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π-Ligands for Generating Transition Metal–Peptide Complexes: Coordination of Amino Acid Derivatives to Tungsten Utilizing Alkyne Ligands

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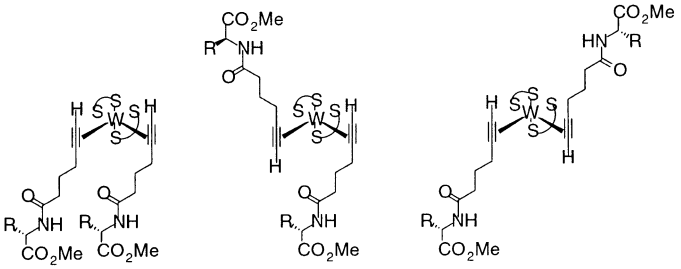
ABSTRACT



Amino acid derivatives bearing an alkyne (AA-CCH) at either the N- or C-terminus readily react with $W(CO)_3(S_2CNMe_2)_2$ to replace the carbon monoxides and form the novel bis-alkyne complexes $W(AA\text{-}CCH)_2(S_2CNMe_2)_2$; the solution behavior of these complexes shows that only the alkyne, and not the other functional groups on the amino acid, bonds to the tungsten.

Most short peptides do not adopt well-defined conformations because the energy differences between the possible conformations open to them are not substantial.[1] The tendency of short peptides to assume a myriad of conformations can be overcome by adding constraints that limit the conformational freedom of the peptide. The addition of covalent constraints has been successfully employed for maintaining peptides in helix, turn, and sheet conformations.[2] In other cases helices and sheets have been generated by coordination of a transition metal to ligands located on the peptide.[2,3]

The use of metal−ligand interactions for controlling peptide conformation is attractive for a number of reasons. First, the generation of a metal−ligand complex can usually be achieved in fewer steps than the somewhat lengthy and complicated syntheses that have been described for covalently constrained peptides. Second, there are a wide variety of transition metal−ligand combinations that might be employed. Third, the transition metal provides an easy spectroscopic handle for assessing the behavior and reactivity of the ordered peptide. Fourth, the presence of a transition metal in the peptide can greatly facilitate the determination of an X-ray crystal structure.

We are seeking to uncover new approaches for controlling peptide conformation through the use of transition metal−peptide interactions. In particular, we are seeking to identify ligands that (1) can be easily introduced anywhere (N-terminus, C-terminus, or side chain) onto a peptide, (2) are unreactive under the normal conditions of peptide synthesis, (3) would readily react with a transition metal complex under

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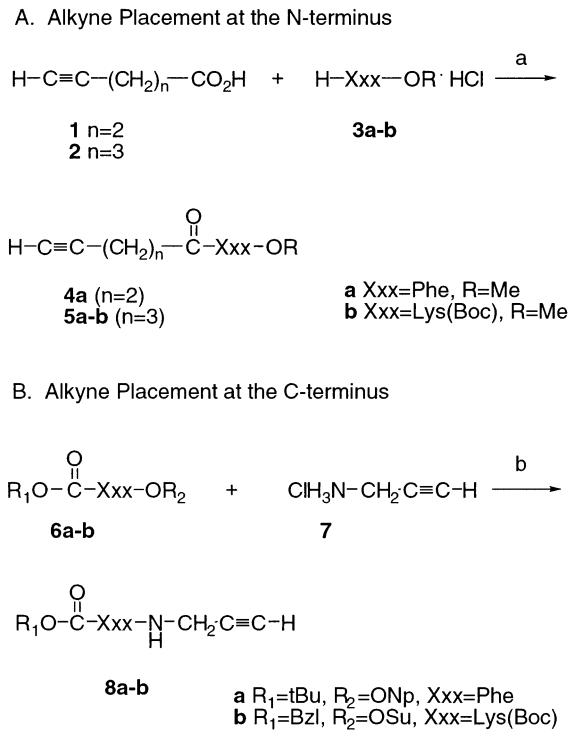
conditions that maintain the structural integrity of the peptide, and (4) could maintain two or more peptides around the transition metal.

