

Reaction of Acetyl and Benzoyl Chlorides with Pyridines and Pyridine *N*-Oxides

V. I. Rybachenko¹, G. Schroeder², K. Yu. Chotii¹, B. Lenska², and A. N. Red'ko¹

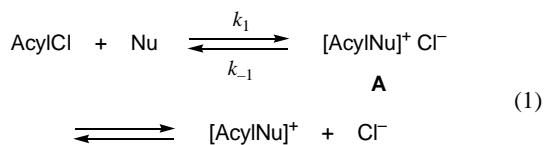
¹ Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine, ul. R. Lyuksemburg 70, Donetsk, 83114 Ukraine
fax: (0622)558524; e-mail: rybach@stels.net

² Faculty of Chemistry, Adam Mickiewicz University, Poland

Received June 12, 2003

Abstract—The rate of formation of *N*- and *O*-acetyl and benzoyl salts of pyridines and pyridine *N*-oxides in acetonitrile and methylene chloride and equilibria therein were studied. The process occurs in one step following the S_N2 mechanism with a small degree of bond rupture in the transition state.

Acylation reactions with carboxylic acid chlorides are known to be catalyzed by organic nucleophiles, such as azines (in particular, pyridines) and azine *N*-oxides [1, 2]. Homogeneous nucleophilic catalysis of acyl transfer involves formation of a labile acyloanium salt **A** by the reaction of substrate with catalyst [reaction (1)] [3, 4].



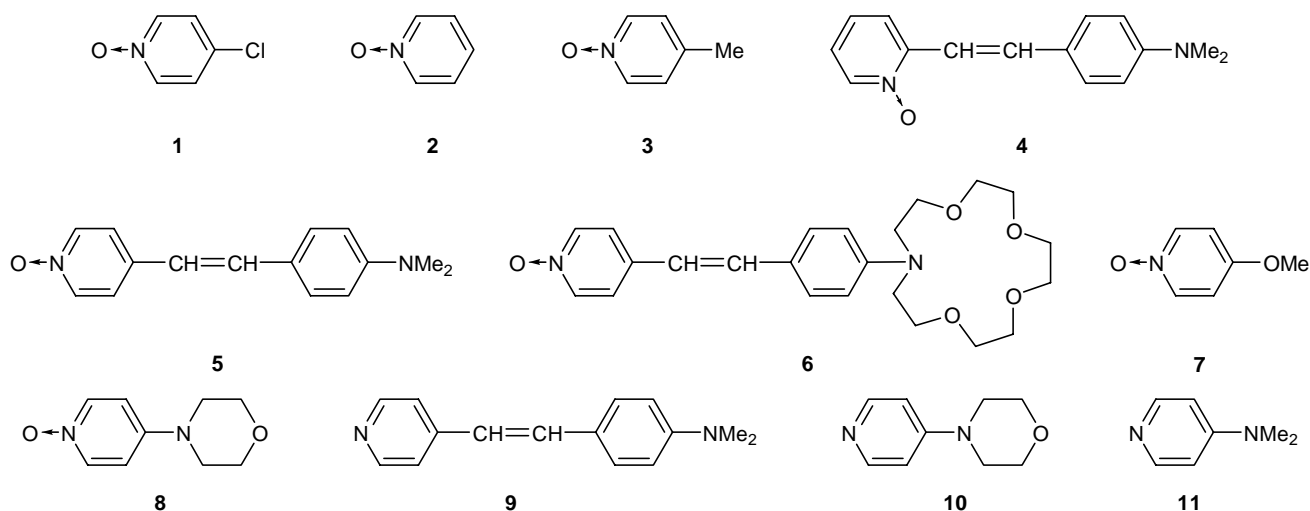
From the viewpoint of basicity [5, 6] it is believed that oxygen-nucleophilic catalysis in aprotic media is more efficient than catalysis by nitrogenous nucleophiles. This is clearly seen with pyridine *N*-oxides and pyridines as examples [7]. However, the reasons for high nucleophilicity of oxygen-containing bases still are not understood. The problem of predicting the reactivity of pyridines and pyridine *N*-oxides remains unsolved as well. These issues require knowledge of the mechanism of reaction (1) and systematic data on its kinetic and thermodynamic parameters. On the other hand, there are no quantitative data on the reactivity of the above nucleophiles even with respect to acetyl chloride. For reactions with benzoyl chloride, the rate constants k_1 were determined by the kinetic study of its catalytic hydrolysis [7] in aqueous acetonitrile, and the rates of reaction (1) with a limited series of nucleophiles in acetonitrile were directly measured [8–10].

