# Metalla Derivatives of Amino Acids and Peptides. 1. Rhena Derivatives of Glycine, L-Alanine, and Glycylglycine. A New N-Terminal End Protecting Group and Heavy-Atom Label

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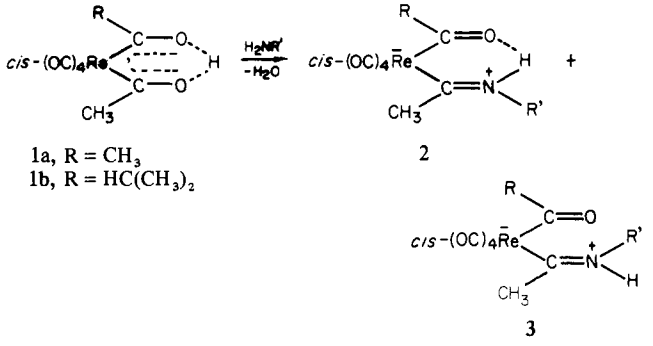
**Abstract:** The rhenaacetylacetone molecule, *cis*-$(OC)_4Re(CH_3CO)_2H$, condenses with ethyl glycinate and ethyl L-alaninate to afford the corresponding rhena-$\beta$-ketoimine derivatives of the amino acid esters, *cis*-$(OC)_4Re[CH_3C(O)][CH_3CN(CHRCO_2CH_2CH_3)(H)]$, where R is H or $CH_3$. The X-ray structure of the ethyl L-rhenaalaninate complex reveals the expected intermolecular hydrogen bonding between rhena groups with no significant structural distortions within the amino acid moiety. Basic hydrolysis of these rhenaamino acid esters affords the rhena derivatives of the free amino acids. When the rhenaglycine complex is treated with DCC and ethyl glycinate, the ethyl rhenaglycylglycinate complex is formed, thus demonstrating the use of the rhena moiety as an N-terminal end protecting group during peptide synthesis. Cleavage of the amino acid derivatives from the rhena moiety using acidic solvolysis and oxidation by iodosobenzene is reported also.

## Introduction

We reported recently the Schiff-base condensation of the rhena-$\beta$-diketones **1** with primary amines to afford rhena-$\beta$-ketoimines which exist as the ketamine tautomers.[1,2] The rhena-$\beta$-ketoimines exhibit geometrical isomerism resulting from their unusual zwitterionic electronic structure which was confirmed by an X-ray structure determination. These isomers are defined by the relative orientation of the iminium ligand substituents and are referred to as the *intra-* or *interisomers* **2** and **3**, respectively,



1a, R = $CH_3$
1b, R = $HC(CH_3)_2$

2



3

depending on whether the molecule exhibits intramolecular or intermolecular hydrogen bonding.[1,2] The X-ray structure of **3**, where R is methyl and R′ is phenyl, revealed a continuous intermolecular N–H···O hydrogen-bonding interaction throughout the lattice between the iminium and acetyl ligands of adjacent rhena moieties.

We now wish to report that the rhenaacetylacetone complex **1a** condenses with ethyl glycinate and ethyl L-alaninate to afford rhena derivatives of these amino acid esters. These complexes represent a new class of amino acid derivatives. The rhena moiety is covalently bonded to only the amino group of the amino acid residue, and it serves as a heavy-atom label for X-ray structural studies. Furthermore, the rhena moiety survives the reaction conditions of classical peptide-coupling chemistry involving base hydrolysis of the C-terminal ester group to the free acid followed by peptide bond formation using dicyclohexylcarbodiimide (DCC). In this capacity, the rhena complex serves as an N-terminal end protecting group during peptide synthesis.

We believe that the rhenaamino acid and -peptide derivatives may make a significant contribution to peptide chemistry in the following four areas: (1) N-terminal end protection during peptide synthesis, (2) heavy-atom labeling of N termini for X-ray structural characterization, (3) effecting unusual transport and tissue distribution properties to amino acids and peptides, and (4) convenient labeling of amino acids and peptides for detection and isolation. This paper reports our initial results concerning the first two areas of interest.

The development of new *classes* of N-terminal end protecting groups is critically important for attaining new selectivity in peptide synthesis as synthetic problems become more challenging.[3] These rhena derivatives have unusually good hydrolytic stability and are removed easily via mild oxidation.

X-ray structural studies of peptides is usually accomplished by using heavy-atom labels which do not perturb the conformation of the native peptide.[4] Preliminary results reported here indicate that the rhena moiety may become a useful heavy-atom label for peptide structure elucidation. The rhena moieties facilitate crystallization via intermolecular hydrogen bonding, and the remainder of the amino acid residue does not participate in this intermolecular hydrogen bonding. Recently, classical coordination of the C-terminus carboxylate anion to the $Mo_2^{4+}$ ion was used to provide a heavy-atom label for C termini.[5]

Synthetic labeling of amino acids and peptides for altering transport properties and for enhancing detection is important also. We anticipate that the organometallic moiety will increase the lipid solubility of these rhena derivatives relative to that exhibited by the free amino acids or peptides. Intracellular oxidation of these rhena derivatives may afford free peptides or simple peptide derivatives. Under these circumstances, these complexes may act as a latent form of amino acid, peptide, or group 7 metal atom.

The only other similar application of transition metal, organometallic chemistry to peptide chemistry was Fischer's use of group 6 carbenoid complexes as reported in 1973.[6] The rhena derivatives reported here have the distinctly different zwitterionic electronic structure which imparts different chemical reactivity and, presumably, affords the observed intermolecular hydrogen bonding in the solid state. Of major importance is the potential incorporation of technetium into amino acids or peptides utilizing the chemistry established for these rhena derivatives. The possibility of such radiolabel incorporation using classical carbenoid

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(4) Blundell, T. L.; Johnson, L. N. "Protein Crystallography"; Academic Press: New York, 1976.
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complex chemistry has not been demonstrated.

## Experimental Section

All reactions were performed under dry, prepurified nitrogen at 25 °C unless stated otherwise. Diethyl ether, THF, and hexane were dried over Na–K alloy with added benzophenone, and methylene chloride was dried over $P_2O_5$.

