

The Studies on Substituent and Kinetic Solvent Isotope Effect in Solvolyses of Phenyl Chloroformates

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The rate constants and kinetic solvent isotope effects (KSIE, $k_{\text{MeOH}} / k_{\text{MeOD}}$) for solvolyses of *para*-substituted phenylchloroformates in CH₃OH, CH₃OD, H₂O, D₂O, 50% D₂O-CH₃OD were determined at 15.0 and 25.0 °C using conductometric method. Kinetic solvent isotope effects for the solvolyses of *para*-substituted phenyl chloroformates were 2.39-2.51, 2.21-2.28, and 1.67-1.69 for methanol, 50% aqueous methanol, and water, respectively. The slopes of Hammett plot for solvolysis of *para*-substituted phenyl chloroformates in methanol, 50% aqueous methanol, and water were 1.49, 1.17 and 0.89, respectively. The Hammett type plot of KSIE, log (KSIE) versus ρ , can be a useful mechanistic tool for solvolytic reactions. The slopes of such straight lines for *para*-substituted phenyl chloroformates are almost zero in methanol, 50% aqueous methanol, and water. It was shown that the reaction proceeds via an associative S_N2 and/or general base catalysis addition-elimination (S_AN) mechanism based on activation parameters, Hammett ρ values, and slopes of Hammett type plot of KSIE.

Introduction

Many acyl transfer reaction and nucleophilic substitution reactions in protic solvent involving esters,¹ amide derivatives² and acid chlorides are third order overall, and it is thought that one molecule of solvent acts as a nucleophile and a second molecule acts as a general base.³ Methanolysis of bromo- and chlorocarboxyl acid proceeds via a second order and third order simultaneously.⁴ The other possible process for the nucleophilic substitution and acyl transfer reactions may be pseudo-second order in which first order with respect to the substrate and methanol, respectively, and may involve methanol as nucleophile with acetonitrile, present in large excess, acting as general base.^{4b} Similar results have been obtained for the aminolyses reaction involving primary and secondary amines.⁵ According to the change of reaction condition as variation of substituent or solvent composition, nucleophilic substitution reaction of acyl halides were reported as an addition-elimination, S_N1 or S_N2 reaction mechanism.^{6,7} Based on product-rate studies, benzoyl chloride solvolyses by an S_N2 mechanism in more polar solvents, where it favors general-base catalyzed or possible addition-elimination pathway (S_AN) in less polar media.⁸

The effect of ring substitution on kinetic solvent isotope effect (KSIE), $k_{\text{SOH}} / k_{\text{SOD}}$, for solvolyses of aromatic compounds has received little attention. Most of the previous work on solvent isotope effects has involved H₂O and D₂O.⁵ In this work we also utilized MeOH and MeOD to show that the KSIE on Hammett's ρ values can be a promising mechanistic tool for identifying different reaction channels in solvolytic reactions. We determined the KSIE for solvolyses of *para*-substituted phenylchloroformate where an oxygen atom is adjacent to the carbonyl group in methanol, water,

and 50% methanol-water mixture. we also estimated activation enthalpy and entropy, ΔH^\ddagger and ΔS^\ddagger to propose transition structure or related properties.

Experimental Section

Para-substituted phenylchloroformates were commercial samples (Aldrich GR-grade > 99%). Merck GR-grade (< 0.1% H₂O) methanol was used without further purification. D₂O and CH₃OD were from Aldrich (99.9% D). Distilled water was redistilled with Buchi Fontavapor 210 and treated using ELGA UHQ PS to obtain specific conductivity of less than 1×10^{-6} mhos/cm. Rates were measured conductometrically at least in duplicate as in previous work.^{8,9}

Results and Discussion

The rate constants and KSIE values for solvolyses of *para*-substituted phenylchloroformate in MeOH-H₂O are summarized in Tables 2-4. Reference to these tables reveals that rate increases in the order *p*-NO₂ > *p*-Cl > *p*-H > *p*-CH₃ > *p*-OCH₃ which is the order of electron withdrawing ability.

