The Mo(η-allyl)$(CO)_2$ Moiety as a Robust Marker Group in Bioorganometallic Chemistry. Unusual Crystal Structure of the Phenylalanine Derivative Mo(C_5H_4-CO-Phe-OMe)(η-allyl)$(CO)_2$

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The MoCp(η-C_3H_5)$(CO)_2$ (Cp = η-cyclopentadienyl) moiety is introduced as a new labeling group in bioorganometallic chemistry. The acid Mo(C_5H_4-CO_2H)(η-C_3H_5)$(CO)_2$ (**2**) was obtained from the reaction of MoCp(η-C_3H_5)$(CO)_2$ (**1**) with BuLi and solid CO_2 followed by aqueous workup. Coupling of **2** to amino acids with various complexity and *C*-terminal functionality by standard peptide chemistry methods yielded the amino acid derivatives Mo(C_5H_4-CO-AA-R)(η-C_3H_5)$(CO)_2$, **3** (**3a**, AA = Phe, R = OCH_3; **3b**, AA = Leu, R = NH_2; **3c**, AA = Gly, R = OCH_3). In addition, the dipeptide derivative Mo(C_5H_4-CO-Leu-Phe-OCH_3)-(η-C_3H_5)$(CO)_2$ (**4**) was synthesized by reacting **2** with H-Leu-Phe-OCH_3. All new compounds are characterized by elemental analysis, IR, MS, and NMR spectroscopy. X-ray analysis on **3a** shows the unit cell to contain two independent molecules, **A** and **B**, which differ mainly by the orientation of the allyl and carbonyl groups with respect to the amino acid substituent on the Cp ring. Furthermore, an allyl-*endo* conformation for both **A** and **B** is observed. This is the first example of such a conformation in the crystal structure of a MoCp(C_3H_5)$(CO)_2$ derivative. In solution, both the *exo* and *endo* isomer are present, as concluded from ^{1}H NMR spectroscopy approximately in a 4:1 ratio. The activation barriers of interconversion were determined to be 62.7 ± 0.5 kJ mol^{-1} (**3a**) and 60.5 ± 0.5 kJ mol^{-1} (**3c**).

Introduction

There is currently considerable interest in the labeling of biomolecules with organometallic compounds, e.g., in biomolecular assays.[1−7] In this context, any potential candidate must meet a number of criteria. Most importantly, the compound must be reasonably stable in aqueous solution. Second, the complex must provide a spectroscopic handle which permits the detection of the bioconjugate in biological media. Attractive techniques include electrochemical detection[1,8−12] and infrared spectroscopy, as suggested by Jaouen, whose group has introduced the so-called carbonylmetallo immuno assay (CMIA).[2,13−16] This immunoassay is based on the IR stretching vibrations of organometallic carbonyl groups with sensitivity comparable to that of radioactive tracers. More recently, they have published examples of a double-[17] and triple-immunoassay[18] based on CMIA technology. As a third prerequesite, the organometallic moiety ought to possess a suitable linker by which it can be covalently attached to the biomolecule. To expand the range of available compounds, we investigate the use of molybdenum allyl dicarbonyl compounds, in particular derivatives of MoCp(η-C_3H_5)$(CO)_2$, **1** (Cp = η-cyclopentadiene).

Throughout the decades following its discovery, Mo(η^5-Cp)(η^3-allyl)$(CO)_2$ (**1**)[19] has played an important role in understanding fluxionality in organometallic complexes. In addition to rotation of the Cp ring, which is a well-understood and common process for Cp ligands, **1** also demonstrates a second motional process, namely, allyl rotation. As early as 1966, it was concluded from

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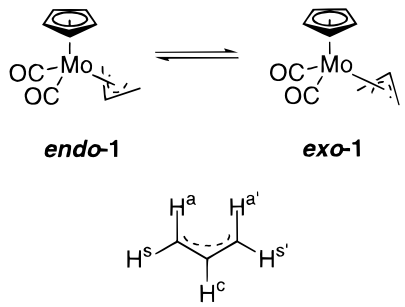
Scheme 1. Two Conformations of 1 and Labeling Scheme for Protons of 1



infrared spectroscopy that two geometrical isomers are present in solution.[20] On the basis of NMR spectroscopic data the two isomers were shown to be due to *exo* and *endo* conformations of the allyl ligand (Scheme 1).[21] Of the two, the *exo* isomer was shown to be the major isomer in solution and was also the only isomer to be found in X-ray crystal structures of **1** and various derivatives thereof.[22−26]

In this work we describe the synthesis of a carboxylic acid derivative of **1** and its coupling to amino acids and peptides along with spectroscopic and structural investigations. The first crystallographic evidence for an *endo*-allyl ligand in MoCp(η-C_3H_5)$(CO)_2$ derivatives is presented.

