Kinetic Evidence for Hydrophobically Stabilized Encounter Complexes Formed by Hydrophobic Esters in Aqueous Solutions Containing Monohydric Alcohols

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Abstract: The pH-independent hydrolysis of four esters, *p*-methoxyphenyl 2,2-dichloroethanoate (**1a**), *p*-methoxyphenyl 2,2-dichloropropanoate (**1b**), *p*-methoxyphenyl 2,2-dichlorobutanoate (**1c**), and *p*-methoxyphenyl 2,2-dichloropentanoate (**1d**), in dilute aqueous solution has been studied as a function of the molality of added cosolutes ethanol, 1-propanol, and 1-butanol. The rate constants for the neutral hydrolysis decrease with increasing cosolute concentration. These kinetic medium effects respond to both the hydrophobicity of the ester and of the monohydric alcohol. The observed rate effects were analyzed using both a thermodynamic and a kinetic model. The kinetic model suggests a molecular picture of a hydrophobically stabilized encounter complex, with equilibrium constants K_{ec} often smaller than unity, in which the cosolute blocks the reaction center of the hydrolytic ester for attack by water. The formation of these encounter complexes leads to a dominant initial-state stabilization as follows from the thermodynamic model. Decreases in both apparent enthalpies and entropies of activation for these hydrolysis reactions correspond to unfavorable enthalpies and favorable entropies of complexation, which confirms that the encounter complexes are stabilized by hydrophobic interactions.

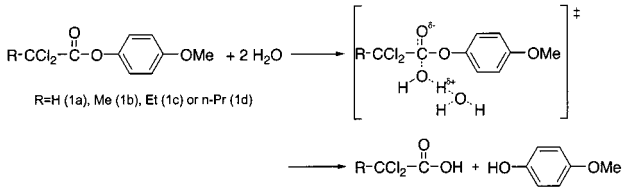
Introduction

Hydrophobic interactions are important noncovalent driving forces for inter- and intramolecular binding and assembly processes in aqueous chemistry and biochemistry.[1] These interactions vary from relatively weak pairwise intermolecular contacts to cooperative bulk association processes. The driving force for these hydrophobic interactions usually originates from a delicate balance between enthalpic and entropic effects, largely due to changes in hydration of the interacting solutes. Both experimental[2] and computational studies[3] have contributed to our present understanding of these rather complex phenomena.

In addition to chemical equilibria, hydrophobic interactions often play a key role in chemical reactions[4] and catalytic processes.[5]

The pH-independent hydrolysis of activated esters, *p*-methoxyphenyl 2,2-dichloroalkanoates **1a**−**d**, in the presence of hydrophobic cosolutes, was chosen for detailed analysis. The hydrolyses of **1a**−**d** proceed via the mechanism shown in Scheme 1.[6,7]

Scheme 1



All these reactions are water-catalyzed between pH 2.0 and 5.5. The reactions proceed via a dipolar activated complex in which two water molecules, one of which, acting as a general base, are involved *with three protons in flight*.

Detailed computer simulations, using both quantum and classical dynamics, revealed that proton tunneling is involved in the rate-determining step,[8] the water molecules involved in the activated complex being therefore subject to severe orientational requirements. Consistent with these views, strongly negative entropies of activation have been found for this reaction.[7]

Previous studies[9] have shown that the hydrolysis of activated esters structurally similar to **1a**−**d**, but also of similar activated amides,[10] is retarded by most hydrophobic cosolutes.[7,9,11−16] In

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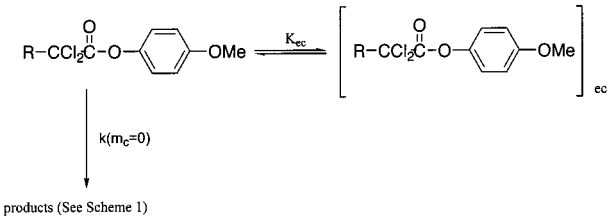
the present study, these rate retardations are interpreted using both a thermodynamic model and a kinetic model.[17]

