

to the benzylic effect, since the $\Delta|\rho_{YZ}|$ values for changes in X from H to p -OCH₃ were 0.03 and 0.24 for the former (reaction (II)) and for the latter (reaction (I)) respectively.

This type of resonance contraction ($\Delta r_{CC} < 0$) can not be experimentally measured nor can be demonstrated with other selectivity parameters such as simple Hammett constants, ρ , or Brønsted constants, β ; the demonstration is only possible, at the present, with an observed increase in the magnitude of cross-interaction constants, ρ_{YZ} .

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Reaction Mechanism for Acyl-Transfer Reactions of Aryl Acetates with Aryloxides

Dong-Sook Kwon, Gwang-Ju Lee, and Ik-Hwan Um*

Department of Chemistry, Ewha Womans University, Seoul 120-750

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Although acyl-transfer reactions have been known significantly important in chemistry and biochemistry and numerous studies have been performed, the reaction has not been well understood.¹⁻³ It has frequently been proposed that acyl-transfer reactions of aryl or thioaryl acetates with various amines and thiolates proceed *via* stepwise mechanisms, i.e. formation and breakdown of tetrahedral intermediates in which the rate-determining step may vary depending on nucleofugalities of the attacking and leaving groups.² However, until quite recently one step concerted mechanisms have also been suggested for most acyl-transfer reactions.³

The arguments concerning with the reaction mechanisms are mainly based on studies of linear free energy relationship (LFER), and the discrepancy seems to originate mostly from difficulties in interpretations of the effect of polar substituents in the attacking and leaving groups on rate constants. The LFERs including Brønsted and Hammett type treatment have been most commonly used for mechanistic investigations.^{4,5} For many decades and for most reactions still today, the most valuable information on the determination of transition state (TS) structure has been obtained from the study of LFER.⁴⁻⁶

Recently we have reported that medium compositions would exert a significant influence on the α -effect as well as on reaction rates for the acyl-transfer reactions of p -nitrophenyl acetate with oxygen centered nucleophiles.⁷ Moreover, we have also observed unusual rate decreases upon addition of an aprotic solvent into the reaction medium. However, a plausible explanation for the results was not given

Table 1. Summary of Second Order Rate Constants (k , $M^{-1}s^{-1}$) for the Reactions of Substituted Phenyl Acetates ($MeC(O)OC_6H_4-X$) with Substituted Phenoxides ($4-Y-C_6H_4O^-$) in H_2O at $25^\circ C$

| Y \ X | $k \times 10^2, M^{-1}s^{-1}$ | | | | | | |
|-------------------------|-------------------------------|-------------------|------------------|-------------------|-----------------------------|----------------------------------|---|
| | 4-NO ₂ (7.14) | 4-CHO (7.66) | 3-CHO (8.00) | 4-COMe (8.05) | 3-NO ₂ (8.35) | 4-Cl-2-NO ₂ (6.46) | 2,4-(NO ₂) ₂ (4.11) |
| MeO(10.20) | 347 | 160 | 68 | 107 | 165 | — | — |
| Me (10.07) ^b | 213 ^b | 99.2 | 32.0 | 60.2 | 115 | — | — |
| H (9.95) | 113 ^b | 53.0 | 16.9 | 33.0 | 64.9 | 1.53 ^c | 12.17 ^d |
| Cl (9.38) | 68.5 ^b | 30.2 ^b | 9.1 ^b | 17.1 ^b | 32.0 ^b | — | — |
| CN (7.73) ^b | 3.00 ^b | 1.31 | 0.24 | 0.53 | 0.83 | — | — |

^aFigures in the parentheses represent the pK_a of phenol taken from reference 12, unless noted otherwise. ^breference 8, ^creference 3d, ^dreference 2d.

Table 2. Brønsted β_{nuc} and Hammett ρ_{nuc} Values for the Reactions of Substituted Phenyl Acetates ($MeC(O)OC_6H_4-X$) with the Various Phenoxides in H_2O at $25^\circ C$

| X | 4-NO ₂ | 4-CHO | 3-CHO | 4-COMe | 3-NO ₂ | 4-Cl-2-NO ₂ | 2,4-(NO ₂) ₂ |
|---------------|-------------------|---------|---------|---------|-------------------|------------------------|-------------------------------------|
| β_{nuc} | 0.79 | 0.80 | 0.93 | 0.89 | 0.91 | 0.64 ^a | 0.38 ^b |
| (r) | (0.991) | (0.992) | (0.990) | (0.993) | (0.996) | — | — |
| ρ_{nuc} | 1.59 | 1.62 | 1.87 | 1.79 | 1.82 | — | — |
| (r) | (0.997) | (0.998) | (0.997) | (0.998) | (0.996) | — | — |

^areference 3d. ^breference 2d.

