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Identical Acyl Transfer Reactions between Pyridine N-Oxides and Their N-Acylonium Salts

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Abstract—28 identical acyl exchange reactions R–CO–Nu$^+$, X$^-$ + Nu between pyridine N-oxides in acetonitrile were studied. Here, X$^-$ = BPh$_4^-$ and R = methyl, N,N-dimethylamino, N,N-diethylamino, 4-morpholino, 1-piperidino, N-methyl, N-phenylamino, or N,N-diphenylamino group. The IR and NMR spectroscopic characteristics of acyloxypyridinium salts were determined, and the quantum-chemical parameters of all reagents calculated. The results were subjected to correlation analysis. It was found that the rate of identical acyl transfer reactions was controlled by the interaction of frontier orbitals in the transition state.

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INTRODUCTION

Apart from their historical and practical importance in organic chemistry in general [1], nucleophilic substitution reactions are of interest, in particular, because they allow us to observe structurally degenerate transformations [2]. An analysis of such reactions is in essence a purely kinetic problem [3] and a priori excludes the use of the principle of Gibbs energy linearity. For this reason, a detailed consideration of identical S$_N$2 reactions is more and more often used [4] as a point of departure for analyzing and predicting nucleophilic reactivity. At the same time, the scope of identical reactions studied experimentally is largely limited to proton [5] and methyl group [2, 4] transfer. This is related to obvious problems of tracking the development of structurally degenerate reactions.

We earlier performed a detailed study of the kinetic and equilibrium characteristics of the transfer of various acyl groups from N-acyloxypyridinium salts (AOPSs) to pyridine N-oxide and its substituted derivatives (Nu),

$$\text{Acyl-Lg}^+,\ \text{X}^- + \text{Nu} \rightleftharpoons \text{Acyl-Nu}^+,\ \text{X}^- + \text{Lg}. \qquad (1)$$

We showed that reaction (1) followed a concerted addition-detachment mechanism (A$_N$D$_N$) and developed through a transition state with a small degree of bond splitting and without the formation of stable tetrahedral intermediate products [6].

This work is concerned with reactions (1) in which the nucleophile and leaving group are identical (Nu≡Lg). The kinetic data were obtained on solutions in acetonitrile for a series of reactions (1), where X$^-$ = BPh$_4^-$; Acyl = CH$_3$CO–(Ac$_1$), (CH$_3$)$_2$NCO–(Ac$_2$), (C$_2$H$_5$)$_2$NCO–(Ac$_3$), 4-morpholinocarbonyl–(Ac$_4$), 1-piperidinocarbonyl–(Ac$_5$), (C$_6$H$_5$)$_2$NCO–(Ac$_6$), and (C$_6$H$_5$)(CH$_3$)NCO–(Ac$_7$); and Lg = Nu = 4-chloropyridine N-oxide (Nu$_1$), pyridine N-oxide (Nu$_2$), 4-methylpyridine N-oxide (Nu$_3$), 4-methoxypyridine N-oxide (Nu$_4$), 4-morpholinopyridine N-oxide (Nu$_5$), and 4-dimethylaminopyridine N-oxide (Nu$_6$). The results obtained are discussed in terms of nucleophile basicities. We determined the vibrational frequencies and carbonyl ^{13}C chemical shifts of the salts and calculated the quantum-chemical characteristics of all the reagents of reactions (1).

EXPERIMENTAL

All reagents were prepared and purified as recommended in [7, 8]. Acetonitrile Aldrich anh was held over molecular sieves 3 Å prior to use. The IR spectra were recorded on a Perkin-Elmer Spectrum BX spectrometer, and the NMR spectra, on a Bruker ARX-400 instrument. The rate constants were calculated ignoring activity coefficients because of reaction (1) symmetry. The reproducibility of the constants obtained was no worse than ±5–7% for reactions 7–18 and 20–28 and ±20% for reaction 19.

