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Rates of Ionization of Phosphoranes

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Abstract: The rates of ionization of $CH_3P(OC_6H_5)_4$ and of several related phosphoranes have been measured by NMR spectroscopy. The equilibrium $CH_3P(OC_6H_5)_4 \rightleftharpoons CH_3P(OC_6H_5)_3^+ + C_6H_5O^-$ (1) is displaced so far toward the left that the ionic products cannot be seen by available NMR techniques, but the spectrum of an equimolar mixture of the phosphorane and of the related phosphonium triflate, $CH_3P(OC_6H_5)_3^+CF_3SO_3^-$, proved to be temperature dependent. Line-shape analyses of these spectra then permit a determination of the rate constant for the dissociation of the phosphorane; temperature-dependent NMR spectra and the corresponding rate constants were also obtained for 1:1 mixtures of $CH_3P(C_6H_5)(OC_6H_5)_3$, of $CH_3P(C_6H_5)_2(OC_6H_5)_2$, of $CH_3P(o\text{-}OC_6H_4CH_3)_4$, and of $CH_3P(p\text{-}OC_6H_4CH_3)_4$ with the corresponding phosphonium cations. Equilibrium constants for some of these reactions have been obtained by conductometric measurements,[2] so that the rate constants for the association of phosphonium cations and phenoxide ion could then be calculated. The relationship of these data to the mechanism for the hydrolysis of phosphate esters is discussed.

The hydrolysis of phosphate esters, in many cases, takes place by way of a trigonal-bipyramidal phosphorane as intermediate.[3-5] An essential step in the formation of the intermediate in acid solution is presumably the addition of water to a protonated ester molecule (eq 2 and 3). The rate constants of reaction 3 are not yet available or susceptible of easy measurement. In order to investigate the rates and equilibria of related additions of nucleophiles to phosphonium salts, some of the physical-organic chemistry of stable phosphoranes has been investigated. This investigation, then, represents a first step in a program aimed, eventually, at a determination of the rate constants of eq 3. In particular, the NMR spectra of several phosphoranes dissolved in various solvents (CD_2Cl_2, THF-d_8, CD_3CN) have been investigated in the hope of observing the equilibrium between salt and phosphorane (eq 1).

$$CH_3P(OC_6H_5)_4 \rightleftharpoons CH_3P(OC_6H_5)_3^+ + C_6H_5O^- \quad (1)$$

$$(RO)_3P{=}O + H^+ \rightleftharpoons (RO)_3P^+OH \quad (2)$$

$$(RO)_3P^+OH + H_2O \underset{k_d}{\overset{k_a}{\rightleftharpoons}} (RO)_3P(OH)_2 + H^+ \quad (3)$$

If these NMR spectra had proved temperature dependent, they might have provided information leading to determination of the rates of the relevant processes. Unfortunately, the equilibria in reaction 1 and in other similar reactions lie so far in favor of the phosphoranes that, starting with pure phosphorane, only signals from these compounds could be detected. However, in favorable cases, when solutions of a phosphorane and of the corresponding phosphonium trifluoromethanesulfonate ("triflate") are mixed, the signals from the methyl groups of cation and phosphorane are both present at low temperatures, but coalesce at higher temperatures.

The experiments here recorded were carried out by two more or less equivalent methods. In the best experiments, the phosphorane and phosphonium triflate were separatedly purified, and then a solution of equivalent quantities of these materials was prepared in a drybox in a suitable solvent, usually trideuterioacetonitrile. In other experiments, a weighed amount of a trifluoromethanesulfonate salt was dissolved or suspended in a solvent with half the molar amount of sodium phenoxide. When the solvent for the reaction was bromobenzene or deuterated methylene chloride, sodium triflate proved insoluble, and could be removed by centrifugation:

$$R_nP(OAr)_{4-n}^+ CF_3SO_3^- + Na^+ArO^- \rightleftharpoons R_nP(OAr)_{5-n} + CF_3SO_3Na \quad (4)$$

On the other hand, sodium triflate is soluble in deuterated tetrahydrofuran; the reaction nevertheless was carried to completion, even when the phosphonium salts were nearly insoluble in the solvent, because of the favorable equilibria for the formation of the phosphoranes. Incidentally, triflate salts were chosen because they are essentially nonnucleophilic. Some experiments were conducted successfully with fluoroborates; in other cases, the decomposition of this anion to yield BF_3 occasioned difficulties.[6]

The temperature-dependent NMR spectra of mixtures of phosphonium salt and phosphorane permit the measure-

ment of the rate constant for equilibration between these species through the ionization process of eq 1; this constant can be shown to be twice that for the dissociation of the phosphorane. The rates and equilibria are sensitive to the structure of the phosphorane with which the experiment is initiated, but complicated by a side reaction to yield ylide. In order to obtain the rate constant for association of phosphonium cation and phenoxide ion, the equilibrium constants for the ionization of several phosphoranes have been determined conductometrically;[2] these associations turn out to occur with the speed of collision. The present paper is concerned with the preparation of the needed salts and phosphoranes, with the variable-temperature NMR spectroscopy, and with the calculations required for the determination of the rate constants for equilibration between phosphonium cations and aryloxide ions.

