residue was examined *via* tlc; after 1 hr a substance with the same mobility as indole ester IIIj was observed. After a total reaction time of 5 hr, the reaction was treated in the above manner; the material thus obtained was recrystallized from acetone–hexane to give 11 mg (22%) of IIIj as white crystals, mp 225–226°. The identity of this material was established by the usual criteria.

Conversion of Ethyl *trans*-3-Amino-2-(2,5-dihydroxy-*p*-tolyl)-crotonate (VII) into Ethyl 5-Hydroxy-2,6-dimethylindole-3-carboxylate (IIIa). A solution of 100 mg of VII in methylene chloride was treated briefly with hydrogen chloride; amorphous material separated. The solvent was removed and a solution of 500 mg (2.56 mmoles total) of VII in methanol was added; this solution was heated under reflux for 5 hr. The cooled solution was treated with 312 mg (2.56 mmoles) of toluquinone; this resulted in immediate generation of a red color. Thin layer chromatography showed two major components, neither having the mobility of the starting materials. After 5 days at room temperature IIIa could not be detected by tlc. The solution was treated with a sodium hydrosulfite solution until the red color was discharged, and the resulting mixture was extracted with methylene chloride. The dried extracts were evaporated, and the residue was recrystallized from acetone–hexane to give 313 mg (52%) of IIIa, mp 222–225°.

In a subsequent experiment the equilibration solution from 600 mg (2.56 mmoles) of VII was treated with 31 mg (0.25 mmole) of toluquinone. The resulting red solution was heated under reflux for 90 min, after which the solvent was removed. The residue was recrystallized from acetone–hexane to give 102 mg (17%) of VII, mp 182–184°. The filtrate was evaporated, and the residue was chromatographed on silica gel. The material eluted with ether was recrystallized from acetone–hexane to give 252 mg (55% based on unrecovered VII) of crystals, mp 215–217°. An additional recrystallization gave 207 mg of IIIa as white crystals, mp 225–227°.

Ethyl *trans*-3-Isopropylamino-2-(2,5-dihydroxy-*m*-tolyl)crotonate (XI). The condensation between toluquinone (6.11 g, 0.05 mole) and ethyl 3-isopropylaminocrotonate (8.56 g, 0.05 mole) was effected in boiling acetone. The cherry red solution was treated with an excess of a sodium hydrosulfite solution, whereupon the red color was discharged. The resulting mixture was distributed between ethyl acetate and water. The dried organic solution was evaporated, and the residue was triturated with ether to give 2.51 g (18%) of ethyl **5-hydroxy-1-isopropyl-2,6-dimethylindole-3-carboxylate** (IIIf) as white crystals, mp 202.0–203.5°. The ethereal filtrate was chilled in the refrigerator for 3 days to give 2.60 g (18%) of white crystals, mp 140–143° after recrystallization from acetone–hexane; λ_{max} 298 mμ (ϵ 22,300); 2.93, 6.16, 6.40, 7.75–7.95, 8.09, 8.24, and 12.64 μ; pmr 65 (3t, J = 7.5 cps), 73.5 (6d, J = 7 cps, $CH(CH_3)_2$), 105 (3s, $=C-CH_3$), 136 (3s, aryl CH_3), 210–258 (3m, OCH_2CH_3 and $CH(CH_3)_2$), 315 (2 broad, O*H*, erased by methanol-d_4), 380, 394 (1d each, J = 2 cps, aryl *H*), 580 cps (1d, J = 9.0 cps, N*H*, erased by methanol-d_4).

Anal. Calcd for $C_{16}H_{23}NO_4$ (293.25): C, 65.51; H, 7.90; N, 4.78. Found: C, 65.65; H, 8.08; N, 5.01.

Acknowledgment. We wish to thank Professors M. Gates and H. E. Zimmerman for helpful discussions. We also thank Mr. G. Morton and Mr. W. Fulmor and staff for spectral data, Mr. L. Brancone and staff for microanalytical data, and Mr. P. Bonenfant, Mrs. J. Davis, and Messrs. R. Mills and D. Munkelt for assistance with the partition chromatography.

Reactions of Phosphinates. The Acid-Catalyzed and Acid-Inhibited Hydrolysis of *p*-Nitrophenyl Diphenylphosphinate

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Abstract: The rates of hydrolysis of *p*-nitrophenyl diphenylphosphinate have been studied in acidic dioxane–water (40:60, v/v). Oxygen-18 studies show that hydrolysis occurs by cleavage of the P–O bond. The dependence of rate on acid concentration passes through a maximum at ~1.5 *M* $HClO_4$. The observed data give a w value (Bunnett) of 12 although ΔS^* is only −27 eu. Measurement of the basicity of dimethylphosphinic acid ($pK_a = -4.0$) and methyl diphenylphosphinate ($pK_a = -4.8$) has shown that phosphinates have very different protonation behavior compared to Hammett bases, and it is clear that very little of the substrate is protonated at the acidity giving a maximum rate of hydrolysis. The observed maximum rate at ~1.5 *M* acid then is not due to extensive protonation of substrate as is true for carboxylic amides nor is it due to solvation effects alone as the Bunnett hypothesis would suggest. Rather, it is primarily due to large changes in activity coefficients with increased acidity, although solvation of the transition state seems to be of some importance in the cause of this phenomenon.

There have been relatively few detailed studies of displacement at phosphorus under acidic conditions.[1] Hudson and Keay studied a variety of phosphonates in aqueous 1 *N* benzenesulfonic acid[2] with results indicating displacement at carbon in alkyl esters and displacement at phosphorus in aryl esters. Dibenzyl phosphate was studied in mildly acidic solution and presumably hydrolyzes by an acid-catalyzed mechanism involving cleavage of the carbon–oxygen band.[3] Oxygen-18 studies and kinetic data indicate that the acid-catalyzed hydrolysis of dimethyl phosphate[4–6] proceeds with complete[4] or nearly complete[6] attack at carbon. A similar analysis of oxygen-18 and kinetic results for monomethyl phosphate[7] is complicated by the rapid hydrolysis of the monoanion. The rates of hydrolysis of both dimethyl phosphate[6] and monomethyl phosphate[7] show linear dependence on acid concentration at constant ionic strength. The rate of

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[1] J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).

