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The Effect of Polarizability on Reactivity of 4-Nitrophenyl Benzoate and Its Sulfur Containing Analogues with Anionic Nucleophiles in Ethanol

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2nd-order rate constants have been measured spectrophotometrically for the reactions of 4-nitrophenyl benzoate (1), S-4-nitrophenyl thiobenzoate (2) and 4-nitrophenyl thionbenzoate (3) with alkoxides, aryloxides and thioaryloxides in absolute ethanol at 25.0 ± 0.1 °C. The substitution of O by polarizable S in the leaving group has little affected the reactivity of 2 toward the charge localized species (e.g. EtO^- and $\text{CF}_3\text{CH}_2\text{O}^-$), while the effect of the similar replacement in the carbonyl group has led to a decrease in reactivity by a factor of 10. However, the reactivity of these esters toward charge delocalized aryloxides has been found to be in the order $1 < 3 \leq 2$. The effect of replaced sulfur atom on reactivity becomes more significant for the reaction with polarizable thioaryloxides, i.e. the reactivity increases in the order $1 < 2 \ll 3$. The difference in reactivity for the present system is attributed to a polarizability effect.

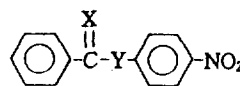
Introduction

Nucleophilic reactivity has been suggested to be governed by many factors, such as basicity of nucleophiles and leaving groups,¹ ionization potential of nucleophiles,² solvation,³ etc.⁴ However, unusual reactivity has often been reported for reactions involving polarizable reactants.⁵ Pearson has attempted to explain the unusual reactivity shown by polarizable reactants in terms of hard and soft acids and bases (HSAB) principle.⁵ The explanations based on the HSAB principle have been satisfactory for many types of reactions in a qualitative manner. However, exceptions have frequently been reported and these could be attributed to a lack of systematic study.

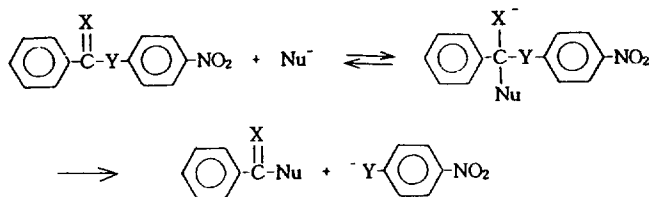
We have chosen the following reaction system in order to study the effect of polarizability on reaction rates systematically. The structure of 1 would not be changed upon the substitution of the oxygen atom by a sulfur atom either in the ether-like oxygen (1→2) or in the carbonyl oxygen (1→3). However, the polarizability of the reaction center would

be considered to increase gradually but significantly. Besides, the nucleophiles employed in the present study are in a wide range of polarizability, such as charge localized alkoxides (EtO^- and $\text{CF}_3\text{CH}_2\text{O}^-$), charge delocalized aryloxides and an oximate (Ox^-), and charge delocalized polarizable thioaryloxides (PhS^- and $p\text{-ClPhS}^-$). Thus, the present study would give us an important information regarding polarizability effect on reaction rates.

Since the acylated coenzyme A, an intermediate in many biological reactions, was known to be a thiol ester, studies of thiol esters have been accelerated.⁶ However thion esters have not intensively been studied due to difficulties in preparations. The substrates studied in the present investigation are biologically important. Therefore, the present study would be considered to help us understand the reactivity of the biologically important compounds.



- 1 : X=Y=O, 4-nitrophenyl benzoate
- 2 : X=O, Y=S, S-4-nitrophenyl thiobenzoate
- 3 : X=S, Y=O, 4-nitrophenyl thionbenzoate



Nu⁻ : alkoxides (EtO⁻ and CF₃CH₂O⁻)
 aryloxides (p-MeOPhO⁻, p-MePhO⁻, PhO⁻,
 p-ClPhO⁻, m-ClPhO⁻, p-CNPhO⁻), oximate (Ox⁻)
 thioaryloxides (PhS⁻ and p-ClPhS⁻)

