Do calix[*n*]arenes really exist as discrete monomers in solution? Comments based on mass spectrometry

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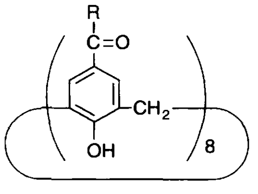
Mass spectrometric measurements have provided unequivocal evidence that calix[*n*]arenes (2_n), which are so far believed to exist as discrete monomers in solution because of strong intramolecular hydrogen bonding, aggregate partially to form dimers and trimers through intermolecular hydrogen bonds. This trend is particularly conspicuous in 2_8 and next in 2_7 and only a very weak dimer peak is observable for 2_6. In contrast, such an aggregate peak is not detected for 2_4 and 2_5. The results are consistent with the prediction offered on the basis of theoretical calculations that 2_4 and 2_5 can adopt a stable C_4- and C_5-symmetrical ring structure, respectively, as well as a stable intramolecular hydrogen-bonding array, whereas 2_6, 2_7 and 2_8 feature a pinched ring conformation as their most stable structure which destabilizes the intramolecular hydrogen-bonding array. The new finding reasonably explains several curious aspects of the behaviour of 2_n such as very poor solubility of 2_8 and gelation in organic fluids.

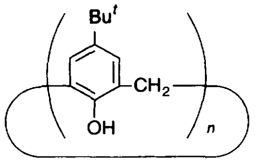
Calix[*n*]arenes are cyclic *n*-mers made up of phenol units linked by methylene bridges.[1] Judging from their polyol structure, they should be soluble in protic solvents such as alcohols. In fact, however, they are not soluble in alcohols but soluble in aprotic solvents, *e.g.* chloroform, toluene and THF.[1] The unusual solubility stems from the hydrogen bonding characteristics of calix[*n*]arenes: the OH groups act both as donor and acceptor of a hydrogen bond and form neat intramolecular hydrogen bonds in a circular array.[1] It has been suggested that the OH groups are not exposed to the solvent medium so the compounds do not show the solubility characteristic of polyols. In fact, vapour pressure osmometry measurements show that calix[*n*]arenes exist as discrete monomers.[2]

Recent studies suggest, however, that the intramolecular hydrogen bonds may be *partially* (or from a dynamic viewpoint, *time-dependently*) cleaved. For example, Aoki and co-workers[3] found that compounds **1** act as gelators of organic fluids, suggested to be a result of aggregation supported by intermolecular hydrogen bonds between the C=O groups on the upper rim and the OH groups on the lower rim. In 1994 it was found that a mixture of 2_8 and buckminsterfullerene (C_{60}) forms a precipitate including these two components in a 1 : 1 ratio, which has made it possible to isolate and purify efficiently C_{60} from carbon soot.[4–6] This precipitate formation has been suggested to be the result of changes in the cone conformation of 2_8 and partial cleavage of the intramolecular hydrogen bonds by C_{60}. Furthermore, recent solid-state measurements of calix[*n*]arenes showed that they can adopt conformations other than the cone which are generated through partial cleavage of the intramolecular hydrogen bonds.[7,8] These findings consistently support the view that the intramolecular hydrogen bonds in calix[*n*]arenes (particularly, those in calix[8]arene) are partially cleaved. It is known that among calix[*n*]arenes (n = 4–8) the solubility of calix[8]arene is particularly poor. This property may be also explained by the partial cleavage of the intramolecular hydrogen bonds that enables the formation of the intermolecular hydrogen bonds.

To find unambiguous evidence for the presence of hydrogen-bonded calix[*n*]arene aggregates we used mass spectrometry.[9] It has already been demonstrated that mass spectrometry is a powerful tool for the detection of trace amounts of unstable complexes which are impossible to detect in solution.[10] We have found that calix[7]arene and calix[8]arene actually form aggregates due to intermolecular hydrogen bonds, whereas the corresponding mass spectral peaks are not found for calix[4]arene and calix[5]arene, and calix[6]arene is a critical compound which divides the monomeric and oligomeric calix[*n*]arenes.



