Intramolecular Catalysis of Sulfonamide Hydrolysis. 3. Intramolecular Acid-Catalyzed Hydrolysis of (*Z*)-2-Carboxy-*N*-methyl-*N*-phenylethenesulfonamide and *N*-Methyl-*N*-phenylmaleamic Acid under Conditions of Varying Water Ordering Effects

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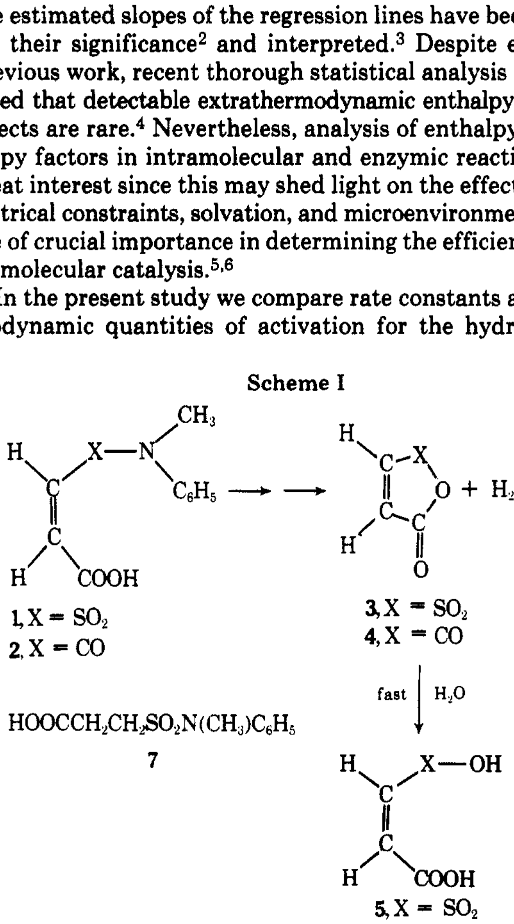
This paper reports rate constants and activation parameters for the intramolecular carboxyl-catalyzed hydrolysis of the title sulfonamide (1) and carbonamide (2) in t-BuOH–H_2O as a function of the mole fraction of water (n_{H_2O}). For both processes, reaction rates are retarded with decreasing n_{H_2O} in the range $n_{H_2O} = 1.00$–0.80. The variation of $\Delta H^{\neq}$ and $-T\Delta S^{\neq}$ as a function of n_{H_2O} shows mirror image behavior. Both quantities pass through extremes at n_{H_2O} ca. 0.95, the solvent composition for which the formation of hydrophobic hydration spheres reaches a maximum. Sulfonamide **7**, the saturated analogue of **1**, hydrolyzes 87 times slower than **1** (at 39.8 °C). This rate difference is predominantly determined by the $\Delta H^{\neq}$ terms, indicating that contributions from rotational entropy of the reactants are not directly reflected in the activation parameters. A tentative explanation for this result is offered in terms of different solvation requirements of the hydrolyses of 1 and 7.

A variety of chemical and biochemical processes in water show enthalpy–entropy compensation upon perturbation of the aqueous environment.[1] It has been proposed that such behavior is a ubiquitous property of water and it has, inter alia, been employed as a diagnostic test for the participation of water in protein processes. In these studies, *linear* ΔH–ΔS relationships of the type $\Delta H = \alpha + T_c\Delta S$ have often been claimed, and the isokinetic temperatures (T_c) derived from the estimated slopes of the regression lines have been tested for their significance[2] and interpreted.[3] Despite extensive previous work, recent thorough statistical analysis has indicated that detectable extrathermodynamic enthalpy–entropy effects are rare.[4] Nevertheless, analysis of enthalpy and entropy factors in intramolecular and enzymic reactions is of great interest since this may shed light on the effects of geometrical constraints, solvation, and microenvironment which are of crucial importance in determining the efficiency of intramolecular catalysis.[5,6]

