Synthesis, Characterization, and Alkali Metal Stability Constants of a New Bis(phosphotriester) Macrobicyclic Polyether Cryptand

Christian B. Allan[†] and Larry O. Spreer[*]

Department of Chemistry, University of the Pacific, Stockton, California 95211

Received May 19, 1994[®]

The synthesis of a new bis(phosphotriester) macrobicyclic polyether cryptand, $O=P[O(CH_2)_2O(CH_2)_2O(CH_2)_2O]_3P=O$ (9), called phosphocrypt, and its acyclic tripodal precursor $O=P[O(CH_2)_2O(CH_2)_2O(CH_2)_2OH]_3$ (8) are described. The new cryptand 9 was synthesized by condensation of 8 and phosphoryl chloride which were simultaneously added under high dilution conditions in the presence of pyridine. The highest yield of 9 (30%) was obtained with a final concentration of 3 mM in vigorously stirred methylene chloride. Both 8 and 9 form stable complexes with K^+ and Rb^+ in water. Log K_s values measured with a cation selective electrode for 8 are 3.6 and 3.0 and 3.7 and 3.6 for 9, respectively. The K_s values for phosphocrypt are 1000-fold greater than those of comparably sized nitrogen bridgehead cryptands. ^1H and ^{13}C NMR indicate 9 is flexible at 20 °C. Molecular dynamics and mechanics calculations indicate that phosphocrypt has more cation–dipole interactions and more favorable conformational changes associated with complexation than comparably sized nitrogen bridgehead cryptands.

Introduction

Since the development of cryptands by Dietrich, Lehn, and Sauvage,[1] there has been a great deal of effort to exploit their remarkable ability for complexation with alkali metals. Cryptands and other polyether compounds are useful as phase transfer catalysts, ion transport agents, and in waste clean-up, and they have potential pharmaceutical uses in imaging and drug delivery.

One area that has not received much attention is the identity of the bridgehead atom. To our knowledge only carbon and nitrogen have been used as bridgehead atoms in simple polyether cryptands,[2] with nitrogen by far the most prevalent. The carbon systems are very difficult to make, and due to their low solubility in water, are not very suitable for aqueous use. There are many examples of macrocyclic ligands that contain phosphorus as phosphine but fewer that contain phosphoryl groups.[3] Liskamp et al. have synthesized an amino acid based cryptand that contains a phosphodiester linkage in one of the rings.[4] Recently several phosphorus bridgehead macrobicyclic systems have appeared in the literature.[5] The main focus of work on these phosphorus bridgehead species has been in transition metal complexation or in studies of host molecules capable of binding neutral organic guests.

We were interested in preparing water-soluble ligands whose alkali metal complexing ability would be independent of pH. Cryptands with phosphoryl bridgehead groups are a reasonable possibility in this regard. This paper describes the synthesis and characterization of a new bis(phosphotriester) macrobicyclic polyether (9) and its acyclic tripodal precursor 8 (Scheme 1). The pH independent aqueous alkali metal complexation properties of 9, which we call phosphocrypt, are also discussed.

Phosphocrypt can be described as replacing the $N(CH_2CH_2)_3$ bridgeheads in 2.2.2 cryptand, $N[(CH_2)_2O(CH_2)_2O(CH_2)_2]_3N$, with phosphato triester groups, $O=P(OCH_2CH_2)_3$. This simple substitution increases the number of potential oxygen binding sites while simultaneously increasing ring size. The replacement also alters the basic conformation of the metal–ligand complexes, since the X-ray structures of nitrogen bridgehead cryptates[6] indicate the conformation is endo-endo, while all our evidence for phosphocrypt indicates the phosphoryl oxygens are in exo positions.

Results and Discussion

Phosphocrypt, $O=P[O(CH_2)_2O(CH_2)_2O(CH_2)_2O]_3P=O$ (9), was made from triethylene glycol and phosphoryl chloride in an overall four step process (see Scheme 1). In the first step triethylene glycol (1) reacts with sodium hydride to generate an intermediate glycoxide that reacts with benzyl chloride (2) to form triethylene glycol monobenzyl ether (3) in 50% yield. Under conditions of excess 1 (3:1), the side product triethylene glycol dibenzyl ether was also formed (25%). Reactions involving 1:1 stoichiometry of 1 and 2 gave lower yields of 3. Fractional vacuum distillation of the crude organic product after ether–water extractions afforded pure 3. In the next step the alkoxide of the monobenzyl ether 3 reacts with phosphoryl chloride (4) to give three main products. The compounds were purified by semipreparative HPLC. The results indicate that 5 and 6 were made along with 7 in ratios of about 5:10:80, respectively. The oxychlorides of 5 and 6 must have been formed initially and then hydrolyzed during the workup. The high ratio of 7 to 5 and 6 was obtained by dropwise addition of $POCl_3$ to the alkoxide which favors 7. In step 3 the hydrogenation of 7 to 8 in absolute ethanol using 10% Pd on activated carbon gave almost quantitative yields.

