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Transition-State Structures for the Hydrolysis of Cyclic and Acyclic Carboxylic Acid Anhydrides[1]

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Proton inventories are reported for the hydrolysis of propionic anhydride at 5, 25, and 45 °C and for succinic anhydride at 25 °C. The secondary β-deuterium isotope effect (k_H/k_D) for acetic anhydride-d_6 hydrolysis was determined at four different temperatures in the range 3.7–45.2 °C and was found to be about 0.95 in all cases. These data are interpreted in terms of significantly different transition states for hydrolysis of propionic and succinic anhydrides. The transition-state structure involved appears to be related to whether the anhydride is cyclic or acyclic.

Introduction

The hydrolysis of carboxylic acid anhydrides has been studied for over half a century, and many different probes of the hydrolytic mechanism have been employed. From their investigations of the temperature dependence of solvent effects on the neutral hydrolysis of several carboxylic acid anhydrides, Robertson and co-workers concluded that there was a significant temperature dependence of the solvent deuterium isotope effect for all of the anhydrides studied.[3,4] The magnitude and direction of the temperature effect did not vary in any discernable pattern as a function of structure. For example, plots of log (k_{H_2O}/k_{D_2O}) vs. $1/T$ for acetic, succinic, and phthalic anhydrides showed maxima while the plots for propionic and benzoic anhydrides showed minima. Their results were initially interpreted in terms of changing solvation and partitioning of the tetrahedral addition intermediate to products or back to reactants. More recently a detailed analysis of the results in terms of changing heat capacities of activation in protium oxide and deuterium oxide using two different models met with limited success.[5] Blandamer et al. were able to fit the data for acetic anhydride very well using the partitioning model and the heat capacity of activation in both solvents. However, the model did not work consistently for the other anhydrides. The data for propionic anhydride could be fitted in protium oxide but not deuterium oxide. Phthalic and benzoic anhydrides were satisfactorily treated by the model in deuterium oxide only while the model would not reproduce the data for succinic anhydride in either protium or deuterium oxides. They were forced to conclude that no simple relationship exists between the heat capacity of activation and the dependence of the solvent deuterium isotope effect on temperature. It seems possible that the solvent isotope effect changes related to partitioning of the tetrahedral addition intermediate could be characterized through kinetic studies in mixtures of protium oxide and deuterium oxide (i.e., proton inventories). Albery and Davies have considered the case of the dependence of the solvent deuterium isotope effect on the atom fraction of deuterium in the solvent in a system involving two consecutive transition states.[6,7] It can be shown that a substantial change in partitioning could be detected by a change in the curvature of a proton inventory plot.

We initially elected to look at the solvolysis of propionic anhydride for the following reasons: (i) the change in solvent deuterium isotope effect measured by Robertson and Rossall[3,4] is substantial (k_{H_2O}/k_{D_2O} ranges from 2.74 to 3.02) over an easily accessible temperature range (5–45 °C); (ii) the curvature in the Eyring plots of ln (k/T) vs. $1/T$ generated from the available data seemed greatest for this anhydride; (iii) proton inventory data were already available for the hydrolysis of acetic anhydride, and this inventory had been interpreted by Batts and Gold.[8] During the course of our study it became obvious that proton inventory data for anhydrides significantly different from propionic anhydride would be useful, so data for succinic anhydride were collected. Secondary β-deuterium isotope effects were determined for the solvolysis of acetic anhydride to further aid our mechanistic interpretation.

Results

The solvolyses of propionic anhydride and succinic anhydride have been investigated under a variety of conditions over a wide range of temperatures. Table I summarizes the data obtained at 5, 25, and 45 °C in protium oxide, deuterium oxide, and mixtures of atom fraction deuterium, n, of the two solvents. Figures 1 and 2 represent the proton inventory data for propionic anhydride at 45 °C and succinic anhydride at 25 °C and accurately represent the quality of the other data (Table I) not shown in plots. Both proton inventories are clearly curved downward. The rate constants and solvent deuterium isotope effects are in good agreement with those in the literature.[4,10-15] The small differences between our results and those of Robertson et al.[3,4] were shown not to be due to the presence of acetonitrile, carbon dioxide, or other

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[1] This research was supported by the Robert A. Welch Foundation and, in part, by the National Institutes of Health (Grant 1 R01 GM25433).

[2] Recipient of a Robert A. Welch Foundation Predoctoral Fellowship.

[3] Rossall, B.; Robertson, R. E. *Can. J. Chem.* **1975**, *53*, 869.

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[14] Ules, S. E. *Recl. Trav. Chim. Pays-Bas* **1933**, *52*, 809.

[15] Robertson et al.[3] did not report rate constants directly but gave an equation that reproduced their rate constants to within their experimental error of 0.5%.

