

Synergistic Effect in the Catalysis by Pyridine *N*-Oxide–Triethylamine Mixture of Acyl Transfer Processes with Participation of Benzoyl, Diethoxyphosphinoyl, and *p*-Toluenesulfonyl Chlorides

I. A. Belousova, V. A. Savelova, Yu. S. Simanenko, and B. V. Panchenko

Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine, ul. R. Luxemburg 70, Donetsk, 83114 Ukraine
e-mail: savelova@infou.donetsk.ua

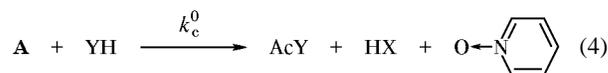
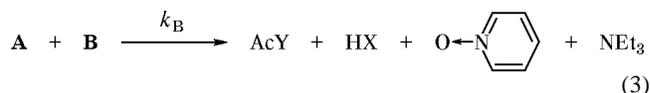
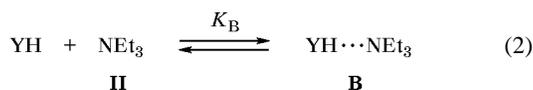
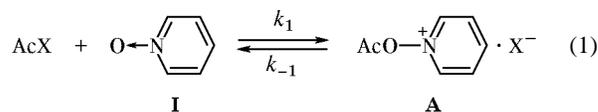
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Abstract—The kinetics of benzylation of substituted phenols with benzoyl chloride in the presence of pyridine *N*-oxide–triethylamine was analyzed with regard to previously reported data on benzylation, phosphorylation, and sulfonylation of phenols and carboxylic acids. A common mechanism of the synergistic effect was established. The synergistic effect decreases in the series $\text{PhCOCl} \gg (\text{EtO})_2\text{POCl} > \text{TsCl}$.

The synergistic effect of a pyridine *N*-oxide–triethylamine mixture in the catalytic acyl transfer processes was studied by us in [1–6]. We examined in detail the kinetic features of phosphorylation [5] and sulfonylation [6] of substituted phenols (4-nitrosophenol, 4-nitrophenol, 2,4-, 2,5-, and 2,6-dinitrophenols, and 2,4,6-trinitrophenol) and 2-(4-dimethylaminophenylazo)benzoic acid (RCOOH) with diethyl chlorophosphate $(\text{EtO})_2\text{POCl}$ and *p*-toluenesulfonyl chloride (TsCl), respectively. Available published data for related reactions with benzoyl chloride as a representative of carboxylic acid derivatives include only the reaction with 4-phenylazophenol [2] and 2-(4-dimethylaminophenylazo)benzoic acid [3]. Therefore, it is difficult to compare with a sufficient reliability synergistic effects in reactions of various compounds, namely carboxylic, phosphoric, and sulfonic acid derivatives. In the present work we studied the kinetics of acylation of 4-nitro- and 4-nitrosophenols with benzoyl chloride in the presence of pyridine *N*-oxide (**I**)–triethylamine (**II**) as catalytic system in dioxane at 25°C. The rates of benzylation of more acidic dinitrophenols and trinitrophenol were too high to include these compounds into the set of substrates for the present study.

A combination of nucleophilic and general base catalysis was proposed previously [2–6] to rationalize synergistic effect in systems containing pyridine *N*-oxide and triethylamine [reactions (1)–(3)]. Here,

A and **B** are intermediates formed by nucleophilic activation of the acylating agent AcX and general base activation of the nucleophile YH; $K_{\text{eq}} = k_1/k_{-1}$ and K_{B} are the equilibrium constants for formation of intermediates **A** and **B**; k_{B} is the rate constant of the reaction of **A** with **B**, leading to final products and regenerating the catalyst.



