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Review Commentary

Mass spectrometry as a tool in dendrimer chemistry: from self-assembling dendrimers to dendrimer gas-phase host–guest chemistry†

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ABSTRACT: Mass spectrometry has played a significant role in dendrimer chemistry, because it serves as an excellent analytical means to determine the purity and analyze the nature of defects even for higher generations. However, a mass spectrometer can also be used as a laboratory to study isolated dendrimer molecules in the gas phase or their host–guest complexes. Since the properties of molecules under environment-free conditions are often quite different from those in solution, their gas-phase chemistry provides valuable new insight into properties which cannot easily be studied in solution. This article summarizes some of our work on characterizing self-assembling metallo-supramolecular dendrimers, on analyzing ionization artifacts, on the differentiation between several, sometimes even isomeric defects through tandem MS experiments, and finally on the analysis of a surprisingly clear dendritic effect occurring in the fragmentation of dendritic host–guest complexes. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: supramolecular chemistry; mass spectrometry; gas-phase chemistry; dendrimers; self-assembly; molecular tweezers; defects; fragmentation mechanisms; dendritic effects

INTRODUCTION

Dendrimers are onion-type polymers which bear branching units in each shell.[1] Consequently, the number of branches and their molecular masses increase exponentially from the core outwards. Since the synthesis of dendrimers most often involves the repetition of two distinct steps for the formation of each generation, the building blocks of the *n*th shell are similar to those in the $(n+1)$th shell, but are located in different microenvironments. This usually causes the NMR spectra of higher-generation dendrimers to exhibit broad signals which cannot easily be assigned to individual shells. The precise characterization of dendrimers thus becomes increasingly difficult with higher generation numbers. In particular, it is hardly possible to provide evidence for their structural integrity or for the presence of defects such as missing branches. Even if the presence of defects might be detected by NMR methods, for example, through signal integrals, their exact nature will hardly become clear on the basis of NMR experiments only. Here, mass spectrometry is an extremely helpful tool.

Indeed, the history of dendrimer chemistry nicely illustrates that the development of a field of research depends much on the availability of suitable methods. When Buhleier, Wehner, and Vögtle published the first synthesis of what back in 1978 was coined 'cascadanes,'[2] an unambiguous characterization of dendrimers with high masses was very difficult. Mass spectrometry would have been the method of choice, but in 1978, none of the nowadays routinely used soft ionization techniques existed. Consequently, it took almost a decade[3] for dendrimer chemistry to develop into a field of intense research. Nowadays, matrix-assisted laser desorption-ionization (MALDI) mass spectrometry is considered to be a highly valuable tool for the routine characterization of dendrimers due to the large mass range of the mass analyzers usually coupled to the MALDI ion source.[4] Also, electrospray ionization (ESI) has been used to ionize dendrimers and transfer them into the gas phase as

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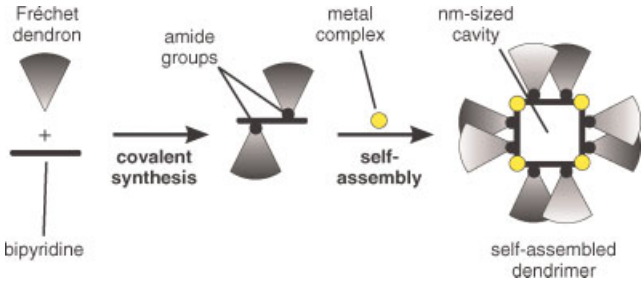
intact species.[5] A central question for a precise mass spectrometric characterization of dendrimers is whether additional signals below the molecular mass of the structurally perfect species are due to fragments formed during the ionization or due to defects[6] originating from the synthesis. In order to distinguish both, it is highly desirable to understand the fragmentation patterns of dendrimer ions in the gas phase which can be unraveled by tandem mass spectrometric experiments (MS/MS).[7] Mass spectrometry may provide even more information, for example, on different sites of protonation in the gas phase[8] as compared to solution, on the self-assembly of dendrimers,[9] or on weak, non-covalently bound host–guest complexes of dendritic species.[10] These results demonstrate the remarkable power of mass spectrometry for a detailed characterization of dendrimers without which the fast pace of development in this field would not have been possible.

Here, we discuss four different aspects of mass spectrometry as a tool for dendrimer chemistry. First, the self-assembly of metallo-supramolecular dendrimers with a cavity at the central core is discussed. Since these species form dynamic combinatorial libraries, mass spectrometry and NMR spectroscopy provide complementary data without which a characterization of these species would be impossible. The second part reports two examples for the generation of artifacts during electrospray and MALDI. Third, MS/MS experiments with mass-selected dendrimer ions are also quite useful to distinguish different, sometimes even isobaric defects. Finally, the last part summarizes a study on host–guest complexes generated from dendritic viologen guests bound inside a Klärner tweezer.[11] An interesting dendritic effect on the fragmentation mechanisms of these host–guest complexes is observed, which can only be examined in the gas phase in the absence of solvents and counter ions.

ANALYTICAL CHARACTERIZATION: DYNAMIC COMBINATORIAL LIBRARIES OF SELF-ASSEMBLING DENDRITIC METALLO-SUPRAMOLECULAR SQUARES

Self-assembly under thermodynamic control is an efficient strategy for the synthesis of larger, more complex species from simple, but suitably programmed building blocks.[12] Scheme 1 shows the application of this approach to the generation of metallo-supramolecular dendrimers with a nanometer-sized cavity at their cores.[13] In a first synthetic step, dendritic wedges are attached to the 3,3′ carbons of 4,4′-bipyridines through amide groups. Mixing them with suitable metal corners such as (dppp)Pd(II) and (dppp)Pt(II) triflates provides access to metallo-supramolecular dendrimers which are of particular interest, (i) because their cavity with its metal–metal edge length of ca. 1.1 nm[14] is suited for guest encapsulation, (ii) because eight amide groups



Scheme 1. Strategy to self-assembling dendrimers: 4,4′-bipyridines decorated with Fréchet dendrons self-assemble with the appropriate metal corners to yield dendron-decorated squares with a nanometer-sized cavity. Since dendrons are attached to the bipyridine through amide bonds, the cavity is surrounded by eight hydrogen bonding-sites

around the seam of the cavity are capable of molecular recognition through hydrogen bonding, while the interior of the cationic squares is hydrophobic and might thus create a special environment for anions with extended hydrophobic surfaces, (iii) because the square is embedded into a dendritic shell, which provides a particular microenvironment and in future may be used to control solubility, and (iv) because a multitude of different isomeric structures can co-exist and interconvert under thermodynamic control in what can be considered as a dynamic library.[15]

Since self-assembly is a reversible process, any self-assembling species can be regarded as part of a dynamic library in which the free building blocks and intermediates on the way to the complete assembly are the minor components coexisting with the final assembly as the major component. Beyond that, the dendritic squares (Scheme 2) discussed here exist as a mixture of up to 54 different isomeric squares due to the positions of the dendrons above and below the square plane (up-down isomers) and due to the torsional angle around the bipyridine aryl–aryl bond which leads to dendrons pointing towards the cavity or away from it (in/out isomers). The superposition of both types of isomers thus gives rise to the dynamic library of up to 54 square isomers shown in Scheme 3.

In such a situation, NMR spectroscopy suffers from a superposition of a large number of sets of signals. Indeed, this was observed for the squares bearing (dppp)Pt(II) corners (dppp = bis-(diphenylphosphino)propane) which gave highly complex ^{1}H and ^{31}P NMR spectra at room temperature. For analogous squares bearing (dppp)Pd(II) corners, simple spectra with only one set of signals were obtained under the same conditions. A temperature dependent study revealed that this finding is due to a ligand exchange process which is remarkably faster for the Pd(II) squares as compared to their Pt(II) analogues. However, it is impossible to decide from the NMR spectra whether the library contains exclusively squares. Other species such as triangles, pentagons, or hexagons could be present. Even open-chain oligomers could be expected.

