

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, BALTIMORE 5, MD.]

The Mechanism of the Reaction of Tris-(hydroxymethyl)-aminomethane and Pentaerythritol with Phenyl Esters

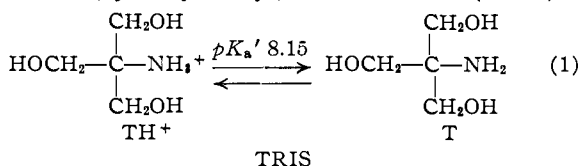
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The apparent second-order rate constants (k_2') for the reaction of tris-(hydroxymethyl)-aminomethane (TRIS) with five substituted phenyl acetates (solvent water, pH 7-10, $T = 30^\circ$, $\mu = 1.0 M$) are related to the fraction of neutral TRIS, $K_a/(K_a + a_H)$, and the hydrogen ion activity, by the expression $k_2' = k_b K_a/(K_a + a_H) + k_a K_a K_w/(K_a + a_H) a_H$. The terms involving k_a and k_b represent the nucleophilic displacement of phenol from ester by neutral TRIS with and without hydroxide ion catalysis. The ratio k_b^H/k_b^D was found to be 1.0 and in competitive studies of the reaction of TRIS with a limited amount of acetic anhydride (pH 5-10) the amino group was found to be the position of greatest nucleophilicity toward the acyl carbon atom. Thus, the term involving k_b has been assigned to an aminolysis reaction occurring without general acid or base catalysis. When the amino group of TRIS is replaced by a fourth $-CH_2OH$ group (to give pentaerythritol) the k_b term is removed from the kinetic expression for k_2' , but the k_a term remains. Therefore, the OH^- catalyzed reaction of TRIS with phenyl acetates is an esterolysis reaction which is not facilitated by the amino group. From the ratio k_{OH}/k_{OD} of 0.55 for the reaction, the mechanism must involve the pentaerythritol or TRIS anion as the nucleophile. The ρ -constants associated with k_a and k_b as well as with the reaction of pentaerythritol with phenyl acetates were determined. The ρ for k_b was found to be unusually small when compared to ρ values obtained previously in the non-general base-catalyzed reaction of other nitrogen bases with these same five substituted phenyl acetates.

Introduction

Tris-(hydroxymethyl)-aminomethane (TRIS) has



received attention as a nucleophile toward the ester bond because of its poly-functioned nature since the combined action of a nitrogen base (histidine) and an aliphatic hydroxyl group (serine) have been suggested to be essential for the high efficiency of catalysis of ester hydrolysis by certain esterases.³ The interesting but cursory observations of previous investigators^{6,7} have suggested to us that a thorough investigation of the kinetics of the reaction of TRIS with esters would be well worthwhile.

Experimental

Compounds.—Tris-(hydroxymethyl)-aminomethane was obtained from Sigma Chemical Co. as a chromatographically pure primary standard. The phenyl esters were prepared by procedures reported previously from this Laboratory.⁴ Dioxane was purified by the method of Fieser⁸ and frozen until used.

pK_a' determinations for TRIS were carried out under nitrogen with a Radiometer type TTT-1a autotitrator and Radiometer Titrograph. The temperature was maintained at $30 \pm 0.1^\circ$ with a Precision Scientific circulating water bath. The pK_a' was obtained by fitting the entire titration curve, after correction for solvent titration, to theoretical dissociation curves. In the determination of pK_a' , conditions of temperature, solvent, ionic strength and TRIS concentration were the same as those employed in the study of the kinetics of reaction of TRIS with the phenyl esters.

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(3) For a compilation of references on this topic see footnotes 1-11 of ref. 4 and footnotes 18 and 19 of ref. 5.

(4) T. C. Bruce and G. L. Schmir, *J. Am. Chem. Soc.*, **79**, 1663 (1957).

(5) T. C. Bruce and J. M. Sturtevant, *ibid.*, **81**, 2860 (1959).

(6) S. A. Bernhard and H. Gutfreund, *Proc. Int. Symp. of Enzyme Chem.*, Marhuxen, Tokyo, 1958, p. 127.

(7) W. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 1778 (1960).

(8) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p. 285.

The determined values of pK_a' were 8.10 when TRIS was at 0.10 M and 8.15 when TRIS was at 0.5 M .

Kinetics.—Reactions were routinely followed spectrophotometrically^{4,9} in 4-ml. quartz cuvettes. The cell compartment of the spectrophotometer (Zeiss PMQII) was modified to accommodate a hollow brass block cuvette holder through which was circulated water at a constant temperature of $30 \pm 0.1^\circ$ (Haake constant temperature circulating bath). The ester, dissolved in *ca.* 0.04 ml. of dioxane, was added (at zero time) to 4 ml. of the aqueous solution of TRIS contained in the cuvette pre-equilibrated to constant temperature. The pH of the TRIS solution was routinely checked prior to and after each experiment to assure against alteration of acidity during each run. Ionic strength was maintained at a calculated value of 1.0 M with KCl (*i.e.*, $TH^+ + K^+ = 1.0 M$). The concentrations of TH^+ and T were calculated from the known pK_a' , the total concentration of added reagent and the pH of the solution. The value of pK_a' employed throughout was 8.15.