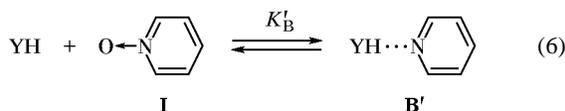
The synergistic effect produced by a mixture of bases **I** and **II** is reflected in the fact that the rate of reaction (3) is considerably higher than the overall rate of the reactions of complex **A** with nucleophilic

reagent YH [nucleophilic catalysis, reaction (4)] and of complex **B** with substrate AcX [general base catalysis, reaction (5)] under the same conditions. The scheme including reactions (1)–(3) was kinetically proved by experimentally observed change of the rate-determining stage depending on the phenol acidity and concentration [5, 6]. This is typical of both phosphorylation [5] and sulfonation processes [6]. For phenols with $pK_a(\text{H}_2\text{O}) > 5$ the rate-determining stage is reaction (3), whereas for more acidic phenols with $pK_a(\text{H}_2\text{O}) < 5$ the rate-determining stage is activation of the substrate, characterized by the rate constant k_1 . As the reaction progresses (and the phenol concentration decreases), the rate-determining stage changes from reaction (1) (k_1) to reaction (3) (k_B).

We also found previously that the kinetics of benzylation of 4-phenylazophenol [$pK_a(\text{H}_2\text{O})$ 8.20] and 2-(4-dimethylaminophenylazo)benzoic acid [$pK_a(\text{H}_2\text{O})$ 5.22] in the presence of catalyst mixture **I/II** conform to the above scheme; i.e., these processes are described by reactions (1)–(3), the latter being the rate-determining stage. Therefore, the kinetics of benzylation of 4-nitrosophenol [$pK_a(\text{H}_2\text{O})$ 6.48] and 4-nitrophenol [$pK_a(\text{H}_2\text{O})$ 7.15] were analyzed in terms of the same scheme.

The reaction rate was measured following the disappearance of phenols by UV spectroscopy at λ 335 (4-nitrosophenol) and 342 nm (4-nitrophenol). The initial reactant concentration ratio was $[\text{YH}]_0 \ll [\text{AcX}]_0 \approx [\text{I}]_0 + [\text{II}]_0$. The apparent pseudofirst-order rate constants k_{ap} (s^{-1}) did not change during the reaction. Their averaged values at $[\text{AcX}]_0 = 0.35\text{--}5.15$, $[\text{I}]_0 = 0.33\text{--}2.94$, and $[\text{II}]_0 = 0.32\text{--}2.87$ M are collected in a summary table which is available from the authors.

In order to calculate the equilibrium concentrations of complexes **A** and **B** it was necessary to know the constants of equilibria (1), (2), and (6).



Indirect estimation of the constant K_{eq} for formation of complex **A** from benzoyl chloride and pyridine *N*-oxide gives a value less than 1 mol/l [2]. Then, at $[\text{AcX}]_0 = 0.35\text{--}5.15$ and $[\text{I}]_0 = 0.33\text{--}2.94$ mM, the equilibrium concentration of intermediate **A** can be calculated by the formula

$$[\text{A}] = K_{\text{eq}} [\text{AcX}]_0 [\text{I}]_0. \quad (7)$$

The equilibrium concentration of complex **B** was calculated by Eq. (8) [5, 6]:

$$[\text{B}] = \frac{K_B [\text{II}]_0 [\text{YH}]_0}{1 + K_B [\text{II}]_0 + K_B [\text{I}]_0} = \alpha_{\text{II}} [\text{YH}]_0, \quad (8)$$

where α_{II} is the fraction of phenol bound into complex **B**:

$$\alpha_{\text{II}} = \frac{K_B [\text{II}]_0}{1 + K_B [\text{II}]_0 + K_B [\text{I}]_0}. \quad (9)$$

