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Catalytic Dephosphorylation of *O*-Phosphoserine by Gyloxylate Ion and Copper(II)

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The β-elimination reaction of *O*-phosphoserine was studied in the presence of glyoxylate ion and Cu(II) at 30.0 °C and over the pH range 3.0–8.0. Equilibrium studies indicate the formation of monoprotonated (III), normal (IV), and monohydroxo (V) Schiff base–metal complexes. The log association constants for the formation of these species from their components are 16.49, 11.56, and 18.14, respectively. In species III the proton resides on the phosphate group and the Schiff base is tridentate. Species IV is a Schiff base complex which may or may not have the phosphate group bound to Cu(II). Species V is like IV except that a hydroxide ion is also bound to the metal ion. In reacting to eliminate phosphate ion, these complexes follow the order III > IV > V with specific rate constants of 1.81×10^3, 3.8×10^4, and 5.0×10^5 s^{-1}, respectively. Substitution of deuterium for the α-hydrogen of *O*-phosphoserine results in a kinetic isotope effect (k_H/k_D) of 3.4 for III and 1.1 and 1.7 for IV and V, respectively. Isotopic-exchange studies indicate that despite the low value of k_H/k_D for the latter two species, a rate-determining proton transfer prevails. The extent of polarization of the α-CH bond plays the major role in determining the order of reactivity of these species.

Introduction

The pyridine carboxaldehyde vitamin B-6 (pyridoxal) is a versatile coenzyme. It is essential to a large number of enzymes catalyzing such amino acid reactions as transamination, racemization, decarboxylation, and the elimination of electronegative substituents from the amino acid β-carbon atom. The reactions proceed by Schiff base formation at the active site of the enzyme. In the absence of the enzyme, slow reaction of these Schiff bases leads to the same products as in the enzymic reactions. Of particular interest to inorganic chemists is the fact that enzyme-free reactions are often strongly catalyzed by metal ions, and many of the mechanisms for vitamin B-6 catalysis are based on qualitative studies of such reaction systems.[1] The possibility that the mechanisms of these reactions are similar to the enzyme-catalyzed cases suggests interesting studies into the means by which metal ions catalyze them. Many studies have been carried out. Of particular relevance to the present work, there have been a number of investigations of the elimination of electronegative substituents from the amino acid β-carbon atom. These include studies of reactions of vitamin B-6 Schiff bases of serine,[2a] threonine,[2b] β-chloroalanine,[3] cysteine,[2a] cystathione, lanthionine,[4] *O*-phosphoserine, *O*-carbamoylserine, azaserine,[5] *O*-phosphothreonine,[5,6] *O*-sulfoserine, and *O*-sulfothreonine.[7]

In searching the literature, one might expect to see detailed analyses of the metal–ligand equilibria in these systems together with kinetic analysis comparing the reactivity of the various molecular species present. However, this has generally proven to be prohibitively difficult because the large number of equilibria involved makes the determination of the various species a very difficult problem and hemiacetal formation with pyridoxal leads to slow equilibria in pyridoxal–amino acid–metal ion ternary systems. In some cases, glyoxylic acid catalyzes the same vitamin B-6 model reactions as does pyridoxal.[9,10] Equilibration times in ternary systems involving glyoxylic acid, amino acids, and metal ions have proven to be amenable to the determination of the stability constants and the corresponding concentrations of the metal complexes formed.[11]

With the hope of reducing a vitamin B-6 model system to a level where it will submit to a full analysis, we have studied the glyoxylate and Cu(II)-catalyzed elimination of phosphate ion from *O*-phosphoserine. Herein we report on the equilibria and kinetics of the system.