We previously determined the equilibrium constants and heats of some reactions of acetyl and benzoyl chlorides with pyridines and pyridine *N*-oxides [11–13]. In the present work we studied the reactivity of these nucleophiles toward acetyl and benzoyl chlorides in aprotic media. The structures of the examined nucleophiles of the pyridine and pyridine *N*-oxide series are shown below.

In all cases, the apparent rates of reactions (1) conform to the second-order kinetics. The rates were measured in acetonitrile using the stopped flow technique under pseudofirst-order conditions, i.e., when $c_{\text{Acy}l\text{Cl}}/c_{\text{Nu}} > 10$. In the kinetic experiments, the nucleophile concentration (and hence the concentration of salt **A**) did not exceed 3×10^{-4} M. The second-order rate constants k_1 for the forward reaction were calculated by the least-squares procedure from the dependence of k_{ap} versus 3–6 analytical concentrations of the acyl chloride.

$$k_{\text{ap}} = k_{-1} + k_1[\text{Acy}l\text{X}]. \quad (2)$$

The plots corresponding to Eq. (2) were linear, and neither signs of hydrolysis nor ion association effects were observed. The thermodynamic parameters of the transition state were calculated from k_1 values at three temperatures in the range from 288 to 308 K. Table 1 contains the obtained rate constants and ΔH^\ddagger and $-\Delta S^\ddagger$ values at 298 K. In addition, the free terms in Eq. (2) (k_{-1} , s⁻¹) are given; these values are frequently used to characterize the backward reaction (see, e.g., [11, 12]).



The equilibrium constants K for BzCl-Nu_{10} , BzCl-Nu_{11} , and AcCl-Nu_{10} were determined in methylene chloride by IR spectroscopy. As analytical frequencies we used those belonging to carbonyl stretching vibrations of acetyl chloride ($\nu_{\text{C=O}}$ 1803 cm^{-1} , $\epsilon = 440 \text{ l} \times \text{mol}^{-1} \text{ cm}^{-1}$) and benzoyl chloride ($\nu_{\text{C=O}}$ 1775 cm^{-1} , $\epsilon = 410 \text{ l} \times \text{mol}^{-1} \text{ cm}^{-1}$). The equilibrium constant for BzCl-Nu_9 was determined in methylene chloride from the reactant concentrations measured by UV spectroscopy [λ_{max} 375 nm (Nu_9), λ_{max} 626 nm (**A**)]. The other thermodynamic parameters of reaction (1), given in Table 1, were obtained by us previously. Also, the known kinetic data and $\text{p}K_{\text{BH}^+}$ values for pyridine *N*-oxides and pyridines in water at 298 K are presented. Table 2 contains the results of statistical processing of the experimental data.

The benzylation rate constants, determined in the present work, are considerably higher than those given in [7] for aqueous acetonitrile. Obviously, this is explained by hydration effects; therefore, these data were not taken into account in further correlations. The data of [8–10], which were obtained in anhydrous acetonitrile, specifically for BzCl-Nu_5 (Table 1), agree with our results within experimental error.

As follows from the data in Table 1, depending on structural factors, the rate constants k_1 for the forward reaction vary over a range of about 4 orders of magnitude. UV monitoring of the reaction between AcCl and Nu_5 shows that the acylation is accompanied by *cis-trans* isomerization of the cation in salt **A**, which occurs at a comparable rate [15]. This process complicates treatment of the kinetic data. Therefore, the lower limit of k_1 is given in Table 1. In the other reactions with styryl-containing nucleophiles, the photochemical transformation is slower than nucleo-

