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Diastereomerically Enriched Analogues of the Water-Soluble Phosphine PTA. Synthesis of Phenyl(1,3,5-triaza-7-phosphatricyclo[3.3.1.1^{3,7}]dec-6-yl)methanol (PZA) and the Sulfide PZA(S) and X-ray Crystal Structures of the Oxide PZA(O) and [Cp*IrCl$_2$(PZA)]

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A diastereomerically enriched analogue of 1,3,5-triaza-7-phosphaadamantane (PTA) was obtained by the reaction of PTA lithium salt with benzaldehyde to give the water-soluble derivative phenyl-(1,3,5-triaza-7-phosphatricyclo[3.3.1.1^{3,7}]dec-6-yl)methanol (PZA, **1**) as a mixture of two diastereoisomers. PZA derivatives phenyl-(1,3,5-triaza-7-phospha-tricyclo[3.3.1.1^{3,7}]dec-6-yl)methanol sulfide [PZA(S), **2**] and oxide [PZA(O), **3**] were also synthesized. The latter was isolated in the solid state, and the X-ray crystal structure of a single diastereoisomer was obtained. Compound **1** was used as a k^1-P monodentate ligand toward iridium(III) moieties, and the piano-stool complex [Cp*IrCl$_2$(PZA)] (**4**) was obtained as a mixture of diastereoisomers both in solution and in the solid state.

During the past few years, there has been a renewed interest in the use of the neutral water-soluble cage monodentate phosphine 1,3,5-triaza-7-phosphaadamantane (PTA)[1] and its structural modifications, as witnessed by the work of many groups in various fields of applications.[2] PTA has a small cone angle (103°) comparable to that of PH_2Me, with the advantage being that it is solid, less toxic, and air-stable, hence easier to handle. Its high water solubility (ca. 253 g/L) makes it an ideal ligand to bring metal and organometallic fragments into the water phase. The renaissance of PTA as a water-soluble ligand has resulted in a large number of coordination compounds being synthesized very recently and their catalytic,[3] medical,[4] and electrochemical properties[5] being investigated, together with mechanistic aspects of Ru-PTA-mediated hydrogen activation in water.[6]

Modifications of the PTA frame have so far been focused on either alkylation at P or N atoms[7,8] or opening of the cage to yield potentially bidentate P,N[9] or tridentate P,N,N[10] derivatives of PTA. Most of these structural changes are relatively far from the coordinating P atom and thus unlikely to impart significant stereoelectronic effects often required for chemo- or enantioselective catalytic applications and for fine-tuning of biological effects in the design of hydrosoluble

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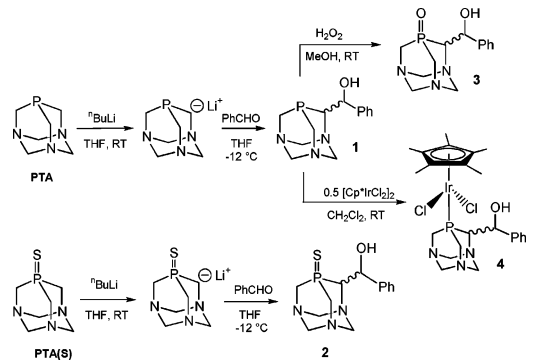
Scheme 1 Syntheses of **1**−**4**



metal-based drugs. Therefore, there is an interest in developing chiral PTA derivatives that are substituted at the methylene groups bridging P and N atoms.

An interesting PTA derivative introducing a binding arm and a chiral center on the C_α to P was obtained by Wong et al. by the reaction of PTA with *n*-BuLi and $ClPPh_2$, resulting in the bidentate phosphine PTA-PPh_2.[11] Although this ligand is not soluble in water and the racemic mixture was not resolved, the method opens for the synthesis of a new class of chiral PTA-based ligands. Herein we present the synthesis of a novel water-soluble multifunctional P,O ligand with two chiral centers, i.e., phenyl(1,3,5-triaza-7-phospha-tricyclo-[3.3.1.1^{3,7}]dec-6-yl)methanol (PZA, **1**), together with the corresponding sulfide [PZA(S), **2**] and oxide [PZA(O), **3**]. In order to test the coordination ability of this ligand, the iridium(III) complex (k^1-P)-[Cp*$IrCl_2$(PZA)] (**4**) was synthesized and its X-ray crystal structure was determined, together with that of **3**.