† Current Address: University of Massachusetts, Department of Chemistry, Lederle Graduate Research Center, Box 34510, Amherst, MA 01003-4510.
® Abstract published in *Advance ACS Abstracts*, October 1, 1994.
(1) Dietrich, B.; Lehn, J.-M.; Sauvage, J.-P. *Tetrahedron Lett.* **1969** 2885–2889.
(2) Dietrich, B.; Viout, P.; Lehn, J.-M. *Macrocyclic Chemistry*; von der Saal, K., Ed.; VCH: New York, 1993.
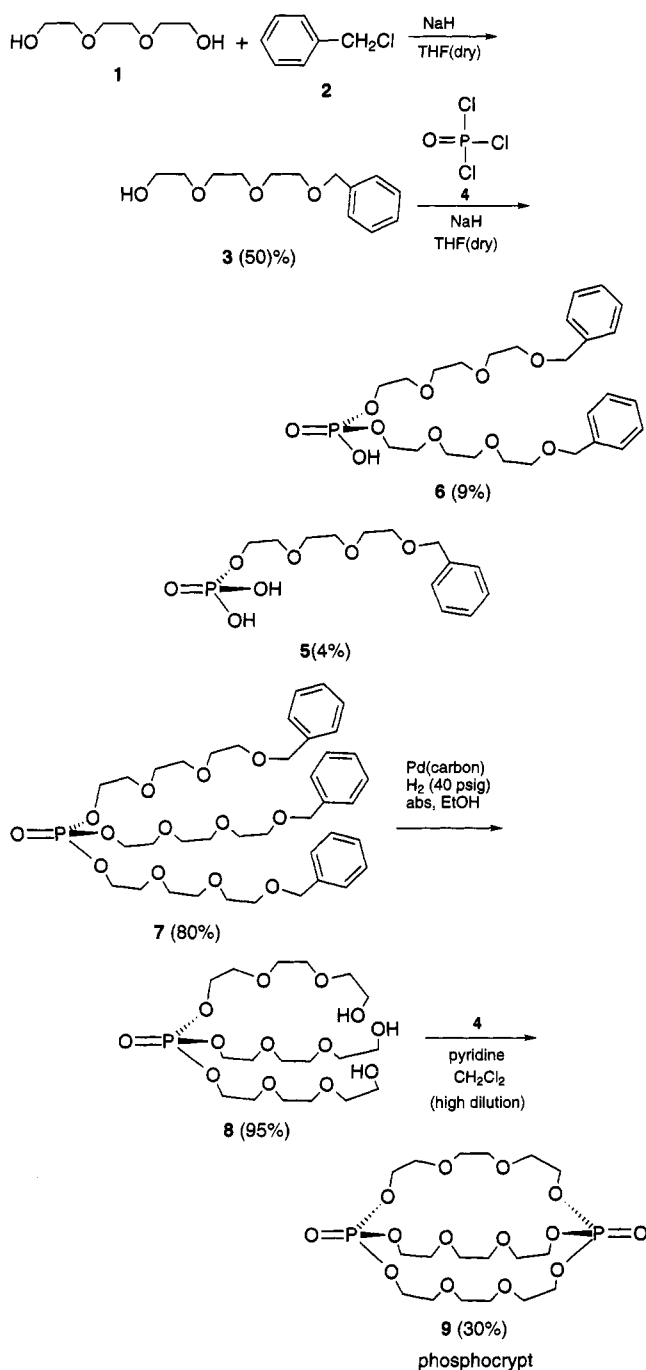(3) Oussaid, B.; Garrigues, B.; Jaud, J.; Caminade, A.-M.; Majoral, J.-P. *J. Org. Chem.* **1993,** *58,* 4500–4503, and references therein. Kaplan, L. J.; Weisman, G. R.; Cram, D. J. *J. Org. Chem.* **1979,** *44*(13), 2226–2233. Reference 10.
(4) van Oijen, A. H.; de Bont, H. B. A.; van Boom, J. H.; Liskamp, R. M. J. *Tetrahedron Lett.* **1991,** *32*(52), 7723–7726.
(5) Mitjaville, J.; Caminade, A.-M.; Mathieu, R.; Majoral, J.-P. *J. Am. Chem. Soc.* **1994,** *116,* 5007–5008, and references therein.
(6) Moras, D.; Metz, B.; Weiss, R. *Acta Crystallogr.* **1973,** *B29,* 388–395.