Table 3. Hammett ρ values for the reaction of substituted phenoxides ($4-Y-C_6H_4O^-$) with various phenyl acetates in H_2O at $25^\circ C$

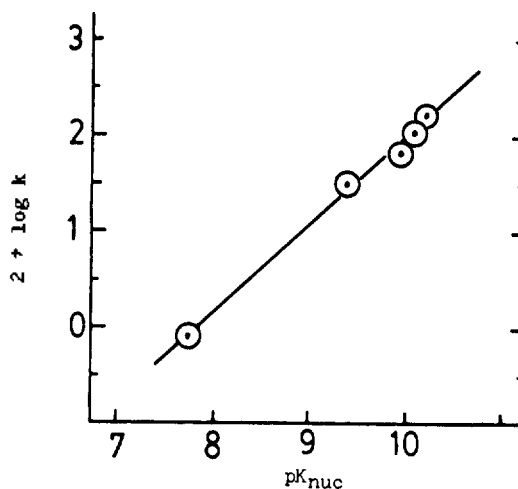
| Y | MeO | Me | H | Cl | CN |
|----------|---------|---------|---------|---------|---------|
| ρ^o | 1.29 | 1.52 | 1.54 | 1.62 | 1.82 |
| (r) | (0.927) | (0.930) | (0.936) | (0.922) | (0.832) |
| ρ^- | 0.63 | 0.72 | 0.71 | 0.79 | 1.07 |
| (r) | (0.854) | (0.841) | (0.828) | (0.855) | (0.930) |

^a ρ^o and ρ^- values are obtained using σ^o and σ^- substituent constants, respectively.

due to lack of information on reaction mechanism. We have, therefore, performed a systematic study of acyl-transfer reactions of substituted phenyl acetates with substituted phenoxides to investigate the reaction mechanism.

In Table 1 are summarized second order rate constants for the acyl-transfer reactions. It is clearly demonstrated that the nucleophilic phenoxide having more strongly electron donating substituent (EDS) is more nucleophilic while the one with more strongly electron withdrawing substituent (EWS) is less nucleophilic. On the contrary the phenyl acetate having stronger EWS on the leaving phenoxide is not always more electrophilic.

Thus more quantitative analyses have been carried out to see whether the present system would give any LFER, and in Tables 2 and 3 are presented the results. Table 2 shows that the logarithmic second order rate constants give very good correlations with basicities of the nucleophilic phenoxides for all the substrates studied (Figure 1 for the *m*-nitrophenyl acetate system as an example). There is no evidence for a break in the Brønsted type of plots for the present system. Since a break in Brønsted type of plots has been often

**Figure 1.** Plot of a Brønsted correlation ($2 + \log k$ vs. pK_{nuc}) for the reactions of *m*-nitrophenyl acetate (MNPA) with substituted phenoxides in H_2O at $25^\circ C$.

observed and interpreted as a change of mechanism in stepwise pathways,² the present results would be considered to indicate that in a given substrate the TS has a constant structure over the range of nucleophiles employed.

In Table 2 is also demonstrated that σ^- constant, among many substituent constants, gives the best correlation with logarithmic rate constants. The best correlation with σ^- constant would be expected, if the nucleophilic attack is involved in the TS of the rate determining step (RDS) whether the reaction proceeds through one step concerted or stepwise mechanisms.⁸ This is based on the argument that the negative charge on the oxygen atom of the phenoxide can be delocalized on the substituent directly by resonance.⁸ According-

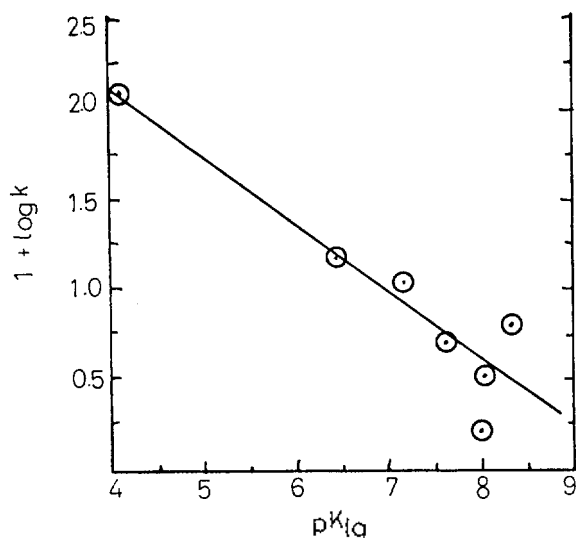


Figure 2. Plot of a Brønsted correlation ($1 + \log k$ vs. pK_{lg}) for the reaction of phenoxide with substituted phenyl acetates in H_2O at $25^\circ C$.