The thermodynamic model for interactions between a reacting molecule and an inert hydrophobic cosolute was developed several years ago.[13,18] This model interprets the rate retardations in terms of the effect of added cosolute on activity coefficients of initial and transition states of the ester undergoing hydrolysis. These coefficients were re-expressed using the procedures described by Wood[19] in terms of pairwise solute−solute interaction parameters. The analysis leads to

$$\ln\left[\frac{k(m_c)}{k(m_c=0)}\right] = \frac{2}{RTm_o^2}[g_{cx} - g_{c\ddagger}]m_c - N\phi M_l m_c \quad (1.1)$$

Here $k(m_c)$ is the (pseudo-)first-order rate constant in an m_c molal aqueous solution of cosolute c, $k(m_c=0)$ the rate constant in the absence of added cosolute, R the gas constant, and T the temperature in Kelvin. Significantly, $[g_{cx} - g_{c\ddagger}]$ is the difference in interaction Gibbs energies between the cosolute c and the reactants x on one hand and the activated complex ‡ on the other hand. Furthermore, M_l is the molar mass of water, N is the number of water molecules involved in the rate-determining step, and ϕ is the practical osmotic coefficient for the aqueous solution where the molality of added solute is m_c. In the present study, $N = 2$ (vide supra). Further, the solutions are very dilute,[20] and hence, ϕ can be taken as unity; m_o is the (hypothetical) ideal reference state and corresponds to 1 mol kg^{-1}. The difference $[g_{cx} - g_{c\ddagger}]$ is denoted as $G(c)$. This analysis of the kinetic results, which involves a direct link between thermodynamics and transition-state theory, has also been employed for completely different reactions, including keto−enol tautomerization,[21] rate-determining electron-transfer reactions,[22] and aquation of iron(II) complexes in aqueous solutions.[23]

Scheme 2



In the analysis of previously reported kinetic data for this class of systems, emphasis was placed mainly on the hydrophobicity of the cosolutes.[9] Rate retardations by added cosolutes follow an additivity scheme in which each methylene unit makes a common contribution to $G(c)$, the SWAG approach (Savage−Wood additivity of group interactions).[19] For hydrolysis reactions similar to those involving esters **1a**−**d**, the change in standard Gibbs energy of activation is largely caused by a stabilization of the initial state by hydrophobic interactions.[24]

In a different approach, the severe orientational requirements on the water orientation in the activated complex[8] prompts the idea of formation of an encounter complex between ester and added solute, in which the cosolute blocks the reaction center from attack by water.

A kinetic scheme based on this molecular picture (Scheme 2) emerges in which ester molecules that are not solvated by cosolute molecules react with a rate constant $k(m_c=0)$. The hydrolysis rate constant for the ester in the encounter complex is assumed to be zero. This assumption leads to the following expression for the observed rate constant

$$k(m_c) = \frac{k(m_c=0)}{1 + K_{ec}m_c} \quad (1.2)$$

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

In the present study, both the hydrophobicity of the cosolute molecules and of the reacting ester were varied. The results of the analysis based on both eqns 1.1 and 1.2 are reported. Furthermore, the isobaric activation enthalpies and entropies for the hydrolysis of **1c** in the presence of hydrophobic cosolutes were determined in order to obtain more information on the thermodynamics of encounter complex formation and to understand the relation between the thermodynamic description and the molecular picture of rate inhibition. We show that both approaches account for the kinetic data.

The study of the thermodynamics and kinetics of encounter complexes in aqueous solution has immediate relevance for a mechanistic understanding of reactions in aqueous media. Generally, the formation of an encounter complex constitutes the first step in the activation process of a bimolecular reaction. Insight into factors governing encounter complex formation aids in a quantitative analysis of second-order rate constants for such chemical transformations.

Results and Discussion

Hydrolysis of 1a−d in the Absence of Cosolutes. (Pseudo)-first-order rate constants at 298.2 K for the hydrolysis of **1a**−**d** in water are summarized in Table 1.

