The Characterization and Synthesis of 1,3-Xylyl 18-Crown-5 Functionalized in the 5 Position With Diphenylphosphine

An Honors Thesis (HONRS 499)

by

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ABSTRACT

1,3-Xylyl-18-crown-5 functionalized on the 5 position of the benzene ring with diphenylphosphine (5-diphenylphosphino-1,3-xylyl-18-crown-5) was synthesized in a three step reaction scheme yielding 1.82% (1.53 g) of pure product. The first step involved a free radical reaction between bromo-m-xylene and N-bromosuccinimide to produce pure 5-bromo-1,3-bis-(bromomethyl)benzene in 28.32% (14.56 g) yield after recrystallization in cyclohexane. The second step involved forming the carbanions by reacting tetraethylene glycol with sodium hydride and reacting this intermediate with 5-bromo-1,3-bis-(bromomethyl)benzene. Following a purification procedure that involved forming the sodium salt of the crown ether, the resulting product was 5-bromo-1,3-xylyl-18-crown-5 in 17.98% (2.33 g) yield. Finally, 5-diphenylphosphino-1,3-xylyl-18-crown-5 was prepared by first using a bromine-lithium exchange reaction involving n-butyl lithium and 5-bromo-1,3-xylyl-18-crown-5 which formed an intermediate that was subsequently reacted at low temperatures with chlorodiphenylphosphine. Purification was accomplished using flash quality silica gel with ethyl acetate as the mobile phase. Carbon and hydrogen analysis of the purified compound confirmed the formula C_{28}H_{43}O_{3}P with 0.75 H_{2}O complexed with the final product.

Infrared spectroscopic studies of the nickel carbonyl complex of this phosphine (Ni(CO)_{3}L) showed a slight decrease (0.2 cm^{-1}) in the vCO frequency as compared to triphenylphosphine. This result indicates that this new phosphine is a slightly better donor than triphenylphosphine towards nickel carbonyl. The addition of alkali metal ions to the Ni(CO)_{3}L complex resulted in increases in the vCO values with lithium ion causing the greatest increase, 0.8 cm^{-1}. This last result indicates that the phosphorus donor ability of this new phosphine can be tuned from approximately the equivalent of, to considerably less than, that of triphenylphosphine.
ACKNOWLEDGEMENTS

I would like to extend a very special thanks to Dr. Bruce N. Storhoff for his assistance and guidance not only on my honors' thesis, but throughout my undergraduate career as a professor and friend. He has been a source of tremendous patience and understanding during difficult times.

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Furthermore, I would like to thank the Ball State Chemistry Department and faculty for always supporting my educational endeavors and allowing me to use their facilities for this project.
INTRODUCTION

In the early 1960s, Charles Pedersen discovered a group of cyclic ethers, commonly known as crown ethers [1]. They are usually named according to the format, x-crown-y, where x is the total number of atoms in the ring and y is the number of oxygen atoms. 18-Crown-6 is a cyclic Lewis base capable of donating electron density to metals through its oxygen atoms, thereby surrounding, or trapping, cations including alkali metals, in the center of the polyether cavity. Different crown ethers solvate different metal cations, depending on the match between ion size and cavity size. Considering 18-crown-6, there is a good match between this cavity and a potassium ion [2].

A second, softer type of Lewis base is the tertiary phosphine. Phosphines of this type (PR₃) are unique in that their electronic and steric properties can be altered in a systematic and predictable way by varying R [3]. They can also stabilize a wide variety of metal complexes of the general type (R₃P)ₙML (L=other ligands such as Cl). Tertiary phosphines have a lone pair of electrons on the central atom that can be donated to a metal. In general terms, the donor abilities, or basicities, of the phosphines parallel the donor abilities of the R groups. For example, the pKₐ values for PMe₃ and PPh₃ are reported to be 8.65 and 2.73, respectively, from data obtained by titrating these phosphines with perchloric acid in nitromethane [4]. The validity of this statement regarding donor abilities can also be seen from the νCO values of complexes with the ligand R₃PNi(CO)₃ [5].

