Proton Inventory of Phthalic Anhydride Hydrolysis. Comments on Analysis of Proton-Inventory Data[1]

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The spontaneous hydrolysis of phthalic anhydride exhibits rate constants k_n in mixtures of deuterium oxide (atom fraction n of deuterium) and protium oxide which are best described by the equation $10^6 k_n = 1058(1 - n + 0.69n)^3(1 - n + 1.33n)$ s^{-1}. This result suggests a hydronium ion and a *gem*-diol-like proton as structural features in the rate-limiting transition-state structure. Two such structures, 3 and 4, are proposed as consistent with this result and previous mechanistic studies. A thorough analysis of nonlinear equations used in proton inventory studies is presented and the criteria for evaluating a "good fit" are discussed.

Water-catalyzed (spontaneous) hydrolyses of a number of reactive acyl compounds have been the subject of recent study.[3-7] The rate-limiting transition-state structure[8] receiving the most support is that involving a water dimer, 1. One H_2O serves as a "general base" and the other H_2O
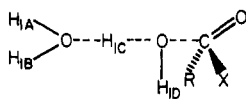
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as the nucleophile. A large part of the support for this structure comes from Brønsted plots, solvent isotope effects, and proton inventories. In proton-inventory studies,[5,6,8] support for 1 arises from a nonlinear dependence of k_n, the observed rate constant in a mixture of H_2O and D_2O, on n, the atom fraction of deuterium in that mixture:

$$k_n = k_0(1 - n + n\phi_1)^2(1 - n + n\phi_{1C}) \qquad (1)$$

where k_0 is the rate constant for hydrolysis in pure H_2O and $\phi_1 (= \phi_{1A} = \phi_{1B})$ and ϕ_{1C} are fractionation factors for H_{1A}, H_{1B}, and H_{1C}. The usual assumption is that ϕ_{1D} is unity. Frequently, the net solvent isotope effects (k_0/k_n where $n \approx 1$) in these cases[5-8] are quite large (>2.5), with $\phi_1 = 0.85 \pm 0.05$ and $\phi_{1C} = 0.5 \pm 0.1$.

The classic example of water-catalyzed hydrolysis involving a transition-state structure like 1 is anhydride hydrolysis. In fact, the proton inventory of acetic anhydride hydrolysis is the benchmark study[8] for the proposal of 1 as a rate-limiting transition-state structure. At 25 °C, the kinetic solvent isotope effect (2.2) for the hydrolysis of phthalic anhydride is unique among those reported (≥2.7) for other anhydrides.[7] The relatively low value of the solvent isotope effect for phthalic anhydride hydrolysis warrants a proton-inventory study to examine whether or not the rate-limiting transition-state structure may be different from 1 or just an atypical example of 1. Furthermore, the recent increase in the number of proton-inventory studies[5,6] prompts us to make some comments on the analysis of proton-inventory data. Thus, the purpose of this report is twofold: to report a proton inventory of the hydrolysis of phthalic anhydride and to discuss the criteria for distinguishing a "good fit" of data to a set of nonlinear equations of n vs. k_n.

Results

Pseudo-first-order rate constants, k_{obsd}, for solvolysis of phthalic anhydride at 25 °C in the presence of acetate buffer (1:9 [HOAc]:[⁻OAc]) have been measured in several

(1) This work was supported in part by the National Science Foundation (Grants GP 38515X and MPS 73-08716).

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Table I. Rate Constants for Spontaneous Solvolysis (k_s)
of Phthalic Anhydride in H_2O–D_2O Mixtures of Atom
Fraction Deuterium n at 25.00 ± 0.05 °C

atom fraction of deuterium, n	$10^6 k_s$, s^{-1}
0.00	1051 ± 4^a
0.10	996 ± 9
0.20	938 ± 8
0.30	876 ± 4
0.40	807 ± 4
0.50	739 ± 3
0.60	680 ± 3
0.70	625 ± 4
0.80	567 ± 3
0.90	518 ± 1
0.99	472 ± 2

^{a} Standard error of estimate.