Experimental Section

Methods. The phosphoranes and phosphonium salts are sensitive to moisture; they were therefore recrystallized under nitrogen in specially dried glass, and transferred and weighed under nitrogen in a Labconco drybox. Melting points, obtained in sealed capillaries, are corrected. ^{31}P NMR spectra were obtained with a Varian XL-100 spectrometer at 40.5 MHz in Fourier transform mode, and chemical shifts are reported relative to that of 85% of phosphoric acid; proton NMR spectra were recorded either at 100 MHz or at 60 MHz and chemical shifts are reported relative to that of tetramethylsilane.

Materials. Methyltetraphenoxyphosphorane[2] melted at 82–84°: NMR ($DCCl_3$) δ 2.22 (d, J_{H-P} = 16 Hz, P-CH_3), 6.70–7.35 (m, aromatic); ^{31}P ($CDCl_3$) + 53.04 ppm relative to 85% H_3PO_4.

Tri-*o*-tolyl phosphite was prepared by refluxing a solution of 19.52 g of *o*-cresol and 9.82 g of hexamethylphosphoramide (Aldrich) in 50 ml of benzene under nitrogen for about 20 hr. After the evolution of dimethylamine had ceased, the benzene was removed at reduced pressure, and the phosphite (14.65 g; 69% of theory) distilled at 187–192° (0.05–0.1 mm); (lit.[7] 248° (11 mm), 238° (11 mm)). The structure was confirmed by ir and proton NMR spectroscopy.

Methyltri-*o*-cresoxyphosphonium trifluoromethanesulfonate. Tri-*o*-tolyl phosphite (3.52 g) and methyl triflate (Willow Brook Laboratories, 1.64 g) were stirred under nitrogen at 60° for 3 hr. Both the proton and the ^{31}P NMR spectra of the resulting viscous, colorless syrup indicated quantitative formation of the phosphonium salt, but attempts to crystallize it have so far failed, and it was used without further purification. Proton NMR ($CDCl_3$) δ 2.18 (s, C-CH_3), 2.82 (d, J_{H-P} = 16 Hz, P-CH_3), 7.25 (aromatic); ^{31}P ($CDCl_3$) −42.22 ppm relative to 85% H_3PO_4.

Methyltetra-*o*-cresoxyphosphorane. Barium *o*-cresoxide was prepared from a mixture of 7 g of *o*-cresol and 10.2 g of barium hydroxide octahydrate in 35 ml of water. After the reaction mixture had been refluxed for 2 hr, it was filtered, the water from the filtrate was removed by rotoevaporation, and the grayish pink crystals were dried in a Fischer pistol over P_2O_5 at 70° under vacuum for 24 hr, ground in a mortar, and then dried again for 24 hr. A mixture of 3.82 g of the syrupy triflate salt described above and 1.30 g of barium *o*-cresoxide was stirred at room temperature in 50 ml of methylene chloride under nitrogen for 24 hr. The precipitate of barium triflate was removed by filtration under nitrogen and the solvent evaporated at reduced pressure. The oily residue was dissolved in hexane and the phosphorane purified by several crystallizations from that solvent. The product (1.02 g; 29% of theory) was dried in vacuo and melted at 102–105°. Anal. Calcd for $C_{29}H_{31}PO_4$: C, 73.40; H, 6.59; P, 6.53. Found: C, 73.39; H, 7.06; P, 6.48. Proton NMR ($CDCl_3$) δ 2.00 (s, C-CH_3), 2.20 (d, J_{H-P} = 16 Hz, PCH_3), 6.70–7.42 (m, aromatic); ^{31}P ($CDCl_3$) +53.03 relative to 85% H_3PO_4.

Tri-*p*-tolyl phosphite was prepared by a procedure that parallels that of Baddiley et al.[8] for tribenzyl phosphite. A solution of 8.25 g of phosphorus trichloride in 20 ml of anhydrous ether was added, with vigorous stirring, to a solution of 19.5 g of *p*-cresol and 14.25 g of pyridine in 50 ml of anhydrous ether. During the addition (30 min), the reaction mixture was maintained at 0° and protected from moisture; the stirring was continued for 2 hr at 0° and then overnight at room temperature. After the pyridinium hydrochloride that precipitated had been removed by filtration under nitrogen and washed with ether, the combined filtrate and washings were concentrated by rotary evaporation and the resulting oil was distilled at 196–200° (0.1 mm); yield, 17.85 g (84% of theory); lit.[7] 285° (11 mm). The structure was confirmed by ir and proton NMR spectroscopy.

