][P]^2 + 2k_{-r}[AP_2][W] + k_5[AP_2][M] + k_7[APM]$
	$APM \overset{k_7}{\rightarrow} C + P + E$	$\frac{d[AP_2]}{dt} = k_r[A][P]^2 - k_{-r}[AP_2][W] - k_5[AP_2][M]$
		$\frac{d[W]}{dt} = k_r[A][P]^2 - k_{-r}[AP_2][W]$
		$\frac{d[M]}{dt} = -k_5[AP_2][M]$
		$\frac{d[APM]}{dt} = k_5[AP_2][M] - k_7[APM]$
		$\frac{d[C]}{dt} = \frac{d[E]}{dt} = k_7[APM]$
K-1E	$A + 2P \underset{k_{-r}}{\overset{k_r}{\leftrightarrow}} AP_2 + W$	$\frac{d[A]}{dt} = -k_r[A][P]^2 + k_{-r}[AP_2][W]$
	$AP_2 + M \overset{k_5}{\rightarrow} APM + P$	$\frac{d[P]}{dt} = -2k_r[A][P]^2 + 2k_{-r}[AP_2][W] + k_5[AP_2][M] + k_7[APM]$
	$APM \overset{k_7}{\rightarrow} B + P$	$\frac{d[AP_2]}{dt} = k_r[A][P]^2 - k_{-r}[AP_2][W] - k_5[AP_2][M]$
	$B \overset{k_8}{\rightarrow} C + E$	$\frac{d[W]}{dt} = k_r[A][P]^2 - k_{-r}[AP_2][W]$
		$\frac{d[M]}{dt} = -k_5[AP_2][M]$
		$\frac{d[APM]}{dt} = k_5[AP_2][M] - k_7[APM]$
		$\frac{d[B]}{dt} = k_7[APM] - k_8[B]$
		$\frac{d[C]}{dt} = \frac{d[E]}{dt} = k_8[B]$

rate constants. The results of this approximation (Table V) are quite sufficient, especially in the case of K-1B model. Therefore, the K-1 model was evaluated.

Approximation C (K1C).

1. Hemiaminal formation (1) was omitted, and the reaction of aminal generation as one step was considered. As can be seen (Table VI), fitting of model K-1C is the best while considering the sum of squares values and relative errors of rate constants. Next, the comparison of the results from numerical calculations and the experimental data for different concentrations of salicylaldehyde (**A**) with diethylmalonate (**M**) are presented (see Supporting Information Figs. 2 and 3). It can be seen that the reaction catalyzed by piperidine is faster than 4-piperidinopiperidine because of higher value of the rate constant of the second step (k_2). Moreover, the equilibrium (Scheme 5) is established more rapidly for the piperidine-catalyzed reaction than in the case of 4-piperidinopiperidine but the values of K_r are similar. These effects could be explained as steric effects because piperidine molecules are smaller than 4-piperidinopiperidine and can react faster.

Table IV Results of Model Fitting: Approximation A

Kinetic Model		4-Piperidinopiperidine	Piperidine
K-1A	SSR	5×10^{-5}	2×10^{-5}
	SD	7.00×10^{-3}	5.00×10^{-3}
	k_1	$6.11 \times 10^{-4} \pm 110\%$	$1.39 \times 10^{-3} \pm 280\%$
	k_{-1}	$2.11 \times 10^{-2} \pm 1700\%$	$9.44 \cdot 10^{-3} \pm 940\%$
	k_2	$2.06 \times 10^{-1} \pm 1700\%$	$4.83 \times 10^{-2} \pm 670\%$
	k_{-2}	$9.17 \times 10^{-4} \pm 62\%$	$7.50 \times 10^{-4} \pm 67\%$
	k_5	$3.42 \times 10^{-4} \pm 16\%$	$4.72 \times 10^{-4} \pm 24\%$
K-2A	SSR		2.9×10^{-5}
	SD		5.00×10^{-3}
	k_1		$4.31 \times 10^{-3} \pm 430\%$
	k_{-1}		$3.89 \times 10^{-3} \pm 440\%$
	k_2	Not estimated	$5.31 \times 10^{-3} \pm 77\%$
	k_{-2}		$4.86 \times 10^{-2} \pm 950\%$
	k'_4		$1.74 \times 10^{-1} \pm 520\%$
	k'_{-4}		$3.94 \times 10^{-2} \pm 880\%$
	k_6		$3.61 \times 10^{-4} \pm 42\%$
K-3A	SSR	7.5×10^{-5}	5×10^{-5}
	SD	8.00×10^{-3}	7.00×10^{-3}
	k_1	$3.03 \times 10^{-4} \pm 360\%$	$2.58 \times 10^{-4} \pm 1100\%$
	k_{-1}	$2.97 \times 10^{-3} \pm 2500\%$	$9.06 \times 10^{-4} \pm 2500\%$
	k'_3	$2.22 \times 10^{-2} \pm 2900\%$	$4.47 \times 10^{-3} \pm 4600\%$
	k'_{-3}	$1.47 \times 10^{-3} \pm 2600\%$	$1.33 \times 10^{-3} \pm 5300\%$
	k_6	$1.36 \times 10^{-4} \pm 26\%$	$2.11 \times 10^{-4} \pm 44\%$

