1,1′-Diphosphaferrocene Derivatives for Labeling of Molecules of Biological Interest. The X-ray Molecular Structures of 4-Oxo-4-(3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocen-2-yl)butanoic Acid and Its Bis-$W(CO)_5$ Complex

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3,3′,4,4′-Tetramethyl-1,1′-diphosphaferrocene (**1**) reacts with succinic anhydride in the presence of $AlCl_3$ to give 4-oxo- 4-(3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocen-2-yl)butanoic acid (**2**) in 80% yield. This complex treated with 1 equiv of $W(CO)_5$(THF) gave a mixture of the products in which the $W(CO)_5$ moiety is coordinated to P(1′) (**3a)** and to P(1) (**3b**) in the ratio ∼ 7:1. With two equiv of $W(CO)_5$(THF) the bis-$W(CO)_5$ adduct (**4**) was obtained and transformed into the corresponding *N*-succinimidyl ester (**5**) by treatment with *N*-hydroxysuccinimide in dichloromethane in the presence of DCC (dicyclohexylcarbodiimide). This activated ester reacts with benzylamine and glycine methyl ester to give the corresponding amides in good yields. The crystal structures of **2** and **4** have been determined by X-ray diffraction. Both structures show unexpected conformations with short intramolecular P- - -P distances, indicating secondary bonding between phosphorus atoms. This contrasts with the X-ray structure of **1** displaying longer P- - -P distance (no secondary bonding) and theoretical calculations showing destabilizing, repulsive P- - -P interactions in the 1,1′-diphosphaferrocene system (Ashe, A. J., III; Al-Ahmad, S. *Adv. Organomet. Chem* **1996**, *39*, 325, and references therein). Apparently, conformational preferences of 1,1′-diphosphaferrocenes are small, since they are so easily changed by small changes in the substitution. Furthermore, the structure of **2** shows intermolecular P- - -P secondary bonding, giving rise to the formation of stacking columns along the *z* axis. The structural differences between **2** and **4** and between the $W(CO)_5$ moiety in **4** and this moiety coordinated to nitrogen in $W(CO)_5$-(azaferrocene) complexes have also been analyzed.

Introduction

Recently, there has been considerable interest toward the synthesis of organo−transition metal complexes which form stable conjugates with molecules of biological and medicinal interest such as proteins, peptides, nucleic acids, and currently used medications.[1−4] Such complexes can be used as labeling reagents in studies of high-affinity interactions such as hormone−receptor, enzyme−substrate, and antigen (hapten)−antibody interactions, in DNA hybridization tests or as carriers of radioisotopes in nuclear medicine. The bioconjugates can

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be readily detected and quantified by various techniques including atomic absorption spectroscopy (AAS),[5] electrochemical methods,[6] and Fourier transform IR spectroscopy.[7] In the latter case metal carbonyl labels are used, detectable in the region of the stretching vibrations of coordinated CO (2100−1850 cm^{-1}), where biomolecules and biological matrixes are practically transparent. An immunoassay technique using metal carbonyl markers (carbonylmetalloimmunoassay, CMIA) was recently introduced and successfully applied for simultaneous quantification of two or three haptenes.[7c,d]

The ferrocene moiety has been coupled with redox enzymes such as glucose and galactose oxidases to enable electronic communication between the enzyme and an electrode ("wiring" of enzymes)[8] and with a variety of medications to afford tracers for electroimmunoassays.[9] Ferrocenyl amino acids have also been synthesized for incorporation into a polypeptide chain to study the role of the peptidic backbone in electron-transfer processes.[10] Finally, ferrocene probes are widely used in studies of molecular recognition processes.[11]

The last two decades have witnessed a remarkable progress in synthetic methods and in the understanding of the structure and reactivity of 1,1′-diheteroferrocenes of the group 15 elements.[12] Similarly to ferrocene, these complexes display more or less reversible redox chemistry, but additionally they are able to bind one or two metal centers through the heteroatom lone pairs.[13] In our opinion these features make them particularly interesting as versatile labeling reagents for in vitro assays, with potential applications in redox enzyme assays or electroctrochemical immunoassays, carbonylmetalloimmunoassays (when a metal carbonyl fragment is bound to the heterometallocene), and radioimmunotherapy (when a suitable radioactive metal fragment is bound to the heterometallocene moiety linked, for example, to an antibody). Obviously these anticipated applications will require a detailed knowledge of biological properties of 1,1′-diheteroferrocenes such as their stability in biological media, ability to cross biological membranes, or toxicity.

In this paper we describe the synthesis, starting from the readily available 3,3′4,4′-tetramethyl-1,1′-diphosphaferrocene (**1**),[14] of 4-oxo-4-(3,3′,4,4′-tetramethyl-1,1′-diphospha-2-ferrocenyl)butanoic acid (**2**), its mono-$W(CO)_5$ complexes **3a** and **3b**, the bis-$W(CO)_5$ complex **4**, and corresponding active *N*-succinimidyl (NS) ester **5**.

This ester is a potential metallocarbonyl diphosphaferrocenyl labeling reagent for biomolecules containing amino groups. Its reactivity was tested toward model compounds: benzylamine and glycine methyl ester. Finally, we have determined the X-ray structures of **2** and **4**. These structures shed new light on the hitherto unclear conformational preference in the 1,1′-diphosphaferrocene system and on secondary bonds involving phosphorus atoms.

