

Nucleophilic Displacements at Carbonyl Compounds

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To cite this article:

Shuchismita Dey. Nucleophilic Displacements at Carbonyl Compounds. *Science Journal of Chemistry*. Vol. 3, No. 3, 2015, pp. 57-61.
doi: 10.11648/j.sjc.20150303.14

Abstract: The nucleophilic displacements at carbonyl center are remarkable. Mainly stepwise mechanism was found in these reactions. The stepwise mechanism with rate-limiting addition of the nucleophile to the carbonyl group to form zwitterionic tetrahedral intermediate was a common type of mechanism. Such as, Dey et al. [1] proposed the pyridinolyses of α -chloroacetanilides proceed via a stepwise mechanism with rate-limiting addition of the nucleophile to the carbonyl group to form zwitterionic tetrahedral intermediate (T^\pm). In some cases concerted mechanism was found. Oh and coworkers [9] reported that a concerted mechanism with a hydrogen bonded cyclic transition state for the aminolysis of aryl *N*-allyl thiocarbamates with benzylamines in acetonitrile. The mechanism change from stepwise to concerted was also found in some cases. It was concluded that the change of the amine from benzylamines to anilines causes a shift of the aminolysis mechanism from a concerted to a stepwise process. This paper includes an exclusive review of literature from 1997 to 2015.

Keywords: Nucleophilic Substitution, Carbonyl Compound, Stepwise, Concerted

1. Introduction

The nucleophilic displacements at carbonyl center has been considered with great interest. The reactions have been considered significantly for the last couple of years. The pioneer researchers in this field contributed a significant number of articles in various Journals. In most of the cases the reaction mechanisms were found stepwise with intermediates. For example, Dey et al. [1], proposed the pyridinolyses of α -chloroacetanilides are proposed to proceed via a stepwise mechanism with rate-limiting addition of the nucleophile to the carbonyl group to form zwitterionic tetrahedral intermediate (T^\pm) followed by a bridged type transition state to expel the leaving group. In another report, Castro et al. [2], reported the reactions of 4-methylphenyl 4-nitrophenyl carbonate (MPNPC) and 4-methylphenyl 2,4-dinitrophenyl carbonate (MPDNPC) with a series of secondary alicyclic amines are subjected to a kinetic investigation in 44 wt% ethanol-water, at $25.0 \pm 0.1^\circ\text{C}$, ionic strength 0.2 M (KCl). The reported mechanism of this system was a stepwise mechanism, through a zwitterionic tetrahedral intermediate (T^\pm), and a change in the rate-determining step, from formation to breakdown of T^\pm as the amine pK_a decreases. An exclusive review in this field is required. This paper includes review on displacement reaction at carbonyl compounds.

2. Results and Discussion

2.1. Stepwise Mechanism in Nucleophile Displacement at Carbonyl Center

Dey et al. [1a] reported, the kinetic studies of the reactions of α -chloroacetanilides ($\text{YC}_6\text{H}_4\text{NRC(=O)CH}_2\text{Cl}$; $\text{R}=\text{H}$ and CH_3) with pyridines have been carried out in dimethyl sulfoxide at 95°C . The pyridinolysis rates were faster with $\text{R}=\text{H}$ than with $\text{R}=\text{H}$ and $\text{R}=\text{CH}_3$ whereas the aminolysis rates with benzylamines were faster with both the substrates. The Brønsted β_X values were in the range from 0.30 to 0.32 and the cross-interaction constants, ρ_{XY} , were small negative values; $\rho_{XY} = -0.06$ and -0.10 for both the substrates. Based on these and other results, the pyridinolyses of α -chloroacetanilides were proposed to proceed via a stepwise mechanism with rate-limiting addition of the nucleophile to the carbonyl group to form zwitterionic tetrahedral intermediate (T^\pm) followed by a bridged type transition state to expel the leaving group. Similar reaction mechanism reported in literature supports this conclusion [1b, c]. The reaction system was as follows,

