the cold trap. The flask contents solidified on cooling. Three recrystallizations of the solid from benzene yielded diphenoxyphenyldifluorophosphorane (2.1 g, 33%) as a colorless crystalline solid, mp 68-70°.

Phenoxydimethyldifluorophosphorane.—Dimethyltrifluorophosphorane (5.90 g, 0.050 mol) was added with stirring to phenyl trimethylsilyl ether (8.30 g, 0.050 mol) in an apparatus similar to that used in the previous experiment. The mixture was stirred under reflux for 6 hr and fluorotrimethylsilane (3.90 g, 81%) was collected in the cold trap. Distillation of the residue *in vacuo* yielded phenoxydimethyldifluorophosphorane (7.2 g, 75%), bp 72–74° (0.2 mm), as a colorless mobile liquid. A gray viscous residue (2.6 g) was left in the flask.

Aryloxyphosphonium Hexafluorophosphates.—The following experiments illustrate the use of sodium fluoride in obtaining aryloxyphosphonium hexafluorophosphates in high yields from certain of the reactions we report.

Tetraphenoxyphosphonium Hexafluorophosphate.—Phosphorus pentafluoride (5.0 g, 0.040 mol) was condensed onto a mixture of phenyl trimethylsilyl ether (13.2 g, 0.080 mol) and sodium fluoride (0.5 g) at liquid nitrogen temperature in a glass reaction tube. On warming the sealed tube to room temperature two immiscible liquid layers formed. Removal of fluorotrimethylsilane left a crystalline solid which was recrystallized from acetonitrile to give tetraphenoxyphosphonium hexafluorophosphate (6.0 g, 54% of purified product) as a colorless, crystalline solid.

Bis(dimethylamino)bis(phenoxy)phosphonium Hexafluorophosphate.—Dimethylaminotetrafluorophosphorane (7.6 g, 0.050 mol) was added to phenyl trimethylsilyl ether (8.3 g, 0.050 mol) in a two-necked flask fitted with a dropping funnel and reflux condenser attached to a cold trap at −78°. The reaction mixture was heated at 80° for 3 days. Fluorotrimethylsilane (2.9 g, 63%) collected in the cold trap. The flask contained two immiscible liquids. The upper layer (9.2 g) was shown by ^{19}F nmr to be mainly unreacted dimethylaminotetrafluorophosphorane. The lower layer was shown by ^{19}F and ^{31}P nmr to be a mixture of hexafluorophosphate and a monosubstituted derivative of PF_6^-, either $(CH_3)_2NPF_5^-$ or $C_6H_5OPF_5^-$. After the viscous liquid stood for 3 weeks, colorless crystals appeared; these were shown by ^{19}F and ^{31}P nmr and analysis to be bis(dimethylamino)bis(diphenoxy)phosphonium hexafluorophosphate (2.0 g, 17% of crude product).

Preparation of Bis(dimethylamino)bis(phenoxy)phosphonium Hexafluorophosphate in the Presence of Sodium Fluoride.—The reaction was carried out in a manner exactly analogous to the preceding experiment. Sodium fluoride (0.1 g) was added to the reaction mixture before heating commenced. Fluorotrimethylsilane (5.0 g, ∼100%) collected in the cold trap. The contents of the flask solidified on cooling. Recrystallization of this solid from acetonitrile yielded bis(dimethylamino)bis(phenoxy)phosphonium hexafluorophosphate (8.6 g, 78%) as a colorless crystalline solid.

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CONTRIBUTION FROM THE W. A. NOYES LABORATORY,
THE UNIVERSITY OF ILLINOIS, URBANA, ILLINOIS 61801

A Nuclear Magnetic Resonance Study of the Interaction of Cobalt(II) and Nickel(II) Ions with Thiamine Pyrophosphate

BY W. D. WHITE AND RUSSELL S. DRAGO*

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Measurements of the ^1H and ^{31}P nmr of thiamine pyrophosphate (TPP) have been made in the presence of Co(II) and Ni(II) ions. Line widths and chemical shifts, $\Delta\omega_m$, were measured as a function of temperature for the phosphorus and hydrogen nuclei. The results indicate that TPP is bound to a metal ion through the pyrophosphate group and through the pyrimidine moiety. The similarity of the observed shifts and line widths with those of the ATP complex suggests the interaction may be similar in the two complexes. Proton nmr studies of the reaction of pyruvate, $CH_3C(O)COO^-$, with TPP indicate that the metal–TPP complex aids in decarboxylation, although no intermediates (*i.e.*, metal–TPP–pyruvate adduct) could be detected. These preliminary studies suggest that the metal–TPP complex acts as a more efficient catalyst toward the decarboxylation of pyruvate than TPP alone.

Introduction

In 1911, Neuberg and Karczaz[1] showed that yeast cells converted pyruvic acid, $CH_3C(O)C(O)OH$, to acetaldehyde and CO_2. The enzyme responsible for this reaction is named pyruvate decarboxylase, and several workers[2] have since shown that this enzyme decarboxylates a variety of other α-keto acids. The activity of the yeast can be destroyed, however, if it is washed with a phosphate buffer at pH 7.8.[3] Activity can be restored if magnesium ions plus an organic cofactor are added to the yeast. This cofactor, named cocarboxylase, was isolated and shown to be the pyrophosphate ester of thiamine (Figure 1).[4]

Other divalent metal ions can be used instead of magnesium to restore activity to the enzyme; those found successful in this respect include Mn(II), Co(II), Cd(II), Ca(II), Zn(II), and Fe(II).[2b,5]

Thiamine pyrophosphate (hereafter referred to as TPP) and divalent metal ions have been found to be necessary for enzyme activity in the carboxylase from

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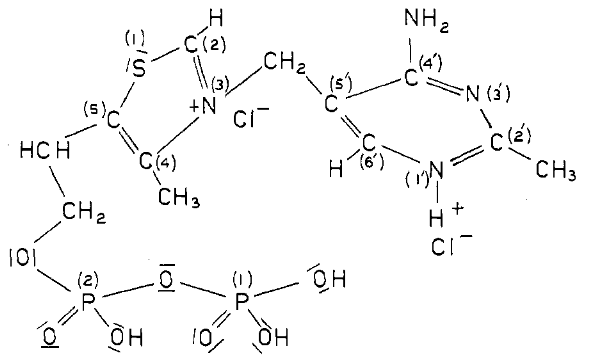

Figure 1.—Structural formula of thiamine pyrophosphate chloride.

wheat germ,[6] *Acetobacter suboxydans*,[7] and in an enzyme isolated from soil bacteria.[8] The function of TPP as a coenzyme in numerous other enzymatic reactions has been reviewed by Metzler.[9] These reactions often involve other coenzymes in addition to TPP and may not require the presence of a divalent metal ion. Only the decarboxylation reaction will be considered in this study.

The present investigation was initiated in order to gain some insight into the interaction between TPP and divalent metal ions. To our knowledge, no metal complexes with TPP have been isolated.

A cobalt(II) complex with the parent vitamin thiamine has been reported by Azizov and Khakimov.[10] The complex, melting at 184°, was found to contain one $CoCl_2$ molecule per thiamine molecule.

