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STRUCTURE AND CONFORMATION OF PYRIDINO- AND DIESTERPYRIDINO-18-CROWN-6 COMPLEXES WITH PRIMARY AMMONIUM SALTS IN SOLUTION AND CRYSTALLINE STATES

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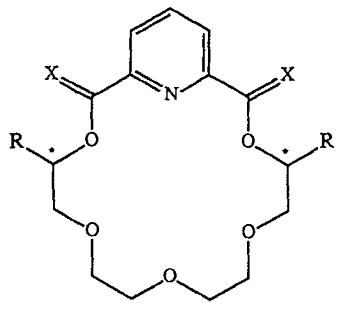
Structures in CD_3OD–$CDCl_3$ mixtures of pyridino-18-crown-6 and diesterpyridino-18-crown-6 complexes with primary ammonium cations containing an α-phenyl group were found to be significantly different. The π–π overlap between the α-phenyl group of the ammonium cation and the pyridine ring of the ligand occurs in the pyridino-18-crown-6 complexes but not in the diesterpyridino-18-crown-6 complexes. The solution structure of a diesterpyridino-18-crown-6 complex with an α-phenyl-containing primary ammonium cation was also found to differ markedly from the corresponding crystal structure in that π–π overlap occurs in the crystal structure, but not in the solution structure.

INTRODUCTION

Pyridino- and diesterpyridino-18-crown-6 ligands form stable complexes with primary ammonium cations in methanol and methanol–chloroform mixtures.[1–3] The primary binding force between these ligands and the primary ammonium cations is that formed by the three hydrogen bonds as shown in Figure 1.[4,5] The chiral members of these ligands, R_2P18C6 (R = Ph) and R_2K_2P18C6 (R = Me, Ph), also exhibit moderate ($\Delta \log K \leqslant 0{\cdot}2$) to significant ($\Delta \log K > 0{\cdot}4$) enantiomeric recognition in forming complexes with α-(1-naphthyl)ethylammonium [$NapCH(CH_3)NH_3^+$] and α-phenylethylammonium [$PhCH(CH_3)NH_3^+$] cations, respectively, in methanol and methanol–chloroform mixtures. In addition to the primary binding force, a second interaction between chiral host and guest molecules is needed to make chiral recognition possible.[6] Examples of this secondary interaction have been given by Pirkle *et al.*[7] and Lipkowitz *et al.*[8] In our case, one candidate for this second interaction is π–π bonding between the α-naphthyl or α-phenyl group of the guest ammonium cation and the pyridine ring of the chiral ligands. Therefore, it is of interest to elucidate further the role of π–π interaction in causing the enantiomeric recognition in these chiral complexes.



X=H: **R₂P18C6** (R=H, Ph, t-Bu, sec-Bu)
X=O: **R₂K₂P18C6** (R=H, Me, Ph)

In this paper, we demonstrate two striking structural

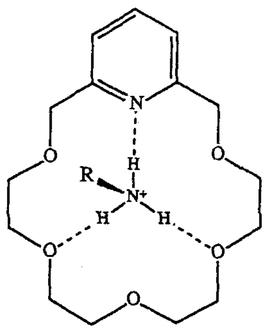


Figure 1. Illustration of the three-point hydrogen bond

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features concerning the presence of this $\pi-\pi$ interaction in the complexes of R_2P18C6 (R = H, Ph, *t*-Bu, *sec*-Bu) and R_2K_2P18C6 (R = H, Me, Ph) with $NapCH(CH_3)NH_3^+$, $PhCH(CH_3)NH_3^+$ and/or $PhCH(CH_2OH)NH_3^+$ in methanol and methanol–chloroform mixtures. We also demonstrate a remarkable difference between the structures of the (*R*, *R*)-Me_2K_2P18C6–(*R*)-$PhCH(CH_2OH)NH_3^+$ complex in a mixture methanol–chloroform (50 : 50, v/v) and in the crystalline state.

