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Reactions of Coordinated Ligands. Part 19:[1] Template Synthesis of a Macrocyclic Secondary Tetraphosphine by Oxidative Demetallation of Crown Phosphine Ni(II) Complexes

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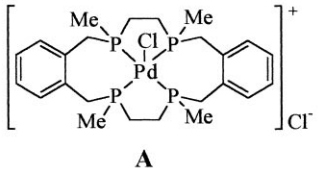
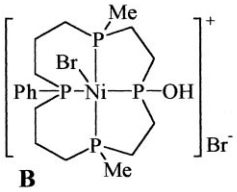
Abstract—The nickel(II) complex **3** containing a 14-membered macrocyclic triphosphine phosphinate ligand is obtained by regioselective oxidation of the crown phosphine nickel(II) complex **2c** with molecular oxygen. The X-ray structure of **3**·H_2O (space group $P2_1/c$) has been determined. Oxidation of the macrocyclic phosphinous acid nickel(II) complex **2a** (P_4 donor set) with H_2O_2/HCl or Br_2 and subsequent demetallation affords the macrocyclic phosphinic acid **5**. Reaction of its methylester **6** with thionyl chloride and subsequent reduction with $LiAlH_4$ gives the novel macrocyclic PH functional tetradentate phosphine **8** in high yields. © 1999 Elsevier Science Ltd. All rights reserved.

Introduction

In a series of papers we have described the high yield syntheses of complexes of macrocyclic tetradentate phosphine ligands (e.g. **A**, **B**) by template mediated coupling reactions of open chain α,ω-PH functional phosphines with bifunctional halides, α- or β-diketones and divinylphosphines.[1–5] Macrocyclic tetradentate phosphine oxides (e.g. **C**) have been obtained by Vincens et al.[6] and Horner et al.[7] in low yield multistage syntheses. Due to the strong macrocyclic effect[8] of crown phosphines their complexes show an extreme stability in solution, both kinetic and thermodynamic in nature. Decomplexation of the phosphine ligands with potassium cyanide could be achieved only in those cases in which the macrocyclic ring system contained the kinetically more labile seven membered chelate rings.[4]



A



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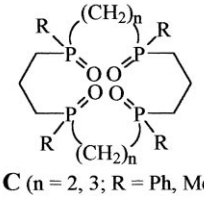

C (n = 2, 3; R = Ph, Me)

Keywords: regioselective oxidation; macrocyclic aminophosphine complex.
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Demetallation of the macrocyclic phosphine complexes should, however, be much easier after oxidation of their phosphorus atoms since phosphine oxides generally form weaker complexes than the corresponding phosphine ligands. Besides molecular oxygen, hydrogen peroxide and bromine have also been considered as reagents for the oxidation of the nickel(II) complexes of type **B** in aqueous solution. Reduction of the macrocyclic tetradentate phosphine oxides obtained by oxidative demetallation should finally lead to the crown phosphine ligands with an isocyclam[9] type structure.

Complexes of macrocyclic tetradentate phosphines and phosphine oxides incorporating radioactive nuclides like ^{99}Tc or ^{109}Pd are of increasing interest as model compounds for radiopharmaceuticals used in tumor targeting and diagnostic nuclear medicine.[10,11]

Results and Discussion

Selective oxidation of the macrocyclic nickel(II) phosphine complex 2c

The work reported in this paper is based upon the macrocyclic aminophosphine complex **1** obtained by template assisted cyclization of H(Me)P–$(CH_2)_3$–P(Ph)–$(CH_2)_3$–P(Me)H with $(CH_2{=}CH)_2$P–NEt_2 (Eq. (1a)) (Scheme 1). The derivatives **2a**, **2b** were synthesized by periphery reactions (Eq. (1b) and (1c)) on **1** in almost quantitative yield. For the oxidation reactions of the complexes **2a**, **2b** only those diastereoisomers were used in which the macrocyclic ring system had the all-*cis* configuration (isomers I). This is

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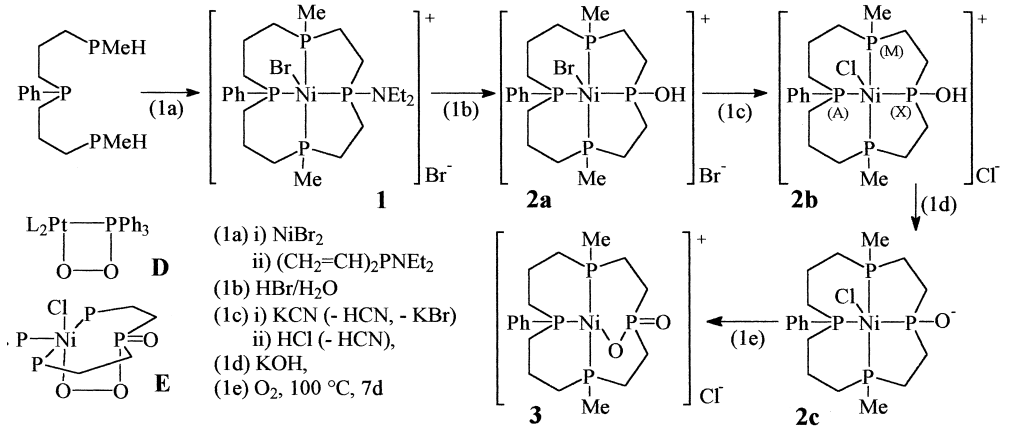