Previous studies[11,12] of adenosine triphosphate (ATP, Figure 2) have established that divalent metal ions, such as Mn(II), Co(II), and Ni(II), bind strongly to the phosphate anions. Binding to the adenosine ring by the metal ion has also been suggested as an important contribution to the overall stability of the metal–ATP complex.[11b,e] The exact point of attachment to the adenosine ring is a point of dispute among several workers. Earlier results[11e] indicated that the ring was inclined at an angle over the metal ion, but later data[12] suggested that the metal ion was bound to one nitrogen only. On the basis of ^{31}P and ^{1}H nmr measurements, the average lifetime of the adenosine ring in the primary coordination sphere of the metal ion was identical with the average lifetime of the triphosphate anion.[11d,e] From this the authors concluded that the ATP breaks bonds at both ends of the molecule simultaneously when it exchanges with the uncomplexed ATP.

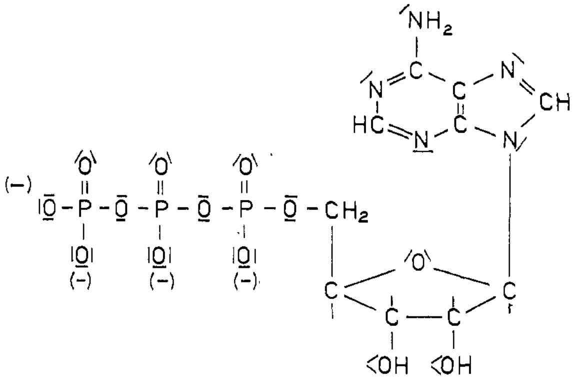

Figure 2.—Structural formula of adenosine triphosphate.

In this paper, we present the results of a ^{1}H and ^{31}P nmr study of the TPP complexes of Ni(II) and Co(II). Temperature studies were conducted in order to determine if any dynamic processes were occurring and to determine $\Delta\omega_i$, the paramagnetic shift of species i. From $\Delta\omega_i$ for Ni(II), an estimate of the hyperfine coupling constant A_i (in hertz) can be calculated from eq 1[13] where ω is the spectrometer frequency (3.76×10^8 radians/sec for protons and 2.54×10^8 radians/sec for phosphorus), k is the Boltzman constant (1.38×10^{-16} erg/deg), T is the absolute temperature, g_{av} and g_N are the Landé splitting factors for the electron and nucleus, respectively, β is the Bohr magneton, and S is the total spin of the system. These data were used to suggest possible binding sites on the ligand where the metal ion is attached. Magnetic moment measurements on the complexes in solution were performed. These results were used to obtain g_{av} in eq 1, and A was calculated from eq 1 for nickel(II) complexes of TPP and compared with data for other Ni(II) complexes.[14]

$$\Delta\omega_m/\omega = -A_i g_{av}\beta_e S(S + 1)/3g_N\beta_N kT \qquad (1)$$

Proton nmr studies were also carried out on solutions of TPP and α-keto carboxylic acids in the absence and presence of metal ion. The concern here was with the evaluation of the extent of metal ion catalysis of the decarboxylation of the α-keto carboxylic acid. It was also of interest to ascertain if a significant interaction of the α-keto carboxylic acid with the metal ion occurred.

Nmr Theory

In radiofrequency spectroscopy, the line shape often depends on relaxation processes which are relatively slow. If the nucleus is involved in some reversible reaction which occurs in a period comparable to the relaxation time, the line shape will be modified.

In the system to be studied, the reaction is the reversible exchange of ligands between the first coordination shell of a metal ion and the uncomplexed ligands. Following conventional notation,[11c,15] we will designate the two environments m and o, respectively. The magnetic resonance behavior of the nuclei in the m and o environments is characterized by the spin–spin and spin–lattice relaxation times T_{2m}, T_{2o}, T_{1m}, and T_{1o}. The average residence time in the m environment, τ_m, divided by the average residence time in the bulk phase, τ_o, is proportional to the ratio of the respective molar concentrations [coordinated ligand]/[ligand], and we have designated this quotient as f. This is only true for dilute solutions, *i.e.*, $f \ll 1$. Rigorously, f is equal

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to $\tau_m/(\tau_m + \tau_o)$, but in systems of interest to us, $\tau_o \gg \tau_m$.

For dilute solutions of paramagnetic ions, Swift and Connick[16] have considered both relaxation and chemical shift effects upon the experimentally observed relaxation times and have carried out a rigorous solution of the Bloch equations, as modified by McConnell[17] for chemical exchange. The following adoption of the equations of Swift and Connick[16] will be used

$$1/T_2 = 1/T_{2o} + f/\tau_m \qquad (2)$$

which is valid in the slow-exchange region and

$$1/T_2 = 1/T_{2o} + f\tau_m\Delta\omega_m^2 \qquad (3)$$

which is valid in the near fast-exchange region. $1/T_2$ is the transverse relaxation time and is related to the line width at half-height, $\Delta\nu_{1/2}$, $1/T_2 = \pi\Delta\nu_{1/2}$.

The experimental quantity $(1/T_2) - (1/T_{2o})$ contains all relaxation effects arising from the presence of unpaired electrons in the spin system. We shall refer to this quantity as $1/T_{2p}$, in keeping with previous notation.[16] It was also shown[16] that the observed frequency shifts are related to exchange rates. In the slow-exchange region

$$\Delta\omega_{\text{obsd}} = -f\Delta\omega_m[1/(\tau_m^2\Delta\omega_m^2)] \qquad (4)$$

for dilute solutions, $f \ll 1$. The relationship

$$\Delta\omega_{\text{obsd}} = -f\Delta\omega_m \qquad (5)$$

holds for the fast- and part of the near fast-exchange region.

In a typical experimental study, the line width of a ligand resonance is studied over as wide a temperature range as possible; then the solution containing the paramagnetic ion is studied over the same range. The quantity $\log fT_{2p}$ is plotted *vs.* the reciprocal temperature; the slope of the resulting plot indicates what conditions apply to the system. If the slope is positive, the system is in the slow-exchange region. If the slope is negative, the system is in the near fast-exchange region. Finally, if the slope is approximately zero, then there is either no exchange, or exchange is so fast that the line width is unaffected by the paramagnetic metal ion.

If the frequency shift is plotted *vs.* $1/T$, the shape of the plot will reflect the regions of exchange. At low temperatures, τ_m is large, and the quantity $1/\tau_m\Delta\omega_m^2$ will be much less than 1. The observed frequency shift will increase (larger downfield shift) as the temperature is raised because τ_m becomes smaller. Finally, when τ_m becomes very small, the observed frequency shift becomes directly proportional to the contact shift, $\Delta\omega_m$. The upfield shift of the resonance is due to the temperature dependence of $\Delta\omega_m$ (eq 1).