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(17) Correlations between ln(k) and several solvent parameters yield less satisfactory results. For example, ln(k) for individual probes correlates reasonably well with the relative permittivity ϵ 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.
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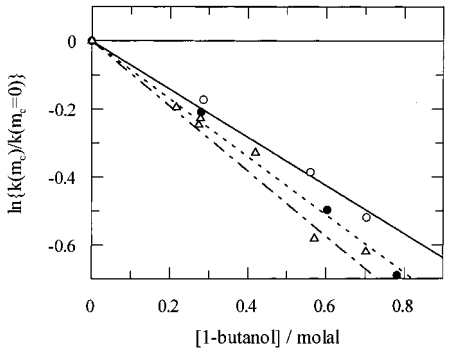

Figure 1. Hydrolysis of **1b** (○), **1c** (●), and **1d** (△) as a function of the concentration of 1-butanol. The lines are the best fits using eq 1.1.

Table 1. (Pseudo-)First-Order Rate Constants for the Water-Catalyzed Hydrolysis of **1a**−**d** in Water at 298.2 K

compd	10^4k (m_c=0)/s^{-1}	compd	10^4k (m_c=0)/s^{-1}
1a	30.9	**1c**	3.06
1b	11.7	**1d**	2.73

Table 2. *G*(*c*) Values for the Hydrolysis of Esters **1a**−**d** in Aqueous Solution at 298.2 K in the Presence of Short-Chain Alcohols[a]

	G(*c*) for given cosolute (J kg mol^{-2})		
ester	EtOH	*n*-PrOH	*n*-BuOH
1a	−304(5)	−474(8)	−709(10)
1b	−338(9)	−555(22)	−833(29)
1c	−400(4)	−592(22)	−1044(54)
1d	−466(22)	−634(52)	−1213(70)

[a] The numbers in brackets are standard errors based on a least-squares fit of the kinetic data using eq 1.1.

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-catalyzed hydrolysis of activated amides was studied using Charton's expanded branching equation.[25,26] The size of the data set in Table 1 does not allow a similar analysis. Unfortunately, the data set cannot be expanded due to the severe solubility problems encountered with more hydrophobic esters.

Thermodynamic Model. Rate constants for the hydrolysis of the esters **1a**−**d** decrease upon increasing cosolute concentration (e.g. Figure 1).[20] The decrease in rate constant is more pronounced for the more hydrophobic cosolutes, in accord with previous observations.[9,14−16]

Analysis of the kinetic data using eq 1.1 yields the *G*(*c*)-values summarized in Table 2.

Assuming the (standard) chemical potential of the transition state to be largely unaffected by the cosolute, a negative *G*(*c*) signifies a lowering of the chemical potential of the initial state. *G*(*c*) decreases upon increasing the hydrophobicity of both added cosolute and ester, indicating increasing stabilization of the initial state ester. The results are summarized in Figure 2(please note that $-G(c)$ is plotted in Figure 2).

In Figure 2, the ordinate shows a scale having constant increments for one methylene unit. The coordinate records *G*(*c*)-values which follow an approximate additivity scheme in accord with the SWAG theory,[19] 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 or sideways in Figure 2).

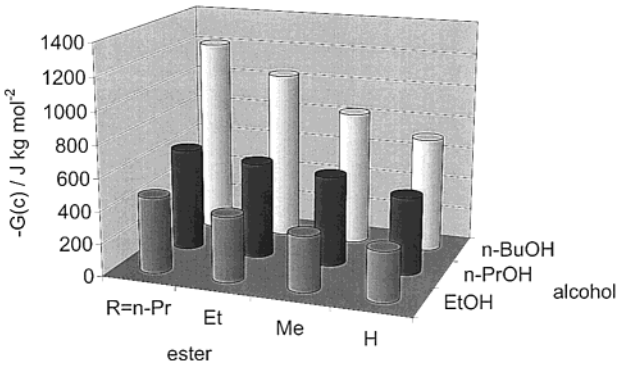

Figure 2. Absolute values of *G*(*c*) in J kg mol^{-2} for different probe−cosolute combinations.

