Further Kinetic Studies of Solvolytic Reactions of Isobutyl Chloroformate in Solvents of High Ionizing Power Under Conductometric Conditions

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Solvolyses of isobutyl chloroformate (**4**) in 43 binary solvent mixtures including highly aqueous media, water, D_2O, CH_3OD, 2,2,2-trifluoroethanol (TFE) as well as aqueous 1,1,1,3,3,3-hexafluoro-isopropanol (HFIP) solvents were performed at 45 °C, in order to further investigate the recent results of D'Souza, M. J[1]. *et al.*; solvolyses of **4** are found to be consistent with the proposed mechanism (Ad_E). The variety of solvent systems was extended to comprise highly ionizing power solvent media ($Y_{Cl} > 2.7$ excepted for aqueous fluorinated solvents and pure TFE solvent) to investigate whether a mechanistic change occurs as solvent compositions are varied. However, in case of 18-solvent ranges having aqueous fluorinated solvent systems (TFE-H_2O and HFIP-H_2O) and/or having $Y_{Cl} > 2.7$ solvent systems, the solvent effect on reactivity for those of **4** are evaluated by the multiple regression analysis as competition with S_N2 - type mechanism. And in pure TFE and 97 w/w % HFIP solvents with high Y_{Cl} and weak N_T, these solvolyses are understood as reactions which proceed through an ionization (S_N1) pathway.

Key Words : Extended Grunwald-Winstein equation, Solvolysis, Kinetic solvent isotope effect, Solvent effect

Introduction

According to the recent results of D'Souza, M. J[1]. *et al.* (**2011**. *Beilstein J. Org. Chem.*) for solvolyses of isobutyl chloroformate (**4**) using the extended Grunwald-Winstein equation [eq. (1)],[2-5] solvent effects on reactivity for those of **4** were revealed to proceed *via* an addition-elimination mechanism with nucleophilic attack at the reaction center (C=O) stabilizing the transition state (TS).

$$\log (k/k_o) = mY_{Cl} + lN_T + c \qquad (1)$$

In eq. (1) k and k_o are rate constant of solvolysis of a substrate RX in a given solvent and 80% ethanol-water, respectively; m is the susceptibility to change in ionizing power (Y_{Cl}: based on solvolysis of 1-adamantyl chloride[4] with $m=1.00$); l is the susceptibility to changes in solvent nucleophilicity (N_T) (N_T: based on the solvolyses of *S*-methyl dibenzothiophenium ion[15]); and c is a constant (residual term).

We have carried out further work because the results reported were obtained using only 18 solvents for the correlation analysis; in particular, the experimental results were obtained without considering highly aqueous solvent systems including aqueous 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), which may influence those of **4** by inducing a mechanistic change[6-9] due to the variation of solvent composition; also, there is a potential problem of possible multicolinearity for solvolytic analyses by two-terms multiple regressions.

Iso-butylchloroformate (**4**) is a chloroformate ester, useful as a pharmaceutical precursors, with geometrical s*yn* confor-mation in 3-D structure.[10-13]

In this work, solvents having ionizing power values (Y_{Cl}) > 2.7 were regarded as highly ionizing power media, such as aqueous fluorinated alcohols, pure water and the solvent ranges 40% MeOH → H_2O, 40% EtOH → H_2O and 30% acetone → H_2O, respectively. Within this range of solvents, there are differences in solvent nucleophilicity (N_T) value (*e.g.*, N_T; −0.74 for 40% EtOH and −2.97 for 97 w/w % HFIP).

Results and Discussions

Solvolysis of **4** in 43 binary solvent mixtures including highly aqueous media, water, D_2O, CH_3OD, 2,2,2-trifluoro-ethanol (TFE) solvent systems as well as aqueous HFIP solvents were performed at 45 °C.

Particularly, kinetic data for highly aqueous binary mixtures (with alcohol and acetone cosolvents) containing water (or D_2O) were obtained from an improved rapid-mixing conductometric technique (see footnote in Table 1) to minimize problems associated with sparingly soluble substrates. Additional kinetic data in 100% H_2O, MeOH, and EtOH, 80% MeOH, 80% EtOH, 97% w/w TFE-water, and 97% w/w HFIP-water at various temperatures are also reported in Table 2.

These specific rates show the phenomena of maximum rates at 45 °C in specific solvent (10% MeOH) and the relative values of $k_{H_2O}/k_{solvent}$ rate-ratios are less than 4-fold for 40% MeOH, 40% EtOH and 30% acetone. Such observations may be a reflection of a significant contribution from solvent nucleophilicity (N_T) into solvolysis rates of **4**, even

Table 1. The rate constants $(k/s^{-1})^a$ for solvolysis of isobutyl chloroformate (**4**) in binary solvent mixtures at 45.0 °C

