Cancer Res. **1977**, *37*, 2455.
5. Eastman, A.; Bresnick, E. *Biochem. Pharmacol.* **1981**, *30*, 2721.
6. Pasini, A. *Inorg. Chim. Acta* **1987**, *137*, 57.
7. Barnard, C. F. J.; Cleare, M. J.; Hydes, P. C. *Chem. Brit.* **1986**, 1001.
8. Sherman, S. E.; Lippard, S. J. *Chem. Rev.* **1987**, *87*, 1153.
9. Van Kralingen, C. G.; Reedijk, J.; Spek, A. L. *Inorg. Chem.* **1980**, *19*, 148.
10. Chow, S. T.; McAuliffe, C. A. *Prog. Inorg. Chem.* **1975**, *19*, 51.
11. Altman, J.; Wilchek, M.; Warshawsky, A. *Inorg. Chim. Acta* **1985**, *107*, 165.
12. Talebian, A. H.; Bensely, D.; Ghiorghis, A.; Hammer, C. F.; Schein, P. S.; Green, D. *Inorg. Chim. Acta* **1991**, *179*, 281.
13. Gandolfi, O.; Apfelbaum, H. C.; Blum, J. *Inorg. Chim. Acta* **1987**, *135*, 27.
14. Gibson, D.; Rosenfeld, A.; Apfelbaum, H.; Blum, J. *Inorg. Chem.* **1990**, *29*, 5125.
15. Appleton, T. G.; Hall, J. R.; Prenzler, P. D. *Inorg. Chem.* **1989**, *28*, 815.
16. Appleton, T. G.; Berry, R. D.; Hall, J. R.; Sinkinson, J. A. *Inorg. Chem.* **1991**, *30*, 3860.
17. Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 673.
18. Appleton, T. G.; Berry, R. D.; Hall, J. R. *Inorg. Chem.* **1985**, *24*, 666.
19. Appleton, T. G.; Hall, J. R.; Neale, D. W.; Thompson, C. S. M. *Inorg. Chem.* **1990**, *29*, 3985.
20. Jhonson, G. L. *Inorg. Syn.* **1966**, *8*, 242.
21. Hoeschele, J. D.; Farrel, N.; Turner, W. R.; Rithner, C. D. *Inorg. Chem.* **1988**, *27*, 4106.
22. Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Aust. J. Chem.* **1986**, *39*, 1347.
23. Khokhar, A. R.; Lumetta, G. J.; Doran, S. L. *Inorg. Chim. Acta* **1988**, *153*, 129.
24. Khokhar, A. R.; :Lumetta, G. J.; Newman, R. A.; Doran, S. L. *Inorg. Chim. Acta* **1988**, *151*, 249.

^1H NMR Study of Imidazole, L-Histidine, and Their Derivatives Coordinated to the Paramagnetic Undecatungstocobalto(II)silicate and -nickelo(II)silicate Anions

Moonhee Ko, Gyung Ihm Rhyu, and Hyunsoo So*

Department of Chemistry, Sogang University, Seoul 121-742, Korea
Received April 13, 1994

^1H NMR spectra of imidazole, 2- and 4(5)-methylimidazole, histamine, L-histidine, L-histidine methyl ester, N_α-acetyl-L-histidine, and L-carnosine coordinated to the paramagnetic undecatungstocobalto(II)silicate ($SiW_{11}Co$) and undecatungstonickelo(II)silicate ($SiW_{11}Ni$) anions are reported. For these complexes the ligand exchange is slow on the NMR time scale and the pure resonance lines of the free ligand and the complexes have been observed separately at room temperature. Two different complexes are formed, depending upon which nitrogen atom of the imidazole ring is coordinated to the cobalt or nickel ion of $SiW_{11}M$. Thus the NMR spectrum of a D_2O solution containing a ligand and $SiW_{11}M$ consists of three sets of lines originating from the free ligand and two complexes. All NMR lines of the $SiW_{11}Co$ complexes have been assigned unequivocally using the saturation transfer technique. The temperature dependence of some spectra are also reported. The NMR spectra of some complexes show that the internal rotation of the substituent on the imidazole ring is hampered by the heteropolyanion moiety even at room temperature.

Introduction

Recently we have reported the ^1H and ^{13}C NMR spectra of some pyridine-type ligands coordinated to paramagnetic heteropolyanions, $[SiW_{11}O_{39}Co^{II}]^{6-}$ and $[SiW_{11}O_{39}Ni^{II}]^{6-}$.[1] The Co^{2+} or Ni^{2+} ion in the heteropolyanion carries a water molecule which can be replaced by various ligands; see Figure 1. Pyridine-type ligands coordinated to $[SiW_{11}MO_{39}]^{6-}$ ($M=Co^{II}$ or Ni^{II}; denoted as $SiW_{11}M$ hereafter) undergo slow exchange on the NMR time scale, exhibiting NMR lines separated from those of free ligands. The slow exchange allowed us to measure the absolute isotropic NMR shifts directly, and to identify the species formed when bidentate ligands such as pyrazine and 4,4'-bipyridyl reacted with $SiW_{11}Co$.

The isotropic NMR shifts ($=\delta_{complex}-\delta_{free\ ligand}$) in paramagnetic system contain contact and pseudocontact contributions. Contact shifts occur when unpaired electron density is transferred from the metal to the ligand nucleus in question, whereas pseudocontact shifts arise from a through-space dipolar interaction between the electronic and nuclear magnetic moments.[2] The pseudocontact shift is proportional to the geometrical factor, $(3\cos^2\theta-1)/r^3$. Therefore, useful information on the conformation of the ligand may be obtained, if the pseudocontact shifts can be determined from the NMR data.

