

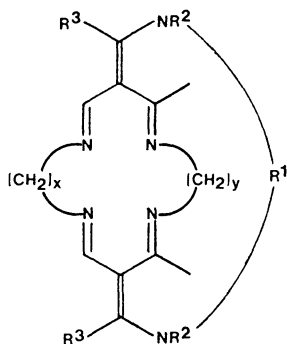
MULTIPLE STRUCTURES FROM A MACRO BICYCLIZATION REACTION -- THE RICH CHEMISTRY OF THE JÄGER MACROCYCLES

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Abstract - The well developed synthetic system for preparation of a highly versatile family of dry cave ligands has yielded two other very different families of equally interesting ligands. The dry cave ligands are designed to provide a protected coordination site for such small molecules as CO and O₂. The second family of ligands is related to the first by dimerization and the resulting complexes contain two identical metal ions separated by an intramolecular void. An intramolecular tautomerization reaction of the coordinated dry cave ligand produces a unique family of clathro-chelate structures in which the metal ion is totally encapsulated by a hexadentate ligand, containing azomethine donor groups.

The development of the chemistry of complexes with macrocyclic ligands has received continuing impetus from the biochemistry of such macrocycle-containing systems as heme proteins, vitamin B₁₂ and siderophores and ionophores. Our interest in mimicking the various functions of the heme proteins has been further stimulated by the compelling potential applications of controlled oxidation reactions of organic molecules. Studies in a number of laboratories on substituted porphyrins have clearly shown that appended structural components (superstructure) can serve, in place of the protein, to control the chemistry at the active site in the heme protein. We have recently reported (1) a very promising new series of bicyclic dry cave ligands (structure 1) that has been designed to provide a protected cavity for the binding of such small molecules as O₂ and CO. The ligands resemble porphyrins only in that they contain four nitrogen donors



R₁ = (CH₂)_n, n = 4-8, m-, p-xylyl, etc.

R₂ = H, CH₃, alkyl, -CH₂C₆H₅

R₃ = H, CH₃, alkyl, C₆H₅, etc.

x, y = 2 or 3

1.

and a macrocycle. In contrast to porphyrins, the ring size may be varied and the ligand is neutral in charge and non-aromatic.

The cobalt(II) complexes formed by the new ligands are exceptionally effective O₂ carriers (2,3). For simplicity in discussion, ligands of structure 1 will be represented by listing in succession R₃, R₂, R₁. For example: CH₃, CH₃, (CH₂)₆ represents structure 1 with vinyl and nitrogen methyl groups and a hexamethylene bridge. Unless otherwise specified, x = y = 3. Table 1 lists values of P₅₀ for materials with which it is appropriate to compare the new O₂ carriers. The cobalt complex of the dry cave ligand has a greater O₂ affinity than any previously characterized cobalt species. Further, it is comparable to iron-myoglobin in O₂ affinity, whereas coboglobin itself has a lesser affinity by about two orders of magnitude.

TABLE 1. P_{50} (25°, Torr) for Selected O_2 Carriers

Compound	P_{50}
Iron-myoglobin	0.7
Cobalt-myoglobin	57.
Cobalt-protoporphyrin-IX ^a	17,800.
Cobalt-picket fence porphyrin ^a	140.
Cobalt-(CH ₃ ,CH ₃ , (CH ₂) ₆ -dry cave) ^b	1.0

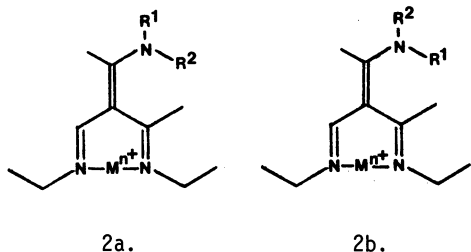
^aIn toluene solution, N-methylimidazole axial ligand.

^bAqueous solution, N-methylimidazole axial ligand, extrapolated value.

It has also been shown that the O_2 affinities of the dry cave complexes can be varied over a very large range by the structural changes implicit in Structure 1 (3).

