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Equilibrium of Acyl Transfer between Pyridine *N*-Oxides and Their Acylonium Salts

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Abstract—Transfer of acyl groups from *N*-acyloxypyridinium salts to pyridine *N*-oxides in acetonitrile was studied. The equilibrium constants of acyl exchange were determined. These quantities vary in the range covering eight orders of magnitude, depending on the structure of the reagents, and are independent of the structure of the acyl group.

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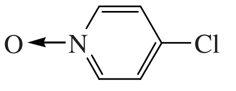
Equilibrium constants are important physicochemical quantities characterizing the reactivity [1, 2]. However, for many organic reactions, in particular, acylation, the available thermodynamic quantities are few or lacking at all [3, 4]. Therefore, the corresponding kinetic data are most often treated using the ionization constants of the reagents [5, 6]. This replacement requires the observance of the linear free energy relationship, which is not always the case. For example, in the coordinates of the Brønsted equation the nucleophilicity of organic compounds changes jumpwise with a change in the nature of the base center [7, 8]. Therefore, the equilibrium constants of acyl transfer reactions are required not only as characteristics of numerous organic [4] and biochemical [5] transformations, but also as necessary parameters for analysis and prediction of their reactivity using modern physically substantiated correlation schemes [9, 10].

Previously [11, 12] we examined the effect of structural factors on the equilibrium constants and heats of the exchange of acetyl and dimethylcarbamoyl groups between pyridine *N*-oxides.

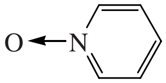
$$\text{Acyl-Nu}_i^+,\text{X}^- + \text{Nu}_j \rightleftarrows \text{Acyl-Nu}_j^+,\text{X}^- + \text{Nu}_i. \qquad (1)$$

In this study we examined how the equilibrium characteristics of reaction (1) are influenced by the structure of the acyl group. For this purpose, we determined by UV and IR spectroscopy and kinetic method the equilibrium constants of reactions (1) in CH_3CN solutions at 298 K, with Acyl = CH_3CO– (Ac_1), $(CH_3)_2NCO$– (Ac_2), C_6H_5CO– (Ac_3), 4-morpholinocarbonyl (Ac_4), 1-piperidinocarbonyl (Ac_5), and $(C_6H_5)_2NCO$– (Ac_6); X^- = BPh_4^- and Nu=.

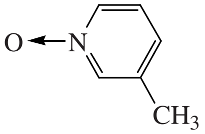
The results are given in Table 1. Also given are the quantities that we obtained previously and also the heats of the reactions, calculated by the AM1 method taking into account the solvent (CH_3CN) effect in the COSMO approximation. The equilibrium constants of reactions (1) were obtained (except system no. 29) for the reactions in which the leaving group (Nu_j) or nucleophile (Nu_i) is 4-(4'-*N*,*N*-dimethylaminostyryl) pyridine *N*-oxide, Nu_9 in our notation. This choice is dictated by the reliability requirements. In CH_3CN, 4-(4'-*N*,*N*-dimethylaminostyryl)pyridine N-oxide (λ_{max} 395 nm) and its *O*-acyl salts (λ_{max} 510 ±5 nm) have well-resolved absorption bands which are not superimposed on bands of other participants of reaction (1). Their very high intensity (ε, respectively, 36000 and 59000 ± 5000 1 mol^{-1} cm^{-1}) allowed simultaneous determination of the equilibrium concentration of the starting compounds and products and reliable monitoring of the reaction kinetics [14] with any combination of participants of reaction (1). The accuracy of the measured quantities is particularly



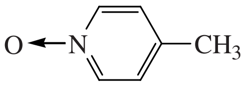
(Nu$_1$)



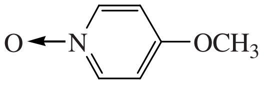
(Nu$_2$)



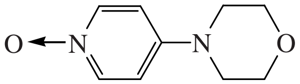
(Nu$_3$)



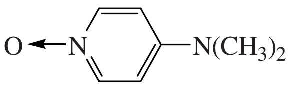
(Nu$_4$)



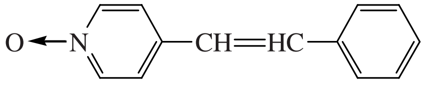
(Nu$_5$)



