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Registry No. **5-c**, 87156-75-0; **5-t**, 87156-76-1; **6**, 33326-56-6; **7-c**, 70388-65-7; **7-t**, 27066-35-9; **8**, 103-29-7; **9**, 95-13-6; **10**, 100-42-5; **11**, 108-88-3; *trans*-cinnamyl benzyl sulfide, 87156-77-2; *trans*-cinnamyl bromide, 26146-77-0; benzyl mercaptan, 100-53-8; triphenyl(3-phenylprop-1-yl)phosphonium bromide, 7484-37-9; triphenylphosphine, 603-35-0; 1-bromo-3-phenylpropane, 637-59-2.

Heat Capacities of Activation for the Neutral Hydrolysis of Two Acyl-Activated Esters in Water-Rich 2-*n*-Butoxyethanol–Water Mixtures. Analysis in Terms of the Pseudo-Phase-Separation Model[1]

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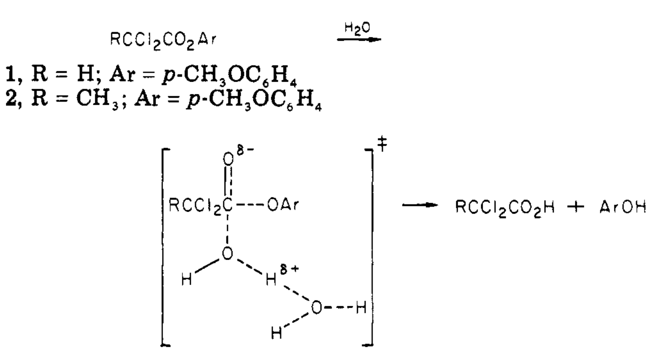
The water-catalyzed hydrolysis of *p*-methoxyphenyl dichloroacetate (1) and 2,2-dichloropropionate (2) in water-rich 2-*n*-butoxyethanol (2-BE)–H_2O exhibits large, *positive* heat capacities of activation (1, $\Delta C_p^{\ddagger} = 224 \pm 51$ cal mol^{-1} deg^{-1}; 2, $\Delta C_p^{\ddagger} = 342 \pm 51$ cal mol^{-1} deg^{-1}; temperature 20–48 °C) at 2 mol % of 2-BE ($n_{H_2O} = 0.98$). These positive $\Delta C_p^{\ddagger}$ values contrast sharply with the negative $\Delta C_p^{\ddagger}$'s found for S_N solvolysis reactions in highly aqueous mixed solvents. By use of a pseudothermodynamic approach, the $\Delta C_p^{\ddagger}$ values as well as positive heat capacities for transfer (ΔC_p^{θ},tr) of two model substrates from water to 2-BE–H_2O are rationalized within the framework of a *pseudo-phase-separation model*. Based on previous thermodynamic and other evidence, this model assumes the onset of microphase separation in 2-BE–H_2O at about $n_{H_2O} = 0.98$ at 25 °C. It is shown that temperature-dependent partitioning of the acyl-activated esters between a water-rich and a cosolvent-rich microphase provides an adequate explanation for the observed heat capacity data. The observed $\Delta C_p^{\ddagger}$ for solvolysis of *tert*-butyl chloride in 2-BE–H_2O at $n_{H_2O} = 0.98$ is also reconcilable with the proposed theory.

Water-catalyzed reactions in highly aqueous mixed solvents often show peculiar kinetic features which presumably reflect the unique solvent structural properties of these reaction media.[2] For example, the pH-independent hydrolysis of *p*-methoxyphenyl dichloroacetate (1) and 2,2-dichloropropionate (2) in 2-*n*-butoxyethanol (2-BE)–H_2O exhibited large and *positive* heat capacities of activation ($\Delta C_p^{\ddagger}$) at a mole fraction of water (n_{H_2O}) of 0.98 (1, $\Delta C_p^{\ddagger} = 224 \pm 51$ cal deg^{-1} mol^{-1}; 2, $\Delta C_p^{\ddagger} = 342 \pm 51$ cal deg^{-1} mol^{-1}).[3] By contrast, S_N solvolyses of a variety of neutral substrates in mixtures of water with a hydrophobic cosolvent invariably show *negative* extremes in $\Delta C_p^{\ddagger}$ in the highly aqueous region.[4,5] In a preliminary report we have argued that the positive $\Delta C_p^{\ddagger}$'s for 1 and 2 did not arise from mixed kinetics or a change in mechanism but probably resulted from hydrophobic interactions between the substrates and 2-BE. In this paper the $\Delta C_p^{\ddagger}$ values for 1 and 2 are analyzed in detail, taking into account recent thermodynamic and other data for the 2-BE–H_2O system which point to the occurrence of a microphase separation at n_{H_2O} ca. 0.98 (25 °C). Within the framework of this *pseudo-phase-separation model* and on employment of a pseudothermodynamic approach, the solvent dependence of $\Delta C_p^{\ddagger}$ can be rationalized. The analysis implies a temperature-dependent partitioning of the ester between the water-rich and cosolvent-rich microphases, leading to positive $\Delta C_p^{\ddagger}$ values, the magnitude depending on the hydrophobicity of the substrate.