Methyltri-*p*-cresoxyphosphonium trifluoromethanesulfonate was prepared from tri-*p*-tolyl phosphite by the same procedure as that used to prepare the ortho isomer. The colorless syrup was used without purification. Proton NMR ($CDCl_3$) δ 2.32 (s, C-CH_3), 2.62 (d, J_{H-P} = 16 Hz, P-CH_3), 7.18 (aromatic); ^{31}P ($CDCl_3$) −41.87 ppm relative to 85% H_3PO_4.

Sodium *p*-Cresoxide. Sodium hydride (10.95 g of a 57% suspension in mineral oil) was rinsed several times with petroleum ether and suspended with stirring in 13 ml of purified tetrahydrofuran. This suspension was cooled in an ice bath, and a solution of 9.75 g of *p*-cresol in 26 ml of THF was added drop by drop with stirring. After the addition was complete, the mixture was stirred overnight at room temperature. Excess sodium hydride was removed by filtration under nitrogen, and the product precipitated by adding the filtrate to 500 ml of *n*-hexane. The precipitate was filtered under nitrogen, washed with hexane, and dried in a Fischer pistol at 56° under vacuum for 24 hr. The white powdery product melted above 260° (lit.[9] mp 123–125°!).

Methyltetra-*p*-cresoxyphosphorane was prepared by stirring a mixture of 5.16 g of methyltri-*p*-cresoxyphosphonium triflate and 1.30 g of anhydrous sodium *p*-cresoxide in 50 ml of methylene chloride under nitrogen for 20 hr at room temperature. The precipitated sodium triflate was removed by filtration under nitrogen, and the solvent evaporated at reduced pressure. The brownish oily residue crystallized from hexane and was purified by several recrystallizations: yield, 1.43 g or 30% of theory; mp 71–74°. Anal. Calcd for $C_{29}H_{31}PO_4$: C, 73.40; H, 6.59; P, 6.53. Found: C, 73.57; H, 6.78; P, 6.39. Proton NMR ($CDCl_3$) δ 2.22 (s, C-CH_3), 2.15 (d, J_{H-P} = 16 Hz, P-CH_3), 6.70–7.25 (m, aromatic); ^{31}P NMR ($CDCl_3$) +52.75 ppm relative to 85% phosphoric acid.

Methyldiphenylphenoxyphosphonium iodide[10] was prepared from phenyl diphenylphosphinite and methyl iodide, and used without further purification. Methyl diphenoxyphenylphosphonium iodide was prepared by parallel procedures from diphenyl phenylphosphonite.[11] Methyltriphenoxyphosphonium iodide was prepared from methyl iodide and triphenyl phosphite; mp 125–130° dec.; lit.[12] 75°, 130°.

Silver trifluoromethansulfonate was prepared according to Hazeldine and Kidd.[13] Phosphonium iodides were converted to the corresponding triflates by dissolving an iodide salt in methylene chloride under argon and adding an equivalent amount of silver triflate in three portions, with vigorous stirring to promote the heterogeneous reaction. After 30 min, the mixture was filtered and rotoevaporated. The resulting triflate salts were recrystallized under nitrogen, in flasks sealed with serum caps, from 1,2-dichlorethane–ether or methylene chloride–ether.

Methyldiphenylphenoxyphosphonium triflate melted at 99–100°. Anal. Calcd for $C_{20}H_{18}F_3PO_4S$: C, 54.29; H, 4.10; P, 7.00; S, 7.24; F, 12.88. Found: C, 54.65; H, 4.16; P, 7.04; S, 7.22; F, 12.89. Proton NMR ($CDCl_3$) δ 2.80 (d, J_{H-P} = 17 Hz, P-CH_3), 7.2, 7.8 (m, aromatic); mass spectrum, base peak 293 (phosphonium cation).

Methylphenyldiphenoxyphosphonium triflate melted at 151.5–152°. Anal. Calcd for $C_{17}H_{18}F_3PO_5S$: C, 52.40; H, 3.96; P, 6.76; S, 6.99; F, 12.44. Found: C, 52.23; H, 3.76; P, 6.31; S, 7.01; F, 12.42. Proton NMR ($CDCl_3$) δ 2.75 (d, J_{H-P} = 17 Hz, PCH_3), 7.4 (aromatic); mass spectrum, base peak 309 (phosphonium cation).

Methyltriphenoxyphosphonium triflate, prepared through the iodide, melted at 96.5–98.5°. It was also prepared when triphenyl phosphite (12.4 g) and methyl triflate (Willow Brook Laboratories; 6.56 g) were stirred under nitrogen at 100°. Although spontaneous refluxing stopped after a few minutes, the heating was continued for an hour. When the mixture was cooled to room temperature, the product crystallized. Anhydrous ether was added, and the white crystals were filtered under nitrogen, washed with anhydrous ether, and dried in vacuo: yield 17.54 g (92% of theory); mp 96.5–98.5°. Anal. Calcd for $C_{20}H_{18}F_3O_6PS$: C, 50.63; H, 3.82; P, 6.53; S, 6.76; F, 12.02. Found: C, 49.96, 51.05; H, 3.93, 3.78; P, 6.49, 6.65; S, 7.08, 7.00; F, 13.14, 10.91. Mass spectrum, parent and

