Kinetic evidence for hydrophobically-stabilised encounter complexes formed by hydrophobic esters and amides in aqueous solutions containing monohydric alcohols

The pH-independent hydrolyses of four activated esters, p-methoxyphenyl 2,2-dichloroethanoate (2.1a), p-methoxyphenyl 2,2-dichloropropanoate (2.1b), p-methoxyphenyl 2,2-dichlorobutanoate (2.1c) and p-methoxyphenyl 2,2-dichloropentanoate (2.1d), and two activated amides, 1-(4-methylbenzoyl)-1,2,4-triazole (2.2a) and 1-(4-n-butylbenzoyl)-1,2,4-triazole (2.2b), in dilute aqueous solution have been studied as a function of the molality of added cosolutes ethanol, 1-propanol and 1-butanol. Rate constants for the neutral hydrolysis decrease with increasing cosolute molality. These kinetic medium effects respond to both the hydrophobicity of the ester and of the monohydric alcohol. The observed rate effects are analysed using both a thermodynamic and a kinetic model. According to the kinetic model a hydrophobically-stabilised encounter complex is formed with equilibrium constants $K_{ec}$ often smaller than unity, in which the cosolute blocks the reaction center of the hydrolytic ester or amide from attack by water. Formation of these encounter complexes leads to a dominant initial-state stabilisation as described by the thermodynamic model set out in Chapter 1. Decreases in both apparent enthalpies and entropies of activation for these hydrolysis reactions correspond to unfavourable enthalpies and favourable entropies of complexation, which confirms that the encounter complexes are stabilised by hydrophobic interactions.

2.1 Introduction

2.1.1 Thermodynamic analysis of 1:1 hydrophobic interactions

Weak hydrophobic interactions between reacting molecules and inert added cosolutes in aqueous solutions have been investigated for over a decade using the thermodynamic analysis presented in Chapter 1.
As mentioned in Chapter 1, previous studies\textsuperscript{2} showed that hydrolysis of activated esters structurally similar to \textit{2.1a-d}, but also of similar activated amides structurally similar to \textit{2.2a,b}\textsuperscript{3} is retarded by many hydrophobic cosolutes, except \(\alpha\)-amino acids. In the past, a variety of cosolutes has been examined in combination with several hydrolytic probes. An overview of previous studies is given in Table 2.1.

\textbf{Table 2.1:} Kinetic solvent effect studies on the hydrolysis of activated amides and activated esters in dilute aqueous media, which have been analysed using Equation 1.9, excluding studies in this thesis.

<table>
<thead>
<tr>
<th>Cosolute</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>mono-, di- and polyhydric alcohols</td>
<td>4,5</td>
</tr>
<tr>
<td>(alkyl substituted) urea(s)</td>
<td>6</td>
</tr>
<tr>
<td>carboxamides</td>
<td>8, 8, 9</td>
</tr>
<tr>
<td>sulfonamides/sulfonyl/sulfoxides</td>
<td>6, 6, 10</td>
</tr>
<tr>
<td>carbohydrates</td>
<td>8, 9</td>
</tr>
<tr>
<td>(N)-alkyl-2-pyrrolidinones</td>
<td>11</td>
</tr>
<tr>
<td>sodium alkylsulfates</td>
<td>12</td>
</tr>
<tr>
<td>(N)-alkylated ammonium bromides</td>
<td>13</td>
</tr>
<tr>
<td>(\alpha)-amino acids</td>
<td>14, 15</td>
</tr>
</tbody>
</table>

Rate retardations caused by added cosolutes often follow an additivity scheme\textsuperscript{16} in which each methylene unit or functional group makes a common contribution to \(G(c)\), the SWAG-approach (Savage-Wood additivity of group interactions).\textsuperscript{17} The observed changes in standard Gibbs energy of activation were found to be mainly caused by a stabilisation of the initial state by hydrophobic interactions.\textsuperscript{18} Hence, \(G(c)\) has been interpreted in terms of stabilisation of the initial state by (hydrophobic) interactions with added cosolutes.

In the analysis of previously reported kinetic data for this class of system, emphasis was placed mainly on varying the structure of the cosolute (see Table 2.1) and in particular on varying the hydrophobicity of the cosolutes.\textsuperscript{2}
2.1.2 TOWARDS A COMBINED THERMODYNAMIC AND MOLECULAR MODEL

In the present study, both the hydrophobicity of cosolute molecules and of reacting esters or amides were varied (Scheme 2.1).

![Scheme 2.1](image)

The activated esters and amides hydrolyse according to the mechanism described in Chapter 1. Results of the analysis based on both a thermodynamic analysis and a molecular model using Equations 1.9 and 2.1, respectively, are reported. Furthermore, isobaric activation enthalpies and entropies for hydrolysis of 2.1c in the presence of hydrophobic cosolutes were determined in order to obtain more information on the thermodynamics of encounter complex formation (vide infra) and to understand the relationship between the thermodynamic description and the molecular picture of rate inhibition. We show that both approaches account for the kinetic data.

2.1.3 ANALYSIS OF KINETIC SOLVENT EFFECTS IN TERMS OF ENCOUNTER COMPLEX FORMATION

The severe orientational requirements on water molecules in the activated complex as described in Chapter 1 prompt the idea of formation of an encounter complex between ester or amide and added solute, in which the cosolute blocks the reaction center from attack by water. Such a model, assuming that the encounter complex is inert, is strongly supported by computer simulations of the hydrolysis reaction described in Chapter 1.

![Scheme 2.2](image)
A kinetic scheme based on this molecular picture (Scheme 2.2) emerges in which ester molecules that are not solvated by cosolute molecules react with a rate constant \( k(m_c=0) \). Since a kinetically observable hydrophobic interaction with cosolute occurs close to the reaction center, the critical orientation of the water molecules for attack at the ester carbonyl group is disturbed and hydrolysis is (largely) inhibited. The hydrolysis rate constant for ester in an encounter complex is therefore assumed to be zero, leading to the following expression for the observed rate constant (Equation 2.1)

\[
k(m_c) = \frac{k(m_c = 0)}{1 + K_{ec} \cdot m_c}
\]

Here \( K_{ec} \) is the equilibrium constant for encounter complex formation in kg mole\(^{-1}\), \( m_c \) the molality of added cosolute, \( k(m_c) \) the observed (pseudo-) first-order rate constant in an \( m_c \) molal solution.