Solvent Composition (%)[b]	rate constant (k/s^{-1})		
	Methanol-water	Ethanol-water	Acetone-water
100	$(5.35\pm0.01)\times10^{-4}$	$(1.49\pm0.03)\times10^{-4}$	-
90	$(1.00\pm0.01)\times10^{-3}$	$(3.11\pm0.06)\times10^{-4}$	$(1.62\pm0.05)\times10^{-5}$
80	$(1.44\pm0.01)\times10^{-3}$	$(4.17\pm0.08)\times10^{-4}$	$(4.94\pm0.01)\times10^{-5}$
70	$(1.83\pm0.03)\times10^{-3}$	$(5.36\pm0.08)\times10^{-4}$	$(1.05\pm0.01)\times10^{-4}$
60	$(2.18\pm0.01)\times10^{-3}$	$(6.51\pm0.04)\times10^{-4}$	$(1.75\pm0.01)\times10^{-4}$
50	$(2.48\pm0.03)\times10^{-3}$	$(8.05\pm0.09)\times10^{-4}$	$(3.03\pm0.01)\times10^{-4}$
40[c]	$(2.50\pm0.01)\times10^{-3d}$	$(1.02\pm0.02)\times10^{-3}$	$(4.85\pm0.04)\times10^{-4}$
30[c]	$(2.82\pm0.01)\times10^{-3d}$	$(1.33\pm0.07)\times10^{-3\,d}$	$(7.30\pm0.01)\times10^{-4c}$
20[c]	$(2.19\pm0.01)\times10^{-3e}$	$(1.69\pm0.01)\times10^{-3d}$	$(1.19\pm0.01)\times10^{-3d}$
10[c]	$(2.85\pm0.01)\times10^{-3f}$	$(2.33\pm0.01)\times10^{-3e}$	$(1.78\pm0.06)\times10^{-3e}$
0[c]	$(2.82\pm0.01)\times10^{-3f}$	$(2.82.\pm0.01)\times10^{-3f}$	$(2.82\pm0.01)\times10^{-3f}$
	MeOD	D$_2$O^{c,f}	
100	$(2.64\pm0.01)\times10^{-4}$	$(1.83\pm0.02)\times10^{-3}$	
	TFE– water^{g,h}	TFE-ethanol^{e,i}	HFIP-water^{g,h}
100	$(2.98\pm0.02)\times10^{-5}$	-	-
97	$(1.15\pm0.05)\times10^{-5}$	-	$(1.37\pm0.01)\times10^{-4}$
90	$(1.27\pm0.02)\times10^{-5}$	-	$(4.42\pm0.08)\times10^{-5}$
80	-	$(5.62\pm0.02)\times10^{-6}$	-
70	$(3.88\pm0.11)\times10^{-5}$		$(6.17\pm0.01)\times10^{-5}$
60		$(1.77\pm0.03)\times10^{-5}$	-
50		$(3.30\pm0.01)\times10^{-5}$	$(1.19\pm0.01)\times10^{-4}$
40		$(4.61\pm0.02)\times10^{-5}$	-
20	-	$(9.98\pm0.02)\times10^{-5}$	

[a]Determined by the conductometric method. [b]v/v basis by alcohol. [c]Using the kinetic apparatus with a turbo-stirrer made by exquisite technique for rapid-mixing in solvent systems corresponding of footnotes of *d*, *e* and *f*, respectively. [d]Injected 4 μL of 5% w/w substrate. [e]Injected 4 μL of 3% w/w substrate. [g]Injected 4 μL of 2% w/w substrate. [h]%w/w basis by fluorinated solvent. [i]% v/v trifluoroethanol.

within a range of higher ionization solvent systems known to favour unimolecular ionization (S_N1) reaction in acid chloride solvolyses.[9a,c]

On the other hand, in case of a higher solvent nucleophilicity[15] of EtOH molecule (N_T: 0.37) relative to H_2O molecule (N_T: −1.38) with a greater of acidity, the relative value of k_{H2O}/k_{EtOH} rate-ratio for hydrolysis/ethanolysis of **4** at 45 °C were found to be a smaller value (*ca.* 19) than expected. Hydrolysis in pure water can be also a clue for inferring that both ionizing power and solvent nucleophilicity terms are important contributors to the observed solvent effect.

These results for solvolyses of **4** mean that contributions from both nucleophilic solvent participation on carbonyl carbon (C=O), and from nucleophilic solvation of TS by polar solvent need to be evaluated in terms of two-term multiple parameters [eq. (1)].[14,15]

The extensive range of solvents for solvolyses of **4**, varying in nucleophilicity and ionizing ability, allow us to deduce an improved evaluation of solvent effects on reactivity and mechanism. Parallel comparisons of our results for **4** were carried out with those of other chloroformates (similarity models) earlier reported, such as *n*-propyl chloroformate (**1**, *n*-Pr),[27] isopropyl chloroformate (**2**, *i*-Pr),[17,18] isopropenyl

Table 2. Rate constants $(k/s^{-1})^a$ for solvolyses of isobutyl chloroformate (**4**) and activation parameters[b]