Partitioning of Acetic Anhydride between the $-NH_2$ and $-CH_2OH$ Functional Groups of TRIS and Lyate Species as a Function of pH .—These experiments were carried out by the following standardized procedure. To 1 ml. of an 0.2 M aqueous solution (2×10^{-4} mole) of TRIS contained in a 1.5-ml. thermostated cell ($30 \pm 0.1^\circ$) under nitrogen was added 0.3 ml. of a 1.0 M solution (3×10^{-4} mole) of acetic anhydride in bis-(2-ethoxyethyl) ether. The addition of the acetic anhydride solution was made with a variable clock-motor driven Agla-micrometer syringe and the pH of the reaction medium was kept constant by addition of base *via* a Radiometer TTT-1a Titrograph assembly¹⁰ employed as a pH -stat.

At the conclusion of the reaction the pH of the reaction medium was lowered to 3.0 by addition of concentrated HCl with a micro-pipet. Employing the Radiometer TTT-1a Titrograph assembly as an automatic recording titrator, the concentration of acetic acid released and the free amino groups remaining were then determined in arbitrary base units as the heights of the titrative curves from pH 3.0 to 6.4 and pH 6.4 to 10, respectively. The concentrations of acetic anhydride and TRIS employed were obtained (in the same arbitrary base units) by titration of the TRIS solution alone and of a blank to which the acetic anhydride was added and allowed to hydrolyze.

The calculation of the % of TRIS acylated on O and N as well as the % hydrolysis of the acetic anhydride was carried out using

$$T_0 = \text{base units of TRIS initial}$$

$$T_f = \text{base units of TRIS after react.}$$

$$AcO_w = \text{base units of acetic acid on complete hydrolysis of acetic anhydride}$$

$$AcO_f = \text{base units of acetic acid after react.}$$

(9) T. C. Bruce and M. F. Mayahi, *J. Am. Chem. Soc.*, **82**, 3067 (1960).

(10) T. C. Bruce and T. H. Fife, *ibid.*, **83**, 1124 (1961).

A = base units equiv. to amide formed
 E = base units equiv. to ester formed
 H = base units equiv. to acetic acid formed from H₂O hydrolysis of acetic anhydride

Then

$$A = T_0 - T_t$$

$$E = 2T_0 \left(\frac{AcO_w - AcO_t}{AcO_w} \right) - (T_0 - T_t)$$

$$H = AcO_w - 2(AcO_w - AcO_t)$$

As a check on the titrimetric experiments the % acylation of TRIS also was determined by the hydroxamic acid method.¹¹ Reactions run at pH 8.0, which by the titrimetric method indicated 70% acylation, were by the hydroxamic acid method 60% acylated. Because the standard employed was not the product of the acylation of TRIS the agreement between the two results is considered satisfactory.

Deuterium Isotope Effect.—The values of k_2' were determined in the manner given under Kinetics and Results ($T = 30$, $\mu = 1.0 M$). The reaction of pentaerythritol with *p*-NPA^{11a} was studied at a pH meter reading of 10.04 (carbonate buffer 0.01 *M*) and the reaction of TRIS with *p*-NPA was studied at a pH meter reading of 8.04. The D₂O employed was obtained from Abbott Laboratories¹² as greater than 99.5% pure. The correction on the glass electrode (metrohm type X) was found to be +0.36 in D₂O.¹² The pseudo-second-order rate constants (k_2') for the reactions were taken as the average value obtained from four separate sets of plots of k_{obs} vs. total reagent. The values obtained were for

	H ₂ O	D ₂ O
Pentaerythritol		
k_2' , l. mole ⁻¹ min. ⁻¹	1.48 ± 0.15	0.95 ± 0.1
TRIS		
k_2' , l. mole ⁻¹ min. ⁻¹	0.0346 ± 0.0014	0.0233 ± 0.0012

After correcting the glass electrode reading to *p*D and taking into account the difference in the dissociation constant of water and D₂O,¹³ the ratio of the third-order rates for the OH⁻ catalyzed reaction of pentaerythritol with *p*-NPA is

$$k_2^H/k_2^D = \frac{1.35 \times 10^4}{2.43 \times 10^4} = 0.55$$

The second-order rate constants for the reaction of neutral TRIS with *p*-NPA were calculated from the apparent second-order constants (k_2') employing the pK_a' of TRIS in H₂O and D₂O (8.72) and the α_H and α_D values at which the k_2' constants were determined. The ratio $k_2^H/k_2^D = 7.9 \times 10^{-2}/7.66 \times 10^{-2} = 1.03$.

Results

In all the kinetic experiments reported herein the total concentration of TRIS (T_T) exceeded that of the esters by 10³ and 10⁴ and thus the conditions of pseudo-first-order kinetics are met.

$$-dE/dt = k_{obs}(E) \quad (2)$$

The values of the experimentally determined pseudo-first-order rate constants (k_{obs}) for ester

(11) The standard procedures of Hestrin [J. Biol. Chem., 159, 21 (1945); 180, 249 (1949)] were employed with the exception that 9 *M* hydroxylamine (pH 8.0) was employed and the reactions were carried out at steam-bath temperature for 45 min. *p*-Nitrophenyl acetate was employed as the primary standard.

