The Effect of the Changing of C-O-C to C-S-C and C=O to C=S on Reactivity of 4-Nitrophenyl Benzoate with Alkali Metal Ethoxides in Ethanol

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Rate constants have been measured spectrophotometrically for the reactions of alkali metal ethoxides with 4-nitrophenyl benzoate, S-4-nitrophenyl thiobenzoate and 4-nitrophenyl thionbenzoate in ethanol at 25°C. Substitution of S for O in the leaving group has not affected reactivity significantly, while the effect of the similar replacement in the acyl group has led to rate decrease by a factor of 10, although pronounced rate enhancements have been expected for both systems. The replacement of O by a polarizable S has also influenced the reactivity of the esters toward alkali metal ethoxides, *i.e.* the reactivity decreases as the size of the metal ion decreases. The alkali metal ions have showed inhibition effect instead of catalytic effect which would have been expected for the present system. The effect of replaced sulfur atom on the reactivity for the present system is attributed to the nature of hard and soft acids and bases.

Introduction

Among many factors influencing nucleophilic reactivity, the effect of polarizability of reactants on nucleophilicity has often been suggested to be important.[1] The best known description based on polarizability is the Pearson's concept of hard and soft acids and bases (HSAB).[2] Although many types of unusual chemical reactivities can be explained in a qualitative manner based on the so-called HSAB principle, exceptions have also been reported frequently,[3] and this could be attributed to the lack of a systematic study.

For a systematic investigation of the Pearson's concept, we have chosen the following esters of I, II, and III as the substrates reacting with alkali metal ethoxides in ethanol. The replacements of the oxygen by a polarizable sulfur atom in the ether like oxygen or in the carbonyl oxygen of carboxylic esters would not cause a structural change. However, the difference in polarizability of the reaction site would be gradually but significantly increased as the substrate changes from I to II and III. Thus the substrates of I-III would be considered to be proper for a systematic study. In addition, the present system would also give us useful informations on the reactions of the biologically important thiol and thion esters.
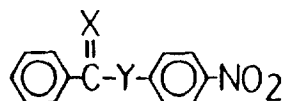

I: X=Y=O   ; 4-nitrophenyl benzoate
II: X=O, Y=S ; S-4-nitrophenyl thiobenzoate
III: X=S, Y=O ; 4-nitrophenyl thionbenzoate

In the present paper, we would like to report a remarkable effect of the replaced sulfur in 4-nitrophenyl benzoate (I; PNPB) on reactivity for the nucleophilic substitution reactions as expressed in equation (1).

Experimental

Materials. Compound I and II were easily prepared by

$$\text{equation (1)}$$

$$M^+ \; ; \quad Li^+ , Na^+ , K^+$$
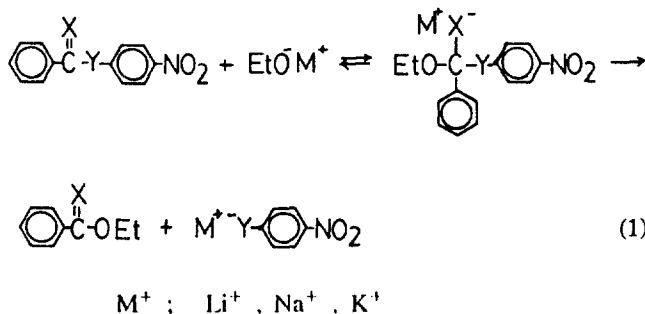
a known procedure and identified by means of melting point and spectral data. Compound III was synthesized from the reaction of thionbenzoyl chloride with 4-nitrophenol and synthesized (mp. 106-107°C, lit. 98-101°C[4a], 106~107°C[4b]). Thionbenzoyl chloride (bp. 58-60°C/0.1 mmHg, lit.[4c] 60-65°C/0.1 mmHg) used was prepared by treatment of SOCl₂ with C₆H₅CS₂H which was prepared from Grignard reaction of CS₂ with C₆H₅MgBr in a dry ether solution. Absolute ethanol was prepared by the method described in the literature[5] under a nitrogen atmosphere. Alkali metal ethoxide solutions were prepared by dissolving corresponding alkali metal in the absolute ethanol under a nitrogen atmosphere. The concentration of the stock solutions of EtOM were titrated against potassium hydrogen phthalate.