H_2O–D_2O mixtures. The rate constant for spontaneous hydrolysis, k_s, is obtained by a linear least-squares fit to eq 2. The concentration of acetate has been varied from

$$k_{obsd} = k_s + k_{OAc}[^-OAc] \qquad (2)$$

0.02 to 0.1 M and the ionic strength has been maintained at 0.1. Values for k_s as a function of n, the atom fraction of deuterium in a given H_2O–D_2O mixture, are reported in Table I. Our values for k_s at n = 0.0 and n = 0.998 are within 1% of those measured by conductometric methods.[7]

The standard errors of estimate for k_s range from 0.2 to 1.0% with a mean of 0.5%. The precision of these measurements is well within the requirements for distinguishing a linear from a two-proton fit, a two-proton from a three-proton fit, and a three-proton from a four-proton fit, 3.5, 1.3, and 0.7%, respectively.[9] Mathematical analyses of these data have been performed by a least-squares curve-fitting procedure.[10]

Discussion

The proton-inventory technique has been successfully employed recently to propose transition-state structures for a number of chemical and biochemical reactions. Details of the theory and methods of application have been presented many times.[11] The basic relationship between k_n and n is expressed in eq 3, where TS refers to transition

$$k_n = k_0 \prod_i^{TS}(1 - n + n\phi_i) \Big/ \prod_j^{RS}(1 - n + n\phi_j) \qquad (3)$$

state and RS refers to reactant state. All exchangeable transition-state hydrogenic sites, i, that contribute to the observed solvent isotope effect constitute the numerator of eq 3, while exchangeable reactant-state protons, j, constitute a similar term in the denominator. The fractionation factor ϕ is an expression of the preference for deuterium at an exchangeable site relative to the deuterium preference in the average solvent site. Since in the reactant state all of the exchangeable sites are solvent molecules, ϕ_j = 1 and the denominator of eq 3 is unity.

Chemical and Mathematical Models. Depending on the transition-state structure proposed, various mathematical models of eq 3 can be analyzed with respect to the

data in Table I. A rate-determining unassisted nucleophilic attack of a water molecule can be described as transition-state structure 2. This structure would be consistent

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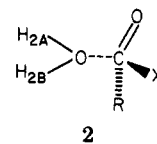
with a quadratic equation (eq 4) where ϕ_2 = ϕ_{2A} = ϕ_{2B} or

$$k_n = k_0(1 - n + n\phi_2)^2 \qquad (4)$$

a variation (eq 5) where $\phi_{2A} \neq \phi_{2B}$. In addition to eq 1,

$$k_n = k_0(1 - n + n\phi_{2A})(1 - n + n\phi_{2B}) \qquad (5)$$

transition-state structure 1 would be consistent with eq 6 (ϕ_{1A} = ϕ_{1B} = ϕ_{1C}) and eq 7. In both cases, only three

$$k_n = k_0(1 - n + n\phi_1)^3 \qquad (6)$$

$$k_n = k_0(1 - n + n\phi_{1A})(1 - n + n\phi_{1B})(1 - n + n\phi_{1C}) \qquad (7)$$

protons (ϕ_{1D} = 1) are contributing to the net solvent isotope effect. Furthermore, mathematical models where all four protons (eq 8–11) are contributing should be consid-

$$k_n = k_0(1 - n + n\phi_1)^4 \qquad (8)$$

$$k_n = k_0(1 - n + n\phi_1)^3(1 - n + n\phi_{1D}) \qquad (9)$$

$$k_n = k_0(1 - n + n\phi_1)^2(1 - n + n\phi_{1C})(1 - n + n\phi_{1D}) \qquad (10)$$

$$k_n = k_0(1 - n + n\phi_{1A})(1 - n + n\phi_{1B})(1 - n + n\phi_{1C}) \times (1 - n + n\phi_{1D}) \qquad (11)$$

ered as well. Inclusion of a term for the fourth proton is not unreasonable in view of the fact that *gem*-diols (models for tetrahedral intermediates) have fractionation factors larger than unity.[12] Since the precision of the measured rate constants is only slightly better than that required (0.7%) to distinguish between a three-proton fit and a four-proton fit, some caution should be applied in proposing a four-proton model over a three-proton model. Finally, a linear model (eq 12) needs to be considered.

