FULL PAPER

A Topological View of Isomeric Dendrimers

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A topological approach to the analysis of isomeric dendrimers by considering their molecular graphs has been applied to correlate various properties of a series of new sulfonimide-based isomeric dendrimers with their structures. According to this approach isomeric dendrimers are referred to as either isographic, that is, having the same graph, or non-isographic, that is, having different graphs. Six sets of non-isographic isomeric dendrimers with four to ten peripheral groups and

one set of three isographic isomers with eight peripheral groups have been designed, synthesized and investigated with regard to their melting, solubility, separation, NMR spectroscopic and mass spectrometric characteristics. The results are discussed in the light of the graph-dependent and -independent properties of the isomers.
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Introduction

Dendrimers play an increasingly important role in many areas of chemistry.[1] The usually applied synthetic routes can be classified into divergent[2] and convergent[3] syntheses, although both have also been combined for the synthesis of POPAM dendrimers decorated with peripheral Fréchet dendrons.[4] Recently, we reported the synthesis of sulfonimide-based dendrimers,[5] which in principle allows us to program dendrimers with individual branching points and peripheral units. The direction of growth of the dendrimers can be determined by the reaction conditions because of the clearly distinguished reactivities of the building blocks, that is, the branching aromatic amines and the intermediate sulfonamides. The synthesis of a particular dendrimer can thus be programmed by selecting the appropriate series of reaction steps.

The deliberate preparation of highly unsymmetrical dendrimers with a specific structure rather than the unintended formation of some minor defects emphasizes the question of how to accurately describe different structural isomers. One way to do this is to use topology by defining and following molecular graphs. The application of topological techniques to the analysis and classification of molecular structures has become increasingly important over the past 30 years. The development in this area gained much impe-

tus from successful syntheses of myriads of molecular catenanes, rotaxanes and knots[6] as well as endohedral fullerenes[7] and orientational isomers of guests encapsulated in self-assembled capsules.[8] Their structures and properties depend not only on their geometry, but also on their topological and stereochemical features.[9] Nowadays, topological theories of graphs and knots[10] are widely used to adequately describe many types of isomerism and chirality. In addition, graph theory has successfully been applied to the systematic analysis of hydrogen-bonding patterns in a large variety of organic crystal structures.[11]

In this contribution, we propose a topological approach to the analysis of isomeric dendrimers by representing their molecular structures as planar graphs. This consideration has been applied to isomeric series of sulfonimide-based dendrimers of different sizes and shapes which were then examined with respect to their graph-dependent and -independent physicochemical and NMR spectroscopic properties, as well as their fragmentation reactions as observed in tandem MS experiments.

Results and Discussion

Topological Considerations

Irrespective of their detailed chemical structure, all dendritic molecules contain a core and one or more shells of branching points, both of a certain valence. In the periphery, they are substituted with terminal groups. These broadly accepted descriptors result in a tree-like graph (Figure 1). This simplified two-dimensional visualization of a dendritic structure is a planar molecular graph consisting of a set of linked symbols for the core, the branching points and the terminal groups. Therefore, the dendrimer graph,

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or simply the dendrograph, in Figure 1 maps the information on the numbers of branching points and terminal groups and on their connectivities. This graphical representation is often used in general discussions on dendrimers because the dendrograph does not contain any data on the chemical composition of the dendrimer. Figure 2 provides the chemical structures and the corresponding dendrographs of two different pairs of isomeric dendrimers (dendroisomers). Dendroisomers can be described by either the same dendrograph or different dendrographs. Isographic isomers can be depicted by the same dendrograph, whereas non-isographic isomers have different dendrographs.[12]
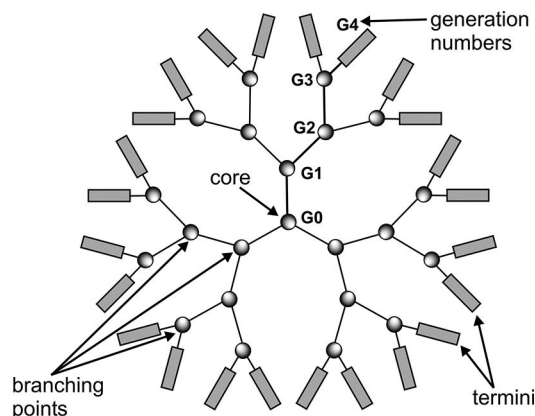

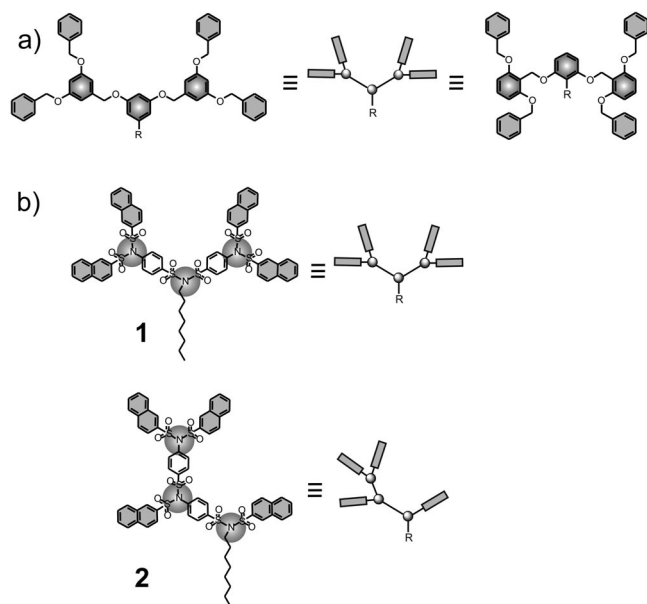Figure 1. Example of a planar graph of a dendrimer, a dendrograph.

