crystalline solid (mp 135-137 °C) in 3.6% overall yield (0.18 g) and had the following spectral data: ^1H NMR ($CDCl_3$) δ 1.95 (s, 6 H), 2.40 (s, 3 H), 3.36 (d, 4 H), 3.48 (s, 3 H), 3.64 (s, 3 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 4.80 (m, 2 H), 6.70 (br s, 2 H), 6.95 (s, 1 H); mass spectrum for $C_{21}H_{30}N_2O_8S_2$ (calcd *m/e* 502.1443, found *m/e* 502.1453).

***N*-Acetyl-*S*-[[3-[[2-(acetylamino)-3-methoxyoxopropyl]-thio]-4,5-dimethoxyphenyl]methyl]-L-cysteine Methyl Ester.** This third addition product to be eluted from the column was isolated as a viscous oil in 1.0% overall yield (0.05 g) and had the following spectral data: ^1H NMR ($CDCl_3$) δ 2.07 (s, 6 H), 3.24 (d, 4 H), 3.60 (s, 2 H), 3.80 (s, 6 H), 3.90 (s, 6 H), 4.90 (m, 2 H), 6.71 (d, 1 H), 6.82 (d, 1 H); mass spectrum for $C_{21}H_{30}N_2O_8S_2$ (calcd *m/e* 502.1443, found *m/e* 502.1458).

Acknowledgment. This research was supported in part by the National Institutes of Health, Grants AG 01757 and AG 01758. We thank Mr. Dick Weisenberger for obtaining the mass spectral data and Dr. C. Cottrell for obtaining the carbon-13 NMR spectra.

Registry No. 4, 616-91-1; 5, 452-86-8; 6, 75625-96-6; 7, 75625-97-7; 8, 75659-24-4.

Salt Effects on the Intramolecular Carboxyl-Catalyzed Hydrolysis of Sulfonamides[1]

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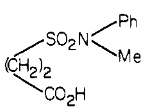
Relatively few studies have been made of solvent and electrolyte effects on intramolecular catalyzed hydrolytic processes.[3] This is surprising since medium effects are believed to play a significant, although probably not dominant,[3b] role in the important class of intramolecular reactions which go on within the enzyme-substrate complex.[4] The present work involves a study of electrolyte effects on the intramolecular carboxyl-catalyzed hydrolysis of the sulfonamides 1 and 2. In previous studies,[1,5] the mechanism of this reaction has been investigated in some detail. All kinetic data are consistent with nucleophilic catalysis, the rate-determining step being breakdown of a pentacovalent sulfur intermediate[1] via a transition state schematically depicted as 3.



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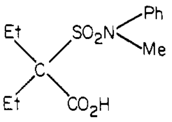

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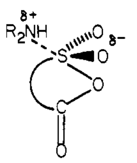

3

Results and Discussion

First-order rate constants for the intramolecular carboxyl-catalyzed hydrolysis of 1 and 2 in a variety of aqueous electrolyte solutions are listed in Table I. Thermodynamic activation parameters are given for hydrolysis in the presence of $MgCl_2$, $CaCl_2$, and n-Bu_4NBr. The effect of HCl on the hydrolysis rate is treated as a salt effect[6] since external acid catalysis cannot compete with intramolecular catalysis in 2.0 M HCl at 55 °C. The magnitudes of the salt effects are expressed as $k_{obsd}^s/k_{obsd}^\circ$ (Table I), which reveal that the hydrolysis of 1 is generally somewhat more affected[7] by the presence of the electrolytes than the hydrolysis of 2. The greater sensitivity of the hydrolysis of 1 to solvation effects was also noted for hydrolysis in some mixed aqueous solvents.[1,8] For example, on going from H_2O to 1:1 (v/v) $EtOH-H_2O$ the rate constant decreases about tenfold for 1 while the rate constant for 2 becomes smaller by a factor of only 4. We assume that this difference is a consequence of the closer proximity of the reacting groups in 2, which implies that the solvation shells of the sulfonamide and carboxyl groups are not independent of each other.[9] Therefore, the solvation change upon transforming the initial state into the transition state 3 will most likely be smaller for 2 than for 1, and this factor may well attenuate the medium effects on the hydrolysis of 2.

