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Polarographic Study of Tl^+, Li^+, Na^+, K^+, and Cs^+ Complexes with Monensin Anion in Dipolar Aprotic Solvents

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Summary. The stability constants, K_s, of monensin complexes with Li^+, Na^+, K^+ and Cs^+ ions were studied by a competitive polarographic method using the $Tl^+/Tl(Hg)$ redox couple as a sensitive electrochemical probe. The K_s values are strongly influenced by the solvents (acetonitrile, propionitrile, acetone, N,N-dimethylformamide, N-methyl pyrolidinone, N,N-dimethylacetamide, dimethylsulfoxide, N,N-diethylformamide and N,N-diethylacetamide were used in experiments) and vary inversely with the Gutmann donicity scale. Molecular mechanics computations revealed the probable structures of the complexes.

Keywords. Monensin complexes; Solvent effect; Molecular mechanics computation.

Polarographische Untersuchung von Tl^+-, Li^+-, Na^+- und Cs^+-Komplexen mit Monesin-Anion in dipolaren aprotischen Lösungsmitteln

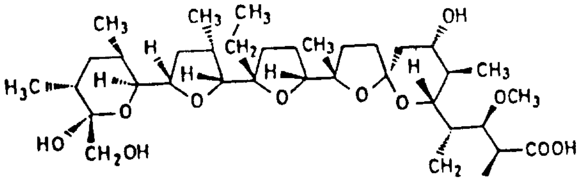
Zusammenfassung. Es wurden die Stabilitätskonstanten K_s von Monesin-Komplexen mit Li^+-, Ma^+- und Cs^+-Ionen mittels einer competitiven polarographischen Methode unter Verwendung der $Tl^+/Tl(Hg)$-Redoxelektrode als sensitiver elektrochemischer Sonde bestimmt. Die K_s-Werte werden stark vom Lösungsmittel (Acetonitril, Propionitril, Aceton, N,N-Dimethylformamid, N-Methylpyrrolidinon, N,N-Dimethylacetamid, Dimethylsulfoxid, N,N-Diethylformamid und N,N-Diethylacetamid) beeinflußt, wobei sie invers zur *Gutmann* schen Donizitätsskala variieren. Die wahrscheinliche Struktur der Komplexe wurde mittels molekularmechanischer Berechnungen ermittelt.

Introduction

It is well known that macrocyclic ligands are capable of forming stable complexes with many cations; most of the results can be found in valuable reviews [1, 2] given by Izatt *et al.* There are at least three factors that make a significant contribution to the binding of cations by these ligands: i) relative cation and ligand size, ii) the ligand topology and the number of the donor sites participating in the binding, and, especially iii) the solvent effect on the selectivity and stability constants of complexes. Of these factors, the third seems to be a somewhat neglected area of research. In Chapt. 7 of Ref. [2] ("Suggestion for Future Work") we can even read; "More data valid in a variety of solvents are needed in order to understand the effect of solvent parameters on thermodynamic and kinetic values".

We have recently been involved in the study of the complexation of thallium(I) [3] and alkali metal cations [4] by crown ethers in dipolar aprotic media. The stability constants of the resulting complexes were found to decrease with the Gutmann donicity [5] of the solvents. During the present work our attention has been focused on the complexes of monensin. The information for understanding their behaviour in solutions is rather sparse. The majority of earlier studies involved methanol as solvent and only in Ref. [6] some dipolar aprotic solvents (acetonitrile, propylene carbonate, N,N-dimethylformamide and dimethylsulfoxide) were included. The results of that work suggest strongly that it would be of interest to compare the stabilities of complexes in a series of aprotic solvents representing a wide variety of donicities.

In addition, the complexes of alkali metal cations with monensin are interesting from the biological and topological point of view. Monensin (hereafter abbreviated as *Mon*H) is known to induce exchange of alkali metal and H^+ ions across biological membranes [7]. X-ray analysis revealed macrocyclic structures of the ligand and its cation complexes; the Na^+ [8] and Li^+ [9] complexes with Mon^- involves coordination by six oxygen atoms.



MonH

In a previous communication [10] we have reported a study of the solvent dependence of the acid dissociation constant of *Mon*H. In this paper we describe a polarographic study of Tl^+, Li^+, Na^+, K^+ and Cs^+ complexes with Mon^- in acetonitrile, propionitrile, acetone, N,N-dimethylformamide, N-methyl pyrolidinone, N,N-dimethylacetamide, dimethylsulfoxide, N,N-diethylformamide and N,N-diethylacetamide. The possible structures of the complexes in methanol are discussed on the basis of molecular mechanics computations.

