



# Second Generation Self-Assembling Dendrimer Combining Supramolecular and Dynamic Covalent Chemistry

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*Dedicated to Prof. Dr. Michael Schmittel on the occasion of his retirement.*

A monodisperse second generation self-assembled dendrimer has been obtained combining supramolecular chemistry and dynamic covalent chemistry as orthogonal binding moieties. A branching unit **18** and a core **5** were connected via a heteroleptic terpyridine zinc complex exploiting the sterical hindrance of mesitylene units in the 6,6''-position of one of the terpyridines as the distinction between the ligands. Solubility problems could be solved by introduction of an ethylhexyl ether. The final sphere of the dendrimer was connected via

imines, hydrazones and oximes, whereby the oxime made from *O*-methylhydroxylamine (**22**) led to a complete turnover of all aldehyde functions. Furthermore, no amine signal was left and also no signals for a diffusion constant of the hydroxylamine **22** were observed. The successful formation of the dendrimers was analyzed by <sup>1</sup>H NMR and DOSY NMR spectroscopy. Furthermore both, the first and second generation dendrimers could be detected by ESI HRMS.

## Introduction

A century ago, the chemical community started to understand macromolecules<sup>[1,2]</sup> and many classes of polymeric compounds have been found or made. Nature provides macromolecules as well as chemical synthesis does. Both classes can be subdivided into

- homo- and heteropolymers (e.g., cellulose vs. proteins), and
- polymers which are monodisperse or not (see also proteins vs. cellulose).

In chemical synthesis, the production of a monodisperse polymer is not straightforward because the usual methods of polymerization (step or chain polymerization) do not allow the control of the chain length. Since the end of the last millennium, however, a mono-disperse class of polymers became available: the dendrimers.<sup>[3]</sup> Building on the seminal results of Vögtle and co-workers who synthesized the first cascade molecules,<sup>[4]</sup> two strategies were established for the synthesis of more or less spherical, mono-disperse molecules: the divergent synthesis (from the inside outwards) and the convergent synthesis (synthesis of dendrons which finally are assembled to a dendrimer).

Besides these classical routes, there is a third approach to mono-disperse dendrimers: the supramolecular one. Hirsch et al.<sup>[5]</sup> used the molecular recognition between isocyanuric acids and so-called Hamilton receptors to assemble dendrimers. Supramolecular dendrimers in general consist of a central unit binding the branching moieties. We will refer to them as core molecule and branching unit. As the last generation does not contain any branching, we will call it caps. By the proper choice of stoichiometry of core molecules, branching units and caps, self-assembled entities of varying molecular weight could be achieved. However, Hirsch et al.'s method did not guarantee mono-dispersity due to the use of identical recognition events in each shell of the self-assembled dendrimer.

Therefore, to obtain a mono-disperse, self-assembled dendrimer, different recognition domains must be used in each shell. For each additional generation of a dendrimer, a new recognition pattern must be chosen. And it must be ensured, that each new recognition is orthogonal to the previous ones.

In 2012,<sup>[6]</sup> we presented a second-generation dendrimer using two orthogonal hydrogen bond patterns. In the first shell, the recognition between a Hamilton receptor and an isocyanuric acid was used. Binding in the resulting supramolecule is achieved by six hydrogen bonds whose orientation is V-shaped. In the second shell, a linear pattern of four hydrogen bonds was used. Due to a different sequence of hydrogen bond donors and acceptors, and due to the different geometry (V-shape vs. linear), the recognition is orthogonal.

Orthogonal recognition has also been used for branching and connecting the resulting dendrons.<sup>[7–9]</sup>

In order to generate dendrimers of larger size, new recognition patterns must be incorporated. The task is therefore to synthesize new branching units (usually of the type AB<sub>2</sub>) with moieties A and B binding orthogonal to one another and to the ones used in the already existing dendrimer.