Instruments. The measurements of melting point were performed with a Buchi 510 melting point apparatus. The kinetic study was performed with a Hitachi U-2000 model UV-Vis spectrophotometer equipped with a Neslab model constant temperature circulating bath to keep the temperature in the UV cell at 25.0±0.1°C.

Kinetics. The reactions were followed by monitoring the replacing 4-nitrophenoxide or 4-nitrothiophenoxide ion at a fixed wavelength (λ_{max} of ArY⁻). Typically, reaction was initiated by adding 5 μl of 0.02 M solution of the substrate in CH₃CN by syringe to a 10-mm UV cell containing 2.50 ml of absolute ethanol and EtO⁻M⁺ solution. Generally, EtO⁻M⁺ concentration was varied over the range $(1-20) \times 10^{-3}$ M while the ester concentration was 4×10⁻⁵M.

Table 1. Kinetic Data for the Reactions of EtO⁻M⁻ with the Substrates I, II and III in Ethanol at 25℃

|	[LiOEt] ×10³,M	k_{obs} ×10²,s⁻¹	[NaOEt] ×10³,M	k_{obs} ×10²,s⁻¹	[KOEt] ×10³,M	k_{obs} ×10²,s⁻¹
PNPB (I)	0.821	0.704	0.542	0.614	0.631	0.621
	1.73	1.79	1.17	1.35	1.35	1.48
	2.62	2.87	1.79	2.12	2.06	2.37
	3.50	3.92	2.41	2.92	2.76	3.24
	4.37	4.94	3.01	3.59	3.44	4.09
	$k_2=12.0$ M⁻¹s⁻¹		$k_2=12.2$ M⁻¹s⁻¹		$k_2=12.4$ M⁻¹s⁻¹	
PNTPB (II)	0.821	0.906	0.542	0.726	0.631	0.749
	1.73	2.09	1.17	1.37	1.35	1.84
	2.62	2.92	1.79	2.38	2.06	2.71
	3.50	3.91	2.41	2.97	2.76	3.63
	4.37	4.78	3.01	3.91	3.44	4.68
	$k_2=10.8$ M⁻¹s⁻¹		$k_2=12.9$ M⁻¹s⁻¹		$k_2=13.7$ M⁻¹s⁻¹	
PNPTB (III)	4.46	0.412	3.10	0.309	3.54	0.352
	8.60	0.716	5.98	0.588	6.82	0.669
	12.4	1.03	8.65	0.827	9.87	0.962
	16.0	1.25	11.1	1.03	12.7	1.22
	19.4	1.49	13.5	1.23	15.4	1.45

Results

Reactions of the alkali metal ethoxides with the substrates of I-III in absolute ethanol were studied spectrophotometrically by monitoring the appearance of the absorption due to the generated 4-nitrophenoxide or 4-nitrothiophenoxide ion. The reactions were carried out under pseudo-first-order conditions with the alkali metal ethoxide concentration in excess of the substrate. Pseudo-first-order rate constants were calculated from the plots of ln $(A_\infty-A_t)$ vs t, which were linear over ca. 90% reaction. Second-order rate constants where possible were obtained from the slopes of the linear plots of k_{obs} vs [EtO⁻M⁺].

In Table 1 are presented the pseudo-first-order rate constants for the reactions of alkali metal ethoxides with the substrates I-III in ethanol at 25℃. The data are shown graphically in Figures 1-4.