Infrared spectra were recorded on a Perkin-Elmer 727 spectrometer as solutions in 0.10-mm sodium chloride cavity cells using the solvent as a reference and a polystyrene film as a calibration standard. Proton NMR spectra were obtained on a JEOL MH-100 NMR spectrometer using $Me_4Si$ as an internal reference. Mass spectra (MS) were recorded on a LKB 9000 spectrometer and optical rotations were measured at the sodium D line by using Schmidt/Haensch and Rudolph Research Autopal III polarimeters. Microanalysis was performed by Galbraith Laboratories, Inc., Knoxville, TN.

Complex **1a**, *cis*-$(OC)_4Re(CH_3CO)_2H$, and iodosobenzene were prepared by literature methods,[7,8] where amino acid esters and dicyclohexylcarbodiimide (DCC) were obtained commercially.

**Preparation of *cis*-$(OC)_4Re[CH_3C(O)][CH_3CN(CH_2CO_2CH_2CH_3)(H)]$ (4).** To a solution of 0.53 g (1.4 mmol) of **1a** in a 5 mL of $CH_2Cl_2$ was added 0.21 g (2.0 mmol, slight excess) of ethyl glycinate. The yellow reaction solution turned to pale lemon yellow within 30 s. The reaction solution was stirred for 18 h, and then the solvent was removed at reduced pressure. The reaction residue was extracted with 22 mL of a 10:1 hexane–$CH_2Cl_2$ solution. After filtration, the volume of solution was reduced to ca. 10 mL, and then, the solution was placed at −20 °C for 16 h to afford 0.58 g (90%) of **4** as a mixture of geometrical isomers (yellow oil plus yellow crystalline needles): IR ($CH_2Cl_2$) $\nu$(CO) 2075 (m), 2000 (s, sh), 1975 (vs), 1937 (s), $\nu$(C≡O, C≡N) 1560 (m), $\nu$(ester) 1737 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ *intraisomer* 1.31 (t, 3, ester $CH_3$), 2.60 (s, 3, $CH_3CO$), 2.70 (s, 3, $CH_3CN$), 4.30 (d, 2, $CH_2N$), 4.31 (quartet, 2, ester $CH_2$), 13.49 (br s, 1, NH), *interisomer* 1.32 (t, 3, ester $CH_3$), 2.48 (s, 3, $CH_3CO$), 2.88 (s, 3, $CH_3CN$), 4.10 (quartet, 2, ester $CH_2$), 4.55 (d, 2, $CH_2N$), 9.58 (br s, 1, NH). Anal. ($C_{12}H_{14}O_7NRe$) C, H, N.

**Preparation of *cis*-$(OC)_4Re[CH_3C(O)][CH_3CN(CH_2CO_2H)(H)]$ (5).** To a solution of 0.30 (0.64 mmol) of **4** in a 4 mL of EtOH at 0 **C** was added 1 molar equiv of KOH (as an EtOH solution). The reaction solution was stirred at 0 °C for 90 min, and then, the solvent was removed at reduced pressure. The reaction residue was cooled to −78 °C after the addition of 10 mL of ether. One molar equiv of HCl (as an ether solution) was added to the flask, and the mixture was stirred at −78 °C for 5 min and at 25 °C for 1 h. The yellow reaction solution was filtered, and the filtrate was dried over $MgSO_4$. Addition of 17 mL of hexane and a reduction of the solution volume at reduced pressure afforded a nearly quantitative yield of **5** as a yellow oil (14% *interisomer*, 86% *intraisomer*): IR ($CH_2Cl_2$) $\nu$(CO) 2080 (m), 2005 (s, sh), 1985 (vs), 1940 (s), $\nu$(acid) 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ *intraisomer* 2.61 (s, 3, $CH_3CO$), 2.68 (s, 3, $CH_3CN$), 4.29 (d, 2, $CH_2N$), 10.30 (br s, 1, $CO_2H$), 12.73 (br s, 1, NH). Anal. ($C_{10}H_{10}O_7NRe$) C, H, N.

**Preparation of *cis*-$(OC)_4Re[CH_3C(O)][CH_3CN[CH_2C(O)NHCH_2CO_2CH_2CH_3][H]]$ (6).** To a solution of 0.098 (0.22 mmol) of **5** in 3 mL of THF at 0 °C was added a slight excess of 1 molar equiv of DCC (as a THF solution). The reaction solution was allowed to warm by removing the 0 °C bath, and within 2 min it became cloudy. A 10% molar excess of ethyl glycinate was added, and the reaction solution was stirred at 25 °C for 16 h. The THF was removed at reduced pressure, and the product was extracted into a hexane/$CH_2Cl_2$ solution. Concentration of the solution afforded 0.052 g (45%) of **6** as a yellow oil (*intraisomer*): IR ($CH_2Cl_2$) $\nu$(CO) 2080 (m), 2010 (s, sh), 1978 (vs), 1938 (s), $\nu$(ester) 1738, $\nu$(amide) 1685 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.32 (t, 3, ester $CH_3$), 2.63 (s, 3, $CH_3CO$), 2.76 (s, 3, $CH_3CN$), 4.13, 4.19, 4.26 (overlap, 4, $OCCH_2N$, $OCH_2$), 4.39 (d, 2, $CH_2N$), 6.89 (br s, 1, OCNH), 13.10 (br s, 1, NH). Anal. ($C_{14}H_{17}O_8N_2Re$) C, H, N.

**Preparation of *cis*-$(OC)_4Re[CH_3C(O)][CH_3CN(L\text{-}CHCH_3CO_2CH_2CH_3)(H)]$ (7).** Complex **7** was prepared and isolated according to the procedure given for **4** except that the reaction time was 4 h. Both *intra* and *inter* (mp 96.5–97.5 °C) isomers were isolated as pure compounds. From 0.50 g (1.5 mmol) of **1a**, 0.38 g of **7** was isolated (60% yield): IR ($CH_2Cl_2$) $\nu$(CO) 2080 (m), 2010 (m, sh), 1968 (vs), 1945 (s), $\nu$(ester) 1740, $\nu$(C≡O, C≡N) 1560, 1580; $^1H$ NMR ($CDCl_3$) $\delta$ *interisomer* (pale yellow solid) 1.31 (t, 3, ester $CH_3$), 1.65 (d, 3, $CH_3C^*$), 2.50 (s, 3, $CH_3CO$), 2.89 (s, 3, $CH_3CN$), 4.31 (quartet 2, $CH_2O$), 4.93 (quintet, 1, CH), 9.33 (br s, 1, NH), *intraisomer* (yellow oil) 1.29 (t, 3, ester $CH_3$), 1.75 (d, 3, $CH_3C^*$), 2.61 (s, 3, $CH_3CO$), 2.69 (s, 3, $CH_3CN$), 4.28 (quartet, 2, $CH_2O$), 4.61 (quintet, 1, CH), 13.49 (br s, 1, NH). Anal. ($C_{13}H_{16}O_7NRe$) C, H, N.