Solvent	T/°C	k/s^{-1}	ΔH$^{\neq}$ kcal mol^{-1}	ΔS$^{\neq}$ cal mol^{-1} K^{-1}
100% MeOH	25	$(9.98 \pm 0.01)\times10^{-5}$	14.9 (14.1)[c]	-26.8 (-29.6)[c]
	35	$(2.35 \pm 0.02)\times10^{-4}$		
	40	$3.53(3.27)^{c}\times10^{-4d}$		
	45	$(5.23 \pm 0.05)\times10^{-4}$		
		$(4.63)\times10^{-4c}$		
	55	$(1.11 \pm 0.01)\times10^{-3}$		
80% MeOH	25	$(3.20 \pm 0.01)\times10^{-4}$	13.6	-29.0
	35	$(6.84 \pm 0.02)\times10^{-4}$		
	45	$(1.44\pm 0.02)\times10^{-4}$		
	55	$(2.85 \pm 0.02)\times10^{-4}$		
100% EtOH	25	$(3.00 \pm 0.02)\times10^{-5}$	14.2 (15.2)^{c,e}	-29.5 (-28.6)^{c,e}
	35	$(6.45 \pm 0.02)\times10^{-5}$		
	45	$(1.49 \pm 0.03)\times10^{-4}$		
		$(1.27)\times10^{-4c}$		
	55	$(3.22 \pm 0.01)\times10^{-4}$		
80% EtOH	25	$(9.00 \pm 0.07)\times10^{-5}$	14.2 (14.0)[c]	-29.6 (-30.4)[c]
	35	$(1.97 \pm 0.02)\times10^{-4}$		
	45	$(4.17 \pm 0.08)\times10^{-4}$		
		$(3.85)\times10^{-4c}$		
	55	$(8.85 \pm 0,01)\times10^{-4}$		
100% H$_2$O	25	$(4.17 \pm 0.05)\times10^{-4f}$	15.8 (15.5)^{g}	-20.6
	35	$(1.11 \pm 0.04)\times10^{-3}$		
	45	$(2.82 \pm 0.01)\times10^{-3}$		
	55	$(6.97 \pm 0.03)\times10^{-3}$		
97% TFE	35	$(3.67 \pm 0.01)\times10^{-6}$	22.0 (21.5)[c]	-12.2
	45	$(1.15 \pm 0.05)\times10^{-5}$		
	55	$(3.48 \pm 0.01)\times10^{-5}$		
		$(2.66)\times10^{-5c}$		
97% HFIP	35	$(4.47 \pm 0.04)\times10^{-5}$	20.3	-15.0
	45	$(1.37 \pm 0.01)\times10^{-4}$		
	55	$(3.62 \pm 0.03)\times10^{-4}$		

[a]Determined as described in footnote *a* in Table 1. [b]Obtained from Erying plots. [c]Quoted in Table 1 or 2 of ref. **1**. [d]Obtained from interpolation using Arrhenius plots. [e]ΔH$^{\neq}$ =12.9 kcal mol^{-1} and ΔS$^{\neq}$ = −29.9 cal mol^{-1}K^{-1}, respectively for **3** (Table 4 of ref. 16). [f] Double injected (2 × 4 μL) of 0.5% (w/w) substrate for each kinetic run.

chloroformate (**3**, *i*-Prop),[16,19] neopentyl chloroformate (**5**, *n*eoP)[20] and 1-adamantylmethyl chloroformate (**6**, 1-AdCH$_2$).
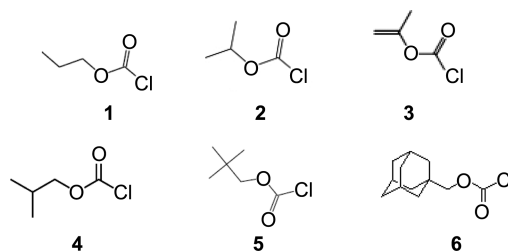
A scatter plot between dependent variables (y=log(k/k_o) for **4**) and two explanatory variables (x$_1$=Y$_{Cl}$, x$_2$=N$_T$) for regression analysis gave non-linear correlations exhibited in
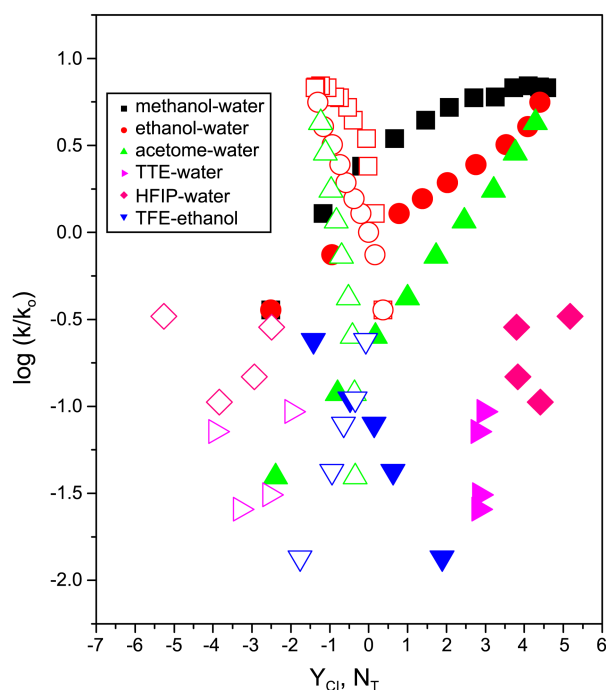
Figure 1. The scatter plots of relationship between dependent variables [log(k/k_o) for **4**] and two explanatory variables (Y_{Cl}, N_T) at 45° for regression analysis. (solid symbols: plots for Y_{Cl}, open symbols: plots for N_T).

Figure 1. The validity for two-terms multiple regression analyses [eq. (1)] for further work of **4** was strongly secured from these relationship observed [y *vs* $x_1 \rightarrow$ r (linear correlation coefficient) = 0.348, p-value (significance probability) = 0.003 and y *vs* $x_2 \rightarrow$ r = 0.439, p-value = 0.000].

When a multiple regression analysis of log(k/k_o) on Y_{Cl} (x_1) and N_T (x_2) of corresponding the two-terms Grunwald-Winstein eq. (1)[4b,14,21] is performed for solvolysis rates of **4** in all solvent systems (41-solvents) chosen for this work at 45.0 °C, it leads to a poor correlation (correlation coefficient, r = 0.857), [with 0.40(±0.05) for *m*, 0.68(±0.08) for *l* and −0.16(±0.10) for c, respectively, in Table 3].

