EFFECT OF STRUCTURE ON THE KINETICS OF THE NUCLEOPHILIC SUBSTITUTION OF ACYLONM IONS

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A study was carried out on 67 reactions involving transfer of acyl groups from the corresponding N-, O-acylonium salts to pyridine N-oxides, highly basic pyridines, and N-methylimidazole in acetonitrile solution. PM3 calculations were carried out for the ionization potentials of the nucleophiles and electron affinities of the N-, O-acylonium cations. A multiparameter correlation was obtained predicting the rate of acyl group transfer.

Acyl transfer has been studied in great detail both experimentally [1] and theoretically [2]. However, the mechanism of many of these reactions has not been established, in particular, for acylonium salt transformations. Depending on structural factors, including the nature of the acyl fragment and medium, the nucleophilic reactions of these compounds have been assumed to proceed through a dissociative mechanism, direct nucleophilic substitution, an associative mechanism featuring a tetrahedral intermediate, and even radical species [4].

In recent work [5], we showed that highly basic pyridines and pyridine N-oxides eliminate leaving groups from acetyl and dimethylcarbamoyl acylonium salts through a simple second-order reaction, i.e., the acyl transfer in these reactions proceeds as an SN2 reaction:

\[ \text{Ac}^+ \cdot \text{Nu}^\prime + \text{Nu} \rightarrow \text{Ac} \cdot \text{Nu}^\prime + \text{Nu}^\prime + X^- \quad (1) \]

The rate constants for reaction (1) are very sensitive to structural factors. These terms range over 10 orders of magnitude and encompass a broad region of chemical kinetics. This feature of reaction (1) is unique for the purpose of quantitative analysis of the reactivity of compounds in nucleophilic substitution at a carbonyl carbon atom. For further elucidation of the mechanism of reaction (1), the scope of the reactions studied was considerably expanded by broadening the range of acylonium salts examined and using a large number of nucleophiles. Kinetic data were obtained for a series of acyl transfer reactions (1), where

\[ \text{Ac} = \text{CH}_3\text{OCO}, \text{CH}_3\text{CO}, (\text{CH}_3)\text{N} \cdots \text{CO}, \text{O} \cdots \text{N} \cdots \text{CO}; \]
\[ \text{X} = \text{BPh}_3; \text{Nu}_1 = \text{Cl} \cdots \text{O} \cdots \text{N} \cdots \text{O} (\text{Nu}_1), \]
\[ \text{O} \cdots \text{N} \cdots \text{O} \cdots \text{O} \cdots (\text{Nu}_2), \text{CH}_3\text{O} \cdots \text{O} \cdots \text{O} \cdots (\text{Nu}_3), \]
\[ \text{C}_2\text{H}_5 \cdots \text{O} \cdots (\text{Nu}_4), \text{CH}_3\text{O} \cdots \text{O} \cdots (\text{Nu}_5), \]
\[ \text{O} \cdots \text{C} \cdots \text{H} \cdots \text{C} \cdots \text{H} \cdots \text{O} \cdots (\text{Nu}_6), \]
\[ (\text{CH}_3)\text{N} \cdots \text{O} \cdots \text{C} \cdots \text{H} \cdots \text{C} \cdots \text{H} \cdots \text{O} \cdots (\text{Nu}_7), \]


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Second-order rate constants were found for all the reactions studied in acetonitrile

\[ k_{\text{obs}} = k_{\text{rev}} + k_2[\text{Ac} - \text{Nu}^+, X^-] \]  

with values of \( k_{\text{rev}} \) close to zero. Most of the values of \( \log k_2 \) in Table 1 were obtained using Eq. (2) for from three to six acylonium salt concentrations under pseudo-first-order conditions with \([\text{Ac} - \text{Nu}^+, X^-] = 0.0005 - 0.003 \text{ mole/liter} \) and \([\text{Nu}] \leq 1 \times 10^{-4} \text{ mole/liter} \). The values of \( k_2 \) for symmetrical reactions Nos. 23 and 39-41 were determined using equimolar reagents by analyzing the entire line shape in DNMR spectra as in our previous work [6]. The rates of "slow" identical reactions Nos. 62 and 63 were determined under analogous conditions by IR spectral observation of deuterated reagent analogs.