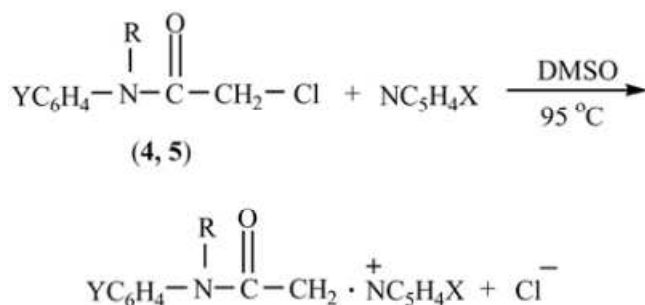


Figure 1. Reaction system of the pyridinolysis of α -chloroacetanilides (with $R=H$ and CH_3) in dimethyl sulfoxide at 95°C [1].

$R = H$ and CH_3 .

$Y = p\text{-CH}_3\text{O}, p\text{-CH}_3, H, p\text{-Cl}$ and $p\text{-NO}_2$.

$X = p\text{-CH}_3\text{O}, p\text{-CH}_3, m\text{-CH}_3$ (only for $R=\text{CH}_3$), $H, m\text{-C}_6\text{H}_5$ and $m\text{-COCH}_3$.

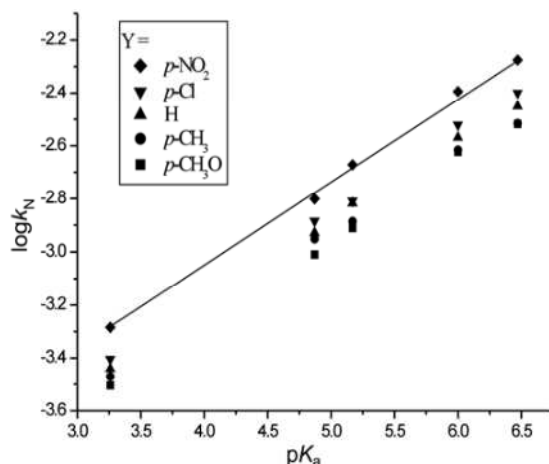
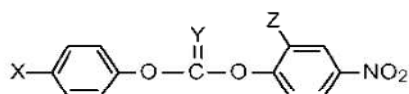


Figure 2. Brønsted plots of $\log k_N$ vs. $pK_a(X)$ for the pyridinolysis of $Y\text{-}\alpha$ -chloroacetanilides ($R = H$) in DMSO at 95°C [1].



$X = H, Y = O, Z = H$	PNPC
$X = H, Y = O, Z = \text{NO}_2$	PDNPC
$X = \text{Me}, Y = S, Z = H$	MPNPTOC
$X = \text{Me}, Y = O, Z = H$	MPNPC
$X = \text{Me}, Y = O, Z = \text{NO}_2$	MPDNPC

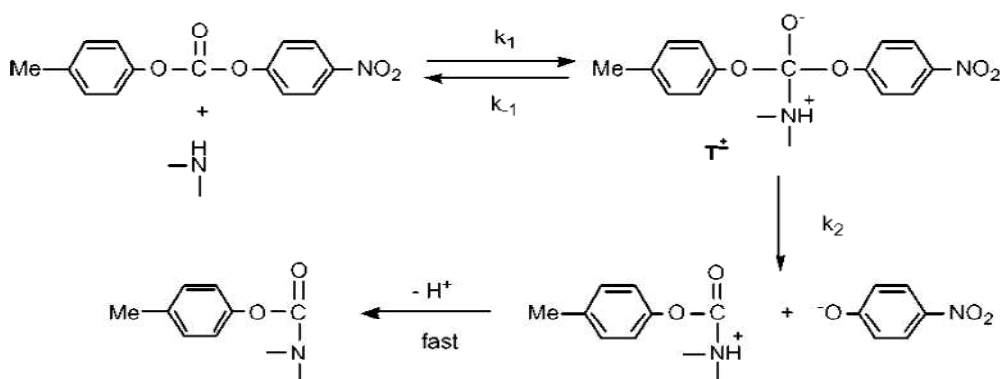
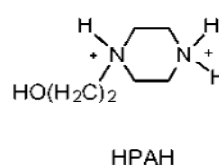
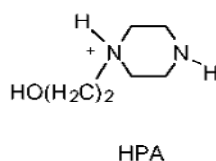


Figure 3. Reaction mechanism [2].

