Synthesis and Alkali-Metal-Ion Complexation of P-Stereogenic Diphosphacrowns

Yasuhiro Morisaki,[a] Ryosuke Kato,[b] and Yoshiki Chujo*[b]

Phosphine is conformationally stable because of the high inversion energy barrier of the phosphorus atom, which allows the phosphorus atom to become a chiral center. Thus, enantiopure P-stereogenic 12-, 15-, 18-, and 21-membered aliphatic phosphines “diphosphacrowns” were synthesized from secondary P-stereogenic bisphosphine as a chiral building block. Their complexation behaviors with alkali metal ions are investigated in comparison with benzo-18-diphosphacrown-6 and benzo-18-crown-6. 15-, 18-, and 21-Membered diphosphacrowns captured alkali metal ions to form 1:1 metal complexes. Unique guest selectivity was observed, as diphosphacrowns encapsulated smaller alkali metal ions than common crown ethers; for example, 18-membered diphosphacrowns interacted more strongly with Na⁺ than K⁺. The difference in guest selectivity between diphosphacrowns and common crown ethers is speculated to result from the cavity size, owing to the large phosphorus atom as well as steric hindrance around the phosphine moiety.

1. Introduction

The first crown ether (dibenzo-18-crown-6) was reported by Pedersen in 1967[a] and represents a host molecule that can encapsulates cationic guests such as alkali metal ions and ammonium.[b] The guest selectivity of crown ethers can be controlled by the ring size, skeleton, and donor atoms. Since their discovery, a variety of crown ether derivatives have been synthesized. For example, various azacrown and thiacrown derivatives,[3, 4] which contain nitrogen and sulfur as donor atoms instead of oxygen, have been prepared. These derivatives exhibit unique guest-encapsulating abilities toward a variety of heavy metal ions in addition to alkali metal ions, and may have applications as heavy-metal ion sensors.

Phosphacrowns possessing trivalent phosphorus atoms as donor atoms have also been synthesized.[5] Phosphine is conformationally stable because of the high inversion energy barrier of the phosphorus atom, which allows the phosphorus atom to become a chiral center.[6] We have developed practical synthetic routes to enantiopure P-stereogenic benzodiphosphacrowns[7a] by using an optically active bisphosphine[8] as a chiral element block. Phosphorus exhibits a high affinity towards transition metals, and phosphines can be used as ligands for transition-metal-catalyzed asymmetric reactions. Previously, we disclosed that diphosphacrowns could coordinate transition metals such as Pt⁴⁺ and Pd⁴⁺; notably, the metals were captured outside of the ring.[7a] However, the complexation of other metal ions has not been investigated. In this study, aliphatic diphosphacrowns (R,R)-1b–e with 12-, 15-, 18-, and 21-membered rings, respectively, were synthesized (Figure 1).[7a]

The complexation of alkali metal ions was investigated, in addition to that by benzo-18-diphosphacrown-6 (R,R)-1a (Figure 1).

2. Results and Discussion

2.1. Synthesis

Aliphatic diphosphacrowns with various ring sizes were synthesized by using a secondary bisphosphine (S,S)-2-BH₃, as shown in Scheme 1. The synthesis of the secondary bisphosphine was established by Crépy and Imamoto.[8] The secondary phosphine proton of (S,S)-2-BH₃ is readily exchanged with Li through the reaction with alkylithium reagents, owing to the electron-withdrawing character of coordinated boranes. The treatment of (S,S)-2-BH₃ with nBuLi afforded the dilithiated species, which could be reacted with electrophiles. Without isolation, ditosylates were added to the dilithiated species to obtain the enantiopure aliphatic diphosphacrown–borane complexes (R,R)-1b–e–BH₃ in moderate isolated yields. Their structures were confirmed by ¹H, ¹³C, and ³¹P NMR spectroscopy (Figures S1–S12 in the Supporting Information) as well as high-resolution mass spectrometry (HRMS). Furthermore, the...
structures of (R,R)-1b–BH₃ and (R,R)-1c–BH₃ were confirmed by using X-ray crystallography (Figure 2 and Table S1). The single crystals were formed from CH₂Cl₂ and hexane (good and poor solvents, respectively), whereas suitable single crystals of (R,R)-1d–BH₃ and (R,R)-1e–BH₃ could not be obtained, because of the long and flexible oligo(ethyleneoxy) chains.