Besides hydrogen bonds, metal complex formation plays an important role in supramolecular chemistry. Pedersen's

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work on the host guest chemistry between crown ethers and metal ions was one of the starting points of supramolecular chemistry and was consequently recognized by awarding the Nobel prize in 1987.<sup>[10]</sup> But metal ion “recognition” has a much longer history, especially the complex formation with transition metals. Macrocyclic receptors have been created parallel to Pedersen’s work,<sup>[11]</sup> non-macrocyclic complexes date back to Werner.<sup>[12]</sup>

To use metal complex formation for the assembly of dendrimers, ordinary complex formation is not conducive. In order to selectively add a new shell in a dendrimer, the metal ion must bind to two different ligands, the core or a branching unit on the inner side, and a different branching unit or a cap on the outer side. Therefore, only heteroleptic complexes - i.e. a complex with two different, usually chelating ligands - can be used. An effective way to construct heteroleptic complexes is the use of ligands L\* with steric bulk in combination with related ones L without steric hindrance.<sup>[13]</sup> For metal ions with a coordination number of 6, 2,2':6',2"-terpyridines may be used, for those with a coordination number of 4, 2,2'-bipyridines or 1,10-phenanthrolines can be chosen. A metal ion M (we will ignore the charges in the following discussion for clarity) and the two ligands L and L\* have to be mixed in a 1:1:1 ratio. A sufficient steric hindrance in ligand L\* will not allow the formation of the complex ML<sub>2</sub>, but MLL\* would be possible. Of course, ML<sub>2</sub> can also be formed, but its formation would leave complexes ML\* and free ligands L\*. Energetically, the latter situation is less favored as the coordination of the metal ion in ML\* is not complete. Only when MLL\* is formed, all metal ions are completely complexed. Therefore, the 1:1:1 mixture of M, L, and L\* leads to the (in most cases) exclusive formation of the heteroleptic complex.

We therefore decided to use heteroleptic complex formation as one recognition event being orthogonal to the hydrogen bonds.

The strategy to synthesize supramolecular dendrimers differs fundamentally from the divergent and convergent synthesis. Those two apply a sequence of reactions which are irreversible. In contrast, the self-assembly approach is thermodynamically controlled. This applies to hydrogen bonded dimers as well as to metal complexes. The binding of all components is dynamic. While most bond forming reactions in organic chemistry are irreversible, especially those used in the traditional divergent or convergent syntheses of dendrimers, there are also reversible reactions. Many of them have been exploited in dynamic covalent synthesis (DCvC).<sup>[14]</sup> Due to their reversibility (and thus thermodynamic control), this reaction may also be applied to the synthesis of self-assembled, supramolecular dendrimers. Of course, also in the dynamic covalent connection, the reacting moieties must not be the same. Thus, disulfide exchange or olefin metathesis cannot be used. We have chosen imine formation.

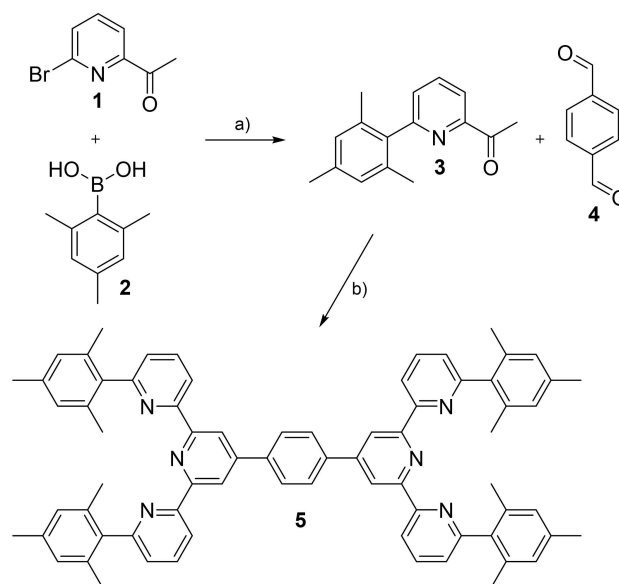
In this work, we present a new branching unit AB<sub>2</sub> which is orthogonal to the hydrogen bond patterns used up to now. The AB<sub>2</sub> unit allows incorporation into dendrimers by a reversible covalent reaction, here formation of imines and related compounds, and by a metal ion complex formation, here the

formation of a heteroleptic terpyridine complex. Both units can be used as recognition sites A or B, and both units can be incorporated in two orientations. Due to simpler synthesis, we chose terpyridines (A) and aldehyde (B) functions for our target molecules AB<sub>2</sub>. This branching unit allows the self-assembly of a second-generation dendrimer combining supramolecular and dynamic covalent chemistry.