RESULTS AND DISCUSSION

The rate constants for identical reactions 7–18 and 20–28 (Table 1) were determined using the IR data and N-oxide analogues completely deuterated in the ring, as

Table 1. Characteristics of identical acyl transfer reactions (k_2^{298} and $\Delta G^{\#}$) in solutions in acetonitrile and spectroscopic characteristics ($\nu_{C=O}$ and $\delta^{13}C$, solutions in acetonitrile) and quantum chemical parameters of reaction (1) reagents

No.	Ac	Nu	k_2^{298}, l/(mol s)	$\Delta G^{\#}$, kJ/mol	$\nu_{C=O}$, cm^{-1}	$\delta^{13}C$, ppm	pK_{BH}^{+}	*IP**, eV (Nu)	*EA**, eV ($AcLg^+$)	E_{p_z}, eV ($AcLg^+$)
1	Ac_1	Nu_1	850[8]	56.2	1838.5	–	0.33	8.963	3.257	0.052
2	Ac_1	Nu_2	1550[8]	54.8	1837.0	142.84	0.79	8.615	2.947	0.210
3	Ac_1	Nu_3	3100[8]	53.1	1834.5	141.52	1.29	8.422	2.634	0.365
4	Ac_1	Nu_4	8900[8]	50.5	1832.5	143.75	2.05	8.264	2.166	0.501
5	Ac_1	Nu_5	26900[8]	47.7	1829.0	140.16	3.25	7.728	1.494	0.854
6	Ac_1	Nu_6	44700[8]	46.5	1825.0	139.57	3.88	7.611	1.535	0.862
7	Ac_2	Nu_1	4.36×10^{-3}	86.5	1802.0	–	0.33	8.963	3.037	1.967
8	Ac_2	Nu_2	4.90×10^{-3}	86.2	1803.5	143.39	0.79	8.615	2.727	2.114
9	Ac_2	Nu_4	79.4×10^{-3}	79.2	1797.5	144.19	2.05	8.264	1.965	2.359
10	Ac_2	Nu_5	1.90×10^{-1}	77.1	1789.0	140.72	3.25	7.728	1.320	2.661
11	Ac_2	Nu_6	7.58×10^{-1}	73.7	1788.0	–	3.88	7.611	1.361	2.680
12	Ac_3	Nu_1	1.12×10^{-3}	89.8	1793.0	–	0.33	8.963	2.993	1.902
13	Ac_3	Nu_2	1.62×10^{-3}	88.9	1793.0	–	0.79	8.615	2.680	2.052
14	Ac_3	Nu_4	16.6×10^{-3}	83.2	1787.5	144.04	2.05	8.264	1.883	2.316
15	Ac_3	Nu_5	26.9×10^{-3}	81.9	1778.5		3.25	7.728	1.268	2.558
16	Ac_3	Nu_6	8.51×10^{-2}	79.1	1778.0		3.88	7.611	1.306	2.588
17	Ac_4	Nu_1	4.89×10^{-2}	80.5	1799.0	–	0.33	8.963	3.086	1.848
18	Ac_4	Nu_4	1.10	72.8	1789.5	–	2.05	8.264	2.019	2.223
19	Ac_4	Nu_6	~10	67	1781.5	–	3.88	7.611	1.415	2.539
20	Ac_5	Nu_1	8.71×10^{-3}	84.8	1794.0	–	0.33	8.963	2.942	2.079
21	Ac_5	Nu_2	13.8×10^{-3}	83.6	1791.5	–	0.79	8.615	2.601	2.210
22	Ac_5	Nu_4	1.38×10^{-1}	77.9	1787.0	–	2.05	8.264	1.842	2.438
23	Ac_5	Nu_5	0.38	75.4	1779.0		3.25	7.728	1.227	2.724
24	Ac_5	Nu_6	1.17	72.6	1778.5		3.88	7.611	1.263	2.754
25	Ac_6	Nu_1	3.98×10^{-2}	81.0	1799.0	–	0.33	8.963	2.898	2.090
26	Ac_6	Nu_2	4.79×10^{-2}	80.5	1793.5	–	0.79	8.615	1.845	2.052
27	Ac_6	Nu_4	1.74	71.6	1791.0	143.63	2.05	8.264	1.845	
28	Ac_7	Nu_1	3.10×10^{-2}	81.6	1796.0	–	0.33	8.963	2.971	2.062

