plane 2 in Figure 4a) are equivalent. In the other orientation, shown in Figure 4b, the nitrate ion is relatively strongly hydrogen-bonded to the ammine ligand NH1, and therefore, the two α-pyrrolidonate rings experience trans effects from the ammine ligands to different degrees and would be inequivalent. These differences of the bridging ligands within the molecule give three different environments for the α-pyrrolidonate rings at a relative statistical weight of 2:1:1. The intensities of the three peaks for C4 in Figure 2a are ca. 1:2:1 and reasonably support the inequivalence of the α-pyrrolidonate rings. The peak for C3 splits only into two but this is probably due to the overlapping of the peaks.

In 3.6 M D_2SO_4, each carbon peak does not show any splitting (Figure 2b) except the satellites for C2, which is due to the Pt nucleus ($I = {}^1/_2$, 33.7%). No isomerization between H-H and H-T isomers is observed.

For comparison, ^{13}C and ^{195}Pt NMR spectra of other α-pyrrolidonate-bridged Pt(III) complexes were measured. The ^{13}C spectrum of **2** is basically the same as the spectrum of **5**, which means ^{13}C chemical shift is not considerably affected by whether the complex is tetranuclear or binuclear or by what the axial coordination ligands are. However, the coupling constants $^3J_{C-Pt}$ for the C2 carbon atom are significantly different (see the Results). The ^{195}Pt NMR spectrum of **2** measured at 0 °C shows two peaks at −843 ppm and −316 ppm. These two values correspond to the inner and outer Pt atoms of the tetranuclear complex and are significantly lower than those reported for the analogous α-pyridonate-bridged binuclear Pt(III) complex $[Pt_2(en)_2(C_5H_4NO)_2(NO_2)(NO_3)](NO_3)_2 \cdot 0.5H_2O$ (−1141 and 541 ppm).[18] The solution of **2** is not stable and, if the measurement is carried out overnight at room temperature the peak at −843 ppm diminishes and a new peak appears at 196 ppm. We infer from the chemical shift that this spectral change corresponds to a structural change from the tetranuclear **2** to a binuclear Pt(III) complex similar to **5** although its axial ligands are unknown. However, no convincing evidence supporting this reaction is available at the moment. The reaction is by no means such one as produces a Pt(II) complex via reduction of **2** by water,[15] since the chemical shift is undoubtedly that of a Pt(III) species. We tried to obtain a ^{195}Pt NMR spectrum of **5** in order to compare the spectrum with that of the reaction product of **2**; however, no reliable spectrum was obtained presumably because a very gradual reaction was occurring in the solution.

The ^{13}C NMR spectrum of binuclear Pt(III) complex **6** (Figure 3) suggests that its structure is basically analogous to that of **5** with Me-Im and a sulfate ion as axial ligands. From steric considerations similar to the nitrate and nitrite coordinations in the Pt(III) dimer **5**, it would be reasonable to assume that Me-Im coordinates to the N_2O_2-coordinated Pt atom and a sulfate ion coordinates to the N_4-coordinated Pt atom.

The ^{195}Pt NMR spectrum of **6** shows two peaks at −845 and +205 ppm, which is in agreement with a H-H binuclear Pt(III) structure. The similarity of these chemical shifts to those of the reaction product of **2** (−843 and +196 ppm) suggests that both complexes have a basically similar structure, i.e., a H-H Pt(III) dimer.

Conclusion

The present study demonstrates for the first time the existence of binuclear and tetranuclear α-pyrrolidonate-bridged Pt(III) complexes. Addition of Me-Im to the tetranuclear Pt(III) complex **2** affords the binuclear Pt(III) complex **5**. Oxidation of the mixed-valent tetranuclear complex **1** electrochemically or with $Na_2S_2O_8$ gives the tetranuclear Pt(III) complex **2**, whereas oxidation of **1** by HNO_3 affords the binuclear Pt(III) complex **5**. These facts suggest that axial coordination of significantly strongly coordinating ligands to the tetranuclear complex leads to formation of binuclear Pt(III) complexes. The stabilities of the binuclear Pt(III) complexes versus platinum reduction by water significantly differ depending on the axial ligands.

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Registry No. **1**, 80612-40-4; **2**, 100992-71-0; **2a**, 100927-47-7; **5**, 125840-55-3; **5**·H_2O, 125840-56-4; **6**, 136504-59-1; Pt, 7440-06-4; ^{195}Pt, 14191-88-9.

Supplementary Material Available: Details of the X-ray data collection (Table S1), anisotropic temperature factors (Table S2), distances of possible hydrogen bondings (Table S4), and a depiction of the crystal packing (Figure S1) (4 pages); the observed and calculated structure factors (Table S3) (12 pages). Ordering information is given on any current masthead page.

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Design, Synthesis, and Structure of a Macrocyclic Tetraamide That Stabilizes High-Valent Middle and Later Transition Metals

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High-valent middle and later transition-metal centers tend to oxidatively degrade their ligands. A series of ligand structural features that prevent discovered decomposition routes is presented. The result of the iterative design, synthesis, and testing process described is the macrocyclic tetraamide H_4[**1**]. H_4[**1**] is the parent acid of the macrocyclic tetraamido-*N* ligand $[\eta^4$-**1**$]^{4-}$, which has been shown to stabilize high-valent middle and later transition-metal complexes unavailable in other systems. The features presented provide insights useful to the development of new compounds for homogeneous oxidations and of model compounds for high-valent reactive intermediates in catalytic oxidations in chemistry and biology. The crystal structures of H_4[**1**] and a copper complex of one of its synthetic precursors reveal intramolecular and intermolecular hydrogen bonding patterns that are relevant to recent developments in the ordering effects of hydrogen bonding on solution and solid-state structures. The synthetic value of these ordering effects is discussed.

Introduction

The range of stable high-valent middle and later transition-metal complexes is limited by the small number of suitable ligands. The metal centers in such species usually possess a strong driving force for gaining electrons, and as the nearest source of electrons, the ligand complement is usually vulnerable to one or more of a variety of processes that range from nondestructive polarization in bonding to destructive oxidation events. It is possible to identify the processes and characterize the mechanisms by which a highly

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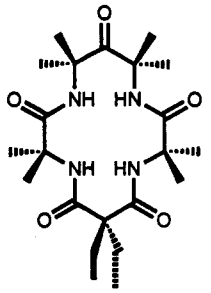
oxidizing metal center may gain electrons from its ligand complement.[2] With this understanding, it is possible to suppress or completely block these mostly undesirable processes by redesigning the ligand complement.[3]

In this paper, we will describe how the interplay between design and testing has been carried out in one specific ligand family to give a ligand that is compatible with highly oxidized middle and later transition-metal species of definitive oxidation states. We present the design history, synthesis, and characterization of $H_4[1]$,



$H_4[1]$

the parent acid of the macrocyclic tetraamido-*N* ligand $[\eta^4\text{-}1]^{4-}$. This tetraanionic ligand is a strong donor and is resistant to oxidative destruction. It has allowed rare high-valent metal centers such as five-coordinate Fe(IV)[3c] and four-coordinate Ni(III)[3e] to be isolated and fully characterized. The insights gained in developing $H_4[1]$ are pertinent to the development of high-valent transition-metal enzyme models and catalytic oxidants.