The electrolytic dissociation constants of acylonium salts in acetonitrile were found in the range from \( 10^{-1} \) to \( 10^{-3} \text{ g-eq/liter} \) [6]. Deviations were not found from pseudo-first-order kinetics or from linearity on plots for Eq. (2), i.e., there was no evidence for ionic association, hydrolysis, or other side reactions. Table 1 also gives the carbonyl group stretching frequencies for the acylonium salts in acetonitrile, ionization potentials (IP) of the nucleophiles and leaving groups in reaction (1), and electron affinities (EA) of the acylonium salt cations, which were calculated using the PM3 approximation.

The transition state indices \( \Delta H^\# \) and \( \Delta S^\# \) (Table 2) of some of the reactions given in Table 1 were determined from the \( k_2 \) values at three temperatures in the range from 20 to 30°C.

Table 1 shows that the rates of these reactions range from very fast (\( \log k_2 > 7 \)) to slow (\( \log k_2 < -5 \)). The activation parameters given in Table 2 are typical for spontaneous (noncatalytic) bimolecular nucleophilic substitution [7]. The low values for the activation enthalpies \( \Delta H^\# \) (15-66 kJ/mole) and entropies \( \Delta S^\# \) (from -44 to -190 J/mole-K) suggest an associative transition state, in which breaking of the bond of the leaving group is insignificant [7, 8]. Negative values of \( \Delta H^\# \) are characteristic for nucleophilic substitution proceeding stepwise through the formation of stable tetrahedral intermediates. Our positive values of \( \Delta S^\# \) indicate a concerted mechanism [1] (\( A_N + D_N \) according to the IUPAC nomenclature).

The set of reactions in Table 1 does not correspond to the requirements of a Hammett reaction series. Thus, the correlatons of \( \log k_2 \) for the entire data set \( k \) using the linear energy correlation principle are incorrect. Let us formally examine reaction (1). Three subprocesses may be delineated in nucleophilic substitution. In our case, these are formation of the acylonium salt–Nu\(^+\) bond, dissociation of the acylonium salt–Nu\(^+\) bond, and redistribution of electron density between the reaction fragments. Description of these subprocesses requires at least three parameters for the reactants and products. In selecting these parameters for the first two subprocesses, we used an approach developed recently for \( S_N 2 \) reactions by Pross and Shaik. In the state correlation diagram method [7], an energy gap on the reactant side must be overcome in bond formation

\[ G = \text{IP}_{\text{Nu}} - \text{EA} \text{AcNu}^+, \]

where \( \text{IP}_{\text{Nu}} \) is the ionization potential of the nucleophile, \( \text{EA} \text{AcNu}^+ \) is the electron affinity of the substrate, while an energy gap on the product side \( G_p \) must be overcome in bond dissociation. Experimental values of \( \text{IP} \) for some of our nucleophiles have been reported [5, 6] but there is virtually no information on the \( \text{EA} \) of acylonium salts. Thus, quantum chemical calculations were used to obtain both terms. In describing the electron density redistribution subprocess, we may use the frequencies for \( \text{C}=\text{O} \) stretching vibrations, which clearly reflect the electron density distribution in the acylonium cations [7]. As seen from Fig. 1, in which the predicted rate constants were determined from the following equation

\[ \lg k_2 = (-247.33 \pm 12.29) + (2.11 \pm 0.45)\text{IP}\text{Ac}^+ + (4.80 \pm 0.47)\text{IP}\text{j} - (1.55 \pm 0.43)\text{EA}_i - (10.05 \pm 0.77)\text{EA}_j + (0.10 \pm 0.01)\nu_{\text{C}=\text{O}}, + \]

\[ + (0.04 \pm 0.01)\nu_{\text{C}=\text{O}}^2 \]

\( n = 67, r = 0.894, S = 1.036 \).