



# The effect of acyl substituents on the $\alpha$ -effect: contrasting $\alpha$ -effect profiles for reactions of 4-nitrophenyl substituted benzoates with neutral and anionic nucleophiles

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**Abstract**—The magnitude of the  $\alpha$ -effect for reactions of 4-nitrophenyl substituted benzoates with a pair of anionic nucleophiles is independent of the electronic nature of the acyl substituent, while the one for the corresponding reactions with a pair of neutral nucleophiles increases as the acyl substituent changes from a strong electron withdrawing substituent to electron donating ones. © 2001 Elsevier Science Ltd. All rights reserved.

The term  $\alpha$ -effect was given to the abnormally enhanced nucleophilic reactivity shown by nucleophiles having an atom with one or more nonbonding electron pairs at the  $\alpha$ -position from the nucleophilic center.<sup>1</sup> The magnitude of the  $\alpha$ -effect has been suggested to be governed by many factors such as the basicity of  $\alpha$ -effect nucleophiles,<sup>2</sup> the magnitude of Brønsted  $\beta_{\text{nuc}}$  values,<sup>3</sup> the hybridization type of electrophiles,<sup>4,5</sup> electrophilic center atoms<sup>6</sup> and solvents.<sup>7–9</sup>

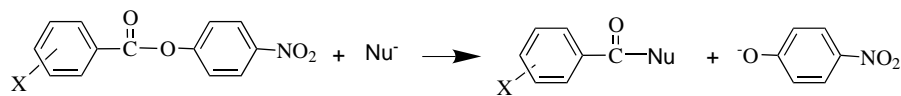
Recently, we have demonstrated that the magnitude of the  $\alpha$ -effect is strongly dependent on the medium for the reaction of 4-nitrophenyl acetate with butane-2,3-dione monoximate ( $\text{Ox}^-$ ) as an  $\alpha$ -effect nucleophile and 4-chlorophenoxide ( $\text{ClPhO}^-$ ) as a corresponding normal nucleophile in  $\text{DMSO-H}_2\text{O}$  and in  $\text{MeCN-H}_2\text{O}$  mixtures of varying compositions.<sup>6–9</sup> The  $\alpha$ -effect ( $k_{\text{Ox}^-}/k_{\text{ClPhO}^-}$ ) increased on addition of DMSO in the reaction medium up to near 50 mol% DMSO, and then decreased upon further addition of DMSO, resulting in a bell-shaped dependence of the  $\alpha$ -effect on solvent composition.<sup>7</sup> However, the  $\alpha$ -effect for the same reactions run in  $\text{MeCN-H}_2\text{O}$  mixtures increased steadily as the mol% MeCN in the medium increased.<sup>8</sup> The bell-shaped  $\alpha$ -effect profile

with a maximum  $\alpha$ -effect at ca. 50 mol% DMSO has also been observed for the corresponding reaction of 4-nitrophenyl diphenyl phosphinate and 4-nitrophenyl benzenesulfonate.<sup>6</sup> Similarly, the increasing  $\alpha$ -effect profile upon addition of MeCN in the medium has been found to be common for the reactions of substituted phenyl acetates in  $\text{MeCN-H}_2\text{O}$  mixtures, although the magnitude of the  $\alpha$ -effect was demonstrated to be significantly dependent on the electronic nature of the substituent in the leaving group.<sup>9b</sup>

It appeared to us as highly informative to investigate the effect of acyl substituents on the  $\alpha$ -effect. Herein we report the first such results for an  $\alpha$ -effect system, kinetic studies of the reactions of 4-nitrophenyl X-substituted benzoates (**1a–1j**) with a pair of anionic nucleophiles,  $\text{Ox}^-$  and  $\text{ClPhO}^-$ , as shown in Eq. (1). Surprisingly, the  $\alpha$ -effect profile obtained from the reactions of **1a–1j** with the anionic nucleophiles contrasts with the one obtained previously from the reactions of **1a–1j** with a pair of neutral nucleophiles, hydrazine ( $\text{NH}_2\text{NH}_2$ ) as an  $\alpha$ -effect nucleophile and glycylglycine (glygly) as a corresponding normal nucleophile.<sup>10a</sup> The  $\alpha$ -effect for the reactions with the anionic nucleophiles,  $k_{\text{Ox}^-}/k_{\text{ClPhO}^-}$ , is independent of the electronic nature of the acyl substituents, while the  $\alpha$ -effect for the corresponding reactions with the neutral nucleophiles,  $k_{\text{NH}_2\text{NH}_2}/k_{\text{glygly}}$ , increases as the acyl substituent changes from a strong electron withdrawing substituent to electron donating ones. Two plausible causes of the contrasting  $\alpha$ -effect profile are discussed.