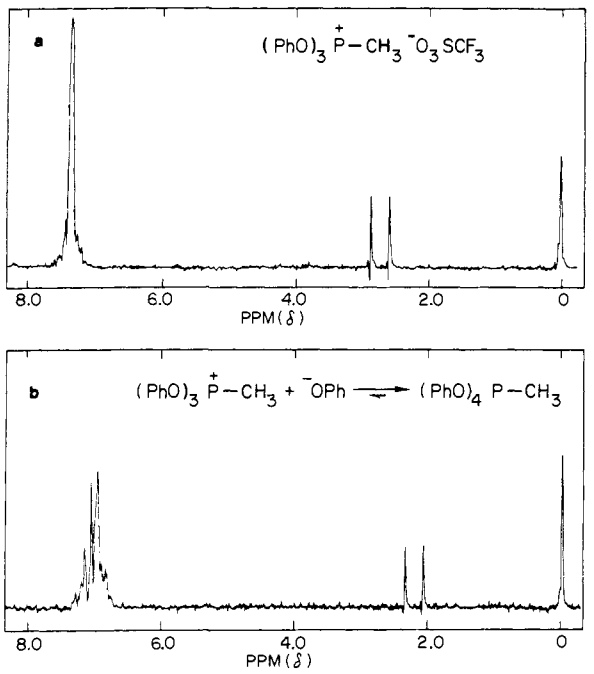

Figure 1. (a) The 60-MHz ^1H NMR spectrum of methyltriphenoxyphosphonium triflate in $CDCl_3$. (b) Spectrum of its reaction product with sodium phenoxide in $CDCl_3$ (i.e., methyltetraphenoxyphosphorane).

base peak, 325 (phosphonium cation); proton NMR ($CDCl_3$) δ 2.75 (d, J_{H-P} = 16 Hz, P-CH_3), 7.4 (m, aromatic); ^{31}P NMR ($CDCl_3$) −41.43 ppm, relative to 85% H_3PO_4. Although neither fluorine analysis is satisfactory, analyses for four other elements, the spectroscopic data, and the sharp melting point leave little doubt as to the identity or purity of the salt.

Methyl-d_3-diphenylphenoxyphosphonium triflate was prepared in analogy with the corresponding nondeuterated material from methyl-d_3 iodide (Merck), mp 99.0-99.5°. The NMR spectrum showed only peaks in the aromatic region. Mass spectrum, base peak 296 (trideuterated phosphonium cation).

Methyldiphenylphosphine oxide melted at 111-112° (lit.[14] 110-111°). **Phenyl methylphenylphosphinate** boiled at 140° (0.1 mm) [lit.[15] 159-160° (3 mm)] and **diphenyl methylphosphonate** boiled at 145-146° (0.9 mm): [lit.[16] 192-192.5° (9 mm)]. The structures were confirmed by NMR, ir, and/or mass spectra.

Ethylphenyldiphenoxyphosphonium trifluoromethanesulfonate. Ethyl trifluoromethanesulfonate (Willow Brook, 2.5 g) was added to a solution of 4.13 g of diphenyl phenylphosphonite in 5 ml of anhydrous either and refluxed for 20 min, whereupon the product suddenly precipitated. The solid was recyrstallized from methylene chloride-ether; mp 107-107.5°. Anal. Calcd for $C_{21}H_{20}F_3PO_5S$: C, 53.59; H, 4.32; P, 6.58; F, 13.18; S, 6.83. Found: C, 53.39; H, 4.27; P, 6.56; F, 12.06; S, 6.79. Proton NMR ($CDCl_3$) δ 1.22 (d of d, J_{H-P} = 24 Hz, 6 Hz), 3.2 (overlapping d of q, J_{H-P} = 12 Hz, 6 Hz), 7.4, 8.0 (m, aromatic); mass spectrum, base peak 323 (phosphonium cation).

Solvents. Acetonitrile-d_3 (Stohler Isotope Chemicals, 99% D) was purified in 30-g batches by a procedure modeled on that used for conductivity studies with nondeuterated solvent.[2] Peroxide-free tetrahydrofuran[17] was refluxed through 4A molecular sieves in a Soxhlet apparatus. CD_2Cl_2 (99.5%) and perdeuteriotetrahydrofuran (99%) were purchased from Merck.

Bromobenzene was distilled from lithium aluminum hydride and stored over molecular sieves.

Methods. The preparation of solutions of equimolar quantities of phosphorane and phosphonium salt for NMR measurements were carried out with moderate precautions against moisture. Transfers to stoppered, weighed NMR tubes were made in a drybox. Quantities of those phosphonium salts that were available only as syrups could not easily be estimated; a small amount was therefore transferred in a drybox for weighing, and then diluted with the proper amount of deuterioacetonitrile, so that 0.3-0.4 ml of solution would contain an amount of salt equivalent to the previously weighed quantity of phosphorane; the NMR solution was then made up in a drybox by adding approximately the correct quantity of the solution to the weighed phosphorane in an NMR tube.

