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Development of a Series of $P(CH_2N{=}CHR)_3$ and Trisubstituted 1,3,5-Triaza-7-phosphaadamantane Ligands

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The synthesis and structure of a series of novel phosphine ligands derived from the condensation of $P(CH_2NH_2)$ with aldehydes are described. Depending on the reaction conditions, either substituted tris(iminomethyl)phosphine, $P(CH_2N{=}CHR)_3$, or 1,3,5-triaza-7-phosphaadamantane structures substituted at the "lower rim", $PTAR_3$, are obtained.

Our group,[1−5] and others,[6] have been interested in the coordination chemistry of the air-stable and water-soluble heterocyclic phosphine 1,3,5-triaza-7-phosphaadamantane (PTA).[7] Recent reports that ruthenium complexes of PTA have shown anticancer activity have created a resurgence of interest in this ligand.[8] A handful of PTA derivatives have appeared in the literature including alkylation of the phosphorus[9] or nitrogen[10] or modification of the triazacyclohexane ring.[11] A few "ring-opened" derivatives involving cleavage of either P−C or N−C bonds have also appeared (Figure 1).[9,12] We have recently reported a general methodology for the modification of the "upper rim" of PTA through lithiation of an α-carbon.[5]

Herein we report a general method for the modification of the "lower rim" of PTA, yielding phosphine derivatives in which the triazacyclohexane ring is trisubstituted. In addition to the synthesis of these ligands, the coordination chemistry and properties of the ligands are described.

Frank and Daigle reported in 1981 that the addition of concentrated HBr to PTA results in the formation of the triammonium salt $P(CH_2NH_3Br)_3$.[13] Careful addition of aqueous sodium hydroxide yields the free triammine $P(CH_2NH_2)_3$.[14] $P(CH_2NHAr)_3$ ligands have recently been utilized as trianionic triamidophosphine donors to early transition metals.[15]

We have utilized $P(CH_2NH_2)_3$ as a precursor to a series of trisubstituted triazaphosphaadamantane ligands. The cyclocondensation of various aldehydes with tris(aminomethyl)phosphine leads to the synthesis of PTA derivatives in which the lower rim of the ligand is trisubstituted. Depending on the reaction conditions and electronics of the aldehyde, either a tris(iminomethyl)phosphine or a triazaphosphaadamantane

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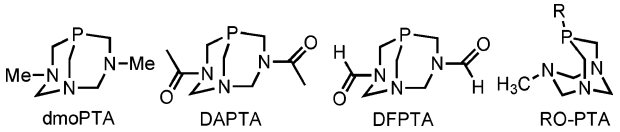
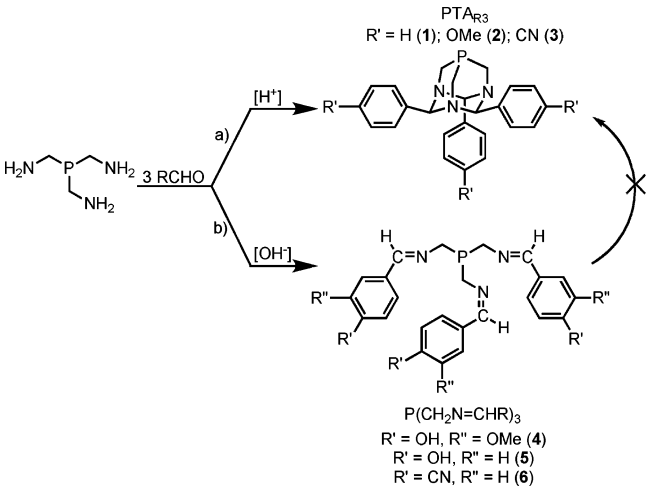


Figure 1. Examples of ring-opened PTA derivatives.

Scheme 1



structure is obtained. Under acidic conditions, condensation is followed by ring closure, yielding the heterocyclic ring triazaphosphaadamantane $PTAR_3$ (R = C_6H_5, C_6H_4OMe, C_6H_4CN; Scheme 1a).[16] However, under basic conditions, tris(iminomethyl)phosphine ligands are obtained from a 3-fold condensation reaction of the aldehyde with tris(aminomethyl)phosphine (Scheme 1b).[17] The tris(iminomethyl)phosphines cannot be converted into $PTAR_3$ ligands by heating or the addition of acid, leading us to conclude that the synthesis of $PTAR_3$ ligands occurs in a stepwise manner (condensation followed by nucleophilic attack and ring closure).