2.2. Complexation: Stoichiometry

The complexation behaviors of (R,R)-1a prepared previously and (R,R)-1b–e with five alkali metal ions (Li⁺, Na⁺, K⁺, Rb⁺, and Cs⁺, respectively) were examined. The removal of boranes from (R,R)-1a–e–BH₃ was carried out by adding excess CF₃SO₃H and successive treatment with KOH; the reaction conditions are shown in the Experimental Section. The complete removal of the boranes was confirmed by using ³¹P NMR spectra, as shown in Figure S13.

The complexation stoichiometry was determined by using Job plots and nonlinear curve fitting. Hexafluorophosphate salts (MPF₆; M = Li, Na, K, Rb, and Cs) were used. The association constants were estimated through titration by using ³¹P NMR spectroscopy, and the data are summarized in Table 1. The complexation of alkali metal ions (Li⁺, Na⁺, and K⁺) with benzo-18-diphosphacrown-6 (R,R)-1a was evaluated by ³¹P NMR spectroscopy (³¹P NMR spectra for Job plots are shown in Figures S15–S17 and for titration are shown in Figures S18–S20). The Job plots are shown in Figures 3a–c; (R,R)-1a formed 1:1 complexes with Li⁺, Na⁺, and K⁺.

With 12-diphosphacrown-4 (R,R)-1b, no change in the chemical shifts of the ³¹P NMR spectra were observed upon addition of the alkali metal ions.
of alkali metal ions (Figure S14), suggesting that \((R,R)-1\)b did not form a complex with alkali metal ions. Generally, 12-crown-4 ring skeletons can capture small alkali metal ions such as Li\(^+\) and Na\(^+\).\(^{[2]}\) However, the 12-membered ring of \((R,R)-1\)b would be too small to encapsulate guest molecules even as small as Li\(^+\), owing to the bulky phosphine moieties.

Complexation of Li\(^+\) and Na\(^+\) by 15-membered ring \((R,R)-1\)c was observed in the \(^{31}P\) NMR spectra (\(^{31}P\) NMR spectra for Job plots are shown in Figures S23 and S24 and for titration are shown in Figures S25 and S26). The Job plots and titration results are shown in Figures S27 and S28, respectively. The Job plots indicate that \((R,R)-1\)c could form 1:1 complexes with Li\(^+\) and Na\(^+\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Log K [(\Delta G^*/k\text{Jmol}^{-1})]</th>
<th>Li(^+)</th>
<th>Na(^+)</th>
<th>K(^+)</th>
<th>Rb(^+)</th>
<th>Cs(^+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzo-18-diphosphacrown-6 ((R,R))-1a</td>
<td>1.50 (−8.42)</td>
<td>3.99 (−22.4)</td>
<td>2.37 (−13.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12-diphosphacrown-4 ((R,R))-1b</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15-diphosphacrown-5 ((R,R))-1c</td>
<td>1.65 (−9.26)</td>
<td>1.00 (−5.61)</td>
<td>3.09 (−17.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18-diphosphacrown-6 ((R,R))-1d</td>
<td>2.44 (−13.7)</td>
<td>4.53 (−25.4)</td>
<td>4.39 (−24.6)</td>
<td>4.23 (−23.7)</td>
<td>3.79 (−21.2)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>21-diphosphacrown-7 ((R,R))-1e</td>
<td>2.37 (−13.3)</td>
<td>3.44 (−19.3)</td>
<td>4.39 (−24.6)</td>
<td>4.23 (−23.7)</td>
<td>3.79 (−21.2)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>benzo-18-crown-6(^{[14]})</td>
<td>2.72 (−15.3)</td>
<td>3.72 (−20.9)</td>
<td>3.96 (−22.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{[a]}\) Calculated by \(^{31}P\) NMR titration in CDCl\(_3\)/CD\(_3\)CN (v/v = 1/1) at 25 °C. \(^{[b]}\) Calculated by \(^{1}H\) NMR titration in CDCl\(_3\)/CD\(_3\)CN (v/v = 1/1) at 25 °C. \(^{[c]}\) Standard free energy change.

Diphosphacrown (\(R,R\))-1d, which has an 18-membered ring, could also capture alkali metal ions (Li\(^+\), Na\(^+\), and K\(^+\)), as indicated by the corresponding Job plots (Figure S35a–c, respectively). \(^{31}P\) NMR spectra for the Job plots are shown in Figures S29–S31 and for the titration are shown in Figures S32–S34.

21-Diphosphacrown-7 (\(R,R\))-3e formed 1:1 complexes with all alkali metal ions (Li\(^+\), Na\(^+\), K\(^+\), Rb\(^+\), and Cs\(^+\)), as shown in Figure S47a–e (\(^{31}P\) NMR spectra for Job plots are shown in Figures S37–S41 and for the titration are shown in Figures S42–S46).