Table I. Proton Inventory Data for the Solvolysis of Propionic Anhydride and Succinic Anhydride in H_2O-D_2O Mixtures of Atom Fraction Deuterium (n)

anhydride (temp, °C)	atom fraction deuterium (n)	no. of runs	10^6k_n, s^{-1}	10^6k_n, s^{-1} (calcd[a])
propionic (5.0 ± 0.1)	0.000	14	384 ± 15[b]	384
	0.406	5	270 ± 6	266
	0.497	5	244 ± 6	243
	0.505	6	238 ± 6	241
	0.989[c]	3	132 ± 4	135
propionic (25.00 ± 0.05)	0.000	22	1423 ± 30	1423
	0.248	4	1117 ± 17	1125
	0.496	9	865 ± 23	867
	0.744	4	638 ± 17	647
	0.992[c]	8	464 ± 6	460
propionic (45.0 ± 0.1)	0.000	5	402 ± 7[d]	402
	0.248	3	323 ± 4[d]	319
	0.496	4	243 ± 3[d]	246
	0.744	3	185 ± 1[d]	184
	0.992[c]	4	134 ± 4[d]	132
succinic (25.00 ± 0.05)	0.000	7	2669 ± 24	2669,[e] 2669[f]
	0.498	4	1687 ± 15	1680, 1712
	0.518	3	1661 ± 9	1647, 1678
	0.997[c]	4	969 ± 4	971, 966

[a] Values were calculated on the basis of the model of eq 1 with $\phi_b^* = 0.87$, and ME = 0.95 (5 °C), 0.88 (25 °C) and 0.89 (45 °C) for propionic anhydride. [b] All error limits are standard deviations. [c] Atom fraction of deuterium determined by Josef Nemeth.[9] [d] Values are 10^5k for propionic anhydride at 45 °C. [e] Based on the model of eq 1 with ME = 1 and $\phi_a^* = \phi_b^* = 0.713$. [f] Based on the model of eq 2 with $\phi_a^* = 0.67$ and $\phi_b^* = 1.2$.

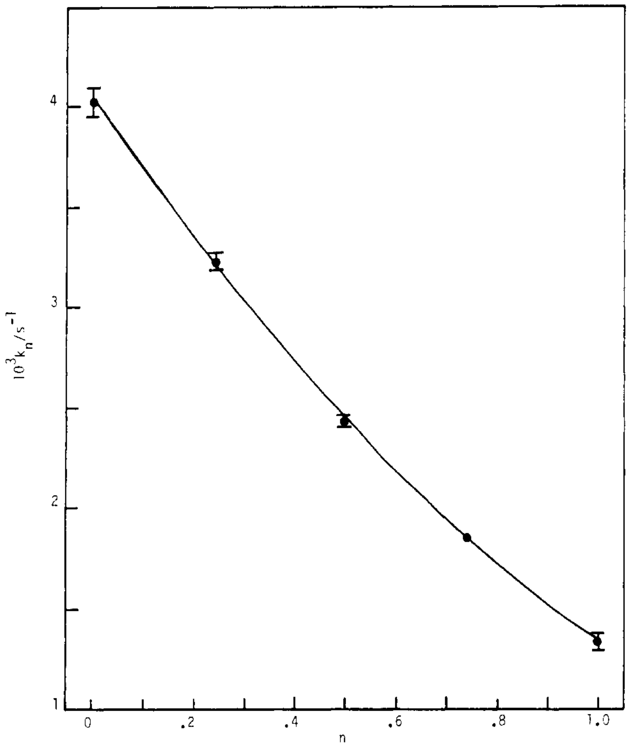

Figure 1. Proton inventory for the hydrolysis of propionic anhydride at 45 °C. The data are taken from Table I. The solid line was calculated on the basis of the model of eq 1 with $\phi_a^* = 0.48$, $\phi_b^* = 10.87$, and ME = 0.89. Error bars are standard deviations. Where error bars are omitted, the circles encompass them. The plots for the data at 5 and 25 °C (not shown) show equally good fits to the model.

determinable variables on the basis of experiments in our laboratories.

The secondary β-deuterium isotope effect for solvolysis of acetic anhydride and acetic anhydride-d_6 was measured at four different temperatures in protium oxide and at a single temperature in deuterium oxide as shown in Table II. In all cases an inverse secondary deuterium isotope effect was observed in direct conflict with the earlier report of Bender and Feng.[16] They reported no isotope effect on the basis of studies done using a pH-stat to monitor the kinetics. However, our values seem much more consistent with the large solvent deuterium isotope effect of $k_{H_2O}/k_{D_2O} = 2.90$ at 25 °C.[8] As a check of our experimental procedure we also list the solvolysis rate constants for acetic anhydride measured by Robertson et al. in parentheses in Table II. The agreement is very good.

