

Kinetics of the pH-independent hydrolyses of 4-nitrophenyl chloroformate and 4-nitrophenyl heptafluorobutyrate in water-acetonitrile mixtures: consequences of solvent composition and ester hydrophobicity

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ABSTRACT: The pH-independent hydrolyses of 4-nitrophenyl chloroformate, NPCF and 4-nitrophenyl heptafluorobutyrate, NPFB in aqueous acetonitrile were studied spectrophotometrically from 15 to 45 °C. The binary solvent composition covers water concentrations from 2.349 to 53.207 and from 2.745 to 53.333 mol L⁻¹ for NPCF and NPFB, respectively. For both esters, the dependence of log (*k*_{obs}), the observed rate constant, on log [water] is sigmoidal. The approximate kinetic orders with respect to water were found to be 2 and 3 for NPCF and NPFB, respectively. $\Delta G^\ddagger$ gradually decreases as a function of increasing [water], due to a complex, quasi-mirror image compensation of $\Delta H^\ddagger$ and $\Delta S^\ddagger$; both parameters increase. The structures of the transition states were probed by a proton inventory study, carried out in the presence of L₂O mole fractions (L = H or D) of 0.190, 0.540, 0.890 and 0.180, 0.529, 0.890, for NPCF and NPFB, respectively. Plots of observed rate constants *versus* the atom fraction of deuterium in the solvent curve downward. Cyclic transition state models were fitted to the kinetic data; these models contain the ester and two water molecules (NPCF) or three water molecules (NPFB). Thus, the sigmoidal dependences of log (*k*_{obs}) on log [water] are not due to a change in the number of water molecules in the transition states as a function of increasing [water]. The binary solvent mixture is micro-heterogeneous; there exists two “micro-domains,” one consists predominantly of coordinated water molecules, the other consists mostly of acetonitrile hydrogen-bonded to water molecules. NPCF is 232 times more soluble in water than NPFB. That is, the former ester is dissolved in the outer, more polar periphery of these micro-domains whereas the more hydrophobic NPFB is dissolved in their inner, less polar interiors. This conclusion is corroborated by comparing the dependence on log [water] of log [*k*_{obs}], and of *E*_T, the empirical solvent polarity parameter, as measured by solvatochromic probes of increasing hydrophobicity. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: 4-nitrophenyl chloroformate; hydrolysis of 4-nitrophenyl heptafluorobutyrate; hydrolysis of proton inventory; solvent effect; solvatochromism

INTRODUCTION

Binary mixtures of water and organic solvents are extensively employed in organic syntheses and in studies of reaction mechanisms of, for example, acyl transfer reactions. The reasons are partially practical and are often connected with solubility constraints. On the other hand, there is an increased interest in understanding the effects of reaction medium, of both pure solvents and binary mixtures on rate and equilibrium constants of chemical and biochemical reactions.^{1–4} The physico-chemical properties of both substrate and components of the

binary mixture affect the solvation of the species of interest, for example, reactants and activated complexes, hence reaction rates and equilibria. In this regard, studies of solvatochromism (effects of the medium on the spectra, absorption or emission, of solvatochromic probes) and thermo-solvatochromism (effects of temperature on solvatochromism) have contributed a great deal to our understanding of the above-mentioned interactions.^{5,6} The reason is that solvatochromic probes may be employed as models for the species of interest, for example, polar reagents and activated complexes. These studies have indicated that the hydrophobic/hydrophilic character and pK_a of both solvatochromic probe and components of the solvent play a central role in determining the composition of the solvation micro-sphere of the probe. This composition is not related in a

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simple way to bulk solvent composition because most mixtures of water with organic solvents are micro-heterogeneous.⁶

As a part of our interest in studying medium effects on reactivity we report here on the pH-independent hydrolyses of two reactive esters, 4-nitrophenyl chloroformate (NPCF) and 4-nitrophenyl heptafluorobutyrate (NPFb) in binary mixtures of water (W) and acetonitrile (MeCN) over almost the entire range of water concentration, from 2.349 to 53.333 mol L⁻¹. Effects of medium composition on the reactions were deduced from kinetic orders with respect to water; kinetic solvent isotope effects, KSICs, that is, $(k_{\text{obs}})_{\text{H}_2\text{O}-\text{MeCN}}/(k_{\text{obs}})_{\text{D}_2\text{O}-\text{MeCN}}$; the dependence of the activation parameters on log [water], and by applying the proton inventory technique to probe the structures of the transition states. Information on the relationship between ester hydrophobicity and the polarity of its reaction site was secured by comparing the dependence on log [water] of log (k_{obs}) and of E_{T} , the empirical solvent polarity parameter; the latter was measured by two solvatochromic indicators of different hydrophobicity.

EXPERIMENTAL

Materials

The reagents were purchased from Acros or Merck. The solvatochromic probes 2,6-dichloro-4-(2,4,6-triphenyl pyridinium-1-yl) phenolate (WB); 1-methylquinolinium-8-olate, QB (structures depicted in Results and Discussion) were available from previous studies.⁶ MeCN was further purified by distillation from P₄O₁₀, then from anhydrous K₂CO₃.⁷ D₂O was distilled under nitrogen. All-glass double distilled water was employed throughout.

NPCF was purified by sublimation under reduced pressure. NPFb was synthesized by refluxing a mixture of 10 mmol distilled heptafluorobutyryl chloride and 12 mmol of sodium 4-nitrophenoxide in 50 mL of anhydrous acetonitrile for 6 h. The solvent was evaporated, the residue was suspended in 25 mL dry chloroform, the suspension filtered, and the ester purified by flash column chromatography, using chloroform as eluent. Yellow oil; yield 78%. Calculated for C₁₀H₄F₇NO₄, %: C, 35.84; H, 1.20, N, 4.18. Analyzed: C, 35.63; H, 1.26; N, 4.25. IR (Bruker Victor-22 FTIR, 0.025 mol L⁻¹ solution in CD₃CN) 1802 cm⁻¹ ($\nu_{\text{C=O}}$); 1521 and 1342 cm⁻¹ (asymmetric and symmetric ν_{NO_2}).

