diazomethane to furnish the pentaester **6**.[12]

Prolonged heating of either PGI_2 methyl ester or the regioisomer **3** afforded a small amount of nonpolar oily product. It appeared to us that this component might be the internal ketal **4** and ought to be accessible as a major product by a carefully controlled reaction conditions, and an experimental study was undertaken.

6-Keto-$PGF_{1\alpha}$ (**2**, R = Me, 0.95 g), upon treatment with powdered molecular sieve 4A (4 g)[13] and kiesel gel (4 g)[14] in dry methylene chloride (50 mL) with vigorous stirring at 25 °C for 4 h followed by filtration and purification by column chromatography, afforded the desired ketal **4** as a principal product (40% yield), whose structure was apparent from ^1H NMR and double-resonance ^1H NMR experiment as well as IR analysis.[15] Structure **4** was further confirmed by the following observations. (1) Hydrolysis of **4** with a mixture of acetic acid–water–tetrahydrofuran gave 6-keto-$PGF_{1\alpha}$ methyl ester. (2) Exposure of **4** to AcOD–D_2O–THF produced the 6-keto-$PGF_{1\alpha}$ methyl ester with no deuterium incorporation.[11] (3) Treatment of **4** with excess *p*-nitrobenzoyl chloride–triethylamine afforded the monobenzoate of allylic alcohol.[16] (4) Silylation of **4** with TMSDEA gave the monotrimethylsilyl derivative by mass spectral assay. (5) The methoxy lactol **5** was produced by methanolysis of **4**. Apart from being of considerable interest with regard to biological activity, the ketal **4** represents an internally protected form of 6-keto-$PGF_{1\alpha}$ methyl ester which allows a variety of useful selective transformations.

In the preliminary test, the *endo*-enol ether **3** shows the higher potency to natural PGE_1 in inhibiting platelet aggregation and the lower to PGI_2 methyl ester, while the internal ketal **4** was almost inactive.[17] Further study of the biological activities of **3** and **4** are in progress and will be published in due course.

References and Notes

(1) (a) C. Pace-Asciak and L. S. Wolfe, *Biochemistry*, **10**, 3657 (1971); (b) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature*, **263**, 663 (1976); (c) R. Gryglewski, S. Bunting, S. Moncada, R. J. Flower, and J. R. Vane, *Prostaglandins*, **12**, 685 (1976); (d) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *ibid.*, **12**, 715 (1976); (e) S. Bunting, R. Gryglewski, S. Moncada, and J. R. Vane *ibid.*, **12**, 897 (1976).

(2) (a) E. J. Corey, G. E. Keck, and I. Székely, *J. Am. Chem. Soc.*, **99**, 2006 (1977); (b) R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *Prostaglandins*, **12**, 915 (1976).

(3) (a) J. L. Marx, *Science*, **196**, 1072 (1977); (b) A. M. Lefer, M. L. Ogletree, J. B. Smith, M. J. Silver, K. C. Nicolaou, W. E. Barnette, and G. P. Gasic, *Science*, in press.

(4) For a recent review, see K. C. Nicolaou, G. P. Gasic and W. E. Barnette, *Angew. Chem.*, in press.

(5) (a) W. C. Chang, S. Murota, M. Matsuo, and S. Tzurufuji, *Biochem. Biophys. Res. Commun.*, **72**, 1259 (1976); (b) C. Pace-Asciak, *J. Am. Chem. Soc.*, **98**, 2348 (1976); (c) W. Dawson, J. R. Boot, A. F. Cockerill, D.-N. B. Mallen, and D. J. Osborn, *Nature*, **262**, 699 (1976).

(6) (a) K. C. Nicolaou, W. E. Barnette, G. P. Gasic, R. L. Magolda, W. J. Sipio, M. J. Silver, J. B. Smith, and C. M. Ingerman, *Lancet*, I, 1058 (1977); (b) K. C. Nicolaou, W. E. Barnette, G. P. Gasic, R. L. Magolda, and W. J. Sipio, *J. Chem. Soc., Chem. Commun.*, 630 (1977); (c) R. A. Johnson, F. H. Lincoln, J. L. Thompson, E. G. Nidy, S. A. Mizsak, and U. Axen, *J. Am. Chem. Soc.*, **99**, 4182 (1977).