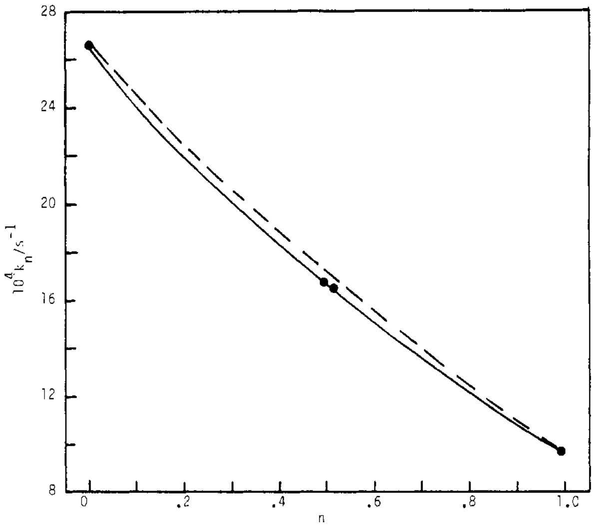

Figure 2. Proton inventory for the hydrolysis of succinic anhydride at 25 °C. The data are taken from Table I. The solid line was calculated on the basis of the model of eq 1 with $\phi_a^* = \phi_b^* = 0.71$, and ME = unity. The dashed line is based on the model of eq 1 with $\phi_a^* = 0.48$, $\phi_b^* = 0.87$, and ME = unity and is shown to emphasize the failure of this model to reproduce the data. The circles encompass the error bars.

Analysis of the proton inventories, completed by using the γ method of Albery,[7] yielded the following γ values: propionic anhydride ($\gamma = 0.57 \pm 0.14$, 0.35 ± 0.09, and 0.38 ± 0.11 at 5, 25, and 45 °C, respectively); succinic anhydride ($\gamma = 0.39 \pm 0.05$ at 25 °C). These values can be compared to the other γ values for anhydride hydrolyses calculated from literature data: acetic anhydride[7,8] ($\gamma = 0.52 \pm 0.08$

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(16) Bender, M. L.; Feng, M. S. *J. Am. Chem. Soc.* **1960**, *82*, 6318.

Table II. First-Order Rate Constants and Secondary β-Deuterium Isotope Effects for the Solvolysis of Acetic Anhydride and Acetic Anhydride-d_6 in Protium Oxide

temp, °C	$10^6 k_H$, s^{-1}	$10^6 k_D$, s^{-1}	k_H/k_D
3.7	618 ± 30[a] (638)[b]	646 ± 22[a]	0.957 ± 0.047[a]
24.4	2513 ± 40 (2560)	2686 ± 7	0.935 ± 0.015
34.3	4326 ± 27 (4390)	4511 ± 34	0.959 ± 0.010
45.2	7340 ± 110 (7340)	7627 ± 200	0.961 ± 0.025
25.0	921 ± 2 (D_2O) (905)	972 ± 11 (D_2O)	0.947 ± 0.010

[a] Error limits are standard deviations. All rate constants are the average of from three to eight replicate pairwise determinations. [b] Values in parentheses are calculated from the data of Robertson et al.[3,4,15] and are included for comparative purposes.

at 25 °C); phthalic anhydride[17] ($\gamma = 0.72 \pm 0.10$ at 25 °C).

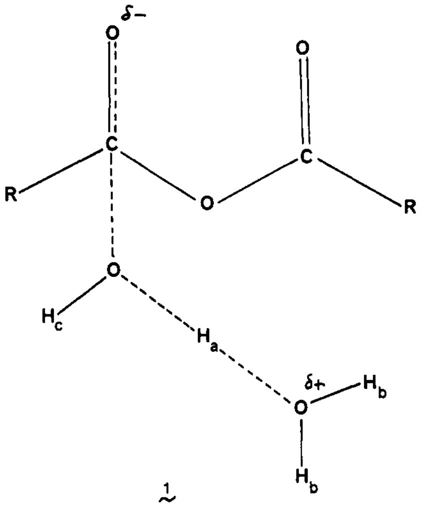
Discussion

The data available on anhydride solvolysis appear to be interpretable in terms of a mechanistic model in which the differences between acyclic and cyclic anhydrides are emphasized. The solvolysis models to be considered have been formulated on the basis of our data and spectroscopic and structural data gleaned from the literature. The data suggest that acyclic, aliphatic carboxylic acid anhydrides exist in solution as a temperature- and solvent-dependent population of nonplanar conformers separated by relatively small energy barriers. The cyclic anhydrides, on the other hand, exist as one, approximately planar, conformation in solution. This idea is consistent with the known electronic and molecular properties of these compounds and this information will prove consistent with the transition-state structures posed based on our proton inventory studies.

Propionic Anhydride Proton Inventories. The theory of proton inventories and discussion of the two common methods used to analyze the data, the γ method and polynomial regression analysis, are available in the literature.[7,18,19] Our experiments were designed to employ the γ method suggested by Albery, but at the suggestion of a referee, we have also analyzed the data by the polynomial regression method. The γ method requires only measurements at $n = 0$, 0.5, and 1.0, and our data were collected with this in mind. The polynomial regressional analysis works best for data collected at very large numbers of values of n. Therefore, the two methods of data analysis give slightly different results in the present study.