The activation parameters for the reaction at 25 °C are summarized in Table 5. The large negative ΔS^\ddagger and large positive ΔH^\ddagger reveal that the solvolytic reaction proceeds via an S_N2. The ΔH^\ddagger is increased as the water content of the mixtures increases, suggesting that bond breaking in the transition state is a little important.

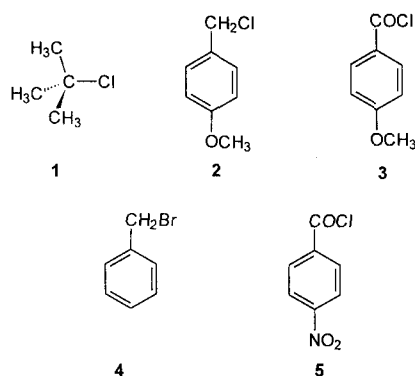
Kinetic Solvent Isotope Effect (KSIE). Several KSIEs are summarized at Table 1 for the reactions which are known to solvolyse by an S_N1, S_N1 type S_N2, S_N2 or S_AN mechanism.^{8,10-17} Solvolysis of *t*-butyl chloride (**1**)¹⁰ is known to proceed by S_N1 with KSIE of 1.06¹⁴ which is close to unity. For both *p*-methoxy benzylchloride (**2**)¹⁸ and *p*-methoxy benzoylchloride (**3**)^{11,12,15} KSIEs are 1.22^{14,15} which is larger

Table 1. Rate constants (s^{-1}) and kinetic solvent isotope effects for solvolyses of various substrates in methanol at 25 °C

Substrate	CH ₃ OH	CH ₃ OD	k_{MeOH}/k_{MeOD}
1	2.90×10^{-6}	2.73×10^{-6}	1.06 ^a
2	2.86×10^{-4}	2.35×10^{-4}	1.22 ± 0.03^b
3	1.13×10^{-2}	9.25×10^{-3}	1.22 ± 0.01^a
4	2.64×10^{-6}	1.94×10^{-6}	1.36 ^b
5	4.29×10^{-2}	1.89×10^{-2}	2.27 ± 0.10^c

^athis work. ^bSee reference 13a. ^cSee reference 16.

than *t*-butylchloride. KSIE of benzylbromide (**4**)¹⁶ which is known to proceed by S_N2 is 1.36¹⁴ and KSIE of *p*-nitrobenzoylchloride (**5**)^{11d} which is known to proceed by $S_A N$ is relatively larger value of 2.27.¹⁴ The increase of KSIE as the substrates varied from S_N1 to $S_A N$ type indicates that the transition state formulated by them was actually a general-base catalysis type in which deprotonation of an attacking nucleophile, methanol, is catalyzed by second methanol molecule.^{11b} Bentley reported a small KSIE value even for the S_N2 solvolyses of methyl tosylate,¹⁹⁻²¹ but he also found larger *l* and KISE values for the $S_N2(p)$ solvolysis of (PhO)₂POCl. Perhaps the small kinetic solvent isotope effects indicate an early transition state, and the large kinetic solvent isotope effects indicate a late transition state in typical S_N2 solvolyses.²¹ Therefore, the large KSIE is important of bond-formation in the transition state nucleophilic displacement reaction.²¹ The KSIE is not criterium of the reaction mechanism but indication of a degree of bond-formation in the transition state of nucleophilic displacement

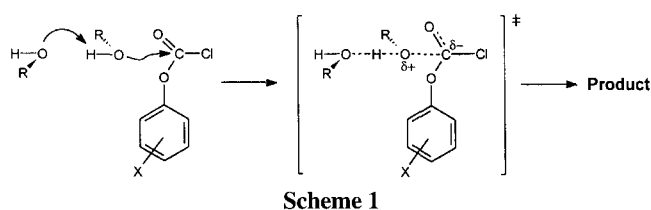
**Table 2.** Rate constants (s^{-1}) and kinetic solvent isotope effects for solvolyses of *p*-substituted phenyl chloroformates in methanol at 15 °C and 25 °C