philic substitution, so that the kinetic dependences can be separated. The acetylation is faster than benzylation by a factor of 2–3, other conditions being equal. The examined reactions give rise to isokinetic relationship (no. 1 in Table 2), which may be regarded as an evidence in favor of a common mechanism of these reactions [16]. The rate constants for the backward reaction (k_{-1}) are appreciably smaller than k_1 , indicating displacement of equilibrium (1) toward the products. However, most experimental k_{-1} values were determined with large errors. Moreover, their variation shows no regular relation. Presumably, the main reason is that salts **A** in acetonitrile solution dissociate into ions [4]: the electrolytic dissociation constants of chloride salts **A** in acetonitrile range from 0.02 to 0.005 mol/l [17, 18]. As a result, k_{-1} depends on the concentration of **A** provided that the dissociation is incomplete [6]. Otherwise (i.e., when the dissociation of **A** is complete), k_{-1} values determined from Eq. (2) make no physical sense as rate constants [19], and hence they cannot be used for determination of the equilibrium constant.

In order to eliminate electrolytic dissociation stage, thermodynamic parameters of reaction (1) should be determined in a less polar medium, e.g., in methylene chloride. According to our previous data [13], the solvent nature has no appreciable effect on the heat of reaction leading to formation of salts **A**. In addition, it is seen from Table 1 that the values of K (l/mol) determined in acetonitrile and methylene chloride are of the same order of magnitude [11]. It is also seen that the state of equilibrium (1) in CH_2Cl_2 varies over a range of more than 6 orders of magnitude, depending on structural factors. The acylation equilibrium is displaced toward the products to a greater extent than

Table 1. Kinetic and thermodynamic parameters of reaction (1) in acetonitrile at 298 K

No.	Acyl	Nu	$k_1, \text{l mol}^{-1} \text{s}^{-1}$	$\Delta H^\ddagger, \text{kJ/mol}$	$-\Delta S^\ddagger, \text{J mol}^{-1} \text{K}^{-1}$	k_{-1}, s^{-1}	$K, \text{l/mol}$	$-\Delta H, \text{kJ/mol}$	$\text{p}K_{\text{BH}^+}$
1	Bz	1	1850	66	-40	—	0.9 ^{a,b}	33.2 ^{a,b}	0.33
2	Bz	2	630 (705) ^c	46	25	0.022	2.8 ^{a,b}	41.2 ^{a,b}	0.79
3	Bz	3	7080	22	97	—	37.2 ^{a,b}	49.8 ^{a,b}	1.29
4	Bz	4	960	16	135	—	—	—	—
5	Bz	5	8860 (6000) ^d	—	—	1.5 (0.012) ^d	—	—	1.43
6	Bz	6	3850	20	109	0.8	—	—	—
7	Bz	7	30 000	—	—	—	1200 ^{a,b}	—	2.05
8	Bz	8	~300 000	—	—	—	—	—	3.25
9	Bz	9	1400 ^e	—	—	0.008 ^e	2.0 ^a	—	6.42
10	Bz	10	11 660 (1700) ^c	12	129	0.4	10 000 ^a	—	8.63
11	Bz	11	33 000 (2700) ^c	—	—	—	150 000 ^a	—	9.7
12	Ac	1	3170	42.7	34.6	11.8	5.8 ^{a,f}	50.3 ^{a,f}	0.33
13	Ac	2	9400	34.1	54.5	7.0	25.0 ^{a,f} 45.2 ^f	60.2 ^{a,f}	0.79
14	Ac	3	51 750	15.3	106	11.4	173 ^{a,f}	78.4 ^{a,f}	1.29
15	Ac	5	>3000	—	—	—	—	66 ^g	1.43
16	Ac	7	240 000	—	—	60	4550 ^{a,f}	—	2.05
17	Ac	8	~900 000	—	—	—	—	—	3.25
18	Ac	10	55 400	7.7	129	4.0	~10 ^{5a}	—	8.63
19	Ac	11	103 400	19.6	86	30	—	125 ^h	9.7

^a Methylene chloride..^b Data of [12].^c In acetonitrile containing 0.4 mol/l of water; data of [7].^d Data of [8].^e Data of [10].^f Data of [11].^g In chloroform; data of [27].^h Data of [13].

benzoylation with structurally related substrates. The benzoylation process is also characterized by a smaller heat effect. We can state (no. 2 in Table 2) that the enthalpies of activation for reaction (1) change in the opposite direction to the reaction heats. In the case of Hammett reaction series (nos. 3 and 4 in Table 2), these quantities give rise to good linear correlations.