Scheme 1. Overall Steps in the Synthesis of Bis(phosphotriester) Macrobicyclic Polyether 9

period. The concentrations were varied from 50 to 3 mM (based on the final concentrations after the addition was complete). Polymer formation was seen under the higher concentration conditions with methylene chloride as the solvent. In THF some polymers formed over the entire concentration range studied. Intramolecular hydrogen bonding in **8** may facilitate the ring closure steps by prearranging the molecule in a conformation suitable for the hydroxy groups to react with the same phosphoryl chloride molecule. Tetrahydrofuran solvent molecules may hinder ring closure by interfering with intramolecular hydrogen bonding in **8**. Methylene chloride, on the other hand, should not interfere with the hydrogen bonding. Indeed the best yields of **9** (30%) were obtained in dilute solutions of methylene chloride. The crude sticky solid remaining after rotory evaporation of the final reaction mixture was dissolved in a minimum of water and run through a cation exchange column (Dowex SX50, Na$^+$ form) to remove pyridine and give pure **9**.

NMR Spectra

The general features of the 300 MHz proton NMR spectra (not shown) for **8** and **9** are similar to those of triethylene glycol (**1**). There are three regions in **1**, two that correspond to the polyether methylene protons closest to the alcohol groups, which are multiplets, and the inner methylene protons that show a singlet due to their symmetry. The singlet is located between the two multiplets. The chemical shifts range from 3.6 to 3.8 ppm relative to tetramethylsilane. The integrated peak ratios indicate the hydroxy protons are unresolved from the nearest methylene protons.

The presence of the phosphoryl group in **8** shifts the two methylene protons on carbon 6 (see Figure 1 for numbering scheme) downfield to 4.2 ppm, and the broadened OH proton moves upfield to 3.1 ppm. The chemical shifts of other protons in **8** are changed very little compared to those of **1** except that the singlet has broadened slightly and the multiplets show additional fine splitting.

The closing of both rings to make **9** simplifies the proton NMR spectrum. Due to the symmetry of the molecule only three regions should be seen, and this is what is observed. Compared to the spectrum of **8**, only the signals at 4.2, 3.7, and 3.6 ppm remain. The multiplet structure is diminished and the signals at 4.2 and 3.7 ppm are very broad at room temperature. The broadness of the proton peaks in phosphocrypt may be due in part to conformational changes associated with the molecule at room temperature. A comparison of the ¹H NMR spectrum for the methylene protons nearest the bridgehead atom between 2.2.2 cryptand and **9** gives some insight to the nature of the broadness. There is some triplet structure in the 2.2.2 cryptand spectrum[8] for these protons. It is reasonable to attribute the differences in the NMR peaks to differences in the nature of the bridgehead. The phosphate ester bonds apparently allow more flexibility in the molecule than amine bonds, so at room temperature the NMR lines are broader for **9**.

The larger ring size in phosphocrypt over those in the 2.2.2 cryptand (22 versus 18 atoms, respectively) may also contribute to its greater flexibility. Gas phase

The ring closure reaction to form the cryptand **9** was the most difficult step. In most work on macrobicyclic polyether syntheses with nitrogen bridgeheads, the crown ether analogue is made first and then the second ring is closed.[7] Our method employs two trifunctional molecules that react in one synthetic step to close both rings. This method of forming macrobicyclic polyether compounds has been called single tripodal capping.[2] High dilution conditions are common for ring closures of this type where multifunctional groups react. Formation of **9** was accomplished by the separate dropwise addition of solutions of both phosphoryl chloride (**4**) and phosphotriester podand **8** to a refluxing pyridine solution, in dry tetrahydrofuran (THF) or methylene chloride, over an 8–12 h

(7) Lehn, J.-M. *Struct. Bonding* **1973**, *16*, 1–71.

(8) This work. See also: Dietrich, B; Lehn, J.-M. *Tetrahedron Lett.* **1969**, No. 34, 2889.

