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Tetrahedral Intermediate in Acyl Transfer Reactions. A Revaluation of the Significance of Rate Data Used in Deriving Fundamental Linear Free Energy Relationships

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Abstract: A theoretical investigation of model mechanisms applicable to acyl transfer reactions in solution has shown that the interpretations of experimental rate constants in terms of mechanistic constants are all subject to an ambiguity that is well-known in principle but usually ignored or incorrectly evaluated in practice. For all models involving reversibly formed tetrahedral intermediates, the experimental constants are products of the form $k_f f_p$ in which k_f is equal to $k_i[H^+]^n$ or to k_i[cat] and f_p is a product distribution fraction. Each accessible pH range can give a maximum of one constant that depends on the pH; there is no way to dissect out the desired mechanistic constants or the equilibrium constants for the several tetrahedral intermediates unless some independent means can be developed to measure the f_p. These conclusions are of major concern to all studies that attempt to relate reactivity to structure. Representative acyl transfer reactions have been reinterpreted. One example of the so-called trialkyl lock acceleration is now shown to amount to a factor of about 4000 for the mechanistic rates in contrast to the factor of 5×10^{10} originally proposed. Most of the decrease in estimate arises from recent reevaluations of the observed rates, but there is a further decrease by a factor of 100 in the mechanistic rates due to considerations treated in the present study. Evidence is also presented that certain acyl transfer reactions in solution may proceed by direct displacement rather than through a reversibly formed tetrahedral intermediate.

We have been interested in the theoretical calculation of steric effects on reaction rates and have sought ways to enlarge the range of experimental data suitable for testing the calculated values.[1] The largest available collection of quantitative data on steric effects is that for esterification and ester hydrolysis.[2] Another potentially useful reaction for the study of steric effects is aminolysis of esters, also an acyl transfer reaction. In order to compare observed rate data with theoretical calculations, it is necessary to be able to interpret the observed values in terms of rate constants for a defined mechanism. This obvious requirement has often been slighted or overlooked altogether.

Acyl transfer reactions in solution are generally believed to proceed through tetrahedral intermediates. Examples that have attracted considerable interest in recent years are aminolysis of esters,[3,4] lactam formation,[5,6] hydrolysis of imidates,[7-14] lactonization,[15,16] and others.[17-24] An alternative mechanism for acyl transfer is direct displacement of the S_N2 type.

Recent gas-phase studies bear on these two mechanisms. The gas-phase bimolecular reactions of methoxide anion and of other anions with phenyl acetate do not give acyl transfer at all but give instead nucleophilic aromatic substitution to form anisole or corresponding products.[25a] However, a termolecular gas-phase acyl transfer to form methyl acetate does occur in reaction of a methanol–methoxide complex with phenyl acetate. These results indicate that the direct bimolecular S_N2 acyl transfer is not favored, but they do not rule out some form of displacement involving a more complex transition state.

The other gas-phase study treated acyl transfer reactions of protonated acetic acid and its derivatives.[25b] In contrast to the methoxide results the acidic gas-phase acyl transfers seemingly do involve a displacement mechanism.

Direct observation of an intermediate would, of course, provide an unambiguous demonstration. Although such intermediates have long been known for carbonyl reactions of aldehydes and ketones, they have not been observed for the carbonyl reactions of esters except for special structures.[21] Nevertheless, most acyl transfer reactions in solution can be understood in terms of postulated tetrahedral intermediates present in low concentrations. Variants of the mechanisms account consistently for details of pH–rate profiles[3-24] and for other data such as isotopic exchange and isotopic effects.[26-28] A critical examination of the mechanisms of acyl transfer leads me to postulate that certain reactions in solution, particularly certain aminolysis reactions, may proceed

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instead through some type of direct displacement rather than through a kinetic intermediate.

The correct mechanistic expressions for a mechanism involving a simple intermediate are well-known:[29]

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_2} C$$

$$k_{obsd} = k_1 f$$

$$f = k_2/(k_{-1} + k_2)$$

If $(k_{-1} + k_2) >> k_1$ so that the steady-state approximation is valid, then under pseudo-first-order conditions k_{obsd} may be expressed as the product of a rate constant k_1 and a distribution factor f (which has a value between 0 and 1). Unless the concentration of B can be directly monitored, there is no way to dissect out the value of k_1. This important property is general whether the mechanisms are simple or complicated. Observed rate constants or the derived phenomenological constants for acyl transfer reactions must always be considered to be complex.

Most structure reactivity correlations (including our own) have failed to appreciate the significance of this ambiguity. Since such reactions as esterification and ester hydrolysis form the basis of many correlations based on the Hammett[30] equation or the Taft equation,[2,31] it is a matter of some importance to examine the consequences of the distribution term. Fortunately it turns out that this term is almost certainly nearly unity for alkaline hydrolysis of esters.

The purpose of the present study is to present a theoretical analysis of representative mechanistic models applicable to acyl transfer reactions and to evaluate the relationships between experimentally accessible rate constants and mechanistic constants.

In the models T represents a family of tetrahedral intermediates while T^+, T^0, and T^- designate the several levels of protonation. The models treated are (1) T^- irreversible, (2) T^+ reversible, (3) T^+ and T^0 irreversible, (4) T^+ and T^- irreversible, (5) T^+, T^0, T^- irreversible, (6) T^+, T^0, T^- reversible, (7) T^+, T^0, T^- irreversible, multichannel.

The first two models apply particularly to ester hydrolysis and present new perspectives for these well-studied reactions. The treatment is based throughout on the steady-state approximation. Since all intermediates are present in low concentrations, the approximation is expected to be reliable. All models assume further that the tetrahedral intermediates are in protonic equilibrium. In consequence the several concentrations are related by the well-known relationships in eq 0.1–0.4.

$$[T^+] = [H^+]^2[T]/D \qquad (0.1)$$

$$[T^0] = [H^+]K_{T^+}[T]/D \qquad (0.2)$$

$$[T^-] = K_{T^+}K_{T^0}[T]/D \qquad (0.3)$$

$$D = [H^+]^2 + [H^+]K_{T^+} + K_{T^+}K_{T^0} \qquad (0.4)$$

The experimental rate constant k_{obsd}, eq 0.5, is usually defined

$$d[P]/([E_{total}][A_{total}]dt) = k_{obsd} \qquad (0.5)$$

in terms of total concentrations of reactants while the rate constant k'_{obsd} applicable in the mechanistic kinetics expressions is based instead on the concentrations of free E and free A, eq 0.6. The

$$d[P]/([E_{free}][A_{free}]dt) = k'_{obsd} \qquad (0.6)$$

well-known relationship between k_{obsd} and k'_{obsd} is shown in eq 0.7–0.9. For acidic reactants f_e and f_a are to be replaced by whatever equivalent form is applicable.

$$k'_{obsd} = k_{obsd}/(f_e f_a) \qquad (0.7)$$

$$f_e = K_{EH}/([H^+] + K_{EH}) \qquad (0.8)$$

$$f_a = K_A/([H^+] + K_{AH}) \qquad (0.9)$$

Table I. Comparison of E_s Values[a]

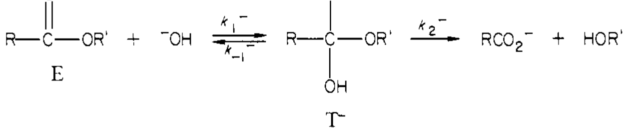
R	$-E_s$	$-E_s'$	$-E_s^b$
CH_3	0	0	0
CH_3CH_2	0.07	0.08	0.05
$CH_3CH_2CH_2$	0.36	0.31	0.35
$CH_3CH_2CH_2CH_2$	0.39	0.31	0.37
$(CH_3)_2CH$	0.47	0.48	0.50
$(CH_3)_2CHCH_2$	0.93	0.93	0.92
$CH_3CH(CH_2CH_3)$	1.13	1.00	1.03
$(CH_3)_3C$	1.54	1.43	1.58

[a] E_s, ref 2a, Table VI; E_s', ref 2b; E_s^b, see text.

