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Studies on the Complexation of Alkali Metal Cations by Macrocyclic Diamides Using Electrospray Ionization Mass Spectrometry (ESI-MS)

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Several macrocyclic diamides have been tested as ligands for complexation of alkali metal cations. Electrospray ionization mass spectrometry was found to be a perfect tool for investigation of host-guest interaction between ligands and cations studied. Effect of the ring size and regioisomerism of the amido groups on complexation properties of ligands were also investigated.

Key words: electrospray ionization, macrocyclic diamides, complexation, alkali metal cations

The supramolecular chemistry, which evolves dynamically in recent decades, highlights the interactions of the macromolecules with the guest molecules and attracts the attention of numerous research groups to this subject [1]. Because of preparation of an enormous number of novel host-guest systems having the potential practical significance, a need emerged for a simple method of analysis of the host-guest interactions, which could compete with the well-known approaches such as X-ray structure analysis, nuclear magnetic resonance techniques, as well as the spectrophotometrical methods [2]. Such an alternative method in question should reflect accurately the interactions present in the investigated solution, as well it should allow simple, economical and – what is of key importance – quick analysis of these interactions.

These requirements are satisfied by the rapidly-developing mass spectrometry using the electrospray ionization (ESI-MS). This technique allows analyzing the broad range of non-covalent interactions of the host molecules having various structure (crown ethers and their derivatives [3–6], proteins [7,8], cages [9–11], cryptands [1], cyclodextrins [12,13]) with various types of guest molecules (metal cations [1–11], small, neutral molecules [12], amino acids [13]). The ESI-MS analysis is quick, enables direct investigation of the solutions of interest, and requires a minute amount of sample. Therefore, this method is suitable for screening of the specifically selective receptors. Keeping in mind that, in order to find practical applications, the potential receptor molecule has to bind strongly and very selectively

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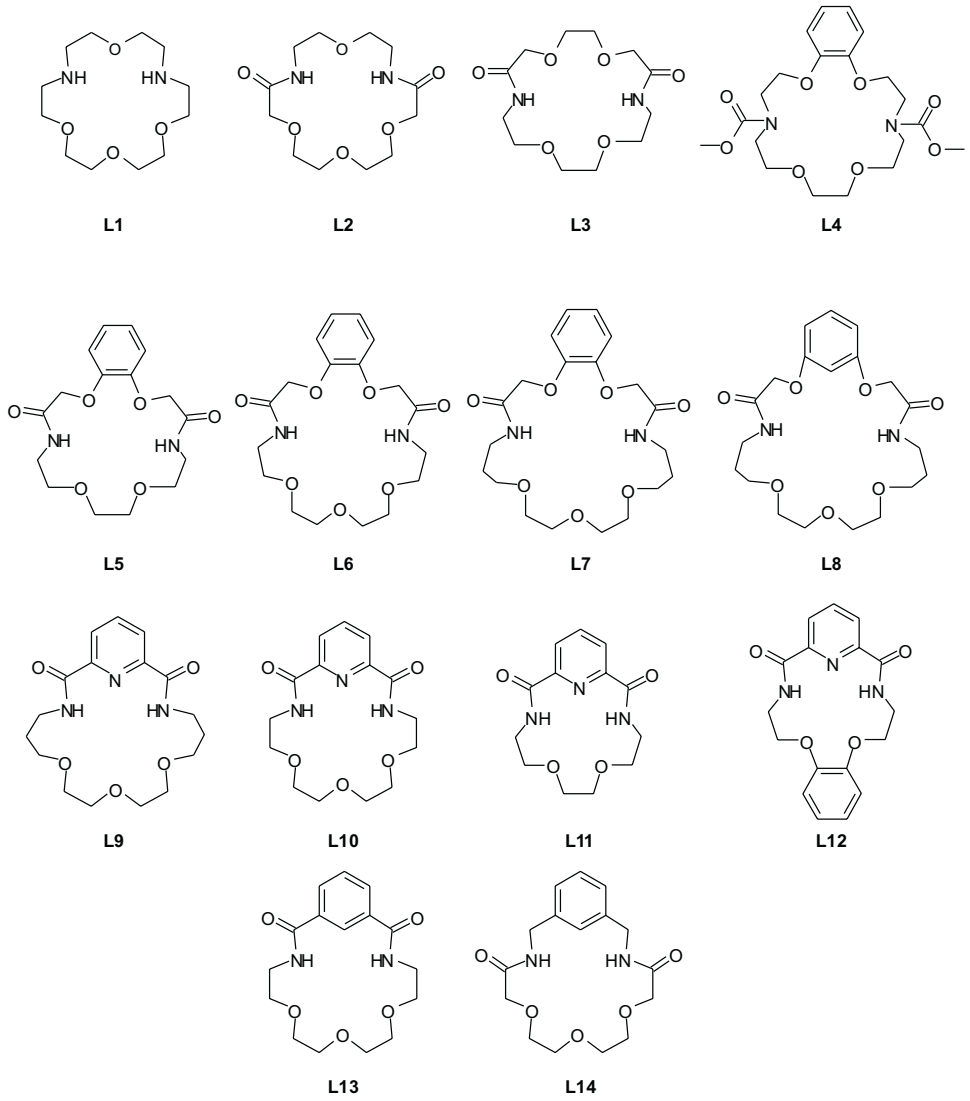
the given host molecule, one can significantly simplify the ESI-MS analysis and cut the test time to minimum.