Kinetic measurements

All binary solvent mixtures were prepared at 25 °C by volume and by weight. In order to suppress any base-catalyzed reaction, the mixtures contained 0.01 mol L⁻¹ HCl or DCl. The (residual) protium concentration in D₂O,

or in DCl/D₂O, hence the deuterium contents of these media, were determined by ¹H-NMR (Varian Innova-300 NMR spectrometer) by using 1,4-dioxane as an internal reference.⁸

Kinetic runs (at least triplicate) were carried out with the aid of Beckman DU-70, or Applied Photophysics SX-18 MV stopped-flow Uv-Vis spectrometers; both are interfaced to PC, and equipped with thermostated cell holders, whose temperatures were controlled within ± 0.05 °C. Preliminary experiments in W-MeCN mixtures ([W] = 53.333 mol L⁻¹) have shown that the observed rate constant, k_{obs} , was independent of ester concentration in the range $(2-8 \times 10^{-5} \text{ mol L}^{-1})$. In subsequent runs the final [ester] was $\approx 5 \times 10^{-5} \text{ mol L}^{-1}$. The reaction progress was followed by monitoring the liberation of 4-nitrophenol at 320 nm, as a function of time. Values of k_{obs} were calculated from log (absorbance) *versus* time plots; these were rigorously linear over more than five half-lives. The agreement between calculated and experimental "infinity" absorbances was routinely checked. The relative standard deviation in k_{obs} , that is, ((standard deviation/ k_{obs}) 100), was ≤ 0.2 , that between k_{obs} of triplicate runs was $\leq 1.0\%$.

Spectrophotometric determination of the empirical solvent polarity parameter, E_{T}

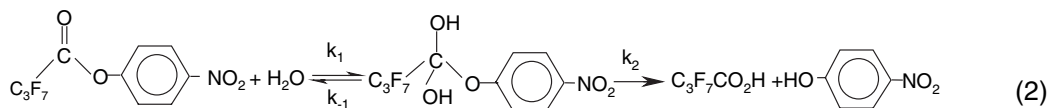
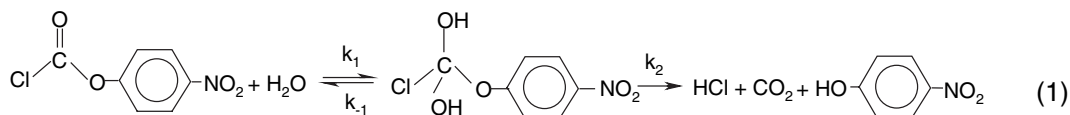
This was carried out as described in detail elsewhere,⁶ by using the Beckman DU-70 spectrometer. The final solvatochromic probe concentration was $2-5 \times 10^{-4} \text{ mol dm}^{-3}$. Values of λ_{max} (calculated from the first derivative of the absorption spectrum) were determined at 25 °C as a function of solvent composition. E_{T} was calculated from:^{5,6}

$$E_{\text{Tprobe}}(\text{kcal/mol}) = 28\,591.5/\lambda_{\text{max}}(\text{nm}).$$

RESULTS AND DISCUSSION

In W-MeCN mixtures, at [W] = 11.076, 33.440 and 53.207 mol L⁻¹, values of k_{obs} for both esters were found to independent of [HCl] in the range 0.001–0.1 mol L⁻¹. This shows that both reactions are water-catalyzed hydrolyses. Simple kinetic pathways for the reactions studied are depicted in Scheme 1.

Hydrolysis of each ester gave one equivalent of 4-nitrophenol and the spectra of both reactions (λ vs. time) showed sharp isosbestic points at 285 nm. Additionally, rigorous pseudo-first order kinetics were always observed; identical k_{obs} were obtained in the presence, or absence of $5 \times 10^{-5} \text{ mol L}^{-1}$ 4-nitrophenol, added to the solution before the start of the kinetic run. That is, the intermediates of the first step of both reactions of Scheme 1 do not accumulate; this (first) step is rate limiting, in



Scheme 1. Pathways for the pH-independent hydrolyses of NPCF and NPFB

agreement with the fact that the 4-nitrophenoxide ion is a better leaving group than the hydroxide ion. Accordingly, the reaction rate is given by:

$$\text{Rate} = k_1[\text{ester}][\text{W}]^x = k_{\text{obs}}[\text{ester}], \text{ since } [\text{W}] \gg [\text{ester}] \quad (3)$$

$$k_{\text{obs}} = k_1[\text{W}]^x \text{ or } \log k_{\text{obs}} = \log k_1 + x \log [\text{W}] \quad (4)$$

Where (x) is the kinetic order with respect to water.

Tables 1 and 2 show the dependence of k_{obs} on solvent composition at different temperatures, for NPCF and NPFB,

respectively; the corresponding activation parameters are listed in Tables 3 and 4. Figures 1 and 2 show plots of $\log k_{\text{obs}}$ versus $\log [\text{W}]$ for NPCF and NPFB, respectively; the corresponding dependence of the activation parameters on $\log [\text{W}]$ is shown in Figs. 3 and 4, respectively. All these results show the following relevant points:

- In all solvent mixtures, NPFB is much more reactive than NPCF, in agreement with the stronger (-I) effect of the $n\text{-C}_3\text{F}_7$ - group relative to the Cl atom;⁹
- As shown by Eqn (4), (x) may be calculated from plot of $\log (k_{\text{obs}})$ versus $\log [\text{W}]$. For NPCF these plots are

Table 1. Hydrolysis of 4-nitrophenyl chloroformate in water (W)-acetonitrile (MeCN) mixtures: observed rate constants (k_{obs} , sec^{-1}) as a function of temperature and medium composition, listed as water molar concentration, $[\text{W}]$, and mole fraction, χ_{W} ^a