The rate constant of hydrolysis in the encounter complex is assumed to be zero, as the largest rate effect will be caused by the direct blocking of the reaction center from attack by water. The influence of encounter complexes in which the cosolute molecule does not directly block attack by water will be more complex, possibly only partially inhibiting reaction. However, incorporating this further complexity in Equation 2.1 is not warranted, as the number of data points does not permit the introduction of more variables (\textit{vide infra}).

Two examples of encounter complexes expected to show more complex behaviour deserve discussion. If the cosolute molecule binds to the hydrolytic probe far (relative to the size of the cosolute molecule) from the reaction centre, it will not block attack by water. Obviously, the rate of hydrolysis in these encounter complexes cannot be assumed to be zero and these encounter complexes will not be observed as a consequence of the absence of a rate effect (\textit{vide infra}). In addition, the effect of cosolutes binding on the side of the carbonyl opposite that on which a water molecule is attacking, is unclear from this molecular picture. Because of the induced change in solvation shell around the amide group, it may have a rate effect. Consequently, the equilibrium constant for encounter complex formation is a minimum value. In the case of a small hydrolytic probe, however, it is expected that essentially all encounter complexes will inhibit reaction as binding can only take place close to the reaction center.

The assumptions described above are summarised in Figure 2.1.
In Figure 2.1, the chemical potential of the hydrolytic probe in “different solutions” is sketched. On the left hand side of the figure (A), the Gibbs energy of activation of the hydrolysis reaction in water without added cosolute is depicted. The Gibbs energy of activation of the hydrolysis reaction in the presence of 1 mol kg\(^{-1}\) of a cosolute binding close to the reactive centre is shown (B). The weak interaction between hydrolytic probe and cosolute (equilibrium constants up to 1.21 kg mol\(^{-1}\), *vide infra*) leads to a lowering of the chemical potential of the hydrolytic probe. The activated complex cannot form an encounter complex as the water molecules involved in the activated complex cannot be removed without destroying the activated complex. In other words, the activated complex has lost its hydrophobicity.

The third, hypothetical, case would occur if a cosolute molecule interacts only far away from the reactive centre. In this case, both reactant state and transition state are lowered, both to exactly the same extent (C). The right hand side of Figure 2.1 (D) depicts the situation in which binding to the hydrolytic probe is possible both close to and remote from the reaction centre. In this case, both the initial and the transition state will be stabilised, but the effect is larger for the initial state, leading to a decrease in the rate of reaction.

It will be clear from the above that there exists a strong link between the molecular picture and the thermodynamic model. This includes the “kinetic invisibility” of encounter complexes involving cosolutes complexing far from the reaction center as, typically, the chemical potential of the transition state is...
assumed to remain unchanged (vide supra). This assumption results in encounters occurring remote from the reaction centre to go unnoticed in the thermodynamical description as well.

2.2. RESULTS AND DISCUSSION

2.2.1 HYDROLYSIS OF HYDROPHOBICALLY MODIFIED ACTIVATED ESTERS AND ACTIVATED AMIDES IN THE ABSENCE OF COSOLUTES

(Pseudo-)first-order rate constants at 298.2K for the hydrolysis of 2.1a-d and 2.2a,b in water are summarised in Table 2.2.

Table 2.2: (Pseudo-)first-order rate constants for the water-catalysed hydrolysis of 2.1a-d and 2.2a,b in water at 298.2K.

<table>
<thead>
<tr>
<th>Compound</th>
<th>10^4k(m_c=0)/s^-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1a</td>
<td>30.9</td>
</tr>
<tr>
<td>2.1b</td>
<td>11.7</td>
</tr>
<tr>
<td>2.1c</td>
<td>3.06</td>
</tr>
<tr>
<td>2.1d</td>
<td>2.73</td>
</tr>
<tr>
<td>2.2a</td>
<td>9.44</td>
</tr>
<tr>
<td>2.2b</td>
<td>8.99</td>
</tr>
</tbody>
</table>

Increasing hydrophobicity of the alkyl chain in the alkanoate moiety of the ester retards the rate of hydrolysis. Previously, the influence of alkyl groups on the water-catalysed hydrolysis of activated amides was studied using Charton’s expanded branching equation.23,24 The size of the data set in Table 2.2 does not allow a similar analysis. Unfortunately, the data set cannot be expanded due to the severe solubility problems encountered with more hydrophobic esters.

Electronic effects are expected to play only a minor role in the observed rate retardation. Substitution of H by Me in going from 2.1a to 2.1b could cause a small rate inhibition resulting from electronic effects on the basis of the Taft substituent parameters σ_i being 0.00 and –0.06, respectively (σ_i for Et equals -0.07).25

Apart from the electronic effect, a decrease in reaction rate will also be caused by the increased intramolecular steric hindrance by the alkyl tail. Upon elongation of the alkyl chain, it is increasingly able to fold back towards the reaction centre. This effect is levelling off between 2.1c and 2.1d, attributed to the fact that there is
MONOMERIC COSOLUTES

hardly any difference in the ability of the alkyl chain to fold back in the direction of the reaction center. A similar effect was found for 1-acyl-(3-substituted)-1,2,4-triazoles when the alkyl chain of the acyl moiety was elongated or branched at the β-position.26

Rates of hydrolysis of the two activated amides 2.2a,b are almost identical (i.e. within 5%). For these probes the alkyl tail was introduced further away from the reaction center. As a result, there is no additional interaction between the alkyl chain and the reaction center introduced upon increasing hydrophobicity. Interpretation of the results of the experiments with added cosolutes is therefore not complicated by this additional interaction.

2.2.2 THE THERMODYNAMIC MODEL

Rate constants for the hydrolysis of the esters 2.1a-d and amides 2.2a-b decrease upon increasing cosolute molality (e.g. Figure 2.2). The decrease in rate constant is more pronounced for the more hydrophobic cosolutes, in accord with previous observations.2

![Figure 2.2: Left: Hydrolysis of 2.1b (o), 2.1c (•) and 2.1d (Δ) as a function of molality of 1-butanol. Right: Hydrolysis of 2.2a (o) and 2.2b (•) as a function of molality of 1-butanol. The lines are the best fits using Equation 1.9. In the fit for 2.2b, only data for molalities up to 0.57 mol kg\(^{-1}\) have been used.](image-url)
Analysis of the kinetic data using Equation 1.9, as described in Chapter 1, yields the \( G(c) \)-values summarised in Table 2.3.