RESULTS AND DISCUSSION

Extensive one-dimensional ^1H NMR studies of R_2P18C6 (R = H, Ph, *t*-Bu, *sec*-Bu) complexes with $NapCH(CH_3)NH_3^+$ and $PhCH(CH_3)NH_3^+$ in $CD_3OD–CDCl_3$ mixtures showed that, in each of these systems, the signals corresponding to the pyridine protons of the ligand underwent a significant upfield shift (up to 0·2 ppm) on formation of the complex.[2] This fact provides strong evidence that in each of the complexes either the naphthyl or the phenol group of the ammonium cation is located close to and has some overlap with the pyridine ring of the ligand. The upfield shift of the pyridine proton signals of the ligand on formation of the complex is caused by the magnetic shielding effect of the overlapping naphthyl or phenyl group of the ammonium cation.[9] If the two aromatic groups are separated by a long distance and do not overlap, either one of the two should experience a magnetic deshielding effect rather than the shielding effect and a downfield shift rather than an upfield shift for their proton signals.

A ^1H NMR study of the R_2K_2P18C6 (R = H, Me, Ph) complexes with $NapCH(CH_3)NH_3^+$, $PhCH(CH_3)NH_3^+$ and $PhCH(CH_2OH)NH_3^+$ showed that in the formation of each complex with $NapCH(CH_3)NH_3^+$, the pyridine proton signals of the ligand underwent an upfield shift (up to 0·15 ppm), whereas in the formation of each complex with $PhCH(CH_3)NH_3^+$ and $PhCH(CH_2OH)NH_3^+$, the pyridine proton signals of the ligand underwent a significant downfield shift (up to 0·15 ppm). The downfield shift of the pyridine proton signals in the latter two instances indicates that the phenyl group of either $PhCH(CH_3)NH_3^+$ or $PhCH(CH_2OH)NH_3^+$ is away from and does not overlap with the pyridine ring of the ligand. Evidence for the separation of the phenyl group from the pyridine ring in the R_2K_2P18C6 (R = H) complex with $PhCH(CH_3)NH_3^+$ and the R_2K_2P18C6 (R = Me) complex with $PhCH(CH_2OH)NH_3^+$ is also found in the ^1H NMR NOESY spectra of these two complexes in $CD_3OD–CDCl_3$ (50 : 50). In these NOESY spectra [Figures 2(a) and (b)], off-diagonal signals correlating the chemical shifts of the pyridine protons (*ca.* 8·1–8·3 ppm) and those of the phenyl protons (*ca* 7·2 ppm) are absent. Instead, off-diagonal signals are present which correlate the pyridine chemical shifts of the ligand and the methyl chemical shift (1·5 ppm) of $PhCH(CH_3)NH_3^+$ [Figure 2(a)] or the methylene chemical shift (*ca* 3·9 ppm) of $PhCH(CH_2OH)NH_3^+$ [Figure 2(b)], indicating that the methyl or methylene protons of the ammonium cation are in close proximity (<5 Å) to the pyridine protons of the ligand. The phenyl group of the ammonium cation, then, must be positioned far away from the pyridine ring of the ligand.

Other major off-diagonal signals in Figures 2(a) and (b) also support the above conclusion. For example, in Figure 2(a), a pair of strong off-diagonal signals are seen to correlate the phenyl proton chemical shifts (*ca* 3·7 ppm) of $PhCh(CH_3)NH_3^+$ and the chemical shifts (*ca* 3·7 ppm) of the ligand's $-OCH_2CH_2-$ protons at the bottom (far from the pyridine ring), indicating that the phenyl group of the ammonium cation is in close proximity to the part of the ligand opposite to the pyridine ring. In Figure 2(b), a pair of off-diagonal signals are seen to correlate the phenyl proton chemical shifts (*ca* 7·0 ppm) of $PhCH(CH_2OH)NH_3^+$ and the chemical shifts (*ca* 4·0 ppm) of the ligand's $-OCH_2CH_2O-$ protons in the region far from the pyridine ring indicating that the phenyl group of the ammonium cation is distant from the pyridine ring.