Albery showed that the number of protonic sites in the transition state contributing to the solvent isotope effect must be greater than γ^{-1}.[7] The γ values obtained at 25 and 45 °C for propionic anhydride and at 25 °C for succinic anhydride hydrolysis indicate that probably three or more protons are responsible for the solvent isotope effect. However, the polynomial regression analysis described by Schowen[19] showed that linear and quadratic terms were significant at the 100% confidence level for propionic anhydride at 25 and 45 °C but that the cubic term was only significant at the 21% level at 25 °C and at the 82% level at 45 °C. For succinic anhydride at 25 °C the linear and quadratic terms were again significant at the 100% confidence levels, but the cubic term was deemed significant only at the 41% level. For propionic anhydride at 5 °C the γ value suggests two or more protons, which is consistent with 100% confidence levels for the linear and quadratic terms. The cubic term was significant at the 61% confidence level in this case.

Thus, the two methods of analysis both strongly support the involvement of two protons with the involvement of a third proton being supported in most instances by the γ analysis and at levels of confidence ranging from 21% to 82% by the polynomial regression analysis. Had the experiments been designed with the polynomial regression analysis in mind, it is likely the agreement would be better.



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It has been argued that the water-catalyzed hydrolysis of esters and related compounds involves a catalytic entity referred to as an immature hydronium ion (the two water molecules usually depicted in the BAc_2 mechanism).[20] This transition-state model involves an "in-flight" proton H_a with an isotopic fractionation factor of about 0.5 and two protons H_b with fractionation factors of about 0.83 as shown in 1.[20] The proton inventories under consideration can be interpreted in terms of a similar model. Equation 1 describes the rate constant obtained in a solvent mixture

$$k_n = k_o\mathrm{ME}^n(1 - n + n\phi_a^*)(1 - n + n\phi_b^*)^2 \qquad (1)$$

of atom fraction deuterium, k_n, in terms of the rate constant in protium oxide, k_o, and in terms of the isotope effect contributions of H_a and the two H_b protons in terms of the isotopic fractionation factors ϕ_a^* and ϕ_b^* for these sites. The term ME^n is a differential medium effect described by Albery.[7] We have assumed the medium effect absorbs the effects of possible activity coefficient changes on transfer of reactants and transition states from H_2O to D_2O, solvation effects, and the change in conformational populations as the temperature changes. It seems reasonable to estimate the magnitude of the differential medium effect on the basis of similar effects measured for transfer from H_2O to D_2O of sodium propionate.[21] This experiment yielded a value for the medium effect of 0.93 at 25 °C. Values of 0.48 and 0.87 for ϕ_a^* and ϕ_b^* coupled

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[17] Gandour, R. D.; Coyne, M.; Stella, V. J.; Schowen, R. L. *J. Org. Chem.* **1980**, *45*, 1733. The γ value was calculated in our laboratory by using data from this reference.

[18] Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275.

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with values of ME of 0.95, 0.88, and 0.89 for the proton inventories of propionic anhydride hydrolysis at 5, 25, and 45 °C reproduce the experimental data very well when substituted into eq 1. These calculated values are shown in Table I, and the solid line of Figure 1 is drawn from them. This is not a unique solution as one could hold ME constant and vary ϕ_a^* or ϕ_b^*, and still have a transition state consistent with the hydronium ion hypothesis. It should be pointed out that the contributions from H_a and H_b of 2.08 and 1.15 to the solvent isotope effect are essentially identical with such protons in the model for acetic anhydride (2.0 for the bridging proton and 1.2 for the others) proposed by Batts and Gold.[8]

β-Secondary Isotope Effect. The measured secondary β-deuterium isotope effects for acetic anhydride-L_6 (L = H or D) also support the transition-state structure. The use of such secondary isotope effect measurements in the characterization of transition-state structures has been treated in a recent review.[22] Even more recently Schowen and co-workers have critically analyzed kinetic isotope effect probes of transition states for carbonyl addition and have proposed a model to explain the anomalous temperature dependencies of some secondary β-deuterium isotope effects in acyl transfer reactions.[23] It is generally agreed that an increase in nucleophilic interaction at carbonyl carbon will decrease hyperconjugative stabilization of the partial positive charge on the reactant carbonyl carbon. This will increase the force constants of the β-CH(CD) bonds to produce an inverse secondary deuterium isotope effect ($k_H < k_D$). The classic experiments of Bender and co-workers in this area were interpreted in exactly this manner.[16]