(11a) Terms employed are: neutral TRIS (T), protonated TRIS (TH⁺), TRIS anion (T⁻), ester (E), TH⁺ $\xrightleftharpoons{K_a}$ T, T $\xrightleftharpoons{K_a}$ T⁻, hydrogen ion activity determined by the glass electrode (α_H), (α_H) × (α_{OH}) = $K_w = 10^{-14}$, *p*-nitrophenyl acetate (*p*-NPA), *m*-nitrophenyl acetate (*m*-NPA), *p*-chlorophenyl acetate (*p*-CIPA), phenyl acetate (PA) and *p*-cresol acetate (*p*-MePA).

(12) This value is smaller than that reported by Glasoe and Long (J. Phys. Chem., 64, 188 (1960)) at 25° and by Mikkelsen and Nielson (ibid., 64, 632 (1960)) at 22.2°. The reason for this is to be found in the linear dependence of *p*(DH) - *p*H on 1/°K. (T. H. Fife and T. C. Bruce, unpublished results).

(13) C. K. Rule and V. K. LaMer, J. Am. Chem. Soc., 60, 1981 (1938).

disappearance (i.e., phenol appearance), determined at any constant pH between 7.0 and 10.0, when plotted vs. T_T (0.05 to 1.0 *M*), gave linear plots. Thus, the reaction is first order in TRIS. In Fig. 1 there are presented plots of k_{obs} vs. T_T at

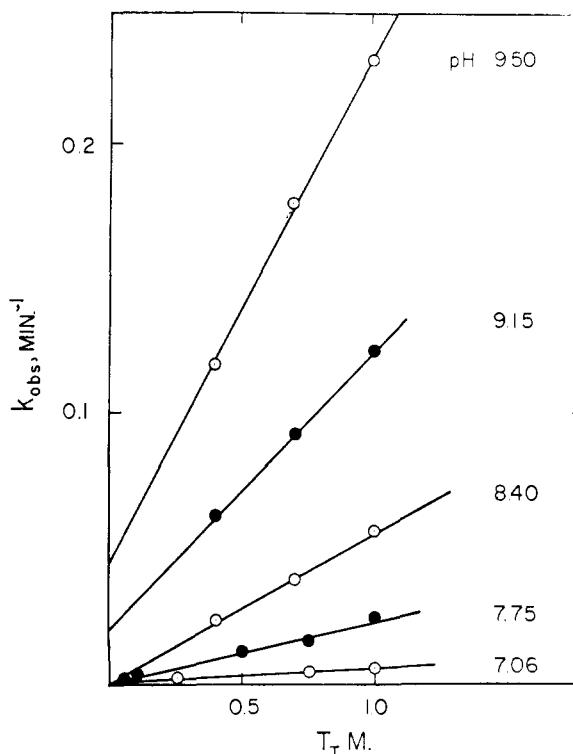


Fig. 1.—Linear plots of the observed first-order rate constants (k_{obs}) for the reaction of TRIS with *p*-NPA vs. total concentration of TRIS (T_T) at various pH values. The slopes of the plots are the pH-dependent apparent second-order rate constants (k_2').

varying pH values for the ester *p*-NPA. The values of the pseudo-second-order rate constants (k_2') were obtained routinely as the slopes of the plots of k_{obs} vs. T_T at each pH.¹⁴

$$k_2' = (k_{obs} - k_{hydro})/T_T \quad (3)$$

Inspection of the values of k_2' reveals that the reaction of TRIS with phenyl esters between pH 7.0 and 10.0 follows the kinetics of eq. 4.

$$-dE/dt = k_b(E)(T) + k_a(E)(T)(OH^-) \quad (4)$$

$$= K_a k_b \frac{(E)(T)T}{K_a + \alpha_H} + \frac{k_a K_w K_a (E)(T)T}{\alpha_H (K_a + \alpha_H)}$$

$$k_2' = \frac{k_b K_a}{K_a + \alpha_H} + \frac{k_a K_w K_a}{\alpha_H (K_a + \alpha_H)}$$

and

$$k_2'(K_a + \alpha_H) = k_b K_a + ((k_a K_w K_a)/\alpha_H)$$

It follows from (4) that a plot of $(K_a + \alpha_H)k_2'$ vs.

(14) The experimentally determined first-order rate constants (k_{obs}) and calculated apparent second-order rate constants (k_2') for the disappearance of esters as a function of the concentration of TRIS and pH ($T = 30^\circ$, $\mu = 1.0$, solvent H₂O) have been deposited as Document number 6553 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the document number and by remitting in advance \$1.25 for photoprints or \$1.25 for 35 mm. microfilm payable to: Chief, Photoduplication Service, Library of Congress.