We have extended this study to imidazole, histidine, and

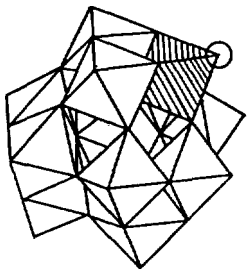


Figure 1. Polyhedral representation of $[SiW_{11}M(H_2O)O_{39}]^{6-}$ (M = Co or Ni). Each octahedron represents a WO_6 or $MO_5(H_2O)$ group. The water molecule coordinated to the Co^{2+} or Ni^{2+} ion is represented by a circle.

their derivatives. Imidazole and histidine are of prime biological importance, and NMR studies of these and their transition metal complexes have been reported by a number of investigators.[3-9] NMR spectra of octahedral cobalt(II) complexes of imidazole and its derivatives were studied.[6] For these complexes the pseudocontact contribution due to the magnetic anisotropy is washed out by rapid dynamic rearrangement of the magnetic axes. Histidine was found to form several different chelates with the Co^{2+} ion.[3]

The heteropolyanion, $SiW_{11}Co$, has advantage over the Co^{2+} ion for studying the complex formation with these ligands. Since the ligand exchange is slow at $SiW_{11}Co$, two different complexes can be identified by NMR. In addition, the magnetic axes in $SiW_{11}Co$ complexes are fixed and the pseudocontact shifts are not washed out. So these heteropolyanions may provide a unique opportunity to get conformational information, if the pseudocontact shifts can be extracted from the measured isotropic shifts. Unfortunately, such analysis is not so easy to carry out, the difficulty arising partly from the sensitivity of the isotropic shifts to the nature of the substituent on the imidazole ring. However, the characteristic NMR spectra of some ligands coordinated especially to $SiW_{11}Co$ may be useful in identifying them in the free state and also in the polypeptides. In this paper we report the ^1H NMR spectra of imidazole, 2-methylimidazole, 4-methylimidazole, histamine, L-histidine (his), L-histidine methyl ester, N_α-acetyl-L-histidine, or L-carnosine coordinated to $SiW_{11}Co$ or $SiW_{11}Ni$.

Experimental

The ligands imidazole, 2-methylimidazole, 4(5)-methylimidazole, histamine, L-histidine, 1-methyl-L-histidine, L-histidine methyl ester, N_α-acetyl-L-histidine, and L-carnosine are commercially available. $K_6[SiW_{11}Co(H_2O)]\cdot nH_2O$ was prepared according to the method of Simmons.[10] The pH of solutions was adjusted by stirring in small amounts of D_2O solutions of H_2SO_4 or NaOD. The pH values of D_2O solutions are given as uncorrected pH meter readings.

^1H NMR spectra were obtained in the Fourier-transform mode with Varian Gemini-300 and -200 spectrometers equipped with a broad band, narrow-bore probe. NMR measurements were made at ambient temperature (22-25℃), and temperature dependence of some spectra were studied at 0-60℃. The residual water resonance in each spectrum was saturated by irradiation with a single radiofrequency pulse which was gated off during acquisition. For a typical experiment 90° pulses (11 μs) were used and the acquisition time was 0.5 s with the pulse repetition time of 1.5 s. A total of 512 transients was accumulated. The spectral width was 25000 Hz and the line-broadening factor used in exponential apodization was 5 Hz. Sodium salt of 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid (TSP) was used as an internal reference.

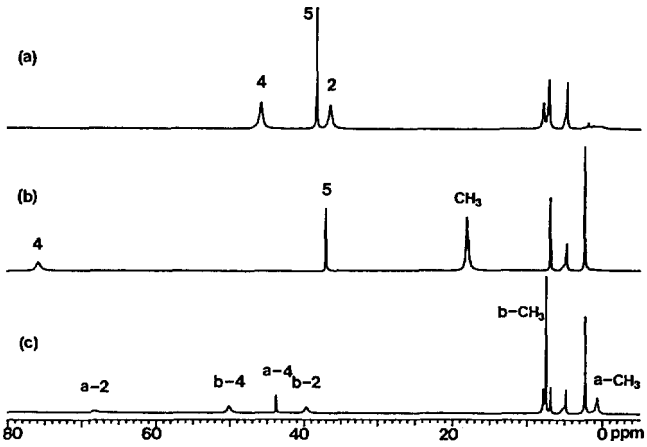
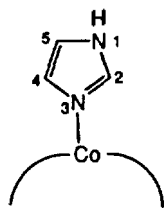


Figure 2. ^1H NMR spectra of D_2O solutions containing $SiW_{11}Co$ and (a) imidazole (pH 8.6), (b) 2-methylimidazole (pH 9.4), and (c) 4(5)-methylimidazole (pH 9.1) in 1 : 1 mole ratio. Chemical shifts in ppm from TSP. The lines originating from the complexes are labeled.

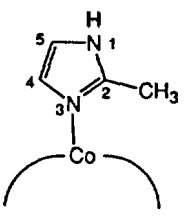
Results

$SiW_{11}Co$ Complexes

Imidazole Derivatives. The ^1H NMR spectrum of a D_2O solution containing imidazole and $SiW_{11}Co$ is shown in Figure 2(a). The protons bonded to nitrogen atoms are completely exchanged with deuterons in a D_2O solution, and their signals are not observed. The two lines at 7.9 and 7.2 ppm are attributed to 2-H and 4-H (5-H) of free imidazole, respectively. Rapid proton exchange makes 4-H and 5-H equivalent for free ligand. The three lines at 36.4, 38.3, and 45.8 ppm originate from the coordinated imidazole, **1**. It has been shown that the line widths are inversely proportional to the sixth power of the metal-nuclei distance.[6,12] Thus the narrow line at 38.3 ppm can be assigned to 5-H, the proton located farthest from the Co^{2+} ion. The line at 36.4 ppm, the intensity of which decreases slowly, is assigned to 2-H which is slowly exchanged with deuteron in a D_2O solution. Finally the line at 45.8 ppm is assigned to 4-H.