$[\text{W}]$, mol L^{-1}	χ_{W}	$k_{\text{obs}} \times 10^2$, 15 °C	$k_{\text{obs}} \times 10^2$, 25 °C	$k_{\text{obs}} \times 10^2$, 35 °C	$k_{\text{obs}} \times 10^2$, 45 °C
2.350	0.115	0.019	0.033	0.054	0.086
4.447	0.202	0.071	0.126	0.221	0.356
7.489	0.313	0.165	0.319	0.579	0.966
11.076	0.418	0.261	0.543	1.024	1.733
14.427	0.504	0.342	0.736	1.421	2.537
20.006	0.614	0.487	1.078	2.242	4.043
26.430	0.717	0.733	1.646	3.485	6.712
33.440	0.807	1.163	2.490	5.450	10.910
42.848	0.903	1.983	4.638	10.098	20.096
48.409	0.948	2.637	6.314	13.280	27.520
53.207	0.986	3.201	7.247	16.520	33.358

^a The rate constants reported are the mean of at least triplicate runs. The relative standard deviation between k_{obs} of a triplicate, that is, ((standard deviation/ k_{obs})100) was $\leq 1.0\%$.

Table 2. Hydrolysis of 4-nitrophenyl heptafluorobutyrate in W-MeCN mixtures: Observed rate constants (k_{obs} , sec^{-1}) as a function of temperature and medium composition^a

$[\text{W}]$, mol L^{-1}	χ_{W}	$k_{\text{obs}} \times 10^2$, sec^{-1} , 15 °C	$k_{\text{obs}} \times 10^2$, sec^{-1} , 25 °C	$k_{\text{obs}} \times 10^2$, sec^{-1} , 35 °C	$k_{\text{obs}} \times 10^2$, sec^{-1} , 45 °C
2.745	0.130	0.011	0.013	0.016	0.018
6.230	0.266	0.080	0.107	0.137	0.162
9.496	0.371	0.174	0.250	0.338	0.442
13.294	0.472	0.295	0.435	0.623	0.841
17.163	0.557	0.417	0.644	0.977	1.404
25.914	0.710	0.847	1.447	2.268	3.335
33.223	0.806	1.894	3.077	4.832	7.351
43.091	0.904	7.531	11.745	17.810	25.290
48.394	0.946	16.40	24.50	35.330	49.570
53.333	0.986	30.00	36.450	63.610	94.320

^a The rate constants reported are the mean of at least triplicate runs. The relative standard deviation between k_{obs} of a triplicate, that is, ((standard deviation/ k_{obs})100) was $\leq 1.0\%$.

Table 3. Activation parameters for the hydrolysis of 4-nitrophenyl chloroformate in W-MeCN mixtures as a function of medium composition^a

[W], mol L ⁻¹	$\Delta H^\ddagger$, kcal mol ⁻¹	$\Delta S^\ddagger$, cal K ⁻¹ mol ⁻¹	$-T\Delta S^\ddagger$, kcal mol ⁻¹ , 25 °C	$\Delta G^\ddagger$, kcal mol ⁻¹
2.350	8.5	-46.0	13.7	22.2
4.447	9.3	-40.7	12.1	21.4
7.489	10.2	-35.9	10.7	20.9
11.076	10.9	-32.3	9.6	20.6
14.427	11.6	-29.6	8.8	20.4
20.006	12.3	-26.2	7.8	20.1
26.430	12.9	-23.5	7.0	19.9
33.440	13.3	-20.6	6.7	19.5
42.848	13.5	-19.4	5.8	19.3
48.409	13.6	-18.5	5.5	19.1
53.207	13.7	-17.7	5.3	19.0

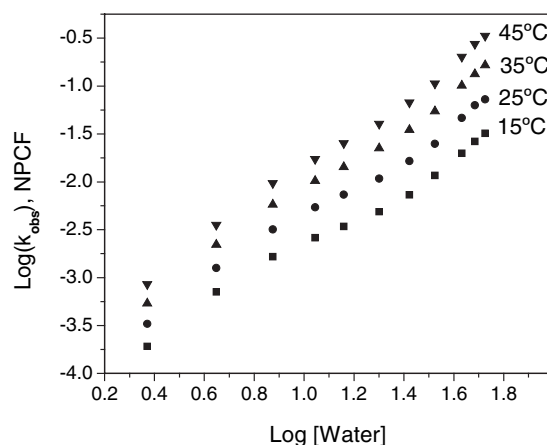
^a The errors are ± 0.1 kcal mol⁻¹ ($\Delta H^\ddagger$ and $\Delta G^\ddagger$) and 0.5 cal K⁻¹ mol⁻¹ ($\Delta S^\ddagger$).

Table 4. Activation parameters for the hydrolysis of 4-nitrophenyl heptafluorobutyrate in W-MeCN mixtures as a function of medium composition^a

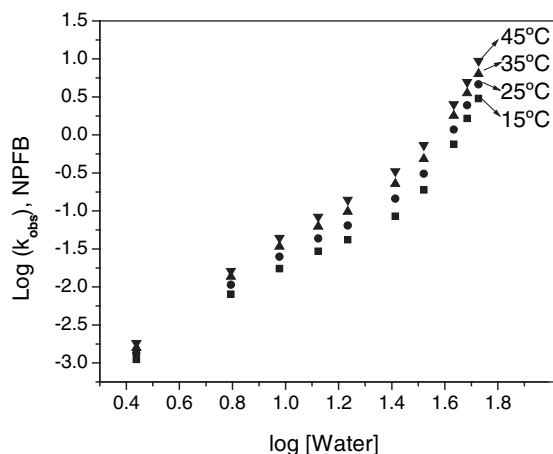
[W], mol L ⁻¹	$\Delta H^\ddagger$, kcal mol ⁻¹	$\Delta S^\ddagger$, cal K ⁻¹ mol ⁻¹	$-T\Delta S^\ddagger$, kcal mol ⁻¹ , 25 °C	$\Delta G^\ddagger$, kcal mol ⁻¹
2.745	2.4	-63.6	19.0	21.4
6.230	3.7	-55.1	16.4	20.2
9.496	5.1	-48.9	14.6	19.6
13.294	5.8	-45.3	13.5	19.3
17.163	6.8	-41.2	12.3	19.1
25.914	7.7	-36.5	10.9	18.6
33.223	7.6	-35.3	10.5	18.2
43.091	6.8	-35.4	10.6	17.4
48.394	6.1	-36.2	10.8	16.9
53.333	6.3	-34.6	10.3	16.6

