

Kinetics of hydrolysis of 4-methoxyphenyl-2,2-dichloroethanoate in binary water–cosolvent mixtures; the role of solvent activity and solute–solute interactions†

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Rate constants are reported for the pH-independent hydrolysis of 4-methoxyphenyl-2,2-dichloroethanoate in aqueous solution as a function of the concentration of added cyanomethane (acetonitrile), polyethylene glycol (PEG 400) and tetrahydrofuran (THF). The concentration of water was varied between *ca.* 25 and 55.5 M. It was found that the variation in water activity yields only a minor contribution to the observed variation in rate constants. Interestingly, for both cyanomethane and PEG 400 $\log(k)$ varies approximately linearly with the molar concentration of water. Medium effects in highly aqueous solutions ($[\text{H}_2\text{O}] > 50 \text{ M}$) of ethanol, 1-propanol, 2-propanol, 1-butanol and 2-methyl-2-propanol have also been determined. Unexpectedly, in this concentration range the alcohols induce significantly smaller effects per unit volume than cyanomethane. The present results are discussed in terms of pairwise interaction parameters. Isobaric activation parameters have been determined and reveal remarkable differences in the nature of the induced medium effects.

Introduction

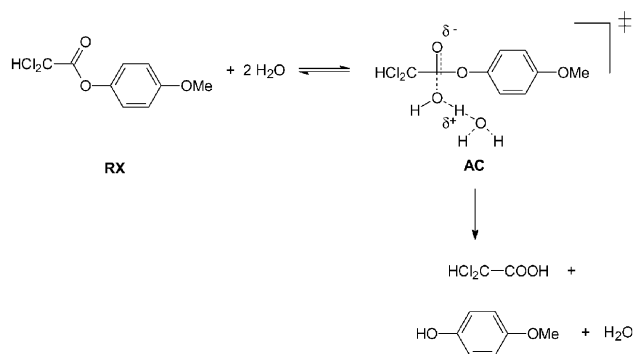
The neutral hydrolysis of 4-methoxyphenyl-2,2-dichloroethanoate (RX) in aqueous solution is second-order in water over an extensive pH range, *i.e.* pH 2–5 (Scheme 1). The reaction mechanism is characterised by a dipolar transition state involving two water molecules with three protons in-flight.^{1,2} The rate constant for ester hydrolysis is quite sensitive to added cosolutes and cosolvents (both will be denoted as cosolvent throughout this paper).^{3,4} Treatments of the kinetic data reported in references 3,4 and employed in many subsequent studies emphasise the effects of added cosolvent, in terms of pairwise interactions, on the reference chemical potentials of initial and transition states and, hence, of the Gibbs energy of activation.⁵ These studies focused on effects in highly aqueous media, *i.e.* at concentrations of cosolvents less than one to two mole percent. In order to obtain a better insight into the kinetics over a more extended range of concentrations of cosolvent, we investigated the rate constant for the pH-independent hydrolysis of RX in aqueous solution as a function of the mole fraction of added cyanomethane, polyethylene glycol (average molecular weight 400, PEG 400) and tetrahydrofuran (THF). None of these cosolvents are directly involved in the hydrolysis of RX and there is no evidence to suggest that either cyanomethane or PEG 400 significantly self-associate. Furthermore, the relationship between the thermodynamic water activity and the reactivity of water has been examined.

Results

Water activities

The chemical potential of water in a binary aqueous mixture (μ_1) is related to the activity a_1 using eqn. 1, where μ_1^* is the chemical potential of pure water (at constant temperature T and ambient pressure p);

$$\mu_1 = \mu_1^* + RT \ln a_1 \quad (1)$$



The activity is related to the activity coefficient ($a_1 = f_1 x_1$). By definition,⁶ $\lim_{x_1 \rightarrow 1} a_1 = 1$ and $\lim_{x_1 \rightarrow 1} f_1 = 1$. In Fig. 1 we compare and contrast the dependence of a_1 on mole fraction x_1 for cyanomethane + water,⁷ PEG 400 + water and THF + water.⁸ Added CH_3CN or THF raises the thermodynamic activity of water above that in the corresponding ideal binary liquid mixture. Similarly, PEG 400 decreases the activity of water more