I shall usually avoid using the phrase "rate-limiting step" since the intended meaning is all too often ambiguous. The pertinent quantities are the rate constants for the steps which lead into the tetrahedral manifold and either the several distribution fractions or else the related rate constant ratios. The best way to make the meaning clear is through reference to the rate constants, fractions, or ratios symbolically.

Model 1. Scheme I. T^- Irreversible.

Scheme I



$$k'_{obsd} = \frac{k_2^-}{k_{-1}^- + k_2^-}k_1^- \qquad (1.1)$$

$$k'_{obsd} = f_p^- k_1^- \qquad (1.2)$$

$$f_p^- = k_2^-/(k_{-1}^- + k_2^-) \qquad (1.3)$$

$$r_p^- = k_2^-/k_{-1}^- \qquad (1.4)$$

For aryl esters it is generally postulated that $k_2^- > k_{-1}^-$; f_p^- should therefore be nearly unity for base-catalyzed hydrolysis of aryl esters. The Hammett $\rho\sigma$ data for aryl benzoates are consistent with this postulate. This point is discussed further below.

Ester $C{=}^{18}O$ exchange provides evidence as to what r_p^- values may be expected for benzoate esters. The $k_{hydrol}/k_{exchange}$ values depend on solvent and on the ester. Typical values are 30–100 for methyl benzoates and 4–10 for ethyl and isopropyl benzoates. Lower values are reported for CF_3COOCH_3.[26-28] If protonic equilibration is fast in T^-, these values indicate that alkoxide loss is faster than OH^- loss. Kirsch proposed that internal H bonding between OH and O^- in T^- might retard loss of OH^- in comparison with OR^- although relative basicities would lead one to expect that loss of OH^- would be faster. Since the two oxygen atoms of a tetrahedral intermediate are about 2.3 Å apart, such a suggestion is plausible. An alternative but related suggestion is that loss of ROH (instead of OR^-) could occur directly through a multicenter transition state; no such channel is available for loss of OH^-.

Proton equilibration in T^- can occur by at least four mechanisms. These are (1) a direct intramolecular proton transfer, (2) a cyclic version involving one or more solvent molecules, (3) reaction with water to form T^0, and (4) reaction with OH^- to form T^{2-}. The reverse of step 3 is expected to be diffusion controlled, and the forward rate constant will therefore be about 10^8. This is based on a pK_a of 11.6 for T^0 as summarized in Table III. Since pK_a for T^- is estimated to be about 15.0, both rate constants for mechanism 4 should be nearly diffusion controlled. Rate constants for mechanisms 1 and 2 are not known, but solvent-promoted exchange for ammonium ions has rate constants in excess of 10^8. If these estimates are correct, then proton exchange in T^- should occur with rate constants approaching diffusion limits.

The rate constants for k_{-1}^- are not known. The rate constant for loss of OH^- from $HOCH_2O^-$ is about 10^3, and rates of loss

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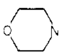
Table II. Product Distributions from Tetrahedral Intermediates R'C(OH)(OR')NR_2(T^o)

R''	OR'	NR	pK_T[a]	pK_{T^o}[b]	f_p^{+}[c]	f_p^{o}[c]	ref
CH_3	$OC_6H_4CH_3$-*p*	$(CH_3)_2N$	6.7	11.7[k]	0.82	1.0	*d*
CH_3	$OC_6H_4CH_3$-*p*	CH_3NH	7.3	11.7[k]	0.88	1.0	*d*
CH_3	$OC_6H_4NO_2$-*m*	CH_3NH	7.0	10.7[k]	0.90	1.0	*d*
CH_3	OC_2H_5	*i*-$PrNCH_3$	10.2	12.6	0	0.35	*e*
CH_3	OCH_2CF_3	CH_3NH	6.5	11.5	0	0.95	*f*
CH_3	$OCH_2CH_2OCH_3$	CH_3NH	9.4	12.3	0	0.8	*f*
CH_3	OC_2H_5	CH_3NH	9.8	12.6	0	0.6	*f*
H	OCH_3		7.7	(12.3)	0	1.0	*g*
CH_3	OCH_3	$C_6H_5CH_2CH(CH_3)NH$	8.5	12.6	0	0.97	*h*
CH_3	OC_2H_5	$(CH_3)_2N$	10.2	12.6	0.04	0.22	*i*
CH_3	OC_2H_5	$(C_2H_5)_2N$	10.3	12.6	0.14	0.28	*i*
CH_3	OC_2H_5	*i*-Pr_2N	10.6	12.6	0.40	0.94	*i*
CH_3	OC_2H_5	$C_2H_5NCH_3$	10.3	12.6	0.08	0.20	*i*
CH_3	OC_2H_5	$C_6H_5NCH_3$	7.9	(12.6)	0	0.86	*i*
CH_3	OC_2H_5	C_6H_5NH	7.7	11.1	0	0.97	*h*
H	OC_2H_5	*p*-$CH_3OC_6H_4NH$	6.7	11.1	0	1.0	*j*
H	OC_2H_5	C_6H_5NH	6.5	11.1	0.05	1.0	*j*
H	OC_2H_5	*p*-ClC_6H_4NH	6.4	10.8	0.08	1.0	*j*
H	OC_2H_5	*m*-$O_2NC_6H_4NH$	6.1	10.3	0.	1.0	*j*
H	OC_2H_5	*p*-$O_2NC_6H_4NH$	5.7	10.1	0.12	0.98	*j*

[a] Apparent. [b] From the linear free energy equation of Table III. For CF_3CH_2O $\sigma_I = 0.42/2.8 + 0.27$. [c] Product distribution fractions, eq 3.4, 4.1, 7.1. [d] Satterthwaite and Jencks.[14] [e] Caswell and Schmir.[36] [f] Pletcher et al.[37] [g] Blackburn and Jencks.[38] [h] Chaturvedi and Schmir.[39] [i] Smith and Schmir.[40] [j] Okuyama et al.[11] [k] σ_I for $OC_6H_5 = 0.47$, $OC_6H_4NO_2$-*m* 0.58, $OC_6H_4NO_2$-*p* 0.60, OC_6H_4Cl-*p* 0.51, $OC_6H_4CH_3$ 0.45.