in [7]. The kinetics of the process was monitored by measuring stretching skeletal heteroring vibration bands of the salt and its deuterated analogue. The frequencies of these bands are virtually independent of the nature of the acyl group and equal 1617 and 1580 cm^{-1} for Nu_1 salts, 1614 and 1572 cm^{-1} for Nu_2, 1632 and 1597 cm^{-1} for Nu_4, 1638 and 1606 cm^{-1} for Nu_5, and 1633 and 1612 cm^{-1} for Nu_6. The rates of reaction 19 (Table 1) were calculated from the NMR spectra over the temperature range 323–343 K with extrapolation to 298 K. The proton signals of the dimethylamino group of 4-dimethylaminopyridine (3.03 ppm) and 1-morpholinocarbonyloxy-4-dimethylaminopyridinium tetraphenylborate (3.18 ppm) were used as indicator signals. The experimental reaction rates obeyed second-order reaction kinetics equations. The concentration of salts in the kinetic experiments did not exceed 1×10^{-2} mol/l. At these concentrations, we did not observe the influence of ionic association on experimental rate constants; that is, AOPSs reacted in the form of ions [7].

The rate constants (k_2^{298}) and Gibbs activation energies ($\Delta G^{\#}$) for identical reactions (1) in acetonitrile at 298 K are listed in Table 1. The table also contains some spectroscopic characteristics of the reagents, including carbonyl group stretching vibration frequencies ($\nu_{C=O}$) and chemical shifts ($\delta^{13}_{C=O}$) of the carbonyl carbon atom of AOPSs in acetonitrile solutions. The ionization potentials of N-oxides (*IP**), the electron

Table 2. Correlation equation parameters for identical acyl transfer reactions (1)

No.	$Y = a + bX$	Reaction number in Table 1	a	b	n	R	S_0
1	$\Delta G^{\neq} = f(\mathrm{p}K^{+}_{\mathrm{BH}})$	1–6	56.8 ± 0.33	-2.76 ± 0.14	6	0.995	0.43
2	$\Delta G^{\neq} = f(\nu_{\mathrm{C=O}})$	1–6	-1334 ± 129	0.76 ± 0.07	6	0.983	0.80
3	$\Delta G^{\neq} = f(\delta^{13}_{\mathrm{C=O}})$	2–6	-147 ± 116	1.40 ± 0.82	5	0.70	2.9
4	$\Delta G^{\neq} = f(\mathrm{p}K^{+}_{\mathrm{BH}})$	7–11	88.0 ± 0.91	-3.64 ± 0.37	5	0.985	1.14
5	$\Delta G^{\neq} = f(\nu_{\mathrm{C=O}})$	12–16	-957 ± 219	0.58 ± 0.12	5	0.940	1.82
6	$\Delta G^{\neq} = f(\delta^{13}_{\mathrm{C=O}})$	8, 9, 10	-104 ± 324	1.31 ± 2.27	3	0.5	5.8
7	$\Delta G^{\neq} = f(\nu_{\mathrm{C=O}})$	1, 7, 12, 17, 20, 25, 28	1275 ± 163	-0.66 ± 0.09	7	0.957	3.52
8	$\Delta G^{\neq} = f(\nu_{\mathrm{C=O}})$	4, 9, 14, 18, 22, 27	1156 ± 239	-0.60 ± 0.13	6	0.913	5.29
9	$\Delta G^{\neq} = f(\delta^{13}_{\mathrm{C=O}})$	4, 9, 14, 27	$-(4.9 \pm 4.5) \times 10^3$	35.2 ± 31.3	4	0.62	14.0
10	$\mathrm{p}K^{+}_{\mathrm{BH}} = f(\nu_{\mathrm{C=O}})$	1–6	505 ± 30	-0.27 ± 0.02	6	0.993	0.19
11	$\Delta G^{\neq} = f(IP^* - EA^*)$	1–28	13 ± 58	10 ± 9	28	0.2	13
12	$\Delta G^{\neq} = f(IP^* - EA^*)$	1–6	140 ± 20	-14.9 ± 3.4	6	0.909	1.8
13	$\Delta G^{\neq} = f(IP^*)$	1–6	-9.75 ± 4.96	7.40 ± 0.60	6	0.987	0.70
14	$\Delta G^{\neq} = f(IP^*)$	20–24	8.90 ± 1.15	5.59 ± 0.47	5	0.976	1.32
15	$\Delta G^{\neq} = f(EA^*)$	1, 7, 12, 17, 20, 25, 28	306 ± 75	-75 ± 25	7	0.81	7.2
16	$\Delta G^{\neq} = f(EA^*)$	2, 8, 13, 21, 26	107 ± 46	-11 ± 18	5	0.34	15
17	$\Delta G^{\neq} = f(E_{p_z})$	1, 7, 12, 17, 20, 25, 28	56.1 ± 4.4	14.0 ± 2.3	7	0.936	4.3
18	$\Delta G^{\neq} = f(E_{p_z})$	6, 11, 16, 19, 24	33.7 ± 7.3	14.9 ± 3.1	5	0.942	4.90
19	$\Delta G^{\neq} = f(IP^* - E_{p_z})$	1–6	-120 ± 26	19.6 ± 3.0	6	0.957	1.26
20	$\Delta G^{\neq} = f(IP^* - E_{p_z})$	1–26, 28	-80.6 ± 9.4	15.1 ± 0.9	27	0.957	3.9