As shown in Table I, all electrolytes except n-Bu_4NBr accelerate the hydrolysis of 1 and 2. Since studies[1,5,8] of mixed aqueous solvent effects have shown that the rates of hydrolysis of 1 and 2 *decrease* with decreasing dielectric constant (ϵ) of the medium, it seems evident that an explanation of the salt effects cannot be given in terms of the reduced dielectric constant in the salt solutions.[10] Furthermore, it is also highly unlikely that "structure-making" and "structure-breaking" effects[11] of the ions represent the dominant factor in determining the kinetic salt effects. For both substrates the electrolyte effects of the single ions follow the sequences $Mg^{2+} > Ca^{2+} > H^+ > Na^+ \approx K^+ > NH_4^+ > Cs^+ > Me_4N^+ > n\text{-}Bu_4N^+$ and $Cl^- \approx Br^- > ClO_4^- > HSO_4^-$. These are not the sequences expected for water-structure perturbation.[12]

We suggest that the kinetic salt effects presented in Table I mainly reflect the hydrogen bonding properties of water molecules as modulated by the presence of the electrolytes.[13] This explanation hinges on the notion that water molecules in the electrostatic field of cations will be better hydrogen bond donors than unpolarized water molecules whereas water molecules in the hydration shells of anions will be better hydrogen bond acceptors. The

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(1) Part V in the series "Intramolecular Carboxyl-Catalyzed Hydrolysis of Sulfonamides". Part IV: Graafland, T.; Wagenaar, A.; Kirby, A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1979**, *101*, 6981.

(2) (a) University of Groningen. (b) University of Cambridge.

(3) See, for example: (a) Bruice, T. C.; Turner, A. *J. Am. Chem. Soc.* **1970**, *92*, 3422; (b) Dafforn, G. A.; Koshland, D. E., Jr. *Ibid.* **1977**, *99*, 7246.

(4) (a) Lumry, R.; Rajender, S. *Biopolymers* **1970**, *9*, 1125. (b) Jencks, W. P. *Adv. Enzymol. Relat. Subj. Biochem.* **1975**, *43*, 219.

(5) Graafland, T.; Engberts, J. B. F. N.; Kirby, A. J. *J. Org. Chem.* **1977**, *42*, 2462.

(6) $k_{obsd}^s/k_{obsd}^\circ = 1.42$ for 2 in 2 M HCl: this value is probably too low as a result of the salt effect on k_{obsd}° in 0.5 M HCl (see Experimental Section).

(7) A rigorous comparison is hindered by the different acidities of the media used for hydrolysis of the two substrates (Experimental Section). However, salt effects measured for the hydrolysis of 1 in the presence of 0.5 N HCl showed that this factor is of minor importance and does not affect the sequences of the salt effects of the single ions.

(8) Graafland, T., unpublished results.

(9) A referee has pointed out that the relative magnitude of the salt effects observed for 1 and 2 might also be affected by the intrinsic difference in volume change upon transferring the initial state into the transition state. See: Long, F. A.; McDevit, W. F. *Chem. Rev.* **1952**, *51*, 119. In terms of this theory the largest effects are expected for 1, but in the absence of ΔV^* values no definite conclusions can be drawn.

(10) It has been calculated that around a single charged ion the dielectric constant at a distance of 6 Å is reduced to 40: Azzam, A. M. *Z. Elektrochem.* **1954**, *58*, 889.

(11) See: Bunton, C. A.; Robinson, L. *J. Am. Chem. Soc.* **1968**, *90*, 5965.

(12) Blandamer, M. J. *Q. Rev., Chem. Soc.* **1970**, *24*, 169.

(13) Compare: (a) Menninga, L.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1976**, *98*, 7652 and references cited therein; (b) Breemhaar, W.; Engberts, J. B. F. N. *J. Org. Chem.* **1978**, *43*, 3618.

