Interactions between metal cations and the ionophore lasalocid. Part 14.[1] Structure of lasalocid–alkali metal cation complex salts in methanol from NMR spectroscopy and computational experiments

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^{13}C and ^{1}H NMR spectra were obtained and totally assigned for all the alkali metal cation complex salts of lasalocid in methanol. Most of the corresponding ^{1}H–^{1}H coupling constants were also accessed. Computational experiments in the solvent methanol involving either Monte-Carlo statistical mechanics simulations or quantum semiempirical calculations in a continuum were also carried out. These data provided insight into the structure and solvation of these species in methanol.

Introduction

Lasalocid (Fig. 1) is a naturally occurring ionophore isolated some 40 years ago[2] from strains of *Streptomyces lasaliencis.* Numerous studies have been devoted to its cation-complexing and translocating abilities. It has been shown that it can interact with most metal cations. Among these, alkali metal cations form a class of particular interest in view of the importance of Na^+, K^+ and even Li^+ in biological exchanges. The equilibria in methanol of lasalocid with all the alkali metal cations have been described in previous papers[3,4] in this series and elsewhere.[5–7] We determined the magnitude of the thermodynamic functions, *i.e.* enthalpies and entropies,[3] volumes and heat capacities[4] associated with complexation reactions in this solvent. Methanol was chosen by us and others for its ability to dissolve the ionophore, its complexes and the alkali metal inorganic salts and also for the ease with which most of the usual physicochemical measurements (electrochemical, thermodynamic, spectroscopic) can be made in it.

Understanding the complexation process requires not only knowing the energies involved and their derived quantities but also having some idea of the structure of the reacting and resulting species. Also, the variations in the thermodynamic properties concerned with the nature of the cation mainly arise from the structure of the complexes formed; *e.g.* ligation sites and conformation of the ligands. These properties can vary from one cation to another. Structural information in solution can be obtained by spectroscopic measurements. For lasalocid, information has been obtained from UV–VIS,[3,5] fluorescence,[5] circular dichroism[5,8] and circular polarization of fluorescence.[9] The disadvantage of these methods is that they reflect the state of the chromophores only, *i.e.* mainly the salicylic moiety and sometimes the ketone group.

Fuller data would be expected from ^{13}C and ^{1}H NMR spectra. The first study of the free acid and the sodium salt of lasalocid in methanol was conducted by Shen and Patel[10] and allowed a partial assignment of the ^{13}C and ^{1}H resonance frequency shifts. For ^{1}H, this was taken further by Anteunis[11] who on the basis of these data suggested structures for these species in methanol. Absence of dimerization of the sodium salt in methanol, contrary to what was observed in chloroform,[10,12] was postulated from ^{13}C relaxation studies.[10] The free acid was shown to be monomeric in both solvents methanol and chloroform.[10,13] In a recent paper,[14] we reported complete assignment in chloroform and methanol of ^{13}C and ^{1}H chemical shifts for lasalocid free acid, its potassium salt and its anion in a non-complex tetraalkylammonium salt. Studies of relaxation times and variation with concentration of the chemical shifts showed that no dimerization occurs in methanol for any of these three species. Examination of chemical shifts and ^{1}H–^{1}H coupling constants then enabled us to propose a rough description of the structure of these three species in methanol solution. From that and previous studies it was suggested that the potassium salt KA had a folded conformation of the ligand, which wrapped the cation.

Two types of complexes could, theoretically, be formed in methanol between lasalocid and a monovalent metal cation M^+; the ligand could either be in the acid form HA or the anion form A^-. This has frequently been observed for other ionophores in this family. For lasalocid the potentiometric study[3] was in this respect inconclusive as regards the formation or not of HMA^+. Recent NMR data, which will be reported elsewhere allowed the determination of formation constants of HMA^+ in methanol for all the alkali metal cations. Some structural features were also, incidentally, established. The work reported here concerns only the neutral complexes, *i.e.* the MA salts in methanol.

A systematic study of the structures of all the alkali metal salts is reported here. Experimental ^{13}C and ^{1}H NMR data are given. These spectroscopic data were used in a systematic computational search for most favoured MA structures in methanol. Gaseous state structures of lasalocid and lasalocid anion had previously been investigated using AM1 semiempirical quantum calculations.[15] These structural aspects were recently specified for the acid using Monte-Carlo sampling simulations, molecular dynamics and thermostatistical computations.[16] This work was extended to methanol solutions[17] using both continuous and discrete models for the solvent. The same was undertaken here for the lasalocid alkali metal salts. Preferred conformations in the gaseous state, accessed using Monte-Carlo sampling, were taken as starting geometries for the studies in methanol. These were carried out using statistical mechanics simulations and a semiempirical quantum approach in a continuum.

The main purpose of this work was to obtain a more accurate picture of the structures of these MA salts in methanol, which could be correlated to their thermodynamic properties in the same solvent, for which abundant data had previously been reported.

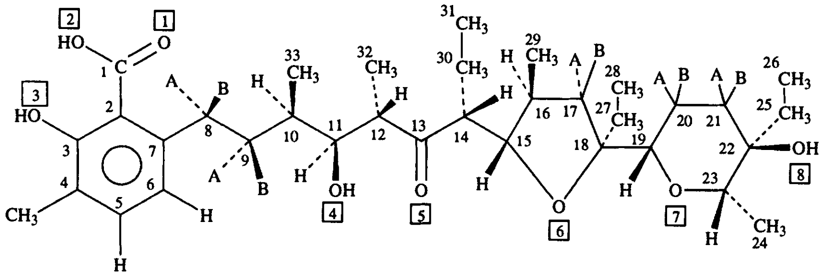


Fig. 1 Lasalocid formula with carbon and oxygen numbering scheme

Experimental

Chemical

Lasalocid was prepared as previously[18] from its commercial sodium salt (Sigma). Its alkali metal salts, including the sodium salt, were prepared in methanol (Merck *pro analysi*) by exact neutralization of lasalocid acid with an alkali metal methoxide solution obtained, as previously described,[19] by either direct reaction of the metal (Li^+, Na^+, K^+) with methanol or electrochemically using the corresponding amalgams (Rb^+, Cs^+). The lasalocid alkali metal salt was isolated by evaporation of the methanol from the solution. To remove traces of water the solid thus obtained was dissolved in acetone and the acetone was evaporated. This procedure was repeated twice. The salt was then dried overnight in a vacuum oven in a polytetrafluoroethylene-coated flat dish.

CD_3OD was prepared by the CEA and distributed by SDS.