Hybrid ligands containing both phospine and crown ethers have the potential for several unique properties. In M(P-crown)ₓ(CO)ᵧ systems, for example, crown complexed alkali metal ions might
activate the CO groups through crown-complexed alkali-metal-to-CO oxygen interactions. Also, the organization of anions involved in reactions catalyzed by phosphine complexes could be assisted by cations complexed in tethered crown ethers. Furthermore, the structure of crown ether groups provides organized and localized ether solvent environments that help catalyst systems in which hard donor sites serve as hemilabile ligands or in systems where a substantial level of solvent organization is needed in the vicinity of a catalytic center. Finally, phosphine-crown ether complexes have been shown to lend phase-transfer qualities to complexes.

To date, the chemical properties of only three crown ether phosphine molecules have been studied to some extent vide infra. Several other compounds of this type have been synthesized and characterized, but not studied. Given the potential for interesting chemical behavior for these compounds, we elected to prepare and study a new type of molecule, I, that will extend the range of known phosphine-crown systems.

LITERATURE REVIEW

In 1982, the first extensively studied phosphine azacrown ether was synthesized by Stephan J. McLain [6]. Aza crowns of type II are elementary in design. The carbon chain between the nitrogen and phosphorus forms a flexible linkage for the crown ether ring. Also, the -CH₂-groups prohibit direct orbital coupling and buffer the electron effect between the aza crown ether and the phosphorus. Within the patent for this molecule, McLain argues that the rate of propylene hydroformylation reactions (CH₃CHCH₂ + CO + H₂) catalyzed by rhodium or cobalt compounds in the
presence of this phosphine azacrown ether is promoted by the presence of alkali metal ions, which interact with the CO oxygen. For example, when the diphenylphosphine (m=1, n=2) was used, the presence of NaPF₆ increased the rate of reaction by a factor of five.

Extensive studies have also been conducted on ferrocenylphosphine ligands modified by monoaza crown ethers of type III [7]. They are extremely complex molecules containing a chiral carbon. Like the previous azacrown ether, the \(-\text{CH}_2\)- chain between the nitrogens provides flexibility to the compound. When this phosphine ligand was modified by monoaza-18-crown-6 and a palladium complex, a \(\pi\)-allylpalladium complex chelated by the two phosphorus atoms was formed, leaving the crown ether portion free. Studies suggest that the aza crown ether can interact with an incoming nucleophile. Therefore, palladium catalysts based on type III have been examined for stereoselectivity and catalytic activity in the allylation of substituted \(\beta\)-diketones using potassium fluoride as an insoluble base in mesitylene. The ligands bearing monoaza-18-crown-6 with an appropriate length of linker chain significantly accelerated the rate of allylation. High enantioselectivity (up to 75% ee) was also observed and is attributed to a ternary complex containing a crown ether, a potassium ion and an enolate anion which attack the \(\pi\)-allylpalladium(II) intermediate.

Most recently, a new class of aza crown ethers functionalized with phosphites have been synthesized and characterized [8]. Type IV compounds are very complex molecules based on two
phosphorus atoms and four crown ether molecules. The molecule also has four optically active carbons, and overall it has C$_2$ symmetry. As seen in the previous two examples, some flexibility exists within the compound due to the -CH$_2$- groups, which also prevent direct orbital coupling between the crown ethers and the phosphorus centers. This molecule is the only example containing more than one crown ether per binding center. It combines with rhodium carbonyl complexes to form active hydroformylation catalysts. As seen in Scheme 1, the hydroformylation reaction conditions are a 1:1 mixture of phosphite IV and Rh(acac)(CO)$_2$ dissolved in CH$_2$Cl$_2$ added to styrene in the presence of CO and H$_2$ at 35°C in pressure bottles. Rates and selectivities for hydroformylation reactions are similar to those of other tartrate-derived diphosphites. It was suggested that future studies using the compound would involve experiments to help understand how secondary interactions between crown ethers in complexes of functionalized alkenes can play a role during catalytic processes such as hydrogenation.