The activation parameters of reaction (1) are typical of spontaneous (noncatalytic) bimolecular nucleophilic substitution processes [1, 20]. Here, it should be noted that nucleophilic substitution reactions involving formation of stable tetrahedral intermediates are characterized by negative enthalpies of activation [21]. Therefore, our ΔH^\ddagger values suggest a concerted [22] rather than stepwise mechanism of the reaction under study. The values of ΔH^\ddagger (~10–60 kJ/mol) and ΔS^\ddagger

(~20–120 J mol⁻¹ K⁻¹) indicate formation of an associative transition state where the degree of dissociation of the bond with the leaving group is not large.

It is known that one-step nucleophilic substitution reactions are largely controlled by the thermodynamic factor [20, 23]. When parameters characterizing equilibrium are lacking (which is usually the case in practice) [5, 7–10], quantitative treatment of the kinetic data utilizes the basicity as a correlation parameter for nucleophilic reactions [2, 6]. Correlations 5, 6, and 8 in Table 2 show that the rate of acylation of pyridines and pyridine *N*-oxides is linear in the nucleophile basicity. Here, the acetylation reaction is more sensitive to structural variations than benzoylation (by a factor of ~2). However, no satisfactory general $\log k - \text{p}K_{\text{BH}^+}$ correlation can be drawn for pyridines

Table 2. Correlation equations for the reactions of pyridines and pyridine *N*-oxides with acetyl and benzoyl chlorides

No.	Reactants ^a	Correlation			
		equation	<i>r</i>	<i>S</i> ₀	<i>n</i> (Nu)
1	AcCl + Nu	$\Delta H^\ddagger = 52.6(\pm 1.9) - 0.32(\pm 0.02) - \Delta S^\ddagger$	0.982	3.47	11
2	AcCl + Nu	$\Delta H^\ddagger = 60(\pm 13) - 0.41(\pm 0.18) - \Delta H$	0.70	14.0	7
3	BzCl + Py → O	$\Delta H^\ddagger = 154.5(\pm 3.5) - 2.65(\pm 0.08) - \Delta H$	0.999	0.984	3 (1–3)
4	AcCl + Py → O	$\Delta H^\ddagger = 92.5(\pm 2.7) - 0.98(\pm 0.07) - \Delta H$	0.999	0.848	3 (1–3)
5	BzCl + Py → O	$\log k_1 = 3.00(\pm 0.09) + 0.64(\pm 0.08)pK^{Nu}$	0.982	0.077	4 (1–3, 5)
6	BzCl + Py	$\log k_1 = 0.46(\pm 0.02) + 0.42(\pm 0.01)pK^{Nu}$	0.999	0.009	3 (9–11)
7	BzCl + Nu	$\log k_1 = 3.48(\pm 0.25) + 0.07(\pm 0.05)pK^{Nu}$	0.5	0.5	7 (1–3, 5, 9–11)
8	AcCl + Py → O	$\log k_1 = 3.15(\pm 0.11) + 1.12(\pm 0.08)pK^{Nu}$	0.995	0.106	4 (1–3, 7)
9	AcCl + Nu	$\log k_1 = 4.24(\pm 0.39) + 0.08(\pm 0.07)pK^{Nu}$	0.5	0.7	6 (1–3, 7, 10, 11)
10	BzCl + Py	$\log k_1 = 3.05(\pm 0.10) + 0.27(\pm 0.03)\log K$	0.996	0.086	3 (9–11)
11	BzCl + Py → O	$\log k_1 = 3.28(\pm 0.02) + 0.36(\pm 0.02)\log K$	0.999	0.023	3 (1–3)
12	BzCl + Nu	$\log k_1 = 3.27(\pm 0.09) + 0.32(\pm 0.03)\log K$	0.962	0.161	6 (1–3, 9–11)
13	AcCl + Py → O	$\log k_1 = 3.07(\pm 0.16) + 0.65(\pm 0.07)\log K$	0.989	0.145	4 (1–3, 7)
14	AsCl + Nu	$\log k_1 = 3.40(\pm 0.22) + 0.29(\pm 0.07)\log K$	0.80	0.45	11

^a Py stands for substituted pyridines, and Py → O, for substituted pyridine *N*-oxides.

and pyridine *N*-oxides (nos. 7 and 9 in Table 2). This means that the basicity cannot be used as a parameter characterizing reactivity of nucleophiles belonging to different series.