Castro et al. [2] [figure 3] reported a stepwise mechanism, through a zwitterionic tetrahedral intermediate (T^\pm), and a change in the rate-determining step, from formation to breakdown of T^\pm as the amine pK_a decreases for kinetics and mechanism of the aminolysis of 4-nitrophenyl and 2,4-dinitrophenyl 4-methylphenyl carbonates in aqueous ethanol.

In another work, Lee et al. [3a] reported Kinetic studies of the reactions of p -nitrophenyl N -phenylcarbamates with benzylamines in acetonitrile at 25.0°C . Lee et al. [3] reported the reaction mechanism as stepwise mechanism

involving rate-limiting breakdown of the zwitterionic tetrahedral intermediate T^\pm based on several grounds. The Hammett (ρ_X and ρ_Y) and Brønsted (β_X) coefficients determined are given in Table 1 for the k_2 step. The exceptionally large magnitudes of these selectivity parameters are consistent with the stepwise mechanism with rate-limiting breakdown of T^\pm ; both ρ_X and ρ_Y should be compared with other corresponding values after taking into account of a non-conjugating intervening group, CH_2 and NH , present in the benzylamine nucleophile and in the N -

phenylcarbamate substrate respectively, which are known to reduce the ρ values by a factor of ca 2-8.9. The large β_X values are also in line with the proposed mechanism, but they are less reliable since the pK_a values used are those in water, not in acetonitrile. However, it is well known that although the absolute pK_a values are different in H_2O and MeCN, the $\Delta pK_a = (pK_a)_{MeCN} - (pK_a)_{H_2O}$ values for the structurally similar amines are nearly the same. Thus the β_X values should be nearly the same in both H_2O and MeCN. Another important

parameter for reaction mechanism is Cross-interaction Constants. This constant indicates important mechanistic information. The ρ_{XY} was positive and relatively large, which was in line with stepwise mechanism; it has been shown both experimentally and theoretically that the sign of ρ_{XY} should be positive in contrast to the negative ρ_{XY} for the S_N2 (nucleophilic substitution bimolecular) reactions. The other articles have been considered to support this proposed mechanism [3b, c].