^a The errors are ± 0.1 kcal mol⁻¹ ($\Delta H^\ddagger$, and $\Delta G^\ddagger$) and 0.5 cal K⁻¹ mol⁻¹ ($\Delta S^\ddagger$).

not strictly linear; a third order polynomial may be conveniently fitted to the data ($r^2 > 0.999$). If linear regression is employed instead, (x) was found to increase from 1.5 to 1.8 as T is increased from 15 to 45 °C. A fourth order polynomial is required to fit the data of NPFb ($r^2 > 0.999$); for the same T range,

**Figure 1.** Plots of $\log(k_{\text{obs}})$ versus $\log[\text{water}]$ for the hydrolysis of 4-nitrophenyl chloroformate in W-MeCN at different temperatures

(x) obtained by linear regression of the data increases from 2.5 to 2.7. These linear regressions, although only approximate, indicate that the transition state, TS, for the hydrolysis of NPFb contains more water molecules than its NPCF counterpart. Note that (x) for the hydrolysis (in W-MeCN) and methanolysis (in

**Figure 2.** Plots of $\log(k_{\text{obs}})$ versus $\log[\text{water}]$ for the hydrolysis of 4-nitrophenyl heptafluorobutyrate in W-MeCN at different temperatures

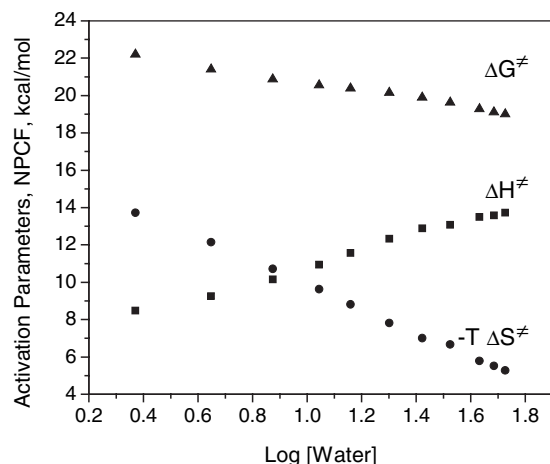


Figure 3. Dependence of the activation parameters for the hydrolysis of 4-nitrophenyl chloroformate on $\log [W]$. The $T\Delta S^\ddagger$ term was calculated at 25 °C

MeOH–MeCN) of (structurally similar) 4-nitrophenyl trifluoroacetate are 3.2 and 2.9, respectively. The plots that generated these (x) were linear because of the very limited protic solvent concentration range employed, 1–5 mol L⁻¹.¹⁰

- iii. The above-mentioned difference in (x) also agrees with the large differences between $T\Delta S^\ddagger$ for both esters. Over the whole solvent composition range, the hydrolysis of NPFB is associated with much more negative entropy of activation than for NPCF, presumably because of the larger number of water molecules involved in its TS. In fact, $\Delta G^\ddagger$ for NPFB is dominated by the $T\Delta S^\ddagger$ term, over the entire water concentration range. This contrasts with the hydrolysis of NPCF, where the above-mentioned entropy dominance is observed only for the water-poor regions, $[W] \leq 5 \text{ mol L}^{-1}$; at higher water concen-

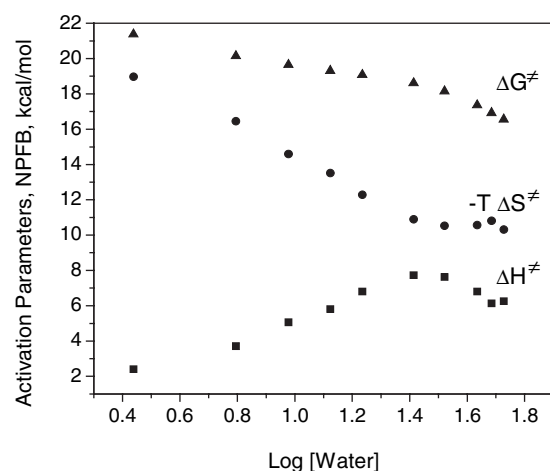


Figure 4. Dependence of the activation parameters for the hydrolysis of 4-nitrophenyl heptafluorobutyrate on $\log [W]$. The $T\Delta S^\ddagger$ term was calculated at 25 °C

trations $\Delta G^\ddagger$ is dominated by variation in the $\Delta H^\ddagger$ term, Tables 3 and 4. The relative importance of these contributions is apparent from Figs. 3 and 4. For NPCF, $\Delta G^\ddagger$ decreases monotonically as a function of increasing $\log [W]$, due to an increase of $\Delta H^\ddagger$, accompanied by quasi mirror-image increase of the corresponding $\Delta S^\ddagger$. This enthalpy–entropy compensation has been observed for several water-catalyzed reactions; among other factors, they reflect variations in the interactions of the components of the binary solvent mixture with the species of interest, reagent state, RS, and/or TS.^{2,11} For NPFB, $\Delta G^\ddagger$ also decreases monotonically as a function of increasing $\log [W]$, due to partial enthalpy–entropy compensation. The energy difference between the $\Delta H^\ddagger$ and $T\Delta S^\ddagger$ curves in the water poor-region is, however, large so that the two curves do not cross (as in case of NPCF). This results in the above-mentioned entropy dominance of the hydrolysis of NPFB;