Conversely, in earlier studies, a specific solvolyses rate studies of **3** (as similarity model) had been carried out by

Ryu, Z. H. *et al.* (2005, *Bull. Korean Chem. Soc.*)[16] and D'Souza, M. J. *et al.* (2011, *Eur. J. Chem.*),[19] respectively. Analysis results (with being essentially identical for conclusion) reported by D'Souza, M. J. *et. al.* (by Ryu, Z. H. *et al.*), in 51 (40) solvent systems containing a highly ionizing media as well as TFE-EtOH solvent systems, gave rise to a good (single type) linear correlation with the values of 0.54 (0.60) for *m*, 1.54 (1.88) for *l* and 0.966 (0.968) for *r*, indicating a single mechanism, regardless of the characteristic of solvent chosen (excluding 97% TFE and 97% HFIP solvent systems from the correlation).[19]

Such phenomenon for **4** may be explained as the dispersion effect caused by differential solvation effect on the reaction center to bring out the different reaction mechanisms; accordingly, solvolyses analysis in solvent systems chosen may be estimated by assuming that unsatisfactory correlation is caused by dual channel mechanism.

For 35-solvent systems including TFE-EtOH solvents, but excluding aqueous fluorinated solvents, a good linear correlation analysis (*r* = 0.953) was obtained from the specific solvolysis rate constants of Table 1 using the extended Grunwald-Winstein equation [eq. (1)], giving log (k/k_o) = 0.62 (±0.02) Y_{Cl} + 1.82 (±0.14)N_t + 0.06 (±0.05) with 158 of F-test value and 0.001 of *p*-value (Table 3, Figure 2).

In case of all analyzed in further work for **4**, *p*-values (significance probability) as criteria for significance of multiple regression analyses [eq. (1)] were observed as $p \leq$ 0.001 (F-test > 45). Statistical variance inflation factor (VIF) were obtained as 5.17 for the multiple regression in 35-solvent systems (Figure 2) and as 1.03 for those in 18-solvent systems (Figure 3); a consequence of our work is that the potential problem of multicolinearity (VIF > 10: problem) could be avoided.

As presented in Table 3, when compared with recent results (evaluated only in highly alcoholic media) reported by D'Souza, M. J. *et al.*, our result exhibits the same large amount of nucleophilic solvent assistance (*l* = 1.82) and correlation coefficient (r), but different magnitude of polar solvation (*m* = 0.53 → 0.62) and those of F-test value. The revised m-value have relevance to a greater number (18 → 35) of solvents available for correlation analysis, indicating

Table 3. Comparison of previous and our results in multiple regression analyses for solvolyses[a] of isopropenyl (**3**) and isobutyl chloroformate (**4**) in chosen solvent mixtures at 10 °C using the extended Grunwald-Winstein equation [eq. (1)]

	log(k/k_o) = mY_{Cl} + lN_t + C						
ROCOCl	*m* (A)	*l* (B)	**c**	n^b	r^c	B/(A+B)^d	F^e
i-Prop (**3**)^{f,g}	0.54^f	1.54^f	0.05^f	50^h	0.968^f	0.74^f	347^f
	0.60^g	1.88^g	0.25^g	40^h	0.968^g	0.76^g	
i-Bu (**4**)	0.53^i	1.82^i	1.81^i	18^i	0.957^i	077^i	82^i
	0.62±0.02	1.82±0.14	0.06±0.05	35^j	0.953	0.75	158
	0.40±0.05	0.68±0.08	-0.16±0.10	41^h	0.857	0.630	45
	0.67±0.08	0.80±0.06	-1.10±0.33	18^k	0.974	0.54	138

^{a}Performed using Origin 6.0 program for multiple regression analysis and values of solvent parameter Y_{Cl} and N_T are quoted from ref 4, 15 and 21. ^{b}Number of solvent. ^{c}Correlation coefficient. ^{d}Fraction of the contribution from solvent nucleophilicity. ^{e}F-test value. ^{f}Data from ref.19. ^{g}Data from ref.16. ^{h}Full range of solvent chosen. ^{i}Data from ref.1. ^{j}Except for the fluorinated aqueous solvents. ^{k}Highly ionizing power media, (Y_{Cl} > 2.7) except for the 100% TFE and 97 HFIP-H_2O solvents.
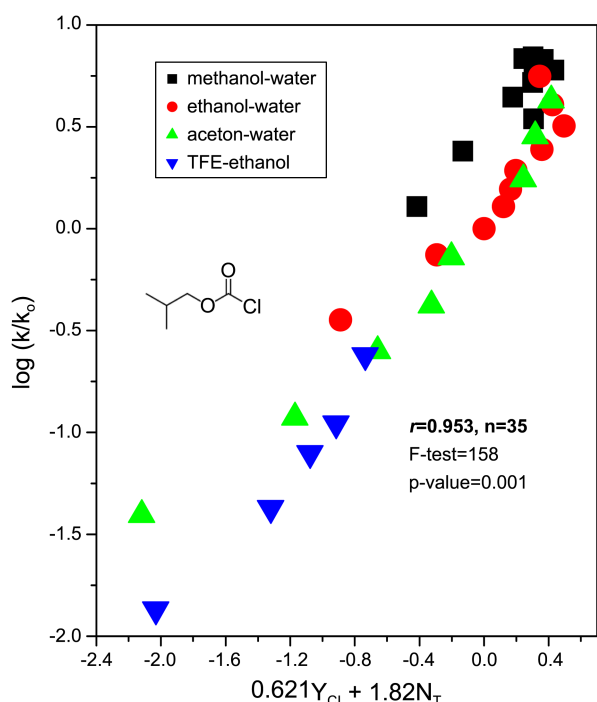
Figure 2. Plot of $\log(k/k_o)$ for solvolysis of isobutyl chlorofomate (**4**) at 45 °C against $(0.652Y_{Cl} + 1.82N_T)$. Except for 100%TFE, TFE-H$_2$O and HFIP-H$_2$O in this correlation.