Scheme I



1, R = H; Ar = p-$CH_3OC_6H_4$
2, R = CH_3; Ar = p-$CH_3OC_6H_4$

Results and Discussion

The hydrolysis of aryl dichloroacetates has been the subject of several mechanistic studies.[6] The pseudo-first-order rate constants (k_{obsd}) are independent of the pH between at least pH 1 and 5.5, and the rate constants for the water reaction of some esters fall on the same Brønsted plot as the rate constants for other general-base catalysts.[7] The mechanism, formulated in Scheme I, is further sup-

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Table I. Pseudo-First-Order Rate Constants and Thermodynamic Activation Parameters for the Neutral Hydrolysis of 1 and 2 in 2-BE-H_2O at 25 °C[a]

compd	n_{H_2O}	$10^5 k_{obsd}$, s^{-1}	$\Delta G^{\ddagger}$, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1	1.000	307	20.66	7.9	−44
	0.995	235	21.04	7.6	−45
	0.980	36.2	22.15	2.2[b]	−67[b]
	0.950	4.67	23.36	10.4	−44
	0.900	2.63	23.70	10.4	−45
2	1.000	115	21.46	7.8	−46
	0.995	84.6	21.65	7.2	−48
	0.980	6.19	23.20	0.8[c]	−75[c]
	0.950[d]	0.65	24.53	9.5	−50

[a] Containing (6.0-10.0) × 10^{-3} mol kg^{-1} of HCl. [b] $\Delta C_p^{\ddagger}$ = 224 ± 51 cal deg^{-1} mol^{-1}, temperature range 20-48 °C. [c] $\Delta C_p^{\ddagger}$ = 342 ± 51 cal deg^{-1} mol^{-1}, temperature range 20-48 °C. [d] No HCl added because of stability problems of the reaction mixture at pH 2.1. A control experiment showed that the rate constant was the same in the acidic and the neutral media.

ported by large solvent deuterium isotope effects ($k_{H_2O}/k_{D_2O} \approx 3$–4), large negative entropies of activation ($\Delta S^{\ddagger}$ = −35 to −44 eu), and results of proton inventory studies.[8] The question of whether or not the reaction pathway involves a tetrahedral intermediate has not been settled completely, but for our discussion of solvent effects the major point is that the hydrophobicity of the reactants is considerably reduced during the activation process.

Rate constants and activation parameters for the neutral hydrolysis of 1 and 2 in water-rich 2-BE–H_2O are listed in Table I. They pertain to the water reaction since solvolysis in pure 2-BE is extremely slow. For both esters $\Delta G^{\ddagger}$ increases continuously with a decreasing mole fraction of water (n_{H_2O}), but the enthalpy and entropy of activation show mirror-image behavior similar to that found in *t*-BuOH–H_2O.[2b,3,9] However, as noted previously, the Eyring plots exhibit strong curvature at n_{H_2O} = 0.98, the tangent at the curved plots increasing with temperature. On the assumption that $\Delta C_p^{\ddagger}$ is temperature independent, the curves were analyzed in terms of the Valentiner equation[1,3,10] by employing a least-squares procedure. The $\Delta C_p^{\ddagger}$ values thus obtained for 1 ($\Delta C_p^{\ddagger}$ = 224 ± 51 cal deg^{-1} mol^{-1}) and 2 ($\Delta C_p^{\ddagger}$ = 342 ± 51 cal deg^{-1} mol^{-1}) are large and positive and contrast sharply with those for several hydrolysis reactions of neutral substrates in water[4] and aqueous mixtures[5] which are usually between −30 and −150 cal deg^{-1} mol^{-1}. For example, the hydrolysis of *t*-BuCl has been studied in several aqueous mixtures, and $\Delta C_p^{\ddagger}$ exhibits minima in the typically aqueous (TA) mixtures[11] around the solvent composition of maximum hydrophobic hydration.[5] In these cases the behavior of $\Delta C_p^{\ddagger}$ has been rationalized in terms of solvent structural effects. More recently, the minimum in $\Delta C_p^{\ddagger}$ was explained by invoking a modified S_N1 mechanism.[12]

Table II. Solubilities (*m*), Gibbs Free Energies, Enthalpies, and Entropies of Transfer of 3 and 4 from H_2O to 2-BE-H_2O at 25 °C[a]

compd	n_{H_2O}	$10^4 m$, mol kg^{-1}	ΔG_{tr}^{θ}, kcal mol^{-1}	ΔH_{tr}^{θ}, kcal mol^{-1}	ΔS_{tr}^{θ}, eu
3	1.00	29.6	0.00	0.0	0
	0.98	90.1	−0.66	6.5[b]	24[b]
4	1.00	11.9	0.00	0.00	0
	0.98	49.0	−0.84	8.9[c]	33[c]
	0.95	419	−2.11	5.1	24

[a] Containing 10^{-3} mol kg^{-1} of HCl. Standard state 1 mol kg^{-1}. [b] ΔC_p^{θ}, tr = 56 cal deg^{-1} mol^{-1}. [c] ΔC_p^{θ}, tr = 134 cal deg^{-1} mol^{-1}.