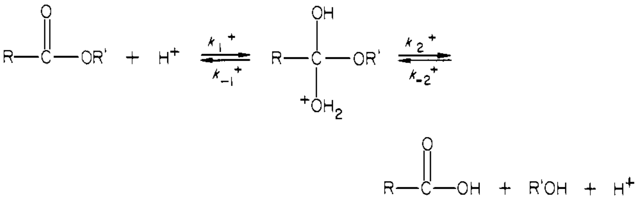
of OH^- from the anions of hydrates of benzaldehydes are about 10^4.[32] A reasonable value for k_{-1}^- might be 10^6 or 10^7. To postulate protonic equilibration in T^- seems more plausible than is the converse.

Isotopic rate ratios $k(^{16}O)/k(^{18}O)$ for labeled alkoxyl oxygen are nearly unity. This observation is consistent with r_p^- large, but it is also consistent with interpretations based on a postulated "early" transition state.

The evidence seems to show consistently that the partitioning ratio f_p^- is large for most examples of hydroxide-catalyzed ester hydrolysis. Hence the observed rates of base-catalyzed hydrolysis of esters may be taken as valid measures of the k_1^- step.

Model 2. T^+ Reversible.

Scheme II



$$\frac{dx}{dt} = k_2^+[T^+] - k_{-2}^+[P] \tag{2.1}$$

$$k'_{obsd} = f_p^+k_1^+ + (1 - f_p^+)k_{-2}^+ \tag{2.2}$$

$$f_p^+ = k_2^+/(k_{-1}^+ + k_2^+) \tag{2.3}$$

$$x_{eq} = \frac{k_1^+k_2^+e - k_{-1}^+k_{-2}^+p}{k_1^+k_2^+ + k_{-1}^+\ k_{-2}^+} \tag{2.4}$$

$$[E]_{eq} = e - x_{eq} \tag{2.5}$$

$$K_{eq} = \frac{k_2^+}{k_{-1}^+}\frac{k_1^+}{k_{-2}^+} = \frac{k_1^+}{k_{-2}^+}\frac{f_p^+}{1 - f_p^+} \tag{2.6}$$

$$r_p^+ = k_2^+/k_{-1}^+ \tag{2.7}$$

The treatment of reversible first-order reactions is well-known,[29] but the presence of T^+ adds further terms. The initial concentration of ester is *e* and of acid is *p*.

As always is true for reversible reactions for which $x_\infty = x_{eq}$, k_{obsd} is a sum of effective forward and effective reverse rate constants, eq 2.2. The experimentally accessible constants, *k*(hydrolysis) and *k*(esterification), can be obtained either by direct measurement of initial rates based on total reactant concentrations or indirectly through the experimental equilibrium constant. However, *k*(hydrolysis) = $f_p^+k_1^+$ while *k*(esterification) = $(1 - f_p^+)k_{-2}^+$.

Since the empirical steric constants E_s are nominally based on experimental rates of acid-catalyzed hydrolysis of esters[2a] while the proposed E_s' values are based on esterification in methanol,[2b] the present analysis asserts that E_s and E_s' pertain to f_ik_i composites rather than to the intended *k* values. The linear free energy expression for a set of reactants having constant bonding, polar, and solvation effects is eq 2.8.[1b] The application of eq 2.8 to each

$$k_{obsd} = a + \rho_sE_s \tag{2.8}$$

of the components of $f_p^+k_1^+$, that is, to eq 2.9, leads to eq 2.10–2.13

$$k'_{obsd} = k_1^+/(1 + k_{-1}^+/k_2^+) \tag{2.9}$$

$$k'_{obsd} = 10^\alpha = \frac{10^\beta}{1 + 10^\gamma} \tag{2.10}$$

$$\alpha = a(obsd) + \rho(obsd)E_s \tag{2.11}$$

$$\beta = a_1^+ + \rho_1^+E_s^0 \tag{2.12}$$

$$\gamma = a_{-1}^+ + \rho_{-1}^+E_s^0 - a_2^+ - \rho_2^+E_s^0 \tag{2.13}$$

in which E_s^0 represents the (inaccessible) steric constant defined in terms of the mechanistic constant k_1^+; in using the k_1^+ constants to define E_s^0 values $\rho_1^+ = 1.0$ by definition. Inspection of the denominator of eq 2.10 shows that there is no simple general relationship between E_s^0 so defined and the conventional E_s values, nor is there any simple relationship for E_s' values based on methanolic esterification and E_s^0 values pertaining to mechanistic step k_{-2}^+.

In the course of evaluating applications of E_s to reactions of esters, I carried out back calculations to derive E_s^b values based on hydroxide hydrolysis of esters.[1b] The purpose was to determine whether there are differences in E_s^b and the conventional Taft

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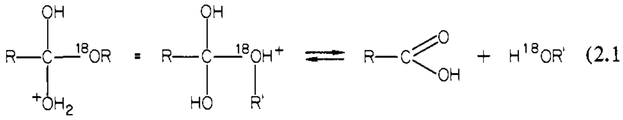
E_s values. From the discussion of Model 1, it is expected that the $E_s{}^b$ are based directly on $k_1{}^-$ values of Scheme I. They should represent the intended set. The $E_s{}^b$ range was defined to be consistent with the E_s range by choosing appropriate ρ_s values in the range 0.95–1.30 that depended on the ester, on the solvent, and on what allowance had been made for residual minor polar effects of alkyl groups. The details are not significant for present purposes; the $E_s{}^b$ are intended to be illustrative, not definitive. The point of interest is the close relationships among the several E_s sets, Table I.

For this limited set at any rate the several definitions of E_s show no worse variability than is usually found among other types of substituent constants used in linear free energy expressions. This implies that $f_p{}^+$ values are not too different for the several members of this set. As the range of substituents and of reaction conditions is extended, the f_p values cannot be expected to remain constant. Use of the f_ik_i composites will suffice for many purposes, but theoretical studies will need to estimate individual effects on f_i and k_i.

A relative constancy among $f_p{}^+$ values provides no information about absolute $f_p{}^+$ values since the $f_p{}^+$ term cancels in the linear free energy expression. There is no reason to suppose that $r_p{}^+$ of eq 2.7 is either very large or very small; $f_p{}^+$ should therefore be not too far from 0.5. On statistical grounds $k_{-1}{}^+ \cong 2k_2{}^+$ and $r_p{}^+ = 0.3$. Steric effects might slightly increase $r_p{}^+$. For ethyl acetate K_{eq} for hydrolysis in water is about 0.30.[33] It appears that similar values apply to other ethyl esters.[34] If $r_p{}^+$ is very large, then $k_1{}^+/k_{-2}{}^+$ must be very small, and there is no sound chemical reason for this assumption.

Isotope effects appear to contradict the above analysis. The $k(^{16}O)/k(^{18}O)$ rate constant ratios for acid-catalyzed hydrolysis of methyl formate and of methyl benzoate based on the alkyl oxygen are nearly 1.00.[27b,28a] The authors conclude, "The lack of an overall isotope effect argues that the energy barrier for expulsion of methanol (from T^0) must be significantly smaller than that for water".[27b] I interpret this to mean that $r_p{}^+$ is predicted to be much greater than unity.