Table 1. Log K_s Values (M^{-1}) for Various Ligands with Potassium and Rubidium in Water^{a,b}

	K$^+$		Rb$^+$
ligand	pH 7	pH 2	pH 7
2.2.2	4.8 (5.4)	3.5	3.8 (4.4)
2.2.3	(2.2)		(2.1)
2.3.3	(<2)		(<0.7)
8	3.6	–	3.0
9	3.7	3.7	3.6

^{a} Measurements were carried out at 25 °C with an ionic strength of 0.01 M Me$_4$NBr. The experimental uncertainties in the log K_s values from this work are ±0.1. ^{b} Literature values are in parentheses from ref 11.
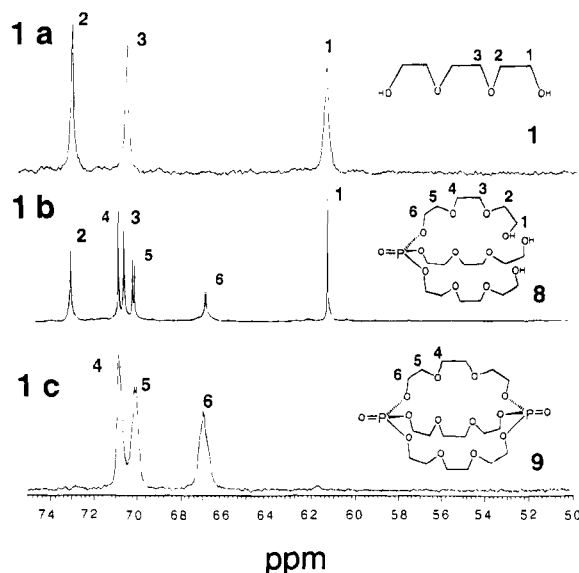
Figure 1. ^{13}C profile in formation of **9**.

molecular dynamics calculations (CAChe, Tektronix, Inc.) at 300 K indicate that a number of different conformations in phosphocrypt have similar energies. In particular conformations where the phosphates move in and out, somewhat like an accordion, generate only small changes in energy and lead to variable cavity sizes. The capability of **9** to change its cavity size is reflected in its lack of selectivity between K$^+$ and Rb$^+$ (see Table 1). Possible synthetic isomers of **9** in which the phosphoryl oxygens exist inside the molecular cavity have not been found, which is in agreement with MMII calculations, which indicates the molecule is very strained in these configurations. Even though the proton spectra are consistent with the structures of **8** and **9**, they offer marginal proof that ring closure has been achieved. Comparison of the ^{13}C spectra for **1**, **8**, and **9** give better evidence of ring closures because of larger chemical shifts and scalar ^{31}P$-^{13}$C coupling. Figure 1 shows the spectra of **1**, **8**, and **9**. The carbon numbering used in the figure gives the assignments and is consistent for all three spectra. The three peaks that correspond to the carbon atoms of triethylene glycol (Figure 1a) are still present in the tripodal ligand **8** with insignificant shifts, but there are also three new peaks (Figure 1b). The new peaks are due to the influence of the phosphoryl group. If ring closure is achieved, the ^{13}C NMR spectrum of **9** should have only three peaks. Not only is this seen, but as shown in Figure 1c, they are at the same positions as carbons 4, 5, and 6 in **8**.

The ^{31}P$-^{13}$C couplings seen in carbons 5 (6.9 Hz) and 6 (5.8 Hz) in **8** are well defined. This is not the case for

the same resonances in **9** because the broadness of the peaks seems to diminish the fine structure. The broadness of the ^{13}C NMR peaks in **9** parallels the ^{1}H peaks and may indicate interconversion between conformational configurations on the NMR timescale. One apparent anomaly in the carbon assignments is that carbon 5 has the larger ^{31}P$-^{13}$C coupling constant in **8**, yet it is further from the phosphorus atom than carbon 6. We offer no explanation for this, but COSY and HETCOR experiments confirm the assignments for **8**, (available in the supplementary material). Also, calculated ^{13}C chemical shifts (Chemwindows) are in complete agreement with the assignments.

The NMR results do not give definitive evidence for the number of rings in **9** or arms in **8**. Positive ion FAB mass spectrometry was used to show that all the products had the expected molecular formulas. Good combustion data were difficult to obtain because of the hygroscopic nature of **8** and **9**. High-resolution mass spectrometry of **9** also provided elemental analysis data.

Lehn and co-workers[9] observed temperature-dependent changes in the ^{1}H NMR spectra of 2.2.2 cryptand upon complexation with alkali metals. Attempts were made to obtain similar information in this work. Although the chemical shifts of the ring protons in **9** moved 3 Hz downfield upon complexation with potassium in D$_2$O at 20 °C, interpretation of these preliminary results is difficult due to the broadness of the signals, and temperature-dependent changes gave as yet unexplained results. The stability of phosphocrypt toward hydrolysis was followed by ^{13}C NMR in D$_2$O at both pD 7 and 1. The compound showed no appreciable changes in the spectrum after 5 days at pD 7, but some decomposition at pD 1 was noted after 24 h.