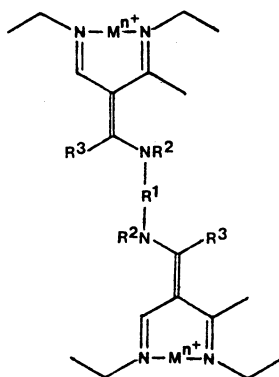
The study of the dry cave complexes has included other metal ions, especially iron, copper and manganese, but they will not be discussed here. Attention is to be focused on the remarkable richness of the synthetic systems that have yielded the dry cave ligands.

Structural studies have revealed that the bridging nitrogen atoms are trigonal planar and this gives rise to the possibility of an unusual kind of stereoisomerism (1,2). Referring back to structure 1, it is useful to direct one's view of the structure toward the edge of the NiN_4 plane so that an unsaturated ring appears above the plane. This produces the projections in structures 2a and 2b. As shown, the bridge group R_1 can be attached to the N-bond that is

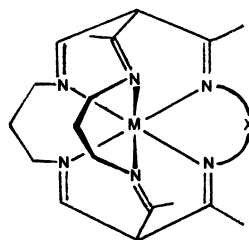


approximately perpendicular to the macrocycle plane, thus placing the bridge essentially just above the metal ion (2a, lid-on isomer), or the bridge may be attached to the N-bond approximately parallel to the NiN_4 plane, placing the bridge to one side of the metal ion (2b, lid-off isomer). Both isomeric structures have been observed. Depending on both the precise natures of the substituents and on the conditions used in the second cyclization step, a closely related dimeric ligand may be formed (structure 3, profile view, after the style of structure 2). This species is of much interest since it contains

two metal ions bound in a single ligand (4,5). These modes of isomerism do not exhaust the rich ligand chemistry of these systems. Under appropriate conditions, certain of the ligands



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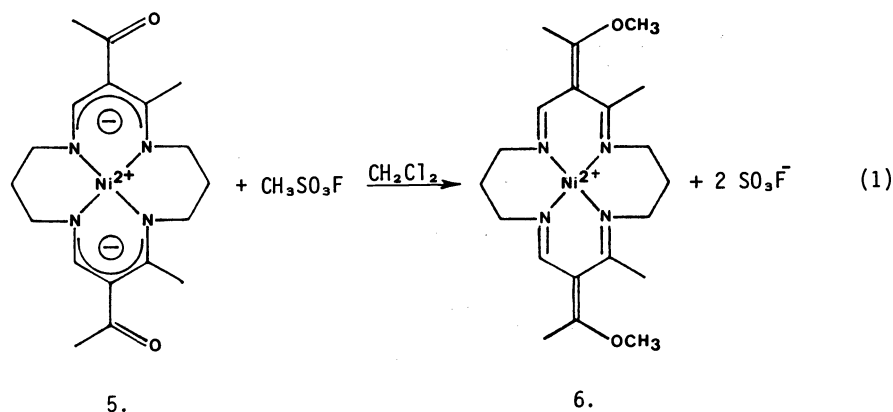


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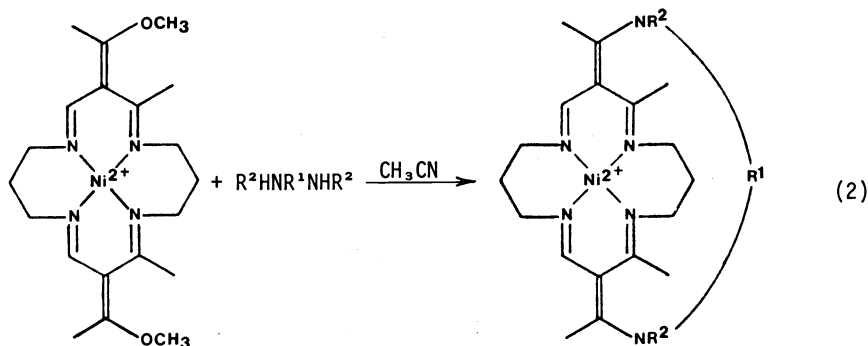
can rearrange into clathro-chelate ligands (for the first such structure see ref. 6) that fully encapsulate the coordinated metal ion (structure 4). Intermediate structures are known in which only one iminoethylidene group has undergone rearrangement.