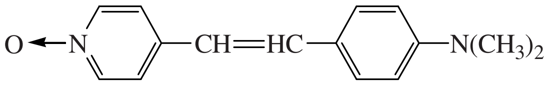
(Nu$_6$)



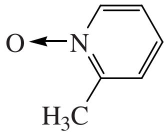
(Nu$_7$)



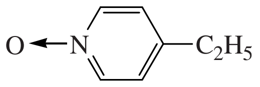
(Nu$_8$)



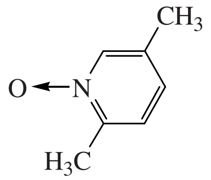
(Nu$_9$)



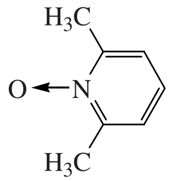
(Nu$_{10}$)



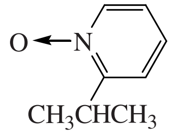
(Nu$_{11}$)



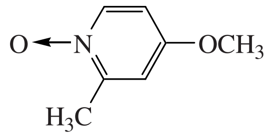
(Nu$_{12}$)



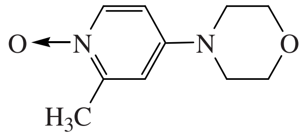
(Nu$_{13}$)



(Nu$_{14}$)



(Nu$_{15}$)



(Nu$_{16}$)

important in this case, because pairwise subtraction of the quantities (log K_{i9} – log K_{j9} = logK_{ij}) for reactions with the same nucleophile (or leaving group) allows calculation of the constants as elements of the corresponding *i*–*j* matrix, most of which cannot be directly determined experimentally but are necessary, e.g., for correlation analysis [10–12]. A special example from the benzoyl transfer (cf. system nos. 26, 27, and 29 in Table 1) confirms that the calculated (1.76 – 0.42 = 1.34) and experimental (log $K_{2,4}$ 1.12) values coincide within the measurement errors.

As seen from Table 1, the equilibrium constants of reaction (1) vary in the range covering eight orders of magnitude depending on the structure of salts, but these changes are associated virtually exclusively with the basicity of the leaving group and/or nucleophile (see, e.g., system nos. 1 and 5, 16 and 19, 30 and 32). The parameter log *K* is the larger, the higher the electron-withdrawing power of substituents in Nu$_i$ (and hence the lower the basicity), which is quite consistent with the concept of the mechanism of nucleophilic substitution reactions [3–5]. At the same time, the structure of the acyl group as a fragment of the acylonium cation, potentially capable to affect the equilibrium of reaction (1), exerts virtually no influence. For example, the equilibrium constants in system nos. 2, 16, 20, 23, 26, 30 or nos. 5, 19, 25, 28, 32 coincide within the measurement error.

Let us consider formally structural factors affecting the equilibrium under consideration. The entropy changes in symmetrical reactions are insignificant [9, 15, 16]; therefore, the free energy of reaction (1) can be presented as follows:

$$\Delta G_{ij} \approx E(\text{Ac-Nu}_i) - E(\text{Ac-Nu}_j), \qquad (2)$$

where $E(\text{Ac-Nu}_i)$ and $E(\text{Ac-Nu}_j)$ are the energies of the breaking and forming bonds, respectively, which, in turn, can be presented as follows:

Table 1. Thermodynamic characteristics (log K_{ij}, $\Delta G_{ij} = -RT\ln K_{ij}$, $-\Delta H_{ij}$)[a] of reaction (1) (solutions in CH_3CN, 298 K)