Figure 2. (a) Examples of isographic dendroisomers (Gorman and co-workers[13]). These are depicted by the same graph, but differ with respect to their constitution. (b) Non-isographic dendroisomers 1 and 2 (this work) have different dendrographs.

Several precedents for isomerism in dendrimer research have been reported in the literature.[13–17] Sometimes, the term "isomers" has not been used in a strict sense[14] to denote compounds with similar structural formulae, but

different elemental compositions. Hawker et al.[15] reported the first detailed study of pairs of Fréchet-type dendrons and their truly isomeric linear analogues. Noticeable differences in hydrodynamic volumes as well as in solubility and crystallinity were observed only for isomers with high
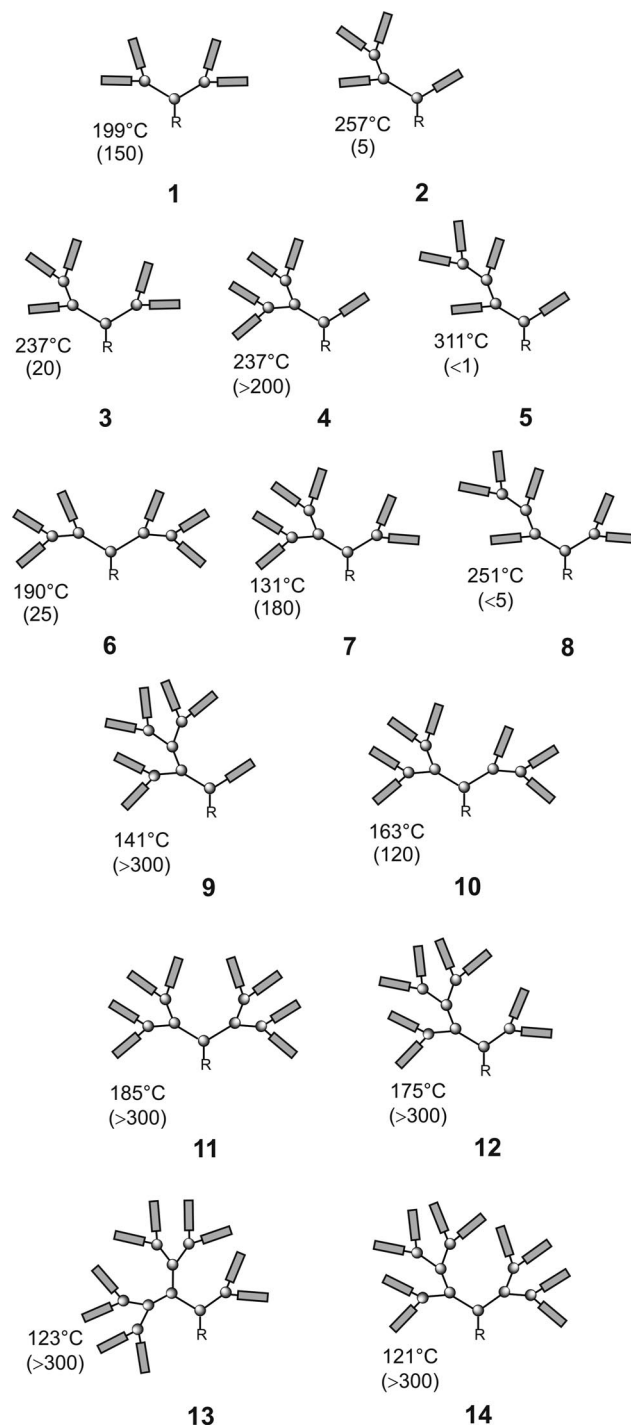

Figure 3. Dendrographs of a series of non-isographic isomers of the sulfonimide dendrimers (R = n-octyl; spheres represent the sulfonimide branching points, lines the p-phenylene linkers, and rectangles represent the 2-naphthyl peripheral groups). See also Figure 2 for reference to compounds 1 and 2. Melting points and solubilities (in parentheses in $mg\,mL^{-1}$) in chloroform are given.

molecular weights (>5 kDa). More recently, Gorman and co-workers[13] investigated the effect of constitutional differences on the encapsulation ability of Fréchet dendrimers. For this purpose, Fréchet-type polyether dendrons were synthesized with either *ortho*- or *meta*-substituted branching points, such as the ones shown in Figure 2a. Isomers with *ortho*-substituted branching points were more hydrophobic at their cores. Finally, a light-induced (*E*)/(*Z*) isomerization of azobenzene-containing dendrimers was used to either decrease[16] or increase[17] their hydrodynamic volumes. The dendroisomers mentioned in the two last examples contain either constitutional or configurational differences at their branching points. Despite these differences, they, however, have the same molecular graphs and are thus isographic dendrimers. As the number of terminal groups increases, the number of possible non-isographic isomers grows almost exponentially. This is why in the present work complete sets of non-isographic isomers were synthesized only for compounds with four and five peripheral groups (**1**–**5**; see Figure 3), whereas for compounds with a higher molar mass only representative isomeric pairs were prepared.