Experimental Section

All synthesis were performed by using standard Schlenck techniques under an atmosphere of argon. THF was dried by refluxing over Na/benzophenone, and all solvents were deoxygenated before use. DMF was of peptide synthesis grade, and all other solvents used were of spectroscopic grade. MoCp(η-allyl)$(CO)_2$ was prepared according to methods published in the literature.[27] The dipeptide Boc-Phe-Leu-OMe (Boc = *tert*-butoxycarbonyl) was prepared by standard methods from Boc-Phe-OH and H-Leu-OMe. All other chemicals were purchased from commercial sources and used as received. Only enantiomerically pure L amino acids were used. Elemental analysis were carried out by H. Kolbe, Analytisches Laboratorium, Mülheim/Ruhr (Germany). Infrared (IR) spectra were recorded on a Perkin-Elmer System 2000 instrument as KBr disks and additionally in CH_2Cl_2 solution where indicated. Frequencies ν are given in cm^{-1}. Mass spectra were recorded by the mass spectrometry service group Mülheim on a MAT 8200 (Finnigan GmbH, Bremen) instrument (EI, 70 eV). Only characteristic fragments are given with intensities (%) and possible composition in brackets. NMR spectra were recorded at room temperature on Bruker ARX 250 (^{1}H at 250.13 MHz and ^{13}C), DRX 400 (^{1}H at 400.13 MHz, ^{13}C and 2D spectra), and DRX 500 (^{1}H at 500.13 MHz, ^{13}C, ^{15}N, 2D). ^{1}H and ^{13}C spectra were referenced to TMS, using the ^{13}C signals or the residual protio signals of the deuterated solvents as internal standards (DMSO-d_6 ≡ 2.49 (^{1}H) and 39.5 (^{13}C), acetone-d_6 ≡ 2.04 (^{1}H) and 29.8 (^{13}C), toluene-d ≡ 2.03 (^{1}H) and 20.4 (^{13}C)). Variable-temperature ^{1}H NMR spectra were recorded in toluene-*d*. However, most signals in these spectra are broad at room temperature due to coalescence in this solvent around 300 K. Therefore, data in this section are reported in acetone-d_6, in which the overall appearance of the spectra resembles spectra in toluene at the low-temperature limit. Positive chemical shift values δ (in ppm) indicate a downfield shift from the standard; only the absolute values of coupling constants are given in hertz. All resonances were assigned by 2D NMR (H−H COSY and ^{1}H−^{13}C HMQC for ^1J and long-range couplings). The following conventions are used: δ/δ' denotes pairs of signals originating from *major*/*minor* isomers. For ^{13}C only data from the *major* isomer are reported. In most cases, signals from the *minor* isomer are of low intensity and thus difficult to detect.

X-ray Crystallographic Data Collection and Refinement. Crystal data for **3a**: $C_{21}H_{21}MoNO_5$, M = 463.33 g mol^{-1}, monoclinic space group $C2$, a = 27.088(4) Å, b = 9.909(1) Å, c = 14.865(2) Å, β = 102.82(2)°, V = 3890.5(9) Å^3, Z = 8, D_{calc} = 1.582 M gm^{-3}, μ(Mo Kα) = 0.707 mm^{-1}, F(000) = 1888. A thin yellow needle of 0.80 × 0.04 × 0.02 mm^3 was mounted on a Nonius Kappa CCD diffractometer system equipped with a cryogenic nitrogen cold stream at 100 K. Graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) was used. Cell constants were obtained from a least-squares fit of a subset of 8943 reflections. A total of 14 178 intensities (6091 independent with R_{int} = 0.1297) were collected by a hemisphere run taking 416 frames at 1.0° in ω. The program MULABS (part of the PLATON99 program suite, A. L. Spek, University of Utrecht, Netherlands, 1999) was used for absorption correction. The Siemens ShelXTL software package (Siemens Analytical X-ray Instruments, Inc.) was used for solution and refinement of the structure. Neutral atom scattering factors of ShelXTL were used. All non-hydrogen atoms were refined anisotropically. H atoms were placed at calculated positions and refined as riding atoms with isotropic displacement parameters. Large anisotropic displacement parameters of the allyl ligand atoms of both crystallographically independent molecules suggest a disorder of these units, but a split atom model did not improve the quality of the structure. The allyl C−C distances were restrained to be equal within certain errors using the SADI instruction (6 restraints); hydrogen atoms were not included for these groups. The absolute structure was determined reliably (Flack parameter −0.03(5)) in accordance with the known stereochemistry (L) of the amino acid. Final R1 = 0.061 (4550 reflections with $I > 2\sigma(I)$), wR2 = 0.141 (all data), 6072 unique reflections used, 2.89° < 2θ < 50°, 507 parameters and 7 restraints, GOOF on F^2 0.999.