[2] R. F. Hudson and L. Keay, *J. Chem. Soc.*, 2463 (1956).

[3] J. Kumamoto and F. H. Westheimer, *J. Am. Chem. Soc.*, 77, 2515 (1955).

[4] P. Haake and F. H. Westheimer, *ibid.*, **83**, 1102 (1961).

[5] C. A. Vernon, Special Publication No. 8, The Chemical Society, London, 1957, p 17.

[6] C. A. Bunton, M. M. Mhala, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3293 (1960).

[7] C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *ibid.*, 3574 (1958).

hydrolysis of α-D-glucopyranose 1-phosphate is linearly dependent on the Hammett acidity function, H_0, and the reaction proceeds with cleavage of the carbon–oxygen bond.[8] The rapid hydrolysis[9] of ethylene phosphate proceeds mainly by attack at phosphorus[4] and there is a significant amount of exchange of the oxygens in ethylene phosphate with oxygen atoms of the solvent.[4] Acid-catalyzed hydrolysis of the fully esterified trimethyl phosphate is obscured by attack of water on the neutral molecule.[10] In this paper we describe our work on the rates and mechanism of acid-catalyzed hydrolysis of *p*-nitrophenyl diphenylphosphinate. In addition to acid catalysis we observe acid inhibition of hydrolysis in more concentrated solutions. The effects on rate of hydrolysis due to increasing concentrations of acid are analyzed by several methods.

Most relevant to the present work, there is a maximum in the rate of acid-catalyzed hydrolysis of triphenyl phosphate at about 1.5 *M* perchloric acid in 75% dioxane–water[5] and *p*-nitrophenyl phosphate has a maximum rate of hydrolysis in aqueous solutions at 5 *M* perchloric acid.[5] The occurrence of maxima in rates of acid-catalyzed hydrolysis of amides as a function of acidity has been interpreted as resulting from extensive protonation of substrate in which case it is clear that addition of more acid would only lower the activity of water and therefore slow the rate of hydrolysis.[11]

The effect of increasing concentration of acid and salt on the rates of hydrolysis of carboxylic anhydrides has also been studied by Bunton and co-workers[12] with the observation of several anomalous effects.

As part of his attempt to improve the analyses of mechanisms of acid-catalyzed reactions by evaluating the role of solvent,[13] Bunnett has included an analysis of the role of solvent in the acid-catalyzed hydrolysis of several phosphates.[14] However, Marburg and Jencks[15] have observed rate decreases in the hydrolysis of acetylimidazolium ion due to increasing concentration of acids or salts which result in a wide range of *w* numbers proposed by Bunnett[13] as a measure of solvation.

Experimental Section

Materials. The solvent, dioxane-water (40:60, v/v), was prepared by the addition of 40 volumes of purified dioxane[16] to 60 volumes of water. The amount of water in the reagent grade perchloric acid was determined by standardization against borax.[17] In acidic solutions dioxane was added to compensate for the water in the perchloric acid. The preparation of *p*-nitrophenyl diphenylphosphinate (I) was accomplished by oxidation of $(C_6H_5)_2PCl$ (obtained from Victor Chemical Co.) with gaseous oxygen to give $(C_6H_5)_2P(O)Cl$ which was treated with a 10% excess of *p*-nitrophenol in pyridine solution. A massive precipitate resulted. Sufficient 10% hydrochloric acid was added to convert all the pyridine to the hydrochloride and the precipitate was filtered and washed with 1% hydrochloric acid and water. Two recrystallizations from acetone provided pale yellow, translucent crystals, mp 149–150°. The infrared spectrum in CCl_4 (Perkin-Elmer Model 421) included absorption at 1340 and 1520 (NO_2), 1435, 1490, 1585, and 1605 (aromatic rings), 1240 (P=O), 1210 cm^{-1} (P–OAr).[18]

Anal. Calcd for $C_{18}H_{14}NO_4P$: C, 63.72; H, 4.16. Found: C, 63.59; H, 4.06.

Dimethyl phosphinic acid was prepared by a known method.[19] Methyl diphenylphosphinate was prepared by Diebert.[20]

Kinetics. Aliquots of the reaction mixtures (about 1.5×10^{-4} *M* in *p*-nitrophenyl diphenylphosphinate) were sealed in rate tubes which were immersed in an oil bath at 75.10°. The reactions were quenched by cooling the sealed tubes in ice and the extent of reaction was measured spectrophotometrically at 318 mμ using a Hitachi-Perkin-Elmer Model 139 spectrophotometer. The spectrum of *p*-nitrophenol shows a maximum at 318 mμ and the diphenylphosphinate ester has an extinction coefficient at 318 mμ which is only $^1/_{11}$ of that for *p*-nitrophenol. Simple arithmetic derivation leads to the equation $\log (OD_\infty - OD) = -kt +$ intercept. Infinity points were measured by complete hydrolysis with base followed by addition of acid and solvent to give the proper acidity and concentration. In a run used to check this, an actual infinity point measurement agreed with the infinity point measured by this method to 0.001 optical density unit. First-order rate constants and the standard deviations were determined graphically and by the least-squares method[21] using the above equation. In some runs, rate constants were obtained by both methods and the results agreed well. The first-order nature of the reaction was proven by carrying some of the reactions to over 90% reaction (4 half-lives) and by the titrimetric run which was carried out at an ester concentration 100 times greater than the corresponding spectrophotometric run.

The rate of hydrolysis at 1.0 *M* perchloric acid was also determined tritrimetrically to confirm the validity of the spectrophotometric method. Following the procedure of Salomaa,[22] quenched aliquots of a reacting solution 0.015 *M* in *p*-nitrophenyl diphenylphosphinate and 1 *M* in perchloric acid were diluted with dioxane to prevent precipitation of diphenylphosphinic acid and then carefully taken to neutrality. A measured amount of standard NaOH solution was added to hydrolyze unreacted ester and the amount of base consumed was then evaluated by addition of excess acid followed by back titration. The rate constant obtained at 75°, 5.05×10^{-4} sec^{-1}, agrees satisfactorily with the spectrophotometric rate constants considering the difference in ester concentration and the inaccuracies inherent in both the spectrophotometric and titrimetric methods.

