(6) J. Z. Gougoutas, *Pure Appl. Chem.*, **27**, 305 (1971).
(7) I. C. Paul and D. Y. Curtin, *Acc. Chem. Res.*, **6**, 217 (1973).
(8) S. R. Byrn, *J. Pharm. Sci.*, **65**, 1 (1976).
(9) A. E. Jungk, M. Luwish, S. Pinchas, and G. M. J. Schmidt, *Isr. J. Chem.*, **16**, 308 (1977).
(10) J. C. Bellows, P. N. Prasad, E. M. Monberg, and R. Kopelman, *Chem. Phys. Lett.*, **54**, 439 (1978).
(11) J. C. Bellows and P. N. Prasad, *J. Chem. Phys.*, **66**, 625 (1977); **67**, 5802 (1977).
(12) P. Georgopoules and J. B. Cohen in "Modulated Structures—1979", J. M. Cowley, J. B. Cohen, M. B. Salamon, and B. J. Wuensch, Eds., American Institute of Physics, New York, 1979, p 21.
(13) B. Dorner and R. Comes in "Dynamics of Solids and Liquids by Neutron Scattering", S. W. Lovesey and T. Springer, Eds., Springer-Verlag, West Berlin and Heidelberg, 1977, p 127, and references therein.
(14) C. N. Sukenik, J. A. P. Bonapace, N. S. Mandel, P. Y. Lau, G. Wood, and R. G. Bergman, *J. Am. Chem. Soc.*, **99**, 851 (1977).
(15) A. Gavezzotti and M. Simonetta, *Nouv. J. Chim.*, **2**, 69 (1978).
(16) Alfred P. Sloan Fellow.

Kaddi Dwarakanath, Paras N. Prasad*[16]
Department of Chemistry
State University of New York at Buffalo
Buffalo, New York 14214

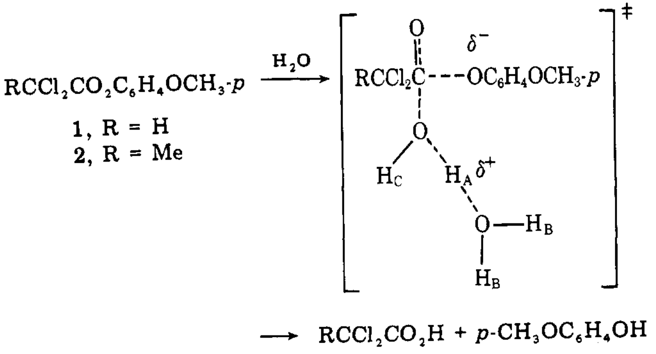
Received January 14, 1980

Hydrolysis of Two Acyl Activated Esters in Water-Rich 2-*n*-Butoxyethanol-Water Mixtures. Effects of Hydrophobic Interactions on Enthalpies, Entropies, and Heat Capacities of Activation[1]

Sir:

Hydrophobic association in aqueous media is of fundamental importance in (bio)chemistry, but the origin of the phenomenon is still not well understood.[2] For many organic reactions in typically aqueous (TA) solutions,[3] there is now ample evidence that the peculiar behavior of thermodynamic activation parameters (such as $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, $\Delta V^{\ddagger}$, and $\Delta C_p^{\ddagger}$) has its origin predominantly in effects due to hydrophobic interactions.[4] Herein we report the observation of large, positive heat capacities of activation ($\Delta C_p^{\ddagger}$) for the neutral hydrolysis of *p*-methoxyphenyl dichloroacetate (**1**) and 2,2-dichloropropionate (**2**) in 2-*n*-butoxyethanol (2-BE)-H_2O at n_{H_2O} = 0.98. These *positive* maxima contrast sharply with the *negative* extrema in $\Delta C_p^{\ddagger}$ which are invariably conjoined with a variety of solvolyses (mainly of the S_N type) of neutral substrates in TA solutions.

