Complexation of phosphoryl-containing mono-, bi- and tri-podands with alkali cations in acetonitrile. Structure of the complexes and binding selectivity

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We present experimental and theoretical studies on new ionophores (L) which possess a high complexation ability for Li$^+$ or Na$^+$ cations. Four tri-podands (R^1–O–C$_2$H$_4$–)$_3$N [R^1 = –CH$_2$–P(O)Ph$_2$ (P1), –C$_2$H$_4$–P(O)Ph$_2$ (P2), -o-C$_6$H$_4$P(O)Ph$_2$ (P3) and -o-C$_6$H$_4$–CH$_2$–P(O)Ph$_2$ (P4)], one bi-podand (R^2–O–C$_2$H$_4$–)$_2$N–CH$_3$ [R^2 = -o-C$_6$H$_4$–CH$_2$–P(O)Ph$_2$ (P5)] and one mono-podand [R^2–O–(CH$_2$–CH$_2$–O)$_3$–R^2 (P6)] containing phosphine oxide terminal groups have been synthesised. Stability constants, enthalpies and entropies of their complexation with lithium, sodium and potassium thiocyanates have been determined in acetonitrile at 298 K by a calorimetric titration technique. We find that tri-podands form a variety of complexes [(M$^+$)$_3$L, (M$^+$)$_2$L, M$^+$L and M$^+$L$_2$)], whereas the bi- and mono-podand form only M$^+$L complexes with Li$^+$ and Na$^+$, and M$^+$L and M$^+$L$_2$ complexes with K$^+$. Formation of poly-nuclear (M$^+$)$_n$L complexes of tri-podands in solution has been confirmed by electro-spray mass spectrometry. At relatively small concentrations of the ligand (C^0_L), P1 binds Na$^+$ much better than Li$^+$, whereas P4 and P5 display a remarkable Li$^+$/Na$^+$ selectivity; at large C^0_L the complexation selectivity decreases. X-Ray diffraction studies performed on monocrystals of complexes of NaNCS with tri-podands P2 and P3 show that Na$^+$ is encapsulated inside a 'basket-like' pseudocavity, coordinating all donor atoms of the tri-podand. Molecular dynamics simulations on P2, P3 and P4 and on their 1:1 complexes with M$^+$ in acetonitrile solution suggest that the structures of M$^+$L complexes in solution are similar to those found for P2 and P3 complexes in the solid state.

Introduction

In recent years, efforts have been made to design ionophores (L) which selectively bind the Li$^+$ cation in solution.[1–9] The best Li$^+$ binders have been found among crown ethers having 12 to 14 membered rings and their derivatives,[2–6] cryptand 2.2.1,[7] tert-butylcalix[4]arenetetraacetate[8] and acyclic ionophores with a quinolyl group.[9]

In this context, molecules containing phosphoryl groups are of particular interest, because of the high binding affinity of the P=O group for 'hard' metal cations. In polar non-aqueous solvents (THF–CHCl$_3$, acetonitrile), mono- and bi-phosphine oxides like Ph$_3$P=O,[10] Ph$_2$P(O)–CH$_2$CH$_2$–P(O)Ph$_2$[10] and β-phosphorylate ethers[11] display a clear preference for Li$^+$ over other alkali cations (M$^+$). Stabilities of their metal complexes are, however, relatively small (in acetonitrile, log β = 2–4[11]), which limits practical applications of these molecules. Phosphoryl-containing mono-podands R–O(CH$_2$–CH$_2$–O)$_n$–R with two terminal fragments (R) bridged by a polyether chain are more efficient complexing agents. The podands with a relatively short chain ($n \leqslant 3$) are Li$^+$ selective and form ML$^+$ complexes which are more stable than those of mono- and bidentate phosphoryl-containing ligands or those of macrocyclic and acyclic polydentate ionophores without any phosphoryl group.[10] Podands can be easily modified by varying substituents at phosphorus, in particular, the 'bridges' between ether oxygens and P=O groups. More than 50 phosphoryl-containing mono-podands and their complexes with alkali, alkaline-earth and rare-earth cations have been synthesized[12–29] and studied by conductometry,[30,31] calorimetry,[32–34] extraction[35] and IR spectroscopy[36–38] methods. Compared to macrocyclic iono-phores (crown ethers, cryptands), mono-podands are not pre-organized. Molecular mechanics and dynamics simulations[39–41] and X-ray diffraction studies[37,38] on their complexes with alkali cations show that the ligands wrap around the cation, forming a helix-like structure, whereas in the uncomplexed ionophores there is no such orientation of their donor groups.[39–41]

It is known that 'octopus-like' tri-podands (acyclic analogues of cryptands) are more efficient complexation agents than their chain-like analogues (mono- and bi-podands, see ref. 42 for the nomenclature)[43–49] and that their binding affinity depends on the nature of donor groups attached to their terminal fragments. Thus, Vögtle et al.[45] have shown that, in mixed methanol–water solution, tri-podands with quinolyl terminal groups form more stable complexes with alkali and alkaline-earth cations than do their analogues with phenyl, or with tropolone terminal groups. One could, therefore, expect remarkable complexation properties (especially for Li$^+$ cation) from tri-podands with three phosphoryl-containing terminal groups, but, to our knowledge, no such ligands have been synthesised so far.

The goal of this study is to design new phorphoryl-containing tri-podands **P1**–**P4** and bi-podand **P5** containing phosphine oxide groups. We report their synthesis, their thermodynamics of complexation with alkali cations in acetonitrile solution, their structure in the solid state and their

P1   **P2**   **P3**   **P4**

O—R =

P5   **P6**

P1

O—R =
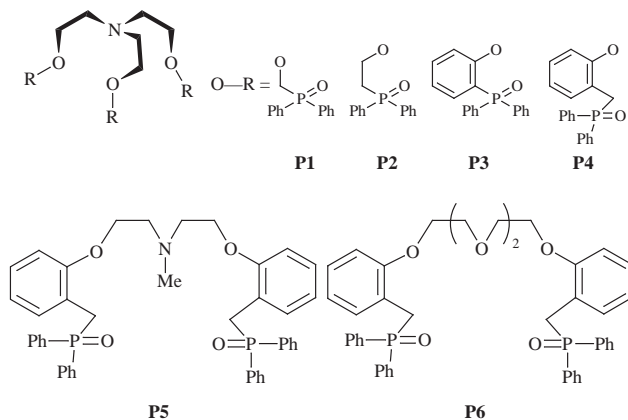
modelling in solution. Their complexation properties in acetonitrile are compared with those of the mono-podand **P6**. All the studied tri-podands have the same number of donor atoms, but differ by the 'bridge' between ether oxygens (O_{eth}) and $P(O)Ph_2$ groups [$-CH_2-$, $-C_2H_4-$, $-C_6H_4-$ and $-o-C_6H_4-CH_2-$ in **P1**, **P2**, **P3** and **P4**, respectively]. Bi-podand **P5** and mono-podand **P6** have the same terminal groups as tri-podand **P4** [R = $-o-C_6H_4-CH_2-P(O)Ph_2$].

In this paper we report studies of the thermodynamics of complexation of these podands with alkali thiocyanates in acetonitrile solution using calorimetric titration techniques. Mathematical treatment of the calorimetric titration curves show that tri-podands form both mono- and poly-nuclear complexes in solution, whose concentrations at equilibrium depend on initial ligand and cation concentrations. The complexation selectivities have been calculated using an approach which takes into account multiple equilibria in solution. The composition of poly-nuclear complexes of tri-podand **P4** in acetonitrile solution has been also assessed by electro-spray mass spectrometry. In order to analyse the cooperativity of their binding sites, the structure of the complexes of tri-podands **P2** and **P3** with NaNCS in the solid state is determined by X-ray diffraction methods. In addition, molecular modelling of tri-podands **P2**, **P3**, **P4** and their 1:1 complexes with Li⁺, Na⁺ and K⁺ cations in acetonitrile is performed in order to gain microscopic insights into the structure of the complexes in solution.

Experimental

Synthesis

The structures of all new compounds were established by analytical data and ¹H and ³¹P NMR spectra. The ¹H and ³¹P NMR spectra were recorded on a Bruker-CXP-200 spectrometer with tetramethylsilane and 85% H_3PO_4 as reference. *J* values are given in Hz. The melting points were measured on a Boetius PHMK-05 instrument.