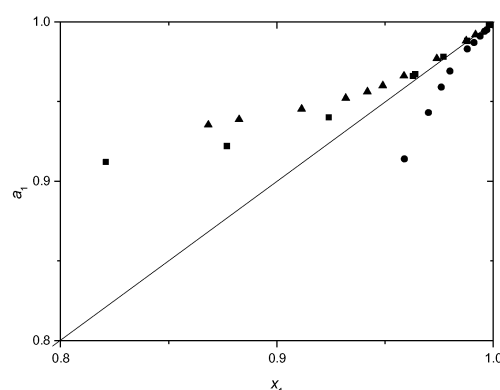


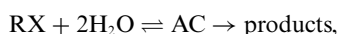
Fig. 1 Thermodynamic water activities in mixtures of water with cyanomethane (■), PEG 400 (●) and THF (▲).

† Electronic supplementary information (ESI) available: the kinetic data and activation parameters that appear in the figures in the paper in tabulated form. See <http://www.rsc.org/suppdata/ob/b4/b414593c/>.

than in the corresponding ideal binary liquid (note that this is largely due to the large molecular size of the oligomer). In dilute aqueous solution, x_1 is a reasonable approximation of a_1 .

Thermodynamic analysis of kinetic data

The chemical reaction under consideration,



involves reactant RX and activated complex AC. Furthermore, n moles of water are part of the activated complex. In this case, n equals two.⁹ The corresponding equilibrium relation in terms of chemical potentials is;

$$\mu_{\text{RX}} + n \cdot \mu_1 = \mu_{\text{AC}}. \quad (2)$$

We relate the three chemical potentials to the composition of the solution using reference concentration $c_r = 1 \text{ mol dm}^{-3}$ for both RX and AC and using the thermodynamic activity a_1 for water;

$$\begin{aligned} \mu_{\text{RX}}^\circ + RT \ln \left(\frac{c_{\text{RX}} \gamma_{\text{RX}}}{c_r} \right) + n \cdot [\mu_1^\circ + RT \ln a_1] \\ = \mu_{\text{AC}}^\circ + RT \ln \left(\frac{c_{\text{AC}} \gamma_{\text{AC}}}{c_r} \right). \end{aligned} \quad (3)$$

γ_{RX} , γ_{AC} and a_1 are all functions of the composition of the aqueous solvent mixture. Furthermore, γ_{RX} and γ_{AC} are defined such that $\gamma_{\text{RX}} \rightarrow 1$ and $\gamma_{\text{AC}} \rightarrow 1$ as $x_1 \rightarrow 1$. From eqn. 3, the standard Gibbs energy of activation is related *via* the equilibrium constant K^\ddagger to the composition of the system and activity of water a_1 using eqn. 4;

$$\Delta^\ddagger G^\circ = -RT \ln \left(\frac{c_{\text{AC}} \gamma_{\text{AC}}}{c_{\text{RX}} \gamma_{\text{RX}} a_1^n} \right) = -RT \ln K^\ddagger. \quad (4)$$

Therefore;

$$c_{\text{AC}} = c_{\text{RX}} \cdot K^\ddagger \frac{\gamma_{\text{RX}}}{\gamma_{\text{AC}}} a_1^n. \quad (5)$$

According to the experiment, the reaction is first-order in RX;

$$\text{Rate of reaction} = k \cdot c_{\text{RX}}. \quad (6)$$

Here k is a (pseudo) first-order rate constant for the given reaction recognising that k depends on the composition of the aqueous solution. Hence, using transition-state theory,¹⁰ rate constant k is given by eqn. 7;

$$k = \frac{k_B T}{h} K^\ddagger \frac{\gamma_{\text{RX}}}{\gamma_{\text{AC}}} a_1^n. \quad (7)$$

If we denote the rate constant in pure water by k_0 and assume that the concentrations of RX and AC are negligibly small, the difference in rate constants between any aqueous mixture and pure water (on a log-scale) is given⁵ by eqn. 8;

$$\ln \left(\frac{k}{k_0} \right) = \ln \left(\frac{\gamma_{\text{RX}}}{\gamma_{\text{AC}}} \right) + n \ln a_1. \quad (8)$$

Eqn. 8 is the key for reactions in aqueous solutions. Rate constant k depends on the composition of the solution because γ_{RX} , γ_{AC} and activity a_1 depend on the composition of the solution. As values for the water activity can be measured, and hence are known, the changes in reactivity of the water can be accounted for in an exact manner.