**Table 2.3**: \( G(c) \)-values for the hydrolysis of esters **2.1a-d** and amides **2.2a,b** in aqueous solution at 298.2 K in the presence of short-chain alcohols.\(^a\)

<table>
<thead>
<tr>
<th>Ester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Cosolute</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>EtOH</td>
</tr>
<tr>
<td>n-PrOH</td>
</tr>
<tr>
<td>n-BuOH</td>
</tr>
<tr>
<td>2.1a</td>
</tr>
<tr>
<td>2.1b</td>
</tr>
<tr>
<td>2.1c</td>
</tr>
<tr>
<td>2.1d</td>
</tr>
</tbody>
</table>

\(^a\) Numbers in brackets are standard errors based on a least-squares fit of the kinetic data using Equation 1.9. \(^b\) Data fitted up to 0.57 mol kg\(^{-1}\).

Assuming the (standard) chemical potential of the transition state to be largely unaffected by the cosolute as mentioned before, a negative \( G(c) \) signifies a lowering of the standard chemical potential of the initial state. \( G(c) \) decreases upon increasing the hydrophobicity of both added cosolute and ester, indicating increasing stabilisation of the initial state ester.

The results are summarised in Figure 2.3 (Please note that minus \( G(c) \) is plotted in Figure 2.3).

**Figure 2.3**: Absolute values of \( G(c) \) in J kg mol\(^{-2}\) for different probe-cosolute combinations.
In Figure 2.3, the $x$- and $y$-axes show scales having constant increments for one methylene unit. The $z$-axis records $G(c)$-values which follow an approximate additivity scheme in accord with the SWAG theory, leading to nearly constant decreases in $G(c)$ upon lengthening the alkyl moiety in the ester with one methylene unit (i.e. stepping either down in Table 2.3, or sideways in Figure 2.3).

For the small range of cosolutes studied, definite conclusions about additivity cannot be drawn. The effects of longer-chain alcohols were not examined because their solubility ranges are small. As was observed for similar hydrolytic probe and cosolute systems, the methylene units closest to the hydrophilic group are partially shielded by the hydrophilic hydration shell of the polar moiety, reducing their hydrophobic effect. Similar shielding effects by nonionic hydrophilic groups have been found by other authors.27

The more hydrophobic the ester the more slowly it hydrolyses. It might therefore seem as if the rate retarding effect of the alkyl chain is amplified by the added cosolute. However, from Table 2.3 and Figure 2.3, it is clear that for all three cosolutes, the increments in $G(c)$ per methylene unit are constant. This pattern indicates that even when the rate of hydrolysis in the absence of cosolute levels off from decreases by 70% to decreases of only 11%, the effect of the cosolute remains the same. In addition, it is very likely that the origin of the rate retardation changes from an electronic effect (going from **2.1a** to **2.1b**) to a steric effect (upon further elongation of the alkyl chain). It is unlikely that both types of effect will be amplified to the same extent, yet the observed increments remain the same.

In order to verify the conclusion that the rate retardations are solely caused by hydrophobic interactions, the cosolute effects on the hydrolysis reactions of **2.2a** and **2.2b** were studied. Apart from an increased hydrophobicity of **2.2b** compared to **2.2a**, both probes have identical reactivity, rate constants of hydrolysis being equal within 5% (*vide supra*). For these activated amides, there are no differences in intramolecular steric interactions or electronic effects that can be amplified by the cosolute. From Table 2.3, it can be seen that also for these probes the rate retarding effect is dependent on hydrophobicity of both the alcohol and the amide. This pattern clearly shows that hydrophobicity of the hydrolytic probe governs the observed rate retardation. A similar correlation between hydrophobicity of the substrate and the observed rate decrease was found previously for the hydrolysis of 1-acyl-(3-substituted)-1,2,4-triazoles,26 while a correlation between cosolute-induced rate decrease and reactivity in pure water was not observed.
2.2.3 A MULTIPLICATIVE SCHEME

In order to further investigate the conclusion that hydrophobically-enhanced 1:1 interactions are the origin of the observed rate decreases, the observed $G(c)$-values (Table 2.2) were written as a matrix that can be written as a matrix product (Equation 2.2 is a least squares analysis).

\[
\begin{pmatrix}
-304 & -474 & -709 \\
-338 & -555 & -833 \\
-400 & -592 & -1044 \\
-466 & -634 & -1213
\end{pmatrix}
= -301.1 \cdot
\begin{pmatrix}
1 \\
1.15 \\
1.34 \\
1.51
\end{pmatrix}
\begin{pmatrix}
1 & 1.50 & 2.49
\end{pmatrix}
\]

(2.2)

Or, in matrix notation:

\[
G(c) = a \cdot ec
\]

(2.3)

Here $a$ is a constant denoting the interaction between $p$-methoxyphenyl 2,2-dichloroethanoate and ethanol. The vectors $e$ and $c$ identify the increment in interaction upon increasing the hydrophobicity of ester and cosolute, respectively, as a multiplication factor. In this matrix notation, the SWAG theory should lead to constant increments in both $e$ and $c$. Indeed, this pattern is effectively followed in $e$, the differences being 0.15, 0.19 and 0.17 (0.17±0.02) indicating that the interactions between probe and cosolute are additive with respect to the probe. However, interactions between probe and cosolute do not seem to be additive with respect to the cosolutes. In this case, additivity is most probably not observed as a result of the small range of cosolutes used.

2.2.4 MOLECULAR DESCRIPTION

In the molecular description leading to Equation 2.1, the observed decrease in rate constant upon increasing the molality of cosolute is accounted for in terms of the formation of an encounter complex by hydrophobic probe and cosolute. Encounter complexes are formed in solution as a result of random movements of molecules and (de)solvation processes. The chances of encounter complex formation increase with increasing size and molality of the solutes. In fact, the formation of encounter complexes is necessary for any bimolecular reaction to occur and the concept of encounter complexes is commonly used in bimolecular photochemical reactions.

Based on typical sizes of solvents and solutes, equilibrium constants for formation of these randomly formed complexes are commonly estimated to range from
0.2 dm$^3$ mol$^{-1}$ to values slightly larger than unity. In aqueous solution, encounter complexes formed from apolar components will be stabilised by hydrophobic interactions and the stabilisation will increase with an increased hydrophobicity of the encounter complexes constituents.

![Figure 2.4](image)

**Figure 2.4**: Hydrolysis of $2.1b$, $2.1c$, $2.1d$, $2.2a$ (o) and $2.2b$ (*) as a function of molality of 1-butanol. The lines are the best fits using Equation (2.1).