For the small range of cosolutes studied, however, definite conclusions about additivity cannot be drawn. The effects of added 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.[16] Similar shielding effects by nonionic hydrophilic groups have been found by other authors.[27]

It is possible to write the observed *G*(*c*) values (Table 2) as matrices that can be written as a matrix product (eq 3 is a least-squares analysis),

$$\begin{pmatrix} -304 & -474 & -709 \\ -338 & -555 & -833 \\ -400 & -592 & -1044 \\ -466 & -634 & -1213 \end{pmatrix} = -301.1 \begin{pmatrix} 1 \\ 1.15 \\ 1.34 \\ 1.51 \end{pmatrix} \begin{pmatrix} 1 & 1.50 & 2.49 \end{pmatrix} \quad (1.3)$$

or, in matrix notation,

$$G(c) = a\mathbf{ec} \quad (1.4)$$

Here *a* is a constant denoting the interaction between *p*-methoxyphenyl 2,2-dichloroacetate 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, most probably as a result of the small range of cosolutes, which was constrained by the solubility of the higher alcohols.

Molecular Description. The observed decrease in rate constant upon increasing the hydrophobicity of the ester 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 concentration of the solutes. In fact, the occurrence of encounter complexes is necessary for any bimolecular reaction to occur and the concept of encounter complexes is commonly used in

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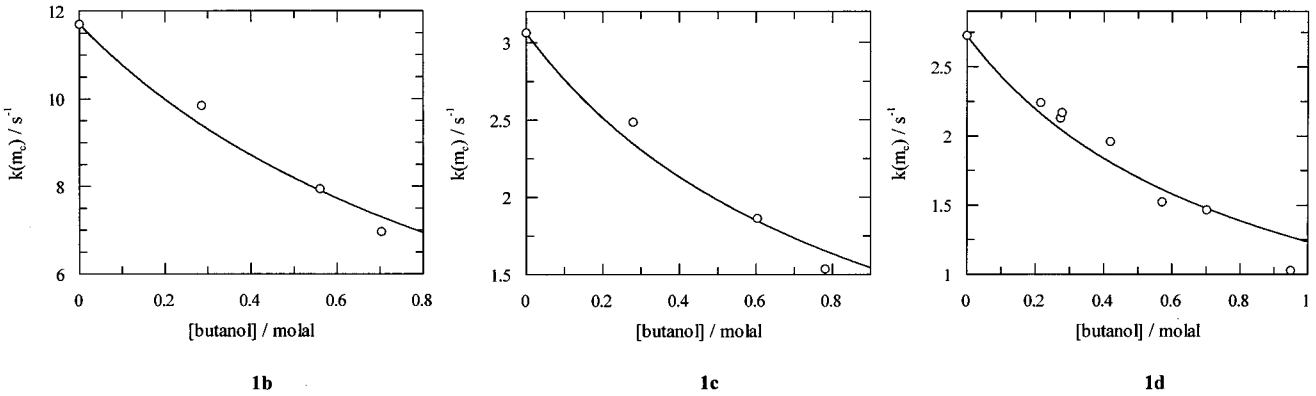

Figure 3. Hydrolysis of **1b**−**d** as a function of the concentration of 1-butanol. The lines are the best fits using eq 1.2.

Table 3. Thermodynamic Parameters for the Hydrolysis of **1a**−**d** in the Presence of Short-Chain Alcohols

	for given cosolute					
	EtOH		*n*-PrOH		*n*-BuOH	
compd	K_{ec} (m_c^{-1})	$\Delta_{ec}G°$ (kJ mol^{-1})	K_{ec} (m_c^{-1})	$\Delta_{ec}G°$ (kJ mol^{-1})	K_{ec} (m_c^{-1})	$\Delta_{ec}G°$ (kJ mol^{-1})
1b	0.34 ± 0.02	2.67 ± 0.15	0.56 ± 0.05	1.44 ± 0.22	0.86 ± 0.07	0.37 ± 0.20
1c	0.45 ± 0.02	1.98 ± 0.11	0.64 ± 0.01	1.11 ± 0.08	1.09 ± 0.10	−0.21 ± 0.23
1d	0.51 ± 0.03	1.67 ± 0.15	0.71 ± 0.04	0.85 ± 0.14	1.21 ± 0.12	−0.47 ± 0.25