(7) ^1H NMR ($CDCl_3$): δ 3.13 and 3.21 (2s, 3 H, OCH_3), 3.66 (s, 3 H, $COOCH_3$).

(8) ^1H NMR analysis of the crude product revealed the presence of a small amount of PGI_2 methyl ester and its stereoisomer, which could be removed by careful column chromatography (TLC R_f value (ether–acetone–Et_3N, 75:25:0.1)): **1**, 0.41; **2**, 0.18; **3**, 0.43.

(9) ^1H NMR ($CDCl_3$): δ 2.22 (m, 1 H, C(12) H), 2.93 (m, 1,H, C(8) H), 3.76 (m, 1 H, C(11) H), 4.03 (m, 1 H, C(15) H), 4.65 (d, 1 H, C(7) H), 4.84 (m, 1 H, C(9) H), 5.47 (m, 2 H, C(13 and 14) H). IR ($CHCl_3$): 1665 cm^{-1} (enol ether).

(10) 5 mm × 1.5 m column of 5% SE-30 on Shimalite-W; column temperature, 260 °C; injection temperature, 280 °C; detector temperature, 260 °C; He, 1.6 kg/cm^2; t_r = 18 mm. Elimination of Me_3SiOH was effected during this operation.

(11) The enol ether **3**, upon treatment with AcOD–D_2O–THF, produced the 7-*d*-6-keto-$PGF_{1\alpha}$ methyl ester: mass spectrum (after trimethylsilylation) *m/e* 511, 421, 350, 325, 278, 263, 217, 199, 173, 143. See ref 2b for the analysis of fragmentation pattern of 6-keto-$PGF_{1\alpha}$ methyl ester. The mass spectra of 5-*d* derivative showed the following peaks: 511, 421, 350, 325, 277, 263, 217, 199, 173, 144.

(12) ^1H NMR ($CDCl_3$): δ 2.07 (s, 3 H), 3.32 (dd, 1 H), 3.57 (dd, 1 H), 3.68 (s, 3 H), 3.70 (s, 3 H), 3.74 (s, 3 H), 4.15–4.55 (m, 2 H). IR ($CHCl_3$): 1735 cm^{-1}. mass spectrum (after trimethylsilylation): *m/e* 402 (M^+), 371, 329, 297, 270, 242, 210, 200, 199, 182, 151, 143, 111.

(13) Freshly powdered and dried in vacuo at 160 °C for 2 h.

(14) Dried in vacuo at 160 °C for 2 h before use.

(15) ^1H NMR ($CDCl_3$): δ 1.90 (m, 2 H, C(7) H), 2.12 (m, 2 H, C(10) H), 2.80 (m, 1 H, C(12) H), 2.87 (m, 1 H, C(8) H), 4.00 (m, 1H, C(15) H), 4.33 (m, 1 H, C(11) H), 4.74 (m, 1 H, C(9) H), 5.44 (m, 2 H, C(13, 14) H). IR (liquid film): 3400 and 1735 cm^{-1} (no enol ether absorption). **4** was homogeneous by GC and TLC (R_f 0.56 (ether–acetone–Et_3N, 75:25:0.1)) analysis. Surprisingly, the NMR spectrum of **4** is almost identical with that of 6,9α-oxido-11,15-dihydroxyprosta-7,13-dienoic acid methyl ester (see C. Pace-Asciak and L. S. Wolfe, *Biochemistry*, **10**, 3657 (1971)), the synthesis of which is undergoing in our laboratories.

(16) ^1H NMR ($CDCl_3$): δ 5.47 (m, 1 H, C(15) H), 7.15–7.4 (AB, 4 H). IR (liquid film): no OH absorption.

(17) When compared with PGE_1, **3** was 11.7 times more potent as an inhibitor of platelet aggregation in ADP induced platelet rich plasma from rat.