## Results and Discussion

In a supramolecular dendrimer, in principle, the sterically hindered terpyridine can be placed on the inner side of the complex or the outer. We decided to connect the sterically hindered ligand L\* to the core (Scheme 1) in order to prevent the formation of insoluble polymers due to homoleptic coupling of several cores to one another. As sterically bulky substituents, mesitylene units were chosen. Because acetylpyridines often serve as terpyridine precursors, a mesityl residue was connected with 5-bromo-2-acetylpyridine (1) via Suzuki cross-coupling in 88% yield employing boronic acid 2.<sup>[15]</sup> The resulting mesityl substituted 2-acetylpyridine derivative 3 was then reacted with terephthalaldehyde (4) following the general procedure of the one-pot terpyridine synthesis from Wang and Hanan.<sup>[16]</sup> The divalent core 5 was obtained in 28% yield.

The AB<sub>2</sub> branching unit, complementary to the core, must possess an unhindered terpyridine L as function A. Two aldehyde moieties as function B allow a connection to the next sphere via condensation with NH<sub>2</sub>-containing molecules. Depending on its specific nature (amine, hydroxyl amine, hydrazine or hydrazide), imine, oxime and hydrazone formations are possible. Since the terpyridine synthesis requires an

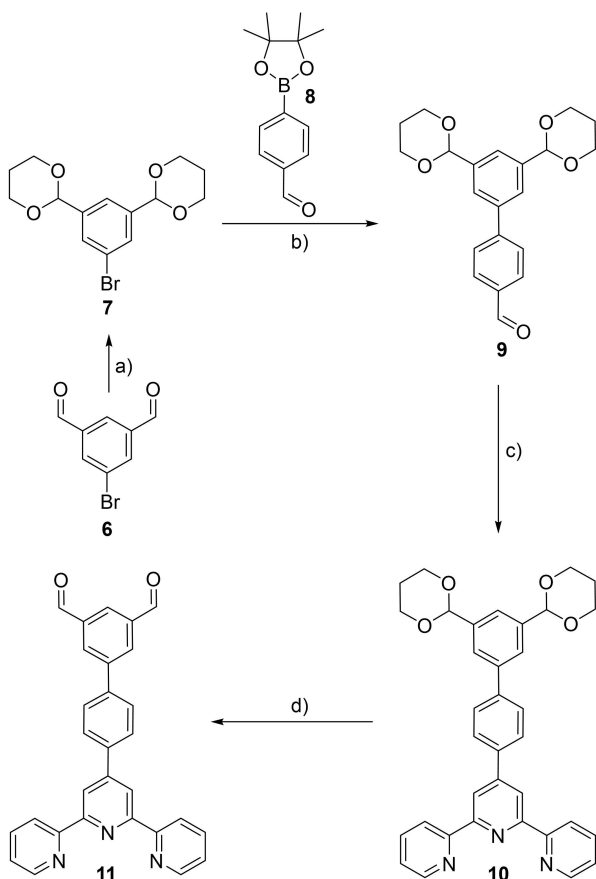


**Scheme 1.** Synthesis of core molecule 5. (a) KOAc, Pd(dppf)Cl<sub>2</sub>, toluene/EtOH/H<sub>2</sub>O 7:2:1, 2 d, 80 °C, 88%, (b) NaOH, aq. NH<sub>4</sub>OH, EtOH, 4 d, 78 °C, 28%.