Note that water is treated in a somewhat unusual manner, *i.e.* for a reaction, second-order in water, we could have written;

$$\text{Rate of reaction} = k \cdot c_{\text{RX}} = k' \cdot c_{\text{RX}} c_1^2, \quad (9)$$

with k' a third-order rate constant and c_1 the molar concentration of water. Eqn. 8 would therefore have become;

$$\ln \left(\frac{k'}{k_0'} \right) = \ln \left(\frac{\gamma_{\text{RX}}^2 \gamma_{\text{AC}}}{\gamma_{\text{AC}}^2} \right) \quad (10)$$

and the standard state for water now also equals $c_r = 1 \text{ mol dm}^{-3}$. The molar activity coefficients for water (γ_1) can be derived from measured activities. However, it is much more convenient to directly use the thermodynamic activities *via* eqn. 8. In this context, we caution against calculating third-order rate constants according to eqn. 9 for mixed aqueous solvents without taking into account non-ideal behaviour, *i.e.* neglecting γ_1 (see ref 10 for examples).

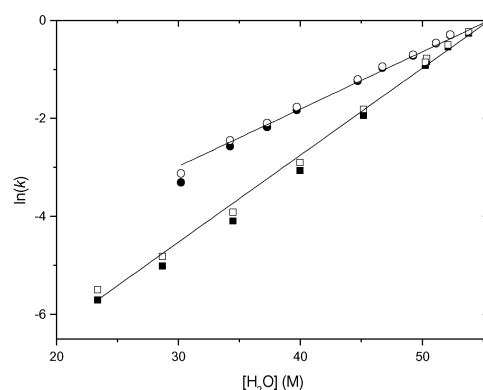
The dependencies of γ_{RX} and γ_{AC} in dilute aqueous media ($x_1 > 0.97$) have previously¹¹ been analysed in terms of (pairwise) interaction parameters. The derivation is based on a molality expansion of the total excess Gibbs energy,^{3,4} of which usually only the first term is considered, which leads to the following equation;

$$\ln \left(\frac{k}{k_0} \right) - 2 \ln a_1 = \frac{2}{m_r^2 \cdot RT} \cdot G(c) \cdot m_2 \quad (11)$$

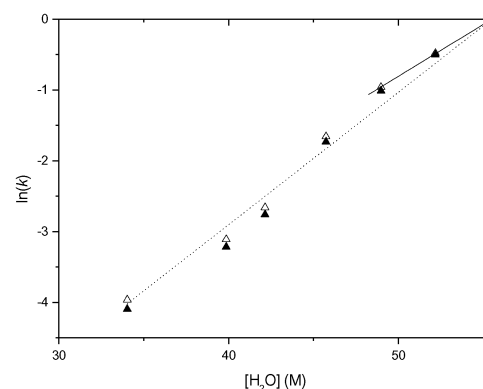
with m_2 the molality of cosolute and m_r the reference molality of 1 mol kg^{-1} . $G(c)$ is interpreted as the difference between the interaction Gibbs energies of the cosolvent [2] with AC and RX ($G(c) = g_{2 \leftrightarrow \text{RX}} - g_{2 \leftrightarrow \text{AC}}$). Eqn. 11 is linear in m_2 and deviations from this linearity can be captured by taking into account higher-order terms of the expansion.

Kinetic data

In Fig. 2, $\ln(k/k_0)$ is plotted *vs.* the concentration of water, as well as $\ln(k/k_0) - 2 \ln a_1$, using the experimentally determined values of a_1 . It is clear that the variation in the water activity hardly contributes to the observed decrease in rate constant. In other words, the main effect on the rate constant results



a)



b)

Fig. 2 Plots of $\ln(k/k_0)$ (black symbols) and $\ln(k/k_0) - 2 \ln a_1$ (open symbols) *vs.* $[\text{H}_2\text{O}]$ for the hydrolysis of RX at 25.0°C in mixtures of water with (a) cyanomethane (\blacksquare, \square) and PEG 400 (\bullet, \circ), and (b) THF ($\blacktriangle, \triangle$). The solid lines represent the fits using eqn. 12.

from changes in chemical potentials of ester (RX) and activated complex as described by $G(c)$.

