Ambidentate Nature of the Two Nitrogen Donor Sites in Imidazole and Related Molecules

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Abstract: The mode of bonding of imidazole, pyrazole, and *N*-methylimidazole to the square planar Schiff base complexes Co(saloph) and Ni(saloph) and the β-diketonate complexes $Co(acac)_2$ and $Ni(acac)_2$ has been investigated. It is found that adducts of all the above complexes in CH_2Cl_2 solution at room temperature undergo rapid intermolecular exchange on the nmr time scale with excess of the bases studied. Through analysis of the contact-shifted nmr of these bases at room temperature and a study of the temperature dependence of these shifts, it is found that imidazole and pyrazole form two types of adducts in solution with the saloph complexes: one where the base is bound through the amine nitrogen and one through the imine nitrogen. The dominant species upon coordination to $Co(acac)_2$ and $Ni(acac)_2$ involves bonding of the imine nitrogen of these bases. Calorimetric data and visible spectra also indicate that these bases form two adducts with the saloph complexes involving the imine and amine nitrogen in solution. Studies are described which indicate that the increased preference of the saloph complexes compared to acac complexes for amine-type donors is enthalpic in nature. *E* and *C* parameters are presented for the imine nitrogen of *N*-methylimidazole and estimates can be made from the studies carried out of the *C*/*E* ratio for the amine nitrogen of this donor.

Binding of imidazole-type molecules to transition metal complexes is a subject of considerable interest because of the frequent occurrence of imidazole derivatives in biologically important metal complexes. For example, in heme proteins the histidine group is thought to be bound to the iron atom[1] and in vitamin B_{12}[2] (cyanocobalamin) a 5,6-dimethylbenzimidazole group is bound axially to cobalt. We report here procedures and examples of determining binding sites in molecules with several donor functional groups. We also describe procedures for characterizing these donor sites which lead to predictions about coordination positions.

Several previous studies of the mode of imidazole bonding include Taube's work with carbon-bound imidazole.[3] Proton and ^{13}C nmr studies showed the existence of imidazole (and many substituted imidazoles) bound through C-2 in $[(NH_3)_5Ru^{II}Im]^{2+}$ and $(NH_3)_4Ru^{III}ImCl_3$. Other nmr studies include imidazole coordination to ruthenium(II) porphyrins. In the study[4,5] of ruthenium carbonylmesoporphyrin IX dimethyl ester, where it was assumed imidazole was bound through the imine nitrogen, it was thought that an intramolecular shuttling process was occurring, making the 4 and 5 proton positions of the coordinated imidazole equivalent. Subsequent work by Faller and Siebert[6] with this complex utilizing multiple resonance techniques led these authors to conclude that intermolecular exchange was more rapid than the intramolecular exchange process with coordinated imidazole. The shortcomings of this interpretation will be discussed. Holm, *et al.*,[7] have studied both inter- and intramolecular site exchange in nitrogenous bases with tetra(*p*-isopropylphenyl)porphinatoruthenium carbonyl. With 3,5-dimethylpyrazole, the rapid exchange mechanism involved the intermolecular mode over the temperature range studied (29–153°). However, with 4,5-dimethylpyridazine and 3,6-dimethylpyridazine, intramolecular exchange is the rapid process over the temperature ranges −24 to 40° and −74 to 18°, respectively.

In the systems cited above, the proton resonances of the coordinated bases shifted upfield from the resonance of the free ligand small amounts due to diamagnetic effects.[8] Previous work in this laboratory with the proton nmr contact shifts of $[Ni(RNH_2)_6]^{2+}$ (R = CH_3, C_2H_5, n-C_3H_7)[9] has revealed large upfield shifts for the amino protons and a downfield shift for the alkyl protons of coordinated amines. The nmr data indicate that in aliphatic amines an attenuation in the magnitude of the C–H proton contact shifts occurs as one proceeds down the chain from nitrogen, in agreement with the expected σ-delocalization mechanism. Upfield shifts for the amino protons have also been observed for $[Ni(bz)_6]^{2+}$ (bz = benzylamine).[10] Contact shift studies of octahedral Ni(II) complexes of pyridine and substituted methyl pyridines[11] show large downfield shifts for the ring protons due mainly to σ-delocalization.

Imidazole and pyrazole contain both a pyridine-like imine nitrogen and a secondary amine nitrogen. Because of the definitive characteristics of the contact shift behavior of alkylamine and pyridine complexes, we feel the proton nmr contact shifts of imidazole bases should be a useful probe into the mode of their bonding to paramagnetic metal complexes.

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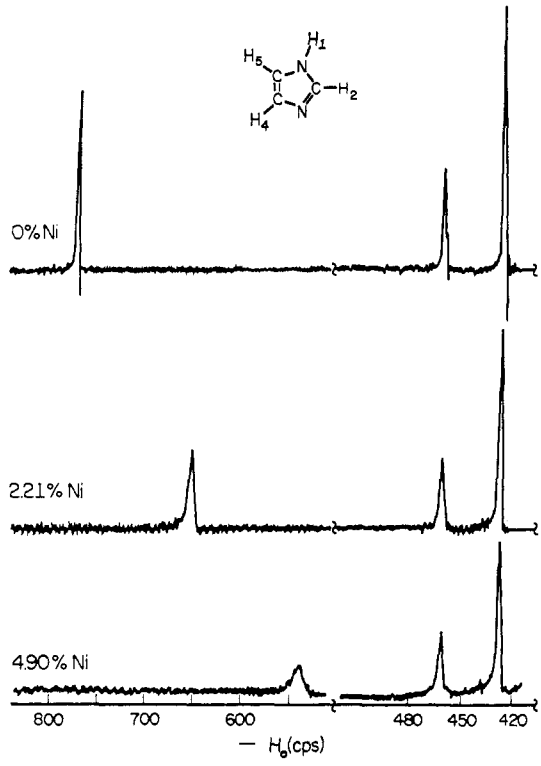

Figure 1. The 60-MHz nmr spectra of CH_2Cl_2–imidazole solution (top spectra) and effect of adding Ni(saloph).