NMR Spectra

All the spectra were recorded on a Bruker MSL 300 spectrometer. ^{13}C, ^{1}H NMR decoupled spectra, J modulated spin-echo spectra, ^{1}H–^{1}H chemical shift correlations (COSY) and ^{1}H–^{13}C correlations were carried out as described in a previous paper.[14]

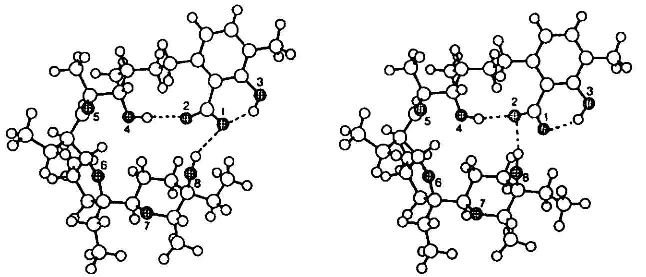
Computations

Semiempirical quantum calculations in a continuum were performed by the PM3 method[20] using the GEOMOS package[21] on a DEC α 3000/300 computer. Monte-Carlo statistical mechanics simulations were carried out with the BOSS program[22] using a DEC α 3000/400 S computer.

Methods and results

Monte-Carlo statistical mechanics on MA complexes *in vacuo*

Statistical thermodynamics computations by Monte-Carlo sampling on MA complexes of lasalocid with alkali metal (Li^+, Na^+, K^+, Rb^+, Cs^+) cations were carried out with the BOSS program[22] in the gas phase. The alkali metal cation and the lasalocid anion were considered as two different species. Atomic charges on the lasalocid anion were calculated using AM1 and then loaded into the parameter file. For these simulations, equilibration was carried out for 3×10^6 configurations. Averaged computed enthalpies and solute–solute energies were recorded over the next 3×10^6 configurations. All alkali metal cations were parametrized according to Aqvist.[23] The starting structures of the various MA complexes were as follows. Two conformations of the ligand resulting from a Monte-Carlo sampling study[24] and labelled 1a and 2a in this paper (Fig. 2) were used. They differ mainly in their head–tail closure bonds, respectively $O(8)H \cdots O(1)$ and $O(8)H \cdots O(2)$, O-1 being the oxygen of the carboxylate already bound to the phenol group O(3)H. The starting conformations of anions **1a** and **2a** were optimized *in vacuo* using the AMBER/OPLS force-field.[25] Conformation **2a** was used for the small cations, and conformation **1a**, which gave rise to a larger complexing cavity was used for the large cations. The cations were located optimally in the co-ordinating cavity with the help of data reported[26] on the cation–oxygen distances in sodium and caesium lasalocid crystals. For Li^+, Na^+, K^+ we used conformation 2a of A^- to cation–oxygen distances of 5.8 for O-1, 3.9 for O-2, 8.0 for O-3, 2.7 for O-4, 2.6 for O-5, 2.4 for O-6, 2.6 for O-7, 2.4 Å for O-8. For RbA and CsA the conformation **1a** of A^- was used and the initial distances to the cation were about 4.7 for O-1, 3.0 for O-2, 7.0 for O-3, 3.3 for O-4, 3.0 for O-5, 3.0 for O-6, 3.1 for O-7, 3.0 Å for O-8. *In vacuo*, the two solutes lasalocid anion and alkali cation were perturbed more frequently than in solution. This means that the co-ordination sites fluctuate; the conformations of the MA complexes are not only representative of local minima and the cross-section of the conformational space is larger than that described in solution.



1a

2a

Fig. 2 Skeleton schemes of the two closed conformations of the anion lasalocid (**1a** and **2a**) resulting from AM1 semiempirical calculations *in vacuo*[24] and showing their hydrogen bonding systems. ○, Carbon; ○, hydrogen; ⊕, oxygen.

The mean energies and the geometric characteristics of the MA complexes *in vacuo* are given in Table 1. The hydrogen bond length and the metal cation–lasalocid oxygen distances are mean values calculated from a Boltzmann distribution. The conformations of these complexes of minimal enthalpy are shown in Fig. 3.

NMR experiments in methanol

Experimental conditions were set to have 100% of the species concerned. These salts were assumed to be monomeric as suggested by ^{13}C relaxation studies.[9,12] Also, no appreciable variations in the ^{1}H and ^{13}C chemical shifts as a function of the salt concentrations were observed in this study. ^{1}H and ^{13}C resonances were assigned independently for each species using one- and two-dimensional spectra as previously.[14] ^{13}C and ^{1}H chemical shifts thus obtained for lasalocid in its complex salts are reported in Tables 2 and 3. Most of the ^{1}H–^{1}H coupling constants were accessed using, as previously,[14] various methods including irradiation. They are reported in Table 4 and ^{1}H and J-modulated ^{13}C NMR spectra of lasalocid rubidium salt in methanol are given as an example in Fig. 4.

In addition, we attempted to follow the complexation by the lasalocid anion of both Li^+ and Na^+ cations using ^{7}Li and ^{23}Na NMR. The lithium chemical shift was found to vary little when adding lasalocid tetramethylammonium salt to a lithium

Table 1 Description of MA complexes of lasalocid with alkali metal cations *in vacuo* according to a Monte-Carlo statistical mechanics computation at 298 K using the BOSS program

	LiA	NaA	KA	RbA	CsA
H [a]	−91.8	−72.7	−62.4	−56.8	−51.0
E_{SX} [b]	−167.7	−141.3	−124.8	−119.3	−111.9
α [c]	23	23	23	18	18
THF [d]	${}^{15}{}_{16}\mathrm{T}$ ${}_{16}\mathrm{E}$	${}^{15}\mathrm{E}$ ${}^{17}{}_{16}\mathrm{T}$	${}^{15}{}_{16}\mathrm{T}$ ${}^{17}\mathrm{E}$	${}^{15}{}_{16}\mathrm{T}$ ${}^{17}{}_{16}\mathrm{T}$	${}^{15}{}_{16}\mathrm{T}$ ${}^{17}\mathrm{E}$
Q_1, Q_2	0.29 0.54	0.31 0.51	0.32 0.46	0.30 0.54	0.30 0.55
φ_1, φ_2	10 39	9 65	27 72	24 58	20 65
THP	${}^{19}\mathrm{C}_{22}$	${}^{19}\mathrm{C}_{22}$	${}^{19}\mathrm{C}_{22}$	${}^{19}\mathrm{C}_{22}$	${}^{19}\mathrm{C}_{22}$
Q_1, Q_2	0.53 0.64	0.53 0.65	0.52 0.67	0.58 0.68	0.56 0.75
θ_1, θ_2	167 178	169 179	168 179	163 178	164 178
[e] O(3)H ··· O(1)	2.25	2.03	2.14	2.06	2.17
O(4)H ··· O(2)	1.90	1.76	1.91	1.89	1.88
O(8)H ··· O(1)	2.65	2.27	2.01	1.93	1.88
[f] M ··· O-1	2.0 [1.9; 2.1]	4.5 [2.2; 4.6]	4.4 [3.9; 4.8]	4.3 [3.5; 4.9]	4.4 [3.3; 4.7]
M^+ ··· O-2	2.0 [1.9; 2.1]	2.4 [2.2; 4.5]	2.6 [2.4; 2.8]	2.6 [2.4; 2.8]	2.7 [2.7; 3.2]
M^+ ··· O-3	4.8 [4.2; 5.0]	6.6 [4.7; 6.7]	6.7 [6.4; 7.0]	6.6 [6.1; 7.2]	6.7 [5.9; 7.1]
M^+ ··· O-4	3.8 [3.3; 4.3]	3.0 [2.6; 4.5]	3.0 [2.8; 3.7]	3.2 [3.0; 3.8]	3.6 [3.5; 4.2]
M^+ ··· O-5	5.3 [4.7; 5.8]	3.2 [2.7; 6.1]	3.3 [2.8; 3.8]	3.3 [2.8; 3.9]	3.2 [2.9; 4.1]
M^+ ··· O-6	5.3 [4.5; 6.1]	2.9 [2.6; 6.1]	2.9 [2.7; 3.4]	3.2 [2.9; 3.7]	3.2 [3.1; 4.1]
M^+ ··· O-7	3.8 [3.2; 4.5]	2.9 [2.4; 4.8]	2.9 [2.6; 3.4]	2.9 [2.8; 3.4]	3.5 [2.9; 3.7]
M^+ ··· O-8	2.1 [2.0; 2.6]	2.5 [2.2; 2.7]	2.8 [2.5; 3.2]	2.9 [2.7; 3.3]	3.4 [2.8; 3.6]

