

Stoichiometry, complex stability, molecular size and conformational variations of metal ion crown ether complexes subject to diffusion coefficients in nonaqueous solutions

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Abstract Both the stoichiometry and complex stability constants of crown ether complexes with metal ions have been determined by examining gradual changes in their diffusional behavior in nonaqueous solution. Diffusion coefficients, D , were evaluated by pulsed field gradient (PFG) NMR titration experiments whilst complex stability constants were determined by nonlinear curve-fitting procedures, D versus c_{sol} , which also allow the treatment of multiple complexation equilibria (1:1 to 1:2 stoichiometries). Differences in the diffusion coefficients of the various free crown ethers with respect to their metal ion complexes indicate great sensitivity to both conformational changes and changes in molecular size upon complexation.

Keywords Metal ions complexation · Complex stability constant · Conformation · Diffusion · Crown ethers · Flexibility · PFG NMR spectroscopy · Stoichiometry

Introduction

Since Pedersen's discovery of macrocyclic polyethers, and especially their ability to form stable complexes with alkali and alkaline earth cations [1], crown ethers and analogous compounds have been the subject of widespread interest [2, 3]. There are two reasons for the continuing interest: (i) the analytical and industrial application of crowns for the selective extraction of cations (or anions after structural modifications) and, (ii) the function of crown ethers as

bioorganic mimics and transport containers for metal ions in biochemical and biological processes [4]. For both applications, aside from generalizations concerning the lipophilicity and hydrophilicity/hydrophobicity of the crown ethers, the determination of the stoichiometry and stability of their complexes are of major interest. For solution-state structure elucidation, NMR spectroscopy is a superior method and a wide variety of techniques are available and many of them have been specifically employed for the aforementioned purposes. In addition to chemical shifts (δ) [5] and spin lattice relaxation times (T_1/s) [6], diffusion-ordered NMR spectroscopy is set to become a highly valued tool for this type of analysis because, in addition to structural information on the stereochemistry of complexation, both the stoichiometries and complex stability constants can be determined in the one analysis. Thus, the diffusion behavior of complexes formed between various crowns and metal ions has been widely employed to clarify the quantitative aspects in several studies [7, 8, 9, 10, 11, 12, 13].

The diffusion coefficients, D , of the free crowns and of their complexes with metal ions/parent ions/solvent molecules are especially dependent on their molecular size and therefore this is the pre-eminent molecular property for which for appropriate conclusions can be drawn [14, 15]. Of note, Geringer in 1989 found only very small changes in D of 18-crown-6 ethers during the titration with CsCl despite the known formation of the strong complex Cs^+ 18-crown-6 [16]. However, it was due to the limitations of the available equipment that precluded the evaluation of the complexational equilibrium by diffusion.

The situation, though, has now changed as diffusion probes have since been developed which, together with gradients of sufficient strength, readily allow the detection

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of variations in the diffusion coefficient in a sensitive manner. Even small changes can be reliably detected and permit the evaluation of differences in D of crowns and their complexes permitting the extraction of useful quantitative information on the complexation equilibria.

The aim of the present paper, firstly for initial experience, is to study the diffusion behavior of the complexation of maleonitrile crown ethers to Ag^+ cations, and then, for a check of applicability, to examine the complexation of Na^+ and K^+ cations using the continuous variation technique. The ensuing results are then compared and evaluated to published values.

Experimental Analysis

Determination of the complex stability constants

The general complexation between a metal ion, M , and a ligand, L , forming the complex M_nL_m can be expressed by the equilibrium [17]:



for which the equilibrium constant, K , is defined as:

$$K = \frac{[M_nL_m]}{[M]^n[L]^m} \quad (2)$$

(where the equilibrium concentrations are in brackets and m and n represent molar ratios). In the case of 1:1 complexation:

$$K = \frac{[ML]}{([M]_t - [ML])([L]_t - [ML])} \quad (3)$$

(where the subscript t indicates total concentration). The equilibrium concentrations are thus [17]:

$$[M] = [M]_t - [ML] \quad (4)$$

and

$$[L] = [L]_t - [ML] \quad (5)$$

For the application of NMR spectroscopy, two extreme cases are considered:

- (a) The rate of exchange of complexation is slow on the NMR timescale. $[L]$ and $[ML]$ are then readily accessible by simple integration of characteristic signals at δ_L and δ_{ML} , respectively. Since the total concentrations are known, K can be calculated from Eq. 3 [18].

- (b) In the case of fast exchange on the NMR time-scale, only signals representing the weighted average of the free and complexed crown are accessible. Thus, in terms of diffusion, the measurable diffusion coefficient is:

$$D_{\text{meas.}(M)} = x_M D_M + x_{ML(M)} D_{ML} \quad (6)$$

[where x are the mole fractions of the metal complex ($x_{ML(M)} = [ML]/[M]_t$) and of the free metal ion ($x_M = [M]/[M]_t$)].