In order to interpret our large and positive $\Delta C_p^{\ddagger}$ values, we have considered several effects other than those due to solvation which could contribute to a curvature in the Eyring plot. These are a change in mechanism, a preequilibrium, and mixed kinetics. A change in mechanism at n_{H_2O} = 0.98 is very unlikely, particularly since the esters do not react with 2-BE. A preequilibrium can also be ruled out since it leads to an apparent contribution to $\Delta C_p^{\ddagger}$ which is always negative.[13] The occurrence of mixed kinetics would mean that the reaction takes place via two distinct routes (a and b). The observed heat capacity is then given by[14] eq 1, with $\alpha = k_a/k_b$. The contribution of

$$\Delta C_p^{\ddagger},\text{obsd} = (1/(1+\alpha))\Delta C_p^{\ddagger},\text{a} + (\alpha/(1+\alpha))\Delta C_p^{\ddagger},\text{b} + (\alpha/(1+\alpha)^2)((\Delta H_a^{\ddagger} - \Delta H_b^{\ddagger})^2/RT^2) \quad (1)$$

the first two terms is dependent on the magnitude and on the sign of $\Delta C_p^{\ddagger}$ for the two distinct routes, but the third term is always positive. Therefore, a positive $\Delta C_p^{\ddagger}$,obsd can be observed even if the separate reactions have negative or zero heat capacities of activation. If we try to reproduce our experimental data by the above equation, $\Delta\Delta H^{\ddagger}$ for the two reactions must be about 13 kcal mol^{-1} for 1 and about 15 kcal mol^{-1} for 2, for the case that $\Delta C_p^{\ddagger}$,a = $\Delta C_p^{\ddagger}$,b = 0 and $k_a = k_b$. If we assume negative values for $\Delta C_p^{\ddagger}$,a and $\Delta C_p^{\ddagger}$,b and take $k_a \neq k_b$, then the difference in $\Delta H^{\ddagger}$ must be even larger. These rather unrealistic results indicate that the observed $\Delta C_p^{\ddagger}$ values for 1 and 2 cannot be reconciled with the occurrence of mixed kinetics. Furthermore, it is not easy to see why mixed kinetics are only significant at n_{H_2O} = 0.98 and not at n_{H_2O} = 0.995 or 0.950. In view of the unexpected $\Delta C_p^{\ddagger}$ values for hydrolysis of 1 and 2 in 2-BE–H_2O at n_{H_2O} = 0.98, the hydrolysis of *t*-BuCl ($\Delta C_p^{\ddagger}$ = −83 cal deg^{-1} mol^{-1} in H_2O)[5] was also studied in this 2-BE–H_2O mixture. The Eyring plot shows a small but significant negative deviation from linearity, and fitting the data to the Valentiner equation leads to $\Delta C_p^{\ddagger}$ = −22 cal deg^{-1} mol^{-1} in the temperature range 10–30 °C. The increase in $\Delta C_p^{\ddagger}$ relative to that in water is again in contrast with the decrease in $\Delta C_p^{\ddagger}$ in water-rich *t*-BuOH–H_2O mixtures ($\Delta C_p^{\ddagger}$ = −194 cal deg^{-1} mol^{-1} at n_{H_2O} = 0.95).[5a] This result provides support for the notion that the positive $\Delta C_p^{\ddagger}$'s for 1 and 2 in 2-BE–H_2O at n_{H_2O} = 0.98 are caused by specific effects in the solvent system and not by the special nature of the hydrolysis reaction under study.

In order to arrive at a reasonable interpretation of the peculiar $\Delta C_p^{\ddagger}$'s, solvent effects on the thermodynamic activation parameters were dissected into initial-state and transition-state contributions. Solvent effects on the thermodynamic parameters of the initial state were ob-

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Table III. Solubility of **4** in 2-BE–H_2O at n_{H_2O} = 0.98 in the Two Pseudophases

temp, K	$10^4 S_1$,[a] mol kg^{-1}	$10^4 S_2$,[b] mol kg^{-1}	$10^4 S_{exp}$,[c] mol kg^{-1}	$10^2 \beta$[d]	$10^4 m_1$,[e] mol kg^{-1}	$10^4 m_2$,[f] mol kg^{-1}	α[g]
278.16	8.40	107	9.30	0.9	8.32	0.98	0.11
283.16	10.1	153	13.6	2.5	9.83	3.79	0.28
288.16	12.3	212	20.7	4.3	11.7	9.02	0.44
293.16	14.9	299	32.0	6.0	14.0	18.0	0.56
298.16	17.8	420	49.8	7.9	16.4	33.4	0.67

[a] Solubility in the water-rich microphase with the assumption that S_1 = 1.5 times the observed solubility in pure water. [b] Solubility in the cosolvent-rich microphase. Assumption: S_2 is equal to the observed solubility in 2-BE–H_2O at n_{H_2O} = 0.95. [c] Experimentally observed solubility of **4** in 2-BE–H_2O at n_{H_2O} = 0.98. [d] Weight fraction of the cosolvent-rich microphase, according to eq 4. [e] Amount of 4 in the water-rich microphase; $m_1 = (1 - \beta)S_1$. [f] Amount of 4 in the cosolvent-rich microphase; $m_2 = \beta S_2$. [g] Fraction of **4** in the cosolvent-rich microphase; $\alpha = m_2(m_1 + m_2)^{-1}$.

tained via temperature-dependent solubility measurements on the model substrates *p*-nitrophenyl acetate (**3**) and *p*-nitrophenyl propionate (**4**).[15] From these data, the Gibbs free energies, enthalpies, and entropies of transfer were calculated (Table II). Both the enthalpy and entropy of the solutes increase upon going to the aqueous mixtures. At n_{H_2O} = 0.98 *positive* heat capacities of transfer (ΔC_p^{θ},tr) were observed which were obtained by fitting the solubilities to eq 2, with ΔC_p^{θ},tr = RB. Herein, $m_{2\text{-BE}}$ and m_{H_2O}

$$\ln (m_{2\text{-BE}}/m_{H_2O}) = AT^{-1} + B \ln T + C \qquad (2)$$

are the solubilities in 2-BE–H_2O and in water, respectively, both expressed in moles per kilogram. At 5 mol % of 2-BE there is no measurable heat capacity of transfer for **4**. In contrast to the situation for water-rich *t*-BuOH–H_2O,[1,2] the positive ΔC_p^{θ},tr cannot be rationalized in terms of hydrophobic interaction between the solute and the organic solvent component. Since solvent structure in 2-BE–H_2O at n_{H_2O} = 0.98 is rapidly broken down upon increasing temperature,[17] hydrophobic interaction between the esters and 2-BE will decrease with temperature. This will lead to a lower enthalpy of transfer at higher temperatures and, consequently, to a negative heat capacity of transfer.