The pH-independent pathway for hydrolysis of **1** and **2** involves a water-catalyzed nucleophilic attack of water on the ester carbonyl.[5] Recently, further support for this mechanism



has been provided by the results of proton inventory studies[6] which show that three protons (H_A, H_B's) contribute to the overall isotope effect.

Recent studies by Desnoyers et al.[7] of the binary system 2-BE-H_2O have revealed that the concentration and temperature dependence of the apparent molal heat capacity and the apparent molal volume are those expected for a TA solution. In fact they are rather similar to those of *t*-BuOH-H_2O, but the various transitions are more pronounced. The sharp peaks in the thermodynamic quantities at about n_{H_2O} = 0.98 are even reminiscent of those of a pseudomicrophase transition and seem to be consistent with a clathrate model for hydrophobic hydration and interaction.[7] In view of these challenging solvent properties, we have measured rates and thermodynamic activation parameters for the neutral hydrolysis of **1** and **2** in this medium (Table I). Notice that $\Delta G^{\ddagger}$ increases continuously with decreasing n_{H_2O} but that $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ exhibit mirror-image behavior and pass through extrema near n_{H_2O} = 0.98. Similar behavior is found for hydrolysis in *t*-BuOH-H_2O,[5c,8] but there is one surprising difference. Whereas plots of $-\ln (kT^{-1})$ vs. T^{-1} show straight lines (with slope $\Delta H^{\ddagger}R^{-1}$) in pure water and at n_{H_2O} = 0.95, there is a strong curvature[9] in these plots (portrayed for **2** in Figure 1) at the "magic mole fraction" in 2-BE-H_2O (n_{H_2O} = 0.98). Analysis in the usual way[10] yields large and *positive* heat capacities of activation: for **1**, $\Delta C_p^{\ddagger} = 224 \pm 51$ cal deg^{-1} mol^{-1}, and for **2**, $\Delta C_p^{\ddagger} = 342 \pm 51$ cal deg^{-1} mol^{-1}. These changes of $\Delta C_p^{\ddagger}$ with n_{H_2O} are *opposite* in sign to those found previously for a number of solvolytic reactions (largely S_N1 or S_N2) in TA solutions.[10,11] Whatever the interpretation of the negative

Table I. Neutral Hydrolysis of **1** and **2** in 2-*n*-Butoxyethanol-H_2O Mixtures (25 °C)[a]

compd	n_{H_2O}	$k_{obsd} \times 10^5$, s^{-1}	$\Delta G^{\ddagger}$, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	temp range, °C
1	1.000	307	20.88	7.9	−44	25-48
1	0.995	235	21.04	7.6	−45	25-48
1	0.980	36.2	22.15	2.2[b]	−67[b]	20-48
1	0.950	4.67	23.36	10.4	−44	24-46
1	0.900	2.63	23.70	10.7	−44	25-48
2	1.000	115	21.46	7.8	−46	25-48
2	0.995	84.6	21.65	7.2	−48	26-48
2	0.980	6.19	23.20	0.8[c]	−75[c]	20-48
2	0.950	0.65	24.53	9.5	−50	30-45

[a] Determined in the presence of 6.0-10.0 × 10^{-3} M HCl to avoid hydroxide-ion catalysis. All rate constants pertain to water reactions since the solvolysis of **1** and **2** in 2-BE is extremely slow. [b] $\Delta C_p^{\ddagger} = 224 \pm 51$ cal deg^{-1} mol^{-1}. [c] $\Delta C_p^{\ddagger} = 342 \pm 51$ cal deg^{-1} mol^{-1}.

