

ferrous porphyrin. Anal. Calcd for $C_{36}H_{44}N_4Fe$: C, 73.46; H, 7.49; N, 9.53. Found: C, 73.58; H, 7.59; N, 9.44. μ_{eff} (295 K) = 4.7 μ_B .

Attempted Preparation of Bis(tetrahydrofuran)octaethylporphyriniron(II), Fe(OEP)(THF)₂. (i) Fe(OEP) (0.5 g) was dissolved in deoxygenated THF and the solution was evaporated to dryness in vacuo at room temperature. This procedure afforded only Fe(OEP), identified by microanalysis, magnetic moment, and Mossbauer spectrum. (ii) Fe(OEP)Cl (0.2 g, 0.32 mmol) and NaBH₄ (0.15 g, 0.39 mmol) were suspended in 40 ml of THF and stirred under an Ar atmosphere for 15 h at room temperature. The reaction mixture was filtered to give a reddish purple solution. Upon removal of THF a brown precipitate was obtained, which was collected by filtration and dried in vacuo. Chemical analysis indicated the product to be Fe(OEP), and this was confirmed by Mossbauer spectroscopy.

Attempted Preparation of Bis(aquo)octaethylporphyriniron(II), Fe(OEP)(H₂O)₂. Fe(OEP) (0.1 g) was reacted with rigorously degassed H₂O (5 ml) at room temperature for 2 h. The water was removed in vacuo and Fe(OEP) was recovered unchanged.

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High Pressure Studies. 21. Volume Changes for Base-Catalyzed Hydrolysis of *p*-Nitrophenyl Esters^{1,2}

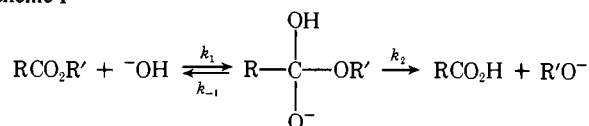
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Abstract: Effects of pressure on the hydroxide ion catalyzed hydrolysis of *p*-nitrophenyl acetate, propionate, dimethylacetate, and trimethylacetate have been determined in 0.005 M Tris buffer (24.5 °C). The activation volumes for hydrolysis are -3, -4, -4, and -10 cm³/mol, respectively. Data are presented indicating that contributions from Tris catalysis and that of other nucleophiles is unimportant under these conditions so that it is likely that these values of ΔV^*_{obsd} correspond to those for hydroxide attack. Since reversion of tetrahedral intermediates to starting esters is unlikely with these systems, the activation volumes are interpreted as directly reflecting the volume change on formation of the transition state leading to the tetrahedral intermediate. The variation in the values of ΔV^*_{obsd} with ester structure may reflect steric effects associated with solvation. The data are contrasted with available pressure results for base-catalyzed hydrolysis of some simple alkyl acetates.

Base-catalyzed hydrolysis of esters of aliphatic carboxylic acids is generally accepted to occur via the reversible formation of a tetrahedral intermediate (Scheme I) so that the rate

Scheme I



constant (k_{obsd}) measured for disappearance of the ester ($\text{RCO}_2\text{R}'$) is given by the combination of rate constants shown in the following equation:⁴

$$k_{\text{obsd}} = k_1[k_2/(k_{-1} + k_2)] \quad (1)$$

The extent of reversibility depends on the structure of R'. For example, k_{-1}/k_2 is much smaller when R'O⁻ is a phenoxide anion than when it is an alkoxide anion, and when R'O⁻ is the very stable *p*-nitrophenoxide anion, k_{-1}/k_2 is essentially zero.⁵

In connection with studies^{1a,6,7} of pressure effects on enzyme-catalyzed hydrolyses of a series of aliphatic *p*-nitrophenyl esters (1), where R is Me, MeCH₂, Me₂CH, and Me₃C, we have determined the effects of pressure on their nonenzymic alkaline hydrolysis rates. Since k_{obsd} equals k_1 for these esters,⁸ the pressure dependence of k_{obsd} directly gives the activation