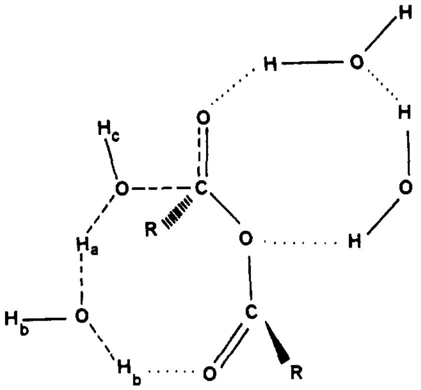
One of Bender's early experiments dealt with the secondary β-deuterium isotope effect for acetic anhydride solvolysis. Bender and Feng reported a value of k_H/k_D = 1.05 ± 0.04.[16] It has always been difficult to rationalize this isotope effect (or the absence of the expected inverse isotope effect) with the observed solvent deuterium isotope effect of $k_{H_2O}/k_{D_2O} = 2.90$ measured by Batts and Gold.[8] The solvent isotope effect presumably arises as postulated above in a mechanism involving significant bonding changes at the carbonyl carbon. Such a transition-state structure should result in a significant inverse secondary β-deuterium isotope effect. We chose to repeat this experiment for this reason and were pleased to find the expected inverse effect over the entire temperature range studied (Table II). In fact, the effect is $k_H/k_D = 0.953 \pm 0.012$ averaged over the four measurements in protium oxide. We can only speculate that the inherent difficulties associated with pH-state kinetics prevented the detection of this effect by the previous workers. The lack of any significant temperature dependence for this effect suggests that a single transition-state structure stands out as the major contributor to this effect. This lack of a strong temperature dependence is easily contrasted with the marked temperature-induced variation of several secondary β-deuterium isotope effects reported by Schowen and co-workers and interpreted in terms of a cascade model involving domination by solvent reorganization and heavy-atom reorganization transition states along parallel reaction paths as a function of temperature.[23] Such a model has been postulated to explain the anomalous temperature dependences of the solvent isotope effects for anhydride hydrolyses reported by Rossall and Robertson.[3,4] The present result seems to indicate that this cascade model should not be invoked to explain the solvent effects since it is not required to explain the secondary β-deuterium isotope effects.

Table III. Approximate Orders with Respect to Water Determined for Carboxylic Anhydride Hydrolysis

anhydride	cosolvent	temp, °C	water order	ref
propionic	acetone	25	4	24
propionic	dioxane	25	4	24
acetic	acetone	25	4	25
acetic	dioxane	25	4	25
isonicotinic	dioxane	25	3	26
2,6-dimethylphthalic	dioxane	65	3.5	27
phthalic	dioxane	25	3.7, 3.0[a]	27, 28

[a] Fagley and Oglukian did not study the reaction above 0.8 mol fraction of water and stated that the participation order with respect to water could change at higher water concentration.[28]

Water Order. The transition state 1 can be considered to be a minimum transition state for acetic and propionic anhydride solvolysis, but it is not entirely consistent with the water-order dependence summarized in Table III. We, therefore, propose the involvement of two additional solvating water molecules. The nonplanarity of the acyclic anhydrides, which is supported by a significant amount of spectroscopic and structural data (see below), makes it sterically possible for one of the H_b protons in 1 to be hydrogen bonded to the carbonyl oxygen atom of the group not undergoing nucleophilic attack. This transition-state structure is represented in 2. This arrangement is appealing since an acidic proton generated by the attack of water on one carbonyl is in a position to immediately protonate the leaving group carbonyl.



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Activation Parameters. The proton inventories for propionic anhydride at three different temperatures have allowed us to determine values for $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ as a function of the atom fraction of deuterium in the solvent. These data are shown in Table IV and were obtained in the following manner. Eyring plots of ln (k/T) vs. $1/T$ were made for the data obtained at each value of n. From the plots (which consisted of only two or three points) the value of $\Delta H^{\ddagger}$ was determined via a linear least-squares fit. This value was used along with the $\Delta G^{\ddagger}$ calculated at 25 °C to calculate $\Delta S^{\ddagger}$ from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$. Figure 3

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(25) Cavasino, F. P.; D'Allessandro, S. *Ric. Sci., Parte 2: Sez. A.* **1964**, *7*, 421.

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(27) Hawkins, M. D. *J. Chem. Soc., Perkin Trans. 2* **1975**, 282.

Table IV. Activation Parameters for the Solvolysis of Propionic Anhydride as a Function of the Atom Fraction of Deuterium (n) in the Solvent at 25 °C[a]

atom fraction deuterium (n)	$\Delta H^{\ddagger}$, kcal/mol	$-\Delta S^{\ddagger}$, eu	$-\Delta G^{\ddagger}$, kcal/mol
0.000	9.74	38.80	21.31
0.248	9.38	40.48	21.46
0.496	9.51	40.55	21.61
0.744	9.40	41.56	21.79
0.992	9.59	41.56	21.78

[a] Determined from the data of Table I.