2.3. Complexation: Association Constant

The association constants (log K) of diphosphacrowns with alkali metal ions were calculated. In the case of \((R,R\))-1a, log K values were estimated to be 1.50, 3.99, and 2.37 m\(^{-1}\), as shown in Figure 4a–c, respectively, and in entry 1 in Table 1. The selectivity followed the order Li\(^+\) < K\(^+\) < Na\(^+\); thus, \((R,R\))-1a interacted with Na\(^+\) more strongly than K\(^+\).

The log K values for \((R,R\))-1c were calculated to be 1.65 and 1.00 m\(^{-1}\), respectively (Figure S28 and entry 3 in Table 1). Although the values were low, interaction with Li\(^+\) was preferred over that with Na\(^+\), despite the 15-membered crown ring.

The log K values of \((R,R\))-1d with Li\(^+\), Na\(^+\), and K\(^+\) were calculated, and the values were 2.44, 4.53, and 3.09 m\(^{-1}\), as shown in Figure S36a–c, respectively, and in entry 4 in Table 1. The selectivity was identical to that of \((R,R\))-1a (Li\(^+\) < K\(^+\) < Na\(^+\)), whereas \((R,R\))-1d and \((R,R\))-1a encapsulated Na\(^+\) more strongly than K\(^+\).

The log K values of \((R,R\))-1e were calculated to be 2.37, 3.44, 4.39, 4.23, and 3.79 m\(^{-1}\) (Figure S48a–e, respectively, and entry 5 in Table 1).

For comparison, we selected benzo-18-crown-6 as a representative crown ether derivative, and the complexation behaviors with alkali metal ions (Li\(^+\), Na\(^+\), and K\(^+\)) were examined under the same conditions. According to the titration results obtained by using \(^1H\) NMR spectroscopy, the log K values with Li\(^+\), Na\(^+\), and K\(^+\) were calculated to be 2.72, 3.72, and 3.96 m\(^{-1}\) (Figure S49 and entry 6 in Table 1). As expected, the order of the selectivity was Li\(^+\) < Na\(^+\) < K\(^+\), which was in accord with previous reports.\(^{[2ab,13]}\)

Generally, 18-membered crown ether derivatives including heteroatom-containing crown ethers have strong affinities toward K\(^+\). For example, the log K values of benzo-18-crown-6 with Na\(^+\) and K\(^+\) in Me\(_2\)SO at 25 °C were
estimated to be 1.70 and 2.85 m⁻¹, respectively[13a] and those in MeOH at 25 °C were estimated to be 4.03 and 5.27 m⁻¹, respectively[13b]. The difference in guest selectivity between diphosphacrowns and common crown ethers is speculated to result from the cavity size as well as steric hindrance around the phosphorus atom. Although a carbon–phosphorus single bond (1.83 Å) is longer than carbon–oxygen single bond (1.50 Å), the atomic radius of the phosphorus atom (0.98 Å) is much larger than that of the oxygen atom (0.48 Å); thus, the cavity size of a diphosphacrown is smaller than that of a common crown ether. Cavity sizes of 18-membered diphosphacrown were estimated to be 4.03 and 5.27 m⁻¹, respectively, total concentration of (R,R)-1a [C₀] is constant.

2.4. Guest-Exchange Study

The guest-exchange behaviors of (R,R)-1a were monitored by using 31P NMR spectra, as shown in Figure 5. Addition of three equivalents of Na⁺ to the (R,R)-1a-K⁺ complex solution led to complete guest exchange, owing to the larger K⁺ value of complexion with Na⁺ [log K(Νa⁺) = 3.99] compared to K⁺ [log K(K⁺) = 2.37] (entry 1 in Table 1). The signal at −11.1 ppm disappeared, and a new signal was observed at −22.5 ppm. On the other hand, when four equivalent free benzo-18-crown-6 moieties were added to (R,R)-1a-K⁺ complex solution, K⁺ was moved to benzo-18-crown-6, which has a larger K⁺ value [log K(K⁺) = 3.96, entry 5 in Table 1] than (R,R)-1a [log K(K⁺) = 2.37, entry 1 in Table 1]. Thus, the signal at −11.1 ppm was shifted to −0.4 ppm, which was the identical chemical shift of free bisphosphate in (R,R)-1a.