Synthesis of Mo(C_5H_4-COOH)(η-allyl)$(CO)_2$ (2). To a solution of MoCp(η-allyl)$(CO)_2$, **1** (1.02 g, 3.95 mmol), in 40 mL of THF was added 3.70 mL of 1.6 M *n*-BuLi in hexane (5.92 mmol) at −78 °C. After 45 min of stirring about 7 g of solid CO_2 was added, and the reaction mixture was stirred for another 10 min at −78 °C. After allowing the mixture to warm to room temperature, about 40 mL of water was added, followed by reduction of the volume to about 25 mL in vacuo. The pH was adjusted to 1 with 6 M HCl, resulting in precipitation of a yellow solid. The precipitate was collected by filtration, washed with water (10 mL) and diethyl ether (5 mL), and dried in vacuo. Yield: 1.06 g (89%) of **2**. Anal. Calcd for $C_{11}O_4H_{10}Mo$ (302.14 g/mol): C, 43.73; H, 3.34. Found: C, 43.62; H, 3.27. IR (cm^{-1}) in KBr: 1930 (vs), 1869 (vs), ν_{CO}, 1681 (s), ν_{COO}; in CH_2Cl_2 solution: 1957 (vs), 1875 (vs), ν_{CO}, 1732 (m), 1713 (s), 1683 (m) ν_{COO}. MS: *m*/*z* 304 (59, M$^+$), 276 (41, [M − CO]$^+$), 248 (97, [M − 2CO]$^+$). ^{1}H NMR (acetone-d_6, 400 MHz, all signals were broadened and signals from the *minor* isomer were difficult to detect with certainty): 5.87 (s, 2H, Cp-$H_{2,5}$), 5.54 (pseudo-t, Cp-$H_{3,4}$), 4.16 (1H, H_c), 2.85 (2 H,

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H_{Allyl}), 0.97 (2 H, H_{Allyl}). ^{13}C NMR (acetone-d_6, 62.9 MHz): 236.8 (*C*O), 166.1 (*C*O_2), 95.1, 94.6 (C_{Cp}), 71.2, 42.4 (C_{allyl}).

General Synthesis of Mo(C_5H_4-CO-AA-R)(η^3-allyl)$(CO)_2$ (AA-R= L-Phe-OMe (3a), L-Leu-NH_2 (3b), and R = Gly-OMe (3c)). Compound **2** (300 mg, 0.99 mmol) and 0.99 mmol of the amino acid hydrochloride (L-phenylalanine methyl ester hydrochloride (214 mg) for **3a**, L-leucinamide hydrochloride (165 mg) for **3b**, or glycine methyl ester hydrochloride (125 mg) for **3c**) were dissolved in 3 mL of DMF. Triethylamine (1.5 mL) and HBTU (HBTU = *O*-(1H-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; 377 mg, 0.99 mmol) were added, and the reaction mixture was stirred for 45 min at room temperature. Upon addition of 40 mL of an aqueous 0.5 M $NaHCO_3$ solution, a yellow precipitate formed, which was collected by filtratrion, washed with water (10 mL), and dried in vacuo. Yield: 420 mg (91%) for **3a**, 310 mg (75%) for **3b**, and 247 mg (67%) for **3c**. The obtained precipitates were of sufficient purity for characterization, but analytically pure samples as well as single crystals of **3a** suitable for X-ray analysis were obtained by slow pentane diffusion in a THF solution at 4 °C.

3a: Anal. Calcd for $C_{21}NO_5H_{21}Mo$ (463.34 g/mol): C, 54.44; H, 4.57; N, 3.02. Found: C, 54.31; H, 4.63; N, 2.98. IR (cm^{-1}) in KBr: 3307 (m, br) ν_{NH}, 1966 (vs), 1945 (vs), 1867 (vs), ν_{CO}, 1742 (s), ν_{COO}, 1623 (s), ν_{CON}; in CH_2Cl_2 solution: 3429 (m), ν_{NH}, 1950 (vs), 1869 (vs), ν_{CO}, 1742 (s), ν_{COO}, 1664 (s), ν_{CON}. MS: *m*/*z* 465 (23, M^+), 437 (3, $[M - CO]^+$), 409 (4, $[M - 2CO]^+$), 367 (83), 254 (100). ^{1}H NMR (acetone-d_6, 400 MHz): 7.50 (br, 1H, N*H*), 7.30 (mult., 4H, H_{Ar}), 7.22 (mult., 1H, H_{Ar}), 5.86 (s, 1H, H_{Cp}), 5.84 (s, 1H, H_{Cp}), 5.53 (pseudo-t, 2H, Cp-$H_{3,4}$), 4.76 (br, 1H, $C_\alpha H$), 3.87/3.63 (mult., 1H, H_c), 3.68 (s, 3H, CH_3), 3.19 (mult., 1H, $C_\beta H$), 2.97 (mult., 1H, $C_\beta H$), 2.79/2.80 and 2.59/2.80 (overlapping mult., 2H, H_{Allyl}), 0.86/1.66 and 0.86/1.5 (overlapping mult., 2H, H_{Allyl}). ^{13}C NMR (acetone-d_6, 125.8 MHz): 237.4, 237.3 (*C*O), 172.6 (*C*O_2), 163.6 (Cp-*C*O), 138.3 ($C_{Ar,q}$), 129.9, 129.3, 127.5 (C_{Ar}), 104.7 ($C_{Cp,\ q}$), 94.1, 91.3 (intensity 2 C), 91.2 (C_{Cp}), 72.4 (C_{allyl}), 54.7 (C_α), 52.4 (*C*H_3), 43.0, 42.9 (C_{allyl}), 37.9 (C_β).

