Spherand Complexation and Decomplexation Rates with Sodium and Lithium Picrates, and Activation Parameters for Decomplexation

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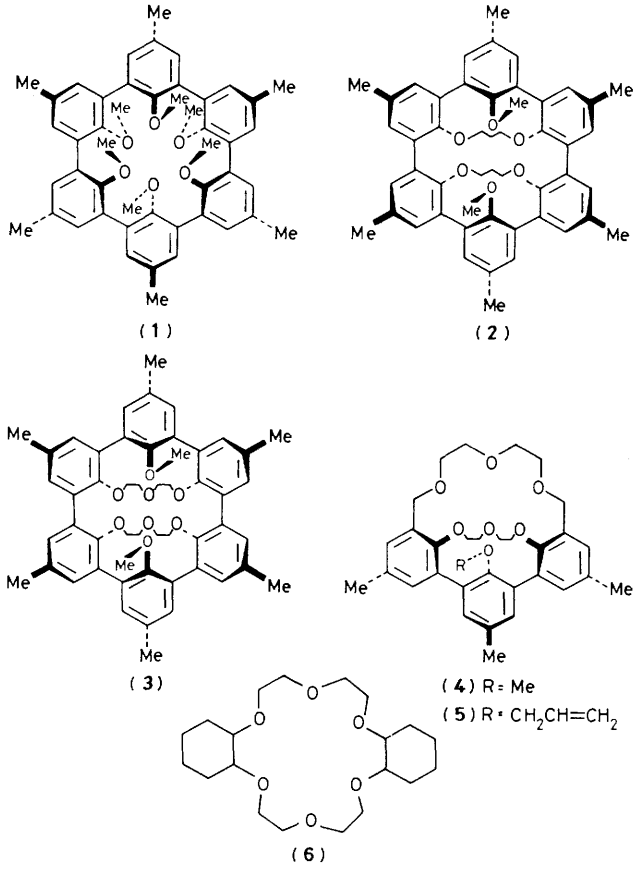
Rate constants have been determined for the complexation and decomplexation of sodium and lithium picrates with three spherands in $CDCl_3$ saturated with D_2O at 25 °C, and the thermodynamic activation parameters have been estimated for decomplexation.

The syntheses of the spherands (**1**),[1] (**2**),[2] and (**3**)[3] have been reported, and the crystal structures of (**1**), (**1**)–LiCl, (**1**)–$NaMeSO_4$,[4] (**2**)–$LiFeCl_4$, and (**3**)–LiCl[3] determined. The binding free energies ($-\Delta G^\circ$ values) of these spherands with NaPic or LiPic [Pic = $C_6H_2N_3O_7$] in $CDCl_3$ saturated with D_2O at 25 °C were too high to be measured by the standard extraction method.[5] We report here a modification of this method applied to (**2**) when complexing NaPic, and of the

hemispherand (4)† when complexing NaPic and LiPic. We also report the rate constants in the same medium for complexation and decomplexation of the free spherands with the two salts, and the activation parameters for the decomplexation. The rate constants were used to calculate the equilibrium constants for association, and the binding free energies.

The association constant (K_a) of (2) with NaPic was determined at 25 °C. Aliquots (10 ml) of 0.001 M (2) in $CDCl_3$ and 0.001 M NaPic in low conductivity water were sealed in a 50 ml Pyrex flask, and the mixture was magnetically stirred at 25 °C. Periodically, 100 μl aliquots of each phase were removed and diluted to a volume of 5 ml with MeCN. Absorbance measurements at 380 nm demonstrated that equilibrium was reached in 18—216 h, depending on the stirring rate. In triplicate runs, K_a (2) determined from aqueous and organic phase absorbance was $(9.2 \pm 1.2) \times 10^9$ l mol^{-1}. Application of the same method to (1) and (3) with NaPic showed that >95% of salt transfer required 30 days, and of (2) with LiPic for 33% transfer required 320 h. Thus K_a values for (1) and (3), and for (2) with LiPic could not be determined directly. Application of the usual method[5] of determining K_a to 0.001 M solutions of (4) and NaPic, or (4) and LiPic, gave K_a (4) = 2.4×10^9 l mol^{-1} and K_a (4) = 2.1×10^5 l mol^{-1}, respectively. Equilibrium was reached within 3 min of vortex mixing for (4) with NaPic compared with only 25% progress toward equilibrium with (2).