Non-linear least-squares fitting of the observed rate data to Equation 2.1 results in the equilibrium constants and standard Gibbs energies of encounter complex formation, $\Delta_{ec}G^0$, given in Table 2.4. Typical examples of the fits are shown in Figure 2.4.
Table 2.4: Thermodynamic parameters for encounter complex formation of 2.1b-d and 2.2a,b in the presence of short-chain alcohols.

<table>
<thead>
<tr>
<th>Ester</th>
<th>Cosolute</th>
<th>Kₑₑ / kg mol⁻¹</th>
<th>ΔₑₑGₒ / kJ mol⁻¹</th>
<th>Kₑₑ / kg mol⁻¹</th>
<th>ΔₑₑGₒ / kJ mol⁻¹</th>
<th>Kₑₑ / kg mol⁻¹</th>
<th>ΔₑₑGₒ / kJ mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EtOH</td>
<td>0.34±0.02</td>
<td>2.67±0.15</td>
<td>0.56±0.05</td>
<td>1.44±0.22</td>
<td>0.86±0.07</td>
<td>0.37±0.20</td>
</tr>
<tr>
<td>2.1b</td>
<td>n-PrOH</td>
<td>0.45±0.02</td>
<td>1.98±0.11</td>
<td>0.64±0.01</td>
<td>1.11±0.08</td>
<td>1.09±0.10</td>
<td>-0.21±0.23</td>
</tr>
<tr>
<td>2.1c</td>
<td>n-BuOH</td>
<td>0.51±0.03</td>
<td>1.67±0.15</td>
<td>0.71±0.04</td>
<td>0.85±0.14</td>
<td>1.21±0.12</td>
<td>-0.47±0.25</td>
</tr>
<tr>
<td>2.1d</td>
<td>n.d.ᵃ</td>
<td>0.24±0.01</td>
<td>3.59±0.11</td>
<td>0.35±0.02</td>
<td>2.60±0.15</td>
<td>0.41±0.06</td>
<td>2.21±0.36</td>
</tr>
<tr>
<td>2.2a</td>
<td>n.d.ᵃ</td>
<td>0.25±0.01</td>
<td>3.41±0.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2b</td>
<td>n.d.ᵃ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) n.d.: not determined

The equilibrium constants for formation of pairwise encounter complexes are in general smaller than unity. The equilibrium constants increase upon increasing the hydrophobicity of the ester and/or the hydrophobic cosolute.

Rewriting ΔₑₑGₒ in a matrix expression similar to Equation 2.2 leads to Equation 2.4 as determined using a weighted least squares fit.

\[
\begin{bmatrix}
2.67 & 1.44 & 0.37 \\
1.98 & 1.11 & -0.21 \\
1.67 & 0.85 & -0.47 \\
\end{bmatrix}
= 10.0 - 7.5 
\begin{bmatrix}
1 & 1.07 & 1.11 \\
1.11 & 1.28 & 1.10 \\
\end{bmatrix}
\]

Or, in matrix notation:

ΔₑₑG₀ = ΔₑₑG(noninteract) - G · Ge Ge 

Here, ΔₑₑG(noninteract) is the unfavourable standard Gibbs energy term associated with bringing ester and cosolute together if there were no favourable interactions between the two. In the present analysis, ΔₑₑG(noninteract) has been set to 10.0 (RTln(0.018)), corresponding to the chance (based on mole fractions) of finding a cosolute molecule near the reaction center in the cosolute reference state of 1 mol kg⁻¹.ΔₑₑG(noninteract) was restricted as the size of the data set does not allow independent determination of all variables. G is the favourable interaction between p-methoxyphenyl 2,2-dichloropropanoate and ethanol. GeGe and GeGe are vectors describing the relative increments in interaction upon increasing the hydrophobicity of ester and cosolute by subsequent additions of one methylene.
unit, respectively. Again, the increment is given as a multiplication by a number >1. The interaction becomes more favourable upon increasing the hydrophobicity of ester and cosolute, in accord with the encounter complex being increasingly stabilised by hydrophobic interactions.

The numbers in Equation 2.5 form the essence of pairwise hydrophobic interactions. They quantify stabilisation of 1:1 interaction complexes in water by hydrophobic effects compared to random interaction in non-aqueous solvents.

2.2.5 MOLECULAR DESCRIPTION – DISTANCE DEPENDENCE

Rate retardations observed for 2.2a,b in the presence of 1-propanol and 1-butanol show an interesting pattern. The effect of the relatively small 1-propanol molecule is moderate for both 2.2a and 2.2b. Increasing the hydrophobicity of the hydrolytic probe to 2.2b induces a small increase in the observed rate retardation. This pattern can be attributed to the increase in binding mainly occurring remote from the reaction center so that the 1-propanol molecule does not substantially affect the hydration shell around the reaction center. As indicated in Figure 2.1 (vide supra), encounter complexes in which the cosolute complexes in a remote position from the reaction center are not expected to inhibit the reaction. These encounter complexes cannot be observed using kinetics alone. They can only be identified using Gibbs energy of transfer studies as they lower the transition state to the same extent as the initial state. With 1-butanol as a cosolute, however, the rate effect on the hydrolysis of 2.2a is already larger than the rate effect of 1-propanol. In addition, the effect of increasing the hydrophobicity of the hydrolytic probe is larger. There are two causes for this effect. First, 1-butanol will form more stable encounter complexes because of its more hydrophobic nature. Second, the 1-butanol molecule is larger than 1-propanol, meaning that the chances of disturbing the hydration shell around the reaction center are also larger.

2.2.6 ACTIVATION PARAMETERS

Enthalpies and entropies of activation for the hydrolysis of 2.1c as a function of the molality of ethanol, 1-propanol and 1-butanol are summarised in Figure 2.5.
Apparent enthalpies of activation $\Delta^\beta H_{\text{app}}$ for the hydrolysis reaction according to Scheme 2.2 are given by Equation 2.6.

$$\Delta^\beta H_{\text{app}} = \Delta^\beta H_w^o - \frac{K_{ec} \cdot [R'Y]}{1 + K_{ec} \cdot [R'Y]} \cdot \Delta_{ec} H^o$$  \hspace{1cm} (2.6)$$

Here, $\Delta_{ec} H^o$ is the enthalpy of formation of the encounter complex and $\Delta^\beta H_w^o$ is the enthalpy of activation for the hydrolysis reaction in the absence of cosolute.