Scheme 1.

indicated by the almost identical AM_2X type $^{31}P\{^1H\}$ NMR spectra (A=P(Ph), M=P(Me), X=P(OH) or P–O^-; Table 1) of **2a**–**c** (which are interrelated by exchange of the apical halogen atoms (Eq. (1c)) and deprotonation of the P–OH unit (Eq. (1d)) and was proved for **2a** by an X-ray structural analysis.[1]

Complex **2c** was chosen primarily for the oxidation with molecular oxygen. If oxygen gas is bubbled through the solution of **2c** in water at 100°C for a couple of days, the mono-oxidation product **3** is obtained (Eq. (1e)) in addition to products of the exhaustive oxidation (see below). At ambient temperature, however, **2c** turned out to be stable towards molecular oxygen. No significant reaction was observed even in the course of a month. The mono-oxidation product **3** shows an AM_2X type $^{31}P\{^1H\}$ NMR spectrum (A=P(Ph), M=P(Me), X=P–O^-). While the δP values for P(A) in **2c** (2.5 ppm) and **3** (13.1 ppm) differ only a little, the $^{31}P\{^1H\}$ NMR signals for P(M) and P(X) are shifted upfield by ca. 40 or 120 ppm, respectively, on formation of **3** from **2c**. No P(A)–P(X) coupling fine structure is observed in the P(A) and P(X) part of the $^{31}P\{^1H\}$ NMR spectrum of **3**. In the starting material **2c**, however, the spins of the P atoms P(A) and P(X) in *trans* position are strongly coupled to each other (^2J(P(A)–P(X))=195 Hz). These spectroscopic data are consistent with the structure proposed for **3**. The oxidation of **2c** to **3** proceeds regioselectively at P–O^-, the additional oxygen atom being inserted between Ni(II) and P–O^- with formation of two six membered chelate ring systems [P(Me)–$(CH_2)_2$–P(=O)–O–Ni] instead of the five membered in **2c**. As a consequence of the ring expansion from five to six[12] the $^{31}P\{^1H\}$ NMR signals of P(X) and P(M) in **3** are shifted upfield with respect to δP(X) and δP(M) of **2c**.

Peroxide type complexes, e.g. **D**, have been proposed as intermediates for the transition metal catalyzed oxidation of phosphines by dioxygen.[13] Similar intermediates (e.g. **E**) may be anticipated for the oxidation of the macrocyclic complex **2c** according to Eq. (1e), which are formed initially

Table 1. $^{31}P\{^1H\}$ NMR data for **2a**–**6**, **8**. Chemical shifts δP relative to H_3PO_4 (85%); coupling constants in Hz, solvent D_2O, if not stated otherwise. For indication of P atoms see formula **2b**, **4**

	δP(A)	δP(L)	δP(M)	δP(X)	J(AL)	J(AM)	J(AX)	J(LX)	J(MX)
2a (isomer I)[a]	9.9		43.7	211.4		63	200		36
2b (isomer I)	3.2		38.3	195.4		62	197		36
2c (isomer I)	2.5		38.4	177.1		59	195		36
3	13.1		−5.5	55.9		85	<1		7
4 (isomer I)	49.2		58.5	42.1		5			57
(isomer II)	49.0		58.6	42.2		5			56
(isomer III)	49.0	58.2	58.4	42.7	5	5		55	55
5 (isomer I)	49.1		58.0	51.0		ca. 5			ca.58
(isomer II)	49.0		58.1	51.2		ca. 5			ca.57
(isomer III)	49.0	57.8	58.0	52.0	ca. 5	ca. 5		ca. 57	ca.57
6 (isomer I)	48.9	57.2	57.4	63.9	5	5		59	57
(isomer II)	48.9	57.1	57.6	63.9	5	5		58	59
(isomer III)	48.9		57.6	63.1		5			59
(isomer IV)	49.0		57.5	63.0		5			60
(isomer V)	48.8		57.3	63.0		5			58
8 (isomer I)[b]	−24.0		−39.7	−60.4		2			11
(isomer II)[b]	−24.1		−39.4	−53.9		2			9
(isomer III)[b]	−24.3	−38.2	−40.0	−57.2	2	<1		18	13
(isomer IV)[b]	−24.4	−38.2	−40.6	−58.3	2	<1		11	17
(isomer V/VI)[b]	−26.0		−40.2	−53.3		<1			12
(isomer V/VI)[b]	−26.7		−40.8	−61.4		<1			12

[a] Solvent H_2O/HBr.
[b] Solvent C_6D_6.