† These new hemispherands were prepared by methods similar to those used for their analogues (refs. 3 and 6). They gave C and H analyses within 0.30% of calculated values, molecular ions in their mass spectra, and expected ^{1}H n.m.r. spectra. The critical ring closure to form (5) (m.p. 208—210 °C) from diethylene glycol and the required bis(benzyl bromide) occurred with 20% yield. Deallylation of (5) with 10% Pd–C in EtOH–*p*-$MeC_6H_4SO_2OH$ gave the monophenol which when methylated with Me_2SO_4 gave (4) (54% overall yield), m.p. 179—180 °C.

Throughout the kinetic studies, $CDCl_3$ saturated at 25 °C with D_2O served as solvent, and all ^{1}H n.m.r. spectra were taken on a Bruker WP-200 instrument. For determination of decomplexation rates, transfers of Na^+ or Li^+ from unlabelled to deuterium-labelled spherands were followed at three temperatures with ^{1}H n.m.r. techniques. Spherands (1)—(3) labelled with deuterium in their methoxy groups were prepared by substituting $(CD_3)_2SO_4$ or CD_3I for the $(CH_3)_2SO_4$ or CH_3I ordinarily used in their syntheses.[1—3] We assumed the absence within experimental error of any hydrogen–deuterium isotope effect on complexation–decomplexation rates, and observed no isotope effect on the equilibria reached with systems (2) and (3). Because of the higher temperatures required for decomplexation of (1)–MPic, equilibrium could not be reached with either ion owing to competing demethylation reactions. With Li^+, the decomplexation rate was so slow that only a limit could be set on the rate constant. The disappearance of the MeO···M^+ protons[1—3] was followed with 12—15 points through two to five half lives in at least triplicate runs at each of three temperatures for each host–guest combination to give first order rate constants with correlation coefficients of 0.99 to 0.95. Table 1 reports the results. Values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ calculated from Eyring plots are reported in Table 2.

Association rate constants (k_1, l mol^{-1} s^{-1}) of (1), (2), and (3) with NaPic were determined at 25 °C by following the ^{1}H n.m.r. changes as NaPic was transferred from (4)–NaPic to each of the three spherands. Whereas transfer from (4)–NaPic to (1), (2), or (3) took >35 min, equilibration between (4)–NaPic, (4), (5),† and (5)–NaPic was complete in <3 min.

Table 1. Decomplexation rate constants.[a]

Host	Guest	Temp/°C	k_{-1}/s^{-1} [b]	$\pm\sigma$ [c]
(1)	NaPic	69.8	1.0×10^{-6}	0.3
(1)	NaPic	84.8	5.6×10^{-6}	0.5
(1)	NaPic	99.8	2.1×10^{-5}	0.5
(2)	NaPic	25.0	2.2×10^{-4}	0.1
(2)	NaPic	40.0	6.0×10^{-4}	0.4
(2)	NaPic	50.0	7.2×10^{-4}	0.2
(2)	LiPic	65.1	7.5×10^{-6}	0.1
(2)	LiPic	79.6	2.6×10^{-5}	0.1
(2)	LiPic	94.8	6.9×10^{-5}	0.8
(3)	NaPic	95.3	4.2×10^{-6}	0.3
(3)	NaPic	110.2	1.0×10^{-5}	0.2
(3)	NaPic	125.2	4.9×10^{-5}	0.8
(3)	LiPic	54.5	2.1×10^{-5}	0.4
(3)	LiPic	69.9	9.3×10^{-5}	0.3
(3)	LiPic	85.4	4.2×10^{-4}	0.9