Using a non-linear least squares analysis based on Equation 2.6 using $K_{ec}$ values obtained from fitting the kinetic data to Equation 2.1, the enthalpies of encounter complex formation were calculated. Using the standard Gibbs energies of encounter complex formation, standard entropies of encounter complex formation were obtained; Table 2.5.
Table 2.5: Thermodynamics of encounter complex formation of 2.1c with short-chain alcohols.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>$\Delta_{ec}G^o$ / kJ mol$^{-1}$</th>
<th>$\Delta_{ec}H^o$ / kJ mol$^{-1}$</th>
<th>$T\Delta_{ec}S^o$ / kJ mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethanol</td>
<td>1.98±0.11</td>
<td>4.95±0.50</td>
<td>2.97±0.52</td>
</tr>
<tr>
<td>1-propanol</td>
<td>1.11±0.08</td>
<td>7.71±0.92</td>
<td>6.60±0.93</td>
</tr>
<tr>
<td>1-butanol</td>
<td>-0.21±0.23</td>
<td>6.68±0.82</td>
<td>6.89±0.85</td>
</tr>
</tbody>
</table>

Formation of encounter complexes is enthalpically opposed and entropically favoured, as expected for hydrophobic interactions$^{36}$ in which water molecules are liberated from their orientationally restricted positions in the hydration shells of the ester and cosolute.$^{37}$ Increasing the hydrophobicity of the cosolute results in a more favourable entropic term, while the changes in the enthalpy are less pronounced. The entropic effect is most pronounced, leading to a lowering of the standard Gibbs energy of encounter complex formation and eventually even to a favourable standard Gibbs energy of encounter complex formation ($K_{ec}>1$). $\Delta_{ec}G^{o}(noninteract)$ (Equation 2.5) is purely entropic and $T\Delta_{ec}S^{o}(noninteract)$ equals -10.0 kJ mol$^{-1}$ whereas $\Delta_{ec}H^{o}(noninteract)$ is zero. Hence, the stabilising effect on encounter complex formation by hydrophobic interactions is brought about by the larger favourable increase in $T\Delta_{ec}S^{o}$ compared to the unfavourable increase in $\Delta_{ec}H^{o}$.

Moreover, from the standard entropy and enthalpy of encounter complex formation, it is anticipated that both the entropy and the enthalpy of the initial state are increased. This, assuming no change in the standard Gibbs energy of the activated complex, is in accord with the observation that with increasing molality of added alcohol, the decrease in apparent entropy of activation is more pronounced than the decrease in apparent enthalpy of activation.

2.2.7 The validity of the assumption of pairwise interactions

Both Equation 1.9 and 2.1 assume the dominance of 1:1 interactions causing the observed rate decreases. According to Figure 2.4, the fitted rate constants tend to deviate from the observed rate constants at higher cosolute molalities. We attribute this trend to higher order interactions. Interestingly, deviation from linearity is not observed in the analysis using Equation 1.9. Traditionally, absence of deviation from linearity has been used as evidence for 1:1 interactions.
In order to assess the possibility of higher-order interactions, estimates were made about the tendency for self-association of the cosolutes and the self-association behaviour of the cosolutes was calculated. Based on the equilibrium constants given in Table 2.4, we contend that the equilibrium constants for self-association $K_{\text{ass}}$ of the alcohols used as cosolutes will be in the order of 0.2 kg mol$^{-1}$ to 0.5 kg mol$^{-1}$. In the following, the self-association of the cosolute molecules is assumed to occur stepwise and in a non-cooperative fashion as shown in Scheme 2.3.

$$
\begin{align*}
R-OH \hspace{1cm} + \hspace{1cm} R-OH & \rightleftharpoons K_{\text{ass}} \hspace{1cm} R-OH \hspace{1cm} + \hspace{1cm} R-OH \\
& \left[ R-OH \right]_n \hspace{1cm} + \hspace{1cm} \left[ R-OH \right]_n & \rightarrow \left[ R-OH \right]_{n+1}
\end{align*}
$$

Scheme 2.3

Based on the above assumptions, it is possible to calculate the molalities of monomer, dimers, trimers, etc. as a function of the total molality of cosolute. Typical examples are given in Figure 2.6.

![Figure 2.6](image_url)

Figure 2.6: Molalities of monomers up to tetramers as a function of the molality of cosolute. Left: Monomers (o) and dimers (∆), Right: trimers (◊) and tetramers (∇) for $K_{\text{ass}}$=0.2 kg mol$^{-1}$ (open symbols) and 0.5 kg mol$^{-1}$ (closed symbols). Only 1 out of 4 calculated data points are shown, curves are based on all data points.

As can be seen from Figure 2.6, the molality of cosolute molecules present in solution as monomers is lower than the total molality of cosolute. Extending equations 1.9 or 2.1 to include terms describing all the possible higher-order interactions is possible. However, this would lead to equations that will not yield significant results when used in the curve fitting procedures, as they would over interpret the available data.
In order to make an estimate of the effect of self-association of the cosolute on the observed kinetics, different quantities were calculated. Considering that 1:1 interaction is still possible with (at least some of) the cosolute molecules constituting the dimer, trimer, etc., the cosolute molality available for 1:1 interactions will be somewhere in between the total molality of cosolute clusters (including monomers) and the total cosolute molality. The results summarised in Figure 2.7 show that the total molality of cosolute clusters (including monomers) varies nearly linearly with total cosolute molality. We therefore contend that the possibility of engaging in 1:1 interactions increases essentially linearly with total cosolute molality.

We assume that higher-order interactions will mainly occur as a result of 1:1 interaction with the clusters present in solution. The possibility to engage in 1:2 and higher order interactions will correlate with (i) the molality of clusters or (ii) the number of higher-order binding sites present in solution. The molality of clusters is given by \( \sum \{ [\text{n-mer}] \} \) whereas the number of higher-order binding sites will correlate roughly with \( \sum \{(n-1)\cdot[\text{n-mer}] \} \), which provides an estimate of the molality of binding sites in between any two cosolute molecules that are part of a cluster. According to Figure 2.7, for small values of \( K_{\text{ass}} \), both terms increase approximately quadratically with cosolute molality. Introducing an additional term into Equation 2.1 to account for the binding to clusters in which 1:2 interaction can take place,
the molality of which is approximated by a quadratic term \( q \cdot m_c^2 \), leads to Equation 2.7.

\[
k(m_c) = \frac{k(m_c = 0)}{1 + K_{ec} \cdot m_c + K_{ecc} \cdot q \cdot m_c^2}
\]  

(2.7)

With \( K_{ecc} \) the equilibrium constant for encounter complex formation with clusters, \( q \) the constant obtained in the quadratic approximation described above. This constant is mainly influenced by \( K_{ass} \) (\( q=0.13-0.15 \) for \( K_{ass}=0.2 \) kg mol\(^{-1}\) and \( q=0.22-0.29 \) for \( K_{ass}=0.5 \) kg mol\(^{-1}\)). All other variables are defined as in Equation 2.1.