Experimental Section

Materials. DL-*O*-phosphoserine and sodium glyoxylate were obtained from Sigma Chemical Co., DL-α-methylserine was obtained from United States Biochemical Corp., and *O*-phospho-α-methylserine was prepared by phosphorylating[12] α-methylserine. DL-(α-^{2}H)-phosphoserine was prepared from serine by deuteration at the α carbon in the presence of pyridoxal and Al(III)[13] followed by phosphorylation.[12] The purity of both of these compounds was checked by potentiometric titrations with standard sodium hydroxide. The extent of deuteration is greater than 80%, determined by integrating the ^{1}H NMR spectrum with sodium acetate as an internal standard. A stock solution of Cu(II) was prepared from the nitrate salt and standardized by titration with the disodium salt of EDTA.[14] Carbonate-free sodium hydroxide was prepared and standardized with potassium hydrogen phthalate.

Equilibrium Measurements. Dissociation constants of the free ligands and equilibrium constants of the metal complexes were determined by potentiometric titration with standard carbonate-free NaOH, in the absence and in the presence of the metal ion, respectively. Stability constant data for the copper(II)–glyoxylate, copper(II)–phosphoserine, and the ternary copper(II)–phosphoserine–glyoxylate systems were obtained by titrating solutions containing 1:1, 1:2, and a 1:1:1 molar ratios of metal ion and ligand(s), respectively. Equilibration times were quite rapid, less than 2 min being required to obtain a stable pH.

In the case of the ternary system, the entire titration involving the addition of about 4 mL of standard NaOH was carried out in four separate steps, each of which involved the addition of 1 mL of base in a time short enough to avoid pH changes due to dephosphorylation. The entire titration curve was then obtained by combining the data of the individual steps and is continuous within experimental error.

Titrations were carried out in a 50-mL jacketed cell serviced by a constant-temperature bath at 30.0 ± 0.1 °C, under CO_2-free nitrogen. The ionic strength of the solution was initially 0.1 M by suitable addition of KNO_3. Standard NaOH was added to the titration cell with a Metrohm Dosimat microburet, and the changes in the pH of the solution during the course of the titration were determined with a Radiometer digital pH meter, Model pHM52. The electrode system was calibrated by direct titration of acetic acid, the observed pH meter readings being compared with the actual hydrogen ion concentration calculated from data tabulated by Harned and Owen.[15] The pH regions below 3.5 and above 10.5 were calibrated using HCl and NaOH solutions, respectively.

The association constants for the free ligands (A = glyoxylic acid, L = phosphoserine) and the stability constants for equilibria 1–7 were computed from the titration data using a corrected version of the computer program SCOGS[16] on an IBM 370/168 computer system.

$$M^{2+} + A^- \rightleftharpoons MA^+ \quad K^M_{MA} \tag{1}$$

$$M^{2+} + HL^{2-} \rightleftharpoons MHL \quad K^M_{MHL} \tag{2}$$

$$M^{2+} + L^{3-} \rightleftharpoons ML^- \quad K^M_{ML} \tag{3}$$

$$ML^- + L^{3-} \rightleftharpoons ML_2^{4-} \quad K^{ML}_{ML_2} \tag{4}$$

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$$M^{2+} + L^{3-} + A^{-} \overset{K^{M}_{MLA}}{\rightleftharpoons} MLA^{2-} \quad (5)$$

$$MLA^{2-} + H^{+} \overset{K^{MLA}_{MHLA}}{\rightleftharpoons} MHLA^{-} \quad (6)$$

$$MLA^{2-} + OH^{-} \overset{K^{MLA}_{MLA(OH)}}{\rightleftharpoons} MLA(OH)^{3-} \quad (7)$$

Kinetic Measurements. The kinetic runs were carried out in a 100-mL water-jacketed cell maintained at 30.0 ± 0.1 °C. The pH of the reaction solution was maintained constant during each kinetic run with a Radiometer pH stat fitted with an autoburet. Buffers were not used because of the previously noted buffer effects on the reaction rates of similar systems.[5]