Experimental

Sodium monensin (Sigma) was purified and converted successively into the free acid and the tetrabutylammonium salt [11]. $TlClO_4$, $LiClO_4$, $NaClO_4$, $KClO_4$ and $CsClO_4$ (high purity commercial reagents) were dried under vacuum at 120 °C. Tetrabutylammonium perchlorate, *TBAP*, was prepared by conversion of $(n\text{-}C_4H_9)_4NI$; it was recrystallized several times from water and dried in vacuo at 60 °C. All the solvents were dried as described in [12] and fractionally distilled at reduced pressure under an argon atmosphere immediately prior to use.

Polarographic and cyclic voltammetric curves were determined in a three electrode system, a Radelkis OH 105 apparatus being used. The working electrode was either a mercury drop electrode with a controlled drop time of 1.0 s or a hanging mercury drop electrode [13]. The auxiliary electrode was Pt-wire. The potentials were measured against an aqueous SCE, a two part salt bridge being used. One arm of this bridge contained solvent and electrolyte exactly as in the polarographic vessel. All solutions were deaerated with pure argon which was passed through molecular sieves, 0.4 nm, and presaturated by bubbling through the solvent. The measurements were performed at a temperature of 23 ± 0.1 °C. The quantum chemical calculations were carried out using a PC 386/387 computer.

Results and Discussion

Thallium(I) ions when studied by polarography and cyclic voltammetry have been found to unergo one-electron reduction to the metal amalgam in all solvents under study (c.f. [3, 14]). The shapes of the waves are in agreement with those characteristic for a reversible one electron transfer. The reversibility of the electrode process is also preserved after an addition of the ligand; it indicates that the exchange between $\mathrm{Tl(I)}_{solvated}$ and $\mathrm{Tl(I)}_{complexed}$ is rapid on the measurement timescale.

The dependence of the shift in half-wave potential upon the excess ligand concentration c_{Mon^-}, was found to be in accordance with the Lingane equation for the complexation of 1:1 type:

$$E'_{1/2} - E^0_{1/2} = -(\mathrm{RT}/F)\ln(K_s[\mathrm{Tl}Mon]c_{Mon^-}) - (RT/F)\ln(i_{\mathrm{Tl}Mon}/i_{\mathrm{Tl(I)}}) \qquad (1)$$

where $E'_{1/2}$ and $E^0_{1/2}$ are the half-wave potentials of the complexed and free (solvated) thallium(I) ion, respectively, $K_s[\mathrm{Tl}Mon]$ is the complex stability constant, whereas the ratio of limiting currents $i_{\mathrm{Tl}Mon}/i_{\mathrm{Tl(I)}}$ is attributed to a change in the diffusion coefficient of Tl^+ on complexation. It is noteworthy that the concentration of supporting electrolyte *TBAP* has no effect on the $E^0_{1/2}$ potential, therefore the measurements reported below were carried out in the presence of 0.05 *M* *TBAP*. Consequently, addition of an increasing amount of the tetrabutylammonium salt of monensin (10–100 m*M*) to the solution containing 0.5 m*M* Tl^+ led us to the stability constants of the Tl*Mon* complex which are presented in Table 1.

Next we have evaluated the stability constants of Li*Mon*, Na*Mon*, K*Mon* and Cs*Mon* complexes. Taking into account extremely negative potentials of the electo-

Table 1. Stability constants of monensin complexes with monovalent cations in various solvents

Solvent	DN[a]	$\log K_s$[b]				
		Tl^+	Li^+	Na^+	K^+	Cs^+
Acetonitrile	14.1	10.6	12.1	12.5	9.7	6.2
Propylene carbonate[c]	15.1	–	11.5	12.0	9.1	5.6
Propionitrile	16.1	9.9	12.2	11.8	9.2	5.6
Acetone	17.0	9.9	11.0	11.7	8.7	5.5
N,N-Dimethylformamide	26.6	7.2	6.0	8.7	7.3	4.4
N-Methyl pyrolidinone	27.3	6.0	4.7	6.6	6.0	4.3
N,N-Dimethylacetamide	27.8	6.0	4.3	6.5	5.6	3.9
Dimethylsulfoxide	29.8	4.5	3.8	5.6	5.1	3.3
N,N-Diethylformamide	30.9	4.1	3.5	5.3	4.6	3.3
N,N-Diethylacetamide	32.2	4.1	2.8	5.2	4.5	3.1