1



2

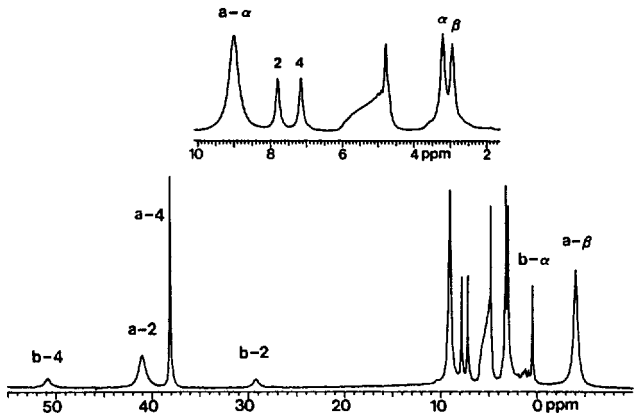


Figure 3. ^1H NMR spectrum of a D_2O solution (pH 9.1) containing $SiW_{11}Co$ and histamine in 1 : 1 mole ratio. Chemical shifts in ppm from TSP.

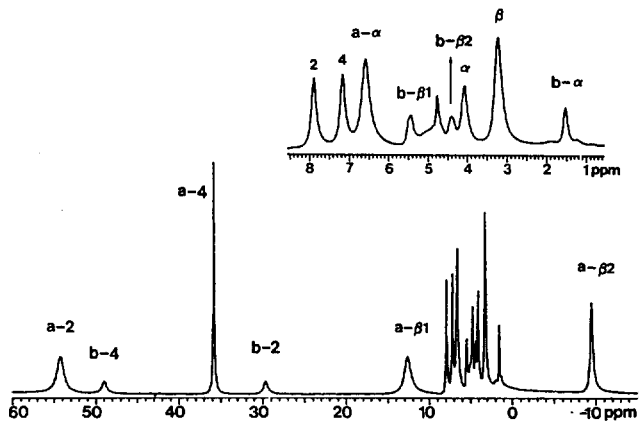
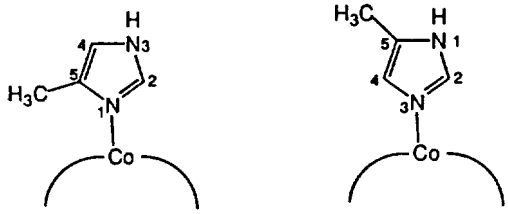


Figure 4. ^1H NMR spectrum of a D_2O solution (pH 7.7) containing $SiW_{11}Co$ and L-histidine in 1 : 1 mole ratio. Chemical shifts in ppm from TSP.

The ^1H NMR spectrum of a D_2O solution containing 2-methylimidazole and $SiW_{11}Co$ is shown in Figure 2(b). The two lines at 6.9 and 2.3 ppm are attributed to 4-H (5-H) and 2-CH_3 of the free ligand. The three lines at 75.8, 37.0, and 18.0 ppm can be readily assigned to 4-H, 5-H, and 2-CH_3 of **2** on the basis of the line widths and relative intensities.

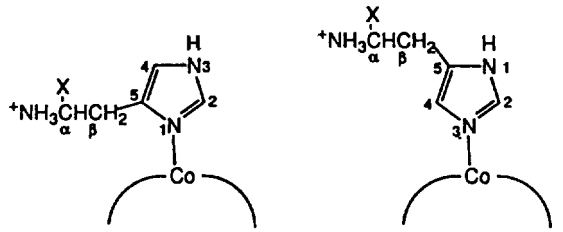
The ^1H NMR spectrum of a D_2O solution containing 4(5)-methylimidazole and $SiW_{11}Co$ is shown in Figure 2(c). The three lines at 7.8, 6.8, and 2.2 ppm are attributed to 2-H, 4-H, 5-CH_3 of the free ligand, respectively. The NMR spectrum shows that two different complexes, **3a** and **3b**, are formed depending upon which nitrogen atom is coordinated to the cobalt ion. The three lines at 68.1, 43.8, and 0.6 ppm are assigned to 2-H, 4-H, and 5-CH_3 of **3a**, and the three lines at 39.7, 50.1, and 7.5 ppm to 2-H, 4-H, and 5-CH_3 of **3b**, respectively.



3a 3b

A methyl group on the imidazole ring has a very remarkable effect on the isotropic shift of a ring proton: the 4-H line of **2** and the 2-H line of **3a** are shifted about 30 ppm downfield from their positions for **1**. On the other hand, the methyl group has little effect on the isotropic shifts of 5-H in **2** and 4-H in **3a**, and the methyl group substituted at the 5 position in **3b** has little effect on the isotropic shifts of 2-H and 4-H.

Histamine. The ^1H NMR spectrum of a D_2O solution containing $SiW_{11}Co$ and histamine in 1 : 1 mole ratio is shown in Figure 3. The four lines at 7.79, 7.14, 3.19, and 2.93 ppm are attributed to 2-H, 4-H, α-H, and β-H of free histamine, respectively. When these lines and the HDO peak at 4.8 ppm are removed, the spectrum consists of two sets of lines with different intensity, indicating that histamine also forms two different complexes, **4a** and **4b**.