Experimental Section

General Remarks. All reactions were carried out under an atmosphere of argon. Solvents were dried by using standard procedures. Chromatographic purifications were carried out on Silica gel 60 (230−400 mesh ASTM), purchased by Merck, using chloroform as eluent. The NMR spectra were determined on Varian Gemini 200 BB (200 MHz for ^1H) in $CDCl_3$ solutions. They were calibrated by using internal Me_4Si (^1H and ^{13}C) or external 85% H_3PO_4 (^{31}P) references. IR spectra were run on a Specord 75 IR spectrometer. The combustion analyses were determined by Analytical Services of the Center of Molecular and Macromolecular Studies of the Polish Academy of the Sciences (Łódź). 3,4,3′,4′-Tetramethyl-1,1′-diphosphaferrocene (**1**) was prepared according to the earlier published procedure.[14]

4-Oxo-4-(3,3′,4,4′-tetramethyl-1,1′-diphospha-2-ferrocenyl)butanoic Acid, 2. To a stirred and cooled to 0 °C suspension of succinic anhydride (0.324 g, 3.24 mmol) in dichloromethane (10 mL) was added $AlCl_3$ (0.573 g, 4.32 mmol) in one portion, and then a solution of DPF (0.600 g, 2.16 mmol) in dichloromethane (5 mL) was slowly added (addition time approximately 45 min). The resulting mixture was refluxed for 3.5 h and hydrolyzed with a mixture of 2 M HCl (15 mL) with ice. The organic layer was separated, and the water layer was extracted with chloroform (3 × 15 mL). The combined extracts were dried with sodium sulfate and evaporated to dryness. Column chromatography (eluent chloroform) and crystallization (dichloromethane−hexanes) afforded pure **2**. Yield: 0.650 g (80%). Mp: 146−148 °C (decomp). ^{1}H NMR: δ 3.99 (d, J_{P-H} = 36.6 Hz, 1H, H-5); 3.73 and 3.69 (dd, J_{P-H} = 36.0 Hz, J_{H-H} = 2.0 Hz, 1H, 1H, H-2′ and H-5′); 2.99 (m, 2H, CH_2); 2.62 (m, 2H, CH_2); 2.39, 2.10, 2.06, 1.98 (singlets, each 3H, Me's).[13] C NMR: δ 205.2 (d, J_{C-P} = 21.7 Hz, CO-ketone); 178.2 (s, CO-acid); 102.6 (d, J_{C-P} = 7.6 Hz), 99.27 (d, J_{C-P} = 7.3 Hz), 99.08 (d, J_{C-P} = 7.2 Hz) and 97.38 (d, J_{C-P} = 5.0 Hz); C3,C3′, C4,′C4′, 84.1−82.4 (m, C2,C2′,C5,C5′); 37.32 (d, J_{C-P} = 12.3 Hz, CH_2), 28.41 (br s CH_2), 15.40, 14.58, 14.04, (s, Me's). ^{31}P NMR: δ −68.68 (td, J_{P-P} = 14.9 Hz, J_{P-H} = 36.0, P1′); −53.15 (dd, J_{P-P} = 14.9 Hz, J_{P-H} = 36.6 Hz, P1). IR ($CHCl_3$): 3300, 2080, 1995, 1720, 1670. Anal. Calcd for $C_{16}H_{20}P_2FeO_3$: C, 50.82; H, 5.33. Found: C, 50.43; H, 5.41.

Reaction of 2 with $W(CO)_5$(THF). A solution of $W(CO)_5$(THF) was prepared by irradiation through Pyrex (external 200 W high-pressure mercury lamp) of $W(CO)_6$ (0.352 g, 1.0 mmol) in THF (150 mL) at room temperature for 1.5 h. In a separate experiment this solution was treated with pyridine. The amount of $W(CO)_5$(py) isolated by column chromatography indicated that 0.79 mmol of $W(CO)_5$(THF) was generated (assuming that reaction with pyridine proceeds quantitatively).

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The photolyte was treated with **2** (0.095 mg, 0.25 mmol), and the resulting solution was stirred at room temperature for 2 h. Removal of solvent, column chromatography (eluent chloroform), and crystallization (CH_2Cl_2−hexanes) afforded pure **4**. Yield: 0.227 g (88%). Mp: 137−139 °C.

^{1}H NMR: δ 4.47 (dd, J_{P-H} = 33.1 Hz, J_{H-H} = 1.4 Hz, 1H, H2′ or H5′); 4.16 (dt, J_{C-P} = 32.8 Hz, J_{H-H} = 1.4 Hz, 1H, H5); 3.52 (dd, J_{P-H} = 33.1 Hz, J_{H-H} = 1.4 Hz, 1H, H2′ or H5′), 2.92 (m, 2H, CH_2) 2.70 (m, 2H, CH_2); 2.37, 2.19, 2.13, 1.95 (singlets, each 3H, Me's). ^{13}C NMR: δ 201.22 (d, J_{C-P} = 16.4 Hz, CO-ketone); 196.80 (d, J_{C-P} = 33.9 Hz) and 196.69 (d, J_{C-P} = 32.7 Hz); W−CO trans to P; 194.27(d, J_{C-P} = 8.2 Hz, W−CO cis to P) and 193.92(d, J_{C-P} = 8.5 Hz, W−CO cis to P); 178.08, (s, CO-acid); 99.61, 99.39, 97.76, 94.98 (doublets, J_{C-P} = 4.2 Hz, C3,C4,C3′,C4′); 86.16 (d, J_{C-P} = 9.9 Hz, C1); 79.35, 79.14, 77.49 (singlets, C1′, C4,C4′); 39.47, 27.82 (singlets, CH_2CH_2); 16.40 (d, J_{C-P} = 4.8 Hz, Me), 13.9 (m, Me's). ^{31}P NMR: δ −27.78 (d, J_{P-H} = 32.8 Hz, satellite bands J_{W-C} = 266.1 Hz, P1); −36.98 (t J_{P-H} = 33.1, satellite bands J_{W-C} = 264.5 Hz, P1′). IR ($CHCl_3$): 2080, 1995, 1960, 1720, 1670. Anal. Calcd for $C_{26}H_{20}O_{13}P_2FeW_2$: C, 30.44; H, 1.96. Found: C, 30.80; H, 2.11.