A series of non-isographic isomers with up to ten peripheral 2-naphthylsulfonyl groups **1**–**14**, as depicted by their dendrographs in Figure 3, were investigated with regard to their melting points, solubility, NMR spectroscopic characteristics, separability and mass spectrometric fragmentation patterns. Additionally, two isographic isomers of the dendrimer **11** with differences in their first (**15**) and second (**16**) generation linkers were prepared and their properties compared.

15 **16**
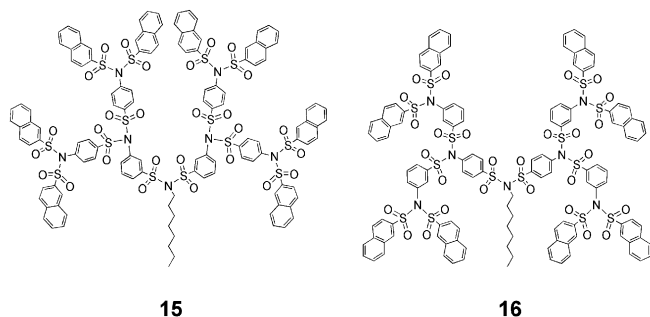
Synthesis and Physical Properties

In order to illustrate the practical utility of the topological approach discussed here, a series of isomeric sulfonimide-based dendrimers (Figure 3) were tailored by choosing the appropriate reaction sequence.[5] The comprehensive synthetic schemes and the characterization data for all the dendrimers mentioned in this work are collected in the Supporting Information. Figure 3 shows the solubility in chloroform of the dendrimers at room temperature and their melting points. For the low-molar-mass dendrimers bearing four to six peripheral groups, the highest melting points were determined for compounds **2**, **5** and **8**, which have the most linear shapes. These compounds also show the lowest

solubility in chloroform. Both trends point to significantly strengthened crystal packing. Most strikingly, the melting point for **8** is more than 100 °C higher than that of its isomer **7**, and a difference in solubility of more than 200 is observed for dendroisomers **4** and **5**. The low solubility of some of the dendrimers studied here may ultimately limit the scope of the programmed synthesis developed previously.[5] The melting points and the solubilities of the available dendroisomer pairs with seven, eight and ten peripheral groups differ less significantly. As a general trend, we note that the differences between isomers vanish almost completely with increasing dendrimer size. This is likely due to the more spherical, globular structure of the larger dendrimers in which the individual dipole moments cancel each other more efficiently compared with smaller structures.

Chromatographic Behaviour

In this study, gel-permeation (GPC), high-performance liquid (HPLC), and simple thin-layer (TLC) chromatography were used to examine the separability of dendrimer mixtures. Different stationary phases were examined for GPC and HPLC.

Figure 4 shows the chromatograms of different pairs of dendrimers of different molecular masses (including the truly isomeric **9**/**10** pair for comparison). One component, dendrimer **9**, was the same in all mixtures for easy comparison. Although a mixture of **1** and **9** is separated almost to the baseline of the two peaks, a mixture of **4** and **9**, which
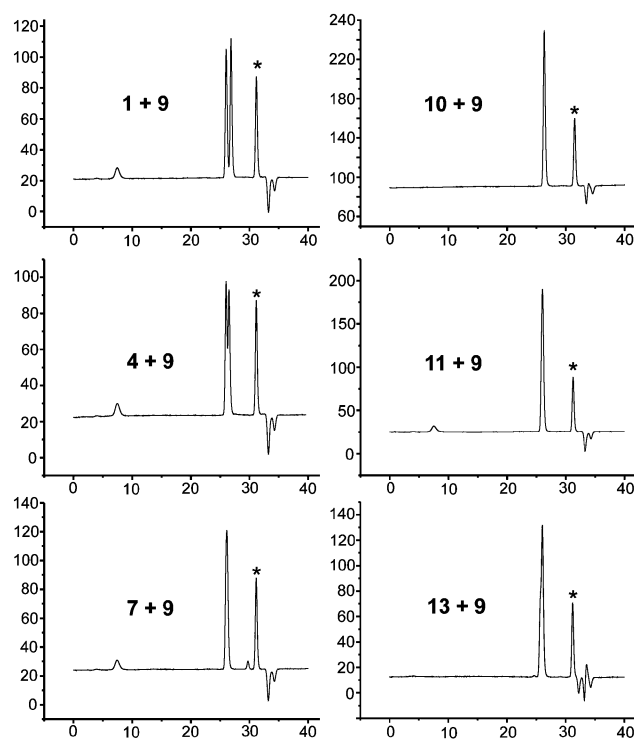

Figure 4. Analytical gel-permeation chromatograms of the dendrimer pairs. Asterisks denote peaks from toluene added as a standard.

are closer in molecular mass, is much more difficult to separate. Mixtures of **9** with larger dendrimers are inseparable on the GPC column used here (molecular weight range: 500 to 3×10^6 Da). Neither was separation obtained for mixtures of isographic isomers **11**, **15** and **16**. This indicates that routinely applied analytical GPC may fail as a tool to examine the structural purity of dendrimers.