The mole fraction of the still unknown metal complex can thus be obtained by:

$$x_{ML(M)} = \frac{(D_M - D_{\text{meas.}(M)})}{(D_M - D_{ML})} \quad (7)$$

and the equilibrium constant, K , by Eq. 8:

$$K = \frac{x_{ML(M)}}{(1 - x_{ML(M)})([L]_t - x_{ML(M)}[M]_t)} \quad (8)$$

If the size of the complex and the free ligand are similar, the diffusional coefficients D_L and D_{ML} will be approximately the same and K can be determined from the one measurement (D_M and D_L are the values of $[M]_t$ and $[L]_t$; a titration study, however, is futile in the absence of NMR-active metal ions).

If differences exist between the molecular sizes of the complex and the free ligand, and thus in their diffusion coefficients, these can be detected with presently available equipment and assessed by the application of Eq. 9 [19]:

$$D_{\text{meas.}(L)} = x_L D_L + x_{ML(L)} D_{ML} \quad (9)$$

(where $x_{ML(L)} = \frac{[ML]}{[L]_t}$, $x_L = \frac{[L]}{[L]_t}$ and

$$x_{ML(L)} = \frac{(D_L - D_{\text{meas.}(L)})}{(D_L - D_{ML})}$$

The equilibrium constant, K_D , can then be expressed as:

$$K_D = \frac{x_{ML(L)}}{(1 - x_{ML(L)})([M]_t - x_{ML(L)}[L]_t)} \quad (10)$$

The unknowns in Eq. 10 in terms of diffusion are the two parameters K_D and D_{ML} . Thus, the titration of $D_{\text{meas.}}$ versus $[M]_t/[L]_t$ allows the determination of both D_{ML} and its complex stability constant K_D .

For evaluation of the titration experiments, curve-fitting software WinEQNMR [20] was employed. The fit of the calculated and experimental dependencies was varied iteratively until both K_D and D_{ML} improved and coincidence was attained. A very useful feature of WinEQNMR is the capability to treat multiple complexation equilibria. Furthermore, the chemical shift dependency derived from

$\delta_{\text{meas.}}$ versus $([M]_t/[L]_t)$ can be evaluated in a quantitative manner in conjunction with the $D_{\text{meas.}}$ evaluation. Thus, when varying the stoichiometry of potential complexes during the data handling by WinEQNMR, two results for K_δ and K_D are obtained and can hence be compared.

Determination of complex stoichiometries

Since correct complex stoichiometry is crucial for correct data analysis, Job's continuous variation method was employed to obtain this information by plotting $[ML]$ versus $[L]_t/\{[M]_t + [L]_t\}$ over a number of titration steps. The maxima of the corresponding Job's plots indicate the stoichiometry present: 1:1 complexation is indicated by a maximal value occurring at 0.5 whilst 1:2 complexation is indicated by a maximal value occurring at 0.66 [21].

Due to the presence of fast exchange on the NMR timescale, $[ML]$ was not directly available and it had to be estimated either from $[L]_t \cdot (\delta_{\text{meas.}} - \delta_{\text{free}})$ or $[L]_t \cdot (D_{\text{meas.}} - D_{\text{free}})$, which are equivalent when the total concentration remains constant [18] (δ_{free} and D_{free} represent the free ligand and $\delta_{\text{meas.}}$ and $D_{\text{meas.}}$ are the values measured at various $[M]_t/[L]_t$ ratios).

NMR measurements

All NMR measurements were performed on a 500 MHz Bruker Avance spectrometer equipped with a Bruker Diff 30 probe linked to a BCU 20 water cooling unit. The sample temperature was calibrated before measurements and kept constant at 298 ± 0.1 K. It was assessed that convection was minimized by acquiring the spectra without sample spinning. ^1H NMR spectra were recorded with 32 k data points zero-filled to 64 k. External TMS was used as standard. The bipolar pulse pair longitudinal eddy current delay (BPP-LED) sequence with sinusoidally shaped gradients was used for measuring diffusion [22].

The term $\ln I$ proved to be linearly dependent on the gradient strength G^2 ; the slope of the curve is related to the self-diffusion coefficient D (cf. Eq. 11).

$$\ln\left(\frac{I}{I_0}\right) = -(\gamma G \delta)^2 D \left(\Delta - \frac{\delta}{3}\right) \quad (11)$$

The gradient strength G was incremented linearly in 16–32 steps, starting from 1.9 G/cm, to generate the 2D data matrix. The diffusion delay ($\Delta = 20$ –40 ms) and maximum gradient strength (up to 180 G/cm) were set to achieve maximal dephasing. The duration of the gradient pulses δ was kept constant at 1 ms and the number of scans (16–128 scans) was also held constant for each of the

various titration steps. The gradient strength was calibrated using the diffusion constant for HDO in D_2O [23]. For the calculation of the diffusion coefficients, the standard Bruker Software Package XWIN-NMR 3.5 was used.