The temperature dependence of the isotropic shift and visible spectra of metal complexes with these bases can reveal whether coordination is occurring through only one nitrogen or if equilibrium concentrations of species coordinated at both nitrogens are present. Coordination at only one nitrogen should give rise to a linear $1/T$ dependence of the contact shift. A single donor site may also produce an isosbestic point in the visible spectrum in the concentration range where only 1:1 base adducts are formed. If coordination occurs at more than one site in the base, neither a linear $1/T$ dependence of the contact shift nor an isosbestic point in the visible spectrum is expected.

Experimental Section

Reagents. Imidazole, pyrazole, and *N*-methylimidazole were obtained from Aldrich Chemical Co. Imidazole was purified by vacuum sublimation; *N*-methylimidazole was fractionally distilled over CaH_2 at 10 mm pressure, the middle fraction being collected. Pyrazole was used without further purification. Baker analyzed pyridine and Fisher piperidine were fractionally distilled from barium oxide at atmospheric pressure. Aldrich *N*,*N*-dimethylacetamide (DMA) was fractionally distilled from BaO twice at 36 mm. Chemical Samples Co. 7-oxabicyclo[2.2.1]heptane (bridged ether) was fractionally distilled three times from CaH_2. Aldrich tetrahydrothiophene (THTP) was fractionally distilled over CaH_2 at atmospheric pressure. Columbia Chemicals dimethylcyanamide (DMCA) was fractionally distilled from BaO at 10 mm. 1-Azabicyclo[2.2.2]octane (quinuclidine) donated by Mallinckrodt Chemical Works, St. Louis, Mo., was purified by sublimation at ~0.5 mm and at room temperature at least three times. Tetrahydrofuran (THF) was stored over CaH_2 for 24 hr, refluxed over CaH_2 for 2 hr, and fractionally distilled from CaH_2 the same day. Chloroform (Baker Spectrograde Analyzed) was washed with H_2O to remove traces of alcohol used as a stabilizer, dried over anhydrous K_2CO_3, distilled not more than 1 day prior to use and stored in the dark at 0°.

Syntheses. Co(saloph), (saloph) = *N*,*N*′-bis(salicylidene)-*o*-phenylenediamino, was prepared by a reported method.[12] *Anal.* Calcd for $CoC_{20}H_{14}O_2N_2$: C, 64.35; H, 3.78; N, 7.51; Co, 15.80. Found: C, 64.23; H, 3.87; N, 7.68; Co, 15.74. Ni(saloph) was prepared in an analogous manner to the cobalt complex. *Anal.* Calcd for $NiC_{20}H_{14}O_2N_2$: C, 64.39; H, 3.78; N, 7.51; Ni, 15.74. Found: C, 64.23; H, 3.65; N, 7.58; Ni, 15.71.

$(Ni(acac)_2)_3$ (acac = acetylacetonato) was prepared by reported procedures.[13] Methanol was removed from the product by drying *in vacuo* at 75° over P_2O_5. The product was recrystallized from methanol. *Anal.* Calcd for $NiC_{10}H_{14}O_4$: Ni, 22.84; C, 46.75; H, 5.49. Found: Ni, 22.85; C, 46.60; H, 5.61. $(Co(acac)_2)_3$ was prepared in an analogous manner to the nickel complex. *Anal.* Calcd for $CoC_{10}H_{14}O_4$: Co, 22.85; C, 46.75; H, 5.49. Found: C, 46.55; H, 5.60; Co, 22.72.

Physical Measurements. The nuclear magnetic resonance spectra were measured with either a JEOLCO C-60H high-resolution nmr spectrometer equipped with a JES-VT-2 temperature control unit or a Varian Associates HA-100 high-resolution nmr spectrometer operating in the field sweep mode equipped with a temperature control unit. Chemical shifts were measured relative to TMS.

The probe temperature for the 60-MHz spectra was measured to ±0.5° using a copper–constantan thermocouple. The probe temperature for the 100-MHz spectra was determined by recording the nmr of ethylene glycol (above 25°) or methanol (below 25°). All complexes were studied in methylene chloride solution. All samples were prepared in a nitrogen-filled dry bag, each nmr tube being fitted with a tight-fitting cap and wrapped with Parafilm.

Solution visible spectra were determined using a Cary recording spectrometer, Model 14 RI.

Thermodynamic Measurements. The description of the modified calorimeter and the procedure for performing the experiments and calculating thermodynamic data have been reported.[14,15] All reagents were kept in stoppered flasks wrapped with Parafilm and stored in calcium sulfate (Drierite) filled desiccators. All glassware was dried in an oven and stored in P_2O_5 filled desiccators. All handling of the chemicals and glassware took place in a glove bag filled with dried nitrogen and containing an open container of P_2O_5. The solvents used to measure enthalpies of reaction with Co(saloph) were degassed with dry N_2 prior to preparation of the solutions. All solutions were prepared in a N_2 atmosphere.

The chloroform–*N*-methylimidazole enthalpy of adduct formation was determined by nmr as previously described.[16] All spectra were run on a Varian Associates HA-100 high-resolution nmr spectrometer as described above. Chloroform chemical shifts were measured relative to the cyclohexane lock signal using a frequency counter. The precision of the chemical shifts is ±0.2 Hz.

Results and Discussion

Imidazole. In CH_2Cl_2 solution, imidazole undergoes rapid proton transfer between the two nitrogens and tautomers exist. The nmr of free imidazole in CH_2Cl_2 at room temperature is shown at the top of Figure 1. The peak at −783 Hz is assigned to H_1, that at −465 Hz to H_2, and that at −428 Hz relative to TMS corresponds to H_4 and H_5. Rapid proton transfer from one nitrogen to the other interconverts an amine nitrogen to an imine nitrogen and makes the 4 and 5 protons equivalent on the nmr time scale. This is called tautomerism in ref 6. Addition of Ni(saloph) to the solution at room temperature produces a marked upfield shift of the H_1 proton (Figure 1), while H_2, H_4, and H_5 are essentially unchanged. Addition of Co(saloph) produces a similar upfield shift in H_1, though the peak is broadened more severely as would be predicted from the longer observed electron relaxation time for five- and six-coordinate complexes of Co(II) compared to

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Ni(II). The free Co(saloph) and Ni(saloph) complexes have square planar structures[17] and the nmr spectra are run in an excess of Lewis base to ensure a significant amount of the 1:1 adduct is formed. In the region of rapid intermolecular exchange, the imidazole resonances observed are a mole fraction weighted average of free imidazole and the contact-shifted resonance of the paramagnetic complex. In view of the large excess of base, nonequivalence of the H_4 and H_5 proton resonances cannot be distinguished.