$$k_n = k_0(1 - n + n\phi) \qquad (12)$$

Although the linear model is difficult to reconcile with likely transition-state structures, it is necessary for comparison with the other models in order to establish the validity of using nonlinear models to explain the data.

Mathematical Analysis. The results of the analyses of the mathematical models are presented in Table II. The equations are grouped according to the number of fitted parameters. Equations with greater than three fitted parameters (eq 7, 10, and 11) have been excluded because the solutions to these equations are identical to those equations with fewer parameters. For example, the best fit to eq 7 is ϕ_{1A} = ϕ_{1B} = 0.62 and ϕ_{1C} = 1.16. A similar situation occurs with eq 10 and 11. The best fit for eq 10 and 11 results when the parameters in these equations resemble the solutions for eq 9. The results presented in Table II represent the best fit for the individual models with no constraints placed on any of the variable parameters. Various initial values have been given to the variable parameters to ensure that the convergence procedure is giving all possible solutions. In the case of eq 1 and 9, two solutions have been obtained.

The criteria for selection of the best fit for a series of nonlinear equations are not well-established. The *F* value

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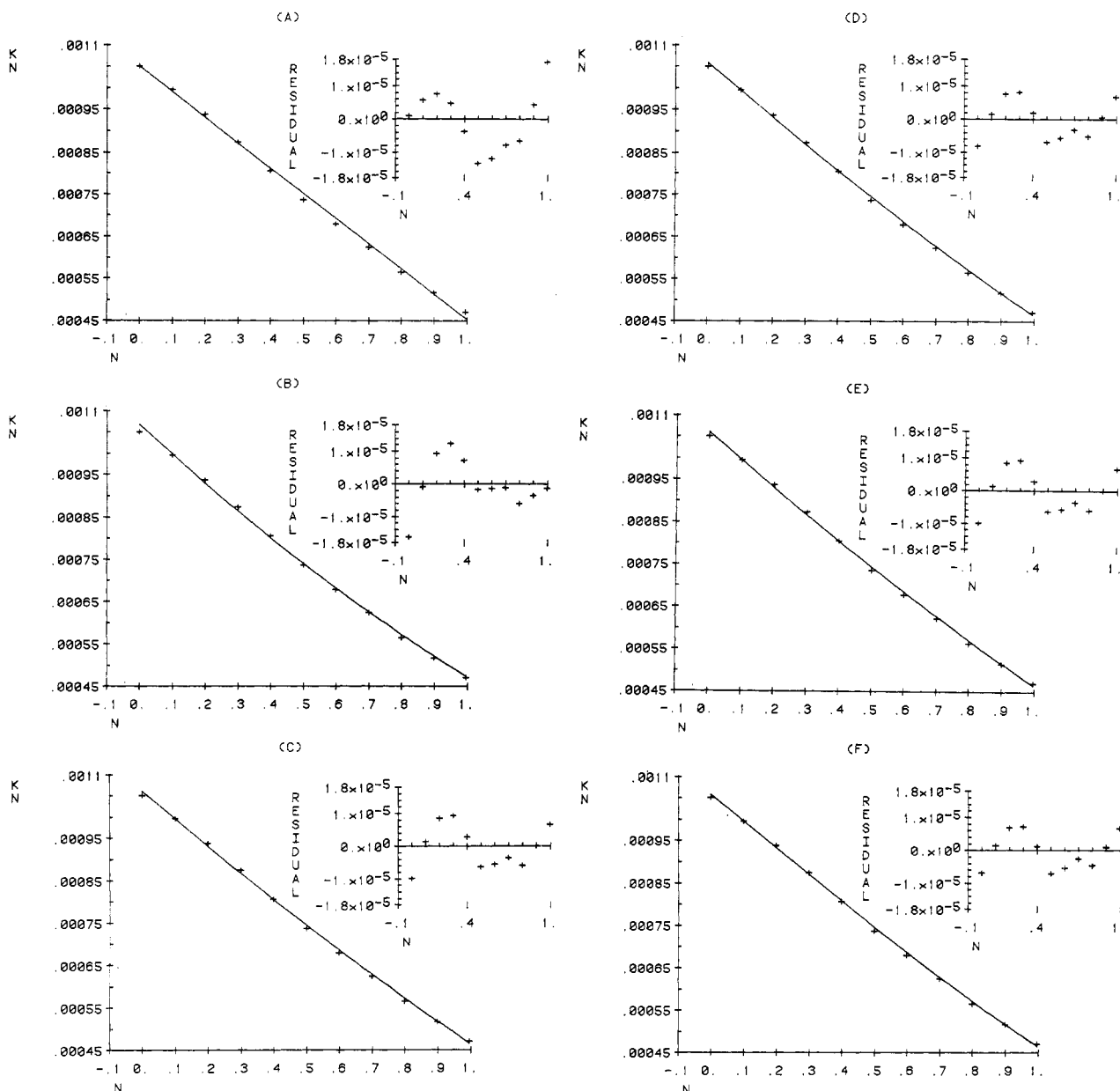
Figure 1. Comparison of mathematical models: (A) eq 12, (B) eq 4, (C) eq 1, solution a, (D) eq 1, solution b, (E) eq 9, solution a, (F) eq 9, solution b with experimental values of k_n (+). Inset plots are residuals (+), k_n(obsd) − k_n(calcd) vs. n. See Table II for parameters of the fitted functions.