Discussion

Effect of Sulfur in C-Y-C on Rate. Significant carbonyl bond shifts to lower frequencies have often been observed when the ether-like oxygen atom of carboxylic esters is replaced by sulfur. This was once attributed to contribution of structure **4** involving participation of sulfur 3d orbitals.[6] However, there is considerable evidence in favour of structure **2** and **3**, and the low carbonyl frequency of the thiol ester has been attributed to vibrational perturbation due to the mass of the C-S bond.[7] An intensive NMR study of thiol esters allowed Idoux *et al.* to conclude that **3** makes little contribution to the structure of a thiol ester relative to an oxygen ester, since the unshared electron pairs on the large sulfur atom are not able to overlap efficiently with the adja-
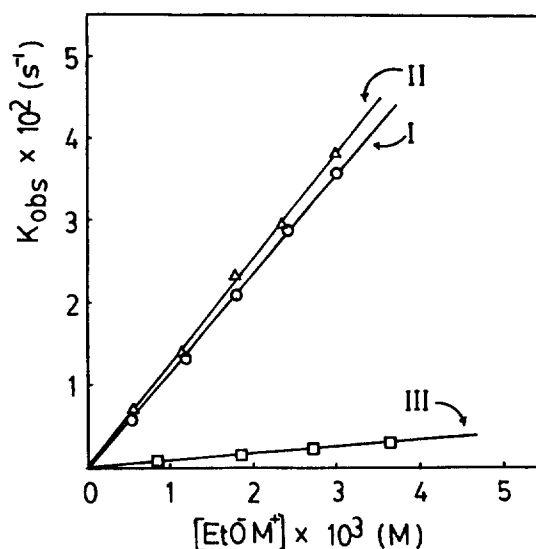
Figure 1. Plots of observed rate constant versus concentration of EtO⁻Na⁺ for the reactions of I, II and III with EtO⁻Na⁻ in ethanol at 25℃.

cent carbonyl group to form a double bond.[8]

X=O, S
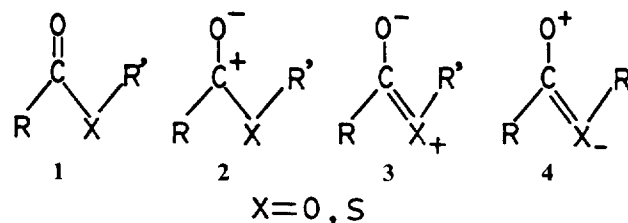
Therefore, the contribution of structure **2** should be more significant for II than I, which should effectively render the carbonyl group of II more enhanced electrophilicity compared to the one in ester I. However, there is no significant reactivity difference between I and II as seen in Table 1 and Figure 1. Furthermore, the basicity of the thiophenoxide is known to be ca. 4 pK_a unit lower than the corresponding phenoxide,[9] and therefore the thiol ester would have been expected to exert a significantly enhanced nucleofugacity compared to the oxygen analogue.

The absence of leaving group effect for the present system might be attributed to the nature of rate-determining-step (RDS). It has been generally believed that the present type of acyl transfer reaction proceeds *via* a rate-determining attack of the anionic nucleophile followed by a fast breakdown of the tetrahedral intermediate. Since the leaving group departure is not involved in the RDS the enhanced nucleofugacity would not be reflected in reactivity. However, the absence of the leaving group effect for the present system can not be attributed solely to the nature of the reaction mechanism, since there is considerable evidence that 4-nitrothiophenoxide is much better leaving group than 4-nitrophenoxide. For example, the thiol ester such as p-nitrothiophenyl acetate has been reported to be up to 300 times more reactive toward polarizable thiophenoxide ions than the corresponding oxygen ester.[10] Thus, the nature of HSAB is also responsible for the present rate data, since ethoxide has been considered to be a hard base and therefore it shows poor
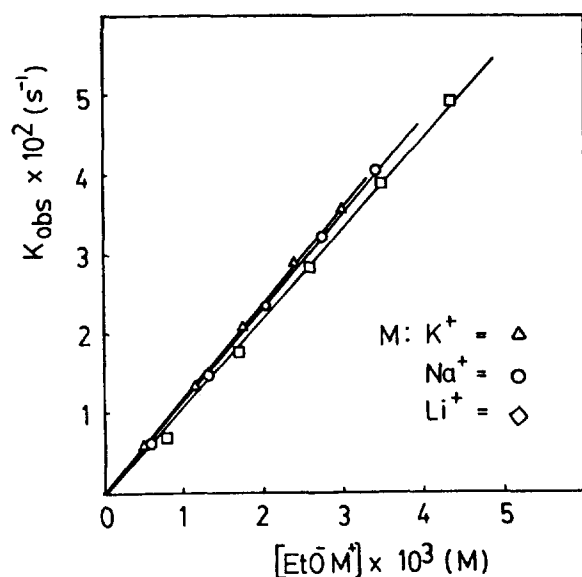
Figure 2. Plots of observed rate constant versus concentration of EtO⁻M⁺ for the reactions of I with EtO⁻M⁺ in ethanol at 25℃.