Unlike analytical GPC, recycling HPLC with a preparative gel-permeation column (molecular weight range: 300–3000 Da) shed more light on the separability of the dendroisomers. The device runs multiple cycles, increasing the probability of mixture separation. We analyzed 1:1 mixtures of non-isographic isomers (**11** + **12** and **9** + **10**) as well as 1:1 mixtures of isographic isomers (**11** + **15** and **11** + **16**). The result is that the two mixtures of the non-isographic isomers could not be separated even after 80 cycles, whereas a mixture of the isographic pair **11** + **16** clearly showed separating peaks after 20 cycles (Figure 5). The second pair of isographic isomers **11** + **15** required 40 cycles to afford complete separation. Other mixtures of differently sized dendrimers were also successfully separated by recycling GPC.
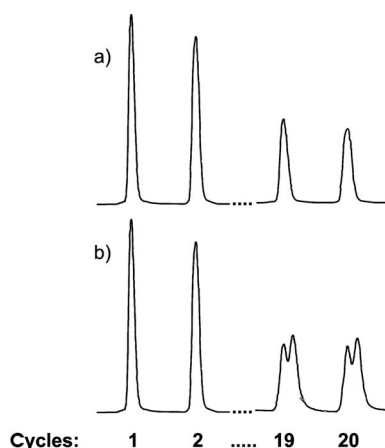

Figure 5. Recycling GPC chromatograms of (a) a 1:1 mixture of non-isographic **11** and **12** (no separation even after 80 cycles); (b) a 1:1 mixture of isographic **11** and **16**.

These results indicate the differences in hydrodynamic volumes induced by the constitutional kinks within their phenylene spacers, thus providing separability for the isographic and geometrically closely related dendroisomers **11**, **15** and **16**. At the same time, non-isographic dendroisomers exhibit matching hydrodynamic volumes despite their strong geometrical dissimilarity. This latter finding is in marked contrast to the observations of Hawker et al. for the aforementioned isomeric polyethers.[15]

Silica gel thin-layer chromatography (TLC) of all the non-isographic isomer mixtures in Figure 3 revealed matching R_f values. Consequently, separation was impossible. In contrast, a mixture of the three isographic dendroisomers **11**, **15** and **16** showed noticeable separation on a TLC plate (CHCl$_3$/SiO$_2$; R_f = 0.40, 0.42 and 0.46, respectively). This implies that the isographic dendroisomers not only have different hydrodynamic volumes but also different polarities

and affinities to the stationary phase. It also means that mixtures of such isomers can be separated by conventional column chromatography although this is not the case for the non-isographic isomers. An HPLC analysis of mixtures of non-isographic isomers in Figure 3 performed using a silica gel column revealed no separation. However, in contrast to analytical GPC, all mixtures of differently sized dendrimers, such as those indicated in Figure 4, were successfully separated by HPLC. The HPLC analysis of mixtures of isographic **11** and **15** or **11** and **16** also showed peak separation.

NMR Spectroscopy

Most of the dendroisomers under study can be easily distinguished by high-resolution ^{1}H NMR spectroscopy. Although many signals of the dendrimers in the aromatic region of the ^{1}H NMR spectra have very similar chemical shifts, the signals for the naphthyl α-protons are highly indicative of differences in symmetry. Figure 6 compares the regions of the naphthyl α-protons in the ^{1}H NMR spectra of the three dendroisomers **3**–**5** which have five peripheral substituents.
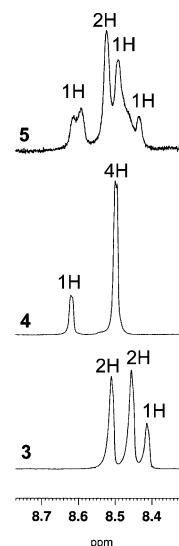

Figure 6. Naphthyl α-proton signals in the ^{1}H NMR (CDCl$_3$) spectra of compounds **3**–**5**.

As seen in Figure 6, one can differentiate between the ratios of non-equivalent peripheral naphthyl substituents in the non-isographic dendroisomers. An additional interesting phenomenon is the multiplicity of the α-proton signals and the variability of their coupling constants. Thus, as shown in Figure 6, the corresponding signals in the ^{1}H NMR spectrum of compound **3** appear as three singlets with relative integral intensities of 2:2:1. The signals of compound **4** are a singlet and a doublet ($^4J_{H,H}$ = 1.5 Hz) with relative intensities of 1:4. Finally, there are two doublets (one proton each) with very large coupling constants ($^4J_{H,H}$ = 5.7 Hz) and two singlets (2:1) in this region of the ^{1}H NMR spectrum of compound **5**. Compounds **9** and **10** were the only pair that could not easily be distinguished by ^{1}H NMR spectroscopy. Both compounds have a low sym-

metry that complicates the aromatic region of their ^{1}H NMR spectra, and both are expected to yield 1:2:4 ratios for the three different sets of naphthyl α-proton signals.