Substrate	temp/°C	CH ₃ OH	CH ₃ OD	k_{MeOH}/k_{MeOD}
<i>p</i> -OCH ₃	15	1.97×10^{-3}	8.32×10^{-4}	2.37
	25	4.14×10^{-3}	1.73×10^{-3}	2.39
<i>p</i> -CH ₃	15	2.28×10^{-3}	9.59×10^{-4}	2.38
	25	4.87×10^{-3}	2.04×10^{-3}	2.35
<i>p</i> -H	15	3.55×10^{-3}	1.43×10^{-3}	2.48
	25	6.94×10^{-3}	2.95×10^{-3}	2.35
<i>p</i> -Cl	15	9.74×10^{-3}	3.87×10^{-3}	2.52
	25	1.90×10^{-2}	8.13×10^{-3}	2.34
<i>p</i> -NO ₂	15	7.26×10^{-2}	2.85×10^{-2}	2.55
	25	1.34×10^{-1}	5.34×10^{-2}	2.51

reaction.

Reference to Table 2, in which KSIE of *para*-substituted phenyl chloroformates are summarized, the magnitude of the KSIE is varied from 2.39 (*p*-methoxy) to 2.51 (*p*-nitro) at 25 °C. KSIE for the *p*-methoxy group which is the strongest electron donating substituent in the Table 2 is larger than the one for the benzyl bromide in Table 1. This implies that the bond-formation in TS, which is an indication of general base catalytic reaction, is important for the solvolytic reaction of phenyl chloroformates (Scheme 1).

KISEs for the reactions in 50% aqueous methanol are summarized in Tables 3 and 4. Reference to the Tables 2, 3 and 4, KSIE values are slightly decreased as increase of water content in the solvent mixture. Bond formation is a little important in the transition structure as water content increases in the solvent mixture, but the general-base catalytic effect is also decreased which is due to the partial bond breaking. However, KSIE of *p*-methoxy phenyl chloroformate which has a strong electron donating substituent is still

**Table 3.** Rate constants (s^{-1}) and kinetic solvent isotope effect for solvolyses of *p*-substituted phenyl chloroformates in 50% methanol at 15 °C and 25 °C

Substrate	temp/°C	50% CH ₃ OH	50% CH ₃ OD	k_{MeOH}/k_{MeOD}
<i>p</i> -OCH ₃	15	9.00×10^{-3}	3.90×10^{-4}	2.31
	25	1.96×10^{-2}	8.88×10^{-3}	2.21
<i>p</i> -CH ₃	15	8.54×10^{-3}	3.68×10^{-3}	2.32
	25	1.80×10^{-2}	8.22×10^{-3}	2.22
<i>p</i> -H	15	1.22×10^{-2}	5.24×10^{-3}	2.33
	25	2.48×10^{-2}	1.10×10^{-2}	2.25
<i>p</i> -Cl	15	2.55×10^{-2}	1.08×10^{-2}	2.36
	25	5.14×10^{-2}	2.25×10^{-2}	2.28
<i>p</i> -NO ₂	15	1.50×10^{-1}	6.36×10^{-2}	2.36
	25	2.05×10^{-1}	1.25×10^{-1}	2.28

Table 4. Rate constants (s^{-1}) and kinetic solvent isotope effect for solvolyses of *p*-substituted phenyl chloroformates in water at 15 °C and 25 °C

Substrate	temp/°C	H ₂ O	D ₂ O	k_H/k_D
<i>p</i> -OCH ₃	15	3.24×10^{-3}	1.96×10^{-3}	1.65
	25	8.76×10^{-3}	5.24×10^{-3}	1.67
<i>p</i> -CH ₃	15	4.00×10^{-3}	2.40×10^{-3}	1.66
	25	1.07×10^{-2}	6.41×10^{-3}	1.67
<i>p</i> -H	15	5.06×10^{-3}	3.04×10^{-3}	1.66
	25	1.33×10^{-2}	7.76×10^{-3}	1.71
<i>p</i> -Cl	15	8.50×10^{-3}	5.00×10^{-3}	1.70
	25	2.25×10^{-2}	1.31×10^{-2}	1.72
<i>p</i> -NO ₂	15	2.89×10^{-2}	1.73×10^{-2}	1.67
	25	7.40×10^{-2}	4.38×10^{-2}	1.69