Figure 3. Plots of observed rate constant versus concentration of EtO⁻M⁺ for the reactions of II with EtO⁻M⁺ in ethanol at 25℃.

reactivity toward the soft substrate.

Effect of Sulfur in C=X on Rate. It has been known that sulfur does not form double bonds with carbon as readily as first-row elements. Also the greatly increased polarizability of the C=S moiety compared to C=O has been demonstrated nicely from NMR studies, *i.e.* ^{13}C and ^{19}F-NMR data showed a marked deshielding effect for a C=S compound in comparison with the corresponding C=O compound.[11] Therefore, the thion ester III would have been expected to show highly increased electrophilicity toward the nucleophilic ethoxide ion. However, unexpectedly, the thion ester III is much less reactive than the corresponding oxygen ester I, as shown in Table 1 and Figure 1. The unusual reactivity of III is not considered to originate from any mechanistic difference between I and III. Instead, the present rate data would be considered to be in accord with the HSAB principle, since III has been reported to be 10⁴ times more reactive than I toward a polarizable nucleophile, 4-Cl-C₆H₄S⁻.[10]

As shown in Figure 1, the thion ester III shows more significant polarizability effect than the thiol ester II. Two factors seem to be operative for this. Firstly, the charge polarization of C=S moiety is more pronounced than that of C=O moiety in the thiol ester II based on NMR study, *i.e.* the down field chemical shifts of carbonyl carbon in thion and thiol esters compared to the one in oxygen analogue have been reported to be ca. 30-50 and 20-30 ppm, respectively.[4b,11] Secondly, the sulfur atom in the thiocarbonyl group of III is directly participating in the rate determining step while the one in the thiol ester II is not, since the departure of the leaving group is not involved in the rate determining step.

Effect of Alkali Metal Ions on Rate. As shown in Figure 1, pseudo-first-order rate constants for the reactions of I, II and III with sodium ethoxide increase linearly as the concentration of EtONa increases. In Figure 2 is also demonstrated that there is no detectable reactivity difference among the alkali metal ethoxides toward I. However, the
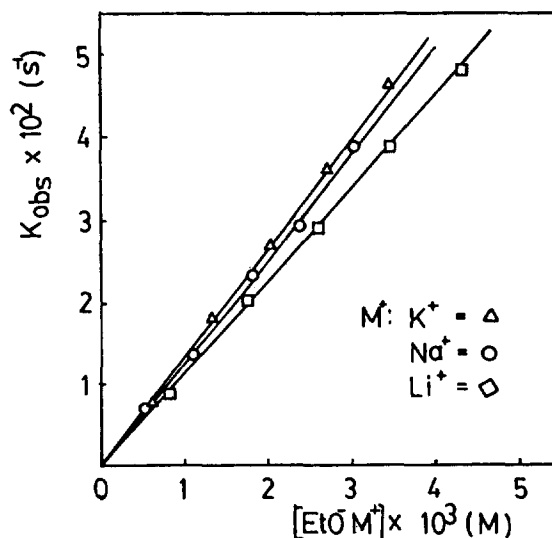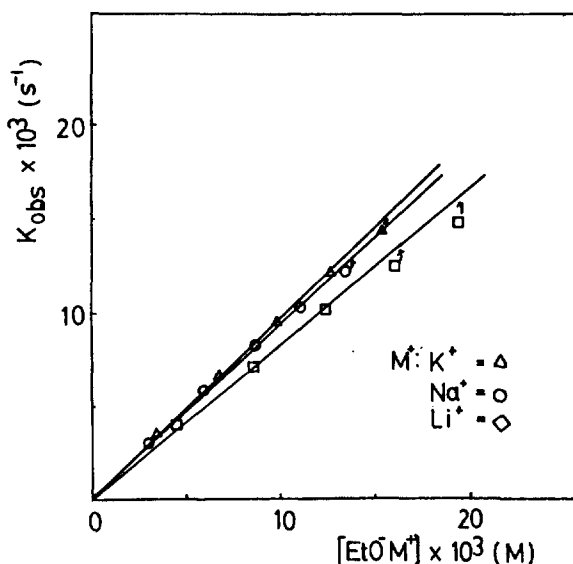