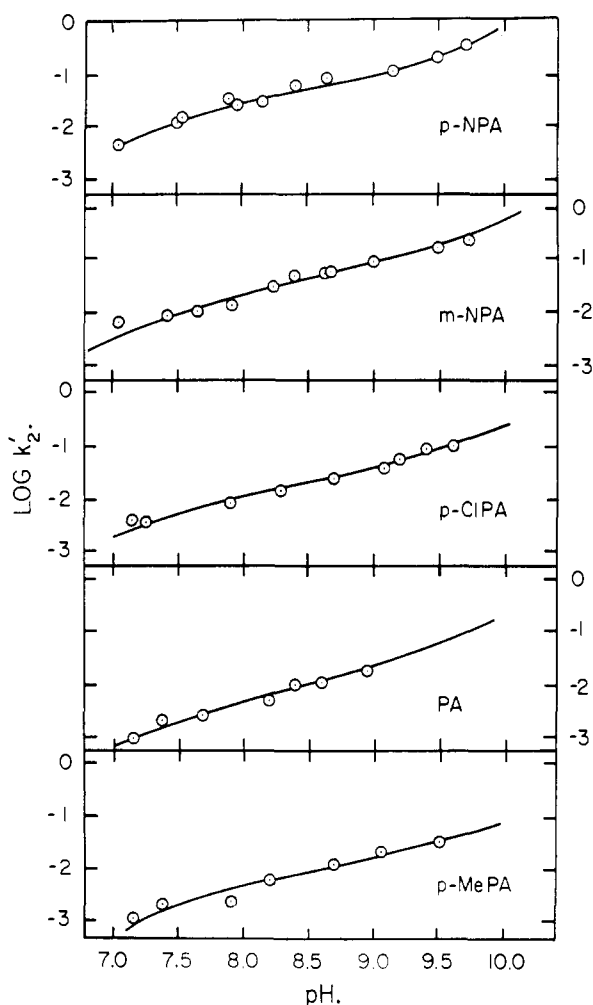


Fig. 2.—pH rate profiles for the reaction of neutral TRIS with five O-acylated phenols ($T = 30^\circ$, $\mu = 1.0 M$, solvent water). The curves are those calculated from eq. 4 employing the constants of Table I.

K_w/a_H should yield a straight line of slope $k_a K_a$ and intercept $k_b K_a$. Plots of this type (not shown) were prepared for each ester and the constants determined. In the plots of $\log k'_2$ vs. pH of Fig. 2 the curves are those calculated from eq. 4 employing the experimentally determined constants which are recorded in Table I.

TABLE I

RATE CONSTANTS FOR THE REACTION OF NEUTRAL TRIS WITH SUBSTITUTED PHENYL ACETATES WITH (k_a) AND WITHOUT (k_b) HYDROXIDE ION CATALYSIS

Substituent on phenyl acetate	k_a , $l.^2 \text{ mole}^{-2} \text{ min.}^{-1} \times 10^{-4}$	k_b , $l. \text{ mole}^{-1} \text{ min.}^{-1} \times 10^2$
<i>p</i> -NO ₂	4.8	6.73
<i>m</i> -NO ₂	4.08	4.97
<i>p</i> -Cl	1.13	2.93
H	1.05	0.99
<i>p</i> -CH ₃	0.86	0.99

The fit of eq. 4 to the experimental points for *p*-NPA is also shown by the solid line of Fig. 3.

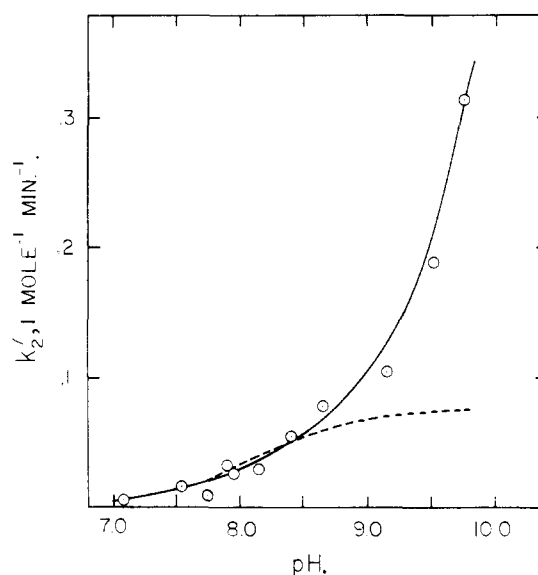


Fig. 3.—The experimental values of the apparent second-order rate constants (k'_2) for the reaction of TRIS with *p*-NPA plotted against the pH values at which they were determined. The dotted line is the expected relationship if the only rate term were for the bimolecular reaction of neutral TRIS with the ester. The solid line is that calculated from eq. 4 and includes terms for the reaction of neutral TRIS and ester with and without hydroxide ion catalysis.