0022-3263/81/1946-0215$01.00/0

Table I. First-Order Rate Constants at 55.2 °C and Activation Parameters[a] for the pH-Independent Hydrolysis of 1 and 2 in Aqueous Electrolyte Solutions

compd	salt	[salt][b]	10^5k_{obsd}, s^{-1}	k^s_{obsd}/k^0_{obsd}[c]	$\Delta G^{\ddagger}$, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1			7.42	1	25.13	21.9	−11
1	$MgCl_2$	1.00	15.0	1.96	24.61	20.3	−15
1	$MgCl_2$	2.00	26.8	3.64	24.11	19.0	−17
1	$CaCl_2$	1.00	14.9	1.99	24.48	19.0	−19
1	$CaCl_2$	2.00	21.1	2.83	24.45	20.9	−12
1	HCl	2.00	13.0	1.75			
1	NaCl	2.00	12.3	1.68			
1	KCl	2.00	12.2	1.65			
1	CsCl	2.00	10.5	1.40			
1	NH_4Cl	2.00	11.6	1.49			
1	Me_4NCl	2.00	7.5	1.01			
1	n-Bu_4NBr	0.40	4.35	0.59	25.12	18.4	−23
1	n-Bu_4NBr	0.80	3.64	0.50	25.05	16.3	−29
1	NaBr	2.00	12.0	1.63			
1	KBr	2.00	12.2	1.63			
1	$NaClO_4$	2.00	9.87	1.36			
1	Na_2SO_4	1.00	7.70	1.04			
2			10.8	1	25.16	24.6	−2
2	$MgCl_2$	1.00	17.9	1.60	24.88	24.4	−2
2	$MgCl_2$	2.00	24.9	2.32	24.58	23.6	−3
2	$CaCl_2$	1.00	18.1	1.66	24.80	23.5	−4
2	$CaCl_2$	2.00	23.4	2.10	24.80	25.2	2
2	HCl	2.00	15.3	1.42			
2	NaCl	2.00	17.0	1.59			
2	KCl	2.00	16.1	1.50			
2	CsCl	2.00	14.7	1.35			
2	NH_4Cl	2.00	15.6	1.39			
2	Me_4NCl	2.00	14.0	1.31			
2	n-Bu_4NBr	0.40	10.2	0.97	25.03	22.9	−7
2	n-Bu_4NBr	0.80	9.2	0.87	25.05	22.5	−8
2	NaBr	2.00	17.2	1.62			
2	KBr	2.00	17.2	1.58			
2	$NaClO_4$	2.00	15.7	1.47			
2	Na_2SO_4	1.00	12.1	1.13			

[a] $\Delta G^{\ddagger}$ and $\Delta S^{\ddagger}$ are given at 25.00 °C. [b] Concentrations in moles per 55.5 mol of H_2O. All solutions contain 3.10^{-2} M HCl (1) or 0.5 M HCl (2) (see text). [c] Ratio of the rate constants in the salt solutions and in water.

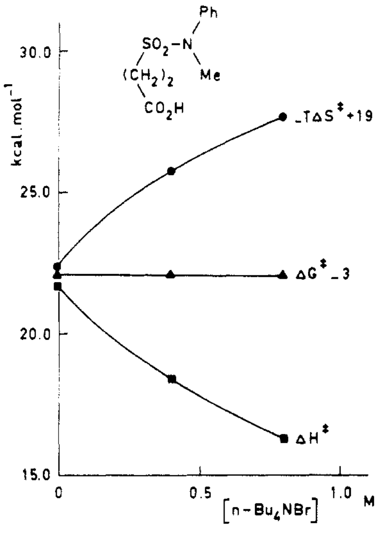

Figure 1. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. molality of n-Bu_4NBr for the intramolecular carboxyl-catalyzed hydrolysis of 1 at 25 °C.

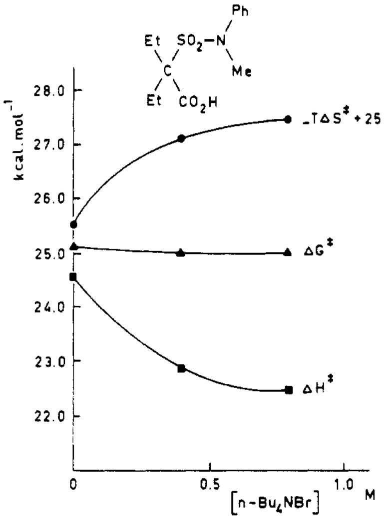

Figure 2. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. molality of n-Bu_4NBr for the intramolecular carboxyl-catalyzed hydrolysis of 2 at 25 °C.

magnitude of the effect will be a function of the charge densities of the distinct ions,[14] consistent with the ion sequences given above. Thus, a plausible explanation for the kinetic salt effects of all inorganic electrolytes may be advanced in terms of electrostatic field effects of the ions operating via polarized water molecules in the hydration shells of the initial state and the transition state. Most likely, the polar transition state will be most susceptible to hydrogen bond stabilization with the amine leaving group as a major hydrogen bonding site.[15] The activation parameters for hydrolysis of 1 and 2 in aqueous $MgCl_2$ and $CaCl_2$ (Table I) are consistent with electrolyte-induced stabilization of the transition state (decrease in $\Delta H^{\ddagger}$ which

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[14] Stokes, R. H. *J. Am. Chem. Soc.* **1964**, *86*, 979.