Mass Spectrometry

Mass spectrometry is a routine tool for dendrimer characterization: matrix-assisted laser desorption/ionization (MALDI) is frequently used[18] due to the common coupling to time-of-flight analyzers that offer a broad mass range. Electrospray ionization (ESI) has also been applied to several classes of dendrimers.[19] Mass spectrometry is particularly useful for an analysis of dendrimer defects[20] which are indistinguishable by most other methods. However, ionization artifacts can make mass spectrometric analysis difficult.[21] In the context of this study, we attempted to distinguish between pairs of non-isographic sulfonimide dendroisomers by analyzing their fragmentation reactions as observed in tandem mass spectrometric experiments.[22]

The dendrimers under study were first ionized by using an electrospray ionization source coupled to a Fourier-transform ion-cyclotron resonance (FTICR) mass spectrometer. All dendrimers described in this article can be ionized as their sodium or potassium adducts, whereas protonation yields only a peak of marginal intensity. This behaviour is in agreement with MS studies on other persulfonylated dendrimers with a polyaminoamine (POPAM) scaffold. For these POPAM-based dendrimers, collision-induced fragmentations indicate that they can be protonated at the amine nitrogen atoms, whereas sodium adduct formation occurs through coordination of the cation to the sulfonimide group. As the dendrimers under study in this work do not bear amine nitrogen atoms, protonation is unlikely. Sodium or potassium attachment, however, is quite favourable. Figure 7a and d shows the ESI mass spectra of dendrimers **1** and **2** as typical examples of the results obtained with the ESI-FTICR instrument.

Only the sodium adducts gave intense enough peaks for the MS/MS experiments. After mass selection of the [M + Na]+ dendrimer ion of interest, a CO_2 laser was used to irradiate the ions in the IR region [infrared multiphoton dissociation (IRMPD); 10.6 μm wavelength] and to induce fragmentation (Figure 7b and c). The fragmentation pattern is highly complex even for the smaller dendrimers under study. Nevertheless, almost all fragments can be assigned to combinations of a few different fragmentation pathways that can be classified into three categories (Scheme 1).

The first reaction gives rise to losses of SO_2, presumably through an *ipso* substitution (process A), as found previously.[5] The 1,2-elimination of octene (process B) from the alkyl side-chain at the focal point represents the second type of fragmentation reaction, which can occur through a simple 1,2-elimination process or, by analogy to ester pyrolysis, through a six-membered transition-state structure, as depicted in Scheme 1; we cannot distinguish between these two mechanisms on the basis of the mass spectrometric experiments.
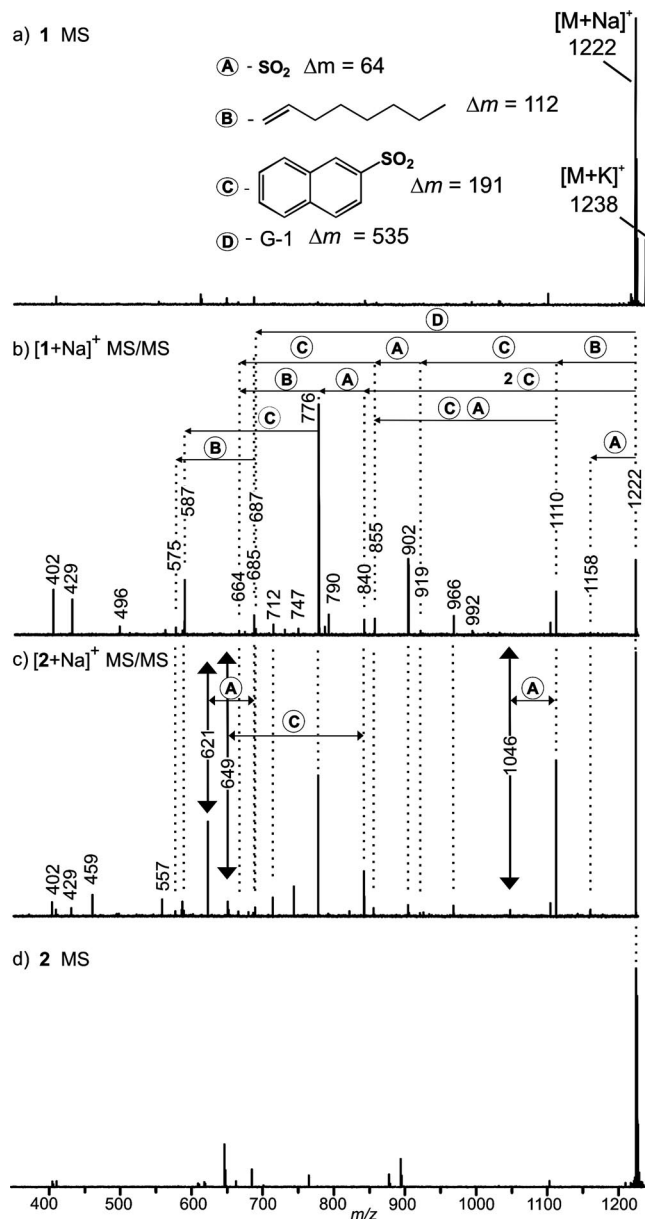

Figure 7. (a) and (d) ESI-FTICR mass spectra of non-isographic dendroisomers **1** and **2** sprayed from methanol/CH_2Cl_2 (3:1). (b) and (c) tandem mass spectra (IRMPD) of dendrimers **1** and **2** after mass selection of the [M + Na]+ ion. Vertical double arrows indicate fragments that appear only in one of the mass spectra and are thus indicative of structural differences.