1 [R = $(CH_2)_nMe$]



$\mathbf{2}_n$ (n = 4–8)

Results and discussion

Optimization of measurement conditions

With our mass spectrometry instrumentation (Hitachi M-2500) it is possible to use two different ionization modes, electrospray ionization mass spectrometry (ESI–MS) and secondary ion mass spectrometry (SIMS). ESI–MS is excellent in detecting unstable complex species, but the highest measurable m/z value is 2000 Da/charge in this instrument. Since the m/z value of 2_8 is 1298, this mode is not suitable for the detection of calix[*n*]arene oligomers. On the other hand, as the highest measurable m/z value in SIMS can be enhanced up to 4500 under the selected measurement conditions, this enables us to detect dimers and trimers.

A typical example for the SIMS (positive) measurement of 2_8 is shown in Fig. 1. It is clearly seen from Fig. 1 that in addition to a peak for $[2_8]^+$ (m/z = 1298), two peaks assignable to $[(2_8)_2]^+$ (m/z = 2596) and $[(2_8)_3]^+$ (m/z = 3894) are observable and except for these two peaks no significantly strong peak appears between $[2_8]^+$ and $[(2_8)_3]^+$. Although the peak intensities of the dimer and trimer are weaker than that for the monomer ($[\text{dimer}]^+/[\text{monomer}]^+ = 0.062 \pm 0.006$ and $[\text{trimer}]^+/[\text{monomer}]^+ = 0.018 \pm 0.004$), the result clearly shows that 2_8 can aggregate through intermolecular hydrogen bonds. It is likely that aggregates greater than the trimer are also formed, but the mass spectrometric method does not give us any useful information about this possibility. On the other

Table 1 Peak intensity ratios of [dimer]$^+$/[monomer]$^+$ and [trimer]$^+$/[monomer]$^+$ (in % for [monomer]$^+$ = 100)[a]

Calix[*n*]arene	Method A[b]		Method B[c]	
	[dimer]$^+$/[monomer]$^+$	[trimer]$^+$/[monomer]$^+$	[dimer]$^+$/[monomer]$^+$	[trimer]$^+$/[monomer]$^+$
2$_4$	nd	nd	nd	nd
2$_5$	nd	nd	0.1 ± 0.1	nd
2$_6$	0.1 ± 0.1	nd	*d*	*d*
2$_7$	0.8 ± 0.4	nd	2.8 ± 0.3	nd
2$_8$	6.2 ± 0.6	1.8 ± 0.4	*d*	*d*

[a] Positive SIMS covering *m*/*z* 0–4500. The value is an average of five repeated scans. nd denotes that the peak is not detected: judging from the accuracy of the measurement system, nd should be smaller than 0.05% relative to [monomer]$^+$. [b] Measurement conditions recorded in the caption to Fig. 1. [c] [**2**$_n$] = 0.05 mol dm^{-3} in chlorobenzene: other measurement conditions are the same as Method A. [d] **2**$_6$ and **2**$_8$ were not soluble in chlorobenzene under the conditions used in Method B.

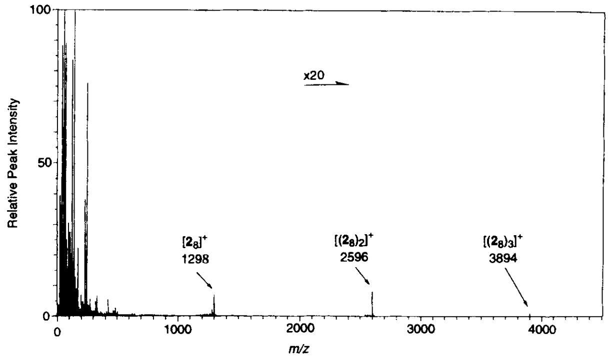


Fig. 1 Positive SIMS mass spectrum for **2**$_8$ in a 2-nitrophenyl octyl ether (NPOE) matrix: 5 µl of a chlorobenzene solution containing **2**$_8$ (0.01 mol dm^{-3}) and 5 µl of NPOE were mixed and 1 µl of the mixture was loaded on the silver target