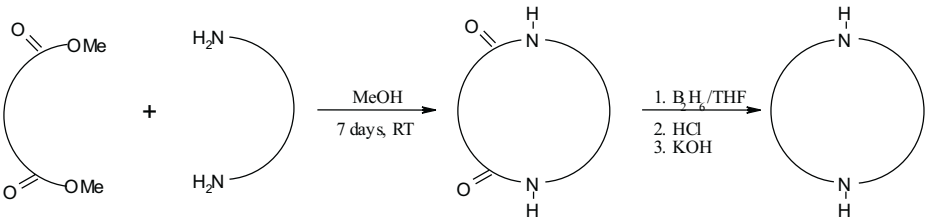
In this paper we present general considerations concerning ESI-MS method as an analytical tool for determination of a general relationship between the diazacoronand structure (ring size, effect of additional heteroatoms, regioisomeric location of the amide carbonyl group) and the complexation properties of these ligands with respect to the alkali metal cations. In our study, we decided to investigate a series of the representative ligands having the structures **L1** to **L14**, shown in Scheme 1.



Scheme 1. Structures of ligands investigated.

EXPERIMENTAL

Materials and sample preparation. The macrocyclic diamides (**L2-L14**) have been prepared according to the general procedure outlined in Scheme 2 [14,15]. Diamine **L1** has been obtained *via* borohydride reduction from diamide **L2**.



Scheme 2. General procedure for preparation of macrocyclic diamides.

The complexation reagents, *i.e*., lithium, sodium, potassium, rubidium and caesium chlorides and hydroxides were purchased from Aldrich. Methanol (HPLC grade, from Merck) and redistilled water were used as the solvents.

All ligands and metal chlorides or hydroxides have been dissolved separately in a 7:3 water:methanol mixture at a concentration of $1 \cdot 10^{-3}$ mol/dm^3. The appropriate solutions (100 μl each) have been mixed 30 minutes before the measurement and made up to 1 ml with the same solvent mixture. The final solution was therefore $1 \cdot 10^{-4}$ mol/dm^3 in both the host and the guest.

Mass spectrometer All measurements were performed using an API-365 (MDS SCIEX) triple quadrupole mass spectrometer equipped with the TurboIonSpray™ ESI source. This source enhances solvent evaporation from spray droplets by use of additional drying gas having controlled flow rate and temperature.

During acquisition of the standard spectra, the first quadrupole was used as the mass analyser, and the next two quadrupoles were set to the maximum ion transmission. The samples were delivered *via* the syringe pump. The flow rate was set to 10 μl/min. In our experiments, this was the lowest flow rate providing a stable and reproducible spray. All the spectra were acquired three times for at least 60 seconds.

Determination of the measurement conditions. The appearance of the mass spectrum recorded using our apparatus depends on several key parameters, which are to be carefully adjusted and standardized. The most significant ones are: the declustering potential, the focusing potential, the ion source geometry (the position of the capillary with respect to the nozzle) and the optional use of drying gas. After preliminary experiments we concluded that there were the ranges of both potentials, where the relative intensities of recorded peaks were fairly constant. In the case of declustering potential, the corresponding range was 30–50 V (see Figure 1), whereas in the case of focusing potential, the proper range was 200–250 V. We established that even the presence of cold drying gas influenced greatly the peak intensities in the mass spectrum. Therefore, we decided to abandon the use of drying gas. In each measurement series, the position of the capillary with respect to the nozzle was kept constant.