In contrast to the observed solution structure of the R_2K_2P18C6 (R = Me) complex with $PhCH(CH_2OH)NH_3^+$ in $CD_3OD–CDCl_3$ (50 : 50), the phenyl group of the ammonium cation is found to be partly overlapping with, rather than being positioned away from, the pyridine ring of the ligand in the crystal structure of the same complex as seen in Figure 3. Quantitative evidence for $\pi-\pi$ interaction and overlap of the aromatic rings is found in the dihedral angle between the pyridine and phenyl groups and the shortest interatomic distances between the phenyl carbons and the atoms of the ligand. The dihedral angle between the least-square planes of the aromatic groups is 7·2°, which indicates that the rings are nearly parallel. The shortest interatomic distances between the carbons of the phenyl group and atoms of the ligand are as follows: C22—N1, 3·37 Å; C23—N1, 3·4 Å; C24—C21, 3·57 Å; C25—C21, 3·67 Å; C26—O3, 3·39 Å; and C27—C3, 3·34 Å. These distances indicate that the aromatic rings partially overlap with the phenyl group being displaced towards C3 and O3. This is shown in Figure 3, although the figure exaggerates the displacement because it is rotated several degrees from a view perpendicular to the planes of the aromatic groups in order to show better resolution of the atoms. It is also seen in Figure 3 that the methylene protons of $PhCH(CH_2OH)NH_3^+$ are located well away (>5 Å) from the pyridine ring of the crown ether ligand, and the OH group of the ammonium cation is hydrogen bonded to one of the four oxygens in a nearby ClO_4^- co-anion (not shown).

These results provide a good example of the crystal structure of a complex being markedly different from the corresponding solution structure. The difference between the structures of the R_2K_2P18C6 (R = Me) complex with $PhCH(CH_2OH)NH_3^+$ in the crystalline state and in the CD_3OD–$CDCl_3$ (50:50) solution also suggests that the cause for the absence of the π–π overlap in the solution structures of the R_2K_2P18C6 complexes with $PhCH(CH_3)NH_3^+$ and $PhCH(CH_2OH)NH_3^+$ is solvent related, rather than resulting from an unfavorable conformational strain. If the conformation of the R_2K_2P18C6 (R = Me) complex with $PhCH(CH_2OH)NH_3^+$ in which the overlap between the phenyl group and the pyridine ring occurs is severely strained and energetically unfavourable, it should not be found in the crystal structure.

Molecular mechanics calculations of a number of R_2K_2P18C6 (R = H, Me) complexes with $PhCH(CH_3)NH_3^+$ and $PhCH(CH_2OH)NH_3^+$ indicate that in the absence of solvent, the energy difference between the two conformations, one with and the other one without the presence of the π–π overlap, is small (<2 kcal mol^{-1}) (1 kcal = 4·184 kJ) in each of the complexes studied. It is also found from the molecular mechanics calculations that the conformation with the π–π overlap in each complex is always slightly favored over that without this overlap. These results provide additional support for the involvement of the solvent in causing the absence of π–π overlap in the solution structures of the R_2K_2P18C6 (R = H, Me) complexes with $PhCH(CH_3)NH_3^+$ and $PhCH(CH_2OH)NH_3^+$.

The molecular mechanics calculations have been extended to a number of R_2P18C6 (R = H, Me) and R_2K_2P18C6 (R = H, Me) complexes with not only $PhCH(CH_3)NH_3^+$ and $PhCH(CH_2OH)NH_3^+$ but also with $NapCH(CH_3)NH_3^+$. It is found in each complex