System no.	Nu_i	Acyl	log K_{ij}[b]	pK_{BH^+} of Nu_i [6, 13], H_2O/CH_3CN	ΔG_{ij}, kJ mol^{-1}	$-\Delta H_{ij}$, kJ mol^{-1}
1	1	Ac_1	2.72	0.33/9.06	–15.6	7.46
2	2	Ac_1	1.76	0.79/9.97	–10.0	–0.01
3	3	Ac_1	1.22 (0.84)	0.92/10.30	–5.9[d]	1.96
4	4	Ac_1	0.48	1.29/11.00	–2.7	–1.65
5	5	Ac_1	–1.35	2.05/12.37	7.7	–7.00
6	6	Ac_1	–3.80	3.25/14.5[c]	21.7	–17.37
7	7	Ac_1	–5.26	3.88/15.62	30.0	–23.64
8	8	Ac_1	0.86	1.10/10.6[c]	–4.9	1.45
9	10	Ac_1	1.28 (0.93)	1.03/10.25	–6.3[d]	–3.08
10	11	Ac_1	(0.30)	1.34/11.0[c]	–1.7	–1.16
11	12	Ac_1	0.93	1.21/10.8[c]	–5.3	–0.73
12	13	Ac_1	1.21	1.37/10.27	–6.9	–3.02
13	14	Ac_1	(0.71)	1.26/10.9[c]	–4.0	0.76
14	15	Ac_1	–1.25	–	7.1	–8.38
15	16	Ac_1	–4.21	–	24.0	–19.14
16	2	Ac_2	(1.99)	0.79/9.97	–11.3	0.21
17	3	Ac_2	1.30 (1.28)	0.92/10.30	–7.4[d]	2.36
18	4	Ac_2	0.51 (0.51)	1.29/11.00	–2.9	–1.49
19	5	Ac_2	–1.57 (–1.62)	2.05/12.37	9.1[d]	–7.01
20	2	Ac_5	1.79	0.79/9.97	–10.2	0.51
21	4	Ac_5	0.32	1.29/11.00	–1.8	–1.06
22	5	Ac_5	–1.30	2.05/12.37	7.4	–7.04
23	2	Ac_6	1.85	0.79/9.97	–10.5	0.74
24	4	Ac_6	0.46	1.29/11.00	–2.6	–0.98
25	5	Ac_6	–1.36	2.05/12.37	7.7	–8.01
26	2	Ac_3	1.76	0.79/9.97	–10.0	0.44
27	4	Ac_3	0.42	1.29/11.00	–2.4	–1.19
28	5	Ac_3	–1.24	2.05/12.37	7.1	–6.83
29	2	Ac_3	1.12[e]	0.79/9.97	–5.9	–0.75
30	2	Ac_4	1.80	0.79/9.97	–10.3	0.50
31	4	Ac_4	0.23	1.29/11.00	–1.3	–0.97
32	5	Ac_4	–1.45	2.05/12.37	8.2	–7.04

[a] *j* 4 in system no. 29 and 9 in the other systems. [b] The error of the UV spectrophotometric determination of constants does not exceed ±0.05 log unit, and that of kinetic determination, ±0.10 log unit. The values obtained from kinetic measurements as $K = k_1/k_{-1}$ are given in parentheses. [c] Calculated by the equation $pK_{BH^+}(CH_3CN) = 1.83pK_{BH^+}(H_2O) + 8.56$ [13]. [d] Averaged equilibrium constants used. [e] Measured by IR Fourier spectroscopy.

$$E = E^0 + \Delta E;\ \Delta E = f(Nu_x). \qquad (3)$$

Assuming [17] that $f(Nu_x) = \rho\sigma_x$ or $f(Nu_x) = \rho' pK_x$, we obtain for any Nu_i-Nu_j pair

$$\Delta G_{ij} = \rho(\sigma_i - \sigma_j) = \rho'(pK_i - pK_j). \qquad (4)$$

It follows from Eq. (4) that the effect of the structure of the acyl group on ΔG_{ij} is described by the reaction constant ρ. This quantity characterizes the sensitivity of a given equilibrium to structural changes in the reactants [17].

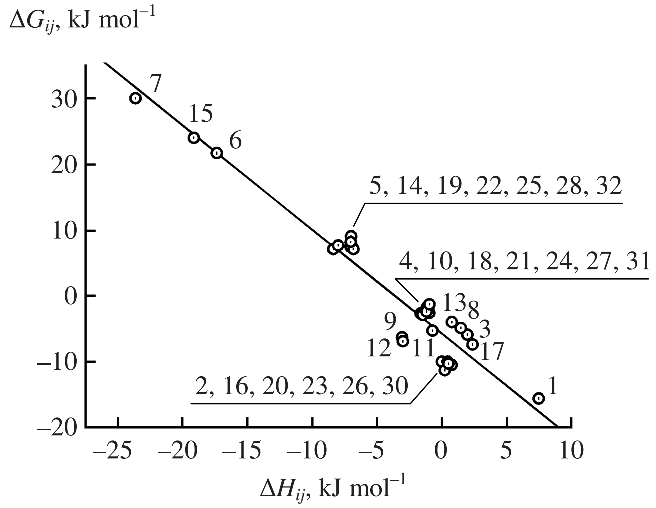
The most suitable method for characterizing the structure of acylonium cations is IR spectroscopy [18]. The integral intensities A_8 of skeleton stretching vibra-