[a] All runs involved solutions of complex and deuteriated host (4—15 $\times 10^{-4}$ M) in $CDCl_3$ saturated at 25 °C with D_2O. Pyrex glass sealed ampoules were used for each point (including those at zero and infinity) for all runs except those involving (2)–NaPic. Ampoules were frozen at −78 °C to stop reactions. With (2)–NaPic, reactions were followed continuously in the ^{1}H n.m.r. instrument probe equilibrated at the desired temperature. The midpoint of 20 scans (accumulation time, 80 s) was used for kinetic points. Aryl and methoxy protons integrated in kinetic runs occurred respectively at δ: (1), 7.167 and 2.848; (1)–NaPic, 7.316 and 2.944; (1)–LiPic, 7.349 and 3.035; (2), 7.600 and 2.800; (2)–NaPic, 7.826 and 2.870; (2)–LiPic, 7.784 and 2.884; (3), 6.950 and 2.128; (3)–NaPic, 6.819 and 1.996; (3)–LiPic, 6.785 and 1.910 [the latter six values were obtained in the presence of 4 mol. equiv. of $Pr(fod)_3$ shift reagent added for each point before analysis (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionato)]. [b] Calculated from the least squares slope of the plot of $-(\ln \{[HG]_t[H^*]_t - ([HG]_t + [H^*]_t)[H]\} \div \{[HG]_t + [H^*]_t\})$ *vs.* time which provides $k_{-1}/[H^*]_t$ values in which $[HG]_t$ and $[H^*]_t$ are respectively the initial concentrations of non-deuteriated complex and deuteriated host, [H] is the concentration at time t of non-deuteriated complex and host, and k_{-1} is the first order decomplexation rate constant. [c] Mean standard deviation of three runs. This error is larger than the least square plots within runs.

Table 2. Complexation and decomplexation rate constants, association equilibrium constants, association free energies, and activation enthalpies and entropies for decomplexation at 25 °C.

					in kcal mol^{-1} [j]		
Host	Guest	k_1/mol^{-1} s^{-1} [a]	k_{-1}/s^{-1} [b]	K_a/l mol^{-1} [c]	$-\Delta G°$ [c]	$\Delta H^{\ddagger}$	$-T\Delta S^{\ddagger}$ [d]
(1)	NaPic [e]	4.1×10^5	3.4×10^{-9}	1.4×10^{14}	19.2	25	4
(1)	LiPic [f]	7.5×10^4	$<1.5 \times 10^{-12}$	$>5 \times 10^{16}$ [g]	>23	—	—
(2)	NaPic [e]	1.2×10^6	2.2×10^{-4}	5.4×10^9	13.3	9	14
(2)	LiPic [h]	3.8×10^5	1.9×10^{-7}	2.0×10^{12}	16.8	18	9
(3)	NaPic [e]	8.6×10^4	1.6×10^{-9}	5.4×10^{13}	18.7	23	6
(3)	LiPic [h]	3.0×10^5	6.7×10^{-7}	4.5×10^{11}	15.9	22	4
(4)	NaPic	—	—	2.4×10^9 [i]	12.8	—	—
(4)	LiPic	—	—	2.1×10^5 [i]	7.3	—	—
(6)	NaPic	—	—	1.7×10^6 [f]	8.5	—	—
(6)	LiPic	—	—	5.1×10^4 [f]	6.4	—	—