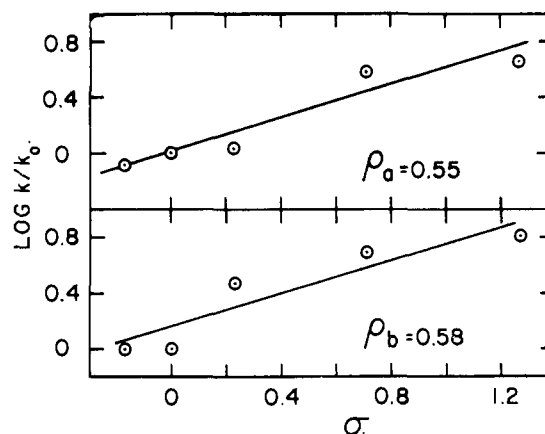


Fig. 4.—Conventional Hammett $\rho\sigma$ plots of the rate constants for the reaction of TRIS and phenyl esters with (ρ_a) and without (ρ_b) hydroxide ion catalysis. The value ρ_b refers to the sensitivity to electronic effects of the aminolysis reaction and ρ_a to the sensitivity to electronic effects of the attack of TRIS anion.

Conventional Hammett¹⁵ $\rho\sigma$ plots of k_a and k_b are presented in Fig. 4.

The question arises as to whether the amino or hydroxyl groups of TRIS serve as the nucleophilic centers in the displacement reactions at the acyl carbon atom. Toward the resolution of this question the reaction of TRIS with acetic anhydride was investigated. The advantage of acetic anhydride as a substrate over the phenyl esters resides in the lower pK_a' for acetic acid as compared to phenol allowing titrimetric determination

(15) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Ch. VII.

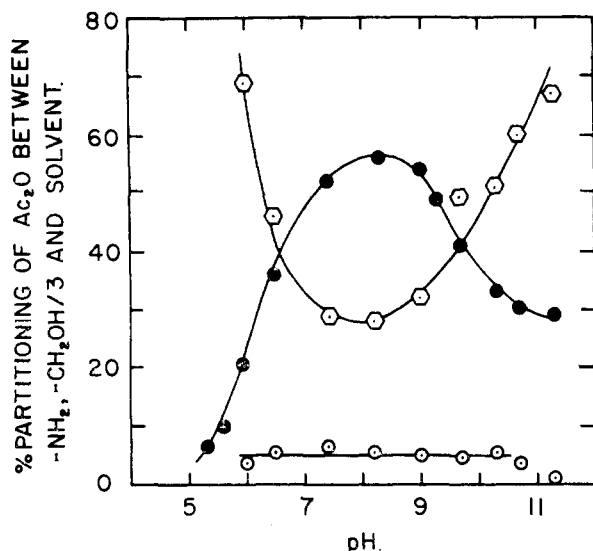


Fig. 5.—Plots of the % partitioning of acetic anhydride between the solvent \circ and the amino \bullet and each hydroxyl group \circ of TRIS.

of the acetic acid produced by hydrolysis and acylation and the amount of N-acylation. The procedure employed (see Experimental for precise details) was to allow TRIS and acetic anhydride (mole ratios of 1:0.8) to react to completion in water at constant pH (pH-stat) and then to titrate the reaction mixture (autotitrator) to determine the quantity of acetic acid produced due to hydrolysis and acylation, the concentration of amino groups which disappears due to N-acylation, and by difference the concentration of hydroxyl groups acylated during the reaction. The experimental data are presented in Fig. 5. Above pH 10, the amount of O-acylation decreases due to the increasing rate of hydrolysis of the acetic anhydride. On the other hand, the amount of N-acylation is strongly pH dependent. The shape of the curve suggests that N-acylation increases with the increase in concentration of T over TH^+ . The decrease in N-acylation above pH 8.5 may be again ascribed to an increase in the rate of solvolysis of the anhydride. In separate experiments it was determined that the rate of the O \rightarrow N acyl shift was much too slow to affect the results obtained.

To determine whether the amino group of TRIS played a role in the OH^- -catalyzed reaction of TRIS with the phenyl acetates the reaction of tetrakis-(hydroxymethyl)-methane-pentaerythritol—with *p*-NPA was investigated. The same conditions of temperature, solvent and reagent concentrations were employed as in the reaction of TRIS with *p*-NPA and the same procedures were used to evaluate k_2' . Constant pH was maintained with 0.01 M carbonate buffer. The reaction at any constant pH was found to be strictly first order in ester and pentaerythritol. The values of k_2' were found to be pH dependent and when $\log k_2'$ was plotted vs. pH, a linear profile of slope 1.1 was obtained (Fig. 6). The rate equation for the reaction of pentaerythritol with *p*-NPA is then

$$-dE/dt = k_c(E)(\text{pentaerythritol})(\text{OH}^-) \quad (5)$$

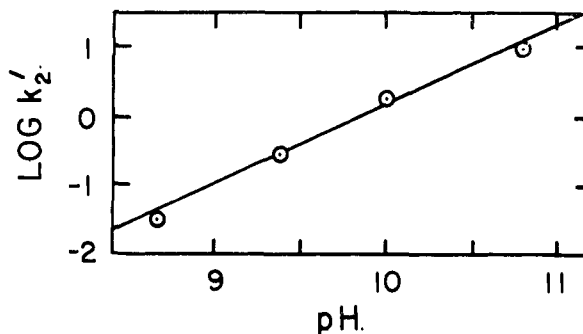


Fig. 6.—Conventional pH rate profile for the reaction of pentaerythritol with *p*-NPA. The slope of the linear plot is 1.1 indicating OH^- catalysis.