Tris[2-(diphenylphosphorylmethoxy)ethyl]amine (P1). A suspension of 11.22 g (34.40 mmol) anhydrous Cs_2CO_3, 6.00 g (25.80 mmol) diphenylphosphinoylmethanol and 2.07 g (8.60 mmol) tris(2-chloroethyl)amine hydrochloride in 40 ml was refluxed in dry dioxane for 14 h and diluted in 150 ml of water. The mixture was extracted with chloroform (3 × 50 ml). The organic phase was washed with water (3 × 30 ml) and the solvent was evaporated *in vacuo*. The residue was chromatographed on a column of Brockmann II alumina and chloroform–Pr^{i}OH, (10:1 v/v) as eluent. After evaporation of the solvents *in vacuo*, the residual oil was dried *in vacuo* (1 Torr, 3 h, 150 °C); yield 4.80 g (70.30%), as glass.
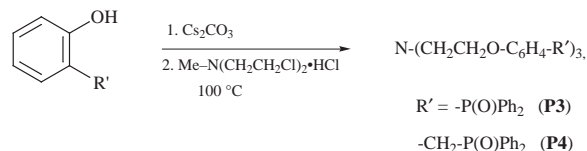
[Calc. for $C_{45}H_{48}NO_6P_3$ (791.79): C, 68.3; H, 6.1; N, 1.8; P, 11.7. Found: C, 68.2; H, 6.0; N, 1.7; P, 11.5%]; δ_H(CDCl$_3$) 2.54 (m, 6H, 3OCH$_2$CH$_2$N), 3.44 (m, 6H, 3OCH$_2$CH$_2$N), 4.14 (d, $^2J_{H-P}$ = 6.0, 6 H, 3P–CH$_2$, Ar), 7.44 (m, 18H, Ar), 7.74 (m, 12H, Ar); δ_P(CDCl$_3$) 27.90.
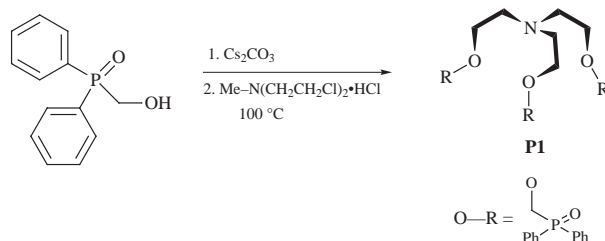
Tris[3-oxa-5-(diphenylphosphoryl)pentyl]amine (P2). 0.11 g (2.00 mmol) of finely ground KOH was added to a solution of 1.09 g (7.30 mmol) of triethanolamine in 20 ml of dry dioxane. The mixture was stirred for 1 h at 20 °C, then 5.00 g (21.90 mmol) of vinyldiphenylphosphine oxide was added. The reaction mixture was held for 48 h at 20 °C, and the solvent was evaporated *in vacuo*. Then 30 ml of water was added to the residue, and extracted with CHCl$_3$ (3 × 30 ml). The organic phase was washed with water (3 × 30 ml) and the solvent was evaporated *in vacuo*. The residue was chromatographed on a column of type L silica gel using chloroform and chloroform–Pr^{i}OH, (10:1 v/v) as eluent. Yield 5.10 g (79%), oil. [Calc. for $C_{48}H_{54}NO_6P_3$ (833.85): C, 69.1; H, 6.5; N, 1.7; P, 11.1. Found: C, 69.0; H, 6.4; N, 1.7; P, 10.9%]; δ_H(CHCl$_3$) 2.60 [m, 12H, 3NCH$_2$CHO + 3CH$_2$CH$_2$P(O)Ar], 3.30 (m, 6H, OCH$_2$CH$_2$N), 3.78 [m, 6H, OCH$_2$CH$_2$, P(O)Ar], 7.40 (m, 18H, Ar), 7.70 (m, 12H, Ar); δ_P(CHCl$_3$) 30.02.

O—R =

P2
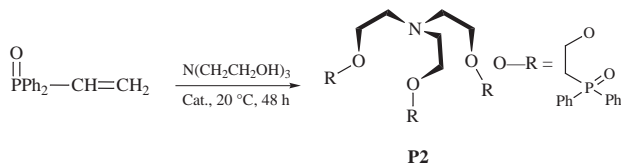
Tris[*o*-(diphenylphosphoryl)phenoxyethyl]amine (P3). P3 was prepared from 10.03 g (30.76 mmol) anhydrous Cs_2CO_3, 5.88 g (20.00 mmol) 2-(diphenylphosphoryl)phenol and 1.3 g (6.66 mmol) tris(2-chloroethyl)amine hydrochloride in 50 ml in dry dioxane. Yield of **P3** 5.15 g (79.00%), as glass. [Calc. for $C_{60}H_{54}NO_6P_3$ (977.97): C, 73.7; H, 5.6; N, 1.4; P, 9.8. Found: C, 73.5; H, 5.6; N, 1.3; P, 9.5%]; δ_H(CDCl$_3$) 2.04 (m, 6H, 3NCH$_2$CH$_2$O), 3.54 (m, 6H, 3OCH$_2$CH$_2$N), 6.84 (m, 3H, Ar), 7.00 (m, 3H, Ar), 7.20–7.80 (m, 36H, Ar); δ_P(CDCl$_3$) 27.20.

N-(CH$_2$CH$_2$O-C$_6$H$_4$-R′)$_3$,

R′ = -P(O)Ph$_2$ (**P3**)

-CH$_2$-P(O)Ph$_2$ (**P4**)

Tris[*o*-(diphenylphosphorylmethyl)phenoxyethyl]amine (P4). A suspension of 8.15 g (25.0 mmol) anhydrous Cs_2CO_3, 5.0 g (16.2 mmol) of 2-(diphenylphosphinylmethyl)phenol and 1.3 g (5.4 mmol) of tris(2-chloroethyl)amine hydrochloride in 50 ml of dry dioxane was refluxed for 14 h and was diluted with 150 ml of water. The mixture was extracted with chloroform (3 × 50 ml). The organic phase was washed with water (3 × 30 ml) and the solvent was evaporated *in vacuo*. The residue was chromatographed on a column of Brockmann II alumina and chloroform and chloroform–Pr^{i}OH, (10:1 v/v) as eluent. After evaporation of the solvents *in vacuo*, the residual oil was dried (1 Torr, 3 h, 150 °C), yield 5.0 g (90%), as glass. [Calc. for $C_{63}H_{60}NO_6P_3$ (1020.04): C, 74.2; H, 5.9; N, 1.4; P, 9.1. Found: C, 74.0; H, 5.8; N, 1.3; P, 9.1%]; δ_H(CDCl$_3$) 2.82 (m, 6H, 3NCH$_2$CH$_2$O), 3.70 (m, 12H, 3ArCH$_2$P + OCH$_2$CH$_2$N), 6.68 (m, 3H, Ar), 6.90 (m, 3H, Ar), 7.10 (m, 3H, Ar), 7.34 (m, 20H, Ar), 7.62 (m, 13H, Ar); δ_P(CDCl$_3$) 24.09.
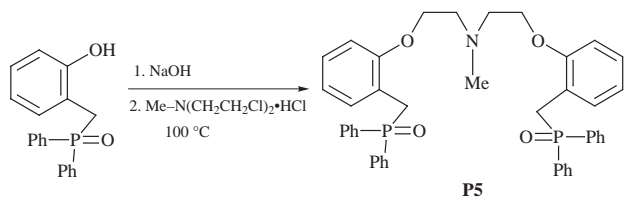
Methyl[bis(*o*-diphenylphosphorylmethyl)phenoxyethyl]amine (P5). A suspension of 5.30 g (16.2 mmol) anhydrous Cs_2CO_3,

Table 1 Thermodynamics parameters (log β, ΔG, ΔH and $T\Delta S$) of complexation of LiNCS with phosphoryl containing podands in acetonitrile at 298 K[a]

Ligand	Reaction[b]	log β	ΔG/kJ mol⁻¹	ΔH/kJ mol⁻¹	$T\Delta S$/kJ mol⁻¹
P1	I	4.08(0.2)	−23.3	−28.1(2.0)	−4.8
P2	I	4.16(0.2)	−23.7	−32.8(2.0)	−9.1
	II	6.04(0.4)	−34.5	−68.4(5.0)	−33.9
	III	9.99(0.5)	−57.0	−46.7(3.0)	10.3
P3	I	4.30(0.10)	−24.5	−10.7(1.0)	13.9
	II	6.35(0.50)	−36.3	−16.6(2.0)	19.6
	III	8.22(0.50)	−46.9	−19.3(3.5)	27.6
P4	I	3.48(0.24)	−19.8	−20.2(2.9)	−0.4
	II	4.56(0.60)	−26.1	−40.7(6.3)	−14.6
	III	7.60(1.1)	−43.2	−27.1(1.2)	16.1
P5	I	4.56(0.15)	−26.1	−17.5(1.5)	8.6
P6	I	4.90(0.02)	−27.9	−25.2(0.3)	2.7

[a] Stability constants β have been calculated with the CHEM-EQUI program[52] using calorimetric titration data. [b] Reactions: I, $M^+ + L = M^+L$; II, $2M^+ + L = (M^+)_2L$; III, $3M^+ + L = (M^+)_3L$; IV, $M^+ + 2L = M^+L_2$.