bimolecular photochemical reactions.[28] On the basis of typical sizes of solvents and solutes, equilibrium constants for formation of these randomly formed complexes are commonly estimated to range from 0.2 L mol^{-1} to values slightly larger than unity.[29] In aqueous solution, encounter complexes will be stabilized by hydrophobic interactions and the stabilization will increase with an increased hydrophobicity of the encounter complexes constituents.

The kinetic scheme (Scheme 2), assuming the encounter complex is inert, is strongly supported by a computer simulation of the hydrolysis reaction.[8] Since the hydrophobic interaction with the 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.[30] This model leads to the kinetic description given by eq 1.2. Nonlinear least-squares fitting of the observed rate data to eq 1.2 results in the equilibrium constants and standard Gibbs energies of encounter complex formation, $\Delta_{ec}G°$, as given in Table 3. Typical examples of the fits are shown in Figure 3.[31]

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 $\Delta_{ec}G°$ in a matrix expression similar to eq 1.3 leads to eq 1.5 as determined using a weighed least-squares fit

$$\begin{pmatrix} 2.67 & 1.44 & 0.37 \\ 1.98 & 1.11 & -0.21 \\ 1.67 & 0.85 & -0.47 \end{pmatrix} = 10.0 - 7.5 \begin{pmatrix} 1 \\ 1.07 \\ 1.10 \end{pmatrix} (1 \quad 1.11 \quad 1.28) \tag{1.5}$$

or, in matrix notation,

$$\Delta_{ec}G° = \Delta_{ec}G(\text{noninteract}) - G\mathbf{G}_{ec}{}^{e}\mathbf{G}_{ec}{}^{c} \tag{1.6}$$

Here, $\Delta_{ec}G$(noninteract) is the unfavorable standard Gibbs energy term associated with bringing ester and cosolute together if there were no favorable interactions between the two. In the present analysis, $\Delta_{ec}G$(noninteract) has been set to 10.0 ($-RT$ ln(0.018)), corresponding to the chance (based on mole fractions) of finding a cosolute molecule near the reaction center. $\Delta_{ec}G$(noninteract) was restricted as the size of the data set does not allow independent determination of all variables. G is the favorable interaction between *p*-methoxyphenyl 2,2-dichloropropanoate and ethanol. $\mathbf{G}_{ec}{}^{e}$ and $\mathbf{G}_{ec}{}^{c}$ are the increments in interaction upon increasing the hydrophobicity of ester and cosolute, respectively. Again, the increment is given as a multiplication by a number > 1. The interaction becomes more favorable upon increasing the hydrophobicity of ester and cosolute, in accord with the encounter complex being increasingly stabilized by hydrophobic interactions.

Activation Parameters. Enthalpies and entropies of activation for the hydrolysis of **1c** as a function of the concentration of ethanol, 1-propanol, and 1-butanol are summarized in Figure 4. Apparent enthalpies of activation $\Delta^{‡}H_{app}°$ for the hydrolysis reaction according to Scheme 2 are given by

$$\Delta^{‡}H_{app}° = \Delta^{‡}H_{w}° - \frac{K_{ec}[R'Y]}{1 + K_{ec}[R'Y]}\Delta_{ec}H° \tag{1.7}$$

Here, $\Delta_{ec}H°$ is the enthalpy of formation of the encounter complex and $\Delta^{‡}H_{w}°$ is the enthalpy of activation for the hydrolysis reaction in the absence of cosolute.

Using a nonlinear least-squares analysis based on eq 1.7 with K_{ec} values as obtained from fitting the kinetic data to eq 1.2, the enthalpies of encounter complex formation were calculated.