**Preparation of Racemic *cis*-$(OC)_4Re[CH_3C(O)][CH_3CN(CHCH_3CO_2H)(H)]$ (8).** Complex **8** was prepared from **7** by using the same procedure given for **5** except that a very slight deficiency of KOH was used and the saponification was conducted at −40 to +5 °C over 2.5 h. From 0.22 g (0.45 mmol) of **7**, 0.075 g of *recrystallized* **8** (36% yield) was isolated as a white solid: mp 131–133 °C; IR ($CH_2Cl_2$) $\nu$(CO) 2080 (m), 1980 (br, vs), 1950 (s), $\nu$(acid) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ *intraisomer* 1.68 (d, 3, $CH_3CH$), 2.67 (s, 3, $CH_3CO$), 2.75 (s, 3, $CH_3CN$), 4.64 (quintet, 1, CH), 9.57 (br s, 1, $CO_2H$), 12.93 (br s, 1, NH). Anal. ($C_{11}H_{12}O_7NRe$) C, H, N.

**Preparation of 8 from Racemic 7 and 6 N HCl.** To a solution of 0.22 g (0.45 mmol) of racemic **7** in 3.5 mL of acetone at 0 °C was added 3.5 mL of 12 N HCl. The yellow reaction solution was warmed to 25 °C and was stirred for 24 h. During this time, the solution turned deep red. After the solvent was removed at reduced pressure, the red residue was extracted with 20 mL of ether. Filtration yielded ca. 0.01 g of a white solid which was identified by $^1H$ NMR ($D_2O$) and melting point as a mixt. of D,L-alanine and D,L-alanine·HCl. The addition of hexane to the ether filtrate and cooling at −20 °C afforded 0.063 g (30% yield) of D,L-**8** which was identified by IR, $^1H$ NMR, and melting point. No other rhena complex or alanine derivative was observed. The origin of the red color was not established.

**Preparation of *cis*-$(OC)_4Re[OC(O)CF_3][CH_3CN(CHCH_3CO_2CH_2CH_3)(H)]$ (9) and $[(OC)_5Re(H_2NCHCH_3CO_2CH_2CH_3)](CF_3CO_2)$ (10) from 7 and Trifluoroacetic Acid (TFA).** A solution of 0.11 g (0.23 mmol) of **7** was stirred in 5 mL of TFA for 19 h, and then the TFA was removed at reduced pressure. Extraction of the yellow residue with 10 mL of ether afforded a nearly colorless solution and a small amount of a yellow oil. The yellow oil (0.013 g) was identified as **10** by $^1H$ NMR (acetone-$d_6$). The ether solution was concentrated at reduced pressure yielding an amber oil. Dissolving the oil in $CH_2Cl_2$/hexane and inducing fractional crystallization by concentrating the solution at reduced pressure and by cooling afforded 0.037 g of **9** as a pure yellow oil and 0.022 g of **10** as a slightly impure yellow oil. Complex **9** (59%): IR ($CH_2Cl_2$) $\nu$(CO) 2100 (m), 2035 (sh, s), 1980 (vs), 1935 (s), $\nu$(carbonyl) 1740 (m), 1715 (m), 1695 (m), $\nu$(C≡N) 1560 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.31 (t, 3, ester $CH_3$), 1.63 (d, 3, $CH_3CH$), 2.85 (s, 3, $CH_3CN$), 4.30 (quartet, 2, $CH_2O$), 4.65 (quintet, 1, CH), 10.68 (br s, 1, NH); MS parent ion at *m/e* 555. Anal. ($C_{13}H_{13}O_8NF_3Re$) C, H, N, F. Complex **10** (35%): IR ($CH_2Cl_2$) $\nu$(CO) 2160 (w), 2080 (w), 2035 (vs), $\nu$(carbonyl) 1740 (m), 1670 (m) $cm^{-1}$; $^1H$ NMR (acetone-$d_6$) 1.29 (t, 3, ester $CH_3$), 1.71 (d, 3, $CH_3CH$), 4.28 (quartet, 2, $CH_2O$), 5.13 (complex multiplet, 1, CH), 5.58 (br s, $NH_2$).

**Oxidation of 7 with Iodosobenzene.** To a solution of 0.103 g (0.21 mmol) of **7** in 5 mL of $CH_2Cl_2$ was added 0.544 g of PhIO in portions until vigorous gas evolution ceased and an IR of the reaction solution indicated the absence of rhena carbonyl bands. A small amount of a colorless oil separated from the reaction solution. The yellow supernatant reaction solution was removed by syringe and concentrated at reduced pressure affording a yellow liquid. An $^1H$ NMR spectrum of this liquid in $CDCl_3$ revealed iodobenzene, $CH_2Cl_2$, and equimolar amounts of acetic acid and *N*-acetyl ethyl-L-alaninate. The liquid was extracted with hexane to remove the iodobenzene and was dissolved in $CDCl_3$ with a small amount of $Na_2CO_3$ present to remove the acetic acid. Evaporation of the solvent at reduced pressure afforded 0.022 g (67% based on **7**) of *N*-acetyl ethyl-L-alaninate as identified by IR, $^1H$ NMR, and specific rotation. The initial colorless oil which separated during the reaction afforded 0.030 g of a tacky off-white solid at reduced pressure: mp 115–125 °C dec; $^1H$ NMR ($D_2O$), only trace organics present. Anal. Calcd: C, 1.07; H, 0.47; Re, 61.77. This solid is tentatively identified as $HReO_4$.