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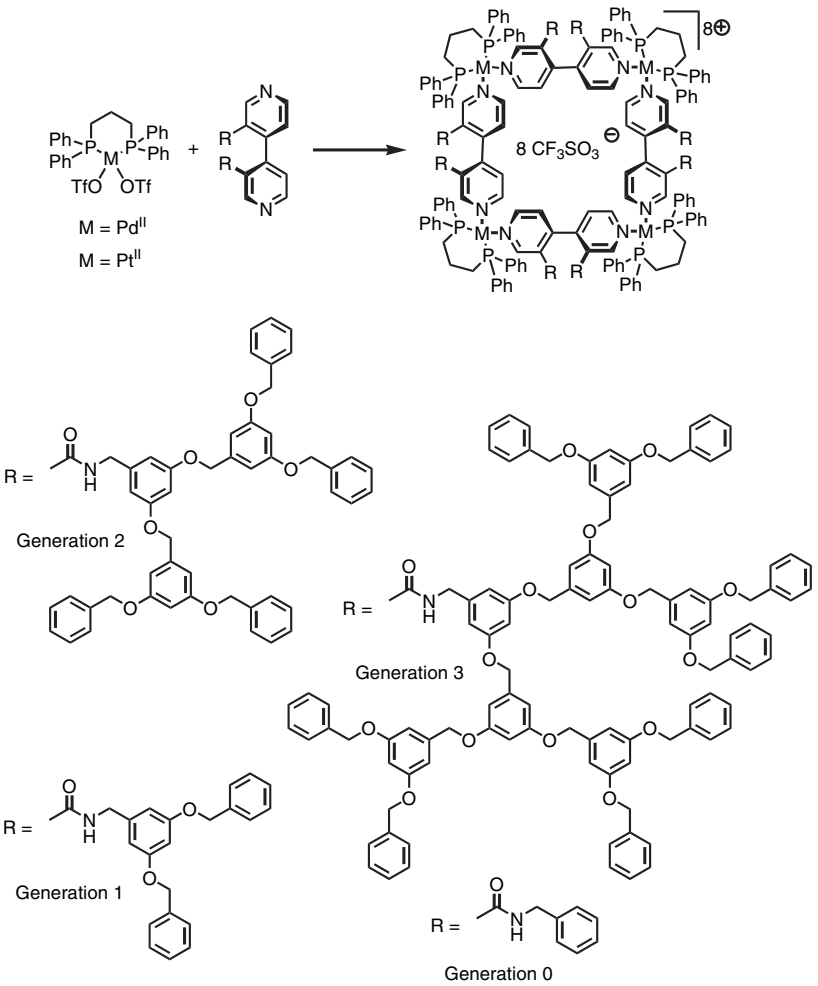

Scheme 2. Metallo-supramolecular squares decorated with Fréchet-dendrons of generation 0 (G0) to generation 3 (G3)

Mass spectrometry is the method of choice to answer this question.[16] Figure 1(a,b) shows the ESI-FTICR mass spectra of the second generation squares bearing (dppp)Pd(II) and (dppp)Pt(II) corners, respectively. Both spectra are quite clean and the experimental isotope patterns are in good agreement with those calculated on the basis of natural abundances. In both spectra, defects are observed. Since two different batches of the dendron-substituted bipyridine ligand were used, the defects differ in both spectra. While missing G1 dendrons are detected in Fig. 1a, Fig. 1b shows signals for squares lacking one G2 dendron. The most important conclusion from these spectra, however, is that the equilibrium does not contain significant amounts of any other cyclic or open-chain oligomer. Squares are formed exclusively. This information together with the complex NMR spectra permits only one conclusion: the complexity of the NMR spectra originates from the presence of at least a significant number out of the 54 possible isomers.

Mass spectrometry can go beyond the analytical characterization in terms of exact mass, charge state, isotope pattern, and detection of defects. Ligand exchange reactions can be examined using the mass spectrometer as a detector for what species are present in solution. These experiments are complemented by temperature-dependent NMR experiments which revealed ligand exchange reactions to interconvert different isomers into each other. This process proceeds significantly faster for Pd(II) squares (one set of NMR signals at room temperature) as compared to the Pt(II) analogues (complex spectra at room temperature, one set of signals at 393 K). The ligand exchange in solution can easily be followed by mass spectrometry (Fig. 2). When two different Pd(II) squares (e.g., G0 and G1) are mixed, an ESI mass spectrum recorded after ca. 30 sec (Fig. 2a) shows inter alia five signals for all different mixed forms in a close-to-statistical ratio (statistical expectation: 1 : 4 : 6 : 4 : 1). Consequently, the ligand exchange within Pd(II) squares is so fast that only the equilibrium situation can be observed. In marked contrast, the analogous Pt(II) squares exchange ligands much more slowly and reach the equilibrium only after 2 days (Fig. 2b). These results are in excellent agreement with the NMR data.

These experiments demonstrate that ESI mass spectrometry yields valuable information on dendrimer size, defects in the dendrimer structure, and even on their

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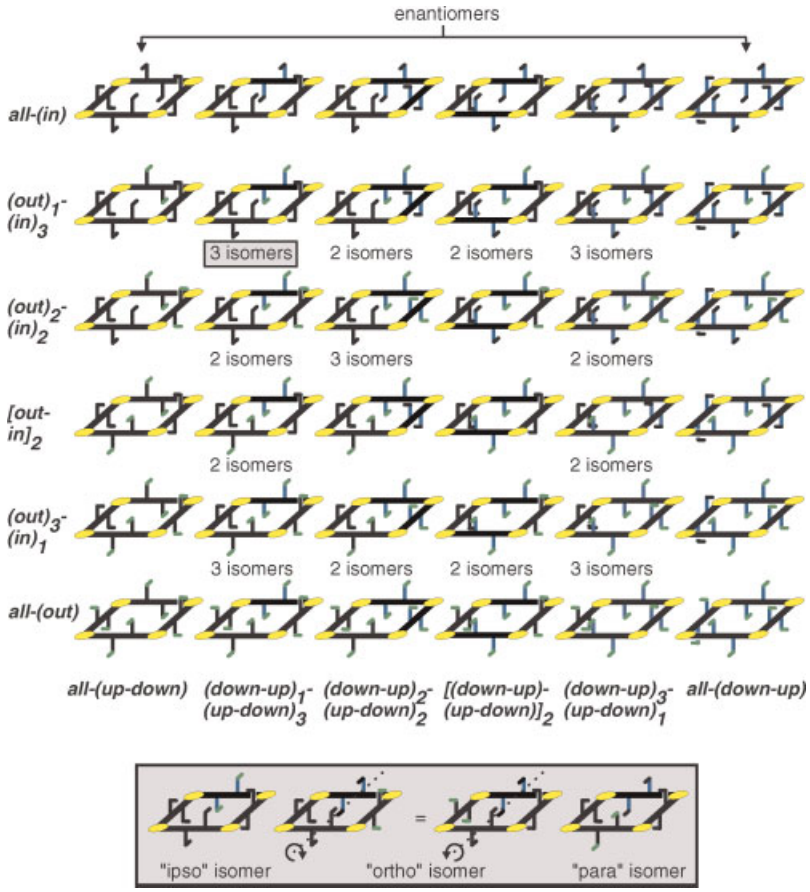

Scheme 3. A superposition of up-down and in/out isomerisms (as indicated by the flags attached to the square scaffolds) give rise to 54 possible isomers which interconvert reversibly with each other. Some of them are enantiomers as indicated above for one example. For some combinations of up-down and in/out isomers, several possibilities exist as exemplarily shown below for the $(out)_1-(in)_3$/$(down\text{-}up)_1-(up\text{-}down)_3$ combination (see small box in second row)

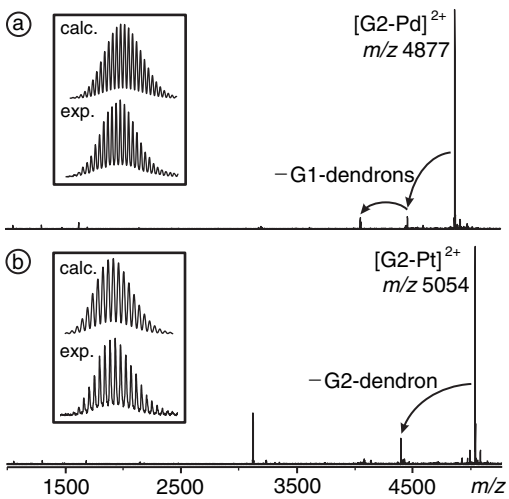

Figure 1. Electrospray ionization Fourier-transform ion-cyclotron resonance (ESI-FTICR) mass spectra of 400 μM acetone solutions of second generation Pd(II) and Pt(II) squares

reactivity in solution. This is not only possible for covalently bound dendrimers, but also for self-assembling species with their relatively weak bonds which often render a mass spectrometric analysis difficult.