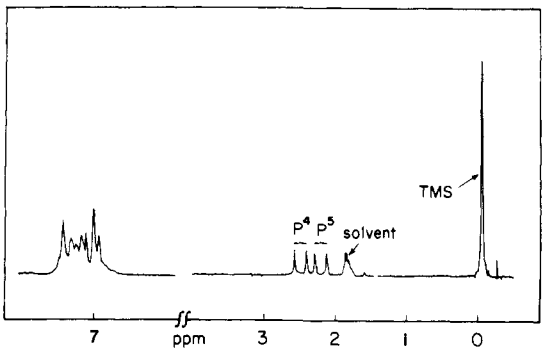

Figure 2. The 100-MHz ^1H NMR spectrum of an equimolar mixture of methyltetraphenoxyphosphorane and methyltriphenoxyphosphonium triflate in acetonitrile-d_3.

Alternatively, weighed quantities of phosphonium triflates and sodium phenoxide were mixed and stirred under argon in the appropriate solvent (THF-d_8 or CD_2Cl_2) in a round-bottom flask. The quantities were chosen in 2:1 molar ratios, so that after reaction the mixture would contain equivalent amounts of salt and phosphorane. The precipitated sodium triflate was removed by centrifugation, and the supernatant transferred by syringe to an NMR tube. Although the reaction is heterogeneous, it proceeded to completion as evidenced by NMR spectroscopy.

Variable-temperature NMR experiments were conducted either with a Varian A-60 or Varian HA-100 spectrometer. Temperatures were calibrated using the chemical shift between the methyl and hydroxyl signals from methanol for low temperatures, and the analogous shifts for ethylene glycol for high temperatures.[18]

Analyses. Samples for analysis were transferred to screw cap bottles in a drybox. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Results

Temperature Dependent NMR Spectra. The proton NMR spectra of phosphoranes and of triflate salts, individually, show different chemical shifts for the signals from the P-CH_3 groups. The spectra from the various phosphoranes, however, gave no indication of the presence of any salt in equilibrium with the phosphorane. A vain attempt was made to find a trace of the phosphonium cation from methyltetraphenoxyphosphorane by using Fourier transform techniques and a CAT to store the results of tracing and retracing the region where the signal from the P-CH_3 group of the salt could appear. The results showed that the equilibrium constant for the dissociation of the phosphorane must be less than 10^{-7} M (cf. the value of 10^{-10} M from ref 2). The proton NMR spectra of the salt and phosphorane in deuteriochloroform and acetonitrile are shown in Figures 1 and 2. The spectrum in acetonitrile-d_3 is less clean for two reasons. First, a signal is also obtained from the residual hydrogen in the solvent, which is only 99% deuterated. Second, acetonitrile has not been obtained entirely anhydrous, so that a small amount of hydrolysis occurs to yield diphenyl methylphosphonate; the small signals from the methyl group of the impurity of the phosphonate ester lie at slightly higher field than those from the phosphorane. At higher temperatures, the doublet from the methyl group of the phosphorane broadens, presumably owing to the formation of ylide (see below).

When equivalent amounts of salt and phosphorane are mixed in deuterioacetonitrile, the 60-MHz NMR spectrum shows a triplet; the upfield signal from the salt overlaps the downfield signal from the phosphorane; at 100 MHz the

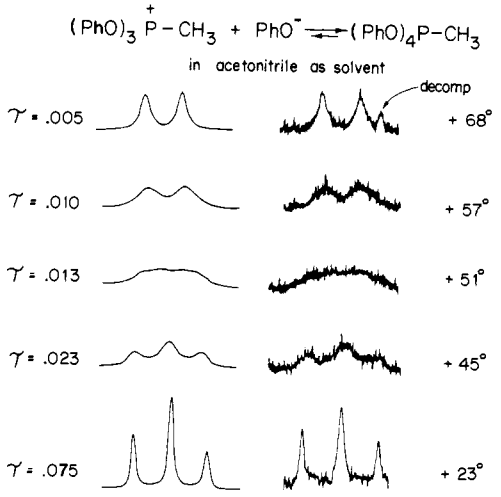

Figure 3. Calculated and observed 60-MHz NMR spectra of a solution of 0.314 *M* methyltetraphenoxyphosphorane and 0.314 *M* methyltriphenoxyphosphonium triflate in acetonitrile-d_3.