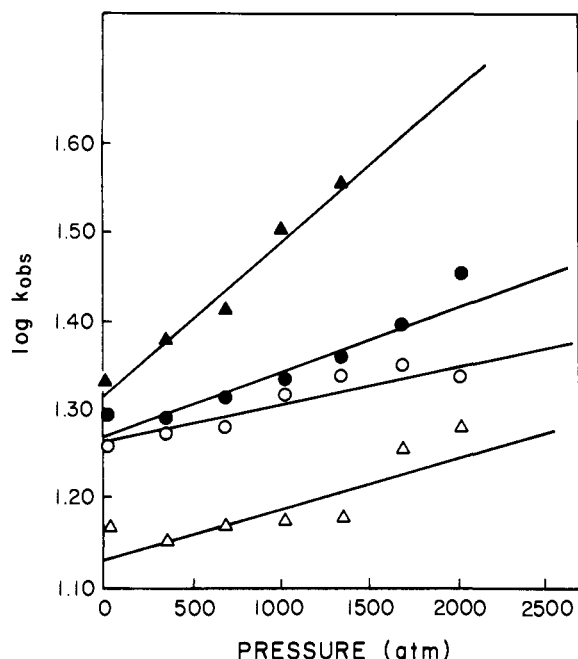
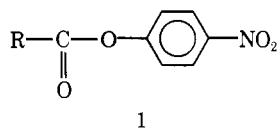


Figure 1. Pressure dependence of $\log k_{\text{obsd}}$ for the alkaline hydrolysis of *p*-nitrophenyl acetate (O), propionate (●), dimethylacetate (Δ), and trimethylacetate (▲) in 0.005 M Tris buffer (24.5 °C). Points for the trimethylacetate have been displaced upward by 1.0 log unit.

Table I. Rate Constants and Activation Volumes for Hydrolysis of *p*-Nitrophenyl Esters ($\text{RCO}_2\text{-}p\text{-NO}_2\text{Ph}$) in 0.005 M Tris Buffer (24.5 °C)^a

P, atm	$k_{\text{obsd}}, \text{M}^{-1} \text{s}^{-1b}$			
	R = Me ^c	R = MeCH ₂ ^d	R = Me ₂ CH ^d	R = Me ₃ C
51	18.0	19.7 ± 0.3	14.6 ± 1.6	2.15 ^e (2.70) ^f
340	18.8	19.5 ± 0.5	14.2 ± 1.0	2.40
680	19.0	21.0 ± 1.1	14.6 ± 0.7	2.61 (3.63)
1021	20.7	21.4 ± 0.9	14.9 ± 0.6	3.19 (3.81)
1361	21.7	22.8 ± 0.7	15.0 ± 1.1	3.61 (4.94)
1701	22.2	25.2 ± 0.3	18.1 ± 1.1	(5.32)
2041	21.4	28.5 ± 2.2	19.1 ± 0.9	(5.68)
ΔV_{obsd}^g	-3	-4	-4	-10 (-11)

^a Ester concentration ca. 10^{-4} M; ionic strength adjusted to 0.028 M with NaCl. ^b $k_{\text{obsd}} = (dP/dt)_0 / ((\text{OH})(\text{ester})_0)$. ^c Buffer pH 7.83. ^d Buffer pH 7.86. ^e Buffer pH 8.02. ^f 0.05 M Tris buffer, pH 8.86, $\mu = 0.008$ M, 25 °C. ^g Units of cm^3/mol .



volume corresponding to the attack of hydroxide on the ester (ΔV^*_1).

Activation volumes for alkaline hydrolysis of a few other esters have been reported.^{9,10} However, the R' groups in these esters were various alkyl moieties so that the observed hydrolysis rate constants cannot be assumed to just equal k_1 . Their activation volumes may include both ΔV^*_1 and a contribution reflecting the pressure dependence of the competition between k_{-1} and k_2 (eq 2).

$$\Delta V_{\text{obsd}} = \Delta V^*_1 + RT \ln (1 + k_{-1}/k_2) / \partial P \quad (2)$$

In principle, the data for the *p*-nitrophenyl esters **1** can be combined with those for systems where return occurs, per-

Table II. Relative Rate Constants for Hydrolysis of *p*-Nitrophenyl Acetate and Dimethylacetate in 0.005 and 0.05 M Tris Buffer (20 °C)^a