Addition of $Ni(acac)_2$ to imidazole produces an appreciable downfield shift in H_1, H_2, H_4, and H_5 (Figure 2). Though $Ni(acac)_2$ exists as a trimer in the solid state, it dissociates into monomeric octahedral complexes when an excess of a strong coordinating ligand is present.[18] Thus, for two different nickel(II) complexes, very different contact shift patterns are observed upon coordination to imidazole. Dipolar contributions to the observed paramagnetic shift are small for nickel(II) complexes[19,20] and cannot account for the different patterns observed in the two nickel(II) complexes studied here. With Ni(saloph), only H_1 is shifted to an appreciable extent, indicating the presence of a species coordinated to nickel through the amine nitrogen, transmitting unpaired spin to H_1 by the spin polarization mechanism. This type of behavior for the N–H proton is characteristic of coordination of ammonia and many amines[9,10] to nickel(II). Imidazole coordination to $Ni(acac)_2$ causes the H_2, H_4, and H_5 resonances to broaden and fall under a single wide peak downfield from the free imidazole resonance. The H_1 resonance in this complex is shifted in an opposite direction relative to that observed for the Ni(saloph) adduct, and H_2, H_4, and H_5 are all appreciably shifted. Consequently, the binding of imidazole to $Ni(acac)_2$ must involve species coordinated at a different site than Ni(saloph) and this site is assigned as N_3, the imine nitrogen. A similar set of circumstances obscured a bit by possible pseudocontact[21] contributions is observed for Co(saloph) and $Co(acac)_2$. As before Co(saloph) has a significant concentration of species bound through the amine nitrogen and $Co(acac)_2$ through the imine nitrogen. These species need not be the only ones present and in view of the uncertainty in the magnitude of the shifts for the pure adducts, it is difficult to ascertain the relative amounts of the different species. However, a different behavior for the binding of the metal toward these nitrogen centers is clearly operative in the two types of complexes. More definitive conclusions arise from the results which follow.

In the rapid exchange region for a system characterized by the equilibrium

$$A + B \rightleftharpoons AB \qquad (1)$$

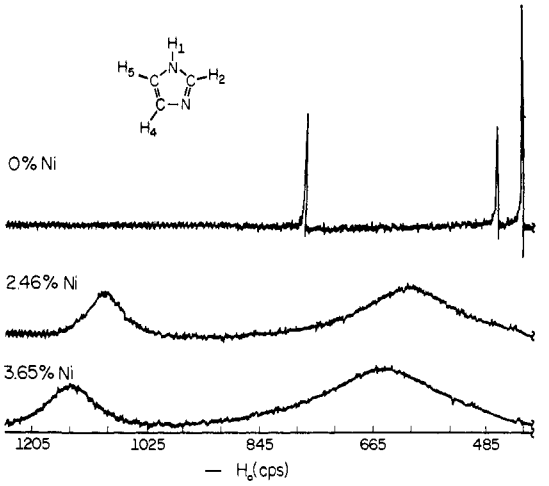

Figure 2. The 60-MHz nmr spectra of adding $Ni(acac)_2$ to a CH_2Cl_2–imidazole solution.

the average chemical shift observed for the base is given by

$$\delta_{obsd} = \delta_{AB}\frac{[AB]}{[B_0]} + \delta_B\left(\frac{[B_0] - [AB]}{[B_0]}\right) = \delta_B + \frac{[AB]}{[B_0]}(\delta_{AB} - \delta_B) \qquad (2)$$

where δ_{AB} is shift of complexed base and δ_B is shift of free base. The equilibrium expression for (1) is given by

$$K = \frac{[AB]}{([A_0] - [AB])([B_0] - [AB])} \qquad (3)$$

when $[B_0] \gg [A]$ and thus $[B_0] \gg [AB]$, eq 3 becomes

$$K = \frac{[AB]}{([A_0] - [AB])[B_0]}$$

and eq 2 becomes

$$\delta_{obsd} = \delta_B + \frac{[A_0]K}{1 + [B_0]K}(\delta_{AB} - \delta_B)$$

This equation can be expressed in terms of the mole fraction of A_0, that is

$$n_{A_0} = \frac{[A_0]}{[A_0] + [B_0]} \simeq \frac{[A_0]}{[B_0]}$$
$$\delta_{obsd} = \delta_B + \frac{n_{A_0}[B_0]K}{1 + [B_0]K}(\delta_{AB} - \delta_B) \qquad (4)$$

Thus, when a simple equilibrium involving the complex and free base is involved, as in eq 1, a plot of n_{A_0} *vs.* δ_{obsd} will yield a straight line in the region where $[B_0] > [AB]$ (see simplification of eq 3). Figure 3 shows the plot for all the different protons in imidazole when $Ni(acac)_2$ is the acid. The straight line indicates that binding is occurring through only one site. When a similar plot is attempted with the acid Ni(saloph), a straight line does not result (Figure 3). The deviation from linearity for the plot of Ni(saloph) and imidazole indicates that the equilibrium cannot be described by an equation of the form of eq 1 and the system likely involves a competitive equilibrium involving both the imine and amine nitrogens. Similar results to those obtained with the nickel(II) complexes are obtained for $Co(acac)_2$ and Co(saloph) and are shown in Figure 4.