$G(c)$ -values have been derived from the kinetic data for cyanomethane, PEG 400, and THF (Fig. 3) and are presented in Table 2. Furthermore, we have determined $G(c)$ -values for several monohydric alcohols (with $x_1 > 0.97$; the water activity was treated as ideal; Fig. 4); these values are also included in Table 2. The $G(c)$ -values reveal that one *molecule* of cyanomethane induces an effect of similar size as one *molecule* of 1-propanol. The large negative value for PEG 400 arises mainly from the relatively large size of the oligomer. Per ethylene oxide unit, the value is *ca.* $-250 \text{ J kg mol}^{-2}$.

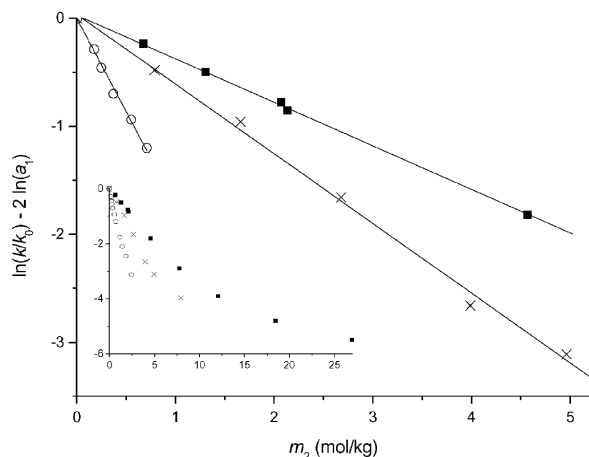


Fig. 3 A plot of $\ln(k/k_0) - 2 \ln a_1$ vs the molality of cosolvent for the hydrolysis of RX at 25.0 °C for cyanomethane (■), PEG 400 (○) and THF (×). Solid lines represent fits using eqn. 11.

Curiously, for cyanomethane and PEG 400 $\ln(k/k_0) - 2 \ln a_1$ is an almost linear function of the molar concentration of water, denoted by $[\text{H}_2\text{O}]$ (Fig. 2). We have fitted the following (linear) equation to the experimental data;

$$\ln\left(\frac{k}{k_0}\right) - 2 \ln a_1 = \frac{1000}{55.5 \times RT} \cdot B \cdot (55.5 - [\text{H}_2\text{O}]) \quad (12)$$

with B in kJ mol^{-1} . The results are summarised in Table 1 and Fig. 2. The parameter B quantifies the difference in activation Gibbs energy, excluding the contribution of the water activity ($\ln \gamma_{\text{RX}} - \ln \gamma_{\text{AC}}$; eqn. 8), in pure water and pure cosolvent,

Table 1 Results from fits using eqn. 12

Cosolvent	$B/\text{kJ mol}^{-1a}$	r^2
CH_3CN	-24.4 (0.3)	0.996
PEG 400	-16.1 (0.2)	0.995
THF	-25.7 (0.7)	0.985

^a Fits including all data points.

Table 2 $G(c)$ -values (obtained with eqn. 11) and initial slopes B^{init} of plots of $\ln(k/k_0) - 2 \ln a_1$ vs $[\text{H}_2\text{O}]$

Cosolvent	$G(c)/\text{J kg mol}^{-2}$	$B^{\text{init}}/\text{kJ mol}^{-1a}$
CH_3CN	-498 (6)	-21.3 (0.4)
PEG 400	-2137 (90)	-16.1 (0.2)
THF	-799 (24)	-20.1 (0.2)
Ethanol	-304 (5)	-11.9 (0.2)
1-Propanol	-474 (8)	-14.0 (0.2)
2-Propanol	-489 (7)	-13.5 (0.3)
1-Butanol	-709 (10)	-16.1 (0.3)
2-Methyl-2-propanol	-596 (10)	-13.0 (0.3)

^a Initial slopes, including only data points at low amounts of cosolvent. Fitted using eqn. 12.