In the present study we compare rate constants and thermodynamic quantities of activation for the hydrolysis of (*Z*)-2-carboxy-*N*-methyl-*N*-phenylethenesulfonamide (1)[7] and *N*-methyl-*N*-phenylmaleamic acid (2) in t-BuOH–H_2O. In both reactions the neighboring carboxyl group provides effective intramolecular catalysis for hydrolysis of the (sulfon)amide bond (Scheme I). In addition, some data have been obtained for **7**, the saturated analogue of **1**. The t-BuOH–H_2O system has been chosen in order to probe into the effect of varying diffusionally averaged "water structure" on the kinetic parameters of the processes[8] shown in Scheme I. There is abundant evidence[9] that the addition of t-BuOH to water leads initially to *increased* water–water hydrogen bonding, until the formation of hydrophobic hydration spheres reaches a maximum at n_{H_2O} ca. 0.95 (n_{H_2O} = mole fraction of water). Further addition of t-BuOH then causes a gradual collapse of the solvent structure. Several physical properties[9] and some chemical processes[1a,5,8,10] respond to these water ordering effects.

Scheme I



1, X = SO_2
2, X = CO

3, X = SO_2
4, X = CO

5, X = SO_2
6, X = CO

$HOOCCH_2CH_2SO_2N(CH_3)C_6H_5$
7

Results and Discussion

Hydrolysis of 1. The intramolecular carboxyl-catalyzed hydrolysis of 1 [$pK_A = 2.01$, $k(D_2O)/k(H_2O) = 1.36$ at pH 1, 40 °C][11] most likely involves rate-determining nucleophilic attack of the carboxylate anion on the sulfur atom of the N-protonated sulfonamide, to yield the cyclic mixed anhydride **3**.[7,12] Rate constants (k_{obsd}) and activation parameters as a function of n_{H_2O} in t-BuOH–H_2O ($n_{H_2O} = 0.80$–1.00) are listed in Table I.

Consistent with the proposed mechanism, reaction rates are retarded markedly with increasing concentrations of t-BuOH. Figure 1 portrays the approximately linear relationship between $\Delta G^{\neq}$ and the dielectric constant (ϵ).[13] There exists no linear correlation between log k_{obsd} and solvatochromism scales like the Z or E_T values. For the sake of comparison, we have also determined some rate constants for hydrolysis of 1 in ethanol–H_2O and 2,2,2-trifluoroethanol (TFE)–H_2O (Table I). Again, k_{obsd} values decrease upon lowering the dielectric constant, the effect being less pronounced in TFE–H_2O than in EtOH–H_2O. The latter effect may indicate increased transition state stabilization by hydrogen bonding interactions with TFE.

In contrast to the monotonic increase of $\Delta G^{\neq}$ in t-BuOH–H_2O, $\Delta H^{\neq}$ and $-T\Delta S^{\neq}$ clearly show mirror image behavior

Table I. Rate Constants and Activation Parameters for the Hydrolysis of 1 and 7 in Various Aqueous Mixtures at Various Mole Fractions of Water (n_{H_2O})

Compd	Solvent system	n_{H_2O}	ϵ	$k_{obsd} \times 10^4$, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1	H_2O	1.00	73.5	11.68[a]	18.6 ± 0.2	−12.4 ± 0.5
1	*t*-BuOH-H_2O	0.96	61.1	8.27[a]	18.1 ± 0.3	−14.8 ± 1.1
1	*t*-BuOH-H_2O	0.95	58.7	6.79[a]	18.1 ± 0.3	−15.1 ± 0.9
1	*t*-BuOH-H_2O	0.94	56.4	5.81[a]	17.7 ± 0.2	−16.8 ± 0.7
1	*t*-BuOH-H_2O	0.90	47.5	3.58[a]	18.6± 0.2	−14.7 ± 0.6
1	*t*-BuOH-H_2O	0.85	38.6	2.43[a]	19.0 ± 0.2	−14.5 ± 0.6
1	*t*-BuOH-H_2O	0.80	31.7	1.82[a]	19.1 ± 0.2	−14.7 ± 0.7
1	EtOH-H_2O	0.95	67.3	9.31[b]		
1	EtOH-H_2O	0.85	56.4	5.23[b]		
1	EtOH-H_2O	0.75	47.5	2.75[b]		
1	TFE-H_2O	0.95	66.1	9.22[b]		
1	TFE-H_2O	0.85	53.2	6.12[b]		
1	TFE-H_2O	0.75	44.5	5.23[b]		
7	H_2O	1.00		0.402[c]	21.9 ± 0.2	−10.8 ± 0.7
7	*t*-BuOH-H_2O	0.95		0.134[c]	20.7 ± 0.2	−16.8 ± 0.7

[a] At 39.8 °C and pH ca. 0.85. [b] At 39.0 °C and pH ca. 0.85. [c] At 49.7 °C and pH ca. 1.50.