The third category comprises direct S–N bond-cleavage reactions that generate an *N*-centred radical that is stabilized by conjugation to the adjacent aromatic ring and two sulfonyl groups. The other fragment is a neutral *S*-centred radical, which again is stabilized to some extent through conjugation. These effects weaken the S–N bond, thus providing a predetermined breaking point. Depending on the size of the substituent, the loss of terminal naphthylsulfonyl branches (process C), a whole first-generation dendron (process D) or even a second-generation dendron (process E) can occur.
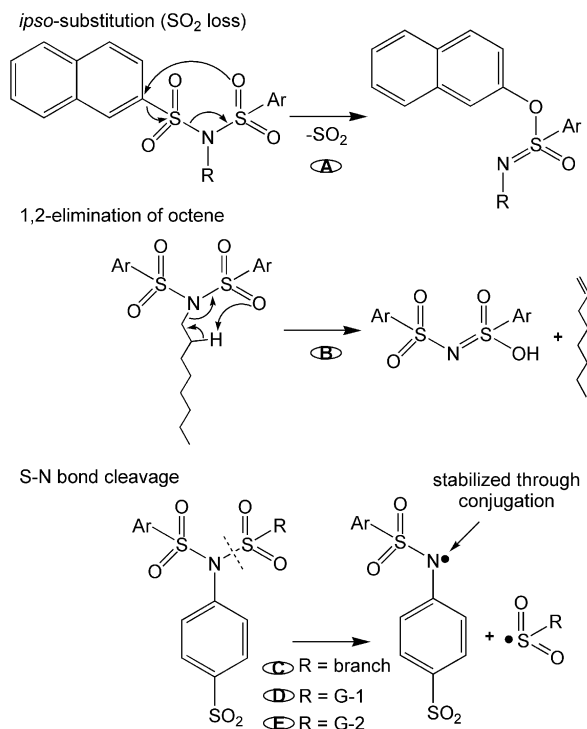
Scheme 1. Three pathways that lead to the fragmentation patterns in the tandem mass spectra.

Figure 8. MALDI-TOF/TOF tandem mass spectra (matrix: dithranol) of mass-selected isomers [2 + Na]+ (top) and [1 + Na]+ (bottom). Vertical double arrows indicate fragments that appear in only one of the mass spectra.

The two MS/MS graphics compared in Figure 7b and c are clearly different with respect to the intensities of the major fragment signals (e.g., m/z = 1110, 840 and 776). These differences are found irrespective of the laser power chosen for the excitation of the ions in the experiment. The fragmentation patterns even differ qualitatively in that several mostly smaller signals are absent for one of the isomers, but are observed in the spectrum of the other (e.g., m/z = 1046, 649 and 621).

The sodium adducts of dendrimers **3** and **4** gave similarly complex IRMPD spectra which again differed significantly from each other. However, dendrimer ions larger than [**3** + Na]+ and [**4** + Na]+ hardly decomposed in the IRMPD experiment, which indicates that they are highly stable molecules sufficiently able to store the energy from the laser beam without fragmenting. Therefore, MALDI-TOF/TOF experiments were performed. Owing to rather high collision energies, the larger dendrimer ions can be expected to fragment more easily. At the same time, rearrangement reactions are less prominent, and direct bond cleavage is preferred. Thus, structural information might be easier to obtain by this technique.[23] In the following we therefore focus on pairs of non-isographic isomers: **1/2**, **3/4** and **9/10**.

The differences observed in the ESI-FTICR tandem MS experiment for [**1** + Na]+ and [**2** + Na]+ were confirmed by the MALDI-TOF/TOF experiment (Figure 8). Qualitatively, the same fragmentation reactions appear, but quantitatively direct bond cleavages (e.g., formation of the fragment at m/z = 1031) are much more pronounced in the MALDI MS/MS experiments.

After assignment of the peaks of the next largest pair of dendrimers **3** and **4** (Figure 9), the two isomers can be
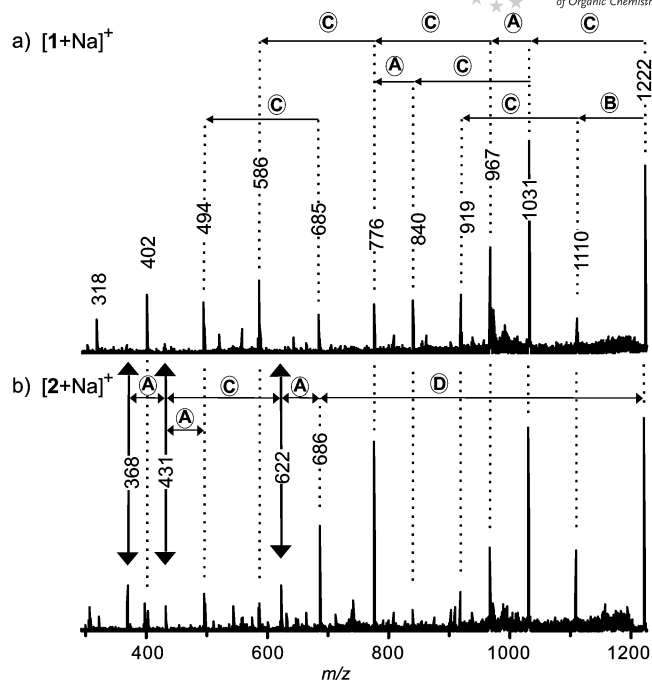