3b: Anal. Calcd for $C_{17}O_4N_2H_{22}Mo$ (414.32 g/mol): C, 49.28; H, 5.35; N, 6.76. Found: C, 49.35; H, 5.42; N, 6.68. IR (cm^{-1}) in KBr: 1947 (vs), 1869 (vs), ν_{CO}, 1684 (s), 1668 s), 1631 (s), ν_{CON}; in CH_2Cl_2 solution: 3515 (w), $\nu(NH_2)$, 3402 (w), ν_{NH}, 1953 (vs), 1870 (vs), ν_{CO}, 1698 (s), 1675 (vs) ν_{CON}. MS: *m*/*z* 416 (16, M^+), 360 (21, $[M - 2CO]^+$), 316 (100). ^{1}H NMR (acetone-d_6, 400 MHz): 7.43 (br, 1H, N*H*), 7.04 (br, 1H, CONH_2), 6.47 (br, 1H, CONH_2), 5.98 (pseudo-t, 1H, H_{Cp}), 5.94 (br, 1H, H_{Cp}), 5.52 (mult., 2H, Cp-$H_{3,\ 4}$), 4.56 (mult., 1H, $C_\alpha H$), 4.1/3.68 (mult., 1H, H_c), 2.88 (mult., 2H, H_{Allyl}), 1.75 (mult., 1H, $C_\gamma H$), 1.61 (mult., 2H, $C_\beta H$), 0.92 (d, 8H, J = 6.5 Hz, 2 CH_3 and 2 H_{Allyl}). ^{13}C NMR (acetone-d_6, 100.6 MHz): *C*O not observed, 175.2, 163.8 (Cp-*C*O), 104.4 ($C_{Cp,\ q}$) 94.2, 93.6, 92.2, 91.9 (C_{Cp}), 72.1 (C_{allyl}), 52.1 (C_α), 42.8, 42.7 (C_{allyl}), 41.9 (C_β), 25.4 (C_γ), 23.6 (*C*H_3), 21.8 (*C*H_3).

3c: Anal. Calcd for $C_{14}O_5NH_{15}Mo$ (373.22 g/mol): C, 45.06, H, 4.05, N, 3.75. Found: C, 45.20; H, 3.98; N, 3.72. IR (cm^{-1}) in KBr: 3279 (m), ν_{NH}, 1946 (vs), 1866 (vs), ν_{CO}, 1753 (s), ν_{COO}, 1629 (s), ν_{CON}; in CH_2Cl_2 solution: 3452 (w), ν_{NH}, 1952 (vs), 1869 (vs), ν_{CO}, 1748 (s), 1667 (s) ν_{CON}. MS: *m*/*z* 375 (43, M^+), 347 (8, $[M - CO]^+$), 319 (65, $[M - 2CO]^+$), 277 (100). ^{1}H NMR (acetone-d_6, 400 MHz) 7.70 (br, 1H, N*H*), 5.89 (pseudo-t, 2H, H_{Cp}), 5.58 (s, 2H, H_{Cp}), 4.04/3.61 (mult. 1H, H_c), 3.99 (d, 2H, J = 5.3 Hz, CH_2), 3.68 (s, 3H, CH_3), 2.91 (mult., 2 H, H_{Allyl}), 0.95/1.77 (mult., 2H, H_{Allyl}). ^{13}C NMR (acetone-d_6, 100.6 MHz) 237.1 (*C*O), 170.8 (*C*O_2), 164.1 (Cp-*C*O), 104.7 ($C_{Cp,q}$), 94.0, 91.8 (C_{Cp}), 72.5 (C_{allyl}), 52.1 (O*C*H_3), 43.0 (C_{allyl}), 41.8 (*C*H_2).