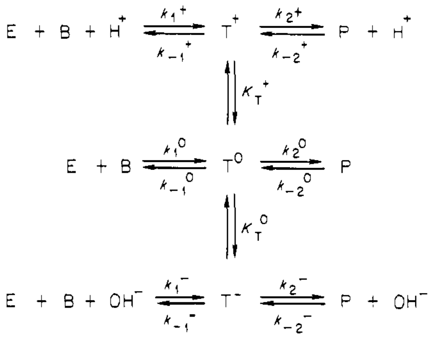
A possible way around the discrepancy was also indicated by the authors. The usual isotope effect is acid strengthening.[35] As shown in eq 2.14, this could lead to an increased rate of loss of the heavy isotope by discriminating in favor of $T^+{}_{HOR'}$. The overall result could presumably be anything from cancellation to a negative isotope effect.



(2.14)

$T^+{}_{H_2O}$ $T^+{}_{HOR'}$

Scheme III



$$\frac{d[T^+]}{dt} = k_1{}^+[E][B][H^+] - (k_{-1}{}^+ + k_2{}^+)[T^+] \cong 0 \quad (3.1)$$

$$\frac{d[T^0]}{dt} = k_1{}^0[E][B] - (k_{-1}{}^0 + k_2{}^0)[T^0] \cong 0 \quad (3.2)$$

$$k_{obsd} = k_1{}^+f_p{}^+[H^+] + k_1{}^0f_p{}^0 \quad (3.3)$$

$$f_p{}^+ = \frac{k_2{}^+}{k_{-1}{}^+ + k_2{}^+} \qquad f_p{}^0 = \frac{k_2{}^0}{k_{-1}{}^0 + k_2{}^0} \quad (3.4)$$

Model 3. Scheme III, Using T+ and T0 Irreversible. Models based on Scheme III assume [B] >> [E] so that pseudo-first-order kinetics obtain. If B does not exist for a given reaction, then it is assumed that in all equations [B] = 1. Model 6 treats the mechanism in its entirety. Models 3–5 treat subsets.

Since T^+ and T^0 are steady-state intermediates and are also in acid–base equilibrium, eq 3.1 and 3.2 must hold. Equations 3.1 and 3.2 must also hold if T^+ and T^0 represent steady-state intermediates that do not interconvert. However, these equations will not hold if the rate of interconversion of T^+ and T^0 is comparable to other rate processes. The usual algebraic substitution leads to eq 3.3 with the f terms defined in eq 3.4. The appropriate regions of a pH-rate profile for a reaction that involves steady-state intermediates T^+ and T^0 will accordingly provide exactly two constants, viz, $k_{H^+} = k_1{}^+f_p{}^+$ and $k_0 = k_1{}^0f_p{}^0$. There are altogether six rate constants and one equilibrium constant in the mechanistic equations. Although the acid–base equilibrium of T^+ and T^0 imposes the constraint shown in eq 3.5, this is not usually of

$$\frac{[T^0][H^+]}{[T^+]} = K_{T^+} = \frac{k_1{}^0(k_{-1}{}^+ + k_2{}^+)}{k_1{}^+(k_{-1}{}^0 + k_2{}^0)} \quad (3.5)$$

practical use since there is no way to extract the desired $k_1{}^+$ or $k_1{}^0$ values nor the equilibrium constant.

There has been some confusion regarding the appropriate kinetics expression in applications of this mechanism to lactone formation. If the derivation is carried out on $[T] = [T^+] + [T^0]$, eq 3.6–3.11 result.[6,9,15,16] Equation 3.11 apparently provides four

$$d[T]/dt = (k_1{}^+[H^+] + k_1{}^0)[E][B] - \\ \{(k_{-1}{}^+ + k_2{}^+)[H^+] + (k_{-1}{}^0 + k_2{}^0)K_{T^+}\}[T]/D \cong 0 \quad (3.6)$$

$$d[P]/dt = (k_2{}^+[H^+] + k_2{}^0K_{T^+})[T]/D \quad (3.7)$$

$$f_p = \frac{f_p{}^+[H^+] + f_p{}^0K'_{T^+}}{[H^+] + K'_{T^+}} \quad (3.8)$$

$$k_f = k_1{}^+[H^+] + k_1{}^0 \quad (3.9)$$

$$K'_{T^+} = K_{T^+}\frac{(k_{-1}{}^0 + k_2{}^0)}{(k_{-1}{}^+ + k_2{}^+)} \quad (3.10)$$

$$k'_{obsd} = f_pk_f = \frac{f_p{}^+[H^+] + f_p{}^0K'_{T^+}}{[H^+] + K'_{T^+}}(k_1{}^+[H^+] + k_1{}^0) \quad (3.11)$$

constants, and the authors report derivation of separate $k_1{}^+$, $k_1{}^0$, $f_p{}^+$, $f_p{}^0$, and K'_{T^+}. It is not entirely obvious, but the denominator of 3.11 is a factor of the numerator. Substitution of eq 3.5 and 3.10 into 3.11 shows that the reduction yields eq 3.3.

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(33) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1964**, *86*, 4651–4654.

(34) (a) Reference 30; p 213. (b) Palomas et al. (Palomas, M. H.; Kaski, T.; Siitonen, T. A. *Ber. Dtsch. Chem. Ges. B* **1942**, *75B*, 336–339) report data for the following equilibria for esterification: $ClCH_2COOCH_3$ 2.8, $ClCH_2CH_2COOCH_3$ 4.7, $CH_3OCH_2CH_2COOCH_3$ 5.4, all at 25 °C.

(35) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275–332.

(36) Caswell, M.; Schmir, G. L. *J. Am. Chem. Soc.* **1979**, *101*, 7323–7329.

(37) Pletcher, T. C.; Koehler, S.; Cordes, E. H. *J. Am. Chem. Soc.* **1968**, *90*, 7072–7076.

(38) Blackburn, G. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 2638–2645.

(39) Chaturvedi, R. K.; Schmir, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 4413–4420.

(40) Smith, V. F.; Schmir, G. L. *J. Am. Chem. Soc.* **1975**, *97*, 3171–3177.

General considerations show that the rate–pH profile for a reaction involving intermediates at just two levels of protonation will yield just two rate constant terms, eq 3.3, and the apparent pK_a of the substrate.

