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(10) National Institutes of Health Predoctoral Trainee.

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Molecular Heteronuclear Chelates. Mixed Metal Chelates of *N,N*¹-Bis(1-phenyl-1,3,5-hexanetrione)ethylenediamine. Preparation and Structure

Sir:

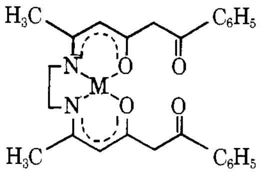
Molecular complexes containing two or more different metal ions in predictable environments are not well known. Such molecules are of interest in the areas of metalloenzymes, homogeneous catalysis, and magnetic exchange interactions. We wish to report the general synthesis and detailed characterization of a series of such complexes. The synthesis of these *pure* mixed polynuclear chelates, hereafter referred to as heteronuclear chelates, employs binucleating ligands in which the coordination sites have different donor atoms, thus associating coordination selectivity with each site. The metals are introduced stepwise with characterization of the intermediate mononuclear and the final heteronuclear products.

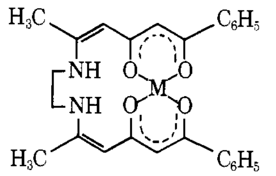
The characterization outlined below includes spectral and magnetic analyses of the compounds prepared as well as three-dimensional X-ray diffraction studies of several members of the series. Correlation of the magnetic and structural results unambiguously establishes the final products as pure heteronuclear complexes.

The new class of ligands employed are the Schiff-bases formed by the condensation of a diamine and a 1,3,5-triketone. These ligands are potentially tetraanionic and by analogy to the chelates of 1,3,5-triketonates can be expected to chelate two divalent metal ions giving a neutral binuclear molecule.[1-5] The Schiff base prepared from 1-phenyl-1,3,5-hexantrione[6] and ethylenediamine, hereafter abbreviated $H_4(BAA)_2en$,[7] is readily prepared in 95% yield by mixing stoichiometric quantities of the reactants in boiling absolute methanol. On cooling to 0°, yellow crystals form which were recrystallized from methanol (mp 171°). Depending upon reaction conditions, $H_4(BAA)_2en$ may be complexed to one or two metal ions. Several examples of each type are discussed below. The analytical results for all the compounds described herein are in excellent agreement with the indicated formulations.

Other related homonuclear chelates have been reported that contain binucleating macrocyclic ligands. Fenton and Gayda[8] reported the preparation of a binuclear complex of the macrocyclic ligand resulting from the condensation of 2,4,6-heptanetrione and ethylenediamine. In addition, Ueno and coworkers[9] and Pilkington and Robson[10] have synthesized several homonuclear complexes using a macrocyclic ligand based on 2,6-disubstituted phenol. There is also one report of a heteronuclear complex of a related ligand in which the metals are Cu(II) and Ni(II).[11] Characterization of this molecule was on the basis of spectral and magnetic data. No structural information is available for any of these chelates.

A number of mononuclear chelates of $H_4(BAA)_2en$ were prepared by allowing 1:1 molar ratios of metal acetates or fresh hydroxides and the ligand to react in H_2O–acetone mixtures. In each case, two isomers (I and II) may result.


I
$M[H_2(BAA)_2en] \cdot N_2O_2$


II
$M[H_2(BAA)_2en] \cdot O_2O_2$

The donor atoms are shown after the general formula as a means of distinguishing between the positional isomers. It is found that, for certain metals, one isomer (I or II) is uniquely produced.

A. $M[H_2(BAA)_2en]$-N_2O_2 Isomer. The mononuclear Ni(II) chelate is an example of isomer I. This complex is readily isolated as red crystals (mp 174°) which are soluble in most organic solvents and insoluble in water. More specifically, the product is extremely soluble in $CHCl_3$ and C_6H_6, but considerably less soluble in acetone and alcohols. Although no structural determination was undertaken, the following spectral and magnetic arguments are sufficient to establish that I is produced as the only product.

