Communications

The Effect of Acyl Substituent on the α-Effect in the Aminolysis of p-Nitrophenyl X-Substituted Benzoates

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Received May 6, 1997

The term α-effect has been given to the abnormally enhanced nucleophilic reactivity shown by a certain group of nucleophiles possessing one or more nonbonding electron pairs adjacent to the nucleophilic center (the α-position) by Edwards and Pearson in 1962.[1] Since then numerous theories have been suggested to explain the cause of the α-effect: (a) destabilization of the ground state (GS) due to electronic repulsion between the nonbonding electron pairs,[2] (b) intramolecular general acid/base catalysis,[3] (c) polarizability,[1] (d) stabilization of the transition state (TS),[4,5] (e) solvent effect.[6,7] However, none of these factors alone is conclusive. Particularly, the effect of solvent on the α-effect has been a subject of controversy.[6,7] Bruice,[6a] Curci,[6b] Ritchie,[6c] and Moss[6d] have suggested that solvent effect is not important for the α-effect, while Depuy[7a] and Wolfe[7b] have claimed that solvent effect is responsible for the α-effect.

Recently, Buncel and Um have demonstrated that the α-effect is significantly solvent dependent.[8,9] The magnitude of the α-effect has been obtained to be increasing with increasing the mole % DMSO in the reaction medium up to near 50% and then to be decreasing upon further additions of DMSO for the reaction of p-nitrophenyl acetate with butane-2,3-dione monoximate and p-chlorophenoxide in DMSO-H₂O mixtures of varying compositions.[8] Interestingly, the magnitude of the α-effect for the corresponding reactions performed in MeCN-H₂O mixtures has been obtained to be increasing with increasing mole % MeCN,[9] indicating solvent effect on the α-effect is significant. However, solvent effect on the GS and TS contributions has not clearly been dissected.

In order to investigate the GS effect on the α-effect, we have performed reactions of p-nitrophenyl X-substituted ben-

zoates with a series of primary amines including two α-effect nucleophiles (hydrazine and hydroxylamine). Aminolyses of carboxylic esters have been widely studied, and the reaction mechanisms are fairly well known.[10,11] However, the effect of acyl substituents on the α-effect as in the present system has not been investigated.
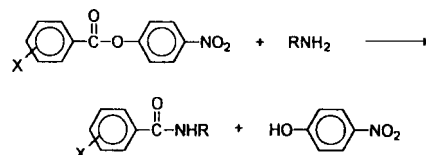
X=4-MeO, 4-Me, H, 4-Cl, 4-CN, 4-NO₂, 3,5-(NO₂)₂

RNH₂=NH₂NH₂, HONH₂, and a series of primary amines

The reaction was followed by monitoring the appearance of the leaving p-nitrophenoxide ion at 410 nm (or p-nitrophenol at 350 nm for the reaction with HONH₂) using a Hitachie U-2000 UV-Vis spectrophotometer for slow reactions ($t_{1/2} > 10$ sec) or an Applied Photophysics SX. 17 MV stopped-flow spectrophotometer for the fast reactions ($t_{1/2} < 10$ sec). All the reactions studied here obeyed pseudo-first-order kinetics up to over 90% of total reaction. The observed rate constants (k_{obs}) was calculated from the equation, $\ln(A_\infty - A_t) = -k_{obs} \cdot t + C$. The plots of kobs versus amine concentration showed linearity in all cases, indicating that general base catalysis often observed in aminolyses of esters is absent in the present system. The apparent second-order rate constants (k_{app}) were calculated from the slope of the plot of kobs vs amine concentration.