Experimental

Materials. Chemicals used in the present study were of the highest quality available from Aldrich, and generally recrystallized or distilled before use. Substrates 1 and 2 were easily prepared by a known procedure^{7a} and identified by means of melting points. Substrate 3 was synthesized from the reaction of thionbenzoyl chloride with 4-nitrophenol.⁸ Thionbenzoyl chloride (bp. 58-60 °C / 0.1 mmHg, lit.⁹ 60-65 °C / 0.1 mmHg) used was prepared by treatment of SOCl₂ with C₆H₅CS₂H which was freshly prepared from Grignard reaction of CS₂ with C₆H₅MgBr in a dry ether solution. Absolute ethanol was prepared by the method described in the literature^{7b} under a nitrogen atmosphere. Potassium ethoxide solution was prepared by dissolving potassium metal in absolute ethanol under a nitrogen atmosphere, and titrated against potassium hydrogen phthalate. Two equivalent amounts of 18-crown-6-ether were used for the reactions of EtO⁻ K⁺ and CF₃CH₂O⁻ K⁺ in order to prevent metal ion catalysis.¹⁰ Other low basic nucleophile solutions were prepared using Me₄NOH·5H₂O and the respective conjugate acid of nucleophile. An equivalent amount of the conjugate acid of nucleophile was added to suppress formation of ethoxide by solvolysis as described previously.¹¹

Instruments. For the slow reaction whose half life is longer than 10 seconds, the kinetic studies were performed with a Hitachi U-2000 model UV-VIS spectrophotometer equipped with a Neslab RTE-110 model constant temperature circulating bath to keep the temperature in the UV cell at 25.0 ± 0.1 °C. For the fast reaction whose half life is shorter than 10 seconds, an Applied Photophysics SX. MV-17 stopped-flow spectrofluorimeter was used.

Kinetics. The kinetic method used in the present study was similar to the one reported previously.¹¹

Results

Pseudo-first-order rate constants (k_{obs}) were calculated from the Guggenheim plots, $\ln(A_{\infty} - A_t) = -k_{obs}t + C$, which were linear over 90% of the total reactions. Second-order rate constants were obtained from the slopes of the linear plots of k_{obs} versus concentration of nucleophile. Generally the intercepts of these plots were very small, indicating that the contribution of ethoxide and/or ethanol to the rate was negligible.

Discussion

Reactions of Charge Localized Nucleophiles. The

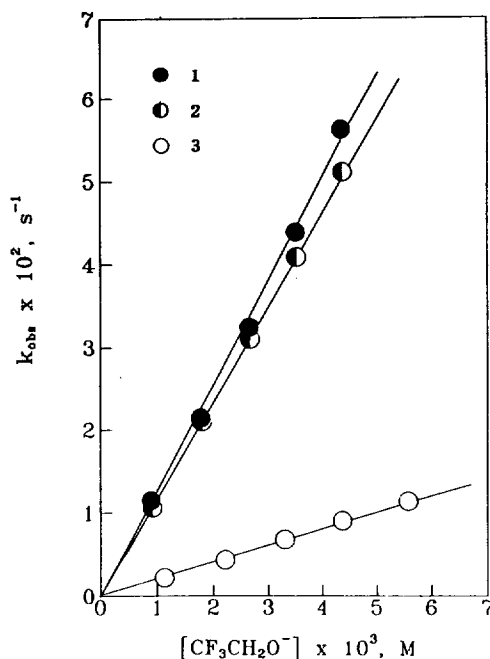


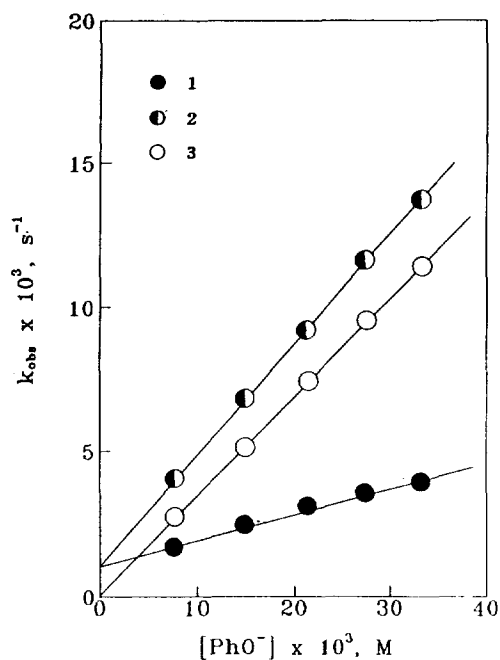
Figure 1. Plots showing dependence of k_{obs} on the concentration of nucleophile for the reactions of 1, 2, and 3 with CF₃CH₂O⁻ in absolute ethanol at 25.0 ± 0.1 °C.

