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Evidence of a Stepwise Acyl-transfer Reaction Mechanism : Nonlinear Hammett Plots for Reactions of *p*-Nitrophenyl Substituted Benzoates with Hydroxide and *p*-Chlorophenoxide

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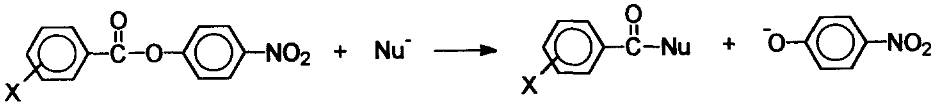
Abstract : The Hammett plots obtained for the title reactions exhibit a break, *i.e.* ρ_{acyl} values decrease from 2.21~2.44 to 1.45~1.52 as the acyl substituent becomes a strong electron withdrawing group ($\sigma > 0.6$). Such a break in the Hammett plots is suggestive of a change in the reaction mechanism and strong evidence of a stepwise mechanism for the acyl-transfer reaction. © 1997 Elsevier Science Ltd.

Due to the great importance of acyl-transfer reactions in chemistry and biochemistry, numerous studies have been carried out to investigate the reaction mechanism.[1-6] However, the mechanism of acyl-transfer reactions has not been completely understood but remains a subject of controversy. Acyl-transfer reactions have been suggested to occur by a stepwise mechanism with an addition intermediate,[1,2] or by a concerted mechanism with a single transition state (TS).[3-6]

Buncel *et al.* have suggested that acyl-transfer reactions proceed via a stepwise mechanism, based on Hammett type studies for reactions of substituted phenyl acetates,[1a,2] sulfonates[1b] and phosphinates[1c] with anionic nucleophiles. However, on the contrary, Williams has concluded that acyl-transfer reactions proceed via a concerted mechanism, based on linear Brönsted type plots obtained from reactions of *p*-nitrophenyl acetate (PNPA) and related sulfonate and phosphinate esters with various substituted phenoxides.[3] Recently, a similar conclusion has been drawn from the studies of isotope effects by Hengge,[4] Marcus effect by Guthrie[5] and structure-reactivity correlations by Jencks.[6a]


(1)

Nu$^-$ = OH$^-$, 4-ClC$_6$H$_4$O$^-$(ClPhO$^-$)
X = 4-MeO, 4-Me, 3-Me, H, 4-Cl, 3-Cl, 4-CN, 4-NO$_2$, 4-Cl-3-NO$_2$, 3,5-(NO$_2$)$_2$

Since the controversy concerning the reaction mechanisms is mainly based on interpretations of the effect of polar substituents in the leaving and attacking group on rates, we have performed the reaction of *p*-nitrophenyl X-substituted benzoates with OH$^-$ and *p*-chlorophenoxide (ClPhO$^-$), equation 1. The substituent in the acyl-moiety can influence both bond formation and fission rates. Therefore, the effect of substituents in the benzoyl moiety would be expected to provide useful information about the reaction mechanism.

The reactions were followed by monitoring the appearance of 4-nitrophenoxide at 410nm using a Hitachi U-2000 UV-Vis or an Applied Photophysics SX. 17 MV stopped-flow spectrophotometer. All the reactions were performed under pseudo-first order conditions at 25.0±0.1℃ in H_2O containing 20 mole % DMSO to eliminate a solubility problem. Second-order rate constants (k_2) were calculated from the slope of the plots of pseudo-first-order rate constants versus nucleophile concentrations (at least five different concentrations). The kinetic results are summarized in Table 1 and demonstrated graphically in Figure 1.

As shown in Figure 1, an electron withdrawing substituent (EWS) in the acyl moiety increases the reaction rate, while an electron donating substituent (EDS) leads to a decrease in rate for both OH$^-$ and ClPhO$^-$ systems. Interestingly, one can see breaks in the present Hammett plots. The effect of the acyl substituents on rates appears to be more sensitive for the electron donating and moderately withdrawing substituents ($\sigma < 0.6$) than for the strongly electron withdrawing ones ($\sigma > 0.6$) for both anionic nucleophiles.

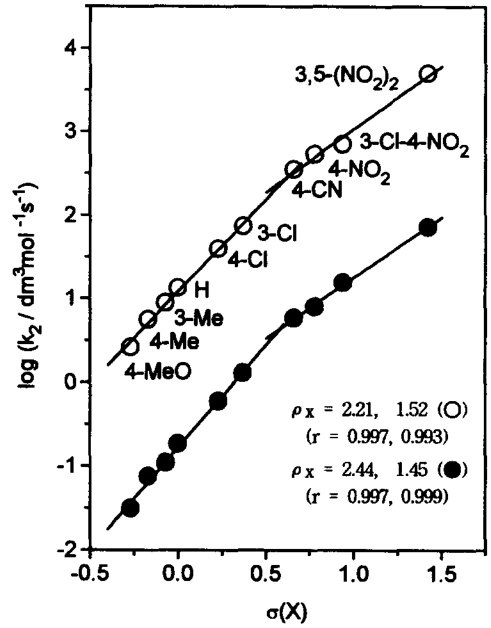


Figure 1. Hammett plots for the reactions of *p*-nitrophenyl X-substituted benzoates with OH$^-$(○) and *p*-chlorophenoxide(●) in H_2O containing 20 mole % DMSO at 25.0±0.1℃.