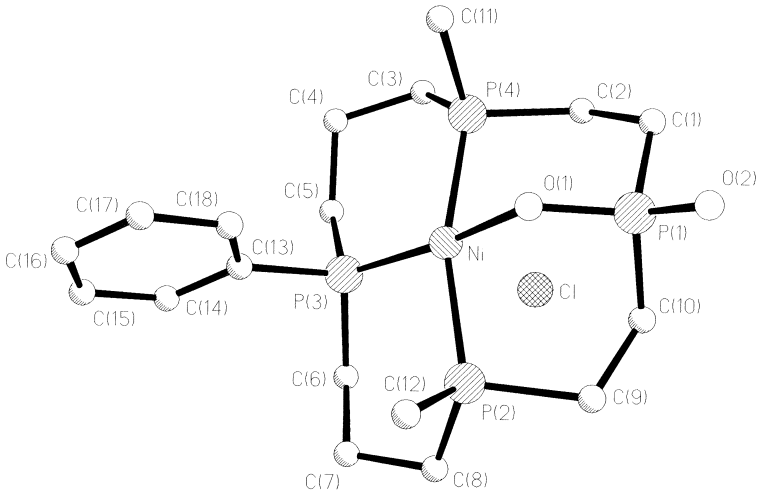


Figure 1. Molecular structure of **3**·H_2O.

by addition of O_2 to the Ni–P(X) bond, the Cl^- ligand being split off simultaneously. Hydrolysis of the Ni–O–O–P peroxo bridge should afford the mono-oxidation product **3** and hydrogen peroxide.

X-Ray structure of 3

The nickel atom in **3** is bound to three P atoms and the oxygen of the 14-membered macrocyclic ligand in a distorted square planar arrangement (P(1)–Ni–P(2,4)= 94.19(4), 96.25(2), O(1)–Ni–P(2,4)=86.12(8), 86.09(8)°) (Fig. 1, Tables 2 and 3). All P atoms are located nearly in a plane. The distance of the nickel atom from the best plane through P(1), P(2), P(3) and P(4) is 0.208 Å. On formation of **3** by oxidation of **2c**[1] the conformation of the macrocycle with respect to the position of the substituents at the P atoms P(1)–P(4) is not changed, the all-*cis* arrangement being adopted in both cases.

Table 2. Atom positional parameters with equivalent isotropic displacement parameters (Å×10^3) for **3**·H_2O (*equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor)

	x	*y*	*z*	*U*(eq)*
Ni	7035(1)	8493(1)	8637(1)	27(1)
Cl	8271(1)	11531(2)	10135(1)	62(1)
P(1)	5291(1)	9119(1)	8821(1)	34(1)
P(2)	7269(1)	6909(1)	9617(1)	38(1)
P(3)	8450(1)	8485(1)	8787(1)	33(1)
P(4)	6615(1)	10409(1)	7851(1)	32(1)
O(1)	5735(2)	8198(3)	8351(2)	33(1)
O(2)	4354(2)	8604(3)	8730(2)	48(1)
O(3)	3379(4)	7013(5)	9445(3)	124(2)
C(1)	5196(3)	10961(4)	8431(3)	44(1)
C(2)	6032(3)	11593(4)	8313(2)	40(1)
C(3)	7481(3)	11626(4)	7766(3)	47(1)
C(4)	8292(3)	10811(5)	7694(3)	53(1)
C(5)	8920(3)	10108(5)	8498(3)	45(1)
C(6)	9331(3)	8104(5)	9803(2)	46(1)
C(7)	9208(3)	6705(6)	10191(3)	59(1)
C(8)	8408(3)	6784(6)	10459(2)	60(1)
C(9)	6479(3)	7457(5)	10095(3)	48(1)
C(10)	6129(3)	9041(5)	9867(2)	41(1)
C(11)	5805(3)	10003(5)	6821(2)	46(1)
C(12)	6956(4)	5072(5)	9238(3)	66(1)
C(13)	8569(2)	7034(4)	8145(2)	34(1)
C(14)	9446(3)	6562(5)	8223(3)	49(1)
C(15)	9515(3)	5453(6)	7726(3)	59(1)
C(16)	8723(3)	4827(5)	7140(3)	56(1)
C(17)	7858(3)	5272(5)	7061(3)	52(1)
C(18)	7778(3)	6367(4)	7562(2)	42(1)

As a result of steric and electronic effects (*trans* influence)[14] of the oxygen atom O(1) inserted into the Ni–P(1) bond, the Ni–P(3) distance is compressed by 0.05 Å while that of Ni–P(2,4) (2.1932(12), 2.1761(12) Å) is elongated compared with the corresponding Ni–P bond lengths in **2a** (2.166(2), 2.159(2) Å).[1]

The formation of a four membered phosphinato chelate ring system,[15] {[–$(CH_2)_2$]$_2$P–O–Ni–O}, is hampered by steric constraints due to the macrocyclic structure of **3**. Within the Ni–O–P═O group the exocyclic P–O bond distance (P–O(2)=1.486(3) Å) is significantly shorter than the endocyclic (P–O(1)=1.545(3) Å) and may be compared with that in $Ph_3P(=O)$ (1.46(1) Å)[16a] and $Ph_2P(=O)(OH)$ (P(═O)=1.486(6) Å)[16b] indicating a higher degree of (P–O)π contribution in the exocyclic P–O bond. The Ni–O(1) distance (1.909(2) Å) is within the range typical for covalent nickel alkoxides,[17a] carboxylates (terminal)[17b] and σ-phosphinates (terminal).[17c]