that contributions from highly ionizing media into stabilization of TS for this reaction **4** are important. That is, the change of *m*-value could be considerable evidence for the existence of tetrahedral-type intermediate (stepwise), which could be stabilized by nucleophilic solvation, and TS-stabilization by nucleophilic solvation for **4** showed more sensitive for than those of **3**.

Considering the nucleophilicity of solvents used which have $N_T > -1.5$ (higher) the value relative to those of aqueous fluorinated solvents, the $0.62Y_{Cl}$ term obtained implicates the degree of the nucleophilic solvation of TS by the charge-dipole interaction with a nucleophilic solvents and the $1.82N_t$ term obtained involves those of the nucleophilic participation by the nucleophile solvent for the stabilization of TS.

Accordingly, the fraction (0.75) of the contribution from solvent nucleophilicity (N_T) as well as the magnitude of the susceptibility ratio ($l/m = 2.94$) between the two-term parameters were induced into being rationalized as a addition-elimination mechanism (Ad$_E$) with the carbonyl addition step being rate determining by using the useful mechanistic indicator [($l/m = 1.9$-3.0 for Ad$_E$, $l/m \leq 0.8$ for I (ionization pathway), respectively].[1]

As shown in Table 4, the value of $[k_{40E}/k_{97T}]_Y$ for **4** was observed as 116 (98)[24a] indicating a loose (polar) TS; the value is smaller than that for **3** with 4.46×10^3. In contrast, the high value of k_{MeOH}/k_{MeOD} (KSIE) in methanol > 2.0 for both **4** and **3** indicates a third order reaction[30-33] involving one molecule of solvent as nucleophile and another as general base catalyst (GBC).[16,30,34] The trend of results for **4** is similar to recently reported results for **6**.[20] In 100% water,

the value of k_{H_2O}/k_{D_2O} ratios are 1.54 for **4** and 2.08 for **3**, respectively, indicating substrates believed to react by the bimolecular mechanism.

Putative cause of this result observed may be a reflection of the difference in rate-limiting step (mechanism) according to the kind of binary solvent mixtures chosen for **4**, but to the variation of solvent composition.

So the $[k_{40E}/k_{97T}]_Y$ ratio could be not a central role as the mechanistic tool available for identifying the two different (dual) reaction channels occurring, although, 40E and 97T of corresponding the range of polar media (see footnote *a* of Table 4) are favorable S$_N$1 solvolyses, and the k_{H_2O}/k_{TFE} ratio with 94 (small value) for **4** as additional data is also supported with our interpretation. These offer another reason for separating solvent systems used for this work into three parts for multiple correlation analysis as follow; (i) the majority of the 35-solvents excluding 6-aqueous fluorinated solvent systems. (ii) the 18-solvent ranges having aqueous fluorinated solvent systems (TFE-H$_2$O and HFIP-H$_2$O) as well as $Y_{Cl} > 2.7$ solvent systems, and (iii) the solvents of highest Y_{Cl} and lowest N_T (pure TFE and 97% HFIP-H$_2$O solvents).

Results from a multiple regression analysis for solvolysis of **4** in solvent systems of corresponding (ii) is obtained as a good linear correlation (r = 0.974, n = 18 and F-test = 138) with $\log(k/k_o) = (0.67 \pm 0.08)Y_{Cl} + (0.80 \pm 0.06)N_T + (-1.10 \pm 0.33)$ and is also tabulated in Table 2 (Figure 3).

Also, considering fraction (0.54) of the contribution from solvent nucleophilicity and the magnitude of the susceptibility ratio ($l/m = 1.19$) between the two-term parameters.
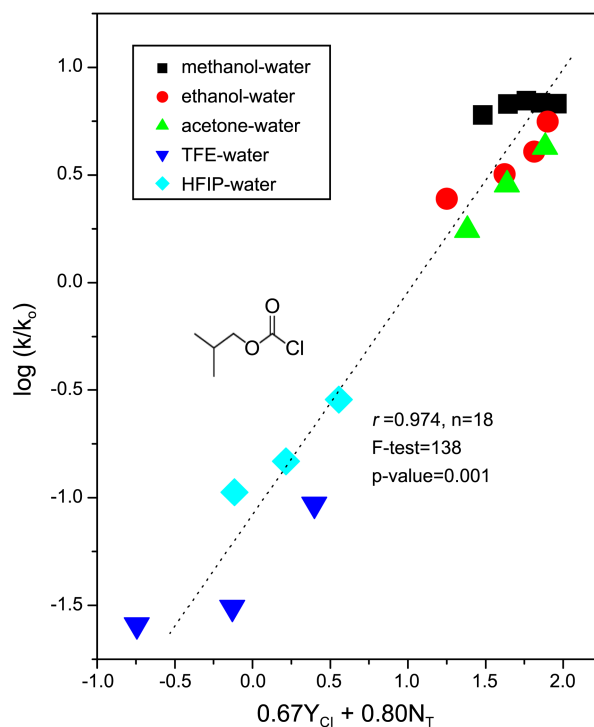

Figure 3. Plot of $\log(k/k_o)$ for solvolyses of isobutyl chloroformate (**4**) at 45 °C against $(0.67Y_{Cl} + 1.88N_T)$ in highly aqueous media ($Y_{Cl} > 2.7$). Except for 100%TFE and 97%HFIP-H$_2$O solvents.