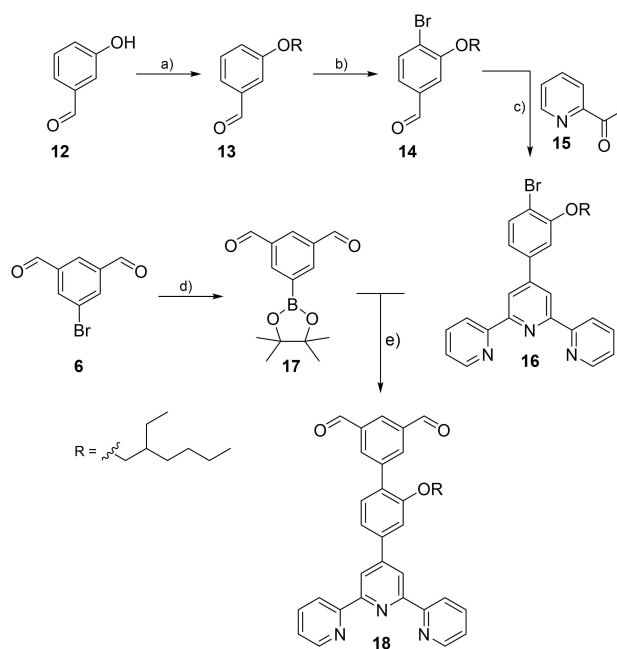
aldehyde as building block, the aldehyde functions B of the AB<sub>2</sub> branching unit needed to be masked during the synthesis.

Therefore, the CHO functions in 5-bromoisophthalaldehyde (**6**) were converted into the corresponding 1,3-dioxanes as reported in the literature in 82% yield (95%<sup>[17]</sup>) using propane-1,3-diol and *p*-toluenesulfonic acid as catalyst (Scheme 2). A subsequent Suzuki cross-coupling reaction of the doubly protected bromide **7** with boronic ester **8** gave biphenyl **9** in 75% yield. The unprotected aldehyde function in **9** introduced by the cross-coupling could now be reacted with 2-acetylpyridine (**15**) in the presence of sodium hydroxide and aqueous ammonia solution to give terpyridine **10** in 68% yield. By reaction with hydrochloric acid, the protecting groups in **10** could be removed quantitatively. Thus, AB<sub>2</sub>-building block **11** could be obtained in 42% overall yield. Even though ligand **11** does dissolve in chloroform, it turned out that its complexes with zinc ions were almost insoluble in this solvent.

An introduction of branched aliphatic residues often enhances the solubility of less soluble molecules in non-polar solvents such as chloroform.<sup>[18]</sup> Scheme 3 illustrates a possible strategy to incorporate an ethylhexyl ether into the AB<sub>2</sub> unit. Starting with 3-hydroxybenzaldehyde (**12**), a 2-ethylhexyl group was introduced via a Williamson ether synthesis to give **13** in



**Scheme 2.** Synthesis of the AB<sub>2</sub> unit **11**. (a) *p*TsOH, propane-1,3-diol, toluene, 1 d, 111 °C, 82%, (b) KOAc, Pd(dppf)Cl<sub>2</sub>, 1,4-dioxane, 2 d, 80 °C, 75%, (c) 2-acetylpyridine (**15**), NaOH, aq. NH<sub>4</sub>OH, EtOH, 3 d, 78 °C, 68%, (d) 2 M HCl, THF, 1 d, room temp., quant.



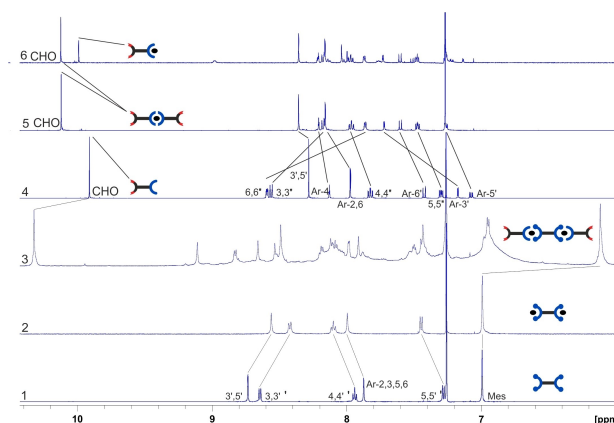
**Scheme 3.** Synthesis of the modified AB<sub>2</sub> unit **18**. (a) 2-Ethylhexylbromide, K<sub>2</sub>CO<sub>3</sub>, DMF, 80 °C, 1 d, 78%, (b) bromine, acetic acid, 1 d, room temp., quant., (c) NaOH, aq. NH<sub>4</sub>OH, EtOH, 5 d, 78 °C, 86%, (d) 4,4',4',5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane, KOAc, Pd(dppf)Cl<sub>2</sub>, 1,2-dimethoxyethane, 1 d, 80 °C, 87%, (e) KOAc, Pd(dppf)Cl<sub>2</sub>, 1,2-dimethoxyethane, 3 d, 80 °C, 29%.

