Chirality in Dendritic Architectures**

H. W. I. Peerlings and E. W. Meijer*

Dedicated to Professor Hans Wynberg on the occasion of his 75th birthday

Abstract: At first glance the topic of chiral dendrimers seems to be a contradiction in terms. However, recent studies reveal that both the building blocks of the dendrimer and the overall dendritic architecture can be chiral and that chirality can be introduced at various levels. The expression of optical activity in these enantiomerically pure dendrimers as a result of conformational (dis)order has proven to be of special interest. In this Concepts article we present the different approaches to introducing chirality in dendritic architectures, organized through their possible impact in fields such as biocompatibility, catalysis, molecular recognition, and surface chemistry. Also, the relation between molecular chirality of core or building block and the macroscopic chirality of dendritic objects is discussed.

Keywords: catalysis · chirality · dendrimers · molecular recognition · surfaces

Introduction

Both the symmetry and the asymmetry in molecular objects have always attracted the interest of chemists.[1] Three-dimensional symmetry in macromolecular or nanosize structures is encountered within the domain of dendrimers and hyperbranched polymers. Dendrimers or cascade molecules are highly branched macromolecules, synthesized stepwise from a central core and leading to a well-defined number of generations and end groups. They are generally described as structures that are spherical and possessing a high degree of symmetry.[2] By now combining chirality or asymmetry with these highly symmetrical dendrimers, a contradiction in terms is in fact introduced. In this article we will discuss the different concepts and approaches to the chirality of dendritic architectures and how these chiral features are expressed in the specific properties of this new class of macromolecules. Although dendrimers are often compared with globular proteins, which are chiral in all their features, we will restrict ourselves here to the discussion of chiral dendrimers only.

The first report on chiral dendrimers dates back to 1979, when Denkewalter described a divergent procedure for the synthesis of high molecular weight dendrimers based on the amino acid lysine.[3] Since that time a large number of publications have appeared on the issue of chirality in dendrimers, derived from natural products or man-made chiral building blocks. Seebach was the first to classify the various possibilities of building chiral dendrimers based on the position of chirality in the molecule.[4] Owing to the recent accounts on the synthesis and properties of chiral dendrimers, we have slightly modified and expanded Seebach's classification. We differentiate between a chiral dendrimer based on 1) chirality of the core only, 2) chirality of the branching unit only, 3) chirality of the end group only, 4) chirality of two or three of these building blocks, 5) constitutionally different branches attached to a chiral core, 6) a rigid chiral conformation, but without any stereocenters or chiral units, and 7) interactions with chiral ligands, which are not covalently attached. All of the chiral dendrimers reported so far are members of one of the above classes, although no examples are yet known for classes 6 and 7. A selected anthology of chiral dendrimers and their classification is given in Figure 1.

Discussion

Challenges of chiral dendrimers: Not only do chiral dendrimers have a high scientific value for the basic understanding of fundamental stereochemical issues, they also have many features that will be of crucial importance to other fields where dendrimers are thought to be useful. Many of the interesting properties and applications envisaged for chiral dendrimers are the result of the typical dendrimer properties, like: 1) a well-defined three-dimensional architecture with a restricted conformational freedom at higher generations, 2) a large number of reactive end groups at the periphery of the dendrimer, and 3) the host–guest properties of dendrimers. When chirality is introduced into these highly branched architectures, it is interesting to raise the

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[**] This concepts article is a personal reflection on the many issues raised by the combination of chirality and dendrimers. The concepts presented here are partly based on several recent reports in the published literature and partly on the highly appreciated discussions with colleagues on as yet undisclosed results. In particular Bert Meijer would like to express his gratitude to Professor Hans Wynberg who stimulated him to explore all aspects of stereochemistry.