A number of other compounds have been prepared and characterized, but they have not been studied extensively. A series of crown ether-modified phosphines of Type V have been synthesized [9]. Picate extractions show 1:1 stoichiometric crown-type complexes with sodium and potassium. When combined with [RhCl(cod)]$_2$, these phosphines show high activities toward catalytic hydrogenation of potassium and cesium cinnamates. Also, when combined with (π-C$_3$H$_5$PdCl)$_2$, these phosphines catalyze the reaction of allyl bromide with powdered sodium or potassium iodide in benzene to give allyl iodide.
Type VI compounds are aminomethylphosphines [10]. Their synthesis involves treatment of 4'-aminobeno-15-crown-5 with diphenylphosphine in the presence of formaldehyde or with the phosphonium salt [Ph₂P(CH₂OH)₂]Cl in the presence of triethylamine. Their nickel(II), palladium(II), and platinum(II) complexes have also been synthesized.

Type VII compounds and their rhodium complexes have been synthesized [11]. These phosphorus crown ethers can solubilize lithium cations into chloroform, and the oxide macrocycles also solubilize sodium cations. tert-Butyl-phosphadibenzo-18-crown-6 complexes the sodium cation, yet phenylphosphadibenzo-18-crown-6, whose cavity is about the same size, does not.

Finally, Type VIII compounds have been synthesized [12]. All of the systems have the abilities to extract sodium and potassium ions comparably to benzo-15-crown-5. IR studies indicate that the azacrown systems (VIII) have better ability than the benzocrown systems (V) to increase the electron density on the nickel center. An X-ray structure of the phosphine oxide of the phenylaza-15-crown-5 derivative demonstrates that the nitrogen atom is essentially planar so that the macrocyclic ring is large and not organized for coordination with spherical ions.
EXPERIMENTAL

Reagents and Materials

N-bromosuccinimide (NBS), 5-bromo-\textit{m}-xylene, tetraethylene glycol, sodium hydride, butyl lithium, and chlorodiphenylphospine were obtained from Aldrich Chemical Company, Inc. The NBS was recrystallized prior to use. The chlorodiphenylphosphine and the tetraethylene glycol were distilled prior to use. The other reagents and solvents were obtained from departmental supplies. The THF was distilled from sodium benzophenone ketyl prior to use.

Methods and Instruments

During and following the butyllithium reaction, reactions and purifications were carried out under a blanket of argon. IR and NMR spectra were recorded on Nicolet 5ZDX and Varian Gemini-200 instruments, respectively. The 5ZDX IR instrument was calibrated with solutions of Ni(CO)$_3$PPh$_3$ for which the $\nu$CO stretching band has been reported to be 2068.9 cm$^{-1}$ [5]. The resident "peak picker" routine was used to determine the peak frequencies. Elemental analyses were carried out by Midwest Microlab Ltd., Indianapolis, IN.
Syntheses [See Scheme 2, p. 10]

5-Bromo-1,3-bis-(bromomethyl)benzene

5-Bromo-\textit{m}-xylene (27.77 g, 0.15 mol) and N-bromosuccinimide (56.10 g, 0.305 mol) dissolved in 525 mL of anhydrous carbon tetrachloride was stirred and brought to reflux. Dibenzoyl peroxide (0.45 g) was added. After refluxing for 60 hours, the solution became yellow in color. The mixture was cooled and filtered. The remaining solution was rotovapped to remove the tetrahydrofuran leaving a yellow-brown oil. The residue was recrystallized in 75 mL cyclohexane using low heat and stirring. After placement in the freezer overnight, white needles fell out of solution as 5-bromo-1,3-bis-(bromomethyl)benzene. The solution was filtered and dried under high vacuum providing 14.56 g (28.32\%) of product.