**Keywords:**  $\alpha$ -effect; amines; kinetics; mechanism; substituent effect.

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(1)

$\text{Nu}^- = \text{MeC(O)C(Me)=NO}^- (\text{Ox}^-)$  and  $4\text{-ClC}_6\text{H}_4\text{O}^- (\text{ClPhO}^-)$

$\text{X} = 4\text{-MeO (1a)}, 4\text{-Me (1b)}, 3\text{-Me (1c)}, \text{H (1d)}, 4\text{-Cl (1e)}, 3\text{-Cl (1f)},$   
 $4\text{-CN (1g)}, 4\text{-NO}_2 \text{ (1h)}, 4\text{-Cl-3-NO}_2 \text{ (1i)}, 3,5\text{-(NO}_2)_2 \text{ (1j)}$

The kinetic study was performed spectrophotometrically by monitoring the appearance of 4-nitrophenoxide ion at 410 nm. All the reactions obeyed pseudo-first-order kinetics up to over 90% of the total reaction, and the observed pseudo-first order rate constants ( $k_{\text{obs}}$ ) were obtained from the well known equation,  $\ln(A_\infty - A_t) = -k_{\text{obs}}t + c$ . Usually, five different concentrations of nucleophiles were employed and replicate values of  $k_{\text{obs}}$  were determined to obtain the second-order rate constants from the slope of linear plots of  $k_{\text{obs}}$  versus nucleophile concentrations. The second-order rate constants obtained in this way are summarized in Table 1.

As shown in Table 1, the second-order rate constants are strongly dependent on the electronic nature of the acyl substituent, i.e. the second-order rate constant for the reaction with  $\text{Ox}^-$  increases from  $6.43 \text{ M}^{-1} \text{ s}^{-1}$  to  $34.2$  and  $15,500 \text{ M}^{-1} \text{ s}^{-1}$  as the acyl substituent X changes from 4-MeO to H and 3,5-( $\text{NO}_2$ )<sub>2</sub>, respectively. A similar result is obtained for the reaction with  $\text{ClPhO}^-$ . It is also seen that  $\text{Ox}^-$  is much more reactive than  $\text{ClPhO}^-$  for all the substrates, indicating the  $\alpha$ -effect is significant in the present reaction system. The effect of acyl substituents on the  $\alpha$ -effect ( $k_{\text{Ox}^-}/k_{\text{ClPhO}^-}$ ) for the reaction of **1a–1j** with  $\text{Ox}^-$  and  $\text{ClPhO}^-$  is demonstrated in Fig. 1 together with the  $\alpha$ -effect for the reaction of **1a–1j** with  $\text{NH}_2\text{NH}_2$  and glygly ( $k_{\text{NH}_2\text{NH}_2}/k_{\text{glygly}}$ ) for comparison. One can see that the magnitude of the  $\alpha$ -effect for the reactions of **1a–1j** with the anionic nucleophiles is much larger than that for the corresponding reaction with the neutral amine nucleophiles. More surprisingly, the  $\alpha$ -effect profile obtained from the reaction of **1a–1j** with  $\text{Ox}^-$  and  $\text{ClPhO}^-$  contrasts with the one obtained from the corresponding reaction with  $\text{NH}_2\text{NH}_2$  and glygly, i.e. the magnitude of

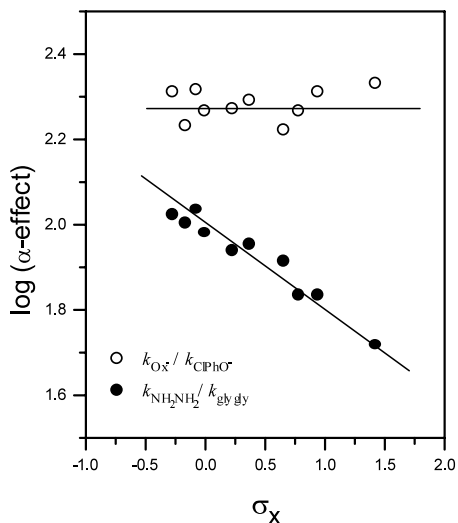
the  $\alpha$ -effect for reactions of **1a–1j** with  $\text{Ox}^-$  and  $\text{ClPhO}^-$  remains independent of the electronic nature of the acyl substituents, while the one for the reaction with  $\text{NH}_2\text{NH}_2$  and glygly increases as the acyl substituent changes from a strong electron withdrawing substituent (EWS) to electron donating substituent (EDS).