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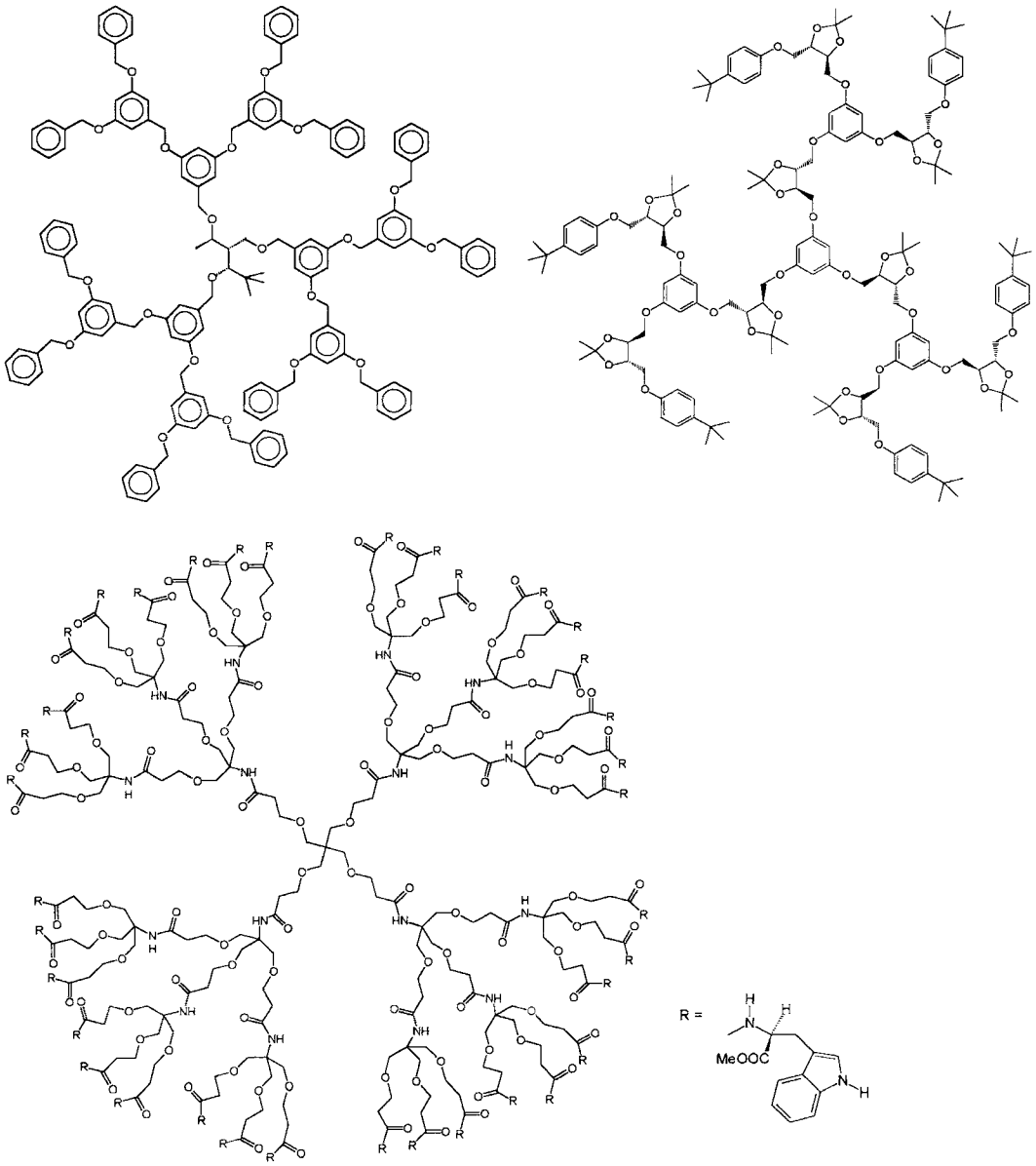

Figure 1. A selected anthology of chiral dendrimers and their classification. Top left: class 1, Seebach's dendrimer with a chiral core [4]. Top right: class 2, Chow's dendrimer with chiral building blocks [5]. Bottom: class 3, Newkome's dendrimer with chiral end groups [6].

following questions and to investigate whether some of the challenges can be brought within the realm of reality:

1) Is there a role in biological systems for well-defined nanosize structures with a periphery of natural products and encapsulated guests?
2) Can dendritic chiral objects close the gap between molecular and macroscopic chirality?
3) Are the surfaces of fractal nature and is it possible to use these curved chiral surfaces?
4) Is chiral clathration possible by making use of chiral recognition in dendritic host–guest systems?
5) Is it possible to have very efficient dendrimer-based catalysts for asymmetric synthesis?

Finally, it is of interest to know whether the chiroptical properties (e.g. optical rotation) of dendrimers differ from those of their linear macromolecular counterparts. The importance of chirality in linear polymers is generally accepted, and for further information the reader is referred to excellent reviews.[7]

Biocompatibility of dendrimers derived from natural products: The most logical way of introducing chirality into dendritic architectures is through the use of natural products, like amino acids, nucleotides, and carbohydrates as building blocks or as end groups. These dendrimers can act as models for the different dendritic structures known in biomacromolecules, while additional features emerge from their possible biocompatibility and availability for interactions with other bioreactive species, including modeling of enzymatic activity.

By far the most intriguing approach to these dendrimers is the use of AB_2 building blocks to construct highly branched macromolecules, based on natural products only.[9, 10] Following Denkewalter's first report,[3] Tam reported on an all-peptide dendrimer.[8] These dendrimers (Figure 2) were made to study their possible role in biological systems and no specific

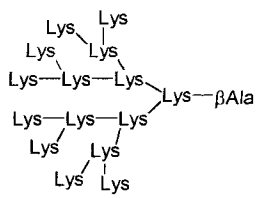

Figure 2. Tam's all-peptide dendrimer [8].