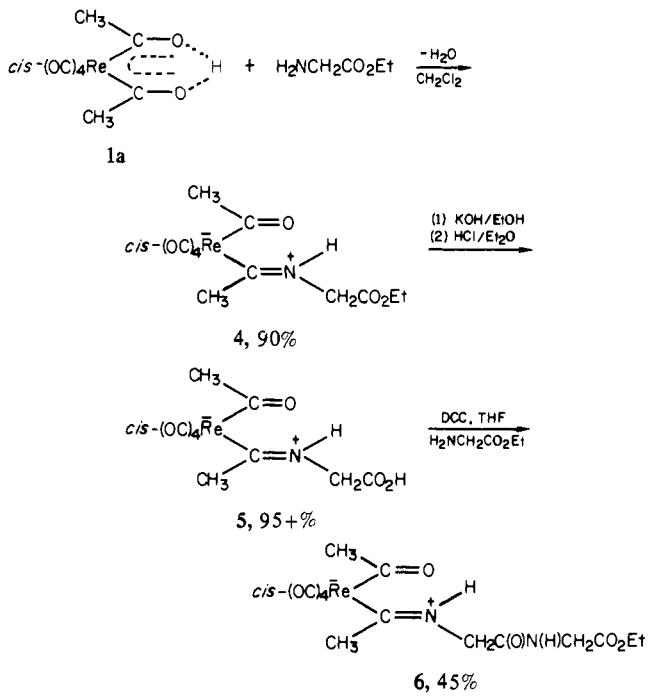
**X-ray Crystallography.** Pale yellow crystals of **7** were crystallized from ether/hexane solution at −20 °C. Collection of the X-ray data and the Lorentz, polarization, and absorption corrections were performed by Molecular Structure Corp., College Station, TX, as a commercial, technical service.

A platelike crystal of dimensions 0.30 × 0.30 × 0.10 mm was mounted in a glass capillary. Preliminary examination of the crystal on the diffractometer showed monoclinic symmetry. The systematic absences indicated the space group $P2_1$ or $P2_1/m$. Cell constants at 23 ± 1 °C obtained from the computer centering of 25 reflections were $a$ = 9.777 (2) Å, $b$ = 7.005 (2) Å, $c$ = 12.995 (3) Å, $\beta$ = 105.83 (2)°, $V$ = 856.3 Å$^3$, and $d$(calcd) = 1.88 g/cm$^3$ with $Z$ = 2.

The data were collected on an Enraf-Nonius CAD4 diffractometer using Mo $K\alpha$ ($\lambda$ = 0.71073 Å) radiation and a graphite crystal incident beam monochrometer. Intensity measurements were made by using $\omega$–$\theta$ scans with a variable $\omega$–$\theta$ scan speed ratio of 2–20°/min (in $\omega$). A total of 2778 reflections in the range $0 < 2\theta \leq 60°$ were collected, of which 2672 were unique and were used to solve and refine the structure. Three

(7) Lukehart, C. M.; Zeile, J. V. *J. Am. Chem. Soc.* **1976**, *98*, 2365.
(8) Saltzman, H.; Sharefkin, J. G. *Org. Synth.* **1963**, *43*, 60.

Scheme I



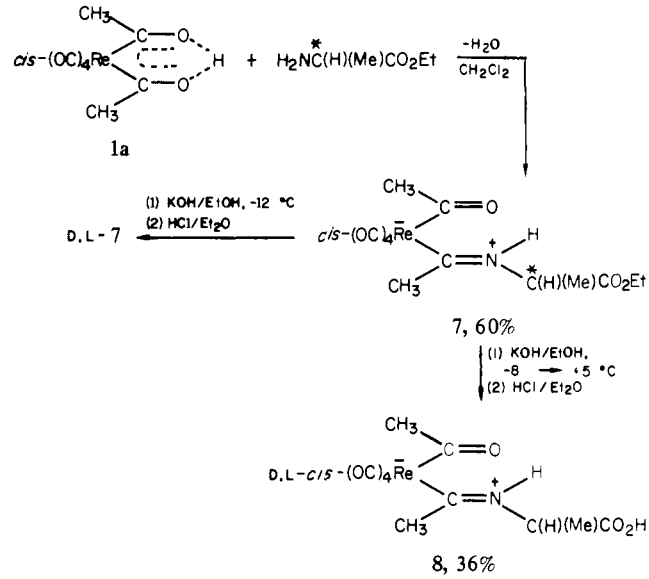

representative reflections were measure every 41 min, and no significant change in intensities was observed. Intensities and standard deviations on intensities were calculated by using the formulas $I = S(C - RB)$ and $\sigma(I) = [S^2(C + R^2B) + (pI)^2]^{1/2}$, where $S$ is the scan rate, $C$ is the total integrated peak count, $R$ is the ratio of scan time to background counting time, $B$ is the total background count, and $p$ is a factor introduced to downweight intense reflections and was set to 0.05. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 75.3 $cm^{-1}$. Relative transmission coefficients ranged from 0.346 to 0.994 with an average value of 0.858, and an empirical absorption correction based on a series of $\phi$ scans was applied to the data.

A measured specific rotation of $[\alpha]_D^{25.8°C} = +15.1°$ ($c$ 0.97, Silanor-C) ensured the optical activity of the sample and verified the proper choice of space group $P2_1$. A sharpened Patterson function revealed the Re position and provided phases for a difference synthesis to locate the remaining atoms. The $y$ coordinate of the Re was held constant at $^1/_4$ to provide a pseudoinversion center at the origin relating the Re atoms. All nonhydrogen atoms, H(1), and H(9) were successfully located and refined. The remaining hydrogens were located but not refined. The presence of extensive false imaging at $^1/_4 - y$ was observed as expected for an acentric space group.

The total refinement was carried out will all nonhydrogen atoms anisotropic. Positional parameters were refined on H(1) and H(9), but the isotropic thermal parameters were not refined. All other isotropic hydrogen atoms were included but not refined. The quantity minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma(F_o)$. Atomic scattering factors were those tabulated by Cromer and Mann[9] except for hydrogen where Stewart's values[10] were used. The anomalous dispersion factors for all atoms except hydrogen were those given by Cromer and Liberman.[11] The final $R$ factor was 0.055 and the weighted $R$ factor, $R^w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$, was 0.047, both calculated with all 2672 unique reflections. The weighting scheme employed is patterned after the method suggested by Hughes.[12] The maximum shift-to-error ratio for the atomic parameters in the final cycle was 0.60.

An ORTEP view of the molecule indicated that the D isomer had been refined initially. Inversion of the nonhydrogen atoms through the origin provided atomic coordinates for the L enantiomorph, which were refined to provide a difference synthesis for the location of the hydrogen atoms. All hydrogen atoms were located, but only the positional parameters of H(1) and H(9) were refined. Total refinement was carried out exactly as before to give a lower final $R$ factor of 0.052 and a weighted $R$ factor, $R_w$ of 0.044, indicating that the L enantiomorph was the correct choice.