The hydrogen-bonding networks found in the crystal structures presented and their relevance to recent studies in other fields are also discussed. The intermolecular hydrogen bonding found in the copper(II) complex of a Schiff base intermediate to the macrocycle provides more supporting evidence for empirical rules developed to predict solid-state interactions.[4] The intramolecular hydrogen bonding in $H_4[1]$ is relevant to recent studies of the solution and solid-state conformations of linear polyamides.[5]

Experimental Section

Materials. All solvents and reagents were reagent grade (Aldrich) except for CH_2Cl_2, concentrated HCl, glacial acetic acid, EtOH, NaOH, and CCl_4 (Fisher, reagent grade) and were used as received.

Physical Measurements. ^1H NMR spectra were measured at 300 MHz on an IBM NR/300 FT-NMR spectrometer or at 90 MHz on a Varian EM-390 spectrometer. ^1H NMR data are reported in δ (ppm) vs $(CH_3)_4Si$ with the deuterated solvent proton residuals used as internal standards. Infrared data were obtained on a Beckman IR 4240 spectrophotometer or on a Nicolet 5DXB FT-IR spectrophotometer. Crystal structures were solved by Crystalytics Co. of Lincoln, NE.

Safety Note. The organic azides produced in the following syntheses are never isolated in concentrated form as oils or as solids in quantities greater than 20 mg.

Synthetic Note. Compounds B–D have been previously prepared.[6] We have modified these procedures as discussed below.

2,4-Dibromo-2,4-dimethylpentanone (B). To 2,4-dimethylpentanone (85 mL, 68.5 g, 0.60 mol) in CCl_4 (1000 mL) was added *N*-bromosuccinimide (NBS) (240 g, 1.35 mol, 2.26 equiv). The mixture was heated under reflux, and benzoyl peroxide (20 mg) was added to the solution. While the solution was heated under reflux (24 h), a pale orange solid (succinimide) floated to the surface of the CCl_4, while unreacted NBS remained on the bottom. Benzoyl peroxide was added to the refluxing mixture (20 mg; 12–24 h intervals) until no NBS was visible; usually, the reaction was complete after 24 h. When the reaction was complete, the solids were collected by filtration and discarded and the CCl_4 was removed from the mother liquor under reduced pressure, leaving a pale yellow oil. To remove residual CCl_4, 95% EtOH (100 mL) was added and the solvents were removed under reduced pressure to leave a yellow oil (159.99 g, 0.59 mol, 98%). ^1H NMR ($CDCl_3$): 2.1 (s).

2,4-Diazido-2,4-dimethylpentanone (C). A solution of B (89.8 g, 0.33 mol) in EtOH (1200 mL, 95%) was added to a solution of NaN_3 (*Caution!*) (47.2 g, 0.726 mol, 2.2 equiv) in water (600 mL). The solution was heated under reflux (16 h) to give a pale orange solution. The EtOH was removed under reduced pressure until the solution became cloudy. The cloudy aqueous solution was extracted with pentane (500 mL) three times, and the combined extracts were dried over Na_2SO_4 and concentrated to 300 mL under reduced pressure. Glacial acetic acid (100 mL) was then added, and the remaining pentane was removed under reduced pressure. It is important to execute this procedure to remove the NaN_3, since the product is exposed to Pd/C in the next step, and care should be taken to avoid the formation of a heavy metal azide. The pentane was removed from a small sample under reduced pressure to give a neat oil (<20 mg) for spectroscopic characterization: ^1H NMR ($CDCl_3$): 1.54 (s). IR (neat): 2115 cm^{-1} ($\nu(N_3)$), 1720 cm^{-1} ($\nu(CO)_{ketone}$).

2,4-Diamino-2,4-dimethylpentanone (D). Glacial acetic acid (50 mL) was added to the HOAc solution from the previous step, and this solution was added to 10% Pd/C (2.7 g). The mixture was hydrogenated at 50 psi (1 week) in a Parr hydrogenator. Because the reaction evolves one N_2 molecule for every H_2 molecule absorbed, the bomb was evacuated and refilled with H_2 10 times. (H_2 from the high-pressure reservoir is not efficiently consumed.) The charcoal was removed by filtration. The HOAc was removed under reduced pressure. After HBr was added (48%, 76 mL), the mixture was dissolved in EtOH. The volatiles were removed under reduced pressure to yield a tan solid, which was washed with a mixture (200 mL) of THF (50%), EtOH (45%), and 48% HBr (5%). The white powdery product was the dihydrobromide salt of D (56.2 g, 48% from B). ^1H NMR ($CDCl_3$/DMSO-d_6) of D·2HBr: 8.62 (6 H, s, br, NH_3), 1.77 (12 H, s, Me). IR (free base, Nujol): 3460–3160 cm^{-1} ($\nu(NH_2)$), 1690 cm^{-1} ($\nu(CO)_{ketone}$). The product must be stored as the dihydrochloride or dihydrobromide salt.

Bis-2,4-(2-bromo-2-methylpropanamido)-2,4-dimethylpentanone (E). The compound D·2HBr (24.25 g, 0.073 mol) and Et_3N (40 mL) were added to CH_2Cl_2 (500 mL). The mixture was dried over Na_2SO_4 (1 h) and then filtered into a three-neck round-bottom flask (1 L) equipped with a reflux condenser and a pressure-equalizing addition funnel. Under a N_2 atmosphere, bromoisobutyryl bromide (20 mL, 0.162 mol) was carefully added to the solution from the addition funnel to avoid boiling the solvent. (*The reaction is VERY exothermic.*) The solution became cloudy upon production of $[Et_3NH]Br$. After being stirred (1 h), the reaction mixture was washed twice with dilute aqueous HCl and twice with dilute aqueous Na_2CO_3. The resultant CH_2Cl_2 solution was dried over Na_2SO_4 to give a clear, pale yellow solution. The CH_2Cl_2 was removed under reduced pressure, yielding the white solid product (32.3 g, 100% yield). Anal. Calcd for E: C, 40.74; H, 5.93; N, 6.34. Found: C, 40.54; H, 5.88; N, 6.24. ^1H NMR ($CDCl_3$): 7.42 (2 H, s, NH), 1.90 (12 H, s, Me), 1.65 (12 H, s, Me). IR (Nujol): 3327 cm^{-1} ($\nu(NH)$), 1724 cm^{-1} ($\nu(CO)_{ketone}$), 1652 cm^{-1} ($\nu(CO)_{amide}$).

Bis-2,4-(2-azido-2-methylpropanamido)-2,4-dimethylpentanone (F). NaN_3 (*Caution!*) (40 g, 0.55 mol, 2.5 equiv) was dissolved in water (500 mL), and the solution was added to a solution of E (95 g, 0.22 mol) in EtOH (800 mL, 95%). The mixture was heated under reflux (30 h). The EtOH was removed under reduced pressure until the solution became cloudy. The aqueous solution was extracted twice with CH_2Cl_2, and the extract was dried over anhydrous Na_2SO_4. It is important to execute this procedure to remove the NaN_3, since the product is exposed to Pd/C in the next step and care should be taken to avoid the formation of a heavy metal azide. The solution was concentrated carefully under reduced pressure so the procedure could be halted before the oil or solid separated. EtOH (ca. 250 mL) was added, and the solution was again

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concentrated under reduced pressure. A small sample was isolated as a solid for spectroscopic characterization. ^{1}H NMR ($CDCl_3$): 7.28 (2 H, s, NH), 1.62 (12 H, s, Me), 1.50 (12 H, s, Me). IR (Nujol): 3440–3260 cm^{-1} (ν(NH)), 2110 cm^{-1} ($\nu(N_3)$), 1713 cm^{-1} ($\nu(CO)_{ketone}$), 1675 cm^{-1} ($\nu(CO)_{amide}$).