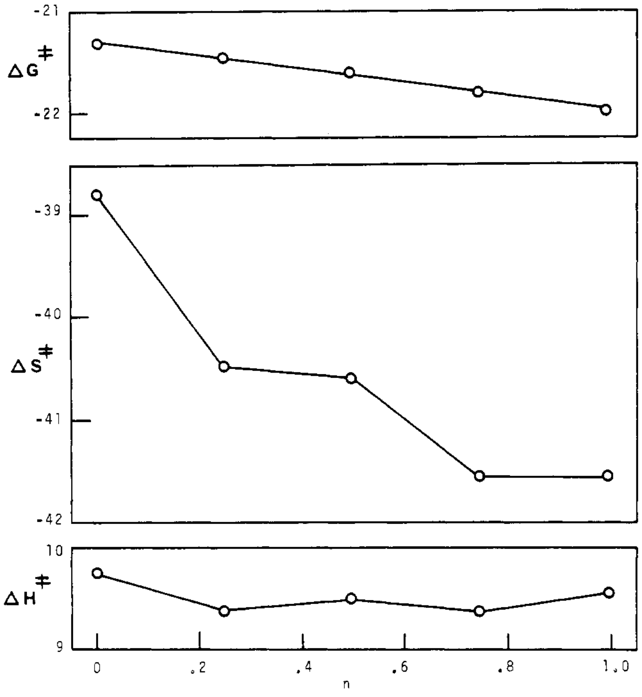


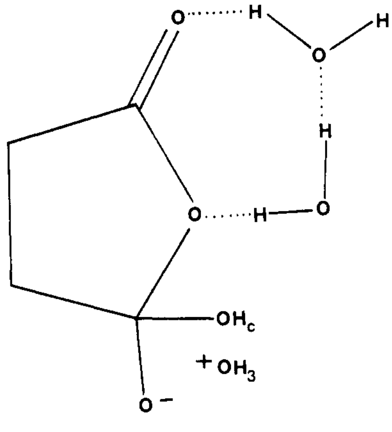
Figure 3. Activation parameters for propionic anhydride hydrolysis at 25 °C as a function of the atom fraction of deuterium in the solvent. Units are ΔG^{*} (kcal/mol), ΔS^{*} (eu), ΔH^{*} (kcal/mol).

shows plots of these activation parameters as a function of the atom fraction of deuterium in the solvent. It is easily seen that ΔH^{*} is essentially invariant as the deuterium content changes while ΔS^{*} shows a significant dependence on n. One can, in fact, calculate from the Eyring equation that the solvent deuterium isotope effect on ΔH^{*} is $k_{H_2O}/k_{D_2O} = 0.78$, an inverse effect, while that on ΔS^{*} is 4.01, a very large normal effect. The exact explanation of this result awaits further experiment but obviously suggests that a major portion of the observed solvent isotope effect of 3.07 is entropic in origin.

Succinic Anhydride. The data obtained for succinic anhydride cannot be fit with the fractionation factors given for propionic anhydride without gross changes in the medium-effect term. In fact, the isotope effect is duplicated with assumption of a medium effect of unity, but the curvature of the proton inventory is poorly reproduced with this model as shown by the dashed line in Figure 2. Our data suggest that the transition state for succinic anhydride hydrolysis is shifted toward the tetrahedral intermediate. A good fit of the data is obtained if the incipient hydronium ion proposed in the earlier transition state (1) is allowed to "mature" and the medium effect is taken to be unity. The calculated values in Table I based upon eq 1 with $\phi_a^{*} = \phi_b^{*} = 0.713$ and ME equal to unity illustrate the fit shown in Figure 2 by the solid line. Molecular models indicate that a hydrogen bond between the catalyzing water molecule and the carbonyl oxygen not suffering attack is unlikely. A transition-state structure such as that proposed by Fagley and Oglukian for phthalic anhydride appears to be more likely.[28] Such a structure is shown as 3. Gandour et al. have recently added additional support for this transition-state structure using the proton inventory technique.[17] This analysis, however, included a fractionation factor of 1.31 for the "*gem*-diol" type proton (H_c in 3). *gem*-Diol protons have been shown to have fractionation factors ranging from 1.23 to 1.28, so their assignment of a value of 1.31 to the proton in question is reasonable.[29] Our analysis above has assumed a fractionation factor of unity for H_c in 3 as we have done for the H_c proton in 2 for the acyclic cases. While we cannot incorporate a greater than unity fractionation factor for H_c in 2 and still fit the proton inventories for propionic anhydride (i.e., too little curvature is generated) with reasonable values for H_a and H_b, we can obtain a fairly reasonable fit with this model in 3. Equation 2 assumes

$$k_n = k_0(1 - n + 0.67n)^3(1 - n + 1.2n) \tag{2}$$

equal fractionation factors of 0.67 for the three hydronium ion protons of 3 and incorporates a value of 1.2 for the "*gem*-diol" proton H_c in 3. Although this equation does not generate enough curvature to fit the experimental values, it does come close and cannot be rigorously excluded (see Table I). Any contribution by a proton with a fractionation factor greater than unity will tend to flatten out the observed curvature. The value of 1.2, which is on the low side for a *gem*-diol proton, still allows a reasonable value for the hydronium ion fractionation factor. Raising the value to 1.25 would require a value of 0.33 for the hydronium ion protons. This is an unreasonable value.



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The above discussion points out the continuing problem of the value of the fractionation factor for protons such as H_c in 2 and 3. In most studies a value of unity has been assumed for this proton, but Gandour's study suggests that a value between unity and ~1.25–1.30 for such a proton may be more realistic for transition states resembling fully developed tetrahedral intermediates.

Schowen et al.[30] have found the solvent deuterium isotope effect for succinic anhydride to be 2.76 regardless of whether succinic anhydride or succinic anhydride-d_4 was used. This value is in excellent agreement with our value of 2.75. They have also found an inverse secondary β-

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[28] Fagley, T. F.; Oglukian, R. L. *J. Phys. Chem.* **1969**, *73*, 1438.

[29] Mata-Segreda, J. F.; Wint, S.; Schowen, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 5608–5609.