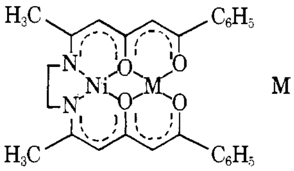
First, the infrared spectrum of $Ni[H_2(BAA)_2en]$ contains an intense unchelated carbonyl band at 1700 cm^{-1} which would be absent if the coordination were O_2O_2. Second, the visible spectrum is essentially identical with that of $Ni(acac)_2en$ where the coordination geometry is the same as in I. Third, the product is rigorously diamagnetic ($\chi_g(\text{obsd}) = -266 \times 10^{-6}$, $\chi_g(\text{calcd}) = -246 \times 10^{-6}$ cgs) and, therefore, the Ni(II) is square planar. $Ni(acac)_2en$, a model for isomer I, is also diamagnetic and square planar.

Although the spectral data cannot be used to assess the purity with respect to positional isomerism, magnetic results may be used in this way. If the Ni(II) were coordinated at the O_2O_2 site, II, its environment would be similar to that found in the bis(benzoylacetonate)nickel(II) chelate which achieves a coordination number of six by binding two adduct ligands such as water or by oligomerization.[12] In either of these environments Ni(II) is paramagnetic with $\chi_m \simeq 5000 \times 10^{-6}$ cgs at 300°K and $15{,}000 \times 10^{-6}$ cgs at 77°K. Thus, very small amounts of isomer II, as an impurity in I, would be easily detected by susceptibility measurements. Inasmuch as the calculated and observed diamagnetism of $Ni[H_2(BAA)_2en]$ are in such good agreement, it is possible to state that isomer I is the only product.

B. $M[H_2(BAA)_2en]$-O_2O_2 Isomer. Two well-characterized mononuclear chelates with structure II have been prepared in which M = Cu(II) and VO(II). Since spectral and magnetic characterizations are not as definitive as in the Ni(II) complex, single-crystal X-ray determinations were carried out. The results confirm that both chelates contain metals bonded to four oxygens.[13] The solubility properties of these complexes are much different than $Ni[H_2(BAA)_2en]-N_2O_2$. They are insoluble in water, fairly soluble in acetone and alcohols, soluble in strongly coordinating solvents, and quite insoluble in nonpolar organic solvents.

Our approach to the systematic synthesis of pure heteronuclear transition metal chelates with the different metals in predictable environments is to make use of the selectivity of different coordination sites within a single ligand molecule.

Syntheses of the heteronuclear chelates discussed below involves using mononuclear $Ni[H_2(BAA)_2en]-N_2O_2$ as a ligand for a second metal to be coordinated at the O_2O_2 site. In order to avoid metal ion rearrangement, we have chosen systems in which one metal ion has a demonstrated preference for the N_2O_2 site and the second a demonstrated preference for the O_2O_2 site. The $Ni[H_2(BAA)_2en]$ was dissolved in hot acetone followed by slow addition of a stoichiometric amount of a metal acetate dissolved in a minimum of water. The heteronuclear chelate, III, precipitates on concentrating and cooling. Yields are typically 60-90%. These neutral chelates are insoluble in water, sparingly soluble in nonpolar solvents, moderately soluble in acetone, and quite soluble in coordinating solvents such as pyridine and DMF.



M = Cu, Zn, UO_2, VO

III

$NiM(BAA)_2en$

Preliminary spectral and magnetic data for these complexes are consistent with III. None of the infrared spectra exhibit bands attributable to unchelated carbonyl groups. The magnetic susceptibility of $NiCu(BAA)_2en$ and $NiVO(BAA)_2en$ indicates the presence of one unpaired electron per molecule; $NiZn(BAA)_2en$ is diamagnetic and $NiUO_2(BAA)_2en$ is slightly paramagnetic, presumably due to some orbital contribution. The EPR spectra of $NiCu(BAA)_2en$ and $NiVO(BAA)_2en$ exhibit normal Cu(II) and VO(II) absorptions without ^{14}N superhyperfine splitting, a further indication that the Ni coordination is N_2O_2 in both cases.

A three-dimensional single-crystal structure determination was carried out on crystals obtained by recrystallization of $NiZn(BAA)_2en$ from pyridine. The crystals were monoclinic $I2/c$ with lattice parameters a = 28.403 (6) Å, b = 8.465 (3) Å, c = 30.220 (9) Å, β = 105.86 (2)°, and Z = 8. Intensity data were collected by the θ-2θ scan technique with graphite-monochromated Mo Kα radiation on a Syntex $P2_1$ diffractometer. Of the 5055 data with $\sin \theta/\lambda < 0.54$, 2559 had $I > 3\sigma(I)$ and were used in the solution and refinement of the structure. The structure was solved by Patterson-Fourier methods and refined by full-matrix (isotropic) and block-diagonal (anisotropic) least-squares refinement. The conventional discrepancy factors at the present stage of refinement are $R = 0.056$ and $R_w = 0.071$.