Exhaustive ligand oxidation in the crown phosphine complex 2a

Using strong oxidizing agents like H_2O_2/HCl or Br_2 in aqueous solution the crown phosphine ligand in the complex **2a** (or **2b**) can be completely oxidized. The phosphine oxide complexes formed may be demetallated by precipitation of Ni(II) as insoluble $Ni(OH)_2$ with potassium hydroxide (Eq. (2a)) (Scheme 2). On protonation of the macrocyclic potassium phosphinate **4** obtained as an intermediate according to Eq. (2a), the phosphinic acid **5** is formed in high yields (Eq. (2c)).

The product was isolated as HCl adduct containing small amounts of HBr bound to the phosphine oxide units (composition **5**·1.2HCl·0.15HBr·H_2O). HCl and HBr could not be removed completely by heating in vacuo (80°C, 10^{-3} mbar). Phosphine oxides form thermally stable adducts with

Table 3. Selected distances (Å) and bond angles (°) in **3**·H_2O

Ni–P(2)	2.1932(12)	Ni–P(3)	2.1235(11)	Ni–P(4)	2.1761(12)
Ni–O(1)	1.909(2)	P(1)–O(2)	1.486(3)	P(1)–O(1)	1.545(3)
P(1)–C(1)	1.807(4)	P(1)–C(10)	1.804(4)	P(2)–C(9)	1.844(4)
P(2)–C(8)	1.815(4)	P(4)–C(2)	1.822(4)	P(4)–C(3)	1.810(4)
C(1)–C(2)	1.525(5)	C(9)–C(10)	1.542(6)	P(3)–C(5)	1.824(4)
P(3)–C(6)	1.821(4)				
P(4)–Ni–P(2)	163.71(4)		P(3)–Ni–P(2)	94.19(4)	
P(3)–Ni–P(4)	96.25(4)		O(1)–Ni–P(3)	168.65(8)	
O(1)–Ni–P(4)	86.09(8)		O(1)–Ni–P(2)	86.12(8)	
Ni–O(1)–P(1)	116.52(14)		O(2)–P(1)–O(1)	114.4(2)	
C(11)–P(4)– Ni	113.6(2)		C(12)–P(2)–Ni	112.3(2)	
C(10)–P(1)–C(1)	110.6(2)		C(6)–P(3)–C(5)	102.3(2)	

hydrogen halides. Thus $Ph_3P{=}O{\cdot}HCl$, which was characterized by X-ray structural analysis, eliminates HCl even at 60°C only very slowly.[18] The composition of the hydrogen halide adduct of **5** was determined by titration with KOH. The potassium salt **4** isolated from this solution still contains small quantities of potassium chloride and bromide.

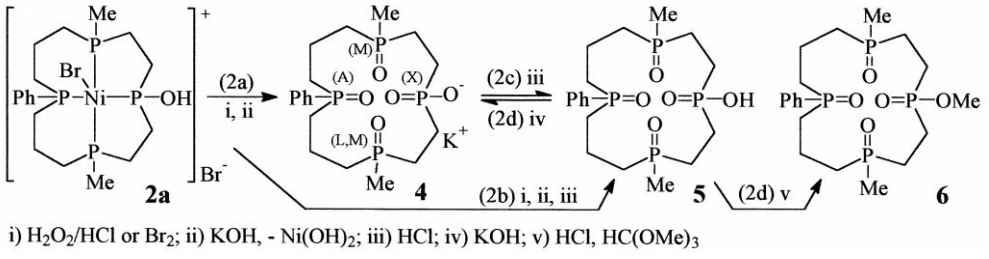
Although only the all-*cis* isomer of **2a** was employed for the oxidative demetallation reactions according to Eq. 2(a)–(c) three isomers of the phosphine oxides **4** and **5** are formed. The $^{31}P\{^1H\}$ NMR spectrum of the aqueous solution of **4** in addition to the 10-line pattern of two AM_2X spin systems shows a set of 14 lines corresponding to one ALMX spin system, indicating the formation of isomers with equivalent or inequivalent MeP(=O) groups, respectively (Table 1). The assignment of the signals of the AM_2X and ALMX spin systems is based on intensity arguments and the $^{31}P–^{31}P$ coupling fine structure. While the signal for $P(=O)O^-$ (X) appears as a triplet with a splitting ($^3J(PP)$=55–57 Hz) typical for systems with P(=O)–C–C–P(=O) fragments,[19] a doublet of doublet fine structure is observed for the MeP(=O) units (L, M). The signals at ca. 49 ppm showing a small triplet splitting of about 5 Hz ($^4J(PP)$)[19] may be assigned to PhP(=O). Protonation of **4** has no significant effect on the δP values of P(A) and P(L,M) while the signal of P(X) ($P(=O)O^-$) in **5** is shifted downfield by ca. 9 ppm (Table 1).