[30] Gandour, R. D.; Stella, V. J.; Coyne, M.; Schowen, R. L., personal communication of unpublished results.

deuterium isotope effect of $k_H/k_D = 0.92$ for total deuteration of the succinic anhydride. This result would also be consistent with our proposed transition state **3**.

Supporting Data. There are considerable data in the literature that support an argument that fundamental differences in anhydride structure that depend on the cyclic or acyclic nature of the anhydride may be refelected in the transition-state structure for hydrolysis as proposed herein.

Large dihedral angles between the carbonyl groups for several acyclic anhydrides have been found in the gas, liquid, and solid phases.[31-34] Ultraviolet spectra obtained in our laboratory are consistent with these observations. The cyclic, constrained succinic anhydride exhibits a single λ_{max} in solution, consistent with a single conformation, whereas acetic and propionic anhydrides exist as sets of conformers (broad λ_{max} with shoulders) interconvertible by rotational motion about the C–O bonds. This population of conformers is observed in both polar and nonpolar solvents, although the relative populations change with the solvent.

Calculation of Pauling bond orders from literature data for succinic,[35] maleic,[36] formic,[37] and acetic anhydrides[31] as well as methyl acetate[38] and succinimide[39] reveals that the resonance interaction of the ether oxygen with the carbonyl is strongly dependent on structure, being more important for cyclic anhydrides.

The anhydrides also differ rather dramatically with respect to their basicities. In all cases, the cyclic anhydrides are much less basic than the acyclic ones. It appears that this difference in basicity can be attributed in large part to differences in resonance stabilization of the protonated carbonyl group. Upon protonation the acyclic anhydride should be more able to assume a conformation that minimizes some of the unfavorable positive dipole interaction interactions.

The previous arguments support the idea that succinic anhydride has greater resonance stabilization than does acetic anhydride. Jencks has pointed out that the difference in the free energies of hydrolysis for acetic and succinic anhydrides is 7.4 kcal/mol.[40] The more favorable hydrolysis of acetic anhydride is controlled by a favorable dominating enthalpy term and not an entropy term. The entropy terms are both large negative values with that for acetic anhydride being more negative by 7 eu.[41] If succinic anhydride is stabilized to a greater extent by resonance than is acetic anhydride, then it is reasonable that acetic anhydride would have a more favorable enthalpy of hydrolysis. Bunton and co-workers suggested an essentially common mechanism of hydrolysis for acyclic, saturated anhydrides and comparable cyclic anhydrides because of comparable rate constants though they did acknowledge differences in activation energies.[42] This observation may be due more to fortuitous circumstances rather than a commonality of transition states. Nucleophiles other than water react more slowly with cyclic anhydrides than with acyclic ones.[43-50] The enthalpies of activation for the hydrolysis of acetic, propionic, succinic, and phthalic anhydrides are 9.6, 9.5, 12.5, and 11.7 kcal/mol, respectively.[3,4] The source of this enthalpic difference for cyclic anhydrides may be their additional resonance stabilization. With this in mind it is interesting to consider the possibility that different modes of attack of the same nucleophile on different anhydrides with the same steric constraints are interpretable in terms of different reactant-state stabilities. If cyclic anhydrides have greater resonance stabilization in the reactant state, this will effectively cause a decrease in the leaving ability of the carboxylate group and thus require a better nucleophile for nucleophilic catalysis when compared to acyclic anhydrides.

If the carboxylate group of cyclic anhydrides is a poorer leaving group than in acyclic anhydrides, then the transition state for addition of water will be reached later for cyclic anhydrides. Thus, the expulsion of the carboxylate may become partially rate limiting. Gandour et al. have considered a possible rate-limiting breakdown of the tetrahedral intermediate in terms of exocyclic vs. endocyclic displacement (i.e., does the leaving group remain attached to the intermediate?).[17] If the cyclic anhydrides are less strongly hydrogen bonded to water in the reactant state as their weaker basicities would suggest, then the attack of the nucleophile may be hindered because the initial charge buildup on the carbonyl oxygen atom may be less effficiently solvated. This may result in a later transition state for cyclic anhydrides. This is exactly the conclusion drawn from our analysis of the proton inventories which support a transition state involving an "immature hydronium ion" for succinic anhydride solvolysis.

Conclusion

Although we have not been able to find direct evidence for the unusual temperature dependence of the solvent deuterium isotope effect for anhydride hydrolysis being due to changes in tetrahedral intermediate partitioning, we have found two significantly different transition states for propionic vs. succinic anhydride. These two transition states are supported by several other studies of anhydride hydrolysis. We also feel that the available data in the literature strongly support the difference in transition states for cyclic and acyclic anhydrides. Whereas the analysis of Blandamer et al.[5] worked for some anhydrides in some solvents but failed the test of generality, the models proposed in this paper, while they do not explain the temperature dependence, do allow us to reproduce the proton inventories obtained.