The structural analysis shows discrete molecules of $NiZn(py)(BAA)_2en$ of structure type III in which the N_2O_2 site is occupied by four-coordinate square planar Ni and the O_2O_2 site is occupied by Zn. The coordinated pyridine completes the five-coordination of the zinc atom. Although the X-ray study cannot distinguish between the scattering of zinc and nickel, the diamagnetism of the complex requires the Ni to be the four-coordinate species as discussed previously. A view of the single molecule is shown in Figure 1.

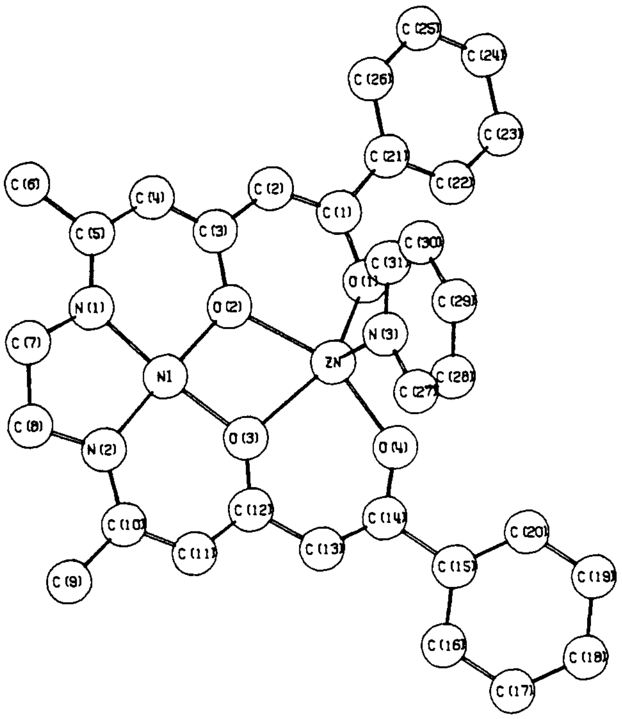


Figure 1. A view of the molecular structure of $NiZn(py)(BAA)_2en$.

The Ni-N and Ni-O distances average 1.844 (8) and 1.847 (6) Å, respectively. The Zn-O distances average 2.089 (6) Å to the bridging oxygens and 1.950 Å to the terminal oxygens. The average value of the basal Zn-O distances is comparable to that in analogous zinc diketonate complexes.[14] The difference between the terminal and bridging distances follows the trend observed in the 1,3,5-triketonate complexes but is greater in magnitude.[15] The apical Zn-N distance is 2.096 (7) Å. The Ni-Zn distance is 3.122 (2) Å.

The nickel is square-planar with no atom in the coordination sphere displaced more than 0.03 Å from planarity. The five-coordinate Zn is displaced from the least-squares basal plane 0.32 Å toward the pyridine, in somewhat typical fashion for five-coordination; oxygen atoms O(1) and O(3) are displaced 0.14 Å away from the pyridine. Distances and angles within the ligand framework are consistent with those previously summarized[14] for comparable compounds.

We believe the use of coordinatively selective sites in binucleating ligands provides an excellent pathway to pure heteronuclear complexes. Characterization by any single physical technique, even structure determination, may not be unambiguous with respect to the position of the metal ions. However, when careful structural, spectral, and magnetic characterizations are used throughout, the exact nature of the complex and its purity can be determined to a high degree of certainty.

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Nuclear Magnetic Resonance Studies of Exchangeable Protons. I. Fourier Transform Saturation-Recovery and Transfer of Saturation of the Tryptophan Indole Nitrogen Proton[1]

Sir:

Proton exchange rates between water solvent and sites on small molecules have been measured by several techniques including NMR.[2] We have measured this rate for the indole nitrogen proton of tryptophan. This proton was studied because its resonance is often visible and assignable in protein NMR spectrum and the protein exchange rate can be measured.[3]

The present measurement may also be of technical interest because it partially bridges the gap between measurements based on line broadening (restricted to rates greater than a few seconds^{-1}) and those based on the real-time observation of the change in intensity of such a resonance when the H/D ratio of the solvent is changed. We use a Fourier transform measurement based on a previously published technique[4] for observation of signals from compounds at millimolar concentration in nearly 100% H_2O, so that the concentrations we use are also unusually low.