The reaction solutions were initially made up to contain 2.0×10^{-3} M each of *O*-phosphoserine, glyoxylic acid, and Cu(II). Fresh solutions of the amino acid and glyoxylate were prepared for each run. The reaction was initiated by adding the requisite volume of Cu(II). Ionic strength was maintained at 0.1 M by suitable addition of KNO_3, and CO_2-free nitrogen was bubbled through to reaction solutions throughout the kinetic run. The rate of dephosphorylation was followed by measuring the amount of inorganic phosphate liberated during the course of the reaction, as a function of time. Aliquots of the reacting mixture were removed at definite time intervals and added to a flask containing the phosphate-developing reagent[17] at ca. 3.0 °C. The low temperature and the high acidity effectively quenches the dephosphorylation reaction. The absorbance was measured at 700 nm with a Beckman spectrophotometer, Model B. First-order rate constants were calculated from these data.

Results

Equilibrium Measurements. Values for the proton association constants of glyoxylic acid and *O*-phosphoserine and association constants for the metal complexes formed in the copper(II)–glyoxylate and copper(II)–phosphoserine binary systems are listed in Table I. In titrations of the 1:1 systems of Cu(II) and either glyoxylic acid or *O*-phosphoserine, precipitates form above pH 4.5 and 4.8, respectively. However, in titrations of the 1:1:1 molar ratios of Cu(II), glyoxylate, and *O*-phosphoserine, Figure 1E, precipitation is not observed and stable pH readings are obtained until the end of the titration. This is an indication of ternary complex formation. Computer analysis shows that the curve may be fit accurately by addition of three ternary complex formation constants to the binary constants previously determined. These ternary constants are reported in Table I. A monoprotonated mixed-ligand species—MHLA (L = *O*-phosphoserine and A = glyoxylate)—is formed first. At higher pH values, the MHLA species loses a proton to form a normal mixed-ligand complex, MLA, which hydrolyzes at still higher pH's to form a monohydroxo species, MLA(OH). The constants listed in Table I have been used to calculate the concentrations of the various complex species as a function of pH, using the computer program COGSNR.[16] The species distribution diagram, Figure 2, shows that MHLA reaches a maximum concentration around pH 4.6 while the concentration of MLA becomes a maximum around pH 6.4. The concentration of MLA(OH) is appreciable at pH 7.5 and increases with increasing pH.

Kinetic Measurements. Kinetic runs carried out with a 1:1 molar ratio of *O*-phosphoserine to Cu(II) or glyoxylate show no detectable dephosphorylation of the amino acid over the pH range 3.0–8.5. On the other hand, kinetic runs carried out with a 1:1:1 molar ratio of *O*-phosphoserine, Cu(II), and glyoxylic acid show rapid dephosphorylation rates, indicating that dephosphorylation occurs only for the ternary complexes. A pH–rate profile, Figure 3, was constructed and shows a rate maximum at pH 4.7. Turbidity was observed in solutions with a pH above 8.5. By solving simultaneous equations in the pH range 7.0–8.0, where the concentration of the monoprotonated species is negligible, specific rate constants were obtained for MLA and MLA(OH). The specific rate constant for the monoprotonated species was then calculated from the rate remaining after subtraction of the contributions of the MLA and MLA(OH) species from experimental rates. The values were checked by constructing a theoretical pH–rate profile for M = L = A concentrations of 2.0×10^{-3} M, utilizing the equilibrium data in Table I. This curve agrees within ex-

Table I

association constant[a]	log K^b	association constant[a]	log K^b
K^{H}_{HA}	3.04 ± 0.01	K^{M}_{ML}	9.32 ± 0.02
K^{H}_{HL}	9.69 ± 0.01	$K^{ML}_{ML_2}$	5.84 ± 0.04
	(9.69 ± 0.01)	K^{M}_{MLA}	11.56 ± 0.10
$K^{HL}_{H_2L}$	5.68 ± 0.01	K^{MLA}_{MHLA}	4.93 ± 0.20
	(5.74 ± 0.01)	$K^{MLA}_{MLA(OH)}$	6.58 ± 0.10
$K^{H_2L}_{H_3L}$	2.10 ± 0.01		
	(2.25 ± 0.02)		
K^{M}_{MA}	2.15 ± 0.02		
K^{M}_{MHL}	5.0 ± 0.02		

[a] A = glyoxylic acid, L = DL-*O*-phosphoserine, M = Cu(II). [b] t = 30.0 °C, μ = 0.1 M (KNO_3). Values in parentheses refer to (DL-α-^{2}H)phosphoserine.