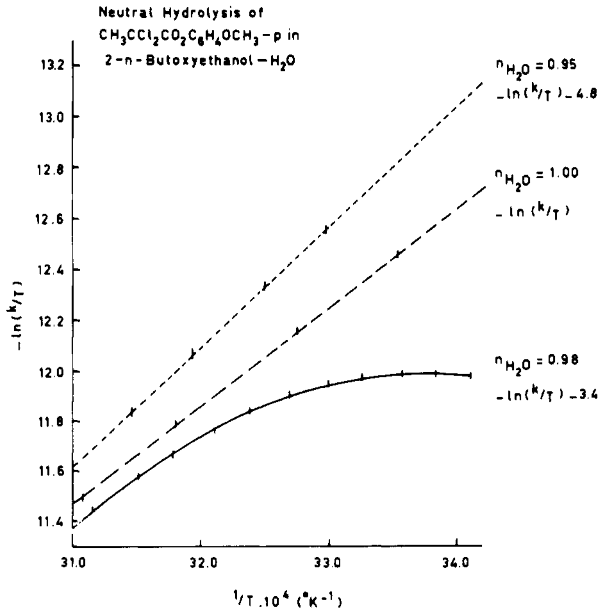


Figure 1. Plots of $-\ln (k/T)$ vs. $(1/T)$ for the neutral hydrolysis of **2** in 2-*n*-butoxyethanol-H_2O. The experimental error in $\ln (k/T)$ is indicated by the lengths of the vertical stripes.

0002-7863/80/1502-4256$01.00/0

extrema in $\Delta C_p^{\ddagger}$ for these reactions might be,[12] our positive heat capacities of activation at $n_{H_2O} = 0.98$ do accord with the occurrence of strong hydrophobic interaction between the substrate and 2-BE.[13] It is well known that hydrophobic hydration of relatively nonpolar solutes like **1** and **2** in water is accompanied by large and positive heat capacities.[2,3,14,15] Hence, hydrophobic interaction, implying destructive overlap of the hydrophobic hydration envelopes of the solute and the cosolvent,[16] will give rise to negative heat capacities. This effect will be much stronger for the nonpolar initial state than for the polar transition state. In TA solutions of extreme heterogeneity, like 2-BE–H_2O, the overall result will be a positive maximum in $\Delta C_p^{\ddagger}$ at the solvent composition of maximum hydrophobic hydration ($n_{H_2O} = 0.98$). In addition, the maximum in $\Delta C_p^{\ddagger}$ will be most pronounced for the most hydrophobic substrate (**2**) as is borne out by experiment. Interestingly, strong $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ compensation is also found for the hydroxide-ion catalyzed reaction of **2** in 2-BE–H_2O (stopped-flow technique; $n_{H_2O} = 1.00$, $\Delta H^{\ddagger} = 5.4$ kcal mol^{-1}, $\Delta S^{\ddagger} = -25$ eu; $n_{H_2O} = 0.98$, $\Delta H^{\ddagger} = 0.3$ kcal mol^{-1}, $\Delta S^{\ddagger} = -46$ eu; $n_{H_2O} = 0.95$, $\Delta H^{\ddagger} = 3.4$ kcal mol^{-1}, $\Delta S^{\ddagger} = -38$ eu). However, within the limits of experimental error a linear Eyring plot is obtained at $n_{H_2O} = 0.98$. This difference with the water-catalyzed process presumably reflects the smaller differences in hydrophobicity between initial state and transition state for the hydroxide-ion catalyzed reaction.

In conclusion, the present results either demonstrate an unprecedented solvent effect on $\Delta C_p^{\ddagger}$ for the neutral hydrolysis of **1** and **2** in a TA solution or may well demand an improved interpretation of the changes in $\Delta C_p^{\ddagger}$ found previously for solvolytic reactions of neutral substrates in water-rich TA mixtures. We are pursuing further kinetic studies to distinguish between these possibilities.

Supplementary Material Available: Pseudo-first-order rate constants for the neutral hydrolysis of **1** and **2** in *t*-BuOH–H_2O and 2-*n*-butoxyethanol–H_2O as a function of solvent composition and at a series of temperatures (Table II) and Gibbs free energies, enthalpies, and entropies of activation for the neutral hydrolysis of **1** and **2** in *t*-BuOH–H_2O in the range $n_{H_2O} = 0.925$–1.000 (Table III) (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Presented at the Euchem Conference on Correlation Analysis in Organic Chemistry, Sept 1979, Assisi, Italy.