replacement of the ether-like oxygen by sulfur atom (1→2) would increase nucleofugality (leaving group ability), since the pK_a of ArSH is about 2 pK_a units smaller than that of the corresponding ArOH.¹² Such an introduction of a sulfur atom has also been reported to increase the charge polarization of the C=O bond based on an intensive IR study of various thiol esters.¹³ However, the charge polarization is considered to be more significant when the carbonyl oxygen is replaced by a sulfur atom (1→3) than the ether-like oxygen (1→2) according to ¹³C NMR studies.¹⁴ ¹³C NMR data showed a marked deshielding effect for the C=S compound in comparison with the corresponding C=O compound,¹⁴ i.e. the chemical shift of carbon was observed to appear 46 ppm down field shift for the thion ester (3) and about 21 ppm for the thiol ester (2) from that of the carbonyl carbon in 1.^{14a} Therefore, the sulfur containing esters (2 and 3) are expected to be more reactive than the corresponding oxygen ester (1) due to increased nucleofugality and/or charge polarization.

As shown in Figure 1, the reactivity of 2 with CF₃CH₂O⁻ is not much different from that of 1 (11.4 M⁻¹s⁻¹ and 13.2 M⁻¹s⁻¹, respectively). A similar result can be seen from Table 1 for the reaction of 1 and 2 with EtO⁻. Since the leaving group ability of 4-nitrothiophenoxide in 2 is expected to be much higher than that of 4-nitrophenoxide in 1, one might expect 2 is significantly more reactive than 1. However, this expectation would only be valid when the leaving group departure is involved in the rate-determining step. In our recent mechanistic study, the reaction of 1 and 2 with anionic nucleophiles has been suggested to proceed *via* a rate-determining formation of an addition intermediate followed by a fast breakdown of it.¹⁵ In this mechanism, the leaving group departure occurs after the rate-determining step. Consequently, it is considered that the enhanced leaving group ability

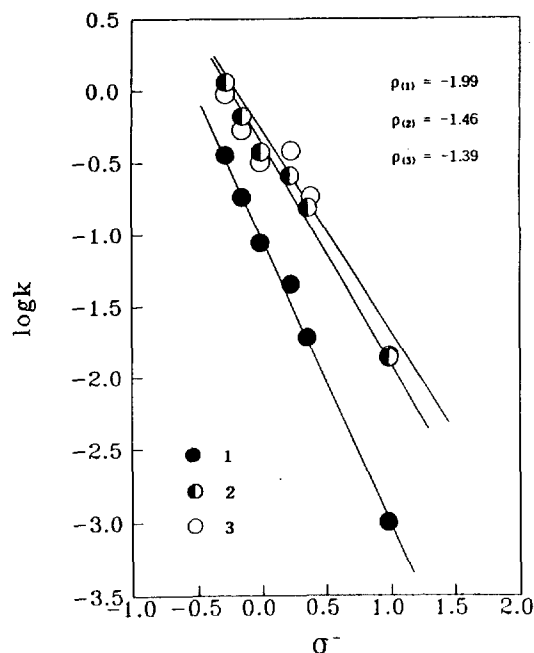
Table 1. Summary of second-order rate constants (k) for the reactions of 1, 2 and 3 with various types of anionic nucleophiles in absolute ethanol at 25.0 ± 0.1 °C.