***N*-Succinimidyl Ester 5.** A solution of **4** (0.102 g, 0.1 mmol), *N*-hydroxysuccinimide (0.012 g, 0.1 mmol), and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 0.1 mL of 1.0 M solution in dichloromethane) in dichloromethane (5 mL) was stirred 45 min at room temperature TLC showed complete disappearance of **4** and formation of a product. The solid formed was filtered off and the filtrate evaporated to dryness and chromatographed (chloroform) to give **5** as an orange-red oil. Yield: 109 mg (96%).

^{1}H NMR: δ 4.46 (dd, J_{H-P} = 33.0 Hz, J_{H-H} = 1.5 Hz, 1H, H2′ or H5′); 4.15 (dt, J_{H-P} = 33.1 Hz, J_{H-H} = 1.3 Hz, 1H, H5); 3.53 (dd, J_{P-H} = 33.3 Hz, J_{H-H} = 1.8 Hz, 1H, H2′ or H5′); 3.0 (m, 4H, CH_2CH_2); 2.84 (s, 4H, succinimide), 2.37, 2.19, 2.14, 1.95 (singlets, each 3H, Me's). IR ($CHCl_3$): 2080, 2000,1975, 1790, 1745, 1680.

Reaction of 5 with Benzylamine. A solution of *N*-succinimidyl ester **5** (106 mg, 0.094 mmol) and benzylamine (15 mg, 0.14 mmol) in dichloromethane (5 mL) was stirred overnight at room temperature The solvent was evaporated and the residue chromatographed using chloroform as eluent to give **6a** as an orange solid. Yield: 71 mg (62%). Mp: 64−66 °C.

^{1}H NMR: δ 7.30 (m, 5H, Ph); 5.90 (t, J_{H-H} = 5.9 Hz, 1H, NH); 4.48 (dd, J_{H-H} = 11.5 Hz, 5.9 Hz, 1H, CH_2 benzyl); 4.36 (dd, J_{H-H} = 11.5 Hz, 5.9 Hz, 1H, CH_2 benzyl); 4.44 (d, J_{H-P} = 34.1 Hz; J_{H-H} = 1.7 Hz, H2′ or H5′); 4.14 (dt, J_{P-H} = 33.2 Hz, J_{H-H} = 1.7 Hz, H5); 3.54 (dd, J_{H-P} = 33.4 Hz, J_{H-H} = 1.7 Hz, 1H, H2′ or H5′); 3.1 (m, 1H CH_2); 2.9 (m, 1H CH_2; 2.6, m, 2H, CH_2); 2.40, 2.19, 2.13, 1.93 singlets, each 3H, Me's). ^{13}C NMR: δ 202.2 (d, J_{C-P} = 15.6 Hz, CO ketone); 197.2 (d, J_{C-P} = 34.5 Hz, W−CO trans to P); 196.8 (d, J_{C-P} = 32.0 Hz, W−CO trans to P); 194.3 (d, J_{C-P} = 8.3 Hz, W−CO cis to P); 194.0 (d, J_{C-P} = 8.5 Hz, W−CO cis to P); 171.2 (s, CO amide); 138.1, 128.7, 127.7, 127.5 (singlets, Ph); 99.6, 99.4, 97.8 (singlets, C4,C3′C4′); 94.0 (d, J_{C-P} = 4.4 Hz, C3); 87.1 (d, J_{C-P} = 8.8 Hz, C2); 79.1−77.3 (m, C2′,C5,C5′); 43.6, 39.7, 30.1 (singlets, methylene carbons); 16.4 (d, J_{C-P} = 4.7 Hz, Me); 14.0 (m, Me's). ^{31}P NMR: δ −32.2 (d, J_{P-H} = 33.2 Hz, satellites ^{183}W, J_{P-W} = 267.3 Hz, P1); −45.7 (t, J_{P-H} = 33.9 Hz, satellites ^{183}W, J_{P-W} = 264.0 Hz, P1′). IR ($CHCl_3$): 2080, 2000, 1995, 1700, 1680. Anal. Calcd for $C_{33}H_{27}NO_{12}P_2FeW_2$: C, 35.55; H, 2.44; N, 1.26; P, 5.56. Found: C, 35.86; H, 2.72; N, 1.45; P, 5.66.

Reaction of 5 with Glycine Methyl Ester. 5 (106 mg, 0.094 mmol) was dissolved in dichloromethane (2 mL). To this solution was added a solution of glycine methyl ester hydrochloride (14 mg, 0.11 mmol) in dichloromethane (2 mL) containing 2 drops of triethylamine, and the resulting solution was stirred overnight at room temperature. The solvent was evaporated to dryness and the residue chromatographed to give **5b** as an orange solid. Yield: 78 mg (71%). Mp: 61−63 °C.

^{1}H NMR: δ 6.12 (t, J_{H-H} = 5.0 Hz, 1H, NH); 4.41 (dd, J_{H-P} = 32.7 Hz; J_{H-H} = 1.4 Hz, 1H, H2′ or H5 ′); 4.20 (t, J_{H-H} = 1.2 Hz, 0.5 H, a half of the H5 signal), 4.02 (d, J_{H-H} = 5.0 Hz, 1.5H, glycine CH_2 + half of the H5 signal); 3,76 (s, 3H, COOMe); 3.56 dd, (J_{H-P} = 33.1 Hz, J_{H-H} = 1.8 Hz, H2′ or H5′); 3.0 (m. 2H, CH_2); 2.55 (m, 2H, CH_2); 2.39, 2.19, 2.14, 1.99 (singlets, each 3H, Me's). ^{13}C NMR: δ 202.1 (d, J_{C-P} = 15.5 Hz, CO ketone); 197.0 (d, J_{C-P} = 34.5 Hz, W−CO trans to P); 196.8 (d, J_{C-P} = 32.5 Hz, W−CO trans to P); 194.3 (d, J_{C-P} = 8.2 Hz, W−CO cis to P); 194.0 (d, J_{C-P} = 8.4 Hz, W−CO cis to P); 171.4 (s, CO); 170.3 (s, CO); 99.6, 99.4, 97.8 (singlets, C4,C3′,C4′); 94.2 (d, J_{C-P} = 4.4 Hz, C3); 87.1 (d, J_{C-P} = 8.8 Hz, C2); 79.1−77.3 (m, C2′,C5,C5′); 52.4 (s, OMe) 41.3, 39.6, 29.7 (singlets, methylene carbons); 16.4 (d, J_{C-P} = 4.7 Hz, Me); 14.0 (m, Me's). ^{31}P NMR: δ −23.9 (d, J_{P-H} = 33.0 Hz, satellites ^{183}W, J_{P-W} = 266.8 Hz, P1); −36.5 (t, J_{P-H} = 33.0 Hz, satellites ^{183}W, J_{P-W} = 264.2 Hz, P1′). IR (KBr): 2080, 2000, 1960. Anal. Calcd for $C_{29}H_{25}NO_{14}P_2FeW_2 \cdot {}^1/_3C_6H_{14}$: C, 33.08; H, 2.66; N, 1.24; P, 5.50. Found: C, 33.15; H, 2.61; N, 1.50; P, 5.70.