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chirality issues were raised. It would, however, be interesting to examine how the conformations and hydrogen-bonding patterns of these dendritic macromolecules differ from their linear counterparts, and circular dichroism could be used for this purpose. The search for dendritic polysaccharides is inspired by the presence of these molecules in natural tissues. A number of groups have been successful in preparing these all-saccharide dendrimers and have expressed an interest in studying their application in the inhibition of infectious diseases.[11] This interest is based on the notion that simple saccharide derivatives are not active, while clusters of saccharides (neoglycoconjugates) are.

In the hope that biological compatibility can be achieved through the presence of the amino acids and saccharides at the periphery of the dendrimer, poly(amidoamine) dendrimers,[12] arborols,[6] arborol-like dendrimers,[13] and poly(propylene imine) dendrimers[14] have been prepared with amino acids and saccharides as end groups. The stereochemical issues of these dendrimers will be discussed below in the section on chiral surfaces, whilst the saccharide dendrimers were the subject of a recent Concept article by Stoddart et al.[15]

Now that dendrimers consisting of or decorated with natural products are accessible, it should be possible to investigate the enzymatic cleavage of these groups from the densely packed dendrimer surface. However, only unsuccessful attempts are known to us.[16] Recently, an enzymatic hydrolysis study was performed on a lactic acid based dendrimer by the group of Seebach.[17]

Chiral objects: The relationship between macroscopic chirality of objects and intrinsic chirality of molecules has puzzled many scientists for decades. When we compare these two forms of chirality (e.g. the mirror image relationship of our hands versus the identical configurations of the molecules that make up both hands), we recognize that somewhere in the growth of matter the molecular chirality is overruled by other packing phenomena. This effect is well-documented and accepted for crystallization.[18] However, it is less known for more disordered structures, despite the fact that a number of chiral aggregates and polymers can be switched between diastereoisomeric conformers, while the configuration at the stereocenters is unaffected.[19, 20] In this section we want to highlight the fact that chiral dendrimers are an attractive class of compound to shed light on the issue of chiral objects in general.

The most appealing form of chiral dendrimer can be viewed in terms of the description that Green and Garetz used for the chirality of atactic polystyrene.[21] Since each molecule of polystyrene is chiral by definition due to its atactic nature, it will be present as a mixture of stereoisomers in which the mirror-image enantiomers are not present, owing to statistical improbability. As a result of the flexibility of the polystyrene chain, the detection of chirality is only theoretical. However, it is possibile that dendrimers can bring this notion within the realm of reality, and this is why we mention our class 6 of chiral dendrimers. Suppose that high-generation dendrimers with highly packed surfaces do indeed have very rigid conformations; each dendrimer will then be chiral and kinetically stable, while it is statistically impossible that its mirror image be present.[22] It should be possible to study these dendrimers with a variety of the recently introduced nanometer-scale techniques with spectroscopy tools like SNOM, AFM, etc. In order to illustrate this type of chirality, four different conformations of our dendritic box, generated by computer, are given in Figure 3. Whether the chirality can be detected then depends on the rigidity of the dendritic object.

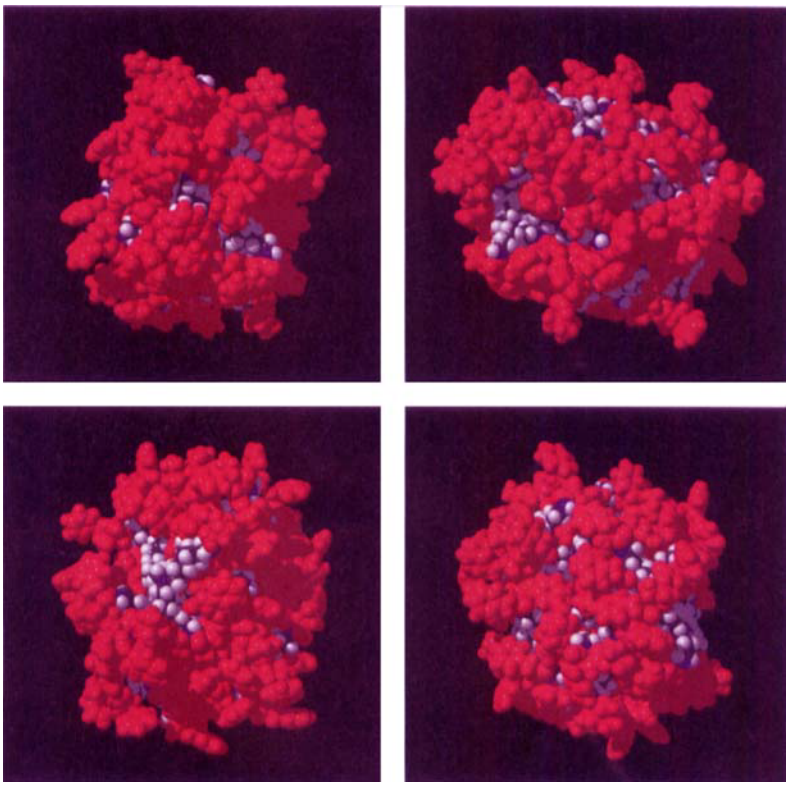

Figure 3. Four conformations of the dendritic box that possess macroscopic chirality.