[a] Mean enthalpy of the MA complex *in vacuo* (kcal $\mathrm{mol^{-1}}$, 1 cal = 4.184 J). [b] Mean intersolute energy (kcal $\mathrm{mol^{-1}}$) between the lasalocid anion and the alkali metal cation. [c] Steric angle α (°) between the benzene and carboxylate planes. [d] Minimum and maximum values of the Cremer ands Pople parameters[27] for the tetrahydrofuran and tetrahydropyran rings, envelope ${}^{x}E$, x being the apex, twist ${}^{y}{}_{z}T$, y and z being out-of-plane, perfect chair form C. [e] Mean H ··· O hydrogen bond length (Å). [f] Mean distance between cation and lasalocid oxygens with in brackets minimal and maximal values.

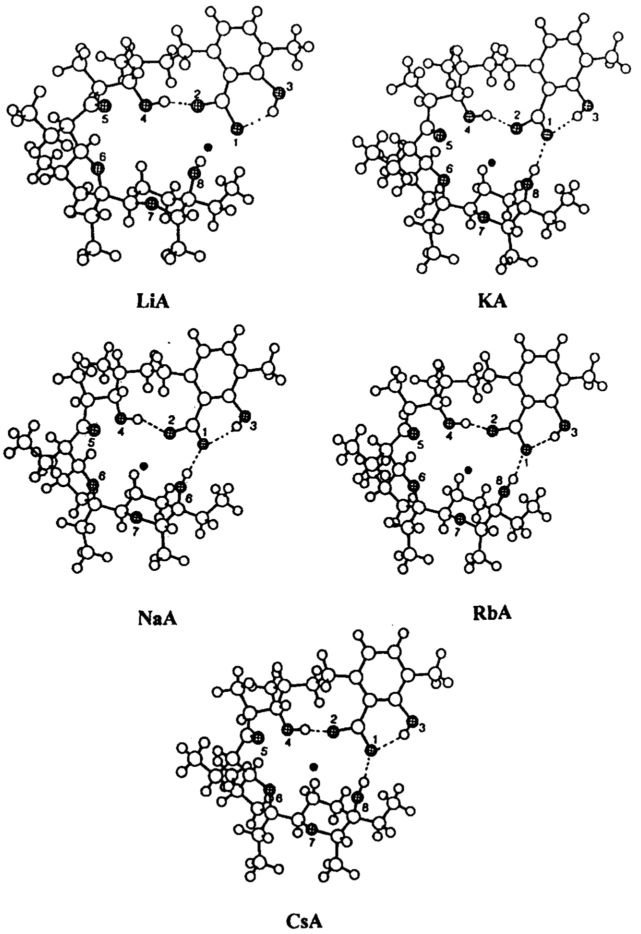


Fig. 3 Skeleton schemes of MA complexes of minimal enthalpy *in vacuo* resulting from Monte-Carlo simulations using the BOSS program. ○, Carbon; o, hydrogen; ◍, oxygen; ●, metal cation.

Table 2 ^{13}C Chemical shifts of lasalocid alkali metal complex salt MA in methanol, at concentration from 0.1 to 0.2 mol $\mathrm{dm^{-3}}$ at room temp. *ca.* 20 °C (unit ppm, accuracy ±0.1, values corrected to 100% MA taking into account the small partial dissociation using association constants in ref. 3)

^{13}C	LiA [b]	NaA	KA [a]	RbA	CsA
1	176.4	177.1	177.5	177.5	177.1
2	118.7	118.4	118.3	118.3	118.2
3	160.6	161.7	161.9	161.7	161.4
4	123.0	124.0	124.2	124.2	123.9
5	132.7	133.1	133.2	133.2	133.0
6	121.3	121.4	121.7	121.5	121.5
7	144.3	144.8	144.8	144.8	144.8
8	33.7	34.2	32.7	33.8	33.7
9	37.5	38.5	37.9	38.8	38.8
10	35.6	35.2	33.7	35.1	35.1
11	76.5	73.2	71.6	72.2	72.1
12	50.4	50.2	49.0	49.8	49.5
13	223.0	220.2	219.1	218.9	217.9
14	56.0	56.6	56.6	56.7	56.9
15	85.4	84.4	84.4	84.9	85.2
16	36.1	35.9	34.3	35.8	36.0
17	38.6	39.0	38.0	39.3	39.6
18	88.2	88.1	88.1	88.2	88.4
19	72.9	70.6	71.1	71.8	72.2
20	21.9	20.9	19.4	20.6	20.6
21	29.3	30.7	30.0	31.1	31.1
22	70.8	71.9	72.2	71.9	72.3
23	76.5	77.1	77.5	77.7	77.8
24	14.0	13.9	13.5	14.2	14.3
25	31.6	32.3	32.0	33.0	33.1
26	6.9	6.7	6.8	6.8	7.0
27	30.7	30.6	29.9	31.1	31.4
28	9.4	9.6	9.5	9.5	9.9
29	15.4	15.6	15.7	15.7	15.8
30	18.6	17.5	15.7	17.0	17.0
31	13.1	12.8	12.2	12.8	13.0
32	13.7	13.0	12.7	13.0	13.0
33	13.8	13.4	13.4	13.5	13.6
34	16.1	16.2	16.4	16.1	16.2

[a] From ref. 14. [b] LiA 0.1 mol $\mathrm{dm^{-3}}$ + LiCl 0.2 mol $\mathrm{dm^{-3}}$.