4a: X = H
5a: X = CO_2^-
6a: X = CH_3OCO

4b: X = H
5b: X = CO_2
6b: X = CH_3OCO

The stronger set contains a characteristic narrow line at 38.0 ppm, which is readily assigned to 4-H of **4a**. Then the strong line at 41.5 ppm is assigned to 2-H of **4a**. The two remaining strong lines cannot be assigned readily. At this stage we have used the saturation transfer technique to identify lines which are connected by chemical exchange among the free ligand and two complexes. When each line of a complex is saturated, the intensities of the lines originating from the corresponding protons in the free ligand and the other complex are reduced. The seven observed lines originating from the two complexes have been completely assigned by this technique; see Figure 3. The line ascribable to β-H of **4b** is hidden under the HDO line at 4.8 ppm at 25 ℃, but shows up at other temperatures.

L-Histidine. The ^1H NMR spectrum of a D_2O solution containing $SiW_{11}Co$ and histidine in 1 : 1 mole ratio is shown in Figure 4. The four lines at 7.88, 7.16, 4.06, and 3.21 ppm are attributed to 2-H, 4-H, α-H, and β-H of free histidine, respectively.[2] When these lines and the HDO peak at 4.8 ppm are removed, the remaining spectrum shows that histidine also forms two isomers, **5a** and **5b**. The stronger set contains a characteristic, narrow line at 35.8 ppm, which is readily assigned to 4-H in **5a**. Then the line at 54.2 ppm is assigned to 2-H in **5a**. The remaining lines have been completely assigned by the saturation transfer experiments; see Figure 4. (The ^1H NMR spectrum 1-methyl-L-histidine coordinated to $SiW_{11}Co$ has also been measured. Only Type

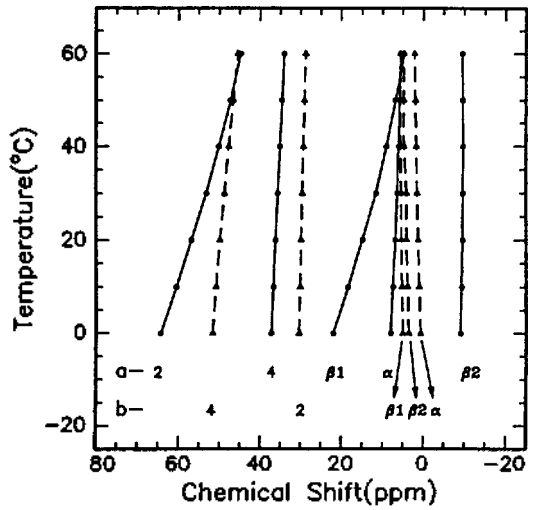


Figure 5. Temperature dependence of the NMR lines for SiW_{11}-Co-histidine complexes **5a** and **5b**.

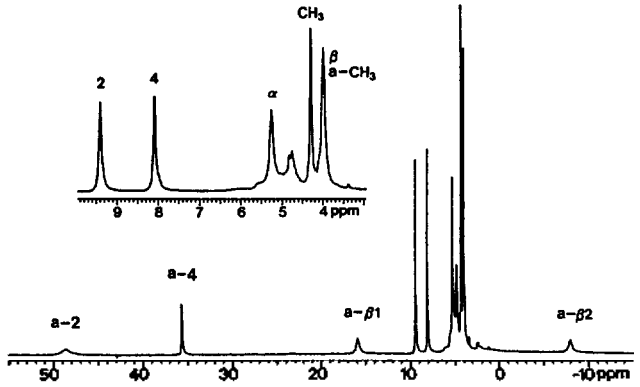


Figure 6. ^1H NMR spectrum of a D_2O solution (pH 4.8) containing $SiW_{11}Co$ and L-histidine methyl ester in 1 : 1 mole ratio. Chemical shifts in ppm from TSP. The line ascribable to α-H of **6a** is probably hidden under the HDO line at 4.8 ppm.

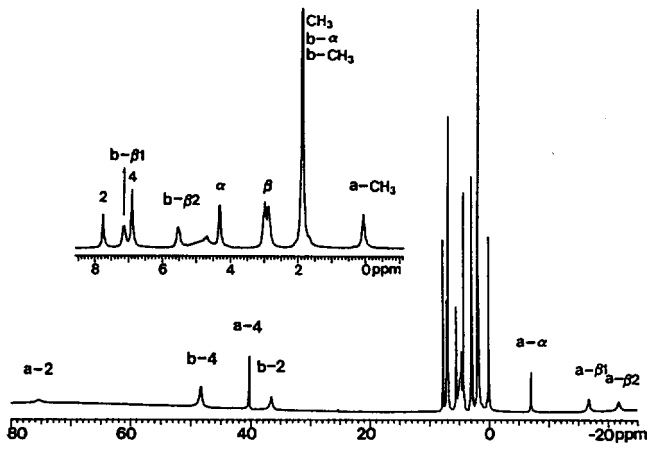


Figure 7. ^1H NMR spectrum of a D_2O solution (pH 8.8) containing $SiW_{11}Co$ and N_α-acetyl-L-histidine in 1 : 1 mole ratio. Chemical shifts in ppm from TSP.