The $\Delta C_p^{\ddagger}$ and ΔC_p^{θ},tr values will now be rationalized in terms of a pseudo-phase separation model, assuming that the 2-BE–H_2O system consists of a water-rich (WR) microphase and a cosolvent-rich (CR) microphase which start to form at about n_{H_2O} = 0.98. The existence of microphases was strongly argued by Desnoyers et al.[17b] on the basis of thermodynamic data for the 2-BE–H_2O system over a large composition range. These microphases do not represent separate phases but are "aggregates" of the hydrophobic cosolvent. The formation of local structures, which will be rather similar to clathrate hydrates, is also suggested by results of spin-lattice relaxation time,[18] ultrasonic absorption,[19] and Rayleigh scattering[20] measurements. All these techniques show that large structural changes occur in 2-BE–H_2O at about 2 mol % (1 mol kg^{-1}) of 2-BE. We contend that the concentration at which microphase separation takes place may be viewed as a "critical micellar concentration" (cmc) which is found for surfactant molecules. For nonionic surfactants the cmc decreases with temperature,[21] and the association number increases with temperature.[22] Solubilization measurements of apolar solutes in these surfactant solutions showed that the amount of solubilizate increases very strongly with temperature.[21] This suggests that the increasing association number provides the micelle more and more with the properties of an apolar solvent system. Assuming that 2-BE–H_2O at n_{H_2O} = 0.98 behaves in a similar manner, it is likely that at higher temperatures more of the CR microphase will be formed. The "cmc" at 25 °C can be estimated on the basis of experimental data for related molecules which do form micelles.[22,23] Starting from the cmc of n-$C_8H_{17}OCH_2CH_2OH$, we estimate a "cmc" for 2-BE of 0.52 mol kg^{-1}. Variation of the number of (CH_2CH_2O) groups has only a small effect on the cmc.[21] Hence we assume that at 25 °C the formation of significant amounts of the microphase will start at a 2-BE concentration of ca. 0.6–0.7 mol kg^{-1} (n_{H_2O} = 0.988–0.986), in accordance with the observation that at 2-BE concentrations below 0.7 mol kg^{-1} no excess absorption was observed in Nishikawa's ultrasonic absorption measurements.[19] Thus, at n_{H_2O} = 0.98 (1 mol kg^{-1} of 2-BE) relatively little of the microphase will be formed, and this fraction is expected to increase with temperature. The composition of the water-rich microphase will not change significantly, and the solubility of an apolar solute in this phase will increase following the normal temperature effect as reflected in the enthalpy of solution ($H_{sol}^{\theta} = -\delta R \ln m/\delta T^{-1}$). In the cosolvent-rich microphase, which can be compared with an apolar solvent, the enthalpy of solution will be higher than in water.[24] This means that as a consequence of the normal temperature effect, the increase in solubility in this microphase with increasing temperature will already be higher than in water. As argued before, the fraction of the cosolvent-rich microphase will increase with temperature, and, consequently, there will be a concomitant faster increase of the solubility with temperature. This will then result

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(15) Previously it has been argued[6b] that the solvatation behavior of aryl acetates is probably not significantly different from that of aryl dichloroacetates. The *p*-methoxyphenyl esters, which would be more suitable model systems, could not be used because of the fairly high solubility of *p*-methoxyphenyl acetate in water and because of the low melting point of this ester which leads to the formation of oils and the accompanying separation problems. Although the hydrophobicity of **3** and **4** is smaller than that of **1** and **2**, the difference in the Rekker *f* value[16] between the model acetate and propionate is the same as that between the corresponding dichloroacetate and dichloropropionate. Therefore, the trend in the transfer parameters for the model substrates as a function of solvent composition will provide a good indication of the different effects of hydrophobic interactions on **1** and **2**.

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in an apparent increase in the enthalpy of solution, expressed in an *apparent positive* heat capacity of transfer from water to 2-BE–H_2O at n_{H_2O} = 0.98. The positive ΔC_p^{-},tr for **4** can be rationalized in terms of this pseudo-two-phase model. In Table III we have separated the observed solubility (S_{exp}) into the amount of the solute in the water-rich microphase (m_1) and in the cosolvent-rich microphase (m_2). These solubilities were calculated by assuming that the solubility in the water-rich microphase (S_1, expressed in moles per kilogram of this microphase) is 1.5 times the observed solubility in pure water, and that in the cosolvent-rich microphase the solubility (S_2, expressed in moles per kilogram of this microphase) is equal to that in 2-BE–H_2O at n_{H_2O} = 0.95. Although we are well aware of the possibility that the assumed values may differ from the (unknown) real values, it seems justifiable to draw qualitative conclusions from these data because changes in the solubilities in the two distinct microphases will only influence the absolute values of the solubilities in the two distinct microphases, but it can be shown that the trend in these values upon changing the temperature will not be affected. From the experimentally observed solubility (S_{exp}) and the solubilities in the two microphases (S_1 and S_2) the weight fractions of the cosolvent-rich microphase (β) were calculated from eq 3 which can be rewritten as

$$S_{exp} = (1 - \beta)S_1 + \beta S_2 \tag{3}$$

eq 4. The data in Table III show that in order to explain

$$\beta = \frac{S_{exp} - S_1}{S_2 - S_1} \tag{4}$$

the experimental solubilities of **4** (as a function of temperature) in 2-BE–H_2O at n_{H_2O} = 0.98, the fraction of the cosolvent-rich microphase (β) has to increase with temperature in a rather constant way from 0.9% at 5 °C to 7.9% at 25 °C. This increase of β is consistent with a supposed decrease of the cmc with temperature.