GENERAL SYNTHETIC PROCEDURES FOR THE DRY CAVE LIGANDS

The extremely general syntheses described here depended on the development of a reagent that was well suited to the bicyclization reaction. The reagent (7,8) is the novel methoxyethylidene-substituted macrocycle (structure 6) first reported from these laboratories several years ago. It is formed by the reaction of the well-known Jäger complex (structure 5) with a strong methylating agent, equation 1. This reagent undergoes a variety of reactions, the

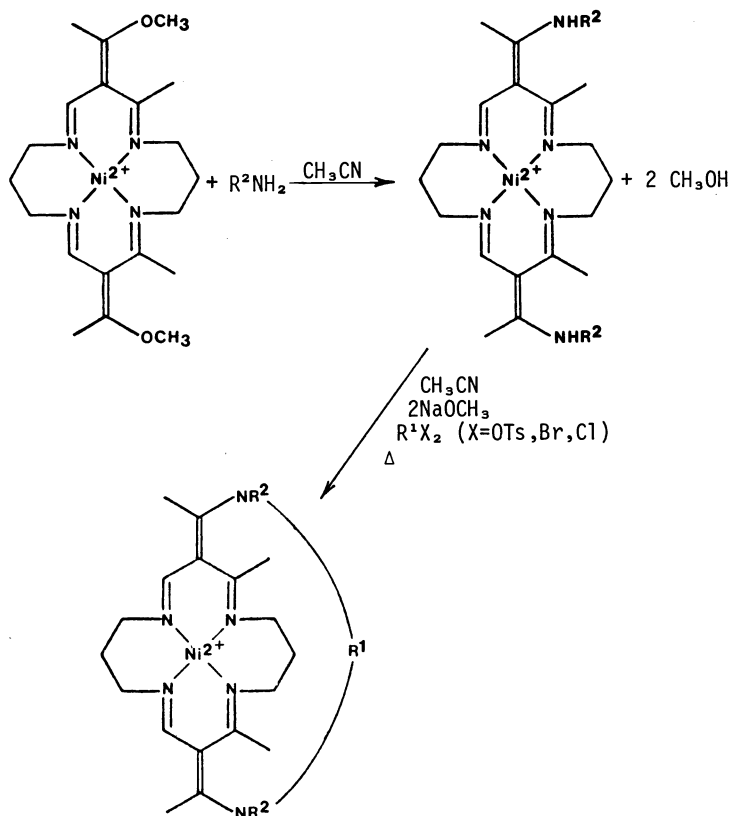


most important being the substitution of the methoxy group by various amino groups (equation 2). This reaction closely parallels amide formation by carboxylate esters and may



be rationalized on the basis of the electron withdrawing effect of the metal ion on the vinyl group. The ring closure reactions are naturally efficient because of the conformation of the methoxyethylidene reagent (8,9). Looking to structure 6, the unsaturated chelate rings rise up on the same side of the NiN₄ plane (x-ray structure, ref. 7) and the saturated chelate rings both project on the other side of the same plane. The resulting saddle shape is ideally suited to the bicyclization reaction. The reaction is generally quite efficient, giving yields in the range 60-90%, when carried out by adding .02M diamine solution dropwise to a .02M solution of the methoxyethylidene complex. Any isomers remain unseparated at this point. High dilution techniques (e.g., slow addition via a peristaltic pump of dilute solutions to a large solvent volume) improve the yields but are needed only in difficult cases. Depending on the availability of reagents, the bicyclization may be more conveniently carried out using a modified regime. As shown in Scheme 1, the methoxyethylidene reagent may first be converted to the bis-alkylamine derivatives and these may then be used in ring closures with various ditosylates or similar reagents.

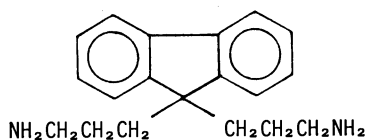
Scheme 1



THE DIMERIC BIMETALLIC COMPLEXES

At least one-third of the ring closures studied gave evidence of isomers. In several cases, these were separated and characterized by the usual methods. In all cases, the isomers are not interconvertible and extensive studies have failed to show evidence for the occurrence of both the lid-on and lid-off isomers for a single specific ligand. A total of seven crystal structures have been solved for compounds containing the dry cave ligands (ref. 1,2 and unpublished results). The lid-on structure was found for only one of these [Fe(CH₃,H,m-xyllyl)Cl]PF₆; the lid-off isomer is the predominant structure for dry cave complexes (10).