Experimental Section

A. Preparation of Samples.—Thiamine pyrophosphate chloride (A grade) was obtained from Calbiochem, Los Angeles, Calif., and used without further purification. The vitamin was stored under refrigeration at all times to prevent contamination. NaOD was prepared by carefully dissolving freshly cut sodium (J. T. Baker) in D_2O (99.4%, Columbia Organic) under a stream of nitrogen. A solution of the vitamin (0.3 M for ^1H studies and 0.5 M for ^{31}P studies) was freshly prepared for each run with the pH adjusted to the range 6.8–7.5 using pH Hydrion paper. Under no circumstances was the pH allowed to rise above 8.0. This minimized the possibility of cleaving[18] the thiazole ring. Half of the TPP solution was used to measure T_{2o}. The metal ion was added to the other half of the solution and this solution was used to measure T_2. D_2O solutions of metal ions were prepared by weighing out appropriate quantities of the anhydrous metal chlorides (prepared from the hexahydrates by heating) to form a stock solution and adding them to volumetric flasks to obtain the desired molarity. For ^{31}P measurements, the metal concentrations ranged from 5×10^{-4} to 10^{-3} M. For ^1H measurements, the metal concentrations ranged from 10^{-2} to 10^{-1} M and ligand concentrations were approximately 0.5 M. Particular care was taken to exclude oxygen from the cobalt solutions, although no apparent oxidation occurred during any of the runs.

B. Recording of Spectra.—Proton magnetic resonance spectra were recorded at 60 MHz on a JEOLCO C-60H or a Varian A-56/60 using a Varian V-6040 variable-temperature controller. Temperatures were measured using an Assembly Products iron–constantan thermocouple. The temperature was measured before and after each spectrum was recorded. Generally, the temperature was raised slowly, recording line widths at selected intermediate temperatures. The temperature was lowered after reaching the maximum temperature, and the previously measured line widths were checked. No appreciable decomposition was observed unless the temperature was held at 100° for an extended period of time. However, over 24 hr, new resonances appeared in the ^1H nmr indicating some decomposition. Therefore, all samples were freshly prepared and never subjected to temperatures over 90° for an extended period of time.

Phosphorus magnetic resonance spectra were recorded at 40.5 MHz in a field of 23,487 G on a Varian HA-100. Variable-temperature studies were carried out on the HA-100 using a Varian V-6040 variable-temperature controller. Temperatures were measured using the same thermocouple arrangement used in the proton studies. Calibration of the phosphorus spectra was accomplished by switching the observing side-band frequency to a new frequency after recording the initial spectrum. The second frequency was provided by a Hewlett-Packard 200-ABR audio oscillator.

Magnetic susceptibilities were determined by the method of Evans.[19] The procedure followed has been previously reported.[20] Corrections were made for the diamagnetic susceptibilities of the ligands and anions using Pascal's constants.

Visible spectra were obtained with a Cary 14 recording spectrometer using 1-cm quartz cells at room temperature.

Results and Discussion

The ^{31}P and ^1H nuclear magnetic resonance spectra of thiamine pyrophosphate in dilute solutions of Co(II) and Ni(II) ions in D_2O have been recorded over the range 0–100°. The pH remained constant in the range 6.8–7.5. Recorded spectra are simulated in Figure 3. The ^1H nmr spectrum of TPP has been previously recorded by several workers,[12,21] and the simulated spectrum appears in Figure 3a. Dioxane was used as the internal standard, and the assignment of the spectrum is relatively straightforward. The resonance at low field (τ 2.1 ppm) is assigned to the 6′ proton of the pyrimidine ring on the basis of its chemical shift being similar to that observed in methylpyrimidine[22] (1.4 ppm) and on the basis of an integrated area corresponding to one proton. The resonance at 4.7 ppm is assigned to the 5′ methylene group that connects the pyrimidine group to the thiazole ring on the basis of its integrated area (2 protons) and a chemical shift similar to that of the *N*-methylthiazolium cation[23] (5.7 ppm).

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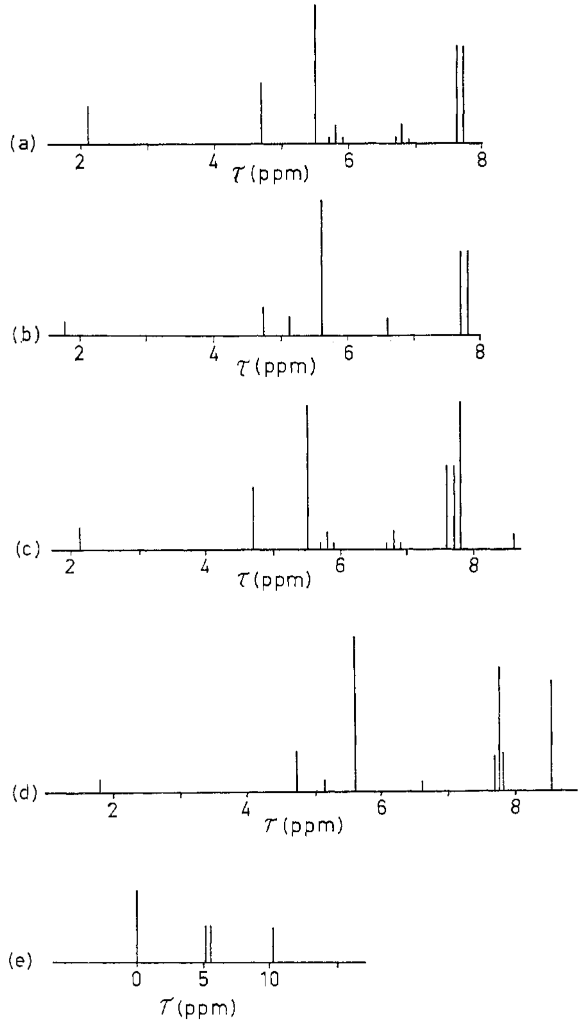

Figure 3.—Simulated nmr spectra: (a) proton nmr spectrum of TPP; (b) proton nmr spectrum of TPP and Co(II); (c) proton spectrum of TPP and pyruvate; (d) proton spectrum of a solution of TPP, pyruvate, and Co(II); (e) ^{31}P spectrum of TPP relative to 85% H_3PO_4.

The resonance at 5.5 ppm is due to D_2O molecules that have been protonated by exchange. The resonance at 5.8 ppm is assigned on the basis of shift and area to the 5-methylene group closest to the oxygen atom, while the upfield resonance at 6.8 ppm is assigned to the methylene group closest to the thiazole ring. Previously workers have observed resonances at 5.98 ppm for the $-CH_2-O-$ moeity[24] and at 7.25 ppm for a methyl group attached to a carbon of the thiazolium ring.[23] The resonances at high field (7.6 and 7.7 ppm) are assigned to the 4-CH_3 and 2′-CH_3 groups, respectively, on the basis of integrated area (3 protons) and chemical shift (7.35 ppm) for methyl groups on a pyrimidine ring[21] and 7.30 ppm for a methyl group on a thiazolium ring.[23,25] Because of the small chemical shift differences between the methyl groups, the assignment of the methyl resonances is not unequivocable and could be reversed. Results from our studies with paramagnetic ions, however, suggest that this assignment is correct, *vide infra*. These assignments are in agreement with those of earlier workers investigating thiamine. The assignment of the methylene groups at the 5 position is unambiguous; in TPP, these are broad peaks with unresolved fine structure from proton and phosphorus spin–spin splitting, but when the pyrophosphate group is hydrolyzed, the resulting $-CH_2-CH_2-OH$ group shows the expected triplet–triplet pattern with chemical shifts of 6.1 and 6.75 ppm, respectively.

