NMR Diffusion Coefficients of *p-tert*-Butylcalix[*n*]arene Systems

Orna Mayzel,[a] Oleg Aleksiuk,[b] Flavio Grynszpan,[b] Silvio E. Biali[b] and Yoram Cohen*[a]

[a] *School of Chemistry, The Sackler Faculty of Exact Sciences, Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel*
[b] *Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel*

The pulsed gradient spin echo (PGSE) NMR technique was used for measuring the diffusion coefficients of neutral and charged calix[*n*]arenes and for probing their association in solution with potential guests.

The enormous recent interest in the synthetic macrocycles calix[*n*]arenes stems from their ability to form inclusion complexes with small organic molecules.[1] *p-tert*-Butylcalix-[4]arene **1a** readily forms inclusion complexes in the solid state,[2] and this ability has been utilized recently with larger calixarenes for the purification of fullerenes.[3] However, few studies have been conducted on the complexation of neutral molecules by the parent *p-tert*-butylcalix[*n*]arenes in solution.[4]

The detection of complex formation by NMR can be achieved by measuring intermolecular NOEs or by monitoring changes in the relaxation times or in the chemical shift of the host or guest upon complexation.[5a–c] Diffusion measurements have been shown to provide a complementary probe for testing complexation in solution.[5d] In principle free hosts and guests should have different diffusion coefficients, but when associated in a complex they should have identical diffusion coefficients, irrespective of whether the chemical shifts of the guest or the host are shifted as a result of the complexation. In this communication we describe the first pulsed gradient spin echo (PGSE) NMR[6] study on calixarenes for probing association in solution. We describe the influence of cavity size and charge on the diffusion coefficients.

For the present study we chose several *p-tert*-butylcalix-[*n*]arenes of different sizes (**1a–d**), two systems which exist in the solid state as inclusion complexes (*i.e. p-tert*-butylcalix-[4]arene–toluene **2**[2] and *p-tert*-butylcalix[4]arene–Cs–MeCN **3**[7]) and the aminocalix[4]arene tosylate system **5**.[8] In the crystal of **2** obtained from toluene, a solvent molecule is located inside the calixarene cavity, whereas in **3** the Cs^+ atom is located inside the cavity, and is coordinated to a MeCN molecule.[2,7] In the case of **5** we were unable to conclude on the basis of the NMR data, whether the tosylate and the calixarene are associated.[8]

Examination of the $CDCl_3$ solutions of the calixarenes **1a–d** shows, in general, the expected trend according to which the larger the macrocycle, the smaller is its diffusion coefficient.† The diffusion coefficient of *p-tert*-butylaminocalix[4]arene **4** was similar to that of **1a**. Interestingly, the larger *p-tert*-butylcalix[8]arene **1d** was found to diffuse slightly faster than expected for its molecular mass. One plausible explanation of

1a *n* = 1
b *n* = 2
c *n* = 3
d *n* = 5

2 R = OH, X = PhMe
3 R = O^-, X = Cs^+····NCMe
4 R = NH_2
5 R = NH_3^+, X = $OTos^-$

Table 1 Diffusion coefficients of *p-tert*-butylcalix[*n*]arenes (*n* = 4, 5, 6, 8) and *p-tert*-butylaminocalix[4]arene in $CDCl_3$ at 283 K[a]

System	$D_{macrocycle}$/ 10^{-5} cm^2 s^{-1}	D_{CDCl_3}/ 10^{-5} cm^2 s^{-1}
1a	0.68 ± 0.01	1.97 ± 0.04
1b[c]	0.57 ± 0.01	1.98 ± 0.02
1c	0.52 ± 0.04	2.02 ± 0.03[b]
1d	0.56 ± 0.01	2.01 ± 0.01
4	0.63 ± 0.01	1.96 ± 0.01
$CDCl_3$	—	2.01 ± 0.01

[a] Values are mean ± standard deviation for at least 3 experiments. [b] Value from only two measurements. [c] **1b** was prepared according to ref. 9.