Scheme II




The maximum electron density on the final difference map was 1.1 e/Å$^3$ near Re. Except as noted previously, calculations were carried out with the XRAY 67 program[13] as implemented and updated on the Vanderbilt DEC-1099 computer. A table of atomic positional and thermal parameters and a listing of observed and calculated structure factors are provided as supplementary material.

## Results and Discussion

The preparation of the ethyl rhenaglycinate complex **4** and its conversion to the ethyl rhenaglycylglycinate complex **6** is shown in Scheme I. Spectroscopic characterization of rhena-$\beta$-ketoimine compounds including the identification and assignment of geometrical isomerism about the C–N double bond is discussed fully elsewhere.[1,2] The rhenaacetylacetone molecule **1a** undergoes a Schiff base condensation with ethyl glycinate affording the ethyl rhenaglycinate complex **4**. Complex **4** is a rhena-$\beta$-ketoimine derivative of ethyl glycinate. Several nonmetalla $\beta$-dicarbonyl enamine derivatives of amino acids and peptides are known also.[14]

The strong covalent binding of the rhena moiety to the amino group of the amino acid ester prompted the investigation of using these rhena derivatives as N-terminus protecting groups in peptide syntheses. When **4** was treated with 1 equiv of KOH in ethanol at 0 °C, the ester was saponified to the carboxylate anion. This rhenaglycinate salt was isolated by removing the ethanol solution at reduced pressure and washing the yellow solid with ether. Protonation in ether at −78 °C with HCl/ether afforded the neutral rhenaglycine complex **5** in essentially quantitative yield. When **5** is treated with ethyl glycinate and dicyclohexylcarbodiimide (DCC) in THF, the ethyl rhenaglycylglycinate molecule **6** is formed in 45% yield. Reaction yields were not optimized and may be artifically low due to the small scale of the reactions and the mechanical losses incurred when small quantities of liquid products were isolated.

This reaction sequence demonstrates the successful use of the rhena moiety as an N-terminus protecting group under classical peptide-coupling conditions. Furthermore, the survival of the rhena moiety under such drastic pH conditions of KOH/ethanol and HCl/ether indicates exceptional chemical stability of the iminium ligand.

To test the effect of rhena derivatization of an optically active amino acid, we treated complex **1a** with ethyl L-alaninate as shown in Scheme II to afford the ethyl L-rhenaalaninate complex **7**. Both the *intra* and *inter* geometrical isomers of **7** were isolated as pure

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(10) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.
(11) Cromer, D. T.; Liberman, D. *J. Chem. Phys.* **1970**, *53*, 1891.
(12) Hughes, E. W. *J. Am. Chem. Soc.* **1941**, *63*, 1737.
(13) Stewart, J. M. "X-Ray 67 Program System for X-Ray Crystallography for the Univac 1108, CDC 3600/6600, IBM 360/50, 65, 75, IBM 7094", Technical Report Tr-67-58; Computer Science Center, University of Maryland: College Park, MD, 1967.
(14) Dane, E.; Drees, F.; Konrad, P.; Dochner, T. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 658.

| compd | $[\alpha]_D^{26°C}$, deg |
|---|---|
| ethyl L-alaninate | +5.0 (*c* 3.76, Silanor-C) |
| 7, *intraisomer* | +36.3 (*c* 0.91, Silanor-C) |
| 7, *interisomer* | +15.1 (*c* 0.97, Silanor-C) |

compounds. Specific rotations (vide infra) indicated that **7** was optically active and probably possessed the L-configuration for the amino acid residue. The large specific rotation of the *intraisomer* presumably results from a lower energy Cotton effect since this isomer is much more colored than the *interisomer*.

The X-ray structure of the *interisomer* of **7** was undertaken to unambiguously characterize a rhenaamino acid derivative, to identify the optical configuration of the amino acid residue and to determine any perturbation of the expected intermolecular N–H···O hydrogen bonding between rhena moieties by the amino acid ester functionality. The crystal structure of **7** consists of discrete monomeric molecular units which participate in a chain network of N–H···O hydrogen bonding. The N–H(1) group of a reference molecule ($x, y, z$) is hydrogen bonded to the acetyl oxygen atom, O(5) of an adjacent molecule ($-x, {}^1/_2 + y, -1 - z$), while O(5) of the reference molecule is hydrogen bonded to H(1) of a second adjacent molecule ($-x, y - {}^1/_2, -1 - z$). These hydrogen-bonding distances are the shortest intermolecular contacts. An ORTEP view of **7** is shown in Figure 1, and interatomic bond distances and bond angles are compiled in Tables I and II, respectively. Selected least-squares plane data are listed in Table III.

Other chemically interesting structural features of **7** are as follows. (1) The coordination about the Re atom is essentially octahedral (the average value for the angles defining the principle coordination axes is 174.2°, and the average value of the angles between adjacent coordination sites is 90.6° except for the C(5)–Re–C(7) angle which is 82.9(5)°). (2) The average values of the terminal carbonyl ligand C–O distances and the Re–C–O angles are 1.129 Å and 177.1°, respectively, which indicate normal terminal coordination of the carbonyl ligands. (3) The C(8) methyl and alanyl ester substituents of the iminium ligands are anti relative to the C(7)–N bond with the methyl group being closer to the acyl oxygen atom, O(5). (4) The sum of the bonding angles about atoms C(5), C(7), N, and C(11) in each case is 360° with individual angles ranging from 110 (1) to 131 (1)°, indicating nearly formalized $sp^2$ hybridization (planes I–III). (5) The atoms C(7), N, C(5), and O(5) are essentially coplanar (maximum deviation from planarity is atom C(5) of +0.11 Å) with the atoms Re, C(8), C(6), and H(1) being displaced from this plane (plane IV) by 1.17, −1.65, −0.52, and −0.66, respectively. (6) There is marked coplanarity among the atoms of the amino acid ester moiety, N, C(9), C(11), O(6), O(7), C(12), and C(13) (maximum deviation from planarity is C(12) of −0.12 Å), with C(7), C(10), and H(1) being displaced from this plane (plane V) by 0.94, −1.37, and −0.71 Å, respectively. This plane intersects plane IV with a dihedral angle of 78.1°. (7) The intermolecular N···O(5) hydrogen bonding distance of 2.92 (2) Å and the N–H(1)···O(5) angle of 171° represent a normal strong N–H···O hydrogen-bonding interaction.[15]

A comparison of the molecular structures of **7** and the rhena-*N*-phenylacetylacetonimine complex (**3** where R is methyl and R′ is phenyl) reveals no significant differences in bond distances and bond angles, relative ligand orientations, or intermolecular hydrogen bonding between the rhena moieties of these two rhena-β-ketoimine molecules.[1] The relatively short acetyl C–O and iminium C–N distances and the relatively long rhenium–acetyl carbon and rhenium–iminium carbon distances substantiate the zwitterionic electronic description for these molecules.[1] Recent $^{13}C$ NMR data for other rhena-β-ketoimine molecules support this unusual electronic structure, also.[16]

The ethyl alaninate ester functionality is attached to the iminium nitrogen atom as a substituent. Refinement of the structure

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(16) Darst, K. P.; Lukehart, C. M. *Inorg. Chim. Acta* **1980**, *41*, 239.