perchlorate solution in methanol, −0.08 ppm at most when most of the lasalocid lithium salt was presumably formed; according to its association constant in methanol.[2] On the contrary, variations in the ^{23}Na chemical shifts under the same conditions were noticeable and though the observed signal resulted from equilibria between $\mathrm{Na^+}$ and NaA no significant

Table 3 ^1H Chemical shifts of lasalocid alkali metal complex salt MA in methanol in the conditions stated in Table 2

^1H	LiA	NaA	KA[a]	RbA	CsA
5	7.05	7.07	7.05	7.05	7.05
6	6.61	6.58	6.60	6.59	6.59
8A	3.36	3.76	3.97	3.96	3.99
8B	2.85	2.50	2.36	2.38	2.76
9A	1.72	1.75	1.67	1.66	1.71
9B	1.52	1.53	1.50	1.50	1.49
10	1.72	1.78	1.70	1.74	1.71
11	3.95	4.29	4.42	4.37	4.37
12	3.11	3.00	2.94	2.93	2.90
14	3.04	2.87	2.78	2.73	2.67
15	3.82	3.85	3.95	4.00	4.09
16	2.20	2.23	2.23	2.28	2.21
17	1.72	1.98	1.97	2.02	2.06
18	1.65	1.56	1.47	1.49	1.48
19	3.83	3.73	3.62	3.61	3.57
20A	1.78	1.94	1.95	2.02	2.00
20B	1.52	1.52	1.54	1.59	1.67
21A	1.72	1.77	1.75	1.83	1.88
21B			1.52	1.75	1.62
23	3.95	3.89	3.67	3.88	3.86
24	1.26	1.29	1.26	1.25	1.23
25A	1.44	1.71	1.58	1.56	1.49
25B		1.46	1.40	1.43	1.49
26	0.98	0.99	1.02	1.02	1.00
27A	1.75	1.92	1.89	1.92	1.90
27B	1.48	1.43	1.89	1.42	1.48
28	0.91	0.93	0.95	0.93	0.94
29	1.08	1.13	1.15	1.13	1.13
30A	1.91	2.00	2.11	2.04	2.07
30B	1.56	1.49	1.46	1.42	1.49
31	0.98	0.94	0.88	0.91	0.90
32	1.08	1.04	1.06	1.00	0.98
33	1.03	0.94	0.92	0.91	0.92
34	2.20	2.20	2.14	2.20	2.21

[a] From ref. 14.

enlargement was obtained. The data were processed by considering the equilibrium constant, the mass balance and the additivity of the chemical shifts. The apparent formation constant so obtained, log $K_1' = 2.3$ at high ionic strength (from $I = 0.4$ to 1.4 mol dm^{-3}, room temp.), is close to the standard value from the potentiometric measurements; log $K_1 = 2.8$ (25 °C, molar scale of concentrations).

Computational studies on MA complexes in methanol

Monte-Carlo statistical mechanics simulations on MA complexes in methanol. The two solutes lasalocid anion and alkali metal cation were placed with 378 methanol molecules[28] in a cubic cell (*ca.* 26.7 × 26.7 × 40 Å^3) with periodic boundary conditions. These calculations were carried out in the isobaric (NPT) ensemble at 25 °C and 1 atm with Metropolis[29] and preferential sampling[30] option. The starting conformations of these simulations in methanol solution were the conformations of minimal enthalpy resulting from the Monte-Carlo simulations in the gas phase. The cut-off was set at 11 Å for both solute–solvent and solvent–solvent interactions and was taken to be very large for intramolecular interactions in the solute. Equilibration was carried out for 3 × 10^6 configurations; averaging for computed energies and distribution functions were performed over the next 3 × 10^6 configurations. Intermolecular interaction energies were obtained using the AMBER/OPLS force-field.[25] The computation of intramolecular and intermolecular energy terms are described in detail in a previous paper.[1]

Integrations of the radial distribution functions $g_{O\cdots HOMe}$ and $g_{OH\cdots OHMe}$ out to a distance of 2.65 Å yielded, respectively, $\eta_{O\cdots HOMe}$ and $\eta_{OH\cdots OHMe}$.

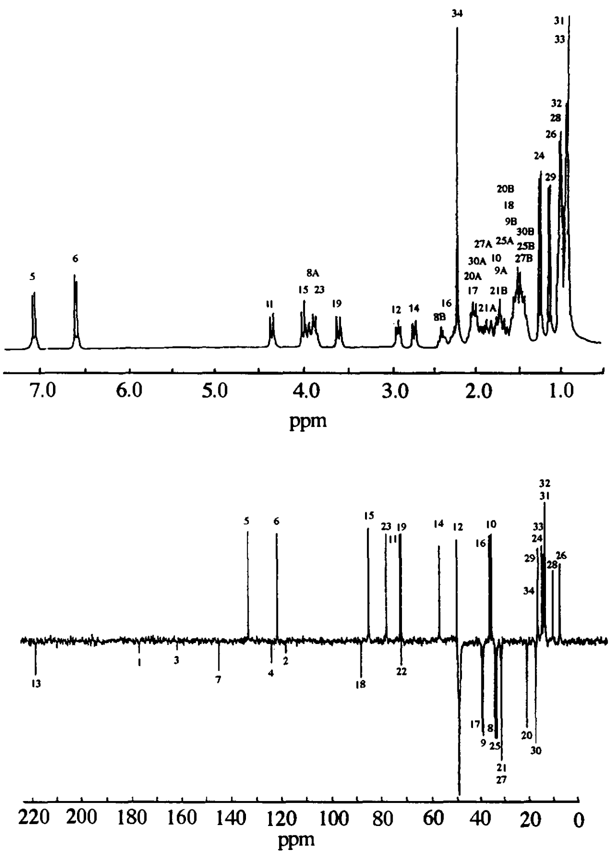


Fig. 4 ^1H and *J*-modulated ^{13}C NMR spectra of lasalocid rubidium salt in methanol (ppm, room temp.)

$\eta_{O\cdots HOMe}$ is the average number of hydrogen bonds between lasalocid oxygens and the hydrogen of methanol. $\eta_{OH\cdots OHMe}$ is the average number of hydrogen bonds between the hydrogen of solute hydroxy groups and the oxygen of methanol. $\eta_H = \eta_{O\cdots HOMe} + \eta_{OH\cdots OHMe}$ is the total average number of hydrogen bonds between the methanol solvent and the lasalocid molecule.