is commonly used when comparing several fits with the same number of adjustable parameters. With this criterion, eq 4 is best among the equations with two parameters, while eq 9 is best among the equations with three parameters. However, it should be stated that by using the F-value criterion alone all equations are significant at the 0.0001 level.

Comparison of the residual sum of squares (or sum of squares due to error) may be more revealing, since this is the criterion for convergence in the modeling program. A residual is the vertical distance on the plot between the observed value and the fitted value. An observed value above the fitted value results in a positive residual, while a value below the fitted gives a negative residual. Thus, the smaller the residual sum of squares, the closer the observed values are to the fitted values.

The standard deviation of the regression is a measure of the precision to which predictions can be made. Since it is the square root of the mean square due to error (residual sum of squares/degrees of freedom), it is a better criterion for comparison of equations with different num-

bers of adjustable parameters than the residual sum of squares. As before, the smaller the value of the standard deviation of regression, the better the fit.

By use of these two criteria, eq 9, solution b, emerges as the best fit. However, the significance of the improvement in fit of an equation with more variable parameters than another must be determined by the partial-F statistic. This statistic compares the additional sum of squares that are accounted for by a new term relative to the size of the random error. The partial F statistic[13] for eq 9, solution b, relative to eq 4 is 8.1. From this value it can be stated at a 0.02 level of confidence that the additional term is very useful to the fit of the data.

Another approach to establishing a good fit is residual analysis. However, this type of analysis is somewhat less

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(13) The partial F statistic is computed by comparing the difference in the residual sum of squares (SS) of the two equations to the mean-square residual (residual SS/degrees of freedom in the residual) for the equation with more adjustable parameters, for example, eq 9, solution b, vs. eq 4: $(601 − 298)/(298/8) = 8.1$.