Mo(C_5H_4-CO-Phe-Leu-OMe)(η-allyl)$(CO)_2$ (4). Boc-Phe-Leu-OMe (190 mg, 0.5 mmol) was dissolved in a mixture of CH_2Cl_2 (3 mL) and CF_3COOH (3 mL) and stirred for 1 h at room temperature. After removal of the solvent, 10 mL of diethyl ether was added and the mixture was taken to dryness again. This step was performed three times in total in order to remove any traces of trifluoro acetic acid. A solution of **1** (151 mg, 0.5 mmol) in DMF (2 mL) and NEt_3 (1 mL) was added, followed by addition of HBTU (190 mg, 0.5 mmol). After stirring at room temperature for 45 min, 30 mL of an aqueous 0.5 M $NaHCO_3$ solution was added, resulting in formation of a yellow precipitate. The solid was collected by filtration, washed with water (10 mL), and dried in vacuo. Yield: 180 mg (62%). Anal. Calcd for $C_{27}O_6N_2H_{32}Mo$ (576.51 g/mol): C, 56.25; H, 5.59; N, 4.86. Found: C, 54.56; H, 6.03; N, 4.49. IR (cm^{-1}) in KBr: 3296 (m), ν_{NH}, 1951 (vs), 1868 (vs), ν_{CO}, 1746 (s), ν_{COO}, 1655 (s), 1629 (s), ν_{CON}; in CH_2Cl_2 solution, 3420 (m), ν_{NH}, 1953 (vs), 1870 (vs), ν_{CO}, 1743 (s), ν_{CO}, 1712 (s), 1682 (s), 1660 (s), ν_{CON}. MS (EI): *m*/*z* 578 (33, M^+), 550 (2, $[M - CO]^+$), 522 (2, $[M - 2CO]^+$), 480 (100, $[M - 2CO - allyl + H]^+$). ^{1}H NMR (acetone-d_6, 500 MHz): 7.61 (br, 1H, N*H*), 7.46 (br, 1H, N*H*), 7.28 (mult., 4H, H_{Ar}), 7.20 (t, 1H, J = 7.1 Hz, H_{Ar}), 5.84 (br, 2 H, Cp$H_{2,5}$), 5.27 (mult., 2H, Cp$H_{3,4}$), 4.79 (br, 1H, $C_{\alpha,Phe}$), 4.52 (br, 1H, $C_{\alpha,Leu}$), 3.78/3.47 (mult., 1H, H_c), 3.66 (s, 3H, O*C*H_3), 3.16 (mult., 1H, $C_{\beta,Phe}$), 2.93 (mult., 1H, $C_{\beta,Phe}$), 2.76/2.72 (mult., 1H, H_{Allyl}), 2.48/2.80 (mult., 1H, H_{Allyl}), 1.71 (br, 1H, $C_{\gamma,Leu}$), 1.60 (t, 2H, J = 6.3 Hz, $C_{\beta,Leu}$) 0.90 (overlapping d, 6H, 2 CH_3), 0.89/1.35 (d, J = 11 Hz, 1H, H_{Allyl}), 0.82/1.17 (d, J = 10.5 Hz, 1H, H_{Allyl}). ^{13}C NMR (acetone-d_6, 100.6 MHz): 237.4, 237.3 (*C*O), 173.5, 173.0 (*C*O_2 and *C*ON), 163.8 (Cp-*C*O), 138.7 ($C_{Ar,q}$), 130.1, 129.2, 127.3 (C_{Ar}), 105.2 ($C_{Cp,q}$), 95.0, 93.6, 91.0, 90.4 (C_{Cp}), 72.7 (C_{allyl}), 55.5 ($C_{\alpha,Phe}$), 52.3 (O*C*H_3), 51.6 ($C_{\alpha,Leu}$), 43.1, 42.9 (C_{allyl}), 41.3 ($C_{\beta,Leu}$), 38.4 ($C_{\beta,Phe}$), 25.4 ($C_{\gamma,Leu}$), 23.2, 21.9 (both *C*H_3).

Results and Discussion

Syntheses. A convenient way of linking organometallic compounds to biomolecules is via a carboxylic acid group.[14,17,18,28−30] To synthesize Mo(η^5-C_5H_4-COOH)(η^3-allyl)$(CO)_2$ (**2**), compound **1** was reacted with *n*-BuLi and solid CO_2 in THF under an atmosphere of argon at −78 °C. After aqueous workup, the carboxylic acid derivative **2** was obtained in good yield. All characterization data are consistent with this compound. Compound **2** serves as an effective precursor to complexes of the amino acids H-Phe-OMe, H-Leu-NH_2, and H-Gly-OMe in a mixture of DMF and NEt_3 in the presence of the coupling reagent HBTU (*O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) at room temperature within 45 min. After addition of aqueous $NaHCO_3$ and isolation of the precipitates by filtration, the compounds Mo(η-C_5H_4-CO-AA-R)(η-allyl)$(CO)_2$, with AA-R = Phe-OMe (**3a**), Leu-NH_2 (**3b**), and Gly-OMe (**3c**), were obtained in yields between 67% and 91% (Scheme 2). No appreciable decomposition of the products was observed even upon prolonged standing of the wet precipitates.