\textit{Reaction of 5-Bromo-1,3-bis-(bromomethyl)benzene with Tetraethylene Glycol to Form 5-Bromo-1,3-xylyl-18-crown-5}

A solution of 5-bromo-1,3-bis-(bromomethyl)benzene (11.85 g, 0.03456 mol) and tetraethylene glycol (5.94 mL, 0.03456 mol) in 200 mL of THF was added dropwise for 48 hours to a refluxing mixture of 2.76 g NaH (60\% in mineral oil) in 300 mL of THF. The reaction mixture was then cooled to 25$^\circ$C. Excess NaH was decomposed by the careful addition of water. The mixture was filtered and rotovapped to remove THF leaving a brown oil. The residue was shaken with dilute hydrochloric acid and CH$_2$Cl$_2$ in a separatory funnel. The aqueous phase was washed with CH$_2$Cl$_2$, and the combined organic phases were dried and put under high vacuum. A brown oil remained.
After dissolving the residue in 50 mL of methanol, 2.5 g NaClO₄ H₂O was added. The mixture was stirred and warmed to 60°C for 15 minutes. It was rotovapped under low heat and then placed under high vacuum for two hours with no heat. The oil was dissolved in 80 mL of ethyl acetate. The mixture was heated and stirred at 60°C and then placed in the freezer. The resulting solid was isolated and dissolved in 50 mL of dichloromethane and water. For further purification, 50 mL of hot heptane was used for recrystallization of the oil. After heating, the heptane was decanted away from the remaining oil and placed in the freezer. White crystals fell out of solution providing 2.33 g (17.98%) of the crown ether.

Target Molecule I, (5-Diphenylphosphino-1,3-xylyl-18-crown-5)

5-Bromo-1,3-xylyl-18-crown-5 (4.00 g, 0.011 mol) was dried thoroughly under high vacuum and then dissolved in 100 mL of freshly distilled THF. While under argon, the solution was cooled to -83.6°C using an ethyl acetate/liquid nitrogen slush. A solution of n-butyl lithium (4.27 mL, 0.011 mol) in hexane was added slowly via syringe over a period of 10 minutes. The solution was stirred an additional 30 minutes at this temperature, and chlorodiphenylphosphine (1.92 mL) was added slowly. After an additional 30 minutes of stirring at -83.6°C, the stirred solution was allowed to warm to 25°C and stirring was continued for an additional 12 hours. Triethylamine (1.00 mL) and aqueous ammonium chloride (5 mL, 20%) were added in sequence. After rotovapping away the THF, a yellow oil remained. The residue was shaken with 50 mL of water and 50 mL of CH₂Cl₂, and the organic layer was dried and placed under high vacuum. The yellow residue was chromatographed on silica gel using ethyl acetate. 1.53 g (35.83%) of the diphenylphosphine crown (target molecule, I) was retrieved.
Ni(CO)$_3$P(Ph)$_2$R Infrared Spectroscopic Study

While under argon, Ni(CO)$_4$ (0.5 mL) and CH$_2$Cl$_2$ (25 mL) were combined into solution. PPh$_3$, the control phosphine, was placed in a test tube covered by a suba-seal. Ni(CO)$_4$ solution (2 mL) and CH$_2$Cl$_2$ (3 mL) were added via syringe. The mixture was shaken for ten minutes until the carbon monoxide gas ceased evolving. After completing the IR analysis of PPh$_3$, the procedure was repeated using diphenylphosphino-1,3-xylyl-18-crown-5. To test for donor ability using the IR, small amounts of the ions lithium, sodium, and potassium, which had been dried under high vacuum, were placed each in test tubes with the diphenylphosphino-1,3-xylyl-18-crown-5 and Ni(CO)$_4$/CH$_2$Cl$_2$ mixture. IR studies were completed on diphenylphosphino-1,3-xylyl-18-crown-5 and on each of the ion complexes. The data are presented in Table 5 on p. 15.
SCHEME 1. Preparative Methods for the Target Molecule, I
RESULTS AND DISCUSSION