H[2]. About 26 g of F were dissolved in EtOH (100 mL) and H_2O (9 mL) and hydrogenated with 10% Pd/C (1.51 g) at 50 psi (4 days) with five purgings (see synthesis of D). The dihydrobromide salt (32.77 g, 82% from E) was obtained after a workup similar to that used for D. ^{1}H NMR (after isolation of the free base of H[2]) ($CDCl_3$): 8.63 (1 H, s, amide NH), 7.60 (1 H, s, amide NH), 1.52 (6 H, s, Me), 1.42 (6 H, s, Me), 1.27 (6 H, s, Me), 1.18 (6 H, s, Me), amine proton resonance broad and underneath methyl singlets. IR (Nujol): 3260–3180 cm^{-1} (ν(NH, weak)), 1679 cm^{-1} ($\nu(CN)_{imine}$), 1648 cm^{-1} ($\nu(CO)_{amide}$).

Bis-2,4-(2-amino-2-methylpropanamido)-2,4-dimethylpentanone (G). The Schiff base H[2] (4.60 g) was dissolved in EtOH (35 mL, 95%), and HBF_4 (5.5 mL, 48%, diluted with 7 mL water) was added. The solution was added to a glass bomb (125 mL volume) which was placed in a silicone oil bath and heated (104–108 °C, 3 h) [*Caution*—Pressure!]. The solution was chilled in an ice bath, and a chilled aqueous syrupy slurry of NaOH was added until the pH was ≈12. The mixture was immediately taken to a viscous, but still freely stirring, sludge without heat under reduced pressure. CH_2Cl_2 was added (150 mL), and the mixture was stirred (5 min). Na_2SO_4 was added rapidly with swirling (10 s) to dry the mixture and was filtered away immediately. The sodium salts were washed several times with CH_2Cl_2, and the combined CH_2Cl_2 solutions were taken to dryness in a weighed round-bottom flask at room temperature under reduced pressure to yield the solid product (4.44 g, 97%). The compound is stored as a solid; it recyclizes in solution. Whenever more than 20% H[2] impurity was found in G, the above procedure was repeated until G was at least 80% pure before proceeding to the next step. ^{1}H NMR ($CDCl_3/CCl_4$) of the free base: 8.19 (2 H, s, amide NH), 1.61 (12 H, s, Me), 1.48 (4 H, s, amine NH_2), 1.34 (12 H, s, Me). ^{1}H NMR (D_2O) of the free base: 1.52 (12 H, s, Me), 1.27 (12 H, s, Me). ^{1}H NMR (D_2O) of G·2HBF_4: 1.24 (12 H, s, Me), 1.21 (12 H, s, Me). IR (Nujol, free base): 3390–3290 cm^{-1} ($\nu(NH)_{amide/amine}$, strong), 1703 cm^{-1} ($\nu(CO)_{ketone}$), 1650 cm^{-1} ($\nu(CO)_{amide}$).

H_4[1]. The diamine G (4.44 g) was dissolved in CH_2Cl_2 (800 mL), and Et_3N (9.9 mL) was added. After diethylmalonyl dichloride (2.45 mL) was added, the reaction was stirred under N_2 (10 h). The reaction was washed three times with dilute aqueous HCl and three times with dilute aqueous Na_2CO_3. After being dried over Na_2SO_4 the solution was concentrated to a pale yellow oil under reduced pressure. Several small portions of boiling CH_2Cl_2 were used to wash the oil into a 150-mL beaker (60 mL total). CCl_4 (40 mL) was added, and the solvent volume was reduced to 50 mL by boiling. Upon cooling, white microcrystalline H_4[1] floated to the surface of the solution. The crystals were filtered and washed twice with CH_2Cl_2 (3 mL) and then twice with pentane (10 mL). The crystalline product was pure (2.06 g, 32.3%, 12.1% from 2,4-dimethylpentanone). Anal. Calcd for H_4[1]·CH_2Cl_2: C, 52.77; H, 7.70; N, 10.70. Found: C, 52.67; H, 7.61; N, 10.63. (The presence of one CH_2Cl_2 per molecule of H_4[1] was quantified by ^{1}H NMR.) Mp: 273–276 °C. ^{1}H NMR ($CDCl_3$): 6.58 (2 H, s, amide NH, broad), 6.22 (2 H, s, amide NH, broad), 2.0 (4 H, broad, methylene), 1.52 (12 H, s, Me), 1.47 (12 H, s, Me), 0.89 (6 H, t, Me–ethyl, J = 7.5 Hz). IR (Nujol): 3500 cm^{-1} ($\nu(NH)_{amide}$, weak), 3450 cm^{-1} ($\nu(NH)_{amide}$, medium), 3405 cm^{-1} ($\nu(NH)_{amide}$, strong), 3377 cm^{-1} ($\nu(NH)_{amide}$, very strong) (all amide NH stretches are very sharp for H_4[1]), 1702 cm^{-1} ($\nu(CO)_{ketone}$), 1680 cm^{-1} ($\nu(CO)_{amide}$), 1645 cm^{-1} ($\nu(CO)_{amide}$). Crystals suitable for diffraction were grown by vapor diffusion of pentane into a 1,2-dichloroethane solution.

CuCl(η^3-2). The diamine G (0.92 g) was dissolved in EtOH (100%, 20 mL), and $Cu(OAc)_2$·$2H_2O$ (0.673 g) was added. NaOH pellets (0.25 g) were added to the solution and dissolved with stirring, while the solution turned dark blue. Removing the EtOH under reduced pressure yielded a dark blue solid (1.43 g). A portion of this solid (0.107 g) was added to dry THF (20 mL), excess NaH was added, and then diethylmalonyl dichloride (0.10 g) was added. A pale blue solid (0.056 g) was isolated from the THF and crystals suitable for diffraction were grown from THF. A compound with identical properties was prepared by reacting $CuCl_2$·$2H_2O$ (0.400 g) with G (0.745 g) and NaOH (0.105 g) in absolute EtOH (20 mL). The compound was purified by removing the EtOH under reduced pressure, dissolving the residue in MeCN, filtering, and adding Et_2O to precipitate the product (0.576 g, 62.1%). IR (Nujol): 3500–3100 cm^{-1} ($\nu(NH)_{amide/amine}$, weak), 1682 cm^{-1} ($\nu(CN)_{imine}$), 1620 cm^{-1} ($\nu(CO)_{amide}$), 1590 cm^{-1} ($\nu(CO)_{amide}$).