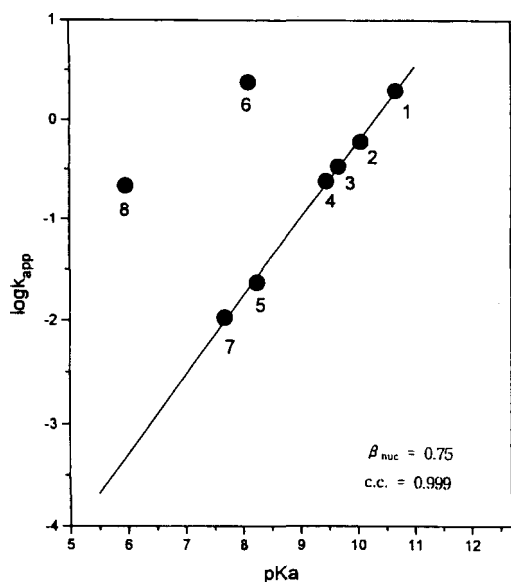As shown in Figure 1, the reactivity of the primary amines increases with increasing amine basicity, which results

Figure 1. A Brönsted type plot for the reaction of p-nitrophenyl benzoate with RNH_2 in H_2O containing 20 mole % DMSO at 25.0 °C. (R=1. Et-, 2. $-CH_2CO_2H$, 3. $-CH_2CH_2OH$, 4. $C_6H_5CH_2-$, 5. $-CH_2CONHCH_2CO_2H$, 6. $-NH_2$, 7. $-CH_2CO_2C_2H_5$, 8. HO-)
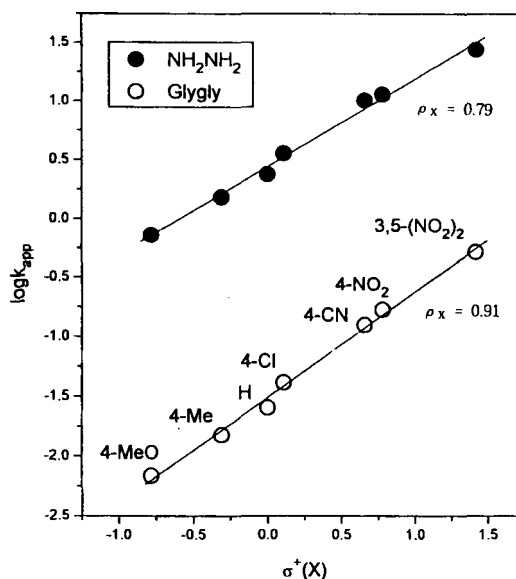

Figure 2. Hammett plots for the reaction of p-nitrophenyl X-substituted benzoates with NH_2NH_2 (●) and glycylglycine (○) in H_2O containing 20 mole % DMSO at 25.0 °C.

in a good linear Brönsted plot. However, NH_2NH_2 and $HONH_2$ show positive deviations from the linearity, suggesting that the α-effect is manifest in the present system. Aminolysis has been understood to proceed in a stepwise mechanism. The rate determining step (RDS) has been suggested to be dependent on the basicity of the leaving group and the incoming amine, i.e. the RDS changes from the leaving group departure to nucleophilic attack as the basicity of amines becomes about 4-5 pKa unit higher than that of the leaving group in most carboxylic esters.[10,11] Since the most basic amine in the present system is $EtNH_2$ and it is only about 3.5 pKa unit more basic than the leaving p-nitrophenoxide, an RDS change would occur beyond $EtNH_2$. Therefore, the linear Brönsted plot clearly indicates that there is no RDS change in the present aminolysis.

The β_{nuc} value obtained in the present system is 0.75, which is slightly smaller than the one (β_{nuc}=1.02) for the reaction of p-nitrophenyl benzoate with a series of substituted phenoxides in the same reaction condition.[12] Since the magnitude of β_{nuc} values represents the degree of electron transfer from the nucleophile to the substrate at the TS,[10-12] one can expect that the degree of electron transfer would be less significant for the amine system (neutral nucleophiles) than the aryloxide system (anionic nucleophiles). Therefore, the smaller β_{nuc} value obtained in the present system compared with the one obtained in the corresponding reactions with the anionic nucleophiles is consistent with expectation.