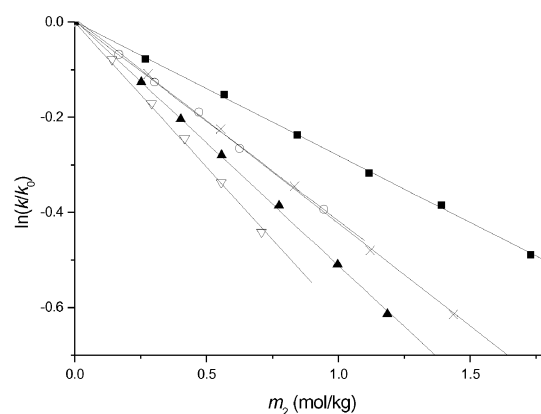


Fig. 4 A plot of $\ln(k/k_0)$ vs the molality of cosolvent for the hydrolysis of RX at 25.0 °C for ethanol (■), 1-propanol (○), 2-propanol (×), 1-butanol (▽) and 2-methyl-2-propanol (▲). Solid lines represent fits using eqn. 11.

under the assumption that the linear dependence extends to pure cosolvent (this may well not be true). In other words, B multiplied by the volume fraction¹² of cosolvent gives the change in activation Gibbs energy in the mixture. For both cyanomethane and PEG 400 a fairly linear correlation is found, which is indicative of the absence of extensive clustering or preferential solvation (the concentration scale is of importance for this conclusion, see below). For THF, the correlation is less good, and some clustering takes place in these mixtures. In this respect, it is worthwhile to compare the present results with previously determined rate constants in water–2-methyl-2-propanol mixtures (Fig. 5).¹³ For this cosolvent a plot of $\log(k)$ vs $[\text{H}_2\text{O}]$ significantly deviates from a linear trend, as one would expect.

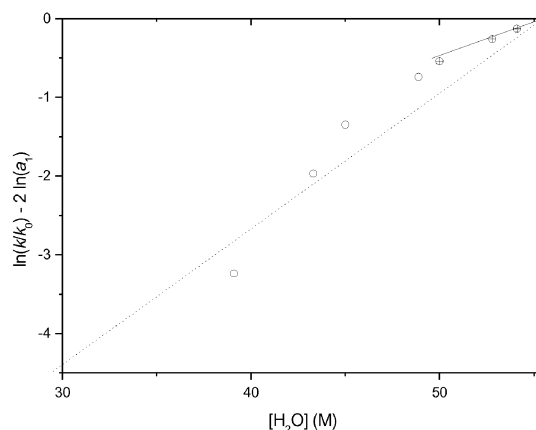


Fig. 5 A plot of $\ln(k/k_0) - 2 \ln a_1$ vs $[\text{H}_2\text{O}]$ for the hydrolysis of RX at 25.0 °C in water–2-methyl-2-propanol mixtures. Data taken from ref. 12 (open circles) and present results (crossed circles). The dotted line indicates the corresponding values for water–cyanomethane mixtures.

The parameter B has been calculated from the data for only dilute aqueous mixtures in order to obtain the *initial slopes* (B^{init} , Table 2). Alcoholysis will be a significant side reaction only at concentrations larger than those used in the present study.¹⁴ As can be seen, in dilute aqueous mixtures ($[\text{H}_2\text{O}] > 50 \text{ M}$) the alcohols induce a significantly smaller effect per unit volume than cyanomethane. This is a surprising result, especially considering the fact that B^{init} varies little among the alcohols (with the exception of 1-butanol, which is however only partially miscible with water). The relatively small variation in the slopes draws attention to the concentration of water as an important factor that governs the solvation properties of aqueous mixtures. The initial slope of cyanomethane is about 13% smaller than the corresponding value of B including all data points (Table 1),