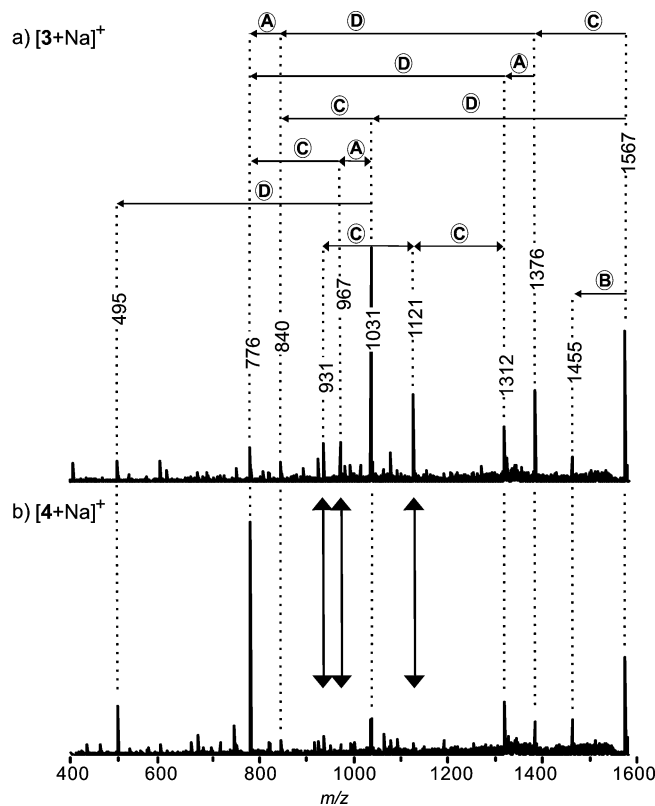Figure 9. MALDI-TOF/TOF tandem mass spectra (matrix: dithranol) of mass-selected isomers [**3** + Na]+ (top) and [**4** + Na]+ (bottom). Vertical double arrows indicate fragments that appear in only one of the mass spectra.

distinguished by close analogy to the smaller dendrimers **1** and **2**. Eye-catching qualitative differences (m/z = 1121, 967 and 931) as well as quantitative changes in intensities (m/z = 1376, 1031, 776 and 495) are clear. The two spectra thus differ significantly and clearly help to differentiate between them.

As expected, the MALDI tandem mass spectra of the largest investigated pair of dendrimers, that is, **9** and **10**, differ in respect of several key fragments (Figure 10) (e.g., m/z = 1812, 1403, 1278, 1188, 932 and 777).
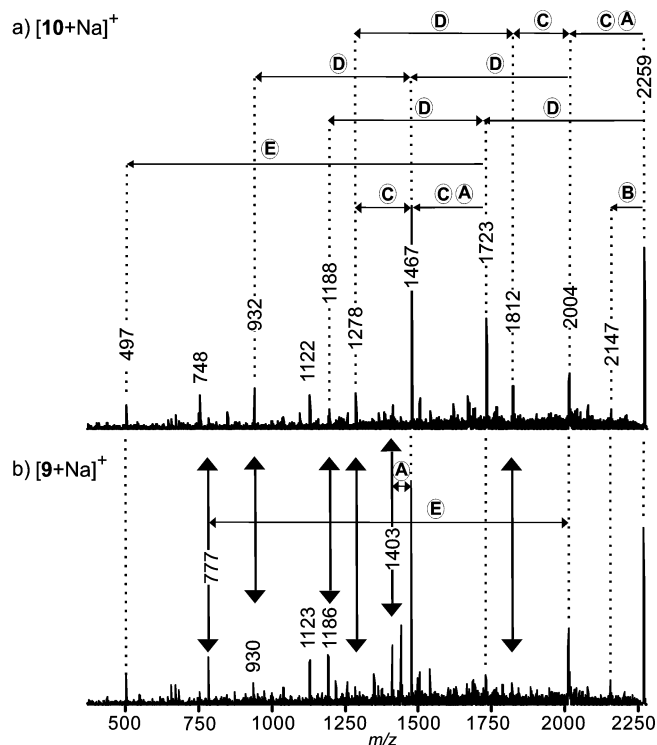

Figure 10. MALDI-TOF/TOF tandem mass spectra (matrix: dithranol) of mass-selected [**10** + Na]$^+$ (top) and [**9** + Na]$^+$ (bottom). Vertical double arrows indicate fragments that appear in only one of the mass spectra.

Although virtually all the peaks in the fragmentation spectra can be assigned, it is not clear in which order they are formed. MS^3 experiments, which would provide clarity here, can only be performed with the FTICR instrument. However, the intensities are not sufficiently high, and the larger dendrimer ions do not easily decompose.