The ^{31}P nmr spectrum of TPP has not previously been recorded, and the simulated spectrum appears in Figure 3e. The chemical shifts were measured relative to 85% phosphoric acid. The upfield resonance is assigned to the P(2) phosphorus (Figure 1) on the basis of its chemical shift (10.17 ppm) being similar to that observed[11a] for the P(2) resonance in adenosine diphosphate ADP (11.1 ppm). The resonance at 5.48 ppm thus belongs to the P(1) phosphorus nucleus, and similar chemical shifts have been observed[11a] for the P(1) phosphorus of ADP (6.3 ppm). The difference in chemical shifts between the two phosphorus nuclei is due to the increased shielding of the methylene group attached to one of the oxygen atoms.

Further proof of the assignment of the ^{31}P nmr spectra can be obtained from the fine structure of each resonance. The low-field resonance is split into a doublet, with $J = 20$ Hz; the upfield resonance is a broad multiplet. The terminal phosphorus nucleus, P(1), interacts only with the P(2) phosphorus, since any other nucleus with $I = {}^1/_2$ is too far removed. The splitting of the P(1) resonance, 20 Hz, can be assigned to –P–O–P– coupling. Similar splittings have been recorded[11,26,27] for other systems involving the –P–O–P– linkage. The upfield resonance is also split by this interaction with the other phosphorus and, in addition, is further split by the adjacent methylene protons. This additional interaction[28] of about 10 Hz results in a multiplet of a doublet of triplets and is unresolvable because the line widths of the components are greater than the splittings. Before proceeding with the interpretation of the nmr spectra of the metal complexes of TPP, we shall describe the temperature dependence of the spectra.

The Ni–TPP System. (a) ^1H Nmr of the 6′-H Proton.—The measured values of fT_{2p} for the 6′-H proton of TPP are shown in Figure 4. Two independent runs were made differing only in solution concentrations. The line widths were recorded as the temperature was increased, and as the temperature was lowered, the line widths were checked against the previously recorded values. No appreciable immediate dissociation of the ligand was noted although heating accelerated the eventual decomposition of the ligand. In addition, no appreciable concentration dependence was noted for fT_{2p}. The temperature dependence of the isotropic shift of the 6′ proton is shown in a plot of $\Delta\omega/f$ in Figure 5. Both Figures 4 and 5 reflect the transitions between the various regions of exchange. In Figure 4, the line width begins to broaden about 0°, assumes its maximum breadth at 30°, and continues narrowing until 80°. At temperatures higher than 80°,

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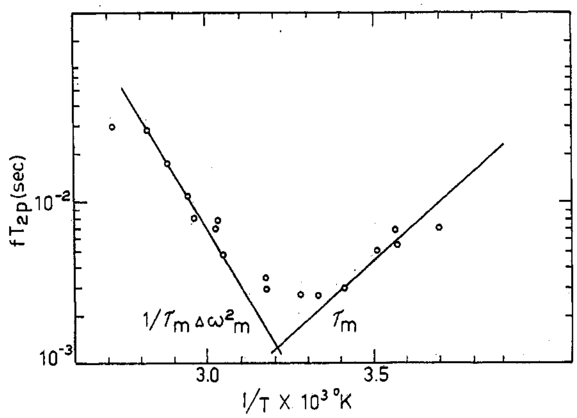

Figure 4.—Log plot of the temperature dependence of the line width of the 6′-H proton in the presence of Ni(II). [Ni(II)] = 0.0776 *M*; [TPP] = 0.45 *M*.

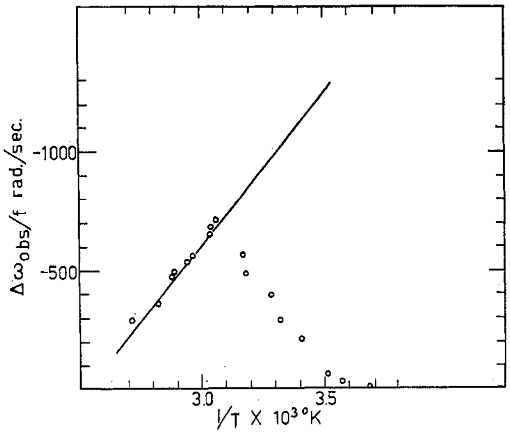

Figure 5.—Frequency shift *vs.* temperature of the 6′-H proton of TPP in a D_2O solution of Ni(II). [Ni(II)] = 0.0776 *M*; [TPP] = 0.45 *M*.

the line width begins to level off. In the region between room temperature ($(1/T) \times 10^3 = 3.3$) and 0° ($(1/T) \times 10^3 = 3.6$), the values of log (fT_{2p}) *vs.* $1/T$ can be fitted to a straight line, from which τ_m can be obtained, $\tau_m = 2.1 \times 10^{-1}$ sec. This region corresponds to the "slow-exchange region." For temperatures higher than 55° ($(1/T) \times 10^3 = 3.05$), the values of log (fT_{2p}) *vs.* $1/T$ can be fitted to a straight line. This region is the so-called "near fast-exchange region" where $fT_{2p} = 1/\tau_m\Delta\omega_m^2$.

The plot of isotropic shift *vs.* $1/T$ (Figure 5) shows a distinct change in slope at 55°. Below 55°, the observed shift increases from 0 to about 700 radians/sec. Above 55°, the observed shift assumes a linear relationship with $1/T$. Below 55°, the observed shift is proportional not only to $f\Delta\omega_m$ but also to the exchange time, τ_m. Since the factor $1/\tau_m^2\Delta\omega_m^2$ is considerably less than 1, the observed isotropic shift is reduced. Above 55°, the observed shift is proportional to $\Delta\omega_m$ only. The small temperature dependence of $\Delta\omega_o$ follows from the temperature dependence of the isotropic shift, which makes up the major part of $\Delta\omega_m$. The extrapolated value of $\Delta\omega_m$ is 1040 radians/sec at 30°.

Finally, if we plot values of ln ($\tau_m kT/h$) *vs.* $1/T$, the slope of the plot will be equal to $\Delta H/R$, and the intercept will be equal to $-\Delta S/R$. This has been done for the Ni–TPP system, and the results are $\Delta H^{\ddagger} \approx 8$ kcal/mol and $\Delta S^{\ddagger} \approx -2$ eu. These results are similar to those observed for other systems containing the Ni(II) ion in octahedral environment.[29]

(b) ^{31}P Nmr of the Pyrophosphate Group of TPP.—The measured values of fT_{2p} for the two phosphorus nuclei in the pyrophosphate side chain of TPP are shown in Figure 6. Both nuclei are plotted on the same graph due to the shortage of data. The line width broadened as the temperature was raised to 60° at which temperature both resonances disappeared into the base line. Below room temperature, the P(1) resonance was a broadened doublet. As the temperature was raised, the doublet coalesced into a singlet at room temperature (30°). The P(2) nucleus remained an unresolved multiplet at all temperatures.