Using Equation 2.7, combining \( K_{ecc} \) and \( q \) in \( K_{ecc}' \), a consistent set of values for \( K_{ec} \) and \( K_{ecc}' \) can be obtained and fitted curves are better than in Figure 2.4; Table 2.6.

**Table 2.6**: Binding constants \( K_{ec} \) and \( K_{ecc} \).

<table>
<thead>
<tr>
<th>ester</th>
<th>EtOH</th>
<th>n-PrOH</th>
<th>n-BuOH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( K_{ec} )</td>
<td>( K_{ecc} )</td>
<td>( K_{ec} )</td>
</tr>
<tr>
<td></td>
<td>/ kg mol(^{-1})</td>
<td>/ kg mol(^{-1})</td>
<td>/ kg mol(^{-1})</td>
</tr>
<tr>
<td>2.1b</td>
<td>0.30</td>
<td>0.055</td>
<td>0.47</td>
</tr>
<tr>
<td>2.1c</td>
<td>0.36</td>
<td>0.080</td>
<td>0.53</td>
</tr>
<tr>
<td>2.1d</td>
<td>0.41</td>
<td>0.099</td>
<td>0.57</td>
</tr>
</tbody>
</table>

\(^{[a]} \) \( K_{ec} \) has been set to \( \sim \frac{d \ln \left\{ k(m_c)/k(m_c=0) \right\}}{d m_c} \) (vide infra).

### 2.2.8 COMPARISON OF THE MODELS

Both thermodynamic model and molecular description account for the observed rate decreases. A link between the two descriptions can be derived for \( K_{ec} \cdot m_c < 1 \),

\[
\ln \left\{ \frac{k(m_c)}{k(m_c = 0)} \right\} = -\ln \left\{ 1 + K_{ec} \cdot m_c \right\} \approx -K_{ec} \cdot m_c
\]  

(2.8)

Comparison of Equation 2.8 and Equation 1.9 shows that the terms in Equation 1.9 describing the interaction between ester and alcohol and the term for the lowering of the water activity in Equation 2.8 are replaced by an equilibrium constant. Hence, the lowering of the standard Gibbs energy of encounter complex formation, as given by the increasing equilibrium constants, is equivalent to a stabilisation of the initial state, as revealed by the negative \( G(c) \).
The inclusion of higher-order terms in Equation 2.1 leading to Equation 2.7 shows a peculiar difference between the thermodynamic model and the molecular picture. 1:1-Interactions are still sufficient for the thermodynamic model to give a reasonable fit, but the fit based on the molecular picture improves quite strongly upon adding a term describing higher-order interactions. The fact that \( \ln\left(\frac{k(m_c)}{k(m_c=0)}\right) \) changes linearly with \( m_c \) in the molality range studied suggests that \( \frac{k(m_c)}{k(m_c=0)} \) varies approximately exponentially with \( m_c \).

\[
\frac{k(m_c)}{k(m_c=0)} \approx e^{-am_c} = \left[ \frac{e^{am_c}}{e^{am_c}} \right]^{-1} \approx \left[ 1 + a \cdot m_c + \frac{1}{2} \cdot a^2 \cdot m_c^2 + \ldots \right]^{-1}
\]  

(2.9)

Comparing Equation 2.9 and Equation 2.7 suggest that \( K'_{ec} \) should equal \( \frac{1}{2} \cdot K_{ec}^2 \), which is indeed observed (Figure 2.8).

![Figure 2.8: \( K'_{ec} \) as a function of \( K_{ec} \) for cosolutes ethanol (o), n-propanol (•) and n-butanol (Δ). The curve indicates \( \frac{1}{2} \cdot K_{ec}^2 \).](image)

As can be concluded from the above, the significance of \( K'_{ec} \) is rather ambiguous. In one explanation, it reflects just another term of the Taylor series approximating an exponential function correctly describing the observed kinetics. Alternatively, the fact that \( K'_{ec} \) happens to be close to \( \frac{1}{2} \cdot K_{ec}^2 \) causes \( \ln\left(\frac{k(m_c)}{k(m_c=0)}\right) \) to vary almost linearly with \( m_c \). In fact, comparable factors in the thermodynamic description could also lead to an overestimate of the molality range in which 1:1 interactions are dominant. This, in turn, could explain the non-additivity of the \( G(c) \)s of some combinations of cosolutes.5,38

The entropy and the enthalpy of the initial state both are increased by the encounter complex formation between ester and cosolute, as described before. Therefore, the molecular description explains previous observations² of the negative \( G(c) \), signifying initial state stabilisation, being accompanied by a strong enthalpic
destabilisation of the initial state, directly in terms of the thermodynamics of encounter complex formation.

Using the molecular model of encounter complex formation, the observed thermodynamics, including the $G(c)$-values, can be fully accounted for.

The inherent advantage of the molecular description is its possibility to link the observed kinetics and thermodynamics to a molecular picture of two interacting molecules. However, one has to keep in mind that an important contribution to the thermodynamics of interaction is caused by water molecules being released from restricted positions in the hydration shells of those molecules.