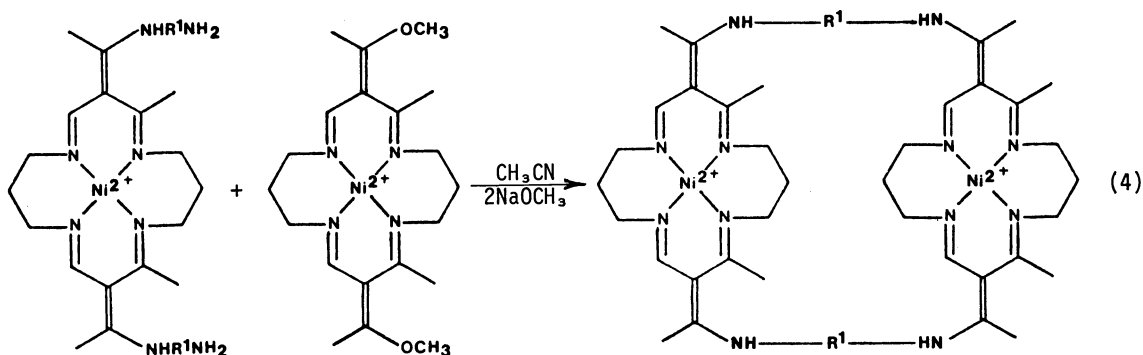
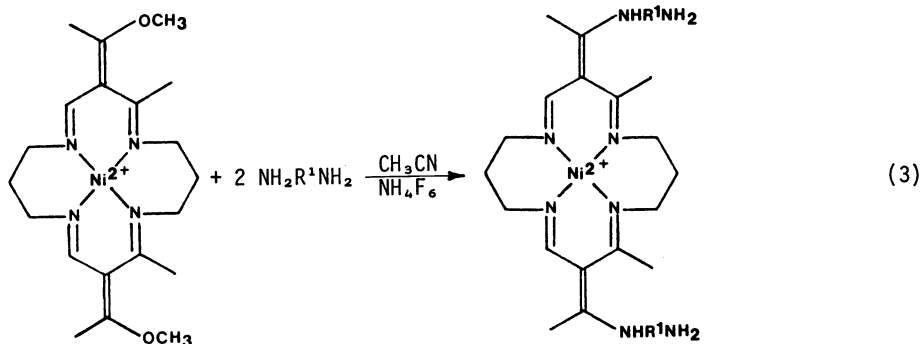
It is important to recognize this point, that the isomerism in question arises from dimerization. Thus, depending on conditions, the bicyclization reaction will produce varying amounts of the monomeric dry cave complex of structure 1 and of the dimeric bimetallic complex of structure 3. This monomer, dimer isomerism has been observed for the ligands characterized by R₃, R₂, R₁ as follows: CH₃,H,(CH₂)_n (n = 4-8); CH₃,CH₃,(CH₂)₁₀; CH₃,H,m-xyllyl; CH₃,H,p-xyllyl; CH₃,H,C₇F₁ (for parent diamine see structure 7).



7.

derivative of nickel (II) (10). Classical molecular weight determinations and related inferential methods were investigated extensively but failed, mainly because of the highly charged electrolyte types involved. It should be emphasized that electrical conductance measurements on dilute solutions including Onsager graphs fail to distinguish adequately between these dimers and monomers. Separate proof of the dimeric structure was achieved by specific synthesis of two of the dimers by the route given in equations 3 and 4.

Certain ligands gave only the monomeric dry cave isomer: CH₃,CH₃,m-xyllyl; CH₃,n-C₄H₉,m-xyllyl; CH₃,C₆H₅CH₂,m-xyllyl; CH₃,CH₃,(CH₂)_n (n = 4-8). Others gave only the dimeric bimetallic isomer: CH₃,CH₃,(CH₂)₂; CH₃,CH₃,(CH₂)₃; CH₃,CH₃,p-xyllyl; CH₃,H,duryl; CH₃,CH₃,duryl. It was possible to classify all of the isomeric structures into either of two types on the basis of chromatographic and solubility behavior and certain features of their nmr spectra. The ultimate proof of the source of the isomerism involved the x-ray structure determination on the dimeric m-xyllyl

