(Figures 1 and 2). Although the hydride ligands were not located, on the basis of steric grounds they are presumably located in the plane defined by P(3)-W-P(4), such that the overall coordination geometry is dodecahedral. Four-membered oxametallacycles,[7] which are of particular interest as potential models for olefin oxidation,[8] are rare compared with five- and six-membered derivatives.[9] Furthermore, four-membered oxametallacycles derived from ortho metalation of aryloxy ligands are surprisingly rare,[10] for which $W(PMe_3)_4H_2(\eta^2\text{-}OC_6H_4)$ represents a structurally characterized example.

More interesting situations arise in the reactions of the monosubstituted phenols, $2\text{-}RC_6H_4OH$ (R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$), in which a variety of potential C-H bond activation reactions are now possible, leading to the formation of either four-, five-, or six-membered oxametallacycles. For example, the reaction of 2-methylphenol gives the five-membered oxametallacycle $W(PMe_3)_4H_2\{\eta^2\text{-}OC_6H_3(CH_2)\}$ as a result of selective sp^3 C-H bond activation of the methyl substituent, in preference to the four-membered ortho-metalated alternative. However, in marked contrast, the corresponding reactions of the 2-ethyl-, 2-isopropyl-, and 2-*tert*-butylphenol derivatives give specifically the four-membered oxametallacycles as a result of selective sp^2 C-H bond activation at the ortho position.

The propensity for the formation of four-membered metallacycles within this system is striking, especially given the marked tendency of ortho-substituted *tert*-butyl groups in other systems to undergo facile metalation, with the resulting formation of six-membered oxametallacycles.[9] Although at present we cannot address the question whether the formation of four-membered versus six-membered oxametallacycles in this system represents a kinetic or thermodynamic preference, we note that one contributing factor may be a consequence of the 18-electron configuration of the tungsten centers in these oxametallacycles. The six-membered oxametallacycle complexes that are derived from aryloxy ligands typically possess electron-deficient metal centers. Structural studies on these oxametallacycles demonstrate that formation of the six-membered ring allows for large M-O-C bond angles, thus enabling favorable lone-pair donation from oxygen to the electron-deficient metal center.[9] Such lone-pair donation would clearly stabilize an oxametallacycle structure of an electron-deficient metal center. However, for the 18-electron complexes described here, lone-pair donation would not be expected to contribute significantly to oxametallacycle stability, and thus the preference for six-membered ring formation would be lessened.

Studies indicate that the four- and five-membered oxametallacycles are also highly reactive. For example, $W(PMe_3)_4H_2(\eta^2\text{-}OC_6H_4)$ is hydrogenated rapidly by H_2 at room temperature to give $W(PMe_3)_4H_3(OC_6H_5)$.[11] Deuterium labeling demonstrates that this reaction proceeds via initial reductive elimination of the metallacycle-hydride unit (eq 2).

$$W(PMe_3)_4H_2(\eta^2\text{-}OC_6H_4) \rightarrow [W(PMe_3)_4H(OC_6H_5)] \xrightarrow{D_2} W(PMe_3)_4HD_2(OC_6H_5) \quad (2)$$

In conclusion, these studies have demonstrated the selectivity with which electron-rich tungsten complexes may form four- and five-membered oxametallacycle complexes, in contrast to the more commonly observed six-membered derivatives that are obtained for electron-deficient metal complexes.

Supplementary Material Available: Tables of spectroscopic data for all new compounds, crystal and intensity collection data, atomic coordinates, bond distances and angles, and anisotropic displacement parameters and ORTEP drawings (21 pages); tables of observed and calculated structure factors for $W(PMe_3)_4H_2(\eta^2\text{-}OC_6H_4)$ and $W(PMe_3)_4H_2\{\eta^2\text{-}OC_6H_2Me_2(CH_2)\}$ (28 pages). Ordering information is given on any current masthead page.

(6) Crystal data for $W(PMe_3)_4H_2\{\eta^2\text{-}OC_6H_2Me_2(CH_2)\}$: monoclinic, $P2_1/n$ (No. 14), a = 9.898 (3) Å, b = 28.065 (9) Å, c = 10.663 (3) Å, β = 104.33 (2)°, V = 2870 (1) Å^3, Z = 4, ρ_{calcd} = 1.45 g cm^{-3}, μ(Mo Kα) = 44.9 cm^{-1}, λ(Mo Kα) = 0.71073 Å (graphite monochromator); 4474 unique reflections with $3° < 2\theta < 48°$ were collected of which 2556 reflections with $F > 6\sigma(F)$ were used in refinement; R = 0.0455, R_w = 0.0451, GOF = 1.274.