78% yield. Subsequent bromination in acetic acid gave 4-bromide **14** in quantitative yield. This aldehyde **14** was then reacted with 2-acetylpyridine **15** in the presence of sodium hydroxide and ammonium hydroxide to give terpyridine **16** in 86% yield. The previously introduced bromine atom in *para*-position, with respect to the terpyridine, allows further synthesis via Suzuki cross-coupling.

The coupling partner, boronate ester **17**, was synthesized from 5-bromoisophthalaldehyde (**6**) following a literature procedure with 4,4',4',5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane, potassium acetate and Pd(dppf)Cl<sub>2</sub> in 87% yield which is comparable to the reported one (85%<sup>[19]</sup>). Subsequent coupling of bromide **16** with boronate ester **17** gave the branching unit **18** in 29% yield. Over all steps, a yield of 20% was achieved. As expected, this modified branching unit **18** showed significantly improved solubility and the metal complexes formed with this ligand showed a very good solubility in chloroform. Summarizing, the introduction of the ethylhexyl ether into the branching unit **18** solved the solubility problems and enables the formation of chloroform soluble heteroleptic metal complexes.

By connecting the branching unit **18** to the core **5** via complex formation, a first-generation dendrimer will be formed. An overview of the synthesized ligands **18** and **5** with schematic representations is shown in Figure 1 together with a schematic illustration of the final second-generation dendrimer.

Before assembling the potential dendrimer, the formation of the heteroleptic complex formed by the core **5** and the branching unit **18** was studied separately. Needless to



**Figure 1.** The sterically hindered di(terpyridine) core **5** and the non-hindered terpyridine branching unit **18** form a heteroleptic complex with zinc ions (first generation of a dendrimer). The outer aldehyde functions can react with amines and related compounds to form imines and imine-like structures (extension to the second generation of the dendrimer). The terpyridines are highlighted in blue. Aldehydes, H<sub>2</sub>N compounds and related condensation products are colored red. Bottom: schematic representation of the second generation tetraoxime ( $M = Zn^{2+}$ ,  $Y = C_6H_4$ ,  $X = C_6H_3OCH_2CH_2NBu$ ; the sterically demanding mesityl residues are abbreviated as grey spheres).

Besides the shift of the mesitylene-*H*-signal in spectrum 3, there is another strong evidence for the formation of the heteroleptic complex **5**·**Zn**<sub>2</sub>·**18**<sub>2</sub>. The aldehyde signal of the branching unit **18** shifts from 9.91 ppm (spectrum 4) to 10.32 ppm (spectrum 3). To prove that this shifted *CHO* signal belongs to the heteroleptic complex **5**·**Zn**<sub>2</sub>·**18**<sub>2</sub>, all other possibly formed complexes were measured separately and their spectra are also shown in Figure 2. Spectrum 4 shows the <sup>1</sup>H

The formation of the heteroleptic complex **5·Zn<sub>2</sub>·18<sub>2</sub>** can be detected in DOSY NMR spectra, too. The determined diffusion coefficient *D* gives information on the solvodynamic radii of particles and therefore allows to classify them by size. Core **5** had a diffusion coefficient *D* of  $5.6 \cdot 10^{-10}$  m<sup>2</sup>/s and for the branching unit **18**, a diffusion coefficient *D* of  $7.4 \cdot 10^{-10}$  m<sup>2</sup>/s was determined. The heteroleptic complex **5·Zn<sub>2</sub>·18<sub>2</sub>** showed a diffusion coefficient *D* of  $3.2 \cdot 10^{-10}$  m<sup>2</sup>/s (see SI), which implies the formation of a larger particle compared to the uncoordi-

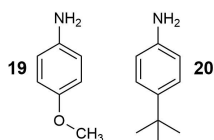
nated ligands. In summary, three different methods [shift of the  $^1\text{H}$  NMR signals, HRMS (ESI) and the diffusion coefficient  $D$  determined by DOSY NMR] successfully showed the complete formation of the heteroleptic complex  $5 \cdot \text{Zn}_2 \cdot 18_2$ .