The conformations of MA complexes of minimal enthalpy with methanol molecules of the first shell of solvation in interaction with the cation are shown in Fig. 5. The enthalpy values, the solute–solute and solute–solvent energies and $\eta_{O\cdots HOMe}$ and $\eta_{OH\cdots OHMe}$ are reported in Table 5. The metal cation–lasalocid oxygen mean distances were calculated using a Boltzmann distribution. They are given in Fig. 6. To compare co-ordination numbers of the alkali cations free in methanol and in the MA complex in methanol, Monte-Carlo statistical mechanics simulations were performed on free cations also placed in a box with 378 methanol molecules. These simulations were achieved using the same conditions as for the MA complexes in methanol. The radial distribution functions between the alkali cation involved and the methanol oxygen atoms were computed (Fig. 7) both for the cation alone in methanol and for the cation in the MA complex in methanol. The radial distribution function tends to 1 as r increases suggesting that these systems can be considered as equilibrated. The integration of the first two peaks of these radial distribution functions provides the mean numbers of near neighbouring methanol molecules n_1 in the first and n_2 in the second solvation shells of the cation. For the co-ordination of the Na^+ cation in the first shell of solvation, our results agree closely with those of Jorgensen.[31] For Li^+, K^+, Rb^+ and Cs^+ free cations, data resulting from MC simulations or MD simulations or X-ray diffraction studies are only available in water.[32] The internuclear $M^+\cdots O$ distances and the co-ordination numbers in methanol were found to be close to their values in water for the first solvent shell. Calculations of

Table 4 Vicinal coupling constants (Hz) of lasalocid anion in MA complexes. For each MA complex, the experimental values are in the first column, the mean coupling constants resulting from the Monte-Carlo simulations in methanol are given in the second column, the coupling constants corresponding to conformations resulting from the PM3 computations in a continuum are reported in the third column

	LiA			NaA			KA			RbA			CsA	
^1H-^1H	Exp.	MC	PM3	Exp.	MC	PM3	Exp.	MC	PM3	Exp.	MC	PM3	Exp.	MC
8A-9A	3.6	3.1	2.8	3.5	2.9	2.8	2.8	3.2	3.1	3.2	3.1	2.6	3.6	2.8
8A-9B	10.8	12.8	12.8	11.2	12.8	12.8	11.4	12.9	12.9	12.0	12.8	12.7	12.0	12.7
8B-9A	10.8	12.8	12.8	11.2	12.7	12.8	11.4	12.9	12.9	12.0	12.8	12.8	12.0	12.8
8B-9B	4.1	4.1	3.6	5.3	4.4	4.0	6.0	3.9	3.6	6.4	3.9	4.2	6.6	4.3
10-33	7.0	6.9	7.2	7.0	6.9	7.2	6.5	6.9	7.2	7.0	6.9	7.3	6.4	6.9
10-11	2.0	4.3	4.2	1.4	4.3	4.2	1.8	4.1	4.2	2.4	3.3	3.5		3.7
11-12	9.6	10.3	10.3	10.2	10.3	10.3	10.2	10.3	10.3	10.0	10.1	10.2	9.9	10.2
12-32	7.0	7.0	7.1	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0
14-30A	8.4	12.3	12.3	10.5	12.3	12.3	10.5	12.2	12.2	10.4	12.3	12.3	10.5	12.3
14-30B	4.2	3.2	2.9	5.6	3.2	2.9	2.5	3.2	2.9	2.4	3.5	3.1	3.2	3.8
14-15	3.0	2.1	2.1	2.2	2.0	2.0	2.5	2.0	2.0	2.4	2.3	2.5	3.2	2.4
15-16	10.8	10.3	10.3	10.2	10.1	10.2	10.2	10.3	10.2	11.2	10.2	10.4	10.4	10.5
16-17A	7.0	4.1	6.6	7.0	6.7	6.8	7.7	6.6	6.7	7.7	6.3	5.8		6.2
16-17B	12.2	11.5	11.4	13.3	11.4	11.2	11.2	11.5	11.4	13.0	11.7	12.0		11.8
16-29	6.5	7.2	7.1	6.3	7.2	7.2	6.5	7.2	7.2	6.4	7.2	7.2	6.4	7.2
19-20A	10.8	11.1	11.1	11.9	11.1	10.9	12.0	11.1	11.1	12.0	11.2	11.2	11.6	11.2
19-20B	3.0	4.5	4.1	2.8	4.5	4.5	2.1	4.3	3.9	2.4	3.3	3.1	2.0	3.3
20A-21A		5.1	5.2		5.0	5.1	4.6	5.1	5.4		3.3	4.1		3.9
20A-21B		13.0	12.8		13.0	12.9	11.2	13.0	12.7		13.2	13.2		13.2
20B-21A		3.7	3.9		3.9	3.9		3.7	3.7	3.0	3.3	4.4		4.0
20B-21B		5.1	5.1		4.9	5.0	5.5	5.1	5.3	4.5	5.5	4.4		4.6
23-24	7.0	6.5	6.6	7.0	6.5	6.5	7.0	6.5	6.5	7.0	6.5	6.5	7.0	6.5
25-26	7.0	7.5	7.5	7.0	7.5	7.5	7.0	7.5	7.5	7.0	7.5	7.5	7.0	7.5
27-28	7.0	7.5	7.5	7.0	7.5	7.5	7.0	7.5	7.5	7.0	7.5	7.5	7.0	7.5
30-31	7.0	7.5	7.5	7.0	7.5	7.5	7.0	7.5	7.5	7.0	7.5	7.5	7.0	7.5

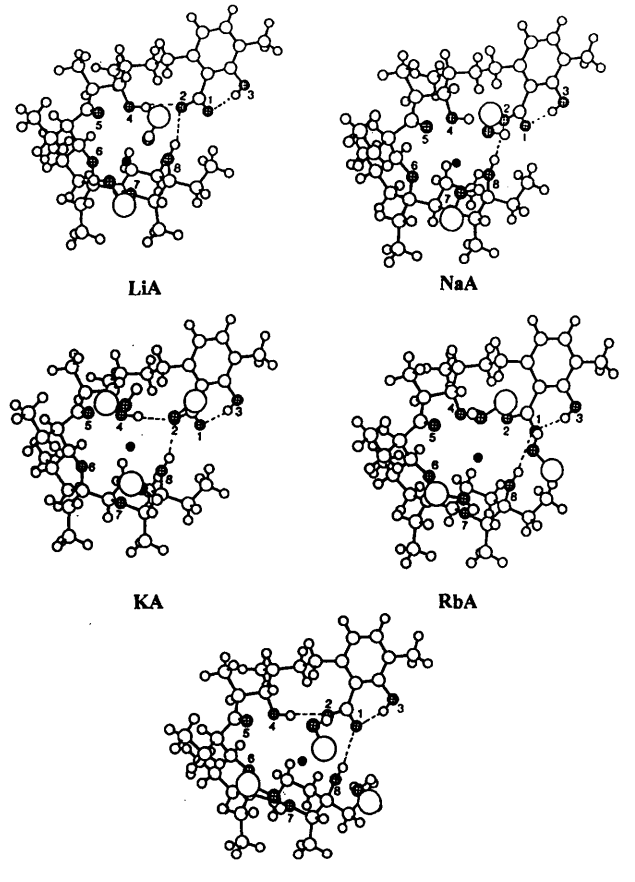

LiA NaA KA RbA CsA

Fig. 5 Skeleton schemes of MA complexes of minimal enthalpy resulting from Monte-Carlo simulations in methanol with methanol molecules of the first solvation shell in interaction with the cation involved. ○, Carbon; o, hydrogen: ⊗, oxygen; ●, metal cation.

the enthalpies of association of MA complexes in methanol from the enthalpies of MA in methanol and those for separate M^+ and A^- ions in methanol yielded incoherent results compared with the experimental data.[3] As underlined by Kollman,[33] it seems to be currently impractical to search for enthalpy differences of less than 10 kcal mol^{-1} (1 cal = 4.184 J).