IONIZATION ARTIFACTS: FALSE-NEGATIVE RESULTS

For a reliable characterization, it is important to know whether and under what conditions the ionization of dendrimers might lead to the generation of artifacts producing signals in the mass spectra for defects which are not present in the sample. An earlier study indicated that MALDI mass spectrometry might lead to the decomposition of photosensitive dendrimers upon irradiation with the MALDI laser.[17] In this study, the photofragments were unambiguously formed during ionization and it was clear that they do not originate from synthesis. Other studies described matrix effects on the mass spectra of dendrimers.[18] Consequently, it is not *a priori* clear that MALDI mass spectrometry always

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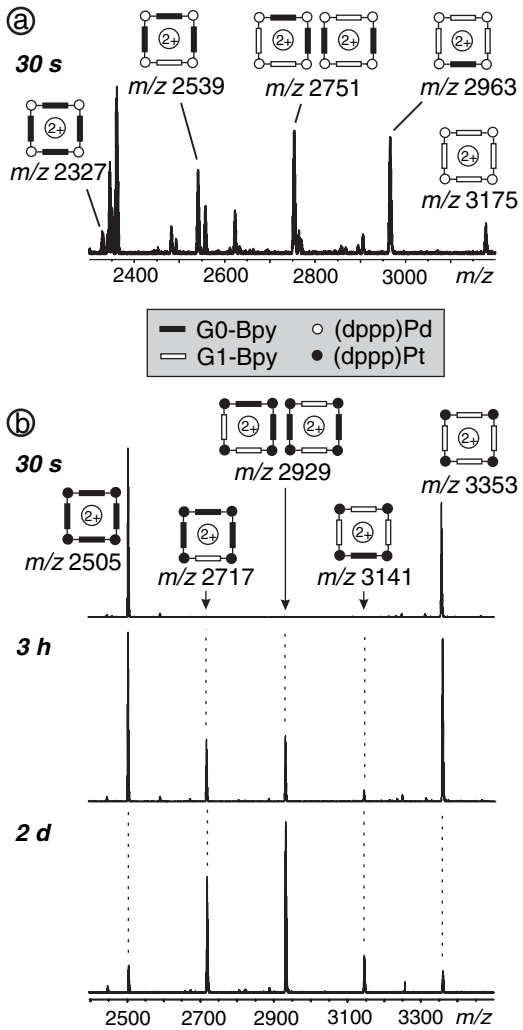

Figure 2. ESI-FTICR mass spectra of 1:1 mixtures of (a) G0 and G1 Pd(II) squares 30 sec after mixing both squares, and (b) of G0 and G1 Pt(II) squares 30 sec, 3 h and 2 days after mixing, respectively

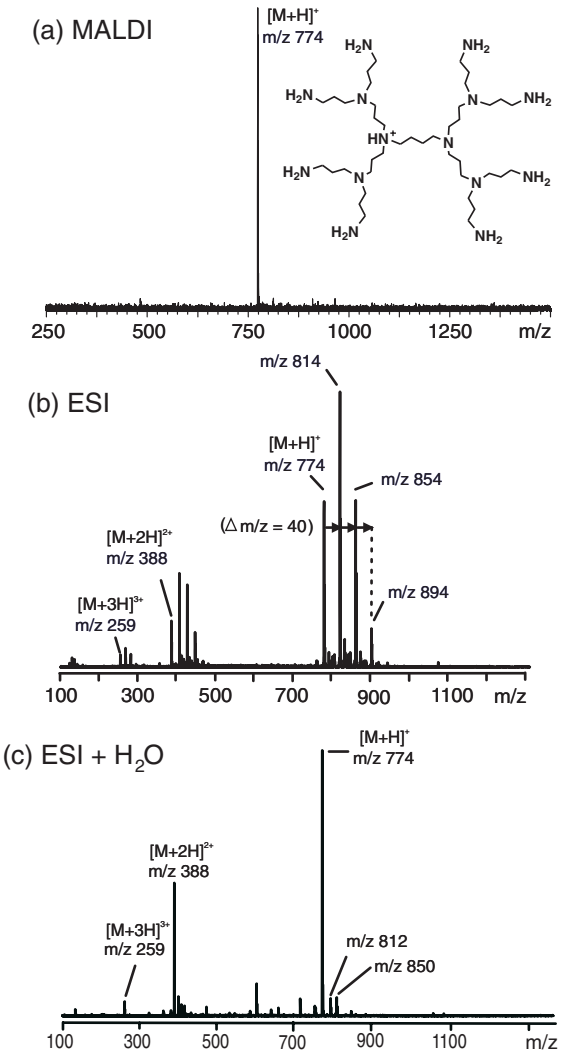

Figure 3. (a) MALDI mass spectrum (matrix: 2,5-dihydroxy-benzoic acid = DHB) of the second generation POPAM dendrimer shown in the inset. (b) ESI-FTICR mass spectrum of a ca. 50 μM solution of G2 POPAM dendrimers in methanol with 1% acetic acid. (c) ESI-FTICR mass spectrum of G2 POPAM dendrimers obtained under the same conditions, but with a dendrimer sample which was stirred in water before ionization

reliably reflects the composition of the sample and one might arrive at the conclusion that ESI may be a better ionization method due to its inherent softness and the absence of any irradiation during the ionization process.

In a recent study,[19] we reported artifacts in the ESI mass spectra of polypropyleneamine (POPAM) dendrimers which were not observed in the corresponding MALDI mass spectra. Figure 3 depicts these findings for a second generation POPAM dendrimer. While only the signal for the singly protonated parent ion appears in the MALDI mass spectrum (Fig. 3a), the ESI mass spectrum (Fig. 3b) contains not only doubly and triply charged species, but also a series of signals above the expected mass with a repetitive distance of 40.031 amu. This mass difference corresponds to additional C_3H_4 fragments in the dendrimer structure. Since the synthesis of POPAM dendrimers involves a Michael addition step with excess acrylonitrile followed by a catalytic hydrogenation of the resulting nitrile-terminated dendrimers, one may conclude that some residual acrylonitrile is reduced to the corresponding imine and undergoes exchange of its NH group against one of the *N*-termini of the dendrimer. Such a reaction would give rise to imine-terminated dendrimer branches. However, ^{1}H and ^{13}C NMR experiments confirm the MALDI results and do not exhibit any signals for such imines above the signal-to-noise ratio. Consequently, we conclude that they can only be present in the sample to a very minor extent. ESI thus overestimates their abundance drastically.

The imine nature of the impurities is supported by the fact that these artifacts almost completely vanish from the ESI mass spectrum when the dendrimer is stirred in water for some minutes before ionization. In turn, the addition of propionic aldehyde to a methanol solution of the

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dendrimer increases the intensity of these signals. The same kind of artifacts is observed for higher generation POPAM dendrimers. In addition, the defects described earlier by Meijer *et al*.[5b] are found then. This example shows that ESI may provide biased data on the purity of dendrimers.

In turn ESI mass spectrometry provides a clear picture of the purity of dendrimers persulfonylated in their periphery (Fig. 4).[20] Clearly, only signals for pseudomolecular ions are observed in the ESI mass spectrum. Signals for defects are hardly visible. The MALDI mass spectrum, however, exhibits a large number of signals corresponding to defects in which sulfonyl groups from the periphery have been replaced by hydrogen atoms. Without the knowledge from the ESI-MS experiment that the dendrimer samples are pure, the MALDI mass spectra may be quite misleading for the synthetic chemist, since exactly the same series of defects would be expected from an incomplete substitution of the periphery with sulfonyl groups. The MALDI mass spectrum thus suggests that the dendrimer synthesis failed although this is certainly not true.