[a] Solvent donor number from Ref. [5]. [b] Error in determination of $\log K_s$ is ±0.1. [c] $\log K_s$ values in PC were extracted from Ref. [6]

reduction of complexed alkali metal cations, we have decided to use a competitive complexation method [15–18]. From the electrochemical properties of the Tl^+, Tl*Mon*/Tl(Hg) system, it is seen that this couple can be used as a sensitive probe to determine $K_s[MMon]$ values (M^+ represents an alkali metal cation). Therefore, in order to determine these values, we have measured the $E^0_{1/2}$ potential in solutions containing 0.5 m*M* Tl^+, and then after successive addition of 5–25 m*M* monensin in the form of its tetrabutylammonium salt ($E'_{1/2}$), and 15–60 m*M* alkali metal cations ($E''_{1/2}$). Reversible or nearly reversible cyclic voltammograms (scan rate 33 mV s^{-1}) were obtained in each case. In general it was observed that $-E^0_{1/2} < -E''_{1/2} < -E'_{1/2}$, the proximity of $E''_{1/2}$ to $E'_{1/2}$ depends on the effectiveness of the competition of M^+ with Tl^+ for the monensin anion. Applying the formalism discussed in details in Ref. [17], we have found the $K_s[MMon]$ values listed in Table 1. Note that the ionic strength was maintained at about 0.05 using T BAP. It is also noticeable that the stability constants of the alkali metal complexes already published in acetonitrile, N,N-dimethylformamide and dimethylsulfoxide [6] agree satisfactorily with our values. Therefore the $K_s[MMon]$ values determined in propylene carbonate by *Cox et al.* [6] are also included in Table 1.

The results in Table 1 show the stability constants for the Mon^- complexes to be quite sensitive to solvent variation. Thus for the Li*Mon* complex a variation

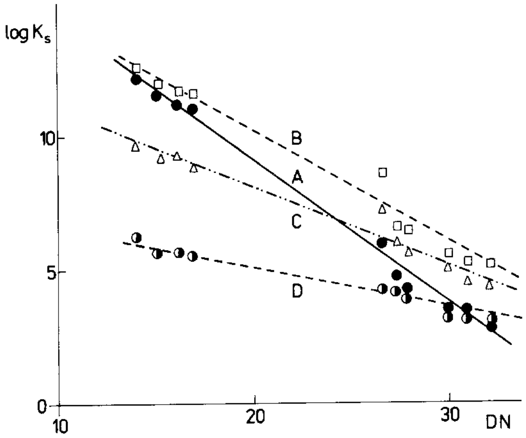


Fig. 1. Dependence of the stability constants of the complexes of alkali metal cations with the monensin anion on the Gutmann donor number of solvents: A – Li^+, B – Na^+, C – K^+, D – Cs^+

Table 2. Parameters of Eq. (2) for the complexation of monovalent cations with monensin anion

Dependent variable	α^a	β^a	n^b	r^c	s^d	F^e
$\log K_s[TlMon]$	-0.368 ± 0.056	16.00 ± 1.43	9	0.9857	0.41	239.5
$\log K_s[LiMon]$	-0.532 ± 0.039	19.69 ± 0.97	10	0.9959	0.33	985.6
$\log K_s[NaMon]$	-0.423 ± 0.061	18.62 ± 1.48	10	0.9851	0.51	263.1
$\log K_s[KMon]$	-0.279 ± 0.048	13.59 ± 1.18	10	0.9784	0.40	179.6
$\log K_s[CsMon]$	-0.154 ± 0.036	8.17 ± 0.61	10	0.9811	0.21	205.4

[a] Errors are determined on the basis of Student's distribution with a confidence level of 0.95. [b] Number of experimental points. [c] Correlation coefficient. [d] Standard deviation in $\log K_s$. [e] The Fisher and Snedecor test

in the stability constant of up to 9 orders of magnitude is observed. It is apparent that complexation increases in strength with a decrease in the donor number of the solvent. This result is in agreement with the trends observed in previously published [6] stability constants for *MMon* complexes. In fact, plots of $\log K_s$ against the Gutmann donor number give satisfactory relationships. The parameters of linear regression in the form of Eq. (2) are listed in Table 2 (see Fig. 1)

$$\log K_s = \alpha DN + \beta. \qquad (2)$$

From the data presented in Table 2 it can be deduced that the desolvation of cations plays a very important role in the complexation. Also the variation of the slope α of linear regression (2) upon the nature of the cation documents this idea. Taking into account the $1/r_c$ value as a measure of the ability of the cation to form a complex with Mon^- the relationship reproduced in Fig. 2 can be obtained. This correlation can easily be interpreted by an application of the Born approach to the thermodynamic of cation solvation, where for univalent cations a linear dependence between free enthalpy of solvation and $1/r_c$ is anticipated. Note that r_c is the cation radius in the Ladd scale which provides a good interpretation of solvation phenomena [19].