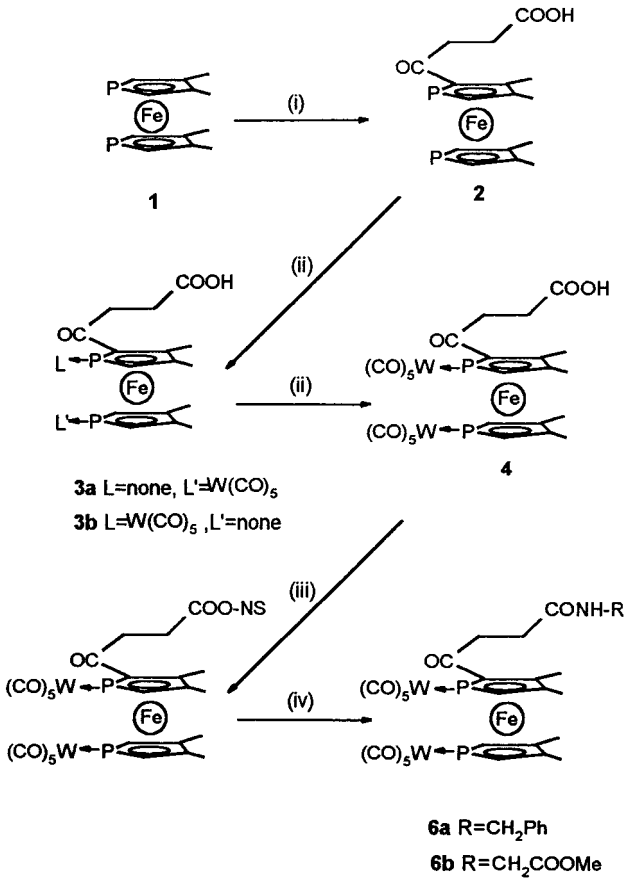
Table 1. Crystal Data and Structure Refinement Details

	2	**4**
	Crystal Data	
formula	$C_{16}H_{20}FeO_3P_2$	$C_{26}H_{20}FeO_{13}P_2W_2$
source of material and habit	red irregular pillars	red irregular pillars
crystal dimens, mm	0.15 × 0.2 × 0.2	0.15 × 0.2 × 0.3
space group	$P2_1/n$	$P2_1/c$
Z	8	4
a, Å	11.367(2)	11.548(2)
b, Å	22.166(3)	11.201(2)
c, Å	14.129(3)	24.902(5)
β, deg	112.36(1)	95.31(3)
V, Å^3	3292(1)	3207(1)
linear abs coeff (μ), mm^{-1}	1.12	7.76
	Data Collection	
diffractometer	Siemens P3	Siemens P3
radiation type (λ), Å	Mo Kα (0.710 73)	Mo Kα (0.710 73)
temp, K	293(2)	293(2)
scan type	$\omega/2\theta$	$\omega/2\theta$
2θ scan range, deg	1.8−48.0	1.8−48.0
data collected (h, k, l)	$-13 \le h \le 14$; $-28 \le k \le 0$; $-18 \le l \le 0$	$-15 \le h \le 14$; $0 \le k \le 14$; $0 \le l \le 32$
no of reflns collected	5236	4940
no. of ind reflns	5024 (R_{int} = 0.0182)	4818 (R_{int} = 0.0173)
no. of reflns with $F_o > 4\sigma(F_o)$	3674	4155
	Solution and Refinement	
system used	SHELXS-97, SHELXL-97	
soln	direct methods	
refinement method	full-matrix least-squares on F^2	
H atoms	refined isotropically using riding model	
$(\Delta/\sigma)_{max}$	0.003	0.001
$R(F)^a$	0.080	0.049
$wR(F^2)^b$	0.171[c]	0.107[d]
$R(F)^a$	0.055 for 3674 reflns	0.039 for 4155 reflns
$wR(F^2)^b$	0.148 for 3674 reflns[c]	0.096 for 4155 reflns[d]

[a] $R(F) = \sum(||F_o| - |F_c||)/\sum|F_o|$. [b] $wR(F^2) = [\sum(w|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2}$. [c] $w = 1/[\sigma^2(F_o^2) + (0.111P)^2 + 7.39P)]$. [d] $w = 1/[\sigma^2(F_o^2) + (0.0685P)^2 + 5.65P)]$, where $P = (\max(F_o^2, 0) + 2F_c^2)/3$.

X-ray Structure Determinations. A summary of crystallographic data collection parameters and refinement parameters are collected in Table 1. In the final least-squares full-matrix refinement, all non-hydrogen atoms for both structures were refined with anisotropic thermal displacement parameters. Hydrogen atoms were included as riding atoms with an idealized geometry (C−H(CH_3) = 0.96, C−H(CH_2) = 0.97, C−H(CH) = 0.98, U_H = 1.5 U_C). Only H atoms of the OH groups were localized from the difference map. U_H were refined isotropically.