From these values we can calculate the amount of the solute in the water-rich microphase ($m_1 = (1 - \beta)S_1$) and in the cosolvent-rich microphase ($m_2 = \beta S_2$). The fraction of the solute in the cosolvent-rich microphase (α) is given by $\alpha = m_2(m_1 + m_2)^{-1}$. The computed values for α, given in Table III, show that the fraction of the solute in the 2-BE-rich microphase increases with temperature. However, at higher temperatures the increment becomes less. This indicates that although the weight fraction of the cosolvent-rich microphase (β) *increases* in a rather constant way, leading to a *fast increase* in the solubility and an *apparent positive* ΔC_p^{θ},tr, the increase of the fraction of the solute in this microphase (α) *decreases* with increasing temperature. We note that the latter behavior of α is necessary in order to account for the experimental heat capacity data. In the case of a less hydrophobic substrate, like **1**, the increase of the solubility in the cosolvent-rich microphase will be less, leading to a lower ΔC_p^{θ},tr and also to a smaller fraction of the solute in the cosolvent-rich microphase as is borne out in practice.

We now turn to the analysis of the kinetic data for hydrolysis of **1** and **2** in 2-BE–H_2O. In the CR microphase the pseudo-first-order rate constants for the hydrolysis of the acyl-activated esters will be reduced as compared with those in the water-rich microphase because the initial state will be stabilized, and simultaneously the transition state will be destabilized. Furthermore, the water concentration is lower in this microphase. For an interpretation of the kinetic data within the framework of the pseudo-phase-separation model we need realistic estimates for the pseudo-first-order rate constants and the enthalpies of activation pertaining to each of the microphases. The rate constant in the water-rich microphase (k_1) was chosen on basis of the following reasoning. The rate constants in pure water and at n_{H_2O} = 0.995 (0.27 mol kg^{-1} of 2-BE) are known. As argued above, the microphase separation will start at ca. 0.7 mol kg^{-1} of 2-BE. If we assume a linear relation between $\Delta G^{\ddagger}$ and the molality of 2-BE, k_1 at 25 °C can be calculated for both substrates: $k_1(\mathbf{1}) = 152 \times 10^{-5}$ s^{-1} and $k_1(\mathbf{2}) = 50 \times 10^{-5}$ s^{-1}. The enthalpy of activation ($\Delta H_1^{\ddagger}$) was taken as 7 kcal mol^{-1} for both substrates (compare Table I). The pseudo-first-order rate constants in the cosolvent-rich microphase (k_2) are more difficult to estimate. At n_{H_2O} = 0.95 and 0.90, the mole fractions at which we expect that the substrate is almost completely dissolved in the cosolvent-rich microphase, the pseudo-first-order rate constants for the hydrolysis of **1** are not equal. At n_{H_2O} = 0.90 the rate constant is reduced, possibly as a result of the reduced water concentration and a change in the microenvironment of the substrate. At higher 2-BE concentration the cosolvent-rich microphase may consist of larger aggregates, leading to a more apolar environment for the substrate in this microphase and, consequently, to a lower pseudo-first-order rate constant at n_{H_2O} = 0.90. The rate decrease at n_{H_2O} = 0.90 may also originate from a reduced contribution of a small fraction of the substrate in the water-rich microphase to the overall rate constant. This fraction will be smaller at n_{H_2O} = 0.90. If this is the valid explanation for the rate decrease at higher 2-BE concentration, k_{obsd} at n_{H_2O} = 0.90 will be a more appropriate estimate for the rate constant in the cosolvent-rich microphase at n_{H_2O} = 0.98 (k_2). However, if the first assumption, namely, a lower water concentration and a more apolar environment for the substrate at n_{H_2O} = 0.90, is true, then k_2 should even by higher than k_{obsd} at n_{H_2O} = 0.95. Since we cannot differentiate between both possibilities, we have taken for k_2 a value which is rather similar to k_{obsd} at n_{H_2O} = 0.95; $k_2(\mathbf{1}) = 5.0 \times 10^{-5}$ s^{-1} and $k_2(\mathbf{2}) = 0.7 \times 10^{-5}$ s^{-1}, both at 25 °C. The enthalpy of activation in the cosolvent-rich microphase ($\Delta H_2^{\ddagger}$) was assumed to be 10 kcal mol^{-1}, comparable with $\Delta H^{\ddagger}$ at n_{H_2O} = 0.95 and 0.90 (Table I). The experimental rate constants at n_{H_2O} = 0.98 (k_{obsd}) and the rate constants in the two microphases (calculated from k(25 °C) and $\Delta H^{\ddagger}$) are given at different temperatures in Tables IV and V for **1** and **2**, respectively.