Figure 4. Plots showing metal ion inhibition for the reactions of III with EtO⁻M⁺ in ethanol at 25℃.

reactivity of II toward EtOM depends on the kind of metal ion as shown in Figure 3. Similarly, as the metal ion changes from K⁺ to Na⁺ and Li⁺ the reactivity of III decreases, and the dependence of the reactivity on the kind of metal ion is more significant than II as shown in Figure 4. A careful examination of Figure 4 reveals that the plots of k_{obs} vs [EtOM] are not linear and the downward curvature is getting more significant as the size of the metal ion decreases.

It has been suggested that ion-paired species are generally less reactive than the dissociated anions in a variety of S_N2 reactions at saturated carbon center.[12] The degree of ion-pair has generally been considered to be getting stronger with increasing concentration and the charge density of the ionic species.[13] Therefore, the present metal ion effect on rate could be attributed to the difference in ion-pair strength,

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since EtO^-Li^+ is least reactive among EtO^-M^+ and would form ion-pair most strongly in ethanol for the present system.

On the contrary, significant catalytic effects of alkali metal ions in ion-paired RO^-M^+ have been found for the reaction of 4-nitrophenyl diphenylphosphinate with ethoxide ion in ethanol, and the catalytic effects were disappeared when the metal ions formed complexes with proper complexing agents such as crown ethers or cryptands.[14] Similarly, the catalytic effects shown by alkali metal ions were disappeared by the use of proper complexing agents for the reaction of diphenyl 4-nitrophenyl phosphate with RO^-M^+.[15] A common aspect of the two esters of phosphinate and phosphate is that the catalytic ability of alkali metal ion increases with decreasing the sizes of metal ions.

Thus the role of metal ion was attributed to stabilization of the negatively charged transition state by electrostatic interaction with cations.[15] This explanation is mainly based on the fact that the order of catalytic effects is in the same order of the effective charge densities, *i.e.* $Li^+>Na^->K^+$ >complexed metal ions with crown ethers. However, such an argument could not be applied to the present system since the reactivity order is completely opposite to the one in the phosphorus centers.

The other explanations suggested are as follow.[14] (1) The ion-paired EtO^-M^+ species would attack simultaneously at the $P=O$ bond to form a four-centered transition state. (2) Pre-equilibrium association of M^- with the oxygen of $P=O$ to increase the charge polarization of $P=O$ bond. (3) The metal ion acts an electrophilic catalyst *via* co-ordination at the phenoxy oxygen to increase nucleofugacity of $4-NO_2-C_6H_4O^-$.
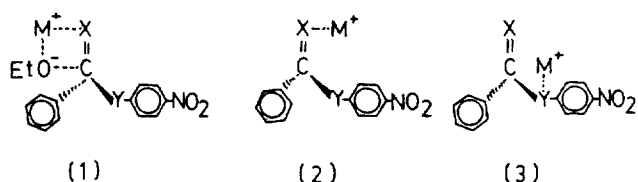
Since the leaving group departure would occur after the rate-determining step, the reactivity would not be affected significantly by an increased nucleofugacity as mentioned above. Therefore, the enhancement of nucleofugacity by electrophilic catalyst of M^+ ions (case (3)) would not be responsible for the present results.

A $P=O$ double bond has been known to be weak and easily polarizable to give P^--O^-, therefore, the presence of metal cation would accelerate the charge polarization of $P=O$ bond. Similarly, a $C=S$ bond is also considered to be highly polarizable as mentioned above. Therefore, one would expect that the presence of metal ion would increase the charge polarization of $C=S$ bond (case (2)). However, the contribution of enhanced charge polarization by pre-equilibrium of the dissociated M^+ with sulfur in $C=S$ moiety would not be significant, since EtO^-M^+ would be present as ion-paired species but not dissociated species in the present solvent system.[14]

The one plausible way to increase charge polarization of the $C=S$ moiety by metal ion is the case (1). Thus, one would expect at least some catalytic effect by alkali metal ion for the substrate containing a $C=S$ bond in a similar

manner to the case in the phosphorus center. However, such catalytic effect observed in the phosphorus center is not present for the reaction of III with EtO^-M^+, but instead, the metal ions inhibit the reaction.