(17) (a) The structure of Co(saloph) is not known, but the closely related Cu(*N,N'*-bis(salicylideneethylenediamine)[17b] and Cu(*N,N'*-salicylidenepropane-1,2-diamine)·H_2O[17c] have been done, the tetradentate ligand essentially planar. The Co(saloph) base adducts are likely square pyramidal as in Co(salen)·NO and related derivatives.[17c] (b) D. Hall and T. N. Waters, *J. Chem. Soc.*, 2644 (1960); (c) F. S. Llewellyn and T. N. Waters, *ibid.*, 2639 (1960); (d) A. Earnshaw, P. C. Hewlett, and L. F. Larkworthy, *ibid.*, 4718 (1965).

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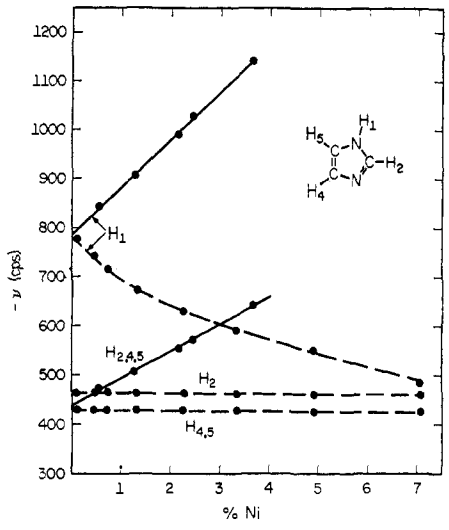

Figure 3. Plot of mole fraction of Ni *vs.* chemical shift (at 60 MHz relative to TMS) of imidazole: broken line = Ni(saloph), solid line = $Ni(acac)_2$.

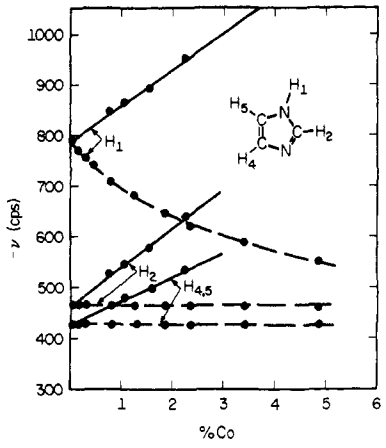

Figure 4. Plot of mole fraction of Co *vs.* chemical shift (at 60 MHz relative to TMS) of imidazole: broken line = Co(saloph), solid line = $Co(acac)_2$.

The existence of more than one species in solution in the Co(saloph)–imidazole system is also indicated by the nonexistence of an isosbestic point in the electronic spectrum of solutions of this adduct. It is necessary, however, to prove that the deviation from linearity in the nmr plot and lack of an isosbestic point are due to coordination at different nitrogens in the 1:1 adduct and not due to the presence of both 1:1 and 2:1 adducts in solution. Evidence to support two different 1:1 imidazole complexes comes from two experiments. An isosbestic point in the visible spectra could not be obtained over a concentration range of imidazole and Co(saloph) comparable to that used in a study[12] of pyridine and Co(saloph) where an isosbestic point was obtained ([Co(saloph)] = 4.23×10^{-4} *M*, [pyridine] = 9.54×10^{-4} to 0.1 *M*). In an nmr study of pyridine and Co(saloph) in CH_2Cl_2 over a concentration range similar to that used in Figure 4 for imidazole, a linear plot for the chemical shift of the α protons of pyridine *vs.* per cent Co(saloph) exists. This fact supports the visible spectral evidence that only the 1:1 adduct is being formed with pyridine and the observed chemical shifts are governed by eq 1. In view of the similar basicity of imidazole and pyridine, *vide infra*, it is safe to assume that imidazole behaves like pyridine in forming only 1:1 adducts with Co(saloph) over the concentration range in Figure 4. The lack of an isosbestic point and the nonlinear chemical shift plot most probably arises from the ambidentate nature of imidazole.

It is of interest to consider the above observations in light of the dynamic processes which are known to occur in free imidazole. We are in effect claiming that coordination to nickel(II) or cobalt(II) acetyl acetonate gives rise to a predominant species by locking one nitrogen into an imine environment. Thus, if proton transfer is occurring, the relative rates give rise to a predominantly imine coordinated species. Simple proton transfer could change this nitrogen to a coordinated amine and, if there is some very small amount of a species in solution coordinated in this way, it could arise from such a proton transfer. If this proton transfer is occurring, the relative rates are such that the predominant species in the nickel(II) or cobalt(II) saloph has the coordinated nitrogen stabilized in an amine environment. It should be emphasized that without ligand dissociation there is no way for the H_4 and H_5 protons to be made equivalent by proton transfer from one nitrogen to the other in the complex. However, rapid proton transfer between the two nitrogens could be occurring in the complex without leading to a direct interchange of bound H_4 and H_5. Accordingly, nonequivalence of H_4 and H_5 in spin saturation experiments cannot be used to infer[6] the "absence of tautomerism in the complex." This nonequivalence does eliminate rapid metal shuttling (*i.e.*, intramolecular donor nitrogen interchange accompanied by proton transfer). Rapid ligand dissociation and exchange of the nitrogens involved in coordination can equilibrate H_4 and H_5, but this need not be the predominant mechanism for tautomerism in the complex. Tautomerism in the complex could occur without ligand dissociation and would lead to a mixture of amine and imine coordinated imidazole. This is one way to account for the equilibrium mixture obtained in the saloph complexes.

Pyrazole. A situation similar to that of imidazole exists with pyrazole binding to Co(saloph) and Ni(saloph). Figure 5 shows the nonlinear behavior of the chemical shift *vs.* per cent nickel for the H_1 proton when Ni(saloph) is added to a pyrazole solution. The pyrazole complexes with $Ni(acac)_2$ exhibit markedly different nmr spectra than those of the corresponding Schiff base complexes. Results similar to those obtained in the Ni(II) system are obtained upon addition of Co(saloph) or $Co(acac)_2$ to a pyrazole solution. Again, the difference in the chemical shift of the $Ni(acac)_2$ and Ni(saloph) adducts as well as the nonlinear plot of chemical shift *vs.* per cent nickel can be explained by species coordinating at the imine and amine nitrogens. A visible spectral study with pyrazole shows results similar to those obtained with imidazole; no isosbestic point could be obtained with Co(saloph) adducts.

