Diffusion Coefficients of Macrocyclic Complexes using the PGSE NMR Technique: Determination of Association Constants

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Diffusion coefficients measurements using the pulsed gradients spin echo (PGSE) NMR technique are used for probing complexation and for determining the association constant (K_a) of macrocyclic host–guest complexes.

Macrocyclic compounds are widely used as synthetic ionophores in transport processes.[1,2] Carrier mediated transport is a complex process which involves, *inter alia*, complexation of the guest by the host at one interface, diffusion of the host–guest complex across the membrane, decomplexation at the second interface as well as back diffusion of the carrier (host) to the first interface.[2b]

Diffusion measurements using the pulsed gradient spin echo (PGSE) NMR technique[3] have been used extensively to study chemical systems.[4] This technique has been used to probe aggregation and association of some nucleotides in aqueous solution[5] and recently diffusional differences have been used to obtain water suppressed spectra of macromolecules.[6] Nevertheless, only very few diffusion studies, most of which were non-NMR studies, have ever been performed on macrocyclic compounds.[7] Surprisingly, these studies were limited to non-complexed macrocycles.[7]

In the present report we use simultaneous measurement of the diffusion coefficients of host–guest systems, using the PGSE NMR technique, to probe complexation and to calculate the association constants (K_a) of macrocyclic complexes. The association constants obtained by the PGSE NMR technique are in good agreement with those obtained by other methods.

In order to probe the complexation and to calculate the association constants of macrocyclic complexes the diffusion coefficients of the two components of the methylammonium chloride complexes of 18-crown-6 **1** and [2.2.2] cryptand **2** were measured. These values were compared with the diffusion coefficients of the free methylammonium chloride and the free complexing hosts under the same conditions. The rationale behind the method is that if the formed complex is very strong, one should obtain an identical diffusion coefficient for both components of the complex. If, on the other hand, the complexation is negligible the diffusion coefficients of the host and the guest in the host–guest solution should be equal to that of each of the free components. For complexes having a moderate binding constant one can use the measured diffusion coefficients to calculate the molar fraction of the bonded guest. For systems in which the complexation–decomplexation processes are fast on the NMR timescale the observed diffusion coefficient (D_{obs}) should be weighted average of the diffusion coefficient of the free guest (D_{free}) and the diffusion coefficient of the complexed guest (D_{com}). Knowing the composition of the prepared host–guest sample enables to calculate the association constant of the complex (K_a).

The diffusion coefficients of the 1:1 solutions of either 18-crown-6 or [2.2.2] cryptand with methylammonium chloride and the respective free components were determined by the PGSE NMR technique according to which the ratio of the echo intensity in the presence and in the absence of pulsed gradients, A_g and A_0, respectively, is given by eqn. (1)[3]

$$\ln (A_g/A_0) = -(\gamma g\delta)^2(\Delta-\delta/3)D \qquad (1)$$

wherein g is the gradient strength of the diffusion gradients (g cm^{-1}), D is the self-diffusion coefficient of the observed spins (cm^2 s^{-1}), γ is the gyromagnetic ratio (rad s g^{-1}), δ is the length of the diffusion gradients and Δ is the time separation between the two diffusion gradients given in s.

Typical spectra obtained in such experiments are shown in Fig. 1. The diffusion coefficients of the various samples studied are computed in Table 1 along with the calculated association constants (log K_a)†.

As expected, the changes in the diffusion coefficients of the host molecules upon complexation are rather small, but much more significant changes are observed in the diffusion coefficients of the guest methylammonium cation upon complexation. The decrease in the diffusion coefficient of the guest probes the formation of a host–guest complex and allows us to determine the association constant of the complex as explained above. The data computed in Table 1 shows the expected trend. The complexation constants for 18-crown-6 and [2.2.2]cryptand with methylammonium chloride are higher in methanol than in water in which ion solvation is much more pronounced. In the same solvent, the complexation constants are higher for the [2.2.2] cryptand as compared to the ones found for 18-crown-6. Cryptands, being bicyclic structures have, in general, higher complexation constants than crown ethers having monocyclic structures.[8] In addition, the observed complexation constants found for 18-crown-6 are in good agreement with literature values obtained by others using different methods. We found log K_a of 0.67 dm^3 mol^{-1} in D_2O as compared to the value of 0.4 dm^3 mol^{-1} found by Noguichi *et al.* for the 18-crown-6 methylammonium perchlorate complex.[9] The value we have obtained for the methylammonium chloride complex of 18-crown-6 in methanol (3.67 dm^3 mol^{-1}) is in a reasonable agreement to the value reported by Izatt *et al.* (4.25 dm^3 mol^{-1}) for the methylammonium iodide complex.[10] The difference between the two values may arise from the difference in the amount of residual water in the methanol solutions used in these two studies.‡

The determination of the binding constant is the first step for determining host-guest interaction. It is therefore not surprising that many different methods have been developed for determining binding and association constants of such systems.[11] The use of NMR methods to calculate binding and association constants of host-guest systems has recently increased and it has been advocated that NMR methods are