To date, most investigations of peptide−ligand chemistry have focused on the use of basic ligands (both natural and unnatural) on the peptide for metal binding.[4] In contrast the ability of π-ligands on the peptide for metal binding has received very little study.[5,6] As an entry into such investigations, we were drawn to the capacity of tungsten and molybdenum dithiocarbamate complexes to form air-stable, d^4 mono- or bis-alkyne complexes.[7] From the literature on these complexes we reasoned that an alkyne met the four criteria for the type of ligand we were seeking.

To probe the feasibility of this ligand, the alkynyl amino acid derivatives shown in Scheme 1 were prepared. The

Scheme 1. Preparation of Alkynyl Amino Acids[a]

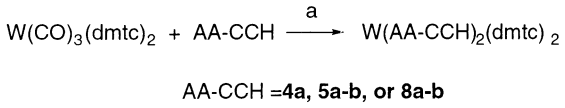


[a] Reagents and conditions: (a) EDC or DCC, DIEA, CH_2Cl_2; (b) DIEA, CH_2Cl_2.

alkyne ligand was readily introduced at the N-terminus via acylation of an amino acid ester hydrochloride (**3a**,**b**) with either 4-pentynoic acid (**1**) or 5-hexynoic acid (**2**), using a carbodiimide mediated coupling reaction to yield the derivatives **4a** and **5a**,**b**, respectively. Alternatively, the alkyne ligand was readily introduced at the C-terminus by reaction of an N-protected amino acid active ester (**6a**,**b**) (either nitrophenyl or hydroxysuccinimidyl esters) with propargylamine hydrochloride (**7**) to yield the derivatives **8a**,**b**.

Two molar equivalents of these alkynyl amino acids (AA-CCH = **4a**, **5a**,**b**, **8a**,**b**) were subsequently reacted with one molar equivalent of $W(CO)_3(S_2CNMe_2)_2$ [$W(CO)_3(dmtc)_2$][8] in refluxing methanol under an inert atmosphere (Scheme 2). Upon addition of the alkynyl amino acid to the rust orange

Scheme 2. Preparation of Bis-Alkyne Complexes[a]



[a] Reagents and conditions: (a) MeOH, reflux, 2−24 h.

solution of $W(CO)_3(dmtc)_2$ the color quickly changed to a deep green, which indicated that the tungsten complex had coordinated the first alkyne ligand.[9] After a period of 2−24 h the solution color eventually changed from deep green to a pale, lemon yellow, which indicated that the tungsten had coordinated the second alkyne ligand.[10,11] Once the solutions had become pale yellow reflux was halted. The methanol was removed by rotary evaporation and the crude tungsten bis-alkynyl amino acid was purified to homogeneity by flash chromatography. Product purity was assessed by thin-layer chromatography.

The products isolated from these reactions were identified as the bis-alkyne complexes $W(AA\text{-}CCH)_2(dmtc)_2$ (AA-CCH = **4a**, **5a**,**b**, **8a**,**b**) with several methods of analysis. First, each purified complex yielded a combustion analysis for carbon, hydrogen, and nitrogen that was consistent with the expected structure of the product.

Second, three of the complexes ($W(AA\text{-}CCH)_2(dmtc)_2$, AA-CCH = **5a**,**b**, **8b**) were analyzed by electrospray mass spectrometry (ESMS). Until recently it was thought that, in general, organometallic species were too fragile for analysis by mass spectrometry. However, the advent of ESMS has allowed for the analysis of organometallics by mass spectrometry.[12] Methanol solutions of these tungsten bis-alkynyl-amino acids yield signals for M + H, M + Na, and M + 2Na ions. Owing to the presence of the four major tungsten isotopes, these ions appear in unique and distinctive patterns. Thus, correlation of the actual ion pattern to the theoretical pattern can serve as confirmation of the structure. Shown in Figure 1 are the theoretical[13] and actual isotope patterns for the M + H ion derived from the complex $W(\mathbf{5b})_2(dmtc)_2$.

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(13) Theoretical isotope patterns were calculated with a program available at a website provided by the University of Sheffield: http://www.shef.ac.uk/chemistry/chemputer/.