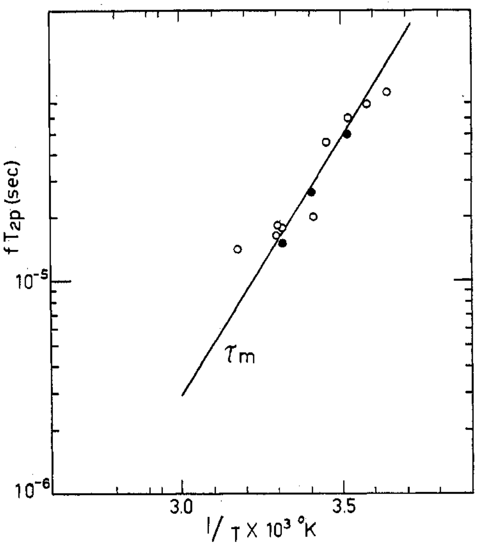

Figure 6.—Log plot of the temperature dependence of the line width of the phosphorus nuclei of TPP in D_2O Solution of Ni(II): ○, P(1); ●, P(2). f = [Ni(II)]/[TPP] = 0.0016.

The calculation of the line width for the phosphorus resonance is complicated by the presence of a spin–spin splitting by the other phosphorus nucleus. If the nucleus under observation is involved in a spin–spin interaction with another nucleus, while at the same time being relaxed by a paramagnetic metal ion, the transverse relaxation time will be affected by the exchange time of the nuclear spin states, τ_o, as well as by the exchange lifetime of the ligand in the primary coordination sphere of the metal, τ_m. If τ_m is shortened appreciably, the coupling of the nuclear spin states will disappear because each nucleus sees only an average field associated with the other nucleus.[30,31] Relaxation by the paramagnetic metal ion is effectively decoupling the nuclei from each other. This phenomenon, known as chemically induced spin decoupling or chemical-exchange spin decoupling, has been observed by previous workers.[32–34]

No appreciable concentration dependence was noted during the line width studies, so we presume we are

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(29) See Table I in ref 15 for a compilation of kinetic parameters concerning Co(II) and Ni(II) ions.

(30) V. Royden, *Phys. Rev.*, **96**, 543 (1954).

(31) A. L. Bloom and J. N. Shoolery, *ibid.*, **97**, 1261 (1955).

(32) B. B. Wayland and R. S. Drago, *J. Amer. Chem. Soc.*, **87**, 2372 (1965).

(33) R. W. Kluiber and W. D. Horrocks, *ibid.*, **88**, 1399 (1966).

(34) L. S. Frankel, *J. Chem. Phys.*, **50**, 943 (1969).

dealing with first-order exchange, but coupling problems prevent an accurate evaluation of the exchange parameters. A very crude value of τ_m for both nuclei at 30° is found to be 2×10^{-5} sec (Figure 6). A rough estimate of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can be given ($\Delta H^{\ddagger} = 10$ kcal/mol, $\Delta S^{\ddagger} = -3$ eu) and the additional broadening due to exchange between spin states is about 3 cycles at room temperature.

The Co-TPP System. (a) ^{1}H Nmr of the 6′-H Proton.—The measured values of fT_{2p} for the 6′-H proton with cobalt(II) are shown in Figure 7. The line width narrows upon raising the temperature and then assumes a constant value at temperatures higher than room temperature. The observed variation of line width below room temperature is characteristic of a spin system in the near fast-exchange region. The relation $fT_{2p} = 1/\tau_m\Delta\omega_m^2$ (eq 3) is consistent with the frequency data obtained in the same region (Figure 8). Above room temperature, the data fit the equation $fT_{2p} = T_{2m}$ (eq 2). The exchange time at room temperature may be calculated from eq 3 if the frequency shift at that temperature is known. The value obtained for τ_m is 1.2×10^{-4} sec. For temperatures above room temperature, T_{2m} is calculated to be 3×10^{-2} sec. The isotropic shift at room temperature $\Delta\omega_m$ is observed to be 570 radians/sec.

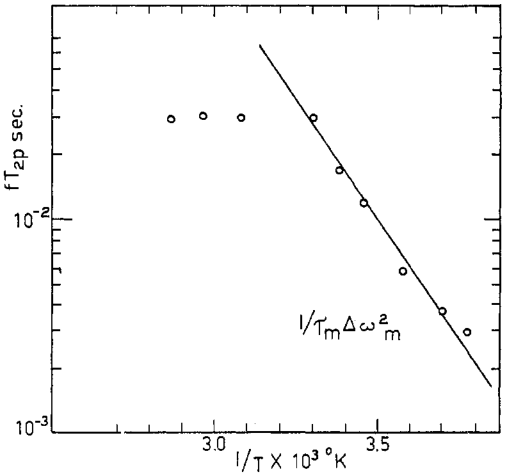

Figure 7.—Log plot of the temperature dependence of the line width of the 6′-H proton of TPP in a D_2O solution of Co(II). [Co(II)]/[TPP] = 0.189.

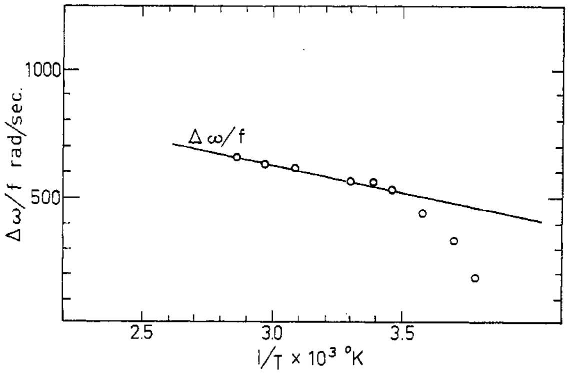

Figure 8.—Temperature dependence of the chemical shift of the 6′-H proton in TPP in a D_2O solution of Co(II). [Co(II)]/[TPP] = 0.189.

It should be noted that the plot of observed shift *vs.* $1/T$ for the proton in the Co-TPP system does not assume a positive slope and decrease with increasing temperature as that for the Ni-TPP system did. With the information available, we cannot rationalize this behavior and this further supports our decision to make only semiquantitative use of our kinetic data.

(b) The ^{31}P Nmr of the Pyrophosphate Group of TPP.—The measured values of fT_{2p} for P(1) and P(2) of the pyrophosphate group of TPP are shown in Figure 9. The frequency shifts *vs.* $1/T$ are shown in Figure 10. The line widths were determined for each peak of the doublet of resonance P(1) by techniques similar to that used in the Ni(II) system for temperatures below 15°. Above 15°, the resonances were broadened by exchange mechanisms. Above 40°, the exchange rate had become very rapid, and the system entered the near fast-exchange region. As before, coupling problems preclude our obtaining accurate rate data and the curves presented mainly summarize our spectral observations.

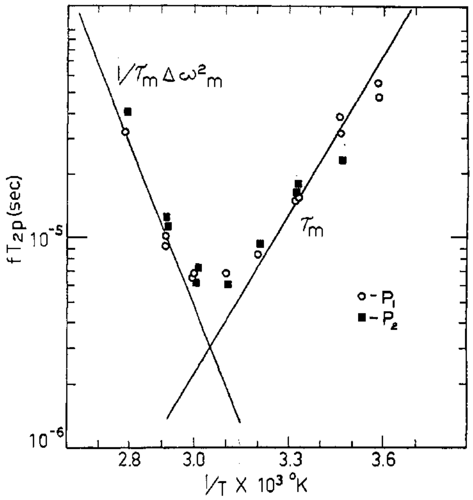

Figure 9.—Log plot of the temperature dependence of the line width of the phosphorus nuclei in TPP in D_2O in the presence of Co(II). [Co(II)]/[TPP] = 0.00156.