The situation becomes much better in going to correlations based on the Brønsted equation. Thus, the reaction series including acylation of pyridine *N*-oxides or pyridines (nos. 10, 11, and 13 in Table 2) show excellent linear correlations, and the series of benzylation of both these is characterized by a good correlation (no. 12). However, the most important is that all the available data exhibit a quite definite tendency, namely symbate variation of the rate and equilibrium constants for reaction (1) (no. 14). Undoubtedly, the equilibrium constant is a better parameter for predicting the reactivity than the basicity constant. The observed impairment of the correlation $\log k - \log K$ on variation of the structure of both reactants involved in reaction (1) is likely to result from the fact that the free term in the Brønsted equation is not a constant [24]. In keeping with the latest concepts [24, 25], this parameter is nothing else than the internal reaction barrier which can be determined from parameters of the corresponding identical reactions [20, 25]. As we showed previously, the rate constants of identical reactions of salts **A** with pyridine *N*-oxides and pyridines differ considerably [26, 27]. Analogous results were obtained by quantum-chemical calculations of identical reactions between acyl chlorides and

halide ions [28, 29]. The above stated leads us to believe that prediction of the reactivity may be improved further via introduction of the internal barrier into correlation no. 14 (Table 2). However, in this case, the reaction series should be extended considerably to obtain statistically significant results.

To conclude, it should be emphasized that our results allow us to understand better such widely used terms as “supernucleophilicity” and “oxygen-nucleophilic catalysis” [1, 2, 6–10, 30] while interpreting homogeneous catalytic effects in the acyl transfer processes. In fact, the reactivity of both nitrogen bases having no hydrogen on the basic center and oxygen bases with respect to acyl halides depends on the state of the reaction equilibrium.

EXPERIMENTAL

The IR spectra were recorded on a Perkin–Elmer Spectrum BX spectrometer (resolution 4 cm⁻¹, Beer–Norton apodization). The rate constants of fast reactions were determined by the stopped flow technique using an Applied Photophysics setup equipped with a temperature-controlling unit (±0.1 K). The electron absorption spectra were recorded on a Specord-200 spectrophotometer; the optical densities were measured in cells maintained at 298 ± 0.1 K. Concentration quantities were used in the calculation of all constants. The equilibrium constant were determined

with an accuracy of no less than $\pm 5\%$, and the rate constants were measured with an accuracy of $\pm(3-7)\%$.

Chemically pure acetyl chloride and benzoyl chloride were distilled twice under reduced pressure in a stream of argon. Pyridines and pyridine *N*-oxides were recrystallized prior to use as described in [15, 27]. Acetonitrile and methylene chloride (from Aldrich) were preliminarily kept over 3-Å molecular sieves.

The authors are grateful to the Mianowski Fund for Support of Science (Poland) for financial help.