From Fig. 6 the value of k_c is $1 \times 10^4 \text{ l.}^2 \text{ mole}^{-1} \text{ min.}^{-1}$. It should be noted that if the statistical difference of three and four hydroxyl groups is considered, k_c is for all practical purposes identical to k_a of eq. 4 for the reaction of *p*-NPA with TRIS. Therefore, the amino group is not involved in the OH^- -catalyzed reaction of TRIS with *p*-NPA.

The question arises as to whether the attack of the hydroxyl groups of TRIS and pentaerythritol on the acyl carbon atom occurs *via* mechanisms involving TRIS anion (T^-) and pentaerythritol anion (specific base catalysis) or *via* a mechanism in which a proton is abstracted by an OH^- ion in the transition state (general base catalysis). A means, generally employed, to resolve this question is to compare the rates in water to those in D_2O . For this purpose the reaction of pentaerythritol with *p*-NPA was studied in D_2O and H_2O . The ratio $k_c^{\text{H}}/k_c^{\text{D}}$ was found to be 0.55. This suggests a specific base-catalyzed mechanism to be involved. The $k_{\text{H}}/k_{\text{D}}$ ratio for the N-acylation of TRIS by *p*-NPA was found to be 1.0, indicating no general base catalysis in this step.

Discussion

Bernhard and Gutfreund⁶ reported that in the reaction of TRIS with *p*-nitrophenyl acetate (H_2O), *p*-nitrophenol and acetate anion were liberated at equal rates. From this observation it was suggested that in the reaction of TRIS with *p*-nitrophenyl acetate a catalysis of hydrolysis is involved without acetylation of the TRIS. Jencks and Carriolo,⁷ in an extension of studies¹⁶ on the nucleophilic displacement of *p*-nitrophenol from *p*-nitrophenyl acetate (aqueous solution), reported that the disappearance of ester and acetylation of TRIS follow the same rate law and from limited kinetic data concluded that the rate of *p*-nitrophenol release from *p*-nitrophenyl acetate was dependent solely on the concentration of the neutral species of TRIS (eq. 4). The authors favored acetylation of a hydroxyl rather than the amino function (pH 8.1). This opinion was based on the fact that the acylated product behaved in its reaction with hydroxylamine more like an aliphatic ester than an amide situated on a tertiary carbon atom.¹¹ With the assumption of initial attack of the aliphatic hydroxyl group and this attack being

(16) T. C. Bruice and R. Lapinski *J. Am. Chem. Soc.*, **80**, 2265 (1958).

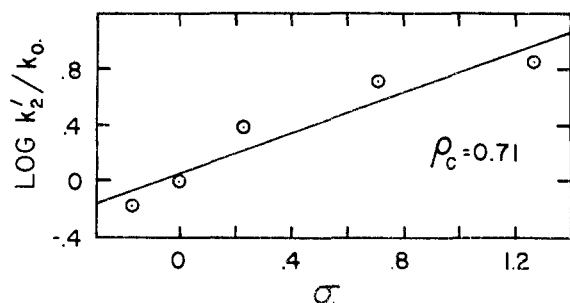


Fig. 7.—Hammett ρ plots for the base-catalyzed esterolysis of phenyl esters by pentaerythritol (least square slope). The values of k_2' were determined at a constant pH of 10.8.

dependent on the state of ionization of the amino group, an intramolecular general base-catalyzed *trans* esterification was postulated.¹⁷

The results of this study indicate that between pH 7.0 and 10.0 two kinetically detectable modes are present for the reaction of TRIS with phenyl acetates.⁴ The two kinetic constants k_a and k_b relate to the reaction of neutral TRIS at the ester carbonyl with and without hydroxide ion catalysis. The value of k_b for the reaction of TRIS with *p*-NPA does not suggest the necessity of a special mechanism to account for the nucleophilicity of TRIS. Thus, the second-order rate constant for the reaction of *t*-butylamine with *p*-NPA is 1.1 l. mole⁻¹ min.⁻¹ and the pK_a' of this base is 10.5.⁷ The Brønsted equation for the displacement of *p*-NP from *p*-NPA is $\log k_{2a} = 0.8pK_a' + C$.¹⁸ If the attacking group in TRIS is the amino function, then we may assume *t*-butylamine and TRIS to belong to the same nucleophilic series (C value of the Brønsted equation being identical). Employing the k_2 value for *t*-butylamine and pK_a' values of *t*-butylamine and TRIS, one can calculate the expected rate constant for the reaction of the TRIS amino group with *p*-NPA. The calculated value of 0.012 l. mole⁻¹ min.⁻¹ is in fair agreement, considering the assumptions made, with that of 0.067 l. mole⁻¹ min.⁻¹ determined in this study as k_b and 0.07 l. mole⁻¹ min.⁻¹ determined by Jencks and Carriuolo as k_2 .