[15] For hydrolysis of N-aryl-substituted sulfonamides, $\rho_{LG} = -0.76 \pm 0.10$ (see ref 1).

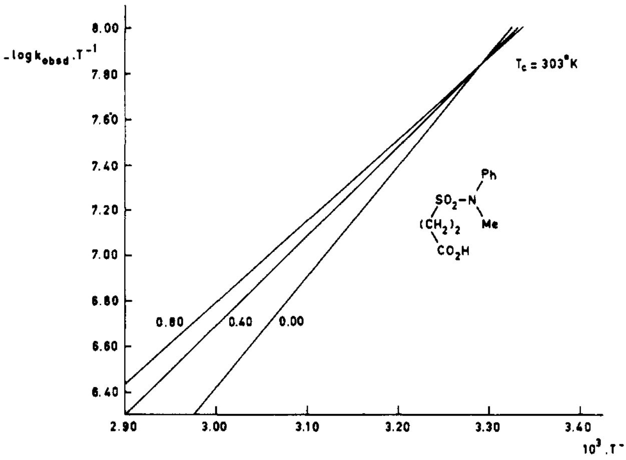

Figure 3. Plots of $-\log k_{obsd}T^{-1}$ vs. T^{-1} for the intramolecular carboxyl-catalyzed hydrolysis of 1 in water and in the presence of 0.40 and 0.80 M n-Bu_4NBr.

more than compensates for the decrease in $\Delta S^{\ddagger}$).

As noted above, n-Bu_4NBr is the only electrolyte used in this study which exerts a negative salt effect. Thermodynamic activation parameters for the hydrolysis of 1 and 2 are plotted as a function of the molality of n-Bu_4NBr in Figures 1 and 2, respectively. Small changes in $\Delta G^{\ddagger}$ are found to conceal large, compensatory changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The most pronounced effects are observed for 1: $\Delta H^{\ddagger}$ decreases by more than 5.5 kcal mol^{-1} upon addition of 0.8 M of n-Bu_4NBr whereas $\Delta S^{\ddagger}$ becomes more negative by 18 eu. These changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are at least an order of magnitude larger than the experimental error in these quantities of activation.[16] Applying Petersen's criterion[17] for the existence of an isokinetic temperature (T_c), $-\log k_{obsd}T^{-1}$ has been plotted vs. T^{-1} for hydrolysis of 1 in water and the two salt solutions (Figure 3). The three straight lines intersect at a single point, which corresponds with T_c = 303 K. The smaller changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for hydrolysis of 2 do not satisfy the Petersen criterion, despite the linear plot of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$. Although a detailed analysis of the variation of these activation parameters would require a dissection into initial-state and transition-state solvation effects,[18] the data strongly suggest the operation of dominant hydrophobic interaction between the substrate and the hydrophobic[12,19] tetra-n-butylammonium cation. This hydrophobic effect, which originates from mutually destructive overlap of the respective hydrophobic hydration spheres, will increase both the enthalpy and the entropy of the initial state,[18,20] leading to the observed trends in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. In the transition state for hydrolysis hydrophobic interaction will be attenuated as a result of the dipolar character of this species. It is noteworthy that in typically aqueous solutions like highly aqueous t-BuOH–H_2O, similar $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ mirror image behavior has been observed as a function of solvent composition.[1,5] However, in that case the initial state is more strongly stabilized, leading to a more manifest decrease of the rate of hydrolysis upon increasing concentration of the additive.

Experimental Section

Materials. The synthesis of sulfonamide 1 (pK_A = 3.44; H_2O, 50 °C) has been described previously.[1] Sulfonamide 2 (p$K_A \approx$ 2.8; H_2O, 50 °C) was prepared according to the standard procedure outlined in part IV[1] and gave the expected amine and diacid upon hydrolysis.