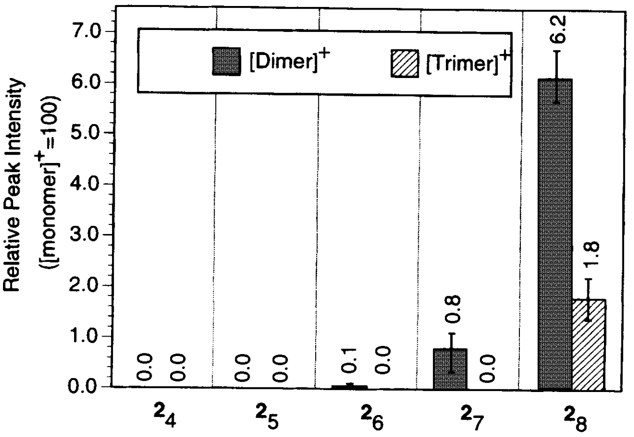


Fig. 2 Peak intensity ratios of [dimer]$^+$/[monomer]$^+$ and [trimer]$^+$/[monomer]$^+$. The measurement conditions are similar to those recorded in the caption to Fig. 1.

hand, both 49,50,51,52,53,54,55,56-octamethylcalix[8]arene and 49,50,51,52,53,54,55,56-octamethyl-5,11,17,23,29,35,41,47-octa-*tert*-butylcalix[8]arene gave only their monomeric peaks. Furthermore, it is inconceivable that the clusters are newly formed in the gas phase under high vacuum (1 × 10^{-4} Pa). The results clearly indicate that the clusters are formed through the hydrogen-bonding interaction in the solution phase.

The above finding encouraged us to continue this study. We thus tried to optimize the measurement conditions so that we can detect the aggregates that may be formed from other calix[*n*]arenes. We screened the positive *vs.* negative mode in SIMS and the effect of matrices. We found that the peak intensity of dimers and trimers becomes weaker when negative SIMS is used instead of positive SIMS. Under the measurement conditions recorded in the caption to Fig. 1, *e.g.* positive SIMS gave [dimer]$^+$/[monomer]$^+$ = 0.062 ± 0.006 and [trimer]$^+$/[monomer]$^+$ = 0.018 ± 0.004 whereas negative SIMS gave [dimer]$^-$/[monomer]$^-$ = 0.010 ± 0.006 and the [trimer]$^-$/[monomer]$^-$ peak was not detected. For **2**$_7$, positive SIMS gave [dimer]$^+$/[monomer]$^+$ = 0.008 ± 0.004 whereas the corresponding peak could not be detected in negative SIMS. The results imply that the ionization potential of positive SIMS is superior to that of negative SIMS. We thus decided to use positive SIMS.

As a matrix we tested glycerine, 3-nitrobenzyl alcohol (NBA) and 2-nitrophenyl octyl ether (NPOE) which are frequently used as matrices for FAB and SIMS ionization. In glycerine all calix[*n*]arenes **2**$_n$ (*n* = 4–8) were sparingly soluble and satisfactory sample solutions could not be prepared. Although the sample solutions prepared in NBA gave the peaks assignable to dimers and trimers, most of them were turbid. In particular, **2**$_8$, which features the worst solubility, resulted in a precipitate. We concluded, therefore, that NBA is not suitable for the quantitative estimation of the relative peak intensity. On the other hand, NPOE is satisfactorily miscible with all calix[*n*]arenes and resulted in clear solutions. We thus decided to use NPOE as a matrix. As a solvent for calix[*n*]arenes we tested chlorobenzene, chloroform and toluene. Among them chlorobenzene showed the highest solubility and was well miscible with NPOE. The combination of NPOE as a matrix and chlorobenzene as a solvent gave the satisfactorily reproducible data. We thus measured the positive SIMS under these optimized conditions.

Relative peak intensities of dimers and trimers *vs.* monomers

We measured the positive SIMS spectra for **2**$_n$ (*n* = 4–8). The results are summarized in Fig. 2 and Table 1. For **2**$_8$, the peaks assignable to dimer and trimer clearly appeared, the peak intensities relative to monomer ([**2**$_8$]$^+$) being 6.2 and 1.8%, respectively. For **2**$_7$ the peak assignable to the dimer was observed (0.8%), but that assignable to the trimer was not detected. The results suggest that the intramolecular hydrogen bonds in **2**$_8$ are less stable and more easily cleaved to form the intermolecular hydrogen bonds than those in **2**$_7$. Neither dimer nor trimer was detected for **2**$_4$ and **2**$_5$ under the same measurement condition.† The results indicate that OH groups in **2**$_4$ and **2**$_5$ predominantly form the intramolecular hydrogen bonds over the intermolecular hydrogen bonds. Recently, we systematically estimated the stability of calix[*n*]arenes (*n* = 4–7) by a computational method using MM3(92).[11] The results showed that in **2**$_4$ and **2**$_5$ the regular intramolecular hydrogen bonds can be formed without deforming their basic cone skeletons (*i.e.* they can keep regular C_4- and C_5-symmetry, respectively), whereas in **2**$_6$ and **2**$_7$ (and maybe also in **2**$_8$ which we could not calculate because of the greater complexity), the

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† However, only when the concentration of **2**$_5$ in chlorobenzene was enhanced to 0.05 mol dm^{-3} from 0.01 mol dm^{-3} did it give a weak dimer peak (0.1%: see Table 1).