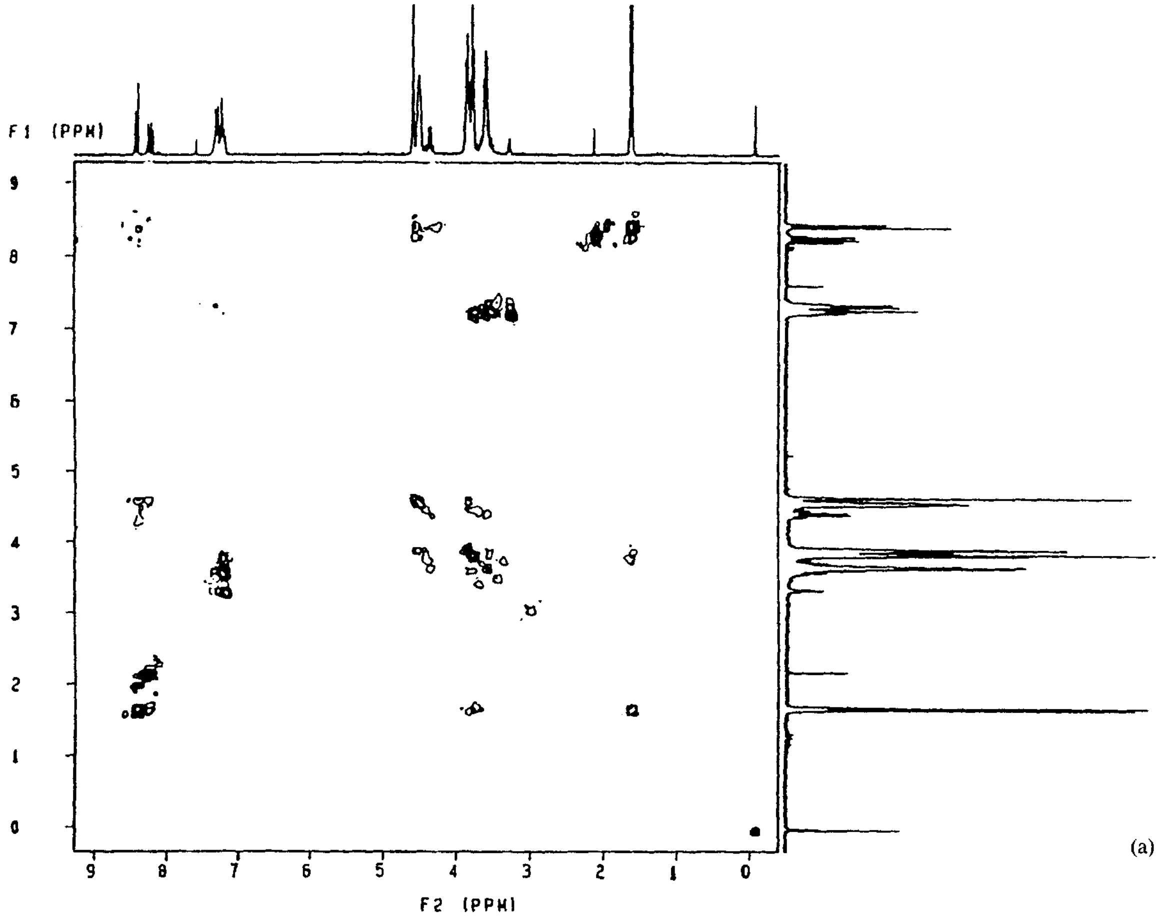

Figure 2. ^1H NMR NOESY spectra of (a) R_2K_2P18C6 (R = H) complex with $PhCH(CH_3)NH_3^+$ and (b) (*R*, *R*)-R_2K_2P18C6 (R = Me) complex with (*R*)-PhCh(Ch_2OH)NH_3^+ in CD_3OD–$CDCl_3$ (50:50, v/v)

that the conformation with the π–π overlap is always favoured slightly over the other, but the energy difference is always small (<3 kcal mol^{-1}).