Table II. Summary of Statistical Analyses of Mathematical Models from Curve-Fitting Procedure

equation	F value	10^8 SD regression	10^{12} SS of residual	calcd $10^6 k_0$	fractionation factors	Figure 1
			A. Two-Parameter Equations			
12	4003	987	877	1049	$\phi = 0.432$	A
4	5843	817	601	1067	$\phi_2 = 0.665$	B
6	3254	1095	1078	1072	$\phi_1 = 0.764$	
8	2473	1255	1417	1075	$\phi_1 = 0.818$	
			B. Three-Parameter Equations			
5	3734	723	418	1061	$\phi_{2A} = 0.51; \phi_{2B} = 0.86$	
1 (a)	3671	729	425	1061	$\phi_1 = 0.93; \phi_{1C} = 0.50$	C
1 (b)	4388	667	356	1059	$\phi_1 = 0.62; \phi_{1C} = 1.16$	D
9 (a)	3652	731	428	1061	$\phi_1 = 0.96; \phi_{1D} = 0.50$	E
9 (b)	5251	610	298	1058	$\phi_1 = 0.69; \phi_{1D} = 1.33$	F

objective than the criteria discussed in preceding paragraphs. In Figure 1 are illustrated plots of the data from Table I (n vs. k_n) along with calculated values of the various equations (Table II) and plots of residuals vs. n. In all six plots there are definite patterns to the signs of the residuals and increasing values of n (e.g., Figure 1(B): $-,-,+,+,+,-,-,-,-,-,-$). For Figures 1A and 1B, eq 12 and 4, respectively, there are two changes in sign, while Figures 1C–F, eq 1, solutions a and b, and eq 9, solutions a and b, respectively, reveal three sign changes. A greater number of sign changes reveals more randomness in the errors. Another approach is to examine the distribution of the residuals, i.e., the number of positive and negative residuals as well as their individual values. Comparison of Figures 1B and 1F, eq 4 and 9, solution b, respectively, illustrates this approach. In Figure 1B there are three positive and eight negative residuals, while in Figure 1F there are six positive and five negative residuals. The values of the residuals range from -1.6×10^{-5} to 1.3×10^{-5} in Figure 1B and from -0.6×10^{-5} to 0.8×10^{-5} in Figure 1F. Thus, residual analysis supports eq 9, solution b, Figure 1F, as the best fit to the data.

Combining all the above criteria suggests that eq 9 is the best fit. Albeit the largest F value is for eq 4, residual analysis, residual sum of squares, and standard deviation of regression indicate a significant improvement in the fit with eq 9, solution b. All the three-parameter equations are equivalent in their pattern of residuals, and eq 1 and 9 have a similar distribution of residuals. Visual inspection of the plot of eq 9, solution b, with the experimental data, Figure 1F, reveals an excellent fit. From the mechanistic viewpoint though, the most crucial test of any acceptable equation is its agreement with the chemistry.

Chemical Analysis. Nucleophilic attack by a water molecule (2) would be consistent with eq 4 as the best fit. The calculated fractionation factor (0.665) is just slightly lower than expected (0.69) for a hydrogen attached to an oxygen with a positive charge.[14] This value for ϕ_2 suggests that if the nucleophilic mechanism is operating and 2 is an accurate picture of the transition state (rate-determining attack), then the charge transfer from oxygen to the carbonyl carbon is completed. If breakdown of a zwitterionic intermediate is rate limiting, then hydrogenic sites on additional solvent molecules needed in the breakdown step must have fractionation factors close to unity.

The protolytic mechanism for hydrolysis (1) would be consistent with eq 1 and 9. In this transition-state model one water molecule serves as a general base to abstract a proton from the attacking water molecule. This model has four protons which could contribute to the overall solvent

isotope effect. The proton H_{1D} is usually assumed to have a fractionation factor of unity. The "in-flight" proton H_{1C} should have a ϕ value close to 0.5 which corresponds to a primary isotope effect of 2.0, a typical value in general-base protolytic reactions.[15] The two protons H_{1A} and H_{1B} ($\phi_{1A} = \phi_{1B} = \phi_1$) should contribute secondary isotope effects with ϕ values dependent on the Brønsted β value. In previous reports,[5] estimates of ϕ_1 have been made from the observed Brønsted β, usually 0.33 ± 0.02, and eq 13,