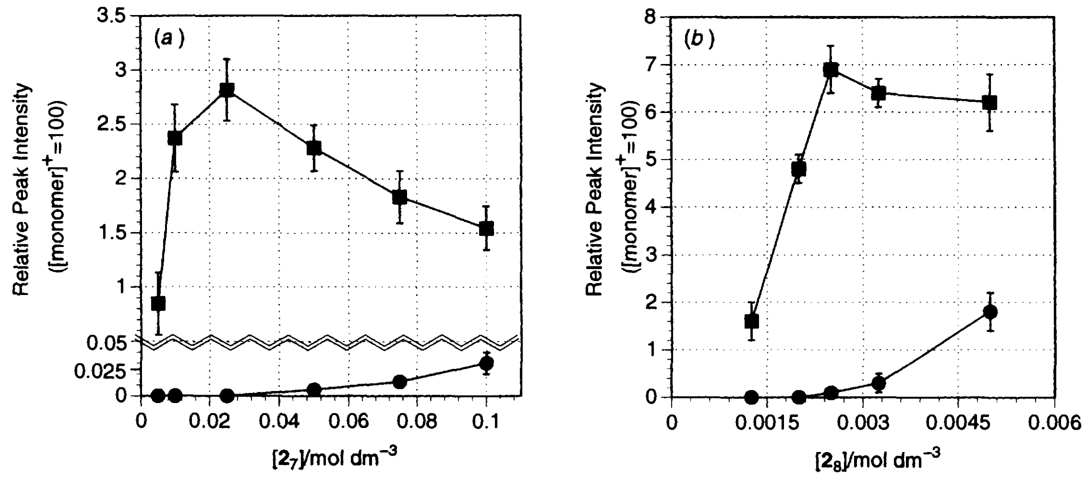


Fig. 3 Peak intensity ratios for $[\text{dimer}]^+/[\text{monomer}]^+$(■) and $[\text{trimer}]^+/[\text{monomer}]^+$(●) plotted against $\mathbf{2}_7$ or $\mathbf{2}_8$ concentration. The calix[*n*]arene is in chlorobenzene : NPOE (1 : 1 v/v).

basic skeleton must be deformed to a pinched cone conformation for OH groups to form the regular intramolecular hydrogen bonds. The results predict that the intramolecular hydrogen bonds in $\mathbf{2}_6$ and $\mathbf{2}_7$ (and maybe also in $\mathbf{2}_8$) are more destabilized than those in $\mathbf{2}_4$ and $\mathbf{2}_5$. The present mass spectroscopic data exactly substantiate this prediction.

Concentration effects

As $\mathbf{2}_8$ resulted in relatively strong peaks for the ionized dimer and trimer, we suspected that contrary to a generally accepted rationale for calix[*n*]arenes,[1] the aggregate of $\mathbf{2}_8$ may be detectable also in solution. If aggregate formation is detectable in solution using ^{1}H NMR spectroscopy, it would be most likely at high concentration and low temperature. We measured the ^{1}H NMR spectra of $\mathbf{2}_8$ (0.86–9.95 mmol dm^{-3}) in [^{2}H$_5$]chlorobenzene at 298 K. However, the chemical shifts of $\mathbf{2}_8$ protons did not change over the experimental error ($\pm$0.0012 ppm). We also measured the ^{1}H NMR spectra of $\mathbf{2}_8$ (2.05 mmol dm^{-3}) at 185–298 K (solvent CD_2Cl_2). Although the δ_{OH} value gradually shifted to lower magnetic field as the medium temperature was lowered (9.96 ppm at 298 K and 10.25 ppm at 185 K), other δ_{CH} values scarcely changed. A similar temperature-dependent δ_{OH} down-field shift is also observed for that of $\mathbf{2}_4$ which does not afford either the dimer peak or the trimer peak. Hence, the shift is attributed to the change in the intramolecular hydrogen bonds.