Syntheses and Characterization

5-Bromo-1,3-bis-(bromomethyl)benzene

5-Bromo-1,3-bis-(bromomethyl)benzene was prepared from the commercially available 5-bromo-m-xylene and N-bromosuccinimide as shown in Scheme 2. This approach using a free radical reaction to brominate methyl groups on aromatic rings is a well established synthetic method [13]. The crude product was recrystallized from stirred and heated cyclohexane. After cooling the solution in the freezer, white needles accumulated as pure product (14.56 g, 28.32%).

Table 1 Selected $^1$H NMR Data of 5-Bromo-1,3-bis-(bromomethyl)benzene

<table>
<thead>
<tr>
<th></th>
<th>ArCH$_2$</th>
<th>ArH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Shifts (δ)</td>
<td>4.4 (4H)</td>
<td>7.2-7.6 (3H)</td>
</tr>
</tbody>
</table>

5-Bromo-1,3-xylyl-18-crown-5

The crown ether precursor for the target molecule, I, was prepared from tetraethylene glycol, sodium hydride, and the previously synthesized 5-bromo-1,3-bis-(bromomethyl)benzene in dry THF as shown in Scheme 2. The tetraethylene glycol reacts with the sodium hydride to form alkoxides on the terminal groups which then act as two nucleophiles towards the brominated methyl group carbons. In order to prevent the side reaction between sodium hydride and water,
the THF must be extremely dry. The THF was distilled from LiAlH₄ into oven dried glassware immediately prior to use.

Purification of the crown ether was accomplished by dissolving the oily residue in methanol and adding sodium perchlorate. The mixture was warmed to 60°C and stirred for fifteen minutes. After placing the residue under high vacuum to completely remove the methanol, the resulting oil was dissolved in ethyl acetate, stirred at 60°C, and then placed in the freezer. A solid formed which was presumed to be the sodium salt (see IX). The idea behind this method is that only the 18-crown-5 will form a complex. For further purification, hot heptane was used to recrystallize the oil resulting after the decomplexation of the sodium ion. After cooling the heptane solution in the freezer, white powdery crystals (2.33 g 17.98%) of the pure crown ether accumulated. This purification procedure was more efficient and easier to accomplish than the chromatography method reported for similar compounds [14].

Table 2 Selected ¹H and ¹³C NMR Data for 5-Bromo-1,3-xylyl-18-crown-5

<table>
<thead>
<tr>
<th>Chemical Shift (δ)</th>
<th>¹H</th>
<th>¹³C</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂CH₂</td>
<td>3.7(16H)</td>
<td></td>
</tr>
<tr>
<td>ArCH₂</td>
<td>4.6(4H)</td>
<td></td>
</tr>
<tr>
<td>ArH</td>
<td>7.3-7.7(3H)</td>
<td></td>
</tr>
</tbody>
</table>
**Diphenylphosphino-1,3-xylyl-18-crown-5, I**

The target molecule was prepared from n-butyl lithium, chlorodiphenylphosphine, and the previously prepared 5-bromo-1,3-xylyl-18-crown-5 shown in Scheme 2. Under conditions of -83.6°C in THF, 5-bromo-1,3-xylyl-18-crown-5 reacts with n-butyl lithium in an exchange reaction to form its lithium-stabilized carbanion and butyl bromide. Then, the chloride on chlorodiphenylphosphine acts as a leaving group in the presence of this carbanion yielding diphenylphosphino-1,3-xylyl-18-crown-5, I. Purification was accomplished using flash quality silica gel chromatography with ethyl acetate as the mobile phase, and this procedure provided 1.53 g (35.83%) of colorless crystals. Since this phosphine is air sensitive, the procedure was carried out under argon. Results from the carbon and hydrogen analysis of C$_{28}$H$_{43}$O$_{5}$P are shown in Table 3. As shown, the analytical results closely match the calculated values if 0.75 H$_{2}$O of hydration is included. Further, the NMR data (see Table 4) are entirely consistent with the proposed formulation and connectivities.