X-ray Data Collection and Structure Refinement of H_4[1]·$C_2H_4Cl_2$ and CuCl(η^3-2)·THF. Crystal data: Single crystals of H_4[1]·$C_2H_4Cl_2$, at 20 ± 1 °C, are monoclinic, space group, $P2_1/c$, C_{2h}^5 (No. 14), with a = 14.193 (4) Å, b = 11.700 (3) Å, c = 18.328 (5) Å, β = 105.03 (1)°, V = 2940 (1) Å^3, and Z = 4 formula units (d_{calcd} = 1.215 g cm^{-3}). A total of 4053 independent reflections having 2θ(Mo K$\bar{\alpha}$) < 45.8° (the equivalent of 0.60 limiting Cu K$\bar{\alpha}$ spheres) were collected on a computer-controlled Nicolet autodiffractometer using full (0.90° wide) ω scans and graphite-monochromated Mo K$\bar{\alpha}$ radiation. The dichloroethane solvent molecule of crystallization is disordered, with its non-hydrogen atoms occupying four of six sites in the lattice at any given time. Single crystals of CuCl(η^3-2)·THF are orthorhombic (space group $Pna2_1$, C_{2v}^9 (No. 33), at 20 ± 1 °C), with a = 15.953 (3) Å, b = 13.711 (2) Å, c = 10.229 (2) Å, V = 2237 (1) Å^3, and Z = 4 formula units (d_{calcd} = 1.385 g cm^{-3}). A total of 2723 independent reflections having 2θ(Mo K$\bar{\alpha}$) < 55° (the equivalent of 1.0 limiting Cu K$\bar{\alpha}$ spheres) were collected on a computer-controlled Nicolet autodiffractometer using full (0.90° wide) ω scans and graphite-monochromated Mo K$\bar{\alpha}$ radiation. The structures were solved using Direct Methods techniques with the Nicolet SHELXTL software package as modified at Crystalytics Co. The resulting structural parameters have been refined to convergence: R_1 (unweighted, based on F) = 0.037 for 1983 independent reflections having $2\theta_{MoK\bar{\alpha}}$ < 45.8° and $I > 3\sigma(I)$ for H_4[1]·$C_2H_4Cl_2$, and R_1 (unweighted, based on F) = 0.035 for 1917 independent reflections having $2\theta_{MoK\bar{\alpha}}$ < 55.0° and $I > 3\sigma(I)$ for CuCl(η^3-2)·THF using counterweighted cascade block-diagonal least-squares techniques and a structural model that incorporated anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The methyl groups were included in the refinements as idealized sp^3 rigid rotors.

Results and Discussion

Design Features. The processes by which ligand complements transfer electrons or electron density to an oxidizing metal center are of two classes: (I) destructive processes and (II) nondestructive processes. The ligand $[\eta^4$-1$]^{4-}$ contains a series of structural features that overcome complications of both classes identified in work with earlier ligands. These protecting structural features can be summarized as follows. Class I complications: (i) The ligand $[\eta^4$-1$]^{4-}$ is *gem*-dimethylated at the saturated carbon atoms α to the nitrogens and β to the metal. The methyl groups replace H substituents on the chelate backbones of earlier ligands that were found to lead to destructive two-electron reductions of the metal (Figure 1a).[2] This type of protection was first employed by Margerum with acyclic ligands.[7] The H substituents can also be replaced by an aromatic group.[3b,d,f] (ii) The ligand $[\eta^4$-1$]^{4-}$ does not contain heteroatom substituents on the chelate backbone with lone pairs capable of significant overlap with the σ^* orbital of the C–C bond in the five-membered chelate rings. Such substituents were found to lead to destructive two-electron reductions of the metal in earlier ligands (Figure 1b).[2] (iii) Heteroatom donors in the chelate system of $[\eta^4$-1$]^{4-}$ are all amido-*N* ligands. In contrast with alkoxide donors of earlier systems, the nitrogen lone pairs have minimal overlap with the σ^* orbitals of the C–C bond in the five-membered chelate rings, an arrangement believed to provide protection against heterolytic ligand oxidative decomposition (Figure 1c). (iv) The macrocyclic structure is believed to protect against homolytic ligand oxidative decomposition, another possible pathway for oxidative decomposition of earlier ligands (Figure 1d).[8] The above four features provide $[\eta^4$-1$]^{4-}$ with superior resistance to oxidative destruction. Nondestructive Class II complications can also occur, and $[\eta^4$-1$]^{4-}$ has been designed to eliminate one of these in particular. The ligand, $[\eta^4$-1$]^{4-}$, has no extended π-systems conjugated with the metal center and is therefore termed an innocent ligand. Noninnocent ligands have extended π-systems conjugated with the metal center, and this leads to ambiguities in the formal oxidation state assignment at the metal center (Figure 1e).[9]

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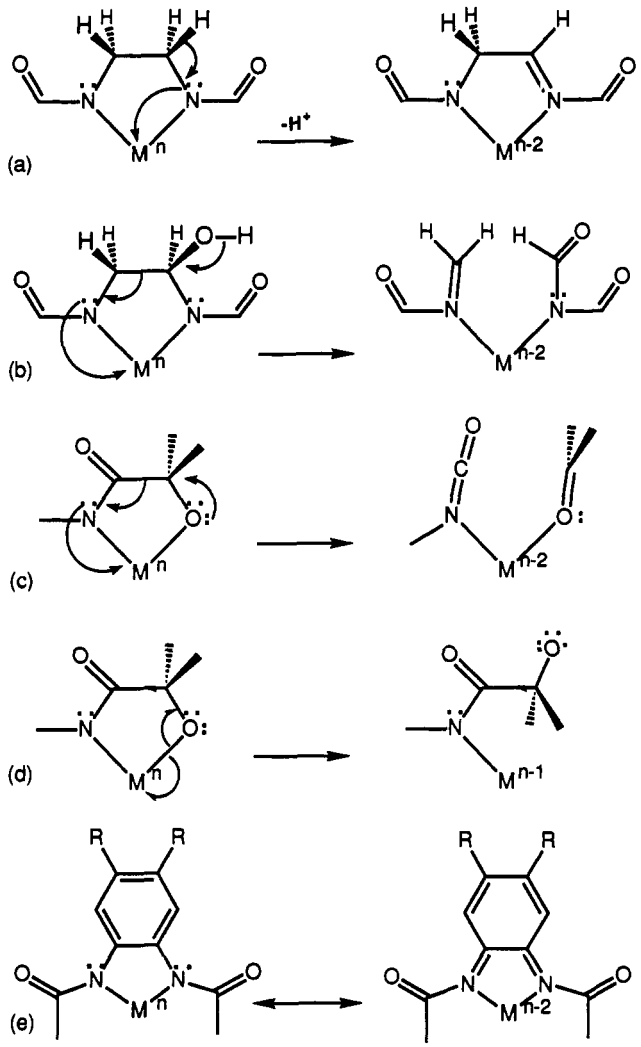


Figure 1. Destructive (a–d) and nondestructive (e) means of transferring electron density from a ligand to a metal. Subsequent homolytic steps not shown in part d also lead to C–C bond scission.

The ligand $[\eta^4\text{-}1]^{4-}$ combines the properties of oxidation resistance and high donor capacity.[10] The combination of these properties has permitted the isolation of stable high-valent middle transition-metal complexes in rare coordination geometries and in definitive rare oxidation states (e.g., five-coordinate Fe(IV)[3c] and four-coordinate Ni(III)[3e]). Crystallographically characterized complexes of $[\eta^4\text{-}1]^{4-}$ are shown in Figure 2. The complexes have low formal reduction potentials (e.g., Fe(IV/III) = +0.645 V vs NHE, Ni(III/II) = +0.130 V vs NHE). CPK models suggest that complexes of $[\eta^4\text{-}1]^{4-}$ will have at least one nonplanar amide arising from ring strain induced by coordination. Dunitz analyses[11] (Figure 3) of all of the structurally characterized complexes of $[\eta^4\text{-}1]^{4-}$ have revealed at least one nonplanar amide in each complex. ($[Et_4N][FeCl(\eta^4\text{-}1)]$:[3c] $\bar{\tau} = -16.9°$, $\chi_N = 7.3°$, $\chi_C = -3.2°$. $[Et_4N][Ni(\eta^4\text{-}1)]$:[3e] $\bar{\tau} = 17.3°$, $\chi_N = 28.6°$, $\chi_C = 2.9°$. $[Me_4N][Co(\eta^4\text{-}1)]$:[3a] $\bar{\tau} = -22.3°$, $\chi_N = -23.8°$, $\chi_C = -0.6°$.) The Cr(V) complex $[Cr(O)(\eta^4\text{-}1)]^-$ has four nonplanar amides.[3d] (The most nonplanar amide in $[(CH_3)_4N][Cr(O)(\eta^4\text{-}1)]$ has $\bar{\tau} = 28.4°$, $\chi_N = 24.0°$, and $\chi_C = 0.6°$.) As discussed below, $H_4[1]$ has one amide that shows significant nonplanarity for an organic amide, even though $H_4[1]$ adopts a conformation significantly different from its coordinated tetraanionic form.