5.0 g (16.2 mmol) of 2-(diphenylphosphorylmethyl)phenol and 1.55 g (8.1 mmol) methyl[bis(2-chloroethyl)]amine hydrochloride in 50 ml dry dioxane was refluxed for 14 h and was diluted with 150 ml of water. The mixture was extracted with chloroform (3 × 50 ml). The organic phase was washed with water (3 × 30 ml) and the solvent was evaporated *in vacuo*. The residue was chromatographed on a column of Brockmann II alumina, chloroform and chloroform–Pr^{i}OH, (10:1 v/v) as eluent. Yield 4.12 g (76%) oil. [Calc. for $C_{43}H_{43}NO_4P_2$ (669.76): C, 73.8; H, 6.2; N, 2.0; P, 8.9. Found: C, 73.5; H, 5.9; N, 1.9; P, 8.6%]; δ_H(CDCl$_3$) 2.45 (s, 3H, NCH$_3$), 2.80 (m, 4H, 2NCH$_2$CH$_2$O−), 3.76 (m, 8H, 2ArCH$_2$P + 2OCH$_2$CH$_2$N), 6.68 (m, 2H, Ar), 6.88 (m, 2H, Ar), 7.10 (m, 2H, Ar), 7.34 (m, 14H, Ar), 7.68 (m, 8H, Ar); δ_P(CDCl$_3$) 30.34.

1,8-Bis[2-(diphenylphosphinylmethyl)phenoxy]-3,6-dioxaoctane (P6). P6 was prepared as reported in reference 30, mp 131.5–133 °C. In the complexation experiments, podands **P1**–**P6** were
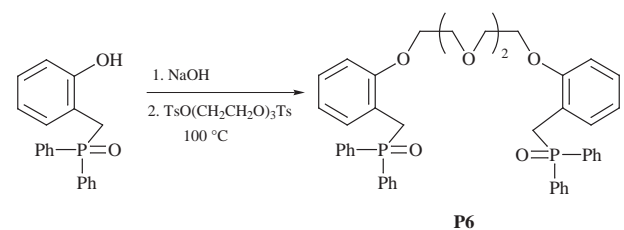
used without any additional purification. The preparation of 'pure for analysis' grade sodium thiocyanate and the monitoring of its water content were performed according to reported procedures.[50] Acetonitrile solvent was dried over P$_2$O$_5$ according to a standard procedure.[51] The water content in acetonitrile were monitored by IR spectroscopy for ν(OH) at 3450–3600 cm⁻¹.

Thermodynamics of complexation in solution

Log β and ΔH values (Tables 1–3) were determined using the calorimetric titration technique. The heats of the reaction were measured on an LKB-2017/112 calorimeter at 298 K by calori-

Table 2 Thermodynamics parameters (log β, ΔG, ΔH and $T\Delta S$) of complexation of NaNCS with phosphoryl containing podands in acetonitrile at 298 K[a]

Ligand	Reaction	log β	ΔG/kJ mol⁻¹	ΔH/kJ mol⁻¹	$T\Delta S$/kJ mol⁻¹
P1	I	3.73(0.4)	−21.3	−22.3(3.0)	−1.0
	II	7.59(0.2)	−43.3	−36.8(2.0)	6.5
	III	7.41(0.5)	−42.3	−73.3(5.0)	−31.0
P2	I	6.06(0.3)	−34.6	−34.8(1.0)	−0.2
	IV	11.23(0.3)	−64.1	−34.3(1.5)	29.8
P3	I	4.32(0.12)	−24.7	−20.7(0.2)	4.0
	II	5.85(0.20)	−33.4	−60.1(2.0)	−26.7
P4	I	3.00(0.5)	−17.1	−19.6(0.3)	−2.5
	IV	4.47(0.30)	−25.5	−17.6(0.8)	7.9
P5	I	2.97(0.03)	−17.0	−16.1(0.3)	0.9
P6	I	4.63(0.15)	−26.4	−33.0(2.0)	−6.5

[a] See footnotes of Table 1.

Table 3 Thermodynamics parameters (log β, ΔG, ΔH and $T\Delta S$) of complexation of KNCS with phosphoryl containing podands in acetonitrile at 298 K[a]

Ligand	Reaction	log β	ΔG/kJ mol⁻¹	ΔH/kJ mol⁻¹	$T\Delta S$/kJ mol⁻¹
P3	I	2.44(0.10)	−13.9	−16.6(1.0)	−2.7
	IV	4.49(0.20)	−25.6	−13.1(2.0)	12.5
P4	I	2.02(0.20)	−11.5	−12.6(0.7)	−1.1
	IV	5.01(0.30)	−28.6	−4.3(1.0)	24.3
P6	I	1.75(0.15)	−10.0	−20.6(3.0)	−10.6
	IV	3.68(0.20)	−21.0	−6.9(1.0)	14.1

[a] See footnote for Table 1.

metric titration. Titration of the ligand solution by the salt and titration of the salt solution by the ligand were both carried out. In the titration experiments the total concentration of the salt (C^o_S) was varied from 0.2 to 34.6 mmol l⁻¹ and that of the ligand (C^o_L) varied from 0.2 to 28.9 mmol l⁻¹.

Equilibria in solution. The stoichiometry of the complexes, stability constants and reaction enthalpies were calculated from the experimental titration curves using the CHEM-EQUI program.[52] This program has been developed for the calculation of equilibrium constants and related thermodynamics values from spectral, thermochemical or electrochemical experimental data (IR, NMR, UV–VIS, fluorescence spectroscopy, potentiometry, calorimetry, conductometry, *etc.*). CHEM-EQUI can use any combination of these data simultaneously to calculate equilibrium constants. It uses several algorithms of minimization (gradient, simplex and Monte-Carlo methods) and various statistical criteria for selecting a model of equilibrium in a solution that most precisely fits to the experimental data.

If ligand L forms with the cation M^+ and the anion X a variety of complexes in solvent S corresponding to different n, m and k [reaction (1)], the CHEM-EQUI program using

$$nM^+ + kX^- + mL \rightleftharpoons M_nL_mX_k \qquad (1)$$
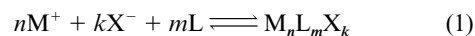
calorimetric data, calculates the stability constants β_j, $j = 1, \ldots, p$ and enthalpies of reactions ΔH_j of these p equilibria by minimizing a weighted error-function $U(\beta, \Delta H)$ [eqn. (2)], where

$$U(\beta, \Delta H) = \sum_{i=1}^{N} w_i(Q_{exp,i} - Q_{calc,i})^2 \Longrightarrow \text{minimum} \quad (2)$$

$Q_{exp,i}$ and $Q_{calc,i}$ are experimental and calculated heats at points along the titration, w_i is the weight of the i-th point of a titration. $Q_{calc,i}$ is calculated for each point of the titration curve as a function of volumes of initial and final samples of each titration (V_b and V_f, respectively), of the concentration of the i-th species (C_i) and of enthalpies ΔH_i and stability constants β_i [eqn. (3)].

$$Q = Q_0 + V_f \sum_{i=1}^{p} \Delta H_i C_i(\beta_1, \ldots, \beta_p) -$$
$$V_b \sum_{i=1}^{p'} \Delta H_i C_i(\beta_1, \ldots, \beta_{p'}) \quad (3)$$

The summation in eqn. (2) is performed over the different types of complexes assumed to be in solution [reaction (1)]. Concentrations C_i are a function of the formation constants β_i [eqn. (4)] and satisfy the mass-balance equation (5), where v_{ij}

$$C_i = \exp(\ln \beta_i + \sum_{j=1}^{q} v_{ij} \ln C_j) \quad (4)$$

$$\sum_{i=1}^{p} v_{ij} C_i = C_j^0; j = 1, q \quad (5)$$

corresponds to the relative stoichiometric coefficient of species j in the reaction in which species i are formed, q is the number of initial reagents (*i.e.* for the complexation of an alkali cation with a podand $q = 2$). Details of algorithms used by CHEM-EQUI are given in ref. 52.