affinity of AOPS cations (EA^*), and the energies of the lower free (subfrontier) molecular orbitals of AOPSs (E_{p_z}) that contained the largest contribution of C=O bond p_z orbitals were calculated ab initio using the 3-21G basis set. The IP^* and EA^* values correspond to vertical processes in which structural changes are frozen.

Structural changes occur in both reagents in identical $\mathrm{S_N2}$ reactions. Table 1 shows that the rate of reaction (1) substantially (by up to eight orders of magnitude) depends on the structure of its participants. The influence of substituents in the nucleophile (e.g., see Table 1, reactions 1–11) and changes in the nature of the acyl group (Table 1, reactions 1, 4, 7, 12, 14, 16, 17, 21, 23, 25, and 26) cause comparable changes in the rate of acyl exchange. The structural effects in the nucleophile and leaving group are traditionally characterized by basicity values [9]. Among the experimental data that describe the structure of the carbonyl center, the vibrational frequency of carbonyl vibrations and ^{13}C=O chemical shifts are most informative. The correlation equation parameters obtained for various groups of reactions (1) using the reagent characteristics specified above are listed in Table 2.

We see that the ^{13}C chemical shift is a poor correlation parameter (Table 2, Eqs. (6) and (9)), but the quality of the $\Delta G^{\neq}$–$\mathrm{p}K^{+}_{\mathrm{BH}}$ (Table 2, Eqs. (1) and (4)) and $\Delta G^{\neq}$–$\nu_{\mathrm{C=O}}$ (Table 2, Eqs. (2), (5), (7), and (8)) dependences well satisfies the formal correlation analysis requirements. However, note that the $\nu_{\mathrm{C=O}}$ values for salts and $\Delta G^{\neq}$ change in the same direction when substituents in Nu are varied (Acyl = const, see Table 2, Eqs. (2) and (5)) and in opposite directions when the nature of the acyl group transferred changes (Nu = const, see Table 2, Eqs. (7) and (8)). The opposite signs of similar correlations are likely caused by changes in the C=O vibrational mode caused by changes in the nearest environment of the carbonyl group [10]. Vibrational frequencies and band intensities then do not give correct information about the electronic structure of the corresponding bonds [11]. In addition, the $\mathrm{p}K^{+}_{\mathrm{BH}}$ and $\nu_{\mathrm{C=O}}$ values (Table 2, Eq. (10)) are closely linked with each other. For this reason, using them together in two-parameter correlations would be incorrect [12]. As concerns one-parameter correlations with $\mathrm{p}K^{+}_{\mathrm{BH}}$ (Table 2, Eqs. (1) and (4)), they cannot be used to separate structural effects in the reagents or, all the more, describe all the reactions studied.

Our detailed analysis of $\Delta G^{\neq}$–p$K_{\rm BH}^{+}$ correlations for identical dimethylcarbamoyl transfer reactions [7] only allowed us to find that the transition state of reactions (1) becomes more "rigid" (shifts toward tetrahedral intermediate products) as the basicity of the nucleophile and leaving group grows. The factors that control the barrier to the reaction and the reasons for barrier changes remain unknown. It is also unclear to what extent the conclusions drawn from our analysis are universal, that is, transferable to other reaction series. For instance, note that identical methyl and acyl transfer reactions (1) are substantially different. The rate of the former drops in the series of the strongest nucleophiles [13] and grows in the series of nucleophiles studied in this work (Table 1; Table 2, Eqs. (1) and (4)).