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(30) If interaction between ester and cosolute occurs far from the reaction center, there will be no difference between the interaction with reactant or activated complex, resulting in the absence of a kinetic effect.

(31) The rate decreases 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 the 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.

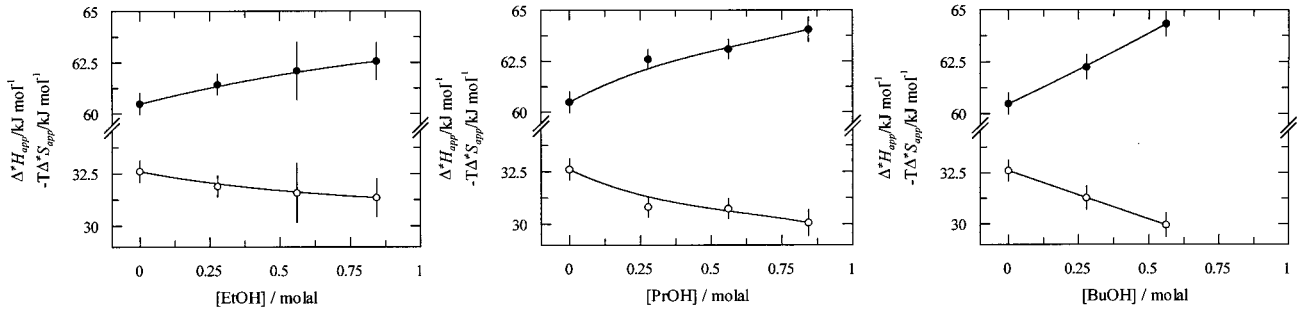


Figure 4. Activation parameters, $\Delta^{\ddagger}H_{app}$ (○) and $-T\Delta^{\ddagger}S_{app}$ (●), at 25 °C of the hydrolysis of **1c** in the presence of ethanol, 1-propanol, and 1-butanol.

Table 4. Thermodynamics of Encounter Complex Formation of **1c** with Short-Chain Alcohols

	$\Delta_{ec}G°$ (kJ mol^{-1})	$\Delta_{ec}H°$ (kJ mol^{-1})	$T\Delta_{ec}S°$ (kJ mol^{-1})
ethanol	1.98 ± 0.11	4.95 ± 0.50	2.97 ± 0.52
1-propanol	1.11 ± 0.08	7.71 ± 0.92	6.60 ± 0.93
1-butanol	-0.21 ± 0.23	6.68 ± 0.82	6.89 ± 0.85

Using the standard Gibbs energies of encounter complex formation, the entropies of encounter complex formation were obtained, Table 4.

The formation of encounter complexes is enthalpically opposed and entropically favored, as expected for hydrophobic interactions[1] in which water molecules are liberated from their orientationally restricted positions in the hydration shells of the ester and cosolute.[32] Increasing the hydrophobicity of the cosolute results in a more favorable entropic term, while the changes in the enthalpy are less pronounced. The entropic effect being most pronounced, leads to a lowering of the standard Gibbs energy of encounter complex formation and eventually even to a favorable standard Gibbs energy of encounter complex formation ($K_{ec} > 1$). 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.

Comparison of the Models. Both the thermodynamic model and the molecular description fit the observed rate decreases. A link between the two descriptions can be derived for $K_{ec}m_c < 1$,

$$\ln\left\{\frac{k(m_c)}{k(m_c=0)}\right\} = -\ln\{1 + K_{ec}m_c\} \approx -K_{ec}m_c \quad (1.8)$$

Comparison of eq 1.8 and eq 1.1 shows that the terms in eq 1.1 describing the interaction between ester and alcohol and the term for the lowering of the water activity in eq 1.8 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 stabilization of the initial state, as revealed by the negative $G(c)$.

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 observations of the negative $G(c)$, signifying initial state stabilization, being accompanied by a strong enthalpic destabilization of the initial state,[15] 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 for linking 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.