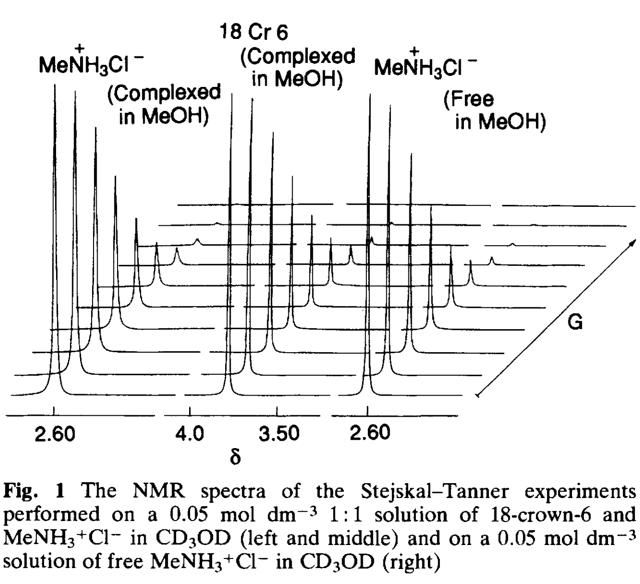

Fig. 1 The NMR spectra of the Stejskal–Tanner experiments performed on a 0.05 mol dm^{-3} 1:1 solution of 18-crown-6 and $MeNH_3^+Cl^-$ in CD_3OD (left and middle) and on a 0.05 mol dm^{-3} solution of free $MeNH_3^+Cl^-$ in CD_3OD (right)

Table 1 Diffusion coefficients and association constants for the methylammonium chloride complex of 18-crown-6 **1** and [2.2.2] cryptand **2** in D_2O and CD_3OD at various temperatures.[a]

Substance	Solvent	T/K	$D_{\mathrm{macrocyclic}}$/ (10^{-5} cm^2/s)	D_{MeNH3}/ (10^{-5} cm^2/s)	log(K_a/dm^3 mol^{-1})
1 and $MeNH_3^+$	D_2O	298	0.55 ± 0.01	1.23 ± 0.02	0.67
1	D_2O	298	0.56 ± 0.01	—	
$MeNH_3^+$	D_2O	298	—	1.36 ± 0.01	
1 and $MeNH_3^+$	CD_3OD	298	1.34 ± 0.01	1.37 ± 0.02	3.69
1	CD_3OD	298	1.35 ± 0.02	—	
$MeNH_3^+$	CD_3OD	298	—	1.70 ± 0.01	
2 and $MeNH_3^+$	D_2O	298	0.46 ± 0.02	0.95 ± 0.04	1.53
2	D_2O	298	0.45 ± 0.04	—	
$MeNH_3^+$	D_2O	298	—	1.38 ± 0.01	
2 and $MeNH_3^+$	D_2O	277	0.21 ± 0.01	0.59 ± 0.01	1.67
2	D_2O	277	0.20 ± 0.01	—	
$MeNH_3^+$	D_2O	277	—	0.72 ± 0.01	
2 and $MeNH_3^+$	CD_3OD	298	1.14 ± 0.03	1.14 ± 0.03	>4
$MeNH_3^+$	CD_3OD	298	—	1.64 ± 0.01	
2 and $MeNH_3^+$	CD_3OD	213	0.28 ± 0.01	0.29 ± 0.01	>4
$MeNH_3^+$	CD_3OD	213	—	0.42 ± 0.06	

[a] Values are means ± standard deviation of at least 3 experiments.

less prone to misinterpretations caused by minor impurities as compared to methods based on UV and fluorescence techniques.[12] These NMR methods are primarily based on changes in chemical shifts upon complexation.[12–14] One of the main sources for systematic errors when determining association constants based on chemical shifts NMR methods is the possibility of confusing acid-base chemistry with binding phenomena, namely, assigning changes in chemical shifts which are due to proton transfer to binding processes.[12] It should be noted that this complication is less severe when extracting the association constant from diffusion measurements since self diffusion coefficients are parameters which are less sensitive to proton transfer than chemical shifts. This fact enables us to easily determine the association constant of methylammonium chloride to [2.2.2] cryptand (see Table 1) although it was clear from the NMR spectra that as expected[15] partial protonation of the cryptand moiety did occur. Using the PGSE NMR method the only assumption made in order to calculate K_a is that D_{com} is taken as the diffusion coefficient of the host in the host–guest solution. The data in Table 1 shows that this assumption is justified as can be concluded from the fact that even the diffusion coefficient of the free host is very similar to the diffusion coefficient of the complexed host in the host–guest solution.

The diffusion method is more suitable for the determination of weak and moderate association constants. Taking into account the range of concentrations normally used in NMR measurements of this kind (10–0.1 mmol), the sensitivity and the accuracy of the diffusion coefficient determination one obtain an upper limits for K_a in the range of 10^3 to 10^5 dm^3 mol^{-1}. It should be noted that large differences in the diffusion coefficients of the host and the guest increase the accuracy of the method.

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Footnotes

† The concentrations of the solutions studied were 0.05 mol dm^{-3} and the host-guest ratio was 1 : 1. The diffusion experiments were carried out on a Bruker 500 MHz ARX NMR spectrometer equipped with a B-AFPA 30 pulsed gradient unit capable of producing Z-gradient of nearly 100 G cm^{-1}. Experiments were carried out in an 5 mm high resolution inverse probe having self shielded gradient coil. The pulsed gradients used were in the range of 0 to 41.57 G cm^{-1}. The total echo time was typically 124 ms. Some experiments using a shorter echo time of 64 ms have also been performed. All diffusion coefficients are averages of at least three experiments and only data having a correlation coefficient (R^2) of more that 0.993 were included.

‡ In our study the amount of residual water in the CD_3OD was estimated to be about 1% based on NMR integration. The amount of residual water if any, is not reported in ref. 10.

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