Stability Constants and Selectivity

Many factors affect the stability and the selectivity of alkali metal cryptate complexes. The difference in free energies between the solvated cryptate complex and the separately solvated alkali metal ion and ligand determine the stability. The selectivity depends on the relative free energy changes between solvation and complexation for different alkali metal ions. These free energies depend on such factors as cavity size, cavity rigidity, ionic radius, solvent, and number of binding sites.[10] Rigid ligands with fixed cavity sizes tend to exhibit greater selectivity than nonrigid ligands.

The aqueous stability constants, log K_s, for **8** and **9** with potassium and rubidium were measured potentiometrically following a previously reported method[11] and are given in Table 1. Included in the table are the literature values for the nitrogen bridgehead 2.2.2, 2.2.3, and 2.3.3 cryptands. In addition to the literature values for the 2.2.2 cryptand, our experimentally determined values are also given. Our values for the 2.2.2 cryptand are somewhat lower than those reported in the literature using the same concentration range. However, stability constants for the 2.2.2 cryptand with alkali metals do show some variations from different laboratories.[10] The cation selective electrode used and the ionic strength are two experimental differences between this work and the literature measurements and may account for some of

(9) Lehn, J.-M.; Sauvage, J.-P.; Dietrich, B. *J. Am. Chem. Soc.* **1970**, 92, 2916–2918.

(10) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, 271–339.

(11) Lehn, J.-M.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1975**, 97, 6700–6707.

the difference in the log K_s values. The literature ionic strength value (0.05 M) is five times higher than our value (0.01 M), and a glass cation selective electrode was used in the literature work whereas we used a liquid-membrane electrode. Five different calibrations and K_s measurements with samples from three different syntheses were used, and our measurements are internally consistent with average uncertainties in the log K_s values of ±0.1. Comparisons of stability constants between **8**, **9**, and the 2.2.2 cryptand are therefore based on our measurements, but all others are based on literature values.

The log K_s values for **8** and **9** with potassium in water at pH 7 are 3.6 and 3.7, respectively. The value for **8** is one of the largest we have seen for an acyclic polyether in water with potassium. It is nearly the same value as that for the cryptand **9**, which is highly unusual for an open chain analogue since macrobicyclic polyether cryptands normally have larger K_s values than their acyclic precursors. The added stability of cryptands over acyclic analogues is referred to as the macrobicyclic effect (or cryptate effect) and has been shown to be mostly of enthalpic origin.[12] The large K_s value in **8** may arise from the formation of intramolecular hydrogen bonds, which could make a pseudo cavity around a spherical cation and mimic the closed ring system in **9**. The log K_s values for **9** with Rb⁺ and K⁺ are very similar while for **8** log K_s decreases for Rb⁺ compared to K⁺. The lack of selectivity of **9** between Rb⁺ and K⁺ suggests the molecule is not rigid, which is supported by the broad lines in the proton and carbon NMR spectra. MMII calculations confirm that phosphocrypt is flexible enough to adjust its cavity size to fit both potassium and rubidium with minimal differences in energy. The P–O–C bonds of the capping group in phosphocrypt must allow more flexibility then the N–C–C linkage in the 2.2.2 cryptand.

The decrease of the stability constant seen in the tripodand **8** on going from K⁺ to the larger Rb⁺ cation may reflect relative changes in hydrogen bonding, solvation, and conformational energies. The gas phase minimum energy of the K⁺ complex of **8** is roughly 22 kcal mol⁻¹ more positive than that of the Rb⁺ complex, yet the K⁺ complex is more stable in solution than the Rb⁺ complex. This suggests that solvation and hydrogen bonding energies are mostly responsible for the differences in the stabilities.

The comparison of stability constants for phosphocrypt and nitrogen bridgehead cryptands with comparably sized rings indicates that phosphocrypt forms much more stable alkali metal complexes than the nitrogen bridgehead systems. Ring sizes larger than 18 in the nitrogen bridgehead cryptands show a dramatic decrease in their ability to complex alkali metals (Table 1). The literature value for the stability constant of the 2.2.3 cryptand, which has 18 and 21 member rings, decreases by a factor of 1000 for potassium in water, compared to the literature value of the 2.2.2 cryptand. It should also be noted that the selectivity for K⁺ over Rb⁺ in the 2.2.2 cryptand is lost in the 2.2.3 ligand. The 2.3.3 cryptand, with 24 and 21 member rings, has completely lost its ability to form stable cryptate complexes with alkali metals within experimental detection limits. By comparison, phosphocrypt, with 22 member rings, has appreciable complexation strength.