As it can be seen (Fig. 2) the thallium(I) ion does not conform to this correlation. One may expect, however, that only the data for hard electron pair acceptors will be on one line. While alkali metal cations are considered to be hard acceptors, Tl^+ is a soft Lewis acid. And this seems to limit correlation presented in Fig. 2 to alkali metal cations only.

Having established the $K_s[MMon]$ values, it was of interest to propose the possible structures of the complexes. One of the most promising tools for the design of molecules is the use of computational techniques such as molecular mechanics in combination with computer graphics [20, 21]. Several reviews [22–25] have been published which describe in detail the procedures and their application to the problems of macrocyclic ligand-guest interaction. In many cases a reasonable agreement between the calculated and experimental values was found and this led us to the application of molecular mechanics to the complexes. According to that we have considered the complexes surrounded by methanol molecules (the parameters for MeOH are well established).

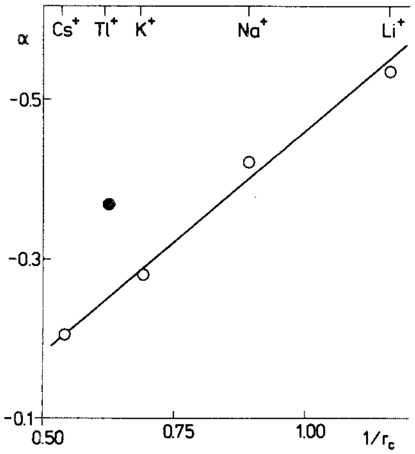
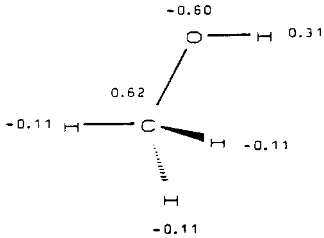


Fig. 2. Plot of the slopes of regression described by Eq. (2) on the reciprocal of the ionic radius of cation (the correlation coefficient for the regression line is $r = 0.9863$)

The calculations were performed with the program AMBER 3.0 [26–28] in which the energy functions had the same form as in Ref. [26]. The parameters were taken from the AMBER force field [27] with the exception of the data for alkali metal cations; the last ones were extracted from [29]. As starting geometry for the computation on *MMon* complexes, the X-ray data available from the literature [9] were used. Because of the dominant role of electrostatic interactions in such systems, much attention has been paid to the partial charges at the Mon^- and MeOH atoms. To this purpose we have calculated a set of atomic charges at a fixed X-ray molecular geometry *via* the molecular electrostatic potential (ESP) fit method (see [30, 31] and references therein). But rather to "deorthogonalize" the MNDO [33–35] density matrix to obtain a proper basis set and next to compute ESP, we used a multicenter multipole expansion of MNDO density matrix with multipoles centered on atoms. In our calculations we used multipole expansion up to dipoles because quadrupole terms had not significant values. Such a procedure ensures the portrayal of the dipole moment of a molecule so that no "scaling" of fitted charges is necessary what was done in Refs. [30, 31]. The construction of the surfaces of points for evaluated ESP was realized by the use of the surface generation algorithm of Connoly [32]. Using shells of 1.5 and 2.0 times the van der Waals radii, with a density of one point to square angstrom, we have obtained the charges rather insensitive to the position of the electrostatic potential points. For the Mon^- anion the accuracy is ±0.01 which corresponds to an error of ±5% i.e. $\pm 1.2\,\mathrm{kJ\,mol^{-1}}$. The derived charges are −0.951 and −0.522 for oxygen atoms of the $-COO^-$ group and for all remaining O-atoms, respectively. In the case of the MeOH molecule the error in evaluation of the electrostatic potential is ±15%; the resulting charges are given in the following scheme:



In order to simulate the complexation reaction we used the model expressed by Eq. (3)

$$Mon^-(\mathrm{MeOH})_6 + M^+(\mathrm{MeOH})_{12} \rightleftarrows MMon(\mathrm{MeOH})_6 + 12\ \mathrm{MeOH}. \qquad (3)$$

The resulting complexation energies, E_{compl}, defined as the difference of the total energy of the complex and the total energies of its components in the lowest energy conformations, are listed in Table 3. These values have not precise physiochemical meaning because the model of complexation is oversimplified. However, it is clear from Table 3 that the computations reproduce qualitatively the experimental trend with respect to binding preferences of alkali metal cations to the Mon^- anion. Indeed, the stability constants of the complexes gradually decrease in the following

Table 3. Calculated complexation energies (kJ/mol^{-1}) for *Mon*$^-$-cation complexes and experimental values of stability constants in methanol