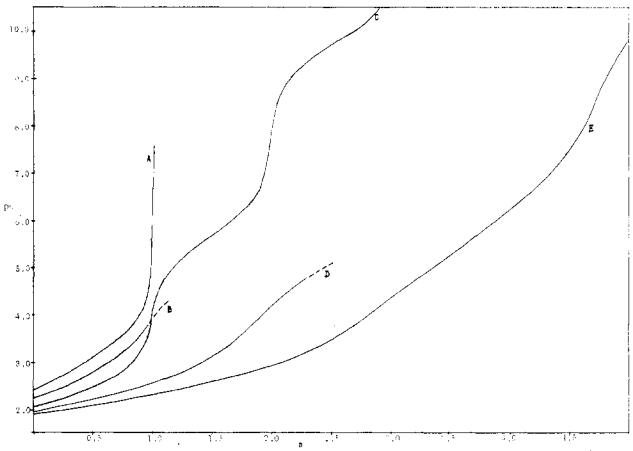


Figure 1. Potentiometric titration curves: (A) free glyoxylic acid, (B) 1:1 Cu(II) + glyoxylic acid, (C) free *O*-phosphoserine, (D) 1:1 Cu(II) + *O*-phosphoserine, (E) 1:1:1 Cu(II) + glyoxylic acid + *O*-phosphoserine. "*a*" is the moles of base added per mole of ligand. For curve E, the absicca represents *m*, the moles of base added per mole of metal ion.

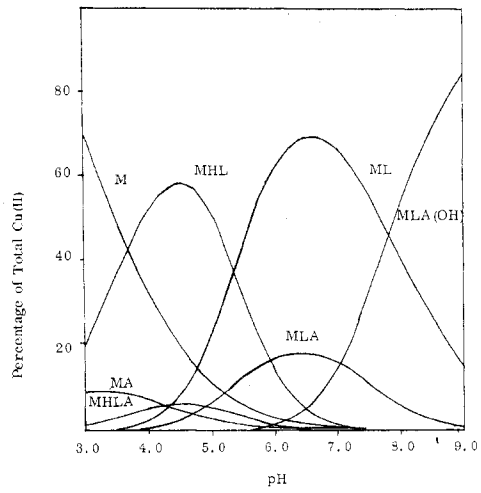


Figure 2. Variation with pH of the composition of a solution of Cu(II) ions (0.002 M), glyoxylic acid (0.002 M), and *O*-phosphoserine (0.002 M). The curves show the percentage of the total Cu(II) present as free metal ion and the species MA, MHL, ML, MHLA, MLA, and MLA(OH), calculated from constants listed in Table I.