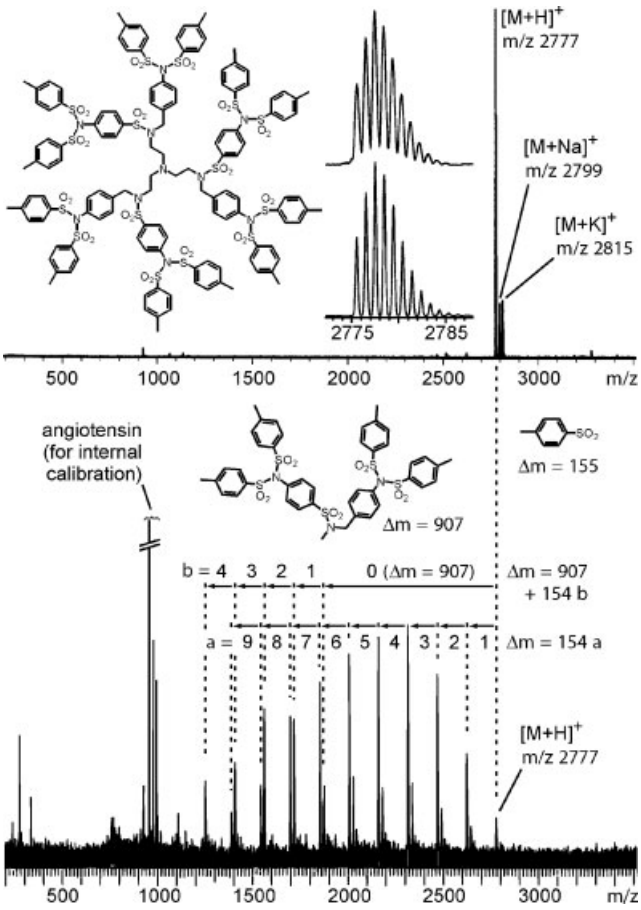

Figure 4. Top: ESI mass spectrum of a 50 μM methanol solution (1% acetic acid) of the persulfonylated dendrimer shown in the inset. Bottom: MALDI mass spectrum (matrix: DHB) of the same dendrimer. Note that the loss of 907 amu corresponds to a fragmentation reaction in the gas phase as evidenced by tandem MS experiments with the ESI-generated, mass selected parent ion

The sulfonyl/proton exchange occurs during the irradiation with the MALDI laser when acidic 2,5-dihydroxybenzoic acid (DHB) is used as the matrix. It is, however, not a photochemical reaction. Neither UV/VIS spectroscopy shows the dendrimers to absorb at the laser wavelength of 337 nm nor are signals for dendrimers observed in the absence of any matrix in an LDI experiment. The latter finding indicates that the laser beam is merely reflected by the sample support and that no light energy is absorbed by the dendrimer alone. Also, the acidity of the matrix is highly important (Fig. 5). With

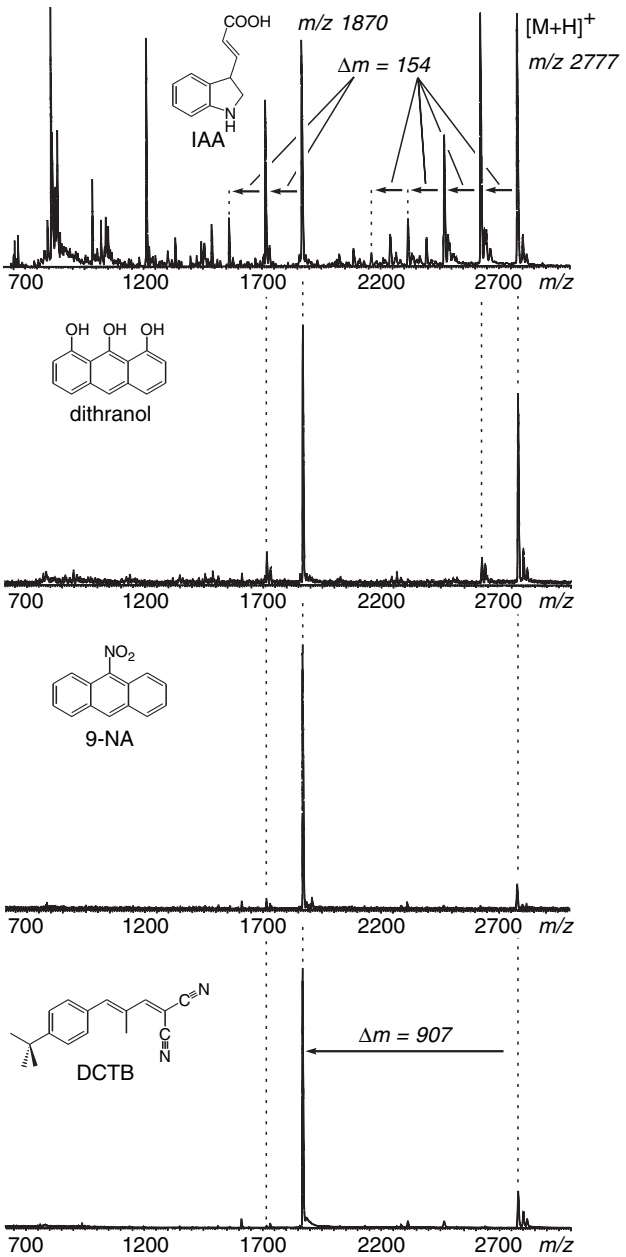

Figure 5. MALDI mass spectra of the second generation persulfonylated dendrimer (Fig. 4) in different matrices of decreasing acidity. From top to bottom: IAA, dithranol, 9-NA, DCTB. All spectra were obtained under the same conditions

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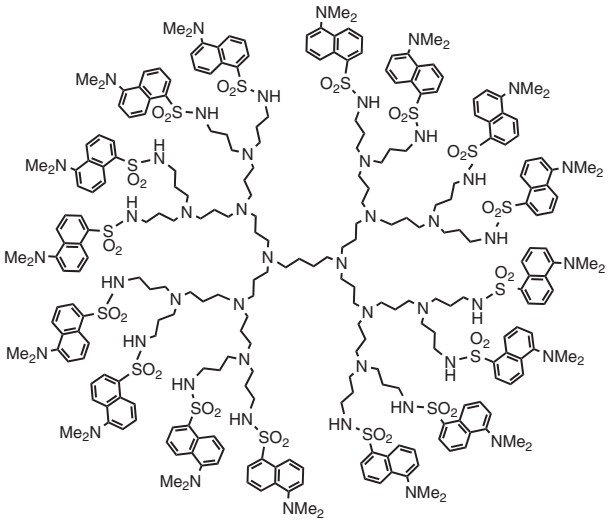