Unlike the negative end in a $P=O$ bond, the one in a $C=S$ bond is considered to be highly polarizable and soft. On the contrary, alkali metal ions have been suggested to be very hard and nonpolarizable.[16] Therefore, the interaction between the soft end of $C=S$ moiety and the hard metal ion would be poor based on the HSAB principle. The hardness order of the alkali metal ions $(Li^+>Na^+>K^+)$ is nicely in accord with the degree of inhibition $(EtO^-\ Li^+>EtO^-\ Na^->EtO^-K^+)$ for the present system, as shown in Figure 4. Thus it is considered that the present metal ion inhibition also originates from the nature of HSAB.

However, more quantitative studies would be required for a complete understanding of the present result. Studies on phosphorus and sulfur centered electrophiles are currently underway.

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Pyrolysis of Carbonate

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# Theoretical Studies on the Gas-Phase Pyrolysis of Carbonate Esters, Hydroxy-Esters and -Ketones[1]

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Gas-phase pyrolyses of carbonate esters, α-and β-hydroxy esters and β-hydroxy ketones have been studied theoretically by the AM1 MO method. Carbonate esters were found to decompose by two types of processes; in the reaction pathway involving an intermediate, the decomposition of the intermediate was rate-limiting, but direct pyrolyses were also possible *via* a six-membered cyclic transition state in which the methoxy oxygen attacks a hydrogen atom on the β-carbon. The hydroxy esters and ketones were found to decompose in a concerted process involving a six-membered cyclic transition state. Successive methylation on the α- and γ-carbon led to an increase in the reactivity in agreement with experiments.

Introduction

In our previous works,[2] we have shown theoretically by the semiempirical MO methods of MNDO and AM1 that the gas-phase pyrolysis of esters, I (X, Y=O or S; R^1, R^2, R^3=H or CH_3; Z=CH_2) proceeds through a six-membered cyclic transition state (TS) conforming to a concerted process of the retro-ene reaction,[3] which can be conveniently interpreted using the frontier orbital (FMO) theory[4] of three-species interactions.[5] We have explicitly shown that the most impor-

(I)
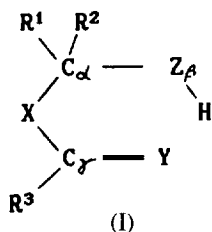
tant step controlling the reactivity is the facility to form a bond between Y and H in I, *i.e.*, the ease of nucleophilic attack of Y upon H; this required a greater π-donating ability of the π-HOMO of the donor (C_γ=Y) and the accepting ability of the σ*-LUMO of the acceptor (C_β-H) for a greater reactivity, the cleavage of the C_α-X bond being of little importance. These theoretical findings supported in general the mechanism proposed based on extensive experimental studies.[6] However our theoretical analysis provided us with a more detailed and concrete understanding for the cyclic concerted reaction mechanism based on orbital properties of the TS as well as the ground state (GS) of the ester decomposition.

In this work we have extended our theoretical investigations of the gas-phase decomposition mechanism using the AM1 method[7] to carbonate esters (I with X, Y=O or S; Z=CH_2; R^1, R^2=H or CH_3; R^3=OCH_3), α-hydroxy esters (I with X, Y=O or S; Z=O; R^1, R^2, R^3=H or CH_3), β-hydroxy esters (I with X=CH_2; Y=Z=O; R^1, R^2=H or CH_3; R^3=OCH_3) and β-hydroxy ketones (I with X=CH_2; Y=Z =O; R^1, R^2=H or CH_3; R^3=CH_3).

Calculation

The computations were carried out with AM1.[7] All geometries were fully optimized. Transition states were located by the reaction coordinate method,[8] refined by the gradient norm minimization,[9] and characterized by confirming only one negative eigenvalue in the Hessian matrix.[10]

Results and Discussion

Pyrolysis of Carbonate Esters. Carbonate esters correspond to formate esters with a methoxy group substituted at the γ-carbon.

Two decomposition pathways, (1) and (2), are possible in

(II)

(III)

$$CH_3OH + CXY \quad (1)$$