Scheme 1. (i) Succinic Anhydride/$AlCl_3$; (ii) $W(CO)_5$(THF), 1 equiv; (iii) *N*-Hydroxysuccinimide/ *N,N′*-Dicyclohexylcarbodiimide; (iv) Benzylamine (Glycine Methyl Ester); NS = *N*-Succinimidyl



Results and Discussion

Syntheses and Characterization. Earlier studies by Mathey and his group[12a−c] showed that 1,1′-diphosphaferrocenes display high reactivity toward electrophiles and undergo typical Friedel−Crafts acetylation when treated with acetyl chloride in the presence of $AlCl_3$. We have found that **1** reacts under mild conditions with succinic anhydride and $AlCl_3$ in dichloromethane to give **2** in 80% yield (Scheme 1).

The structure of **2** was confirmed by the spectral as well as elemental analysis data. We have also determined its X-ray structure (vide infra).

We were interested in the coordinating properties of **2** toward photochemically generated $W(CO)_5$(THF). Ligating properties of **1** toward various metal centers, including $M(CO)_5$(THF), where M = Cr, Mo, W, have earlier been studied by Mathey et al.[13] However, **2** contains two nonequivalent P atoms, and therefore the problem of the selectivity of the complexation arises. We have found that when **2** was treated with 1 molar equiv of $W(CO)_5$(THF) at room temperature for 2 h, two products are formed in the ratio ∼7:1 along with some amount of unreacted **2**. We were unable to separate them, but analysis of the ^{31}P NMR spectrum of their mixture made possible their identification. The signals assigned to the major product appear at −40.2 and −47.9 ppm. In the ^{1}H undecoupled spectrum the former signal is a triplet of doublets (J_{P-H} = 33.2 Hz, J_{P-P} = 8.9 Hz) and therefore should be assigned to P(1′), whereas the latter, a doublet of doublets (J_{P-H} = 35.6 Hz, J_{P-P} = 8.9 Hz), corresponds to P(1). Only the signal of P(1′) shows characteristic satellite bands due to ^{183}W (J_{P-W} = 262.1 Hz). The major product of the reaction is therefore **3a**. On the same basis the minor product of the reaction, displaying signals at −29.7 (this signal shows ^{183}W satellites (J_{P-W} = 267.5 Hz)), and −60.2 ppm was identified as **3b**. The ratio of **3**/**3b** of 7:1 indicates that the $-COCH_2CH_2COOH$ chain renders coordination to P(1) slighty more difficult, presumably by combination of steric and electronic effects.

Treatment of **2** with two or more equivalents of $W(CO)_5$(THF) gave the bis-$W(CO)_5$ adduct (**4**) in good yield. This complex was isolated and characterized by spectral and elemental analysis data as well as by X-ray structure determination (vide infra). Its ^{31}P NMR spectrum displays the ^{183}W satellites at both signals (−27.78, −36.98 ppm). In contrast to mono-$W(CO)_5$ complexes **3a** and **3b** no coupling between ^{31}P nuclei is observed in the spectrum.

The complex **4** was then transformed into the corresponding *N*-succinimidyl ester **5** by a standard treatment with *N*-hydroxysuccinimide (NHS) and *N,N′*-dicyclohexylcarbidiimide (DCC) in dichloromethane. We characterized this compound only by IR and ^{1}H NMR spectra.

Once the synthesis and characterization of **5** was completed, it was still necessary to verify its reactivity toward amino groups since inactivation of organometallic NS-esters toward nucleophiles has been reported.[15] Therefore, we tested the reactivity of **5** toward model amines: benzylamine and glycine methyl ester (the latter can be considered as a model of the terminal amino function in peptides and proteins).

The reaction of **5** with these amines procceded smoothly and completely in dichloromethane at room temperature to give the corresponding amides **6a** and **6b** isolated in 62−71% yield (Scheme 1). This means that reactivity of the activated ester function in **5** is quite normal. Obviously, coupling of **5** with peptides or proteins should be carried out in water or mitures of water with organic solvent. Although **5** is almost totally insoluble in water, we hope than it will work similarly to an osmium cluster studied by Osella et al. in water−organic solvent mixtures.[2i] Another possibility is offered by the reverse micelle systems.[16]

It is worthy to note that the IR spectra of derivatives **4**−**6a,b** are quite similar in the region 2100−1900 cm^{-1} (region of stretching vibrations of coordinated carbon monoxide). The lack of the influence of the modification of the organic chain means that IR spectra represent good fingerprints for the presence of the diphosphaferrocene-$W(CO)_5$ marker in biomolecules.

The unit cell of **2** contains two crystallographically independent, almost identical, molecules (**2a**/**2b**). A view of the molecule **2a** (with its numbering scheme) is given in Figure 1.

The atoms in molecule **2b** are numbered 20 + *X*, where *X* is the number of the corresponding atom in

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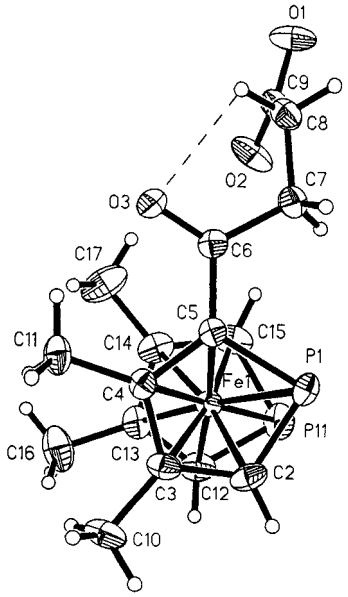


Figure 1. Ortep plot of **2a** (30% probability level) showing the adopted numbering scheme. View along the vector perpendicular to the phospholyl rings.