(2) Franks, F. In "Water. A Comprehensive Treatise", Franks, F., Ed.; Plenum Press: New York, 1975; Vol. 4, Chapter 1.

(3) TA solutions have been defined as those in which the cosolvent induces long-range order in the hydrogen-bond regime. The solution thermodynamics are dominated by large negative entropies, pronounced heat capacity effects, and peculiar volumetric behavior. See Franks, F. In "Water. A Comprehensive Treatise", Franks, F., Ed.; Plenum Press: New York, 1973; Vol. 2, Chapter 1.

(4) Reviews: (a) Engberts, J. B. F. N. In "Water. A Comprehensive Treatise", Franks, F., Ed.; Plenum Press: New York, 1979; Vol. 6, Chapter 4. (b) Blandamer, M. J.; Burgess, J. *Chem. Soc. Rev.* **1975,** *4,* 55.

(5) (a) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1961,** *83,* 1743. (b) Fife, T. H.; McMahon, D. M. *Ibid.* **1969,** *91,* 7481. (c) Engbersen, J. F. J. Ph.D. Dissertation, University of Groningen, 1976. For the water-catalyzed process it is not clear whether or not a tetrahedral intermediate is formed, but this question does not seriously influence our discussion of solvent effects.

(6) Karzijn, W.; Engberts, J. B. F. N., unpublished work.

(7) (a) Roux, G.; Perron, G.; Desnoyers, J. E. *J. Phys. Chem.* **1978,** *82,* 966; (b) *J. Solution Chem.* **1978,** *7,* 639.

(8) These data are recorded in the microfilm edition. The largest extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (at $n_{H_2O} \sim 0.96$) are found for the most hydrophobic substrate (**2**).

(9) At higher temperatures, rates are higher than expected on the basis of an Eyring plot of kinetic data obtained at lower temperatures, despite the increase of $\Delta H^{\ddagger}$ with temperature. This is inherent in transition-state theory, which can be shown as follows. If θ is a reference temperature and $T > \theta$, then $\Delta G_T^{\ddagger} = \Delta H_T^{\ddagger} - T\Delta S_T^{\ddagger} = \Delta G_\theta^{\ddagger} + \Delta C_p^{\ddagger}(T - \theta) - T\Delta C_p^{\ddagger}\ln(T/\theta)$. Thus, $d(\Delta G_T^{\ddagger})/dT - d(\Delta G_\theta^{\ddagger})/dT = -\Delta C_p^{\ddagger}\ln(T/\theta)$. Owing to the dominant entropy term, the deviation of the Gibbs free energy of activation from that expected on basis of the Eyring equation differs in sign from the temperature dependence of $\Delta H^{\ddagger}$.

(10) (a) Robertson, R. E. *Prog. Phys. Org. Chem.* **1967,** *4,* 213. (b) Kohnstam, G. *Adv. Phys. Org. Chem.* **1967,** *5,* 121. Recently, Blandamer, Scott, and Robertson (Robertson, R. E., personal communication) have advanced a new method for the calculation of $\Delta C_p^{\ddagger}$ values which appears to avoid some problems in the statistical analysis of the experimental data. However, in our case the original treatment is sufficiently accurate to establish the large positive $\Delta C_p^{\ddagger}$ values of which the sign and relative magnitude is interpreted in the present paper.

(11) (a) Robertson, R. E.; Sugamori, S. E. *J. Am. Chem. Soc.* **1969,** *91,* 7254; (b) *Can. J. Chem.* **1972,** *50,* 1353.

(12) Recently, Robertson has revised the traditional interpretation of the magnitude of $\Delta C_p^{\ddagger}$ for S_N displacement reactions in water: Robertson, R. E. *Tetrahedron Lett.* **1979,** 1489.