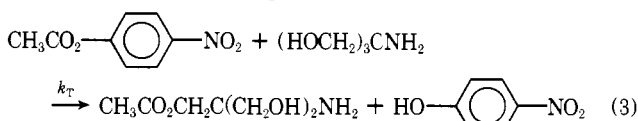
R	P, atm	$k_{0.05}^b / k_{0.005}$	$(k/(\text{OH}))_{0.05} / (k/(\text{OH}))_{0.005}$	$k_{\text{OH}}/k_{\text{T}}^c \times 10^{-4}$	$k_{\text{OH}}(\text{OH})^d / k_{\text{T}}(\text{T})$
Me	1	3.29	1.89	2.82	4.7
	2041	2.99	1.71	0.813	5.5
Me ₂ CH	1	1.74	1.00	<i>e</i>	<i>e</i>
	680	1.87	1.08	21.4	61
	2041	2.71	1.55	1.11	7.5

^a 0.005 M Tris, pH 7.60; 0.05 M Tris, pH 7.84. ^b See text for definition of k ; subscript denotes total buffer concentration. ^c Calculated from the equation $k = k_{\text{OH}}(\text{OH}) + k_{\text{T}}(\text{T})$ using data from experiments at both 0.005 and 0.05 M total buffer concentration. ^d Calculated for 0.005 M total buffer concentration. ^e Not calculable because $k_{\text{OH}} \gg k_{\text{T}}$.

mitting an evaluation of the latter term of eq 2.⁶ In this paper we present our most recent results for the systems **1**. In an earlier publication we reported preliminary results for three of the four esters **1**. The present data are substantially different for *p*-nitrophenyl dimethylacetate.

Results and Discussion

The second-order rate constants for disappearance of **1** are presented in Table I and plotted vs. pressure in Figure 1. The activation volumes obtained from these plots are included in Table I. We believe that these values of k_{obsd} and ΔV^*_{obsd} for the esters **1** reflect the rates, and their pressure dependence, of the reaction between the ester and hydroxide ion (i.e., k_1 and ΔV^*_1); however, it is necessary to consider other possible competing reactions of these esters which could liberate the *p*-nitrophenoxide anion. In particular, it is known that the buffer Tris (tris(hydroxymethyl)aminomethane) reacts with *p*-nitrophenyl acetate (eq 3).^{11,12}



The rate constant k , defined according to eq 4a and 4b, in-

$$dP/dt = k(\text{ester}) \quad (4a)$$

$$k = k_{\text{OH}}(\text{OH}) + k_{\text{T}}(\text{Tris}) + k_{\text{N}}(\text{N}) \quad (4b)$$

cludes the various contributions leading to formation of *p*-nitrophenoxide ion. Since the quantities $k/(\text{OH})$ (Table II) are greater for 0.05 M Tris than for 0.005 M Tris, with the exception of the atmospheric pressure data for *p*-nitrophenyl dimethylacetate, Tris catalysis is clearly indicated. The other nucleophile present in these systems is water, but it is a poor nucleophile compared with hydroxide. Jencks' data indicate values ranging from ca. 1×10^9 to 1.5×10^9 for the rate constant ratio $k_{\text{OH}}/k_{\text{H}_2\text{O}}$ for *p*-nitrophenyl acetate at 25 °C.^{11,13} Under the conditions of our experiments for *p*-nitrophenyl acetate (Table I), the ratio $k_{\text{OH}}(\text{OH})/k_{\text{H}_2\text{O}}(\text{H}_2\text{O})$ is 11.5,¹⁴ indicating that nucleophilic attack by water is not important. Comparable data for the other esters are not available, but there is no reason to believe that nucleophilic attack by water is more significant with these other systems than it is with the acetate.