The above results suggest that mass spectrometry is the sole analytical method for detecting the aggregation properties of calix[*n*]arenes. Therefore, we decided to estimate concentration effects by mass spectrometry. Neither dimer nor trimer was detected for $\mathbf{2}_4$. In the case of $\mathbf{2}_5$, it gave a dimer peak (0.1% relative to [monomer]$^+$) when the concentration of $\mathbf{2}_5$ in chlorobenzene was enhanced to 0.05 mol dm^{-3}, however, the trimer was not detected. In the case of $\mathbf{2}_6$, it gave a dimer peak (0.1% relative to [monomer]$^+$) when the concentration of $\mathbf{2}_6$ in chlorobenzene was 0.01 mol dm^{-3}. In general, the solubility of $\mathbf{2}_8$ is very poor, so that we could prepare the concentration in chlorobenzene : NPOE (1 : 1 v/v) solution only up to 5.0 mmol dm^{-3}. On the other hand, $\mathbf{2}_7$ is more soluble and we could enhance the concentration up to 100 mmol dm^{-3}. As shown in Fig. 3, $\mathbf{2}_8$ gave stronger peaks for [dimer]$^+$/[monomer]$^+$ and [trimer]$^+$/[monomer]$^+$ than $\mathbf{2}_7$ in spite of the lower concentration and in both calix[*n*]arenes the [dimer]$^+$/ [monomer]$^+$ ratio afforded a maximum at 25 mmol dm^{-3} for $\mathbf{2}_7$ and 2.5 mmol dm^{-3} for $\mathbf{2}_8$ whereas the [trimer]$^+$/ [monomer]$^+$ ratio increased with increasing calix[*n*]arene concentration. It is considered that when the formation of dimers proceed, the equilibrium in these systems is gradually shifted upon the trimers. Conceivably, the poor solubility in $\mathbf{2}_8$ is understood in association with the high aggregative nature: the intramolecular hydrogen bond array is easily destabilized, which facilitates the formation of intermolecular hydrogen bonds and eventually causes the precipitation of aggregated $\mathbf{2}_8$.

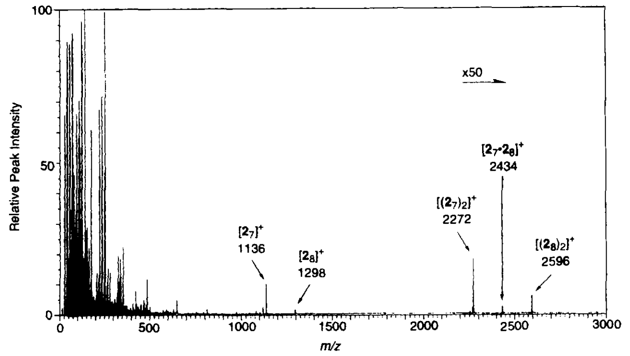
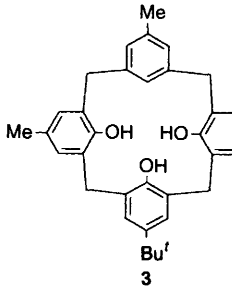


Fig. 4 Positive SIMS mass spectrum for a mixture of $\mathbf{2}_7$ and $\mathbf{2}_8$ in a 10 : 1 mole ratio: the sample solution consists of 100 mmol dm^{-3} $\mathbf{2}_7$ in chlorobenzene (5 µl), 10 mmol dm^{-3} $\mathbf{2}_8$ in chlorobenzene (5 µl) and NPOE (15 µl)