PM3 semiempirical quantum calculations in a continuum. In the self consistent reaction field approach,[34] the solvent is considered to be a dielectric continuum and the solute is placed in a cavity. The solute is submitted to an electrostatic potential, the potential of reaction field, due to the polarization of the solvent by the solute charge distribution, which is represented by a multipole expansion. To define the cavity, we use the ellipsoidal approximation.[35] The dielectric permittivity of methanol was set to 32.66 at low frequency and to 5.55[36] at infinite frequency. The relative permittivity of the cavity was taken as equal to 1. The conformations of MA complexes resulting from Monte-Carlo simulations *in vacuo* were optimized beforehand by the PM3 method in the gas phase using the GEOMOS program.[21] The conformation obtained was modified little and the alkali metal cation–lasalocid oxygen distances were included in the fluctuation intervals of the values computed by Monte-Carlo simulations (Table 1). Among the conformations of MA complexes saved during these Monte-Carlo simulations in methanol solutions, only conformations of minimal enthalpy of each complex were optimized by the GEOMOS program using the PM3 method in a methanol continuum. The conformations resulting from these computations are described in Table 5. In the present state, the caesium atom is not parametrized in the GEOMOS program. Only the LiA, NaA, KA and RbA complexes were, therefore, studied.

Discussion

Gaseous state structure of the MA complexes

For all the alkali metal cations and irrespective of the initial

Table 5 Description of MA complexes of lasalocid with alkali metal cations in methanol according to Monte-Carlo statistical mechanics computations at 298 K using the BOSS program

	LiA	NaA	KA	RbA	CsA
H[a]	−3422	−3378	−3348	−3355	−3327
E_{XX}[b]	−107.1	−110.7	−91.9	−114.7	−109.2
E_{SX}[c]	−193.5	−177	−166.8	−134.1	−130.6
$\eta_{COO^- \cdots HOMe}$	2.9	3.5	2	2.6	1.9
$\eta_{O(3) \cdots HOMe}$	0.5	0.1	0.1	—	0.1
$\eta_{O(3)H \cdots OHMe}$	0.9	0.1	0.6	—	—
$\eta_{O(4) \cdots HOMe}$	—	0.1	—	—	—
$\eta_{O(4)H \cdots OHMe}$	—	0.6	0.2	—	—
$\eta_{O(5) \cdots HOMe}$	0.1	—	—	—	0.5
$\eta_{O(8) \cdots HOMe}$	—	0.3	0.3	0.1	0.2
$\eta_{O(8)H \cdots OHMe}$	—	—	0.5	0.1	—
Total	4.4	4.7	3.7	2.8	2.7
[d]O(3)H ··· O(1)	1.96	1.95	1.95	2.05	2.06
O(4)H ··· O(2)	2.02	1.95	2.09	1.98	2.38
O(8)H ··· O(1)				2.49	
O(8)H ··· O(2)	2.26	2.16	2.47		2.39

[a] Mean enthalpy of the system ($A^- + M^+ + 378\ CH_3OH$) (kcal mol^{-1}). [b] Mean solute–solute energy E_{XX} (A^-, M^+) (kcal mol^{-1}). [c] Mean solute–solvent energy E_{SX} [(A^-, M^+) − (methanol)] (kcal mol^{-1}). [d] Hydrogen bond length OH ··· O (Å) calculated using a Boltzmann distribution.

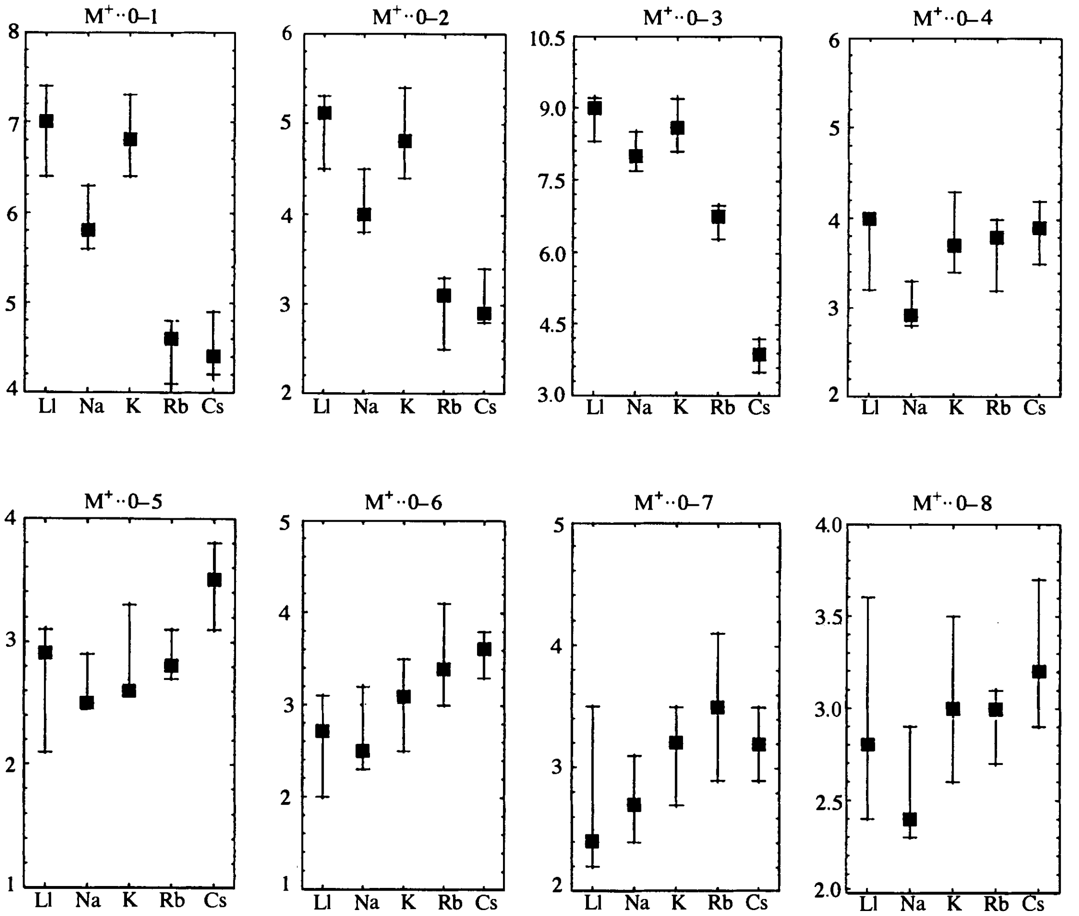


Fig. 6 Alkali metal cation–lasalocid oxygen distances (Å) with the maximal deviation in the MA complex in methanol resulting from Monte-Carlo simulations in methanol. (■, Mean value; |—|, minimal to maximal values).

conformation of the anion, the computed structures of the alkali metal lasalocid complex salts involve a conformation of type **1a** for the lasalocid anion. This corresponds to a head–tail closure through an O(8)H ··· O(1) bond, O-1 being also bound to the phenol oxygen O-3. This head–tail closure is stronger as the size of the cation increases as shown by the decrease in this bond length. The internal hydrogen bond O(4)H ··· O(2) is maintained in all cases. As a function of the cation, no strong changes occur in the tetrahydrofuran and tetrahydropyran ring conformations as shown by the weak variations of the Cremer and Pople parameters in Table 1.