Ligands **1** and **2** were straightforwardly prepared by reacting benzaldehyde with the lithium salts of PTA[11] and PTA(S),[12] respectively, while **3** was obtained by oxidizing **1** using aqueous H_2O_2 (35%), as for PTA(O).[13] Finally, complex **4** was prepared by reacting **1** with the dimer [Cp*IrCl(μ-Cl)]$_2$[14] in CH_2Cl_2, as shown in Scheme 1 (see the Supporting Information for details). The synthesis of **1** results in a racemic mixture (1:1) of two diastereoisomers, as expected from the presence of two chiral centers, and is confirmed by the $^{31}P\{^1H\}$ NMR spectrum in D_2O, which consists of two singlets at −103.4 and −106.6 ppm in a 1:1 ratio slightly upfield shifted with respect to PTA (−96.2 ppm).

The formation of a pair of diastereoisomers is also evident in the case of **2** showing $^{31}P\{^1H\}$ NMR singlets (deuterated dimethyl sulfoxide, DMSO-d_6) at −10.5 ppm (21.9%) and −14.1 ppm (78.1%), similar to PTA(S) (−20.01 ppm).[12] In the case of **3**, the oxidation of PZA was monitored by $^{31}P\{^1H\}$ NMR in D_2O. Two singlets at 1.99 and 1.41 ppm in an approximate 1:1 integration ratio were observed soon after the reaction was started, and no remaining PZA could be detected. After 5 min, the formation of a white precipitate was observed, accompanied by a decrease of the intensity of the high-field singlet, to reach a final ratio of 1:0.76 in solution at room temperature. The precipitate was filtered, dried, and redissolved in DMSO-d_6. The $^{31}P\{^1H\}$ NMR spectrum (−3.38 ppm, s) indicates that the precipitate contains only the most insoluble diastereoisomer.

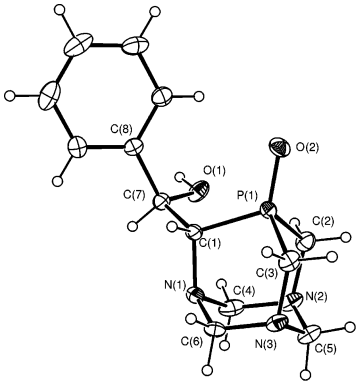


Figure 1. Asymmetric units of (*R*,*S*-*S*,*R*)-**3**. Ellipsoids are shown at 30% probability.

Gas chromatography−mass spectrometry (MS) data of **1**−**3** reveal peaks corresponding to the parent cations at *m*/*z* = 263 for **1**, 295 for **2**, and 279 for **3**, respectively. The electrospray ionization (ESI)-MS analysis of **4** indicates the presence of the cationic species [Cp*IrCl(PZA)]$^+$ (*m*/*z* = 628). The IR spectra of **2** and **3** (KBr pellets) show the presence of the P═O and P═S groups with bands at 1153 and 610 cm^{-1}, respectively, which compare well to those of PTA(O) (1167 cm^{-1})[15] and PTA(S) (629 cm^{-1}).[15b]

Compound **1** shows remarkably high water solubility ($S_{20\ °C}$ = 1.05 g mL^{-1}), about 4 times more soluble than PTA.[2] PZA dissolves also in MeOH, EtOH, and chlorinated solvents and is poorly soluble in tetrahydrofuran. Compound **2**, on the other hand, is much less soluble in water, alcohols, and chlorinated solvents but soluble in DMSO, while one diastereoisomer of **3** is only sparingly soluble in DMSO and precipitates from water solutions (vide supra). The iridium complex **4** is only sparingly soluble in water ($S_{20\ °C} = 1.8 \times 10^{-3}$ g mL^{-1}), as is the corresponding PTA complex [Cp*$IrCl_2$(PTA)] ($S_{20\ °C} = 2.2 \times 10^{-3}$ g mL^{-1}).[16] Slow concentration of a methanol solution of **1** in air resulted in crystals suitable for X-ray diffraction analysis. The compound isolated in the solid state turned out to be the oxide **3**, as shown in Figure 1. This suggests that **1** is more sensitive to oxidation than PTA, in agreement with findings by Wong

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et al.,[11] who observed that the bidentate phosphine ligand PTA-PPh_2 was slowly oxidized over time in a CH_2Cl_2 solution. The X-ray crystal structure of **3** shows that only the *R,S-S,R* diastereoisomer is present in the asymmetric unit. By dissolution of a few crystals in DMSO-d_6, it was possible to confirm that it corresponds to the species with a $^{31}P\{^1H\}$ NMR singlet at −3.38 ppm.