The amino acids differ in complexity (see NMR data below) and *C*-terminal protecting groups (OCH_3 for **3a** and **3c**, NH_2 for **3b**). To investigate whether coupling of **2** could be expanded to larger biomolecules, the dipeptide H-Leu-Phe-OMe was reacted with **2** in an analogous manner, resulting in isolation of Mo(η-C_5H_4-CO-Leu-Phe-OMe)(η-allyl)$(CO)_2$ (**4**). The isolated **3a**−**c** and **4** were already of good purity, but analytically pure samples could be obtained by slow pentane diffusion into a THF solution at +4 °C. All characterization data are consistent with the proposed constitution. To further

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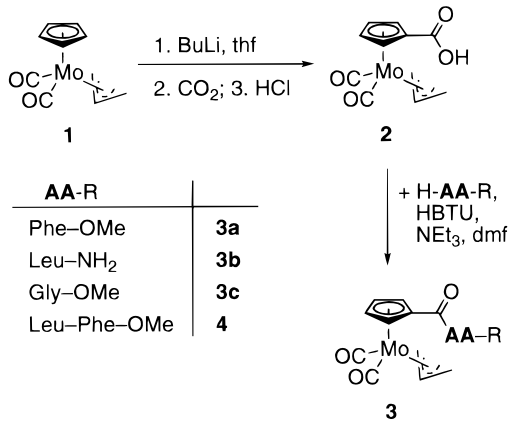
Scheme 2



elucidate the solid-state structures, a single crystal of **3a** was subjected to X-ray analysis.

X-ray Single-Crystal Structure of 3a. X-ray structure determination reveals the presence of two crystallographically inequivalent molecules in the unit cell. The two molecules **A** and **B** are depicted in Figure 1 together with the labeling scheme; relevant bond lengths and angles are summarized in Table 1. The Mo atoms in both molecules are coordinated by the same ligands, namely, two carbonyl groups, an allyl ligand, and a substituted Cp. The geometry of the two molecules differs in the arrangement of the allyl and carbonyl ligands around the Mo atom and the folding of the Phe substituent. In molecule **A**, the allyl ligand is located toward the substituent on the Cp ring, while the carbonyl ligands point toward the unsubstituted part of the Cp ring. In molecule **B**, the Phe substituent is folded upward and the Mo(allyl)$(CO)_2$ unit has undergone a 150° rotation about the Mo−Cp(centroid) axis compared to **A**. Thus, the relative orientation of the allyl and carbonyl ligands is the opposite from **A**. Rotation

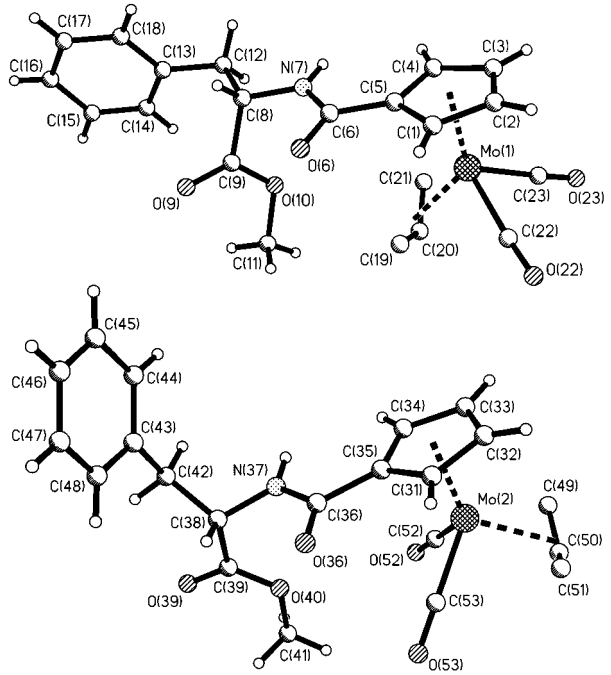


Figure 1. Plot of the two independent molecules named **A** (top) and **B** (bottom) of **3a**. See text for details and Table 1 for geometrical information.

Table 1. Selected Bond Lengths (Å) and Angles (deg) for 3a

Molecule A			
Mo(1)−C(1)	2.315(7)	Mo(1)−C(2)	2.327(10)
Mo(1)−C(3)	2.348(9)	Mo(1)−C(4)	2.363(8)
Mo(1)−C(5)	2.354(7)	Mo(1)−C(19)	2.250(11)
Mo(1)−C(20)	2.264(10)	Mo(1)−C(21)	2.52(2)
Mo(1)−C(22)	1.977(12)	Mo(1)−C(23)	1.968(12)
C(22)−Mo(1)−C(23)	78.2(5)	C(20)−Mo(1)−C(22)	90.9(5)
C(20)−Mo(1)−C(23)	90.3(4)	C(19)−C(20)−C(21)	142.3(12)
Molecule B			
Mo(2)−C(31)	2.313(9)	Mo(2)−C(32)	2.382(8)
Mo(2)−C(33)	2.399(10)	Mo(2)−C(34)	2.361(9)
Mo(2)−C(35)	2.309(7)	Mo(2)−C(49)	2.402(11)
Mo(2)−C(50)	2.261(11)	Mo(2)−C(51)	2.366(12)
Mo(2)−C(52)	1.952(11)	Mo(2)−C(53)	1.952(11)
C(52)−Mo(2)−C(53)	80.4(4)	C(50)−Mo(2)−C(52)	88.1(5)
C(50)−Mo(2)−C(53)	93.0(4)	C(49)−C(50)−C(51)	142(2)

about the metal−Cp axis is a process with a low activation energy barrier.[31] To our knowledge, the concomitant presence of two *different* rotational isomers of this kind in one unit cell has been rarely noted. Two examples are the $W(CO)_3X$ (X = Me, I) fragment in the crystal structures of an activated ester in $(\eta\text{-}C_5H_4R)W(CO)_3X$.[32]