It has to be pointed out that the careful selection of the ion source parameters is very important for obtaining correct results of the measurements. Unfortunately, this point is usually not addressed sufficiently in majority of publications dealing with ESI studies of the host-guest interactions. It is especially important in the case when the significant differences in solvation energies of the analyzed ions are expected. Correct above-mentioned four ion source parameters can equalize to some extent the response factors of the different complex ions making direct comparison of their abundances more meaningful.

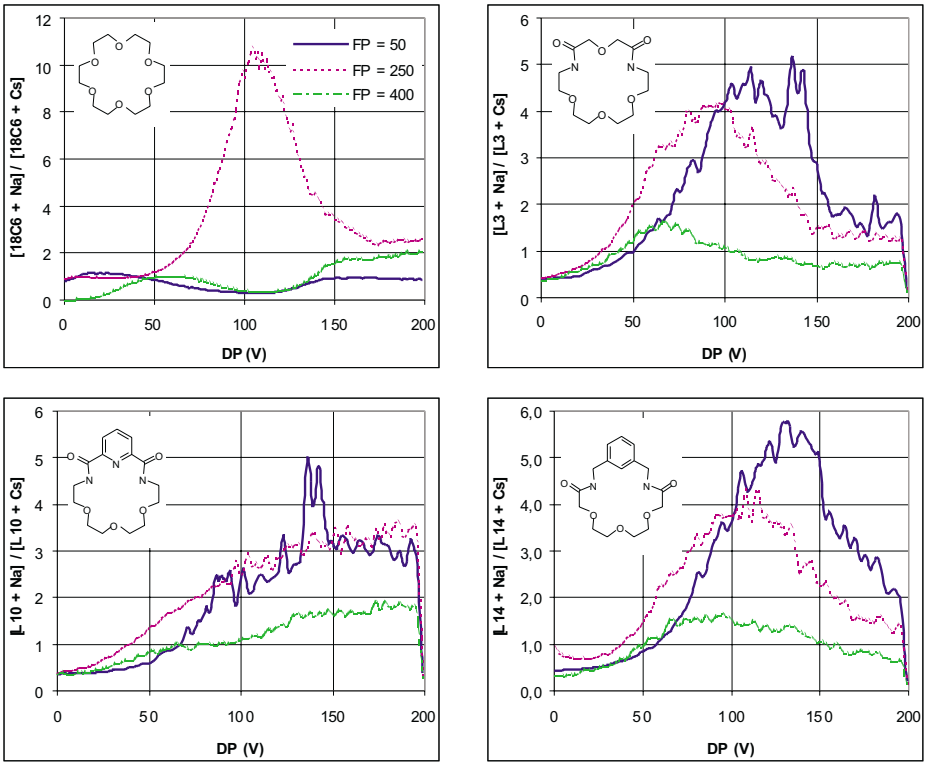


Figure 1. Normalized [L+Na]/[L+Cs] ratio for four different ligands as a function of declustering potential (DP) for different focusing potential (FP) values. This experiment shows that the optimal declustering potential values are in the range of 30–50 V. In this range, there is no significant influence of the focusing potential values on the peak intensity ratio ([L + Na]/[L + Cs]).

RESULTS AND DISCUSSION

Choice of the subjects of study. Having established the parameters of the measurement, we focused on the analysis of the cyclic bisamides and their reduced derivatives.

We have noticed in the preliminary experiments, that diazacoronand **L1** has a very high affinity to the proton. The equimolar solution of amine **L1** and amide **L2** (or **L3**) as well as an alkali metal chloride gave the mass spectra, where the highest peak corresponded always to the protonated amine and the intensities of all other peaks corresponding to the complex ions were less than 27% of that highest, protonated molecular ion peak $[\mathbf{L1}+H]^+$ (see Table 1). Such a situation made it impossible to analyze precisely the interactions in the solution, because we did not know what fraction of the ligand was complexated with metal cation and what fraction was protonated.

Trying to minimize the undesired ligand protonation, we used the alkali metal hydroxides instead of the chlorides. The mass spectra of the resulting solutions displayed significant quantitative changes (see Table 2). In the cases of rubidium and cesium, the strongly alkaline reaction medium eliminated completely the protonation of cyclic amines. However, in the case of sodium, the protonation of the amine competed with the formation of sodium complexes; in the cases of lithium and potassium, the protonation of the amine still predominated. As the consequence we had to exclude ligand **L1** from our studies and all further experiments were performed for the ligands containing amido groups.