Scheme 4. Dansyl-decorated G3 POPAM dendrimer

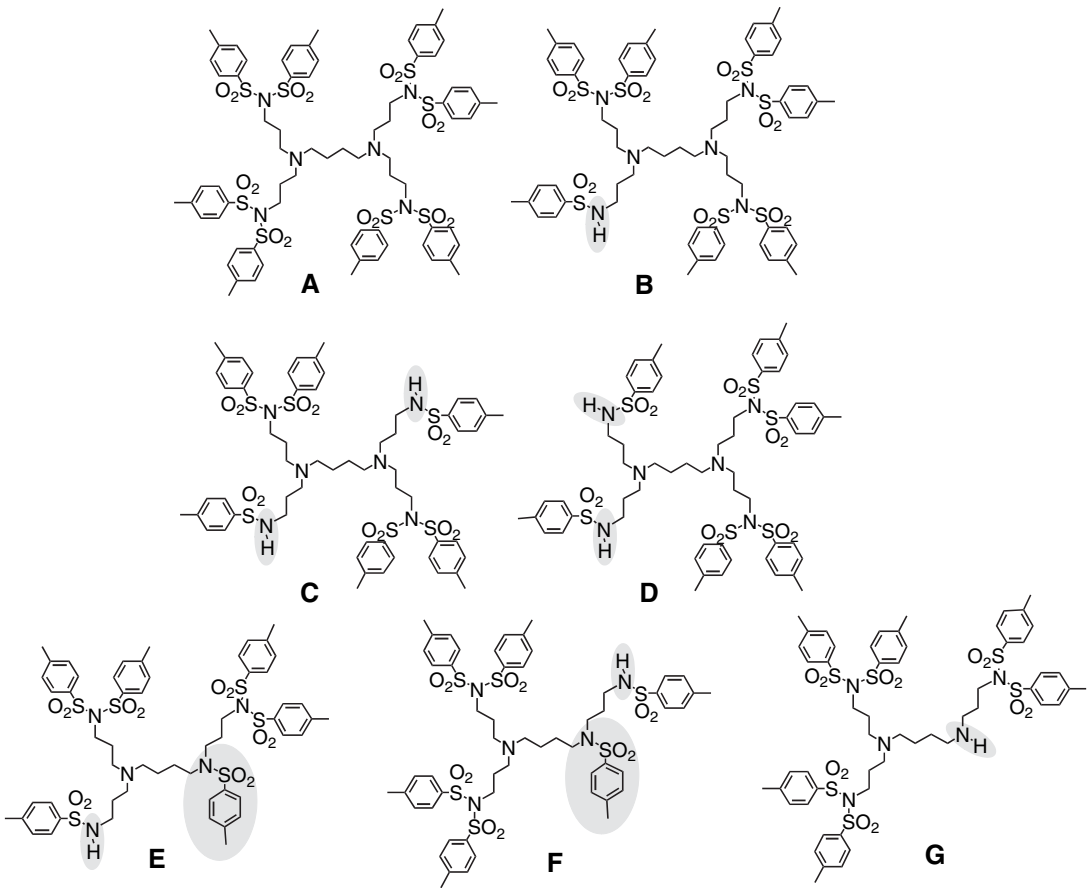
non-acidic matrices, parent ions are observed only accompanied by a fragment from an MS/MS-confirmed gas-phase dissociation reaction appearing at a distance of 907 amu below the parent ion.

Similarly, if the dendron periphery is decorated with dansyl groups (Scheme 4), which indeed absorb the laser light, the same degradation occurs in acidic matrices.[19] The acid-mediated thermal reaction prevails and leads to the replacement of dansyl groups against protons as described above ($\Delta m = 233$ amu). In the absence of a matrix (the LDI experiment), photochemical cleavages can nevertheless be observed which lead to a different series of fragmentation products with peak distances of $\Delta m = 235$ amu, because the sulfonyl group leaves together with a proton from the dendrimer backbone likely generating imino termini.

The two examples presented in this chapter demonstrate both ionization methods to generate artifacts under certain circumstances. In both cases false-negative results are obtained. Consequently, the synthetic chemist using mass spectrometry for the characterization of dendrimers should crosscheck seemingly negative results by using different matrices and/or by comparing different ionization methods.

DENDRIMER PURITY AND STRUCTURE: DIFFERENTIATING DEFECTS BY TANDEM MS EXPERIMENTS

Attempts to pertosylate G1 POPAM dendrimers resulted not only in the fully substituted product **A**, but also in mixtures of defect variants **B–G** as shown in Scheme 5.[20,21]



Scheme 5. Persulfonylated G1 POPAM dendrimer A and defects B–G generated during the synthesis

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The ability of an FTICR mass spectrometer to select only one out of a large number of different ions present in the instrument cell allows us to select defect ions of a certain molecular mass which can then be studied by collision-induced fragmentation experiments with respect to their fragmentation reactions. Singly protonated, mass-selected dendrimer ions $[\mathbf{A}+\mathrm{H}]^+$ cleanly fragment as described earlier by Meijer *et al*.[8] (Scheme 6, Fig. 6, top trace).

A non-symmetrical defect dendrimer such as **B** can be protonated at each of the two central amino nitrogen atoms. Consequently, two different fragments are possible as seen in the MS/MS spectrum (Fig. 6, second row). When two sulfonyl groups are missing, two isomeric structures are possible: One symmetrical isomer **C** with one missing sulfonyl group on each side of the dendrimer and a second isomer **D** which lacks two sulfonyl groups on the same side of the molecule. Mass selection of the ions at *m/z* 1241 and collision-induced fragmentation (Fig. 6, third row) results in three different fragments. This is only possible, if both isomers significantly contribute to the mass-selected ions. From this spectrum, we can safely conclude that both isomers are formed in significant amounts. Finally, defects are formed in which the dendrimer scaffold is not intact anymore. For those structures formally lacking one propylene amine branch and two sulfonyl groups, isomers **E**–**F** may be generated. The MS/MS spectrum (Fig. 6, bottom), however, nicely shows that isomer **E** is the major structure contributing to the ions at *m/z* 1184. The large intensity of the fragment signal at *m/z* 648 indicates the presence of **E**, while a fragment with *m/z* 802 would be expected from **F** and **G**. The corresponding signal is hardly visible in the MS/MS spectrum. Consequently, **F** and **G** are only very minor components among the ions at *m/z* 1184. For the second-generation dendrimers, similar arguments apply and these data make clear that the structure of different defect structures can be assigned through tandem MS experiments.

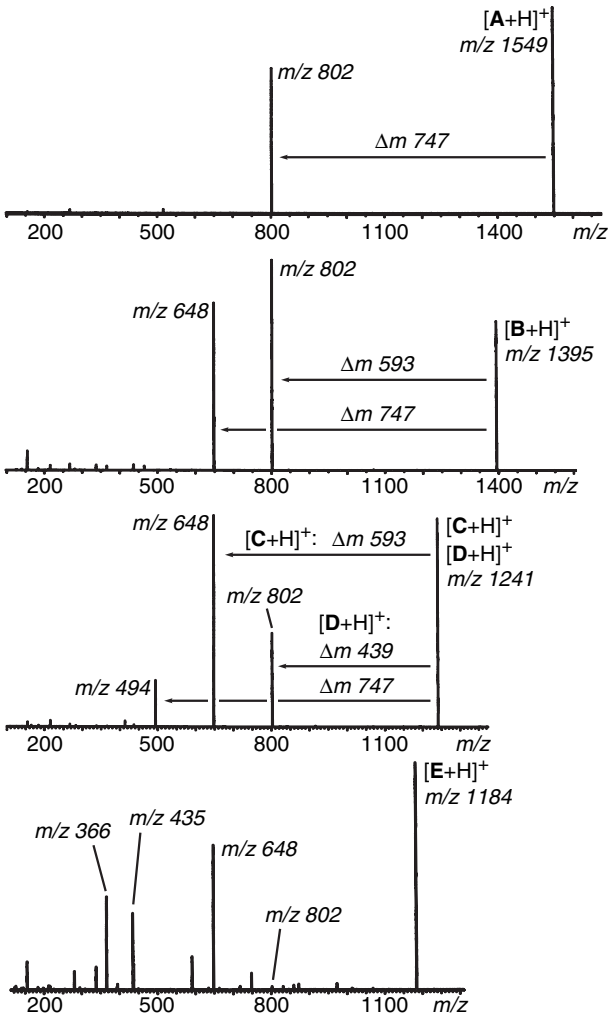
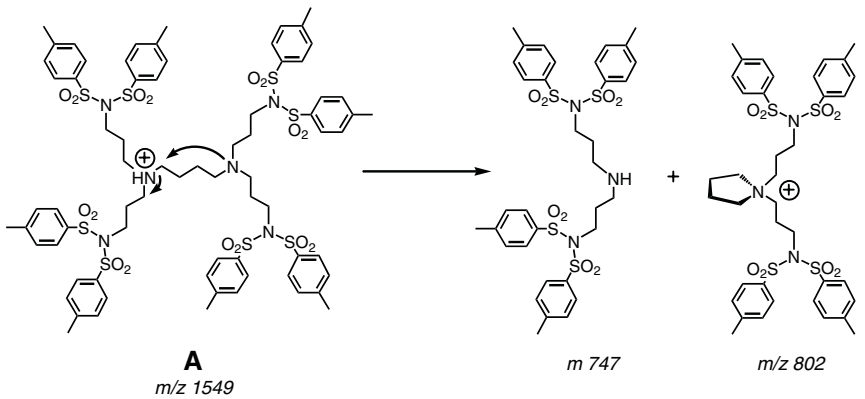