large value of 1.65 at 25 °C in water. Since this value is larger than the one for *t*-butyl chloride (1.06) in methanol, the possibility that the phenyl chloroformates solvolyse *via* an S_N1 mechanism in water can be excluded. The KSIE of 1.65-1.70 at 15 °C in Table 4 are smaller than the KSIE of Table 3 at same temperature, but they are still larger than the value of benzyl bromide (1.36). This leads to the conclusion that the reaction proceeds *via* associative S_N2 mechanism or general base catalyzed addition-elimination reaction mechanism.¹⁷

Hammett Relationship.²³ In Figure 1 we present the Hammett plots¹⁸ for the solvolyses of *p*-substituted phenyl-

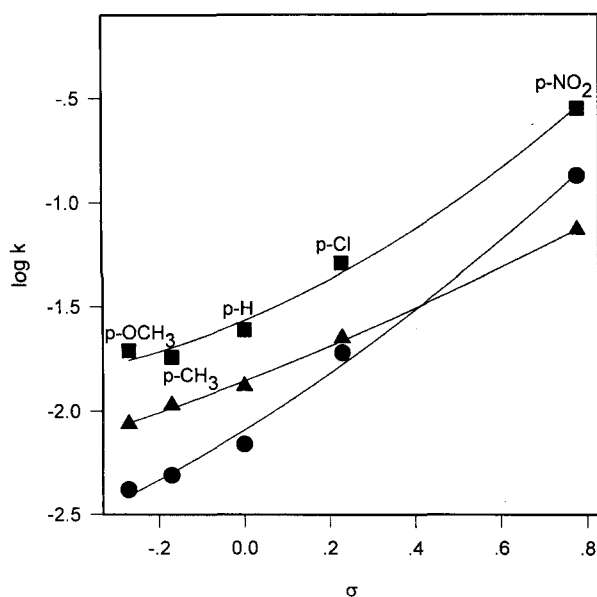


Figure 1. Hammett plot for the solvolysis of *p*-substituted phenyl chloroformates in CH₃OH, 50% CH₃OH, H₂O at 25 °C (solvent codes: methanol; ●, 50% methanol; ■, water; ▲).

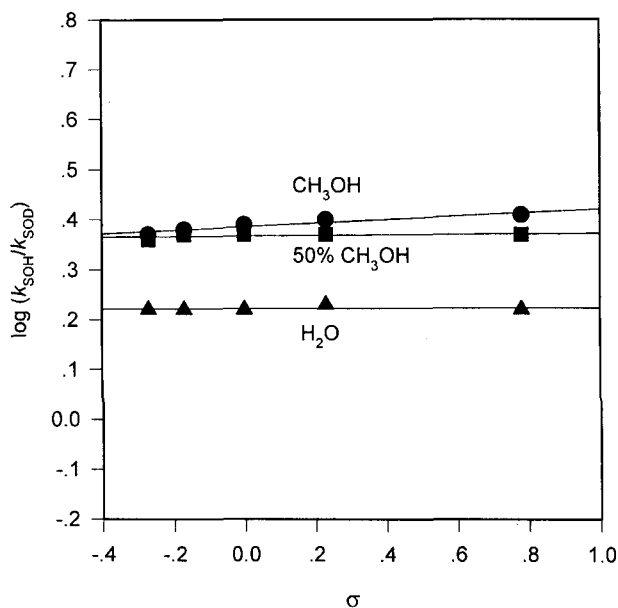


Figure 2. Plot of $\log(k_{SOH}/k_{SOD})$ vs σ for the solvolyses of *p*-substituted phenyl chloroformates in CH₃OH, 50% CH₃OH, H₂O at 15 °C.