(13) Alternatively, the positive $\Delta C_p^{\ddagger}$ values could be reconciled with hydrolysis of **1** and **2** via two distinct routes (mixed kinetics). See, for example, Winter, J. G.; Barron, J. P.; Scott, J. M. W. *Can. J. Chem.* **1975,** *53,* 1051. However, this possibility should be discarded, since, in order to reproduce the experimental $\Delta C_p^{\ddagger}$ values, the difference in $\Delta H^{\ddagger}$ between the two reaction paths must be ~13 kcal mol^{-1} for hydrolysis of **1** and ~15 kcal mol^{-1} for hydrolysis of **2**. This is clearly unrealistic. In this calculation it is assumed that, for the two distinct reactions, $\Delta C_p^{\ddagger} = 0$ and $k_1 = k_2$; otherwise the difference in $\Delta H^{\ddagger}$ becomes even larger. We also note that it is not easy to see why mixed kinetics is only significant at 2 mol% of 2-BE.

(14) de Visser, C.; Perron, G.; Desnoyers, J. E. *Can. J. Chem.* **1977,** *55,* 856.

(15) de Visser, C.; Perron, G.; Desnoyers, J. E. *J. Am. Chem. Soc.* **1977,** *99,* 5894.

(16) Compare Desnoyers, J. E.; Arel, M.; Perron, G.; Jolicoeur, C. *J. Phys. Chem.* **1969,** *73,* 3346.

Herman A. J. Holterman, Jan B. F. N. Engberts*
Department of Organic Chemistry
The University of Groningen, Nijenborgh 16
9747 AG Groningen, The Netherlands

Received February 8, 1980

Formation of Vitamin D_3 in Synthetic Lipid Multibilayers. A Model for Epidermal Photosynthesis

Sir:

Formation of vitamin D_3 (cholecalciferol, **3**) in fluid solution photolysis of 7-dehydrocholesterol (7-DHC, **1**) has been studied in considerable detail.[1] The locus of in vivo photobiogenesis of **3** is the epidermis.[2a,c,3] Several important differences exist between the two systems. The most obvious is that, once the primary photoprocess takes place in epithelial cells, circulation may remove the product to sublayer sites where further absorption of light is precluded. Thus a true photoequilibrium may not occur. As would be expected, the biological reaction is more economic in terms of selectivity and specificity. Holick et al. have shown that previtamin D_3 (precholecalciferol, **2** is essentially the only photoproduct formed from **1** in rat skin epithelial cells.[3] Apparently photochemical ring opening of the provitamin **1** to previtamin D_3 (**2**) and subsequent thermal conversion at body temperature into the vitamin occurs specifically in the skin, while in solution competing photoreactions of close quantum yield lead to photoequilibria involving tachysterol$_3$ (**4**), lumisterol$_3$ (**5**), and more complicated photoisomers[4] as well as solvent addition products[5] (Scheme I).

At least in part the differences between the two systems might share a conformational origin ultimately based upon the ordered milieu of the epidermis vs. the relatively disordered environment of fluid solution. Another important point is that the atmosphere absorbs essentially all radiation below λ 300–310 nm.[6] The absorption maximum of **1** occurs at shorter wavelength, namely, 280 nm. A series of weak absorption bands of the diene which occur around 330 nm (ϵ 50) may account for epidermal photosynthesis, and the mechanism of the ring opening is possibly different from that occurring at shorter wavelengths. Accordingly, as a step toward probing both the medium effect as well as the wavelength variation, the photolysis of **1** at ~280 and 310 nm in the anisotropic environment of synthetic ordered lipid multibilayers as a model for the epidermal photosynthesis was studied.

The first objective was to prepare a series of saturated synthetic lipid multibilayers incorporating 7-dehydrocholesterol (**1**) as a structural component and determine that these

0002-7863/80/1502-4257$01.00/0