The chiral dendrimers of class 5 represent a second type of chiral object in which constitutionally different branches are attached to a (chiral) core. We have investigated this type of chirality by synthesizing the dendrimers A and B in which four Fréchet wedges of different generation are attached to a core based on pentaerythritol (Figure 4).[23] A multistep synthesis afforded both compounds in their racemic form. Unfortunately, these dendrimers could not be obtained in their enantiomerically pure form, since all separation techniques available to us were unable to discriminate between enantiomers of this kind. Therefore, chiral dendrimer C was prepared, consisting of three different generations of Fréchet wedges and a chiral glycerol derivative (Figure 5).[24] In this case the polymer could be obtained in enantiomerically pure form for both (*R*) and (*S*) enantiomers, owing to the synthetic procedure and the starting material (*S*)-solketal. Optical rotation, optical rotatory dispersion (ORD), and circular dichroism (CD) studies on dendrimer C showed that no optical activity could be detected. Therefore, we

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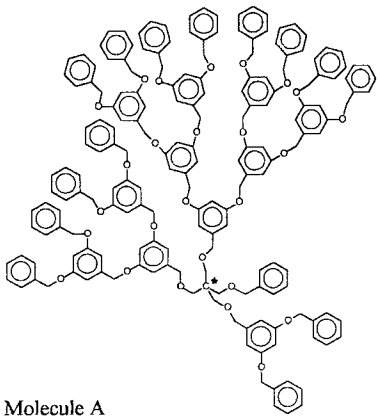
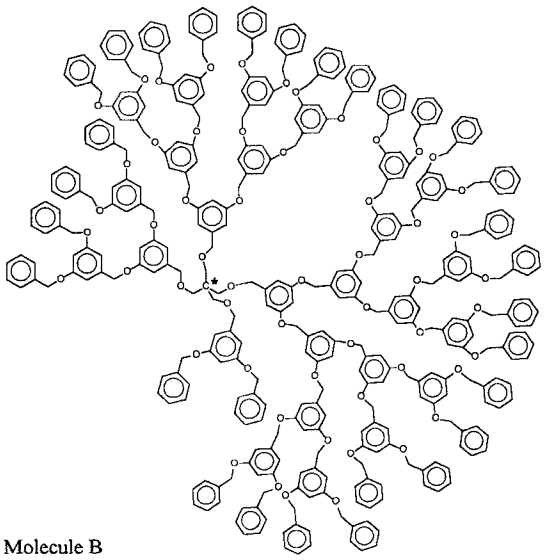


Molecule A



Molecule B

Figure 4. Chiral dendrimers A and B consisting of a chiral core to which four constitutionally different wedges are attached [23].

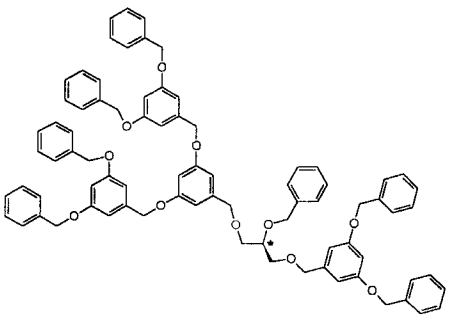


Figure 5. The enantiopure chiral dendrimer C synthesized from solketal [24].

referred to this compound as being cryptochiral,[25] and in fact it is the macromolecular analogue of 4-ethyl-4-propylundecane, reported by the group of Wynberg in 1965.[26] The conformational flexibility and the lack of difference in the electronic properties of the substituents are used to explain the zero rotation. As a result it is difficult to ascertain whether the local chirality of the core is expressed in the mesoscopic chirality of dendrimer C. Studies to increase the rigidity in this class of chiral dendrimer are in progress, with the aim of preparing macroscopic rigid chiral objects.