Model 4. Scheme III, Using T^0 and T^- Irreversible. Equation 4.1 follows analogously to the derivation of eq 3.3.

$$k'_{obsd} = k_1{}^0 f_p{}^0 + k_1{}^- f_p{}^-[OH^-] \qquad (4.1)$$

Model 5. Scheme III, Using T^+, T^0, and T^- Irreversible. Equation 5.1 follows analogously to the derivation of eq 3.3.

$$k'_{obsd} = k_1{}^+ f_p{}^+[H^+] + k_1{}^0 f_p{}^0 + f_1{}^- f_p{}^-[OH^-] \qquad (5.1)$$

Model 6. Scheme III, Using T^+, T^0, and T^- Reversible. Equation 6.1 is derived by the procedures used above. There are in principle

$$k'_{obsd} = (k_1{}^+ f_p{}^+[B] + (1 - f_p{}^+)k_{-2}{}^+)[H^+] + (k_1{}^0 f_p{}^0[B] + (1 - f_p{}^0)k_{-2}{}^0) + (k_1{}^- f_p{}^-[B] + (1 - f_p{}^-)k_{-2}{}^-)[OH^-] \qquad (6.1)$$

three equilibrium constants, eq 6.2, one for each level of protonation.

$$K_{eq}{}^+ = (k_1{}^+ k_2{}^+)/(k_{-1}{}^+ k_{-2}{}^+)$$

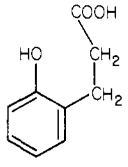
$$K_{eq}{}^0 = (k_1{}^0 k_2{}^0)/(k_{-1}{}^0 k_{-2}{}^0)$$

$$K_{eq}{}^- = (k_1{}^- k_2{}^-)/(k_{-1}{}^- k_{-2}{}^-) \qquad (6.2)$$

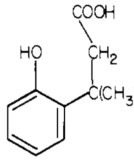
However, it is generally assumed that the equilibrium constant is pH independent.

With minor transformations, eq 6.1 is applicable to the reverse reaction.

The use of these equations may be illustrated by application to the important lactone reactions studied by Cohen[41a] and by Schmir.[41b] Three acids (**1**–**3**) will illustrate applications of the method.



1



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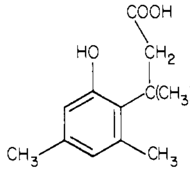


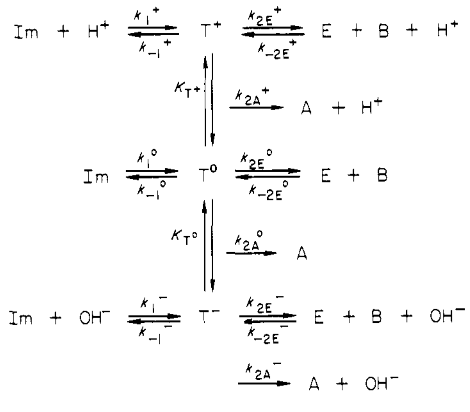
3

Lactone formation is subject to catalysis by hydronium ion, and there is also a so-called hydroxide catalysis which can better be interpreted as reaction of phenoxide ion with the unionized carboxyl group. There are also other kinetics terms not of concern at present. As a starting point we may consider the equilibrium constants for lactone formation. These are respectively 8.2 × 10^{-3}, 280, and 6 × 10^5; and **3** therefore has a K_{eq} value almost 10^8 larger than does **1**. The differences in the equilibrium constants arise primarily from the differential steric crowding of the acids compared to the lactones.

Due to the unfavorable lactone equilibrium for **1**, it was not possible to measure directly the rate of lactonization. The rate constant was instead calculated by measuring the acid-catalyzed hydrolysis of the lactone and dividing this into the equilibrium constant. It can easily be shown that the value k_{H^+} so obtained is comparable with the corresponding values obtained for **2** and **3** by direct measurement; all are estimates of $k_1{}^+ f_p{}^+$.

The three k_{H^+} values are 7 × 10^{-5}, 2.8 × 10^{-2}, and 26. The ratio of rate constants for **3**/**1** is 4 × 10^5. However, the quantity of theoretical significance is the ratio of the unobservable $k_1{}^+$ values. To get an order of magnitude estimate, we may postulate that $f_p \cong K_{eq}/(1 + K_{eq})$. This postulates that for an equilibrium constant of 1 the partitioning factor is 0.5. While such a result is not required, it is reasonable. For acids **2** and **3** $f_p{}^+$ is predicted to be nearly unity, but for acid **1** it is predicted to be about 0.01. Therefore, the values of $k_1{}^+$ for acids **2** and **3** are nearly equal to the observed k_{H^+}, while the value for **1** should be 100 times as large, or about 7 × 10^{-3}. This reduces the estimated rate ratios **3**/**1** from 4 × 10^5 to about 4000.

Scheme IV



The conclusions of this analysis are sensible on structural grounds. Relief of steric strain should be much larger for the lactones than for the tetrahedral intermediates. That the ratios of the equilibrium constants are much larger than ratios of the corrected rate constants is in qualitative accord.

Model 7. Scheme IV, Using T^+, T^0, and T^-. In Scheme IV Im represents imidate, E ester, B amine, and A amide.

Hydrolysis of imidate esters has been studied extensively.[4,7–14] Products are a mixture of amide and of ester. An example is hydrolysis of $(CH_3)_2N^+{=}C(CH_3)OC_6H_4{-}CH_3{-}p$ which gives $CH_3CO{-}N(CH_3)_2$ and $CH_3CO{-}OC_6H_4{-}CH_3$. Of particular interest is the expectation that the imidate will provide an alternative entry to the same tetrahedral intermediates that are involved in ester aminolysis. Thus a study of the products of hydrolysis of appropriate imidates should permit observation of the partitioning ratio for ester aminolysis. Such a study has been carried out by Satterthwaite and Jencks[4,14] for the example cited above and for the corresponding methylamine derivative. Their important example is now analyzed in the framework of the general procedures developed in the present study.

The observed rate constant for imidate hydrolysis in terms of the mechanism of Scheme IV is summarized in eq 7.1 and 7.2.

$$k'_{obsd}(Im) = k_1{}^+[H^+]\frac{k_{2E}{}^+ + k_{2A}{}^+}{k_{-1}{}^+ + k_{2E}{}^+ + k_{2A}{}^+} + k_1{}^0\frac{k_{2E}{}^0 + k_{2A}{}^0}{k_{-1}{}^0 + k_{2E}{}^0 + k_{2A}{}^0} + k_1{}^-[OH^-]\frac{k_{2E}{}^- + k_{2A}{}^-}{k_{-1}{}^- + k_{2E}{}^- + k_{2A}{}^-} \qquad (7.1)$$

$$\frac{[T^-]}{[T^0]} = \frac{K_{T^0}}{[H^+]} = \frac{k_1{}^-}{k_1{}^0}\,\frac{k_{-1}{}^0 + k_{2E}{}^0 + k_{2A}{}^0}{k_{-1}{}^- + k_{2E}{}^- + k_{2A}{}^-} \qquad (7.2)$$

The reverse reaction of ester aminolysis is not included in these equations since it is possible to choose conditions for which the reverse process is negligible. The corresponding reactions for ester aminolysis are given in eq 7.3 and 7.4.

$$k'_{obsd}(aminol) = k_{-2E}{}^0\frac{k_{2A}{}^0[B]}{k_{2E}{}^0 + k_{2A}{}^0} + k_{-2E}{}^-[OH^-]\frac{k_{2A}{}^-[B]}{k_{2E}{}^- + k_{2A}{}^-} \qquad (7.3)$$

$$\frac{[T^-]}{[T^0]} = \frac{K_{T^0}}{[H^+]} = \frac{k_{-2E}{}^-}{k_{-2E}{}^0}\,\frac{k_{2E}{}^0 + k_{2A}{}^0}{k_{2E}{}^- + k_{2A}{}^-} \qquad (7.4)$$