Oxygen-18 Experiments. The hydrolysis of *p*-nitrophenyl diphenylphosphinate was carried out in dioxane-water (60:40, v/v), so that a higher concentration of ester could be used. The ester was dissolved in 14.4 ml of dioxane, and 2.66 ml of 61% perchloric acid (enough to give finally a 1.0 *M* solution) and 8.0 ml of 1.91 atom % oxygen-18-enriched water[23] were added. The reaction mixture was kept at 75.7° for 20.5 min. It was then cooled, distilled water was added, and the solution was partially vacuum evaporated in order to remove dioxane. Additional water (50 ml) was added to give a white precipitate (mixture of diphenylphosphinic acid and the *p*-nitrophenyl ester) which was removed by filtration. Chloroform was used to extract more material from the aqueous, acidic solution. Unhydrolyzed *p*-nitrophenyl diphenylphosphinate was separated from diphenylphosphinic acid by extracting a chloroform solution of the mixture with 0.5% sodium formate solution which removed diphenylphosphinic acid with minimal hydrolysis of *p*-nitrophenyl diphenylphosphinate. The

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[8] C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3588 (1958).

[9] J. Kumamoto, J. R. Cox, and F. H. Westheimer, *J. Am. Chem. Soc.*, **78**, 4858 (1956).

[10] P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, 2670 (1961).

[11] (a) V. K. Krieble and K. A. Holst, *J. Am. Chem. Soc.*, **60**, 2976 (1938); (b) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000 (1957); (c) R. B. Martin, *J. Am. Chem. Soc.*, **84**, 4130 (1962).

[12] (a) C. A. Bunton and S. G. Perry, *J. Chem. Soc.*, 3070 (1960); (b) C. A. Bunton, N. A. Fuller, S. G. Perry, and I. H. Pitman, *ibid.*, 4478 (1962); (c) C. A. Bunton, J. H. Fendler, N. A. Fuller, S. G. Perry, and J. Rocek, *ibid.*, 5361 (1963).

[13] J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

[14] See ref 13, p 4981.

[15] S. Marburg and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 232 (1962).

[16] A. I. Vogel, "Practical Organic Chemistry," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1957, p 177.

[17] C. A. Bunton, J. B. Ley, A. J. Rhind-Tutt, and C. A. Vernon, *J. Chem. Soc.*, 2327 (1957).

[18] E. M. Popov, M. I. Kabachnik, and L. S. Mayants, *Russ. Chem. Rev.*, 30, 362 (1961); K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962.

[19] G. M. Kosolapoff and R. M. Watson, *J. Am. Chem. Soc.*, **73**, 5466 (1951).

[20] P. Haake and C. Diebert, work in progress.

[21] W. J. Youden, "Statistical Methods for Chemists," John Wiley and Sons, Inc., New York, N. Y., 1951. The standard deviation (σ) was determined by $\sigma = \sqrt{\Sigma\Delta^2/(N-2)}$, where Δ = deviation of each point and N = number of points.

[22] P. Salomaa, *Suomen Kemistilehti*, **32B**, 81 (1959).

[23] Atom % oxygen-18 = $a = [^{18}O/(^{18}O + ^{16}O)] \times 100$. The atom % excess ^{18}O is this value less the normal abundance of ^{18}O in the material in question.

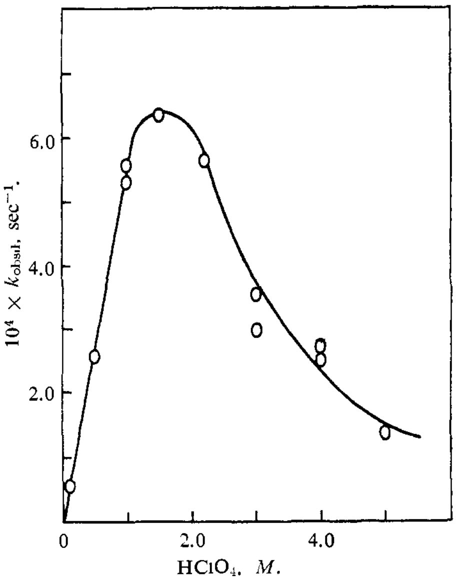


Figure 1. Dependence of rate of hydrolysis of *p*-nitrophenyl diphenylphosphinate on acid concentration.

p-nitrophenyl diphenylphosphinate is, of course, exceedingly sensitive to alkaline hydrolysis. In trial experiments we found that sodium acetate solution was too basic to be used for extraction, but the *p*-nitrophenyl ester appeared to be stable to sodium formate solution. The experimental results indicate that we were not entirely successful in avoiding hydrolysis during this extraction.

The chloroform solution was dried, then evaporated, and the residue was recrystallized from acetone to give *p*-nitrophenyl diphenylphosphinate. Acidification of the sodium formate solutions produced white needles of diphenylphosphinic acid. Unhydrolyzed ester and product acid were also isolated from a blank run in unenriched solvent. Control experiments showed diphenylphosphinic acid did not exchange its oxygens under the conditions of the ester hydrolysis and product work-up.

Diphenylphosphinic acid and *p*-nitrophenyl diphenylphosphinate were analyzed for oxygen-18 by heating with mercuric cyanide[24] to convert the oxygens to carbon dioxide.[20] Mass spectral analyses were performed with a CEC Model 21-620 mass spectrometer with an isotope ratio attachment to give the 46/44 mass ratio and with a CEC Model 21-401 mass spectrometer to give the 46/(44 + 45) mass ratio. The latter machine requires a comparison standard for reliability; tank CO_2 was used.

Acidity Constant Measurements. Fuming sulfuric acid was titrated with water until fuming stopped to determine the SO_3 content[25] and to give 100.0% sulfuric acid. Sulfuric acid solutions below 95.5% were made up from a standardized 95.5% stock solution. As a control the concentration of the 65% solution was checked by basic titration.

Two per cent solutions of dimethylphosphinic acid were prepared on a weight basis in varying concentrations of H_2SO_4. The chemical shift in the nmr spectrum of the methyl protons was determined for each solution using $(CH_3)_3Si(CH_2)_3SO_3Na$ as a standard[26] in 0-55% H_2SO_4 and $(CH_3)_4N^+Br^-$ as a standard in 55-103.2% H_2SO_4. The chemical shift of the methyl protons in methyl diphenylphosphinate was determined relative to $(CH_3)_4N^+Br^-$ as a standard. The measurements on $(C_6H_5)_2PO_2CH_3$ were done at 75° using a Varian A-60 nmr spectrometer equipped with a variable temperature probe.