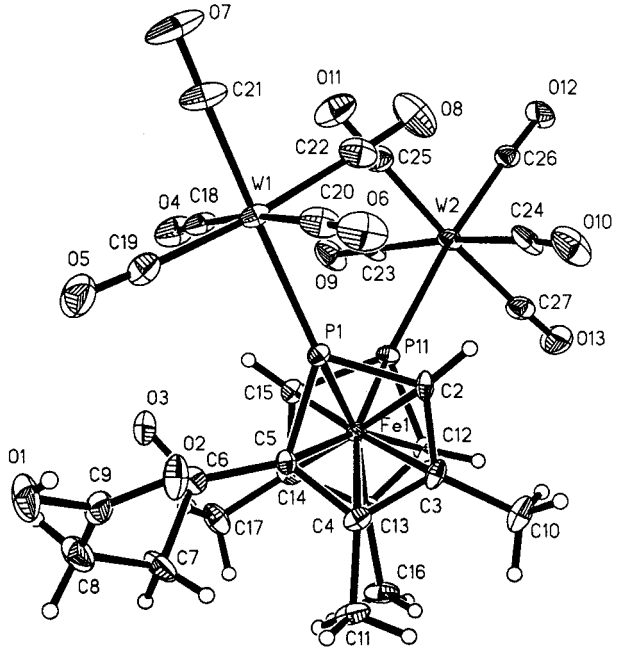
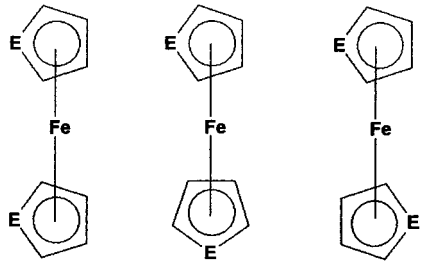


Figure 2. Ortep drawing of **4** (30% probability level). View along the vector perpendicular to the phospholyl rings.

the molecule **2a**. The view of molecule **4,** also along the vector perpendicular to the phospholyl planes, is given in Figure 2.

Conformations of 1,1′-diheteroferrocenes, $(C_4H_4E)_2Fe$, can be conveniently described as a function of the dihedral angle θ, defined as the angle between the planes normal to each C_4H_4E ring that contain both Fe and E atoms.[12c,e] When the heteroatoms are syn-eclipsed (C_{2v} symmetry), $\theta = 0°$. When they are anti (C_{2h} symmetry), $\theta = 180°$. The intermediate gauche or partially eclipsed conformations of C_2 symmetry have $0° < \theta < 180°$.

The computational studies (using extended Hückel,[12d,h,i] Fenske−Hall,[12g] and MS Xα[12i] methods) on 1,1′-diphosphaferrocene showed destabilization of the eclipsed



C_{2v} $\theta = 0°$ C_2 $0° < \theta < 180°$ C_{2h} $\theta = 180°$

Figure 3. Possible conformations of 1,1′-diheteroferrocenes as a function of angle θ. E = P, As, Sb, Bi; θ is the dihedral angle between the planes normal to each C_4H_4E ring that contain both Fe and E atoms.

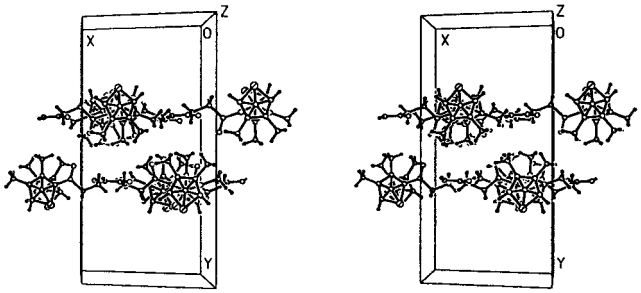


Figure 4. Molecular packing of **2**.

conformation in comparison to C_2 conformations with $\theta > 100°$. The X-ray structures of 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene[17] and 3,3′,4,4′-tetramethyl-2,2′-diphenyl-1,1′-diphosphaferrocene[18] are in full agreement with these results ($\theta = 145°$ for the former and $\theta > 100°$ for the latter). Hovewer, the eclipsed conformation was recently reported for crystalline 2,2′,5,5′-tetraphenyl-1,1′-diphosphaferrocene[19] and explained as a result of intramolecular $\pi-\pi$ interactions of the phenyl substituents providing an extra stabilization energy. The C_{2v} conformation is also forced for 1,1′-diphosphaferrocene chelate complexes in which both lone pairs of the phosphorus atoms are ligated to a metal center.[13,20] In contrast to 1,1′-diphosphaferrocenes, their analogues containing heavier heteroatoms (especially Sb or Bi) show a tendency to adopt in the solid state the eclipsed conformation, which was explained as a result of a secondary bonding between heteroatoms (defined as a covalent bond with fractional bond order which involves interatomic distances longer than the sum of the covalent, but shorter than the sum of the van der Waals radii).[12d,f,21]

Taking account of all these facts, we were surprised to find that molecules **2a** and **2b** display nearly eclipsed conformations with low values of θ: 28.4(3)° and 27.9(3)°, respectively. The intramolecular distance between the phosphorus atoms is 3.522(2) and 3.513(2) Å in **2a** and **2b**, respectively, indicating a secondary bonding.

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Table 2. Selected Bond Lengths [Å] and Angles [deg] and Their Average Values[a]