[a] Average of triplicate runs that involve NaPic, and of multiple runs involving different kinds of competition experiments for LiPic. [b] Values from Table 1 extrapolated to 25 °C. [c] Calculated from equations, $K_a = k_1/k_{-1}$ and $-\Delta G° = RT \ln K_a$. [d] $-T\Delta S^{\ddagger}$ values calculated at 25 °C. [e] The complexation rates were measured by mixing equal volumes of a solution 0.003 M in (4) and 0.0027 M in NaPic with a 0.002 M solution of (1), (2), or (3). The ^{1}H n.m.r. changes were followed (20 scans per point) for the ArOMe protons of the spherands or the $ArCH_2$ protons of (4) in the spectrometer probe at 25 °C. With (1) and (3), plots of time against $\ln(b + [S]) - (\{([C]_i + [S]_i)/b\} \ln\{[S] \div (b + [S])\})$ gave straight lines whose slopes provided k_1K_a (4) values. Definitions: $[C]_i$, $[S]_i$, and [S] respectively are the concentrations of (4) initially, of spherand initially, and at time t; $b = [CG]_i - [S]_i$ in which $[CG]_i$ is the initial concentration of (4)–NaPic; K_a (4) is the association constant for forming (4)–NaPic. With (2), the decomplexation of (2)–NaPic competed with that of (4)–NaPic. Accordingly, time was plotted against $[1/(2c)] \ln(a + b[S] + c[S]^2) - \{[C]_i + [S]_i + b/(2c)\} \{1/\sqrt{-(4ac - b^2)}\} \ln(\{2c[S] + b - \sqrt{-(4ac - b^2)}\} \div \{2c[S] + b + \sqrt{-(4ac - b^2)}\})$ to give straight lines of slope k_1. Definitions: $a = -\{([S]_i[C]_i + [S]_i^2)/K_a$ (2)$\}$ where K_a (2) is the association constant for forming (2)–NaPic; $b = \{([CG]_i - [S]_i)/K_a$ (4)$\} - (2[S]_i + [C]_i)/K_a$ (2); $c = \{1/K_a$ (4)$\} - \{1/K_a$ (2)$\}$. [f] To a 300 μl aliquot of a 0.0017 M solution of (3) in a quartz tube submitted to ultrasonic mixing was added a 250 μl aliquot of a solution, 0.03 M in (6), 0.0188 M in NaPic, and 0.00602 M in LiPic. The relative amounts of (1), (1)–NaPic, and (1)–LiPic were measured by ^{1}H n.m.r. integrations of MeO and total picrate protons (5 s delays between scans). The ratio of the complexation rate constants, k_1^{Na}/k_1^{Li} was determined in four runs to be 5.5 ± 0.2 where the initial NaPic to LiPic concentration ratio varied from 3:1 to 5:1. From this ratio and the determined value for k_1^{Na}, k_1^{Li} was calculated. The ratio was calculated from the equation: $k_1^{Na}/k_1^{Li} = (K_a^{Na}/K_a^{Li})\{\ln([CG_1]/[CG_1]_i)\} \div \{\ln([CG_2]/[CG_2]_i)\}$, in which K_a^{Na} and K_a^{Li} are the respective association constants for forming (6)–NaPic and (6)–LiPic; $[CG_1]$ and $[CG_2]$ are the respective final concentrations of (6)–NaPic and (6)+LiPic; $[CG_1]_i$ and $[CG_2]_i$ are the respective initial concentrations of (6)–NaPic and (6)–LiPic. The value of K_a^{Na} was determined in triplicate by the published extraction method (ref. 5) and that of K_a^{Li} in triplicate by a modified method in which 500 μl aliquots of 0.050 M (6) in $CDCl_3$ and 0.015 M LiPic in D_2O were mixed by vortexing, and the layers were separated and analysed as before. [g] These minimum values are based on the estimated maximum values for decomplexation rates which were slower than those for demethylation at <100 °C. [h] A 250 μl aliquot of a 0.0017 M solution of (1) was mixed with a 250 μl aliquot of a 0.0018 M solution of (2), and a ^{1}H n.m.r. spectrum provided the relative amounts of each spherand. To the solution in a quartz tube subjected to ultrasonic mixing was added a 50 μl aliquot of a solution 0.01 M in (6) and 0.0085 M in LiPic. The ^{1}H n.m.r. spectrum of the mixed solution was measured immediately. Integrals for both MeO and ArH protons of complexed and uncomplexed spherands were used in the analyses. The rate constant ratio, k_1 (2)/k_1 (1), was determined in triplicate runs to be 5 ± 1. Similarly, k_1 (3)/k_1 (1), from triplicate runs was 4.0 ± 0.5. From these ratios and the determined value for k_1 (1), values of k_1 (2) and k_1 (3) were calculated. The ratios were calculated with this equation: k_1 (n)/k_1 (1) = $\ln([S_2]/[S_2]_i) \div ([S_1]/[S_1]_i)$ in which k_1 (n) is k_1 (2) or k_1 (3); $[S_2]$ is the final and $[S_2]_i$ the initial concentration of (2) or (3); $[S_1]$ is the final and $[S_1]_i$ the initial concentration of (1). Control experiments demonstrated that once complexed with Li^+, the complexes of (1), (2), or (3) decomplexed very slowly on the human time scale. Any prolonged exposure of (1), (2), or (3) to soft glass, or short exposure during mixing, results in Na^+ being extracted from the glass and becoming complexed. [i] See text. [j] 1 cal = 4.184 J.

The association rates for forming (4)–NaPic or (5)–NaPic are much faster than those for forming (1)–NaPic, (2)–NaPic, or (3)–NaPic. Thus the role of (4)–NaPic was to provide a pre-equilibrium concentration of NaPic low enough to bring the rates of Na^+ transfer into (1), (2), or (3) onto the human time scale. Table 2 reports the values of k_1 obtained in triplicate runs with 15—20 kinetic points obtained during 1.5—4 half-lives. Correlation coefficients varied from 0.999 to 0.980. Unlike those of (1)–NaPic and (3)–NaPic, the decomplexation rate for (2)–NaPic was sufficiently fast that it had to be taken into account in the kinetic treatment (see footnote e, Table 2).