The 18-crown-6 ether and metal salts were purchased from Fluka and Aldrich; the syntheses and characterizations of the maleonitrile crown ethers have been described elsewhere [24]. Ligands and salts were dried under high vacuum for three days prior to use. Deuterated solvents were purchased from Deutero and used without further purification.

The NMR titration experiments were performed using the described continuous variation technique. The sum of the concentration of metal salt and ligand was held constant at 0.02 M while the total molar ratio $[L]:[M]$ was varied from 14:0 to 1:13 in 14 steps. Both the chemical shifts ($\delta_{\text{meas.}}$) and diffusion coefficients ($D_{\text{meas.}}$) at each step were determined by examination of a suitable ^1H NMR signal.

Results and Discussion

Initial titration experiments corroborated the expected fast exchange of the complexation equilibria on the NMR timescale. Thus, only population-weighted averages of the chemical shifts and diffusion coefficients were available, and since K_δ/K_D could not be determined directly, titration experiments were necessary. The values of K , δ_{ML} and D_{ML} were thus evaluated by curve-fitting procedures employing WinEQNMR.

Because the molecular sizes of the crowns increase upon complexation, the diffusion coefficients consequently reduce in value—the origin therefore proves to be the increasing hydrodynamic radius of the complexes with respect to the free crowns.

Complexation of 18-crown-6 ether

These studies were performed for the purpose of evaluating the protocol at hand. The complexation of 18-crown-6 to various cations in different media has been extensively studied [25, 26, 27]. Both δ and D were evaluated (see Fig. 1) and regression lines in the D -Job's plot were employed for clearer determination of the stoichiometry.

Both plots indicate 1:1 complexation for Ag^+ -18-crown-6. Thus, this exemplary study appears to be a useful test for WinEQNMR software. The corresponding complexation constants, K_δ and K_D , are given in Table 1 together with previously reported values. Similar studies with the same 1:1 stoichiometry result were performed for the complexation of Na^+ and K^+ by 18-crown-6 ether; results and previously reported values are also given in Table 1.

Fig. 1 Job's plots for $\text{Ag}^+ \cdot \mathbf{1}$ in methanol- d_4 : ■ δ -Job's plot (at 500 MHz, δ/TMS external), ● D -Job's plot. Additional lines in the D -Job's plot help to locate the maximum

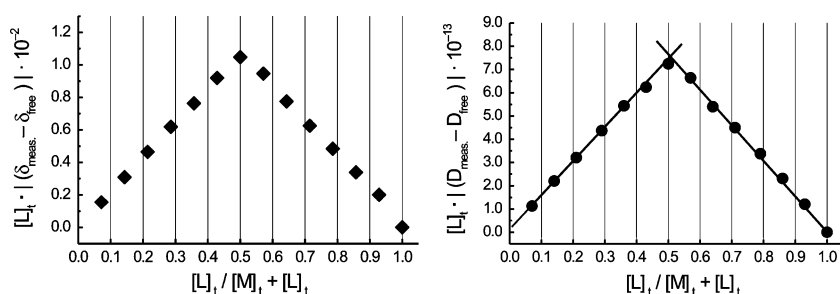
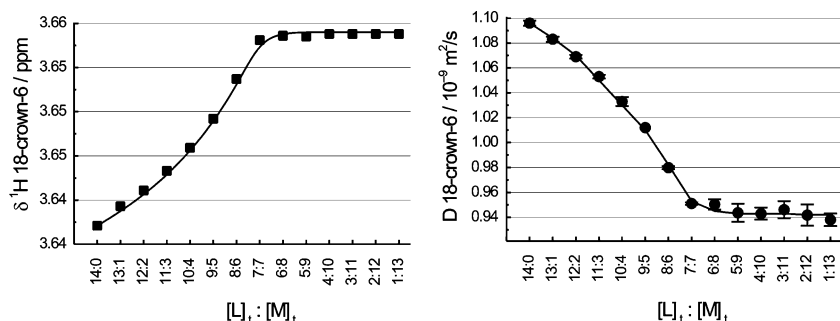


Table 1 Stoichiometries and stability constants for 18-crown-6 ether complexes

Complex	Solvent	Estimated complex stoichiometry M:L	$\lg K_D \text{ M} + \text{L} = \text{ML}$	$\lg K_\delta \text{ M} + \text{L} = \text{ML}$	$\lg K$ Lit.
$\mathbf{1} \cdot \text{AgBF}_4$	methanol- d_4	1:1	4.54	5.04	4.58–4.60 [26]
$\mathbf{1} \cdot \text{NaSCN}$	acetonitrile- d_3	1:1	4.27	4.51	4.21 [27]
$\mathbf{1} \cdot \text{KSCN}$	acetonitrile- d_3	1:1	4.9	4.56	5.46 [27]

Fig. 2 Titration curves of $\text{Ag}^+ \cdot \mathbf{1}$ in methanol- d_4 : ■ δ_{meas} , ^1H (at 500 MHz, δ/TMS external), ● D_{meas} , 18-crown-6. The solid lines visualize fitted values. Bars show the experimental error in D_{meas} .