In preparative experiments involving the reaction of TRIS with alkyl and benzyl halides¹⁸ as well as with esters,¹⁹ one obtains, in high yield, the *n*-alkylamine or amide. Similarly, in our competitive experiments with acetic anhydride we find that the amino group of TRIS as compared to the hydroxyl groups is the most effective nucleophile toward the acyl carbon atom of acetic anhydride. Furthermore, the ratio of k_H/k_D (1.0) for the constant k_b does not add support to a general base-catalyzed reaction.²⁰ It is most logical to

(17) The apparent high efficiency of the postulated intramolecular catalysis was pointed out by the fact that the hydroxyl group of TRIS would be $\sim 10^4$ as reactive as water. It may be noted that this mechanism bears a striking resemblance to the mechanisms favored by Cunningham [*Science*, **125**, 1145 (1957)] Dixon and Neurath [*J. Am. Chem. Soc.*, **79**, 4558 (1959)] and Spencer and Sturtevant [*ibid.*, **81**, 1874 (1959)] for the acylation step in the reaction of *p*-NPA with chymotrypsin.

(18) J. S. Pierce and J. Wotiz, *ibid.*, **73**, 2594 (1951).

(19) J. S. Pierce, C. D. Lunsford, R. W. Raiford, J. L. Rush and D. W. Riley, *ibid.*, **73**, 2595 (1951).

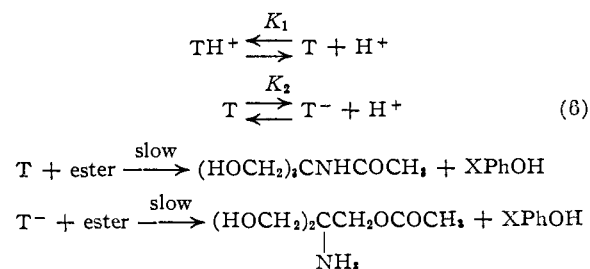
(20) The value of k_b^H/k_b^D may be of doubtful diagnostic value

conclude, therefore, that the non-catalyzed reaction of TRIS at the ester bond represents a non-general base-catalyzed aminolysis reaction which proceeds at a rate not greatly different from that expected of a *t*-butylamine of pK_a' 8.1.

Our finding that pentaerythritol (in which the amino group of TRIS is replaced by a fourth hydroxymethyl group) reacts with *p*-NPA via an OH⁻ catalyzed esterolysis and that the rate constant for this reaction is comparable to that for TRIS establishes the OH⁻ catalyzed reaction of TRIS with the phenyl esters to be an esterolysis reaction in which the hydroxy groups act as the nucleophile.

From the comparative acidity of pentaerythritol²¹ and water, one must assume that at any pH the concentration of pentaerythritol anion and OH⁻ are approximately equal. Since the rate of nucleophilic attack at the ester carbonyl is dependent on the pK_a' of the base^{7,18} we might also assume that the pentaerythritol anion would be comparable to OH⁻ as a nucleophile. When these considerations are combined with the ratio k_c^H/k_c^D of 0.55 for the pentaerythritol reaction we are compelled to assign a mechanism of specific base catalysis to k_c and k_a . The value of 0.55 for the deuterium isotope effect on k_c is comparable to that of 0.65 obtained for the OH⁻ catalyzed formation of epoxide from chlorohydrin.²² The latter reaction represents a case of pre-equilibrium formation of alkoxide followed by a slow intramolecular nucleophilic displacement of chloride ion. In the calculation of the ratio of k_c^H/k_c^D no account was taken of the difference in concentration of pentaerythritol anion at constant acidity in D₂O and H₂O. If such a correction is made, the ratio would be somewhat closer to 1.0 since alcohols are weaker acids in D₂O than in H₂O.²³ That the value of k_c^H/k_c^D is much smaller than 1.0 adds weight to the reaction being specific base catalyzed.²⁰

In summary, the reaction of TRIS with the phenyl esters is given by (6).



The ρ -values for the hydroxide ion specific base-catalyzed reaction of the hydroxyl groups of TRIS and pentaerythritol with substituted phenyl acetates are the first to be measured for a specific base-catalyzed esterolysis. The determined values (0.55 and 0.71, Figs. 4 and 7) are smaller than that for the hydroxide ion-catalyzed hydrolysis of the same esters ($\rho = 1.0$).⁹ The ρ -value for the aminol-

since it has been found that the general base-catalyzed aminolysis of phenyl esters by amines does not exhibit an isotope effect (see W. Jencks and J. Carriuolo, *ibid.*, **82**, 675 (1960)).

(21) P. Ballinger and F. A. Long, *ibid.*, **82**, 795 (1960).

(22) P. Ballinger and F. A. Long, *ibid.*, **81**, 2347 (1959).

(23) P. Ballinger and F. A. Long, *ibid.*, **81**, 1050 (1959).

ysis of phenyl esters by TRIS (0.58) is quite small when compared to that for ammonolysis (1.8)⁹ and aminolysis by imidazoles (1.7–1.9)^{4,24} but compares favorably to that for general base-catalyzed ammonolysis (0.56).⁹ However, our data do not support the aminolysis reaction with TRIS to be general base catalyzed. It would then appear as though the special molecular surroundings of the amino group of TRIS have a profound effect on its reaction at the ester carbonyl. Some plausible mechanisms are under further investigation. The rates of reaction of T⁻ and pentaerythritol anion with *p*-NPA are comparable to that reported by

(24) T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, **80**, 148 (1958).