In this study, we used eqns. (2)–(5) to model the simultaneous equilibria corresponding to various stoichiometries of the complexes involving different combinations of n, $m = 1$–3 and $k = 0$–3. As a criterion of reliability of the model we used the Hamilton R-factor[53,54] and residuals ($Q_{exp} - Q_{calc}$) analysis for fitness.[55,56]

Calculations of complexation selectivity. If ligand L forms complexes of the same stoichiometry with cations M_a^+ and M_b^+, the selectivity of complexation can be defined as a ratio of the stability constants of these complexes. This approach does not work if L forms a variety of complexes [M_aL^+, $(M_a^+)_2L$, $(M_a^+)_3L$, ...]. In this case, to calculate the complexation selectivity $Sel(M_a^+)$ of L for any particular cation M_i^+ for the system containing the mixture of the cations and one ligand, we used eqn. (6), where the numerator corresponds to the total

$$Sel(M_a^+) = (\sum_i v_{ai} C_i)/(\sum_b \sum_k v_{kb} C_b) \quad (6)$$

concentration of the complexed cation M_a^+, and the denominator corresponds to the total concentration of all complexed metal cations. Concentrations C_i in eqn. (6) are calculated using eqn. (4). It follows from eqn. (6), that $Sel(M_a^+)$ varies from 0 to 1. Since equilibrium concentration of the $(M^+)_nL$ complexes depends on the ratio $k_C = C_{M^+}^0/C_L^0$ of overall concentrations of the metal ($C_{M^+}^0$) and of the ligand (C_L^0), eqn. (6) allows us to calculate the complexation selectivity as a function of k_C.

It should be noted that the calculations of $Sel(M_a^+)$ used for the system containing the mixture of cations and one ligand (or for the mixture of ligands and one cation), are based on stability constants determined by titration experiments in systems containing only one type of cation. In this work we estimated $Sel(M_a^+)$ for the hypothetical mixed solution of Li$^+$, Na$^+$ and K$^+$ thiocyanates at the same initial concentration of 0.03 M and $C_L^0 \leqslant 0.08$ M.

The reliability of the method was checked by comparison of stability constants (log β) of test reactions calculated with the CHEM-EQUI program[52] using calorimetric titration data with those measured independently.

For the reaction of 18-crown-6 + KNCS in water, using the potentiometric titration method, we have obtained log $\beta = 1.98 \pm 0.05$, which is practically identical to the value calculated with CHEM-EQUI and is in good agreement with results reported in ref. 57 (log $\beta = 2.03$, calorimetric titration) and 67 (log $\beta = 2.06$, potentiometric titration) for the reaction of 18-crown-6 + KCl in water.

For the test reaction 15-crown-5 + KI in methanol we have found a reasonable agreement between calculated stability constants (log $\beta = 3.46 \pm 0.05$ and 5.95 ± 0.07 for M$^+$L and M$^+$L$_2$, respectively) with those obtained in ref. 59 using a calorimetric titration method (log $\beta = 3.35$ and 6.00 for M$^+$L and M$^+$L$_2$, respectively).
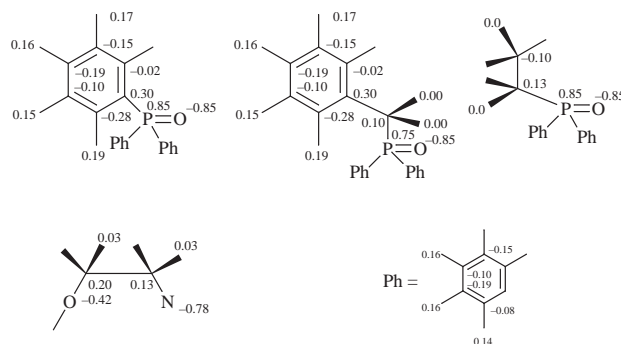
Fig. 1 Charge distributions

Mass spectrometry
The stoichiometry of the complexes of tri-podand **P4** with LiNCS and with NaNCS in acetonitrile solution has been determined by an electro-spray mass spectrometry method using as Plasma Quard mass spectrometer (VG, England).

X-Ray diffraction study
The crystals of the **P2**·NaNCS ($0.30 \times 0.20 \times 0.15$ mm) and **P3**·NaNCS ($0.32 \times 0.30 \times 0.15$ mm) complexes were chosen for X-ray diffraction experiments. The unit cell parameters were determined using the centering of 12 reflections with 2θ in the range of 20–25°. An automated four-circle diffractometer Nicolet P3 using Mo-Kα radiation with a β-filter was used both for unit cell determination and data collection. The reflections with $I \geqslant 3\sigma$ were used for structure refinement. The structures were solved using direct methods with the SHELXTL program[60] and refined with full-matrix least-squares on F^2 anisotropically with the SHELXL-93 program.[61] Hydrogen atoms were localized in difference Fourier maps and refined isotropically. Crystal data and results of the refinement are given in Table 4.†

Molecular modeling studies in acetonitrile solution
The AMBER4.1 program package was employed for molecular mechanics and molecular dynamics simulations on tri-podands **P2**–**P4** and their complexes with alkali cations in acetonitrile. The electrostatic potential atomic charges (Fig. 1) were calculated by an MNDO method using MOPAC-5 program.[62] They were multiplied by the factor 1.42 which scales MNDO ESP charges to the *ab initio* 6-31G* values.[63] The cation parameters employed were those found by Åqvist to reproduce relative and absolute free energies of hydration.[64] For acetonitrile we used the OPLS model, where CH$_3$ is represented in the united atom approximation.[65] The initial structures of the complexes were modeled using the MacroModel 5.5 program[66] and were first energy minimized *in vacuo*.
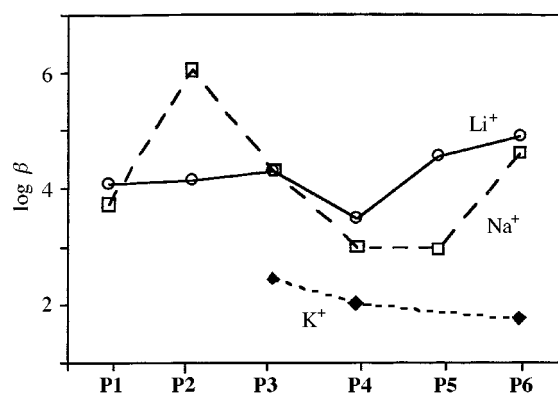
To simulate the solution state, a single complex 'molecule' was placed in a solvent box, which was a 'cube' of 28–30 Å length, containing 374–380 acetonitrile molecules, with periodic boundary conditions. The solute was placed at the center of the box and all solvent molecules within 3 Å and beyond 12 Å from the solute were deleted. In solution, the C–H bonds were constrained to constant values with SHAKE, in conjunction with a time step of 2 fs. In the gas phase, the time step was 1 fs, without SHAKE.