Nu ⁻ (pK_a NuH)		$k \times 10^2, M^{-1}s^{-1}$		
		1	2	3
1. EtO ⁻	(16.0) ^a	1160	1260	140
2. CF ₃ CH ₂ O ⁻	(12.4)	1320	1140	238
3. <i>p</i> -CNPhO ⁻	(7.95)	0.100	1.40	1.40
4. <i>m</i> -ClPhO ⁻	(9.02)	1.89	15.1	16.4
5. <i>p</i> -ClPhO ⁻	(9.38)	4.52	27.6	34.7
6. PhO ⁻	(9.95)	8.91	38.8	33.3
7. <i>p</i> -CH ₃ OPhO ⁻	(10.2)	18.4	69.3	55.5
8. <i>p</i> -CH ₃ OPhO ⁻	(10.2)	36.7	114	102
9. Ox ⁻	(9.44)	1740	2710	2840
10. <i>p</i> -ClPhS ⁻	(7.50)	0.0761	1040	5180
11. PhS ⁻	(7.80)	2.87	1570	7360

^a pK_a values were taken from ref. 12.**Figure 2.** Plots showing dependence of k_{obs} on the concentration of nucleophile for the reaction of 1, 2 and 3 with PhO⁻ in absolute ethanol at 25.0 ± 0.1 °C.

could not influence the reactivity of 2.

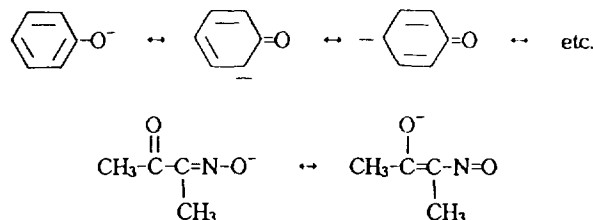
Since the electrophilicity of the thion ester (3) would be much greater than that of the corresponding oxygen ester (1) due to enhanced charge polarization of the C=S bond, one might expect that 3 would be more reactive than 1. However, on the contrary to the expectation, the former is up to 10 folds less reactive than the latter, as shown in Figure 1 and in Table 1 toward the charge localized alkoxides (EtO⁻ and CF₃CH₂O⁻). The negative charge in the alkoxides is highly localized on the oxygen atom, which increases the hardness of the nucleophilic center. Therefore, the interaction between the polarizable substrate (3) and nonpolarizable alkoxide is considered to be very weak based on the

**Figure 3.** Hammett plots for the reaction of 1, 2 and 3 with aryloxides in absolute ethanol at 25.0 ± 0.1 °C.

HSAB principle.⁵ This argument is evident from the fact that the reactivity of ethoxide toward 3 is comparable with that of *p*-methoxyphenoxide ($1.40 M^{-1}s^{-1}$ and $1.02 M^{-1}s^{-1}$, respectively), although the former is about 6 pK_a units more basic than the latter.¹² Thus, the unusual low reactivity of ethoxide toward 3 appears to indicate that polarizability effect on rate is significant in the present reaction system.

Reactions of Charge Delocalized Nucleophiles.

The negative charge on the aryloxides and the oximate can be delocalized by resonance as shown below. Therefore, one would consider that these nucleophiles are polarizable and would exhibit significant rate enhancement toward the polarizable substrates 2 and 3. In fact, 2 and 3 are more reactive than 1 as shown in Figure 2 and Table 1. Such a reactivity order is an opposite result obtained from the reactions of charge localized and nonpolarizable alkoxides (EtO⁻ and CF₃CH₂O⁻) as shown in Table 1. Therefore, one might attribute the enhanced reactivity of 2 and 3 toward the charge delocalized aryloxides and oximate to a polarizability effect, based on the HSAB principle.



Hammett plots have been constructed for the reactions of the substrates (1, 2, 3) with 6 aryloxides. As shown in Figure 3, good Hammett correlations can be seen for all the substrates, indicating that the reactions proceed in a same mechanism.¹⁶ Interestingly, when an electron withdrawing substituent is placed on an aryloxide, the reactivity