Table 4. Values of solvolysis rate ratios, $[k_{40E}/k_{97T}]_Y{}^a$, in 40% (v/v) ethanol-water (40E) compared with 97% (w/w) trifluoroethanol-water (97T), kinetic solvent isotope effect (KSIE)[b] in methanol, and the magnitude of the susceptibility ratio (l/m) between the two-term parameters for various alkyl chloroformate (ROCOCl)

ROCOCl	R = n-Pr[c] (1)	i-Pr[d] (2)	i-Prop[e] (3)	i-Bu (4)	neoP[f] (5)	1-AdCH$_2$[g] (6)	MeOTs
$[k_{40E}/k_{97T}]_Y$	-	-	4.46×10^{3h}	116(98)[i]	-	84[j,k]	500[l]
k_{MeOH}/k_{MeOD}	2.17[m]	(1.35)	2.33(2.08)	2.20(1.54)	-	2.19	1.11[n]
l/m	2.80	0.54 (0.48)[o]	3.13 (2.83)[p]	2.94 (3.43)[q] (1.19)[r]	3.67	3.25	-
$n/n_t{}^s$	22/28[t]	20/24[u] (26/26)[o]	40/40 (50/51)[p,v]	34/41[w] (18/23)[q,x]	13/21[w]	18/27	-

[a]Subscribed Y symbol means that very similar solvent ionizing power (Y_{Cl}), but the different nucleophilicity (N_T) (Y_{Cl} of 2.75, N_T of −0.74 for 40% ethanol/water and Y_{Cl} of 2.85, N_T of −3.30 for 97% w/w trifluoroethanol/water). [b]KSIE = k_{MeOH}/k_{MeOD} and value is parenthesis in k_{H_2O}/k_{D_2O}. [c]Ref. 22 at 40 °C. [d]Ref. 17 at 40 °C. [e]Ref. 16 at 10 °C. [f]Ref. 20 at 45 °C. [g]Ref. 23 at 40 °C. [h]$[k_{40E}/k_{97T}]_Y = 1.08 \times 10^{-3} s^{-1}$ (ref. 16)/2.42 × 10^{-7} s^{-1} (ref. 19) at 10 °C. [i]Ref. 24a. [j]Ref. 24b at 40 °C. [k]88 (25 °C) value for Bu^{t}COCl (ref. 25) with k_{MeOH}/k_{MeOD} = 1.46 and l/m = 0.83, (S$_N$1/S$_N$2 mechanism) excluding TFE-ethanol systems for correlation analysis at 10 °C. [l]Ref. 26. [m]Ref. 27 at 25 °C. [n]Ref. 28. [o]Ref. 18 at 45 °C. [p]Ref. 19. [q]Ref. 1. [r]Result obtained from condition presented in footnote k of Table 3. [s]n/n_t = number of solvents used for correlation/ available total number of solvents. [t]Except for 100%TFE, 97%TFE and all HFIP-H$_2$O solvents. [u]Except for pure MeOH, pure EtOH, 90% MeOH and 90% EtOH, but including fluorinated solvents. [v]Except for only 97% HFIP. [w]Except for aqueous fluorinated solvents (TFE-H$_2$O and HFIP-H$_2$O solvents, respectively). [x]Except for aqueous TFE solvents, no kinetic run for HFIP-H$_2$O solvents.

According to criteria for mechanism presented previously, this probably means the prediction for S$_N$2 mechanism with equivalent contribution from nucleophilic solvation and nucleophilic participation for TS-stabilization in solvolysis of **4**.

As a result, owing to the different solvation of TS according to whether the majority of 35-solvents or 18-highly ionizing media ($Y_{Cl} > 2.7$) media, dual channel mechanism can be explained by an addition-elimination (Ad$_E$) pathway with predominant nucleophilic participation, described as a carbonyl addition channel and S$_N$2 pathway with change of nucleophilic solvent assistance, and specially, in case of (iii), the data points for pure TFE and 97% HFIP solvents are excluded (deviated) from 18-solvent systems data points in linear correlation analyses, these reaction, the consideration of an essential characteristic of these solvents with the solvents of highest Y_{Cl} and lowest N_T supposes that these reaction are preceding through an S$_N$1 (ionization) pathway with preferential partial charge separation, described as a cationic reaction channel.

For solvolyses group comprised of **1**, **3** and **6** similar to the value of k_{MeOH}/k_{MeOD} (KSIE) in methanol (> 2.0), TFE-EtOH solvent systems, with possibility for third order reaction[30,31] based on a general base catalyst (GBC) by solvent molecules, were also contained of the data points in the multiple regression analysis by two term parameters [eq. (1)], but aqueous fluorinated solvent TFE-H$_2$O and/or HFIP-H$_2$O solvents became removal from data points, and the other side, for those consisted of **2** and **3**, the analysis results having the data points only excepted for a less aqueous media (see footnote *u* of Table 4) and those having the data points used almost all solvent available (see footnote *v* of Table 4), respectively, were shown in Table 4. The substrate (**4**) discussed also corresponds to the former type in the multiple correlation analysis.