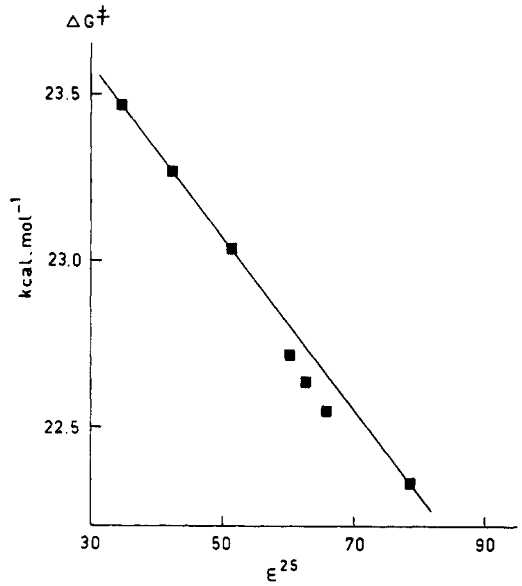


Figure 1. Plot of $\Delta G^{\ddagger}$ vs. ϵ for the intramolecular carboxyl-catalyzed hydrolysis of 1 in *t*-BuOH–H_2O at 25 °C.

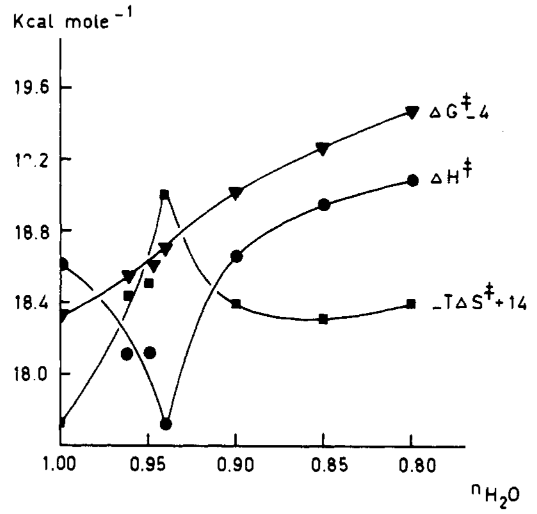


Figure 2. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the intramolecular carboxyl-catalyzed hydrolysis of 1 in *t*-BuOH–H_2O at 25 °C.

(Figure 2). Although the overall changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are well outside experimental error, the variations are too small to justify a rigorous test for linear $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ compensation. However, our results demonstrate for the first time that a simple, intramolecular catalyzed hydrolysis may change from a process in which entropy changes primarily modulate $\Delta G^{\ddagger}$ (n_{H_2O} = 1.00–0.94) to one in which enthalpy changes primarily control changes in $\Delta G^{\ddagger}$ (n_{H_2O} = 0.94–0.80). This change occurs around the "magic mole fraction" of water (n_{H_2O} = 0.95) in the *t*-BuOH–H_2O solvent system. Previously, several chemical phenomena have been found to pass through extremes at high water concentrations in alcohol–water mixtures.[9] This also applies to some protein reactions as illustrated by the enthalpy of denaturation of ribonuclease,[14] which exhibits a maximum at n_{H_2O} ca. 0.85 in EtOH–H_2O at 10 °C. There is considerable evidence in several cases that this type of behavior reflects changes in "water structure" induced by the cosolvent and accompanying changes in the magnitude of hydrophobic interaction between reactants and *t*-BuOH.[8,10]