Another remarkable feature of **3a** in this crystal structure is the *endo* conformation of the allyl ligand. All solid-state structures reported so far for $Mo(\eta\text{-}C_3H_5)(CO)_2$ complexes with different Cp derivatives show an allyl-*exo* conformation,[22−26] although an equilibrium between both geometrical isomers in solution has been demonstrated.[21,23,33−35] An *endo* conformation was found crystallographically for the methyl-allyl derivative $Mo(\eta^5\text{-Cp})(\eta^3\text{-2-}CH_3{-}C_3H_4)(CO)_2$,[36] for which the *exo* conformation was considered unfavorable due to steric interaction of the methyl group with the Cp ring. An allyl-*endo* conformation was also observed in the Mo nitrosyl iodo complex $Mo(\eta^5\text{-Cp})(NO)(I)(\eta^3\text{-allyl})$. However, the allyl ligand in this complex was unsymmetrically bound in a $\sigma{-}\pi$ mode, which also had a significant impact on the mechanism of allyl *endo*−*exo* interconversion in solution.[22]

The crystal structure of **3a** clearly shows that the *endo* form is favored in both molecules, but large anisotropic displacement parameters of the allyl carbon atoms indicate a significant dynamic or static disorder. Since C−C distances of the allyl fragments were restrained to be equal within error, no discussion of these bond lengths is possible. All other relevant bond lengths and angles for **A** and **B** are equal within 2σ. The Mo−carbonyl distances are similar to the distances reported for **1** and its derivatives. The average Mo−C_{Cp} distances (**A**, 2.34 Å; **B**, 2.35 Å) are similar to those reported in the literature for **1** (average Mo−C_{Cp} = 2.33 Å)[22] and $Mo(\eta\text{-}C_5H_4\text{-}C(O)CH_3)(\eta\text{-allyl})(CO)_2$ (average Mo−C_{Cp} = 2.35 Å).[23]

In the crystal lattice, **3a** forms chains with alternating molecules **A** and **B**. Previously a helical arrangement

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in the unit cell packing of an alkyne phenylalanine derivative[37] and a zigzag orientation between neighboring ferrocene amides was observed.[38] In **3a**, the monoclinic space group C_2 implies translational symmetry such that all molecules **A** or **B** in a chain show the same orientation. Hydrogen bond interactions are present between amide groups of neighboring molecules (N(7)···O(36) 2.879 Å and N(37)···O(6) 2.919 Å).

IR Spectroscopy. The presence of hydrogen bonds in **3a** in the solid state is also clearly reflected in the IR spectra. In KBr, the ν_{NH} stretching vibration is rather broad and centered around 3307 cm^{-1}, whereas it shifts to 3429 cm^{-1} in CH_2Cl_2 and becomes much sharper. Analogous differences are observed for **3b**, **3c**, and **4**, which indicates that also in these compounds hydrogen bonds of the amide-NH are present in the solid state. A similar behavior has been noted for ferrocene derivatives of alkynyl amino acids.[37,38] Intramolecular hydrogen bonding is also crucial for structurally organizing β-turn mimetics based on ferrocene dicarboxylic acid.[39,40] In an early paper, King reported the presence of four carbonyl bands in the IR spectrum of **1** in cyclohexane solution. The bands owing to the *endo* and *exo* isomer were separated by approximately 10 cm^{-1}. For all compounds in this work only two carbonyl bands are found (see Experimental Section), although both isomers are known to be present in an approximate 4:1 ratio, as concluded from ^{1}H NMR spectroscopy (vide supra). However, it should be noted that low-polarity solvents are mandatory for obtaining small line width in solution IR spectra. Because of limited solubility all IR spectra in this work needed to be recorded in CH_2Cl_2, and therefore any small difference might be obscured by the natural line-broadening in this solvent. In fact, for applications as biological markers the signal-to-noise ratio would even be enhanced as a consequence of this overlap.

NMR Spectroscopy. X-ray crystallography at 100 K revealed the *endo* conformation of the allyl ligand to be the major component in the crystalline solid. In solution at higher temperatures, however, the situation is more complex and both isomers are present. The ratio of interconversion between the two depends on solvent and temperature (see Supporting Information). In acetone at 300 K, the ratios of the *major*/*minor* isomer are 80:20 (**3a**) and 79:21 (**3c**), being very similar to the ratios in toluene at 223 K (78:22 for **3a**, 79:21 for **3c**; all values determined by careful integration of suitable groups of signals in the ^{1}H NMR spectra). A more pronounced solvent dependence of the *endo*−*exo* ratio has been reported before and was rationalized by the different dipole moments of the two isomers.[34,35] The *exo* isomer has a higher dipole moment, and,thus, it is more stabilized in polar solvents. Evidently, the overall dipole moment of the amino acid derivatives described in this work is dominated by these substituents and there is only a minor contribution, if any, from the metal−allyl moiety. The activation barriers for the *endo*-*exo* rearrangement is also dependent on solvent polarity. Qualitatively, ^{1}H NMR spectra in acetone at room temperature correspond to low-temperature spectra in toluene with well-separated signals for both isomers (see spectra D and C in the Supporting Information). Variable-temperature spectra in toluene provide the assignment of interconverting *endo*−*exo* pairs of signals, but the high-temperature limit could not be reached in acetone. However, positive cross-peaks in 2D NOESY spectra originating from chemical exchange[41] furnished the same unambiguous assignment for acetone solutions.