The formation of the additional AM_2X and the unsymmetrical ALMX diastereoisomer of **4** or **5** on oxidation of **2a** with H_2O_2/HCl or bromine must be due to inversion of configuration at the phosphorus atoms of the RP(=O) groups (R=Me, Ph) of the macrocyclic ring system in the acidic media. Racemization of optically active phosphine oxides $R^1R^2R^3P{=}O$ under the influence of acids (HCl, HBr) and peroxides was first reported by Horner et al.[20a,b] and Denney et al.[20c]

If **2a** (or **2b**) is oxidized with H_2O_2 in neutral or basic medium after demetallation one AM_2X diastereoisomer (I) of **4** is obtained preferably, however, as indicated by the $^{31}P\{^1H\}$ NMR spectrum. Under these conditions, racemization at the phosphorus atoms obviously occurs much more slowly than in acidic media. This is in agreement with the observations of Horner et al.[20b] who found, that (−)-methyl-*n*-propylphenylphosphine oxide is configurationally completely stable in MeOH/NaOH, while in concentrated HCl it racemizes very quickly. On heating isomer I of **4** with concentrated HCl, three diastereoisomers are formed by inversion of configuration at phosphorus. The $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture (after addition of a slight excess of KOH) shows the line patterns of two AM_2 X (I, II) and one ALMX spin system (III) of **4** in about the statistic ratio of 1:1:2 (Fig. 2).

Acidification of **5** and subsequent reaction with trimethyl *ortho*-formate $HC(OMe)_3$ yields the methyl ester **6** of the macrocyclic phosphinic acid **5** (Eq. (2d)). Four main diastereoisomers, showing AM_2X (two) and ALMX line patterns (two) can be identified in the $^{31}P\{^1H\}$ NMR spectrum of **6**. Further resonances of low intensity may be attributed to an additional diastereoisomer (AM_2X). While the δP values of P(A) (PhP(=O)) and P(L,M) (MeP(=O)) are changed little on formation of **6** from **5**, the $^{31}P\{^1H\}$ NMR signal of the P(=O)(OMe) group of **6**, lying in the δP range typical for dialkylphosphinic acid esters $R_2P(=O)(OR')$[21] is shifted about 12 ppm downfield compared with δP(X) in **5**. The signals observed at δC=52.5–53 ppm ($^2J(P(X)–C)\approx 7$ Hz) in the $^{13}C\{^1H\}$ NMR spectrum of **6** may be assigned to the OMe group in **6**.

The mass spectrum of **6** exhibits the parent ion peak at *m*/*e* 466 and fragment peaks at *m*/*e* 451 (M^+-CH_3) or 435 (M^+-OCH_3) indicating that the periphery reaction according to Eq. (2d) was indeed successful.



Scheme 2.

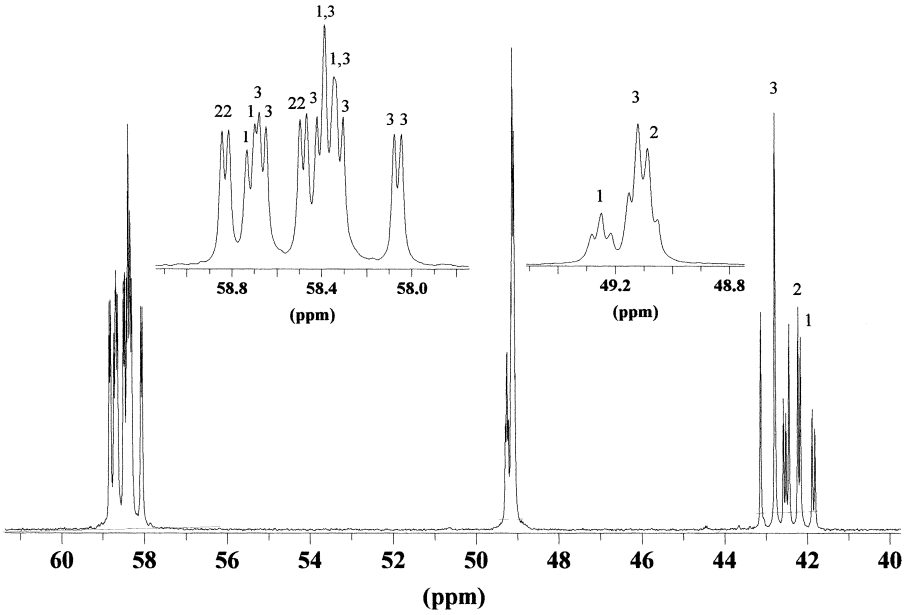


Figure 2. 161.89 MHz $^{31}P\{^{1}H\}$ NMR spectrum of **4** (solvent water; 1=isomer I, 2=isomer II, 3=isomer III)