Table 2. IR characteristics of ν_{8a} and ν_{8b} vibrations of a series of *N*-acyloxypyridinium tetraphenylborates (solutions in CH_3CN)

Comp. no.	Nu	Acyl	ν_{8a}, cm^{-1}	ν_{8b}, cm^{-1}	$A_8 \times 10^{-3}$, $l\ mol^{-1}\ cm^{-2}$
1	Nu_2	Ac_1	1614.0	1582.0	1.30
2	Nu_2	Ac_2	1613.5	1582.0	1.38
3	Nu_4	Ac_1	1629.0	1576.5	2.99
4	Nu_4	Ac_2	1628.0	1576.0	3.16
5	Nu_5	Ac_1	1631.0	1574.5	11.98
6	Nu_5	Ac_2	1632.0	1573.5	12.83
7	Nu_7	Ac_1	1642.0	1573.5	32.10
8	Nu_7	Ac_2	1644.0	1575.0	31.60

tions of the ring (ν_{8a} and ν_{8b}, assignment according to [19]) of a series of *N*-acyloxypyridinium cations are given in Table 2. These quantities are essentially constant in pairs of system nos. 1–2, 3–4, 5–6, and 7–8, i.e., are independent of the structure of the acyl group but strongly depend on the substituent in the ring (cf. A_8 for system nos. 1, 3, 5, 7 and 2, 4, 6, 8, Table 2).

It is known [20] that the quantities A_8 are determined by the effects of n,π conjugation between the substituent in the ring and the reaction center. Hence, the constancy of A_8 indicates that the electronic interaction of the onium fragment of the cation and the carbonyl carbon atom is independent of the structure of the acyl group. Therefore, the whole set of the examined reactions can be considered as a common reaction series. This conclusion is additionally supported by the fact that all the examined reactions show a good isothermodynamic correlation (see figure) between the free energies and calculated heats[1] of reaction (1):



Correlation between the equilibrium constants and calculated heats of reactions (1) (numbering of reaction systems is the same as in Table 1).

$$\Delta G^0_{i\text{–}9} = (-5.76\pm0.61) + (1.58\pm0.08)(-\Delta H^0_{i\text{–}9}); \qquad (5)$$

$$n\ 31;\ r\ 0.962;\ S_0\ 3.00.$$

The observance of Eq. (5), in turn, suggests [19] that the mechanism of the reactions studied is the same and the whole reaction series follows the linear free energy relationship [21]. The latter can be readily verified. The experimentally measured equilibrium constants of reaction (1) can be presented as two equivalent reaction series consisting of 29 systems,[2] in which either the nucleophile (Nu_i = const = Nu_9) or the leaving group (Nu_j = const = Nu_9) is varied. For the case of variation of the leaving group, we have the following linear correlation:

$$\log K_{i9} = (3.54\pm0.09) - (2.32\pm0.06)pK_{BH^+}; \qquad (6)$$

$$n\ 29,\ r\ 0.992;\ S_0\ 0.23.$$

The high quality of correlation (6) is a one more evidence of the conclusion that equilibrium of the reactions under consideration is insensitive to the structure of the acyl fragment of the acylonium cations and depends only on the structure of the nucleophile and leaving group. As seen from Eq. (4), correlation (6) can be written in the form of an equation symmetrical with respect to the participants of reaction (1) and covering all possible combinations of Nu_i and Nu_j:

$$\log K_{ij} = (0\pm0.11) + (2.29\pm0.03)(pK_{BH^+} - pK_{BH^+}); \qquad (7)$$

$$n\ 125,\ r\ 0.992;\ S_0\ 0.35.$$

From Eq. (6) or (7), we can estimate pK_{BH}+ for Nu_{15} and Nu_{16}: 2.06 and 3.34,3.34.an estimateinations off an equation symmetrical with respect to the ucture of the acyl fragment of the acyloniumelationshi respectively.

The reaction constant (ρ 2.32) in Eqs. (6) and (7) actually indicates that the equilibrium of the acyl

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[1] Note that the calculated heats of reaction (1) reasonably agree with the experimental results (few in number) that we obtained previously [17].