(7) Examples of four-membered oxametallacycles include $(AsPh_3)_2Pt\{OC(CN)_2C(CN)_2\}$,[7a,b] $(PPh_3)_2Pt(CH_2OCH_2)$,[7c] $(\eta^5\text{-}C_5Me_5)(PMe_3)Ir(OCMe_2CH_2)$,[7d] $(\eta^5\text{-}C_5H_5)_2Ti\{OC(CH_2)CH_2\}$,[7e] $(\eta^5\text{-}C_5H_5)_2[Zr(OC_6H_8)]_2$,[7f] and $(\eta^5\text{-}C_5Me_5)_2Zr(OCPh{=}CPh)$.[7g] (a) Schlodder, R.; Ibers, J. A.; Lenarda, M.; Graziani, M. *J. Am. Chem. Soc.* **1974**, *96*, 6893-6900. (b) Lenarda, M.; Ros, R.; Traverso, O.; Pitts, W. D.; Baddley, W. H.; Graziani, M. *Inorg. Chem.* **1977**, *16*, 3178-3182. (c) Hoover, J. F.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 6466-6468. (d) Klein, D. P.; Hayes, J. C.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 3704-3706. (e) Ho, S. C.; Hentges, S.; Grubbs, R. H. *Organometallics* **1988**, *7*, 780-782. (f) Vaughan, G. A.; Hillhouse, G. L.; Lum, R. T.; Buchwald, S. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1988**, *110*, 7215-7217. (g) Vaughan, G. A.; Hillhouse, G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 7994-8001.

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Peptide Architecture. Design of Stable α-Helical Metallopeptides via a Novel Exchange-Inert Ru^{III} Complex

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There is considerable interest in the design of linear polypeptides that can adopt stable and well-defined solution conformations. Such systems can serve as models for the study of the early events in protein folding[1] as well as possess substantial utility in the design of peptide-based therapeutic agents.[2] However, in spite of a few encouraging results, design of short monomeric peptides with stable secondary structure conformations in water has not been forthcoming.[3] Here we report for the first time the utility of an exchange-inert metal complex[4,5] in the formation of remarkably stable α-helical peptides. Formation of a macrocyclic *cis*-$[Ru(NH_3)_4L_2]^{3+}$ complex, where L_2 are the side chains of two histidines in positions i and $i + 4$ of a peptide, is shown to be a simple and effective method for constraining the intervening chain in an α-helical conformation and effecting helix nucleation. A 17-residue polypeptide functionalized in this way has a melting

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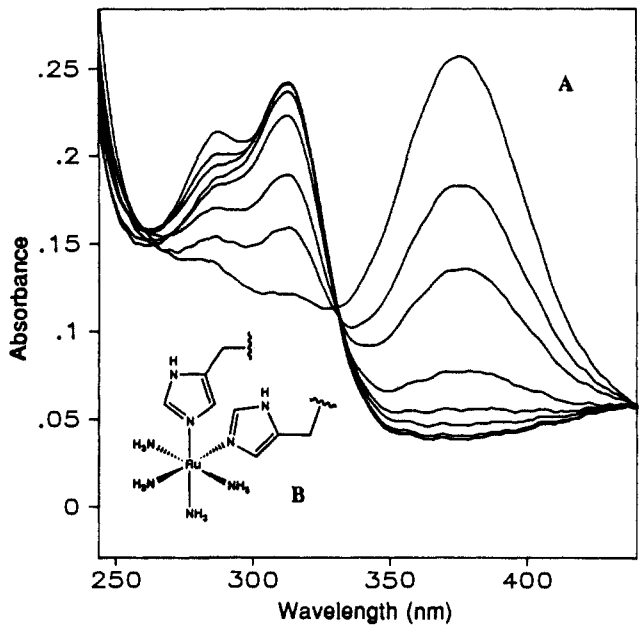

Figure 1. (A) Absorption spectra of tetraaminеruthenium(III)–peptide **1** complex (6.0×10^{-5} in water) at pH 4.7 (maxima at 313 nm), 5.5, 6.6, 7.1, 7.5, and 7.9 (maxima at 376 nm). (B) *cis*-$[Ru(NH_3)_4(His_2\text{-peptide})]^{3+}$ chromophore.