After 1000 steps of conjugate gradient energy minimization, the MD simulations were run for 50–200 ps at 300 K in the (N, V, T) ensemble starting with random velocities. A residue based

Table 4 Complexes **P2**·NaNCS and **P3**·NaNCS in the solid state, crystal data and structure refinement

	P2·NaNCS	**P3**·NaNCS
Empirical formula	$C_{49}H_{54}N_2NaO_6P_3S$	$C_{61}H_{54}N_2NaO_6P_3S$
Formula weight	914.9	1059.0
Crystal system	Orthorhombic	Trigonal
Space group	$P2_12_12_1$	$R3$
Unit cell dimensions		
$a/\text{Å}$	17.735(4)	16.736(2)
$b/\text{Å}$	17.740(4)	16.736(2)
$c/\text{Å}$	15.681(3)	35.302(7)
Density (calculated)/g cm^{-3}	1.232	1.232
Absorption coefficient/mm^{-1}	0.220	0.200
$F(000)$	1928	3324
Size of the crystal/mm	$0.30 \times 0.20 \times 0.15$	$0.32 \times 0.30 \times 0.15$
θ range for data collection/°	1.62 to 23.98	2.87 to 25.04
Reflections collected	2820	2870
Final R indices [$I > 2\sigma(I)$]		
R_1	0.0412	0.0617
wR_2	0.1079	0.1798
Goodness-of-fit on F^2	0.958	1.090
Extinction coefficient	0.0016(7)	0.0008(3)
Diffractometer	Nicolet P3	Nicolet P3
Collection method	$\theta/2\theta$	$\theta/2\theta$
Radiation type	Mo-Kα	Mo-Kα
Temperature/K	293(2)	293(2)
Wavelength/Å	0.710 69	0.710 69
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Standards number	3	3
Standards interval count	100	100
Standards decay (%)	1	1

Fig. 2 Stability constants of the M$^+$L complexes (M$^+$ = Li$^+$, Na$^+$; L = **P1**–**P6**) in acetonitrile. Some of these complexes are in equilibrium with other stoichiometric arrangements (see Tables 1–3).

cut-off of 10 Å was used for non-bonded interactions, taking the ion pair as a single residue. The temperature was controlled by velocity scaling in the gas phase, and by coupling to a thermal bath in solution.

To analyse the energy contributions of different molecular fragments in the binding of M$^+$, the ionophores were 'dissected' into a 'tripod' fragment [N(CH$_2$CH$_2$O)$_3$] and three terminal groups [R = -C$_2$H$_4$–P(O)Ph$_2$ (**P2**), = -o-C$_6$H$_4$–P(O)Ph$_2$ (**P3**) and = -o-C$_6$H$_4$–C$_2$H$_4$–P(O)Ph$_2$ (**P4**)]. The interaction energies of the cation-terminal group ($E_{M^+\ldots R}$) and cation-ligand ($E_{M^+\ldots L}$) have been recalculated from the MD trajectories; their statistical fluctuations are about 12–20 kJ mol^{-1}.

Results

Thermodynamics of complexation

Stability constants, free energies, enthalpies and entropies of complexation of the podands **P1**–**P6** with M$^+$ in acetonitrile at 298 K are presented in Tables 1–3. In complexes with the Li$^+$ and Na$^+$ cations, tri-podands **P1**–**P4** display different stoichiometries compared to the bi-podand **P5** and the mono-podand **P6**. Thus, the tri-podands form with Li$^+$ and

Na$^+$ mono-nuclear M$^+$L, poly-nuclear (M$^+$)$_2$L, (M$^+$)$_3$L and bi-ligand M$^+$L$_2$ complexes, whereas mono- and bi-podands form only M$^+$L complexes. Ionophores **P3**, **P4** and **P6** form both M$^+$L and M$^+$L$_2$ complexes with K$^+$.

In previous work on similar phosphoryl-containing podands[12–29] the complexation selectivity has been determined based on the hypothesis that only 1 : 1 complexes are present. Here they are considered in equilibrium with other stoichiometric arrangements. In the following, we first discuss the relative stabilities of 1 : 1 complexes of podands **P1**–**P6**. This is followed by an analysis of the other equilibria.

Stabilities of 1 : 1 complexes. Results presented in Tables 1–3 and in Fig. 2 show that the stabilities of 1 : 1 complexes with tri-podands (log β) depend on the rigidity of the 'bridge' between the ether oxygens and phosphoryl groups. Thus, **P1** and **P4** prefer Li$^+$ over Na$^+$, **P2** prefers Na$^+$, whereas the stabilities of the Li$^+$ over Na$^+$ complexes of **P3** are nearly the same. Bi-podand **P5** and mono-podand **P6** form with Li$^+$ more stable complexes than with Na$^+$. Complexes of all podands with K$^+$ are weaker than those with smaller cations. Surprisingly, the stabilities of 1 : 1 complexes of tri-podands with Li$^+$ are smaller than those of mono-podands. Thus, for the podands **P4**–**P6** having the same terminal groups, the stability of the Li$^+$L complexes decreases in the order **P6** > **P5** > **P4**, and for the LNa$^+$ complexes this order is **P6** > **P4** $\geqslant$ **P5**. These results are difficult to rationalise on the basis of only cation–ligand interactions because tri-podand **P4** has more donor centres ($N_d = 7$) than bi-podand **P5** ($N_d = 5$) and mono-podand **P6** ($N_d = 6$). Presumably, solvent, counterion and conformational effects play important roles in the stabilities of these complexes. In the LM$^+$ complexes of tri-podands, the cation is encapsulated in the pseudo-cavity formed by the ionophore and is shielded from the solvent (see structures below). In the 1 : 1 complexes of mono- and bi-podands in acetonitrile, additional stabilisation may come from solvent molecules which coordinate to M$^+$. A similar stabilisation by solvent molecules may take place with poly-nuclear complexes of tri-podands which cannot be of a fully converging type like 1 : 1 complexes.

Relative population of complexed forms of (M$^+$)$_n$L$_m$ as a function of the ratio of overall concentrations of L and M^+. The treatment of the calorimetric data shows that equilibrium
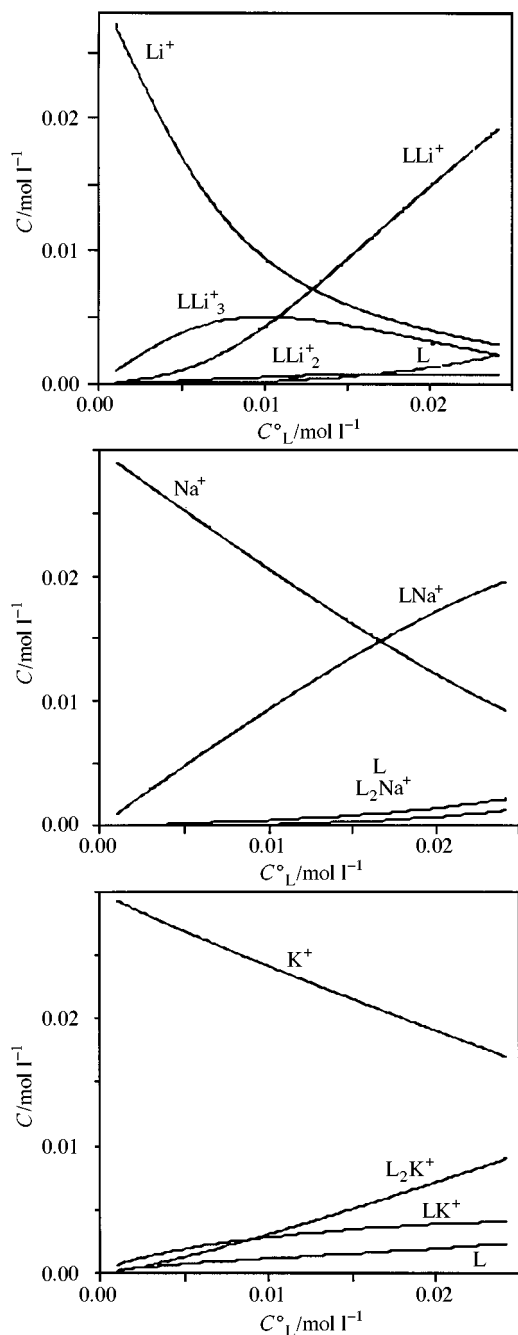
Fig. 3 Equilibrium concentrations of tri-podand **P4**, of the M^+ cation [$M^+ = Li^+$ (top), Na^+ (middle) and K^+ (bottom)] and of their $(M^+)_nL_m$ complexed forms in acetonitrile as a function of the overall ligand concentration (C°_L, mol l^{-1}) at the overall concentration of a cation $C^\circ_{M^+} = 0.03$ mol l^{-1}

concentrations of free ligand, of M^+ and of the complexes [M^+L, $(M^+)_2L$, $(M^+)_3L$ and $(M^+)L_2$] depend on the ratio $k_C = C^\circ_{M^+}/C^\circ_L$. Thus, when the Li^+ cation is in excess ($C^\circ_L < 0.01$ M, which corresponds to $k_C > 3.3$), tri-podand **P4** forms mostly $(M^+)_3L$ complexes, whereas at higher ligand concentrations, the 1:1 complexes become dominant (Fig. 3). For the Na^+ complexes of **P4**, the M^+L form is more populated than the M^+L_2 one at any k_C. The population of the 1:1 form of the complexes of **P4** with K^+ is relatively high only at high excess of the cation ($C^\circ_L < 0.008$ M, $k_C > 4$); at higher concentrations of the ligand, the M^+L_2 complex dominates over the M^+L one (Fig. 3).