One explanation for the facts stated above is the following. In the absence of the solvent, the π–π overlap is slightly favoured in the structure of each of the R_2P18C6 or R_2K_2P18C6 complexes with $NapCH(CH_3)NH_3^+$, $PhCH(CH_3)NH_3^+$ and $PhCH(CH_2OH)NH_3^+$ because of the π–π interaction. In the presence of the solvent, the keto oxygens in each R_2K_2P18C6 molecule are solvated and the π–π overlap may happen only at the cost of removing the solvent molecules from the keto oxygens of the ligand in each R_2K_2P18C6 complex with $NapCH(CH_3)NH_3^+$, $PhCH(CH_3)NH_3^+$ and $PhCH(CH_2OH)NH_3^+$. The phenyl group has fewer π electrons and is smaller than the naphthyl group. In addition, it is evident in Figure 3 that good overlap of the phenyl and pyridino groups would result in a large distortion of the three-point hydrogen bonding. This problem is not found in the crystal structure involving the naphthyl group.[5] Hence it is probable that the π–π interaction between the phenyl group of the ammonium cation and the pyridine ring of R_2K_2P18C6 is not energetic enough to overcome the cost to remove the solvent molecules from the keto oxygens of the ligand. Hence the π–π overlap between the phenyl group of the ammonium cation and the pyridine ring of the ligand is not observed in solution. On the other hand, the π–π interaction of the naphthyl group with the pyridine ring is sufficiently energetic to allow π–π overlap in the solution. The R_2P18C6 molecules do not have keto functions which could be solvated so the phenyl or naphthyl groups of the ammonium cations can be overlapped with the pyridine ring of the ligand, as was observed, with no need to overcome the above-mentioned desolvation energy.

As a support to this explanation, it was found that the maximum downfield shift of the ligand pyridine