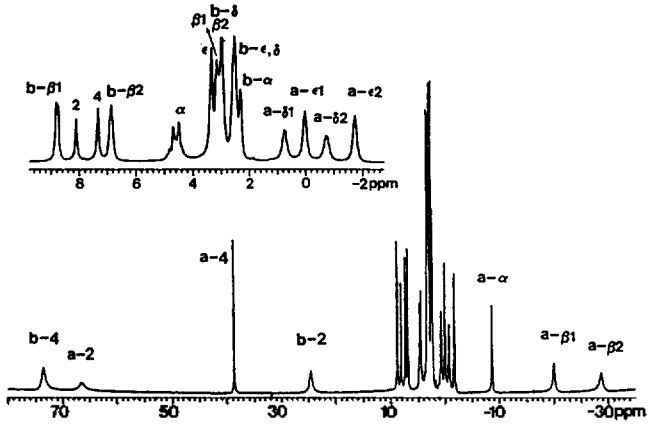


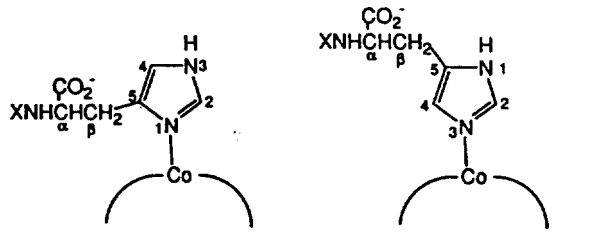
Figure 8. ^1H NMR spectrum of a D_2O solution (pH 9.2) containing $SiW_{11}Co$ and L-carnosine in 1 : 1 mole ratio. Chemical shifts in ppm from TSP.

b complex can be formed for this ligand, and its spectrum is similar to that of **5b**.)

While a single line is observed for the CH_3 group in **2**, **3a**, or **3b** or for the β-CH_2 group in the histamine complexes **4a** or **4b**, the two lines ascribable to the β-CH_2 group in **5a** are split by 22 ppm at 25 ℃, indicating that the β-CH_2 group in **5a** is not rotating freely. In order to study the temperature dependence of these lines, we have measured NMR spectra at various temperatures between 0 and 60 ℃ (Figure 5). As the temperature is lowered, the separation between the two β-H lines of **5a** increases. On the other hand, the two lines ascribable to the β-protons in **5b** are split by 1 ppm and the splitting is nearly independent of temperature. This behavior suggests that the β-CH_2 group in **5b** is rotating freely at 0–60 ℃. Since the two β-protons in L-histidine are not chemically equivalent even when the β-CH_2 group is rotating freely, the two β-H lines need not coincide.

L-Histidine Methyl Ester. The NMR spectrum of L-histidine methyl ester coordinated to $SiW_{11}Co$ is similar to that of $SiW_{11}Co$(his) (Figure 6). It is noted that the lines originating from **6b** are very weak; these lines disappear below pH 4.8. In addition, the lines of the free ligand are shifted downfield, indicating that the substitution rate of this ligand is faster than that of L-histidine.

N_α-Acetyl-L-histidine. The ^1H NMR spectrum of N_α-acetyl-L-histidine coordinated to $SiW_{11}Co$ also consists of two sets of lines (Figure 7). One notable feature is that the β1-H, β2-H, and α-H lines of **7a** are shifted upfield by more than 10 ppm from the corresponding lines in the histidine



7a: X = CH_3CO
8a: X = $^+NH_3CH_2CH_2CO$

7b: X = CH_3CO
8b: X = $^+NH_3CH_2CH_2CO$

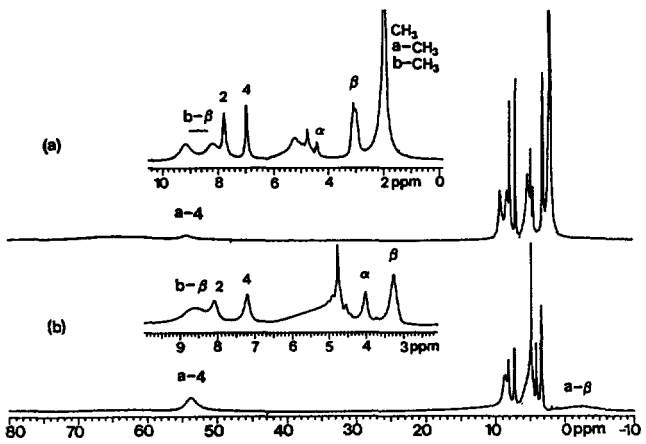


Figure 9. ^1H NMR spectra of D_2O solutions containing $SiW_{11}Ni$ and (a) N_α-acetyl-L-histidine (pH 8.6) and (b) L-histidine (pH 7.2) in 1 : 1 mole ratio. Chemical shifts in ppm from TSP.

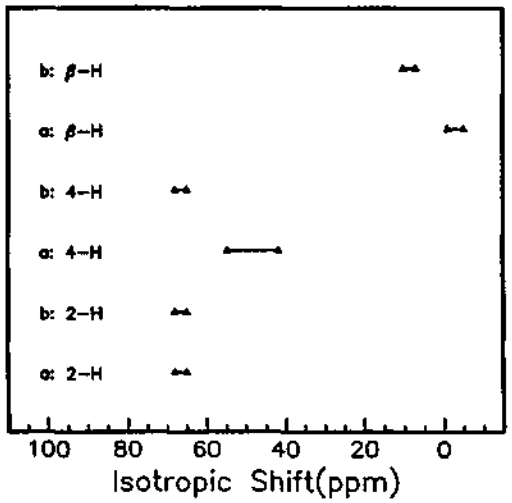


Figure 10. Ranges of isotropic shifts for various protons in ligands containing an imidazole ring coordinated to $SiW_{11}Ni$.