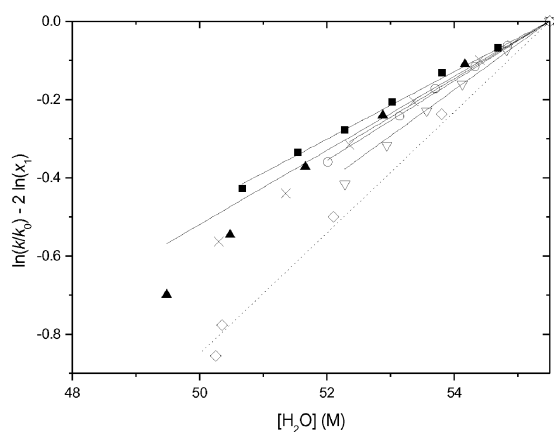
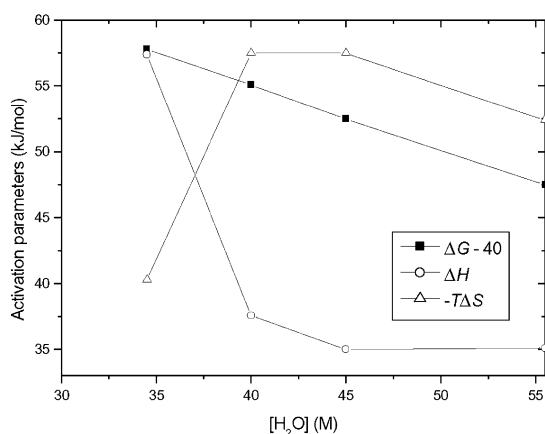


Fig. 6 A plot of $\ln(k/k_0) - 2 \ln a_1$ vs $[\text{H}_2\text{O}]$ for the hydrolysis of RX at 25.0 °C in water-alcohol mixtures. Symbols as in Fig. 4, except for cyanomethane (\diamond).

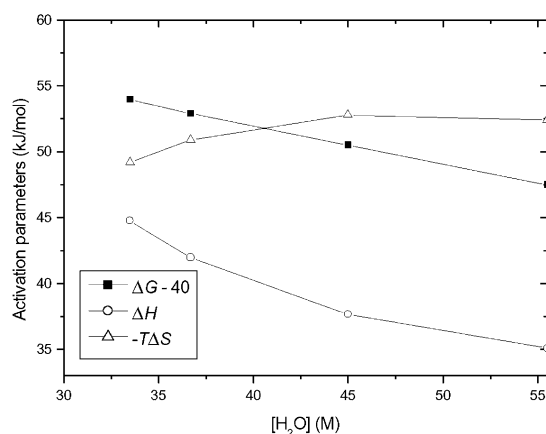
despite the near linear appearance of the plot of $\ln(k/k_0) - 2 \ln a_1$ vs $[\text{H}_2\text{O}]$. In fact, except for PEG 400, the initial slope is invariably smaller than the slope at intermediate concentrations. A comparison of Fig. 4 and Fig. 6 shows that the linear dependencies of $\ln(k/k_0) - 2 \ln a_1$ on the molal scale turn into downward concave dependencies on a molar scale for most of the alcohols. Over a wider concentration range, the nearly linear dependencies of $\ln(k/k_0) - 2 \ln a_1$ on the molar concentration

of water for cyanomethane and PEG 400 (Fig. 2) contrast with the upward concave plots of the same data on a molal scale (inset Fig. 3) or a mole fraction scale (not shown). In any case, linearity depends on the concentration scale, and interpretations should consider what exactly is varied on a particular concentration scale. In particular, these results should be taken as a warning to be cautious of interpreting a linear dependence as evidence for the absence of higher-order interactions.