The corresponding titration for Ag^+ complexation (δ/D versus $[\text{L}]_1/[\text{M}]_1$) is displayed in Figure 2. Up to a 1:1 molar ratio, the observed signal is deshielded and D decreases; afterwards, both δ and D remain effectively constant. The successful complexation of Ag^+ ion with 18-crown-6 thus renders the parameters δ_{ML} and D_{ML} accessible. The titration behavior of Ag^+ complexation is typical for these kinds of compounds and the results obtained for K_δ and K_D are reliable in comparison to the literature values obtained by other methods (cf. Table 1).

For both Na^+ and K^+ , 1:1 complexation with 18-crown-6 ether is well known. The complexes differ in stability with the K^+ complexes more stable than the Na^+ complexes [27]. Hence, the reliability of the method was put to the test: the δ - and D -Job's plots for Na^+ complexation are given in Figures 3 and 4 and for K^+ complexation in Figures 5 and 6. In the two cases, both 1:1 complexation and reliable complexation constants were obtained (cf. Table 1). However, whilst the δ -Job's plots obtained are excellent, the D -Job's plots show an increasing scatter of

Fig. 3 Job's plots for $\text{Na}^+ \cdot \mathbf{1}$ in acetonitrile- d_3 : ■ δ -Job's plot (at 500 MHz, δ/TMS external), ● D -Job's plot. Additional lines in the D -Job's plot help to locate the maximum

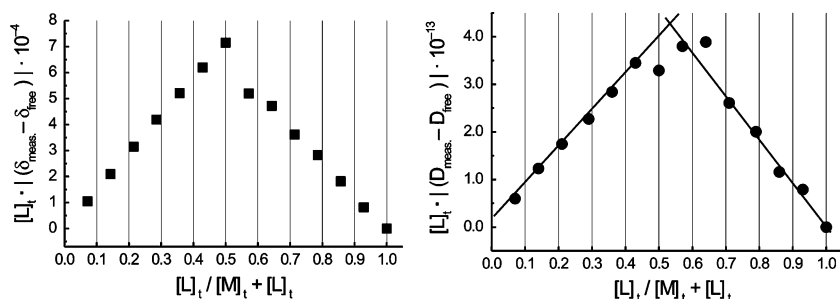


Fig. 4 Titration curves of $\text{Na}^+ \cdot \mathbf{1}$ in acetonitrile- d_3 : ■ $\delta_{\text{meas.}}^1\text{H}$ (at 500 MHz, δ/TMS external), ● $D_{\text{meas.}}$ 18-crown-6. The solid lines visualize fitted values. Bars show the experimental error in $D_{\text{meas.}}$.

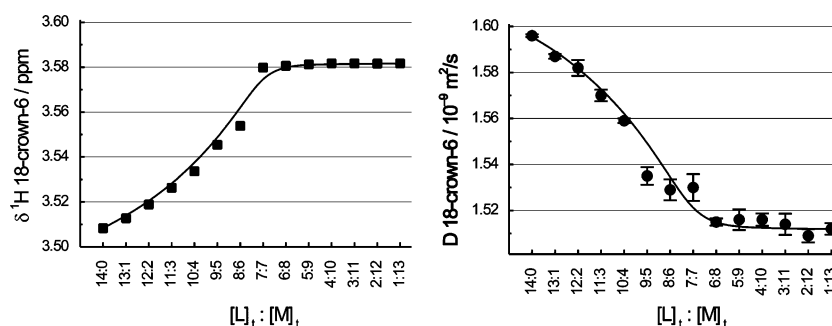


Fig. 5 Job's plots for $\text{K}^+ \cdot \mathbf{1}$ in acetonitrile- d_3 : ■ δ -Job's plot (at 500 MHz, δ/TMS external), ● D -Job's plot. The additional lines in the D -Job's plot help to locate the maximum