Variable Temperature Nmr Studies. Further evidence for two-site coordination in imidazole and pyrazole comes from a variable temperature nmr study. The observed isotropic shift, $\Delta\nu_{iso}$, is the sum of contact and pseudocontact contributions. The contact shift

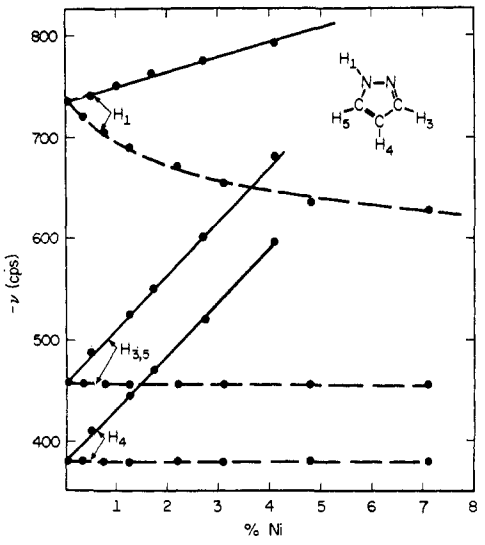

Figure 5. Plot of mole fraction of Ni *vs.* chemical shift (at 60 MHz relative to TMS) of pyrazole: broken line = Ni(saloph), solid line = $Ni(acac)_2$.

is given by the Bloemberg equation[21]

$$\frac{\Delta\nu_p}{\nu_0} = \frac{-A_i g_{av}^2 \beta_e^2 S(S+1)}{g_N \beta_N 3kT} \quad (5)$$

where ν_0 is the probe frequency, A_i the nuclear spin–electron spin coupling constant, g_{av} the average g value of the electron, β_e the Bohr magneton, g_N the nuclear g value, β_N the nuclear magneton, S is the total electron spin of the system, k the Boltzmann constant, and T is the absolute temperature. The pseudocontact shift for an axially symmetric system is given by[22]

$$\left(\frac{\Delta\nu_p}{\nu_0}\right)_i = \frac{-\beta_e^2 S(S+1)}{45kT} F(g) \frac{(3\cos^2\theta_i - 1)}{R_i^3} \quad (6)$$

where $F(g)$ is a function of the principal components of the g tensor, θ_i the angle between the principal axis of the molecule and a vector from the metal to the ith nucleus, and R_i the length of this vector. From the above equation, it can be seen that the isotropic shift should have a linear $1/T$ dependence and a zero intercept. Many systems give linear $1/T$ behavior but have substantial intercepts. Various sources of contributions to this intercept exist and have been reported.[23]

In the fast exchange region, $Ni(acac)_2$ and imidazole (−6 to 39°) produce a linear plot of $-\nu_{H_1}$ *vs.* $1/T$ (Figure 6). However, in a similar temperature region for the systems involving Ni(saloph) with imidazole (−15 to 40°) and pyrazole (−5 to 39°) nonlinear behavior is observed for the chemical shift of H_1 *vs.* $1/T$. This nonlinear behavior is consistent with Ni(saloph) binding at both the imine and amine nitrogens in imidazole and pyrazole with different equilibrium constants and enthalpies for binding at each site in these two molecules. With different enthalpies for the two sites, equilibrium constants will have different temperature dependences, and the fraction of the nickel involved in the respective complexes at each temperature will vary causing the observed nonlinear behavior. In the

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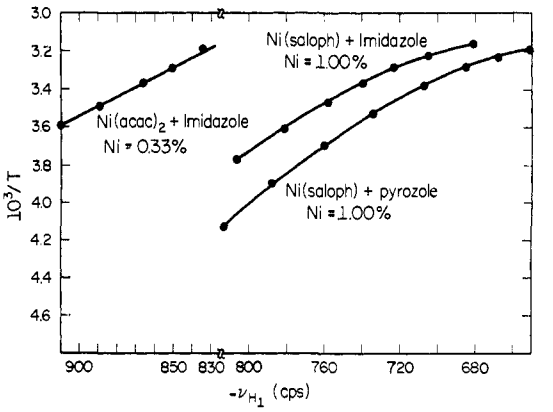

Figure 6. Plot of chemical shift of the H_1 proton of imidazole *vs.* $1/T$ for indicated metal complex adducts.

two Ni(saloph) plots, the curvature for the H_1 proton is to higher field as the temperature is decreased. This indicates that in both cases, as the temperature is decreased, the fraction of Ni(saloph) bound at the amine nitrogen experiencing an upfield shift is increased. In view of the greater temperature dependence of the amine bound nitrogen, a larger enthalpy of adduct formation must exist for the amine nitrogen than for the imine nitrogen toward this acid. As we shall see subsequently, this comparative enthalpy information is most valuable.

***N*-Methylimidazole.** The *N*-methyl protons undergo substantially smaller shifts and shift in the opposite direction of that observed for the N–H proton of imidazole upon coordination to $Ni(acac)_2$ and $Co(acac)_2$ (see Figure 7). The H_2, H_4, and H_5 protons of *N*-methylimidazole are shifted in a similar manner to those of imidazole indicating similar modes of coordination *via* the imine nitrogen in these complexes. A straight line plot of chemical shift *vs.* per cent nickel is obtained (Figure 7) for this donor with $Ni(acac)_2$ and $Co(acac)_2$. An isosbestic point is also obtained in the visible spectra of both these systems (Figure 8). These observations strongly support the existence of one type of complex involving the imine nitrogen.

As with imidazole, *N*-methylimidazole forms two complexes in solution with both Ni(saloph) and Co(saloph). The nmr is not quite as valuable on this system because very small shifts are observed. However, the visible spectrum does not contain an isosbestic point even though the complexes and free acid have overlapping absorbances in the visible region. This strongly suggests the presence of two complexes in solution in addition to the free acid.