- iv. In principle, the above-mentioned non-linear dependence of $\log (k_{\text{obs}})$ on $\log [W]$, Figs. 1 and 2, may be taken to indicate that the number of water molecules in the TS depends on $[W]$. Examples of such dependence are known, for example, (x) for the spontaneous hydration of chloral varies from *ca.* 4 to *ca.* 2 when $[W]$ is increased from 0.25 to 46.3 mol L⁻¹.^{12a} the TS for the hydration of 1,3-dichloroacetone contains one, two, or three molecules of water, depending on whether the reaction is carried out in the presence of surfactant (inverse) aggregates in *n*-hexane, or in aqueous dioxane, respectively.^{12b–d} Finally, the number of water molecules in the TS of the imidazole-catalyzed hydrolysis of N-4-nitrophenyltrifluoroacetamide in W–MeCN was reported to increase from one to four as a function of increasing $[W]$.^{12e}
- v. A handle on the structures of the TSs may be obtained by submitting the kinetic data to analysis by the proton inventory technique, PI. The use of PI to probe the structures of TSs is documented,^{3,4,8,13} so that only a brief account will be given here. The observed KSIE is employed to estimate the number of hydrogens (hence water molecules in the present reactions) that participate in the TS. This number and other chemical information, for example, activation parameters, enable one to suggest a structure for the TS. The observed rate constant, k_n , in the presence of H₂O–D₂O mixtures is related to the observed rate constant in pure H₂O, k_o , by the equation:

$$k_n/k_o = \frac{\prod_{i \text{ TS}} (1 - n + n\phi_i^\ddagger)}{\prod_{j \text{ RS}} (1 - n + n\phi_j)} \quad (5)$$

Where (n) is the atom fraction of deuterium in the solvent. All TS hydrogens (i) and all RS hydrogens (j) that contribute to the isotope effect possess a term in the

Table 5. Dependence of the observed rate constants (k_n) for the hydrolysis of 4-nitrophenyl chloroformate on the atom fraction of deuterium (n) in mixtures of MeCN–H₂O–D₂O at different L₂O mole fractions, χ_{L_2O} at 25 °C^a

$\chi_{L_2O} = 0.190$			$\chi_{L_2O} = 0.540$			$\chi_{L_2O} = 0.890$		
(n)	Expl. $k_n \times 10^2$ (sec ⁻¹)	Calc. $k_n \times 10^2$ (sec ⁻¹)	(n)	Expl. $k_n \times 10^2$ (sec ⁻¹)	Calc. $k_n \times 10^2$ (sec ⁻¹)	χ_D	Expl. $k_n \times 10^2$ (sec ⁻¹)	Calc. $k_n \times 10^2$ (sec ⁻¹)
0.0 ^b	0.116	0.116	0.0 ^b	0.886	0.886	0.0 ^b	4.571	4.571
0.238	0.101	0.101	0.241	0.767	0.771	0.250	4.050	4.049
0.487	0.087	0.087	0.478	0.665	0.666	0.495	3.550	3.568
0.724	0.075	0.074	0.720	0.561	0.567	0.732	3.134	3.131
0.969	0.062	0.062	0.969	0.480	0.473	0.969	2.731	2.723
KSIE	1.89		1.89			1.71		
φ_a	0.726 ± 0.001		0.722 ± 0.003			0.764 ± 0.001		

^a Expl. = Experimental k_n ; Calc. = Calculated k_n by using Eq. (8); $k_n/k_0 = (1 - n + n\varphi_a)^2$, where φ_a is the fractionation factor of protons H_a of TS2 of Fig. 5; KSIE = kinetic solvent isotope effect, that is, $(k_{\text{obs}})_{\text{H}_2\text{O}-\text{MeCN}}/(k_{\text{obs}})_{\text{D}_2\text{O}-\text{MeCN}}$; L = H or D.

^b Calculated rate constant for the reaction in pure H₂O.

numerator and denominator, respectively, of right hand side of Eqn (5). Each hydrogen site is associated with a fractionation factor, defined by Eqn (6):

$$\varphi_{\text{site}} = \frac{[\text{D}/\text{H}]_{\text{site}}}{[\text{D}/\text{H}]_{\text{solvent}}} \quad (6)$$

That is, φ_{site} expresses the preference of deuterium for the site relative to that of bulk solvent. Analysis of the present reaction is simplified by the following: under reaction conditions, MeCN does not undergo H/D exchange with D₂O (conclusion based on integration of the ¹H-NMR peak of MeCN as a function of time); NPCF and NPFb carry no exchangeable hydrogens; φ of the other reactant, water, is unity, by definition. Consequently, the denominator of Eqn (5) is unity, and we need consider only the hydrogens of the TS.

Tables 5 and 6 show the dependence of k_n on (n) at three different mole fractions of L₂O, χ_{L_2O} , where L = H or D; these cover the three regions of the plots of Figs. 1 and 2. The procedure usually employed is to draw TS structures that are chemically sound, and to test how these structures agree with experimental KSIE. Our objective is to determine the dependence, if any, of the structure of the TS on χ_{L_2O} .

Based on the above-mentioned values of (x), any TS containing one water molecule may be ruled out. Therefore, we consider transition states that contain two, or three water molecules, as depicted in Fig. 5 (for sake of simplicity, we draw (H_a) symmetrically between the oxygen atoms).