The association constants of aliphatic diphosphacrown (R,R)-1d with alkali metals were larger than those of benzodiphosphacrown (R,R)-1a; for example, the log K(Νa⁺) value of (R,R)-1d was 4.53 m⁻¹, whereas that of (R,R)-1a was 3.99 m⁻¹. Therefore, the relative encapsulating selectivity among Li⁺, Na⁺, and K⁺ was examined. K(Νa⁺)/K(K⁺) and K(K⁺)/K(Li⁺) of (R,R)-1d were 27.2 and 4.5, respectively, whereas K(Νa⁺)/K(K⁺) and K(K⁺)/K(Li⁺) of (R,R)-1a were 32.1 and 7.3, respectively. Thus, the relative encapsulating selectivity of the benzodiphosphacrown was higher than that of the aliphatic diphosphacrown. Aliphatic diphosphacrowns have flexible ethyleneoxy chains, resulting in larger encapsulating abilities and lower encapsulating selectivities than benzodiphosphacrowns.

3. Conclusions

P-Stereogenic 12-, 15-, 18-, and 21-membered diphosphacrowns were synthesized from secondary P-stereogenic bisphosphine as a chiral building block. 15-, 18-, and 21-Membered diphosphacrowns captured alkali metal ions, and the corresponding Job plots indicated the formation of 1:1 metal complexes. Notably, unique guest selectivity was observed, as diphosphacrowns encapsulated smaller alkali metal ions than common crown ethers. For example, 18-membered diphosphacrowns interacted more strongly with Na⁺ than K⁺. The relative encapsulating selectivity of the benzodiphosphacrown...
was greater than that of aliphatic diphosphacrown, owing to the phosphorus atom being larger than oxygen as well as the steric hindrance around the phosphorus atom. The flexible ethylenylene chain of the aliphatic diphosphacrowns resulted in a larger encapsulating ability and lower encapsulating selectivity than the rigid phenylene skeleton of the benzodiphosphacrown.

**Experimental Section**

**General**

$^1$H (400 MHz) and $^13$C (100 MHz) NMR spectra were recorded on a JEOL JNM-EX400 spectrometer, and samples were analyzed in CD$_2$CN or CDCl$_3$ by using Me$_4$Si as an internal standard. $^{31}$P (161.9 MHz) NMR spectra were also recorded on a JEOL JNM-EX400 spectrometer, and samples were analyzed in CD$_2$CN or CDCl$_3$ by using H$_2$PO$_4$ as an external standard. The following abbreviations are used: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, and br: broad. HRMS spectra were obtained on a Thermo Fisher Scientific EXACTATIVE for electron-spray ionization (ESI). Optical rotations were measured on a Rudolph Research Analytical AUTOPOL IV instrument by using CHCl$_3$ as a solvent. Analytical thin-layer chromatography was performed with SiO$_2$ 60 Merck F$_254$ plates. Column chromatography was performed with Wakogel C-300 SiO$_2$ or MERCK ALO$_6$ 90 active basic.

**Materials**

THF and EtO$_2$ were purchased and purified by the GlassContour solvent purification system.$^{[14]}$ Dehydrated-grade toluene and EtOH were purchased and used without further purification. Bisphosphine (S,S)-2-BH$_4$ was synthesized following the method described in the literature.$^{[9]}$ The other materials were purchased and used without further purification. Alkali metal salts RbPF$_6$ and CsPF$_6$ were prepared by using the procedure in the literature.$^{[15]}$ All reactions were performed under an Ar atmosphere using standard Schlenk techniques.

**Synthesis of P-Stereogenic Diphosphacrowns**

A typical procedure is as follows. A THF solution (30 mL) of (S,S)-2-BH$_4$ (117.0 mg, 0.50 mmol) was added to a solution of anhydride (0.5 mL) of triethylene glycol ditosylate (229.3 mg, 0.50 mmol) was added with a syringe. The reaction mixture was warmed to room temperature and then stirred for 2 h at 50 °C. The solution was cooled to room temperature. After stirring for 48 h, the reaction was quenched upon addition of H$_2$O (30 mL). The organic layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine and dried over MgSO$_4$. After filtration, the solvent was removed in vacuo. The residue was subjected to column chromatography on SiO$_2$ with EtOAc and hexane (v/v = 2/1) as an eluent. The solvent was removed in vacuo to afford (R,R)-1-b-BH$_4$ (120.4 mg, 0.35 mmol, 69%) as a colorless solid.

$^{[16]}$H NMR (CDCl$_3$, 161.5 MHz) δ = -31.3 ppm (br d, $J_{P-H}$ = 65.7 Hz), 70.2 ppm; $^{[15]}$P (H NMR (CDCl$_3$, 161.5 MHz) δ = +35.5 ppm (br d, $J_{P-H}$ = 13.2 Hz), 94.2 Hz; HRMS (ESI) calcd for [C$_{6}$H$_{12}$P$_{2}$O$_{4}$Na]$^{+}$ 401.3290, found 401.3283.