In order to study the effect of acyl substituents on the reactivity and the α-effect, reactions of p-nitrophenyl X-substituted benzoates with NH_2NH_2 and glycylglycine (glygly) were performed, and the kinetic results are demonstrated graphically in Figure 2. As shown in the figure, the reactivity of the benzoate esters increases with increasing the electron withdrawing ability of the substituent X, and good linear Hammett plots are obtained for both NH_2NH_2 and glygly systems. It is noted that σ^+ constants give excellent

correlation with log k and large positive ρ_X value are obtained, eg 0.75 and 0.88 for the NH_2NH_2 and glygly system, respectively. The present result is quite interesting and unusual, since negative ρ_X values have been obtained in most cases when σ^+ constants give better correlation than σ constants.

The Hammett ρ_X value for the NH_2NH_2 appears to be slightly smaller than the one for the glygly system. Since NH_2NH_2 is more reactive than glygly toward all the substrates studied, the reactivity-selectivity principle (RSP)[13] appears to be operative in the present system. However, the ρ_X value in the present aminolysis are considered to be significantly smaller than the one for the corresponding reactions with anionic nucleophiles. In our recent study, ρ_X values have been obtained to be in a range of 2.17-2.80 for the reactions of p-nitrophenyl X-substituted benzoates with aryloxides in the same reaction condition.[14] The difference in the charge type between the neutral amines and anionic aryloxides might influence the magnitude of ρ values, as discussed in the preceeding section. However, such a difference in the charge type is not considered to be solely responsible for the significant difference in the ρ_X values. The difference in the reaction mechanism between the two systems is considered to be more responsible for such a large difference in ρ_X value. It has been suggested that the reaction of aryl benzoates with anionic nucleophiles proceeds via rate determining nucleophilic attack, and followed by fast leaving group departure.[12,14] In this mechanism, the electronic nature of the acyl substituents would influence the reaction rate significantly and would result in large ρ_X values (ρ_X=2.17-2.80 in the reactions with aryloxides)[14]. However, on the contrary, aminolysis of carboxylic esters as in the present system has been understood to proceed via rate-determining leaving group departure.[10,11] In this mechanism, an electron withdrawing group (EWG) would accelerate the nucleophilic attack process but retard the leaving group departure process. Consequently, the electronic
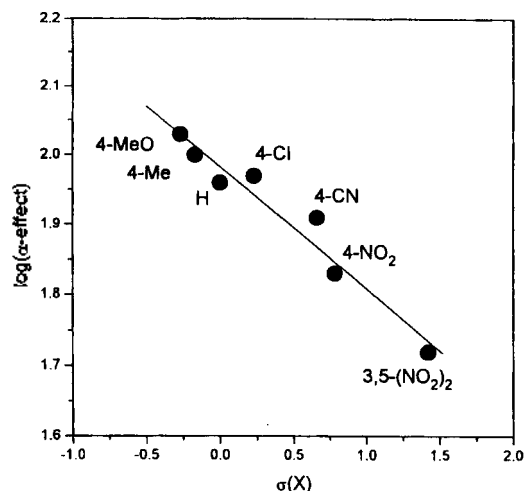
Figure 3. A plot showing dependence of α-effect (kNH_2NH_2/kglygly) on the acyl substituents for the reaction of p-nitrophenyl X-substituted benzoates with NH_2NH_2 and glycylglycine in H_2O containing 20 mole % DMSO at 25.0 °C.

nature of the acyl substituents would be compensated by the opposite substituent effect and result in small ρ_X values (ρ_X=0.75-0.88 in the present system). Therefore, the significant difference in ρ_X values between the amine and aryloxide systems is considered mainly due to difference in reaction mechanism.

In Figure 3 has been demonstrated the magnitude of the α-effect against σ constants. As shown in the figure, the magnitude of the α-effect decreases with increasing electron withdrawing ability of the acyl substituents. The magnitude of the α-effect has been suggested to be influenced by many factors, such as the hybridization type of the electrophilic center (sp > sp^2 > sp^3),[13] the magnitude of Brönsted β_{nuc} values,[15] solvents,[7-9] polarizability[4,16] and the basicity of α-effect nucleophiles.[9a,17] However, the dependence of the α-effect on the acyl substituents as in the present system has never been observed. In the present system, solvent, the basicity of nucleophiles and the hybridization of the substrate are constant. Besides, the acyl substituents would not change the polarizability of the reaction center and β_{nuc} value significantly.