Table IV. Calculated Rate Constants[a] for Hydrolysis of 1 in 2-BE–H_2O at n_{H_2O} = 0.98 within the Framework of the Pseudo-Phase-Separation Model

temp, K	$10^5 k_1$,[b] s^{-1}	$10^5 k_2$,[c] s^{-1}	$10^5 k_{obsd}$,[d] s^{-1}	α[e]
293.25	123	3.71	33.7	0.75
297.95	151	4.94	36.4	0.78
303.06	187	6.68	39.3	0.82
308.81	237	9.27	45.4	0.84
314.61	298	12.8	54.5	0.85
320.96	379	17.9	68.0	0.86

[a] $\Delta H_1^{\ddagger}$ = 7 kcal mol^{-1}, k_1 (25 °C) = 152×10^{-5} s^{-1}, $\Delta H_2^{\ddagger}$ = 10 kcal mol^{-1}, and k_2 (25 °C) = 5×10^{-5} s^{-1}. [b] Rate constant in the water-rich microphase. [c] Rate constant in the cosolvent-rich microphase. [d] Observed rate constants at n_{H_2O} = 0.98. [e] Fraction of the substrate in the cosolvent-rich microphase as calculated according to eq 5.

The values for α (the fraction of the substrate in the cosolvent-rich microphase) have been calculated for different temperatures by fitting k_{obsd} to eq 5 (Tables IV and

$$k_{obsd} = (1 - \alpha)k_1 + \alpha k_2 \tag{5}$$

V). The α values indicate that at 25 °C about 80% of **1**

Table V. Calculated Rate Constants for Hydrolysis of 2 in 2-BE–H_2O at $n_{H_2O} = 0.98$ within the Framework of the Pseudo-Phase-Separation Model[a,b]

temp, K	$10^5 k_1$, s^{-1}	$10^5 k_2$, s^{-1}	$10^5 k_{obsd}$, s^{-1}	α
293.25	40.4	0.519	6.14	0.86
297.95	49.6	0.619	6.15	0.89
303.12	61.7	0.938	6.55	0.91
308.81	77.8	1.30	7.41	0.92
314.66	98.1	1.79	9.04	0.93
320.96	125	2.50	11.4	0.93

[a] $\Delta H_1^{\ddagger} = 7$ kcal mol^{-1}, k_1 (25 °C) = 50×10^{-5} s^{-1}, $\Delta H_2^{\ddagger} = 10$ kcal mol^{-1}, and k_2 (25 °C) = 0.7×10^{-5} s^{-1}. [b] See footnotes *b–e* in Table IV.

and about 90% of **2** should be incorporated into the cosolvent-rich microphase to obtain a good reproduction of the experimental data. From the solubility measurements of **4** we have concluded that at this temperature about 70% of the solute will be in this microphase (Table III). The trend in α is in accordance with the differences in hydrophobicity as indicated by Rekker *f* values[16] (f(**1**) = 2.83, f(**2**) = 3.36, f(**4**) = 2.48). The α values also reflect another trend which was found in the solubility measurements, namely, that the increase of the fraction of the substrate in the cosolvent-rich microphase diminishes upon going to higher temperatures.

Several assumptions are involved in our estimation of k_1 and k_2 which are difficult to verify. Changes in these rate constants have the following effects. For example, if $k_1(1) = 180 \times 10^{-5}$ s^{-1} instead of 152×10^{-5} s^{-1} and $k_2(1)$ is kept constant at 5.0×10^{-5} s^{-1}, we obtain the data listed in Table VI (supplementary material). It shows that this rather large change in k_1 has only a minor effect on the absolute value of α, and the trend in α with variation of the temperature is the same. The increase of k_1 would result from a decrease of the 2-BE concentration in the water-rich microphase, in other words, a lower 2-BE concentration at which the "phase separation" starts. Adopting the linear relation between $\Delta G^{\ddagger}$ and the molality of 2-BE in the water-rich microphase, the "phase separation" starts at 0.54 mol kg^{-1} of 2-BE for $k_1(1) = 180 \times 10^{-5}$ s^{-1} (for $k_1(1) = 152 \times 10^{-5}$ s^{-1} the "phase separation" starts at 0.7 mol kg^{-1} of 2-BE). If $k_1(1)$ is kept constant at 152×10^{-5} s^{-1} and $k_2(1) = 2.5 \times 10^{-5}$ s^{-1} instead of 5.0×10^{-5} s^{-1}, we obtain the data listed in Table VII (supplementary material). It shows that α becomes only slightly smaller on using the lower value for k_2. These calculations reveal that the applied changes in k_1 and k_2 have only a minor effect on the absolute value of α and, most importantly, that the *trend* in α with variation of temperature remains the same. Thus, within the framework of the pseudo-phase-separation model, knowledge of the exact values for k_1 and k_2 is not crucial for the explanation of the experimental rate constants in 2-BE–H_2O at $n_{H_2O} = 0.98$.

In conclusion, we submit that the *positive* $\Delta C_p^{\ddagger}$ values, which are "hidden" in k_{obsd}, can be explained by taking into account *a temperature dependent partitioning of the substrate between the two microphases*. The magnitude of $\Delta C_p^{\ddagger}$ will be largely determined by the hydrophobicity of the substrate. A more hydrophobic substrate has a larger fraction in the cosolvent-rich microphase, and this leads to a higher value for $\Delta C_p^{\ddagger}$.

The above theory also explains the absence of a $\Delta C_p^{\ddagger}$ at the other mole fractions. At $n_{H_2O} = 0.995$ the concentration of 2-BE is too low to form a cosolvent-rich microphase. At this solvent composition, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ will be smaller than for hydrolysis in water as a result of hydrophobic interactions between the substrate and 2-BE. This effect will be larger for **2** than for **1**. At $n_{H_2O} = 0.95$ and $n_{H_2O} = 0.90$ the substrate will be almost completely dissolved in the cosolvent-rich microphase, and again no deviation from linearity will be observed in the Eyring plot.