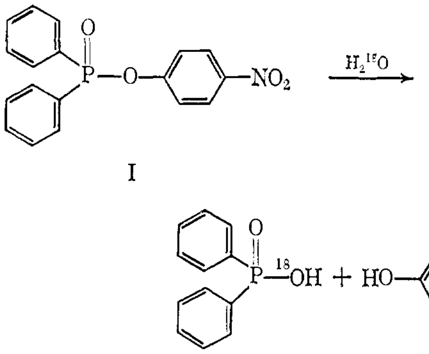
Results

The observed rates of acid-catalyzed hydrolysis of *p*-nitrophenyl diphenylphosphinate (I) are given in Table I. The rate constants are seen to pass through a maximum at about 1.5 *M* $HClO_4$ as shown in Figure 1. Maxima are also observed in the logarithmic dependence of k_{obsd}[27] on H_0 or log C_{H^+} (Figure 2) with initial slopes of 0.7 for the H_0 plot and 1.0 for the log C_{H^-} plot (as the linear portion of Figure 1 demands). The rate constants obtained at 1.0 *M* give $\Delta H^* = 16.5$ kcal/mole, $\Delta S^*_{75} = -27$ eu, and $\Delta F^*_{75} = 25.8$ kcal/mole.[28]

Table I. Rates of Hydrolysis of *p*-Nitrophenyl Diphenylphosphinate at 75.1° in Dioxane–Water (40:60, v/v)

C_{HClO_4}[a]	Temp, °C	$10^5 k_{obsd}$, sec^{-1}	H_0[b]	$C_{solvent}$ (free)[a,c]
0				38.0
0.1	75.1	5.6 ± 0.1	1.76	37.6
0.5	75.1	25.8 ± 1.2	0.99	36.0
1.0	75.1	55.1 ± 1.5	0.39	34.0
1.0	75.1	53.3 ± 2.3		
1.0	75.1	50.5[d]		
1.0	55.2	10.9		
1.0	65.0	21.1		
1.0	84.9	86.3		
1.5	75.1	63.5 ± 1.8	0.05	32.0
2.2	75.1	56.4 ± 0.6	−0.40	29.2
3.0	75.1	35.5 ± 1.2	−0.97	26.0
3.0	75.1	29.8 ± 1.4		
4.0	75.1	25.3 ± 0.2	−1.65	22.0
4.0	75.1	27.4 ± 0.3		
5.0	75.1	13.8 ± 0.3	−2.09	18.0

[a] Units of concentration are moles/liter. [b] H_0 = Hammett acidity function = $pK_{BH^+} - \log (C_{BH^+}/C_B)$. [c] $C_{solvent}$ (free) = $\Sigma C_{solvent} - 4C_{HClO_4}$. [d] Titrimetric rate—all others done spectrophotometrically.



I

II

(1)

The results of experiments designed to determine the position of bond cleavage are shown in Table II. Because diphenylphosphinic acid does not exchange any of its oxygens under the conditions of the experiment and work-up and because the phosphinyl oxygen of the ester is not enriched during hydrolysis, enrichment for the isolated $(C_6H_5)_2PO_2H$ (II) in Table II must be multiplied by 2 to get the per cent P-O bond cleavage: [2(0.855 − 0.203)/(1.710 − 0.200)]100 = 87%. Since there was a chance for dilution of the label by hydrolysis of I during work-up in the extraction with sodium formate solution (see the Experimental Section), within experimental error the per cent of P-O bond cleavage indicates complete hydrolysis by a mechanism involving attack at phosphorus and breaking of the P-OAr bond (eq 1). The alternative result, breaking the Ar-OP bond, would involve nucleophilic aromatic

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(24) M. Anbar and S. Guttmann, *Intern. J. Appl. Radiation Isotopes*, **4**, 233 (1959).

(25) J. C. D. Brand, *J. Chem. Soc.*, 585 (1946).

(26) G. V. D. Tiers and R. I. Coon, *J. Org. Chem.*, **26**, 2097 (1961).

(27) Observed first-order rate constants = k_{obsd} (third column of Table I).

(28) Enthalpy of activation determined from plot of log k_{obsd} *vs.* $1/T$; free energy of activation determined from k_{obsd} at 75.10°.[29]

(29) A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961.

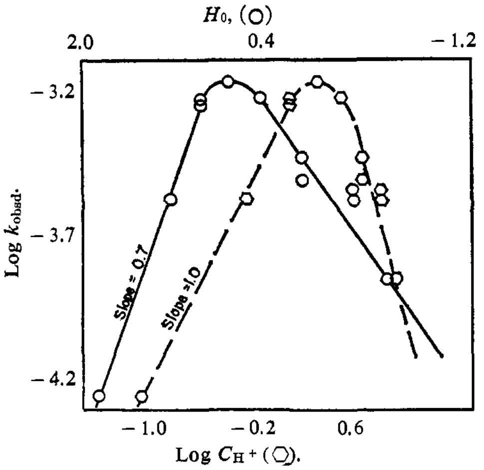
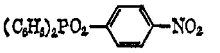


Figure 2. Dependence of log k_{obsd} for hydrolysis of *p*-nitrophenyl diphenylphosphinate on log C_{H^+} and log h_0 = $-H_0$.

displacement with water as nucleophile. Since this would be expected to be a much higher energy process than displacement at phosphorus, we did not repeat the above experiments. The amount of enrichment found in the unhydrolyzed *p*-nitrophenyl diphenylphosphinate is within experimental error of zero, although a thorough study should be made of acid-catalyzed hydrolyses to determine if exchange of phosphinyl oxygen can occur competitively with hydrolysis.