Nature of the Donor Centers. The different behavior of these multifunctional donors toward the two different type acids studied suggests that the nature of the nitrogen donor centers in a given molecule is different. We have shown[24] that the acid–base be-

(24) For a review, see R. S. Drago, *Struct. Bonding (Berlin)*, 15, 73 (1973). The approach is modeled after Mulliken's description of the bonding in charge transfer complexes and is similar to the qualitative suggestions of Ahrland, Chatt, and Davies[25] that the acids be described as class A or class B. It differs from the hard–soft acid–base concept for these terms require that the parameters have a functional form that cannot possibly account for observed acid–base behavior even in a satisfactory qualitative way.[26]

(25) S. Ahrland, J. Chatt, and N. Davies, *Quant. Rev., Chem. Soc.*, 12, 265 (1958).

(26) R. S. Drago, *Inorg. Chem.*, 12, 2211 (1973).

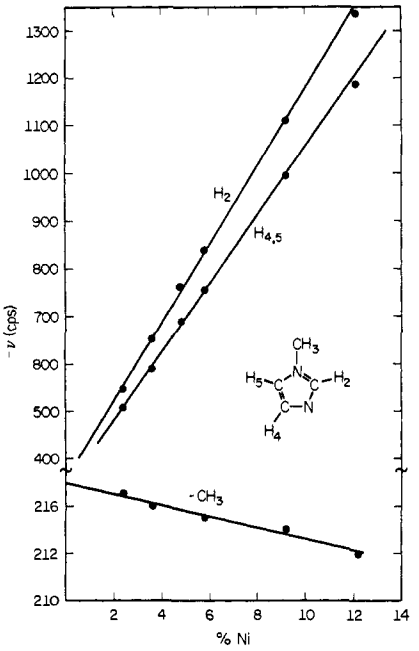

Figure 7. Plot of mole fraction of $Ni(acac)_2$ *vs.* chemical shift (at 60 MHz relative to TMS) of *N*-methylimidazole.

havior of many systems can be quantitatively correlated and qualitatively understood if two different characteristic bonding properties of the acids and bases are considered. We have chosen, for convenience, to describe these properties in terms of the tendency of an acid or base to undergo electrostatic bonding and covalent bonding. The former property is given the symbol E and the latter property the symbol C. For systems on which thermodynamic data are available, the enthalpies are quantitatively correlated by[27,28]

$$-\Delta H = E_A E_B + C_A C_B \qquad (7)$$

where the subscripts refer to acid and base.

An nmr investigation was undertaken to gain further support for the coordination nature of the metal center in these complexes. $Ni(acac)_2$ was added to a solution containing equal amounts of piperidine (C_B = 9.29, E_B = 1.01) and pyridine (C_B = 6.40 and E_B = 1.17). Chemical shifts of protons on both bases showed linear dependence with the per cent nickel present, yet the pyridine protons shifted only 72% of the amount expected if no piperidine were present[29] and the piperidine protons only 28% of the shift if no pyridine were present.[29] However, when Co(saloph) is added to an equimolar mixture of pyridine and piperidine, the pyridine protons shift only 7% of the shift in the absence of piperidine.

One might be tempted on the basis of the data presented here to conclude that the imine nitrogen of *N*-methylimidazole has a substantial C property and E property (by analogy to pyridine where C = 6.40 and E = 1.17) and that the amine nitrogen in the molecule probably has a comparable or larger C property and a smaller E property. Both $Co(acac)_2$ and $Ni(acac)_2$ take advantage of the E property of the donor in forming 2:1

(27) R. S. Drago, G. C. Vogel, and T. E. Needham, *J. Amer. Chem. Soc.*, **93**, 6014 (1971).
(28) R. S. Drago and B. B. Wayland, *J. Amer. Chem. Soc.*, **87**, 3571 (1965).
(29) J. A. Happe and R. L. Ward, *J. Chem. Phys.*, **39**, 1211 (1963).

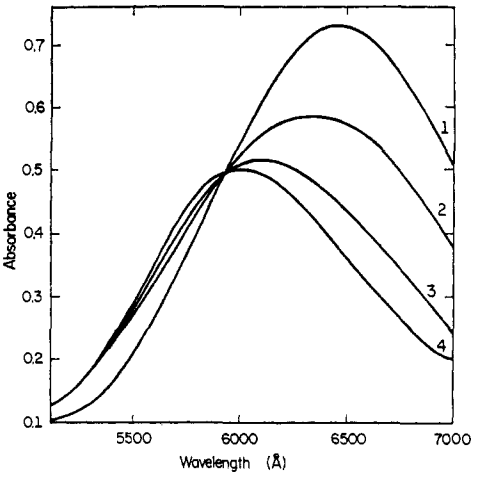

Figure 8. Spectral changes upon addition of *N*-methylimidazole to a CH_2Cl_2 solution containing 7.06×10^{-2} *M* $Ni(acac)_2$. *N*-Methylimidazole added: 1, 7.90×10^{-2} *M*; 2, 1.12×10^{-1} *M*; 3, 1.46×10^{-1} *M*; 4, 1.46 *M*.

adducts. Consequently, the imine nitrogen is the donor center toward these acids. We can crudely state that the selection of imine donor type center for the bases studied here is dominated by the E property of the $Ni(acac)_2$ and $Co(acac)_2$ complexes. The bonding to the Co(saloph) and Ni(saloph) complexes on the other hand has more important relative contributions from the C term (*i.e.*, covalency) and, if it were dominated by the C property, it would have formed complexes exclusively with the amine-type donor centers, but, since two adducts exist in solution, we have mixed E–C behavior.

We have emphasized in an earlier publication[30] that the type of speculation in the previous paragraph is fraught with difficulty. The observations of the reactivity toward the acetylacetonate complexes are free energy considerations, and free energy is often a poor indication of the strength of binding. For example, inferences from free energy data led to an incorrect assessment of the nature of the cobalt center in methylcoboloxime.[30] The qualitative observation regarding the relative amounts of the different complexes formed is a free energy consideration and, in the case of acetylacetonate complexes, the observation could be dominated by entropy terms. In the methylcobaloxime system mentioned above, free energies showed a strong preference for binding sulfur donors instead of oxygen donors, but measured enthalpies showed the bond strength was slightly greater for the oxygen donors. In the systems described here, the temperature dependence of the nmr spectra does provide a relative enthalpic preference for the binding of the amine compared to the imine donor sites in the saloph complexes as discussed above.