This difference in stability constants between comparably sized nitrogen bridgehead ligands and our phosphoryl bridgehead ligand **9** is striking, and the reasons for the difference are undoubtedly complicated. Certainly the fact that phosphocrypt has 12 potential oxygen binding sites while the 2.3.3 cryptand has only 10 binding sites (8 oxygen and 2 nitrogen) suggests this must play some role in the difference in stability constants. Moreover, the stabilities will ultimately be determined by the number of binding sites that actually interact with the alkali metal and by conformational changes associated with complexation. The ability of the ligand to adjust its cavity size should determine how many binding sites are used. In the ligands 2.2.3 and 2.3.3 the cavity size apparently becomes too large so that contact between cation and binding sites introduces deformations and increased intraligand repulsions which destabilize the complexes.[11]

MMII calculations were performed in order to compare cavity sizes between phosphocrypt and the nitrogen bridgehead 2.2.2, 2.2.3, and 2.3.3 cryptands to give insight into the size–stability relationship between the different complexes. The N–N distance in the 2.2.3 cryptand, measured from the minimized conformation (augmented MMII) is 6.3 Å, and 7.3 Å for the 2.3.3 cryptand.[13] In phosphocrypt the P–P distance is calculated to be 7.0 Å. Thus the cavity size, based on the distance between the bridgehead atoms, of the 2.3.3 nitrogen bridgehead cryptand is closest to that of phosphocrypt. As discussed before, experimental evidence indicates that **9** is flexible, and MMII calculations on **9** show that deformations and intraligand repulsions upon complexation are considerably less than the nitrogen bridgehead systems, so the larger stability constants with Rb⁺ and K⁺ in phosphocrypt over the 2.3.3 cryptand probably arise from more overall cation–dipole interactions and more favorable conformational changes.

The aqueous stability constants with potassium at pH 2 are also reported in Table 1 for the 2.2.2 cryptand and phosphocrypt. The log K_s value for phosphocrypt (3.7) is the same at both pH 7 and pH 2. The values for the 2.2.2 cryptand decrease from 4.8 to 3.5. This is not surprising since the protonation of the nitrogens in the 2.2.2 compound influences the formation of its crypate complexes. In fact pH-metric titrations are one method used to experimentally determine stability constants for N-bridgehead cryptands.[11]

For a comparison to the protonated 2.2.2 cryptand, we have synthesized the 2.2.2 cryptand N-oxide.[15] At both pH 7 and pH 2 the log K_s value is 3.0 for the 2.2.2 cryptand N-oxide with potassium in water. This value is similar to that of the 2.2.2 cryptand at pH 2 (log K_s = 3.5). The N-oxide has positively charged nitrogens so the similar stability constants may reflect the electrostatic similarity of the N-oxide with the protonated cryptand.

(12) Kauffmann, E.; Lehn, J.-M.; Sauvage, J.-P. *Helv. Chim. Acta* **1976**, *59*, 1099–1111.

(13) The intramolecular bridgehead distance measured from our calculations for the 2.2.2 cryptand for the endo–endo conformation is 5.71 Å, which agrees with previously calculated values (ref 14). Values for the 2.2.3 and 2.3.3 cryptands are also calculated for the endo–endo conformation.

(14) Geue, R.; Jacobson, S. H.; Pizer, R. *J. Am. Chem. Soc.* **1986**, *108*, 1150–1155.

(15) Unpublished results, see: Christian B. Allan. Ph.D. Dissertation, University of the Pacific, Stockton, CA. Anal. Calcd for $C_{18}H_{36}N_2O_8$·5H₂O: C, 43.37; H, 9.24; N, 5.62. Found: C, 43.34; H, 9.40; N, 5.42.

Conclusion

The synthesis of a new bis(phosphotriester) polyether macrobicyclic cryptand 9 has been described. The compound shows good complexation properties with both potassium and rubidium in water but shows no selectivity between these two alkali metals. We have shown that complexation of potassium by phosphocrypt (9) is pH independent between pH 7 and pH 2. The log K_s values with rubidium are about the same for phosphocrypt and the 2.2.2 cryptand at pH 7, but for comparable ring sizes the stability constants for phosphocrypt are much greater than the nitrogen bridgehead cryptands.

The phosphotriester podand 8 has remarkably high stability constants with both potassium and rubidium in water for an open chain polyether and compares favorably to cryptate complexes. It is inexpensive to make and overall synthetic yields are high, and this compound might prove useful in applications such as waste cleanup.