bond	molecule **2a**	**2b**	av in **2a** and **2b**	**4**	av in **4**
Phospholyl Rings					
C(2 or 22)−C(3 or 23)	1.418(8)	1.426(8)		1.414(12)	
C(3 or 23)−C(4 or 24)	1.422(7)	1.416(7)		1.419(12)	
C(4 or 24)−C(5 or 25)	1.433(7)	1.427(7)	1.417(2)	1.432(11)	1.419(5)
C(12 or 32)−C(13 or 33)	1.397(8)	1.395(8)		1.411(12)	
C(13 or 33)−C(14 or 34)	1.410(8)	1.421(8)		1.429(13)	
C(14 or 34)−C(15 or 35)	1.423(9)	1.421(9)		1.411(12)	
P(1 or 21)−C(5 or 25)	1.805(5)	1.808(5)	1.806(4)	1.778(8)	
P(1 or 21)−C(2 or 22)	1.753(6)	1.750(6)		1.745(7)	
P(11 or 31)−C(12 or 32)	1.744(7)	1.751(6)	1.748(3)	1.749(9)	1.748(5)
P(11 or 31)−C(15 or 35)	1.743(7)	1.748(7)		1.751(9)	
C(2 or 22)−P(1 or 21)−C(5 or 25)	88.4(3)	88.4(3)		90.0(4)	
C(12 or 32)−P(11 or 31)−C(15 or 35)	88.8(3)	89.0(3)	88.7(2)	90.3(4)	90.2(3)
W(1 or 2)−P(1 or 11)−C(2 or 12)			130.9(3)	128.8(3)	
W(1 or 2)−P(1 or 11)−C(5 or 15)			136.5(2)	137.2(3)	
Fe Coordination					
Fe(1 or 2)−P(1 or 21)	2.282(2)	2.280(2)		2.257(2)	
Fe(1 or 2)−P(11 or 31)	2.290(2)	2.289(2)	2.285(1)	2.262(2)	2.259(1)
Fe(1 or 2)−C(2 or 22)	2.073(5)	2.074(2)		2.089(8)	
Fe(1 or 2)−C(3 or 23)	2.081(5)	2.081(5)		2.081(7)	
Fe(1 or 2)−C(4 or 24)	2.087(5)	2.083(5)		2.098(8)	
Fe(1 or 2)−C(5 or 25)	2.076(5)	2.082(5)	2.078(7)	2.078(1)	2.091(3)
Fe(1 or 2)−C(12 or 32)	2.085(6)	2.083(5)		2.077(7)	
Fe(1 or 2)−C(13 or 33)	2.081(5)	2.080(5)		2.111(8)	
Fe(1 or 2)−C(14 or 34)	2.066(6)	2.080(5)		2.101(8)	
Fe(1 or 2)−C(15 or 35)	2.067(6)	2.066(5)		2.094(8)	
Intramolecular P···P Secondary Bonds					
P(1)(21)···P(11)(31)	3.522(2)	3.513(2)	3.737(2)		
Intermolecular P···P Secondary Bonds					
P(1)···P(21)^{i}	3.498(2)				
P(11)···P(31)^{ii}	3.723(2)				

W Coordination in 4

W(1)−P(1)	2.448(2)	W(2)−P(11)	2.457(2)	2.452(1)
W(1)−C(18)	2.029(11)	W(2)−C(23)	2.054(11)	
W(1)−C(19)	2.032(12)	W(2)−C(24)	2.060(13)	
W(1)−C(20)	2.049(12)	W(2)−C(25)	2.048(13)	2.043(4)
W(1)−C(22)	2.038(14)	W(2)−C(27)	2.033(12)	
W(1)−C(21)	2.002(11)	W(2)−C(26)	2.019(10)	2.011(7)

[a] Symmetry code: (i) *x*, *y*, 1−*z*; (ii) *x*, *y*, 1+*z*.

Structures of **2a** and **2b** show also an intermolecular P···P secondary bonding, giving rise to formation of stacking columns along the *z* axis (see Figure 4).

Figure 5 shows a view of this column along the *y* axis. Molecules **2a** and **2b** are situated alternately in the chain. They are two kinds of intermolecular P- - -P interactions: the first between phosphorus atoms belonging to more substitued rings and the second between P atoms belonging to less substituted rings. The intermolecular distances P(1)- - -P(21) and P(11)- - -P(31)^{i} are 3.498(2) and 3.723(2) Å, respecively. The interacting phospholyl rings are nearly parallel. The intra- and intermolecular angles between their four-carbon planes are from 1.3(2)° to 1.7(2)°. In the column Fe atoms are not ideally collinear. The angle formed by three succeeding Fe atoms is 159.8(5)°. The distances Fe(1)−Fe(2) and Fe(2)−Fe(1)^{i} are 7.177(2) and 7.175(2) Å, respecively. The structure of **2** provides the first example of intermolecular secondary interactions between P atoms in the diphosphaferrocene system. However, such interactions were reported for a heavier diheteroferrocene system: octamethyl-1,1′-distibaferrocene.[12d] In our opinion this type of crystal may show interesting electrical properties.

The structure of **4** shows a larger value of θ, 52.6(4)°. This may be attributed to the steric interactions between the $W(CO)_5$ groups. The intramolecular P1−P11 distance of 3.737(2) Å indicates weaker secondary bonding.

The above results clearly show that secondary bonding between heteroatoms exists not only in heteroferrocenes containing heavy pnictogens such as As, Sb, and Bi but also in 1,1′-diphosphaferrocenes. The latter system can populate conformers with low values of θ (<53°) and short intramolecular separations between the heteroatoms even in the absence of such factors as intramolecular interactions between substituents or constraints due to coordination of two phosphorus atoms to a metal center. The most reasonable conclusion to be drawn from these facts is that conformational preferences in 1,1′-diphosphaferrocenes are small, and they can be easily changed by small changes in the substitution. Thus it would seem that the prior (using extended Hückel,[12d,h,i] Fenske−Hall,[12g] and MS Xα[12i] methods) computational studies on 1,1′-diphosphaferrocene do not give a correct description of the conformational preferences of this system, and higher level computation work is called for.