REFERENCES

- Jencks, W.P., *Catalysis in Chemistry and Enzymology*, New York: Dower, 1987.
- Litvinenko, L.M. and Oleinik, N.M., *Mekhanizmy deistviya organicheskikh katalizatorov: Osnovnyi i nukleofil'nyi kataliz* (Mechanisms of Action of Organic Catalysts: Base and Nucleophilic Catalysis), Kiev: Naukova Dumka, 1984, p. 263.
- Fersht, A.R. and Jencks, W.P., *J. Am. Chem. Soc.*, 1969, vol. 91, p. 2125.
- Titov, E.V., Chotii, K.Yu., and Rybachenko, V.I., *Zh. Obshch. Khim.*, 1981, vol. 51, p. 682.
- Savelova, V.A., Belousova, I.A., Litvinenko, L.M., and Yakovets, A.A., *Dokl. Akad. Nauk SSSR*, 1984, vol. 274, p. 1393.
- Savelova, V.A. and Oleinik, N.M., *Mekhanizmy deistviya organicheskikh katalizatorov* (Mechanisms of Action of Organic Catalysts), Kiev: Naukova Dumka, 1990, p. 296.
- Savelova, V.A., Popov, A.F., Solomoichenko, T.N., Sadovskii, Yu.S., Piskunova, Zh.P., and Lobanova, O.V., *Russ. J. Org. Chem.*, 2000, vol. 36, p. 1465.
- Titskii, G.D. and Turovskaya, M.K., *Ukr. Khim. Zh.*, 1993, vol. 59, p. 423.
- Titskii, G.D., Turovskaya, M.K., and Yakovets, A.A., *Mendeleev Commun.*, 1995, no. 4, p. 161.
- Titskii, G.D., Turovskaya, M.K., and Korzhenevskaya, N.G., *Ukr. Khim. Zh.*, 1996, vol. 62, p. 58.
- Rybachenko, V.I., Chotii, K.Yu., Kozhevina, L.I., and Titov, E.V., *Zh. Fiz. Khim.*, 1984, vol. 58, p. 1341.
- Chotii, K.Yu., Rybachenko, V.I., and Titov, E.V., *Zh. Obshch. Khim.*, 1987, vol. 57, p. 1612.
- Semenova, R.G., Gol'dshtein, I.P., Grebenyuk, L.V., Makarova, R.A., and Rybachenko, V.I., *Zh. Fiz. Khim.*, 1997, vol. 71, p. 235.
- Reimers, J.R. and Hall, L.E., *J. Am. Chem. Soc.*, 1999, vol. 121, p. 3730.
- Schroeder, G., Leska, B., Gierczyk, B., and Rybachenko, V.I., *Pol. J. Chem.*, 2001, vol. 75, p. 1947.
- Linert, W. and Jameson, R.F., *Chem. Soc. Rev.*, 1989, vol. 18, p. 477.
- Titov, E.V., Makarova, R.A., Rybachenko, V.I., Chotii, K.Yu., and Goncharova, L.D., *Teor. Eksp. Khim.*, 1988, vol. 24, p. 227.
- Titov, E.V., Rybachenko, V.I., Goncharova, L.D., and Semenova, R.G., *Zh. Fiz. Khim.*, 1980, vol. 54, p. 3099.
- Shmid, R. and Sapunov, V.N., *Neformal'naya kinetika* (Informal Kinetics), Moscow: Mir, 1985, p. 263.
- Trushkov, I.V., Chuvylkin, N.D., Koz'min, A.S., and Zefirov, N.S., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1995, p. 804.
- Jedrzejczak, M., Motie, R.E., Satchel, D.P.N., Satchel, S.S., and Wassef, W.N., *J. Chem. Soc., Perkin Trans. 2*, 1994, p. 1471.
- Williams, A., *Concerted Organic and Bio-Organic Mechanisms*, Florida: CRC, 2000.
- Carroll, F.A., *Perspectives on Structure and Mechanism in Organic Chemistry*, California: ITP, 1998.
- Pross, A., *J. Org. Chem.*, 1984, vol. 49, p. 1811.
- Masel, R.I., *Chemical Kinetics and Catalysis*, New York: Wiley, 2001.
- Rybachenko, V.I., Schroeder, G., Chotii, K.Yu., and Kovalenko, V.V., *Teor. Eksp. Khim.*, 1998, vol. 34, p. 96.
- Rybachenko, V.I., Schroeder, G., Chotii, K.Yu., Titov, E.V., Grebenyuk, L.V., Lenska, B., and Kovalenko, V.V., *Russ. J. Gen. Chem.*, 2001, vol. 71, p. 1608.
- Zhong, M. and Brauman, J.I., *J. Am. Chem. Soc.*, 1999, vol. 121, p. 2508.
- Lee, I., Lee, D., and Kim, C.K., *J. Phys. Chem. A*, 1997, vol. 101, p. 879; Wilbur, J.L. and Brauman, J.I., *J. Am. Chem. Soc.*, 1994, vol. 116, p. 5839.
- Savelova, V.A., Solomoichenko, T.N., Ved', T.V., Sadovskii, Yu.S., and Simanenko, Yu.S., *Zh. Org. Khim.*, 1993, vol. 29, p. 666.