Figure 6. Collision-induced fragmentation reactions with mass-selected $[A+H]^+$ (top trace) and its defects $[B+H]^+$, a mixture of $[C+H]^+$ and $[D+H]^+$, and $[E+H]^+$ (from top to bottom)



Scheme 6. Fragmentation mechanism of singly protonated dendrimer A

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DENDRITIC EFFECTS: GAS-PHASE HOST–GUEST CHEMISTRY OF DENDRITIC VIOLOGEN-TWEEZER COMPLEXES

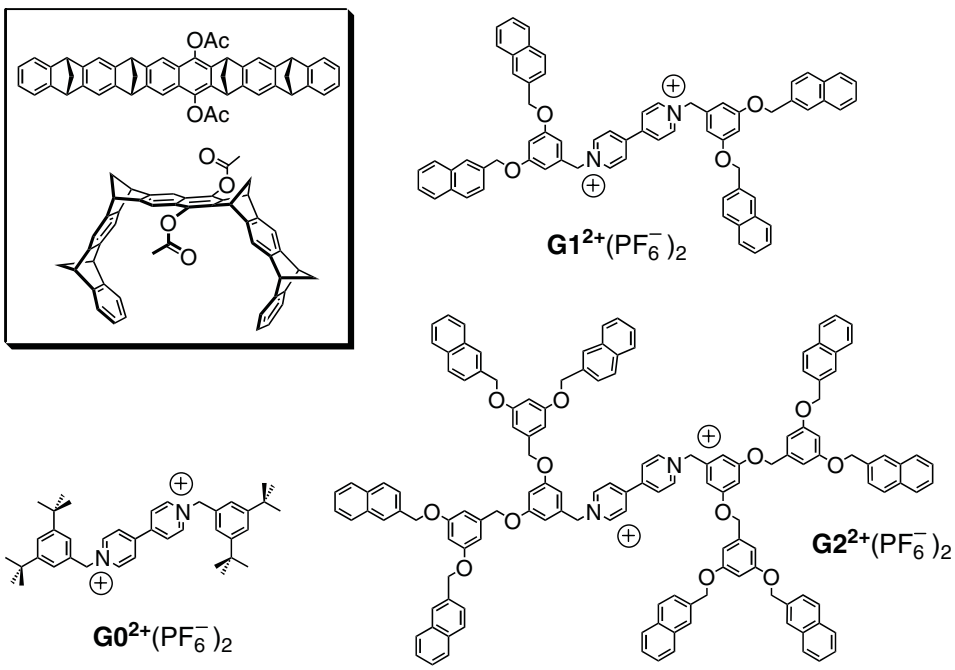
Non-covalent complexes are a particular challenge for mass spectrometry, because it is often rather difficult to ionize them as intact species due to the weak interactions within the complexes. From solution studies, it was known that the Klärner tweezer shown in Scheme 7 (inset) with its extended aromatic surfaces binds electron-deficient viologen dications. This is also true for the dendron-decorated viologens in Scheme 7. All attempts to generate the dication $\mathbf{G0}^{2+}$ without accompanying counterions in the absence of the tweezer failed. Likely, this dication is a short-lived metastable ion, which on the timescale of the FTICR mass spectrometric experiments decomposes due to charge repulsion before it can be detected. Interestingly, the $\mathbf{G1}^{2+}$ dication is stable enough to be detected under extremely mild ionization conditions, while it is no problem at all to produce naked $\mathbf{G2}^{2+}$. Clearly, there is a trend towards higher stabilities.

The first interesting result is found when the molecular tweezer is added to the sample solutions.[22] The mass spectra change drastically and show rather intense signals for the 1:1 complexes which are formed either as singly charged complexes due to the presence of an anion in the complex or as dications without accompanying anions. This is even true for $\mathbf{G0}^{2+}$ indicating that the tweezer is capable of stabilizing the dication, presumably by charge-transfer interactions.

The second surprise was observed in the collision-induced dissociation reactions (Fig. 7). When the first isotope peak of the tweezer-$\mathbf{G0}^{2+}$ dication was isolated in the FTICR cell and subjected to collisions, we expected to see the loss of the tweezer followed by an immediate consecutive fragmentation of the remaining dication (bottom pathway in Scheme 8). However, a fragment was observed which corresponds to the loss of a 3,5-di-tert-butylbenzyl cation (Fig. 7a) giving rise to the singly charged tweezer-benzylbipyridinium intermediate shown in the upper pathway in Scheme 8. From this MS/MS experiment, we conclude that at least part of the tweezer-$\mathbf{G0}^{2+}$ dication fragments through this mechanism and that benzyl-N bond cleavage can at least compete with the tweezer loss.

The FTICR mass spectrometer permits to conduct a double resonance experiment, in which this intermediate at *m*/*z* 1059 is expelled from the cell during the whole reaction time. Thus, all its consecutive fragments should vanish as well. This experiment results in a drastic decrease of the benzylbipyridinium fragmentation product at *m*/*z* 359 (Fig. 7b) revealing that the tweezer-$\mathbf{G0}^{2+}$ complex almost completely decomposes through the upper channel in Scheme 8.

The same reactivity is observed for the first-generation viologen-tweezer complex. However, the MS/MS spectrum of the complex of second-generation viologen and tweezer is completely different. Here, the major fragmentation product is the viologen dication formed through tweezer loss. The intermediate of the upper



Scheme 7. Molecular tweezer (inset) and dendron-decorated viologen dications $\mathbf{G0}^{2+}$–$\mathbf{G1}^{2+}$ which form host–guest complexes with the tweezer in dichloromethane

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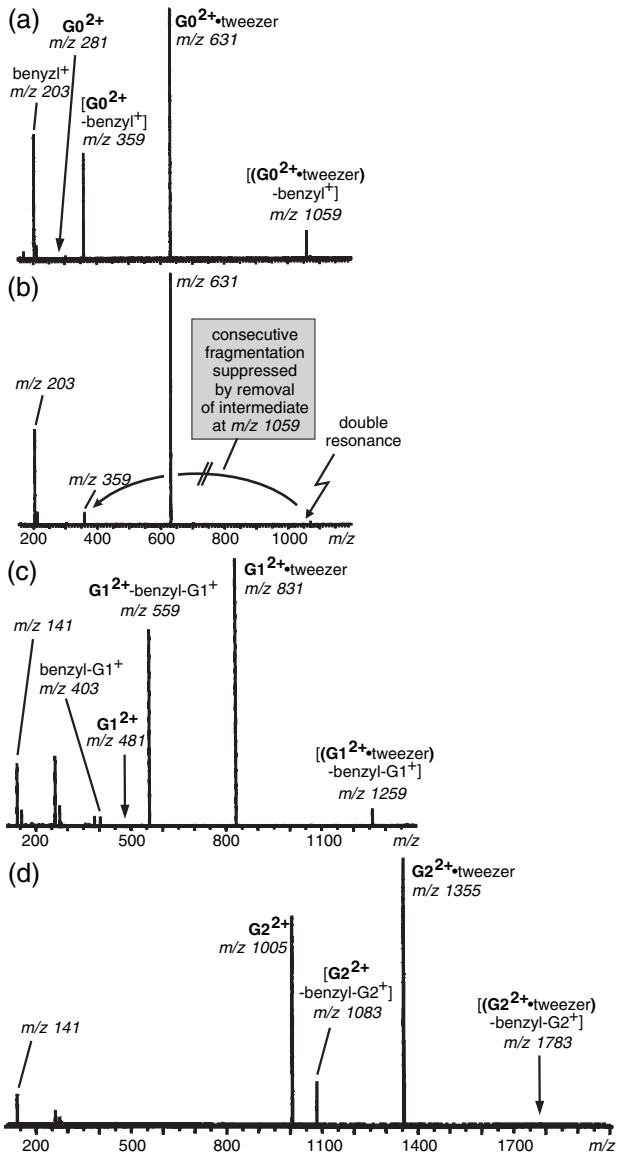
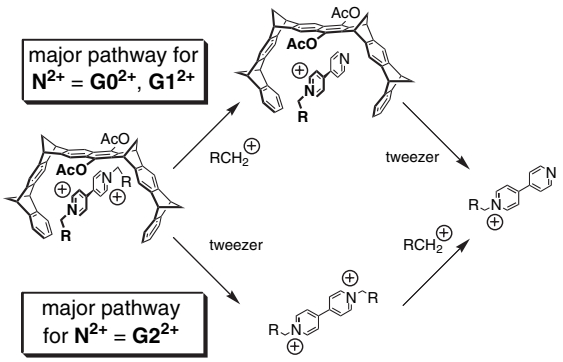