Synthesis of the tertiary secondary crown phosphine 8

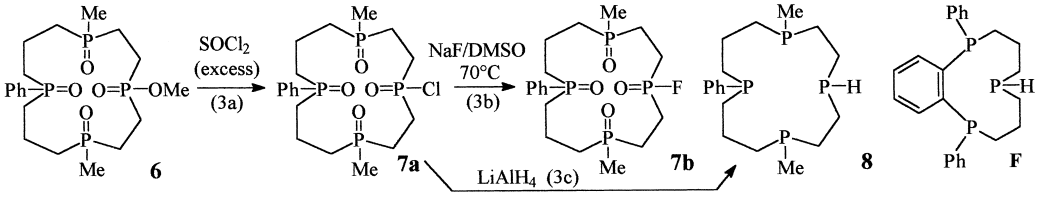
The macrocyclic phosphinic acid ester **6**, accessible by template assisted ring closure and periphery reactions (Eq. 1(a) and (b)), oxidative demetallation (Eq. (2b)) and *O*-methylation of **5** (Eq. (2d)) in high yields, was expected to give the macrocyclic PH functional phosphine **8** on reduction with $LiAlH_4$.

All attempts to synthesize **8** by direct reduction of the phosphinic acid ester **6** with $LiAlH_4$ were not successful, however, probably due to the very low solubility of **6** in suitable solvents like ether or tetrahydrofuran. On treatment of **6** with excess thionyl chloride a product **7a** is formed (Eq. (3a)) (Scheme 3), which in contrast to **6** reacts cleanly with $LiAlH_4$ at 20°C to give the macrocyclic phosphine **8** in very good yields (Eq. (3c)). Chlorination of phosphinic acid esters with $SOCl_2$ is a well established synthetic route to phosphinic acid chlorides.[22]

The $^{31}P\{^{1}H\}$ NMR spectrum of **7a**, dissolved in DMSO, shows broadened resonances with $^{31}P–^{31}P$ coupling fine structure which may be assigned to three diastereoisomers (δP(Me) ca. 54 ppm, δP(Ph) ca. 41 ppm and δP(Cl) ca. 50 ppm). No complete assignment of the individual ^{31}P NMR resonances could be achieved due to signal overlapping and line broadening. For a further identification of the intermediate **7a** it was transformed into the fluoro derivative **7b** by Cl/F exchange with NaF in DMSO (Eq. (3b)). The chemical shift values δF (ca. −76 ppm) or δP (ca. 73 ppm), respectively, for the P(=O)F unit and the ^{1}J(P–F) coupling (ca. 1020 Hz) observed for **7b** in the $^{19}F\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectrum are in ranges typical for phosphinic acid fluorides.[21]

The macrocyclic tertiary secondary phosphine **8** synthesized according to Eq. (3a) and (3c) was obtained as a mixture of, mainly, two symmetrical (I, II) and two unsymmetrical diastereoisomers (III, IV) as indicated by the observation of two AM_2X and two ALMX line patterns in an intensity ratio of about 5:7:3:3 in the $^{31}P\{^{1}H\}$ NMR spectrum (Table 1). While the signals for P(X) (P–H group) show triplet fine structure (^{3}J(PP)) in case of the symmetrical isomers, a doublet of doublet splitting was observed for the unsymmetrical diastereoisomers. The P(Me) groups in the symmetrical isomers give rise to only one resonance (P(M), doublet of doublets), for the unsymmetrical isomers with inequivalent P(Me) groups two sets of signals (P(L,M)) being observed, however. Two additional diastereoisomers (V, VI) are formed in lower quantities (each about 5%) in addition to the major isomers I–IV. Isomers V and VI may be assigned to a symmetrical structure as evidenced by the $^{31}P–^{31}P$ coupling triplet fine structure of the signals for P(X).

The large doublet splitting (^{1}J(PH)=190–200 Hz) of the resonances in the −50 to −65 ppm range of the ^{31}P NMR spectrum supports the assignment of the $^{31}P\{^{1}H\}$ NMR



Scheme 3.

resonances and proves the structure given above for the macrocyclic secondary tertiary phosphine **8**. In the mass spectrum of **8** intense peaks for M^+-H=371, M^+-CH_3=357 and $M^+-C_2H_4$=344 *m/e* are observed. Vapor phase osmometry gave an apparent molecular weight of 376 in CH_2Cl_2 (theoretical 372).

Only a very few examples for PH functional macrocyclic phosphines and their $Mo(CO)_3$ complexes have been reported in the literature so far.[23] Kyba and Liu[23a] obtained the 11 membered ditertiary secondary phosphine **F** in a multistage high dilution macrocyclization of (*o*-$PhPLi)_2C_6H_4$ with bis(3-chloropropyl)(1-naphthylmethyl)-phosphine sulfide in a low total yield of ca. 15%. The 1-naphthylmethyl PH protecting group was removed by treatment with excess potassium naphthalenide. Trisecondary 1,5,9-triphosphacyclododecane has been obtained by Edwards et al.[23c] using template mediated cyclization reactions similar to those reported by Norman et al.[23b]

Experimental

Apparatus and materials

All manipulations were carried out by using standard vacuum line and inert atmosphere techniques. The complexes **1**, **2a**–**2c** were prepared as reported earlier by us.[1,2] The ^{31}P, ^{19}F and ^{13}C NMR spectra were obtained by using JEOL FX 90Q and Bruker AC 250 and AC 400 spectrometers equipped with standard ^1H, ^{19}F, ^{31}P and ^{13}C probe accessories. ^{31}P (relative to external 85% H_3PO_4), ^{19}F (relative to internal CCl_3F) and ^{13}C, ^1H (relative to internal Me_4Si) chemical shifts downfield from the standard are given positive values. Mass spectra were determined on a Varian MAT 311a instrument at 70 eV.