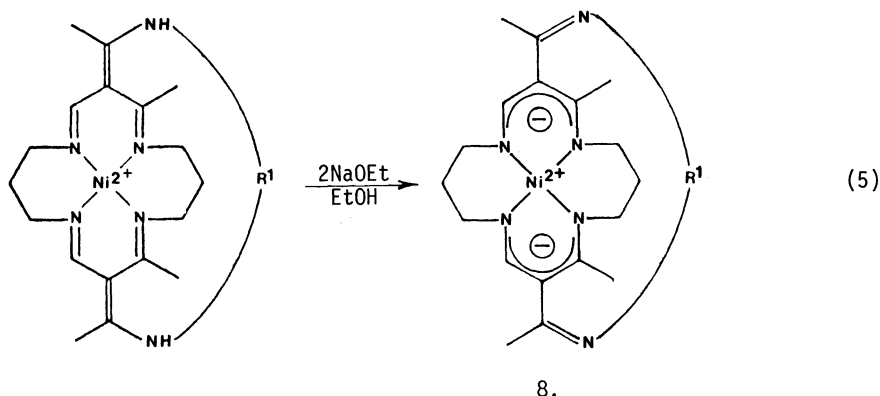


In a number of cases, the separation of the monomer and dimer is conveniently accomplished by fractional crystallization. The dimer commonly separates first from acetonitrile-ethanol solution and is easily purified. The more soluble monomer may be difficult to obtain in pure form, especially if it is much less abundant than the dimer. Chloride or bromide salts of the isomeric mixtures are readily separated by CM-Sephadex column chromatography using aqueous solutions. The tetrapositive dimer is held on the ion exchange column much more strongly than the dipositive monomer. It follows that this chromatographic behavior may also be used to assign structure (dimer versus monomer). Reverse phase HPLC behavior has also been developed as a criterion for identifying these isomers.

The lid-on, lid-off nomenclature can also be applied to the orientation of the linking groups in the dimeric complexes. The x-ray structure of the dimeric *m*-xylene-linked nickel (II) complex shows these linkages to be in the lid-on locations. This is implied in structure 3 and is generally expected on the simplest of steric grounds. The formation of the dimer brings very bulky groups into juxtaposition and it has been shown that bulky groups favor the lid-on position (8). This has been combined with a specific feature of the ¹³C nmr spectra to provide a very convenient preliminary identification technique for the isomers in cases where R₂ and R₃ are both CH₃. For the lid-on dimers, the resonances for these two carbon atoms are separated by about 5-6 ppm and occur near 15-16 and 20-21 ppm from TMS. In contrast, the lid-off monomers show resonances that fall within one ppm of each other and often overlap, at about 20-21 ppm. The single monomer that has the lid-on structure provides a critical test for this correlation. For a monomer, it does indeed show an unusually large separation in these CH₃ resonances, which occur at 20.7 and 14.4 ppm.

NEUTRAL DERIVATIVES OF THE DRY CAVE AND BIMETALLIC COMPLEXES

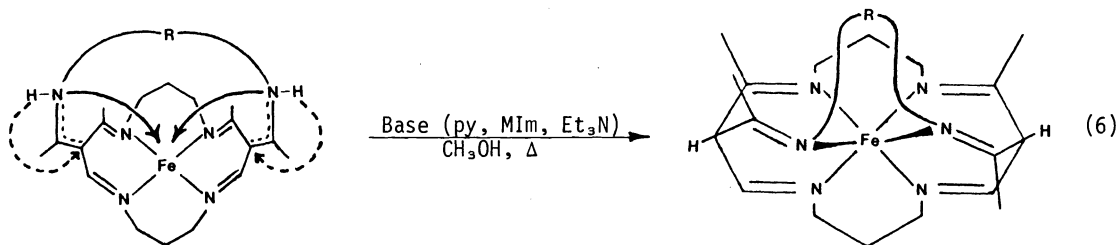
The dry cave complexes for which $R_2 = H$ are readily doubly deprotonated (equation 5) to give



neutral molecules containing structure 8. The deprotonation occurs at the bridge nitrogens; the site of deprotonation was demonstrated using derivatives of nonbridging amines (8). The bridged complexes for which $R_1 = (CH_2)_4$ and *m*-xylyl serve to illustrate the behavior of these species. The infrared spectra show the loss of the hydrogen from nitrogen by disappearance of the N-H absorption from the 3400 cm^{-1} region. Molar conductance shows the species to be nonelectrolytes. Molecular weights were obtained both by osmometry and from the parent peaks in the mass spectra of the neutral derivatives. The neutral *m*-xylyl bridged complex was treated with methyl fluorosulfonate and the product was shown to contain the methylated bridge nitrogens as expected. The neutral complexes are an interesting new family of compounds in their own right; however, they have been very useful as intermediates in the synthesis of selected dry cave and dimeric bimetallic complexes and as derivatives which can be used to prove the molecular weights of those other complexes.