[2] We have not found in the literature the values of pK_{BH}+ for Nu_{15} and Nu_{16}. For Nu_9, pK_{BH}+ 1.43 [11].

transfer is more sensitive to structural effects than the protonation equilibrium. However, the parameters pK_{BH}+ of *N*-oxides, used in correlations (6) and (7), were measured in water, and log K_{ij}, in acetonitrile. Let us take for the correlation the parameters pK_{BH}+ of *N*-oxides in CH_3CN (Table 1). As a result, we obtain the equation similar to (7):

$$\log K_{ij} = (0\pm0.18) + (1.23\pm0.01)(\mathrm{p}K_{\mathrm{BH^+}} - \mathrm{p}K_{\mathrm{BH^+}}); \qquad (8)$$

$$n\ 125,\ r\ 0.997;\ S_0\ 0.20.$$

The quality of correlation of (8) is appreciably higher than that of (7), despite the fact that many of the values of pK_{BH}+ in acetonitrile are calculated and not measured. A considerably lower absolute value of the reaction constant in (8) is apparently due to the solvent effect. Formally the proton is the same acid residue as Acyl in reaction (1). Therefore, closeness of ρ in Eq. (8) to unity (1.23) clearly shows once again that the nature of the group being transferred in acyl exchange (1) exerts a minor influence on the reaction equilibrium.

EXPERIMENTAL

All the nucleophiles were prepared and purified as in [11, 12]. Acetonitrile (Acros for HPLC) were kept over 3 Å molecular sieves before use.

The IR spectra were recorded on a Perkin–Elmer Spectrum BX spectrophotometer (resolution 4 cm^{-1}). The accuracy of determining the frequencies and integral intensities was ±0.5 cm^{-1} and ±5%, respectively.

The electronic absorption spectra of the participants of reaction (1) were recorded on a Specord UV-Vis spectrophotometer. The optical densities were measured on an SF-26 spectrophotometer in a temperature-controlled cell at T 298±0.1 K.

The equilibrium constants for system nos. 1–5, 8–28, and 30–32 were calculated knowing the equilibrium concentrations of the two participants of reaction (1), which were determined from the optical densities of the solutions at wavelengths of about 510 ($\mathrm{Acyl\text{-}Nu_9^+}$) and 395 nm ($\mathrm{Nu_9}$). For system nos. 6 and 7, we determined only the equilibrium concentrations of $\mathrm{Nu_9}$ from the absorption at λ 395 nm.

The rate constants of fast reaction nos. 3, 9, 10, and 13 were determined on an Applied Photophysics stopped-flow installation with a temperature-control unit (±0.1 K).

Quantum-chemical calculations were performed by the AM1 method using the HyperChem 4 program package.

1-Acetyloxy-4-(4'-*N,N*-dimethylaminostyryl)pyridinium tetraphenylborate. 4-(4'-*N,N*-Dimethylaminostyryl)pyridine *N*-oxide (0.075 g) was dissolved in a small amount of acetic anhydride (~3 ml). To the resulting solution, a fourfold excess of sodium tetraphenylborate (~0.42 g) was added in the dark, and the mixture was vigorously stirred for 10–15 min. Then ~100 ml of diethyl ether was added, and after 30–40 min the precipitate (dark violet crystals) was filtered off. Yield ~0.14 g (~80%). The salt is photosensitive, and all manipulations with it were performed in the red light. ^{1}H NMR spectrum (200 MHz; acetone-d_6), δ, ppm (J, Hz): 8.55 d (2H, Py^{α}, J 7.0), 8.03 d (2H, Py^{β}, J 7.0), 7.93 d (2H, –CH=CH–, J 16.4), 7.64 d (2H, Ph, J 8.0), 7.21 d (2H, –CH=CH–, J 16.3), 7.34 m [8H, $\mathrm{BPh_4^-}$ (*o*-H)], 7.05 d (2H, Ph, J 8,0), 6.92 m [8H, $\mathrm{BPh_4^-}$ (*m*-H)], 6.76 m [4H, $\mathrm{BPh_4^-}$ (*p*-H)], 3.07 s [6H, $(CH_3)_2N$–], 2.42 s (3H, CH_3). Found, %: C 81.8; H 6.3; N 4.4. $C_{41}H_{39}BN_2O_2$. Calculated, %: C 81.7; H 6.5; N 4.6.

The other salts were prepared as in [11, 12].

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