We have characterized these ligands by ^{31}P and ^{1}H NMR spectroscopy and X-ray crystallography. The two isomeric products may be quickly identified utilizing ^{31}P NMR spectroscopy. The $PTAR_3$ complexes exhibit ^{31}P NMR chemical shifts at approximately −110 ppm, upfield of PTA (−97 ppm, $CDCl_3$), whereas the $P(CH_2N{=}CHR)_3$ compounds exhibit ^{31}P NMR chemical shifts between −18 and −25 ppm (Table 1). The tris(iminomethyl)phosphines are somewhat air-sensitive relative to the cage compounds, forming phosphine oxide over the course of a day in solution or a few days in the solid state.

Table 1. ^{31}P NMR Data for $PTAR_3$ and $P(CH_2N{=}CHR)_3$

R group	$^{31}P\{^{1}H\}$ NMR	% yield
	$PTAR_3$	
C_6H_5 (**1**)	−111.6[a]	69
C_6H_4OMe (**2**)	−112.1[a]	67
C_6H_4CN (**3**)	−110.9[a]	41
	$P(CH_2N{=}CHR)_3$	
$C_6H_3(OH)(OMe)$ (**4**)	−23.7[b]	70
C_6H_4OH (**5**)	−23.1[c]	55
C_6H_4CN (**6**)	−18.1[a]	65

[a] In $CDCl_3$. [b] In DMSO-d_6. [c] In CD_3OD.

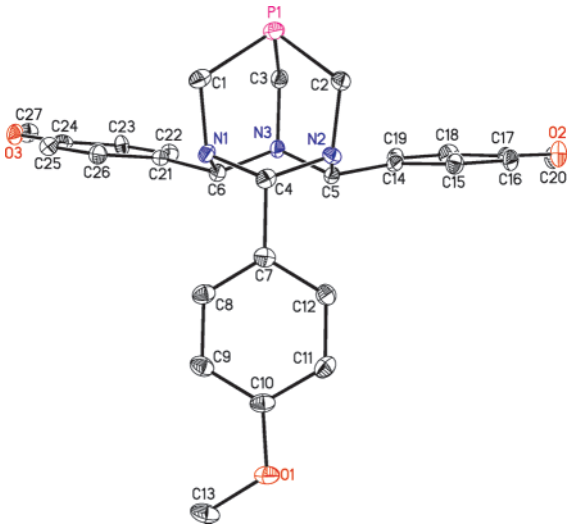


Figure 2. Thermal ellipsoid plots (50% probability) showing the molecular structures of **2**. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): P−C_{ave} = 1.863(2), N−C_{ave} = 1.480(3), C4−C7 = 1.525(3), C5−C14 = 1.514(3), C6−C21 = 1.526(3), C−P1−C = 95.61(11)°.

The substitution pattern of the triazacyclohexane ring is consistently two equatorial and one axial substituent (R), when R = aryl. Density functional theory calculations on the various possible isomers of $PTAR_3$ (e.g., eee, eea, eaa, and aaa) reveal that the eea isomer observed is indeed the lowest in energy by ∼3 kJ/mol relative to the next lowest energy isomer (eee).[18] NMR spectroscopy shows only one isomer present in solution, and based on X-ray crystallography, it is only the eea isomer that is isolated. Figure 2 contains a thermal ellipsoid representation of the anisole derivative of $PTAR_3$, including selected bond lengths and angles.[19] Crystals of the triiminophosphine derived from vanillin (4-hydroxy-3-methoxybenzaldehyde) have also been obtained (Figure 3).[19]

(16) General procedure for the synthesis of $PTAR_3$ ligands. Tris(aminomethyl)phosphine trihydrobromide (1.819 g, 5.0 mmol) and sodium hydroxide (600 mg, 15 mmol) were added to a 100 mL Schlenk flask in a drybox. Freshly distilled methanol (50 mL) was added via syringe, resulting in a clear solution. Hydrogen chloride (2.0 M) in Et_2O (50 μL, 0.10 mmol) and the appropriate aldehyde (25 mmol) were added to the flask and the reaction stirred overnight under nitrogen. The solvent was removed under reduced pressure, resulting in a white solid. Methylene chloride (100 mL) was added to the residue and the solution washed with water (2 × 50 mL). The organic layer was dried over anhydrous potassium carbonate and filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from a minimum of CH_2Cl_2 (5 mL), followed by the addition of 120 mL of absolute ethanol and storage at −5 °C overnight. The product was collected as a white crystalline solid in 40−70% yield, following two washings with 15 mL of ethanol and drying under vacuum.