Setting apart the case of LiA, the co-ordinating sites are identical for the different cations: oxygen O-2 and oxygens O-4 to O-8. However, the mean distances from the cation to each of the co-ordinating oxygens increase slightly as the size of the cation increases, which also corresponds, as reported in Table 1, to a decrease in the negative values of the computed overall cation–ligand interaction energy. The cation-co-ordinating oxygen distances here obtained are larger than those observed in the crystalline state[26] for NaA and CsA but there is an appreciable fluctuation of these distances as shown by the minimal and maximal values in Table 1. This is particularly striking for NaA. In this complex, the fluctuations of the $M^+ \cdots$O-2 and $M^+ \cdots$O-8 distances are weak. However,

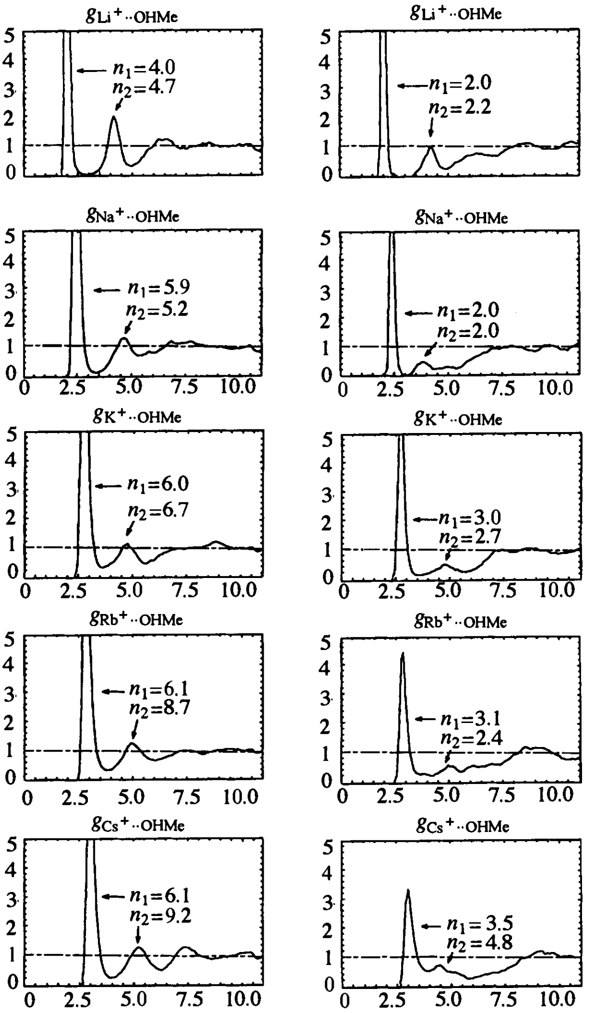


Fig. 7 Radial distribution functions for the free cation (M^+ + 378 CH_3OH) (left) and the cation in the complex (MA + 378 CH_3OH) (right) for all the alkali metal cations at 298 K in methanol from the Monte-Carlo simulations using the BOSS program. n_1 Mean number of solvent molecules in first solvation layer, n_2 mean number of solvent molecules in second solvation layer.

the distances of M^+ from the central oxygens fluctuate widely as if the cation had some freedom of rotation around an O-2, O-8 hinge, from a location at the centre of the crown slightly above its mean plane, as observed in the crystalline state, to a location approximately 2 Å away. These fluctuations, though weaker, also occur with the other cations.

Lithium in the mean structure computed here is strongly bound to oxygen O-8 and, unlike the other cations, to the two oxygens of the carboxylate in an equivalent way. It is thus far from oxygens O-5 and O-6 and occupies an eccentric location in the usual co-ordinating crown. Its strong anchoring to the three terminal oxygens of lasalocid anion results in small fluctuations of the oxygen–cation distances. This strong interaction of Li^+ with oxygen O-1 also means a loosening of the O(8)H ··· O(1) hydrogen bond and an appreciable aperture in the head–tail closure, as already observed,[1] with stronger effects, for Mg^{2+}.

Structure of the MA complexes in methanol

Those experimental ^1H–^1H coupling constants that could be obtained are compared in Table 4 to the corresponding constants calculated for some of the computed structures. The method of calculation used was that of Durette and Horton,[37] which seems well suited to this type of molecule.[16,24] Two series of calculations were performed: one of the mean values (according to a Boltzmann distribution[24]) corresponding to the conformations arising from the Monte-Carlo simulations, and the other value corresponding to conformations arising from the PM3 computations in a continuum. The results, as shown in Table 4, were almost identical for the two series of calculations.

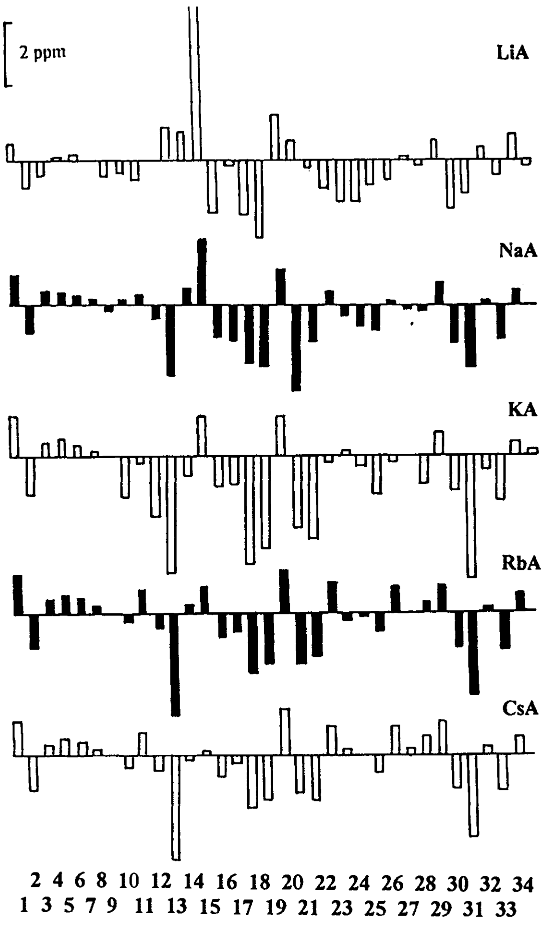


Fig. 8 Variation of the ^{13}C chemical shift from the free lasalocid anion in methanol to the various lasalocid alkali metal salts in methanol for all the carbons of the molecule (numbering as in Fig. 1)