$$\phi_1 = (\phi_1^{RS})^{1-\beta}(\phi_1^{PS})^\beta \tag{13}$$

where PS refers to product state. Substituting unity for ϕ_1^{RS} and 0.69 for ϕ_1^{PS} (ϕ for a hydronium ion proton) gives an estimate of $\phi_1 \approx 0.88$. In our case, the Brønsted β can be estimated from the calculated value of ϕ_1. Of the two solutions to eq 1, solution a agrees with the above discussion better than solution b. The Brønsted β estimated from $\phi_1 = 0.93$ is 0.20, a decidedly small value. However, solution a is a poorer fit than solution b, but a chemical model for solution b is more difficult to picture. The ϕ_{1C} value of 1.16 would actually represent ϕ_{1D}, since ϕ values for *gem*-diol hydrogens are known to be larger than unity.[12] For solution b, ϕ_1 must be some combination of ϕ_{1C} and ϕ_{1A} (or ϕ_{1B}), since ϕ_{1A} or ϕ_{1B} would not be expected to have a ϕ value smaller than 0.69 (cf. ϕ for hydronium ion[14]). This dilemma is resolved by examining solution b of eq 9.

Solution b of eq 9 strongly implies that there is a full hydronium ion in the transition state since $\phi_1 = 0.69$! The ϕ_{1D} value of 1.33 suggests a *gem*-diol proton. Two transition-state structures, 3 and 4, would be consistent with

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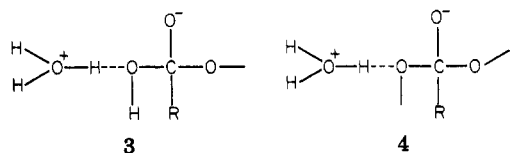
these ϕ values. Structure 3 represents a "very late" version of 1, rate-determining formation of the tetrahedral intermediate. Structure 4 represents a "very early" transition state for rate-determining breakdown of the intermediate. It is also possible that both 3 and 4 contribute with both formation and breakdown partially rate limiting. The large ϕ value of 1.33 (cf. ϕ for *gem*-diols[12] 1.23–1.28) could be explained by the presence of the oxyanion and/or the fact that the intermediate has three oxygens attached to the same carbon. In any event, these suggested transition-state structures from our proton-inventory work must be compared in the light of previous work.

Comparisons with Previous Work. Rossall and Robertson[7] in their temperature-dependence studies of

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kinetic solvent isotope effects in solvolysis of anhydrides have proposed that the breakdown step might be partially rate determining. Hawkins,[16] from his kinetic studies, favors the transition-state structure 1 proposed by Batts and Gold.[8] Fagley and Oglukian[17] suggest from their studies in dioxane–water mixtures that the transition-state structure for solvolysis is highly solvated. Thus, all of these authors favor at least two water molecules or their equivalent as part of the transition-state structure.

Mechanistic Possibilities. Our proton-inventory study is consistent with the hypothesis[7] of two partially rate-determining steps, k_1 and k_2. The only difficulty with this

$(T^- \cdot H_3O^+)$
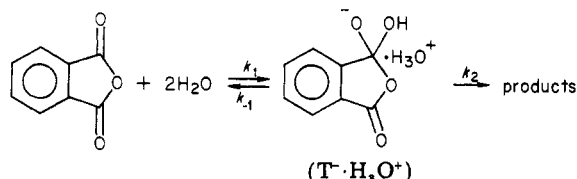
hypothesis is explaining why k_{-1} is of similar magnitude to k_2. On the basis of leaving-group abilities, the carboxylate group should be better than hydroxide but perhaps not as good as acid-catalyzed removal of OH. The latter suggestion requires a tight ion pair of T^- and H_3O^+ as well as preferential catalysis of OH departure over carboxylate departure. Another suggestion to explain the similar magnitudes of k_{-1} and k_2 is an intramolecular effect. In this case, it is an exocyclic vs. endocyclic displacement problem,[18] viz., whether or not the leaving group remains attached to the intermediate. This concept developed from hydrolysis studies of dicarboxylate half-esters suggests that the carboxylate is a much better nucleophile in intramolecular reactions than in intermolecular reactions. This enhancement in nucleophilicity is directly proportional to the equilibrium constant for cyclic anhydride formation.[19] The carboxylate on a phthalate half-ester can displace leaving groups as poor as 2,2,2-trifluoroethoxy.[20] Thus, this tendency toward cyclization should make a ring-opening reaction like k_2 relatively more difficult than might be expected from an analysis of the basicities of the potential leaving groups.

