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COMMUNICATION

Pronounced calcium binding selectivity with diamide derivatives of 12-N_2O_2 and the importance of desolvation

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The complexation of alkali and alkaline-earth cations with two N-substituted amide derivatives of 1,7-dioxa-4,10-diazacyclododecane has been studied in methanol and water by calorimetric and potentiometric methods. High stability (e.g. log K_{CaL} = 11.2: 298 K, MeOH) and selectivity ($10^{7.1}$ over Na^+) for calcium ions in methanol is shown by the secondary amide derivative, and although significantly higher enthalpies of complexation are found for the tertiary amide analog (resulting from lesser differential ligand solvation), accompanying lower entropies of complexation lead to somewhat lower binding free energies for IIa cations. In water, both the complex stability and the selectivity for the more charge dense ions is reduced.

It is well established that the addition of ligating amide substitutents to cation binding neutral ligands leads to an increased selectivity towards more charge dense cations. This factor has been used for example to optimise Li^+/Na^+ selectivity in 14-crown-4 derivatives,[1] to promote calcium binding in simple amide[2] and peptide[2,3] derivatives of [12]-N_2O_2[2a], [15]-N_2O_3 and [18]-N_2O_4 and to improve the transport of sodium in polyaza-polyoxa-coronands.[4] In order to better understand the relative importance of ligand desolvation during cation complexation, we have measured the enthalpy and free energy of binding of certain Group Ia and Group IIa cations with two closely related ligands, 1 and 2, based on a [12]-N_2O_2 coronand. In the case of 1, incorporating two secondary amide groups, the ligand is expected to be more strongly solvated (by protic solvents) as a result of hydrogen-bonding between the amide NH and a solvent heteroatom and associated secondary solvation interactions. This enthalpic term† which is unfavourable with respect to the free energy of cation complexation, will to some extent be compensated by a favourable entropy term, as the more ordered solvent molecules are released following cation binding. In the tertiary amide, 2, hydrogen bonding interactions between the carbonyl oxugen and the solvent hydroxyl group probably occur to a similar extent as in 1.

With both 1 and 2, we have previously shown[2] the strong ligation of the amide carbonyl oxygen in formation of 1:1 complexes by ^{13}C NMR and IR methods of analysis, and that it is this binding which discriminates in favour of the more charge dense ions.

In aqueous solution, the stability constants for formation of the 1:1 complex were measured by standard potentiometric methods followed by iterative data analysis. No discrimination for Na^+/K^+ was seen (*Table 1*), although good selectivity for calcium was noted, over Na^+/K^+. Similar values have been reported for the binding of these ions by both N,N′-diamide derivatives of [15]-N_2O_3, [18]-N_2O_4 and the related 'peptide' derivatives.[2,3] In these complexes, it is likely that cation desolvation dominates the energetics of binding.

In methanol (where cation desolvation is less pronounced), stability constants for 1:1 complex formation were determined using calorimetric methods of analysis. With the Group Ia ions (Table 2), the stability constants were, as expected, between 10^2 and

Table 1 Stability constants for complexation of water in 1 and 2 with cations (298 K, I = 0.1 mol dm^{-3} NMe_4NO_3; ±0.05)

Ligand	Na^+	K^+	Ca^{2+}	pKa_1	pKa_2
1	2.65	2.70	4.74	6.73	4.84
2	2.55	2.60	5.11	7.19	3.98

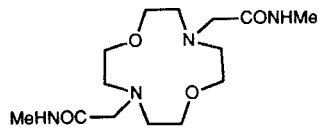
† Strictly, it is the differential enthalpy and entropy of solvation of the free ligand compared to the complex which is more important.

10^3 times higher than in water, with lithium being bound most strongly, with modest selectivity over sodium. For Ca^{2+}, Sr^{2+} and Ba^{2+}, high complex stabilities were observed ($\log K \geqslant 5$) so that values of the 1:1 formation constant could not be obtained directly. Instead, competitive calorimetric titrations were performed with 1 in the presence of either 18-crown-6, [222]-cryptand or 1,10-diaza-18-crown-6, in order to estimate the stability constant. Using the known values[5] of $\log K_{ML}$ and ΔH for complexes of 18-crown-6 (Ca^{2+}), [222]-cryptand (Ca^{2+}) or 1,10-diaza-18-crown-6 (Sr^{2+}, Ba^{2+}), values of ΔH and $\log K$ were calculated. With ligand 2, the $\log K$ values with Sr^{2+} and Ca^{2+} were obtained in a slightly different manner. A solution of free Ca^{2+} (or Sr^{2+}) ions was added to a solution containing the ligand and sodium (or Li^+) ions. Agreement between the indirectly measured enthalpies of complexation and the directly measured values was good (Tables 2 and 3). The high values obtained with 1 (e.g. [Ca. 1^{2+}], $\log K = 11.2$; [Sr. $1]^{2+}$, $\log K = 8.17$) suggest that there must be a very favourable overall entropy of complexation given the lower enthalpy of complexation expected because of the greater energy needed to desolvate ligand 1 (compared to 2).