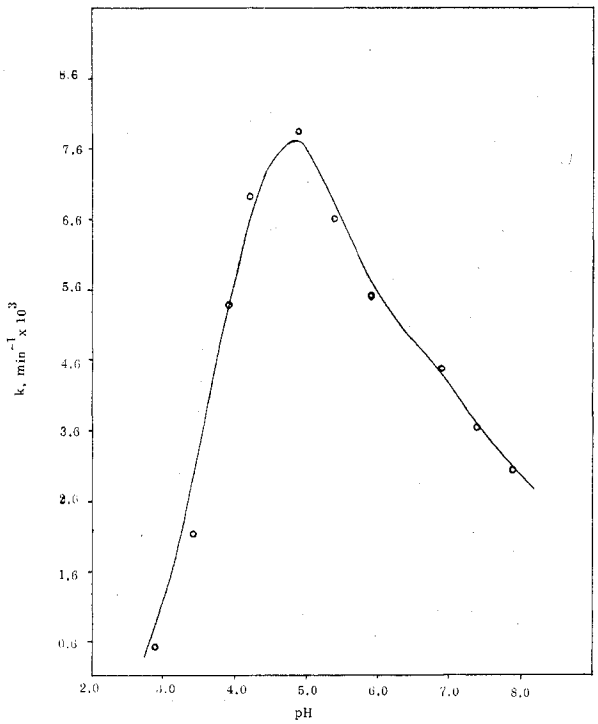


Figure 3. pH–rate profile for the dephosphorylation of *O*-phosphoserine in the presence of Cu(II) and glyoxylic acid: (—) calculated curve, (O) experimental points.

Table II

species[b]	$10^{-4}k_H$,[a] s^{-1}	$10^{-4}k_D$,[a] s^{-1}	k_H/k_D
MHLA	18.1	5.3	3.4
MLA	3.8	3.4	1.1
MLA(OH)	0.5	0.3	1.7

[a] t = 30.0 °C, μ = 0.1 M (KNO_3). [b] M = Cu(II), A = glyoxylic acid, L = *O*-phosphoserine.

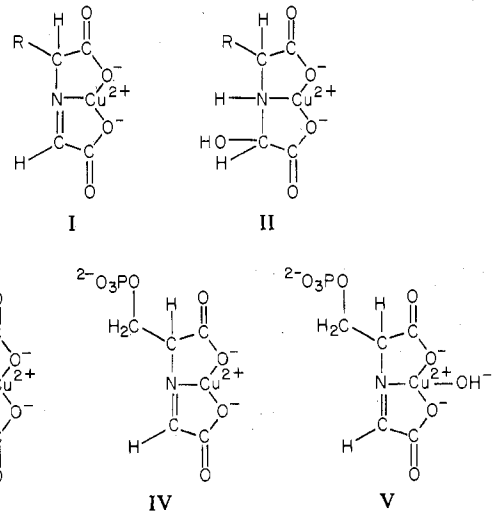
perimental error to one determined by experiment. Specific first-order rate constants for the dephosphorylation of MHLA, MLA, and MLA(OH) appear in Table II.

Several other brief but significant experiments were carried out. A kinetic isotope effect was clearly demonstrated using DL-(α-^{2}H)phosphoserine. For MHLA k_H/k_D = 3.4 and for MLA and MLA(OH) k_H/k_D = 1.1 and 1.7, respectively. For MLA and MLA(OH), studies were carried out to determine whether the α H of the amino acid moiety is eliminated prior to the rate-determining step. The reaction was run at pD 7.2 in D_2O. Aliquots were taken out at varying times, the Cu(II) was removed by solvent extraction with dithizone in carbon tetrachloride, and the proton NMR spectra were recorded with a Varian A60 spectrometer. Exchange of the α proton could not be detected when 50% of the *O*-phosphoserine had reacted. No detectable dephosphorylation is observed for *O*-phospho-α-methylserine over the pH region 3.0–8.0.

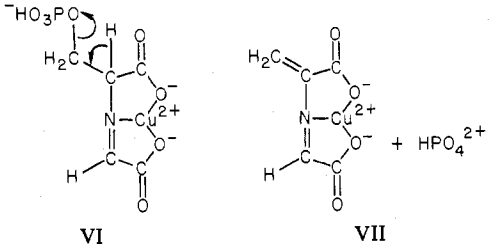
Discussion

Structures of Schiff Base Complexes. The structures of the Schiff base complexes MHLA, MLA, and MLA(OH) may reasonably be inferred from the equilibrium data in Table I. The formation constants of amino acid–glyoxylate Schiff base complexes with metal ions reported previously[11] are consistent with our data. Schiff bases form hydrates but the degree to which the equilibrium in I → II participates in these systems may not be inferred from our data.