Complexation selectivity. The relative selectivities $Sel(M_a^+)$ of podands **P1–P6** for the M^+ cations, calculated for $C^0_{M^+} = 0.03$ M by eqn. (6) are presented in Fig. 4. Since $Sel(M_a^+)$ is a
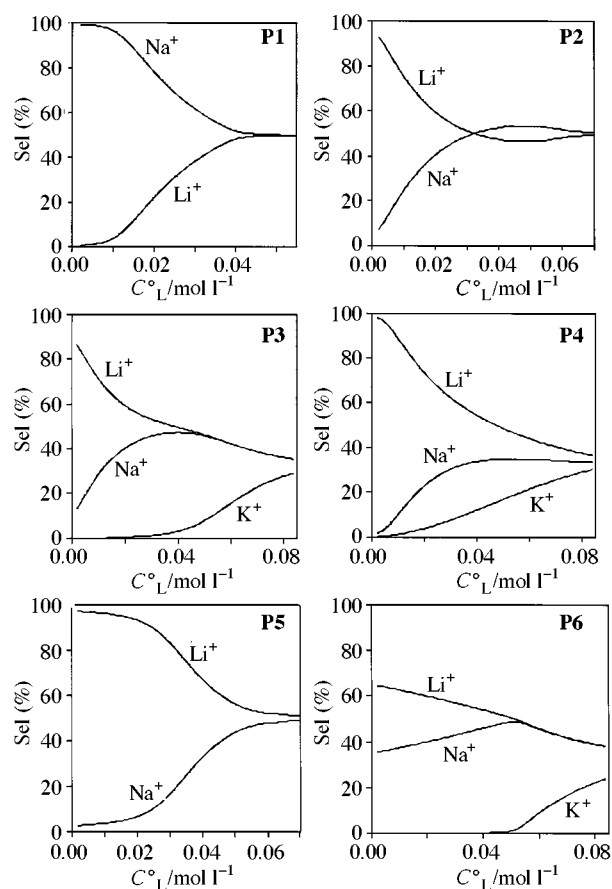

Fig. 4 Complexation selectivity $Sel(M_a^+)$ of podands **P1–P6** as a function of concentration of the ligand (C°_L, mol l^{-1}) calculated for the concentration of cations $C^\circ_{M^+} = 0.03$ mol l^{-1}

function of the number of types of complexes and of their stabilities, it does not necessarily correspond to the relative stabilities of M^+L complexes. Thus, tri-podand **P1** (Fig. 4) displays a Na^+ selectivity for $C^\circ_L = <0.05$ M, although its 1:1 complex with Li^+ (log $\beta = 4.08$) is more stable than the one with Na^+ (log $\beta = 3.73$). This is because **P1** forms with Li^+ only M^+L complexes, whereas Na^+ complexes of M^+L, $(M^+)_2L$ and $(M^+)_3L$ types are present in solution. Analogously, tri-podand **P2**, whose 1:1 Na^+ complex (log $\beta = 6.06$) is more stable than that with Li^+ (log $\beta = 4.16$), displays a Li^+ selectivity at $C^\circ_L < 0.03$ M ($k_C = 1$) (Fig. 4). This podand forms complexes M^+L, $(M^+)_2L$ and $(M^+)_3L$ with Li^+, and M^+L and ML_2^+ complexes with Na^+. Selectivities $Sel(M_a^+)$ for the podands **P3–P6** at $C^\circ_L < 0.04$ M (Fig. 4) qualitatively correspond to the order of stabilities of their M^+L complexes ($Li^+ > Na^+ > K^+$).

It follows from the plots $Sel(M_a^+)$ *versus* C°_L (Fig. 4) that at small concentrations, tri-podands **P2–P4** and bi-podand **P5** display a remarkable Li^+ selectivity: at $C^\circ_L = 0.002$ M ($k_C = 16.5$), $Sel(L^+) = 0.93$, 0.87, 0.98 and 0.97 for **P2**, **P3**, **P4** and **P5**, respectively. Mono-podand **P6** does not discriminate well Li^+ from Na^+: $Sel(Li^+) = 0.65$ at $C^\circ_L = 0.002$ M ($k_C = 16.5$). Variation of the 'bridge' between the O_{eth} atoms and P=O fragments dramatically change the Li^+/Na^+ selectivity of tri-podands. Thus, tri-podand **P1** with a $-CH_2-$ 'bridge' instead of a $-CH_2-CH_2-$ one in **P2**, is almost 100% selective for Na^+ at small C°_L. The discrimination properties of all ionophores diminish when the ligand concentration increases: at $C^\circ_L > 0.04$ M ($k_C = 0.75$), $Sel(Li^+) \simeq Sel(Na^+)$.

One may conclude that tri-podand **P4** and bi-podand **P5** discriminate Li^+ from Na^+ better than tri-podands **P2–P3** and mono-podand **P6**, whereas tri-podand **P1** selectively binds Na^+. It should be noted that the highest Li^+/Na^+ selectivity (for **P4** and **P5** podands) or Na^+/Li^+ selectivity (for **P1** podand) is
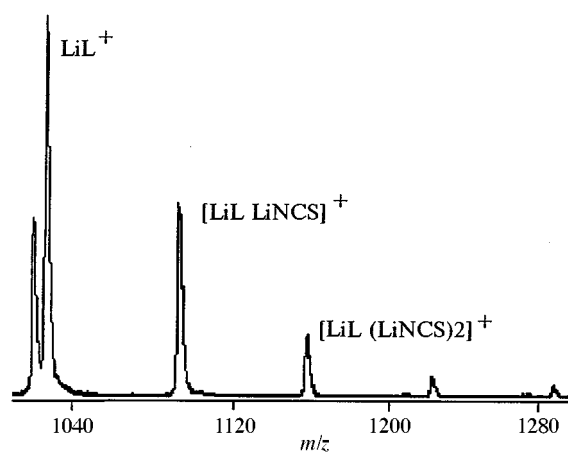
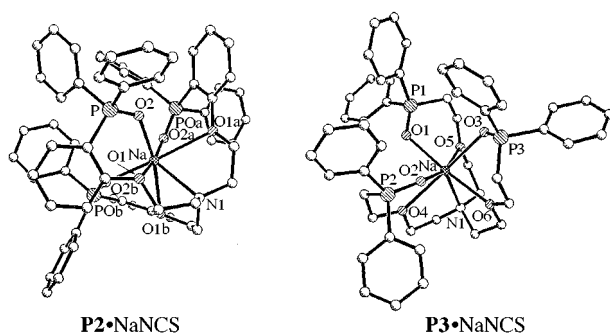**Fig. 5** The mass-spectrum of the complexes of LiNCS formed with tri-podand **P4** in acetonitrile solution

P2·NaNCS   **P3·NaNCS**

Fig. 6 Complexes **P2·NaNCS** (left) and **P3·NaNCS** (right) in the solid state

achieved at small concentrations ($C°_L$ < 0.002 M, i.e. k_C > 16.5) of the ligand. This is important from the practical point of view, because it may allow one to use small amounts of the ionophores in analytical devices.