**Table 3 Analysis of Diphenylphosphino-1,3-xylyl-18-crown-5**

<table>
<thead>
<tr>
<th>Element</th>
<th>% Theory No H$_{2}$O</th>
<th>% Theory 0.75 H$_{2}$O</th>
<th>% Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>69.98</td>
<td>68.07</td>
<td>68.08</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>6.92</td>
<td>7.04</td>
<td>6.93</td>
</tr>
</tbody>
</table>
Table 4 Selected $^1$H and $^{31}$P NMR Data for Diphenylphosphino-1,3-xylyl-18-crown-5

<table>
<thead>
<tr>
<th></th>
<th>$^{31}$P</th>
<th>$^1$H</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CH2CH2</td>
<td>ArCH2</td>
</tr>
<tr>
<td>Chemical Shift ($\delta$)</td>
<td>-5.0</td>
<td>3.7(16H)</td>
</tr>
</tbody>
</table>

**Donor/Acceptor Properties of the P(III) Center**

The donor/acceptor properties of this phosphine were compared to those of triphenylphosphine using infrared spectra of the corresponding Ni(CO)$_2$L complexes which were produced by a reaction between the specified phosphine and Ni(CO)$_4$. In theory, the phosphine is capable of donating its lone pair of electrons to the d orbitals of the nickel center, which in turn can donate this electron density to the CO $\pi^*$ orbitals through backbonding. The increased electron density in the antibonding orbitals of CO slightly decrease its bond order causing increased internuclear distance and decreased bond energy. Therefore, the vCO stretch decreases when the phosphine lone pair is free for donation. However, the R groups on the phosphine can affect its lone pair and change its donor ability. Also, cations that fit strategically within the crown ether cavity can decrease the phosphine’s donor ability by preventing electron donation from the crown ether, thereby causing an increase in vCO.

The data collected from this experiment are presented in Table 5 and leads to the following conclusions. As expected, the Type I phosphine showed a slight decrease in vCO compared to PPh$_3$ indicating that the crown ether group (the CH$_2$ groups on the phenol ring) donates some
electron density to the phosphine, thereby increasing the overall electron density that the phosphine is capable of donating to the nickel atom. The ion studies indicate that complexation with cations, especially lithium ion, reduces the ability of the phosphine center in the target molecule to donate electrons to the nickel center. Sodium and potassium ions also reduced the donor ability of the target molecule phosphine to that of triphenylphosphine. A Ni(CO)₃PPh₃ study was conducted as a control. Since the observed bands were within 0.1 cm⁻¹, it could be concluded that the results were due to the complexation by the crown ether portions of the ligands.

### Table 5 Ni(CO)₃L νCO studies

<table>
<thead>
<tr>
<th>Compound</th>
<th>None</th>
<th>Li⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>I¹</td>
<td>2068.7</td>
<td>2069.5</td>
<td>2068.9</td>
<td>2069.0</td>
</tr>
<tr>
<td>V (n=5)²</td>
<td>2068.3</td>
<td>2069.4</td>
<td>2069.0</td>
<td>2068.5</td>
</tr>
<tr>
<td>VIII (n=5)³</td>
<td>2066.3</td>
<td>2066.9</td>
<td>2067.8</td>
<td>2066.2</td>
</tr>
<tr>
<td>VIII (n=6)</td>
<td>2066.3</td>
<td></td>
<td>2066.4</td>
<td>2067.7</td>
</tr>
<tr>
<td>PPh₃</td>
<td>2068.9</td>
<td></td>
<td>2068.9</td>
<td>2068.8</td>
</tr>
</tbody>
</table>

¹See page 2 for structure. ²See page 4 for structure. ³See page 5 for structure.
REFERENCES