In the molecule **4** both W atoms display a distorted octahedral coordination with similar W−P bond lengths of 2.448(2) and 2.457(2) Å. These bonds are distinctly shorter than the W−P bonds in $W(CO)_5$(triphen-

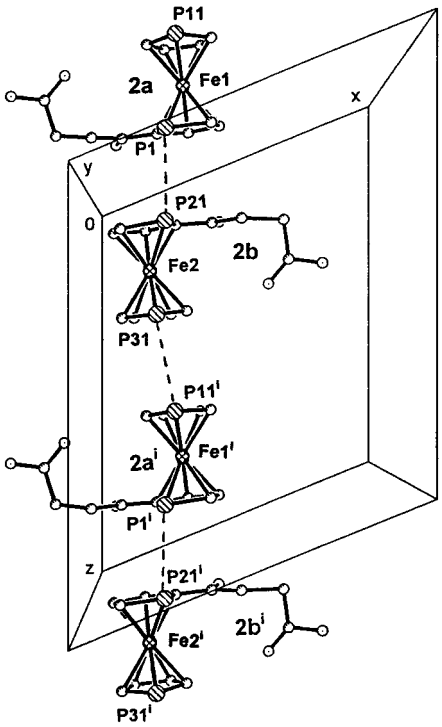

Figure 5. View along *y* axis on the stacking column of molecules **2a** and **2b**. H atoms and CH_3 groups are omitted for clarity.

ylphosphine) and $W(CO)_5$(trimethylphosphine) complexes, where the mean W−P bond lengths are 2.545(1) and 2.516(3) Å, respectively.[22a,b] They are also shorter than normalized to W−P, W−N bonds observed in $W(CO)_5$(azaferrocene) complexes,[23] where the average W−N bond is 2.271(5) Å, which after normalization to W−P gives 2.67 Å (as the difference between $r_P - r_N$ Pauling's atomic radii is 0.40 Å). Thus W−P bonds in **4** are short and strong. In both $W(CO)_5P$ moieties the W−P bonds are not exactly coplanar with the phospholyl rings. The deviations of W(1) and W(2) atoms from the least-squares planes of these rings are 0.579(9) and 0.714(10) Å, respectively, and the angles between the W(1)−P(1) and W(2)−P(11) bonds and the normal to these rings are 76.7(3)° and 73.6(3)°, respectively. These angles may be considered as the measure of the steric hindrance on binding to $W(CO)_5$. The W−C bonds cis to phosphorus in **4** are equivalent with the mean value of 2.043(4) Å, which is nearly identical to the values observed in $W(CO)_5$(azaferrocene) and other $W(CO)_5L$ complexes.[22,23] However, the trans W−C bonds with the mean value 2.011(7) Å are distinctly longer than the average value of these bonds of 1.962(4) Å observed in $W(CO)_5$(azaferrocene) complexes.[23] The W−P and trans W−C bond lengths provide information on the coordinating properties of the 1,1′-diphosphaferrocene system. The long trans W−C bonds in **4** indicate that the W atom in $W(CO)_5$(1,1′-diphosphaferrocene) complexes shows less tendency for π-back-bonding to CO than in the azaferrocene complexes. This fact, together with relatively short W−P bonds, suggests significant π-acceptor properties of the 1,1′-diphosphaferrocene system. It is worthy noting that such properties were already suggested by Mathey et al.[13] on the basis of IR spectral data.

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Table 3. Hydrogen Bonding Geometry [Å, deg][a]

D−H···A	D−H[b]	H···A[b]	D···A	D−H···A[b]
	Crystals of **2**			
O(1)−H(1)···O(22)^{i}	0.93	1.77	2.642(6)	153
O(21)−H(21)···O(2)^{ii}	0.93	1.72	2.642(6)	167
C(8)−H(8A)···O(3)	1.08	2.39	2.782(7)	100
C(28)−H(28A)···O(23)	1.08	2.42	2.772(7)	98
	Crystals of **4**			
O(1)−H(1)···O(2)^{iii}	0.93	1.81	2.690(12)	155

[a] Symmetry codes: (i) $1-x, y, 1-z$; (ii) $1+x, y, 1+z$; (iii) $1-x, -y, -z$. [b] Values normalized following: Jeffrey, A.; Lewis, L. *Carbohydr. Res.* **1978**, *60*, 179. Taylor, R.; Kennard, O. *Acta Crystallogr.* **1983**, *B39*, 133.

The conformation of the $COCH_2CH_2COOH$ chain in **2** and **4** is different. In **4** carbonyl oxygen O(3) and P(1) are in trans conformation with respect to the C(5)−C(6) bond, whereas in **4** the same atoms are in cis conformation. Furthermore the P−W coordination of the phosphole ring disturbs the coplanarity of this ring with the C═O carbonyl bond (in **4** the torsion angle P(1)−C(5)−C(6)−O(3) is 26.9(1.1)°, and in **2** the average value of this angle is − 173.0(4)°). In **4** certain reduction of π electron delocalization between C(5)−C(6) and C(6)−O(3) bonds can be observed. The lengths of these bonds in **4** are 1.476(12) and 1.201(11) Å, respectively, and in **2** their average values are 1.459(7) and 1.224(6) Å.

There are intermolecular short O−H···O hydrogen bonds between neighboring carboxylate groups and in **2** also intramolecular C−H···O hydrogen bonds. Table 3 gives the geometry of these bonds. The molecules of **4** form centrosymmetrical dimers by two O−H···O bonds, which gives nearly eclipsed conformation on the C(8)−C(9) bond with the O(2)−C(9)−C(8)−C(7) torsion angle of 5.6(1.7)°. In the crystals of **2** O−H···O hydrogen bonds are formed between molecules **2a** and **2b** from neighboring stacking columns of molecules connected by intermolecular secondary P···P bonds. They also generate the eclipsed conformation on the C(8)(28)−C(9)(29) bonds with the torsion angles O(2)(22)−C(9)(29)−C(8)(28)−C(7)(27) of 19.8(8)° and 18.4(8)°, respectively. The $COCH_2CH_2COOH$ groups in the molecules **2a** and **2b** have an eclipsed conformation also on the C(6)(26)−C(7)(27) bonds caused by the C(8)(28)−H···O(3)(23) hydrogen bonds. The torsion angles C(8)(28)−C(7)(27)−C(6)(26)−O(3)(23) are 15.6(8)° and 14.1(7)°, respectively.

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Supporting Information Available: Crystal data for **2** and **4** (19 pages). Ordering information is given on any current masthead page.

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