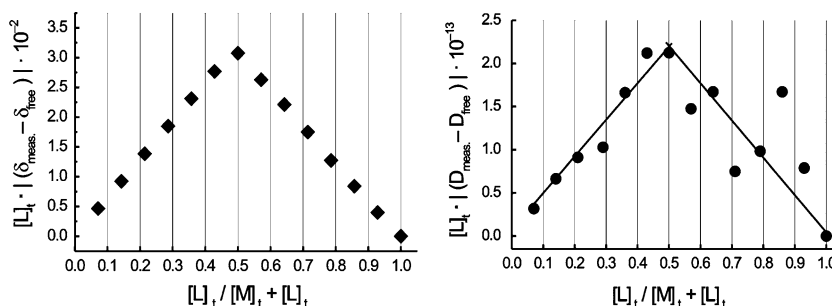
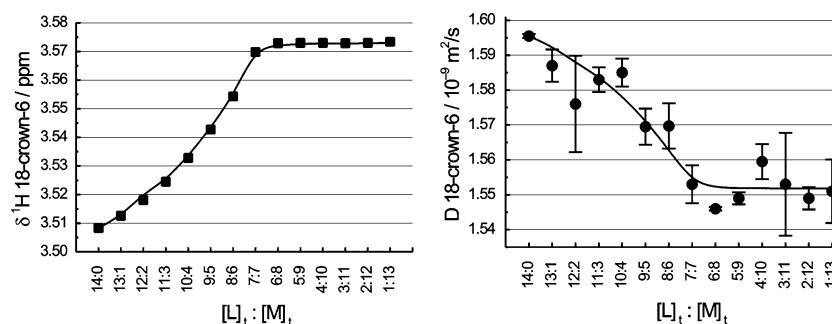


Fig. 6 Titration curves of $\text{K}^+ \cdot \mathbf{1}$ in acetonitrile- d_3 : ■ $\delta_{\text{meas.}}^1\text{H}$ (at 500 MHz, δ/TMS external), ● $D_{\text{meas.}}$ 18-crown-6. The solid lines visualize fitted values. Bars show the experimental error in $D_{\text{meas.}}$.



values in the case of Na^+ after 1:1 complexation was attained (and in the case of K^+ , both before and after). As a consequence, K_D values are smaller than their corresponding K_δ values and the values determined previously; in the case of K^+ , regression lines for finding the correct stoichiometry of complexation were a necessity. However,

K_D values in terms of size are still sufficient in precision and can be usefully employed for discussing molecular interactions in a quantitative manner.

The complexation of Ag^+ was also studied in different solvents; details of the diffusion studies are presented in Table 2. Most remarkable is the large difference in

Table 2 Diffusion behavior of 18-crown-6 ether complexes

Complex	Solvent	Estimated complex stoichiometry M:L	$D_L [10^{-9} \text{m}^2/\text{s}]$	$r_{\text{HL}} [\text{\AA}]^a$	$D_{\text{ML}} [10^{-9} \text{m}^2/\text{s}]$	$r_{\text{HML}} [\text{\AA}]^a$	$\Delta D_{L-\text{ML}} [10^{-9} \text{m}^2/\text{s}]$	$D_{\text{MLL}} [10^{-9} \text{m}^2/\text{s}]$
1 · AgBF_4	methanol- d_4	1:1	1.096	3.31	0.940	3.85	0.156	–
1 · NaSCN	acetonitrile- d_3	1:1	1.596	3.83	1.506	4.06	0.090	–
1 · KSCN	acetonitrile- d_3	1:1	1.596	3.83	1.550	3.94	0.046	–
2 · AgBF_4	nitromethane- d_3	1:1; 1:2	1.066	3.20	0.77	4.44	0.296	0.67
3 · AgBF_4	nitromethane- d_3	1:1; 1:2	0.940	3.63	0.797	4.30	0.143	0.65
4 · AgBF_4	acetonitrile- d_3	1:1	1.690	3.62	1.35	4.52	0.340	–

^a η [mPa s] at 298 K: acetonitrile- d_3 , 0.357; methanol- d_4 , 0.602; nitromethane- d_3 , 0.639 [30].

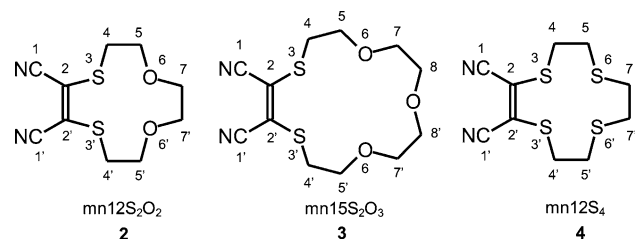
diffusion for free and 1:1 complexed Ag^+ -18-crown-6 ether in methanol. On this basis, extremely strong interaction differences with the solvent were concluded.

The hydrodynamic radius of 18-crown-6 in methanol was found to be only 3.31 Å whilst in acetonitrile it was determined to be 3.83 Å, thereby indicating stronger solvation in this latter case [28]. These differences in solvation influence diffusion and this, of course, carries over to the diffusion behavior after complexation. The observed differences, moreover, are readily comprehensible.