The new bis(phosphotriester) cryptand 9 offers unique characteristics that may be further exploited to give a variety of useful applications. Initial measurements indicate they form more stable alkali metal complexes than similarly sized nitrogen bridgehead systems. Studies of their host−guest chemistry may give further insights into rational macrobicyclic polyether and other macrocyclic ligand design. It will be interesting in the future to compare the complexation properties of 9 with those of the corresponding phosphanes to see if the presence of the phosphoryl group plays a roll in complexation. Finally, selectivity of new phosphoryl bridgehead cryptands for alkali metals may be improved by common methods such as the addition of groups to the polyether bridges that hinder flexibility and by changes in polyether bridge lengths to decrease the cavity size. We are currently exploring some of the many possible variations based on the simple concept of utilizing phosphoryl groups as a bridgehead atom in polyether cryptand ligands.

Experimental Section

NMR spectra were recorded on a Varian Gemini 300 broadband system in CDCl$_3$ at 20 °C with internal TMS reference for proton and carbon spectra and phosphoric acid as an external reference for phosphorus spectra. Infrared spectra were recorded on a Nicolet 5DX FTIR as neat liquids or KBr pellets. Refractive indices were measured with a Bausch & Lomb refractometer. All mass spectra were obtained as FAB$^+$ in nitrobenzyl alcohol (U.C. Berkeley). All HPLC separations were performed with a Waters 600E quarternary solvent delivery system equipped with a 990 photodiode array detector. Column: Jordi Gel RP 500 1 × 10 cm DVB polymer (Jordi Associates, Inc., Bellingham, MA). Mobile phases: (A) 90% water/10% acetonitrile/0.1% trifluoroacetic acid (TFA) and (B) 100% acetonitrile/0.1% TFA. Semipreparative separations were performed under the same conditions except the column dimensions were 2.54 × 10 cm. Gradients with initial concentrations ranging from 50 to 80% B were frequently used with a flow rate of 1.5 mL min^{-1} for analytical separations and 6.0 mL min^{-1} for semipreparative work.

Thin layer chromatography was performed using Whatman C18 reversed phase TLC plates with fluorescent indicator. The mobile phase was 75% ethanol/25% water. In addition to UV detection, the plates were developed in a beaker containing iodine crystals.

All inorganic compounds were reagent grade and used without further purification. Pyridine (<0.01% water) and phosphoryl chloride (99%) were distilled and stored under argon. The 2.2.2. cryptand (Aldrich) was used without further

purification. Reagent grade triethylene glycol and benzyl chloride were distilled under vacuum before use. All solvents were reagent grade and dried over activated molecular sieves (4A), except tetrahydrofuran, which was dried over sodium metal with added benzophenone and distilled directly into the reaction vessel. Methylene chloride was stored for 48 h over activated molecular sieves (3A) and then distilled from calcium hydride directly into the reaction vessel. All glassware was dried in a 150 °C oven for at least 24 h prior to use. All HPLC grade mobile phases were filtered through 0.45 μm millipore membrane filters prior to use.

Stability constants were measured potentiometrically following a known procedure using the same concentrations.[11] Measurements in this work were carried out with an ionic strength of 0.01 M Me$_4$NBr (literature measurements were performed with 0.05 M Me$_4$NBr). A liquid-membrane cation selective electrode (ORION no. 931900) was used in this work with a double junction reference electrode and a Beckman Φ11 pH meter that reads to ±0.1 mV. Sulfuric acid was used to adjust sample and calibration solution pH for the measurements at pH 2. The pH did not change throughout the calibrations and log K_s measurements. Interference from hydrogen ions was negligible down to pH 2.

Preparation of Triethylene Glycol Monobenzyl Ether (3). Sodium hydride (25.3 g of 97% powder, 1.02 mol) was added to dry THF (500 mL) at 0 °C under argon. To this solution was added 400 mL of triethylene glycol (450 g, 3.00 mol) dropwise until the evolution of hydrogen gas ceased. The temperature increased to about 20 °C at the end of the addition, at which time 115.1 mL (126.6 g, 1.00 mol) of benzyl chloride was added. The mixture was brought to reflux for 16 h, cooled, filtered, and rotory evaporated. The resulting viscous liquid was added to 300 mL of ether, extracted two times with water, and dried over anhydrous magnesium sulfate, and the ether was stripped off by rotory evaporation. Fractional vacuum distillation of the crude product gave 97g of pure 3 (135−137 °C, 0.15 mm, n_d^{22} = 1.5050). The water layers were combined and continuously extracted with ether for 7 days, and the ether layer was worked up as before. Fractional vacuum distillation yielded 24 g more of the desired product (130−132 °C, 0.10 mm). Total yield = 50.4% (121 g, 0.504 mol). NMR: ^{1}H δ 7.33 (m, 5H), 4.55 (s, 2H), 3.72−3.54 (m, 12H), 2.05 (broad s, 1H). IR: 3470, 2880, 1160, 770, 700 cm^{-1}.