A rapidly increasing number of papers have been addressing the formation of well-defined dendrimers made out of chiral building blocks and the use of their optical activity in the study of interactions within the dendrimers. Seebach[27] reported a number of compounds based on this principle, where chirality stems from the core, or from both the core and the branching units. In a fundamental study examining the contributions of the different chiral units to the overall optical activity, Chow[5, 28] synthesized layered dendrimers with both configurations of tartaric acid derivatives. He indicated that the optical activity could be determined by the number of (*R*)- and (*S*)-tartaric acid units and that the individual chiral units did not influence each other. McGrath[29] and Sharpless[30] recently reported several chiral objects. The work of McGrath et al. is of great value, because they describe in detail the difficult analysis of the optical rotation for dendrimers of class 4, in which the core, branching units, and end groups are chiral.[29] Using a series of model compounds (Figure 6), they show that the optical activity

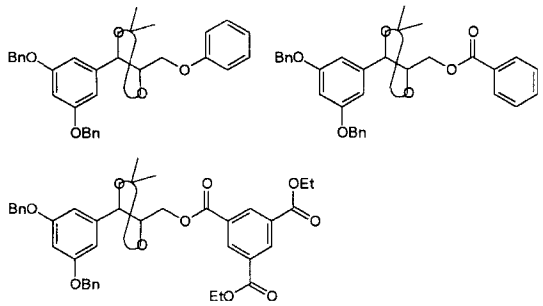


Figure 6. Model compounds used to determine the optical activity of the McGrath dendrimer [31].

of a building block is dependent on where the unit is positioned within the dendrimer and that the optical rotation is not just additive, because the chemical identity of a unit in the core changes with increasing generation. Hence, small deviations from additivity are explained by the constitutional differences between the units.[31] In this respect, high molecular weight dendrimers and linear polymers differ significantly. Within linear polymers the chiral repeating units are similar, whereas the same chiral repeating units within a dendrimer are constitutionally and environmentally different.

Chiral surfaces: Over the last decades much attention has been focused on two-dimensional surface interactions, especially those of Langmuir–Blodgett films. When dendrimers that are approaching their sterically induced stoichiometry are modified on the surface with chiral end groups, they can be viewed as curved surfaces in which the end groups are positioned with the help of covalent bonds. This can lead to very specific interactions between the various end groups, since it is almost impossible to obtain crystalline-like properties on a curved surface. A large number of reports have dealt with the properties of the curved surfaces of dendrimers, however, only a few studies have made use of chiral surface units to form chiral dendrimers.

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In the first example of a chiral dendrimer of class 3,[6] Newkome et al. modified arborols with the enantiomerically pure amino acid tryptophan. The modification was performed for a number of generations; however, no peculiarities in the chiroptical behavior were found (the optical activity per end group was roughly constant for all generations). The same constant optical rotation per end group was observed in a series of saccharide-modified poly(propylene imine) dendrimers.[14a]

Studies on the dendritic boxes,[14b, c] in which the poly(propylene imine) dendrimers were modified with various protected amino acids, showed that the optical activity decreases with increasing generations of dendrimer (Figure 7). This decrease is

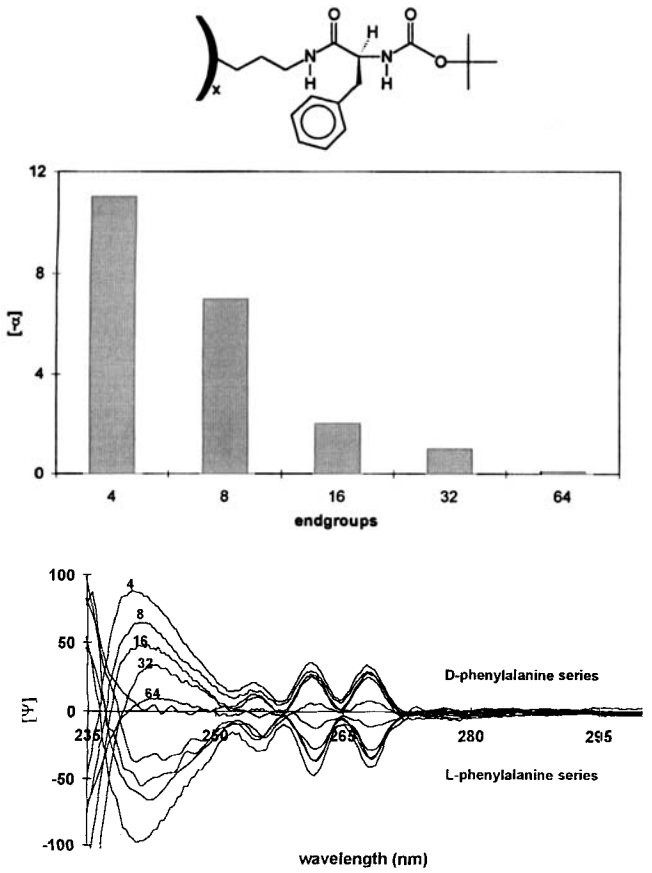

Figure 7. Chiroptical features of the *N*-*t*-BOC-L-phenylalanine-modified poly(propylene imine) dendrimers: dependence of optical activity [α] on generation and the specific ellipticity Ψ for the D- and L-phenylalanine series.