3-Carboxy-*N*-methyl-*N*-phenyl-3-pentanesulfonamide (2): mp 91.3–92.3 °C; NMR ($CDCl_3$) δ 0.95 (t, 6 H), 2.15 (q, 4 H), 3.35 (s, 3 H), 7.1–7.5 (m, 5 H), 10.9 (s, 1 H). Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91; S, 11.24. Found: C, 54.6; H, 6.8; N, 4.8; S, 11.1.

The salts used in all experiments were of analytical quality and were obtained either from Merck AG or from Aldrich. They were used as received, except n-Bu_4NBr which was crystallized twice from ethyl acetate–ether. Salt concentrations are expressed in the aquamolality scale (M; moles of salt per 55.5 mol of water). The water used in the kinetic measurements was demineralized and distilled twice in an all-quartz distillation unit.

Kinetic Measurements. Rates of hydrolysis of 1 and 2 were determined by following the decrease in absorbance at a suitable wavelength in the UV (usually at 235 nm). The k_{obsd} values were reproducible to within 2%. Thermodynamic activation parameters were calculated from rate constants measured at four different temperatures in the range of ca. 50–65 °C. Estimated errors in $\Delta H^{\ddagger}$ are ±0.2 kcal mol^{-1} and in $\Delta S^{\ddagger}$ are ±1 eu. The rate constants were determined at pH values in the middle of the horizontal part of the log k_{obsd}–pH profile, i.e., at 3.10^{-2} M HCl for 1 and at 0.5 M HCl for 2.

Registry No. 1, 62416-04-0; 2, 75599-75-6.

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[16] For a thorough statistical analysis of enthalpy–entropy compensation, see: Krugg, R. R.; Hunter, W. G.; Grieger, R. A. *J. Phys. Chem.* **1976**, *80*, 2335, 2341.

[17] Petersen, R. C. *J. Org. Chem.* **1964**, *29*, 3133.

[18] Engberts, J. B. F. N. In "Water, a Comprehensive Treatise"; Franks, F. Ed.; Plenum: New York, 1979; Vol. 6, Chapter 4. Although 2 has more hydrophobic surface area than 1, it may be argued that the *change* in hydrophobic interaction during the activation process is less than in the case of 1 in view of the closer proximity of the reacting groups in 2. This might explain the more pronounced $\Delta H^{\ddagger} - \Delta S^{\ddagger}$ compensation for 1.

[19] (a) Wen, W.-Y. *J. Solution Chem.* **1973**, *2*, 253. (b) Perron, C.; Desrosiers, N.; Desnoyers, J. E. *Can. J. Chem.* **1976**, *54*, 2163. (c) Wen, W.-Y.; Hung, J. H. *J. Phys. Chem.* **1970**, *74*, 170. (d) Tenne, R.; Ben-Naim, A. *Ibid.* **1976**, *80*, 1120.

[20] Compare: (a) Engbersen, J. F. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1975**, *97*, 1563. (b) Engbersen, J. F. J. Ph.D. Thesis, University of Groningen, 1976.

Synthesis and Wittig Reaction of 1-(Triphenylphosphoranylidene)-3-methoxy-2-propanone[1]

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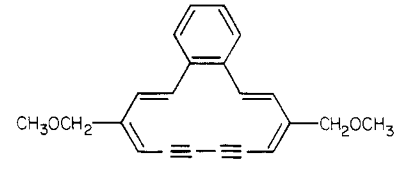
Received June 2, 1980

In order to synthesize dehydroannulenes containing methoxymethyl substituents [e.g., 4,11-bis(methoxymethyl)-6,8-didehydrobenz[14]annulene (1)][1] by the method of Darby et al.,[3] we required a simple method to transform an aldehyde (2) to the corresponding 1-methoxy-3-buten-2-one derivative (4). We now describe the



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[1] Taken in part from the Ph.D. thesis of T. W. Bell, University of London, 1980.

[2] Present address: Department of Chemistry, Cornell University, Ithaca, NY 14853.

[3] Darby, N; Cresp, T. M.; Sondheimer, F. *J. Org. Chem.* **1977**, *42*, 1960.

0022-3263/81/1946-0217$01.00/0