Values of $k_{\text{OH}}/k_{\text{T}}$ were evaluated for the acetate and dimethylacetate at two different pressures. The last column in Table II shows that $k_{\text{OH}}(\text{OH})$ is at least five times greater than $k_{\text{T}}(\text{Tris})$ for both esters using 0.005 M Tris buffer. Since the difference between $k_{\text{OH}}(\text{OH})$ and $k_{\text{T}}(\text{Tris})$ is greater for the

Table III. A Comparison of Aliphatic Substituent Constants for R with Values of $\log k_{\text{obsd}}$ for Hydrolysis of $\text{RCO}_2\text{-}p\text{-NO}_2\text{Ph}^a$

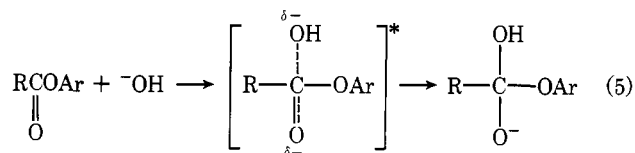
R	σ^*	E_s	$\log k^b$	$\Delta\sigma^*$	ΔE_s	$\Delta \log k$
Me	0	0	1.255	-0.1	-0.1	0.0
MeCH ₂	-0.10	-0.07	1.294	-0.1	-0.4	-0.1
Me ₂ CH	-0.19	-0.47	1.164	-0.1	-1.1	-0.8
Me ₃ C	-0.30	-1.54	0.332			

^a Values of σ^* and E_s from ref 15. ^b From Table I at 51 atm.

dimethylacetate than for the acetate, it seems likely that $k_{\text{OH}}(\text{OH})/k_{\text{T}}(\text{Tris})$ for the propionate must be at least as large as for the acetate and that $k_{\text{OH}}(\text{OH}) \gg k_{\text{T}}(\text{Tris})$ for the trimethylacetate. The similarity in values of k_{obsd} (Table I) for the trimethylacetate in 0.005 M Tris (24.5 °C) and in 0.05 M Tris (25 °C) support this latter contention. Therefore, we feel that the values of k_{obsd} in Table I are reasonably close to the values of k_{OH} for the four esters.

At each pressure the relative values of k_{obsd} are in the order $\text{Me} \approx \text{MeCH}_2 > \text{Me}_2\text{CH} \gg \text{Me}_3\text{C}$, and this order would be expected both on the basis of steric effects (as reflected by the aliphatic substituent constants E_s) and the classical view of polar effects (as reflected by the values of σ^* for the R groups) (Table III).¹⁵ A comparison of the change in rate as R is varied, with the corresponding changes in E_s and σ^* (Table III), however, shows that steric effects are the predominant factors influencing rate. The values of $\Delta \log k$ are much more comparable with those of ΔE_s than to those of $\Delta\sigma^*$. There is a crude linear correlation between $\log k_{\text{obsd}}$ and E_s which gives a value of S equal to ca. +0.6.¹⁶ There is no correlation between k_{obsd} and σ^* . The apparent absence of a polar effect probably reflects the overwhelming influence of the *p*-nitrophenyl group on electron density at the carbonyl group which swamps differences between the R groups.

The alkaline hydrolysis rates for all of the *p*-nitrophenyl esters are increased by pressure yielding negative values of ΔV^*_{obsd} (Table I), which reflect the volume difference between the transition state leading to formation of the tetrahedral intermediate, and the reactants (eq 5). Bimolecular reactions



usually have negative activation volumes since the transition state involves bonding between two previously discrete molecular species. Ie Noble estimates that bond formation in a bimolecular reaction involves a volume change of $-10 \text{ cm}^3/\text{mol}$,¹⁷ but even more negative values of ΔV^* have been observed.¹⁸

Changes in solvation also contribute to ΔV^*_{obsd} and in the reactions of these esters the formation of the transition state might be expected to involve net desolvation and a volume increase. Hydroxide ions are tightly solvated, but charge dispersal in the transition state would make the latter less highly solvated. This balance of effects seems likely in view of the small negative values of ΔV^*_{obsd} for hydrolysis of the acetate, propionate, and dimethylacetate.