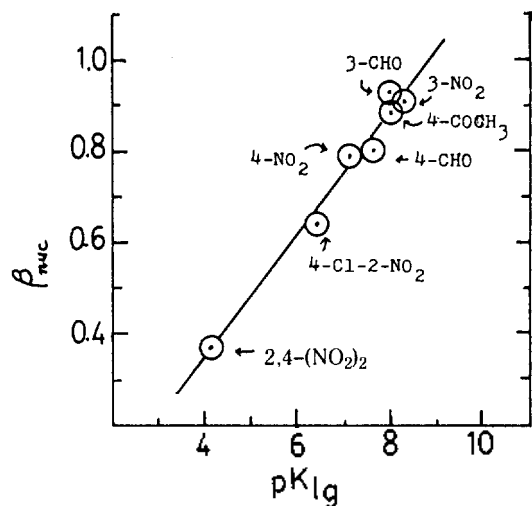
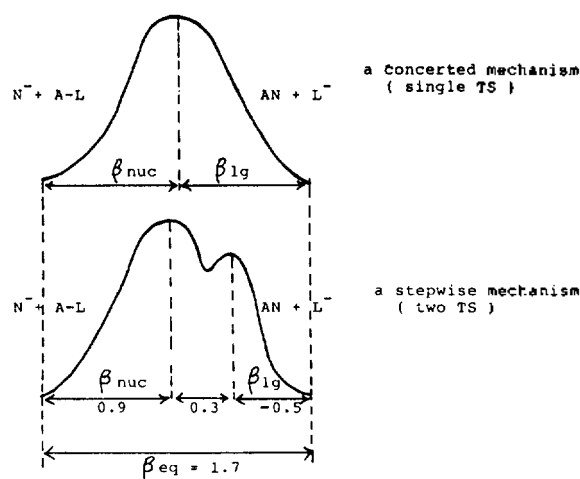


Figure 3. Dependence of β_{nuc} on pK_{lg} for the reactions of substituted phenyl acetates with substituted phenoxides. Data are from Table 2.

ly, the good LFER presented in Table 2 could be considered that the attack of a nucleophile to the carbonyl carbon of a substrate is definitely involved in the RDS.

For a further examination of our present results, we have correlated β_{nuc} with basicity of leaving group (pK_{lg}). As shown in Figure 3, the Brønsted β_{nuc} gives a nice correlation with pK_{lg} . Although a small deviation is observed, it seems to be negligible and does not affect our argument. Therefore such a good correlation seems to be quite consistent with the Hammond postulate,⁹ if one admits β as a measure of the degree of bond formation (or break) at TS.^{10,11} Besides, the present system obeys nicely the reactivity-selectivity principle (RSP),¹¹ if one takes β as a measure of sensitivity parameter. Such an observation of RSP for the present system would not be expected if the nucleophilic attack is not involved in the RDS.^{8,11}

In contrast to the good LFER obtained for the reactions of



Scheme 1. A schematic energy diagram for reaction of N^- with AL to produce AN and L^- .

a given phenyl acetate with various nucleophilic phenoxides, a poor LFER is observed for the reactions of a given nucleophilic phenoxide with various phenyl acetates, as plotted in Figure 2. Furthermore the Hammett correlations used σ^- constant give extremely poor results as demonstrated in Table 3. Slightly better but still poor correlations are obtained when σ^o constants are used instead of σ^- scale. Therefore the present result is considered to indicate that leaving group departure is neither advanced at the TS nor involved in the rate determining step.

To support our argument, analyses of Brønsted β values have been performed. If the present acyl-transfer reaction proceeds *via* a concerted mechanism with a single TS, then one would expect the sum of β_{nuc} and $-\beta_{lg}$ be equal to the known value ($\beta_{eq} = 1.7$) for the present system¹³ as shown in Scheme 1. Since the sum of β_{nuc} and $-\beta_{lg}$ for the present system would not exceed 1.4¹⁴, there would be present another TS indicating a step-wise mechanism.¹⁵

Thus it is proposed that the present acyl transfer reactions proceed *via* a stepwise mechanism rather than *via* a concerted one, *i.e.* rate determining nucleophilic attack to form a tetrahedral intermediate followed by fast breakdown of it.

