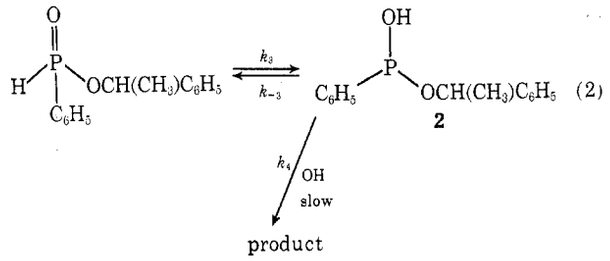
ide ion at phosphorus. By analogy to these and other studies the mechanism that is occurring in the basic region (above pH 9) is attack of hydroxide ion with the probable formation of a pentacoordinate intermediate (the formation of this intermediate has not been unambiguously established in the alkaline hydrolysis of noncyclic phosphorus compounds).

The high rate of reaction of **1** may be simply a more rapid rate due to the phosphorus atom being more liable to attack because of the lack of steric hindrance to the approaching hydroxide ion. A more attractive possibility is that the bimolecular reaction may be occurring through a trivalent species (eq 2) (*e.g.*, **2**). This mechanism implies that trivalent phosphorus esters would have an unusually fast rate of hydrolysis when compared to pentavalent compounds. This is substantiated by the rapid rate of hydrolysis of triethylphosphite (TEP) ($k_{10°} = 5.77 \times 10^{-3}$ sec^{-1}).[7] Comparison of the rate ratio of TEO to diethyl phosphonate



(2)

(DEP)[8] at 80° shows that the hydrolysis of the trivalent species is unusually fast (TEP/DEP = 4670). Assuming k_4 for **2** to be very similar to the rate of hydrolysis of TEP (4.3 sec^{-1} at 80°), the value of k_3/k_{-3} would then be approximately 2×10^{-5}. This is in agreement with physical observations that the trivalent species could not be detected by spectral techniques.[8]

Acid-catalyzed exchange of the hydrogen bound to phosphorus and the oxidation of dialkyl phosphonates has been found to occur through the phosphite form (trivalent species).[9-12] In these reactions the rate-determining step was found to be the formation of the trivalent species.

Thus the trivalent species is a very attractive intermediate in the alkaline hydrolysis of phosphinate esters containing a P–H bond. Further evidence will be needed to definitely establish this hypothesis.

Experimental Section[13]

Preparation of Materials. A. 1-Phenylethyl Phenylphosphinate.—*N*,*N*′-Dicyclohexylcarbodiimide (5.00 g, 0.0242 mol, Aldrich) was added to a refluxing solution of phenylphosphinic acid (3.44 g, 0.0242 mol, Aldrich) in 200 ml of anhydrous benzene. After refluxing for 30 min, 1-phenylethanol (2.96 g, 0.0242 mol) was added dropwise and the mixture was refluxed for 30 min. The solution was cooled to room temperature and *N*,*N*′-dicyclohexylurea was removed by filtration. The benzene was removed on a rotary evaporator. The colorless oil was dissolved in 100 ml of diethyl ether and a small amount of solid material was removed by filtration. Removal of the ether on the rotary evaporator yielded 5.90 g (99%) of 1-phenylethyl phenylphosphinate as a colorless oil. The nmr spectrum[14] of the ester in chloroform-*d* showed bands at δ 7.3 (m, 10 H), 7.30 and 7.60 (2d, 1 H, J_{P-H} = 566 and 564 Hz), 1.55 and 1.63 (2 d, 3 H), and 5.60 (m, 1 H).

Anal. Calcd for $C_{14}H_{15}O_2P$: C, 68.35; H, 6.12; P, 12.58. Found: C, 68.18; H, 6.05; P, 12.46.

B. 1-(*p*-Methylphenyl)ethyl Phenylphosphinate.—1-(*p*-Methylphenyl)ethyl phenylphosphinate was synthesized in the same manner from 3.0 g (0.145 mol) of 1-(*m*-chlorophenyl)-ethanol to yield 6.06 g (96%) of the desired product. The infrared spectrum of the neat ester showed bands at 2370 (w), 1230 (s), 1125 (s), 955 (s), and 822 cm^{-1} (m). The nmr spectrum[14] of the ester in chloroform-*d* showed bands at δ 7.4 (m, 5 H), 7.18 (s, 4 H), 7.3 and 6.6 (2d, 1 H, J_{P-H} = 570 and 577 Hz), 1.48 and 1.61 (2d, 3 H, $CHCH_3$), 5.5 (m, 1 H), and 2.15 and 2.22 (2s, 3 H).