Table V Results of Model Fitting: Approximation B

Kinetic Model	Kinetic Model	4-Piperidinopiperidine	Piperidine
K-1B	SSR	7×10^{-5}	2×10^{-5}
	SD	8.00×10^{-3}	5.00×10^{-3}
	k_2	$4.61 \times 10^{-3} \pm 17\%$	$7.36 \times 10^{-3} \pm 16\%$
	k_{-2}	$1.00 \times 10^{-3} \pm 22\%$	$8.33 \times 10^{-4} \pm 18\%$
	k_5	$4.72 \times 10^{-4} \pm 14\%$	$5.28 \times 10^{-4} \pm 14\%$
K-2B	SSR	6×10^{-5}	3×10^{-5}
	SD	8.00×10^{-3}	5.00×10^{-3}
	k_2	$4.72 \times 10^{-3} \pm 26\%$	$5.50 \times 10^{-3} \pm 21\%$
	k_{-2}	$2.94 \times 10^{-2} \pm 1100\%$	$1.56 \times 10^{-2} \pm 610\%$
	k'_4	$2.03 \times 10^{-1} \pm 620\%$	$4.39 \times 10^{-2} \pm 450\%$
	k'_{-4}	$3.78 \times 10^{-2} \pm 950\%$	$3.00 \times 10^{-2} \pm 390\%$
	k_6	$2.11 \times 10^{-4} \pm 30\%$	$3.61 \times 10^{-4} \pm 40\%$
K-3B	SSR	8×10^{-5}	5×10^{-5}
	SD	9.00×10^{-3}	7.00×10^{-3}
	k'_3	$3.17 \times 10^{-4} \pm 17\%$	$2.33 \times 10^{-4} \pm 25\%$
	k'_{-3}	$2.17 \times 10^{-4} \pm 23\%$	$2.64 \times 10^{-4} \pm 27\%$
	k_6	$1.53 \times 10^{-4} \pm 13\%$	$2.31 \times 10^{-4} \pm 27\%$

The model K-1C was studied in more detail (models K-1D and K-1E). But taking into consideration more elementary steps gave poor results of the models fitting. Since there is no significant change of fitting quality comparing 4-piperidinopiperidine with piperidine-catalyzed reaction, it could be postulated that second N-atom (tertiary) of 4-piperidinopiperidine does not influence directly the reaction mechanism. This is in an agreement with the previous results presented in Table I, in which DABCO and Et_3N did not catalyze the reaction.

It was also interesting to analyze the kinetic results in the case of a significant excess of one of the substrates. When salicylaldehyde (**A**) was in excess (i.e.,