The Satterthwaite and Jencks analysis was based on the assumption that the k_{-1} terms are negligible. This assumption makes the distribution fractions of eq 7.1 equal to unity, and thus the observed rate constants, k_0 and k_{OH^-}, may be equated with the respective mechanistic constants $k_1{}^0$ and $k_1{}^-$. The acid–base equilibrium for T^0 and T^- is therefore given by eq 7.5, and the

$$\frac{[K_{T^0}]}{[K_w]} = \frac{k_{OH^-}}{k_0}\,\frac{(k_{2E}{}^0 + k_{2A}{}^0)}{(k_{2E}{}^- + k_{2A}{}^-)} = \frac{k_{-2E}{}^-}{k_{-2E}{}^0}\,\frac{(k_{2E}{}^0 + k_{2A}{}^0)}{(k_{2E}{}^- + k_{2A}{}^-)} \qquad (7.5)$$

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[41] (a) Milstien, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158–9165. (b) Caswell, M.; Schmir, G. L. *Ibid.* **1980**, *102*, 4815–4821.

Table III. p*K* Values for Alcohols and for Tetrahedral Intermediates $R_1R_2R_3COH$ in Water, 25 °C, Based on $pK = a + \rho_I \Sigma \sigma_I$

R_1	R_2	R_3	σ_1[a]	σ_2[a]	σ_3[a]	pK_a(obsd)	pK_a(calcd)[b]
CCl_3	H	H	0.41	0	0	12.24[c]	12.44
CF_3	H	H	0.42	0	0	12.37[c]	12.37
CHF_2CF_2	H	H	0.45	0	0	12.74[c]	12.15
$CHCl_2$	H	H	0.31	0	0	12.89[c]	13.18
HCC	H	H	0.30	0	0	13.55[c]	13.26
CH_2Cl	H	H	0.16	0	0	14.31[c]	14.29
CH_3OCH_2	H	H	0.08	0	0	14.8[c]	14.88
H	H	H	0	0	0	15.5[c]	15.47
CF_3	CF_3	H	0.42	0.42	0	9.22[d]	9.27
CF_3	CF_3	OH	0.42	0.42	0.27	6.45[d,e]	6.97[e]
CF_3	CHF_2	OH	0.42	0.33	0.27	7.67[d,e]	7.64[e]
CHF_2	CHF_2	OH	0.33	0.33	0.27	8.90[d,e]	8.30[e]
CF_3	CH_3	OH	0.42	−0.05	0.27	10.45[d,e]	10.44[e]
C_6H_5	OH	H	0.10	0.27	0	12.0[e,f]	12.43[e]
CH_3	H	H	−0.05	0	0		15.84
CH_3	OR[g]	OH	−0.05	0.27	0.27		11.55[e]
CH_3	NHR[g]	OH	−0.05	0.17	0.27		12.29[e]
CH_3	NH_2R^+[g]	OH	−0.05	0.60	0.27		9.11[e]
CH_3	OH	OH	−0.05	0.27	0.27		6.9[h]
CH_3	OH	O^-	−0.05	0.27	−0.16		10.1[h]

[a] Exner σ_I values.[42] [b] $pK = 15.472 - 7.390\Sigma\sigma_I$; $s_{pK} = 0.34$, $s_{\text{intercept}} = 0.16$, $s_\rho = 0.27$, $r^2 = 0.9844$. [c] Ballinger and Long.[43] [d] Satterthwaite and Jencks.[14] [e] Statistical factor of 2; pK_a(calcd) = p*K* from equation in footnote *b* − 0.30. [f] Bell and Sorensen.[44] [g] Any alkyl group. [h] For $R_1R_2R_3CNH_2R^+$. These are the major tautomers of T^+ and of T^0.

the ratio of mechanistic constants for aminolysis, k_{-2E}^-/k_{-2E}^0, must equal the ratio of mechanistic constants for imidate hydrolysis and hence also the corresponding ratio of experimental constants, k_{OH^-}/k_0. This means that the detailed analysis based on Scheme IV is in accord with the conclusions of the authors, namely that the ester aminolysis rates should show a pH–rate profile similar to the imidate product profile. The fact that there is a discrepancy led the authors to abandon the hypothesis of common tetrahedral intermediates in rapid protonic equilibrium in favor of a postulate of rate-limiting proton transfers among the tetrahedral intermediates. See Tables II and III; note that pK_a of T^+ is 6–7.

There are, however, other possibilities. One is that the k_{-1} constants for imidate hydrolysis are not negligibly small. Another is that aminolysis of the aryl esters does not go through a tetrahedral intermediate but rather by some sort of direct displacement. This latter hypothesis is considered in more detail below.

Discussion

There are two general ways to proceed with an evaluation of the significance of phenomenological rate data. If there is evidence that $r_p = k_2/k_{-1}$ is large, then f_p will be nearly unity and the phenomenological constants will correspond to the mechanistic rate constants. Such appears to be true for hydroxide-catalyzed ester hydrolysis as indicated above for model 1. A reaction with a favorable equilibrium constant may also be expected to have f_p nearly unity. Such is probably true for lactone formation.

If the equilibrium constant is less than about 10, then the f_p value may be considerably less than unity and may vary with the structure of the substrate. One possible approach is to hope that the composite term $k_f f_p$ will reflect the trends of interest. If the trends correspond with those found for a series for which f_p is about unity, then this hope may have been fulfilled. Such appears to be true of esterification of alkyl-substituted acids as indicated in model 2. The correspondence may not extend to further structural variations such as unsaturation or aryl substitution, and it may not extend to esters in which polar effects are varied. The matter needs to be investigated.

The sensitivity or insensitivity of acyl transfer to the breaking of the bond between the leaving group and the acyl carbon atom provides important evidence about f_p. The most widely available data concerns the hydrolysis, alcoholysis, and the aminolysis of aryl esters. Since the presence of electron-attracting groups accelerates the addition step, it is necessary to examine whether the reaction follows σ or whether it follows σ^-. Rate-limiting cleavage of ArO–C bonds or other bonds results in a requirement for σ^-.[42,45,46]

If f_p is nearly unity, then acceleration of the cleavage of the C–OAr bond cannot increase the phenomenological rate; further increase in k_2^- of model 1, for example, cannot significantly increase f_p.

There is extensive evidence that electron-attracting groups increase both the rate constants and the equilibrium constants for addition to the carbonyl group of aldehydes and ketones. Data for *gem*-diols have been summarized by Bell.[47] Both rate and equilibrium data have been presented, for example, by Anderson and Jencks for carbinolamine formation from aromatic aldehydes and semicarbazide.[48] For p*K* values of adducts see Table III.