Katsuichi Shimoji, Yoshitaka Konishi, Yoshinobu Arai, Masaki Hayashi*

Ono Pharmaceutical Co., Ltd., Research Institute, Shimamoto, Osaka, 618 Japan

Hisashi Yamamoto

Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822

Received November 4, 1977

Conformational Equilibrium in the Backbone of Cyclic Tripeptides[1]

Sir:

NMR measurements and x-ray studies of cyclic tripeptides such cyclo[Pro_3],[2,3] cyclo[Hyp-Pro_2],[3] and cyclo[Sar_3][4] indicate a C_3 symmetric backbone conformation ("crown").[5] We have now synthesized the *N*-benzylglycine (Bzl·Gly) containing cyclic tripeptides of the general structure cyclo-[Pro_x-Bzl·Gly_{3-x}] (**1**, x = 0; **2** x = 1; **3**, x = 2) with the aim

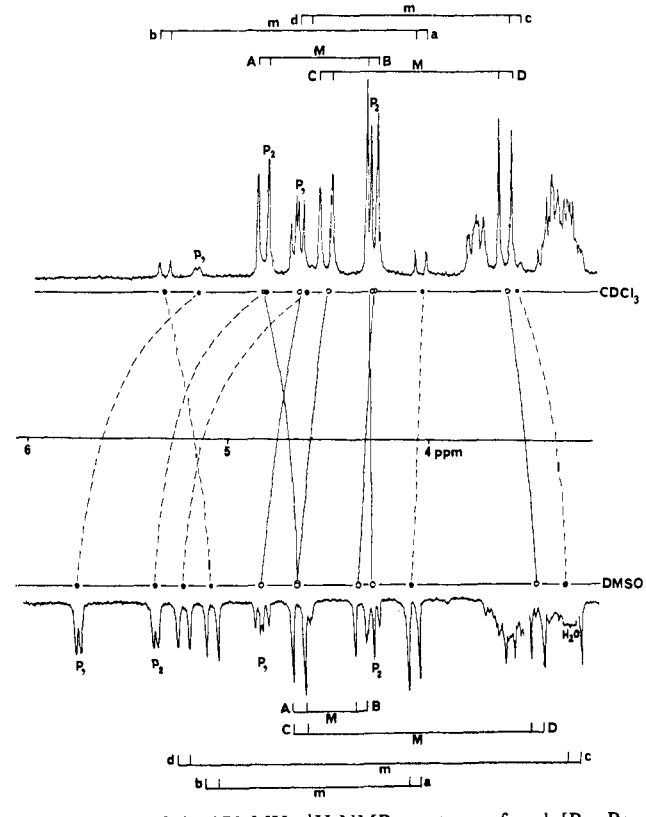


Figure 1. Part of the 270-MHz ^1H NMR spectrum of cyclo[Pro-Pro-Bzl·Gly] in $CDCl_3$ (top) and Me_2SO (inverted on bottom).

0002-7863/78/1500-2548$01.00/0

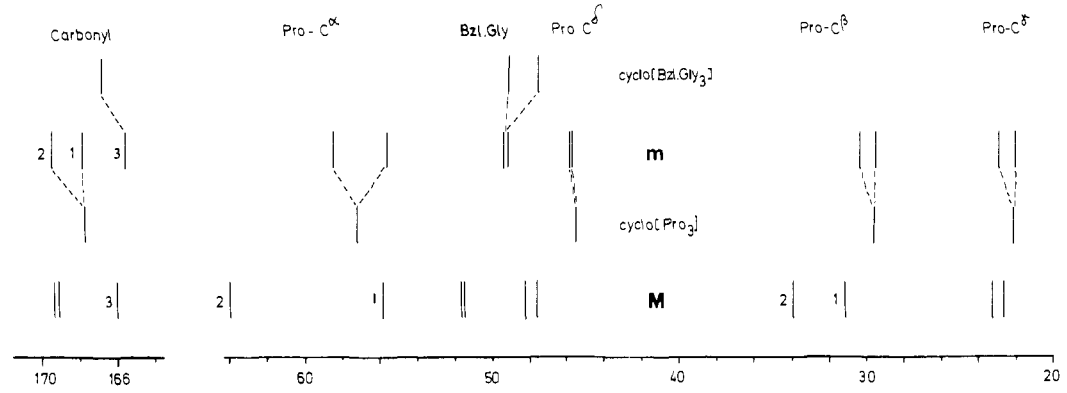
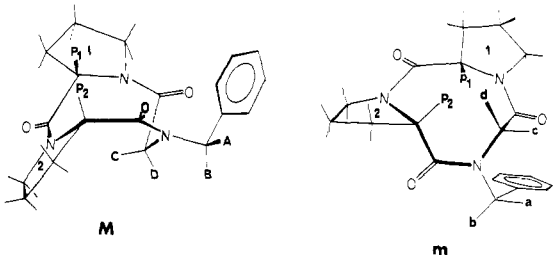