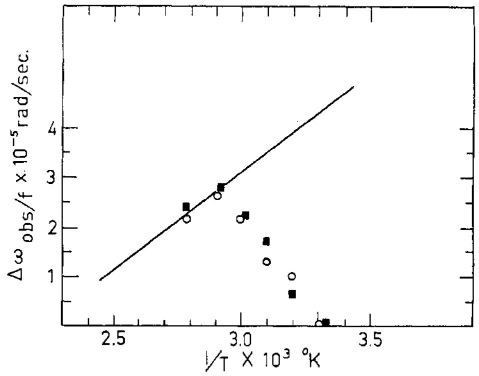

Figure 10.—Temperature dependence of the chemical shift of the phosphorus nuclei in TPP in D_2O solutions of Co(II): O, P(2); ●, P(1). [Co(II)]/[TPP] = 0.00156.

Apparently, the values of τ_m for both phosphorus nuclei, 1.65×10^{-5} sec, are similar as are the isotropic shifts at room temperature (4.3×10^{5} radians/sec). Crude thermodynamic data for the first-order exchange are $\Delta H^{\ddagger} \approx 10$ kcal/mol and $\Delta S^{\ddagger} = -0.4$ eu.

Summary of the Temperature Studies.—Our proposed model for the metal complex involves a 1:1 complex between the TPP and the metal ion. The metal ion binds to the pyrimidine ring and to the pyrophosphate group. The binding at the pyrophosphate group occurs through the oxygen atoms, and since both phosphorus nuclei have equal exchange lifetimes and equal chemical shifts, the central metal ion probably binds to an oxygen atom on each phosphorus. Our data, however, cannot distinguish between the chelate model proposed above and a situation where the metal ion is rapidly exchanging between both oxygen atoms and not bound to both simultaneously.

The effect of the metal binding to the oxygen atoms is most pronounced in the chemical shift of the phosphorus atom. Unpaired spin from the metal d orbitals is introduced into the TPP molecular orbitals *via* overlap of the d orbitals with p orbitals on the oxygen atom. At the phosphorus atom, the unpaired spin enchances the local field around the nucleus, and the net applied field is reduced.[35] The immediate result is that the resonance shifts to low field.

For the Ni(II) complex, we may estimate the isotropic hyperfine coupling constant, A, for the 6′-H proton and the phosphorus nucleus. (The huge nonzero intercept in an extrapolation of $\Delta\omega_m$ *vs.* $1/T$ to zero leads to potential sources of error in the absolute magnitude.) The results (+0.34 MHz for the 6′-H proton and 8 MHz for the phosphorus nucleus) suggest that considerable unpaired spin density is transmitted to the TPP ligand by the metal ion. The sign of the coupling constant, positive in both cases, is related to the direction of the chemical shift, downfield in both cases, while the magnitude of the coupling constant is related to the magnitude of the frequency shift.

Binding to the Pyrimidine Ring.—The binding site to the pyrimidine ring can be at one of three positions (Figure 1): the 1′ or 3′ ring nitrogen or the 4′-amino nitrogen. To determine which nitrogen was the donor atom, isotropic shifts were determined for the protons of TPP at several different metal:ligand ratios. The results are shown in Table I.

TABLE I

^{1}H CHEMICAL SHIFTS (Hz) FOR M^{II}–TPP COMPLEXES[a]

f[b]	6′-H	2′-CH_3	5′-CH_2	4-CH_3	5-CH_2	5-$CH_2$$\mathit{CH}_2$–
$M^{II} = Co^{II}$						
0.189	−16	+9	+5	+6	−18	−60
0.37	−26	+18	+10	+10	−26	−100
0.55	−46	+21	+13	+14	−40	−140
1.0	−60	+27	+12	+18	...[c]	−169
$M^{II} = Ni^{II}$						
0.178	−18	+1	−1	+2	−4	...[c]
0.355	−46	+2	−3	+4	−10	...[c]
0.53	...[d]	+1	−6	+8	...[c]	...[c]

[a] Chemical shifts in D_2O at pH 7 relative to dioxane standard. [b] Mole fraction M(II):TPP. [c] Resonance obscured by another. [d] Too broad to assign shift.

Large downfield shifts are observed for the 5-CH_2– and 5-CH_2CH_2– protons. These shifts are consistent with our previous interpretation of the phosphorus nmr.

In the Co–TPP complex, a downfield shift is observed for the 6′-H and upfield shifts for the 2′-CH_3, 5′-CH_2, and 4-CH_3 protons. In the Ni–TPP complex, downfield shifts are observed for the 6′-H and 5′-CH_2 protons, and upfield shifts for the 2′-CH_3 and 4-CH_3 protons (*cf.* Figure 3b).

Previous studies[36] have shown that cobalt(II) bound to an aromatic nitrogen heterocycle causes a large downfield shift at the ortho position for a proton, a small upfield shift at the ortho position for a methyl group, and small upfield shifts for meta and para methyl groups. Protons in the para position have been observed to shift upfield.[37] When nickel(II) is substituted for cobalt(II), small downfield shifts are observed for meta groups and a proton in the para position. The shifts at other positions are essentially unchanged. Nickel bound to the amino group in a series of substituted anilines[38] causes equal shifts at the meta position for both a proton and a methyl group. In the case of the proton, the shift is to downfield; in the case of the methyl group, the shift is upfield.

Reference to Figure 1 will show that the complex most consistent with the above data is one in which the 1′ nitrogen on the pyrimidine ring is involved in bonding. Binding in the 3′ position is unlikely since the 6′-H proton would have to shift upfield in the Co(II) complex. The binding site at the amino group can be eliminated since the shifts for the meta proton and methyl group in the Ni(II) complex are not equal, or nearly so. Further confirmation of our model comes from studies made with space-filling models. TPP can be "wrapped" around a metal ion without bond straining only if the 1′ nitrogen is pointing toward the metal ion. Attempts to rearrange TPP so that the 3′ nitrogen or the 4′-amino group pointed toward the metal ion were unsuccessful without serious interaction between the amino group and the thiazole ring.

A rigorous interpretation of the mode of interaction between the pyrimidine nitrogen and the metal ion cannot be made. The observed shifts are much smaller than those expected for a fully coordinated species. In $Ni(C_5H_5N)_6^{2+}$, for example,[37] the α, β, and γ protons were observed to shift −3820, −1420, and −445 Hz downfield, respectively. A 5800-Hz shift was observed[12] for the 8-H in adenosine coordinated to bis(acetylacetonato)nickel(II). Thus, much larger shifts are expected for a coordinated pyrimidine fragment. If the pyrimidine is in the first coordination sphere of the nickel(II), it must be in rapid equilibrium with a large mole fraction of complex in which the pyrimidine is not coordinated but in which water is occupying this coordination position. Alternately, the combination of a large ligand field from the coordinated phosphate and possible ring constraints could lead to a weak bond (long distance) to pyrimidine and small contact shifts. The similarity in the magnitude of the shift and half-width of the resonance of TPP and ATP is suggestive of similar modes of interaction. In this latter system, it has been suggested[12] that the pyrimidine nitrogen interacts by hydrogen bonding to a water molecule which is coordinated to the metal ion. In other hydrogen-bonding systems[39] involving $CHCl_3$ and $Co(C_6H_5)_3P)I_3^-$, the sign of the spin density changes in the hydrogen bond; *i.e.*, α spin on the complex gives rise to β

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(35) At constant frequency, $H_{\text{nuc}} = H_{\text{appl}} + H_{\text{loc}}$.