Experimental Section

Materials. Propionic anhydride (Aldrich) was purified by distillation as was acetic anhydride (Fisher). In some cases the

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propionic anhydride was allowed to reflux over magnesium turnings for 24 h before distillation. Deuterium oxide (99.8 atom % deuterium; Aldrich) was distilled from barium nitrate to remove basic impurities. Reagent grade acetonitrile was distilled from calcium hydride or phosphorus pentoxide. Deuterium oxide (99.75 atom % deuterium; Bio-Rad) and acetic anhydride-d_6 (99+%-deuterium; Aldrich) were used as received. Succinic anhydride was purified by multiple recrystallizations from ethanol–chloroform followed by vacuum sublimation.

Methods. Kinetic data were obtained by following the rate of propionic anhydride disappearance at 245 nm with a Cary 118C UV–vis spectrophotometer equipped with a thermostated cell holder and compartment. Expanded absorbance ranges were used to monitor the kinetics as the usual initial substrate concentrations (about 10^{-3} M) gave absorbances conveniently displayed on the 0.1–0.2 absorbance range. The runs were followed for at least 3 half-lives (up to 5 or 6 in many cases). Infinity absorbances were determined at 10 half-lives. Reactions were usually initiated by injecting 25 μL of a solution of propionic anhydride in acetonitrile into 3 mL of thermally equilibrated water (protium oxide, deuterium oxide, or a mixture of the two). Some runs were done by injecting propionic anhydride directly in the absence of acetonitrile to check this solvent effect. A nonlinear least-squares computer program was used to determine the rate constants. Plots of log $(A_t - A_\infty)$ vs. time were used in a confirmatory manner. In most cases 25 or more data points were used for each determination. Repetitive scans of the ultraviolet spectra of some of the anhydrides in various solvents were made by using a Cary digital repetitive scan accessory. The hydrolysis of succinic anhydride was followed in a similar fashion at 222.5 nm as was acetic anhydride at 245 nm. The protium oxide and deuterium oxide solutions were prepared by combination of the appropriate volumes of the purified reagents. The deuterium content of the pure deuterium oxide solutions and some of the H_2O–D_2O mixtures was determined by Josef Nemeth.[9] The secondary β-deuterium isotope effect for acetic anhydride hydrolysis was determined by injecting 10 μL of a substrate solution in acetonitrile into water. Alternating runs with the labeled and unlabeled compounds were done. The γ values for the proton inventories were determined by using a computer program, GAMISO, provided by Professor John Albery and modified to run on our computer.

Acknowledgment. We thank Mr. Phil Huskey for performing the polynomial regression analysis.

Registry No. Propionic anhydride, 123-62-6; succinic anhydride, 108-30-5; acetic anhydride, 108-24-7; deuterium, 7782-39-0; water-d_2, 7789-20-0; water, 7732-18-5.

Intramolecular Hydrogen-Bonding Catalysis of Ester Aminolysis in Acetonitrile

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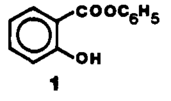
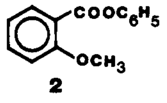
o-Hydroxyphenyl benzoate (3) reacts with 1,3-diaminopropane and 1,4-diaminobutane in acetonitrile according to a two-term rate law (eq 1). The first term of this equation becomes constant when the amine concentration is greater than 0.2 M. Addition of hexamethylphosphoric triamide (HMPT) or tetra-n-butylammonium chloride inhibits this reaction path completely while leaving almost unaffected the path related to the second term of eq 1. These and other results lead to the conclusion that **3** forms a hydrogen-bonded complex with diamines through its o-OH group. HMPT and Bu_4NCl can also form hydrogen-bonded complexes with **3** in competition with diamines, thus inhibiting the reaction path related to the first term of eq 1, whose mechanism is not defined by the present data. On the other hand, the second term of eq 1 relates to a mechanism of intramolecular catalysis by the o-OH group of **3** promoted by bases or in general by hydrogen-bond acceptors. These results stress the importance of hydrogen bonding in intramolecular catalysis in aprotic solvents.

In aprotic media hydrogen-bonding interactions of reagents or addenda with the solvent are absent or low so that the catalytic or inhibiting effect of hydrogen-bond donors or acceptors on the rates of reaction can be studied. This is the case of the intramolecular catalysis of ester aminolysis in acetonitrile by the o-hydroxyl group, which displays reactivity characteristics that cannot be detected in aqueous solvents.

It has been shown that neighboring hydroxyl groups lead to higher rates of aminolysis of esters. Phenyl salicylate, **1**, reacts 132 times faster than phenyl o-methoxybenzoate, **2**, with n-butylamine in acetonitrile.[1]

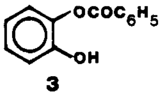


1



2

o-Hydroxyphenyl benzoate, **3**, reacts at least 850 times faster than o-methoxyphenyl benzoate, **4**, with n-butylamine in the same solvent.[2]



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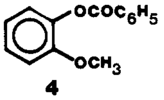

4

However, the mechanisms suggested for catalysis in these reactions of **1** and **3** are different: general acid catalysis was proposed for **1**,[1] and general base catalysis for **3**.[2] The kinetic features displayed by the two substrates are so different that they can hardly be attributed to the same catalytic role of the hydroxyl group. More recently it was suggested that the neighboring OH group of **3** can also react as a general acid.[3] Although we had not ex-

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