Figure 2. Representation of the ^{13}C NMR spectra of cyclotripeptides in $CDCl_3$ (δ from Me_4Si): m, crown conformation; M, boat conformation of cyclo[Pro^1-Pro^2-Bzl-Gly^3] compared with cyclo[Bzl-Gly]$_3$ and cyclo[Pro$_3$].

of eventually obtaining cyclic tripeptides free of N substituents by final removal of the *N*-benzyl groups.[6]

Our NMR investigations surprisingly show that these peptides and also cyclo[Pro_2-Sar] (**4**)[7] exhibit two equilibrating conformations (M and m). We have proven, that the predominant conformation M of cyclo[Pro_2-Bzl-Gly] and of cyclo[Pro_2-Sar] in $CDCl_3$ is not the "crown" but a "boat" conformation (**3**, 90% M, 10% m; **4**, 85% M, 15% m). The results



of compound **3** are discussed more in detail. With increasing solvent polarity (acetone, acetonitrile, Me_2SO) the proportion of the m conformation, which we assign to be the "crown" one, increases to >50%. The NMR spectra and the solvent-induced shift of **3** are shown in Figure 1. NMR double-resonance experiments in different solvents were performed to assign the AB systems of the *N*-benzylglycyl residue and the α protons of the prolyl residues. The exchange of the signals of the one conformation with those in the other was proven by saturation transfer at 85 °C in Me_2SO and is indicated by the same letter in Figure 1 (e.g., A $\rightleftharpoons$ a, $P_1 \rightleftharpoons p_1$).

The NMR spectra of m for **3** show the following characteristics. (a) The resonances of the prolyl C^{α} protons appear as a doublet, as do those of cyclo[Pro$_3$], which has been shown to be in the "crown" conformation.[3] This doublet indicates that the coupling of the C^{α} proton to one of the C^{β} protons is near zero and, to the other, ~6.7 Hz. These couplings are consistent with a Dreiding model of the "crown" conformation, in which the dihedral angle between the prolyl C^{α} proton and the pro-R proton[8] on C^{β} is 90°. (b) The proton chemical shift values of the *N*-benzylglycyl residue are similar to those of **1**, which mainly prefers the "crown" conformation[6] (a, 4.06 vs. 4.22 ppm; b, 5.34 vs. 5.54 ppm; c, 3.65 vs. 3.74 ppm; d, 4.65 vs. 4.56 ppm; solvent $CDCl_3$). (c) The ^{13}C chemical shift values of the *N*-benzylglycyl residue are similar to those of **1** in $CDCl_3$,[6] and those of the prolyl residues are similar to those of cyclo[Pro$_3$], as can be seen in Figure 2.