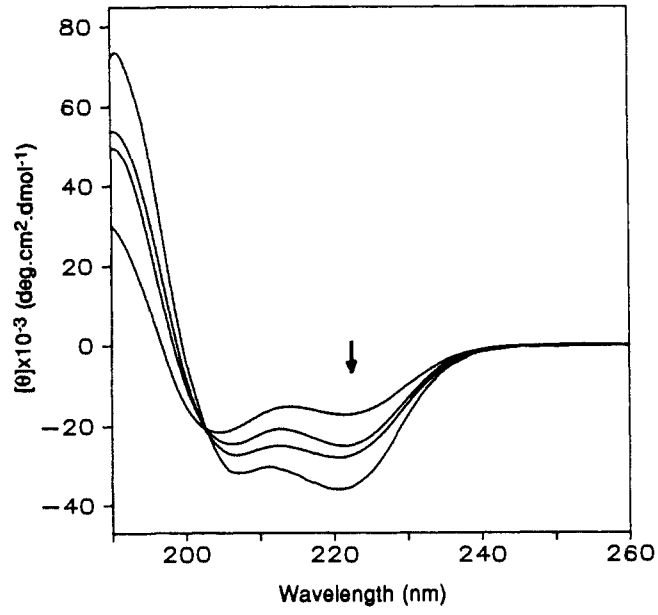

Figure 2. CD spectra of ruthenium(III)-complexed peptides **1** and **2**. From top curve (arrow) to the bottom: (a) *cis*-$Ru(NH_3)_4$–peptide **2**, 6.3×10^{-6} M in water, pH 6.0, at 20 °C and (b) at 0 °C; (c) *cis*-$Ru(NH_3)_4$–peptide **1**, 5.0×10^{-6} M in water, pH 6.1, at 20 °C and (d) at 0 °C.

temperature of 35 °C and exhibits 80% α-helicity at 21 °C.

In a recent study, we described the use of labile transition-metal complexes in the formation of α-helical peptides.[6] In order to extend the scope and utility of this methodology to systems suitable for study under normal physiological conditions, peptide–metal complexes must be designed which are considerably more resistant to ligand exchange. However, unlike the exchange-labile ions which can be easily incorporated by virtue of their rapid exchange rates, formation of exchange-inert metallopeptide complexes is rather difficult.[5a] In peptides and proteins where a number of reactive side-chain functionalities are present, chemoselectivity in the formation of an exchange-inert metal complex is the paramount issue and is primarily dependent on the careful choice of metal ion, its oxidation state, and the ligands employed.[5] The high affinity of aquopentaammineruthenium(II) for surface-accessible histidine residues[7] prompted us to examine the feasibility of forming stable macrocyclic *cis*-$[Ru(NH_3)_4(His_2\text{-peptide})]^{3+}$ complexes of peptides **1** and **2** and further explore the utility of this approach in the induction and stabilization of the α-helical conformation. These peptides have, in addition to two histidines, two aspartic acid and two lysine residues in the relative *i* and *i* + 4 positions and are therefore good models to test the chemoselectivity of the complex-forming reaction. Peptides **1** and **2** were modified in the presence of *cis*-$[Ru(NH_3)_4(H_2O)_2]^{2+}$ in a degassed Tris buffer (50 mM, pH 7.1) for 6 h.[8] The reaction mixture was air oxidized, and the metallopeptide was purified by either ion exchange or reversed-phase chromatography.[9]

peptide **1**: acetyl-AEAAAKEAAAK*H*AAA*H*A-$CONH_2$

peptide **2**: acetyl-AEAAAK*H*AAA*H*EAAAKA-$CONH_2$

Chemoselective functionalization of histidine residues is supported by NMR studies. The histidine C-2 and C-4 protons of peptide **2** occurring at δ 8.52 and 8.51 and at 7.20 and 7.19 undergo dramatic upfield shifts to δ 7.47 and 7.15 and at 6.98 and 6.83, respectively, upon attachment to a tetraammineruthenium(II) moiety. On the other hand, the histidine signals in the Ru(III)–peptide complex display paramagnetic shifting[10] and appear as broad peaks at δ 0.56 and −0.78.[11] Furthermore, the absorption spectrum of the Ru(III) complex of peptide **1** shows ligand to metal charge transfer bands at 287 and 313 nm below pH 6.5 which shift to 376 nm above pH 8 with an isosbestic point at 331 nm[12] (Figure 1). The pronounced shift in absorption maxima with increasing pH is consistent with the behavior of the Ru(III) ions containing coordinated imidazoles and is attributed to N–H deprotonation at the "pyrrole nitrogen".[13] The absorption data give a pK_a value of 7.5 for the imidazole N–H of the coordinated histidine, which is 7 orders of magnitude lower than the pK_a of uncomplexed histidine.[14] The spectral similarity with the simple ruthenium(III)–imidazole complexes and the characteristically facile metal-ion-promoted imidazole N–H ionization[15] further support the formation of the desired complex.