The bulk of the measurements were of what we call the apparent relaxation rate, measured by the technique of saturation-recovery: a long (~0.1 sec) selective (a few milligauss) preirradiation pulse is applied at the exact indole NH resonance frequency, followed by a delay before the observation pulse (which flips the indole N proton by about 45° while not flipping the solvent protons[4]). Neither the preirradiation nor the observation pulse affect the water protons appreciably. Thus the water protons act as a pool of nuclear magnetization. The indole N protons recover their magnetization after preirradiation at a rate which is the sum of their magnetic spin-lattice rate and their specific chemical exchange rate with the water protons.

Except as noted, all experiments were performed on tryptophan (Sigma) (20 m*M*; 80% H_2O, 20% D_2O) and adjusted with minimal dilute NaOH or HCl to approximately the desired pH. Samples were placed in 10-mm NMR tubes for several hours before each measurement, and pH was measured directly in the tube prior to and usually just after each NMR run. The pH measurements were performed with a London GK2321C electrode, and we report the meter readings without correction for the 20% D_2O isotope effect. The NMR data were obtained with a Bruker WH-90 Fourier transform spectrometer connected to a data-handling and control system based on a Nova computer, built along lines described previously.[4] Saturation recovery runs usually consisted of observations at 10 to 20 delay times. In each case the data always showed a single exponential recovery when plotted. About 2 min of accumulation (32 transients) was used per point at 20 m*M* concentration. The peak height of the indole NH line, rather than its integral, was used in these measurements since this peak is always relatively broad (~10 Hz) and field inhomogeniety drift is not a problem.

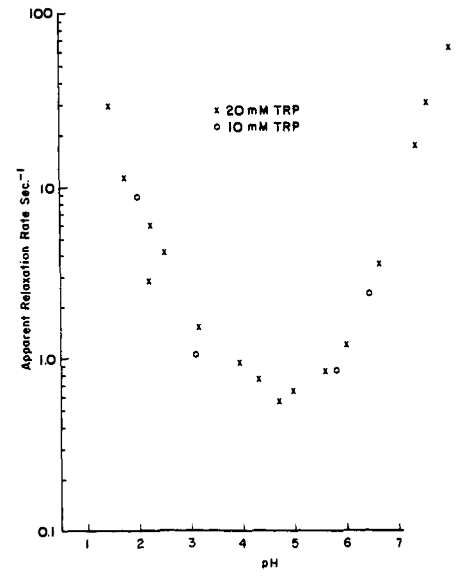

Figure 1. Apparent relaxation rates for the tryptophan indole nitrogen proton at 27°, in unbuffered aqueous (80% H_2O, 20% D_2O) solvent. As discussed in the text, the broad minimum represents primarily magnetic relaxation, while the higher rates represent chemical exchange. At acid pH the rate does not appear to be quite proportional to hydronium ion concentration. If this is not experimental error, it may be a result of minor perturbation by the carboxyl group which titrates in this range. The catalytic rate constant quoted in the text is estimated from the lowest pH points and is, therefore, that of the cation.

The observed apparent rates are plotted in Figure 1. At the pH extremes this rate is much greater than the spin-lattice relaxation rate (due to dipolar interaction with other nuclei). Therefore the observed relaxation rate is the specific chemical exchange rate. The same rate can be inferred from line width measurements but the saturation-recovery method is less subject to uncertainties.

From the measurements at extreme pH values we infer hydroxide and hydronium ion catalytic constants of 8×10^7 and 8×10^2 l./(mol sec), respectively, at 300°. Crude temperature runs at pH 7.2 and 2.2 indicate that enthalpies of activation for the specific rate constants are 1 and 2 kcal/mol, respectively. These temperature measurements were performed at essentially constant pH so that the hydronium catalytic constant has an enthalpy of activation of 2 kcal/mol while the hydroxide catalytic constant is about 15 kcal/mol after correction for the enthalpy of dissociation of H_2O of about 14 kcal/mol. There was no measurable dependence on tryptophan concentration (between 10 and 20 m*M*).

In the central region of Figure 1 (pH ~4.7) the apparent relaxation rate is dominated by processes other than ex-