In the molecular structure of (*R,S-S,R*)-**3**, the P atom is tetrahedrally bound to three C atoms and one O atom with O−P−C angles [ave 116.8(3)°] larger than the C−P−C ones [ave 101.2(3)°; Figure 1].[17]

The P═O oxygen forms a strong intermolecular hydrogen bond with the hydroxyl group of a neighboring PZA(O) molecule [O(1)···O(2)#1 distance = 2.717(6) Å].[18] As a consequence of this intramolecular hydrogen bonding, a 1D infinite chain parallel to the *b* axis is formed (Figure S1 in the Supporting Information), which could account for the poor solubility of this diastereoisomer. This weak solid-state interaction lengthens the P(1)−O(2) distance [1.490(1) Å] in **3** of ca. 0.02 Å more than the P−O distances of oxides of PTA and derivatives previously described in the literature.[7b,15b,19] For the latter compounds, the O atom is not involved in hydrogen bonding. The P(1)−C(1) and C(1)−N(1) [1.833(6) Å and 1.502(6) Å, respectively] bonds belonging to the upper rim of PZA(O) are slightly longer than the corresponding P(1)−C(2), P(1)−C(3) and C(2)−N(2), C(3)−N(3) bonds [ave 1.813(6) and 1.489(7) Å, respectively] of PTA.[15b] Crystals of **4**, suitable for X-ray diffraction analysis, were obtained by slow concentration of a dichloromethane/ethanol solution of **4** (Figure 2).[20] The X-ray analysis reveals the P coordination of the PZA ligand, with the Ir atom coordinated octahedrally by the two chloride ligands and the Cp* ring occupying three contiguous sites of the coordination polyhedron. In a CD_2Cl_2 solution, the $^{31}P\{^1H\}$ NMR spectrum shows two singlets of comparable intensity at −59.3 and −72.3 ppm, indicating that both diastereoisomers are present as observed in the solid state. The hydroxyl group is disordered over two sites, with an occupancy of 51.6%. There are evident intramolecular hydrogen bonds between Cl(2) and the disordered hydroxyl group [O(1a)−Cl(2) = 3.319(6); O(1b)−Cl(2) = 3.112(6) Å].

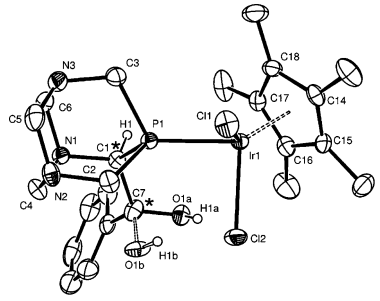

Figure 2. ORTEP diagram of **4**. Ellipsoids are shown at 30% probability. The hydroxyl group is disordered over two sites with an occupancy of 51.6% for O(1a). Only the H atoms involved in the hydrogen bonds or bonded to the stereocenter C(1) are shown.

The presence of such hydrogen bonds influences the Cl(2)−Ir(1) distance as well as the length of the Ir(1)−P(1) bond. We have recently described[16] the X-ray crystal structure of [Cp*$IrCl_2$(PTA)] (**5**), whose structural parameters can be compared to those belonging to **4**. In **5**, the Ir−Cl distances are both 2.418(4) Å, while in **4**, Ir(1)−Cl(1) is 2.4127(10) Å and Ir(1)−Cl(2) is slightly longer at 2.4273(10) Å. The Ir−P bond is 2.2971(9) Å in **4**, and it has to be compared with 2.274(3) Å of **5**. On the contrary, the Cp*(centroid)−Ir distance is 1.8187(16) Å in **4**, while in **5**, it is 1.812(5) Å. Also, the adamantane cage in **4** is more asymmetric than that in **5**, and in particular the P(1)−C(1) bond is 0.01 Å longer than the other two P−C bonds.

The synthesis of **1** represents an important step toward the full exploitation of the synthetic protocol for the functionalization of the "upper rim" of PTA. Work aiming at the resolution of PZA and the synthesis of other enantiomerically pure water-soluble PTA derivatives and at their applications in both enantioselective catalysis and biological applications is in progress.