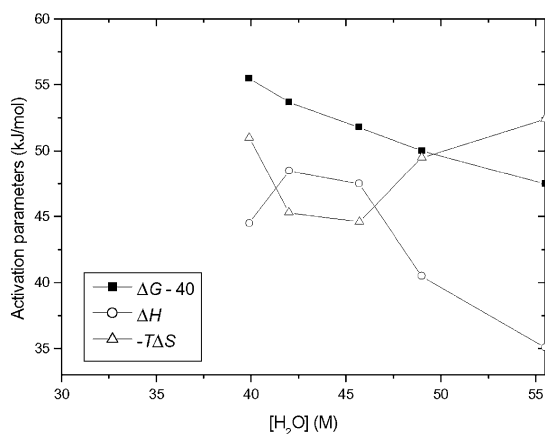
Isobaric activation parameters ($\Delta^\ddagger G$, $\Delta^\ddagger H$ and $\Delta^\ddagger S$) have been determined and are shown in Fig. 7. The activation enthalpies and entropies reveal remarkable differences between the different water-cosolvent mixtures. In particular, whereas for THF the activation enthalpy initially increases and is responsible for the decrease in rate constant, in the case of 2-methyl-2-propanol the activation enthalpy decreases and the decrease in rate constant is caused by a more strongly negative activation entropy. For PEG 400, the decrease in rate constant is also an enthalpy-driven process but the activation parameters vary much more gradually in this case. A similarly small variation in activation parameters is observed for cyanomethane down to *ca.* 40 M of water but the decrease in rate constant is entropy-driven. Below 40 M of water, the solvation properties of the mixtures most likely change dramatically. The initial increase in $-T\Delta^\ddagger S$ for 2-methyl-2-propanol may be attributed to a stabilisation of RX by hydrophobic interactions. It is surprising that for THF rather the opposite is found (*i.e.* $\Delta^\ddagger H$ increases). It is possible that the activated complex is only affected slightly by the alcohols but much more severely by *e.g.* cyanomethane or THF.



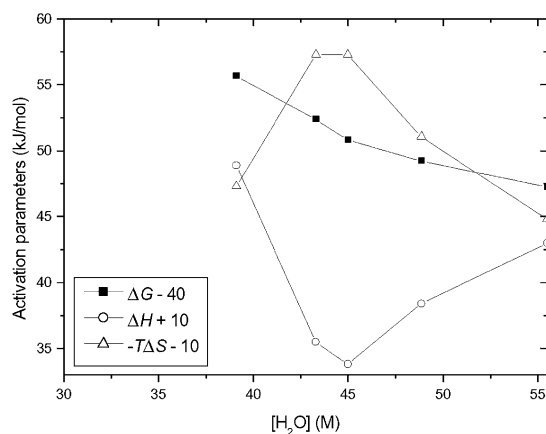
a)



b)



c)



d)

Fig. 7 Isobaric activation parameters ($\Delta^\ddagger G$, $\Delta^\ddagger H$, and $\Delta^\ddagger S$) at 25.0 °C for the hydrolysis of RX in mixtures of water with (a) cyanomethane, (b) PEG 400, (c) THF and (d) 2-methyl-2-propanol.

Discussion

In the present study, rate constants have been obtained for a fairly wide range of cosolvent concentrations and interesting patterns in the dependence of the kinetic medium effects on the composition of the medium have been found. The linearity of plots of $\ln(k/k_0) - 2 \ln a_1$ vs $[\text{H}_2\text{O}]$ for cyanomethane and PEG 400 extends to high concentrations of cosolvent, *i.e.* to a regime where 'pairwise interactions' between ester and cosolvent is a rather inappropriate term. Nevertheless, the effects in this regime appear to be similar, if not the same, as in the dilute regime. Here, we will more closely examine 'pairwise interactions'.

The data show that cyanomethane induces effects that are significantly larger than those induced by the alcohols. Does this difference only result from differences in pairwise interactions? Alternatively, not only pairwise (1 : 1) interactions affect the rate, but also changes in the properties of the solvent mixture as a whole. The approximate linearity with volume fraction suggests that the solvation shells have a statistical composition (*i.e.* corresponding to the macroscopic composition) and that the probe-solvent and probe-cosolvent interactions are relatively weak. Deviations from this 'ideal' case may result from *e.g.* clustering of probe and cosolvent molecules or from 'bulk' changes, such as modified hydrogen-bond donor capacity, because of solvent-cosolvent interactions. In the analysis using pairwise and higher-order interaction parameters, solvent-cosolvent interactions do not directly play a role but this approximation is most likely too severe. Although higher-order terms can be included to account for deviations from linearity, this ignores the fact that we are not dealing with dilute aqueous solutions. An underlying theme of the interaction parameter approach is that if a solution is sufficiently dilute, cosolvent molecules move individually in solution together with a hydration shell (cosphere). Occasionally, a solute and cosolute molecule meet and interact (mainly *via* the cospheres). In this scheme, a triplet interaction term is a logical extension to account for non-ideal behaviour. However, at intermediate concentrations the number of water molecules available for these cospheres is limited and cospheres are by no means independent. Therefore, it is possible that cosolvent-water interactions 'directly' affect the immediate surroundings of solute molecules (*i.e.* cospheres merge into a continuous phase).