Table 6 Description of conformations of MA complexes resulting from PM3 computations in a methanol continuum at 298 K using the GEOMOS program

	LiA	NaA	KA	RbA
α[a]	23	22	23	18
[b]THF	$_{16}E$	$_{16}E$	$_{16}E$	$_{16}E$
q (Å)	0.35	0.36	0.37	0.40
φ (°)	38	35	30	46
THP				
Q (Å)	0.56	0.53	0.55	0.56
θ (°)	178	173	177	165
[c]O(3)H ··· O(1)	1.83 (130)	1.84 (130)	1.82 (129)	1.84 (128)
O(4)H ··· O(2)	2.05 (168)	1.89 (172)	2.28 (171)	2.32 (148)
O(8)H ··· O(1)				2.40 (123)
O(8)H ··· O(2)	2.19 (159)	2.44 (132)	2.18 (158)	
d				
M^+ ··· O-1	7.01	5.80	6.66	4.67
M^+ ··· O-2	5.08	4.02	4.68	3.22
M^+ ··· O-3	8.95	7.93	8.52	6.96
M^+ ··· O-4	3.72	3.13	3.71	3.78
M^+ ··· O-5	2.68	2.83	3.08	3.33
M^+ ··· O-6	2.29	2.71	3.07	3.44
M^+ ··· O-7	2.31	2.76	3.08	3.24
M^+ ··· O-8	2.89	2.74	3.10	3.45

[a] Steric angle α (°) between benzene and carboxylate planes. [b] Parameter of Cremer and Pople[27] for the tetrahydrofuran and tetrahydropyran rings, envelope ^xE, *x* being the apex. [c] Mean hydrogen bond length (Å) with its valence angle (°). [d] Cation–lasalocid oxygens distances (Å).

A good general consistency is observed between calculated and experimental $^1H-^1H$ coupling constants. This suggests that the mean conformations in solution of the ligand lasalocid anion in these complexes are similar to the mean conformations computed here. However, some systematic differences can be noted though it is not possible to assert that they correspond to true conformational differences and do not arise spuriously from the method of calculation of the coupling constants. Also, the fine evolution of these coupling constants as a function of the cation, mainly perceptible for LiA as compared to the other complexes, is not truly restored by the computations. Nevertheless, even for lithium the computed structures are roughly consistent with the experimental ones. Particularly, the recentring of Li^+ in the co-ordination crown from the gas-phase structure to the methanol solution structure of LiA is probably real.

In Fig. 8 the variations of the ^{13}C chemical shifts from the free lasalocid anion to the lasalocid anion in the MA complexes in methanol are reported for all the carbons of the molecule. This diagram, though its interpretation is not staightforward,[1] emphasizes the main changes involved in both the anion conformation and the cation co-ordination as a function of the cation involved. From the strong low-field shift of the C-13 signal in the LiA complex, strong involvement of O-5 in the co-ordination of the Li^+ cation can be suggested. This involvement thus decreases as the size of the cation increases as shown in Fig. 8, by the decrease in the C-13 low-field shift, which practically vanishes for CsA. This corresponds well to the $M^+ \cdots$ O-5 distance increase from LiA to RbA reported in Table 6. This evolution of the O-5 co-ordination comes with an appreciable high field shift of the signals of C-11 and C-30, two carbons in the environment of O-5. This may correspond to conformational changes, which are nevertheless not clearly marked on the corresponding $^1H-^1H$ experimental coupling constants, except possibly from Li^+ to Na^+ for J_{14-30A} and to a lesser extent for J_{11-12} and from Na^+ to K^+ for J_{14-30B} and not marked at all in the computed constants. From the diagram in Fig. 8 other co-ordinations can mainly be inferred for O-6 and O-7. Perturbations on the salicylate group are weak for lithium and somewhat greater for the other cations.

What is suggested by both types of computation (Fig. 6 and Table 6) is that the involvement of O-2 in the co-ordination of the cation, which is rather weak or negligible for the small cations, becomes appreciable for rubidium and caesium; concurrently, the co-ordination strength for O-8, and also for O-5, O-6 and O-7 decreases.

Compared to the situation in the gaseous state, the fluctuation of the cation–oxygen distances is weak though a little larger for the small cations. The location of the cation is governed not only by its co-ordination to the oxygens of the ionophore but also by the residual solvation of both the cation and the lasalocid anion ligand. In this respect, as shown in Table 5, the statistical Monte-Carlo sampling in methanol suggests strong solvation of the salicylate group in the MA complexes. For the small cations, the number of solvent molecules bound to this group is of the same order as that found for the free lasalocid anion in analogous conditions. This could explain why in these computations the type **2a** conformation of the anion involving the $O(8)H \cdots O(2)$ hydrogen bond closure is favoured in methanol (Tables 5 and 6) unlike what is suggested in the gaseous state (Table 1). Only for RbA does the co-ordination of the cation to O-2 favour the closure of the pseudo-crown through the $O(8)H \cdots O(1)$ bond and a concomitant decrease in the salicylate group solvation. Residual solvation of the other oxygens is weaker.

For the cations, radial distribution functions reported in Fig. 7 show the extent of their residual solvation. Approximately half of the methanol molecules bound to the free cation stay in the complex. No marked changes are observed in the distances between the cation and the oxygens of the first solvation layer. However, the interactions with the oxygens of the second solvation layer are much weaker, resulting in a more diffuse layer.

Hence, the following picture of the lasalocid alkali metal cation complexes in methanol emerges. The ionophore anion is closed through a head–tail hydrogen bond of O(8)H with O-2 or O-1 according to the size of the cation, which determines the size of the cavity. The ionophore anion thus constitutes a half-sphere of co-ordination; the complementary half-sphere is formed by the oxygens of the nearest methanol molecules (see Fig. 5). As regards co-ordination by the ligand a clear gap is observed between K^+ and Rb^+; change in the cavity size, involvement of O-2 in the co-ordination, appreciable decrease in the ligand solvation. This is clearly marked in the cation–ligand interaction energies computed in methanol (Table 5), which thus results in corresponding variations in the computed enthalpies of the MA complex–methanol systems: though a decrease in this interaction energy is observed from NaA to KA and from RbA to CsA a sharp break occurs from KA to RbA. The same was observed[4] for the apparent molal heat capacity of these complexes in methanol, which decreases from LiA to KA and from RbA to CsA and abruptly increases from KA to RbA. There is thus both theoretical and experimental evidence for a marked structural change between KA and RbA.

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