Table II. Hydrolysis of *p*-Nitrophenyl Diphenylphosphinate in O^{18}-Enriched Water

	Atom % oxygen-18[a]		
Compd isolated	Initial	Blank experiment, unenriched solvent	From hydrolysis in enriched solvent
H_2O	. . .	0.200	1.710
$(C_6H_5)_2PO_2H$	0.199	0.203, 0.203	0.855
	0.201, 0.203	0.205, 0.205[b]	0.209[b]

[a] Defined in ref 21. [b] Using Model 21-401 mass spectrometer; all other results on Model 21-620 mass spectrometer.

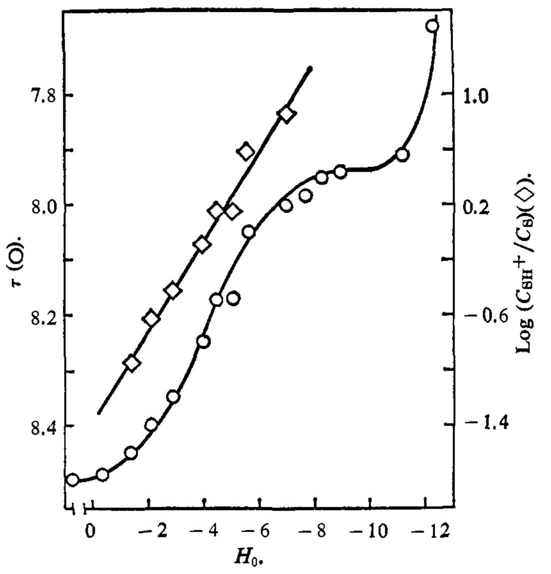


Figure 3. Protonation of $(CH_3)_2PO_2H$ measured by chemical shift, and the dependence of log (C_{SH^+}/C_S) on H_0.

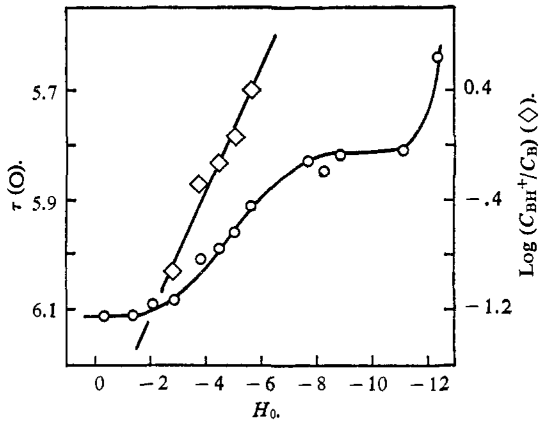


Figure 4. Protonation of $(C_6H_5)_2PO_2CH_3$ measured by chemical shift, and the dependence of log (C_{SH^+}/C_S) on H_0.

The basicities of methyl diphenylphosphinate (III) and dimethylphosphinic acid (IV) were determined by nmr measurements; the plot of chemical shift (in τ units) against H_0 for dimethylphosphinic acid is shown in Figure 3 and for methyl diphenylphosphinate in Figure 4. Both plots show reasonable sigmoid curves with pK_a values from the half-titration value of −4.3 and −4.7, respectively. The cause of the rapid increase in chemical shift in very concentrated and fuming H_2SO_4 is an interesting question which is currently under investigation. An important question in all kinetic studies of acid catalysis is whether the substrate is behaving as a Hammett base. Since proton exchange should be very fast, eq 2 should determine the observed chemical shift, δ_{obsd}

$$(\delta_{SH^+})(C_{SH^+}) + (\delta_S)(C_S) = \delta_{obsd}[(C_S) + (C_{SH^+})] \quad (2)$$

The values of (C_{SH^+}/C_S) can then be obtained as a function of acidity

$$(C_{SH^+}/C_S) = (\delta_S - \delta_{obsd})/(\delta_{obsd} - \delta_{SH^+}) \quad (3)$$

Plots of log (C_{SH^+}/C_S) against H_0 are included in Figures 3 and 4, and give the following H_0 dependence of log (C_{SH^+}/C_S)

$$(CH_3)_2PO_2H\text{: } \log(C_{SH^+}/C_S) = 0.35(-4.0 - H_0) \quad (4)$$

$$(C_6H_5)_2PO_2CH_3\text{: } \log(C_{SH^+}/C_S) = 0.46(-4.8 - H_0) \quad (5)$$

Since the slopes, 0.35 and 0.46, are quite different from 1.0, phosphinates appear to be very different from the bases used to determine the H_0 scale.[30,31] These equations also define pK_a values on the H_0 scale, −4.0 for protonated $(CH_3)_2PO_2H$ and −4.8 for protonated $(C_6H_5)_2PO_2CH_3$, which were used rather than those indicated by the sigmoid plots of Figures 3 and 4. Because the intercepts of the straight-line plots of Figures 3 and 4 were used to evaluate these pK_a values, there is some uncertainty in them, and a further dif-

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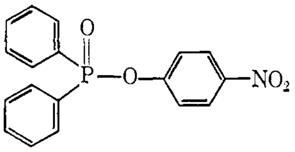
[30] M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

[31] (a) J. T. Edward and I. C. Wang, *Can. J. Chem.*, **40**, 966 (1962); (b) J. T. Edward and H. Stollar, *ibid.*, **41**, 721 (1963).

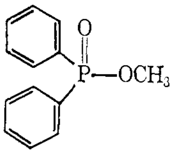
ficulty involves our measurements at 75° using H_0 values for 25°.

The pK_a of protonated I could not be evaluated from ultraviolet spectral measurements because of insufficient change of spectrum on protonation. The nmr spectrum was too complex and the compound was too insoluble to use nmr measurements. We therefore have used known pK_a values[32] for analogous carbon compounds to correct the pK_a's observed here to that of the conjugate acid of I. From pK_a = −4.8 determined by us for the conjugate acid of $(C_6H_5)_2PO_2CH_3$, one estimates pK_a = −5.2 for $(C_6H_5)_2P(O^+H)OC_6H_5$ (pK_a = −2.1 for $C_6H_5C(O^+H)NHCH_3$, but pK_a = −2.5 for $C_6H_5C(O^+H)NHC_6H_5$[32]). There are no available data on *p*-nitrophenyl esters or *p*-nitroanilides, but an approximate estimate of pK_a = 5.7 for protonated I can be made (pK_a = −6.9 for $C_6H_5C(O^+H)CH_2C_6H_5$ and pK_a = −7.4 for $C_6H_5C(O^+H)CH_2C_6H_4NO_2$[32]).[33] It is more difficult to compare our measurement of the pK_a of IV-H$^+$ with that of III-H$^+$, but the agreement appears reasonable considering the pK_a's of the conjugate acids of benzoic acid (−7.3) and acetic acid (−6.2).[32] The pK_a of protonated triphenyl phosphate reported by Vernon and co-workers[5] to be −2.8 also appears reasonable since there will be π bonding in each P–OAr bond resulting in somewhat greater electron density on the phosphoryl oxygen of $(C_6H_5O)_3P{=}O$ than on the phosphinyl oxygen of $(C_6H_5)_2PO_2CH_3$.