Thus, we conclude that m represents the expected "crown" conformation of cyclo[Pro_2-Bzl-Gly] (**3**) with a cis conformation in all peptide bonds. In the other conformation (M) the ^{13}C chemical shift data of prolyl C^{β} and C^{γ} also support the cis conformation of both prolyl peptide bonds,[9] whereas the *N*-benzylglycyl residue might have a cis or trans peptide bond. Considerations of appropriate models exclude the possibility of a trans peptide bond in a cyclic peptide of this size, which would cause considerable ring strain and strong transannular interactions. Therefore we assume M to be the "boat" conformation, which also has all-cis peptide bonds and which differs through an inversion of the *N*-benzylglycyl C^{α} protons from the "crown" one. This conclusion is supported by the quartet structure of the prolyl C^{α} proton signals, which show strong coupling with both protons at C^{β} (dihedral angles measured on Dreiding models: Pro^1 $\theta(H^{\alpha}$, pro-R $H^{\beta}) = -130°$, $\theta(H^{\alpha}$, pro-S $H^{\beta}) = -10.0°$; Pro^2 $\theta(H^{\alpha}$, pro-R $H^{\beta}) = -10.0°$, $\theta(H^{\alpha}$, pro-S $H^{\beta}) = +20°$). The change of the ψ angle (N-C^{α}-C-N′) of Pro^2 from +90° in the "crown" to about +30° in the "boat" is accompanied by an extremely large downfield shift of the signals of C^{α} (63.9 ppm) and C^{β} (33.9 ppm) (Figure 2).

Signal coalescences between 100 and 170 °C in Me_2SO correspond to a barrier of ~20 kcal/mol for the process m $\rightleftharpoons$ M. Such a barrier was also observed for the ring inversion of cyclo[Sar$_3$][10] and cyclo[Bzl-Gly$_3$] (**1**).[6] Hence, our experiments give evidence for the assumption of Dale[10,11] that the process "crown" $\rightleftharpoons$ "boat" is responsible for the highest barrier in the complete ring inversion of cyclo[Sar$_3$] (**5**) (crown $\rightleftharpoons$ boat $\rightleftharpoons$ boat′ $\rightleftharpoons$ crown′). Such a complete ring inversion must always be observable when all amino acids are achiral (degenerated process). In cyclotripeptides with chiral amino acids steric hindrance of the inside orientated groups (related positions in M and m of **3**: C, p_1, p_2, d) determines the population of the conformations. Those with chiral amino acids of different chirality should prefer the "boat" conformation, whereas, if they contain three amino acids of the same chirality, such as cyclo[Pro$_3$], the "crown" conformation is preferred. For the same reason the observation of the process "crown" = "boat" requires at least one achiral amino acid in the molecule.

We were able to detect two conformations not only in the NMR spectra of **2**, **3**, and **4** but also in cyclo[Bzl-Gly$_3$] (**1**) and cyclo[Sar$_3$] (**5**).[12] The latter prefer the crown conformation but, in solvents of low polarity ($CDCl_3$), small amounts of the flexible boat are populated (^1H NMR (δ in parts per million): **1** (10%), singlets at 4.10 (Bzl-CH_2) and 4.67 ($C^{\alpha}H_2$); **5** (6%), singlets at 4.20 ($C^{\alpha}H_2$) and 3.11 (CH_3)). The equivalence of the α protons in these peptide conformations exhibit fast interconversions between six possible boat conformations as originally stated by Dale.[11] The broadening ($b_{1/2}$ = 16 Hz) of the $C^{\alpha}H_2$ singlet at 4.20 ppm of **5** at 75 °C in $C_2D_2Cl_4$ corresponds to $\Delta G^{\ddagger}_{75} \sim 18.4$ kcal/mol ($\Delta G°_{298} = 1.6$ kcal/mol). This proves a common barrier of the processes crown $\rightleftharpoons$ boat and complete ring inversion.[10]

Acknowledgments. We thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for financial support. We are indebted to Professor H. Rüterjans,

University of Münster, for the preliminary NMR measurements at 270 MHz.