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Supporting Information Available: General methods, syntheses, and NMR data for **1**−**4**, Figure S1, and X-ray crystallographic files in CIF format for **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Summary of the crystallographic data for **3**: $C_{13}H_{18}N_3O_2P$, M_w = 279.27, monoclinic, $P2_1/c$, a = 10.485(3) Å, b = 11.337(4) Å, c = 11.004(5) Å, β = 97.97(3)°, V = 1295.4(8) Å^3, Z = 4, ρ_{calc} = 1.432 Mg/m^3; μ = 0.214 mm^{-1}, F(000) = 592, crystal size = 0.50 × 0.50 × 0.05 mm^3, collected/unique = 2408/2277 [R(int) = 0.0587], R1 = 0.0787, wR2 = 0.1391 [$I > 2\sigma(I)$]; R1 = 0.1930, wR2 = 0.1708 (all data). The data collection was performed at room temperature on an Enraf Nonius CAD4 diffractometer equipped with a graphite monochromator and Mo Kα radiation. Selected bond distances (Å) and angles (deg): P(1)−O(2), 1.490(4); P(1)−C(1), 1.833(6); P(1)−C(2) 1.808(6); P(1)−C(3), 1.818(5); N(1)−C(1), 1.502(6); N(1)−C(4), 1.469(8); N(1)−C(6), 1.468(7); N(2)−C(2), 1.493(7); N(2)−C(4), 1.457(8); N(2)−C(5), 1.461(8); N(3)−C(3), 1.485(7); N(3)−C(5), 1.461(8); N(3)−C(6), 1.455(7); C(1)−C(7), 1.527(7); O(2)−P(1)−C(1), 117.7(2); O(2)−P(1)−C(2), 117.7(3); O(2)−P(1)−C(3), 115.0(2); C(1)−P(1)−C(2), 103.7(3); C(1)−P(1)−C(3), 100.0(3); C(2)−P(1)−C(3), 100.0(3); C(1)−N(1)−C(4), 112.3(4); C(1)−N(1)−C(6), 111.4(4); C(2)−N(2)−C(4), 110.0(4); C(2)−N(2)−C(5), 110.7(5); C(3)−N(3)−C(5), 110.0(5); C(3)−N(3)−C(6), 109.8(4); C(4)−N(1)−C(6), 108.4(5); C(4)−N(2)−C(5), 109.3(5); C(5)−N(3)−C(6), 108.3(5).

(18) The symmetry transformation used to generate the equivalent atom is as follows: #1, $-x + 1$, $y + 1/2$, $-z + 1/2$.

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(20) Summary of the crystallographic data for **4**: $C_{23}H_{33}Cl_2IrN_3OP$, M_w = 661.59, monoclinic, $P2_1/c$, a = 8.87890(17) Å, b = 13.626(2) Å, c = 20.3750(4) Å, β = 90.4071(18)°, V = 2465.0(4) Å^3, Z = 4, ρ_{calc} = 1.783 Mg/m^3, μ = 5.719 mm^{-1}, F(000) = 1304, crystal size = 0.40 × 0.20 × 0.20 mm^3, collected/unique = 16383/7502 [R(int) = 0.0294], absorption correction = Ψ scan, R1 = 0.0292, wR2 = 0.0557 [$I > 2\sigma(I)$]; R1 = 0.0600, wR2 = 0.0671 [all data]. The data collection was performed at room temperature on an Oxford Diffraction Excalibur 3 diffractometer equipped with Mo Kα radiation. Selected bond distances (Å) and angles (deg): Ir(1)−P(1), 2.2971(9); Ir(1)−Cl(1), 2.4127(10); Ir(1)−Cl(2), 2.4273(10); Ir(1)−Cp*(centroid), 1.8187(16); P(1)−C(1), 1.864(4); P(1)−C(2), 1.853(4); P(1)−C(3), 1.837(4); O(1a)−Cl(2), 3.319(6); O(1b)−Cl(2), 3.112(6); P(1)−Ir(1)−Cl(1), 85.55(4); P(1)−Ir(1)−Cl(2), 88.70(4); Cl(1)−Ir(1)−Cl(2), 89.38(4); P(1)−Ir(1)−Cp*(centroid), 133.20(4); Cl(1)−Ir(1)−Cp*(centroid), 123.49(4); Cl(2)−Ir(1)−Cp*(centroid), 123.38(4).