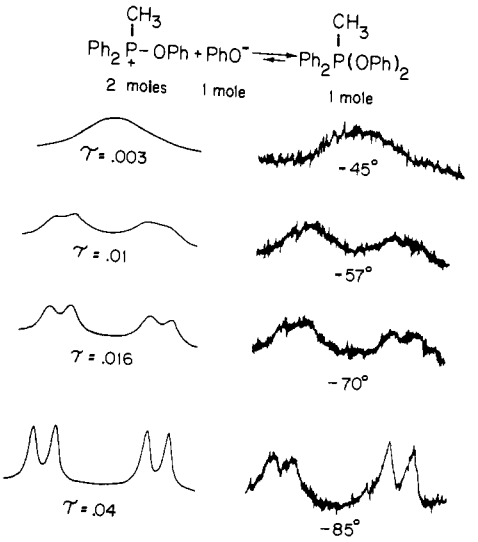

Figure 4. Calculated and observed 100-MHz NMR spectra of a solution of 0.31 *M* methyldiphenylphenoxyphosphonium triflate and 0.14 *M* sodium phenoxide in THF-d_8.

doublets from the two P-CH_3 groups are entirely separated. The effect of raising the temperature with a mixture of phosphorane and salt is shown in Figure 3. The two doublets merge at 51°, but at 68° a new doublet appears halfway between those of salt and phosphorane. (Similar, but less easily analyzed changes occur in the aromatic region of the spectra.) The spectroscopic behavior of methyltetra-*o*-cresoxyphosphorane, and of methyltetra-*p*-cresoxyphosphorane, each mixed with the corresponding triflate salt, show similar behavior, where the signals from the aromatic methyl groups as well as from the P-CH_3 groups merge as the temperature is raised. Because the signals from the P-CH_3 groups of these cresyl derivatives are partially hidden under the much larger peaks from the aromatic methyl groups, these spectra are somewhat harder to treat quantitatively than those from the phenoxy compounds.

The reaction between methyltriphenoxyphosphonium triflate and methyltetraphenoxyphosphorane was also observed in perdeuteriotetrahydrofuran, where the reactions were carried out by mixing 2 equiv of salt with 1 equiv of sodium phenoxide. Although similar phenomena were recorded in this solvent, the reactions at high temperature were complicated by the formation of ylide.

The reaction between methyldiphenylphenoxyphosphonium triflate and sodium phenoxide and the reaction between methylphenyldiphenoxyphosphonium triflate and sodium phenoxide were also carried out in THF-d_8 and in CD_2Cl_2, respectively. The NMR spectrum of an equimolar solution of methyldiphenylphenoxy salt and the corresponding phosphorane (prepared from a 2:1 mixture of salt and phenoxide) shows just one doublet at room temperature. This doublet collapses at +48°, presumably because of ylide formation. At low temperatures, also, the doublet collapses, and at −45° in THF-d_8, the NMR signal appears as a broad band. The separate doublets from the cation and phosphorane are apparent at still lower temperatures and are clear at −85° (Figure 4).

Similar experiments at low temperatures with methylphenyldiphenoxyphosphonium triflate and sodium phenoxide could not be performed because of difficulties with solubilities. Neither the salt nor the product phosphorane was soluble enough in THF-d_8 for measurements; solutions in CD_2Cl_2 could be prepared at room temperature, but at low temperatures product separated from this solvent. However, the P-CH_3 group of the triflate salt in CD_2Cl_2 gave rise to a doublet centered at δ 2.65, whereas that of the phosphorane (prepared from an equimolar mixture of salt and sodium phenoxide) gave rise to a doublet centered at δ 2.37. A mixture of equal quantities of phosphorane and phosphonium salt gave rise to a doublet at δ 2.50. The spectrum at room temperature, then, corresponds to that expected for rapid equilibration between salt and phosphorane.

Relative Equilibrium Constants. Although in every case here examined, the equilibrium between salt and phenoxide ion is too far to the side of phosphorane to permit determination of the constant by NMR spectroscopy, the relative positions of the equilibria could be determined. Mixing 1 mol of methyltriphenoxyphosphonium triflate and 1 mol of methyldiphenylphenoxyphosphonium triflate with 1 mol of phenoxide ion gave rise to methyldiphenylphenoxyphosphonium ion and methyltetraphenoxyphosphorane (as would be expected from the equilibrium constants reported in the accompanying article[2]).

Ylide. At some temperature for each phosphorane–phosphonium salt mixture, the NMR signals from the P-CH_3 groups consist of a doublet that represents the average between the signals for the two components. At higher temperatures, this doublet collapses to a singlet, where the position of the singlet varies somewhat according to the time of heating and temperature; these phenomena, however, are fully reversible on cooling the solutions. Evidence that this behavior results from ylide formation is as follows.

In addition to the changes in the spectrum noted above, a signal from the hydroxyl group of phenol can be seen at a δ of about 9. Most of the phenol probably arise from the salt or phosphorane by hydrolysis induced by adventitious moisture. Nevertheless, as the temperature is raised, the signal from the phenolic hydrogen atom broadens and moves significantly to higher fields. This suggests that the phenol is in equilibrium with the other components, presumably by way of the formation of ylide from the phosphonium salt. Since the NMR signal from the phenolic hydrogen is around δ 9, that of the salt is around 2.8 ppm, that of the phosphorane at 2.2 ppm, and that of the ylide probably near 0.1 ppm,[19] the equilibration is a complicated one. Since the δ values are so disparate, equilibration will not become apparent on the NMR time scale until the rate constant for the equilibration is much greater than that for the equilibration processes between salt and phosphorane. Since the behavior of the phenol signal shows that the equilibration with ylide can nevertheless be detected, ylide formation must indeed be rapid.