Table I. Interatomic Bond Distances (in Å, with Esd's) for *cis*-$(OC)_4Re[CH_3C(O)][CH_3CN(L\text{-}CHCH_3CO_2CH_2CH_3)(H)]$

| | | | |
|---|---|---|---|
| Re–C(1) | 1.98 (2) | C(5)–O(5) | 1.21 (2) |
| Re–C(2) | 1.95 (2) | C(7)–O(8) | 1.52 (2) |
| Re–C(3) | 2.02 (2) | C(7)–N | 1.29 (2) |
| Re–C(4) | 1.95 (2) | N–H(1) | 1.04 (15) |
| Re–C(5) | 2.21 (2) | C(9)–C(10) | 1.52 (3) |
| Re–C(7) | 2.18 (2) | C(9)–H(9) | 0.87 (18) |
| C(1)–O(1) | 1.13 (3) | C(9)–C(11) | 1.54 (2) |
| C(2)–O(2) | 1.15 (3) | C(9)–N | 1.47 (2) |
| C(3)–O(3) | 1.11 (3) | C(11)–O(6) | 1.19 (2) |
| C(4)–O(4) | 1.13 (2) | C(11)–O(7) | 1.31 (2) |
| C(5)–O(6) | 1.49 (3) | C(12)–O(7) | 1.48 (2) |
| | | C(12)–C(13) | 1.47 (3) |

Table II. Bond Angles (in Deg, with Esd's) for *cis*-$(OC)_4Re[CH_3C(O)][CH_3CN(L\text{-}CHCH_3CO_2CH_2CH_3)(H)]$

| | | | |
|---|---|---|---|
| C(1)–Re–C(2) | 92.0 (7) | Re–C(5)–O(5) | 124 (1) |
| C(1)–Re–C(3) | 172.9 (7) | Re–C(5)–C(6) | 122 (2) |
| C(1)–Re–C(4) | 88.9 (7) | C(6)–C(5)–O(5) | 113 (2) |
| C(1)–Re–C(5) | 90.1 (6) | Re–C(7)–C(8) | 118.8 (9) |
| C(1)–Re–C(7) | 87.1 (6) | Re–C(7)–N | 131.2 (8) |
| C(2)–Re–C(3) | 94.9 (7) | C(8)–C(7)–N | 110 (2) |
| C(2)–Re–C(4) | 91.3 (7) | H(9)–C(9)–C(10) | 78 (1) |
| C(2)–Re–C(5) | 176.4 (6) | H(9)–C(9)–C(11) | 129 (10) |
| C(2)–Re–C(7) | 94.3 (6) | H(9)–C(9)–N | 116 (8) |
| C(3)–Re–C(4) | 89.4 (7) | C(10)–C(9)–C(11) | 110 (2) |
| C(3)–Re–C(5) | 83.1 (6) | C(10)–C(9)–N | 112 (2) |
| C(3)–Re–C(7) | 93.9 (6) | C(11)–C(9)–N | 107 (2) |
| C(4)–Re–C(5) | 91.6 (6) | C(9)–C(11)–O(6) | 126 (2) |
| C(4)–Re–C(7) | 173.2 (4) | C(9)–C(11)–O(7) | 110 (2) |
| C(5)–Re–C(7) | 82.9 (5) | O(6)–C(11)–O(7) | 125 (2) |
| Re–C(1)–O(1) | 176 (2) | C(13)–C(12)–O(7) | 109 (2) |
| Re–C(2)–O(2) | 178 (2) | H(1)–N–C(7) | 119 (6) |
| Re–C(3)–O(3) | 178 (2) | H(1)–N–C(9) | 115 (6) |
| Re–C(4)–O(4) | 176 (2) | C(7)–N–C(9) | 126 (2) |
| | | C(11)–O(7)–C(12) | 116 (2) |

Table III. Selected Least-Squares Planes[a] and Atomic Deviations from the Planes for *cis*-$(OC)_4Re[CH_3C(O)][CH_3CN(L\text{-}CHCH_3CO_2CH_2CH_3)(H)]$

| atom | dev, Å | atom | dev, Å |
|---|---|---|---|
| Plane I: | $-0.1288I + 0.9195J + 0.3714K = -2.7135$ | | |
| Re[b] | −0.0045 | H(1) | −0.1210 |
| C(7)[b] | 0.0169 | C(9) | 0.0807 |
| C(8)[b] | −0.0052 | C(5) | −1.8424 |
| N[b] | −0.0072 | O(5) | −2.7417 |
| Plane II: | $-0.0741I - 0.7578J + 0.6482K = -0.6599$ | | |
| Re[b] | −0.0052 | C(7) | −1.6648 |
| C(5)[b] | 0.0209 | N | −1.8302 |
| O(5)[b] | −0.0088 | | |
| C(6)[b] | −0.0069 | | |
| Plane III: | $-0.8170I + 0.3435J + 0.4631K = -4.5000$ | | |
| O(6)[b] | −0.0086 | C(12) | −0.0621 |
| O(7)[b] | −0.0068 | C(13) | −0.4441 |
| C(9)[b] | −0.0058 | C(10) | −1.3691 |
| C(11)[b] | 0.0213 | N | 0.2503 |
| | | H(1) | −0.4473 |
| Plane IV: | $0.2092I - 0.3775J + 0.9021K = -3.4074$ | | |
| C(5)[b] | 0.1120 | Re | 1.1742 |
| O(5)[b] | −0.0757 | C(6) | −0.5151 |
| C(7)[b] | −0.1478 | C(8) | −1.6526 |
| N[b] | 0.1115 | H(1) | −0.6582 |
| Plane V: | $-0.7656I + 0.3381J + 0.5472K = -4.5451$ | | |
| N[b] | 0.0371 | Re | 2.5461 |
| C(9)[b] | −0.0746 | C(10) | −1.3691 |
| O(6)[b] | −0.0846 | H(1) | −0.7075 |
| O(7)[b] | 0.1092 | C(7) | 0.9441 |
| C(12)[b] | 0.1226 | | |
| C(13)[b] | −0.1186 | | |

[a] Equations of the planes are expressed as $PI + QJ + RK = S$ in orthogonal ångstrom space (see test for angles of intersecting planes). [b] Atoms used in calculating the planes.