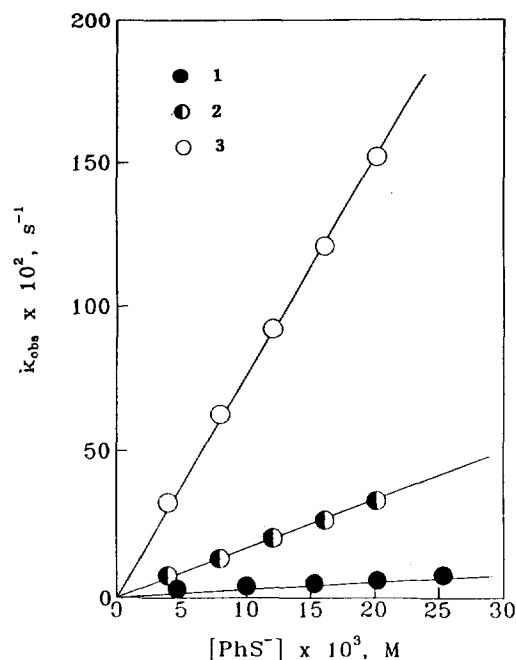


Figure 4. Plots showing dependence of k_{obs} on the concentration of nucleophile for the reaction of 1, 2 and 3 with PhS^- in absolute ethanol at 25.0 ± 0.1 °C.

of 3 becomes higher than that of 2. On the contrary, 3 is less reactive than 2 toward the aryloxide containing an electron donating group. In consequence, the magnitude of the Hammett ρ value decreases as the polarizability of the substrate increases, *i.e.* $\rho(1) > \rho(2) > \rho(3)$. Such a decreasing trend of the ρ value is consistent with the proposal¹⁷ that the coulombic interaction between the electrophile (LUMO) and the nucleophile (HOMO) becomes less important but the orbital interaction plays a more important role as the polarizability of the reactant increases. Therefore, it appears to give more credence to the argument that the enhanced reactivity of 2 and 3 originates from a polarizability effect.

However, a careful examination of Table 1 reveals that the sulfur containing substrates 2 and 3 are 3-14 folds more reactive than the oxygen analogue (1) toward the aryloxides and only 1.4 folds more reactive toward the Ox^- . Such rate enhancements are not as significant as predicted based on the HSAB principle.

Although the negative charge on the aryloxides and Ox^- could be delocalized by resonance, the nucleophilic center atom of these nucleophiles is the oxygen atom. Since O is a highly electronegative atom, the polarizability of these nucleophiles would not be significant. This would account for the fact that rate enhancements in the present system are much smaller than would be expected.

Reactions of Charge Delocalized and Polarizable Nucleophiles. As shown in Figure 4, PhS^- is extremely unreactive toward 1. Furthermore, the reactivity of PhS^- is much smaller than that of PhO^- toward 1 (*e.g.* $k^{\text{PhS}^-}/k^{\text{PhO}^-} = 0.32$) as demonstrated in Table 1. One might attribute the low reactivity of PhS^- toward 1 to its low basicity, since the pK_a of ArSH is much smaller than that of the corresponding ArOH .¹² A similar result can be seen for the correspon-

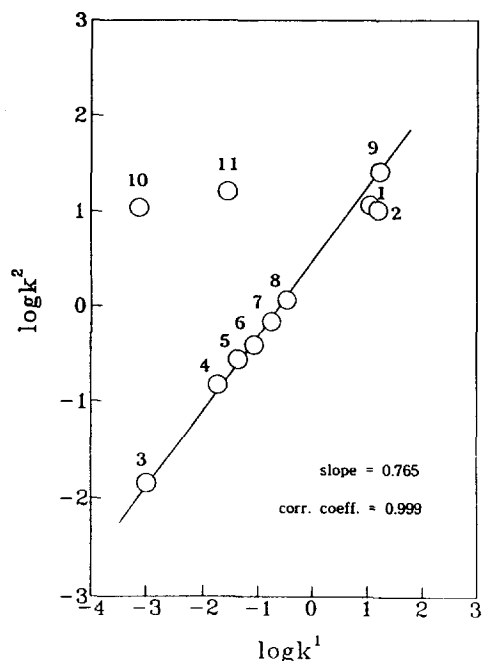


Figure 5. Plots of logarithmic second-order rate constant for the reaction of 2 ($\log k^2$) vs. logarithmic second-order rate constant for the reaction of 1 ($\log k^1$). The numbers refer to the nucleophiles in Table 1.