most pronounced for the larger amino acids such as L-tyrosine and L-phenylalanine. The vanishing optical activity is not due to racemization, concentration, temperature, or solvent effects. From model studies, it became clear that the optical rotation of the *N*-*t*-BOC-L-phenylalanine unit is very sensitive to the local environment and can have a positive or negative value, depending on the solvent. It is now assumed that the local environment of the *N*-*t*-BOC-L-phenylalanine end group changes as the packing becomes more dense on going to higher generations. As the packing becomes more dense, the end groups will have a number of different frozen-in conformations, which will yield an average optical rotation for all end groups of almost zero. When a chiral end group is used that does not have a solvent-dependent optical rotation, a roughly constant optical rotation for the dendrimers of different generation is obtained. This is illustrated in Figure 8 for chiral dendrimers with almost the same molecular volume. In this case the optical rotation of the end group is independent of the solvent, and the increase in generation does not influence the overall optical activity. This result does not mean that these end groups are not densely packed, but rather that the end group is not sensitive to differences in packing.

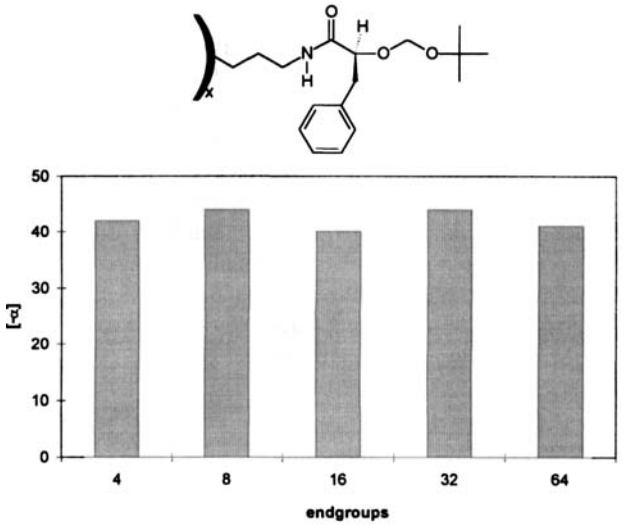

Figure 8. Optical activity versus generation for the acetal-functionalized dendrimers.

From the discussion above, we can conclude that the *N*-*t*-BOC-L-phenylalanine unit in the dendritic box is a special case and can be used as probe for the local environment of the end group of a dendrimer. The issue of dense packing at the periphery of a dendrimer has been further investigated by the introduction of an alkyl-chain spacer between the *N*-*t*-BOC-L-phenylalanine unit and the end of the branching of the dendrimer. The dendrimers of the first (with four end groups) and of the fifth generation (with 64 end groups) were synthesized and compared with the chiral dendrimer without spacers (Figure 9). The opti-

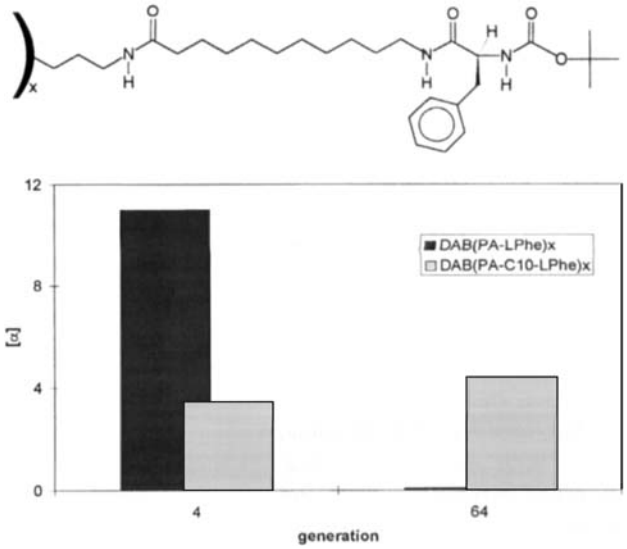

Figure 9. Influence on density of packing observed on introducing an alkyl chain spacer between the surface of the dendrimer and the chiral end group.

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cal activity remains constant for both derivatives with a spacer at $[\alpha]_D^{20} = 4$, which is in sharp contrast to the decrease from $[\alpha]_D^{20} = 11$ to 0.1 for the dendritic box without a spacer. The difference between $[\alpha]_D^{20} = 4$ and 11 is caused by mass effects. Hence, with a spacer the end group can freely adopt its preferred conformation, and the *N*-*t*-BOC-L-phenylalanine unit has been shown to be a useful probe for the local density of a dendrimer surface.