Figure 7. (a) Collision-induced dissociation (CID) of mass selected tweezer-$\mathbf{G0^{2+}}$ dications. (b) Double resonance experiment with the same ions, in which the fragment at m/z 1059 was ejected from the reaction cell during the whole experiment. (c) CID experiment with the tweezer-$\mathbf{G1^{2+}}$ complex. (d) CID experiment with tweezer-$\mathbf{G2^{2+}}$ complex revealing a complete change in reactivity. Tweezer loss is the major fragmentation pathway here giving rise to dicationic $\mathbf{G2^{2+}}$ at *m/z* 1005

channel in Scheme 8 is completely absent. Clearly, the reactivity switches between the two channels depending on the size of the dendrons.

An explanation for this surprisingly clear dendritic effect invokes stabilization of the dications through backfolding of the dendron branches as suggested by molecular modeling (Fig. 8). While $\mathbf{G0^{2+}}$ is unable to backfold the benzyl substituents and thus does not benefit from internal solvation through the formation of intramolecular charge-transfer-complexes, $\mathbf{G1^{2+}}$ can approach the viologen core with the naphthylmethyl



Scheme 8. Two competing channels for the decompositions of tweezer-dendrimer complexes in the gas phase. The reactivity switches from the upper channel to the lower channel depending on the dendron size—a remarkable dendritic effect, which is not found in solution, where counterions and solvent molecules stabilize the viologen dications.

groups into a geometry favorable for dication stabilization. Even more so, $\mathbf{G2^{2+}}$ not only has more flexibility, but also provides the electron-rich, oxygen-substituted branching units which can form internal charge-transfer complexes even more efficiently. This explanation is not only in line with the trend of dication stability observed when the viologens were ionized in the absence of the tweezer. It also rationalizes the reactivity change. If tweezer binding competes with internal solvation through backfolding, the binding energy of the tweezer should decrease with increasing dendron size. Vice versa, increasing dendron size stabilizes the dication and thus reduces charge repulsion which certainly is a significant driving force for the cleavage of benzyl-*N* bonds that produces two separated monocations.

The gas-phase experiments with the tweezer-dendrimer host–guest complexes add valuable insight into the reactivity of such species which cannot be gained from solution studies. In solution, not only solvent molecules change the properties of the complexes. Even more important, the counterions significantly stabilize the dications and reduce charge repulsion. Also, reversible binding which constantly leads to an exchange of the guest hampers the analysis of such a reaction. Such an exchange is not possible in the gas phase, because the complexes are isolated from each other in the high vacuum of a mass spectrometer.

CONCLUSIONS

The work summarized here spans from the characterization of dynamic libraries of self-assembling metallosupramolecular dendrimers to the gas-phase reactions of host–guest complexes with dendritic viologen guests. Mass spectrometry is a valuable tool for studying fragmentation mechanisms and for distinguishing defects

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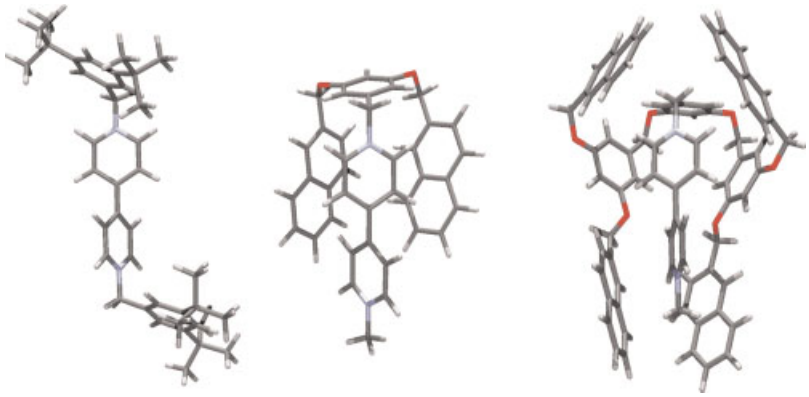

Figure 8. Lowest-energy conformations of the viologen derivatives substituted by two 3,5-di-*t*-butylbenzyl groups (**G0**$^{2+}$), by methyl and the G1 dendron (model compound for **G1**$^{2+}$), and by methyl and the G2 dendron (model compound for **G2**$^{2+}$) calculated by Monte-Carlo conformer search using the MMFF force field implemented in SPARTAN 04

formed in an imperfect synthesis from artifacts originating in the ionization procedures. Mass spectrometry also provides the experimental methodology to study dendrimers under environment-free conditions which provides insight into their intrinsic reactivity unaffected by solvent molecules and counterions. Thus, mass spectrometry is much more than merely a tool for the characterization of dendrimers and its potential for dendrimer chemistry has not yet fully been appreciated by many dendrimer chemists. Nevertheless, we are confident that dendrimer chemistry will see many more applications of mass spectrometry with all its facets in the future.