Conclusion

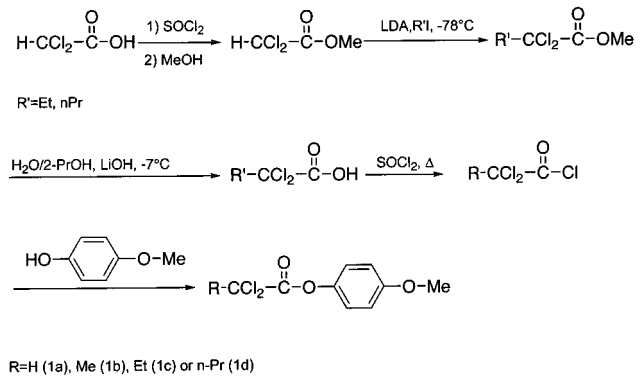
Inert cosolutes can influence reactions in solution by forming encounter complexes. In aqueous solution, these encounter complexes can be stabilized by hydrophobic interactions. This results in enhanced cosolute effects on chemical reactions as the unfavorable entropy term associated with bringing the molecules together is partially or completely (depending on concentration) compensated by the release of water molecules from the hydration shell. For the water-catalyzed 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 stabilization as given by $G(c)$. The stabilization of the encounter complex by hydrophobic interactions results in a decrease in both apparent enthalpy and apparent entropy of activation.

Experimental Section

Kinetics. 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 six different temperatures in the interval between 20.0 ± 0.1 and 50 ± 0.1 °C (except for the 1.5 mol% 1-propanol and the 0.5 mol% 1-butanol solutions for which measurements were performed at four and five temperatures, respectively). 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 **1a**−**d** in acetonitrile into about 15 mL of an aqueous solution of cosolute in the concentration range of 0−2 mol % (up to 1.68 mol % for 1-butanol, below the solubility limit of 1.92 mol %) 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

(32) The changes in $\Delta^{\ddagger}H°$ and $\Delta^{\ddagger}S°$ as a function of cosolute concentration are consistent with recent computer simulations, which show a favorable entropy of association of two methane molecules in water, provided a sufficiently close approach in the aqueous medium. See: Smith, D. E.; Zhang, L.; Haymet, A. D. J. *J. Am. Chem. Soc.* **1992**, *114*, 5875.

Scheme 3



more hydrophobic esters. 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-catalyzed hydrolysis takes place.

Materials. Cosolutes were of analytical grade and were purchased from Merck. The esters were synthesized using the route shown in Scheme 3.

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: 200 MHz) and VRX 300 (^{1}H: 300 MHz) spectrometers. IR spectra were recorded using a Perkin-Elmer 841 infrared spectrophotometer. Methyl dichloroacetate was obtained by reacting dichloroacetic acid with thionyl chloride and subsequent esterification with methanol.[33] ^{1}H NMR ($CDCl_3$, ppm): δ 3.92 (3H, OCH_3, s), 5.97 (1H, HCCl_2, s). IR (CCl_4, cm^{-1}): 1773, 1753.

(a) Methyl 2,2-Dichlorobutanoate. An adapted literature procedure[34] was used. To a solution of 5.8 mL (40 mmol) of anhydrous diisopropylamine and 20 mL of sodium-dried tetrahydrofuran (THF), 14.4 mL of a 2.5 M solution of BuLi in hexane (36 mmol) was added slowly at −78 °C. After stirring for 5 min, 4.0 g (28 mmol) of methyl 2,2-dichloroacetate 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 and filtered, and ether was removed by evaporation. Distillation in a Kugelrohr apparatus (120 °C, ca. 10 mmHg) gave 4.153 g (24 mmol, 60%) of product. ^{1}H NMR ($CDCl_3$, ppm): δ 1.16 (3H, CH_2CH_3, t), 2.46 (2H, $CH_3CH_2CCl_2$, m), 3.89 (3H, OCH_3, s).^{13}C NMR ($CDCl_3$, ppm): δ 8.0, 37.1, 52.8.