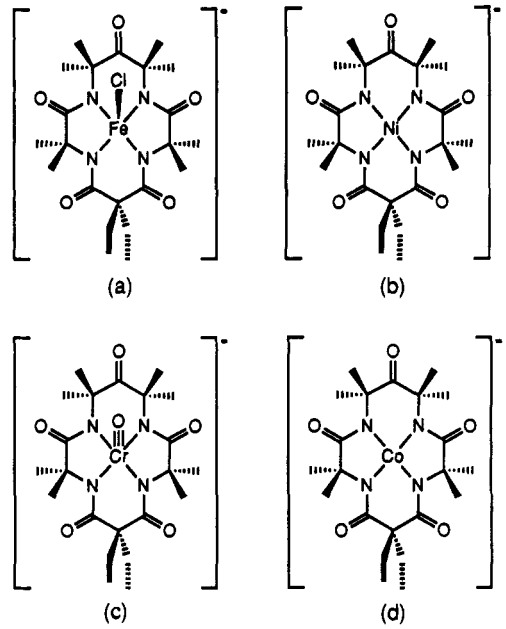


Figure 2. Crystallographically characterized complexes of $[\eta^4\text{-}1]^{4-}$: (a) $[Fe^{IV}(Cl)(\eta^4\text{-}1)]^-$; (b) $[Ni^{III}(\eta^4\text{-}1)]^-$; (c) $[Cr^{V}(O)(\eta^4\text{-}1)]^-$; (d) $[Co^{III}\text{-}(\eta^4\text{-}1)]^-$.

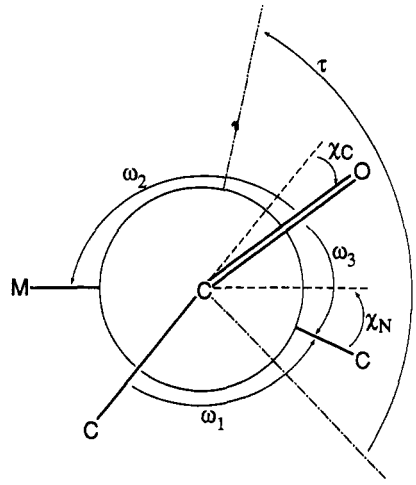


Figure 3. Dunitz amide nonplanarity parameters. For $H_4[1]$ and the unligated amide of $CuCl(\eta^3\text{-}2)\cdot THF$, M = H.

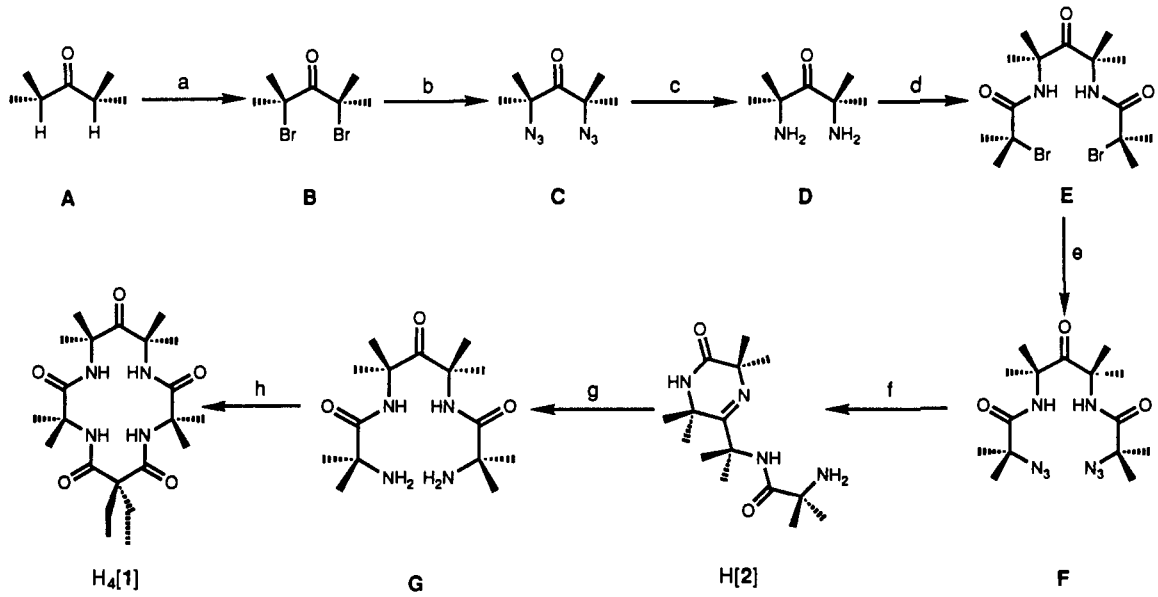
With related macrocyclic tetraamido-*N* ligands, it has been possible to prepare stable Mn(V)–oxo complexes,[3b] as well as stable highly oxidizing complexes of cobalt.[3f] We have previously discussed the unusual conditions needed to metalate $[\eta^4\text{-}1]^{4-}$ and related macrocyclic tetraamido-*N* ligands;[3f] all first-row metals from chromium to copper have been coordinated in high yields.

Synthesis. The synthesis of $H_4[1]$ is presented in Scheme I. The 2,4-dimethylpentanone (A) is brominated with NBS in high yield to give the dibromide (B). Conversion to the diazide (C) (which is never isolated in quantities greater than 20 mg), followed by reduction, yields the diamine (D). Although D may be produced in large quantities, it must be stored as its dihydrohalide salt. Acylation of D with bromoisobutyryl bromide proceeds nearly quantitatively to give the diamide dibromide (E), which is readily converted to the diamide diazide (F). Reduction of F with $(NH_4)_2S$, neutral ethanolic $Pd/C/H_2$, $Pd/C/H_2$ in acetic acid,

(10) For the elucidation of the strong σ-donor strength of amido-*N* ligands, see, for example: (a) Margerum, D. W. *Pure Appl. Chem.* **1983**, *55*, 23–34. (b) Margerum, D. W. *Oxidases Relat. Redox Syst., Proc. Int. Symp., 3rd, 1979* **1982**, 193–206.

(11) The twist angle τ and the pyramidalization terms χ_C and χ_N are obtained from the primary torsion angle data ω_1, ω_2, and ω_3 as follows: $\tau = (\omega_1 + \omega_2)/2$; $\chi_N = (\omega_2 - \omega_3 + \pi) \bmod 2\pi$; $\chi_C = (\omega_1 - \omega_3 + \pi) \bmod 2\pi$. Here we use the modified twist angle, $\bar{\tau}$: $\bar{\tau} = (\tau)$ and π.[10d,e] $\bar{\tau}$ maximizes at ±90° and can be interpreted as the angle between the idealized positions of the $p\pi$ orbitals on C and N. (a) Dunitz, J. D.; Winkler, F. K. *J. Mol. Biol.* **1971**, *59*, 169–182. (b) Dunitz, J. D.; Winkler, F. K. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1975**, *B31*, 251–263. (c) Warshel, A.; Levitt, M.; Lifson, S. *J. Mol. Spectrosc.* **1970**, *33*, 84–99. (d) Collins, T. J.; Coots, R. J.; Furutani, T. T.; Keech, J. T.; Peake, G. T.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1986**, *108*, 5333–5339. (e) Collins, T. J.; Workman, J. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 912–914 and references therein.