Partial oxidation of 2c

A slow stream of air was bubbled through a capillary into a solution of 1.00 g (2.08 mmol) of **2c** (isomer I) in 50 mL of water at reflux temperature for 7 d. The reaction mixture was concentrated in vacuo (20°C, 10^{-3} mbar) to 10 mL and washed twice with 50 mL of CH_2Cl_2. The aqueous phase was separated, the solvent stripped off under reduced pressure and the remaining residue was extracted twice with 50 mL of CH_2Cl_2. The extracts were concentrated under reduced pressure to 15 mL. The precipitate formed on addition of methyl(*tert*-butyl)ether was collected by filtration and dried in vacuo (20°C, 10^{-3} mbar). Yield: 0.34 g (33%) **3**. Anal. Calcd. for $C_{18}H_{31}ClNiO_2P_4$ (M_r=497.5): C, 43.46; H, 6.28; Cl, 7.13. Found: C, 43.04; H, 6.38; Cl, 7.10.

On slow evaporation of a CH_2Cl_2 solution of **3**, yellow crystals of composition **3**·H_2O were obtained which were used for the X-ray structural analysis. $^{13}C\{^1H\}$ NMR (D_2O): δ133.8 (d, *J*=10.1 Hz), 133.7 (d, *J*=2.0 Hz), 130.4 (d, *J*=10.2 Hz), 127.6 (d, *J*=48.7 Hz), 24.3 (d, *J*=88.1 Hz, broad), 24.2 (dt, *J*=34.0, 5.1 Hz), 22.9 (dt, *J*=4.7, 16.2 Hz), 21.0 (dt, *J*≈5, 15 Hz), 17.1 (s, broad), 7.6 (t, *J*=14.1 Hz).

Exhaustive oxidation of 2a. Preparation of 5

To a solution of 3.00 g (4.94 mmol) of **2a** (isomer I) in 100 mL of H_2O excess bromine (12.0 g; 75.1 mmol) was added dropwise and the reaction mixture was stirred for 4 h at ambient temperature. After evaporation of all volatiles, 0.1N KOH was added until the reaction mixture showed a pH value of 8–9. The nickel(II) hydroxide formed was filtered off and the filtrate evaporated to dryness in vacuo. The solid residue was extracted twice with 40 mL of ethanol. After addition of 1 mL of conc. HCl the solvent was removed in vacuo. The solid obtained was extracted with a mixture of 10 mL of isopropanol and 60 mL of CH_2Cl_2. Removal of the solvents from the extract under reduced pressure gave a colorless powder which was dried in vacuo (20°C, 10^{-3} mbar). Yield: 2.34 g (90%). According to the elemental analysis, the product contained, in addition to water, appreciable amounts of chlorine and bromine, obviously bound to **5** as HCl and HBr which could not be removed even on prolonged heating in vacuo at 80°C. The contents of HCl and HBr were determined by titration with 0.1N KOH. The composition of the product calculated on the basis of the elemental analysis and the results of the titration may be given as $C_{18}H_{32}O_5P_4\cdot1.2HCl\cdot0.15HBr\cdot H_2O$ (M_r=526.3): C, 41.08; H, 6.77; Br, 2.28; Cl 8.08. Found: C, 41.26; H, 6.61; Br, 2.05; Cl, 8.19.

Preparation of 4

0.46 g (0.87 mmol) of the product obtained above were dissolved in 30 mL of water and the solution was neutralized with 0.1N KOH. The solvent was removed in vacuo and the residue extracted with a mixture of 20 mL of CH_2Cl_2 and 2 mL of isopropanol. After filtration the extract was evaporated in vacuo to dryness yielding a colorless powder which was dried in vacuo. Yield: 0.41 g (93%). According to the elemental analyses, the product contained small quantities of potassium chloride and bromide. Anal. Calcd. for $C_{18}H_{31}KO_5P_4\cdot H_2O$ (M_r=508.4): C, 42.52; H, 6.54. Found: C, 42.18; H, 6.76.