For the final formation of a second-generation dendrimer, the aldehyde groups of branching unit **18** had to react with suitable partners, amines, and related compounds, to give imines or imine-like structures such as oximes and hydrazones. One equivalent of the  $\text{H}_2\text{N}$ -compound per aldehyde group was added in every case.

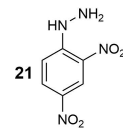
## Imines

The first experiment used *p*-anisidine (**19**, Figure 3) as amine. Unfortunately, the solubility of the dendritic structure decreased while the imine formed causing the dendrimer to precipitate from chloroform. The NMR did not show any remaining aldehyde signal and no signals for the heteroleptic complex  $5 \cdot \text{Zn}_2 \cdot 18_2$  at all and no signals of remaining *p*-anisidine (**19**) (see SI).

To increase the solubility, the 4-*tert*-butylaniline (**20**, Figure 3) was tried next, but even though there still are some NMR signals that could be assigned to the heteroleptic complex  $5 \cdot \text{Zn}_2 \cdot 18_2$ , the signals were very broad and difficult to analyze. The aromatic signals of the amine compound could not be observed anymore. The aldehyde signal is expected to vanish completely by a 100% conversion to an imine and a new signal for the imine proton should be observable. Due to the broad signals, the formation of an imine could not be confirmed. In contrast, three different aldehyde signals were found: 10.31 ppm (heteroleptic complex  $5 \cdot \text{Zn}_2 \cdot 18_2$ , see above), 9.98 ppm (this one can be assigned to the 1:1 complex of the branching unit **18** with zinc), and 10.30 ppm. The signal at 10.30 ppm may indicate an at least partial formation of an imine (e.g., one or two of the four possible aldehyde components could have reacted). Measuring the same sample after four weeks did not show this signal anymore but showed even more broadened signals instead. Taking this into account, 4-*tert*-butylaniline (**20**) appears to be a better alternative compared to *p*-anisidine (**19**) for connecting the second generation via imine formation. But still, the imines did not form completely and due to broad signals, the formation of the second-generation dendrimer cannot be proven (see SI).



**Figure 3.** *p*-Anisidine (**19**) and 4-*tert*-butylaniline (**20**) were used to form imines.



**Figure 4.** 2,4-Dinitrophenylhydrazine (**21**) was used to form hydrazones.

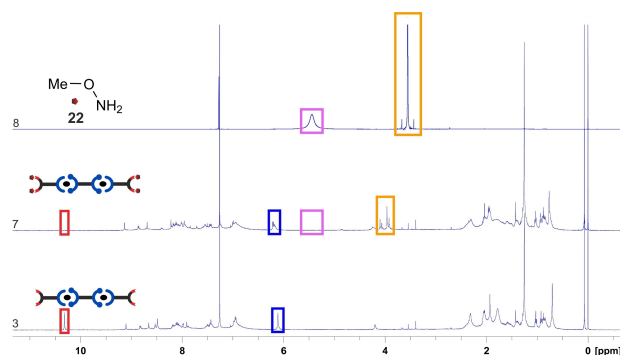
## Hydrazones

An alternative for extending heteroleptic complex  $5 \cdot \text{Zn}_2 \cdot 18_2$  via its aldehyde groups is the formation of a hydrazone upon reaction with a hydrazine. Therefore, 2,4-dinitrophenylhydrazine (**21**, Figure 4) was used as  $\text{H}_2\text{N}$  containing compound.

A comparison of the  $^1\text{H}$  NMR spectra of the heteroleptic complex  $5 \cdot \text{Zn}_2 \cdot 18_2$  (which is the first generation) with the one after the addition of the hydrazine clearly shows that a new aldehyde signal appears [signal at 10.28 ppm right next to the aldehyde signal that belongs to the heteroleptic complex  $5 \cdot \text{Zn}_2 \cdot 18_2$  (10.31 ppm)]. This indicates at least a partial formation of the desired hydrazone. Even more interesting, there is a new singlet at 8.27 ppm which could belong to the  $\text{CH}$  of the new hydrazone. A complete assignment is not possible due to other broad signals and the formation of multiplets which also shift a bit during the (partial) formation of the hydrazone. The mesitylene signal shows a shift from 6.11 ppm to 6.21 ppm which is broadened (see SI).