(36) J. A. Happe and R. L. Ward, *J. Chem. Phys.*, **39**, 1211 (1963).

(37) R. E. Cramer and R. S. Drago, *J. Amer. Chem. Soc.*, **92**, 66 (1970).

(38) R. W. Kluiber and W. D. W. Horrocks, Jr., *Inorg. Chem.*, **6**, 430 (1967).

(39) M. F. Rettig and R. S. Drago, *J. Amer. Chem. Soc.*, **88**, 2966 (1966).

spin at the proton. However, this is not entirely analogous to the nickel–ATP system and, though suspect, this structure cannot be eliminated for the TPP complex. It should be emphasized that if water is involved either *via* a metal-coordinated water–hydrogen bond or a competitive equilibrium, the nature of the complex observed in aqueous solution could be very different from that of the complex formed between the protein and the coenzyme. In the latter case, conditions are expected to be much more hydrophobic, drastically reducing the effective water concentration. These studies cannot resolve the above possibilities.

Magnetic Moment Results.—We have proposed that TPP complexes with metal ions in solution. Presumably, the free positions in the primary coordination sphere of the metal are occupied by D_2O (or HDO) molecules. Indeed, small chemical shifts are observed for the HDO resonance when metal ions are added to D_2O solutions of TPP. These shifts have been interpreted[40] as resulting from delocalization of unpaired spin density from the metal ion to the HDO ligand.

The effective magnetic moments μ_{eff} of the TPP complexes were determined by the Evans method.[25] The results have been summarized in Table II. The observed magnetic moment of the Ni(II) complex is 3.26 BM and of the Co(II) complex is 5.15 BM. Typical experimental values of μ_{eff} for octahedral Ni(II) complexes range between 2.8 and 3.3 BM, while for Co(II) complexes, μ_{eff} ranges between 4.8 and 5.2 BM. Tetrahedral complexes of Ni(II) have μ_{eff} between 3.3 and 4.0 BM, while tetrahedral complexes of cobalt have moments between 4.1 and 4.8 BM.[41] An unequivocal assignment of the local symmetry about the metal ion cannot be made on the basis of magnetic moment data alone. However, visible spectra of the complexes in solution suggest[42] that the metal ion is six-coordinate.

TABLE II

MAGNETIC MOMENT DATA

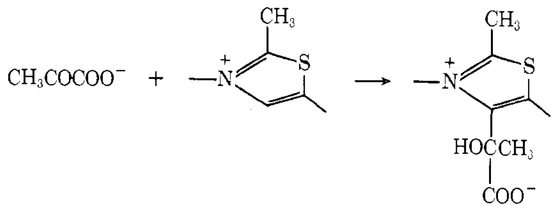
Compd	$\Delta\nu^a$	χ_c^b	χ_d^c	χ_m^d	μ_{eff}^e	g_{av}^f	g_{av}^g
$NiTPP \cdot 3D_2O$	40.0	4,140	200	4,340	3.26	2.31	2.26
$CoTPP \cdot 3D_2O$	35.6	10,300	200	10,500	5.15	2.56	2.93

[a] Frequency shift of the dioxane resonance in hertz. [b] Molar susceptibility of the complex in 10^6 ml/mol. [c] Molal susceptibility of the ligand and anions in 10^6 ml/mol. [d] Calculated from the equation $\chi_m = \chi_c + \chi_d$. [e] Calculated from the equation $\mu_{\text{eff}} = 2.84\sqrt{\chi_m T}$, where T is the absolute temperature of the solution in degrees Kelvin. [f] Calculated from the equation $\mu_{\text{eff}} = g_{\text{av}}\sqrt{S(S+1)}$, where S is the total spin of the metal ion ($^3/_2$ for Co(II) and 1 for Ni(II)). [g] Calculated from the equation $g_{\text{av}} = 2(1 - 4k^2\lambda_0/10Dq)$, where k is the orbital reduction factor (0.92 for Ni(II)), λ_0 is the spin–orbit coupling constant (-315 cm^{-1} for Ni(II)), and $10Dq = 8300$ cm^{-1} for Ni^{II}TPP in D_2O. For Co^{II}TPP, g_{av} was calculated from the equation $g_{\text{av}} = {}^1/_{15}(3g_{\parallel} + 4g_{\perp})(g_{\parallel} - g_{\perp})$ taken from ref 35. $g_{\parallel} = 2$ and $g_{\perp} = 4$ (see text and R. Breslow, *J. Amer. Chem. Soc.*, **79,** 1762 (1957); **80,** 3719 (1958)).

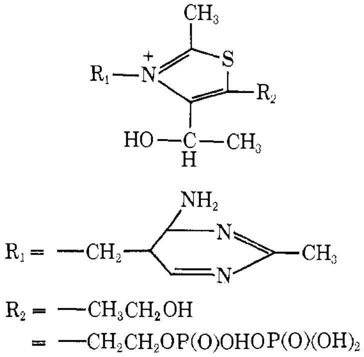
Nmr Studies of the Catalytic Decarboxylation of Pyruvate.—We have proposed that TPP forms a tridentate complex with a metal ion, and presumably in enzymatic systems, the remaining sites are occupied by enzyme substituents (such as histidine, carboxylic acid anion, etc.). The mechanism for the catalytic decarboxylation of pyruvate by TPP in the presence of carboxylase enzyme

$$H^+ + CH_3COCOO^- \xrightarrow[\text{TPP}]{\text{enzyme}} CH_3CHO + CO_2$$

became apparent when Breslow[43] found that the 2 proton on the thiazolium ring exchanged readily with D_2O at room temperature and pH 7.0. He proposed that pyruvate formed an adduct with the thiazolium carbanion after the proton was ionized



and, subsequently, the adduct eliminated CO_2. The product, α-hydroxyethylthiamine diphosphate, can either hydrolyze the hydroxyethyl substituent off



or form a carbanion at the α carbon of the hydroxyethyl group and react again with pyruvate to form α-acetolactate, $CH_3COC(COO^-)OHCH_3$. The hydroxyethylthiamine compound has been isolated,[44] and its nmr spectrum examined.[45] As expected, the α carbon of the hydroxyethyl substituent exchanges slowly with D_2O at pH 8.1.

The decarboxylation reaction also proceeds slowly in the absence of an enzyme. We were interested in following the nonenzymatic reaction *via* nuclear magnetic resonance to see if our model system functioned so as to catalyze decarboxylation of pyruvate.