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 - Since β_{1g} for the MNPA system is not reported, we chose the known value for *p*-cyanophenyl acetate (PCPA) system ($\beta_{1g} = -0.51$). It is because *p*-cyanophenol and *m*-nitrophenol have similar *pK_a* values and therefore β_{1g} of MNPA would be close to that of PCPA.
 - A similar argument could be obtained from an analysis of the effective charges on the oxygen atoms of the attacking and leaving aryloxides at the TS. The effective charges on the oxygen atoms of both attacking and leaving aryloxides are suggested to be -0.25 for PNPA system by Williams *et al.*³ However our present data give the effective charges of -0.1 and +0.2 for the oxygens of attacking and leaving aryloxides, respectively, indicating a stepwise mechanism. We are grateful to one of the referees for the kind suggestion concerning the effective charge.

One-Pot Synthesis of Ketones Using *N*-Methyl-*N*-(2-Pyridinyl)-*N'*-Propylene Urea

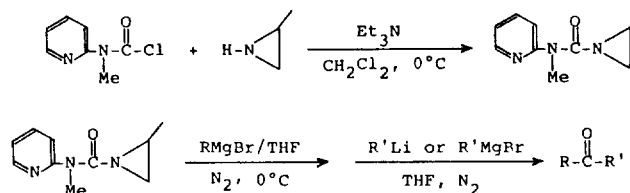
Jae In Lee

Department of Chemistry, College of Natural Science,
Duksung Women's University, Seoul 132-714

Received February 24, 1990

Reaction of carboxylic acid derivatives with organometallics is well-known and widely used for the synthesis of ketones. However, its synthetic application is limited due to the formation of undesired tertiary alcohols, produced by the further addition of the organometallics to the product.¹ Several types of active esters² having pyridinyl ligand have been developed to circumvent this limitation. For instance, the reaction of *S*-(2-pyridinyl) thioates,^{2c} 2-pyridinyl esters,^{2d} and *N*-methyl-*N*-(2-pyridinyl) carboxamides^{2f} with Grignard reagents is especially useful for the successful synthesis of ketones. Active amides³ have also been proposed as acylating reagents to prevent such a side reaction by generating tetrahedral intermediates with Grignard or organolithium reagents. However, there are few reports on the ketone synthesis by sequential additions of two organometallic reagents to the substrate such as *S*-phenyl carbonochloridothioate.⁴

We now wish to report a one-pot synthesis of ketones from Grignard and organolithium reagents using *N*-methyl-*N*-(2-pyridinyl)-*N'*-propylene urea.⁵ The reagent was conveniently prepared by the reaction of *N*-methyl-2-pyridine-carbamoyl chloride,⁶ generated from 2-(methylamino)pyridine and phosgene, with 2-methylaziridine in the presence of triethylamine in methylene chloride at 0°C. The reagent was



easily separated by aqueous work-up and obtained in 92% yield after a short pathway silica gel column chromatography.

The success of ketone synthesis using *N*-methyl-*N*-(2-pyridinyl)-*N'*-propylene urea depends largely on, in the first step, selective substitution of 2-(methylamino)pyridinyl group without concomitant displacement of the 2-methylaziridyl group. We have achieved this goal by dropwise addition of Grignard reagents to *N*-methyl-*N*-(2-pyridinyl)-*N'*-propylene urea at 0°C. Thus, when *N*-methyl-*N*-(2-pyridinyl)-*N'*-propylene urea was treated with 1 equiv of phenylmagnesium bromide at 0°C over a period of 15–20 min, 1-benzoyl-2-methylaziridine was obtained in 93% yield and there were no observable side products such as benzophenone. However, the reaction was carried out in a one-pot way; After completion of the first step, the second organolithium or Grignard reagent was added to the mixture without the isolation of *N*-acylaziridine intermediates.

The results of the synthesis of various ketones was summarized in the Table 1 and the present method appeared especially effective for the synthesis of aromatic ketones. The reaction of the first step works well for aliphatic and aromatic magnesium bromide and was not influenced by the kind of electron withdrawing or donating group in 4-substituted phenylmagnesium bromide under the present reaction conditions. In the second step, reaction of Grignard reagents with the *N*-acylaziridine intermediates required a little longer time than organolithium reagents in most cases. Sig-