Table 1. Summary of Second-order Rate Constants (k_2) for the Reaction of *p*-Nitrophenyl X-substituted Benzoates with OH$^-$ and *p*-Chlorophenoxide in H_2O Containing 20 mole % DMSO at 25.0±0.1℃.

X / Nu$^-$	k_2, dm^3 mole^{-1} s^{-1}									
	4-MeO	4-Me	3-Me	H	4-Cl	3-Cl	4-CN	4-NO_2	4-Cl-3-NO_2	3,5-(NO_2)$_2$
OH$^-$	2.64	5.65	8.90	13.4	39.6	73.8	354	531	715	5,010
ClPhO$^-$	0.0316	0.0754	0.110	0.185	0.604	1.30	5.92	8.01	15.4	72.7

Such a break in Hammett plots has never been observed for reactions similar to the present study. Kirsh *et al.* performed the alkaline hydrolysis of *p*-nitrophenyl X-substituted benzoates (5 different substituents, *e.g.* X= 4-NMe_2, 4-Me, H, 4-Cl, 4-NO_2) in H_2O containing 33% MeCN, and found linear Hammett correlation with a large ρ_{acyl} (2.01) value and a good correlation coefficient (0.999).[7] However, the difference between the previous and our present results is not considered due to the difference in the reaction medium. One can consider that Kirsh *et al.* could not observe such a break because the substituents used in the previous study did not include a strong enough EWS such as 3,5-$(NO_2)_2$, and the number of substituents was not as many as in the present system. In fact, in our present alkaline hydrolysis, one can also obtain a straight line with a large ρ_{acyl} value (2.15) and a good correlation coefficient (0.998) if only 5 different substituents (4-MeO, 4-Me, H, 4-Cl, 4-NO_2) are included.

A downward curvature in Brönsted type plots for reactions of *p*-nitrophenyl acetate (PNPA) with various anionic nucleophiles has been ascribed by Jencks to progressive solvation of highly basic nucleophiles rather than a change in the reaction mechanism.[6b] However, a break in Hammett or Brönsted type plots has generally been interpreted as a change in the reaction mechanism.[8] In our present system, the Hammett plots are clearly consisting of two linear lines for both OH^- and $ClPhO^-$ systems. Therefore, the present nonlinear Hammett plots are considered to be solid evidence of a change in the reaction mechanism, rather than due to solvation since the nucleophiles are kept constant to OH^- and $ClPhO^-$.

Nucleophilic attack would be accelerated by an EWS in the acyl moiety but retarded by an EDS. Therefore, a large positive ρ_{acyl} value might be expected for the bond formation process between the anionic nucleophiles and the acyl carbon atom. In the present system, the ρ_{acyl} value in the region of the electron donating and moderately electron withdrawing substituents ($\sigma < 0.6$) has been calculated to be 2.21 and 2.44, for the reaction with OH^- and $ClPhO^-$, respectively. In many cases, the effect of substituents in the leaving group for alkaline hydrolysis of substituted phenyl benzoates or acetates was reported to be much less sensitive than the one in acyl moiety.[7,9] Such a large ρ_{acyl} value in the present system might be understood in terms of a proximity effect *i.e.*, the substituent in the acyl moiety is one atom closer to the reaction centre than the one in the leaving group.[7,9] However, the nature of reaction mechanism would be more responsible for the large ρ_{acyl} value than the proximity effect. A ρ_{acyl} value of 2.76 was reported for the equilibrium addition reaction of OH^- to substituted benzaldehydes by Bove and Zuman.[10] The calibration of the present ρ_{acyl} (2.21~2.44) by 2.76 results in 0.80~0.88, which indicates that the negative charge developed at the transition state (TS) remains mostly on the acyl moiety but is only slightly transferred to the leaving group for both reactions with OH^- and $ClPhO^-$. Therefore, one can suggest that the present acyl transfer reactions for the substrates containing electron donating and moderately electron withdrawing acyl substituents ($\sigma < 0.6$) proceed via a step-wise mechanism, in which the nucleophilic attack by the anionic nucleophiles to form an addition intermediate is the slow step and leaving group departure is little advanced at the rate determining

TS.

On the other hand, leaving group departure would be inhibited by an EWS but favored by an EDS in the acyl moiety. Accordingly, one might expect relatively a small ρ_{acyl} value if leaving group departure is involved in the RDS whether in a stepwise or a concerted mechanism due to the compensation effect. In fact, the ρ_{acyl} value in the present system has been obtained to be 1.52 and 1.45 for the reaction with OH^- and $ClPhO^-$, respectively, in the region of the strong EWSs ($\sigma > 0.6$). The calibration of these ρ values by 2.76 results in 0.55 and 0.53 for OH^- and $ClPhO^-$, respectively, which is about 31~40% smaller than the values obtained from the EDSs and weak EWS ($\sigma < 0.6$). These reduced ρ values clearly suggest that the negative charge at the rate determining TS is transferred from the acyl moiety to the leaving group to a certain extent, indicating that leaving group departure is involved in the RDS in the strong EWS region. Therefore, it is proposed that the reaction mechanism changes as the acyl substituent varies from EDS to strong EWS ($\sigma > 0.6$), and our finding of a break in the Hammett plots is strong evidence of a stepwise mechanism for the present acyl-transfer reactions.

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