Supplementary Material Available: ^{1}H NMR spectra (270 MHz) of cyclo[Pro-Bzl-Gly_2], cyclo[Pro_2Sar], and cyclo[Bzl-Gly]$_3$ (Figures 3-5) and interpretation of conformational behavior in cyclotripeptides (Table 1) (6 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Conformations of Peptides. 3. For part 2, see Y. A. Bara, A. Friedrich, H. Kessler, and M. Molter, *Chem. Ber.*, in press.
(2) M. Rothe, K. D. Steffen, and I. Rothe, *Angew. Chem., Int. Ed. Engl.*, **4**, 356 (1965); M. Rothe, R. Theysohn, D. Mühlhausen, F. Eisenbeiß, and W. Schindler in "Chemistry and Biology of Peptides", J. Meienhofer, Ed., Science Publications, Ann Arbor, Mich., 1972, p 51.
(3) C. M. Deber, D. A. Torchia, and E. R. Blout, *J. Am. Chem. Soc.*, **93**, 4893 (1971).
(4) J. Dale and K. Titlestad, *Chem. Commun.*, 656 (1969).
(5) The flexibility of the prolyl pyrrolidine ring allows cyclo[Pro_3] to assume different crystal conformations. Interconversions of this kind are fast with respect to the NMR time scale and are not considered here. See M. E. Druyan, C. L. Coulter, R. Walter, G. Kartha, and G. K. Ambady, *J. Am. Chem. Soc.*, **98**, 5496 (1976).
(6) P. Krämer, Doctoral Thesis, Frankfurt a.M., 1976. The mass spectra prove that the compounds are not cyclic dimers or oligomers.
(7) First prepared by M. Rothe et al.[2]
(8) For the definition of prochirality, see D. Arigoni and E. L. Eliel, *Top. Stereochem.*, **4**, 127 (1969).
(9) I. Z. Siemion, T. Wieland, and K. H. Pook, *Angew. Chem., Int. Ed. Engl.*, **14**, 712 (1975); R. Deslauriers and I. C. P. Smith, *Top. Carbon-13 NMR Spectrosc.*, **2**, 1 (1976), and references cited therein.
(10) J. Dale and K. Titlestad, *Acta Chem. Scand., B*, **29**, 353 (1975); J. Schaug, *ibid.*, **25**, 2771 (1971).
(11) J. Dale, *Top. Stereochem.*, **9**, 199 (1976).
(12) We wish to thank Professors J. Dale and K. Titlestad for providing us with the sample of **5**.

H. Kessler,* P. Kondor, G. Krack, P. Krämer
Institute of Organic Chemistry, Laboratory Niederrad Theodor-Stern-Kai 7, D-6000 Frankfurt a.M. 70, Germany
Received October 5, 1977

cyclo-Triphosphorus (δ-P_3) as a Ligand in Cobalt and Nickel Complexes with 1,1,1-Tris(diphenylphosphinomethyl)ethane. Formation and Structures

Sir:

Compounds formed by the reaction of white phosphorus with metal complexes are quite rate. Only recently some rather unstable compounds of the types $[RhCl(PR_3)_2(P_4)]$,[1] $[Fe(CO)_4]_3P_4$,[2] and $[Fe(CO)_3P_2]_n$,[2] which have been suggested to contain P_4 or P_2 molecular units, have been reported. However definitive conclusions about their structures have not been reached. The compound $[CoPCp]_4$ has been found to possess a cubane-like geometry with phosphorus and cobalt atoms at the vertices of a distorted cube.[3]

We have been using over several years the tri(tertiary phosphine), 1,1,1-tris(diphenylphosphinomethyl)ethane, $CH_3C(CH_2PPh_2)_3$, L, as an efficient ligand to form metal complexes with coligands of various types.[4] By reacting white phosphorus with cobalt(II) and nickel(II) aquoions in presence of L, the complexes $[CoL(P_3)]$ and $[LNi(P_3)NiL]Y_2$ (Y = BF_4, BPh_4) containing the *cyclo*-triphosphorus δ-P_3 group as a ligand were obtained. To our knowledge the existence of this molecular unit either free or bound has not been ascertained before.

Equimolecular quantities of $Co(BF_4)_2 \cdot 6H_2O$ in butanol and L in THF were allowed to react, at 50 °C and under inert gas atmosphere, with an excess of white phosphorus. After ~10 min yellow-orange crystals of the $[CoL(P_3)]$ complex (**1**) precipitated. They were filtered off and recrystallized from methylene chloride–butanol. Anal. Calcd for $C_{41}H_{39}CoP_6$: C, 63.41; H, 5.06; Co, 7.58; P, 23.93. Found: C, 63.56; H, 5.28; Co, 7.30; P, 24.92.