This hypothesis was vindicated following an analysis of the enthalpy and entropy of complexation of 1 and 2 with various cations (Table 3). With the secondary amide ligand, 1, lower enthalpies of complexation (than with 2) were measured (calorimetrically) but large favourable entropies of complexation were found. With ligand 2, the enthalpy of complexation was consistently higher than with 1 (averaging 17.7 kJ mol^{-1} i.e. 8.9 kJ mol^{-1} per amide) while entropies of complexation were considerably less than with 1. The 'compensating effect' of ΔH and ΔS in the binding of cations to macrocyclic ligands is a well-defined phenomenon,[6] but in this case the large positive $T\Delta S$ term in the binding of cations with 1 must be made up from a significant ligand desolvation contribution.

The very large difference in entropies of complexation found with 1 and 2 may be rationalised in terms of the changes in the degree of solvent ordering around the ligand. Ligand 1 must induce considerable ordering of the methanol molecules (in both the primary and secondary solvation shells) in a manner not attainable with 2. There are many possible solvation models for this, but an attractive putative structure is represented in 3, wherein the NH groups allow selective inclusion of methanol giving an ordered 'solvate'.

As pointed out earlier,[2c] the differential enthalpy of complexation for 1 vs 2 is primarily associated with amide NH...OHMe hydrogen-bonding which occurs with 1 but not 2. The value of 8.9 kJ mol^{-1} for each amide NH...OHMe hydrogen bond is an estimate of the hydrogen bond strength, but is probably a lower



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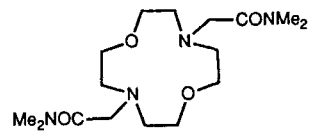

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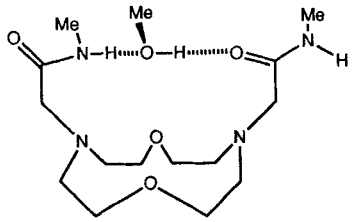

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Table 2 Stability constants for complexation in methanol for 1 and 2 with cations (298 K, CH_3OH)

Ligand	Li^+	Na^+	K^+	Rb^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
1	4.41	4.07	n/d	n/d	11.2[a] (>8.87)[b]	8.17[c]	7.49[c]
2	5.38	4.72	3.85	3.08	7.68[e]	7.12[d]	4.94

[a] Obtained by competition with [222]-cryptand whose ΔH and ΔG values of complexation are known.[5]
[b] Competition with 18-crown-6 only allows a limit to be set.
[c] Competition with 1,10-diaza-18-crown-6 ([22]).
[d] Competition titration of Sr^{2+} with [2. Na]$^+$.
[e] Competitive titration of Ca^{2+} with [2. Na]$^+$; a value of 7.80 was found for the related reaction between Ca^{2+} and [2. Li]$^+$, for which $\log K' = 2.42$ and $\Delta H = -36.5$ kJ mol^{-1}.

Table 3 Enthalpies and entropies of complexation in methanol for reaction of 1 and 2 with cations[a] (298 K; kJ mol^{-1})

Ligand		Li^+	Na^+	K^+	Rb^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
1	$-\Delta H$	2.4	9.2	2.0	0.65	30.4	16.4	17.0
	$T\Delta S$	22.8	14.0	n/d	n/d	33.5	30.2	25.7
2	$-\Delta H$	12.7	26.0	25.7	22.7	46.0[c]	35.8[b]	33.0
	$T\Delta S$	18.0	0.8	−3.8	5.2	−2.2	+4.8	−4.8

[a] Measurements were made with a Tronac Model 450 calorimeter in anhydrous methanol.
[b] A value of 36.6 kJ mol^{-1} was obtained from the competitive titration of Sr^{2+} + [2. Na]$^+$, for which $\log K' = 2.40$ and $\Delta H = -10.6$ kJ mol^{-1}.
[c] A value of 49.5 kJ mol^{-1} was obtained from the competitive titration of Ca^{2+} with the sodium complex [2-Na]$^+$, for which $\log K' = 2.96$ and $\Delta H = -23.5$ kJ mol^{-1}.
[d] Salts used were: $SrBr_2$, $LiClO_4$, $NaClO_4$ or $NaNO_3$ and $Ca(NO_3)_2$, $Ba(ClO_4)_2$, KI, and RbI. No allowance has been made for specific anion complexation, although this is an approximation.

limit since the NH group will certainly be hydrogen-bonded to solvent in the complexed state.

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