In order to show that the preference of the acetylacetonate complexes for a base with a larger E number (*i.e.*, pyridine) is enthalpic, the following experiment was carried out. In CH_2Cl_2, solutions of pyridine and $Ni(acac)_2$ ([pyridine] = 1.002 *M*, $[Ni(acac)_2]$ = 0.081 *M*), as well as one containing piperidine and $Ni(acac)_2$ ([piperidine] = 1.007 *M*, $[Ni(acac)_2]$ = 0.081 *M*), straight lines were obtained for the chemical shift of

(30) R. L. Courtright, R. S. Drago, J. A. Nusz, and M. S. Nozari, *Inorg. Chem.*, **12**, 2809 (1973).

Table I. Measured and Calculated Enthalpies of *N*-Methylimidazole and Co(saloph)

Base	Acid	E_A	C_A	$-\Delta H_{measd}$[a]	Solvent	$-\Delta H_{corr}$[b]	$-\Delta H_{calcd}$[c]
N-Methylimidazole	*m*-FC_6H_4OH[d]	4.422	0.5058	8.5	*n*-Hexane	8.5	8.7
	$Cu(hfac)_2$[d,e]	3.391	1.434	16.1	CCl_4	16.1	16.0
	Methylcobaloxime[29]	9.00	1.53	13.8	CH_2Cl_2	22.1	22.1
	$Zn(NSi(CH_3)_3)_2$[f]	4.94	1.09	14.4	*n*-Hexane	14.4	14.4
	$CHCl_3$[g]	3.02	0.159	4.4	Cyclohexane	4.4	4.2
	HFIP[h]	5.93	0.623	8.3	Benzene	11.1	11.1
Pyridine	Co(saloph)[i]			10.4	CH_2Cl_2	12.5	

[a] In units of kcal/mol. [b] For a discussion of elimination of solvation contribution, see R. S. Drago, M. S. Nozari, and G. C. Vogel, *J. Amer. Chem. Soc.*, **94**, 90 (1972). [c] Calculated using $E_B = 0.895$, $C_B = 9.294$. [d] J. A. Nusz and R. S. Drago, submitted for publication. [e] $Cu(hfac)_2$ = bis(hexafluoroacetylacetonato)copper(II). [f] K. Fisher and R. S. Drago, manuscript in preparation. [g] Enthalpy determined by nmr. [h] HFIP = 1,1,1,3,3,3-hexafluoropropanol, R. M. Guidry and R. S. Drago, *J. Phys. Chem.*, **78**, 454 (1974). [i] C. M. Shramm, Senior Thesis, University of Illinois, 1973.

the base protons *vs.* $1/T$ in the fast exchange region (38 to −5.5°). In a solution containing both pyridine (1.002 *M*), and piperidine (1.007 *M*) with $Ni(acac)_2$ (0.081 *M*) straight lines were observed for the chemical shift of both the pyridine and piperidine protons *vs.* $1/T$, but the slope of the pyridine protons was 56.7% of that of the pyridine–$Ni(acac)_2$ solution, while the slope of the piperidine protons was 42.4% of the piperidine–$Ni(acac)_2$ slope. In this mixed system, the observed slope has contributions not only from the temperature dependence of $\Delta\nu$ for a paramagnetic material (eq 5 and 6) but also from changes in the relative amounts of the pyridine and piperidine complexes, *i.e.*, the temperature dependence of the equilibrium constants. The fact that pyridine has a larger relative slope than piperidine in the mixed solvent is taken to indicate that the pyridine adduct concentration has a larger temperature dependence and hence a larger enthalpy of complexation with $Ni(acac)_2$ than piperidine. Since pyridine has a larger *E* number and smaller *C* number than piperidine, we find a preference for the *E* character of these two donors by the acetylacetonate complexes. Experimental limitations (low equilibrium constants and low solubility) prevent a comparable study of the saloph complexes. However, the enthalpic preference of the saloph complex for the amine as opposed to imine nitrogen of *N*-methylimidazole indicates a larger relative importance of the *C* term of the donor toward this acid. Thus, the free energy and enthalpy variations parallel one another in these systems.

With the above discussion in mind, it was of interest to obtain thermodynamic data on the interaction of *N*-methylimidazole with various Lewis acids to determine its *E* and *C* numbers. The calorimetric data obtained were analyzed[31] with a computer program that assumes an equilibrium situation of the type in eq 1. The results of this analysis for six acids are summarized in Table I and the raw data are contained in the microfilm edition of this journal.[32] The good fits obtained indicate that methylimidazole is forming only one complex in solution and we shall show is binding only through the imine nitrogen toward all of these acids. The first six acids listed in Table I have known E_A and C_A parameters, so a series of equations in terms of two unknowns, C_B and E_B can be written using eq 7. The fact that there is a unique solution to these equations implies that there is only one type of donor center in all these systems. In view of the dominance of the *E* term in the $CHCl_3$ system ($C_A = 0.159$ and $E_A = 3.02$), the imine nitrogen is most probably involved in all these systems.