Jencks and co-workers²⁵ for the reaction of N,O-diacetylserine anion with *p*-NPA. By the same criteria employed to evaluate the nucleophilicity of the anion of N,O-diacetylserine we must also assume that T⁻ and pentaerythritol anion are about 10² to 10³ stronger nucleophiles toward *p*-NPA than a normal alkoxide ion.

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(25) B. M. Anderson, E. H. Cordes and W. P. Jencks, *Federation Proc.*, **19**, 46 (1960).

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Diphenylcyclobutadienoquinone. Synthesis and Structure^{1,2}

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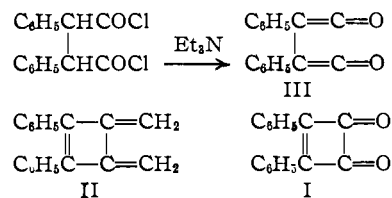
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Diphenylcyclobutadienoquinone, the dioxo analog of diphenyldimethylenecyclobutene, was first sought as a product from a reaction designed to give bis-phenylketene. Failure to find the diketone amongst a complex mixture of products obtained upon dehydrochlorination of α,α' -diphenylsuccinyl chloride prompted a direct synthesis of the cyclobutenedione. This was achieved readily by acid hydrolysis of 1,2-diphenyl-3,3,4,4-tetrafluorocyclobutene. The latter compound was prepared by reaction of perfluorocyclobutene with phenyllithium. The bright yellow crystalline diketone had good thermal stability. All physical and chemical studies confirmed its structure. Permanganate oxidation of the diketone gave only benzoic acid and a Baeyer–Villiger oxidation converted it to diphenylmaleic anhydride. The infrared, ultraviolet and n.m.r. spectra supported the conclusion that the diketone was at hand. In ethanol solution, the diketone transformed to diethyl α,α' -diphenylsuccinate, presumably *via* a bis-ketene intermediate. Phenylation of perfluorocyclobutene gave an accessory product (10%) which, on the basis of extensive chemical and physical studies, is best described as 1,2,3,4-tetrafluoro-1,4-diphenyl-1,3-butadiene.

In this Laboratory the convergence of two research trails focused attention on the diketone diphenylcyclobutadienoquinone, diphenylcyclobutenedione (I). Investigations concerned generally with the chemistry of bis-ketenes⁵ led to a study of 1,2 or α -bis-ketenes, while examination of certain highly unsaturated four-membered ring hydrocarbon systems suggested that it would be pertinent to examine oxo analogs of some of these small ring compounds.

In this context the diketone I is of especial interest. It is, first of all, the dioxo counterpart of diphenyldimethylenecyclobutene (I), described earlier,⁶ and hence comparison of its stability with that of the triene II would be of theoretical interest. Secondly, the diketone I is a valence

tautomer of bis-phenylketene (III) and it might, therefore, be found as a product from a reaction designed to produce the ketene III. Finally, the



diketone I could serve as an intermediate for the realization of *bona fide* cyclobutadienes.

The likelihood that the diketone I would be isolable was supported by the knowledge that Smutny and Roberts had synthesized phenylcyclobutadienoquinone⁷ and its stability made it possible for them to carry out a most thorough study of the cyclobutenedione system.⁸

Reaction of α,α' -diphenylsuccinyl chloride with triethylamine in benzene proved to be completely disappointing. Although evidence for reaction, precipitation of the amine hydrochloride, was noted, infrared analysis of the supernatant benzene solution did not show the presence of ketenoid products, *i.e.*, no strong infrared absorption band at *ca.* 4.8 μ was observed. A complex mixture of products actually was isolated from the above reaction, but only one was obtained which appeared

(1) This is the eleventh publication concerned with the chemistry of small carbon rings. For the preceding paper in this series see A. T. Blomquist, Y. C. Meinwald, C. G. Bottomley, P. W. Martin, *Tetrahedron Letters*, No. 24, pp. 13–17 (1960).

(2) For preliminary communications of portions of this investigation see: (a) Abstracts of Papers Presented at the National Meeting of the American Chemical Society in Boston, Mass., April, 1959, p. 54-O; (b) Abstracts of Papers Presented at the Sixteenth National Organic Chemical Symposium of the American Chemical Society, Seattle, Wash., June 15–17, 1959, p. 11.

(3) Supported by funds from the Sage Fellowship, Summer, 1957; Procter and Gamble Fellow, Summer, 1958; American Cyanamid Fellow, Summer, 1959; Allied Chemical and Dye Fellow, 1959–1960.

(4) The work reported here was abstracted from part of the dissertation presented by Eugene A. LaLancette in June, 1960, to the Graduate School of Cornell University in partial fulfillment of the requirements for the degree Doctor of Philosophy.

(5) A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.*, **79**, 202 (1957).

(6) A. T. Blomquist and Y. C. Meinwald, *ibid.*, **81**, 667 (1959).

(7) E. J. Smutny and J. D. Roberts, *ibid.*, **77**, 3420 (1955).

(8) E. J. Smutny, M. C. Caserio and J. D. Roberts, *ibid.*, **82**, 1793 (1960).