It has been reported[34] that TFE solvent (media of low nucleophilicity) could play a prominent role as the solvent to make stabilization of long-lived carbocationic intermediate, for pure TFE and 97% HFIP solvents excepted from data points of two-term parameters correlation [eq. (1)] in solvolyses of **4**, these solvents behavior for **4** may act as a molecule of ionization. Whereas, in case of solvolyses of **3** with those a good correlation, almost all solvents (containing aqueous fluorinated solvents, without 97% HFIP) behavior may act as a molecule of nucleophile.

A linear rate-rate profile for solvolyses of **3** at 10 °C and those of **4** at 45 °C, with linear slope 1.02 (r = 0.972) implying identical mechanisms, is shown in Figure 4. However,
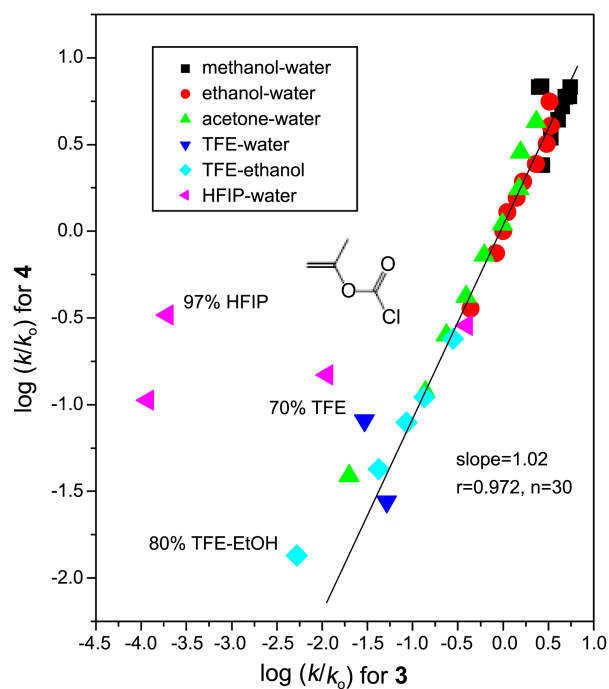
Figure 4. Rate-rate profile for solvolyses of isopropenyl chloroformate (**3**) at 10 °C and isobutyl chloroformate (**4**) at 45 °C in various solvent systems. (data for **3** from ref. 16).
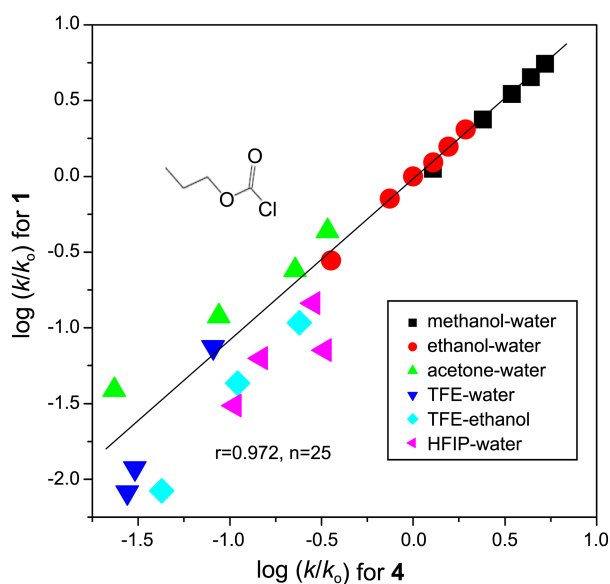
Figure 5. Rate-rate profile for solvolyses of **1** at 40 °C and **4** at 45 °C in various solvent systems. (data for **1** from ref. 23).

data points of corresponding aqueous HFIP solvents deviate significantly (with differential solvation of TS accompanying different mechanism).

A major cause for a greater rate constants for **4** of pure TFE and 97%(w/w) HFIP (as shown in Table 1), compared with the general trend of rates in aqueous fluorinated solvents, consistent with preceding explanation showing that a carbocationic reaction channel is dominant, and those of **4** in 97% TFE (97% HFIP) has a less negative $\Delta S^{\neq} = -12.2$ (−15.0) cal mol^{-1} K^{-1} than the other solvent ($\Delta S^{\neq} = -26.8 \sim -29.6$ cal mol^{-1} K^{-1}) investigated including water ($\Delta S^{\neq} = -20.6$ cal mol^{-1} K^{-1}) in Table 2. These results provide support for the validity of our elucidation of the role in solvents.

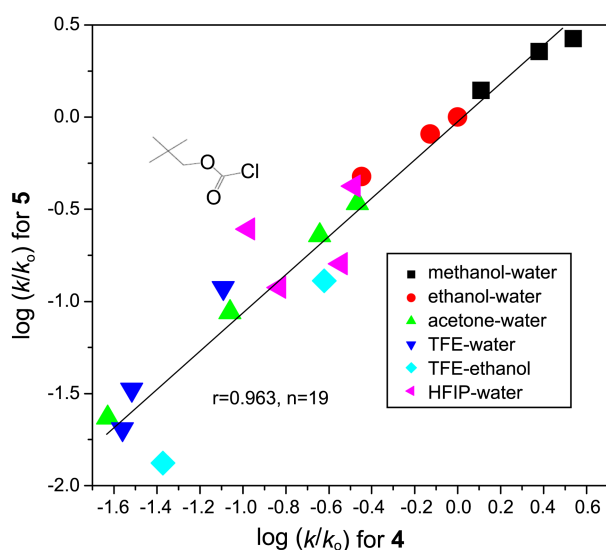To compare with reactivity for solvolyses of **1**, **4**, **5**, and **6**,