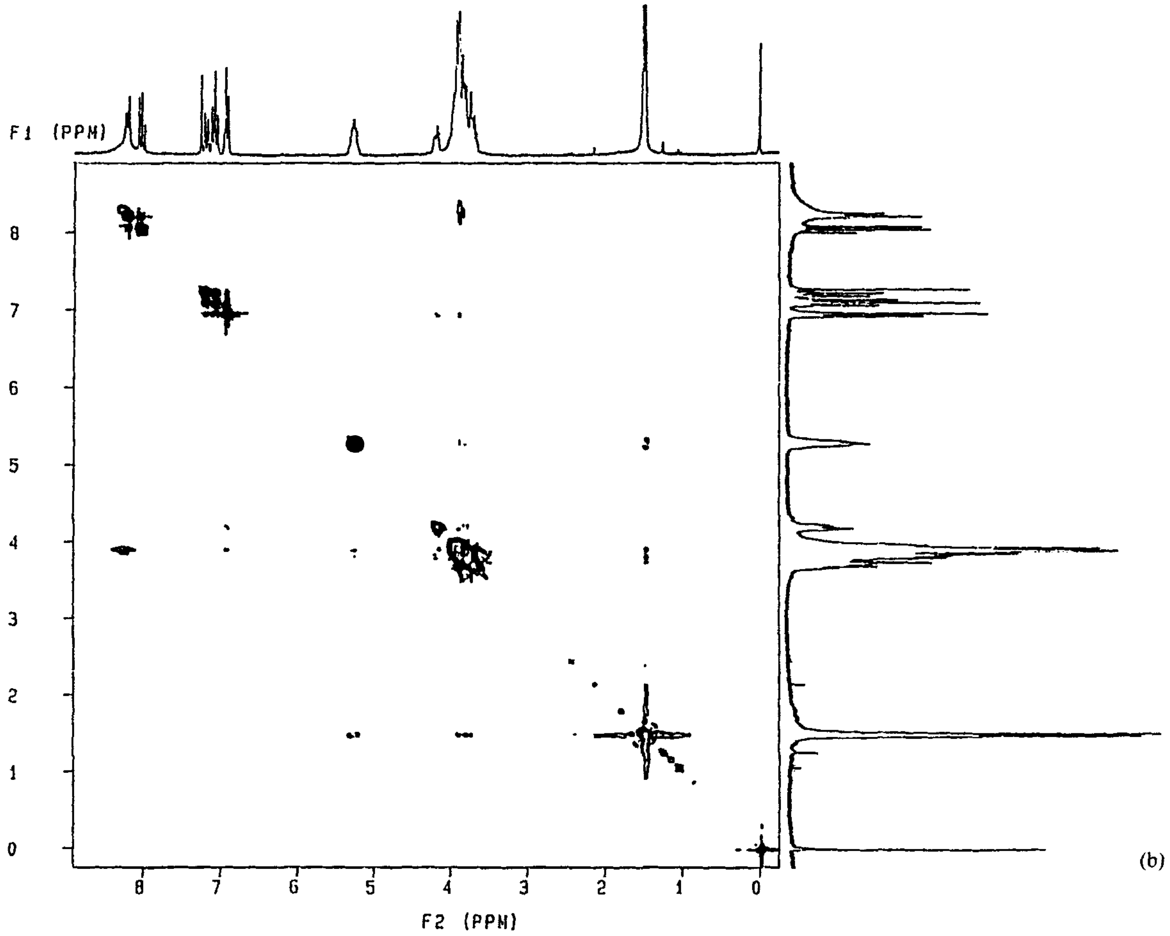

Figure 2. (*Continued*)

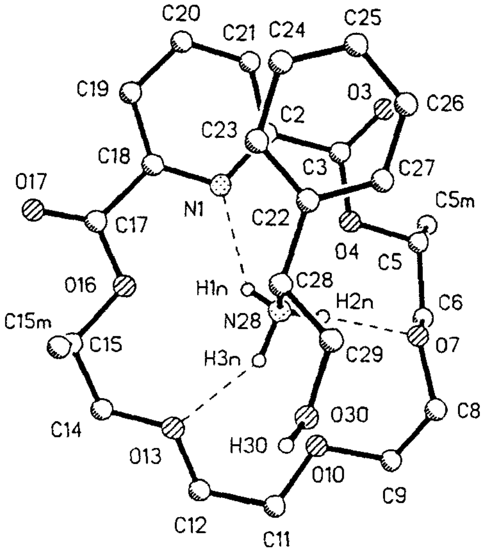

Figure 3. Crystal structure of the (*R*, *R*)-R_2K_2P18C6 complex with (*R*)-$PhCh(CH_2OH)NH_3^+ClO_4^-$. The ClO_4^- and the hydrogen atoms bonded to carbon atoms are omitted for clarity

proton signals in the formation of the R_2K_2P18C6 (R = ME) complex with $PhCH(CH_3)NH_3^+$ was reduced significantly from 0·15 to 0·5 ppm on changing the solvent from $CD_3OD–CDCl_3$ (50 : 50) to pure $CDCl_3$. This indicates that the distance between the α-phenyl group of the ammonium cation and the pyridine ring of the ligand is much less in pure $CDCl_3$ than in $CD_3OD–CDCl_3$ (50 : 50). Chloroform is a much weaker solvating agent than methanol toward the keto oxygens of the ligand, hence the keto oxygens of the ligand are much less solvated in pure $CDCl_3$ than in $CD_3OD–CDCl_3$ (50 : 50), allowing the α-phenyl group of the ammonium cation to be closer to the pyridine ring of the ligand.

EXPERIMENTAL

Materials. Chiral ligands R_2K_2P18C6 (R = H, Me, Ph) and R_2P18C6 (R = H, Ph, *t*-Bu, *sec*-Bu) were prepared according to published methods.[10–12] The ammonium perchlorate salts studied were prepared by treating the free amines (Aldrich) with dilute aqueous perchloric acid (Mallinckrodt). The salts were crystallized from the resulting aqueous solution followed by recrystallization from a chloroform (Fisher)–acetonitrile (Fisher) mixture. The deuterated solvents CD_3OD and $CDCl_3$ were obtained from Aldrich and were used without further purification.

^1H NMR spectra. ^1H NMR spectra were recorded in either CD_3OD or $CD_3OD–CDCl_3$ mixtures with tetramethylsilane as internal reference using a Varian Gemini 200 MHz NMR spectrometer.