However, we have no clear explanation for the scatter of diffusion values around 1:1 complexation. One reason may be convection, and although a lot of effort has been directed towards eliminating such influences on the measurement of D , a detrimental effect nonetheless seemed to prevail. In terms of measurement of D in different solvents, and hence in media of different viscosity, convection is potentially a source of serious error. But convection becomes less important with increasing viscosity of the medium [29] and methanol has proven to be less fluid than acetonitrile [30] (cf. Table 2).

Complexation of maleonitrile crown ethers 2–4

Thiacrown ethers and mixed oxa,thia-crown ethers with a fixed maleonitrile structural fragment are significant in their ability to selectively complex a number of interesting transition metal ions [31–37]. Both the conformation and flexibility of the maleonitrile crowns 2–4 (see Scheme 1) have been studied by NMR spectroscopy ($\delta_{1\text{H}}$, $\delta_{13\text{C}}$, $^n\text{J}_{\text{H,H}}$, T_1) and accompanying molecular modeling examination. The complexation of 2 and 3 with Bi(III), Sb(III), Ag(I), Pt(II) and Pd(II) ions was studied in detail wherein also the counter ion, solvent and concentration influences were considered. The stereochemistry, complex stability and structure of the complexes in solution were determined employing a new structural algorithm which delivers complete structural information in solution without consideration of the solid-state structures at all. Solution-state structures are especially valuable in the case of employing crowns as transport container mimics for bioorganic models.



Scheme 1

In the present study, both the solution stoichiometries and complex stability constants of 2–4 complexes with

AgBF_4 salts were investigated. Subject to crown solubility, nitromethane and acetonitrile were employed as solution media. Former studies have provided considerable information on the complexation of Ag^+ cations: both 1:1 and 2:1 complexes, and also a polymer-like solvated structure, have been found [32]. Thus, the diffusional behavior of dithiadioxo- and tetrathia-crown ethers 2–4 subject to Ag(I) complexation were studied in order to attain deeper insight into the complexational behavior of this interesting and valuable metal.

The examination of both δ - and D -Job's plots of the complexation of 2 with AgBF_4 (Fig. 7) and the corresponding dependencies of δ/D versus complexation (Fig. 8) look very interesting—the maximum in Figure 7 (ca. 0.58) is slightly larger than 0.5 (thereby implying 1:1 complexation), though smaller than 0.66 (1:2 complexation). Obviously, both complex species contribute to the obtained results as exchange is fast on the NMR timescale.

For this reaction therefore, different models to describe the Ag(I) complexation to dioxo/dithia crown 2 were tested:



In order to find consensus between experiment and the theoretical model to simulate Ag(I) complexation of 2 using WinEQNMR, the participation of 1:2 complexation needed to be considered. It can be excluded, though, during the titration between $[\text{L}]_t$ and $[\text{M}]_t$ over the range from 14:0 to 7:7 on the basis of the linear dependence displayed therein (see Fig. 8). After 7:7 however, the titration curve departs from linearity and exhibits complex behavior which cannot be simulated by the model representations. But this effect can be interpreted: excess ligand obviously coordinates with AgL forming AgL_2 complexes (all in fast exchange) and thus AgL_2 additionally contributes to the experimentally observed weighted averages of the chemical shift and diffusion coefficient. An additional increase in δ_{meas} and a decrease in D_{meas} are the experimental consequences and which are evident in the corresponding dependencies shown in Figure 8.

The corresponding complex stability constants, obtained for the two modes of complexation are given in Table 3. Also, in the case of the larger trioxa-dithia-crown ether 3 which complexes to AgBF_4 , the best fit was obtained for 1:1 complexation (cf. Fig. 9) even if the D correlation is actually slightly above 0.5. However, linear dependencies from 7:7 to 1:13 are much better (cf. Fig. 10) than in the former case and prove 1:1 complexation exclusively in the case of crown ether 3 (complex stability constants are included in Table 3). The 15-membered ring system in 3 has one additional ether bridge compared with 2, thus the

Fig. 7 Job's plot for $\text{Ag}^+ \cdot 2$ in nitromethane- d_3 : ■ δ -Job's plot (at 500 MHz, δ/TMS external), ● D -Job's plot. Additional lines in the D -Job's plot help to locate the maximum

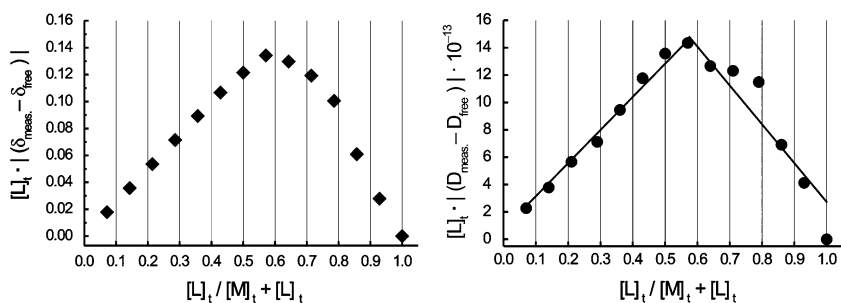


Fig. 8 Titration curves of $\text{Ag}^+ \cdot 2$ in nitromethane- d_3 : ■ δ_{meas} , $\text{H}7/7'$ (at 500 MHz, δ/TMS external); ● D_{meas} , $\text{mn}12\text{S}_2\text{O}_2$. The solid lines visualize fitted values. Bars show the experimental error of D_{meas} .