The equilibrium constants K_B for 4-nitrosophenol [5] and 4-nitrophenol [6] in dioxane were measured previously by UV spectroscopy; the K_B value for 4-nitrosophenol was also measured in the present work by the same method (see table). The α_{II} values calculated therefrom range from 0.002 to 0.009. Taking into account that the fraction of phenol bound into complex **B** (at given $[\text{I}]_0$ and $[\text{II}]_0$) is very small ($\leq 1\%$), the equilibrium concentration $[\text{B}]$ could be calculated by simplified formula (10), as it was done in [2, 3] for 4-phenylazophenol and 2-(4-dimethylaminophenylazo)benzoic acid:

$$[\text{B}] = K_B [\text{II}]_0 [\text{YH}]_0. \quad (10)$$

Insofar as treatment of the kinetic data by Eqs. (8) and (10) gives the same results, we used Eq. (8) as more accurate.

In keeping with the scheme including reactions (1)–(3), the latter being the rate-determining stage, and taking into account Eqs. (7)–(9), the gain in the apparent rate constant Δk_{ap} is expressed by the following equation [5, 6]:

$$\begin{aligned} \Delta k_{\text{ap}} &= K_{\text{eq}} k_B \alpha_{\text{II}} [\text{AcX}]_0 [\text{I}]_0 \\ &= k_B'' \alpha_{\text{II}} [\text{AcX}]_0 [\text{I}]_0, \end{aligned} \quad (11)$$

where $k_B'' = K_{\text{eq}} k_B$ and $\Delta k_{\text{ap}} = k_{\text{ap}} - k_{\text{ap}}^{\text{II}}$ (here, $k_{\text{ap}}^{\text{II}}$ is the apparent pseudofirst-order rate constant in the presence of triethylamine alone). At the given reactant concentrations, the value of $k_{\text{ap}}^{\text{II}}$ which reflects the contribution of reaction (5) to k_{ap} was calculated using the data of [7]. However, this contribution is insignificant: it does not exceed 2%. The contribution of reaction (4) was not taken into account at all while calculating Δk_{ap} ; in keeping with the data of [2], it is much smaller than the contribution of reaction (5). Thus reaction (3) appears to be the only path leading

Kinetic parameters for acylation of phenols and 2-(4-dimethylaminophenylazo)benzoic acid with benzoyl chloride, diethyl chlorophosphate, and *p*-toluenesulfonyl chloride in dioxane at 25°C; $k_B'' = K_{eq} k_B$, $\eta = K_{eq} k_B / (K_B k_B^0)$

R in RC ₆ H ₄ OH	K_B , 1 mol ⁻¹	K_B' , 1 mol ⁻¹	PhCOCl			(EtO) ₂ P(O)Cl			<i>p</i> -MeC ₆ H ₄ SO ₂ Cl		
			$k_B'' \times 10^{-6}$, l ² mol ⁻² s ⁻¹	k_B^0 ^a [7]	η	k_B'' , l ² × mol ⁻² s ⁻¹	k_B^0 ^a [5]	η	k_B'' , l ² × mol ⁻² s ⁻¹	k_B^0 ^a [8]	η
4-NO	10.0 ± 0.13 [5]	7.28 ± 0.26	4.43 ± 0.29	22.9	1.5 × 10 ⁴	347 ± 14	0.149	2.3 × 10 ²	–	–	–
4-NO ₂	3.17 ± 0.9 [5]	6.08 ± 0.83 [6]	3.73 ± 0.42	1.5	7.8 × 10 ⁵	224 ± 17	0.0652	1.1 × 10 ³	40.2 ± 5.7	0.0723	1.8 × 10 ²
4-PhN=N	1.3 ± 0.5 [2]	4.42 ± 0.07 [2]	0.031 ± 0.0030 [2]	5.79	4.1 × 10 ³	–	–	–	–	–	–
RCOOH ^b	6.9 ± 1.5 [3]	0.90 ± 0.05 [3]	0.37 ± 0.02 [3]	1.92	2.8 × 10 ⁴	290 ± 12	0.101	4.2 × 10 ²	42.6 ± 6.8	0.0763	8.1 × 10 ¹

^a 1 mol⁻¹ s⁻¹.