Scheme I. Synthesis of $H_4[1]$[a]



[a] Key to synthesis steps: (a) NBS, CCl_4, Δ; (b) NaN_3, $EtOH/H_2O$, Δ; (c) Pd/C, H_2, HOAc; (d) bromoisobutyryl bromide, Et_3N, CH_2Cl_2; (e) NaN_3, $EtOH/H_2O$, Δ; (f) Pd/C, H_2, $EtOH/H_2O$; (g) $EtOH/H_2O$, HBF_4 (pH = 1), 104–108 °C (3 h), NaOH; (h) diethylmalonyl dichloride, Et_3N, CH_2Cl_2.

or basic ethanolic $Pd/C/H_2$ yields not the diamide diamine (G), but the Schiff base (H[2]).

The most important challenge for obtaining reasonable yields of $H_4[1]$ via the described synthetic route involves mastering the diamide diamine/Schiff-base equilibrium. We will now treat this segment of the synthesis in detail. The best method we have found for hydrolyzing H[2] is to heat it at 104–108 °C in a bomb in an aqueous ethanolic solution of HBF_4 (pH = 1) for 3 h. Fortunately, no amide hydrolysis is observed under these conditions. Once opened, the system will not recyclize in aqueous acid. However, with the free base, the amine/imine equilibrium favors the imine such that cyclization of G proceeds to completion. The diamine G has an approximate half-life of 12 h in CH_2Cl_2. The base used to produce G prior to macrocyclization is important. When an aqueous solution of $G{\cdot}2HBF_4$ is neutralized with $[Me_4N][OH]$, H[2] is obtained quantitatively upon workup. However, aqueous NaOH yields exclusively G. Both H[2] and G have high solubility in water and CH_2Cl_2. Thus, extraction of the free base from dilute aqueous solutions with CH_2Cl_2 is ineffective. If the neutral aqueous solution is pumped to dryness and CH_2Cl_2 is added, the yield of extracted G is low (G probably binds sodium). If the aqueous solution is pumped to a low volume and then extracted with CH_2Cl_2, G can be obtained in quantitative yield. Small amounts of water probably prevent G from binding sodium tightly.

Once the synthesis of G has been mastered, $H_4[1]$ can be isolated from the reaction of G with diethylmalonyl dichloride. On the basis of the characterization of side products from related systems, we speculate that the major side products in the macrocyclization are four-membered ring cyclic imides.[3f]

Many different procedures were investigated in the process of mastering the production of pure G and its subsequent macrocyclization. One procedure involved binding G to a transition metal so that a template-assisted macrocyclization could be attempted. We were led to this approach because H[2] formation is inhibited by sodium ion as described above. However, when copper(II) salts are reacted with G, a copper(II) complex of $[2]^-$ can be obtained in quantitative yield. This species adds to the characterization of H[2]. The ligand $[2]^-$ is tridentate, binding through the imine nitrogen, a deprotonated amide, and the remaining primary amine.

Structural Studies. The crystal structure of $H_4[1]$ is shown in Figure 4. The amide C–O bonds are indistinguishable at the 3σ confidence level (average 1.22 Å). At the 3σ confidence level,

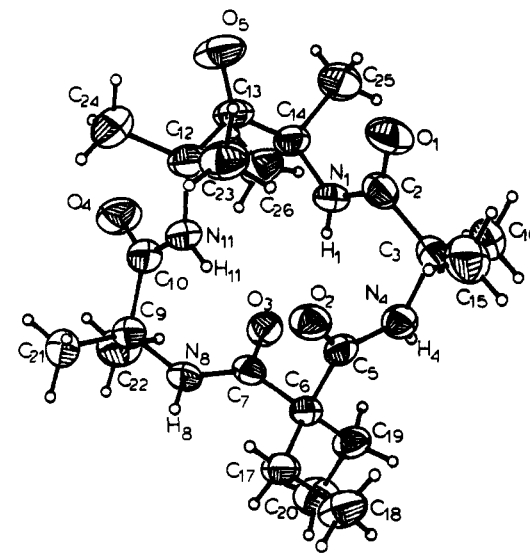


Figure 4. ORTEP drawing of the molecular structure of $H_4[1]$, with all non-hydrogen atoms drawn to encompass 50% of electron density. Selected bond distances (Å): O_1–C_2 = 1.211 (5), O_2–C_5 = 1.219 (5), O_3–C_7 = 1.233 (5), O_4–C_{10} = 1.224 (6), O_5–C_{13} = 1.211 (5), N_1–C_2 = 1.342 (5), N_4–C_5 = 1.341 (6), N_8–C_7 = 1.331 (5), N_{11}–C_{10} = 1.349 (5).

the C–O bond of the ketone is the same length as the amide C–O bonds (1.21 Å). The amide C–N bonds are also indistinguishable at the 3σ confidence level (average 1.34 Å). The Dunitz amide nonplanarity parameters are as follows: $\bar{\tau}$ = 8.6°, χ_N = −10.1°, χ_C = 5.2° ($N_1C_2O_1$); $\bar{\tau}$ = −2.7°, χ_N = 7.6°; χ_C = −6.9° ($N_4C_5O_2$); $\bar{\tau}$ = −8.6°, χ_N = −3.7°, χ_C = −7.3° ($N_8C_7O_3$); $\bar{\tau}$ = 12.3°, χ_N = −5.0°, χ_C = 5.3° ($N_{11}C_{10}O_4$). The $\bar{\tau}$ value of 12.3° signifies nonplanarity for an organic amide. The structure of $CuCl(\eta^3$-2)·THF is shown in Figure 5. The complex is square planar. The largest deviation from the mean plane defined by the copper atom, the coordinated nitrogen atoms, and the chlorine atom is 0.09 Å for the copper atom. As expected from its high σ-donor capacity, the shortest bond to copper is made by the deprotonated amide (1.884 (4) Å), followed by the bond to the amine (2.012 (4) Å), the bond to the imine (2.049 (4) Å), and the bond to chloride (2.236 (2) Å). The average amide C–N bond length (1.33 Å) is longer than the imine C–N bond (1.286 (6) Å). The copper