An alternative possibility consistent with mathematical model suggests a transport step as rate determining. This transport step involves the dissociation of the tight ion pair $(R^- \cdot H_3O^+)$ formed either by the protolytic mechanism 1 or by a relatively fast proton transfer from phthalic anhydride hydrate (T^0) to water.

Conclusion and Caveats. Transition-state structures 3 and/or 4 for phthalic anhydride hydrolysis are consistent with the mathematical model that best describes the ex-

T^0

$(T^- \cdot H_3O^+) \xrightarrow{\text{slow}} T^- + H_3O \xrightarrow{\text{fast}} \text{products}$
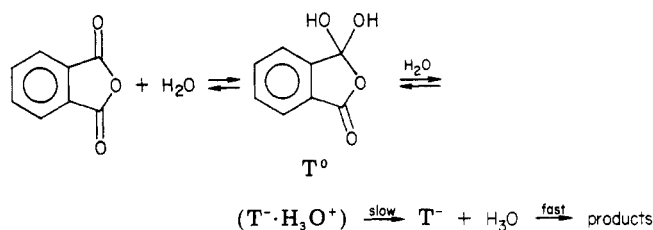
perimental data. These structures have been suggested by others[7] as well. The notion that the breakdown step k_2 is partially (or wholly) rate determining can be rationalized by the endocyclic-displacement hypothesis[18] discussed above. An alternate suggestion that a transport step, dissociation of $(T^- \cdot H_3O^+)$, is rate-limiting is consistent with the model as well.

This proton-inventory study is another example of the utility of this technique in providing detailed information about transition-state structures. This study demonstrates that with enough data points (≥ 11) of high precision, a statistically significant evaluation of a series of nonlinear functions can be made. The novel result from this analysis is the suggestion of a hydrogenic site with a ϕ value greater than unity. The recent equilibrium measurements[12] of fractionation factors greater than unity for protons attached to oxygens of *gem*-diols add support to this novel finding.

Experimental Section

Materials. Sodium acetate and acetic acid were purified as described.[21] Potassium chloride (Baker reagent grade) was dried in an oven at 130 °C for 24 h. Dioxane was distilled from lithium aluminum anhydride. Water was double distilled and deuterium oxide (Aldrich, gold label) was redistilled. Phthalic anhydride was recrystallized from benzene.

Solvent mixtures were prepared gravimetrically. Buffer solutions also were prepared gravimetrically and contained a ratio of acid–base of 1:9. Four buffer solutions were prepared for each solvent mixture: 0.025, 0.05, 0.075, and 0.1 M in acetate. Ionic strength was maintained at 0.1. Five buffer solutions were prepared in "pure" water: 0.02, 0.04, 0.06, 0.08, and 0.1 M in acetate.

Kinetic Procedure. The instrumentation employed has been described elsewhere.[22] Experiments were conducted in thermostated cell holders and were initiated after thermal equilibration. Initiation of reaction was accomplished by injection of 25 μL of a 4 × 10⁻² M solution of anhydride in dioxane into 3 mL of buffer contained in a 1-cm cuvette. A decrease in absorbance was monitored at 298 nm.

Registry No. Phthalic anhydride, 85-44-9.

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