^b RCOOH is 2-(4-dimethylaminophenylazo)benzoic acid.

to the final products. This suggests a strong synergistic effect of catalysts **I** and **II** in the benzylation of phenols.

As follows from the summary table, the k_B'' value calculated by Eq. (11) remains constants in experiments with various concentrations [AcX]₀, [**I**]₀, and [**II**]₀ or [**I**]₀ + [**II**]₀ (30 runs for 4-nitrophenol and 22 runs for 4-nitrosophenol). This is in full agreement with the proposed mechanism of synergistic effect for phenols with $pK_a(H_2O) > 5$, indicating that the reactions with PhCOCl, (EtO)₂POCl, and TsCl follow the same mechanism [scheme (1)–(3)] where reaction (3) is the rate-determining stage. The averaged k_B'' values for benzylation of 4-nitrophenol and 4-nitrosophenol are given in table together with the data reported previously for acylation of phenols and 2-(4-dimethylaminophenylazo)benzoic acid with benzoyl chloride [2, 3], diethyl chlorophosphate [5], and *p*-toluenesulfonyl chloride [6].

To estimate the synergistic effect η in systems where intermediates **A** and **B** do not accumulate in appreciable amounts and the rate-determining stages are reactions (3)–(5), it is reasonable to use Eq. (12):

$$\eta = \frac{K_{eq} k_B}{K_B k_B^0 + K_{eq} k_c^0} \quad (12)$$

Here, $K_{eq} k_B$, $K_B k_B^0$, and $K_{eq} k_c^0$ are the apparent rate constants corresponding to a combination of nucleophilic and general base catalysis, general base catalysis, and nucleophilic catalysis, respectively.

Insofar as in all the examined systems the contribution of nucleophilic catalysis is negligible [2, 3, 5, 6],

the $K_{eq} k_c^0$ in the denominator can be neglected. Table gives the synergistic effects η defined as the ratio $K_{eq} k_B / (K_B k_B^0)$. It is seen that η strongly depends on the nature of the acylating agent. The greatest catalytic effect of mixture **I/II** is observed for benzoyl chloride. The corresponding effects for diethyl chlorophosphate and *p*-toluenesulfonyl chloride are lower by about 2 and 3 orders of magnitude, respectively. While analyzing these results, one should keep in mind that K_B does not depend on the acylating agent. Furthermore, the ratio k_B/k_B^0 which characterizes the reactivity difference between the activated (**A**) and nonactivated (**AcX**) acylating agent also should not depend strongly on its nature. Moreover, we could expect *a priori* that the above ratio should increase in going from PhCOCl to (EtO)₂POCl and then to TsCl (in keeping with the reactivity–selectivity principle) rather than decrease as does the quantity η . Hence the different synergistic effects in the acylation of phenols and carboxylic acid with PhCOCl, (EtO)₂POCl, and TsCl should be treated in terms of the difference in the equilibrium constants K_{eq} . For example, the ratio of K_{eq} in the formation of *N*-benzyloxy- and *N*-(*p*-tolylsulfonyl)-4-dimethylaminopyridinium chloride (CH₂Cl₂, 25°C) [9, 10] is about two orders of magnitude.

EXPERIMENTAL

Spectrophotometric measurements were performed on a Specord UV-Vis instrument. The progress of reactions was monitored following the disappearance of nucleophile. The apparent pseudofirst-order rate constants k_{ap} were calculated by standard procedure

[11]. Linear dependences were processed by the least-squares procedure.

Dioxane [12], pyridine *N*-oxide [13], and triethylamine [14] were purified by known methods. Benzoyl chloride was repeatedly distilled under reduced pressure. *p*-Toluenesulfonyl chloride was twice recrystallized from petroleum ether, mp 70–71°C [15]. Phenols were purified as described in [5]; their melting points coincided with those given in [15].

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