C. 1-(*m*-Chlorophenyl)ethyl Phenylphosphinate.—1-(*m*-Chlorophenyl)ethyl phenylphosphinate was synthesized in the same manner from 3.3 g (0.024 mol) of 1-(*p*-methylphenyl)-ethanol to yield 4.00 g (97%) of the desired product. The nmr spectrum[14] of the ester in chloroform-*d* showed bands at δ 7.5 (m, 9 H), 7.4 and 7.6 (2d, 1 H, J_{P-H} = 570 and 577 Hz), 1.62 and 1.72 (2d, 3 H) and 5.5 (m, 1 H).

Kinetic Methods.—Rates were measured by standard techniques (pH-Stat method) using a Radiometer automatic titration apparatus which consisted of a TTT 1c automatic titrator, a ABU 1c autoburette (with a 2.5-ml burette), a TTA 3c titrator assembly, and a 2c recorder.

Registry No.—**1**, 33521-92-5; 1-(*p*-methylphenyl)-ethyl phenylphosphinate, 33521-93-6; 1-(*m*-chlorophenyl)ethyl phenylphosphinate, 33521-94-7.

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(13) Analysis is by the Microanalytical Laboratory of the Department of Chemistry, University of California.
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Spectrophotometric Determination of the Second Dissociation Constants of the Aminoisoquinolines

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The first protonation of nitrogen heterocycles containing amino substituents on the ring has been shown to occur at the ring nitrogen and not at the substituent amino group.[1-4] Albert[5] has compiled a large number of ionization constants corresponding to this first and second protonation as determined by various workers. In previous work done in this laboratory, we have updated or determined the second pK_a' values for the isomeric aminopyridines and aminoquinolines.[6] It is of interest to investigate the relative basicity of the primary amino group for the isomeric aminoisoquinolines (in terms of pK_a') by ultraviolet spectroscopy and compare their values to those obtained from the above pyridine and quinoline compounds. The second pK_a' values for the aminoisoquinolines along with the temperature at which they were determined are given in Table I.

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TABLE I

SECOND DISSOCIATION CONSTANTS OF AMINOISOQUINOLINES

Compd	Registry no.	First pK_a'	Second pK_a'	Spread[a]	Concn, M	Temp, °C	Analytical wavelength, mμ
Isoquinoline		5.40[b]				20	
1-Aminoisoquinoline	1532-84-9	7.62[c]	−9.59	0.10	4×10^{-5}	23.4 ± 0.5	236
3-Aminoisoquinoline	25475-67-6	5.05[b]	−4.20	0.06	1×10^{-4}	23.5 ± 0.5	391
4-Aminoisoquinoline	23687-25-4	6.28[b]	−2.29	0.05	4×10^{-5}	25.0 ± 1.0	248
5-Aminoisoquinoline	1125-60-6	5.59[b]	1.07	0.06	2×10^{-5}	25.0 ± 1.0	257
6-Aminoisoquinoline	23687-26-5	7.17[b]	−0.59	0.07	4×10^{-5}	25.0 ± 0.5	263
7-Aminoisoquinoline	23707-37-1	6.20[b]	1.13	0.06	2×10^{-5}	24.5 ± 0.5	254
8-Aminoisoquinoline	23687-27-6	6.06[b]	0.18	0.06	2×10^{-5}	25.0 ± 1.0	247

[a] The spread may not exceed ±0.06 units for pK_a' values above zero and ±0.10 for values below zero.[7] [b] A. Albert, R. Goldacre, and J. N. Phillips, *J. Chem. Soc.*, 2240 (1948). [c] A. R. Osborn, K. Schofield, and L. N. Short, *ibid.*, 4191 (1956).

TABLE II

ULTRAVIOLET SPECTRA OF AMINOISOQUINOLINES[a]