One might attribute the contrasting  $\alpha$ -effect profile to a difference in the reaction mechanism between the reactions with the anionic nucleophiles and with the neutral amine nucleophiles. It has generally been understood that aminolyses of carboxylic esters proceed through an addition intermediate and the rate determining step (RDS) is dependent on the basicity of the leaving group and the amine nucleophile.<sup>10–12</sup> The RDS of aminolysis reactions has been suggested to change from breakdown of the addition intermediate to products to formation of the intermediate as the amine nucleophile becomes more basic than the leaving group by 4–5  $\text{p}K_{\text{a}}$  units.<sup>10–12</sup> The RDS of the reactions of **1a–1j** with  $\text{NH}_2\text{NH}_2$  and glygly has been reported to be the breakdown of the addition intermediate, since these amines are only ca. 1  $\text{p}K_{\text{a}}$  unit more basic than the leaving 4-nitrophenoxide.<sup>10a</sup> On the other hand, acyl-transfer reactions with anionic nucleophiles have been suggested to proceed either through a one-step concerted<sup>13</sup> or through a stepwise mechanism.<sup>14</sup> However, the RDS of the acyl transfer reaction with anionic nucleophiles as in the present system has been suggested to be the nucleophilic attack process, whether the reaction proceeds concertedly or in stepwise fashion.<sup>14</sup> Therefore, the difference in the RDS between the reactions with amines and with the anionic nucleophiles might be a plausible cause of the contrasting  $\alpha$ -effect profile shown in Fig. 1.

**Table 1.** Summary of second-order rate constants for reactions of 4-nitrophenyl X-substituted benzoates with  $\text{Ox}^-$  and  $\text{ClPhO}^-$  in water containing 20 mol% DMSO at  $25.0 \pm 0.1^\circ\text{C}$

X	$k_{\text{Ox}^-} (\text{M}^{-1} \text{s}^{-1})$	$k_{\text{ClPhO}^-} (\text{M}^{-1} \text{s}^{-1})$
4-MeO	6.43	0.0316
4-Me	12.9	0.0754
3-Me	22.8	0.110
H	34.2	0.185
4-Cl	113	0.604
3-Cl	254	1.30
4-CN	990	5.92
4-NO <sub>2</sub>	1470	8.01
4-Cl-3-NO <sub>2</sub>	3160	15.4
3,5-(NO <sub>2</sub> ) <sub>2</sub>	15500	72.7

The magnitude of the  $\alpha$ -effect has been suggested to be governed by the ground-state (GS) and transition-state (TS) energies.<sup>7–9</sup>  $\text{Ox}^-$  has recently been reported to be 5.7 kcal/mol less solvated than  $\text{ClPhO}^-$  in 20 mol% DMSO.<sup>7b</sup> This difference in the GS energy between  $\text{Ox}^-$  and  $\text{ClPhO}^-$  should be responsible for the  $\alpha$ -effect shown by  $\text{Ox}^-$  to a certain degree. However, the GS energy difference between these nucleophiles is constant, since  $\text{Ox}^-$  and  $\text{ClPhO}^-$  were used for all the reactions of **1a–1j**. Similarly, the GS energy difference between  $\text{NH}_2\text{NH}_2$  and glygly is also constant. Accordingly, if the GS contribution to the  $\alpha$ -effect is more responsible than the TS contribution, one can expect that the magnitude of the  $\alpha$ -effect would be constant. As shown in Fig. 1, the  $\alpha$ -effect for the reactions with  $\text{Ox}^-$  and  $\text{ClPhO}^-$  is nearly constant, indicating that the GS contribution to the  $\alpha$ -effect is more significant than the TS contribution. However, the  $\alpha$ -effect for the



**Figure 1.** The effect of acyl substituents on the  $\alpha$ -effect for reactions of **1a–1j** with  $\text{Ox}^-$  and  $\text{CPhO}^-$ , and with  $\text{NH}_2\text{NH}_2$  and glygly in 20 mol% DMSO at  $25.0 \pm 0.1^\circ\text{C}$ . The  $\alpha$ -effect data for the reactions with  $\text{NH}_2\text{NH}_2$  and glygly were taken from Ref. 10a.

reactions with  $\text{NH}_2\text{NH}_2$  and glygly increases as the acyl substituent changes from a strong EWS to EDS, indicating that the GS contribution to the  $\alpha$ -effect is less significant than the TS contribution for the reactions with the neutral amine nucleophiles. Therefore, it is proposed that the difference in the GS and TS contributions to the  $\alpha$ -effect is another plausible cause of the contrasting  $\alpha$ -effect profile found from the reaction with the anionic nucleophiles and with the neutral amine nucleophiles.

More quantitative analysis of the GS and TS contributions to the  $\alpha$ -effect is currently under way together with the studies of other charged  $\alpha$ - and normal-nucleophile pairs to determine whether this reactivity is, in fact, general.

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