CLATHRO-CHELATE DERIVATIVES OF IRON (II)

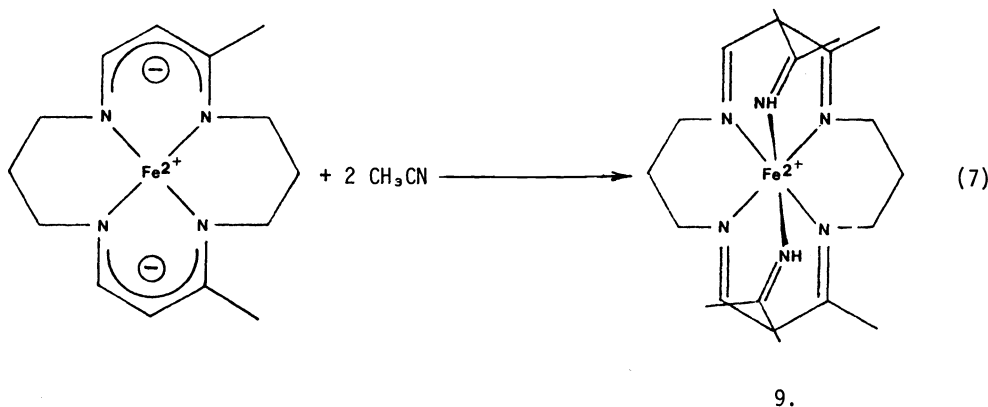
When a nitrogen base, such as imidazole or pyridine, is made available to a high spin, 5-coordinate, chloro complex of iron (II), the usual expectation is displacement of the chloride by the nitrogen base and, when possible, addition of a second mole of the base to form a low spin, 6-coordinate complex. Those monomeric dry cave complexes for which R_2 is H (i.e., those containing secondary amines in the bridge), react quite differently. In fact, they undergo a tautomerization reaction to form complexes having structure 4. This transformation is illustrated for conceptual purposes in equation 6. Although predicted some time



ago (11), only a few clathro-chelates are known and these are of relatively recent origin (6,12-14). Characteristically, they have been synthesized by template reactions with the ligating atoms already in place. Once formed, the clathro-chelate ligand cannot be easily displaced from the metal ion and therefore is not available for separation and subsequent chelation to a different metal ion. The present case is unique in that an intramolecular ligand structural rearrangement leads to formation of the clathro-chelate. In fact, the ligand is synthesized as a dry cave ligand on nickel, removed, chelated to iron (II) as a dry cave ligand and then rearranged *in situ* to the clathro-chelate: The cryptates of Lehn (15) are close analogs of the clathro-chelates but differ because of their commodious interiors and extreme flexibility which permit addition to and removal from certain metal ions without alteration in ligand structure.

The ligands of structure 4 are closely related to the sexadentate chelates (structure 9) formed by the electrophilic addition of acetonitrile to the unsubstituted Jäger macrocycles

(16,17). This reaction is shown in equation 7. It is significant that the imine groups in structure 9 occupy mutually cis positions. The newly formed imine functions in the clathro-