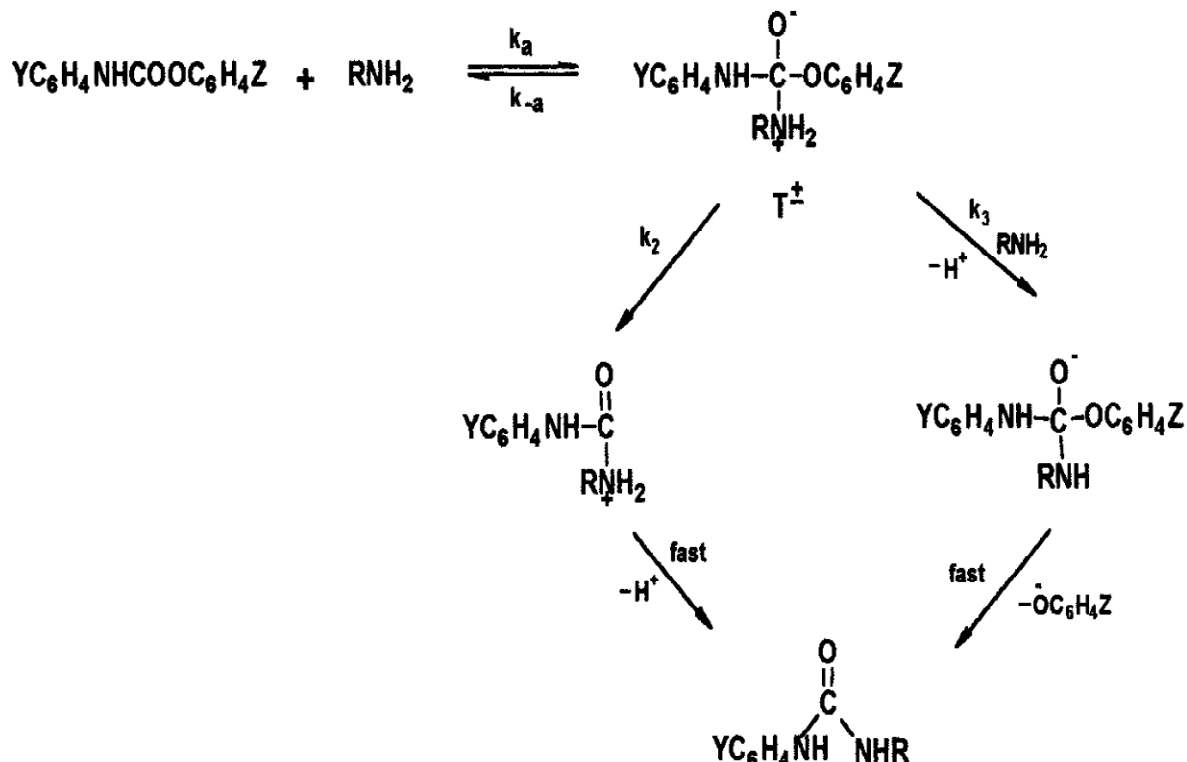


Figure 4. Reaction system of the reactions of *p*-nitrophenyl *N*-phenylcarbamates with benzylamines in acetonitrile at 25.0 °C [3].

For further verification of the similar mechanism Lee et al. [4] reported the mechanism of the anilinolysis of *S*-aryl *N*-arylthiocarbamates in acetonitrile. Authors concluded, The aminolysis reactions of *S*-aryl *N*-arylthiocarbamates ($YC_6H_4NH-C(=O)-SC_6H_4Z$) with anilines in acetonitrile showed rates were more influenced by the nucleophilicity of the nucleophile than the nucleofugality of the leaving group, but the change in the effective charge from reactants to the TS for formation of the tetrahedral intermediate was slightly greater in the leaving group (β_Z from -0.07 to -0.14) than in the nucleophile (β_X 0.04–0.12). The magnitude of the Brønsted coefficients were in the range of values that were consistent for a stepwise mechanism with rate-limiting formation of the zwitterionic tetrahedral intermediate. Signs of cross-interaction constants, ρ_{XY} (>0), ρ_{XZ} (>0) and ρ_{YZ} (<0), were all consistent with a stepwise mechanism.

In another report Lee et al. [5] reported a stepwise mechanism with rate-limiting expulsion of the phenoxide leaving group for the aminolysis reactions of ethyl aryl carbonates with benzylamines in acetonitrile at 25.0°C. Lee et al. [5] reported that, the aminolysis of ethyl aryl carbonates in acetonitrile proceeds by a stepwise mechanism with rate-

limiting expulsion of the phenoxide leaving group from the zwitterionic tetrahedral intermediate, T^\pm . Two reaction pathways, catalyzed and uncatalyzed paths, compete in most of the reactions; base catalyzed is not required for the reactions involving strong nucleophiles ($X = p-CH_3O$, $p-CH_3$) with a strong substituent ($Z = p-NO_2$). The proposed mechanism is based on (i) the large magnitude of ρ_X and especially of ρ_Z , (ii) the relatively large normal kinetic isotope effects ($k_H/k_D > 1.0$) involving a deuterated benzylamine nucleophile, (iii) the greater k_H/k_D values for the catalyzed path, and (iv) the low DH and DS values for both pathways, but with lower values for the base-catalyzed path than for the uncatalyzed reaction.