Mass spectrometry of the complexes in solution

The existence of polynuclear complexes of tri-podands found from the fitting of the calorimetric data was confirmed by electro-spray mass spectrometry studies on the complexes of **P4** with the salts of Li^+ and Na^+ in acetonitrile. For the LiNCS complexes, the mass spectrum contains five peaks with m/z = 516.7, 1026.7, 1091.7, 1157.7 and 1221.7 corresponding to the species $[Li_2L]^{2+}$, $[LLi]^+$, $[LLi(LiNCS)]^+$, $[LLi(LiNCS)_2]^+$ and $[LLi(LiNCS)_3]^+$, respectively (Fig. 5). For the solution containing NaCl, **P4** and traces of water, peaks corresponding to $[NaHL]^{2+}$ (m/z = 521.7), $[HL]^+$ (1020.5) and $[NaL]^+$ (1042.5) cations are observed. Thus, mass spectrometry results are consistent with calorimetric data, which show that **P4** forms poly-nuclear complexes with Li^+, but not with Na^+ cations. Also noteworthy was the presence of SCN^- anion coordinated to the Li^+ complex.

Structure of the complexes in the solid state

Both **P2·NaNCS** and **P3·NaNCS** structures consist of separated complex Na^+L and anion SCN^-. The Na^+ cation has a coordination number of 7 and is encapsulated into a 'basket-like' podand molecule (Fig. 6). Its coordination sphere includes three phosphoryl oxygens (O_{ph}), three ether oxygens (O_{eth}) and the nitrogen atom; its coordination polyhedron may be described as a 'two-apexed' slightly distorted tetragonal bipyramid. The $Na^+ \cdots O_{eth}$ distances are 2.5–2.7 Å (in the complex with **P2**) and 2.6–2.7 Å (in the complex with **P3**). The $Na^+ \cdots N$ (2.6 Å) and $Na^+ \cdots O_{ph}$ (2.3 Å) distances are similar in both complexes. The N atom of the ligand has a

Table 5 Selected average distances (Å) in the complexes of tri-podands **P2**–**P4** with alkali cations (M^+ = Li^+, Na^+ and K^+) simulated by MD in acetonitrile[a]

		Li^+	Na^+	K^+
$M^+ \cdots O_{eth}$	**P2**	2.9–3.1	2.7–2.8	2.8–3.0
	P3	3.2–3.8	2.6–2.7	2.8
	P4	3.1–4.2	2.5–2.7	3.2–3.5
$M^+ \cdots O_{ph}$	**P2**	1.9	2.3	2.6
	P3	1.9	2.3	2.7
	P4	1.9	2.3	2.6
$M^+ \cdots N$	**P2**	2.8	2.5	2.7
	P3	2.1	2.7	2.8
	P4	2.4	2.4	2.7
$N \cdots \langle O_{ph} \rangle$[b]	**P2**	3.3	3.5	3.9
	P3	2.8	3.9	4.1
	P4	2.9	3.4	3.7
$M^+ \cdots \langle O_{eth} \rangle$[c]	**P2**	1.4	1.1	1.4
	P3	1.6	1.1	1.2
	P4	1.5	0.8	1.4
$M^+ \cdots \langle O_{ph} \rangle$[d]	**P2**	0.7	1.1	1.2
	P3	0.7	1.3	1.4
	P4	0.7	1.2	1.1

[a] Statistical fluctuations are 0.2 Å. Distances between [b] N and the plane of phosphoryl oxygens ($N \cdots \langle O_{ph} \rangle$), [c] M^+ and the plane of ether oxygens ($M^+ \cdots \langle O_{eth} \rangle$), [d] M^+ and phosphoryl oxygens ($M^+ \cdots O_{ph}$), M^+ and the plane of phosphoryl oxygens ($M^+ \cdots \langle O_{ph} \rangle$).
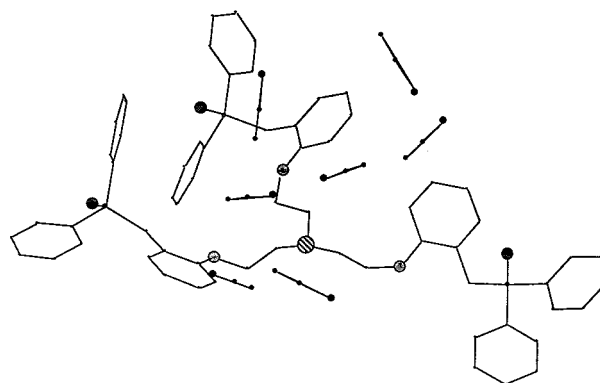

Fig. 7 Tri-podand **P4** in acetonitrile. Snapshot after 50 ps of MD simulations.

typical tetragonal environment. In the complex with the more rigid ligand **P3** the C–N–C and Na–N–C angles are close to their 'ideal' values (109.2–109.8°), whereas in the complex $[Na·P2]^+NCS^-$ they are 104–114°, which corresponds to a more distorted tetrahedron.

Molecular dynamics simulations on tri-podands P2–P4 and on their M⁺L complexes (M^+ = Li^+, Na^+ and K^+) in acetonitrile solution

In order to gain microscopic insights into the structure of the complexes in solution, molecular dynamics simulations of tri-podands **P2**, **P3**, **P4** and of their 1:1 complexes with Li^+, Na^+ and K^+ cations have been performed in acetonitrile. In the uncomplexed tri-podands, all P=O groups diverge from the pseudo-symmetry axis (Fig. 7). As they have no pseudo-cavity suitable to encapsulate a cation, these free ligands are not pre-organized for 1:1 complexation.

In the M^+L complexes of **P2**–**P4**, the cation is encapsulated in the pseudo-cavity delineated by all seven donor atoms of the ligand (Figs. 8 and 9), and shielded from the solvent. Schematically, M^+ sits between the plane of the three ether oxygens $\langle O_{eth} \rangle$, and that of the three phosphoryl oxygens $\langle O_{ph} \rangle$ (Fig. 9). The size of the pseudo-cavity, roughly estimated by the $N \cdots \langle O_{ph} \rangle$ distance, increases regularly with the size of cation (Table 5). The coordination patterns of M^+ also vary as a function of a cation's size. In the Li^+L complexes, the small Li^+
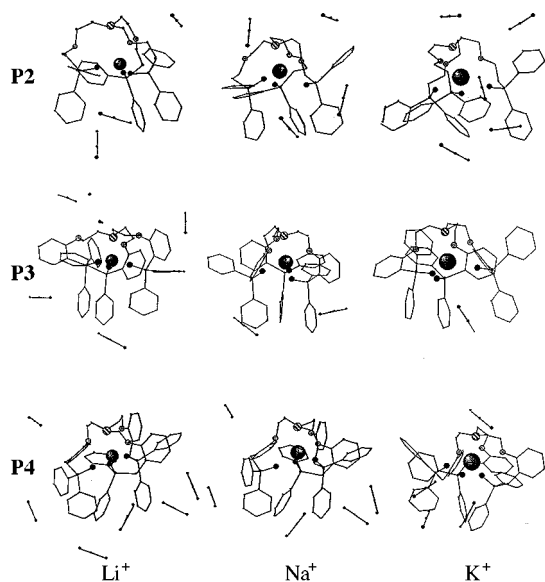
Fig. 8 1:1 complexes of tri-podands **P2**, **P3** and **P4** with alkali cations ($M^+ = Li^+$, Na^+, and K^+) in acetonitrile. Snapshots after 50 ps of MD simulations.
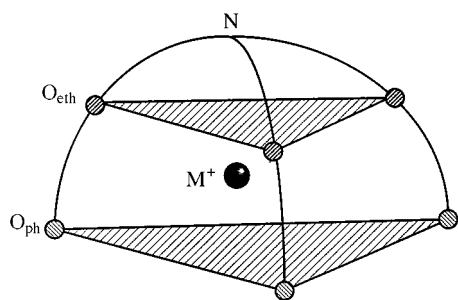

Fig. 9 Schematical representation of the coordination sphere of the M^+ cation in its complex with a tri-podand

cation is situated much closer to the phosphoryl oxygens than to other donor atoms. The $Li^+ \cdots O_{ph}$ distances are approximately the same for any L (1.93 Å), whereas the cation's separation from the O_{eth} atoms (2.9–4.2 Å) and from the nitrogen (2.1–2.8 Å) is much larger. In the Na^+L and K^+L complexes, the cation has similar distances with all donor atoms of the ligand (Table 5).