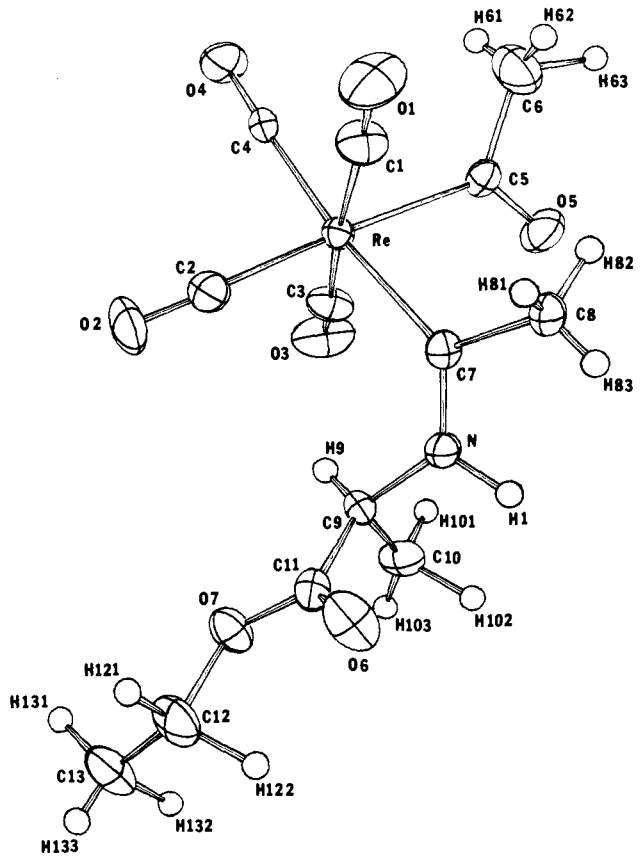



**Figure 1.** An ORTEP view of **7** (*interisomer*) showing the atomic numbering scheme (ellipsoids at 20%).

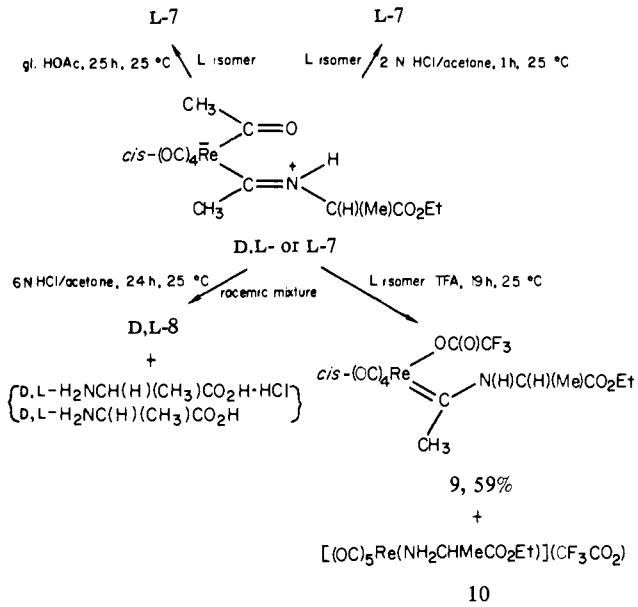
for both enantiomorphs using the *entire* data set confirmed the L configuration at C(9). The bond distances within the ethyl L-alaninate moiety of **7** and those of L-alanine[17] agree to within $\pm 1.8\sigma$, and the largest discrepancy between related bond angles within these molecules is 6°, arising from a slight opening of the C(9)–C(11)–O(6) angle in **7**. In both **7** and L-alanine the backbone atoms, C(9), C(11), O(6), and O(7), are essentially coplanar (plane III) with the N and C(9) methyl carbon atoms being, respectively, 0.25 and 1.34 Å from this plane in **7** and 0.45 and 1.38 Å from this plane in L-alanine.

The molecular structure of **7** clearly demonstrates that the ethyl L-alaninate ester functionality does not perturb the expected intramolecular hydrogen bonding involving the rhena moieties and that the structure of the amino acid residue is not significantly perturbed by the rhena moiety. These structural results may indicate that these rhena derivatives can be used as heavy-atom labels for peptide structure determinations.

For synthetic and biological applications it is important to determine (1) the enantiomeric stability of C(9) in **7** toward base, (2) the hydrolytic stability of the iminium linkage in these rhenaamino acid derivatives, and (3) a method for removing the amino acid residue from the rhena moiety. The specific rotation of an ethanol solution containing an *intra-* and *interisomeric* mixture of **7** was measured periodically at 25 °C over a 20-h period. During this time, the specific rotation varied only within experimental error, $[\alpha]_D^{25°C} = +25.8 \pm 0.7°$ (*c* 1.08, EtOH), indicating that C(9) did not racemize in the presence of a very small concentration of ethoxide ion. As shown in Scheme II, treating an ethanol solution of **7** with 1 equiv of KOH/ethanol at −12 °C for 18 h followed by low-temperature protonation afforded only racemic **7** with no saponification of the ester group. However, treating **7** with KOH/ethanol for 1 h at higher temperature (−8 to +5 °C) followed by protonation afforded the racemic rhenaalanine complex **8**. Therefore, **7** racemizes readily in the

(17) Lukehart, C. M.; Zeile, J. V. *J. Organomet. Chem.* **1975**, *97*, 421.

Scheme III




presence of added base, and racemization of **7** will occur during basic solvolysis of the ester group. The facile racemization of **7** parallels that of L-alanine derivatives and indicates that basic reaction conditions should be avoided.