Table I

Phosphorane	Solvent	T, °C	τ, sec	T	τ, sec	T	τ, sec	T	τ, sec	T	τ, sec
$(C_6H_5O)_4PCH_3$	CD_3CN	23	0.075	45	0.023	51	0.013	57	0.010	68	0.005
$(o\text{-}CH_3C_6H_4O)_4PCH_3$	CD_3CN	23	0.25	41	0.17	63	0.035	76	0.015	84	0.009
$(p\text{-}CH_3C_6H_4O)_4PCH_3$	CD_3CN	24	0.07	39	0.03	48	0.017	58	0.011	80	0.005
$(C_6H_5O)_2P(CH_3)(C_6H_5)_2$	THF-d_8	−85	0.04	−70	0.016	−57	0.01	−45	0.003		

$$(C_6H_5O)_3P^+\text{-}CH_3 + C_6H_5O^- \rightleftharpoons (C_6H_5)_3P{=}CH_2 + C_6H_5OH \quad (5)$$

In order to test for exchange reactions that would occur if ylides are formed under the conditions of our experiments, two separate solutions were prepared: one of methyl-d_3-diphenylphenoxyphosphonium triflate in bromobenzene, the second of ethylphenyldiphenoxyphosphonium fluoroborate.[20] Each was mixed with an equivalent quantity of sodium phenoxide in bromobenzene so as to prepare the corresponding phosphorane. The trideuterio compound showed almost no signal in the region around δ 2.4 where signals from *P*-methyl protons appear in this solvent. The signals of the ethyl group in ethylphenyltriphenoxyphosphorane reveal a doublet of triplets for the C-CH_3 group, with δ 1.18 and $J_{H\text{-}P}$ = 24 Hz and $J_{H\text{-}H}$ = 6 Hz, while the signal for the methylene group appears as a sextet (presumably an overlapping doublet of quartets) centered at δ 2.7. Subsequently the two solutions were mixed; an NMR spectrum taken as soon as possible after mixing (about 5 min) gave evidence of complete exchange. In particular, the doublet from the *P*-methyl group was plainly visible at δ 2.4, with $J_{H\text{-}P}$ = 14 Hz; this signal dominates the *P*-methyl-*P*-methylene region. The signals from the *C*-methyl group had also changed and were consistent with those expected for the overlap of signals from a mixture, with CH_3 groups adjacent to CH_2, CHD, and CD_2 groups.[6] Of course, the preparative production of ylides requires strong bases such as *tert*-butoxide[21] ion. In the present work, however, very little ylide needs to be formed in order to facilitate the rapid equilibration among protons; this kinetic phenomenon is not inconsistent with the need for strong bases in preparative work.

Discussion

Equilibria. The NMR results here recorded show qualitatively that the equilibrium of eq 1, between a phosphonium cation and phenoxide ion, lies far to the side of the phosphorane for the examples here cited, i.e., for reactions with aryloxide ions of methyltriphenoxyphosphonium ion, methylphenyldiphenoxyphosphonium ion, methyldiphenylphenoxyphosphonium ion, and the analogous tetracresylate compounds. The equilibrium is farthest to the side of the phosphorane with the compounds containing the most oxygen atoms bound to phosphorus, whereas methyltriphenylphosphonium cation does not react with phenoxide ion to produce a phosphorane at all. This last example, however, is not a reflection of a generalized polar effect, or lack thereof. The phosphorane that would result from the reaction of the cation with phenoxide ion, i.e., methyltriphenylphenoxyphosphorane, would have only one electronegative group attached to phosphorus; trigonal bypyramidal geometry would demand that one of the substituents attached to phosphorus by a C-P bond occupy an apical position. Such phosphoranes are inherently unstable.[4,5,22-24]

Rates of Equilibration. By mixing equimolar quantities of salt and phosphorane, temperature-dependent NMR spectra are obtained, and these spectra allow the calculation of the rate of equilibration between salt and phosphorane. In each case, the signals obtained for the equilibrium mixture lie appropriately between those for salt and phosphorane, and in all examples but one, two doublets can be observed at low temperatures, and one doublet at high temperatures. In the one remaining case, equilibration had been established at room temperature, but low-temperature measurements were unsuccessful. The temperature at which equilibration becomes rapid on the NMR time scale is highest for the tetraphenoxyphosphorane, and lowest for methyldiphenyldiphenoxyphosphorane; thus the rates of dissociation parallel the equilibrium data,[2] with the most highly dissociated phosphorane showing the highest rates (or lowest temperature at which the rates become fast on the NMR time scale).