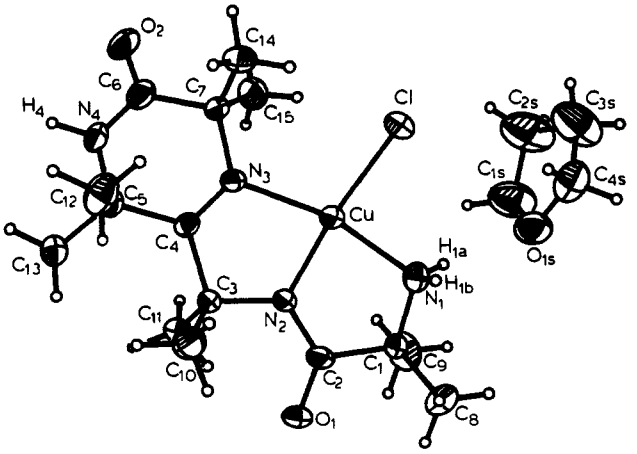


Figure 5. ORTEP drawing of the molecular structure of $CuCl(\eta^3\text{-}2)\cdot THF$, with all non-hydrogen atoms drawn to encompass 50% of electron density. Important bond distances (Å) and angles (deg): Cu–N_1 = 2.012 (4), Cu–N_2 = 1.884 (4), Cu–N_3 = 2.049 (4), Cu–Cl = 2.236 (2), O_1–C_2 = 1.248 (6), O_2–C_6 = 1.227 (6), N_2–C_2 = 1.340 (6), N_3–C_4 = 1.286 (6), N_4–C_6 = 1.324 (6); Cl–Cu–N_1 = 89.6 (1), Cl–Cu–N_2 = 168.4 (1), Cl–Cu–N_3 = 105.6 (1), N_1–Cu–N_2 = 83.3 (2), N_1–Cu–N_3 = 164.1 (1), N_2–Cu–N_3 = 81.0 (1).

complex has no nonplanar amide ($N_2C_2O_1$: $\bar{\tau}$ = 0.7°, χ_N = 4.4°, χ_C = −3.0°. $N_4C_6O_2$: $\bar{\tau}$ = −7.6°, χ_N = −2.6°, χ_C = −4.2°).

The directing effects of hydrogen bonding in the solid state and the solution state have long been a subject of interest and have recently come under considerable study.[4,5] $CuCl(\eta^3\text{-}2)$ has three potential hydrogen donors, H_{1a}, H_{1b}, and H_4, and all three are involved in intermolecular hydrogen bonding. H_{1a} hydrogen bonds to the oxygen atom of the THF molecule of crystallization (H–A = 2.31 (4) Å; DH–A = 174 (3)°). H_{1b} hydrogen bonds to the oxygen atom of the uncoordinated amide (H–A = 2.08 (5) Å; DH–A = 166 (3)°). H_4 hydrogen bonds to the oxygen atom of the coordinated amide (H–A = 2.10 (5) Å; DH–A = 150 (3)°). These data are consistent with Etter's empirical general rule of hydrogen bonding, which states that a molecule will use all good proton donors and acceptors in hydrogen bonding.[4] Crystalline $H_4[1]$ forms intramolecular hydrogen bonds diagonally across the ring with H_1 bonded to O_3 (H–A = 2.39 (3) Å; DH–A = 155 (2)°; with an additional close contact with N_4, H–A = 2.43 (3) Å; DH–A = 108 (2)°), and H_{11} bonded to O_2 (H–A = 2.36 (3) Å; DH–A = 156 (2)°; with an additional close contact with N_8, H–A = 2.42 (3) Å; DH–A = 106 (2)°). A third hydrogen bond is formed intermolecularly with H_8 bonded to O_5 (H–A = 2.47 (3) Å; DH–A – 142 (2)°). These hydrogen bonds are long, but within the accepted range of 1.7–2.5 Å found for amide NH···O_{amide} hydrogen bonds in globular proteins.[12] In a recent structural paper, Gellman and co-workers have noted the tendency of linear malonamide-containing triamides to form nine-membered-ring intramolecular hydrogen bonds and have discussed the relationship of this bonding to the 10-membered-ring β-turn conformation observed in proteins.[5a] It is interesting to note that the intramolecular H–O hydrogen bonds of $H_4[1]$, which also contains the malonamide fragment, are each part of nine-membered rings. The H–O bond distances and the N–H–O bond angles are comparable to those found by Gellman and co-workers. Of the four potential hydrogen bond donors of $H_4[1]$, only one is unused.

Under the nondilute macrocyclization conditions employed in the synthesis of $H_4[1]$, a lower yield of macrocycle than observed and a higher yield of polymer might be expected. The structure of $H_4[1]$ indicates that the relatively high yield obtained (32%) might be attributable to a template effect arising from one or more internal hydrogen bonds in monoacyclated G, the immediate precursor to the macrocycle. Macrocyclizations templated by intramolecular hydrogen bonds have been proposed previously.[13]

(12) Baker, E. N.; Hubbard, R. E. *Prog. Biophys. Mol. Biol.* **1984**, *44*, 97–179.

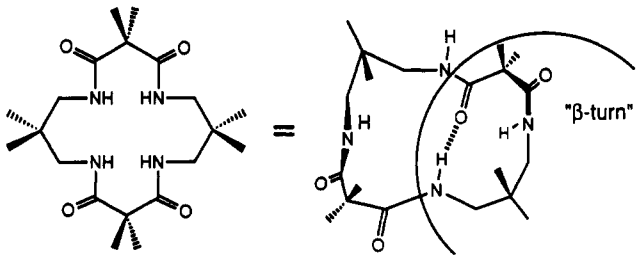


Figure 6. Macrocyclic tetraamide synthesized by Vellacio, Punzar, and Kemp. The representation on the right is the actual structure they proposed for the molecule, based on inspection of models. The hydrogen bond they postulated is indicated.

An important example is the intramolecular hydrogen bond template claimed by Kemp and co-workers in the reaction of 2,2-dimethyl-1,3-diaminopropane with dimethylmalonyl dichloride to form the 16-membered ring tetraamide (Figure 6).[14] Their relatively high yield (28%) of macrocycle, obtained under nondilute conditions (0.1 M concentration of reagents, 0 °C, MeCN), was suggested as supporting evidence for an intramolecular hydrogen-bond template effect. The hydrogen bond they proposed was also related to the β-turn and involved a 10-membered ring containing a malonamide fragment.

The good yield of $H_4[1]$ might also be favored by the rigid-group effects of the amide bonds. Rigid-group effects are well documented in the macrocyclic literature.[15] Thus, ortho-disubstituted aromatic rings, cis double bonds, fused ring systems, etc. incorporated into an acyclic precursor will help increase the yield of macrocycle by eliminating unprofitable degrees of rotational freedom in the precursor. Beneficial rigid-group effects have been elegantly demonstrated by many groups.[16] In organic amides, the trans conformation is favored, for steric reasons, over the cis conformation. The trans conformation favors macrocyclization, since all of the amides in $H_4[1]$ are trans. The barrier to rotation about the carbonyl carbon–nitrogen bond of an amide is approximately 20 kcal mol^{-1}, so the macrocyclic geometry of the amide bonds of the precursor is held more or less in place. It is useful to note that H[2] contains a cis amide, and that the approximate 12-h half-life of G might be attributable to the steric trans-amide preference and the hindered C–N amide bond rotation.

Conclusion

Because so few ligands are compatible with high-valent and highly oxidizing middle and later transition metals, stable analogues of many reactive intermediates in metal-centered biological and nonbiological oxidations remain to be prepared and studied. We are learning that an oxidizing metal center has many mechanisms available for removing electrons from its ligand environment so that a number of ligand design criteria need to be satisfied. In this paper, we have presented the design history and synthesis of an innocent macrocyclic tetraamide ligand that

(13) (a) Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 214–216. (b) Ogawa, S.; Yamaguchi, T.; Gotoh, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 976–978. (c) Owston, P. G.; Peters, R.; Ramsammy, E.; Tasker, P. A.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **1980**, 1218–1220.

(14) Vellacio, F. Jr.; Punzar, R. V.; Kemp, D. S. *Tetrahedron Lett.* **1977**, 547–550.

(15) For treatments of macrocyclic synthetic methodology as applied to transition-metal chemistry, see: (a) Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: New York, 1989. (b) *Coordination Chemistry of Macrocyclic Compounds*; Melson, G. A., Ed.; Plenum Press: New York, 1979.