(b) Methyl 2,2-Dichloropentanoate was synthesized analogously using propyl iodide. ^{1}H NMR ($CDCl_3$, ppm): δ 1.00 (3H, CH_2CH_3, t), 1.59 (2H, $CH_3CH_2CH_2$, sextet), 2.40 (2H, $CH_2CH_2CCl_2$, m), 3.89 (3H, OCH_3, s). ^{13}C NMR ($CDCl_3$, ppm): δ 11.9, 17.0, 45.6, 52.8, 84.3, 166.6. IR (CCl_4, cm^{-1}): 1748, 1768.

(c) 2,2-Dichlorobutanoic Acid was synthesized from methyl 2,2-dichlorobutanoate according to a literature procedure.[35] ^{1}H NMR ($CDCl_3$): δ (ppm): 1.19 (3H, CH_3CH$_2$, t), 2.47 (2H, $CH_3CH_2CCl_2$, q), ^{13}C NMR ($CDCl_3$, ppm): δ 7.0, 36.1, 83.4, 165.3, IR (CCl_4, cm^{-1}): 1732.

(d) 2,2-Dichloropentanoic Acid was synthesized analogously using methyl 2,2-dichloropentanoate. ^{1}H NMR ($CDCl_3$, ppm): δ 1.00 (3H, CH_2CH_3, t), 1.65 (2H, $CH_3CH_2CH_2$, sextet), 2.41 (2H, $CH_2CH_2CCl_2$, m). ^{13}C NMR ($CDCl_3$, ppm): δ 11.9, 17.1, 45.5, 84.3, 166.6. IR (CCl_4, cm^{-1}): 1734.

(e) 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): δ 13.1, 18.3, 46.6., IR (CCl_4, cm^{-1}): 1779, 1799.

(f) 2,2-Dichlorobutanoyl Chloride and 2,2-Dichloropropanoyl chloride were synthesized analogously from 2,2-dichlorobutanoic acid and 2,2-dichloropropanoic acid, respectively.

(1) 2,2-Dichlorobutanoyl Chloride. ^{1}H NMR ($CDCl_3$, ppm): δ 1.20 (3H, CH_3CH$_2$, t), 2.53 (2H, $CH_3CH_2CCl_2$, q). ^{13}C NMR ($CDCl_3$, ppm): δ 7.0, 36.0, 88.5, 165.5. IR (CCl_4, cm^{-1}): 1773, 1802.

(2) 2,2-Dichloropropanoyl Chloride. ^{1}H NMR ($CDCl_3$, ppm): δ 2.36 (3H, CH_3CCl_2, t). IR (CCl_4, cm^{-1}): 1778, 1795.

(g) *p*-Methoxyphenyl 2,2-Dichloroacetate (1a) was synthesized according to a literature procedure.[6]

(h) *p*-Methoxyphenyl 2,2-Dichloropentanoate (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 3 h 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 colorless 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 CH_2Cl_2/*n*-hexane as the eluent. ^{1}H NMR ($CDCl_3$, ppm): δ 1.07 (3H, CH_3CH$_2$, t), 1.82 (2H, $CH_3CH_2CH_2$, sextet), 2.53 (2H, $CH_2CH_2CCl_2$, m), 3.81 (3H, CH_3O, s), 7.00 (4H, phenyl, AB system).

(i) *p*-Methoxyphenyl 2,2-Dichlorobutanoate (1c) and *p*-Methoxyphenyl 2,2-Dichloropropanoate (1b) were synthesized analogously.

(1) p-Methoxyphenyl 2,2-dichloropropanoate. ^{1}H NMR ($CDCl_3$, ppm): δ 2.43 (3H, CH_3CCl_2, s), 3.85 (3H, CH_3O, s), 7.00 (4H, phenyl, AB-system).

(2) p-Methoxyphenyl 2,2-Dichlorobutanoate. ^{1}H NMR ($CDCl_3$, ppm): δ 1.36 (3H, CH_3CH$_2$, t), 2.58 (2H, $CH_3CH_2Cl_2$, q), 3.81 (3H, CH_3O, s), 7.00 (4H, phenyl, AB-system).

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