With the MALDI-TOF/TOF instrument we are limited to MS^2 experiments. For the time being we can only draw the following conclusions from these experiments. (i) Non-isographic dendrimer ions with the same elemental composition give distinguishable MS/MS fingerprints. (ii) ESI-FTICR and MALDI-TOF/TOF mass spectra support each other in that similar fragmentation patterns and similar differences between non-isographic isomer ions are observed. Nevertheless, quantitatively, direct bond cleavage is shown to be preferred in the MALDI-TOF/TOF spectra. (iii) Owing to the complexity of the spectra, it is not yet possible to determine the structure of an unknown dendrimer directly from the fragmentation pattern.

Conclusions

On the basis of the results obtained in this work we have been able to draw conclusions about the graph-dependent and -independent properties of isomers of sulfonimide-based dendrimers. Isographic sulfonimide-based dendroisomers are distinguishable by recycling GPC, silica gel HPLC and silica gel TLC. The non-isographic sulfonimide dendroisomers cannot be separated by any of the chromatographic techniques applied in this work. Therefore, for both types of isomers, chromatographic separation is the graph-independent property. The graph-dependent properties of the non-isographic isomers are their melting points, solubility, NMR spectroscopic and mass spectrometric characteristics. The number of sets of signals in the ^{1}H NMR spectra permits a clear-cut assignment of the symmetry of the dendrimers under study. In addition, tandem MS of pairs of non-isographic isomers exhibits differences in their fragmentation pathway. Both methods are complementary to each other. Isomers **9** and **10**, for example, which could not easily be distinguished by ^{1}H NMR spectroscopy, still give rise to different MS/MS patterns. The dendroisomers and their mixtures are therefore a good benchmark for modern analytical tools and separation science. The topological description of dendrimers from the standpoint of the graph theory proposed in this work is handy and will certainly be helpful in the analysis of their structure–property relationship.

Experimental Section

Electrospray Mass Spectrometry: The mass spectrometry experiments were performed with a Varian/IonSpec QFT-7 FTICR mass spectrometer equipped with a superconducting 7 Tesla magnet and a micromass Z-spray ESI ion source utilizing a stainless steel capillary with a 0.75 mm inner diameter. The different dendrimers were dissolved in either CH$_2$Cl$_2$/MeOH (3:1) or CH$_2$Cl$_2$/MeOH (1:3) depending on the solubility of the sample. These solutions were introduced into the source with a syringe pump (Harvard Apparatus) at flow rates of approximately 2 µL min^{-1}. Parameters were adjusted as follows: capillary voltage: 3.8 kV; extractor cone: 10 V; sample cone: 10 V; source temperature: 40 °C; temperature of desolvation gas: 40 °C. No nebulizer gas was used for the experiments. The ions were accumulated in the instrument's hexapole long enough to obtain useful signal-to-noise ratios. Next, the ions were introduced into the FTICR analyzer cell, which was operated at pressures below 10–9 mbar, and detected by a standard excitation and detection sequence. After mass selection of the [M + Na]$^+$ dendrimer ion of interest, a CO$_2$ laser was used to irradiate the ions in the IR region [infrared multiphoton dissociation (IRMPD); 10.6 µm wavelength] and to induce fragmentation. For each measurement, 5–10 scans were averaged to improve the signal-to-noise ratio.

MALDI Mass Spectrometry: Mass spectrometry analyses were performed with a Bruker Daltonics ultraflex II MALDI-TOF/TOF mass spectrometer. The three most important parameters for successful MALDI-TOF/TOF mass spectra are all related to sample preparation. (i) The use of dithranol as the matrix gave the highest intensities (dihydroxybenzoic acid, sinapinic acid and others did not give satisfying results). (ii) A small amount of sodium chloride

was added and increased the abundances of the sodium adducts significantly. (iii) It was most efficient to directly mix a dichloromethane/methanol solution (ratios of 3:1 to 1:3 depending on the sample solubility) of the sample with a chloroform solution of the matrix (700-fold excess of the matrix over the sample).

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[12] The following nomenclature is suggested to accurately describe the dendrographs even when the commonly used term "generation" becomes somewhat blurred in highly unsymmetrical dendrimers. The dendrographs depicted in Figures 2 and 3 can be classified by at least three numbers. The first number depicts the total number of peripheral groups and the following two figures indicate numbers of peripheral groups on the left and right branches. For example, the dendrograph descriptors for compounds **1** and **2** (Figure 2), each bearing four peripheral groups, are 4-2/2 and 4-3/1. As the dendrograph becomes large, additional figures are introduced to specify the structure of branched subunits recursively. For example, the dendrograph corresponding to compound **9** in Figure 3 is described as 7-(6-(4-2/2)/2)/1. This notation describes a dendrograph with a total of seven peripheral groups, six of which are on one branch attached to the focal point. The distribution of the six groups is recursively described by similar notation. Four of them are attached symmetrically to one sub-branch; the other two are attached to the other. The dendrograph descriptors can be used to encode or decode the structure of any dendrimer. The number of all possible dendrographs can as easily be calculated by a recursive algorithm as the number of isomers for linear and branched alkanes. Two isomers with four peripheral groups are possible, three with five, six with six, eleven with seven and so on if the core and the branching points are bivalent. Analogously, the nomenclature can easily be extended to dendrimers with a higher number of substituents at the core and/or the branching points. It is flexible enough even for dendritic structures that have different valencies at the core and at the branches.

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