Compd	Solvent	pH or H_0	Species[b]	λ_{max}, mμ	Log ϵ_{max}
1-Aminoisoquinoline	95% Ethanol[e]		N	239, 300, 331	4.25, 3.81, 3.70
	$NaOH-H_2O$	~12	N	246, 290, 324	4.10, 3.81, 3.56
	$H_2SO_4-H_2O$	−4.00	M	236, 270, 281, 327, 337	4.37, 3.79, 3.83, 3.81, 3.70
	$H_2SO_4-H_2O$	−10.37[c]	D	236, 268, 279, 324, 335	4.44, 3.66, 3.66, 3.77, 3.74
3-Aminoisoquinoline	$NaOH-H_2O$	~12	N	229, 268, 277, 287 351	4.03, 3.08, 3.11, 2.96, 2.85
	$Na_3BO_3-H_2O$[d]	9.21	N	231, 269, 278, 288, 353	4.74, 3.67, 3.73, 3.58, 3.42
	$H_2SO_4-H_2O$	0.00	M	237, 277, 296, 391	4.79, 3.59, 3.28, 3.63
	$H_2SO_4-H_2O$	−8.00	D	237, 275, 339	4.67, 3.36, 3.63
4-Aminoisoquinoline	95% Ethanol[e]		N	246, 250, 338	4.04, 4.03, 3.79
	0.01 *N* NaOH[e]	~12	N	238, 308, 332	4.08, 3.64, 3.75
	$Na_3BO_3-H_2O$[d]	9.21	N	210, 240, 248, 310, 332	4.68, 4.10, 3.94, 3.64, 3.74
	0.01 *N* HCl[e]	~2	M	216, 230, 317, 357	4.48, 3.63, 3.54, 3.92
	Glycine-HCl[d]	3.28	M	217, 238, 262, 316, 354	4.50, 4.07, 3.59, 3.55, 3.94
	$H_2SO_4-H_2O$	1.00	M	248, 284, 353	4.07, 3.38, 3.34
	$H_2SO_4-H_2O$	−9.98	D	233, 274, 335	4.66, 3.43, 3.69
5-Aminoisoquinoline	95% Ethanol[e]		N	228, 238, 336	4.23, 4.27, 3.79
	0.01 *N* NaOH[e]	~12	N	238, 327	4.27, 3.70
	$Na_3BO_3-H_2O$	9.21	N	205, 238, 332	4.48, 4.22, 3.70
	0.01 *N* HCl[e]	~2	M	226, 258, 336, 380	4.23, 4.11, 3.54, 3.50
	Glycine-HCl[d]	3.07	M	208, 259, 340, 378	4.56, 4.18, 3.53, 3.53
	$H_2SO_4-H_2O$	3.00	M	257, 356	4.18, 3.54
	$H_2SO_4-H_2O$	−9.98	D	224, 259, 331	4.70, 3.30, 3.70
6-Aminoisoquinoline	$NaOH-H_2O$	~12	N	238, 297, 323	4.66, 3.98, 3.44
	$Na_3BO_3-H_2O$[d]	9.21	N	234, 239, 296, 304, 326	4.60, 4.61, 3.83, 3.84, 3.47
	$NaC_2H_3O_2-HC_2H_3O_2$[d]	4.27	M	231, 238, 266, 337, 352	4.43, 4.34, 4.32, 4.01, 4.03
	$H_2SO_4-H_2O$	3.00	M	230, 263, 333, 348	4.45, 4.33, 4.04, 4.06
	$H_2SO_4-H_2O$	−4.00	D	223, 263, 320, 328	4.71, 3.54, 3.65, 3.69
7-Aminoisoquinoline	$NaOH-H_2O$	~12	N	230, 271, 279, 345	4.60, 3.91, 3.85, 3.38
	$Na_3BO_3-H_2O$[d]	9.21	N	231, 273, 349	4.56, 3.90, 3.40
	Glycine-HCl[d]	3.22	M	218, 254, 289, 385	4.14, 4.58, 3.82, 3.35
	$H_2SO_4-H_2O$	3.60	M	254, 283, 385	4.63, 4.03, 3.48
	$H_2SO_4-H_2O$	−2.00	D	233, 263, 307, 328	4.65, 3.50, 3.65, 3.66
8-Aminoisoquinoline	$NaOH-H_2O$	~12	N	222, 238, 342	4.33, 4.18, 3.67
	$Na_3BO_3-H_2O$[d]	9.21	N	207, 224, 307, 345	4.61, 4.36, 3.51, 3.68
	Glycine-HCl[d]	3.05	M	209, 250, 325, 417	4.54, 4.26, 3.41, 3.66
	$H_2SO_4-H_2O$	3.00	M	247, 323	4.13, 3.48
	$H_2SO_4-H_2O$	−4.00	D	227, 257, 327	4.69, 4.32, 3.74

[a] The absorption peaks pertaining to this work were recorded between 220 and 400 mμ. [b] N = neutral molecule, M = monocation, D = dication. [c] The dication may not be 100% isolated at this H_0 value. Albert states that a species is considered isolated when the spectrum changes 1% or less in one pH unit. From −10.20 to −10.37 the maximum change in the spectrum is 3.6%. [d] See footnote *c*, Table I. [e] Reference 3.