In recent years, nucleophilic substitution reactions, including nucleophilic substitution at the carbonyl center [14], have more and more often been analyzed using the model of the Shaik–Pross cross-diagrams [1, 13]. In this approach, reactivity is written in terms of the electron affinity EA^* of the electrophile (AcLg$^+$) and the ionization potential IP^* of the nucleophile as

$$\Delta G^{\neq} = A(IP^*_{\rm Nu} - EA^*_{\rm AcLg+}) - B, \qquad (2)$$

where A is the value characterizing the curvature of the intersecting potential functions (for instance, parabolas) and B is the resonance interaction energy of orbitals in the transition state. We cannot use (2) for our purposes without invoking the results of quantum-chemical calculations (Table 1). In addition, we must assume that A and B are constant values.

Let us consider correlations between the experimental and calculated reaction characteristics (Table 2, Eqs. (11)–(20)). Processing all the reactions studied in the coordinates of Eq. (2) does not give satisfactory results (Table 2, Eq. (11)). At the same time, there is a correlation for Acyl = const (Table 2, Eq. (12)), which is, however, physically meaningless. Indeed, it predicts a decrease in the barrier to reaction as the energy gap ($IP^* - EA^*$) to be overcome by the reactants in reaction (1) increases. Formally, failures of both correlations can be related to the assumptions made (A, B = const) and the calculated quantum-chemical parameters IP^* and EA^* proper. No verified methods for the determination and control of the A and B values have been suggested [1, 13], but the assumption that they are constant in series of related reactions is considered a good approximation [15].

For this reason, we concentrated on the calculated IP^* and EA^* values. Correlations of $\Delta G^{\neq}$ with IP^* (Table 2, Eqs. (13) and (14)) are satisfactory, but correlations with EA^* are not. The latter values do not reflect the expected changes in the electronic structure of AcLg$^+$ in reaction series with one and the same nucleophile (Table 2, Eqs. (15) and (16)), that is, "take no notice" of changes in the nature of the acyl group.

The electron affinity of a molecule or ion is usually taken to equal [13] (Table 1) the energy of the lowest unoccupied molecular orbital (LUMO). This EA^* value may fail to describe structural effects in cations explicitly because of the special features of LUMO localization. An analysis of the MOs of AcLg$^+$ indeed showed that the lowest unoccupied molecular orbital of all cations did not contain a contribution of the p_z orbital of the carbonyl group, that is, exactly the atomic orbital (AO) of the reaction center that experienced the frontal attack of a nucleophile in reaction (1) [16]. For this reason, we selected those LUMOs of AcLg$^+$ (subfrontier orbitals with respect to that determining the EA^* value) that contained the largest contributions of the p_z orbital of C=O. In the majority of cases (except no. 27, Table 1), the coefficients of the p_z AO in the selected LUMOs were of 0.4–0.6. The energies of these orbitals, E_{p_z}, are listed in Table 1.

It follows from Table 2 that the quality of correlations with E_{p_z} is much better than the quality of correlations with EA^* (Table 2, compare Eqs. (17) and (18) with (15) and (16) or (19) with (12)). Moreover, setting the energy gap of the reaction equal to $IP^* - E_{p_z}$ not only gives physically meaningful results (Table 2, compare (19) and (12)) but also allows a unified correlation to be used for processing data on all the identical acyl transfer reactions studied (Table 2, Eq. (20)), which is, in our view, a very interesting result. Note in conclusion that, as distinct from the MO characteristics considered, the other calculated quantum-chemical parameters, such as bond orders and charges on atoms of the reagents of reaction (1), do not correlate with the $\Delta G^{\neq}$ values; for this reason, we neither give nor discuss them.

To summarize, the results obtained lead us to conclude that reactivity in identical acyl transfer reactions is controlled by the interaction of frontier orbitals in the transition state. The particular localization of MOs on electrophile fragments, especially, its reaction center (carbonyl group) should be taken into account in constructing correlations and selecting frontier LUMOs.

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