In TS1, the proton bridge, H_a, contributes a primary isotope effect. H_b which is converted from an OH of water to an OH of the tetrahedral intermediate does not contribute to the isotope effect, i.e., $\varphi_b = 1$. H_c of the

Table 6. Dependence of the observed rate constants (k_n) for the hydrolysis of 4-nitrophenyl heptafluorobutyrate on the atom fraction of deuterium (n) in mixtures of MeCN–H₂O–D₂O at different L₂O mole fractions, χ_{L_2O} at 25 °C^a

$\chi_{L_2O} = 0.180$			$\chi_{L_2O} = 0.529$			$\chi_{L_2O} = 0.890$		
(n)	Expl. $k_n \times 10$ (sec ⁻¹)	Calc. $k_n \times 10$ (sec ⁻¹)	(n)	Expl. $k_n \times 10$ (sec ⁻¹)	Calc. $k_n \times 10$ (sec ⁻¹)	(n)	Expl. $k_n \times 10$ (sec ⁻¹)	Calc. $k_n \times 10$ (sec ⁻¹)
0.0 ^b	0.036	0.036	0.0 ^b	0.572	0.572	0.0 ^b	10.090	10.090
0.238	0.029	0.028	0.241	0.446	0.445	0.247	7.965	7.986
0.487	0.022	0.022	0.478	0.342	0.341	0.497	6.155	6.178
0.724	0.016	0.016	0.720	0.251	0.252	0.731	4.758	4.760
0.969	0.012	0.012	0.969	0.179	0.179	0.969	3.582	3.554
KSIE	3.22		3.34			2.92		
φ_a	0.679 ± 0.001		0.668 ± 0.001			0.697 ± 0.002		

^a Expl. = Experimental k_n ; Calc. = Calculated k_n by using Eq. (9); $k_n/k_0 = (1 - n + n\varphi_a)^3$, where φ_a is the fractionation factor of protons H_a of TS3 or TS4 of Fig. 5; KSIE = kinetic solvent isotope effect, that is, $(k_{\text{obs}})_{\text{H}_2\text{O}-\text{MeCN}}/(k_{\text{obs}})_{\text{D}_2\text{O}-\text{MeCN}}$; L = H or D.

^b Calculated rate constant for the reaction in pure H₂O.

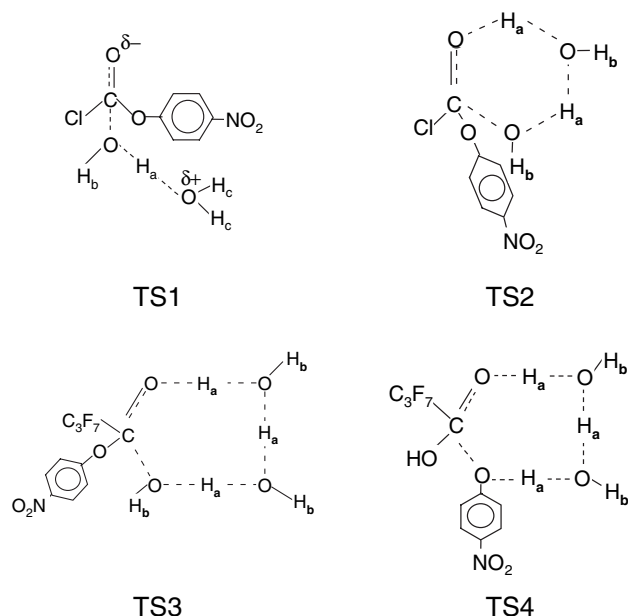


Figure 5. Suggested transition state structures for the hydrolysis of 4-nitrophenyl chloroformate, TS1 and TS2, and of 4-nitrophenyl heptafluorobutyrate, TS3 and TS4

“general base” water molecule contributes a secondary isotope effect. By the same line of reasoning, only H_a of the other TSs contributes to the KSIE. According to TS1, the dependence of k_n/k_o on (n) is given by:

$$\frac{k_n}{k_o} = (1 - n + n\varphi_a)(1 - n + n\varphi_c)^2 \quad (7)$$

Although this equation reproduces the kinetic data reasonably, the errors in the fractionation factors calculated are much larger (between 5 and 10 times) than φ_a and φ_c . Additionally, φ calculated are different from what is expected. For $\chi_{L_2O} = 0.540$, φ_a and φ_c are

similar, ≈ 0.81 ; this is unreasonable for a primary and a secondary KSIE. For $\chi_{L_2O} = 0.190$ and 0.890 , $\varphi_a = 0.989$ and 0.928 and $\varphi_c = 0.720$ and 0.797 , respectively. Again, φ_a is much larger than expected for this proton (*ca.* 0.5), whereas φ_c is less than expected, at least for $\chi_{L_2O} = 0.190$. Provided that the second water molecule acts as a “general base,” that is, its rate constant lies on the line of the Brønsted equation plot, the fractionation factor for H_c of TS1 may be calculated from: $\varphi_c = 0.69^\beta$,⁸ and should be *ca.* 0.8. The latter calculation is based on $\beta = 0.59$, calculated for general base-catalyzed hydrolysis of 4-nitrophenyl trifluoroacetate in 0.56 mol L^{-1} water in acetonitrile.¹⁴ The fact that the fractionation factors calculated by Eqn (7) depend on χ_{L_2O} mean that the degree of proton transfer in the TS depends (somewhat erratically) on χ_{L_2O} , there is no chemical ground for this dependence, that is, TS1 may be safely rejected.

The cyclic TS2 also involves the ester plus two water molecules, protons H_a are transferred in a six-membered ring. The corresponding dependence of k_n/k_o on (n) is given by:

$$k_n/k_o = (1 - n + n\varphi_a)^2 \quad (8)$$

This equation reproduces the data satisfactorily, as can be seen from the calculated k_n of Table 5 and from Fig. 6. Values of φ_a are practically independent of χ_{L_2O} , in the range 0.190–0.540, and is only slightly higher (by 5%) in the water-rich region. Consequently, the structure of the TS appears to be the same, over the whole water concentration range. Equation (9) (NPCF plus three water molecules) also reproduces k_n/k_o , with $\varphi_a = 0.82 \pm 0.01$, although with larger errors in φ , and larger differences between experimental and calculated k_n (rate constants not listed). The value of (x) , and the fact that $(\Delta S^\ddagger_{\text{NPCF}}) \gg (\Delta S^\ddagger_{\text{NPFB}})$ over the whole $[W]$ range, argues against TSs that contain the same number of water molecules, namely three, for both esters. That is,