Table 5. Activation parameters for solvolysis of *p*-substituted phenyl chloroformates at 25 °C

Substrate	solvent	ΔH^\ddagger (kcal/mol)	ΔS^\ddagger (cal/mol)	ΔG^\ddagger (kcal/mol)
<i>p</i> -OCH ₃	H ₂ O	16.4	-13.1	20.3
	50% MeOH	12.8	-23.4	19.8
	MeOH	12.4	-30.8	21.2
<i>p</i> -CH ₃	H ₂ O	16.3	-12.7	20.1
	50% MeOH	12.4	-24.8	19.8
	MeOH	12.0	-28.8	20.6
<i>p</i> -H	H ₂ O	15.9	-13.6	20.0
	50% MeOH	11.2	-28.2	19.6
	MeOH	10.8	-32.0	20.3
<i>p</i> -Cl	H ₂ O	15.9	-12.5	19.6
	50% MeOH	11.2	-26.8	19.2
	MeOH	10.8	-30.0	19.7
<i>p</i> -NO ₂	H ₂ O	15.5	-12.5	19.2
	50% MeOH	10.0	-27.3	18.1
	MeOH	10.0	-28.8	18.6

chloroformate at 50% methanol-water and water, respectively. The slopes (Hammett ρ) of the plots are all positive and decreases in the order methanol (1.49, $r = 0.991$, standard deviation (s.d) = 0.06) > 50% methanol (1.17, $r = 0.993$, s.d. = 0.02) > water (0.89, $r = 0.995$, s.d. = 0.02). The magnitude and sign of these ρ values represent that the transition state of the reaction has the structure where the large negative charge is developed at the reaction center by moving some of electron of nucleophile to the reaction center of substrate, indicating that bond formation is dominant at the transition structure. All compounds in methanol are characterized by a larger slope and also by the fact that all compounds fall on a single straight line. In contrast, in more polar aqueous media the slope is smaller and the strongly electron-donating substituent, *p*-OCH₃ (also *p*-CH₃ in water) deviates slight positively from straight line. This is consistent with associative S_N2 or addition-elimination mechanism discussed above in methanol, suggesting the reduction of general-base catalyst in more polar aqueous solvent.

In Figure 2 we present the plots of $\log(k_{SOH}/k_{SOD})$ vs Hammett's σ values in methanol, 50% aqueous methanol and water, respectively.¹⁷ The straight line is a good indicative of the single mechanism for the substituents of this work.

Analysis with Cross Interaction Coefficients.¹⁹ It may be possible to correlate the magnitudes of the slope with $|\rho_{XY}|$, a measure of the degree of bond formation in the transition state, and hence with the different channels of the reaction path for each separate straight line. The plots in Figures 2 can be represented as

$$\frac{\Delta(\log k_{SOH}/k_{SOD})}{\Delta\sigma_Y} = \Delta\rho_Y \quad (1)$$

where $\Delta\rho_Y$ is the change in ρ_Y due to the change in nucleophile (also solvent) from SOH to SOD.¹⁷ If we divide this value of $\Delta\rho_Y$ by the difference in nucleophilicity of nucleophiles (expressed by a hypothetical substituent constant),

$\Delta\sigma'_X$ the result is none other than the cross-interaction constant ρ_{XY} and can be defined by equation (2).

$$\rho'_{XY} = \frac{\Delta\rho_Y}{\Delta\sigma'_X} \quad (2)$$

Assuming approximately the same $\Delta\sigma'_X$ for MeOH and H₂O, the magnitude of ρ'_{XY} , which is inversely proportional to the distance between reaction centres, is proportional to $\Delta\rho_Y$. Hence the magnitude of $\Delta\rho_Y$ in equation (1), i.e. the slopes of the straight lines in Figures, should represent the relative degree of bond formation in the transition state. Therefore a larger value of $\Delta\rho_Y$, i.e. slope, for methanolysis is consistent with a general-base catalyzed associative S_N2 pathway, in which extensive bond formation has progressed in the transition state; in contrast, a smaller $\Delta\rho_Y$ in more polar media represents a lesser degree of bond formation in the transition state, indicating that a mechanism of associative type, S_N2 or S_AN with tight transition structure or typical associative S_N2, applies in water.

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