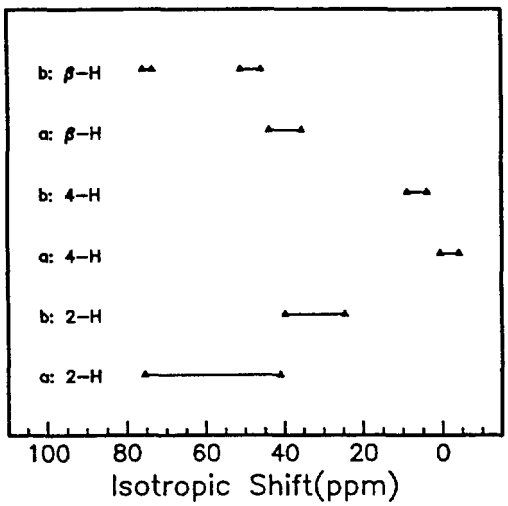


Figure 11. Ranges of isotropic shifts for various protons in ligands containing an imidazole ring coordinated to $SiW_{11}Co$. The isotropic shifts for β-H in Type a complexes of L-histidine and its derivatives are not included.

complex. Similar shifts are observed for L-carnosine coordinated to $SiW_{11}Co$ (see below).

L-Carnosine. L-Carnosine is a naturally ocurring dipeptide found in muscle of man and of numerous animals. It also forms two different complexes with $SiW_{11}Co$ as shown in Figure 8. Here again β1-H, β2-H, and α-H lines of **8a** are shifted upfield from the corresponding lines in the histidine complex.

$SiW_{11}Ni$ Complexes

The ^1H NMR spectra of various ligands coordinated to $SiW_{11}Ni$ are not so well resolved as the spectra of the $SiW_{11}Co$ complexes. Shown in Figure 9 are NMR spectra of L-histidine and N_α-acetyl-L-histidine coordinated to $SiW_{11}Ni$.

Discussion

Linkage Isomerism. For most ligands discussed in this paper, comparable amounts of N_1 and N_3 linkage isomers were formed. One exception is the L-histidine methyl ester complex of $SiW_{11}Co$, which forms the N_3 linkage isomer predominantly. Similar linkage isomerism was observed for square-planar complexes of platinum and palladium with L-histidine and its derivatives.[20]

It is interesting to note that N_1 linkage isomers are formed, while α-picoline is not coordinated to $SiW_{11}Co$ because of steric hindrance between the methyl group and the heteropolyanion.[1] Apparently the smaller ring C-C-C angle in the imidazole ring makes the difference. But the internal rotation of a bulky β-CH_2R group in an N_1 linkage isomer is hampered by the heteropolyanion moiety (see below).

Isotropic Shifts. The ranges of isotropic shifts for various protons in the $SiW_{11}Ni$ complexes are shown in Figure 10. It is noted that the isotropic shifts for each proton fall within a narrow range. It has been shown that the pseudocontact contribution to isotropic shifts is small for $Ni(acac)_2(ptl)_2$ (ptl = pyridine-type ligand).[13-15] For an octahedral Ni(II) complex, which has orbitally non-degenerate $^3A_{2g}$ ground state with excited states far removed in energy, the orbital contribution is small and so is the magnetic anisotropy. Even when a Ni(II) complex deviates considerably from octahedral symmetry, the pseudocontact shifts have been found to be small. A Ni^{2+} ion in octahedral symmetry has two unpaired electrons in e_g orbitals which have σ symmetry. Therefore, the unpaired electron density will be transferred from the d_{z^2} orbital to the σ orbital system of the ligand. So isotropic shifts in octahedral Ni(II) complexes may be attributed mainly to the contact shift by the σ electrons.

The results for $SiW_{11}Ni$ complexes show that various substituents have relatively little effect on the contact shifts by σ electrons. It is also noted that the isotropic shifts for the protons in the $SiW_{11}Ni$ complexes decrease with the increasing number of bonds between the nucleus in question and the nickel ion. A similar phenomenon was also observed for the pyridine-type ligands coordinated to $SiW_{11}Ni$.[1]

On the other hand, the isotropic shifts for some protons in $SiW_{11}Co$ complexes show strong dependence on the substituents (Figure 11). The isotropic shifts of 2-H in both types

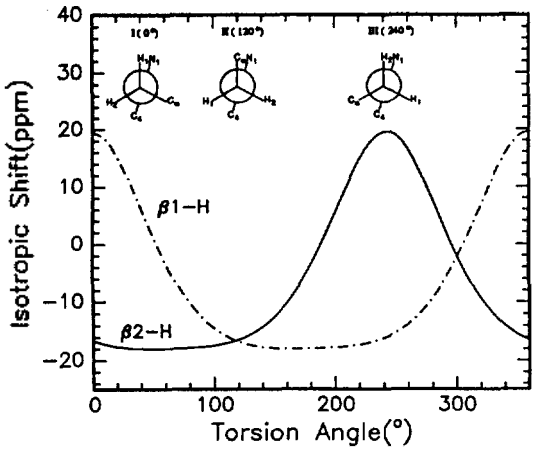


Figure 12. Isotropic shifts of β1-H and β2-H in Type **a** of SiW_{11}-Co(his) as a function of the torsion angle about H_1-C_β-C_5-N_1.

of complexes, for example, are scattered in a range of 55 ppm, whereas those of 2-H in $SiW_{11}Ni$ complexes fall within a range of 3 ppm. Since the pseudocontact shift should remain constant for 2-H in different $SiW_{11}Co$ complexes, the variation of the isotropic shift must come mainly from the contact shift by the π electron. But the effects of the substituents on the contact shifts by the π electron are not easy to estimate quantitatively.

Restricted Rotation of the β-CH_2 Group. The β-CH_2 groups in Type **a** complexes of L-histidine and its derivatives coordinated to $SiW_{11}Co$ exhibit two lines, indicating that the CH_2 groups are not rotating freely. The separation between these two lines increases with decreasing temperature, as is shown in Figure 5 for L-histidine.