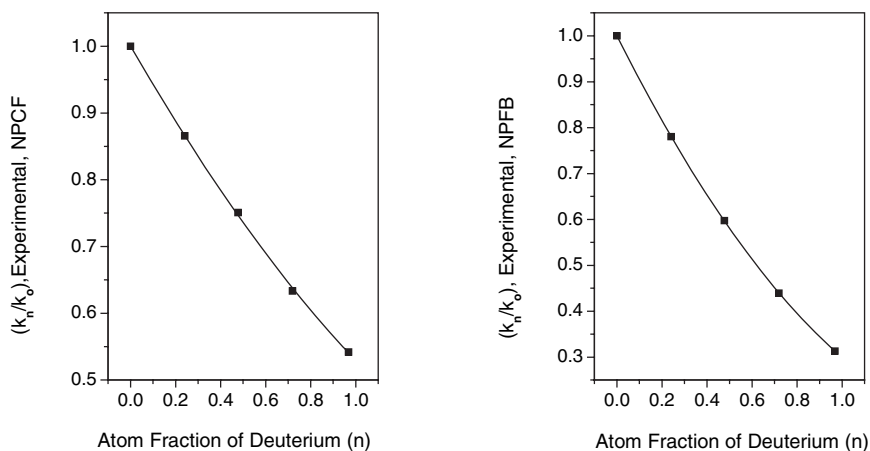


Figure 6. Typical results for the application of the proton inventory technique to the hydrolysis at χ_{L_2O} ($L = H$ or D) of 0.540 and 0.529, for 4-nitrophenyl chloroformate and 4-nitrophenyl heptafluorobutyrate, respectively. The points are experimental and the solid lines were calculated by Eqs. (8) and (9), respectively

assigning TS3 or TS4 to the hydrolysis of NPCF is not warranted.

$$\frac{k_n}{k_o} = (1 - n + n\varphi_a)^3 \quad (9)$$

The same line of reasoning may be employed in order to consider TS2 unlikely for the hydrolysis of NPFB. Additionally, data treatment according to Eqn (8) resulted in larger errors in both (φ_a) and k_n (rate constants not listed), compared with those calculated by Eqn (9), see Fig. 6. Application of the latter equation to the k_n/k_o data resulted in fractionation factors that are independent of χ_{L_2O} , similar to what has been obtained for NPCF. The results may be also conveniently reproduced according to TS4, an alternative to TS3. In this model, NPFB is rapidly hydrated by a single water molecule, followed by a rate-limiting decomposition of the hydrate involving two additional water molecules. A point in favor of TS4 is that the equilibrium constants for the hydration of trifluoromethyl derivatives of carbonyl compounds are >1 , and these reactions are exothermic.¹² The exothermic pre-equilibrium may explain the relatively small values of $\Delta H^\ddagger$, Table 4, since the latter quantity is the sum of the enthalpies of (exothermic) pre-equilibrium and (endothermic) rate limiting step. It is worth noting that the average φ_a for NPFB, 0.682 ± 0.014 , is similar to those calculated for the pH-independent hydrolyses in aqueous acetonitrile of 4-nitrophenyl trifluoroacetate (0.697 ± 0.005), and 4-methylphenyl trichloroacetate (0.707 ± 0.003) for which cyclic TSs, similar to TS3 and TS4 have been suggested.^{3i,10}

- vi. Finally, we address the relevance of ester hydrophobicity and the micro-heterogeneity of the binary mixture to the kinetic data, in particular to $\log(k_{\text{obs}})$ versus $\log[W]$ plots. A measure of the hydrophobic character of the ester is its partition coefficient between n -octanol and water, $\log P$, defined as:¹⁵

$$\log P = \frac{[\text{substance}]_{n\text{-octanol}}}{[\text{substance}]_{\text{water}}} \quad (10)$$

Although the partition coefficient experiment could not be carried out because of the susceptibility of these esters toward hydrolysis, values of $\log P$ may be conveniently calculated from group contribution;¹⁵ they were found to be 1.658 and 4.023 for NPCF and NPFB, respectively. That is, the former ester is 232 times more soluble in water than the latter one. Before discussing the relevance of this large difference in hydrophobicity, it is instructive to briefly discuss the microscopic structure of W-MeCN mixtures as a function of their composition. When the organic solvent is added to water it replaces the uncoordinated water molecules. The limit of χ_w beyond which MeCN cannot be accommodated within the cavities of water is $\chi_w \approx 0.85$. Below this χ_w , solvent micro-heterogeneity

sets in, and there exists two “micro-domains,” one highly structured consisting predominantly of coordinated water molecules, and a relatively disordered one containing mostly acetonitrile, hydrogen-bonded to water. Addition of more MeCN leads to a change in the relative concentrations of the two micro-domains but their compositions do not vary appreciably. At $\chi_w \leq 0.3$ the water clusters have become few and far apart that new interactions set in. W-MeCN interactions become important, this results in the formation of complexes, for example, $(\text{MeCN})_m\text{-W}$ where $m = 1\text{--}4$. At still lower χ_w values, the structure of acetonitrile dominates, and species such as $(\text{MeCN})_m$ are abundant. It should be born in mind, however, that the onset of formation of the different regions is not sharp, and is dependent on the method used to study the solvent system.^{16–18} Using electron impact mass spectroscopy, it has been shown that hydrophobic substrates, partition in favor of hydrophobic micro-domain of the binary mixture.¹⁸ Consequently, if NPCF and NPFB are present in the same nano-droplet, then the former ester is expected to be solubilized at its (more polar) periphery, whereas the latter one is expected to be solubilized in its (less polar) central part. A similar difference in solubilization sites has been shown to occur in aqueous micelles. Thus NPCF is solubilized at the (polar) micellar interface, whereas a relatively hydrophobic ester, 4-nitrophenyl 2,2-dichloropropionate, is solubilized in the (less polar) micellar interior.¹⁹ Another approach to corroborate the presence of the two esters in micro-environments of different polarities is to compare the response to solvent composition of two independent processes: hydrolysis of the esters and solvatochromism of two probes, 2,6-dichloro-4-(2,4,6-triphenyl pyridinium-1-yl) phenolate (WB); 1-methylquinolinium-8-olate, QB, see structures in Fig. 7.