$^{[16]}$H NMR (CDCl$_3$, 161.5 MHz) δ = +32.6 ppm (br d, $J_{P-H}$ = 63.8 Hz), HRMS (ESI) calcd for [C$_{6}$H$_{12}$P$_{2}$O$_{4}$Na]$^{+}$ 404.3106, found 404.3109.

**Removal of Borane from Diphosphacrown**

All sample preparation procedures were performed under an Ar atmosphere. To a solution of (R,R)-1-BH$_4$ (0.10 mmol) in degassed dry toluene (0.5 mL), CF$_3$SO$_2$H acid (0.5 mL, 6 mol%) was added through a syringe. After stirring for 2 h at room temperature, toluene was removed in vacuo. The residue was dissolved in degassed EtOH (3 mL) and added to degassed KOH aqueous solution (1.1 g, 20 mmol KOH in 20 mL H$_2$O). After stirring for 5 h at 50 °C, the solution was allowed to cool to room temperature. Then, extraction with degassed EtO$_2$ was carried out. The organic layer was dried over MgSO$_4$ and purified with column chromatography on Al$_2$O$_3$ (active basic) to obtain (R,R)-1 as a colorless solid.

**Determination of Stoichiometry by Job Plot**

The “total concentration of (R,R)-1 and MFP$_x$”, and the “solvent ratio (CDCl$_3$/CD$_2$CN, v/v = 1/1)” were both constant, and (R,R)-1 in CDCl$_3$ solution and MFP$_x$ in CD$_2$CN solution were added to a NMR tube at various ratios. In each case, the $^1$H NMR and $^{31}$P NMR spectra were monitored, and the data were analyzed by using the Job plot method. The stoichiometry was obtained from the x coordinate at the maximum in the Job plot curve. In this case, the y axis is $|\Delta|$ = |$H/(H+G)$|; $|\Delta|$ = absolute value of chemical shift variation upon complexation, $|H|$ = concentration of (R,R)-1, and $|G|$ = concentration of MFP$_x$. The x axis is the mole fraction of (R,R)-1, $|H|$ / ($|H|$ + $|G|$). For $x = 0.5$, the stoichiometry of the binding is 1:1.
Determination of Association Constants

Determination of the association constants for the (R,R)-1–MPF₆ complexes was carried out by means of an NMR titration technique in CDCl₃/CD₃CN (v/v = 1/1) at 25 °C. The concentration of (R,R)-1, [H₆]₀, in CDCl₃ was kept constant, while the concentration of MPF₆ [G], in CD₃CN was varied. These two solutions were mixed, and ¹H and ³¹P NMR spectra were recorded. The host–guest complexation equilibrium has a sufficiently fast exchange rate compared to the NMR timescale, showing only one set of resonances for the ligand protons and phosphorus. The association constants were determined through nonlinear curve-fitting analysis with complexation-induced downfield or upfield shifting of the data for the host protons upon the addition of a guest. In this case, the association constants calculated individually from the chemical shift variation of protons and phosphorus were almost identical; therefore, all binding constants were calculated from the data of ³¹P NMR spectra. The y axis is |ΔΔ|, and the x axis is [G]. The association constant K and |ΔΔ|max were calculated from Equation (1) by using nonlinear curve fitting:

|ΔΔ| = 

\[ |ΔΔ|max = \frac{1}{2} [K[G] + K[H₆] - (1 + K[H₆] + K[G])^2 - 4 K^2[G][H₆]^{0.5}] \]

Guest-Exchange Study

A stock solution of (R,R)-1a (1.6 × 10⁻³ mol) in CDCl₃/CD₃CN (v/v = 1/1) was prepared, and a ³¹P NMR spectrum was recorded (state I). Then, three equivalents of KPF₆ were added to the solution, and the ³¹P NMR spectrum was subsequently recorded (state II). To the stock solution containing (R,R)-1a and KPF₆ NaPF₆, [3 equiv against (R,R)-1a] was added, and the ³¹P NMR spectrum was again recorded (state III). In addition, to the stock solution containing (R,R)-1a and KPF₆, benzo-18-crown-6 [4 equiv against (R,R)-1a] was added, and the final ³¹P NMR spectrum was recorded (state IV).

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Keywords: alkali metals · chirality · crown ethers · enantioselectivity · P-stereogenic phosphate

[10] CCDC 1454966 and 1454880 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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