Formation of hetero-dimers

Here, we tried to detect the peak for hetero-dimers formed from $\mathbf{2}_7$ and $\mathbf{2}_8$. The purposes of this experiment are to compare the relative aggregation ability between $\mathbf{2}_7$ and $\mathbf{2}_8$ and to rule out the possibility that the [dimer]$^+$ peak may be assignable to a trace amount of concomitant calix[14]arene or calix[16]arene. When $\mathbf{2}_7$ and $\mathbf{2}_8$ were mixed in a 1 : 1 mole ratio, the [dimer]$^+$ and [trimer]$^+$ peaks for $\mathbf{2}_8$ appeared very strongly, whereas those for $\mathbf{2}_7$ appeared very weakly and the peak assignable to the $\mathbf{2}_7{\cdot}\mathbf{2}_8$ hetero-dimer could not be detected. This indicates that the aggregation ability of $\mathbf{2}_8$ is much stronger than that of $\mathbf{2}_7$. We thus prepared a solution containing $\mathbf{2}_7$ and $\mathbf{2}_8$ in a 10 : 1 mole ratio and subjected it to mass spectroscopic measurement. As shown in Fig. 4, the peak m/z = 2434 assignable to the $\mathbf{2}_7{\cdot}\mathbf{2}_8$ hetero-dimer appeared in addition to the homo-dimeric $(\mathbf{2}_7)_2$ and $(\mathbf{2}_8)_2$ peaks. The peak intensity ratios (relative to $[\mathbf{2}_7]^+$ = 100) were 14.8 ± 0.8% for $[\mathbf{2}_8]^+$, 4.0 ± 0.5% for $[(\mathbf{2}_7)_2]^+$, 0.7 ± 0.3% for $[\mathbf{2}_7{\cdot}\mathbf{2}_8]^+$ and 1.6 ± 0.4% for $[(\mathbf{2}_8)_2]^+$. The results indicate that the hetero-dimer can be formed when less destabilized calix[*n*]arene (*i.e.* $\mathbf{2}_7$) exists in excess over the more destabilized calix[*n*]arene (*i.e.* $\mathbf{2}_8$).



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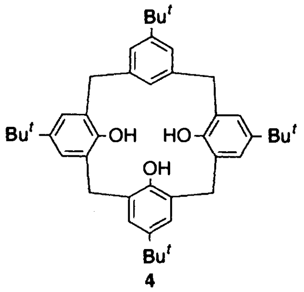

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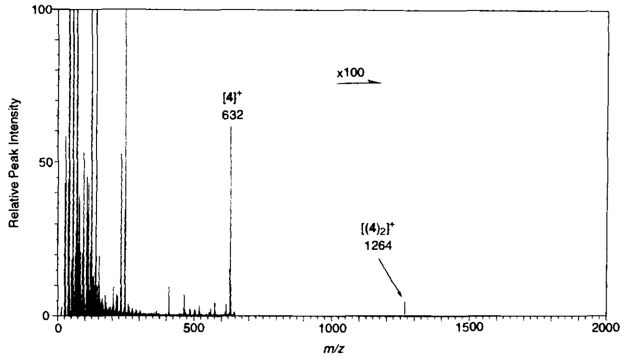

Fig. 5 Positive SIMS mass spectrum for **4** in a 2-nitrophenyl octyl ether (NPOE) matrix: 5 μl of a chlorobenzene solution containing **4** (0.04 mol dm^{-3}) and 5 μl of NPOE were mixed and 1 μl of the mixture was loaded on the silver target

Aggregation of mono-OH-depleted calix[4]arenes

In contrast to calix[*n*]arenes, which can form a 'closed', circular intramolecular hydrogen-bonding array, partially-OH-depleted calix[*n*]arenes lose such a symmetrical structure. In such a case some of the OH groups are exposed to the bulk solvent and therefore can enjoy the formation of intermolecular hydrogen bonds. Previously, Fukazawa *et al.*[12] found that the ^{1}H NMR chemical shifts of a mono-OH-depleted calix[4]arene **3** are concentration-dependent. They attributed this dependency to the aggregation of **3** caused by the intermolecular hydrogen-bond formation between OH groups.[12] This was also confirmed by us with compound **4**.[13] We wanted to know how strong the peaks for the [dimer]$^+$ and [trimer]$^+$ of these calixarenes are, since the aggregate formation can be readily detected even by ^{1}H NMR spectroscopy.

The positive SIMS spectrum for **4** is shown in Fig. 5. The peak which corresponds to [dimer]$^+$ appeared at $m/z = 1265$, but contrary to our expectation, the peak intensity ratio of [dimer]$^+$/[monomer]$^+$ was very weak (0.1%) and the peak which corresponds to [trimer]$^+$ was not observed. First, we considered that the weak peak intensity is due to the low concentration because as shown in Fig. 3 for $\mathbf{2}_7$ and $\mathbf{2}_8$, the plots for the [dimer]$^+$ intensity *vs.* calix[*n*]arene concentration afford a maximum and those for the [trimer]$^+$ intensity *vs.* calix[*n*]arene concentration increase with increasing calix[*n*]arene concentration. However, the peak intensity for the [dimer]$^+$ of **4** did not increase appreciably even though the concentration was enhanced.