In view of the absence of thermodynamic data for the initial state of 1 in *t*-BuOH–H_2O, we have not attempted a more detailed interpretation. We only note that the minimum of $\Delta H^{\ddagger}$ at the n_{H_2O} of maximum water–water interaction may be reconciled with maximal hydrogen bond stabilization of the polar transition state when the structural integrity of the solvent reaches a maximum.[10]

It is interesting to compare the kinetic parameters for the intramolecular catalyzed hydrolysis of 1 with those of 7 (pK_A = 3.58). The pH-rate profile for 7 is shown in Figure 3. This sulfonamide hydrolyzes via a similar pathway to 1, as indicated by the solvent deuterium isotope effect $k(D_2O)/k(H_2O)$ = 1.29 (at 38.6 °C, pH 1.53), but the catalytic efficiency of the COOH group is less than in 1 [k_{obsd} (1)/k_{obsd} (7) = 87 at 39.8 °C]. Since an additional mode of rotation is available in 7, one could argue that the rate difference finds its major origin in different entropic contributions[15] to the efficiency of the intramolecular catalyzed process.[16,17] In fact, the difference in $\Delta G^{\ddagger}$ is brought about primarily by different enthalpic contributions at both n_{H_2O} = 1.00 and 0.95 (Table I). A possible explanation involves the consideration of different solvation changes upon hydrolysis of 1 and 7. Thus, we suggest that the

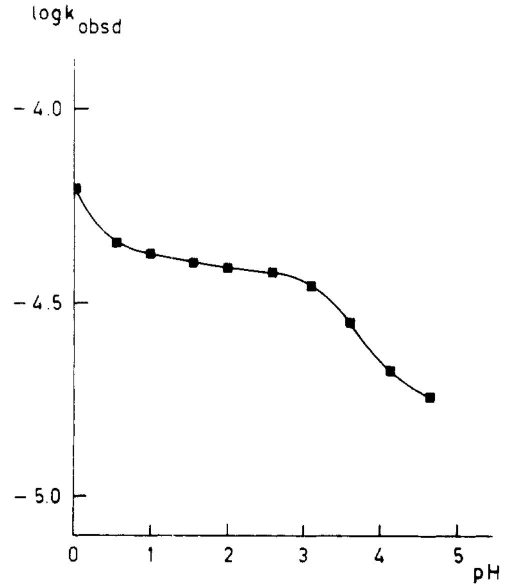


Figure 3. pH–rate profile for the hydrolysis of 7 in water at 49.5 °C.

Table II. Rate Constants (k_{obsd}) and Activation Parameters for the Hydrolysis of 2 in *t*-BuOH-H_2O at 40 °C

	pH 2.85			pH 0.87
n_{H_2O}	$k_{obsd} \times 10^4$, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	$k_{obsd} \times 10^4$, s^{-1}
1.00	2.88	19.3 ± 0.2	−13.0 ± 0.7	24.2
0.96	1.43	18.7 ± 0.2	−16.5 ± 0.7	14.6
0.95	1.22	18.2 ± 0.2	−18.2 ± 0.7	12.5
0.94	1.09	18.6 ± 0.3	−17.4 ± 1.0	11.1
0.90	0.681	19.6 ± 0.3	−15.3 ± 1.0	7.28
0.85	0.467	19.6 ± 0.3	−15.9 ± 1.0	5.78
0.80	0.341	19.8 ± 0.2	−15.9 ± 0.7	5.09