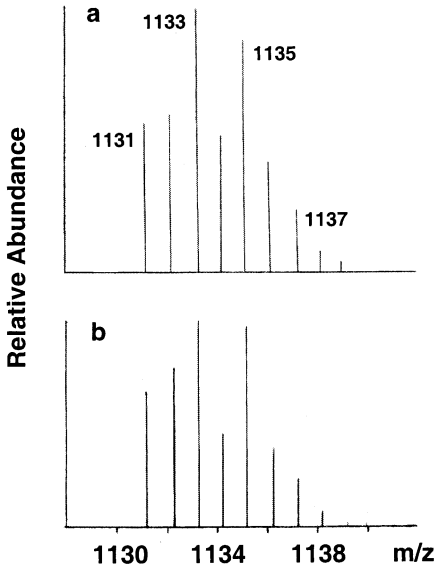


Figure 1. (a) The theoretical isotope pattern expected for the M + H ion in the ESMS spectrum of W(**5b**)$_2$(dmtc)$_2$. (b) The ESMS of the lysine bis-alkyne complex, W(**5b**)$_2$(dmtc)$_2$. The spectrum shows the M + H ions in the region from *m*/*z* 1128 to 1142.

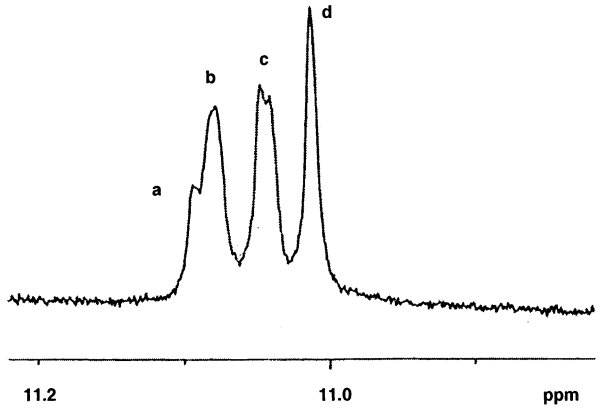


Figure 2. The ^{1}H NMR spectrum of W(**5b**)$_2$(dmtc)$_2$ dissolved in $CDCl_3$ in the region between 10.8 and 11.2 ppm. The resonances that appear here arise from the terminal alkyne hydrogens in the tungsten bis-alkyne complexes. Four separate resonances (labeled **a**−**d**) for terminal alkyne hydrogen are seen. Resonances **b** and **c** are derived from the cis isomer, while resonances **a** and **d** are derived from the trans′ and trans″ isomers.

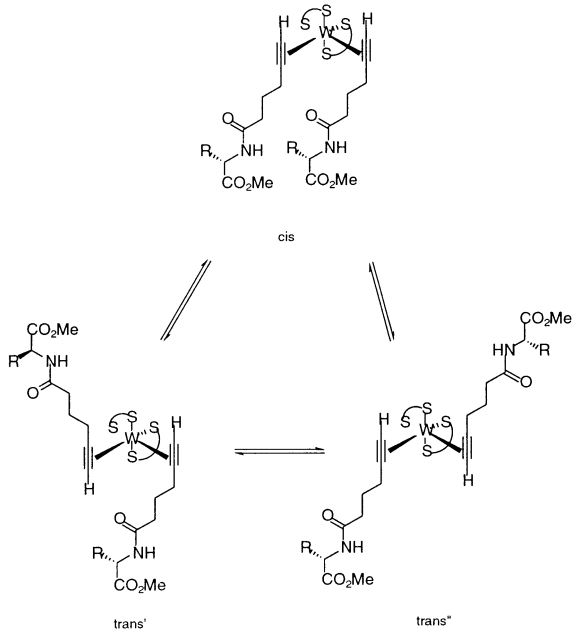
That the theoretical and actual isotope patterns form a nearly identical match confirms the structure of W(**5g**)$_2$(dmtc)$_2$.

To confirm that only the alkynes, and not the other functional groups associated with the amino acid derivatives, were bonding to the tungsten, the UV−visible spectra of each complex was recorded. Each complex was colored yellow, both in the solid state and in solution, and each complex displayed nearly identical absorption spectra that are characterized by a shoulder peak located around 330 nm. Both the yellow color of the complexes and the nearly identical UV−visible spectra indicate that only the alkyne, and not the other functional groups associated with the amino acid derivative, bonds to the tungsten.