In light of prospective applications within biological systems it was of interest to determine the influence of (chiral) substituents on the Cp ring on the activation barrier for *exo*−*endo* interconversion. Therefore, ^{1}H NMR variable-temperature measurements were performed on **3a** and **3c** in toluene. Coalescence of most signals was observed between 223 and 353 K. For **3c**, six signals were observed at low temperature for the allyl ligand, three for the *endo,* and three for the *exo* isomer. In contrast, three signals were observed for the allyl ligand at high temperature, due to rapid *exo*-*endo* interconversion on the NMR time scale (2:2:1 ratio, *syn*, *anti*, and central proton). For **3a**, however, 10 signals for the allyl protons were observed at the low-temperature limit (Supporting Information, spectrum C), which turned into five signals of equal intensity at high temperature (Supporting Information, spectrum A). Unlike the simpler **3c**, **3a** has a chiral center, and thus both *syn* and both *anti* protons are magnetically inequivalent. Consequently, a separate signal with coupling to all other protons is observed for each allyl resonance.

From suitable groups of signals, the activation energies for the allyl rotation in toluene were determined to be $\Delta G^{\ddagger} = 62.7 \pm 0.5$ kJ mol^{-1} for **3a** and $\Delta G^{\ddagger} = 60.5 \pm 0.5$ kJ mol^{-1} for **3c**.[42] The small difference may be attributed to steric factors from the large phenylalanine substituent. Thus, the influence of the chiral center is not reflected in the *exo*−*endo* interconversion activation barrier. In fact, the activation energies for **3a** and **3c** are only slightly lower than for the parent complex **1** ($\Delta G^{\ddagger} = 64.7 \pm 0.5$ kJ mol^{-1} in cyclohexane).[34] Apparently, either substituent on the Cp ring has a negligible influence on the allyl ligand rotation, probably because it is directed away from the metal center and not sterically influencing the allyl ligand.

Concluding Remarks

In this work we report the functionalization of MoCp(η-C_3H_5)$(CO)_2$ (**1**) with a carboxylic acid group and subsequent coupling of this complex with amino acids and peptides under mild conditions in high yield. The organometallic moiety provides an attractive IR-spectroscopic handle and is stable in aqueous solvents. Thus, it is well-suited for applications in biological assays.[2,13,14] The amino acids and peptide were chosen such that the feasability of this chemistry could be established with

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different *C*-terminal groups (methyl ester and amide) and compounds of varying complexity. While the glycine derivative **3c** is achiral, **3a** and **b** possess one chiral center and the dipeptide **4** possesses two. To our knowledge, the X-ray crystal structure of **3a** is the first example with an allyl-*endo* configuration of a simple Mo(η-C_3H_5)$(CO)_2$ complex. Furthermore, it is one of the rare examples in which two isomers that differ primarily by rotation about the metal−Cp axis are present in the unit cell. Rotation about the metal−Cp axis in organometallic compounds is generally a process with an activation barrier below 2 kcal mol^{-1}.[31] Allyl *exo*−*endo* interconversion, on the other hand, has a much higher activation barrier, and indeed both isomers can be readily observed. The influence of the stereochemical centers present in **3a**, **3b**, and **4** results in inequivalence of the *syn* and *anti* hydrogen atoms of the allyl ligand. Consequently, five signals for both the *exo* and *endo* isomer can be observed in the ^{1}H NMR spectrum. The allyl *exo*−*endo* interconversion activation barriers of **3a** and **3c** have been determined. They are similar for both compounds and in the range reported for complex **1**.[21,34]

Jaouen and co-workers have demonstrated good utility of (benzene)Cr$(CO)_3$ derivatives for immunological assays.[17,43−45] The Mo congener is more difficult to prepare and much less stable. Generally, there are only very few reports on molybdenum compounds for the labeling of biomolecules.[46−49] This work shows that the Mo(allyl)$(CO)_2$ moiety shows good stability in aqueous media and is very well-suited for the covalent labeling of amino acids and peptides. Studies to identify further Mo(allyl)$(CO)_2$ derivatives for use in bioorganometallic chemistry are being conducted in our group.

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Supporting Information Available: Plot of VT NMR spectra of **3a** in toluene and of **3a** and **3c** in acetone at room temperature. This material is available free of charge via the Internet at http://pubs.acs.org.

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