Molecular mechanics calculations. The search comparison of the lowest energy conformations of the R_2P18C6 (R = H, Me) and R_2K_2P18C6 (R = H, Me) complexes with several primary ammonium cations were done using CHARMm[13] and PCMODEL[14] programs on a Silicon Graphics workstation and an IBM-compatible 386SX personal computer, respectively.

The conformational spaces for the crown ethers and the ammonium salts were searched independently using grid search techniques. The lowest energy conformation was distinctly different from that found in the crystal structure of the crown ether. Two conformations of the crown were used in the interaction studies: that with the lowest energy one and another that was energy minimized from the x-ray coordinates. The conformational space of each complex was searched by rotating the ammonium salt within the crown ether cavity and by holding the ammonium portion bound within the cavity and rotating the rest of the salt around the C—N bond. Several local minima were found through this search scheme. In some there was π–π overlap between the pyridine ring of the ligand and the α-aromatic group (either naphthyl or phenyl) of the ammonium salt. For each complex, all local minima were within 5 kcal mol^{-1} of each other.

The force field employed in the molecular mechanics calculations does not include an explicit term for π–π interactions. The CHARMm force field uses a Lennard–Jones 12–6 potential and a Coulombic term. The occurrence of hydrogen bonding and π–π interactions is implicitly detected and calculated by these terms. We have performed extensive calculations[11,12] on pyridino-18-crown-6 complexes with organic ammonium cations using a similar non-bonded energy term (a Lennard–Jones 9–6 term and a Coulombic term) without specific terms for hydrogen bonding and π–π overlap consistent with those features observed in the crystal structures of R_2K_2P18C6 (R = Me) complexes with (*R*)- and (*S*)-$NapCH(CH_3)NH_3^+ClO_4^-$.

X-ray structural determination. Single crystals of the (*R*, *R*)-R_2K_2P18C6 (R = Me) complex with (*R*)-$PhCH(CH_2OH)NH_3^+Cl_4^-$ were grown from a $CD_3OD–CDCl_3$ (50 : 50) solution. A suitable crystal was mounted on a Siemens R3m/V automated diffractometer which utilized monochromatic Mo Kα radiation. The orientation matrix and the lattice parameters for the crystal were obtained using 50 carefully centred reflections ($7·47 < 2\theta < 29·84$) in a least-squares procedure. The material crystallized in the monoclinic space group $P2_1$ with $a = 10·453(3)$ Å, $b = 12·621(4)$ Å, $c = 10·78762)$ Å, $\beta = 95·43(2)°$ and $V = 1416·9(7)$ $Å^3$ with $Z = 2$. The structure determination summary is included in the supplementary material.* The summary includes crystal data and solution and refinement procedures. The structure was obtained using direct methods and refined using a full-matrix least-squares procedure with 2153 observed data $[F > 3\sigma(F)]$. All non-hydrogen atoms were refined anisotropically. Positions of hydrogen atoms bonded to carbon atoms were calculated based on known geometrical conditions and these atoms were allowed to ride on their neighboring atoms. The methyl groups were refined as rigid bodies. The isotropic thermal parameter of these hydrogen atoms was set equal to approximately 1·2 times the initial equivalent isotropic thermal parameter of the neighbouring atom and was not refined. Hydrogen atoms of the $-NH_3$ group were refined while that of the alcohol hydrogen was treated in the same manner as the hydrogen bonded to carbon atoms. The final R values for the refinement were $R = 0{\cdot}058$ and $R_w = 0{\cdot}044$.