Table 1. A competition between the ligands **L1**, **L2** and **L3** with respect to Li^+, Na^+, K^+, Rb^+ and Cs^+ introduced in the form of their chlorides. (The intensities of $[\mathbf{L2}+H]^+$ and $[\mathbf{L3}+H]^+$ were negligible in all cases.) The standard deviation is ± 10% of the listed number.

Ligands	M^+	Relative peak intensities, [%]		
		$[\mathbf{L1}+H]^+$	$[\mathbf{L1}+M]^+$	$[\mathbf{L2}+M]^+$
L1+**L2**	Na^+	100.0	22.5	19.5
	K^+	100.0	16.1	12.0
	Rb^+	100.0	6.2	11.2
	Cs^+	100.0	3.1	11.2
		$[\mathbf{L1}+H]^+$	$[\mathbf{L1}+M]^+$	$[\mathbf{L3}+M]^+$
L1+**L3**	Na^+	100.0	26.7	20.1
	K^+	100.0	22.8	15.8
	Rb^+	100.0	9.4	16.5
	Cs^+	100.0	3.0	11.9

Table 2. A competition between the ligands **L1**, **L2** and **L3** with respect to Li^+, Na^+, K^+, Rb^+ and Cs^+ introduced in the form of their hydroxides. The standard deviation is ± 10% of the listed number.

Ligands	M^+	Relative peak intensities, [%]			
		$[\mathbf{L1}+H]^+$	$[\mathbf{L2}+H]^+$	$[\mathbf{L1}+M]^+$	$[\mathbf{L2}+M]^+$
L1+**L2**	Li^+	100.0	24.1	3.1	64.0
	Na^+	38.3	18.8	9.9	100.0
	K^+	100.0	25.3	28.8	60.1
	Rb^+	–	–	100.0	18.8
	Cs^+	–	–	100.0	14.6
		$[\mathbf{L1}+H]^+$	$[\mathbf{L3}+H]^+$	$[\mathbf{L1}+M]^+$	$[\mathbf{L3}+M]^+$
L1+**L3**	Li^+	100.0	13.7	3.4	63.4
	Na^+	93.7	16.8	19.1	100.0
	K^+	100.0	1.5	42.3	13.4
	Rb^+	–	–	100.0	10.6
	Cs^+	–	–	100.0	7.8

The experiment described above consist in comparing the selectivity of two different ligands with respect to one cation. It is to be noted that such an experiment does not allow for drawing any exact quantitative conclusions regarding the values of stability constants of the particular complexes. The reported results are useful merely for estimating which of the ligands is more selective towards one particular cation, but any quantitative determination of this selectivity is not possible.

As it is well known, the response factors depend on the solvation energy of the given ions [3]. In order to perform a quantitative analysis of the results one should introduce the corresponding coefficients for correction of the different ligands response factors. Such a procedure is possible but quite tedious [6,16,17] and unnecessary from the viewpoint of this work. If we are looking for a good, selective ligand for practical application, then we expect this ligand to bind the guest ion at least several times better than the other competing ligands, so the estimation of selectivity is sufficient without making additional corrections. As it has been proved by the work from Brodbelt laboratory [6], the differences between the response factors for ligands with similar structures (*e.g.* crown ethers with the different ring sizes) usually do not exceed 3 to 5 times and in some cases even uncorrected values give better results. Therefore, it is rational to assume that the peak intensity ratios higher than 5:1 are indicative for the stronger complexing properties of one from the two competeing ligands. We believe that the ESI-MS technique is an excellent method for rapid determination which one of the investigated ligands interact more strongly with a given cation and whether the differences in the structure influence significantly their selectivity. Simplicity and the speed of the method is especially important in the case when a large number of ligands has to be screened for the complexation properties.

Effect of the ring size. A general conclusion from the comparison of pairs of benzocoronands (**L4** to **L8**) is that the amide having a larger ring size (and very likely a larger macrocyclic cavity) always forms the complexes with the alkali metal cations stronger than its smaller counterpart (see Table 3).

Table 3. A competition between the benzocoronands with respect to Li^+, Na^+, K^+, Rb^+ and Cs^+ introduced in the form of their chlorides; the values given in the table are reproducible within ± 10%.