Preparation of 6

To a solution of 3.6 g (5.93 mmol) of **2a** (isomer I) in a mixture of H_2O (10 mL) and conc. HCl (10 mL) excess hydrogen peroxide (10 mL, 30%) was added dropwise. The temperature of the reaction mixture increased and bromine was evolved. Upon addition of further conc. HCl (10 mL) and H_2O_2 (1 mL) the green colored solution was heated for 3 h at 70°C. All volatiles were then stripped off under reduced pressure and the solid obtained was dissolved in 50 mL of water. Potassium hydroxide (0.1N aqueous solution) was added until the solution showed a pH value of about **8**. The $Ni(OH)_2$ precipitated was filtered off and the solvent was removed under reduced pressure (20°C, 10^{-3} mbar). The solid was extracted twice with 30 mL of EtOH. After acidifying the extracts with HCl the solvent was removed in vacuo. The residue obtained was dissolved in a mixture of 30 mL of MeOH and 10 mL of trimethyl orthoformate $HC(OMe)_3$ and the solution was heated at reflux for 18 h. All volatiles were stripped off in vacuo and the residue was extracted twice with 20 mL of CH_2Cl_2. Upon addition of 100 mL of petrolether 40/60 to

Table 4. Crystal and refinement data for $3 \cdot H_2O$

Chemical formula	$C_{18}H_{33}ClNiO_3P_4$	$F(000)$	1072
Formula weight	515.49	Crystal size (mm)	0.36×0.32×0.18
Space group	$P2_1/c$	2θ range (°)	2.30–25.06
a (Å)	15.691(4)	index range	0–18, 0–10, −21 to 19
b (Å)	9.134(3)	Reflections collected	4329
c (Å)	18.002(4)	Independent reflections	4169(R_{int}=0.0731)
β (°)	114.11(2)	Absorption correction	Semiempirical
V (Å^3)	2355.0(11)	Min./max. transmission	0.5195/0.6594
Z	4	Refinement methods	Full-matrix least squares on F^2
T (°C)	20	Data/restraints/parameters	4161/0/246
λ (MoK$_\alpha$) (Å)	0.71073	Final indices [$I>2\sigma(I)$]	R_1=0.0389; wR_2=0.0905
Crystal system	Monoclinic	R indices (all data)	R_1=0.0609; wR_2=0.1395
d_{calc} (g cm^{-3})	1.454	Largest diff. peak and hole (eÅ^{-3})	0.589/−0.291
μ (cm^{-1})	12.25		

the extract (concentrated to 20 mL in vacuo) a colorless solid was precipitated. In order to remove traces of HCl, the solid was dissolved in 20 mL of water and the solution was neutralized with 0.1N KOH. After evaporation of the solution in vacuo the solid was extracted with CH_2Cl_2. Removal of the solvent left a colorless powder. According to the elemental analysis, the product contained water and small quantities of KCl. Yield 2.64 g (88%). $\mathbf{6} \cdot 2H_2O$. Anal. Calcd. for $C_{19}H_{38}O_7P_4$ (M_r=502.4): C, 45.42; H, 7.62. Found: C, 45.02; H, 7.60.

Preparation of 8

(a) Reaction of 6 with thionylchloride. 2.37 g (4.72 mmol) of solid **6** (mixture of isomers) was added in small portions to excess thionylchloride (10 mL). Under a vigorous reaction, gas (SO_2) was evolved. When the evolution of gas ceased, the reaction mixture was stirred at ambient temperature for 18 h. Thionylchloride was then removed by evaporation in vacuo to leave a light brown solid which was washed twice with 10 mL of CH_2Cl_2. **7a** was characterized by $^{31}P\{1H\}$ NMR spectroscopy and transformation to the fluoro derivative **7b** by Cl/F exchange with NaF at 70°C using DMSO as the solvent (see text).

(b) Preparation of 8. To a suspension of 2.0 g (52.7 mmol) of $LiAlH_4$ in 200 mL of tetrahydrofuran 2.30 g of the product obtained under (a) were added during a period of 2 h and the reaction mixture was stirred at 20°C for 12 h. After addition of 50 mL of water a clear solution was formed. It was decanted from the solid materials. After extraction with 200 mL of ether the combined THF and ether solutions were evaporated to dryness. The solid obtained was washed twice with 10 mL of water and dissolved in 60 mL of ether. The solution was filtered and the solvent was distilled off in vacuo. The residue obtained was dried in vacuo (20°C, 10^{-3} mbar). Yield: 1.46 g (83%). **8**. Anal. calcd. for $C_{18}H_{32}P_4$ (M_r=372.3): C, 58.06; H, 8.66; P, 33.27. Found: C, 57.35; H, 8.49; P, 33.20; MS: *m*/*e* 371 (M^+-H); molecular weight (osmometrically, CH_2Cl_2): 376.

X-Ray crystallography

Important crystallographic details are listed in Tables 2–4. Experimental data for the X-ray structural analysis of $\mathbf{3} \cdot H_2O$ are collected in Table 4. Crystals of $\mathbf{3} \cdot H_2O$ were mounted in glass capillaries under argon. The measurements were made at 293 K with a Siemens P4/V diffractometer employing graphite filtered MoK$_\alpha$ radiation (λ=0.71073 Å). The structure was solved by using direct methods and refined by full-matrix least squares. In the final refinement cycles, all non-hydrogen atoms were refined anisotropically. The H atoms were included at geometrically calculated positions with isotropic displacement parameters. All calculations were carried out using the SHELXTL programs.[24]

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