Table 2 Diffusion coefficients of 1 : 1 solutions of *p-tert*-butylcalix[4]arene derivatives, potential guests and the respective free guests in $CDCl_3$[a]

System	Temperature/K	$D_{macrocycle}$/ 10^{-5} cm^2 s^{-1}	D_{guest}/ 10^{-5} cm^2 s^{-1}	D_{CDCl_3}/ 10^{-5} cm^2 s^{-1}
2	298	0.78 ± 0.01	2.17 ± 0.04[b]	2.34 ± 0.01
Toluene	298	—	2.21 ± 0.01	2.35 ± 0.01
3	283	0.75 ± 0.02	2.02 ± 0.02[c]	2.05 ± 0.03
MeCN	283	—	1.98 ± 0.02	2.05 ± 0.01
5	298	0.71 ± 0.04	0.71 ± 0.05	2.35 ± 0.01
Tosylate[d]	298	—	0.88 ± 0.04[d]	2.34 ± 0.01

[a] Values are mean ± standard deviation for at least 3 experiments. [b] Value for the toluene. [c] Value for the MeCN. [d] Value for the tosylate of the *p-tert*-butylanilinium salt **6**.

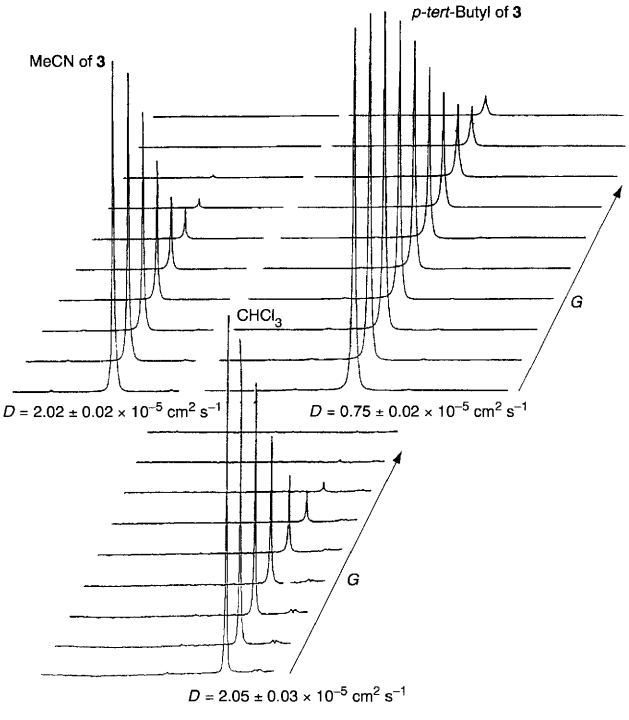

Fig. 1 500 MHz ^{1}H NMR spectra of the Stejskal–Tanner experiments[6] performed on a $CDCl_3$ solution of **3**. For clarity only the peak of the *p-tert*-butyl group of the calixarene moiety is shown.

this observation may be that the large cavity of **1d** allows free diffusion of the chloroform molecules through it. All the computed diffusion coefficients of these systems were found to be smaller than those of the potential guests toluene, MeCN or $CHCl_3$ (Tables 1 and 2). The diffusion coefficient of chloroform in the $CDCl_3$ solution is also reported in all cases as it has been used as an internal reference for the estimation of the accuracy of the diffusion measurements.

The dissolution of the solid state complex **1a**·toluene in $CDCl_3$ gave a solution of the calixarene in a 1 : 1 ratio with the potential guest. The diffusion coefficients obtained for the pair **1a**–toluene were identical to those determined for each of the free partners (Table 1). This shows that in the $CDCl_3$ solution the toluene is not associated to the calixarene, a result which is in agreement with the ASIS study of Bauer and Gutsche who estimated the association constant of **1a** with toluene in $CDCl_3$ to be 1.1.[4] Examination of a $CDCl_3$ solution of **3**, showed that the diffusion coefficient of the MeCN is much higher than that of the calixarenic moiety of **3** (Fig. 1). The value obtained for MeCN is almost equal to that of the free MeCN in $CDCl_3$. This indicates that in the $CDCl_3$ solution, the MeCN molecule is not associated to the macrocycle by second sphere coordination[10] as observed in the crystal.‡

The diffusion coefficients of both the tosylate and the protonated aminocalixarene in $CDCl_3$ were found to be identical (Table 2), indicating that both species are associated in solution. Since, in the case of **5**, the calixarene and the potential guest are oppositely charged, we examined also the diffusion behaviour of *p-tert*-butylanilinium tosylate **6** as a model for the diffusion behaviour of the tosylate anion where no *endo*-calix complexation is possible. We found that the diffusion coefficients of the anilinium and the tosylate ions were identical within experimental error (*i.e.* $0.89 \pm 0.04 \times 10^{-5}$ and $0.88 \pm 0.04 \times 10^{-5}$ $cm^2\ s^{-1}$, respectively). This suggests that the system exists in the $CDCl_3$ solution as an ion pair, with both ions diffusing as a single entity. This demonstrates that although the PGSE NMR method can conclusively indicate whether two molecules of dissimilar *D* values are associated, as with other spectroscopic methods it cannot 'prove' that the guest is located within the cavity of the host.