The structure and bonding in these complexes was further confirmed by their ^{1}H NMR spectra. Resonances from both the alkynylamino acid and the dithiocarbamate were present and possessed area integrations consistent with the bis-alkyne structure. Further, the ^{1}H NMR spectra all showed a set of resonances located around 11.1 ppm that possessed a relative integration equal to two hydrogens. These resonances in the ^{1}H NMR spectrum of W(**5b**)$_2$(dmtc)$_2$ are shown in Figure 2. As noted in previous work with bis-alkyne complexes derived from simple, terminal alkynes, the alkyne hydrogen resonates around 11.0 ppm.[10] The similar location of the alkyne hydrogen in these alkynylamino acid complexes indicates again that only the alkyne is involved in the bonding to the tungsten.

As seen in Figure 2, the terminal alkyne hydrogens in these complexes do not appear as a simple singlet; rather, they appear as a complex pattern of resonances. This complex pattern for the terminal alkyne hydrogens serves as a window on the conformational behavior of these bis-alkyne complexes. When two terminal alkynes coordinate to tungsten or molybdenum to form bis complexes, there are several possible arrangements of the alkynes relative to each other (see Scheme 3). The two alkynes can be cis to each other,

Scheme 3. Conformational Isomers



or they can be trans to each other. Owing to the presence of the dithiocarbamate ligands there are two different trans orientations (trans′ and trans″ in Scheme 3). The trans′ and trans″ conformations are differentiated by the magnetic environments of the terminal alkyne hydrogens. Although the two terminal alkyne hydrogens in the trans′ conformation

are identical with each other, they are distinctly different from the two terminal alkyne hydrogens in the trans″ conformation. In the ^{1}H NMR spectrum each of the two trans conformers should give rise to one signal arising from the terminal alkyne hydrogens. In contrast, in the cis arrangement, the two terminal alkyne hydrogens are in different magnetic environments so this conformer should give rise to two separate signals in the ^{1}H NMR spectrum. This pattern of resonances can then be further complicated by long-range coupling and/or the presence of conformational isomers associated with the amino acid.

As seen in Figure 2, four signals are visible for the terminal alkyne hydrogens in W(**5b**)$_2$(dmtc)$_2$. The other bis-alkyne complexes derived from the alkynylamino acids shown in Scheme 1 also display similar patterns with their terminal alkyne hydrogens. The appearance of these signals indicates that these complexes adopt all three conformations about the metal: cis, trans′, and trans″ (Scheme 3). This behavior is similar to that of bis-alkyne complexes derived from simple, terminal alkynes; they also adopt all three conformations in solution.[10] This conformational isomerism is manifested in other parts of the ^{1}H NMR spectra of these complexes, where, for example, multiple peaks are seen for the amide NH protons and the dithiocarbamate methyl groups. The overall appearance of the ^{1}H NMR spectra is consistent with a dynamic system in which there is an equilibrium between the three conformers. For our purposes, the observation that these alkynylamino acid complexes can adopt the cis conformation is encouraging, because this is the orientation that would permit hydrogen bonding (or other intermolecular attractions) between two adjacent peptides linked to the tungsten via an alkyne appendage.

The results presented here demonstrate that the alkyne meets the four criteria needed for coordination of peptides to a transition metal. The alkyne is unreactive during normal peptide synthesis. It is easily appended to the N- or C-termini (or by extension, to acid or amine side chain groups) of amino acid derivatives with use of standard amide bond forming reactions. The alkyne readily reacts with W(CO)$_3$(dmtc)$_2$ to form novel bis-alkyne complexes, and the peptide backbone of these amino acid derivatives does not inhibit or interfere with the transition metal−ligand chemistry. That these complexes also can adopt a cis arrangement of the two alkyne ligands, even with an attached amino acid, demonstrates that these species have the potential to order the conformation of larger alkynylpeptides through interstrand hydrogen bonding. Studies to explore this possibility are in progress.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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