Cation	E_{compl}	$\log K_s$[a]
Li^+	−356	3.6_0
Na^+	−383	6.3_7
K^+	−379	4.9_7
Rb^+	−361	4.2_8
Cs^+	−330	3.5_9

[a] Literature data [6]

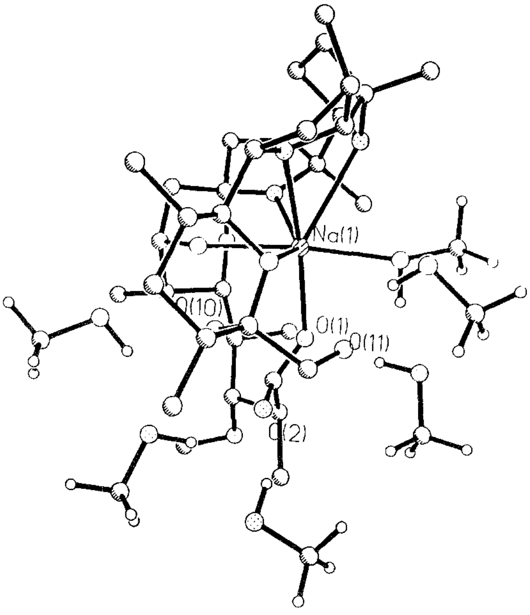


Fig. 3. 3D view of the molecular mechanics minimized complex of the monensin anion with Na^+ cation and six methanol molecules. For simplicity, the hydrogen atoms of *Mon*$^-$ anion are not shown in the diagram

order Na*Mon* > K*Mon* > Rb*Mon* > Li*Mon* > Cs*Mon*, and there is much agreement with the order of E_{compl}.

Figure 3 presents a 3D image of the molecular mechanics minimized complex of the monensin anion with Na^+ cation and methanol molecules. As can be seen, the conformation of the ligand is more deformed to what is found from X-ray data [8, 9]. Such deformation are also observed for all remaining complexes under consideration; the ligand wraps around the cation in a way similar to that presented in Fig. 3. Simultaneously the first solvation shell of the complexed cation is completed by one MeOH molecule. Solvent draws out the cation from the ligand cavity and makes the ligand structure more loose in comparison to the crystal structure (appropriate data are tabulated in Table 4).

Becasue *MMon* complexes in methanol are more or less spherical, they may be characterized by appropriate radii of giration R_G, defined by

$$R_G^2 = \Sigma m_i R_i^2 / \Sigma m_i \tag{4}$$

Table 4. *MMon* complexes in methanol: resulting values from molecular mechanics computations

Cation	$M^{+}\cdots\mathrm{O}^{a}$	CN^{b}	$\mathrm{O}\cdots\mathrm{H}\cdots\mathrm{O}^{c}$	$R_G{}^{d}$	$CM\cdots M^{+e}$
Li$^+$	1.80	3	2.64	4.31	0.96
Na$^+$	2.53	7	2.64	4.31	0.92
K$^+$	2.77	9	2.65	4.35	1.09
Rb$^+$	2.97	10	2.66	4.38	1.49
Cs$^+$	3.12	10	2.70	4.42	1.72

[a] Average distance between the cation and the coordinated oxygen atoms (in Å). [b] Coordination number of cation. [c] Average distance between the carboxylic and hydroxylic oxygen atoms (in Å). [d] Radius of giration (in Å). [e] Distance of the cation from the center of mass of Mon^- (in Å)

where the atom i of mass m_i is placed at a distance R_i from the center of mass of Mon^-. It is seen from Table 4 that the R_G values are independent of the cationic size for Li$^+$ and Na$^+$, and raises from K$^+$ to Cs$^+$. Although the ligand is forced to blow up, it still forms a circle. This is evident from O···H···O distances which denote average O1···O11 and O2···O10 distances (Fig. 3): R_G increases twice as much as O···H···O. Interestingly, however, the distance between the cation and the center of mass fits to some extent the stability constants of the complexes. Comparing the data of the last column of Table 4 and the log K_s values (Table 3) it may be suggested that the distance decreases gradually as the stability of the complexes increases going from Na$^+$ to Cs$^+$. For Li$^+$ the situation is somewhat different. The geometry found here indicates that the position of the cation changed so that it is in close contact with the carboxylic oxygen atom O1 of the ligand but still only one methanol molecule binds to Li$^+$. In all remaining complexes the cation is roughly located over the center of the cavity.

Thus, this study has shown that molecular mechanics computations reproduce qualitatively the changes in the stability of *MMon* complexes in methanol. It gives confidence on the correctness of the designed structures.

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