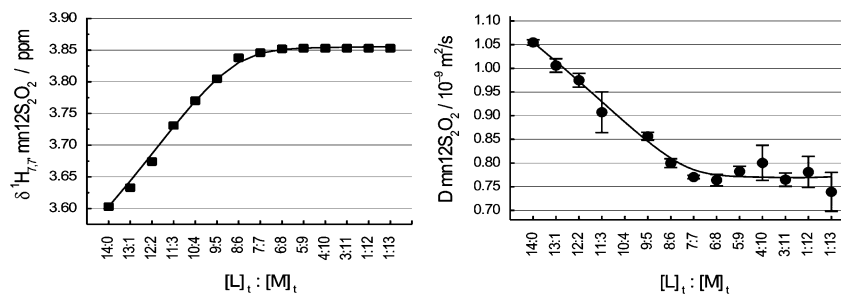


Table 3 Stoichiometries and stability constants of maleonitrile ethers

Complex	Solvent	Estimated complex stoichiometry M:L	$\lg K_{1,D}$ M + L = ML	$\lg K_{1,\delta}$ M + L = ML	$\lg K_{2,D}$ ML + L = MLL	$\lg K_{2,\delta}$ ML + L = MLL	$\lg K$ Lit.
2 · AgBF_4	nitromethane- d_3	1:1; 1:2	4.18	4.04	2.06	2.10	–
3 · AgBF_4	nitromethane- d_3	1:1; 1:2	5.29	4.98	1.27	1.41	–
4 · AgBF_4	acetonitrile- d_3	1:1	3.42	3.27	–	–	4.78 [35]

Fig. 9 Job's plot for $\text{Ag}^+ \cdot 3$ in nitromethane- d_3 : ■ δ -Job's plot 4/4' (at 500 MHz, δ/TMS external), ● D -Job's plot. Additional lines in the D -Job's plot help to locate the maximum

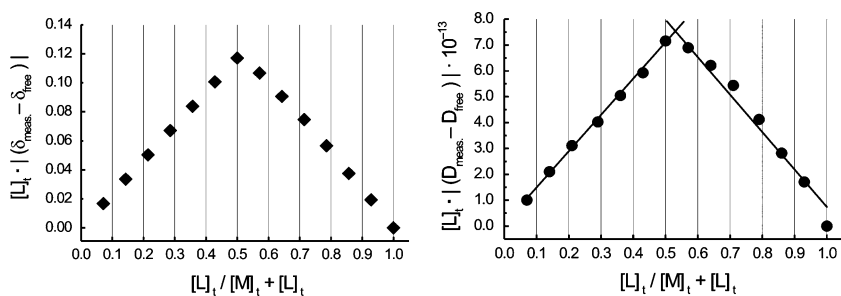


Fig. 10 Titration curves of $\text{Ag}^+ \cdot 3$ in nitromethane- d_3 : ■ δ_{meas} , $\text{H}4/4'$ (at 500 MHz, δ/TMS external); ● D_{meas} , $\text{mn}15\text{S}_2\text{O}_3$. The solid lines visualize fitted values. Bars show the experimental error in D_{meas} .

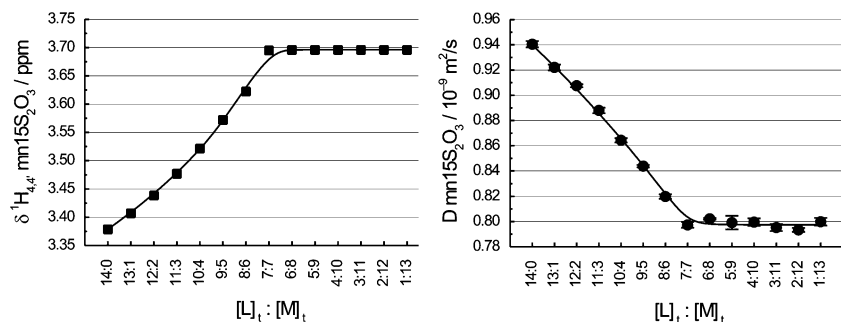


Fig. 11 Job's plot of $\text{Ag}^+ \cdot 4$ in acetonitrile- d_3 : ■ δ -Job's plot H 4/4' (at 500 MHz, δ/TMS external), ● D -Job's plot. Additional lines in the D -Job's plot help to locate the maximum