The contribution of the podand's terminal groups [R = $-C_2H_4-P(O)Ph_2$ (**P2**), $-o$-$C_6H_4-P(O)Ph_2$ (**P3**) and $-o$-$C_6H_4-CH_2-P(O)Ph_2$ (**P4**)] in the binding of M^+ has been calculated from the MD trajectories of the complexes. These calculations show that the three terminal groups contribute about 60% in the binding in the three Li^+L complexes but only 30–40% in the three Na^+L and K^+L complexes, which relates to the structural differences between these two types of complexes.

Discussion

### The terminal groups effect on the complexation properties of podands

Phosphoryl-containing terminal groups are known to enhance the alkali cations binding capability of mono-podands (L) compared to glyms (G) which possess the same number of donor atoms.[10] Depending on the flexibility/rigidity of terminal group and the length of the polyether chain, the difference between $\log \beta$ stability constants varies from 1 to 5 for complexation of Li^+ cation in mixed solvent THF–CHCl$_3$. In acetonitrile this effect becomes even stronger.[10] These results are in agreement with the solvent extraction studies,[41] in which

ionophores L extract alkali and alkaline earth picrates from water to chloroform much better than polyethylene glycols with the same number of donor atoms.

Molecular dynamics simulations performed on the complexes of alkali cations with phosphoryl-containing tri-podands (this work) and monopodands[39–41,68] unambiguously demonstrate that P=O groups efficiently interact with M^+, especially with small Li^+ cations. Thus, in the complexes with tri-podands **P2**–**P4**, Li^+ sits much closer to the oxygens of phosphoryl groups than to other donor atoms of the ligand. This explains why the three terminal groups of tri-podands contribute about 60% of Li^+–ligand interaction energy.

Li^+/Na^+ complexation selectivity of phosphoryl-containing podands as a function of their topology, flexibility and the number of binding sites

Here we discuss the Li^+/Na^+ complexation selectivity of phosphoryl-containing podands as a function of the conformational flexibility of terminal groups, of the number of binding sites and of their topology. We compare the complexation properties of **P1**–**P6** and of their analogues **I–VII** studied recently by Solov'ev et al.[11]
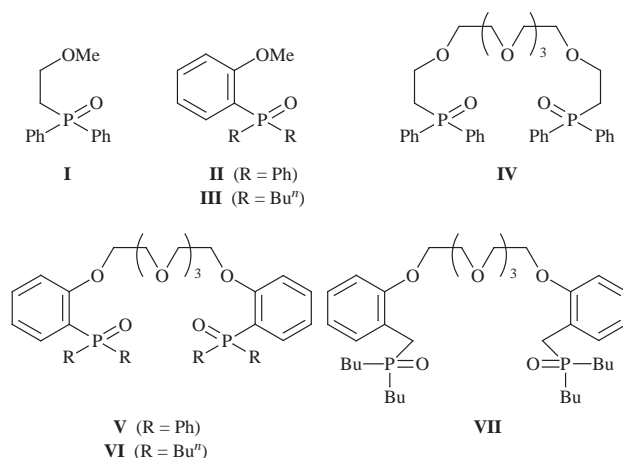
Bidentate molecules **I–III** are Li^+ selective [Sel(Li^+) = 0.8–0.9 at $k_C > 3.3$]. This is typical for ionophores whose P=O group is the main binding site.[11,27,68,69] Although **I–II** display a good Li^+/Na^+ selectivity, their metal complexes are 1.5–2 orders of magnitude less stable than those of podands **IV–VII**[11] and of **P1**–**P6**.

Flexibility/rigidity of podands' terminal groups can be an important factor for the Li^+/Na^+ discrimination. Thus, mono-podands **IV** and **VII** with relatively flexible terminal groups, selectively bind Li^+ [at $k_C = 16.5$, Sel(Li^+) = 0.89 and 0.51 for **IV** and **VII**, respectively]. More rigid podands **V** and **VI** possess a high Na^+-selectivity [at $k_C = 16.5$, Sel(Na^+) = 0.99 and 0.77 for **V** and **VI**, respectively].[11] Interestingly, podands **IV–VII** form poly-nuclear complexes $(Li^+)_2L$ or $(Li^+)_3L_2$, but not with Na^+. It seems that complexation selectivity of tri-podands is less sensitive to the conformational rigidity of their terminal groups. Thus, **P2** podand (with a flexible, $-CH_2-CH_2-$ 'bridge') and **P3** (with a rigid $-C_6H_4-$ 'bridge') display similar Sel(Li^+) selectivity at $C^\circ_L < 0.03$ M. The length of 'bridges' between O_{eth} atoms and $P(O)Ph_2$ groups is a more important parameter which modifies binding selectivities of tri-podands. Tri-podand **P1** (with $-CH_2-$ bridges) prefers Na^+, whereas the analogues **P2**–**P4** with longer 'bridges' are Li^+ selective. The **P4** podand with the longest 'bridge' displays a Li^+/Na^+ selectivity higher than either of the other tri-podands.

Topology of a podand also plays an important role in its binding selectivity. Thus, the chain-like mono-podand **V** (Na^+ selective)[11] has seven donor atoms and the same terminal groups as octopus-like tri-podand **P3**, which is Li^+ selective

(Fig. 4). Cryptand 2.2.1 (with also seven donor atoms) forms in acetonitrile very stable complexes with small alkali cations, but it does not prefer Li$^+$ (log β = 10.3) over Na$^+$ (log β > 11.3).[70] In the same solvent, the Li$^+$ complex of the cryptand 2.1.1 (log β > 10) is slightly more stable than the Na$^+$ complex (log β > 9).[71] *tert*-Butylcalix[4]arenetetraacetate forming 1:1 complexes with alkali cations in MeCN,[8] prefers Li$^+$ (log β = 6.4) over Na$^+$ (log β = 5.8), but it does not display a Li$^+$/Na$^+$ selectivity [Sel(Li$^+$) = 0.80] as high as do **P4** and **P5** podands.

Small crown ethers[2–6,71] and acyclic ionophores with a quinolyl group[9] display a high binding affinity toward Li$^+$ in some organic solvents and in biphasic water/organic solvent systems, but they were not studied in acetonitrile and cannot be compared to podands **P1**–**P6**, as far as their Li$^+$/Na$^+$ selectivities is concerned.

Among podands studied so far in acetonitrile (**P1**–**P6** and **I**–**VII**[11]), **P4** and **P5** molecules display the highest Li$^+$/Na$^+$ selectivity.

Conclusions

This work is devoted to the synthesis, experimental and theoretical studies on new ionophores: four tri-podands, one bipodand and one mono-podand containing phosphine oxide terminal groups. Using a calorimetric titration technique we have determined their stability constants, enthalpies and entropies of complexation with lithium, sodium and potassium thiocyanates in acetonitrile at 298 K. It has been found that in solution, tri-podands form a variety of complexes [(M$^+$)$_3$L, (M$^+$)$_2$L, M$^+$L and M$^+$L$_2$], whereas bi- and mono-podands form only M$^+$L complexes with Li$^+$ and Na$^+$, and M$^+$L and M$^+$L$_2$ with K$^+$. The formation of poly-nuclear (M$^+$)$_n$L complexes of tri-podands in solution has been confirmed by electro-spray mass spectrometry measurements.

It has been shown that the complexation selectivity of podands varies as a function of their concentration because of formation of the complexes of different stoichiometries. At small concentrations of the ligand, the tri-podand **P1** with −CH$_2$−P(O)Ph$_2$ terminal groups prefers Na$^+$, whereas the other ionophores selectively bind Li$^+$. Tri-podand **P4** and bi-podand **P5** with R = −C$_6$H$_4$−CH$_2$−P(O)Ph$_2$ terminal groups *display in acetonitrile the highest Li$^+$/Na$^+$ selectivity compared to any other podand studied so far.* The remarkable complexation selectivities of tri-podands **P1** for Na$^+$ and **P4** for Li$^+$, surprisingly, are mostly related to the formation of poly-nuclear (M$^+$)$_n$L complexes where the P=O groups act separately, rather than to 1:1 complexes with strong cooperativity of binding sites.

Structural studies in the solid and liquid phases (X-ray crystallography and molecular dynamics simulations) highlight the role of P=O containing terminal groups in the cation binding in 1:1 complexes.

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