(16) For recent examples by Stoddart et al., see: (a) Ashton, P. R.; Isaacs, N. S.; Kohnke, F. H.; Mathias, J. P.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1258–1261. (b) Ashton, P. R.; Isaacs, N. S.; Kohnke, F. H.; Stagno D'Alcontres, G.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1261–1263. (c) Kohnke, F. H.; Mathias, J. P.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1102–1110. (d) Ortholand, J.-Y.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1394–1395. (e) Ashton, P. R.; Goodnow, T. T.; Kaifer, A. E.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1396–1399.

successfully stabilizes rare high-valent middle and later transition-metal centers of definitive oxidation states.

The structural properties of the polyamides produced in this study are relevant to current work on the ordering effects of hydrogen bonding. It is reasonable to assume that a combination of hydrogen-bond templates and restricted rotation about the C–N bonds contributes to the good yield of H_4[1] obtained under nondilute conditions. It is likely that manipulating solvent polarity to encourage hydrogen bond templates or to break up undesirable hydrogen bonds is an underutilized technique in the synthesis of amide-containing macrocycles.

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Registry No. A, 565-80-0; B, 17346-16-6; C, 73082-76-5; D·2HBr, 134389-70-1; E, 134389-66-5; F, 134389-67-6; G, 134389-69-8; G·2HBF$_4$, 136424-55-0; H[2]·2HBr, 136392-01-3; H_4[1]·CH_2Cl_2, 136392-02-4; H_4[1]·$C_2H_4Cl_2$, 136392-03-5; CuCl(η^3-2)·THF, 136392-05-7; diethylmalonyl dichloride, 54505-72-5; bromoisobutyryl bromide, 20769-85-1.

Supplementary Material Available: Listings of atomic coordinates, anisotropic thermal parameters for non-hydrogen atoms, bond lengths involving non-hydrogen atoms, bond angles involving non-hydrogen atoms, and close contacts involving hydrogen atoms and complete details of the crystal structure analysis for H_4[1]·$C_2H_4Cl_2$ and CuCl(η^3-2)·THF (32 pages); listings of structure factor amplitudes (18 pages). Ordering information is given on any current masthead page.

Contribution from the Department of Chemistry, Gorlaeus Laboratories, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Synthesis, Structure, and Spectroscopic Properties of Bismuth Citrate Compounds. 1. Crystal Structures of $K_{5-x}(NH_4)_x[Bi_2(cit)_2(Hcit)](H_2O)_y$ (x = 0.25, y = 13) and $(NH_4)_8[Bi_2(cit)_2(Hcit)_2(H_2O)_4](H_2O)_2$

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Received April 9, 1991

This paper describes the synthesis, characterization, and structure of five different products all containing Bi(III) and citrate. These compounds have the general formula $K_{5-x}(NH_4)_x[Bi_2(cit^{4-})_2(Hcit^{3-})](H_2O)_y$ (**1**, x = 0.25–1.0, y = 13), $K_{3-x}(NH_4)_x[Bi(cit^{4-})]_3(H_2O)_y$ (**2**, x = 0–0.5, y = 3–5), $K_{3-x}(NH_4)_x[Bi(cit^{4-})]_3(H_2O)_6$ (**3**, x = 1–2, y = 6), $K_{3-x}(NH_4)_x[(BiO)_2Bi(cit^{4-})_2](H_2O)_6$ (**4**, x = 2–3, y = 6), and $(NH_4)_4[Bi(cit^{4-})(Hcit^{3-})(H_2O)_2](H_2O)$ (**5**). Compounds **1** and **5** have been fully characterized by using three-dimensional X-ray analysis; compounds **2**–**4** have been characterized by elemental analysis and spectroscopy only. The compound $K_{4.75}(NH_4)_{0.25}[Bi_2(cit)_2(Hcit)](H_2O)_{13}$ (**1**) crystallizes in the space group $P\bar{1}$ with a = 11.801 (4) Å, b = 12.973 (3) Å, c = 15.856 (5) Å, α = 98.15 (2)°, β = 108.39 (2)°, γ = 100.91 (2)°, V = 2208.1 Å^3, and Z = 2. The asymmetric unit, which contains two Bi ions on a distance of 4.17 Å, is linked to another unit by an inversion center to form a tetranuclear subunit with additional Bi–Bi distances of 5.82 and 5.85 Å. These tetranuclear units are linked into a two-dimensional network with large meshes, which contain the potassium and ammonium ions and the lattice water molecules. The compound $(NH_4)_4[Bi(cit)(Hcit)(H_2O)_2](H_2O)$ (**5**) crystallizes in the space group $P2_1/c$ with a = 8.998 (2) Å, b = 9.492 (8) Å, c = 27.021 (6) Å, β = 99.42 (2)°, V = 2274.2 Å^3, and Z = 4. The asymmetric unit, which contains one Bi ion, is paired to itself into a dinuclear subunit with a Bi–Bi contact of 5.97 Å. In both compounds the bismuth ions are coordinated by nine oxygens of the citrate anions, with two of the citrate carboxylic groups being bidentately bonded to each bismuth ion, which in compound **5** two of the nine oxygens are water oxygens. One of the nine oxygens coordinated to each bismuth ion is an alcoholic oxygen. The distance to this alcoholic oxygen appears to be the shortest Bi–O contact (about 2.12 Å), the longest Bi–O distance being ca. 3.0 Å. The oxygen to oxygen (water and citrate) and nitrogen (ammonium) distances lie in a range that is characteristic for hydrogen bonding. Compounds **2** and **3** are obtained from solutions of different Bi/cit ratios. Whether type **2** or type **3** is formed is determined by the amount of ammonia in the solutions, but the several batches of type **2** (and also of type **3**) are structurally the same (on the basis of IR, X-ray powder). Compound **4** can be obtained from bismuth citrate solutions containing an equimolar ratio or small excess of H_4cit. The solution behavior of the crystalline compounds obtained has been investigated by using ^{1}H and ^{13}C NMR spectroscopy. All compounds, except for type **4**, show a similar behavior. At low pH (<7), rapid ligand exchange is observed and all citrates are averaged on the NMR time scale. At high pH the citrates are hardly coordinated to Bi(III). However, under high-concentration conditions (high solubility is attained only under basic conditions), coordinated citrates can be detected besides uncoordinated ones. In the case of compound **4**, coordinated citrates are detected even in the low-pH regions. These coordinated citrates become averaged (rapid exchange) by adding free citrate and by raising the pH.

Introduction

Bismuth is the least toxic metal of the As, Sb, Bi triad, which is unusual, since toxicity normally increases down a group in the periodic table. In fact, bismuth and its salts were once widely used in the treatment of syphilis and yaws. Furthermore, bismuth compounds have been used in medicine for two hundred years in a variety of gastrointestinal disorders, also because of their demulcent properties.[2]

Among the modern, bismuth-based ethical pharmaceuticals, DE-NOL (trademark of Gist-brocades N.V.), having colloidal bismuth subcitrate (CBS) as active ingredient, is probably the most interesting. This compound, which is a complex bismuth salt of citric acid (H_4cit), is a very effective peptic ulcer healing agent, and its pharmacological properties were thoroughly investigated from the viewpoint of pharmacology in the last two decades.[3]

The use of CBS in peptic ulcer patients also resulted in significantly lower relapse rates when compared with other ulcer-healing agents.[3] These lower relapse rates are now known to be

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