It is not yet clear why the [dimer]$^+$/[monomer]$^+$ ratio for **4**, the aggregation of which can be detected by ^{1}H NMR spectroscopy, is much weaker than that for $\mathbf{2}_8$, the aggregation of which cannot be detected by ^{1}H NMR spectroscopy. As a possible rationale, $\mathbf{2}_8$ actually aggregates in solution, but the proton chemical shifts in ^{1}H NMR spectroscopy are less affected by the anisotropy effect of benzene π-systems. Anyhow, the discrepancy observed between ^{1}H NMR spectroscopy and mass spectrometry suggests that in some cases the mass spectroscopic data do not necessarily reflect the solution data. This problem should be further investigated in order to use mass spectrometry as a tool for quantitative analysis.‡

Conclusions

It has so far been believed as a generally accepted concept, that calix[*n*]arenes exist as discrete monomers in solution due to the formation of stable intramolecular hydrogen bonds. This concept can reasonably explain several physical properties characteristic of calix[*n*]arenes *e.g.* solubility in aprotic solvents,[1] ν_{OH} in IR spectra[14] and pK_a values.[15] However, there have appeared a few more recent findings which suggest the aggregation of calix[*n*]arenes in solution: they are related to particularly poor solubility of calix[8]arenes[1] and gel formation.[3] In general, physical methods for molecular-weight determination give the averaged value and therefore are not suitable to the detection of partially aggregated species. Although we know that it is premature to feed the mass spectroscopic data straightforwardly back to the solution, the present study, together with several lines of the above mentioned side-evidence, shows that calix[7]arenes and calix[8]arenes aggregate as a dimer and a trimer, indicating that the intramolecular hydrogen bonds are partially cleaved to allow the formation of intermolecular hydrogen bonds. The unexpected findings are due to the powerful capability of mass spectrometry which features facile molecular-weight determination combined with high sensitivity.

Experimental

SIMS measurements

All experiments were performed using a Hitachi M-2500 mass spectrometer. The spectra were obtained in the positive ion mode. Spectra were recorded immediately after the sample was installed. Xe$^+$ was employed as a primary ion and accelerated at 5.8 kV. Secondary ions were accelerated at 1.7 kV. The mass range *m*/*z* 0–4500 was scanned (scan cycle time 8.0 s). The source pressure was typically *ca.* 1×10^{-4} Pa. The signal intensities were averaged over five scans by using a Hitachi M-0301 data system and recorded as the sum of the corresponding isotopic peaks. For the SIMS experiments the calix[*n*]arene (1.25–100 mmol dm^{-3} in 5 μl chlorobenzene) (1 μl = 1 mm^3) and 2-nitrophenyl octyl ether (NPOE) as a matrix (5 μl) were mixed. Then, 1 μl of the mixture was loaded on the silver target.

Materials

Calix[4]arene $\mathbf{2}_4$, calix[6]arene $\mathbf{2}_6$ and calix[8]arene $\mathbf{2}_8$ were purchased from Sugai Chemical Industry Co. Compounds $\mathbf{2}_n$ ($n = 5$ and 7) were prepared according to the references: $\mathbf{2}_5$[16a,b] and $\mathbf{2}_7$.[16c,d] Mono-OH-depleted calix[4]arene **4** was prepared according to the method described previously.[17] Other reagents were commercially available purest grade and were used without further purification.

Miscellaneous

The ^{1}H NMR apparatus used here was a Bruker ARX300 spectrophotometer.

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‡ The ^{1}H NMR spectra for **3** and **4** were measured in CD_2Cl_2.[12,13] If APCI (Atmospheric Pressure Chemical Ionization) mode is adopted, the sample solutions prepared with these solvents can be subjected to mass spectroscopic measurements. The CH_2Cl_2 solution containing **4** (0.010 mol dm^{-3}) gave [dimer]$^+$/[monomer]$^+$ = 0.10 ± 0.03, which was much greater than that obtained from positive SIMS. Unfortunately, APCI mode could not be applied to $\mathbf{2}_8$ because of the molecular-weight limitation (< 2000).

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