(17) General procedure for the synthesis of tris(iminomethyl)phosphine ligands, $P(CH_2N{=}CHR)_3$. Tris(aminomethyl)phosphine trihydrochloride (461 mg, 2.0 mmol) and sodium hydroxide (240 mg, 6 mmol) were dissolved in 40 mL of freshly distilled methanol, resulting in a clear solution. After stirring for 30 min, the solvent was removed and the residue dissolved in 7 mL of CH_2Cl_2 and filtered to remove NaCl. CH_2Cl_2 was removed under vacuum and the residue dissolved in 40 mL of methanol. Sodium hydroxide (15 mg, 0.37 mmol) and the appropriate aldehyde (10 mmol) were added to the solution. The resulting mixture was stirred overnight and the solvent removed under vacuum. The residue was recrystallized at −5 °C from either THF or $CHCl_3$ and diethyl ether. The product was obtained as a yellow solid in 55−70% yield, following washing with diethyl ether (2 × 10 mL) and drying under vacuum. This proceeds well with the bromide salt, $P(CH_2NH_3Br)_3$; however, for separation reasons, the chloride salt, $P(CH_2NH_3Cl)_3$, is preferred.

(18) Calculations were performed on optimized structures using the LANL2DZ basis set at the B3LYP level of theory as implemented in *Gaussian03*.

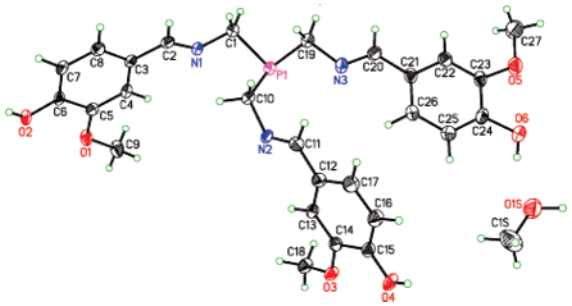


Figure 3. Thermal ellipsoid plots (50% probability) showing the molecular structures of **4**. Selected bond lengths (Å) and angles (deg): P−C_{ave} = 1.857(3), N1−C2 = 1.278(3), N2−C11 = 1.304(3), N3−C20 = 1.274(3), C1−P1−C19 = 97.88(12), C10−P1−C19 = 100.41(13)m C1−P1−C10 = 98.02(12).

Table 2. Spectroscopic, ^{31}P NMR and ν(CO), Data for *trans*-ClRh(PTAR$_3$)$_2$CO Compounds in $CHCl_3$, Where R = H and PTAR$_3$ = PTA

Rh(CO)Cl(PR$_3$)$_2$	^{31}P{^{1}H} NMR	$^1J_{P-Rh}$ (Hz)	ν(CO) (cm^{-1})
PR$_3$ = PPh$_3$[20,22]	−29.6	129	1979
PR$_3$ = P(CH$_2$OH)$_3$[23]	10.8	117	1960
PR$_3$ = PTAR$_3$			
R = H[23]	−60.1	127	1963
R = C_6H_5 (**7**)	−54.4	117	1979
R = C_6H_4OMe (**8**)	−55.3	117	1978
R = C_6H_4CN (**9**)	−54.4	121	1987

Modification of the triazacyclohexane ring of PTA is interesting because it affords the ability to alter the sterics of the phosphine while making minimal changes to the electronics. Comparison of ν(CO) for a series of *trans*-Rh(CO)Cl(PTAR$_3$)$_2$ complexes indicates that these ligands are similar electronically (Table 2). The PTAR$_3$ ligands (**1**−**3**) are less electron-donating than PTA. When R = C_6H_5 (**1**) or C_6H_4OMe (**2**), the electronic parameter is similar to that of PPh$_3$ [ν(CO) = 1979 cm^{-1}];[20] however, when R = C_6H_4-CN (**3**), the ligand is significantly less electron-donating (Table 2). Of interest is that the steric bulk of the PTAR$_3$ ligands is some distance from the phosphorus and, therefore, any metal center. For example, the *trans*-PdCl$_2$(PTAR$_3$)$_2$ complex synthesized by the reaction of PdCl$_2$(COD) with 2 equiv of PTAR$_3$ yields compound **10**, depicted in Figure 4. We have examined the steric demand of the PTAR$_3$ and triimine ligands utilizing the *Solid G* program developed by Guzei and Wendt.[21] Not surprisingly, θ for the PTAR$_3$ ligands (112° for **2**) is somewhat larger than that for PTA (θ = 105°; Table 3).