The imine nitrogen of methylimidazole has different *E* and *C* numbers ($E_B = 0.934$ and $C_B = 8.961$ from solving the six equations discussed above) than pyridine ($E_B = 1.165$ and $C_B = 6.404$). The *C*/*E* ratio indicates the relative importance of covalent to electrostatic interactions. The value for methylimidazole is 10.46 compared to 5.496 for pyridine. The *E* and *C* numbers for the amine nitrogen of methylimidazole could be obtained only if two or more acids could be found which coordinate exclusively at that site. We have not been able to accomplish this. However, the qualitative behavior of competitive complexation suggests that the amine nitrogen has a slightly larger *C*/*E* ratio and parameters of comparable magnitude to those of the imine nitrogen. This assignment is supported by the nmr studies utilizing piperidine which possesses similar *E* and *C* numbers to the imine nitrogen of *N*-methylimidazole. Pyridine, with a larger *E* number than piperidine, coordinated preferentially with $Ni(acac)_2$. However, with Co(saloph), piperidine coordinated almost exclusively because of its larger *C* number. Because *N*-methylimidazole coordinates to $Ni(acac)_2$ through only the imine nitrogen, the amine nitrogen must have a smaller *E* number than that of piperidine. Since both nitrogens of *N*-methylimidazole coordinate to Co(saloph), the *C* number of the amine nitrogen must be larger than that of the imine nitrogen. This would make the *C*/*E* ratio of the amine nitrogen larger than that of the imine nitrogen which is in agreement with previous calorimetric investigations on tertiary amines and the imine containing bases (*e.g.*, pyridine *C*/*E* = 5.496, 4-picoline *C*/*E* = 6.795, triethylamine *C*/*E* = 11.191, trimethylamine *C*/*E* = 14.282).

Since Co(saloph) forms 1:1 complexes, it was of interest to obtain thermodynamic data for this acid which could be case in the *E* and *C* formalism. Interesting results were obtained. Of the bases attempted, measurable heat evolution at reasonable base concentrations (less than ~0.3 *M*) was obtained only with pyridine and *N*-methylimidazole. Dimethylacetamide, tetrahydrothiophene, dimethylcyanamide, dimethyl sulfoxide, and bridged ether all resulted in small heat evolution at reasonable base concentrations. The heat evolved upon pyridine addition gives a good fit to a

(31) R. M. Guidry and R. S. Drago, *J. Chem. Educ.*, submitted for publication.

(32) See paragraph at end of paper regarding supplementary material.

1:1 equilibrium constant expression, but *N*-methylimidazole does not. Thus, the calorimetric evidence confirms the lack of an isosbestic point in the visible study and suggests that coordination to Co(saloph) is taking place through two different donor sites.

These are potentially very significant implications, the finding that both nitrogens of imidiazole are fundamentally different types (*i.e.*, different *C/E* ratio) of donor centers. In electron transfer enzymes, coordination at different basic sites could stabilize different oxidation states and facilitate electron transfer. In other atom or group transfer enzymes, a change in donor center could ease the electron demands made on the metal in the transition state. These are possibilities to consider in systems where binding of imidazole-type molecules is involved in enzyme function.

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Supplementary Material Available. A listing of experimental data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-2743.

Ternary Complexes in Solution. XVIII.[1,2] The Stability Enhancement of Nucleotide-Containing Charge-Transfer Adducts through the Formation of a Metal Ion Bridge

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Abstract: The formation of a charge-transfer adduct between 2,2′-bipyridyl and the purine moiety of adenosine, inosine, AMP^{2-}, IMP^{2-}, ATP^{4-}, and ITP^{4-} is connected with the appearance of an absorption that may be best measured by recording difference spectra (λ_{max} 294 nm). With the aid of this absorption and Benesi–Hildebrand plots, it is possible to determine the stability of these charge-transfer adducts. Their stabilities are independent of the presence of phosphate groups, and they are all of the same order (log K_{CT} = 0.9–1.4). In the presence of Cu^{2+} the absorption is shifted toward larger wavelength, λ_{max} 313 nm. Based on this observation it is concluded that the purine moiety acts as the acceptor in the mentioned charge-transfer adducts. The coordination of Cu^{2+} to 2,2′-bipyridyl does not significantly influence the stability of the adducts formed with adenosine or inosine (log $K_{CT} \simeq 1.5$). However, the stability of the charge-transfer adducts formed with the nucleotides is dramatically increased in the presence of Cu^{2+} [Cu(bipy)(AMP) and Cu(bipy)(IMP), log $K_{CT} \simeq 3.7$; $Cu(bipy)(ATP)^{2-}$ and $Cu(bipy)(ITP)^{2-}$, log $K_{CT} \simeq 7.2$]. This stability increase is the result of the metal ion bridge formed between 2,2′-bipyridyl and the phosphate groups of the nucleotides, thus linking the two aromatic moieties together which form the charge-transfer adduct. A comparison of the mentioned stabilities with the stability constants, $K^{Cu(bipy)}{}_{Cu(bipy)(NP)}$, due to $Cu(bipy)(NP)^{0,2-}$ (where $NP^{2-,4-}$ = AMP^{2-}, IMP^{2-}, ATP^{4-}, ITP^{4-}) reveals that both stabilities are about the same, log $K_{CT} \simeq$ log $K^{Cu(bipy)}{}_{Cu(bipy)(NP)}$. Indeed, the mixed-ligand 2,2′-bipyridyl–Cu^{2+}–nucleotide complexes exist in a folded form that allows a charge-transfer interaction between the pyridyl and purine moieties. The structure of these complexes is shortly discussed, and their biological implications are indicated by taking into account that certain side chains of amino acids (like indole and imidazole) are capable of forming charge-transfer adducts with nucleic bases. Hence, provided that steric conditions are favorable, the stability of these adducts may be considerably increased by the formation of a metal ion bridge between the two involved aromatic moieties.

Nucleotides and their derivatives are involved in many basic processes of life. To these belong the reactions where nucleoside di- and triphosphates participate. Virtually all enzymes requiring these phosphates as substrates need in addition a divalent metal ion;[3] in fact, there are a number of examples showing that the metal ion–nucleotide complex rather than the free nucleotide itself is the true substrate in enzymatic reactions.[4] Hence, it is not surprising that metal ion–nucleotide interactions are studied rather intensively,[5,6] but still the detailed roles of metal ions are not widely known.

Furthermore, up to now mainly simple binary metal ion–nucleotide complexes have been studied,[5,6] but the reactions proceed within higher order species, like enzyme–metal ion–substrate complexes; hence, we believe that many of the unanswered questions may be approached by studying simple ternary complexes.[7,8]

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