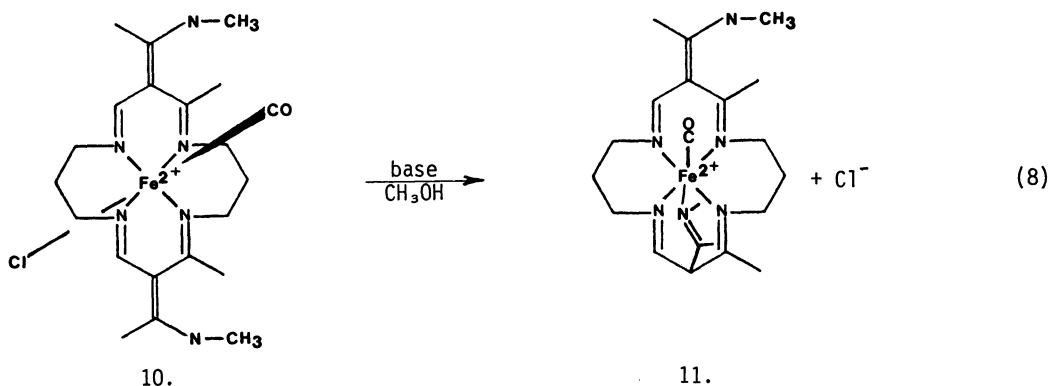


chelate (structure 4) must occupy cis positions and the bridge of the dry cave precursor pre-oriens the groups appropriately. The complexes of structure 9 provided essential information for the facile characterization of the new clathro-chelates. Clathro-chelates have been derived from the dry cave ligands: $\text{CH}_3, \text{H}, (\text{CH}_2)_5$; $\text{CH}_3, \text{H}, (\text{CH}_2)_6$; and $\text{CH}_3, \text{H}, \text{C}_7\text{F}_1$; and the unbridged complex $\text{CH}_3, \text{H}, (\text{CH}_3)_2$. The complexes of structure 4 contain low spin, 6-coordinate iron (II) and a sexadentate ligand that has six unconjugated azomethine groups. Infrared spectroscopy signals the rearrangement by disappearance of the NH stretching mode and by alterations in the spectral region characteristic of C=N groups. New bands occur in the $1605\text{-}1640\text{ cm}^{-1}$ range. Proton nmr confirms structure 4. The bridgehead proton and the adjacent imine carbon proton (H-C=N-) couple and appear as doublets at about 5.7 and 8.7 ppm (from TMS), respectively, with $J_{\text{H-C-N}}$ about 5 Hz. This and other nmr features are closely similar to those of the previously characterized complexes having structure 9.

The electronic spectra contain typical metal to ligand ($\text{M} \rightarrow \pi^*$) charge transfer bands with their colors arising from a band at about 450 nm with a molar extinction coefficient of greater than 6000 and a high energy shoulder at about 400 nm. A second absorption occurs near 300 nm. These are typical charge transfer transitions for low spin iron (II) complexes with imine donors (e.g., $\text{Fe}(\text{bipy})_3^{2+}$). The bands for the clathro-chelate derivatives occur at somewhat lower energies than was found for the analogous species of structure 9 (around 420 nm). For the iron complexes of structure 4, the most dramatic change accompanying the intramolecular rearrangement is the change in oxidation-reduction properties. The $\text{Fe}^{2+}/\text{Fe}^{3+}$ couple for the dry cave complexes generally appears at around -0.400V vs Ag/Ag^+ in CH_3CN . In contrast, the clathro-chelates exhibit $\text{Fe}^{2+}/\text{Fe}^{3+}$ couples at potentials near $+0.380\text{V}$. This change of some 0.8V represents a great stabilization of iron (II) with respect to oxidation. Consequently, the clathro-chelate complexes are indefinitely stable in the air while the parent dry cave complexes react with oxygen, as they were designed to do.

PRODUCTS OF PARTIAL REARRANGEMENT

For certain ligands or under certain circumstances, only one side of the dry cave ligand undergoes the tautomeric rearrangement. The *m*-xylene bridged species $[\text{Fe}(\text{CH}_3, \text{H}, \text{m-xylyl})\text{Cl}]^+$ undergoes this partial rearrangement. Because of the steric limitations of the inflexible bridging group, only one of the nitrogen atoms from the bridge can be brought into the coordination sphere. The complex contains low spin iron (II) and chloride ion acts as the sixth ligand. The infrared and proton nmr spectra contain features typical of both structures 1 and 4, as would be expected. The unbridged complex $(\text{CH}_3, \text{H}, (\text{CH}_3)_2)$ can be caused to undergo partial rearrangement of the corresponding pentadentate ligand by subjecting its CO derivative to rearrangement conditions (equation 8) the CO stretching frequency occurs at 1989 cm^{-1} .



The $\text{Fe}^{2+}/\text{Fe}^{3+}$ couple for the partially rearranged m-xylene derivative occurs at -0.25V causing it and its homologs to be slightly less sensitive to oxygen than their dry cave counterparts.

ACKNOWLEDGEMENT

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