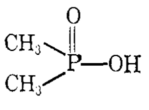
I

pK_a = −5.7 (estd)



III

pK_a = −4.8



IV

pK_a = −4.0

Discussion

The slope of 1.0 for the initial part of the plot of log k_{obsd} against log C_{H^+} (Figure 2) indicates water attack on protonated ester in the rate-determining step according to the Zucker–Hammett hypothesis.[34] The decrease in rate for $C_{H^+} > 1.5$ *M* is not due to extensive protonation of the substrate as is true for amides[11]—the pK_a's indicate that less than 0.01% of I is protonated under our conditions for hydrolysis. Instead the rate behavior we have observed can be explained qualitatively and semiquantitatively in terms of non-Hammett base behavior and a high degree of solvation in the transition state. We also hope to demonstrate that this is an exemplary case of the potential pitfalls in treatments of acid-catalyzed kinetics that use the Bunnett and Zucker-Hammett hypotheses without adequately considering the dangers in neglecting the differences in activity coefficient behavior of substrate and Hammett bases and of transition state and protonated Hammett bases.

Recently, an attempt has been made by Bunnett[35] to treat acid-catalyzed reactions in more sophisticated fashion by modifying the Zucker–Hammett treatment[34] to include solvation effects as indicated in the scheme below (eq 6 and 7) which results in eq 8.[36]

$$S + H^+ \underset{K_a}{\rightleftharpoons} SH^+ \qquad (6)$$

$$SH^+ + wH_2O \xrightarrow{k} \text{products} \qquad (7)$$

$$k_{obsd} = (k/K_a)h_0 a_{H_2O}{}^{w}\frac{f_{BH^+}f_S}{f_B f_{ts}} \qquad (8)$$

Both the Zucker–Hammett and Bunnett treatments require that the activity coefficient ratio, $(f_{BH^+}f_S)/(f_B f_{ts})$, be constant. Bunnett's treatment requires a knowledge of the activity of water as a function of acidity; although such data are available for aqueous solutions, they are not, to our knowledge, available for acidic solutions in 40% dioxane–water. Consequently we have made use of the demonstrated relation between a_{H_2O} and the concentration of free solvent based on 4 moles of solvent removed for every mole of acid in solution.[37] Although this is necessary because of the lack of data on activities of water for our system, it has the advantage of considering dioxane as well as water. It has been reported[38] that dioxane is important in solvating protons in dioxane–water solutions, and dioxane could also be important in solvating the transition state in the hydrolysis studied here. Figure 5 shows the result of plotting (log k_{obsd} − log h_0) = (log k_{obsd} + H_0) against log $C_{solvent}$(free); a straight line is obtained as predicted by Bunnett but the slope of 12 is difficult to rationalize as the "hydration of transition state less substrate on a scale set by the water balance in protonation of an indicator base."[35] It seems unlikely that the unreasonably high slope found here is due to plotting against log $C_{solvent}$(free) since we have plotted (log k_{obsd} − log h_0) for the acid-catalyzed hydrolyses of methyl formate[39] and methyl benzoate[40] against log$C_{solvent}$(free) (calculated as for Table I) and find slopes of 4 and 7, respectively, which are equal to the *w* values found by Bunnett[41] in his plots against log a_{H_2O}.

The fact that Figure 5 gives a straight line may seem quite remarkable and significant considering the extreme deviation from linearity of the plots in Figure 2, but it nevertheless is dangerous to draw any conclusions from such a linear log–log plot without careful examination of the validity of the assumption and the reasonableness of the results. In the case of treatments

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[32] E. M. Arnett, *Progr. Phys. Org. Chem.*, 1, 223 (1963).

[33] Use of the benzyl phenyl ketones as models will probably underestimate the base-weakening effect of the *p*-nitro group because the benzyl methylene prevents direct transmission of the resonance effect of the nitro group. However, use of these models may be fairly reasonable since in our substrate the phosphorus atom might serve to insulate the P=O group more than would be expected from experience with carboxylic esters: the carbonyl carbon of a carboxylate must use the same p orbital for π interactions with the two attached oxygens, but the phosphorus atom in a phosphinate can use two different d orbitals for π bonding to the attached oxygens.

[34] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter IX.

[35] See ref 13, pp 4974, 4975.

[36] Symbols in eq 8 are defined by eq 6 and 7 except that a_{H_2O} = activity of water and f_{BH^+}, f_S, f_B, and f_{ts} are the activity coefficients for protonated Hammett base, substrate, Hammett base, and transition state, respectively.

[37] K. N. Bascombe and R. P. Bell, *Discussions Faraday Soc.*, **24**, 158 (1957); this relation appears to hold through 8 *M* acid, $H_0 \sim -4$. This range includes all our data.

[38] E. Grunwald, G. Baughman, and G. Kohnstam, *J. Am. Chem. Soc.*, **82**, 5801 (1960).

[39] R. P. Bell, A. L. Dowding, and J. A. Noble, *J. Chem. Soc.*, 3106 (1955).

[40] C. T. Chmiel and F. A. Long, *J. Am. Chem. Soc.*, 78, 3326 (1956).

[41] See ref 13, p 4960, reactions 60 and 66.