The conformation of the complex is shown in Figure 3. Positional and thermal parameters for the non-hydrogen atoms of the complex are contained in Table 1. The computer drawing clearly shows that the two aromatic portions of the complex in the solid state do overlap, which is unlike the situation in the solution-state structure. The three-point hydrogen bonding arrangement for RNH_3^+ with similar hosts (see Figure 3) is present. In addition, the alcohol hydrogen of the cation is hydrogen bonded to O3Cl of the anion. The hydrogen bond data are included in Table 2. Bond lengths and angles along with isotropic displacement coefficients for the non-hydrogen atoms and atomic parameters for the hydrogen atoms are included in the supplementary material.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($Å^2 \times 10^3$) for non-hydrogen atoms of the crystalline (R, R)-R_2K_2P18C6 (R = Me) complex with (R)-$PhCH(CH_2OH)NH_3^+ClO_4^-$

Atom	x	y	z	U(eq)[a]
Cl	4209(2)	1287	544(2)	75(1)
O1Cl	4421(4)	1017(5)	1823(4)	108(2)
O2Cl	5314(5)	1128(6)	43(6)	143(3)
O3Cl	3167(5)	676(6)	18(4)	126(3)
O4Cl	3871(7)	2353(5)	422(7)	164(4)
N1	1535(4)	−1621(3)	5707(3)	37(1)
C2	1130(5)	−1181(4)	6728(5)	41(2)
C3	−180(5)	−703(5)	6656(5)	50(2)
O3	−567(4)	−217(4)	7513(4)	72(2)
O4	−889(3)	−876(3)	5567(3)	51(1)
C5	−2185(5)	−429(5)	5437(6)	61(2)
C5M	−3065(7)	−1061(7)	6181(9)	111(4)
C6	−2609(5)	−434(6)	4056(7)	75(3)
O7	−1810(4)	212(4)	3409(4)	67(2)
C8	−2270(7)	424(7)	2108(7)	98(3)
C9	−2420(7)	−487(7)	1316(6)	87(3)
O10	−1303(3)	−1138(4)	1418(3)	61(1)
C11	−809(6)	−1381(6)	281(5)	69(3)
C12	91(6)	−2284(6)	460(5)	65(2)
O13	1159(3)	−2007(3)	1328(3)	54(1)
C14	1955(6)	−2903(5)	1588(5)	64(2)
C15	3076(5)	−2626(5)	2500(5)	55(2)
C15M	3947(6)	−1770(5)	2089(6)	71(3)
O16	2548(3)	−2294(3)	3657(3)	54(1)
C17	3216(5)	−2562(5)	4727(5)	51(2)
O17	4122(4)	−3133(4)	4791(4)	81(2)
C18	2713(5)	−2059(4)	5831(5)	40(2)
C19	3496(5)	−2054(5)	6949(5)	58(2)
C20	3083(6)	−1548(6)	7960(5)	67(2)
C21	1885(6)	−1112(5)	7856(5)	58(2)
C22	1901(4)	876(4)	4692(4)	37(2)
C23	3076(5)	777(5)	5371(5)	48(2)
C24	3269(5)	1179(6)	6569(5)	61(2)
C25	2292(6)	1693(5)	7083(5)	62(2)
C26	1115(6)	1814(5)	6392(5)	56(2)
C27	924(5)	1403(4)	5214(5)	45(2)
C28	1701(4)	416(4)	3394(4)	38(2)
N28	758(4)	−476(3)	3343(3)	41(1)
C29	1250(6)	1230(5)	2414(5)	60(2)
O30	969(4)	741(4)	1249(3)	68(2)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 2. Hydrogen bond data for the crystalline (R, R)-R_2K_2P18C6 (R = Me) complex with (R)-$PhCH(CH_2OH)NH_3^+ClO_4^-$

Atom			Distance (Å)		Angle (°)
D	H	A	D...A	H...A[a]	D−H...A[a]
N28	H1N	N1	2·977(6)	2·23	143
N28	H2N	O7	2·829(6)	1·93	169
N28	H3N	O13	2·966(6)	2·12	142
O30	H30	O3Cl	2·761(6)	1·87	137

[a] E.s.d. values for distances and angles involving H atoms are estimated at 0·03 Å and 2°, respectively, as positions of H atoms were not refined.

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* Supplementary material, which includes a structure determination summary, bond lengths and angles and anisotropic displacement coefficients for the non-hydrogen atoms and atomic parameters for hydrogen atoms for the complex, is available from the authors (N.K.D.).

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