### 2.3 Conclusion

Inert cosolutes can influence reactions in solution by forming encounter complexes. In aqueous solution, these encounter complexes can be stabilised by hydrophobic interactions. This results in larger cosolute effects on chemical reactions as the unfavourable entropy term associated with bringing the molecules together is partially or completely (depending on molality) compensated by the release of water molecules from the hydration shell. For the water-catalysed hydrolysis of the activated esters used in the present study, the formation of encounter complexes, with equilibrium constants $K_{ec}$ often smaller than unity, leads to an initial state stabilisation as given by $G(c)$. The stabilisation of the encounter complex by hydrophobic interactions results in a decrease in both apparent enthalpy and apparent entropy of activation.
2.4 EXPERIMENTAL

2.4.1 KINETIC EXPERIMENTS

Aqueous solutions were prepared by weight immediately before use. Water was distilled twice in an all-quartz distillation unit. All reactions were monitored at 288 nm and at 25.0±0.1°C (in the determination of the G(c)-values) and at least 6 different temperatures in the interval between 20.0±0.1°C and 50.0±0.1°C (except for the 1.5mol% 1-propanol and the 0.5mol% 1-butanol solutions for which measurements were performed at 4 and 5 temperatures, respectively, in the interval between 20.0±0.1°C and 50.0±0.1°C). Reactions were followed for at least six half-lives using a Perkin-Elmer lambda 2, lambda 5 or lambda 12 spectrophotometer. Good to excellent first-order kinetics were obtained, the error in the rate constants being 2% or less. Esters were injected as 20-30 µl of stock solutions containing 2.1a-d in cyanomethane into about 15 ml of an aqueous solution of cosolute in the concentration range of 0-2mol% (up to 1.68 mol% for 1-butanol, below the solubility limit of 1.92mol%) followed by sonication of the solution for 5 min. The sonicated solutions were centrifuged, decanted and diluted to about 20 ml. Of the resulting solution, 6-7 ml aliquots were transferred into a 2.000 cm path length stoppered quartz cuvette. The resulting concentrations of hydrolytic probe were about 10⁻⁵ mol dm⁻³ or less. All these precautions were taken in order to prevent problems due to the low solubility of the more hydrophobic esters. Amides were injected as 5-7 µl of stock solutions containing 2.2a,b in cyanomethane into about 2.8 ml of an aqueous solution of cosolute in the molality range of 0-1.15 mol kg⁻¹ for n-propanol and 0-0.87 mol kg⁻¹ for n-butanol in a stoppered 1.000 cm quartz cuvette. The resulting concentrations were about 10⁻⁵ mol dm⁻³ or less. The pH of all solutions was adjusted to 3.6±0.3 using aqueous HCl. The pH was checked again at the end of each kinetic experiment and was found to be 3.6±0.3, well within the pH-range in which solely water-catalysed hydrolysis takes place.

2.4.2 MATERIALS

Cosolutes were of analytical grade and were purchased from Merck. The esters were synthesised using the route shown in Scheme 2.4.
The starting materials for the syntheses were purchased from Aldrich and were used as received. NMR spectra were recorded on Varian Gemini 200 (\(^1\)H: 200MHz) and VRX 300 (\(^1\)H: 300MHz) spectrometers. IR-spectra were recorded using a Perkin Elmer 841 infrared spectrophotometer. Methyl dichloroethanoate was obtained by reacting dichloroethanoic acid with methanol in the presence of sulfuric acid.\(^{39}\) \(^1\)H-NMR (CDCl\(_3\), ppm): 3.92 (3H, OC\(_2\)H\(_3\), s), 5.97 (1H, HCCl\(_2\), s), IR (CCl\(_4\), cm\(^{-1}\)): 1773, 1753. 1-(4-Methylbenzoyl)-1,2,4-triazole \(2.2b\) and 1-(4-n-butylbenzoyl)-1,2,4-triazole \(2.2b\) were synthesised according to literature procedures.\(^{40}\)

**Methyl 2,2-dichlorobutanoate.** An adapted literature procedure\(^{41}\) was used. To a solution of 5.8 ml (40 mmol) of anhydrous diisopropylamine 20 ml of sodium-dried THF, 14.4 ml of a 2.5M solution of BuLi in hexane (36 mmol) was added slowly at -78°C. After stirring for 5 min, 4.0 grams (28 mmol) of methyl 2,2-dichloroethanoate were added and stirring continued for another 15 min. Next, 2.9 ml (28 mmol) of ethyl iodide was added. The mixture was stirred for another 15 min and then allowed to reach room temperature. The reaction mixture was poured out into a saturated NH\(_4\)Cl solution and 60 ml of ether was added. The ether layer was separated from the aqueous layer and washed with water and brine. The ether layer was dried over sodium sulfate, filtered and ether was removed by evaporation. Distillation in a Kugelrohr apparatus (120°C, circa 10 mm Hg) gave 4.153 g (24 mmol, 60%) of product. \(^1\)H-NMR (CDCl\(_3\)): \(\delta\) (ppm): 1.16 (3H, CH\(_2\)CH\(_3\), t), 2.46 (2H, CH\(_3\)CH\(_2\)CCl\(_2\), m), 3.89 (3H, OCH\(_3\), s). \(^{13}\)C-NMR (CDCl\(_3\), ppm): 8.0, 37.1, 52.8.
Methyl 2,2-dichloropentanoate was synthesised analogously using n-propyl iodide. $^1$H-NMR (CDCl$_3$): $\delta$ (ppm): 1.00 (3H, CH$_2$CH$_3$, t), 1.59 (2H, CH$_3$CH$_2$CH$_2$, sextet), 2.40 (2H, CH$_3$CH$_2$CCl$_2$, m), 3.89 (3H, OCH$_3$, s). $^{13}$C-NMR (CDCl$_3$, ppm): 11.9, 17.0, 45.6, 52.8, 84.3, 166.6, IR (CCl$_4$, cm$^{-1}$): 1748, 1768.

2,2-Dichlorobutanoic acid was synthesised from methyl 2,2-dichlorobutanoate according to a literature procedure.$^{42}$ $^1$H-NMR (CDCl$_3$): $\delta$ (ppm): 1.19 (3H, CH$_3$CH$_2$, t), 2.47 (2H, CH$_3$CH$_2$CCl$_2$, q), $^{13}$C-NMR (CDCl$_3$, ppm): 7.0, 36.1, 83.4, 165.3, IR (CCl$_4$, cm$^{-1}$): 1732.

2,2-Dichloropentanoic acid was synthesised analogously using methyl 2,2-dichloropentanoate. $^1$H-NMR (CDCl$_3$): $\delta$ (ppm): 1.00 (3H, CH$_2$CH$_3$, t), 1.65 (2H, CH$_3$CH$_2$CH$_2$, sextet), 2.41 (2H, CH$_2$CH$_2$CCl$_2$, m). $^{13}$C-NMR (CDCl$_3$, ppm): 11.9, 17.1, 45.5, 84.3, 166.6, IR (CCl$_4$, cm$^{-1}$): 1734.