For hydrolysis of *t*-BuCl in 2-BE–H_2O, $\Delta C_p^{\ddagger}$ is increased by 61 cal deg^{-1} mol^{-1} upon going from water to $n_{H_2O} = 0.98$ (vide supra). This rather small change in $\Delta C_p^{\ddagger}$ as compared with that for the hydrolysis of **1** and **2**, is most likely a consequence of the relatively low hydrophobicity of *t*-BuCl (Rekker *f* value[16] is 2.32) which decreases the preference of the substrate to dissolve in the cosolvent-rich microphase and leads to a smaller range in the apparent heat capacity. In addition, it may well be that the solvolysis of *t*-BuCl in the 2-BE-rich microphase exhibits a negative heat capacity, as was found previously by Viana et al.[25] for the solvolysis of *t*-BuCl in *tert*-butyl alcohol.

Recently, Kanerva and Euranto[26] reported large and positive $\Delta C_p^{\ddagger}$ values for the neutral hydrolysis of chloromethyl dichloroacetate in 2-BE–H_2O at $n_{H_2O} = 0.98$ in the temperature range 25–45 °C. Interestingly, the Eyring plot is S shaped at lower temperatures, indicating a change from a positive $\Delta C_p^{\ddagger}$ (25–45 °C) to a negative $\Delta C_p^{\ddagger}$ (2.5–20 °C). These results can be rationalized in terms of the pseudo-phase-separation model. At lower temperatures the "phase-separation" starts at higher 2-BE concentrations, and thus, there will be hardly any cosolvent-rich microphase. This leads to a reduced or no apparent positive contribution to the negative $\Delta C_p^{\ddagger}$, which one would expect on basis of the negative $\Delta C_p^{\ddagger}$ in water and at $n_{H_2O} = 0.988$. At $n_{H_2O} = 0.975$ the Eyring plot is also S shaped. However, the change from a positive to a negative $\Delta C_p^{\ddagger}$ is found at about 7.5 °C. This is in complete accord with the above explanation. We anticipate that further studies of rate processes in typically aqueous solutions,[11] showing nonideal thermodynamic behavior, will reveal more examples of dramatic changes of $\Delta C_p^{\ddagger}$ in the water-rich solvent composition range.

Experimental Section

Materials. Compound **1** was synthesized as described by Engbersen[6b] by using freshly distilled dichloroacetyl chloride. Compound **2** was prepared from 2,2-dichloropropanoic acid.

2,2-Dichloropropanoic Acid. Through a refluxing mixture of 54.3 g (0.5 mol) of 2-chloropropanoic acid and 1.7 g (12 mmol) of PCl_3 was bubbled chlorine for ca. 4 h. During the reaction a few small portions of PCl_3 (~0.7 g, 5 mmol) were added, and the temperature raised from 120 to 190 °C. After the chlorination was stopped, about 2 mL of water was added, and the yellow-brown solution was distilled (84–86 °C, 11 mmHg) affording a colorless liquid. The ^1H NMR spectrum indicated that the distillate was a mixture of 2-chloropropanoic acid [6%; δ 1.77, (d, 3 H), 4.48 (q, 1 H)], 2,2-dichloropropanoic acid [73%; δ 2.35 (s, 3 H)], 2,2,3-trichloropropanoic acid [11%, δ 6.10 (s, 2 H)], and 2,2,3,3-tetrachloropropanoic acid (10%; δ 6.10, s, 1 H). For purification this mixture of acids was converted into the dicyclohexylamine salts by dissolving it in 150 mL of acetonitrile and adding dicylohexylamine until the solution remained alkaline. The salts were isolated and recrystallized from 96% EtOH. After one recrystallization hardly any mono- and trichloro-substituted compounds were present. Only contamination with the salt of the tetrachloro acid gave further complications. After repeated recrystallizations a few percent remained in the precipitate. For recovery of the acid, 24.0 g (0.074 mol) of the dicyclohexylamine salt was added to 200 mL of water and 100 mL of ether. This solution was acidified with concentrated HCl. More water was added in order to dissolve the formed dicyclohexylammonium

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chloride. The layers were separated, the aqueous layer was extracted with ether, and the combined ethereal layers were dried over $MgSO_4$. After evaporation of the solvent 9.38 g (0.053 mol) of 2,2-dichloropropanoic acid was obtained contaminated with about 2% of 2,2,3,3-tetrachloropropanoic acid.

***p*-Methoxyphenyl 2,2-Dichloropropionate (2).** A mixture of 6.87 g (0.048 mol) of 2,2-dichloropropanoic acid (containing about 2% of 2,2,3,3-tetrachloropropanoic acid) and 6.5 g (0.055 mol) of $SOCl_2$ was refluxed for 3 h. Distillation of the reaction mixture under reduced pressure (50 °C at ca. 100 mmHg) gave 3.8 g (0.024 mol) of 2,2-dichloropropanoyl chloride. The chloride was converted into **2** by following the same procedure as described for **1** (yield 86%). The ester was purified by using HPLC [silica gel (60 mesh) column, 5 μm; CH_2Cl_2/*n*-hexane, 50:50]: mp 25.0–26.4 °C; ^1H NMR ($CDCl_3$, Me_4Si) δ 2.38 (3 H, s), 3.72 (3 H, s), 6.70–7.15 (4 H, m); IR 1760 cm^{-1} (C=O). Anal. Calcd for $C_{10}H_{10}Cl_2O_3$: C, 48.22; H, 4.05; Cl, 28.47. Found: C, 48.09; H, 4.05; Cl, 28.34.