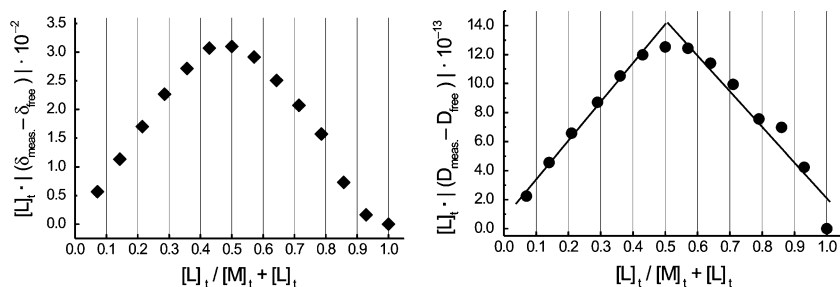
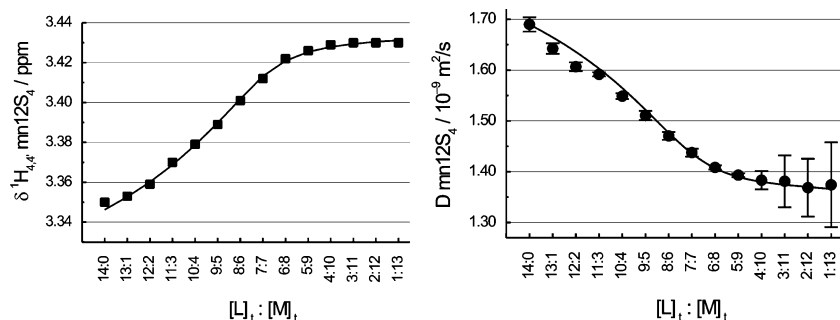


Fig. 12 Titration curves of $\text{Ag}^+ \cdot 4$ in acetonitrile- d_3 : ■ δ_{meas} , $^1\text{H}_{4,\text{et}}$ (at 500 MHz, δ/TMS external); ● D_{meas} , $\text{mn}12\text{S}_4$. The solid lines visualize fitted values. The bars show the experimental error of D_{meas} .



larger cavity of **3** is better able to host the Ag^+ cation than the cavity of **2**. When the cavity is too small, cations tend towards 1:2 complexation, as has been observed in other cases [4]. Thus, the difference in hydrodynamic radii between **3** and the silver complex $\text{Ag}^+ \cdot 3$ will be smaller in **3** compared with **2** and this is impressively corroborated by the corresponding diffusion behavior (cf. $\Delta D_{\text{L-ML}}$ in Table 2).

For the small 12-membered tetrathia-crown ether **4**, 1:1 complexation to AgBF_4 was also detected by both δ - and D -Job's plots (cf. Fig. 11) even if the cavity must be too small to completely host the silver cation (titration curves are presented in Figure 12). It is clear that sharp points characterizing the stoichiometry of the complexes were not obtained and overall changes in $\Delta\delta/\Delta D$ are smaller and not very indicative. In addition, when fitting the dependencies, only weak complexation of Ag^+ to **4** was obtained (cf. Table 3). However, even in this case of very low complexation, both the chemical shift and diffusion coefficient can be employed to precisely determine both the stoichiometry and complex stability of the crown ether complex $\text{Ag}^+ \cdot 4$.

The complex stability constants, estimated by the present methodology, corroborate the results of the δ - and D -titration studies, viz.:

- (i) Stability of the 1:1 complex of $\text{Ag}^+ \cdot 3$.
- (ii) The 1:1 complex $\text{Ag}^+ \cdot 2$ is more stable than the corresponding $2 \cdot \text{Ag}^+ \cdot 2$ (1:2) complex.

- (iii) Contribution of $3 \cdot \text{Ag}^+ \cdot 3$ (1:2) complex is only minor as supported by experiment.

Conclusions

We have shown that it is possible to determine both the stoichiometry and stability constants of metal ions crown ether complexes in solution by evaluating the diffusion behavior of the ligands. Thus, the diffusion coefficient also seems to be an appropriate NMR parameter for the description of even multiple complexation equilibria. In the case of $\text{Ag}^+ \cdot 2$, only the diffusion measurements provided relevant information for the existence of solution complexes with stoichiometry higher than 1:1. The quality of the results obtained is strongly dependent on the difference of the diffusion coefficient between free and complexed crown ether. With small $\Delta D_{\text{L-ML}}$ values, it is often difficult to determine the stoichiometry and stability constant accurately. This difference between D_{L} and D_{ML} quantifies the change of the conformation and the extent of solvation during complexation as a sum parameter. A further limitation is the necessity of the use of solvents with high viscosity due to the detrimental influence of convection effects. Nevertheless, excellent and reproducible results, comparable to values obtained by other methods, are able to be obtained.

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