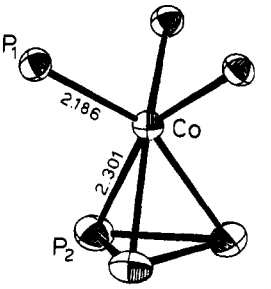


Figure 1. Inner skeleton of $[CoL(P_3)]$. The P–Co–P angles formed by the L and P_3 ligands are 93.6 (1) and 55.5 (1)°, respectively.

The $[LNi(P_3)NiL](BF_4)_2$ complex (**2**) was obtained by reaction at room temperature and under nitrogen atmosphere of $Ni(BF_4)_2 \cdot 6H_2O$ (1 mmol), L (1 mmol), and white phosphorus (excess), in THF–butanol solution. By concentration of the resulting solution, red-brown crystals precipitated. Anal. Calcd for $C_{82}H_{78}B_2F_8Ni_2P_9$: C, 60.29; H, 4.81; Ni, 7.18; P, 17.06. Found: C, 60.00; H, 5.14; Ni, 6.95; P, 17.17. The solution of this complex in acetone was added to a solution of $NaBPh_4$ in butanol and large crystals of the $[LNi(P_3)NiL](BPh_4)_2 \cdot 2(CH_3)_2CO$ complex (**3**) precipitated. Anal. Calcd for $C_{136}H_{130}B_2Ni_2O_2P_9$: C, 73.76; H, 5.91; Ni, 5.30; P, 12.58. Found: C, 73.61; H, 6.57; Ni, 5.15; P, 12.92.

All complexes are air stable, also in solution of THF, methylene chloride, nitroethane.

The cobalt derivative is diamagnetic and a nonelectrolyte in methylene chloride solution. The complex **3** is 1:2 electrolyte in nitroethane solution. The effective magnetic moments of the compounds **3** and **2**, respectively, are equal to 1.92 μ_B (at 293 K) and to 1.9 ± 0.1 μ_B (from 85 to 293 K) for the dimeric units. This is in agreement with the existence of one unpaired electron in both dimers.

The structures of **1** and **3** were established by single-crystal x-ray diffraction studies. Complex **1** crystallizes in space group $R3$ with the following cell constants: a = 10.57 (1) Å, α = 109.5 (1)°, Z = 1. Compound **3** belongs to space group $P1$ with a = 17.53 (1), b = 15.86 (1), c = 13.88 (1) Å; α = 111.7 (1), β = 91.2 (1), γ = 115.4 (1)°; Z = 1.

Intensity data were collected on a Philips computer controlled PW 1100 diffractomerter (Mo Kα monochromatized radiation λ = 0.7107 Å) by the ω–2θ scan technique within $2\theta \leq 55°$ and $2\theta \leq 45°$ for complex **1** and **3**, respectively. Both structures were solved by the heavy-atom method and refined at the present stage to R = 0.048 over 1340 observed reflections ($I \geq 3\sigma(I)$) and R = 0.11 over 4285 observed reflections ($I \geq 3\sigma(I)$) for complex **1** and **3**, respectively. The rather high R value for complex **3** is due to the quality of the data affected by decomposition of the crystal and by the presence of disordered acetone molecules in the lattice which have not been yet included in the model. Refinement of both structures is still in progress.

The inner coordination geometries of the two complexes are shown in Figures 1 and 2. The metal atom in the cobalt complex is coordinated by the three phosphorus atoms of L and by the three phosphorus atoms of the P_3 unit. The two ligands are in a staggered position. The configuration of the nickel derivative is that of a triple-decker sandwich compound, with the P_3 unit bridging the two NiL moieties. The P–P distances in the *cyclo*-triphosphorus units of the two complexes, ranging from 2.13 to 2.16 Å, are indicative of covalent P–P bonds.

The electronic configurations of the complexes may be approached as follows. The 3d and 4s metal orbitals, which span the a_1 and e representations in C_{3v} symmetry, have nonzero overlap with the orbitals containing the lone pairs of the three

0002-7863/78/1500-2550$01.00/0