Chiral clathration: Host–guest interactions and clathration in a dendritic architecture are intriguing properties of dendrimers, especially if they can be achieved with chiral recognition. No examples of enantioselective clathration in chiral dendrimers have been reported so far, but a small number of related experiments are worth mentioning. We have shown that induced circular dichroism (ICD) can be obtained from achiral guest molecules encapsulated into the chiral dendritic box. The ICD effects found are small and in agreement with the conformational disorder in the shell of the dendritic box. However, these ICD spectra could be used to discuss the possible orientational order of the encapsulated guest. An exciton-coupled ICD spectrum has been recorded for four molecules of Rose Bengal encapsulated in a dendritic box (Figure 10).[32] It will be a real challenge to study the interaction of chiral guest molecules with the many chiral dendritic hosts now available, discussed above in the section on chiral objects.

The potential in this area of stereoselective chemistry is illustrated by the exciting report, from the group of Seebach, of high diastereoselectivity in the formation of chiral dendrimers.[33] A chiral triol core was treated with two dendritic wedges differing only in the chirality of the building blocks (Figure 11). In one case three wedges were found to react with the triol core, whilst in the other only two wedges were attached. A large number of reference experiments were performed to verify this observation.

Investigations into the field of enantioselectivity in clathration, encapsulation, and dendrimer formation are still in their infancy, but there is exciting potential here, both scientifically (e.g. modeling enzymatic activity and molecular recognition) and technologically (e.g. separation of enantiomers and sensors).

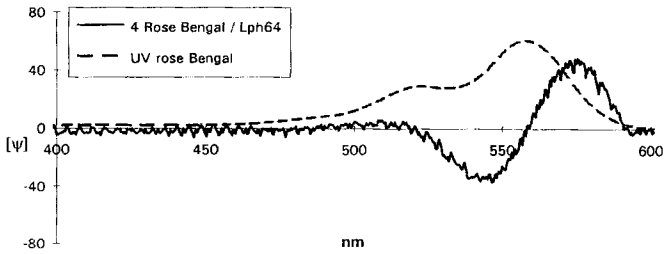

Figure 10. Induced CD effect for encapsulated Rose Bengal molecules in a dendritic box [32].

Catalysis: Dendrimers have the potential to become important carriers for catalysts due to the homogeneous nature of the systems with most of the catalytic sites exposed to the solvent on the one hand, and the possibility of isolating these three-dimensional nanosize systems by (ultra)filtration techniques on the other hand. The first reports in this area are described by the group of van Koten;[34] here, dendritic aryl nickel complexes