Compound **3** was synthesized by following the same procedure as used for **1**. The ester (mp 77.0–77.7 °C, lit.[27] mp 79–80 °C) was recrystallized from 60% EtOH. Ester **4** was synthesized according to the procedure of Funasaki.[28] Recrystallization from 80% EtOH–H_2O gave crystals with a melting point of 61.7–62.2 °C (lit.[29] mp 62–63 °C).

The water used in the kinetic and the solubility measurements was demineralized and distilled twice in an all-quartz distillation unit. *t*-BuOH was obtained from Merck and 2-*n*-butoxyethanol from Aldrich. Both solvents were of the highest grade available and were used as such. The solvent mixtures employed in the experiments were all made up by weight. The cosolvent was added to the appropriate amount of water containing 10^{-2} mol kg^{-1} of HCl in the kinetic experiments and 10^{-3} mol kg^{-1} of HCl in the solubility measurements.

Solubility measurements (5–30 °C) were carried out as follows. To 5 mL of the solvent mixture under study in a Slenk vessel was added 5–50 mg of the solute (**3** or **4**). The mixture was magnetically stirred in a thermostated bath (±0.05 °C) for ca. 6 h in order to obtain a saturated solution. This solution was filtered under pressure. After dilution with water containing 10^{-3} mol kg^{-1} of HCl, the concentration of the solute was determined in duplicate by measuring the absorbance at 273 nm (the absorption maximum of **3** and **4**). A correction was made for the absorbance of *p*-nitrophenol, which was formed by hydrolysis. The concentrated solution was diluted until the absorbance at 273 nm was between 0.5 and 1.0. The original solution was stirred for an additional 2 h, after which the concentration of the solute was again determined in duplicate. If any discrepancy was observed between both sets of measurements, the procedure was repeated a third time.

The solubilities were reproducible to within 1%, and they were determined at five or six temperatures between 5 and 30 °C. The Gibbs free energy, enthalpy, and entropy of transfer were determined by standard methods.[2b] Estimated errors in $\Delta C_{tr}{}^{\theta}$, $\Delta H_{tr}{}^{\theta}$, and $\Delta S_{tr}{}^{\theta}$ are 0.02 kcal mol^{-1}, 0.3 kcal mol^{-1}, and 1 eu, respectively. Transfer parameters for transfer of a water molecule can be neglected[30] relative to those for transfer of **1** and **2**.

Kinetic Measurements. Reaction rates and thermodynamic activation parameters for hydrolysis of **1** and **2** were determined as outlined previously.[31] The solvolysis rates of *t*-BuCl in 2-BE–H_2O were determined conductometrically by using a Wayne–Kerr Autobalance Universal Bridge B642 connected with a Philips P.W. 9512/01 electrode (cell constant $C = 0.71$ cm^{-1}). To 11 mL of the neutral solvent mixture was added 22 μL of a 0.1 mol kg^{-1} HCl solution to obtain a suitable starting conductivity. The reaction medium was thermostated (±0.01 °C), and 3–10 μL of a concentrated solution of t-BuCl in acetonitrile was added (resulting in a substrate concentration between 0.8×10^{-4} and 2.0×10^{-4}M). The reactions were followed for at least 5 half-lives, and from the change in conductivity (recorded with a Kipp recorder), the rate constants were calculated by using the Guggenheim method. The rate constants were determined at nine temperatures between 15 and 35 °C and could be reproduced within 0.7%.

The estimated errors in ΔG^{*}, ΔH^{*}, and ΔS^{*} are 0.02 kcal mol^{-1}, 0.2 kcal mol^{-1}, and 1 eu, respectively.

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Supplementary Material Available: Tables VI and VII containing calculated rate constants for hydrolysis of **1** (2 pages). Ordering information is given on any current masthead page.

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Effect of Seven-Membered Ring Fusion on Thermal Pericyclic Processes of Vinylallenes and Other Seco Steroids Related to *A*-Homovitamin D[1]

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Reaction of the allenylcopper species **10** and iodo ketone **13** produced a 2.4:1 mixture of *A*-homovinylallenones **1c** (6*R*) and **2c** (6*S*). The absolute configurations of **1c** (6*R*) and **2c** (6*S*) were assigned by comparison of their ^{13}C NMR and ^1H NMR spectra to the six- (**1b** and **2b**) and five-membered-ring (**1a** and **2a**) vinylallenes. Thermolysis of **1c** (100 °C, 3 h) yielded **3c** (12%), **14** and **15** (12%), **16** (25%), **17** (24%), and **18** (10%). A similar distribution was obtained for **2c**: **3c** (12%), **14** and **15** (16%), **16** (24%), **17** (24%), and **18** (16%). The thermal rearrangements of the *A*-homovinylallenes **1c** and **2c** occur under much milder conditions than the previously studied six- (**1b** and **2b**) and five-membered-ring (**1a** and **2a**) vinylallene series, and the product distributions differ significantly.

Vitamin D type vinylallenes (**1** and **2**, Scheme I) undergo competitive thermal [1,5]-sigmatropic shifts to afford *E* (**3**) or *Z* (**4**) intermediate trienes. Thermal studies of the five- (**1a** and **2a**) and six-membered (**1b** and **2b**) A-ring vinylallene ketones have revealed that the required thermal

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