## Oximes

The third class of compounds for the formation of imine-like structures are hydroxylamines, leading to oximes. *O*-Methylhydroxylamine (**22**) was chosen and added in stoichiometrical amounts with respect to each aldehyde function. The spectra of the hydroxylamine, of the heteroleptic complex  $5 \cdot \text{Zn}_2 \cdot 18_2$ , and of a 4:1 mixture of those two are compared in Figure 5.



**Figure 5.** Comparison of the  $^1\text{H}$  NMR spectra of the first-generation supramolecular dendrimer  $5 \cdot \text{Zn}_2 \cdot 18_2$  (spectrum 3) with the second-generation containing oxime connections (spectrum 7), and *O*-methylhydroxylamine (**22**) (spectrum 8). The molecular structures of the building blocks are shown in Figure 1, important signals are color coded: aldehyde = red, mesitylene = blue, amine = purple, methoxy = orange.

The strongest evidence for the formation of the oxime is the complete vanishing of the aldehyde signal at 10.32 ppm (spectrum 7, red). Also, the broad H<sub>2</sub>N signal at 5.44 ppm of the hydroxylamine **22** (spectrum 8, purple) completely vanished (spectrum 7).

This means that all four aldehyde functions fully reacted with the hydroxylamine to form the oxime and bind the caps in the second-generation self-assembled dendrimer. All other signals also undergo at least small shifts (Figure 5, spectrum 7). Notable is the shift of the two signals at 8.53 ppm and 8.49 ppm either to 8.41 ppm or into the multiplet at 8.23 ppm–7.99 ppm. The shape of this multiplet also changed a bit. Also, new signals at 7.85 and 7.71 ppm appear which were probably hidden in one of the multiplets before.

Interestingly, the mesitylene signal (Figure 5, blue) at 6.11 ppm vanishes and a multiplet at 6.13–6.25 ppm appears. This could either indicate the splitting of the mesitylene-*H* into a multiplet or it could arise from another signal at a similar chemical shift. The HSQC clearly shows only one correlated signal for this multiplet and the HMBC shows <sup>3</sup>*J* couplings as expected for the mesitylene-*H*, manifesting the assumption of a splitting of the mesitylene-*H* into a multiplet. Also, the integration of this multiplet (8 when compared to the 12 hydrogen atoms of the oximes' methyl groups) indicates that the multiplet must arise from a splitting of the mesitylene-*H*.

To find out what causes this multiplet, a MM+ forcefield calculation of the structure of **5·Zn<sub>2</sub>·18<sub>2</sub>·22<sub>4</sub>** was carried out with hyperchem (see SI). The result shows that the center pyridine ring of the sterically unhindered ligand **18** is stacked between two mesitylene units of core **5**. Typically for  $\pi\pi$  stacking, the rings are not exactly on top of each other but slightly offset. This causes the methyl group in 4-position of one of the mesitylene units to occupy the chemical space in front of the aromatic system carrying the ethylhexyl ether and preventing this system from a completely free rotation. The calculation also shows a dihedral angle of 61° between the mesitylene units and the pyridines they are attached to. This twist and the unsymmetry discussed above are the reason that all mesitylene hydrogen atoms have different chemical environments. Therefore, a multiplet instead of a singlet is observed. Taking a closer look at this multiplet between 6.25 and 6.13 ppm, it may be the result of an overlay of an AB double doublet for the hydrogen atoms of the mesitylene ring close to the ethylhexyl ether and a broad signal for the ones further away of the bulky residue.

Assuming this restriction of rotation, also the signal of the methyl group (Figure 5, orange) of the former hydroxylamine deserves a closer look. First of all, it has to be kept in mind that oximes can possess an *E* and a *Z* configuration.<sup>[20]</sup> This can be detected in the spectrum of the homoleptic complex **Zn·18<sub>2</sub>·22<sub>4</sub>** (see SI). In the case of the heteroleptic complex **5·Zn<sub>2</sub>·18<sub>2</sub>·22<sub>4</sub>**, there is a similar pattern, but this pattern can be detected twice (at 4.10, 4.07 and 3.97, 3.92 ppm). Thus, a total of four singlets exists for the methyl groups of the oximes. This can be explained by the different chemical environment of the two oximes at one former isophthalaldehyde in combination with the *E/Z* isomery. The different environment could be

caused by the ethylhexyl ether. But only, if a rotation between the two aryl rings is slow on the NMR time scale.