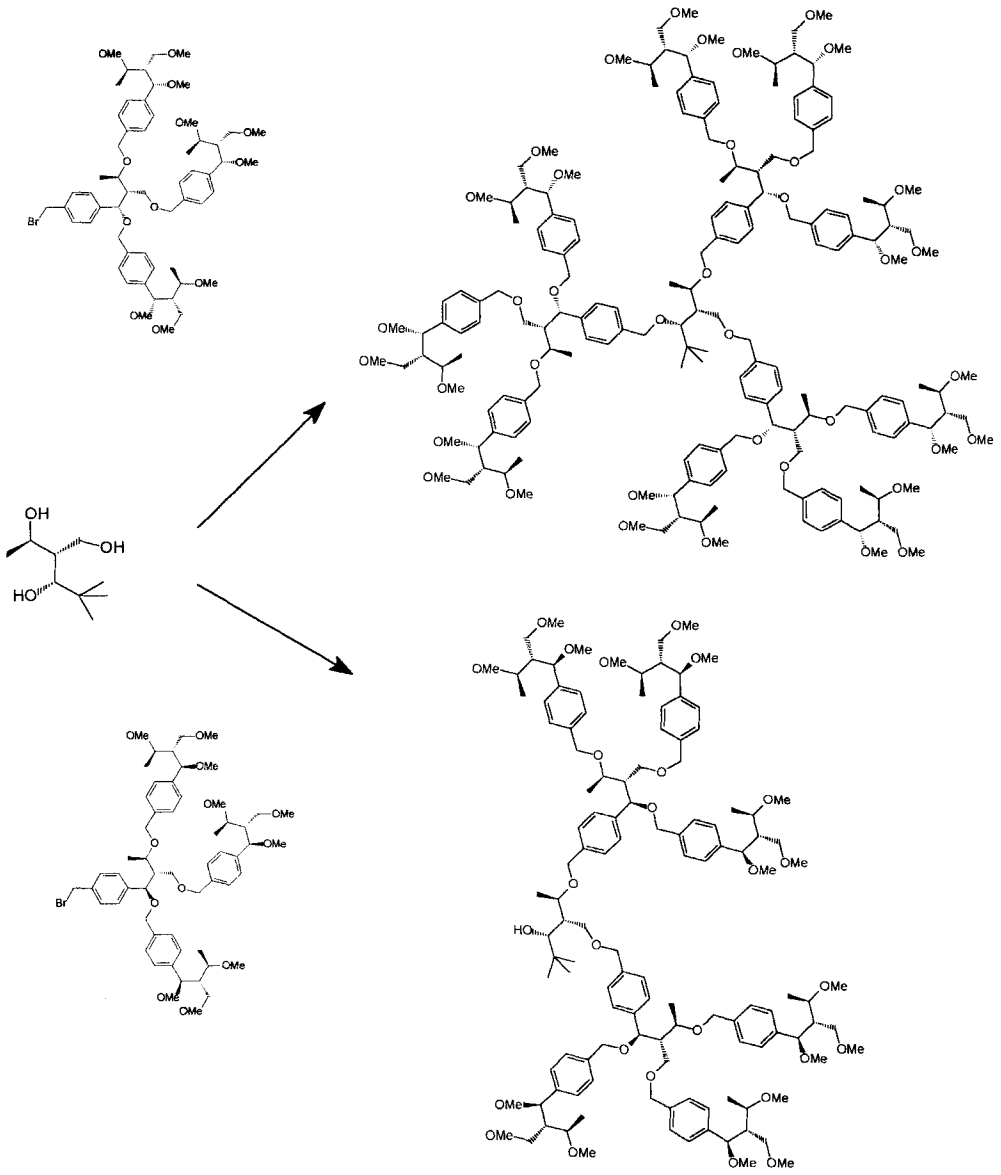

Figure 11. Diastereoselectivity in dendrimer formation [33].

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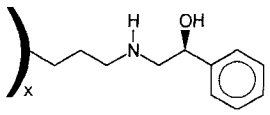
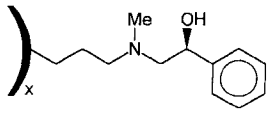
were used as catalysts for the Kharash addition of tetrachloromethane to methyl methacrylate. Obviously, asymmetric catalysis in such systems is not only of general interest, but also shows the scope and limitations of this approach in detail. Initial results with low-generation chiral dendrimers have shown that these multiply substituted molecules act as simple models, but their isolation by ultrafiltration is still a distant goal.[35–37]

In our group we made many attempts to modify the NH_2 end groups of poly(propylene imine) dendrimers into enantiomerically pure ligands for the addition of diethylzinc to benzaldehyde.[38] Two types of derivatives were used for this purpose and the preliminary results are given in Table 1. In all cases studied,

Table 1. The use of modified poly(propylene imine) dendrimers as catalysts for the addition of diethylzinc to benzaldehyde [38].



Catalyst 1



Catalyst 2

End groups	Catalyst 1 Yield (%)	e.e. (%)	Catalyst 2 Yield (%)	e.e. (%)
1	82	36	86	27
2	75	36	77	25
4	54	11	86	25
8	58	9	64	24
16	63	13	57	18
32	49	10	70	18
64	57	7	68	18

both the chemical yields and the enantiomeric excess decreased with increasing generation of the dendrimers. Although it proved to be very difficult to obtain catalytically active dendrimers in high purity, we propose that the loss of activity is caused by multiple interactions on the dendritic surface (see also the section on chiral surfaces). As a result of the denser packing of the end groups at the periphery of higher generations, a number of different conformations can be envisaged, resulting in the presence of different catalytic sites. A possible solution for this problem could be found by introducing an alkyl chain as a spacer between the surface of the dendrimer and the chiral group that acts as the catalyst. We have already shown that this spacer minimizes the interactions between the chiral end groups (see above) and that these types of molecules can easily be isolated by membrane filtration. In the near future we will analyze their activity as catalysts.

This field of research can be regarded as a revisitation of polymer-supported chemistry, and the results found for dendrimers should therefore be compared with those found for modified linear macromolecules. We expect that by proper design the chiral dendritic catalysts will have a great future. Unfortunately, a large number of trial and error experiments, many of which have only yielded negative results, have had to be performed in order to establish the scope and limitations of these systems.

Reflections and Conclusions

The study of chirality in dendritic architectures is only in its infancy, but the initial reports have already shown that many intriguing stereochemical issues are involved. A number of hypotheses are proposed to explain the chiroptical properties (optical rotations, etc.) found for dendrimers with chirality in the core, the branching unit, and/or the end groups. These ideas should be confirmed with more examples, but it is clear from the chiroptical studies of chiral dendrimers that they differ in many aspects from their linear macromolecular counterparts. Despite the fact that many intriguing applications of chiral dendrimers can be envisaged, it is still too early to draw conclusions on whether these ideas will remain in the realm of fantasy or whether chiral dendrimers will indeed play a prominent role in catalysis, molecular recognition, and biocompatibility. It is also to be expected that the studies on chiral dendrimers may help in the understanding of chiral aspects of globular proteins. We will continue pursuing our aim to prepare macroscopic chiral objects based on dendrimers, even if the results may only be of fundamental interest to stereochemists active in the domain of mesoscopic structures.

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