The species MHLA, MLA, and MLA(OH) probably have the structures shown as III, IV, and V, respectively. The pK for deprotonation of III to IV is 4.93 whereas the pK for the phosphate dissociation of phosphoserine is 5.68. The similarity of these figures suggests that the proton of MHLA is on the phosphate moiety. The lower pK for MHLA does not necessarily indicate that the phosphate group of MLA is bound to Cu(II). To do so would require the formation of a seven-membered chelate ring and phosphate binding to a weak Cu(II) axial site. The lower pK for MHLA is equally consistent with the increased polarization of the phosphate group by coordination to Cu(II) through the imino and carboxylate moieties.



Mechanistic and Catalytic Considerations. Dephosphorylation of *O*-phosphoserine may take place by either hydrolysis or an elimination reaction involving cleavage of the α-CH bond.[18] In the present study no detectable dephosphorylation of *O*-phospho-α-methylserine was observed over the pH range 3.0–8.0. The mechanism of *O*-phosphoserine dephosphorylation is therefore elimination as in VI → VII. Elimination



itself may proceed by several different pathways depending on whether the α hydrogen bond breaking is rate determining or not. For the species MHLA, a kinetic isotope effect of 3.4 was observed when the α proton was replaced by deuterium. In this case the rate-determining step is clearly the cleavage of the α proton. For the species MLA and MLA(OH), however, the kinetic isotope effect is 1.1 and 1.7, respectively, raising the question as to whether the mechanism might be E1cB in which the α proton is cleaved prior to the rate-determining phosphate elimination. If such a mechanism were operating, it should result in incorporation of deuterium at the α carbon of the unreacted phosphoserine when the reaction is carried out in D_2O. This, however, was not observed when the unreacted phosphoserine was recovered at various times and its NMR spectrum examined. Therefore it seems that the mechanism of dephosphorylation for the MLA and MLA(OH) species is the same as that for MHLA. Values of k_H/k_D as low as 1.4 have been reported for the phosphate elimination from phosphoserine itself.[19] The E1cB mechanism has been shown not to be operating, and a highly nonlinear transition state has been suggested. Presumably the strongly

anionic phosphate group is responsible for the distortion.

The striking result of the present study is the importance of the polarization of the α-CH bond of a given Schiff base species in determining its reactivity. In species III, the combined polarizing effects of the proton on the phosphate group and the divalent metal ion leads to the high reaction rates. At the other extreme, species V lacks the proton on its phosphate group and, further, the effective charge on Cu(II) is reduced by binding to the hydroxide ion. This leads to a reaction rate which is about 36 times lower than that of III.

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Registry No. DL-*O*-phosphoserine, 17885-08-4; glyoxylic acid, 298-12-4; Cu^{2+}, 15158-11-9; D, 16873-17-9; ML_2^{4-}, 67711-55-1; MLA^{2-}, 67711-56-2.

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Mixed-Valence Thiophosphorus Compounds. Fluoro- and (Trifluoromethyl)(thiophosphorylthio)phosphines with Chiral Phosphorus Centers

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Reactions of the acids $(CF_3)_2PS_2H$ and F_2PS_2H with the fluoro(trifluoromethyl)aminophosphine $CF_3(F)PN(CH_3)_2$ and the reaction of the new acid $F(CF_3)P(S)SH$ with the fluoro- or (trifluoromethyl)aminophosphines $X_2PN(CH_3)_2$ (X = F, CF_3) provide new isomeric (thiophosphorylthio)phosphines XYP(S)SPX'Y' (X, Y, X', Y' = F, CF_3) with chiral phosphorus centers. The compounds were characterized chemically and by NMR spectroscopy. Geminal CF_3–CF_3 (9.0 Hz for CF_3 on pentavalent P; 7.2 Hz for CF_3 on trivalent P) and F–F (82.5 Hz for F on pentavalent P; 92.5 Hz for F on trivalent P) coupling constants are revealed in the NMR spectra of the molecules as a result of the presence of the chiral phosphorus centers. Directly bound geminal fluorine atoms on trivalent P show large chemical shift difference between the two fluorine atoms (4.4 ppm) accompanied by substantially different $^1J_{PF}$ coupling constants (1370 and 1291 Hz). Similar but smaller differences prevail between geminal CF_3 substituents. Reaction of the new acid $F(CF_3)P(S)SH$ with $CF_3(F)PN(CH_3)_2$ gave a mixture of (thiophosphorylthio)phosphine isomers each with two chiral phosphorus centers. Only partial assignment of the major features of this spectrum could be made.