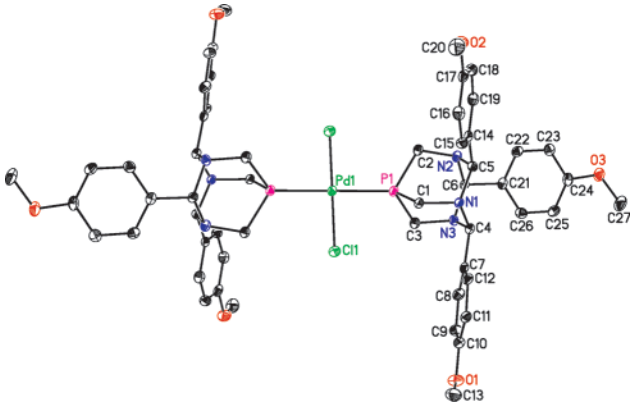


Figure 4. Thermal ellipsoid plots (50% probability) showing the molecular structures of **10**. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd1−P1 = 2.2980(9), Pd1−Cl1 = 2.2983(9), P−Pd−P = 180.00(3), Cl−Pd1−Cl1 = 180.00(3), P1−Pd1−Cl1 = 87.68(3).

Table 3. Cone Angle and Percentage of Sphere Coverage by the PTAR$_3$ and P(CH$_2$N=CHR)$_3$ Ligands As Calculates by *Solid G*[21]

	θ^a	%^{b}		θ^a	%^{b}
PTA	105	19.6	**2**	112	21.9
PMe$_3$[c]	111	21.8	**4**	149	36.5
PPh$_3$[c]	128	28.1			

[a] *Solid G* cone angle (deg). [b] Percentage of metal shielded by the ligand. [c] See ref 24.

In conclusion, we have reported here the first example of substitution of the N−CH_2−N methylenes of PTA. The modifications described have led to an interesting series of phosphine ligands in which the cone angle is large yet near the metal center the ligand is sterically similar to the parent PTA ligand. We are currently exploring the scope of the ligand synthesis and further details of the properties of the ligands.

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Supporting Information Available: Detailed experimental procedures, crystallographic details in CIF format, and NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) X-ray diffraction data were collected at 100 (±1) K on a Bruker APEX CCD diffractometer with Mo Kα radiation (λ = 0.710 73 Å) and a detector-to-crystal distance of 4.94 cm. Data collection was optimized utilizing the APEX 2 software suite. Data integration, correction for Lorentz and polarization effects, and final cell refinement were performed using *SAINT+* and corrected for absorption using *SADABS* as implemented within the APEX 2 software. Structures were solved using direct methods, followed by successive least-squares refinement on F^2. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were located on the difference map for each structure or refined in idealized positions using a riding model. Crystallographic details may be found in Table 1-S of the Supporting Information. A complete list of bond lengths and angles as well as all calculated atomic coordinates and anisotropic thermal parameters may be obtained from the Cambridge Crystallographic Data Centre. Crystal data for compound **2** (CCDC 661303): $C_{27.50}H_{30}N_3O_3P$, MW = 516.96, triclinic, *P*1̄, *Z* = 2, *a* = 7.0594(3) Å, *b* = 10.9914(5) Å, *c* = 17.0315(7) Å, α = 76.0650(10)°, *β* = 86.2170(10)°, *γ* = 74.0730(10)°, *V* = 1233.39(9) Å^3, 15 186 reflections, 4568 independent reflections (R_{int} = 0.0410), R1 = 0.0450, and wR2 = 0.1024. Crystal data for compound **4** (CCDC 661305): $C_{28}H_{34}N_3O_7P$, MW = 555.55, triclinic, *P*1̄, *Z* = 2, *a* = 9.7133(6) Å, *b* = 11.2111(7) Å, *c* = 13.3168(8) Å, α = 99.750(4)°, *β* = 97.639(4)°, *γ* = 100.634(4)°, *V* = 1384.34(15) Å^3, 21 006 reflections, 5149 independent reflections (R_{int} = 0.0620), R1 = 0.0506, and wR2 = 0.01204. Crystal data for compound **10** (CCDC 661304): $C_{56}H_{64}N_6O_6Cl_6P_2Pd$, MW = 1298.17, monoclinic, *P*2(1)/*c*, *Z* = 2, *a* = 14.7270(3) Å, *b* = 22.0291(4) Å, c = 8.75330(10) Å, α = 90°, *β* = 98.8130(10)°, *γ* = 90°, *V* = 2806.24(8) Å^3, 28 103 reflections, 6452 independent reflections (R_{int} = 0.0727), R1 = 0.0479, and wR2 = 0.1126.

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