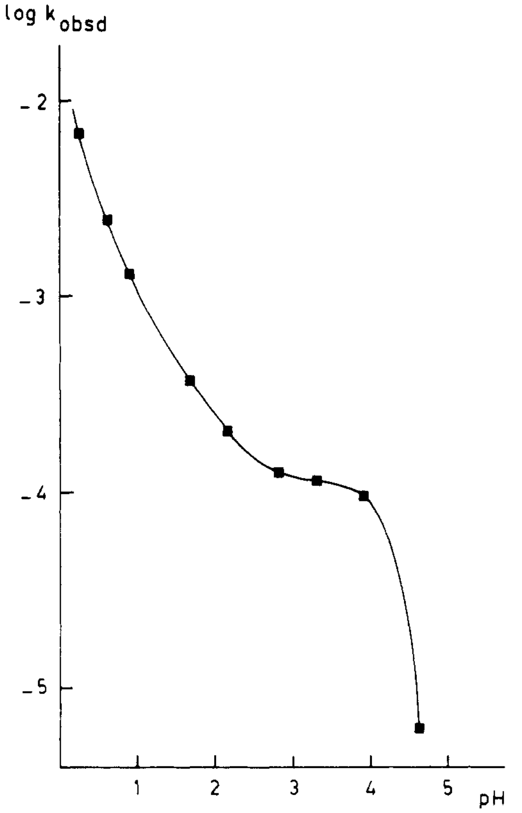


Figure 4. pH–rate profile for the hydrolysis of 2 in *t*-BuOH–H_2O, n_{H_2O} = 0.95 at 40.9 °C.

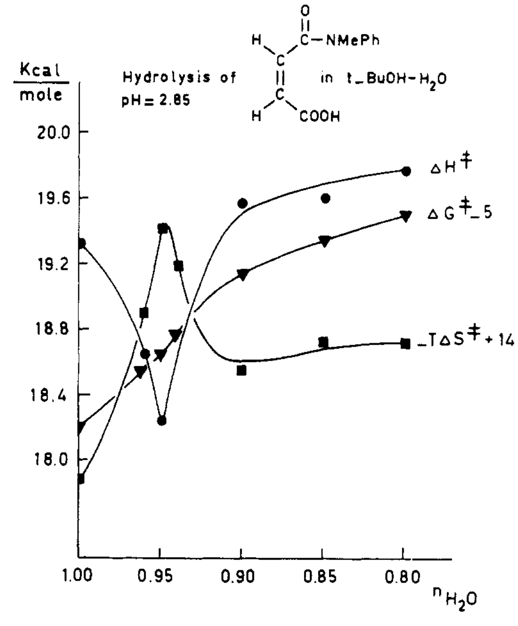


Figure 5. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the intramolecular carboxyl-catalyzed hydrolysis of 2 in *t*-BuOH-H_2O at pH 2.85 (25.0 °C).

entropy loss due to bringing together the sulfonamide and carboxyl groups in 7 will be largely cancelled by the entropy gain from partial desolvation of both groups when they are located in proper proximity necessary for reaction. Since the latter process, which is of course absent in the hydrolysis of 1, will be associated with a net loss of free enthalpy, the rate difference between 1 and 7 will then appear in $\Delta H^{\ddagger}$ rather than in $\Delta S^{\ddagger}$. A similar type of analysis has been advanced by Larsen[18] in his discussion of Jenck's theory[5,6] for the driving force for rate accelerations in intramolecular and enzymic reactions in aqueous media.

Hydrolysis of 2. Carbonamide hydrolysis catalyzed by a neighboring carboxyl group has been studied in detail.[19] Usually, a tetrahedral intermediate is formed upon nucleophilic attack of the carboxylate group on the O-protonated carbonamide function which subsequently breaks down in a rate-determining step.

The log k_{obsd}–pH profile for the acid-catalyzed hydrolysis of 2 is shown in Figure 4 and indicates that the rate of hydrolysis of 2 rapidly increases below pH ca. 2. This is in accord with recent work[20] which showed that the hydrolysis of maleanilic acids is much more susceptible to general acid catalysis than that of maleamic acids.[21] Since we are most interested in the solvent dependence of the activation parameters for the "water reaction" (which most likely involves rate-limiting decomposition of the tetrahedral intermediate), we have measured the pH-independent rate constant (k_{obsd}) as a function of temperature (Table II) at pH ca. 2.8 in *t*-BuOH-H_2O. For comparison, rates are given for the same n_{H_2O} at pH 0.85 (ca. 90% general acid catalysis). At both pH values the rate constants decrease with decreasing n_{H_2O} but show no simple correlation with macroscopic solvent parameters like ϵ and $(\epsilon - 1)/(2\epsilon + 1)$ or with solvatochromism scales like Z or E_T values. As in the case of 1, the monotonic increase of $\Delta G^{\ddagger}$ for the "water reaction" of 2 conceals mutually compensating changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. As shown in Figure 5,

$\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ pass through extrema located around $n_{H_2O} = 0.95$, the solvent composition of maximum structural integrity.