Figure 6. Rate-rate profile for solvolyses of **5** at 45 °C and **4** at 45 °C in various solvent systems. (data for **5** from ref. 20).
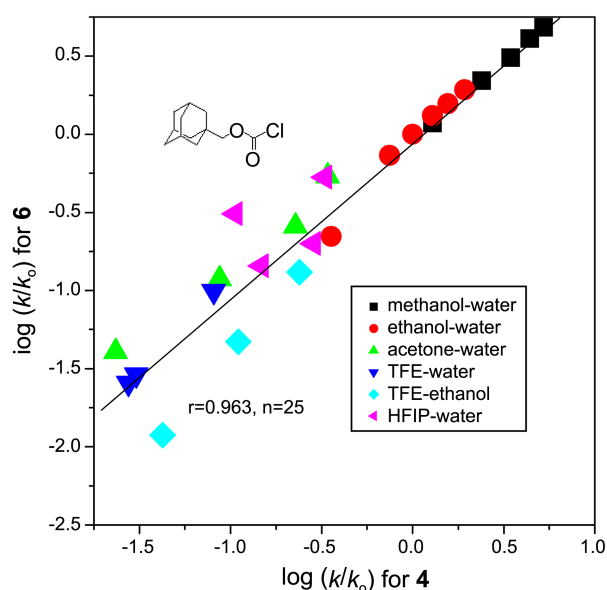

Figure 7. Rate-rate profile for solvolyses of **6** at 40 °C and **4** at 45 °C in various solvent systems. (data for **6** from ref. 24).

plots of logarithms of rate constants (rate-rate profiles) for solvolyses of **4** *vs* rates for **1**,[23] **5**,[20] and **6**,[24] respectively were attempted and these results show good linear correlations (as mentioned in Figure 5, Figure 6 and Figure 7, respectively) with the slopes of almost unity and linear coefficients (r) of 0.963-0.972 (n = 19-25) reduced, due to dispersion phenomena in fluorinated solvent systems. Consequently, these solvolyses show essential identical solvent effects on reactivity.

Conclusions

Values of *l/m* provide useful mechanistic criteria for the solvent effect in solvolytic reactions of acid chlorides [(*l/m* = 1.9-3.0 for Ad$_E$, *l/m* ≤ 0.8 for I (ionization pathway).[1] For solvolyses of **4**, *l/m* = 2.94 in a majority of the solvents (35), confirming that a tetrahedral-type intermediate (stepwise) led to a carbonyl addition mechanism (Ad$_E$); also, nucleophilic solvation was significant, and there was no mechanistic change caused by variation of solvent compositions.

However, in case of 18-solvent ranges having aqueous fluorinated solvent systems (TFE-H$_2$O and HFIP-H$_2$O) as well as Y_{Cl} > 2.7 solvent systems, the effect on reactivity for those of **4** (*l/m* = 1.20) are evaluated by the multiple regression analysis as competition with S$_N$2-type mechanism, and S$_N$1-type mechanism undergoes in pure TFE and 97% HFIP solvents. And TS-stabilization by nucleophilic solvation for **4** showed more sensitive for than those of **3**, due to solvolyses of **4**, in which could not find out a considerable contribution of stoichiometric solvation effect, compared with those of **3**[16] analyzed by third order reaction model.

For solvolyses of **1**,[23] **4**, **5**[20] and **6**,[24] considering the relatively values, for [k_{40E}/k_{97T}]$_Y$, k_{MeOH}/k_{MeOD}, *l/m* and n/n$_t$ given in Table 4, a consistent pattern of solvent effect on reactivity and mechanism were exposed and the sterically-

hindrance effect[36] of aliphatic group adjacent to the site of nucleophilic attack from the rear for these solvolyses could not found.

In conclusion, solvolyses of **4** show various spectra of mechanisms from Ad_E through S_N2 to S_N1 mechanism, according to the choice of solvent.

Experimental

Isobutyl chloroformate (Sigma-Aldrich ≥ 99%) was used as received. All solvents used for kinetic in this work were dried and distilled by standard methods (as described previously[3]); 1,1,1,3,3,3-hexafluoro-2-propanol was Aldrich reagent (AR:99%) and methanol-*d* was Aldrich reagent (> 99.5 ± > % D).

Specific rate constants for solvolytic reaction **4** proceed as pseudo-first type were determined using a general conductometric method[34] and calculation of those were performed by the Origin 6.0 program using the Guggenheim equation[37] from data monitored automatically. These were determined conductometrically at least in duplicate; typically injected 4 μL of 10% w/w substrate in dry acetonitrile into the kinetic apparatus containing 2 mL of each solvent mixture; associated standard deviations, and detailed methods are presented in footnotes of Table 1 and Table 2.

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25. (a) Data Estimated rate constant, k_{40E}, is 5.01×10^{-4} s^{-1} by using polynomial regression (log k *vs* solvent composition, ref. 1). (b) Estimated rate constant, k_{40E}, using polynomial regression with 3rd order and r = 0.9981 (log $k_{(ref. 23)}$ *vs* solvent composition), as 4.57×10^{-4} s^{-1} and then, $[k_{40E}/k_{97T}]_Y = 4.57 \times 10^{-4}$ s^{-1}/5.40×10^{-4} s^{-1} = 84, at 40 °C.
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