Rate Constants. Quantitatively, the temperature-dependent spectral changes can be analyzed by using the equations for a simple two-site exchange process.[25] Fortran programs, written for an IBM 1130 and alternatively for a PDP 11/45 computer, reproduced the spectra and led to the determination of rate constants for equilibration. To what do these constants refer? The rate constants will be the sum of that for the forward and backward reaction in the equilibration process; for the particular set of experimental conditions here used, i.e., for the case where equal quantities of salt and phosphorane are present (together with only a trace of phenoxide ion), the rate constant refers to the dissociation of the phosphorane.

For the NMR process

$$P^4 + ArO^- \underset{k_d}{\overset{k_a}{\rightleftharpoons}} P^5$$

where P^4 stands for the phosphonium cation, and P^5 for the phosphorane.

$$K_{eq} = (P^5)/(P^4)(PhO^-) = k_a/k_d$$

where $k_a(PhO^-) = 1/\tau_A$ and $k_d = 1/\tau_B$. Since (PhO^-) is negligible in these experiments, and since the concentrations of phosphorane and salt were equal,

$$k_a(PhO^-) = k_d$$

and

$$\tau = \frac{\tau_A \tau_B}{\tau_A + \tau_B} = \frac{1}{k_d + k_a(PhO^-)} = \frac{1}{2k_d}$$

The appropriate τ values are listed in Table I.

The NMR spectra for the equilibration between phosphonium salt, aryl oxide, and phosphorane, when the aryl oxide is *o*- or *p*-cresylate, shows exchange for the signals from the *C*-methyl as well as for those arising from the *P*-methyl groups. This, however, is a three-site exchange among the *C*-methyl groups of all three components: salt, phosphorane, and aryl oxide. No attempt has yet been made to analyze this three-site process quantitatively.

Identification of the Rate Process. In view of the finding reported in the accompanying paper,[2] that phosphorane and phenoxide ion react with a favorable equilibrium constant to yield a hexacovalent phosphorus anion, the question must be considered as to whether the phenomena here described could be accounted for by some more complex reaction than

that shown in eq 1, so that the reported time constants might refer to some process other than the dissociation of the phosphorane. This possibility can be disposed of on two counts. First, the temperature-dependent NMR spectra were determined in the presence of a quantity of the phosphonium salt equivalent to that of the phosphorane. Since the equilibrium for the reaction of the cation with phenoxide is even more favorable than that with the phosphorane,[2] the rate is also probably much greater. Second, the reaction between methyltriphenoxyphosphonium triflate and phenoxide ion was carried at two different concentrations, 0.314 and 0.153 M, and yielded practically the same rate constants. Such would not have been the case had the dominant reaction been second order in phosphorane, as required by the hypothesis that the hexacovalent anion is involved in the measured rate.

In the accompanying paper,[2] the equilibrium constants have been obtained for the dissociation of three of the phosphoranes. Using these equilibrium constants and the rate data presented here, the conclusion has been drawn that the reaction of these phosphonium salts with phenoxide ion in acetonitrile proceeds with the speed of collision. An extension of these results to other nucleophiles and other solvents is in progress.

Acknowledgment. This work was supported by the National Science Foundation, under Grant No. GP 2098. D.P. gratefully acknowledges a predoctoral fellowship from the National Institutes of Health. I.S. recieved financial support from the Zlato and Joyce Baloković Fund, administered by the Yugoslav Academy of Sciences and Harvard University, while on leave of absence from the Rudjer Bošković Institute of Zagreb. Special thanks go to Mr. Hampar Janjigian, and Dr. Wm. Hull for assistance with the NMR measurements, and to the NSF under Grant No. GP 30965X for assistance in the purchase of the NMR instrument. We are also indebted to Professors J. D. Roberts and Delos DeTar for helpful discussions, and to Charles Lerman for assistance with the computer programming.

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Computer-Assisted Synthetic Analysis. Synthetic Strategies Based on Appendages and the Use of Reconnective Transforms

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Abstract: Computational procedures are developed corresponding to synthetic strategies based on the antithetic (retrosynthetic) disconnection and reconnection of appendages in a target molecule. The reconnective mode is also used to guide the antithetic analyses of target structures containing medium rings. The importance of stereochemical considerations in the reconnective modes is stressed. A definition of "ring" and "branch" appendages is made. In addition, effective methods for the unambiguous recognition of the identicality of two appendages in a molecule are presented. The procedures are completely general since the appendages may include rings and chiral centers. The identicality of different aromatic resonance structures is also recognized. The appendage matching procedure involves a rapid tree search using a "branch atom by branch atom" matching technique. The method described herein is suitable for application to substructure searching in other areas, e.g., in chemical information retrieval systems.

An important aspect of the project at Harvard to devise a program for computer-assisted synthetic analysis has been the development and testing of general synthetic strategies. Many of the strategies currently employed by the program (LHASA) are based on common molecular features. For example, functional groups and rings are the most obvious synthetically significant structural features in a target molecule.[1] They have led to the formulation in LHASA of functional group oriented chemistries[2] and a strategy based on the recognition and antithetic (retrosynthetic) disconnec-