Introduction

Studies of the symmetrically substituted mixed-valence (thiophosphorylthio)phosphines $F_2P(S)SPF_2$ (I)[1] and $(CF_3)_2P(S)SP(CF_3)_2$[2] (II) were recently extended[3] to include nonsymmetrically substituted compounds $F_2P(S)SP(CF_3)_2$ (III) and $(CF_3)_2P(S)SPF_2$ (IV). We have now synthesized the new acid $CF_3(F)P(S)SH$ which, when reacted with fluoro(trifluoromethyl)(dimethylamino)phosphine,[4] $F(CF_3)PN(CH_3)_2$, or the related phosphine sulfide[5] $F(CF_3)P(S)N(CH_3)_2$ gave additional mixed-valence compounds with chiral phosphorus centers. The new compounds $F(CF_3)P(S)SP(CF_3)_2$ (V), $F(CF_3)P(S)SPF_2$ (VI), $(CF_3)_2P(S)SP(CF_3)F$ (VII), $F_2P(S)SP(CF_3)F$ (VIII), and $F(CF_3)P(S)SP(CF_3)F$ (IX) described herein allow the determination of geminal F–F and CF_3–CF_3 NMR coupling constants. In addition the existence of two isomers of IX was demonstrated by NMR spectroscopy.

Results and Discussion

A. Synthetic Considerations. The general synthetic route for mixed-valence compounds[1-3] (eq 1) gave good yields of VII and VIII from the appropriate acid and $CF_3(F)PN(CH_3)_2$. The new compounds were characterized by spectroscopy and by alkaline hydrolysis with identification of residual CF_3P ions in the hydrolysate[8] (where possible) and also by means of the reaction of the mixed-valence compound with dimethylamine which gave, without rearrangement of X and Y with X' and Y', the aminophosphine and dithiophosphinic acid salt.

$$2XYP(S)SH + X'Y'PN(CH_3)_2 \rightarrow XYP(S)SPX'Y' + (CH_3)_2NH_2^+XYPS_2^- \quad (1)$$
X, Y = F, CF_3

$$XYP(S)SPX'Y' + 2(CH_3)_2NH \rightarrow (CH_3)_2NH_2^+XYPS_2^- + X'Y'PN(CH_3)_2 \quad (2)$$
X, Y, X', Y' = F, CF_3

All syntheses of the acid $CF_3(F)P(S)SH$ yielded a product contaminated with a little $F_2P(S)SH$. Addition of elemental sulfur to $CF_3(F)PN(CH_3)_2$ at elevated temperatures, previously shown to be nonstoichiometric,[5] gave $CF_3(F)P(S)N(CH_3)_2$ and smaller quantities of $CF_3P(S)[N(CH_3)_2]_2$, $CF_3P(S)F_2$, and $F_2P(S)N(CH_3)_2$.[9] These undesirable products may arise from rearrangement reactions of the desired compound at the elevated temperatures required. Separation of $F_2P(S)N(CH_3)_2$[9] from the desired major component $CF_3(F)P(S)N(CH_3)_2$ by conventional vacuum techniques was difficult, and propagation through the synthetic chain (vide infra) to $CF_3(F)PS_2H$ and the mixed-valence compounds gave no improvement in the ease of separation.

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