2,2-Dichloropentanoyl chloride. A mixture of 1.94 g (11.4 mmol) of 2,2-dichloropentanoic acid and 2.74 g (23 mmol) of SOCl$_2$ was refluxed for 3 h. Distillation of the reaction mixture under reduced pressure gave 1.13 g (6 mmol, 53%) of 2,2-dichloropentanoyl chloride. $^{13}$C-NMR (CDCl$_3$, ppm): 13.1, 18.3, 46.6, IR (CCl$_4$, cm$^{-1}$): 1779, 1799.

2,2-Dichlorobutanoyl chloride was synthesised analogously from 2,2-dichlorobutanoic acid. 2,2-Dichlorobutanoyl chloride: $^1$H-NMR (CDCl$_3$): $\delta$ (ppm): 1.20 (3H, CH$_3$CH$_2$, t), 2.53 (2H, CH$_3$CH$_2$CCl$_2$, q), $^{13}$C-NMR (CDCl$_3$, ppm): 7.0, 36.0, 88.5, 165.5, IR (CCl$_4$, cm$^{-1}$): 1773, 1802.

2,2-Dichloropropanoyl chloride was synthesised analogously from 2,2-dichloropropanoic acid. 2,2-Dichloropropanoyl chloride: $^1$H-NMR (CDCl$_3$): $\delta$ (ppm): 2.36 (3H, CH$_3$CCl$_2$, t), IR (CCl$_4$, cm$^{-1}$): 1778, 1795.

$p$-Methoxyphenyl 2,2-dichloroethanoate 2.1a was synthesised according to a literature procedure.$^{43}$

$p$-Methoxyphenyl 2,2-dichloropentanoate 2.1d. To 3 ml of absolute ether, equimolar amounts (6 mmol) of 2,2-dichloropentanoyl chloride and $p$-methoxyphenol and pyridine were added. The mixture was stirred for 3h at room temperature. Pyridine salts were filtered off and the solvent was evaporated. The crude ester was dissolved in petroleum ether 40/60. On cooling, a two-phase system was formed. The upper colourless layer was separated and the solvent was removed by evaporation, yielding the crude ester. The ester was further purified by
column chromatography over silica, using 1:1 CH₂Cl₂/n-hexane as the eluent. ¹H-NMR (CDCl₃, ppm): 1.07 (3H, CH₃CH₂, t), 1.82 (2H, CH₃CH₂CH₂, sextet), 2.53 (2H, CH₂CH₂CCl₂, m), 3.81 (3H, CH₃O, s), 7.00 (4H, phenyl, AB-system).

**p-Methoxyphenyl 2,2-dichlorobutanoate 2.1c** was synthesised analogously.  
*p-Methoxyphenyl 2,2-dichlorobutanoate:* ¹H-NMR (CDCl₃, ppm): 1.36 (3H, CH₃CH₂, t), 2.58 (2H, CH₃CH₂CCl₂, q), 3.81 (3H, CH₃O, s), 7.00 (4H, phenyl, AB-system).

**p-Methoxyphenyl 2,2-dichloropropanoate 2.1b** was synthesised analogously.  
*p-Methoxyphenyl 2,2-dichloropropanoate:* ¹H-NMR (CDCl₃, ppm): 2.43 (3H, CH₂CCl₂, s), 3.85 (3H, CH₃O, s), 7.00 (4H, phenyl, AB-system).

**1-(4-n-Butylbenzoyl)-1,2,4-triazole 2.2b.** To a suspension of 0.71 g (10.3 mmol) of freshly recrystallised 1,2,4-triazole in 50 ml of dry (distilled from P₂O₅) ether, a solution of 1.00 g (5.09 mmol) of 4-(n-butyl)benzoyl chloride was added. The suspension was stirred overnight at room temperature. The liquid was removed via a cannula. The ether was evaporated under reduced pressure and petroleum-ether 40-60 was added. The liquid fraction was removed via a cannula again, after which the petroleum-ether was evaporated under reduced pressure. Yield 1.01 g (4.39 mmol, 86%) ¹H-NMR (CDCl₃, ppm): 0.89 (3H, CH₃CH₂, t), 1.32 (2H, CH₃CH₂CH₂, sextet), 1.59 (2H, CH₃CH₂CH₂CH₂, pentet), 2.66 (2H, CH₂CH₂Ph, t), 7.30 and 8.11 (4H, phenyl, AB-system), 8.06 (1H, triazole-H, s), 9.02 (1H, triazole-H, s).

### 2.5 Acknowledgement

Laura Pastorello is gratefully acknowledged for performing the synthesis of some of the compounds used in this chapter and for performing the initial kinetic experiments. Marten de Rapper is thanked for excellent technical support. Theo Rispens and Sijbren Otto contributed to the chapter by countless enlightening discussions.
2.6 References and Notes


(16) Apart from additivity within series of compounds, promising results are obtained in the attempt to determine an additivity scheme describing all cosolutes used in combination with one particular probe. M. Wijnhold, personal communication.


(19) Correlations between ln(k) and several solvent parameters yield less satisfactory results than the analyses using Equations 1.9 and 2.1 as presented in this Chapter. For example, ln(k) for individual probes correlates reasonably well with the relative
permittivity $\varepsilon$ for aqueous solutions within a series of concentrations using only one cosolute. Plotting $\ln(k)$ vs relative permittivity for solutions of different alcohols, however, results in different correlations for different alcohols.

(20) In terms of the Marcus Theory description in Chapter 1, this corresponds to an increase in the work function.


The rate decrease cannot be caused by the decreased water concentration alone. Based on known densities of aqueous solutions (see *e.g.*: Jolicoeur, C.; Lacroix, G., *Can. J. Chem.* 1976, 54, 624), the water concentration in dilute aqueous solutions used in the present study can be calculated. Considering that the hydrolysis reactions are second-order in water, the decreased water concentration in, for example, a 0.57 m solution of 1-propanol would result in a rate decrease of 6.5%, whereas experimentally rate effects around 25% are found for the different probes.

(34) This is one of the possible choices for $\Delta G(\text{noninteract})$. The advantage of this choice is that it is the same for all different cosolutes. Other possible choices include values based on the molar volume of the cosolute.

(35) $\Delta G(\text{noninteract})$ and $G$ are not independent. For a rather wide range of $\Delta G(\text{noninteract})$, a good fit is possible with a different value for $G$.


The changes in $\Delta^sH^o$ and $\Delta^sS^o$ as a function of cosolute concentration are consistent with recent computer simulations, which show a favourable entropy of association of

(38) Rispens, T. *et al.*, to be published.