$\log P$ of these two probes were found to be 1.79 and -0.63 , for WB and QB, respectively,^{6c} that is, the latter probe is 263 times more soluble in water than the former one. Figure 8 shows plots of the dependence of $\log(k_{\text{obs}})$ and $E_T(\text{probe})$ on $\log[W]$, at 25 °C. For convenience, we employed reduced $\log(k_{\text{obs}})$ and reduced $E_T(\text{probe})$, so that results of different substrates (esters and probes)

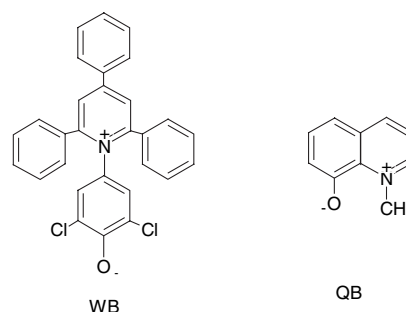


Figure 7. Structures of solvatochromic probes employed

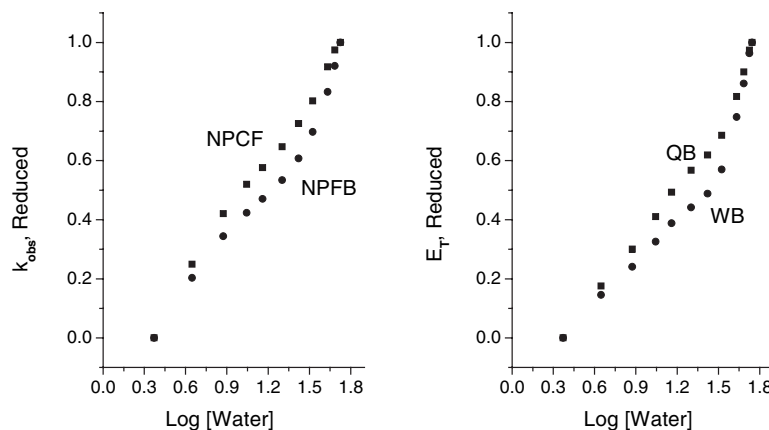


Figure 8. Plots of the dependence of $\log(k_{\text{obs}})$ and of $E_{\text{T}}(\text{probe})$ on $\log[W]$, at 25 °C. Reduced $\log(k_{\text{obs}})$ and reduced $E_{\text{T}}(\text{probe})$ are employed, so that results of different species (esters, probes) may be directly compared. Values of E_{T} in pure water and pure MeCN are, respectively, 64.62 and 52.97 kcal mol⁻¹ (QB) and 70.24 and 54.72 kcal mol⁻¹ (WB).

may be directly compared. The plots show a *remarkable resemblance*, the more hydrophobic substrates (NPFB and WB) deviate more from the ideal (i.e., linear) behavior than the less hydrophobic ones (NPCF and QB).

The non-linear dependence of $\log(k_{\text{obs}})$ on $\log[W]$ probably reflects the effects of preferential solvation of RS and/or TS; a similar rationale has been employed to explain the non-linear dependence of E_{T} on χ_{W} in several binary mixtures.^{5,6} Because Gibbs free energies of transfer of several non-electrolytes from water to mixtures of water and aprotic solvents are relatively insensitive to solvent composition,²⁰ it is plausible that kinetic solvent effects on the RS are not dominant and we concentrate on the TS. Acetonitrile is known to solvate positive centers stronger than negative ones. On the other hand, the water molecule is capable of solvating both types of centers effectively. Thus the dipoles that are generated in TS2 to TS4 are more efficiently solvated by water, so that the activation parameters should be sensitive to the state of water in the solvent mixture. The initial addition of acetonitrile to water results in a decrease of k_{obs} and increase in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ since uncoordinated water molecules would be considerably more polar, that is, of higher kinetic reactivity than their coordinated counterparts.² After this region, the effect of preferential solvation on k_{obs} and the activation parameters becomes apparent. For example, most of the variation in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ occurs below $\chi_{\text{W}} \approx 0.7$. The differences between the enthalpies and entropies of activation, that is, between those calculated for the largest and smallest water concentrations are: ($\Delta\Delta H^{\ddagger}$) = 5.25, 3.85 kcal mol⁻¹; T($\Delta\Delta S^{\ddagger}$) = 8.45 and 8.66 kcal mol⁻¹, for NPCF and NPFB, respectively. $\Delta\Delta H^{\ddagger}$ may reflect the activities of water in the different solubilization sites in MeCN-W nano-clusters.

CONCLUSIONS

(i) The kinetic order with respect to one of the components of a binary solvent mixture should be based on rate constants obtained over a sufficiently wide range of solvent composition. Care should be exercised when kinetic orders with respect to water are interpreted in terms of the number of water molecules in the TS. The reason is that slopes of plots of $\log(k)$ versus $\log[\text{water}]$ are most probably affected by the micro-heterogeneity of the medium, and the concomitant preferential solvation of RS and/or TS by one component of the mixture; (ii) the complex (sigmoidal) dependence of $\log(k_{\text{obs}})$ on $\log[W]$ is not due to a change in the structure of the corresponding TS as a function of increasing $[W]$; (iii) the TS of both esters contain different numbers of water molecules, 2 and 3 for NPCF and NPFB, respectively; (iv) solvatochromic probes may be fruitfully employed in order to mimic the response of chemical reactions to variation of solvent composition. Thus solvation of WB and QB and hydrolysis of both esters seem to be sensitive to the same solute-solvent interactions, namely, hydrogen bonding and dipolar interactions, these are modulated by the water-acetonitrile interactions.

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