Table VI Results of Model Fitting: Approximations C, D, and E

Kinetic Model	Kinetic Model	4-Piperidinopiperidine	Piperidine
K-1C	SSR	5×10^{-5}	2×10^{-5}
	SD	7.00×10^{-3}	5.00×10^{-3}
	k_r	$3.58 \times 10^{-3} \pm 15\%$	$6.14 \times 10^{-3} \pm 16\%$
	k_{-r}	$6.28 \times 10^{-4} \pm 20\%$	$6.39 \times 10^{-4} \pm 18\%$
	k_5	$3.47 \times 10^{-4} \pm 7.9\%$	$4.44 \times 10^{-4} \pm 11\%$
K-1D	SSR	5×10^{-5}	2×10^{-5}
	SD	7.00×10^{-3}	4.00×10^{-3}
	k_r	$3.69 \times 10^{-3} \pm 36\%$	$9.14 \times 10^{-3} \pm 33\%$
	k_{-r}	$6.58 \times 10^{-4} \pm 65\%$	$1.86 \times 10^{-3} \pm 67\%$
	k_5	$3.50 \times 10^{-4} \pm 16\%$	$7.06 \times 10^{-4} \pm 31\%$
	k_7	$5.83 \times 10^{-3} \pm 2200\%$	$8.61 \times 10^{-5} \pm 52\%$
K-1E	SSR	4×10^{-5}	1×10^{-5}
	SD	6.00×10^{-3}	4.00×10^{-3}
	k_r	$4.14 \times 10^{-3} \pm 29\%$	$6.89 \times 10^{-3} \pm 16\%$
	k_{-r}	$2.55 \times 10^{-3} \pm 60\%$	$1.98 \times 10^{-3} \pm 36\%$
	k_5	$7.56 \times 10^{-4} \pm 25\%$	$8.50 \times 10^{-4} \pm 23\%$
	k_7	$7.89 \times 10^{-2} \pm 5700\%$	$2.78 \times 10^{-1} \pm 950\%$
	k_8	$4.17 \times 10^{-5} \pm 26\%$	$3.33 \times 10^{-5} \pm 22\%$

$[A]_0 \gg [M]_0$), the rate of malonate (**M**) consumption corresponded to the pseudo-first order kinetics: $-d[M]/dt = k_{obsM}[M]$.

This is in agreement with the proposed mechanism (K-1C). An excess of salicylaldehyde (**A**) shifts the equilibrium to the products side. It could be assumed that the amine catalyst forms the aminal, and free amine is not present; in other words, the first stage (i.e., aminal **AP2** formation) is irreversible. Since the concentration of the aldehyde (**A**) was approximately constant and the catalyst regenerated fast, a pseudo-first-order reaction with respect to malonate (**M**) was observed.

It should be stressed that the presence of a phenolic group with essential acidic properties in salicylaldehyde (**A**) and in all the intermediate compounds can influence the course of the condensation and the effect must be take into consideration. First, it shifts the equilibrium of the acid–base reaction to the product side; the basic catalyst is present in a protonated form. For that reason, carbanion generation from diethyl malonate is inhibited, and thus formation of β-hydroxy compound (Scheme 2) is depressed. It was already found that *p*-hydroxybenzaldehyde did not react with various compounds containing an active methylene group without a base catalyst, because of the acidity of the hydroxyl phenolic group [10a]. In addition, deamination of β-amino compound (i.e., **AP2**) (Scheme 3) can be accelerated in the presence of H^+ and both phenolic group and piperidinium ion can be its source [7].

In the case of an excess of malonate (**M**) (i.e., $[M]_0 \gg [A]_0$), the pseudo-zero-order reaction rate was observed with respect to aldehyde (**A**) (see Supporting Information Fig. 4): $-d[A]/dt = k_{obsA}$. It means that under such conditions there is another rate-limiting step, and salicylaldehyde takes part neither in this step nor in the earlier steps. It could suggest that in the excess of active methylene compound the Hann–Lapworth mechanism is preferred, but on the basis of additional experiments under such conditions with Et_3N, which has a similar basicity as piperidine, we did not observe the condensation reaction. The phenomenon could be justified taking into consideration formation of stable enolate—piperidinium complex, as the first step of the reaction. The decomposition of the complex may be slower than the next steps and thus determine the overall condensation rate.

CONCLUSIONS

The condensation reaction of salicylaldehyde and diethylmalonate in the presence of piperidine or 4-piperidinopiperidine in a toluene solution proceeds via the Knoevenagel mechanism. Taking into consideration the complexity of the investigated reaction, while based only on kinetic modeling and catalytic tests, it is hard to predict details of the Knoevenagel mechanism, i.e., which reaction paths are preferred: via aminal (which is most probable), iminium ion, or both. In excess of one of the substrates, additional processes might carry out that may strongly influence the reaction or even may change the reaction mechanism.

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