ding reaction of 1 toward $p\text{-ClPhS}^-$ (*e.g.* $k^{p\text{-ClPhS}^-}/k^{p\text{-ClPhO}^-} = 0.02$). However, on the contrary to the reaction of 1, the sulfur centered nucleophiles are significantly more reactive than the corresponding oxygen centered ones toward polarizable substrates 2 and 3, *i.e.* PhS^- is 40 and 221 times more reactive than PhO^- toward 2 and 3, respectively. If the nucleophilic reactivity is mainly governed by the basicity of the nucleophiles, one would expect that the less basic thiophenoxide is also less reactive than the more basic phenoxide toward 2 and 3. In fact, the present result is opposite to the expectation, which implies that the basicity of a nucleophile cannot be a measure of the nucleophilicity for the reactions involving polarizable reactants as in the present system. This argument can be further supported from the fact that PhS^- is 52 folds more reactive than EtO^- toward 3, although the former is about 8 pK_a units less basic than the latter.

It has generally been considered that the nucleophilic center of ArS^- is highly polarizable due to the large size of S atom and charge delocalization by resonance as is in the ArO^- system. Therefore, the high polarizability of the sulfur centered nucleophiles is considered to be responsible for the unusual high reactivity of these nucleophiles toward the polarizable substrates 2 and 3. On the contrary, the low reactivity of these polarizable nucleophiles toward the oxygen ester 1 would be attributed to the difference in polarizability between the reactants, on the basis of the HSAB principle.

In order to examine the effect of polarizability on reaction rates, logarithmic second-order rate constant for the reaction of 1 ($\log k^1$) against that for the corresponding reactions of 2 ($\log k^2$) and 3 ($\log k^3$) is plotted in Figures 5 and 6, respectively. As shown in Figure 5, the charge delocalized oxyanionic nucleophiles (ArO^- and Ox^-) fall on a linear line. The cha-

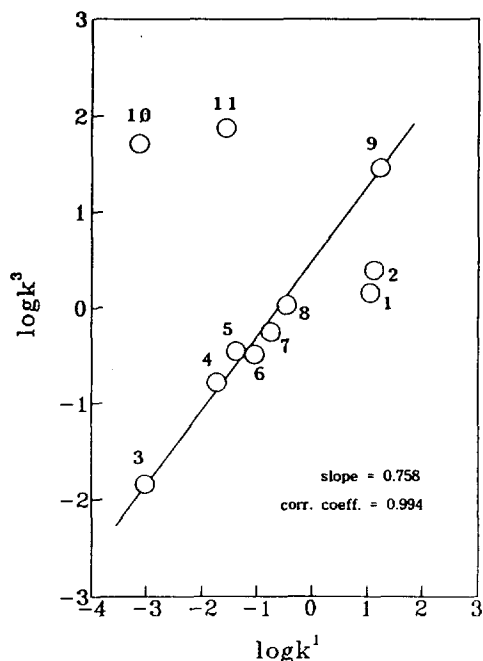


Figure 6. Plots of logarithmic second-order rate constant for the reaction of 3 ($\log k^3$) vs. logarithmic second-order rate constant for the reaction of 1 ($\log k^1$). The numbers refer to the nucleophiles in Table 1.

rges localized alkoxides (EtO^- and $\text{CF}_3\text{CH}_2\text{O}^-$) exhibit only small downward deviations from the linear line, while the polarizable PhS^- and $p\text{-ClPhS}^-$ deviate significantly upward. Such deviations are even more significant when the rate comparison is made for the more polarizable substrate 3. As shown in Figure 6, the polarizable PhS^- and $p\text{-ClPhS}^-$ deviate more positively while nonpolarizable EtO^- and $\text{CF}_3\text{CH}_2\text{O}^-$ do more negatively from the linear line composed of the charge delocalized ArO^- and Ox^- . Therefore, the deviations observed in these Figures appear to reflect the fact that the effect of polarizability on rate is important and the HSAB principle is operative in the present system.

Conclusion

Substitution of O by polarizable S in the leaving group or in the carbonyl group of 1 influences the reactivity significantly, depending on the degree of polarizability of the attacking nucleophiles. The reactivities of polarizable substrates 2 and 3 increase significantly toward polarizable nucleophiles (ArS^-), and decrease toward nonpolarizable nucleophiles

(RO^-), indicating that the effect of polarizability on rate is significant in the present system.

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