Three factors can contribute to the temperature dependence of the NMR lines: (1) 1/kT dependence of the isotropic shift,[2] (2) the rate of the ligand exchange at the cobalt ion, and (3) restricted rotation of the β-CH_2 group. Let us consider the 1/kT dependence of the isotropic shifts first. The isotropic shift of β1-H in **5a** at 0 ℃ is 19.3 ppm. If the isotropic shift exhibits only the 1/kT dependence, then the isotropic shift at 60 ℃ should be 15.8 ppm. Thus the 1/kT dependence of the isotropic shift can account for less than 4 ppm of the 18 ppm shift of the β1-H line at 0-60 ℃.

The second factor is the rate of the ligand exchange. When the ligand exchange is slow at low temperatures, separate lines will be observed for the free ligand and two complexes. As the temperature and thus the rate of ligand exchange increases, the β1-H line is expected to be shifted upfield and the β2-H line downfield toward the lines of the corresponding β-protons in the free ligand and **5b**. While the β1-H line is shifted in the correct direction, the β2-H line remains virtually unmoved. Moreover, the width of the β1-H line remains unchanged during a shift of 17 ppm, while a large line-broadening should accompany any shift of a line by chemical exchange. These results suggest that the ligand exchange at 0-60 ℃ is not fast enough to shift the lines significantly.

Therefore, it is concluded that the restricted rotation of the β-CH_2 group is mainly responsible for the temperature dependence of the β-H lines. Model building shows that rotation of the substituent in **5a** is hampered by the heteropolyanion moiety. It is probable that only a few rotamers are populated even at high temperatures and that the coordinated L-histidine is gradually frozen into a rotamer as the temperature is lowered. In order to identify the rotamers involved, we have tried to estimate the isotropic shifts as a function of the torsion angle α about H_1-C_β-C_5-N_1.

The isotropic shift ($\Delta\delta_{iso}$) may be represented as a sum of the pseudocontact contribution ($\Delta\delta_{pc}$), and the contact shifts by σ electrons ($\Delta\delta_\sigma$) and by the π electron ($\Delta\delta_\pi$).

$$\Delta\delta_{iso}=\Delta\delta_{pc}+\Delta\delta_\sigma+\Delta\delta_\pi \quad (1)$$

The pseudocontact shift for a given nucleus i in an axial system can be expressed as[2]

$$\Delta\delta_{pc}=-\frac{N_A}{12\pi}\frac{(3\cos^2\theta_i-1)}{r_i^3}(\chi_\parallel-\chi_\perp) \quad (2)$$

Here N_A is Avogadro's constant, θ_i is the angle betweem the principal axis of the complex and the radius vector from the metal ion to the nucleus, i; r_i is the distance between the metal ion and the nucleus, i; and $\chi_\parallel$ and $\chi_\perp$ are magnetic susceptibility components parallel and perpendicular to the principal axis.

The geometrical factors $(3\cos^2\theta-1)/r^3$ have been calculated by using the crystal structure data for L-histidine[16] and the N-Co distance, 2.08 Å.[17] In the absence of the magnetic data, the magnetic anisotropy is represented by $f(\chi_\parallel-\chi_\perp)_o$, where $(\chi_\parallel-\chi_\perp)_o$ is the value for pyridine (abbreviated as py below) coordinated to bis(2,4-pentanedionato)cobalt(II), $Co(acac)_2$[8], and f is a proportionality constant.

The contact shift resulting from the transmission of the σ-type electrons is assumed to be the same as the isotropic shift for $SiW_{11}Ni$(his), −6.26 ppm at 0 ℃. It has been shown that the contact shift by σ electrons for $Co(acac)_2(py)_2$ is similar to the isotropic shift for $Ni(acac)_2(py)_2$.[13]

Finally, the contact shift by the π electron may be estimated from the average isotropic shift of a freely-rotating β-CH_2 group. The value, −6.19 ppm at 0 ℃, for β-CH_2 in the Type **a** complex of $SiW_{11}Co$(histamine) was chosen. Only one line was observed for β-CH_2 in this complex, indicating that this group was rotating freely. The average isotropic value may be expressed as

$$-6.19=\langle\Delta\delta_{pc}\rangle+\Delta\delta_\sigma+\langle\Delta\delta_\pi\rangle \quad (3)$$

where $\langle\Delta\delta_{pc}\rangle$ and $\langle\Delta\delta_\pi\rangle$ represent average values for the freely-rotating β-CH_2 group. It has been shown that the hyperfine coupling constant of the proton in the C-C-H system is propotional to $(0.08+\cos^2\theta)$, where θ is α−90.[19] Since $\Delta\delta_\pi$ should exhibit the same angular dependence, it may be written

$$\begin{aligned}\Delta\delta_\pi&=h(0.08+\cos^2\theta)\\&=h\{0.08+\cos^2(\alpha-90)\}\end{aligned} \quad (4)$$

where h is a proportionnality constant. Since the average value of $\cos^2\theta$ is 0.5, the following expression is obtained.

$$\langle\Delta\delta_\pi\rangle=h(0.08+\langle\cos^2\theta\rangle)=0.58\ h \quad (5)$$

Substituing this in Eq. (3), we obtain

$$\begin{aligned}-6.19&=0.69\ f-6.26+0.58\ h\\h&=0.12-1.19\ f\end{aligned} \quad (6)$$

Combining Eqs. (1), (4), and (6), we obtain

$$\Delta\delta_{iso}=\Delta\delta_{pc}-6.26+(0.12-1.19f)\times\{0.08+\cos^2(\alpha-90)\} \quad (7)$$

The $\Delta\delta_{iso}$ values calculated as a function of the torsion angle for $f=1.07$ are shown in Figure 12. It is found that the angular variation is determined mainly by the pseudocontact contribution, the contribution of $\Delta\delta_{\pi}$ is being less than 1.4 ppm for the entire range. Rotamers I ($\alpha=0°$) and III ($\alpha=240°$) exhibit a large difference in the $\Delta\delta_{iso}$ values for the two β-protons. L-Histidine hydrochloride monohydrate has the conformation of rotamer I in the crystal.[16]