We believe that in the near future when NMR instruments equipped with gradient coils become commonplace, PGSE studies for probing complexation will become routine.

This research was supported by the Wolfson research award administered by the Israel Academy of Sciences and Humanities (Y. C.).

Received, 16th February 1995; Com. 5/00957J

Footnotes

† 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 a Z-gradient of nearly 100 G cm^{-1}. Experiments were carried out in a 5 mm high resolution inverse probe having self shielded gradient coils. The pulsed gradients were incremented from 0 to *ca.* 41.57 G cm^{-1}. The pulsed gradients were of 2 ms duration separated by a 60 ms delay and the total echo time was 124 ms.

‡ The complex was prepared according to ref. 7. The ^{133}Cs NMR of the isolated complex was found to be identical to that reported[7] (δ −234 relative to 0.5 mol dm^{-3} CsBr in D_2O as an external reference).

References

1 For reviews on calixarenes see: C. D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge, 1989; *Calixarenes: A Versatile Class of Macrocyclic Compounds*, ed. J. Vicens and V. Böhmer, Kluwer, Dordrecht, 1991; S. Shinkai, *Tetrahedron*, 1993, **49**, 8933.

2 G. Andretti, R. Ungaro and A. Pochini, *J. Chem. Soc., Chem. Commun.*, 1979, 1005; G. A. Facey, R. H. Dubois, M. Zakrzewski, C. I. Ratcliffe, J. L. Atwood and J. A. Ripmeester, *Supramolecular Chem.*, 1993, **1**, 199.

3 J. L. Atwood, G. A. Koutsantonis and C. L. Raston, *Nature*, 1994, **368**, 229; T. Suzuki, K. Nakashima and S. Shinkai, *Chem. Lett.*, 1994, 699.

4 See for example: L. J. Bauer and C. D. Gutsche, *J. Am. Chem. Soc.*, 1985, **107**, 6063.

5 Many have used conventional NMR techniques to probe complexation see for example (*a*) C. D. Gutsche, M. Iqbal and I. Alam, *J. Am. Chem. Soc.*, 1987, **109**, 4314; (*b*) J. P. Kintzinger and J.-M. Lehn, *J. Am. Chem. Soc.*, 1974, **96**, 3313; (*c*) T. Wang, J. S. Brandshaw and R. M. Izatt, *J. Heterocyc. Chem.*, 1994, **31**, 1097, and references cited therein; (*d*) Few examples have been reported in the literature in which the PGSE NMR technique has been used to detect association between molecular species: R. Rymden and P. Stilbs, *Biophys. Chem.*, 1985, **21**, 145; R. Rymden, J. Carlfors and P. Stilbs, *J. Incl. Phenom.*, 1983, **1**, 159; O. Mayzel and Y. Cohen, *J. Chem. Soc., Chem. Commun.*, 1994, 1901. For self-association of charged systems using the PGSE NMR method see Y. Cohen and A. Ayalon, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 000.

6 E. O. Stejskal and J. E. Tanner, *J. Chem. Phys.*, 1965, **42**, 288. For excellent reviews on the PGSE technique see: P. Stilbs, *Prog. NMR Spectroscopy*, 1987, **19**, 1; E. W. Lang and H.-D. Ludemann, *Prog., NMR Spectroscopy*, 1993, **25**, 507.

7 J. M. Harrowfield, M. I. Odgen, W. R. Richmond and A. H. White, *J. Chem. Soc., Chem. Commun.*, 1991, 1159.

8 O. Aleksiuk, F. Grynszpan and S. E. Biali, *J. Org. Chem.*, 1993, **58**, 1994.

9 D. R. Stewart and C. D. Gutsche, *Org. Prep. Proc. Int.*, 1993, **25**, 137.

10 For a review on second sphere coordination see: H. M. Colquhoun, J. F. Stoddart and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 487.