Deviations from the 'overall' trend (on a molar scale) occur in highly aqueous media (*i.e.* $|B^{\text{min}}| < |B|$). It is cyanomethane that acts largely 'ideally' in dilute aqueous mixtures. This may be the result of cyanomethane disrupting the hydrogen-bond network already at low concentrations (reflecting the effects in mixtures with a high cyanomethane content). For the alcohols, the hydrogen-bond network, although affected, may remain initially intact which accounts for the relatively small effects in dilute aqueous media (note that cyanomethane is usually referred to as structure-breaking and alcohols as structure-making). These results support the view that in dilute solutions apolar groups affect the rate mainly *via* cosolute-water interactions, either *via* cosphere-cosphere interactions or *via* 'bulk' alterations of the properties of water.

The activation parameters reveal that the nature of the kinetic medium effects depend strongly on a particular cosolvent. Furthermore, the activation parameters indicate that group additivity in terms of enthalpy and entropy is at best limited to structurally closely related compounds. Changes in the 'bulk' solvation properties play an important role and are responsible for the widely varying values of $\Delta^\ddagger H$ and $\Delta^\ddagger S$. We conclude that thinking about medium effects in terms of 'solvation' is useful or perhaps even necessary for dilute aqueous mixtures. Interaction parameters may provide detailed information about solute-solute interactions but comparison is best limited to structurally closely related compounds.

Conclusions

The rate constant of the pH-independent hydrolysis of esters RX in mixed aqueous solvents is determined mainly by changes in the Gibbs energies of RX and AC. The (small) variations in the water reactivity (water activity) hardly play a role in the observed medium effects. Interestingly, nearly linear dependencies of $\log(k)$ on the molar concentration of water are found for cyanomethane and PEG 400 as cosolvents. In contrast, 2-methyl-2-propanol significantly deviates from this trend. Isobaric activation parameters reveal remarkable differences in the induced medium effects by the different cosolvents. Whereas for 2-methyl-2-propanol and cyanomethane the decrease in rate constant initially is entropy-driven, it is enthalpy-driven for PEG 400 and THF. Truly pairwise interactions between molecules in aqueous solution most likely only occur in rather dilute mixtures, *i.e.* with $[\text{H}_2\text{O}]$ at least 54 M. At lower concentrations of water, the hydrogen-bond network of water may already become affected by the presence of (co)solutes and not necessarily to equal extents.

Experimental

4-Methoxyphenyl-2,2-dichloroethanoate (RX) was prepared using a standard procedure.¹⁵ PEG 400 was used as supplied (Aldrich). Cyanomethane was purified by passing the liquid through an Al_2O_3 column and THF was distilled. All alcohols were analytical grade. The water used in all experiments was demineralised and distilled twice in an all-quartz distillation unit. Aqueous solutions were prepared by weight. Density data were taken from ref. 16. The pH of the solutions was adjusted to 3.4 using $\text{HCl}(\text{aq.})$. The progress of reaction was monitored at 288 nm for between five and six half-lives using a Perkin-Elmer spectrophotometer. Approximately 5 μl of a stock solution of the ester in cyanomethane ($0.0143 \text{ mol dm}^{-3}$) was added to a prethermostatted reaction medium solution placed in a quartz cell. Good pseudo-first-order kinetics were observed. Standard errors in the rate constants were 2–3% (1–2% for mixtures containing alcohols). Isobaric activation parameters have been calculated from rate constants in the temperature range of 20–40 °C.

Activities of aqueous solution containing PEG 400 were measured using a water activity meter (Decagon Devices INC., WA 99163, USA). An aqueous solution is held in a closed thermostatted vessel. The wall of the latter includes a small temperature-controlled mirror which is illuminated. The reflected beam is monitored. The temperature of the mirror is lowered such that at a recorded mirror temperature the mirror clouds by condensation of water in the vapour phase. The detector of the reflected beam records this temperature. The system is calibrated using $\text{NaNO}_3(\text{aq.})$ in the thermostatted vessel such that a direct link is established between the temperature at which the mirror fogs and the activity of water in the solution.

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