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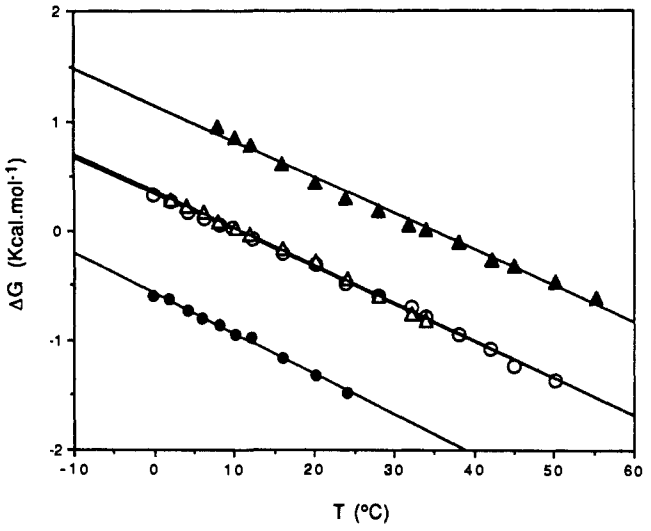

Figure 3. Plot of ΔG vs temperature for the unfolding of free and ruthenium-complexed peptides **1** and **2** [(5.0–6.3) × 10^{-6} M, in 20 mM MES, pH 6.0]: (●) peptide **2**; (○) Ru(III)–peptide **2**; (△) peptide **1**; (▲) Ru(III)–peptide **1**.

Restriction of the conformational mobility of peptides **1** and **2** by the formation of an exchange-inert macrocyclic Ru(III) complex affords remarkably stable α-helical metallopeptides (Figure 2). The analysis of CD spectra[16] of Ru(III)-complexed peptides **1** and **2** at 21 °C in water indicates 80% ($[\theta]_{222}$ = −28 000 deg·cm²·dmol⁻¹) and 50% ($[\theta]_{222}$ = −17 300 deg·cm²·dmol⁻¹) α-helicity, respectively.[17] In contrast, the free peptide **1** under similar conditions is 45% helical ($[\theta]_{222}$ = −16 000 deg·cm²·dmol⁻¹) while uncomplexed peptide **2** exhibits the CD spectrum of a random coil structure.[16] In order to assess differences in helix stability between the metal-ion-complexed and uncomplexed forms of peptides **1** and **2**, the conformational stability of each peptide in the presence and absence of transition-metal ions was determined from heat denaturation studies.[18] The analysis of the thermal denaturation curves afforded linear ΔG vs T and van't Hoff plots (Figure 3). The data suggest that the formation of the exchange-inert Ru(III) complex contributes up to 1 kcal·mol⁻¹ toward the stability of the α-helical conformation and dramatically increases the melting temperature of both peptides by about 25 °C. Complexed peptides **1** and **2** exhibit melting temperatures of 35 and 9.5 °C, respectively, while the corresponding free peptides have T_m values of 11 and −15.5 °C.

The above study unequivocally establishes that exchange-inert metal complexes can be effectively exploited in designing highly stable α-helical metallopeptides. The availability of a simple methodology for the formation of stable α-helical peptides can have considerable utility in the de novo design of biologically active peptides.

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Enantioselective Catalysis of the Triplex Diels–Alder Reaction: Addition of *trans*-β-Methylstyrene to 1,3-Cyclohexadiene Photosensitized with (−)-1,1′-Bis(2,4-dicyanonaphthalene)

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The discovery of enantioselective photochemical sensitization reactions has been pursued with modest success since 1965 when Hammond and Cole reported that triplet energy transfer from an optically active amide gives a 7.7% enantiomeric excess (ee) of *trans*-1,2-diphenylcyclopropanes.[1] Similarly, Takamuku and co-workers observe modest enrichments from isomerization of *trans*-cyclooctenes sensitized by optically active esters.[2] Inoue and co-workers described an unusual temperature dependence for this reaction.[3] The differential recognition of excited molecules bound to chiral surfaces by optically active quenchers was recently reported by Avnir and co-workers.[4] Despite a massive effort to develop chiral Lewis acids that will induce optical activity in cycloadducts formed by the Diels–Alder reaction,[5] only Vondenhof and Mattay have considered a photochemical route to this goal.[6] They describe use of an optically active sensitizer in a radical cation Diels–Alder reaction, but do not report an enantiomeric excess in the cycloadducts that result.

We recently described the [4 + 2] cycloaddition of electron-rich dienes to electron-rich dienophiles in nonpolar solvents catalyzed by irradiation of electron-deficient arene sensitizers.[7] This process

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