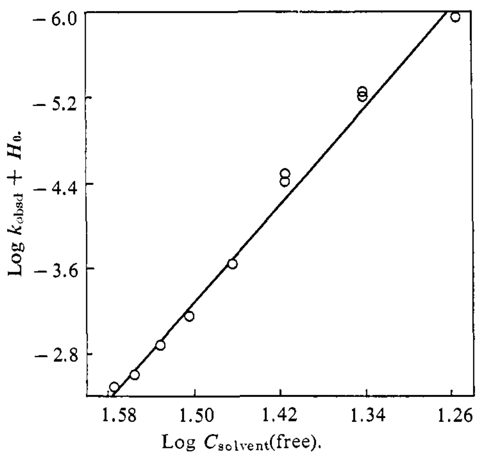

Figure 5. Dependence of log $k_{\text{obsd}} + H_0$ on log C_{solvent}(free).

of acid-catalyzed kinetics by the Zucker–Hammett hypothesis or by Bunnett's method an important assumption is that the activity coefficient ratio in eq 8 is constant so that, for example, it will not affect the slope of Figure 5. Recently a number of substrates have been found[42] to give acid–base behavior in concentrated acidic solutions differing from Hammett bases as we have also observed (Figures 3 and 4). Equations 4 and 5 are based upon a general treatment of protonation in strong acids according to eq 9 which requires that

$$\log (C_{\text{SH}^+}/C_{\text{S}}) = a(\text{p}K_{\text{SH}^+} - H_0) \qquad (9)$$

the activity coefficient ratio $(f_{\text{S}}f_{\text{BH}^+}/f_{\text{SH}^+}f_{\text{S}})$ vary with acidity as follows.[43]

$$\log \frac{f_{\text{S}}f_{\text{BH}^+}}{f_{\text{SH}^+}f_{\text{B}}} = (1 - a)(H_0 - \text{p}K_{\text{SH}^+}) \qquad (10)$$

That is, when $a = 1$, S is a Hammett base. But if $a \neq 1$, log $(f_{\text{S}}f_{\text{BH}^+}/f_{\text{SH}^+}f_{\text{B}})$ will vary linearly with H_0 and will pass through zero at $H_0 = \text{p}K_{\text{SH}^+}$ as the linearity of Figures 3 and 4 and previous studies[42] demonstrate. Since the activity coefficient ratio involved in the Zucker–Hammett[34] and Bunnett[13] treatments should be very similar to this one we can also expect a variation with H_0 according to

$$\log \frac{f_{\text{S}}f_{\text{BH}^+}}{f_{\text{ts}}f_{\text{B}}} \sim (1 - a)(H_0 - \text{p}K_{\text{SH}^+}) \qquad (11)$$

It is just this variation that the Zucker–Hammett and Bunnett treatments neglect. With many substrates variation of the activity coefficient ratio (eq 11) may only give Zucker–Hammett plots with slopes somewhat different from 1.0.[44] However, the meaning of particular values of the slopes of Bunnett plots seems to be suspect until the substrates in question are shown to be Hammett bases. Lane has pointed out that this difficulty can be circumvented[42e] by using eq 9 to get values of log $(C_{\text{SH}^+}/C_{\text{S}})$ and, if $C_{\text{S}} \sim C_{\text{S}}(\text{total})$, eq 13 can be used to evaluate solvation effects

$$k_{\text{obsd}}C_{\text{S}} = k(C_{\text{SH}^+})a_{\text{H}_2\text{O}}{}^{n}\frac{f_{\text{SH}^+}}{f_{\text{ts}}} \qquad (12)$$

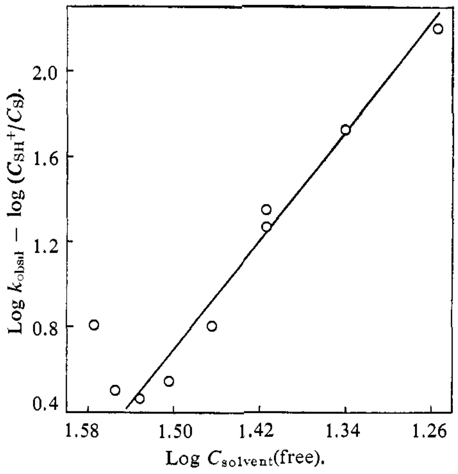

Figure 6. Evaluation of solvation in hydrolysis by plot of log k_{obsd} − log $(C_{\text{SH}}{}^+/C_{\text{S}})$ against log C_{solvent}(free).

or

$$\log k_{\text{obsd}} - \log (C_{\text{SH}^+}/C_{\text{S}}) = \log a_{\text{H}_2\text{O}} + \log k\frac{f_{\text{SH}^+}}{f_{\text{ts}}} \qquad (13)$$

The activity coefficient ratio in eq 13 should change only slightly, if at all. Thus for our data Figure 6 shows the plot of log k_{obsd} − log $(C_{\text{SH}^+}/C_{\text{S}})$ against C_{solvent}(free) and the slope gives $n \sim 6$ rather than the 12 observed for w in the Bunnett plot (Figure 5). This value contrasts with $n \sim 2$ found by this method for the acid-catalyzed hydrolysis of ethyl acetate.[42e] Our result must be viewed with reservation since our pK measurements were carried out on methyl diphenylphosphinate and the *p*-nitrophenyl ester might well have a different value of a (eq 9) which would then change Figure 6 to give a different slope.

The use of ΔS^* as a measure of the role of solvent has been suggested by Long.[45] Our measurements indicate that $\Delta S^* = -27$ ev for the acid-catalyzed hydrolysis of I. This is a value in agreement with an A_2 mechanism[45] but does not agree very well with a solvation number of 6. Since the acid-catalyzed hydrolysis of phosphinates is an A_2 process, the transition state must contain water for nucleophilic attack on the protonated substrate, and solvent could also be required for proton removal from the attacking H_2O, for solvation of the leaving group, and for proton transfer. If it were known whether the displacement is direct or an addition–elimination process through a pentacoordinated phosphorus intermediate, it would be possible more completely and accurately to assign the role of solvent.