The complexation rate constant (k_1, l mol s^{-1}) of (1) with LiPic at 25 °C was determined by competition experiments between NaPic and LiPic to give the ratio of rate constants, from which that for LiPic was calculated. Solutions of known ratios of NaPic- to LiPic-complexes of dicyclohexano-18-crown-6 (6) (commercial material) were mixed with solutions of (1), and the relative amounts of (1), (1)–NaPic, (1)–LiPic, and total picrate were determined by ^{1}H n.m.r. measurements. Control experiments showed that once formed the complexes of (1) did not undergo exchange under the reaction conditions. Table 2 gives the results. The complexation rate constants of (2) and (3) with LiPic were determined by competition experiments between (1) and (2) for LiPic, and between (1) and (3) for LiPic. The ratios of rate constants were derived and from these the k_1 values for (2) and (3) complexing LiPic were calculated (see Table 2).

The association and dissociation *rate constants* at 25 °C were used to calculate the association *equilibrium* constants and free energies of complexation for (1), (2), and (3) with NaPic and LiPic. These values are only approximate. Comparison of the values of $-\Delta G°$ obtained by direct measurement of the association constant between (2) and NaPic (13.6 kcal mol^{-1}) and that calculated from the rate constants (13.3 kcal mol^{-1}) provides calibration. Also listed in Table 2 for comparison are K_a values obtained by the extraction method for the hemispherand (4) and the crown (6).

The decomplexation rate constants of the spherand complexes vary by $>10^8$, whereas the complexation rate constants vary by only *ca.* 10^1. Thus the $>10^7$ variation in the equilibrium constant is governed largely by the difference in the dissociation rate constants. This correlation implies that the transition states (common to complexation and decomplexation) resemble the decomplexed state more than the complexed, and the widely differing free spherand structures are relatively little perturbed in the transition states. The crystal structures of the spherands and their complexes[3,4] show the same conformational organization in their uncomplexed and complexed states: one in which a cavity lined with electrons is surrounded by hydrocarbon. To reach these electrons, guests

must pass through lipophilic sleeves of diameters too small to accommodate metal ion plus ligands. Thus disengagement of the ionic guest from its solvent ligands, and re-engagement of the ion with the electrons of these spherands cannot be a concerted process. The Na^+ and Li^+ ions in the transition states are largely surrounded by hydrocarbon units. In reaching the transition states from the non-complexed side, the ions must shed their co-ordinating ligands and enter the sleeves. This process does not structurally perturb the spherands much, so the transition state energies and rates are little affected by the structural differences between the spherands. For decomplexation, the starting complexes differ structurally in the number of oxygen atoms ligated (5—7), in the compression of their oxygen atoms, and in deformations of their bond angles.[3,4] Thus the free energy differences in the complexes themselves seem to be mainly responsible for the >9 kcal mol^{-1} difference in the binding free energies of the spherands. The enthalpic and entropic contributions to the activation free energies for decomplexation of the five measurable spherand complexes reinforce rather than cancel one another.

When the metal–ligand relationships are the most complementary in any given ligand class, the order for binding LiPic and NaPic in $CDCl_3$ saturated with D_2O at 25 °C is spherands > cryptands‡ > hemispherands > crowns > open-chain polyethers. We attribute the superior binding power of spherands to the fact that the ligating sites are fully organized during synthesis rather than during complexation. With the other classes, the guest must generate its own cavity by displacing inward-turned methylene groups from the occupied centres of the macroring systems.[7] The guests must also break hydrogen bonds between outward-turned unshared electron pairs of the host's oxygen atoms and solvent in the conformationally flexible cryptands, hemispherands, crowns, and open-chain polyethers. These electron pairs are sterically unavailable for solvation in the spherands. This fact also explains why when the ionic diameter of cations becomes too large for the preformed cavity (*e.g.*, with K^+) no complexation of any kind occurs.

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‡ Cryptand–LiPic and cryptand–NaPic complexes were equilibrated with (**2**) in $CDCl_3$ saturated with D_2O at 25 °C (ref. 3).

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