It has often been suggested that the GS of α-effect nucleophiles is destabilized either by desolvation or by the electronic repulsion between the nonbonding electron pairs.[2,7] Since the nucleophiles are kept constant (hydrazine and glygly), the difference in GS destabilization between the two nucleophiles would be also constant no matter what the acyl substituent is. Therefore, one might expect constant α-effect if the GS effect were responsible for the α-effect in the present system. However, the present result is contrary to the expectation, indicating that the GS effect is not responsible for the α-effect. This is consistent with Bruice's observation that the GS solvation effect between NH_2NH_2 and glygly is negligible for the α-effect observed in the reactions with malachite green.[6a] Therefore, it is proposed that GS destabilization is less important than TS stabilization for

the α-effect observed in the present aminolysis.

References

1. Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16.
2. Edwards, J. O.; Ibne-Rosa, K. M. *J. Am. Chem. Soc.* **1962**, *84*, 763.
3. Jencks, W. P.; Gerstein, J. *J. Am. Chem. Soc.* **1965**, *86*, 4655.
4. Buncel, E.; Wilson, H. *J. Chem. Educ.* **1987**, *64*, 475.
5. Hoz, S.; Buncel, E. Isr. *J. Chem.* **1985**, *26*, 313.
6. (a) Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 4400. (b) Curci, R.; Di Furia, F. *Int. Chem. Kinet.* **1975**, *7*, 341. (c) Ritchie, C. D.; Minasz, R. J.; Kamego, A. A.; Sawada, M. *J. Am. Chem. Soc.* **1977**, *99*, 3747. (d) Moss, R. A.; Swarup, S.; Ganguli, S. *J. Chem. Soc. Chem. Commun.* **1987**, 860.
7. (a) DePuy, C. H.; Della, E. W.; Filley, J.; Grabowski, J. J.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2481. (b) Wolfe, S.; Mitchell, D. J.; Schlegel, H. B.; Minot, C.; Eisenstein, O. *Tetrahedron Lett.* **1982**, *23*, 615.
8. (a) Buncel, E.; Um, I. H. *J. Chem. Soc., Chem. Commun.* **1986**, 595. (b) Tarkka, R. M.; Buncel, E. *J. Am. Chem. Soc.* **1995**, *117*, 1503.
9. (a) Um, I. H.; Oh, S. J.; Kwon, D. S. *Tetrahedron Lett.* **1995**, *36*, 6903. (b) Um, I. H.; Yoon, H. W.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1993**, *14*, 425. (c) Um, I. H.; Jung, J. K.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1993**, *14*, 12. (d) Um, I. H.; Hahn, G. J.; Lee, G. J.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1992**, *13*, 642.
10. (a) Castro, E. A.; Pizarro, M. I.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 5982. (b) Oh, H. K.; Shin, C. H.; Lee, I. *J. Chem. Soc. Perkin Trans. 2.* **1995**, 1169. (c) March, J. *Advanced Organic Chemistry*; Wiley: New York, 1985; Chapts 10 and 16.
11. Um, I. H.; Kwon, H. J.; Kwon, D. S.; Park, J. Y. *J. Chem. Res. (M).* **1995**, 1801.
12. Um, I. H.; Jeon, J. S.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1991**, *12*, 406.
13. Buncel, E.; Wilson, H.; Chuaqui, C. *J. Am. Chem. Soc.* **1982**, *104*, 4896.
14. Um, I. H.; Min, J. S.; Jeon, J. S.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1995**, *16*, 569.
15. Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 3248.
16. Um, I. H.; Kim, G. R.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1992**, *13*, 632.
17. (a) Hudson, R. F.; Hansell, D. P.; Wolfe, S.; Mitchell, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1406. (b) Terrier, F.; MacCormark, P.; Kizilian, E.; Halle, J. C.; Demerseman, P. *J. Chem. Soc., Perkin Trans. 2* **1991**, 153.