Preparation of Tris(triethylene glycol monobenzyl ether) Phosphate (7). Sodium hydride (10.1 g of 95% powder, 0.400 mol) was added to dry THF (350 mL) at 8 °C under argon, followed by the dropwise addition of 3 (97 g, 0.404 mol) over a 2 h period. The murky brown mixture was stirred for an additional 30 min, and then phosphoryl chloride (12.4 mL, 20.4 g, 0.133 mol) was added dropwise so that the temperature did not exceed 10 °C. The cloudy lighter brown solution was extracted with ether and water after the addition was complete. The ether layer was dried over anhydrous sodium sulfate and the ether removed by rotory evaporation, giving 90 g of a viscous product (78−80% pure, HPLC, TLC) which was either used crude or was purified in the synthesis of 8. Crude yield: 88.6%. NMR: ^{1}H δ 7.35 (m, 5H), 4.55 (s, 2H), 4.18 (m, 2H), 3.65 (m, 10H); ^{13}C 11 lines; ^{31}P (s, −5.97). IR: 2884, 1250, 1160−915, 760, 700 cm^{-1}. MS: m/e 765 (M + H)$^+$.

Preparation of Tris(triethylene glycol) Phosphate (8). A mixture of 7 (5.05 g, 6.61 mmol) and 10% Pd (10 g on activated carbon) in absolute ethanol (70 mL) was hydrogenated (40 psig) in a Paar apparatus until TLC and HPLC indicated all the benzyl ether groups had been cleaved (3 h). The solution was filtered twice, and the solvent and toluene were removed by rotory evaporation. The crude oily product, 3.108 g (6.29 mmol) was used without further purification in the synthesis of 9. Yield: 95.2%. Pure product from HPLC: n_d^{22} = 1.4639. NMR: ^{1}H δ 4.21 (m, 2H), 3.8−3.5 (m, 10H), 3.18 (broad s, 1H); ^{13}C δ 72.6, 70.5, 70.2, 69.8 (d, $J(^{31}$P−^{13}C) = 6.9 Hz), 66.7 (d, $J(^{31}$P−^{13}C) = 5.8 Hz), 61.4; ^{31}P δ −5.63 (broad s). IR: 3470, 2885, 1460, 1355, 1270, 1160−930, 887, 828 cm^{-1}. MS: m/e 495 (M + H)$^+$.

Preparation of 2,5,8,11,13,16,19,22,23,26,29,32-Dodeca-oxa-1,12-diphospha-1,12-dioxobicyclo[10.10.10]dotria-contane (Phosphocrypt) (9). The compound was synthesized under argon in a flask containing dry methylene chloride (50 mL) and pyridine (488 μL, 6.0 mmol) at reflux. Two pressure-equilibrating dropping funnels were used for the dropwise addition of **4** (188.9 μL, 2.0 mmol in 75 mL of methylene chloride) and **8** (1.0 g, 2.0 mmol in 75 mL of methylene chloride) to the vigorously stirred pyridine solution over an 8 h period. After the addition was complete, the solution was refluxed for 3 more hours and rotory evaporated to a white solid (pyridine HCl) which was then dissolved in a minimum amount of water and run through a strong cation exchange column (Dowex SX50) in the sodium form. The aqueous separation was followed by the presence of chloride in the eluate (AgNO$_3$). Fractions were collected beginning with the first negative AgNO$_3$ test. Each fraction was extracted with methylene chloride four to five times, dried over anhydrous sodium sulfate, and rotory evaporated. From these fractions the product **9** was obtained as a very hygroscopic solid. Yield: 328 mg (30%). NMR: ^{1}H δ 4.20 (broad m, 4H), 3.70 (broad m, 4H), 3.65 (s, 4H); ^{13}C δ 70.5, 69.8 (broad d, $J(^{31}P-^{13}C) = 6.9$ Hz), 66.8 (broad, d, $J(^{31}P-^{13}C) = 5.8$ Hz); ^{31}P δ −5.95. IR: 2890, 1458, 1268, 1155−940, 828, 751 cm^{-1}. MS: m/e 539 (M + H)$^+$. HRMS: calcd for C$_{18}$H$_{37}$O$_{14}$P$_2$ (M + H)$^+$ 539.1657, found: 539.1658.

Supplementary Material Available: Copies of ^{1}H NMR spectra of **3**, **9**, and the 2.2.2 cryptand N-oxide and COSY and HETCOR spectra of **8** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.