The solvolytic stability of **7** under acidic conditions was examined as shown in Scheme III. Complex **7** was recovered unchanged in high yield after standing in glacial acetic acid for 25 h and in 2 N HCl/acetone solution for 1 h at 25 °C. In each case, no water-soluble products were isolated. Dissolution of racemic **7** in 6 N HCl/acetone solution and standing at 25 °C for 24 h afforded **8** in 30% yield via acid hydrolysis of the ester group along with a very low yield of D,L-alanine and D,L-alanine·HCl. No other rhena complexes or alanine derivatives were isolated. The hydrolytic stability of **7** appears to be unusually high since acid hydrolysis of the ester group can occur without complete cleavage of the amino acid from the rhena moiety.

In attempting to remove the amino acid residue from the rhena moiety, we treated complex **7** with neat trifluoroacetic acid (TFA) at 25 °C for 19 h. The only products isolated from this reaction were the neutral (aminocarbenoid) (trifluoroacetate) rhenium complex **9** and the ionic ethyl alaninate rhenium complex **10**. Compound **9** is well characterized, whereas **10** is isolated as a slightly impure oil. However, the IR and $^1$H NMR spectra as well as the solubility properties of **10** are consistent with ethyl alaninate acting as an amine ligand, as shown. The specific rotations of **9** and **10** were not measured; and, no free alanine derivatives were isolated. This reaction clearly demonstrates that the rhena-$\beta$-ketoimine amino acid derivatives are much more stable to acid solvolysis than Fischer's group 6 carbenoid amino acid derivatives since TFA rapidly cleaves the amino acid residue from the metal atom of the carbenoid compounds.[6]

For possible synthetic applications, a high-yield procedure for completely cleaving the amino acid residue from the rhena moiety is desirable. Previous results indicated that organometallic complexes similar to these Re(I) complexes are susceptible to oxidation by using mild oxidizing agents such as iodosobenzene.[17] When **7** was treated with iodosobenzene in methylene chloride solution at 25 °C, a vigorous evolution of gas (CO, presumably) occurs. The reaction solution was monitored by IR as solid iodosobenzene was added in portions. Upon reacting, the solid iodosobenzene disappeared with a concomitant decrease in the concentration of **7**. After ca. 11 equiv of iodosobenzene was added to the reaction solution, the IR spectrum of it revealed organic carbonyl bands but no absorptions due to carbonyl ligands. An $^1$H NMR spectrum of the crude reaction residue showed iodobenzene and a 1:1 mixture of acetic acid and *N*-acetyl ethyl-L-alaninate. Presumably, the acetyl and iminium ligands of **7** were oxidized to the carbonyl

product with the acetate anion being protonated by an endogenous proton source.

Subsequent workup afforded a 67% isolated yield of *N*-acetyl ethyl-L-alaninate. The measured specific rotation, $[\alpha]_D^{26°C}$, of +6.4° (*c* 0.933, Silanor-C) indicates that the L configuration of the amino acid has been maintained throughout the oxidation reaction. The fate of the rhenium is less certain although elemental analysis of the only Re-containing product suggests that a rhenium oxide having the empirical formula, ca. $HReO_4$, is formed.[18] The need for such an apparent excess of iodosobenzene is not obvious. Oxidation of the carbonyl ligands to $CO_2$ would nearly fit the observed reaction stoichiometry; however, this explanation is not very reasonable when considering the heterogeneous reaction conditions, and the rapid evolution of the gaseous product. Although the above oxidation reaction effectively cleaves the amino acid residue from the rhena moiety, the formation of the *N*-acetyl amino acid derivative is rather inconvenient if the free amino acid derivative is desired.

Future study of the synthesis and structures of rhena derivatives of amino acids and peptides is planned. The compatability and selectivity of rhena derivatization in the presence of more reactive functional groups will be examined, and the search for more convenient rhena cleavage reactions will be continued.

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**Supplementary Material Available:** Tables listing the atomic positional and thermal parameters and the observed and calculated structure factors (14 pages). Ordering information is given on any current masthead page.

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# Molecular Species Containing Persistent Voids. Template Synthesis and Characterization of a Series of *lacunar*-Nickel(II) Complexes and the Corresponding Free Ligands

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**Abstract:** A new family of lacunar ligands has been synthesized in the form of their nickel(II) complexes by a template process. The new species were designed to provide a protected void, or cavity, in the vicinity of a coordination site in order to facilitate the binding of small molecules to the metal ion. The nature of the ligand greatly limits collapse of the cavity, and the height and flexibility of the roof vary with the length of the homologous bridging group which varies from tetramethylene to octamethylene. The shorter dimethylene and trimethylene bridges are too short to span the cavity while longer bridges produce complicated systems containing isomers. The electron density at the metal ion is insensitive to bridge length so that the previously reported great change in $O_2$ affinity by the cobalt(II) complexes arises from steric effects.

Molecular structures containing sizable, noncollapsing voids are of significance for a variety of reasons, some fundamental and others associated with their applications in the study of other fundamental chemical processes. Macrocyclic ligands constitute one of the more primitive classes of such structures, being almost two dimensional. These substances are well-known because of their exceptional coordinating properties toward metal ions, even the larger alkali-metal ions.[1] Cram and associates[2] have pioneered the study of guest–host complexation between such host molecules and organic guest molecules. The cyclodextrins have long fascinated chemists because of the persistent void in their structures and the provocative interaction between the void and co-solutes.[3] With appropriate substituents, such structures have been studied as enzyme models.[4] Collman et al. appended four pivaloylamide groups on the same side of porphyrin and extended the void represented by the coordination site substantially in the third dimension, thereby producing highly effective reversible oxygen carriers of the iron and cobalt complexes.[5] An exemplary void-containing structure was created by Baldwin et al., who synthesized a "capped porphyrin" having a benzene ring suspended above the porphyrin.[6] A number of observations have suggested that conformational changes in the capped porphyrins may produce variations in the height of the cavity.[7] The simpler strapped

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(7) The $O_2$ binding constants do not increase as the chain length increases for the "roof-supports" (Linard, J. E.; Ellis, P. E., Jr.; Budge, J. R.; Jones, R. P.; Basolo, F. *J. Am. Chem. Soc.* **1980**, *102*, 1896–1904) despite the fact that the X-ray structure for the free ligand shows that the capped porphyrin with the short roof supports has a remarkably low roof (Jameson, G. B.; Ibers, J. A. *Ibid.* **1980**, *102*, 2823–2831).

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