Similar sensitivity is found in hydroxide-catalyzed hydrolysis of esters. The values will be presented first as an analysis of the observed rate constants (the phenomenological constants here). For many esters the ρ_i value is about 12.[1b] Recalculation of values for a series of $RCOOC_6H_5$ esters also gives ρ_i about 12.[42,49] Hirsch carried out an extensive evaluation of substituent effects in the hydrolysis of ArCOOAr′ and found that ρ(Ar) is 2.0 for all sets.[50] This corresponds to $\rho_i \sim 12$.[1b]

Several sets of data are available for Hammett correlations for aryloxy esters. For the Kirsch data ρ(Ar′) values were about 1.2 with (p-NO_2) = 0.89. This is closer to the normal σ (0.81)[42] than to σ^- (1.27). Earlier sets of data have been recalculated with modern values as shown in eq 10.1 and 10.2 for the data for

$$\log k = 1.901 + 1.025\sigma (s_{\log k} = 0.025,\ s_\rho = 0.03) \tag{10.1}$$

$$\log k = 2.319 + 0.920\sigma (s_{\log k} = 0.111,\ s_\rho = 0.13) \tag{10.2}$$

Ar′.[51,52] These are based on $\sigma(p\text{-}NO_2) = 0.81$.

The data of Schowen[53] for methanolysis have been recalculated

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Table IV. Methanol Exchange in Methyl Aryl Carbonates
$XC_6H_4OCO_2CH_3 + CH_3O^- \rightarrow XC_6H_4O^- + CH_3OCOOCH_3$

X	σ	σ^-	log k^a (25 °C)	log k^b (calcd σ)	log k^c (calcd σ^-)
p-NO_2	0.81	1.27	1.211	1.230	1.136
p-CHO	0.47	1.04	0.719	0.673	0.915
p-$COCH_3$	0.47	0.82	0.652	0.673	0.703
p-CO_2CH_3	0.44	0.66	0.594	0.624	0.549
p-Br	0.26	0.26	0.382	0.329	0.165
p-Cl	0.24	0.24	0.316	0.296	0.145
H	0	0	−0.155	−0.097	−0.085
p-CH_3	−0.14	−0.14	−0.284	−0.327	−0.220
p-CH_3O	−0.12	−0.12	−0.328	−0.294	−0.201

[a] Derived from data of Mitton et al.[53] The Arrhenius parameters were either recalculated[55] or else $\Delta S^{\ddagger}$ was recomputed from $\Delta H^{\ddagger}$ and one $k(t)$ value.[56] From these matching $\Delta H^{\ddagger} - \Delta S^{\ddagger}$ pairs, k(25 °C) was calculated. The reported $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ values have been rounded and hence do not properly reproduce k(25 °C). [b] $\log k = 0.0972 + 1.6388\sigma$; $s_{\log k} = 0.04$, $r^2 = 0.994$. [c] $\log k = -0.0856 + 0.9621\sigma^-$; $s_{\log k} = 0.15$; $r^2 = 0.930$.

on the standard Hammett basis and are shown in Table IV and eq 10.3. The correlations are better with σ than with σ^-.[54]

$$CH_3O^- + CH_3OCOOC_6H_4X \rightarrow CH_3OCOOCH_3 + {}^-OC_6H_4X \qquad (10.3)$$

The data for both hydrolysis and for alcoholysis are consistent with mechanistic rate constants that require little sensitivity to the value of k_2^- of model 1. They constitute good evidence that f_p is about unity for these esters.

Results for aminolysis of aryl esters follow a different pattern than observed in hydrolysis. Cordes has reported rate constants for reactions of $CH_3COOC_6H_4X$ with piperidine ($\rho = 2.1$), with ethylenediamine ($\rho = 1.9$), with glycine ethyl ester ($\rho = 2.2$), and with morpholine ($\rho = 2.6$).[57] In each case the reaction is best correlated by $\sigma^-(p\text{-}NO_2)$. Recalculation of the data for ammonolysis of $RCOOC_6H_5$[49] gives $\rho_i = 8.0$ for the acyl group, corresponding to a Hammett ρ of about 1.3. Thus in contrast to the ester results the aminolysis reactions have a larger sensitivity to electron-attracting groups in the leaving ArO group than in the acyl group.

These data show clearly that in aminolysis reactions of aryl esters the rates are sensitive to the leaving ability of the aryloxy group. For the tetrahedral mechanism this result requires that the f_p value must be sufficiently small that an increase in k_2 can cause a significant increase in f_p. This requirement is in conflict with the results of the imidate ester studies. As summarized in Table II, the reported partitioning ratios in favor of amide product are large. One possible explanation is that aminolysis of aryl esters does not involve a kinetically significant tetrahedral intermediate, that some sort of direct displacement occurs instead. This postulate also requires that the transition state for aminolysis must differ geometrically from that for imidate hydrolysis. This is a problem that deserves further study.[58]

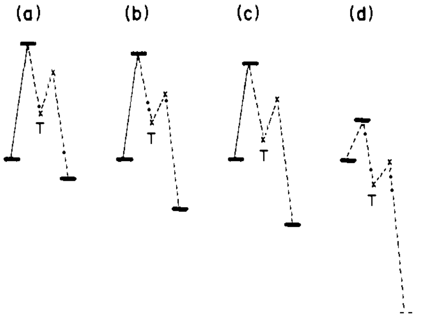

Figure 1. Reaction state diagrams for hydroxide-catalyzed hydrolysis of esters. Solid lines designate experimental energy levels. Energies for the tetrahedral intermediates are speculative. Taking energy of reactants as zero, $\Delta G^{\ddagger} = 16.3$ and $\Delta G = -1.7$ for ethyl acetate (a), 14.9 and −7.4 for phenyl acetate (b), 13.6 and −9.4 for p-nitrophenyl acetate (c), 5.5 calculated for $CF_3COOC_6H_4NO_2$-p (d), and $\Delta G \sim -20$. See text for references.

Data for other acyl transfer reactions are less plentiful. The value of the $k(^{16}O)/k(^{18}O)$ ratio for hydrazinolysis based on the methoxyl oxygen atom of methyl formate is reported to be 1.062 at pH 7.85.[27a] This means that the breaking of the $C\text{–}OCH_3$ bond is kinetically significant. At pH 10 the value is 1.0048, interpreted as little sensitivity to bond breaking.[27b] Hydrazinolysis of methyl benzoate at pH 7.9 gave a ratio of 1.041, consistent with the methyl formate data.[28a] These studies were concerned with estimating the extent of bond making in the transition state.

Enthalpies, Entropies, and Free Energies of Activation. The entropy for combination of two molecules into one is about −26 to −30 cal K^{-1} mol^{-1}.[60–63] The entropy effect of strong hydrogen bonding is perhaps about −5 cal K^{-1}mol^{-1} per bond based on ammonium ion data.[64] The entropy data are based on the standard state of 1 M for all species. The $\Delta S^{\ddagger}$ for the aminolysis reaction should be about −25 to −30, that for hydrolysis should be about the same for adding HO^- to ester since H-bonding effects should be comparable for HO^- and for T^-.

A few experimental activation entropies are available for aminolysis. For the nine pairs derived from three amines, $EtNH_2$, piperidine, and morpholine, and from three acetates, C_6H_5, p-$O_2NC_6H_4$, and 2,4-$(O_2N)_2C_6H_3$, all except two are reported to have $\Delta S^{\ddagger} = -24$ (±2). The two exceptions are $CH_3COOC_6H_5$ with piperidine and with ethylamine, both with $\Delta S = -33$.[65] Most of these entropy values accord with the predicted value.