The preliminary results are shown in Figure 3c. The ^1H nmr of CH_3COCOO^- consists of a resonance at τ 7.8 due to the methyl group and a very small peak at τ 8.7 due to the methyl group of hydrated pyruvate.[46] The concentration of the hydrated form is small enough so that its nmr spectrum essentially is nonexistent. Pyruvate in the presence of TPP undergoes decarboxylation and a new resonance appears at τ 8.7. The intensity of the pyruvate resonance at τ 7.8 decreases as the intensity of the resonance at τ 8.7 increases. After

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(40) C. C. McDonald and W. D. Phillips, *J. Amer. Chem. Soc.*, **85,** 3737 (1963).

(41) B. N. Figgis, "Introduction to Ligand Fields," Interscience, New York, N. Y.

(42) Both complexes exhibit weak bands (ε 5–10) characteristic of aqueous metal ion spectra. Tetrahedral complexes have extinction coefficients of 100–500: T. M. Dunn, "Modern Coordination Chemistry," Interscience, New York, N. Y., 1960.

(43) R. Breslow, *J. Amer. Chem. Soc.*, **79,** 1762 (1957); **80,** 3719 (1958).

(44) L. O. Krampitz, I. Suzuki, and G. Greull, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **20,** 971 (1961).

(45) J. J. Mieyal, R. G. Votaw, L. O. Krampitz, and H. Z. Sable, *Biochim. Biophys. Acta*, **141,** 205 (1967).

(46) G. Ojelund and I. Wadso, *Acta Chem. Scand.*, **21,** 1408 (1967).

4 hr, the peak at τ 8.7 is approximately 25% of the height of the peak at τ 7.8. To a fresh solution of TPP and pyruvate, cobalt(II) ion was added, and its spectrum is shown in Figure 3d. The resonance at τ 8.5 is now as large as the resonance at τ 7.7. Previous studies[9,44] of the nonenzymatic systems CH_3COCOO^-–TPP and CH_3COCOO^-–thiamine have shown that pyruvate is decarboxylated and condensed to α-acetolactate, $CH_3COCOH(COO^-)CH_3$, without appreciable accumulation of the intermediate, α-hydroxyethylthiamine pyrophosphate. We can tentatively assign the resonance at τ 8.5 in Figure 3c (τ 8.7 in Figure 3d) to the $CH_3COH(COO^-)$– methyl group and the resonance at τ 7.7 (τ 7.8 in Figure 3d) to the CH_3COCOO^- methyl group and the $CH_3COCOH(COO^-)$– methyl group.

The participation of the metal ion–TPP complex in the decarboxylation reaction is likely since the 6′-H proton exhibits a downfield shift indicating that the TPP is still complexed to the metal ion. No metal ion–TPP–pyruvate complex could be detected in the composited nmr spectrum, but this is consistent with previous studies on these systems.[44] The effect of the metal ion–TPP complex is tentatively to increase production of the α-acetolactate at the expense of the pyruvate. Previous studies[9] did not observe this catalytic effect, but this could have been due to the higher pH at which these studies were carried out.

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CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY,
THE UNIVERSITY OF GEORGIA, ATHENS, GEORGIA 30601

Chalcogen Chemistry. V. Complexes of Organotellurium Trihalides with Tetramethylthiourea[1]

BY KENNETH J. WYNNE* AND PHILIP S. PEARSON

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A series of organotellurium trihalides has been found to give molecular tetramethylthiourea (tmtu) complexes of the general formula $RTeX_3$tmtu, where R = CH_3, C_2H_5; X = Cl, Br, I; R = *p*-$CH_3OC_6H_4$; X = Cl. These are moisture-sensitive, crystalline solids which appear to be monomeric in organic solvents such as chloroform and nitrobenzene. Square-pyramidal coordination around tellurium with an apical organo group and tmtu coordinated through sulfur is proposed for these complexes and is consistent with our infrared spectral data.

Introduction

In a recent communication we described the preparation of a new class of five-coordinate tellurium compounds.[2] We began our investigation into this area in order to test the applicability of a bonding theory we have proposed to explain structural variations observed in chalcogen and organochalcogen(IV) halides.[1a] Our approach led to the prediction that the central atom in an organochalcogen trihalide should exhibit a limiting coordination number (CN) of five, achieved in the solid state by halogen bridging. To test whether organotellurium trihalides could act as acceptors and to determine whether the nature of this interaction would be consistent with our predictions, we examined the reactions of a variety of organotellurium trihalides with tetramethylthiourea (tmtu). Our results are reported below.

Experimental Section

General Data.—Due to the moisture sensitivity of the compounds prepared in this study, all preparations and handling operations were carried out in a dry atmosphere achieved through the use of dry nitrogen filled polyethylene glove bags.

Spectra.—Infrared spectra were obtained using Perkin-Elmer Model 621 and Beckman IR-11 spectrophotometers. Far-ir solution spectra were recorded on samples in 0.5- or 3.0-mm polyethylene cells. Solids were run as freshly prepared Nujol mulls between polyethylene plates in the 33–500-cm^{-1} region and on AgCl plates in the 500–4000-cm^{-1} region. Proton nuclear magnetic resonance data were obtained using a Perkin-Elmer Hitachi Model R-20 spectrometer. Chemical shifts were measured *vs.* internal tetramethylsilane.

Chemicals.—Tetramethylthiourea (Eastman) was recrystallized from anhydrous ethyl ether prior to use. Reagent grade nitrobenzene was used directly after storage over Linde 5A Molecular Sieves, which had been previously heated *in vacuo* at 300° for 24 hr. All other solvents were distilled from P_2O_5 and stored over molecular sieves.

Methyltellurium trichloride[1a] and tribromide,[3] ethyltellurium trichloride,[1d] and *p*-methoxyphenyltellurium trichloride[4] were prepared by reported procedures. The preparation of new organotellurium trihalides or those prepared in a manner different from that found in the literature is outlined below.

Methyltellurium Triiodide.—This compound was prepared by adding $(CH_3)_2Te_2$[3,5] (5.0 g, 17.5 mmol) in 50 ml of CH_2Cl_2 to a solution of I_2 (15.0 g, 60.0 mmol) in 100 ml of CH_2Cl_2. Methyltellurium triiodide (14.0 g, 76.5% yield) precipitated as a violet powder, mp 175–178°, lit.[6] mp 180°. *Anal.* Calcd for CH_3I_3Te: C, 2.30; H, 0.58; I, 72.74. Found: C, 2.26; H, 0.54; I, 72.59. This compound is virtually insoluble in common organic solvents and could not be further purified thus accounting for the poor analytical results.

Ethyltellurium Triiodide.—This compound was prepared by adding $(C_2H_5)_2Te_2$[1d] (5.0 g, 16.0 mmol) in 50 ml of CH_2Cl_2 to a solution of I_2 (13.0 g, 51.0 mmol) in 100 ml of CH_2Cl_2. Cooling

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[1] Parts I–IV, respectively: (a) K. J. Wynne and P. S. Pearson, *Inorg. Chem.*, **9**, 106 (1970); (b) K. J. Wynne, *ibid.*, **9**, 299 (1970); (c) K. J. Wynne, *ibid.*, **10**, 1868 (1971); (d) K. J. Wynne and P. S. Pearson, *ibid.*, **10**, 1871 (1971).

[2] K. J. Wynne and P. S. Pearson, *Chem. Commun.*, 556 (1970).

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