The method selected for these determinations was that used by Albert for the determination of the second dissociation constant of 3-aminopyridine[7-9] and which we previously used.[6]

It can be seen that the second pK_a' value of 1-aminoisoquinoline is in the same general area of those of 2-aminopyridine ($pK_a' = -8.1$) and 2-aminoquinoline ($pK_a' = -9.08$).[6] This is probably due to the close proximity of the two positive charges on the molecule and some interaction with the peri hydrogen atom. In the case of 3-aminoisoquinoline where there exists two adjacent positive charges, however, the second pK_a' is considerably less than would be expected for an amino substituent α to the ring nitrogen. At first glance, the value obtained for the second pK_a' of 4-aminoisoquinoline is larger than that for a β-amino group, *e.g.*, 3-aminoquinoline ($pK_a' = -0.40$),[6] but it may be pointed out that this value is in the general area of 3-aminopyridine ($pK_a' = -1.5$).[6]

In the cases of the 6- and 8-aminoisoquinoline and 5- and 7-aminoquinoline, the pK_a' value should be less than those found for 5- and 7-aminoisoquinoline and 6-aminoquinoline owing to the second protonation of the additional ionic resonance forms described by Albert.[5]

The ultraviolet spectra of the 1-, 4-, and 5-aminoisoquinolines in 0.10 *N* hydrochloric acid have been recorded by Ewing and Steck.[3] It seems that they were not concerned with pure electronic species, for they have a mixture of mono- and dications in the 5 isomer. The ultraviolet spectra of all the pure mono- and dicationic species of the aminoisoquinolines were determined in sulfuric acid of accurately known pH and H_0 values. The results, as well as those of other workers, are recorded in Table II.

The effect on the ultraviolet spectra of monoprotonation of the isomeric aminoisoquinolines has been described previously.[10] Upon diprotonation, 1-, 6-, and 8-aminoisoquinoline undergo small changes in all the absorption bands. Large hypsochromic shifts occur of the long wavelength band for 3-, 4-, and 5-aminoisoquinolines. 7-Aminoisoquinoline is partly anomalous in that it exhibits large shifts in all the ultraviolet absorption bands. The data in Table II for all of the isomers of the aminoisoquinolines show that the spectra of all their dications resemble those of the isoquinolinium ion, which is to be expected since the same phenomena occur with the aminoquinolines.[6]

Experimental Section

The experimental procedure used was that of Brown and Plasz[6] except for 1-aminoisoquinoline. A stock solution of this amine was prepared by weighing out 0.0721 g (0.0005 mol) of the solid and dissolving it in 500 ml of Baker Analyzed sulfuric acid. It was then diluted to the proper H_0 by the addition of water and/or sulfuric acid and the pK_a' value was determined as above.

The preparation and purification of the aminoisoquinolines is described below.

1-Aminoisoquinoline.—This compound was purified by vacuum sublimation at 85°, mp 120–121° (lit.[11] 122–123°).

3-Aminoisoquinoline.—This compound was purified by vacuum sublimation at 140°, mp 175–176° (lit.[12] 178°).

4-Aminoisoquinoline.—This compound was recrystallized twice from benzene, mp 107–108° (lit.[13] 108.5°).

5-Aminoisoquinoline.—This amine was recrystallized from benzene–hexane, vacuum sublimed at 105–110°, and recrystallized again from benzene–hexane, mp 129° (lit.[13] 128–129°).

6-Aminoisoquinoline.—6-Acetamidoisoquinoline (0.1 g) was refluxed with 10 ml of 20% sodium hydroxide in water for 1 hr. After cooling, the amine was crystallized, removed by filtration, and sublimed under vacuum at 190°, mp 217–217.5° (lit.[14] 217–218°).

7-Aminoisoquinoline.—This compound was prepared by the method of Osborn and Schofield.[10] Purification was accomplished by recrystallization from benzene and sublimation under vacuum at 160°, mp 203–204° (lit.[10] 204°).

8-Aminosoquinoline.—This compound was purified by vacuum sublimation at 100° followed by recrystallization from heptane, mp 173–174° (lit.[15] 173–174°).

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The Effect of Solvent and Cation on the Isomer Ratio of the Enolates of 3-Methylcyclohexanone[1a]

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If the enolization of an unsymmetrical ketone is carried out in the presence of excess ketone, the enolate mixture is thermodynamically controlled, whereas, if it is carried out with excess base, the mixture is kinetically controlled. The difference between kinetic and thermodynamic control has been demonstrated with a number of different ketones.[2-5] House and Kramer[6] have shown that the enolate mixture can be quenched with acetic anhydride to produce a mixture of enol acetates in the same isomer ratio as that of the original enolates.

This paper reports studies of the equilibrium and kinetic control of the enolization of 3-methylcyclohexanone and of the effect of changing the solvent or cation on the equilibrium mixture.

The preparation of the mixture of lithium enolates followed the procedure described by Huff[7] and was essentially similar to that previously described by other authors.[6] In a flame-dried apparatus, under nitrogen pressure, triphenyl methane was dissolved in the appropriate solvent, and to this a solution of phenyllithium in diethyl ether was added. 3-Methylcyclohexanone was then added with a syringe, and, after an appropriate length of time, the enolate mixture was quenched with excess acetic anhydride. In the case of equilibrium control, the ketone was in excess and the enolate mixture was stirred for over 18 hr before being

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