Within experimental error, the values of ΔV^*_{obsd} for the acetate, propionate, and dimethylacetate are very similar (-3 to $-4 \text{ cm}^3/\text{mol}$); however, that for the trimethylacetate ($-10 \text{ cm}^3/\text{mol}$) is decidedly more negative. The activation volume (ΔV^*_{obsd}) is given by the following equation:

$$\Delta V^*_{\text{obsd}} = (V_{\text{ts}} - V_{\text{ester}}) - V_{\text{OH}} \quad (6)$$

Table IV. Comparison of Activation Volumes for Ester Hydrolysis with Reaction Volumes for Aldehyde Hydration and Carboxylic Acid Ionization

R	RCO_2Ar^a ΔV^*_{OH}	RCHO^b $\Delta V_{\text{hydration}}$	RCO_2H^c $\Delta V_{\text{ionization}}$
CH ₃	-3	-8	-11
CH ₃ CH ₂	-4	-12	-13
(CH ₃) ₂ CH	-4	-13	-14
(CH ₃) ₃ C	-10	-12	(-18) ^d

^a From Table I; units of cm^3/mol . ^b Reference 21; units of cm^3/mol . ^c Reference 20; units of cm^3/mol . ^d This number may be a little less negative.

Table V. A Comparison of Activation Volumes for Alkaline Hydrolysis of a Series of Alkyl Acetates ($\text{CH}_3\text{CO}_2\text{R}$) with that for Hydrolysis of *p*-Nitrophenyl Acetate (24.5 °C)

R	T, °C	ΔV^*_{obsd} cm^3/mol	$\Delta V^*_{\text{obsd}} - \Delta V^*_1$ cm^3/mol
CH ₃	25 ^a	-9.9	-7
CH ₃ CH ₂	25 ^a	-8.8	-6
	20 ^b	-5.6	-3
(CH ₃) ₂ CH	20 ^b	-5.6	-3
CH ₃ (CH ₂) ₃	20 ^b	-5.6	-3
(CH ₃) ₂ CHCH ₂	20 ^b	-6.3	-3
CH ₃ (CH ₂) ₄	20 ^b	-5.8	-3

^a Reference 9. ^b Reference 10. ^c The value chosen for ΔV^*_1 is $-3 \text{ cm}^3/\text{mol}$ corresponding to ΔV^*_{OH} for *p*-nitrophenyl acetate (Table I).

in which V_{ts} , V_{ester} , and V_{OH} are the partial molar volumes of transition state, ester, and hydroxide ion, respectively. Since V_{OH} is independent of the ester, it has not been grouped with the first two terms. It might be expected that increasing the size of R would decrease the solvation (increase the volume) of the neutral ester more than that of the negative transition state.¹⁹ Thus the difference $V_{\text{ts}} - V_{\text{ester}}$ would become more negative with increasing size of R, leading to increasingly negative values of ΔV^*_{obsd} .

Although the activation volumes do not show a smooth change with variation in R, support for this proposal is found in the relative ionization volumes for the homologous carboxylic acids (Table IV).²⁰ Solvation effects must be of primary importance in determining these values and the same sharp discontinuity is observed between the ionization volumes of dimethyl- and trimethylacetic acid as is observed for ester hydrolysis. Interestingly, this discontinuity is not observed in the reaction volumes for hydration of the homologous aldehydes (Table IV); a reaction which had been suggested as a model for ester hydrolysis.²¹

Earlier, we indicated that activation volume data for the *p*-nitrophenyl esters **1** might be combined with pressure data for simple aliphatic esters to probe the extent of reversion of the tetrahedral intermediate to starting ester (see Scheme I, and eq 1 and 2). The data which are available for simple aliphatic esters are those shown in Table V and are all for various alkyl acetates.^{9,10} If the value of ΔV^*_1 (eq 2) is chosen as that for *p*-nitrophenyl acetate ($-3 \text{ cm}^3/\text{mol}$) and the various activation volumes in Table V are equated to ΔV^*_{obsd} (eq 2), the resulting values of $RT \partial \ln(1 + k_{-1}/k_2)/\partial P$ obtained from $\Delta V^*_{\text{obsd}} - \Delta V^*_1$ are the negative quantities in Table V, indicating that the ratio k_{-1}/k_2 decreases with pressure; i.e., reversion of the tetrahedral intermediate becomes less competitive with its conversion to product as pressure is increased

(Scheme I). This is reasonable since RCO_2H should be more highly solvated than RCO_2R making its formation more favored by pressure because of a smaller molar volume.