Nadar et al. [6] reported enhanced reactivity in the ammonolysis of phenyl thioacetates in aqueous medium the ammonolysis of thioesters proceeds through a simple bimolecular nucleophilic substitution pathway with a zwitterionic tetrahedral addition intermediate (T^\pm), whereby its formation is rate-determining (k_1 step). Comparison of this reaction of thioesters with a similar reaction of analogue oxyesters shows a mechanistic difference. Further, for thioesters there is a rate enhancement with larger k_N values.

The change in mechanism and enhanced reactivity observed by substitution of the oxygen atom by sulphur atom on the phenyl moiety.

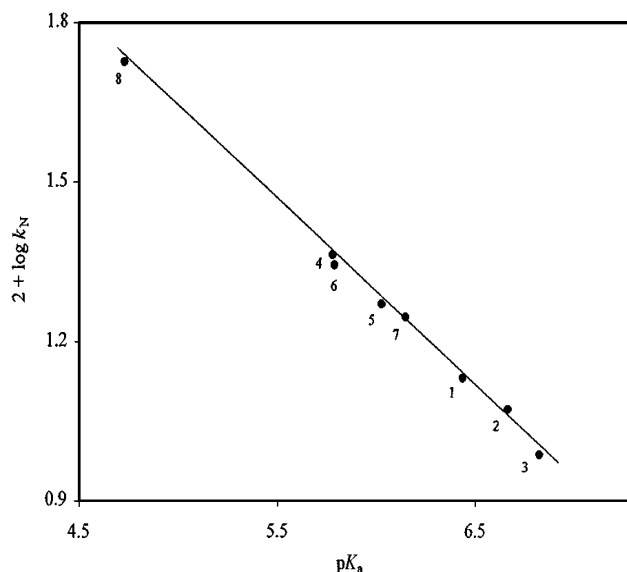


Figure 5. Brønsted-type plot obtained in the aminolysis of substituted phenyl thiolacetates in aqueous medium, 18 °C, ionic strength 0.1 M (KCl) [6].

Um et. al. [7a] reported that the aminolyses reactions of *p*-nitrophenyl acetate in water and dimethyl sulfoxide proceed through rate-determining breakdown of the addition intermediate mechanism. This conclusion was drawn based on the linear Brønsted-type plot with a large slope ($\beta_{nuc} = 0.76\text{--}0.82$) for both reactions run in H_2O and in DMSO. One can obtain useful information about the reaction mechanism from the magnitude of the β_{nuc} value for aminolysis reactions. It has generally been reported that a small β_{nuc} value (0.3 - 0.1) is obtained when the aminolysis reaction proceeds through a rate-determining formation of an addition intermediate, but a large β_{nuc} value (0.8 - 0.1) for aminolysis in which the RDS is rate determining breakdown of the addition intermediate. Um et al. [7b-f] reported similar mechanism found in literature representing strong evidences in support of this conclusion.

Castro et. al. [8] reported kinetics and mechanisms of the reactions of 3-methoxyphenyl, 3-chlorophenyl, and 4-cyanophenyl 4-nitrophenyl thionocarbonates with alicyclic amines. The reactions of 3-methoxyphenyl, 3-chlorophenyl, and 4-cyanophenyl 4-nitrophenyl thionocarbonates with a series of secondary alicyclic amines were studied kinetically in 44 wt % ethanol-water at 25.0 °C and an ionic strength of 0.2 M (KCl). Pseudo-first-order rate coefficients (k_{obsd}) were obtained for all reactions (amine excess was used). The reactions of substrates with piperidine, piperazine, and 1-(2-hydroxyethyl) piperazine exhibit linear k_{obsd} versus amine concentration plots with slopes (k_1) independent of pH. In contrast, the plots were nonlinear upward for the reactions of substrate with morpholine, 1-formylpiperazine, and piperazinium ion. For all these reactions, a reaction scheme was proposed with a zwitterionic tetrahedral intermediate T^\pm ,

which can be deprotonated by an amine to yield an anionic intermediate (T^-). When the nonlinear plots were fit through an equation derived from the scheme, rate and equilibrium microcoefficients were obtained. The Brønsted-type plots for k_1 were linear with slopes 0.22, 0.20, and 0.24 for the aminolysis of substrates, indicating that the formation of intermediate is rate-determining.