Let us assume that I is the dominant conformation at low temperatures. In order to simplify the discussion, we will further assume that I is the only rotamer populated at 0℃, and that another rotamer is also populated at higher temperatures. The temperature dependence of the isotropic shift for β1-H can be explained in terms of either II ($\alpha=120°$) or III. If either of them is populated at higher temperatures, the average isotropic shift will decrease with increasing temperature. The calculated average isotropic shift is 1 ppm when rotamers I and II (or III) are populated equally, and this value agrees with the observed value at 60℃. Intuitively III looks the more likely rotamer to be populated at high temperatures. However, if III is populated significantly, the isotropic shift of β2-H should increase with increasing temperature. On the other hand, if II is populated at higher temperatures, the isotropic shift will be nearly temperature independent, as was observed.

So the experimental data indicate that rotamer II contributes to the isotropic shifts at high temperatures. However, model building shows that this rotamer is not energetically favorable because of strong steric hindrance between the $-C_{\alpha}H(NH_3^+)(COO^-)$ group and the heteropolyanion moiety. After considerable effort, we cannot still give a satisfactory explanation about the temperature dependence of the isotropic shifts of the β1-H group.

Effects of Substituents. It is noted that the line of 2-H, a ring proton, also exhibits a large temperature dependence, which cannot be accounted for by the 1/kT dependence alone. This indicates that the unpaired electron density at 2-H is affected significantly by the conformation of the substituent. The effect of the substituent is reflected also in the isotropic shifts (at 25℃) of 2-protons in various derivatives of imidazole and L-histidine coordinated to $SiW_{11}Co$ (Type a complexes): histamine, 33.2; L-histidine methyl ester, 39.2; L-histidine, 46.3; L-carnosine, 58.3; 4-methylimidazole, 60.3; N_{α}-acetyl-L-histidine, 67.7 ppm. The isotropic shifts of β2-protons, the lines of which appear at the highest field, are also sensitive to the nature of the substituents for Type a complexes: histamine, −7.0; L-histidine, −12.7; N_{α}-acetyl-L-histidine −24.7, L-carnosine, −31.7 ppm.

The sensitivity of the isotropic shifts to the nature and conformation of the substituent on the imidazole ring and the large isotropic shifts of 2-H and β2-H in Type a complexes may make $[SiW_{11}Co(H_2O)O_{39}]^{6-}$ a useful probe or shift reagent for identifying various derivatives of imidazole and histidine. But the same property makes it difficult to separate the contact and pseudocontact contributions to the isotropic shifts. It remains a challenging problem to abstract accurate pseudocontact shifts from NMR data, and thus to obtain detailed information on the conformations and internal rotations of L-histidine and related compounds coordinated to $SiW_{11}Co$.

Acknowledgment. The financial support of the Korea Ministry of Education is gratefully acknowledged. The use of NMR spectrometer is financially supported by the Organic Chemistry Research Center.

References

1. Ko, M.; Rhyu, K. I.; So, H. *Bull. Korean Chem. Soc.* **1993**, *14*, 500.
2. Bertini, I.; Luchinat, C. *NMR of Paramagnetic Molecules in Biological Systems*; Benjamin/Cummings: Menlo Park, CA, 1986.
3. McDonald, C. C.; Phillips, W. D. *J. Am. Chem. Soc.* **1963**, *85*, 3736.
4. Martin, R. B.; Mathur, R. *J. Am. Chem. Soc.* **1965**, *87*, 1065.
5. Fratiello, A.; Schuster, R. E.; Bartonili, G. *J. Am. Chem. Soc.* **1970**, *92*, 2304.
6. Bertini, I.; Canti, G.; Luchinat, C.; Mani, F. *J. Am. Chem. Soc.* **1981**, *103*, 7784.
7. Banci, L.; Bertini, I.; Luchinat, C.; Scozzafa, A. *J. Am. Chem. Soc.* **1987**, *109*, 2328.
8. York, J. L.; Millet, F. S.; Minor, L. B. *Biochemistry* **1990**, *19*, 2583.
9. Faarr-Jones, S.; Wong, W. Y. L.; Gutheil, W. G.; Bachovchin, W. W. *J. Am. Chem. Soc.* **1993**, *115*, 6813.
10. Simmons, V. E., Ph.D. Thesis, Boston University (1963).
11. Weakley, T. J. R; Malik, S. A. *J. Inorg. Nucl. Chem.* **1967**, *29*, 2935.
12. Koenig, S. H. *J. Magn. Reson.* **1978**, *97*, 2113.
13. Happe, J. A.; Ward, R. L. *J. Chem. Phys.* **1963**, *39*, 1211.
14. Doddrell, D.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 6839.
15. Morishima, I.; Yonezawa, T.; Goto, K. *J. Am. Chem. Soc.* **1970**, *92*, 6651.
16. Fuess, H.; Hohlwein, D.; Mason, S. A. *Acta. Cryst.* **1977**, *B33*, 654.
17. Candin, R; Harding, M. M. *J. Chem. Soc. (A)* **1970**, 384.
18. Horrocks, W. D.; Hall, D. D. *Inorg. Chem.* **1971**, *10*, 2368.
19. Ayscough, P. B. *Electron Spin Resonance in Chemistry*; Methuen, London, 1967; p 77.
20. Appleton, T. G.; Pesch, F. J.; Wienken, M.; Menzer, S.; Lippert, B. *Inorg. Chem.* **1992**, *31*, 4410.