However, we are comparing our data with those determined by others, and in view of the ca. $3 \text{ cm}^3/\text{mol}$ difference in ΔV^*_{obsd} for ethyl acetate from two different groups (Table V), the values of $\Delta\Delta V^*$ may not remain the same when all data that are compared come from the same laboratory. We propose to test this by determining values of ΔV^*_{obsd} for a variety of acetates **3** where R is varied from alkyl through phenyl and finally again to *p*-nitrophenyl to obtain a spectrum of results as the stability of the $\text{R}'\text{O}^-$ varies.

Experimental Section

Materials. The esters *p*-nitrophenyl acetate, dimethylacetate, and trimethylacetate used in this study were those described in our earlier report.⁶ *p*-Nitrophenyl propionate was prepared from *p*-nitrophenol and propionyl chloride in pyridine.^{22,23} Recrystallization from chloroform-hexane gave crystals, mp 63–64 °C (lit.²³ 62.5–63 °C). The purity of the esters was checked by monitoring the absorption spectrum at 400 nm before and after basic hydrolysis in 0.1 M NaOH. A stoichiometric amount of *p*-nitrophenoxide ion was formed.

Tris buffers were prepared from "Tris-HCl" and "Tris Base" obtained from the Sigma Chemical Co. The weights of "Tris-HCl" and "Tris Base" were carefully determined so as to permit good calculations of "Tris" concentrations. The 0.005 M Tris buffers were prepared by tenfold dilution of stock solutions of 0.05 M buffers. pH values at atmospheric pressure were determined at the reaction temperatures. The pH values at high pressures were calculated from the atmospheric pressure pH values, the known compression of water at high pressures, and the pressure dependences of the ionization constants of Tris-HCl and water.^{3,6,24,25}

Ester Hydrolysis. The esters were hydrolyzed in 0.005 M Tris buffers at 24.5 °C. Hydrolysis was monitored by observing the change in absorbance at 400 nm due to the pseudo-zero-order production of *p*-nitrophenoxide ion at less than 5% conversion.

To a 5-ml volumetric flask was added 200 μl of ester stock solution. The stock solution of *p*-nitrophenyl propionate was $2.9 \times 10^{-3} \text{ M}$ in the solvent acetonitrile; the other ester stock solutions were the same as previously reported.⁶ This was then diluted volumetrically with 0.005 M Tris buffer maintained at constant ionic strength with sodium

chloride. The kinetics were followed by the procedures previously reported.^{3,6}

High-Pressure Optical Cell. Complete details of the high-pressure apparatus and techniques have been reported.^{3,6}

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- (2) Support by the National Science Foundation through Grant MPS 72-05018 is gratefully acknowledged.
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Intramolecular Nucleophilic Aminolysis of Aliphatic Esters. Cyclization of Methyl 2-Aminomethylbenzoate to Phthalimidine

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Abstract: Methyl 2-aminomethylbenzoate cyclizes at 30 °C in H_2O to phthalimidine with apparent hydroxide ion catalysis. The value of the second-order rate constant k_{OH} ($7 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$) is $\sim 10^5$ -fold greater than that for hydrolysis of methyl benzoate. The slope of a plot of $\log k_0$ vs. pH is 1.0 at pH values above 8.60 and 2.0 at pH values less than 8.60. Pronounced general-base catalysis is observed in the cyclization reaction. The Brønsted coefficient β for a series of general-base catalysts is 1.0, which is the value expected for a proton-transfer reaction in the thermodynamically unfavorable direction. Thus, it is probable that the rate-determining step in the general-base-catalyzed cyclization is proton transfer which is not concerted with bond making or breaking. The k_{OH} values are closely similar for the cyclization of methyl 2-aminomethylbenzoate, ethyl 2-hydroxymethylbenzoate, and *tert*-butyl 2-mercaptomethylbenzoate, even though the nucleophilic groups differ greatly in basicity.

Chemical intramolecular reactions bear a striking resemblance to corresponding enzymatic reactions proceeding through an enzyme-substrate complex.^{1,2} Consequently, the

study of intramolecular catalysis has been of great importance in attempts to understand the mechanism of enzyme action. In determining the relative efficiency of intramolecular nu-