2.2. Other Mechanism

In some reports [9, 10] it was observed that the reaction of some $C=O$ substrates proceed through concerted mechanism. Oh and coworkers [9] reported that a concerted mechanism with a hydrogen bonded cyclic transition state for the aminolysis of aryl *N*-allyl thiocarbonates with benzylamines in acetonitrile based on the negative cross-interaction constant, failure of RSP.

Um et al. reported [10] concluded that the catalyzed reaction (i.e., breakdown of T^\pm to the products) proceeds through a concerted mechanism with a six-membered cyclic TS (i.e., TS cycl in Scheme 2) rather than via the alternative stepwise pathway with an anionic intermediate T^- . This proposal was based on the following data: (1) The catalytic effect decreases with increasing basicity of the incoming amine (a comparative Brønsted-type plot). This was possible only when a second amine molecule relays protons from the aminium moiety of T^\pm to the aryloxy leaving group. (2) A large negative entropy of activation is caused by restriction of the rotational and vibrational degrees of freedom in the cyclic TS. (3) An inverse DKIE is observed for the uncatalyzed reaction (i.e., $Kk_2^H/Kk_2^D = 2.88/3.10 = 0.93$), but a normal primary DKIE is obtained for the catalyzed process, in which the deprotonation and the donation of a proton by a second amine molecule occur in the RDS (i.e., $Kk_3^H/Kk_3^D = 22.4/6.94 = 3.23$). The proposed TS for the catalyzed route, TS_{cycl}, also bears a strong similarity to that previously advanced in the S_NAr reaction of 1-(*Y*-substituted phenoxo)-2,4-dinitrobenzenes with cyclic secondary amines in the same reaction medium (i.e., acetonitrile).

The change in mechanism was also found in some reaction systems. For example, Lee et al. [11a] reported the aminolysis reactions of *S*-aryl *N*-arylthiocarbonates ($YC_6H_4NH-C(=O)-SC_6H_4Z$) with anilines in acetonitrile are studied. The reaction rates are more influenced by the nucleophilicity of the nucleophile than the nucleofugality of the leaving group, but the change in the effective charge from reactants to the TS for formation of the tetrahedral intermediate is slightly greater in the leaving group (β_Z from -0.07 to -0.14) than in the nucleophile (β_X 0.04–0.12). The magnitude of the Brønsted coefficients were in the range of values that were consistent for a stepwise mechanism with rate-limiting formation of the zwitterionic tetrahedral intermediate. Signs of cross-interaction constants, ρ_{XY} (>0), ρ_{XZ} (>0) and ρ_{YZ} (<0), are all consistent with a stepwise mechanism. It was concluded that the change of the amine from benzylamines to anilines causes a shift of the aminolysis mechanism from a concerted to a stepwise process. These results have been explained based on other works [11b-e].

3. Conclusion

The nucleophilic displacement reactions were considered with high priority in organic chemistry. The series of reactions in this category conclude significant mechanism. It was observed based on extensive experiments that the mechanism include stepwise with intermediates, concerted and in some cases mechanism change from stepwise to concerted. Most of the possible mechanism have reviewed in this article which would be helpful researchers in this field. Important findings of this review article can be summarized as; most of the reactions at carbonyl center proceed through stepwise mechanism. A few proceed through concerted and some of the reactions in this category found to proceed through a mechanistic change.

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