Components of the solution (1:1:1)		Peak intensity ratio				
A	B	$[A+Li]^+/[B+Li]^+$	$[A+Na]^+/[B+Na]^+$	$[A+K]^+/[B+K]^+$	$[A+Rb]^+/[B+Rb]^+$	$[A+Cs]^+/[B+Cs]^+$
L4	**L5**	1.3	3.9	3.2	4.8	3.7
L6	**L5**	5.3	6.2	5.2	6.0	8.1
L7	**L5**	6.2	9.8	10.1	11.2	13.2
L8	**L5**	2.3	3.9	3.5	5.1	5.3

The following examples concern the pairs of ligands (**L9** to **L12**) possessing the additional electron donating complexation centres, which are the pyridinium moieties. An analysis of the results for this group of ligands confirms again the conclusion that the larger ring size favours the complexation of the metal cations. One can see that the presence of the pyridinium nitrogen (**L10**) enhances the complexation and that the additional benzo moiety in the ether part of the ligand (**L13**) interferes with complexation with all investigated cations (see Table 4).

Table 4. A competition between the ligands **L9**-**L13** with respect to Li^+, Na^+, K^+, Rb^+ and Cs^+ introduced in the form of their chlorides; the values given in the table are reproducible within ± 10%.

Components of the solution (1:1:1)		Peak intensity ratio				
A	B	$[A+Li]^+/[B+Li]^+$	$[A+Na]^+/[B+Na]^+$	$[A+K]^+/[B+K]^+$	$[A+Rb]^+/[B+Rb]^+$	$[A+Cs]^+/[B+Cs]^+$
L9	**L10**	1.3	2.1	2.2	1.7	1.5
L10	**L11**	1.7	4.0	6.7	8.1	7.1
L10	**L12**	6.4	13.0	17.2	19.5	25.1
L11	**L12**	3.5	5.3	3.6	3.8	3.7
L10	**L13**	1.4	3.5	2.8	2.5	2.3

Regioisomerism of the amido group. Because mass spectrometry excludes the experiments for a pair of isomers, therefore the information on the relative selectivity of isomeric ligands can be obtained indirectly, by analysing their behaviour with respect to the same reference compound. The method is expected to be quite accurate, because the response factors for complexes of the isomeric ligands should be similar.

The data reported in Table 5 show clearly that the regioisomeric cyclic amides **L13** and **L14** differ significantly in their complexation abilities. The complexes of **L14** are much more stable for all cations studied. Interestingly, the relative complexation ability od **L14** grows monotonically with the increasing size of the cation, from about 7 for lithium up to 91 for ceasium. This behaviour can be rationalized by much higher flexibility of the structure of that ligand as compared with **L13**.

Table 5. A competition between two isomeric ligands **L13** and **L14** with respect to Li^+, Na^+, K^+, Rb^+ and Cs^+ introduced in the form of their chlorides. Ligand **L2** was used as the reference compound. The values given in the table are reproducible within ± 10%.

Components of the solution (1:1:1)		Peak intensity ratio				
A	B	$[A+Li]^+/[B+Li]^+$	$[A+Na]^+/[B+Na]^+$	$[A+K]^+/[B+K]^+$	$[A+Rb]^+/[B+Rb]^+$	$[A+Cs]^+/[B+Cs]^+$
L2	**L13**	4.3	6.9	6.3	6.8	8.2
L2	**L14**	0.60	0.35	0.21	0.11	0.09
Values calculated from the results given above:						
L14	**L13**	7.2	20	30	62	91

CONCLUSIONS

The ESI-MS technique satisfies all requirements for a modern analytical method for screening the selectivity of the host-guest interactions. It performs particularly well in searching for the most selective receptor for a given cation. In such circumstances, one can skip the additional measurements aiming to make corrections in the peak intensities because of differing response factors. These factors depend mainly on the solvation energy of cations, although the size, conformation and charge of the host molecule, viscosity of the solvent and the temperature and other parameters of the ion source, are also important. However, the ESI-MS approach is very efficient for a fast, preliminary analyses of synthetic ligands sets in order to find compounds with the strongest complexation properties.

The results obtained by us for compounds shown in Scheme 1 led to the following conclusions:

– it is not possible to use ESI-MS technique for reliable estimation of the relative complexation efficiences of the diazacoronands with free amino groups (**L1**) due to their very high proton affinities;
– geometric fit in recognition of alkali metal cations is substantial feature;
– macrocyclic N,N′-bismethoxycarbonyl derivative is slightly better receptor than macrocyclic diamide;
– pyridine containing macrocyclic diamides are slightly better receptors than their benzo-analogues;
– alkali metal cation recognition depends on the position of the amido functionality respect to the aromatic ring.

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