In conclusion, we note that the rates of the intramolecular carboxyl group assisted hydrolysis of **1**, **2**, and **7** are retarded by the addition of organic cosolvents to water. The gradual increase of $\Delta G^{\ddagger}$ is composed of larger, mutually compensating changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

Despite the difference in mechanism, the hydrolysis of both **1** and **2** exhibits extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ at $n_{H_2O} = 0.95$ in *t*-BuOH–H_2O, which is the solvent composition of maximum water ordering. The extremes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ most likely reflect secondary solvation effects due to the formation of hydrophobic cavity type hydration spheres induced by the addition of the first 5 mol % of *t*-BuOH. In addition, comparison of the activation parameters for **1** and **7** provides further evidence for the notion[5] that contributions from rotational entropy of the reactants generally cannot be determined from the observed entropy of activation as measured in aqueous reaction mixtures.

Experimental Section

Materials. Sulfonamide **1** was synthesized as reported previously.[7] The new compounds **2** and **7** were prepared according to standard procedures and gave the expected acid and amine upon hydrolysis.

***N*-Methyl-*N*-phenylmaleamic acid (2),** mp 111.3–111.8 °C. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.42; H, 5.53; N, 6.75.

2-Carboxy-*N*-methyl-*N*-phenylethanesulfonamide (7), mp 144.5–144.7 °C. Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76; S, 13.18. Found: C, 49.37; H, 5.36; N, 5.89; S, 13.08.

The water used in the kinetic measurements was demineralized and distilled twice in an all-quartz distillation unit. D_2O was obtained from Reactor Centrum Nederland (99.94 ± 0.05% D_2O) and was used as such. *t*-BuOH and TFE were obtained from Aldrich and anhydrous EtOH was obtained from Merck and were of the best quality available. The solvent mixtures were all made up by weight.

Kinetic Measurements. The rates of hydrolysis of **1**, **2**, and **7** were determined by following the change of the absorbance at 235, 240, and 224 nm, respectively. The reactions were carried out in 1-cm quartz cells, which were placed in the adequately thermostated (±0.05 °C) cell compartment of a Beckman Model 24 spectrophotometer. About 5 μl of a concentrated solution of the sodium salt of **1** in H_2O, of **2** in *t*-BuOH, and of **7** in EtOH were added to the aqueous reaction media in the cuvette (3 mL) by means of a capillary pipet and under vigorous shaking. Initial substrate concentrations were ca. 5×10^{-5} M for **1** and **2** and ca. 10^{-4} M for **7**. Measurements were taken for at least 3 half-lives. Accurate pseudo-first-order kinetics were observed and k_{obsd} values were reproducible to within 2%. In the mixed solvent systems pH measurements were complicated by the presence of the organic cosolvent. However, this constitutes no serious problem since the k_{obsd} values refer to pH-independent rate constants. In all cases the breakdown of the cyclic anhydride intermediate was too fast to influence the observed rate. Activation parameters were calculated from k_{obsd} values at four different temperatures in the range of 34.5–48.5 °C for **1**, 39.5–52.0 °C for **2** at pH 2.85, and 38.5–54.0 °C for **7**. The errors listed in Tables I and II are statistical errors.

Registry No.—**1**, 59632-54-1; **2**, 62416-03-9; **7**, 62416-04-0.

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(16) The different rates may also be partly determined by the different geometries of the reactive syn-planar conformations of **1** and **7** which are transferred into the cyclic mixed anhydride. However, we contend that these factors will be primarily reflected in $\Delta H^{\ddagger}$ and will not affect significantly our discussion of the $\Delta S^{\ddagger}$ values.

(17) For the intramolecular COOH-catalyzed hydrolysis of carbonamides the situation is quite different and may reflect the difference in rate-determining step, i.e., breakdown of the cyclic, tetrahedral intermediate. Compare (a) T. Higuchi, L. Eberson, and A. K. Herd, *J. Am. Chem. Soc.*, **88**, 3805 (1966); (b) A. J. Kirby and P. W. Lancaster, *J. Chem. Soc., Perkin Trans. 2*, 1206 (1972).

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