Our discussion has depended greatly on the H_0 scale as a measure of acidity, but one should be able to explain Figure 1 without reference to the Hammett scale. From eq 12 one obtains eq 14.[34] This considered together with the behavior shown by other substrates undergoing A_2 hydrolyses[44] leads again to the conclusion that solvation and activity coefficient behavior

$$k_{\text{obsd}} = \frac{k}{K_{\text{a}}}a_{\text{H}^+}a_{\text{H}_2\text{O}}{}^{n}\frac{f_{\text{S}}}{f_{\text{ts}}} \qquad (14)$$

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[42] (a) See ref 31a; (b) see ref 31b; (c) A. R. Katritzky, A. J. Waring, and K. Yates, *Tetrahedron*, **19**, 465 (1963); (d) M. J. Janssen, *Rec. Trav. Chim.*, **82**, 1197 (1963); (e) C. A. Lane, *J. Am. Chem. Soc.*, **86**, 2521 (1964). These references cover measurements on amides, thiolactams, benzamides, thioamides, and ethyl acetate, respectively.

[43] Derived from eq 9 using $(a_{\text{SH}^+}a_{\text{B}}/a_{\text{BH}^+}a_{\text{S}}) = (K_{\text{BH}^+}/K_{\text{SH}^+})$.

[44] F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957).

[45] (a) F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963); (b) F. A. Long and R. Bakule, *J. Am. Chem. Soc.*, **85**, 2313 (1963).

must be important. The solvation part clearly enters through the a_{H_2O} term and has been adequately discussed above. Consideration of Figure 1 and the activity coefficients in eq 14 indicates that f_S/f_{ts} is decreasing with increasing acidity. We qualitatively observed greater solubility of our substrate in more acidic solutions in agreement with a marked decrease in f_S. Although salting in of a neutral organic molecule is not expected, it might be explained by our use of a mixed solvent; if water preferentially solvates protons, this leaves a greater effective concentration of dioxane for solvation of the neutral substrate. The acid-catalyzed hydrolysis of a phosphinate soluble in water should be studied to resolve this question by elimination of the dioxane problem.

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Analysis of the Optical Rotatory Dispersion of Polypeptides and Proteins. IV. A Digital Computer Analysis for the Region 190–600 mμ[1,2]

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Abstract: The lack of methods for resolving complex optical rotatory dispersion curves into their component Cotton effects has prevented an adequate comparison of experiment and theory. A nonlinear, least-squares curve fitting approach to the interpretation of optical rotatory dispersion data is shown to be effective in both resolving overlapping Cotton effects and revealing small Cotton effects obscured by larger ones adjacent to them. The application of this method to the optical rotatory dispersion data (from 600 to 190 mμ) of various α-helical polypeptides in solution yields results agreeing with the conclusions from the combination of circular dichroism and polarized ultraviolet absorption spectra which support the exciton (for $\pi \rightarrow \pi^*$) and one-electron (for $n \rightarrow \pi^*$) models. The method is also applied to the optical rotatory dispersion of the random form of poly-α-L-glutamic acid and the poly-L-proline II helix. For the former, three Cotton effects are found centered at 197.6, 216.6, and 235 mμ with rotational strengths -14.2×10^{-40}, 1.9×10^{-40}, and -0.13×10^{-40} erg cm^3, respectively. For the poly-L-proline II helix, two Cotton effects are found centered at 206.9 and 221.0 mμ with rotational strengths -33×10^{-40} and 5×10^{-40} erg cm^3, respectively. It is concluded that further theoretical work is needed before assignments can be made for the optically active transitions of the "random" polypeptide conformation and the poly-L-proline II helix.

In 1956, Moffitt[3] predicted that when the peptide chromophore is incorporated into an α helix, the 185-mμ $\pi \rightarrow \pi^*$ monomer transition would be split into two perpendicularly polarized components separated by 2800 cm^{-1} (~10 mμ). In 1961, studies[4] on the far-ultraviolet polarized absorption spectra of oriented films of α-helical polypeptides revealed two transitions near 190 mμ with the predicted polarization and approximately the predicted energy separation. Thus, it seemed that the validity of the application of the exciton model to polypeptides was established. Moffitt[3] also predicted that the two components of the split $\pi \rightarrow \pi^*$ transition would have large rotational strengths of opposite sign but equal absolute magnitude. He assumed that the $n \rightarrow \pi^*$ peptide transition near 220 mμ would make a negligible contribution to the optical activity. A year later Moffitt, Fitts, and Kirkwood[5] reported that certain terms in the original Moffitt treatment which would give rise to additional optical activity for the exciton band had been neglected; however, this additional contribution was not evaluated until 1964.[6] Therefore, even with these revisions, it was expected that all the optical activity above 170 mμ would arise from the 190-mμ exciton band, the perpendicular and parallel components of which were predicted to be separated by 10 mμ.

Thus, in 1960–1961, when the optical rotatory dispersion (ORD) of some proteins and α-helical polypeptides was measured to 225 mμ,[7,8] it was surprising to discover a sizeable trough at 233 mμ. This was thought to be due to a negative Cotton effect located near 225 mμ and was assigned to the $n \rightarrow \pi^*$ transition. It was also pointed out at the time that an alternative ex-

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(1) Polypeptides. LII. For the previous paper in this series, see *J. Am. Chem. Soc.*, **88**, 2041 (1966).

(2) We are pleased to acknowledge the support (in part) of this work by U. S. Public Health Service Grants AM-07300-01, -02, and -03.

(3) (a) W. Moffitt, *Proc. Natl. Acad. Sci. U. S.*, **42**, 735 (1956); (b) W. Moffitt, *J. Chem. Phys.*, **25**, 467 (1956).

(4) W. B. Gratzer, G. Holzwarth, and P. Doty, *Proc. Natl. Acad. Sci. U. S.*, 47, 1785 (1961).

(5) W. Moffitt, D. D. Fitts, and J. G. Kirkwood, *ibid.*, **43**, 723 (1957).

(6) (a) I. Tinoco, Jr., *J. Am. Chem. Soc.*, **86**, 297 (1964); (b) I. Tinoco, Jr., R. W. Woody, and D. F. Bradley, *J. Chem. Phys.*, **38**, 1317 (1963); (c) R. W. Woody, Dissertation, University of California, Berkeley, Calif., 1962, as quoted in G. Holzwarth, Dissertation, Harvard University, 1964.

(7) N. S. Simmons and E. R. Blout, *Biophys. J.*, 1, 55 (1960).

(8) N. S. Simmons, C. Cohen, A. G. Szent-Gyorgyi, D. B. Wetlaufer, and E. R. Blout, *J. Am. Chem. Soc.*, **83**, 4766 (1961).