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REFERENCES

1. (a) Zeng F, Zimmerman SC. *Chem. Rev.* 1997; **97**: 1681–1712. (b) Archut A, Vögtle F. *Chem. Soc. Rev.* 1998; **27**: 233–240. (c) Smith DK, Diederich F. *Chem. Eur. J*. 1998; **4**: 1351–1361. (d) Bosman AW, Jansen HM, Meijer EW. *Chem. Rev.* 1999; **99**: 1665–1688. (e) Newkome GR, He E, Moorefield CN. *Chem. Rev.* 1999; **99**: 1689–1746. (f) Nierengarten J-F. *Chem. Eur. J*. 2000; **6**: 3667–3670. (g) Schlüter AD, Rabe JP. *Angew. Chem*. 2000; **112**: 860–880; *Angew. Chem. Int. Ed*. 2000; **39**: 864–883. (h) Newkome GR, Moorefield CN, Vögtle F. *Dendrimers and Dendrons. Concepts, Syntheses, Applications*. Wiley-VCH: Weinheim/Germany, 2001. (i) Haag R. *Chem. Eur. J*. 2001; **7**: 327–335. (j) Hecht S, Fréchet JMJ. *Angew. Chem*. 2001; **113**: 76–94; *Angew. Chem. Int. Ed*. 2001; **40**: 74–91. (k) Fréchet JMJ, Tomalia DA. *Dendrimers and other dendritic polymers*. Wiley: New York, 2001. (l) Grayson SMG, Fréchet JMJ. *Chem. Rev.* 2001; **101**: 3819–3868.
2. Buhleier E, Wehner W, Vögtle F. *Synthesis* 1978: 155–158.
3. The earliest reports available after the initial article by Vögtle *et al.*: (a) Tomalia DA, Baker H, Dewald JR, Hall M, Kallos G, Martin S, Roeck J, Ryder J, Smith P. *Polymer J*. 1985; **17**: 117–132. (b) Newkome GR, Yao Z-Q, Baker GR, Gupta VK. *J. Org. Chem.* 1985; **50**: 2003–2004.
4. See, for example: (a) Kawaguchi T, Walker KL, Wilkins CL, Moore JS. *J. Am. Chem. Soc*. 1995; **117**: 2159–2165. (b) Schwartz BL, Rockwood AL, Smith RD, Tomalia DA, Spindler R. *Rap. Commun. Mass Spectrom*. 1995; **9**: 1552. (c) Leon JW, Kawa M, Fréchet JMJ. *J. Am. Chem. Soc*. 1996; **118**: 8847–8859. (d) Wendland MS, Zimmerman SC. *J. Am. Chem. Soc*. 1999; **121**: 1389–1390. (e) Rheiner PB, Seebach D. *Chem. Eur. J*. 1999; **5**: 3221–3236. (f) Bu L, Nonidez WK, Mays JW, Tan NB. *Macromolecules* 2000; **33**: 4445–4452. (g) Zhou L, Russell DH, Zhao M, Crooks RM. *Macromolecules* 2001; **34**: 3567–3573. (h) Chen H, He M, Cao X, Zhou X, Pei J. *Rap. Commun. Mass Spectrom*. 2004; **18**: 367–370.
5. Selected examples: (a) Kallos GJ, Tomalia DA, Hedstrand DM, Lewis S, Zhou J. *Rap. Commun. Mass Spectrom*. 1991; **5**: 383–386. (b) Hummelen JC, van Dongen JLJ, Meijer EW. *Chem. Eur. J*. 1997; **3**: 1489–1493. (c) Tolic LP, Anderson GA, Smith RD, Brothers II HM, Spindler R, Tomalia DA. *Int. J. Mass Spectrom*. 1997; **165**(166): 405–418. (d) Puapaiboon U, Taylor RT. *Rap. Commun. Mass Spectrom*. 1999; **13**: 508–515. (e) Watanabe S, Sato M, Sakamoto S, Yamaguchi K, Iwamura M. *J. Am. Chem. Soc*. 2000; **122**: 12588–12589. (f) Cohen SM, Petoud S, Raymond KN. *Chem. Eur. J*. 2001; **7**: 272–279. (g) Rio Y, Accorsi G, Nierengarten H, Rehspringer J-L, Hönerlage B, Kopitkovas G, Chugreev A, Van Dorsselaer A, Armaroli N, Nierengarten J-F. *New J. Chem*. 2002; **26**: 1146–1154. (h) Iavarone AT, Williams ER. *J. Am. Chem. Soc*. 2003; **125**: 2319–2327.
6. Representative examples for the analysis of defects through mass spectrometry: (a) Liu M, Fréchet JMJ. *Polymer Bull*. 1999; **43**: 379–386. (b) Wolter EK, Cloninger MJ. *Org. Lett*. 2002; **4**: 7–10. (c) Engel GD, Gade LH. *Chem. Eur. J*. 2002; **8**: 4319–4329. (d) Zhang W, Tichy SE, Pérez LM, Maria GC, Lindahl PA, Simaneck EE. *J. Am. Chem. Soc*. 2003; **125**: 5086–5094. (e) Zimmerman SC, Zharov I, Wendland MS, Rakow NA, Suslick KS. *J. Am. Chem. Soc*. 2003; **125**: 13504–13518.
7. See, for example: (a) Puapaiboon U, Taylor RT, Jai-nhuknan J. *Rap. Commun. Mass Spectrom*. 1999; **13**: 516–520. (b) Koster S,

DOI: 10.1002/poc

Duursma MC, Guo X, Benthem RATM, de Koster CG, Boon JJ, Heeren RMA. *J. Mass Spectrom*. 2002; **37**: 792–802. (c) Adhiya A, Wesdemiotis C. *Int. J. Mass Spectrom*. 2002; **214**: 75–88. (d) Neubert H, Knights KA, de Miguel YR, Cowan DA. *Macromolecules* 2003; **36**: 8297–8303. (e) He M, McLuckey SA. *Rap. Commun. Mass Spectrom*. 2004; **18**: 960–972.
8. Weener J-W, van Dongen JLJ, Meijer EW. *J. Am. Chem. Soc*. 1999; **121**: 10346–10355.
9. Corbin PS, Lawless LJ, Li Z, Ma Y, Witmer MJ, Zimmerman SC. *Proc. Natl. Acad. Sci. USA* 2002; **99**: 5099–5104.
10. (a) Ong W, Kaifer AE. *Angew. Chem*. 2003; **115**: 2214–2217; *Angew. Chem. Int. Ed*. 2003; **42**: 2164–2167. (b) Yamada T, Ge M, Shinohara H, Kimura K, Mashiko S. *Chem. Phys. Lett*. 2003; **379**: 458–465. (c) Broeren MAC, van Dongen JLJ, Pittelkow M, Christensen JB, van Genderen MHP, Meijer EW. *Angew. Chem*. 2004; **116**: 3541–3646; *Angew. Chem. Int. Ed*. 2004; **43**: 3557–3562.
11. Klärner F-G, Kahlert B. *Acc. Chem. Res*. 2003; **36**: 919–935.
12. (a) Whitesides GM, Mathias JP, Seto CT. *Science* 1991; **254**: 1312–1319. (b) Philp D, Stoddart JF. *Angew. Chem*. 1996; **108**: 1242–1286; *Angew. Chem. Int. Ed*. 1996; **35**: 1154–1196. (c) Swiegers GF. In *Encyclopedia of Supramolecular Chemistry*, Atwood JL, Steed JW (eds). Marcel Dekker: New York, 2004, pp. 1263–1269.
13. Baytekin HT, Rang A, Engeser M, Schalley CA. Unpublished results.
14. Molecular modelling using the augmented MM2 force field implemented in the CACHE 5.0 program (Fujitsu Ltd. 2001, Krakow, Poland), crystallography of similar complexes, and STM experiments of analogous structures yield similar size estimates. See: (a) Stang PJ, Cao DH, Saito S, Arif AM. *J. Am. Chem. Soc*. 1995; **117**: 6273–6283. (b) Aoyagi M, Biradha K, Fujita M. *Bull. Chem. Soc. Jpn*. 1999; **72**: 2603–2606. (c) Safarowsky C, Merz L, Rang A, Broekmann P, Hermann BA, Schalley CA. *Angew. Chem*. 2004; **116**: 1311–1314; *Angew. Chem. Int. Ed*. 2004; **43;** 1291–1294.
15. (a) Lehn J-M. *Chem. Eur. J*. 1999; **5**: 2455–2463. (b) Otto S, Furlan RLE, Sanders JKM. *Drug Discov. Today* 2002; **7**: 117–125. (c) Rowan SJ, Cantrill SJ, Cousins GRL, Sanders JKM, Stoddart JF. *Angew. Chem*. 2002; **114**: 938–993; *Angew. Chem. Int. Ed*. 2002; **41**: 898–952.
16. (a) Schalley CA, Müller T, Linnartz P, Witt M, Schäfer M, Lützen A. *Chem. Eur. J*. 2002; **8**: 3538–3551. (b) Sakamoto S, Fujita M, Kim K, Yamaguchi K. *Tetrahedron* 2000; **56**: 955–964. For a review, see: (c) Schalley CA. *Mass Spectrom. Rev*. 2001; **20**: 253–309.
17. Blais J-C, Turrin C-O, Caminade A-M, Majoral J-P. *Anal. Chem*. 2000; **72**: 5097–5105.
18. (a) Chessa G, Scrivanti A, Seraglia R, Traldi P. *Rap. Commun. Mass Spectrom*. 1998; **12**: 1533–1537. (b) Kaneko R, Wada Y. *J. Mass Spectrom*. 2003; **38**: 526–530. (c) Demelbauer UM, Zehl M, Plematl A, Allmaier G, Rizzi A. *Rap. Commun. Mass Spectrom*. 2004; **18**: 1575.
19. Baytekin B, Werner N, Luppertz F, Engeser M, Brüggemann J, Bitter S, Henkel R, Felder T, Schalley CA. *Int. J. Mass Spectrom*. 2006; **249**(250): 138–148.
20. Felder T, Schalley CA, Fakhrnabavi H, Lukin O. *Chem. Eur. J*. 2005; **11**: 5625–5636.
21. Vögtle F, Fakhrnabavi H, Lukin O, Müller S, Friedhofen J, Schalley CA. *Eur. J. Org. Chem*. 2004: 4717–4724.
22. Schalley CA, Verhaelen C, Klärner F-G, Hahn U, Vögtle F. *Angew. Chem*. 2005; **117**: 481–485; *Angew. Chem. Int. Ed*. 2005; **44**: 477–480.

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