The reactions hydrazine with aryl acetates has $\Delta S^{\ddagger} = -30$ for the k_2 of the term k_2[ester][hydrazine] and −45 for k_3 of the term k_3[ester][hydrazine].[16] The values may be rather uncertain since they were extracted from complex experimental data.[66] The entropies correspond fairly well with transition states derived from two molecules and from three molecules, respectively, as implied by the kinetics expressions.

Results for hydroxide-catalyzed hydrolysis of esters reflect a more complex situation than predicted. Hydrolysis of RCOOEt with R = alkyl in 70% aqueous acetone has $\Delta S^{\ddagger} = -42$,[66] in 85% ethanol −32,[69] and in 40% aqueous dioxane perhaps about −30.[68–70]

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(54) The authors provided unusually extensive data for computing $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and attempted to account for these values directly.[53] The strong correlation between these quantities makes it very difficult to derive reliable separate $\Delta H^{\ddagger}$ or $\Delta S^{\ddagger}$ sets that are useful in structure–reactivity analyses. The recalculations reported in Table IV showed that the error limits on $\Delta H^{\ddagger}$ and on $\Delta S^{\ddagger}$ are about 2.5 times as large as estimated.[53] Much of the apparent variation in $\Delta S^{\ddagger}$, for example, lies within expected error limits. For a set of nine substituents, $\Delta S^{\ddagger} = -17.7 \pm 1.2$ cal K^{-1} mol^{-1}, and for this set the hypothesis $\Delta S^{\ddagger}$ = constant may better represent the situation than does the hypothesis that the individual values are meaningful. Of the four exceptions two, p-CHO(−12.0) and p-O^-(−34.8), might reasonably be expected to show special interactions with CH_3OH. The other two, p-NO_2 (−20.7) and p-CH_3(−21.2 recalculated, −17.1 reported), have no obviously special properties. The overall high quality of the kinetics data is reflected in the excellent $\rho\sigma$ representation of the interpolated k(25 °C) values (Table I).

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An extensive set of data for methoxide exchange, eq 10.3, has $\Delta S^{\ddagger} = -18$, and for $CH_3COOAr + CH_3O^-$, $\Delta S^{\ddagger} = -21$.[54] Entropies for ionic reactants in methanol are affected to an unknown extent by ion pairing, and in water presence of ions complicates the prediction of the entropy for hydroxide-catalyzed hydrolysis. It is certainly possible that one or more extra molecules of water are hydrogen bonded in the transition states.

Energy diagrams for reaction coordinate states can be constructed in part for hydroxide-catalyzed hydrolysis of esters. Figure 1 shows the known energy values for three esters.[71,72] For ethyl acetate $\Delta G^{\ddagger} = 16.3$ kcal mol^{-1} and ΔG(products − reactants) for hydrolysis to neutral products is −1.7 kcal mol^{-1}. The corresponding values for phenyl acetate are 14.9 and −7.4; for *p*-nitrophenyl acetate they are 13.6 and −9.4. For an ester ZCOOZ′ such as $CF_3COOC_6H_3(NO_2)_2$ having strongly polar substituents, $\Delta G^{\ddagger}$ is predicted to be about $5.5 = 16.3 - (0.47(12) + 0.26(8)1.4$ and $\Delta G = -20$ or less. The energies shown for the tetrahedral intermediates T and for the second transition state are speculative.

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(70) Rate data reported[69] at 20 °C and at 50 °C yield the following Arrhenius activation energies for RCOOMe + NaOH in 40% aqueous dioxane; units are k_{cal}/mol: Me 10.9, Et 10.0, *n*-Pr 11.4, *n*-Bu 9.8, *i*-Bu 10.9, *i*-Pr 10.0, *s*-Bu 10.7, *t*-Bu 10.9. The data are anomalous in that most of the rate variations here are due to the *A* factor (the $\Delta S^{\ddagger}$ term) while in other studies[67–68] $\Delta S^{\ddagger}$ values are relatively constant for the series. The $\Delta S^{\ddagger} = -27$ for methyl acetate.

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Cadmium Binding by Biological Ligands. 1. Formation of Protonated Polynuclear Complexes between Cadmium and D-Penicillamine in Aqueous Solution

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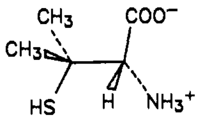
Abstract: Extensive alkalimetric titrations of the cadmium–D-penicillamine system in aqueous solutions have revealed the presence of several protonated polynuclear metal complexes in the pH 4–8 region. Over 1000 pH measurements (glass electrode), in 15 separate titrations, were collected with a computer-controlled titrator. The solutions [25 °C, 0.2 M (KNO_3) ionic strength] contained 1–5 mM cadmium nitrate and a 3-fold (or more) excess of D-penicillamine. The functional behavior of the data was consistent with the equilibrium model employing the species $Cd(pen)H^+$, $Cd_3(pen)_4H_2$, the "core + link" series $Cd_2(pen)_5H_3[Cd(pen)H]_n^{n-3}$, $n = 0, 1, 2...$, $Cd(pen)_2^{2-}$, and $Cd(pen)_2OH^{3-}$.

The amino acid D-penicillamine, I, has attracted considerable



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attention in heavy metal poisoning.[1,2] Although the molecule is effective in chelation therapy for copper, lead, and mercury poisoning, it appears to *elevate* the toxicity of cadmium, for reasons not entirely understood.[3]

The interpretation of the biological binding mechanisms of cadmium can be assisted by the understanding of the metal binding mechanisms in simple aqueous solutions containing a controlled and limited number of ligands. Unfortunately, the vast majority of older studies of cadmium reactions with sulfhydryl ligands are incomplete. Such reactions can be much more complicated than first realized, due to the propensity of sulfhydryl groups to bridge metal ions to form polynuclear complexes.[4] In aqueous solution the determination of the composition of such species is often a difficult endeavor, especially when several polynuclear species exist simultaneously with comparable concentrations.[5]

Past studies of the equilibrium complexation reactions of the cadmium–penicillamine system have not substantiated the presence of polynuclear complexes in low ionic strength (≤0.2 M) aqueous solution for metal concentrations at the millimolar level. Kuchinkas and Rosen,[6] Lenz and Martell,[7] and Sugiura et al.[8] interpreted equilibrium data with the species Cd(pen) and $Cd(pen)_2$, where pen = penicillamine. Corrie et al.,[9] in the most comprehensive study to date, proposed a model consisting of several protonated mononuclear complexes. Apparently at the 3 M ionic strength used, polynuclear complexes are not observed to form. Sovago et al.[10] suggested that the methyl groups on penicillamine sterically hinder the formation of certain polynuclear complexes. In the solid state, however, penicillamine is known to coordinate cadmium in a polymeric fashion.[11,12] In contrast to the case of penicillamine, cysteine forms polynuclear species with cadmium in dilute solution, as first indicated by Perrin and Sayce.[13]

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