The DOSY NMR spectrum also does not show any signals with a diffusion constant expected for the hydroxylamine **22** (which possesses a diffusion constant around 3.1·10<sup>-9</sup> m<sup>2</sup>/s). Instead, the observed diffusion constants were ca. 3.2·10<sup>-10</sup> m<sup>2</sup>/s. This is comparable to the diffusion constants found for the heteroleptic complex **5·Zn<sub>2</sub>·18<sub>2</sub>** with the free aldehyde functions. It is plausible, that the DOSY still shows similar diffusion constants since the formation of four oximes (exchange of O by NOME) does not have a big impact on the size, and thus the diffusion constant of the whole dendrimer.

The second-generation dendrimer **5·Zn<sub>2</sub>·18<sub>2</sub>·22<sub>4</sub>** was also detected by high resolution mass spectrometry (ESI). Two differently charged ions were detected due to different numbers of triflate counter ions associated to the complexes: 1346.4646 (calcd. 1346.4612,  $\Delta = 2.52$ ), C<sub>152</sub>H<sub>146</sub>F<sub>6</sub>N<sub>16</sub>O<sub>12</sub>S<sub>2</sub>Zn<sub>2</sub><sup>2+</sup>; 847.9894 (calcd. 847.9899,  $\Delta = -0.68$ ), C<sub>151</sub>H<sub>146</sub>F<sub>3</sub>N<sub>16</sub>O<sub>9</sub>S<sub>1</sub>Zn<sub>2</sub><sup>3+</sup>.

## Conclusion

A sterically hindered diterpyridine core **5** and an AB<sub>2</sub> moiety **11** containing a terpyridine and two aldehydes were successfully synthesized. Due to the insolubility of the complexes formed with **11** in CDCl<sub>3</sub>, this ligand could not be used as a branching unit for the formation of a dendrimer. Therefore, an ethylhexyl ether was introduced into the branching unit **18**. The increased solubility made the formation of the first-generation dendrimer **5·Zn<sub>2</sub>·18<sub>2</sub>** possible. The structural assignment was supported by the shifts of the <sup>1</sup>H NMR, DOSY NMR experiments, and ESI HR mass spectra.

Second generation dendrimers were planned to result via formation of imines or imine-like structures, combining dynamic covalent chemistry with supramolecular chemistry. The successful conversion of all four aldehyde groups was observed by using the *O*-methylhydroxylamine (**22**) for the formation of a tetraoxime. Both, the aldehyde signal of the heteroleptic complex **5·Zn<sub>2</sub>·18<sub>2</sub>** and the H<sub>2</sub>N signal of the hydroxylamine vanished completely in the <sup>1</sup>H NMR spectra – a proof for the formation of the second-generation dendrimer! Even though the DOSY NMR did not show a larger species compared to the first-generation dendrimer, it also did not show any signals that could be assigned to unreacted *O*-methylhydroxylamine (**22**), giving another proof for the formation of the second-generation dendritic structure. It was also possible to detect the second-generation dendrimer **5·Zn<sub>2</sub>·18<sub>2</sub>·22<sub>4</sub>** via ESI HR mass spectrometry.

In summary, it was possible to form a self-assembling second generation dendrimer with a molecular weight of 2996 g·mol<sup>-1</sup> combining supramolecular chemistry and dynamic covalent chemistry using the orthogonal binding motifs of heteroleptic complex formation and oxime building. The presented AB<sub>2</sub> unit is also orthogonal to other recognition motifs such as the previously used<sup>[6]</sup> hydrogen bond patterns. Thus, significantly larger self-assembling dendrimers should be accessible by combining the different hydrogen bond patterns,



the heteroleptic complex and oxime formation in one dendrimer.

## Experimental Section

**Preparation of the complexes:** Due to the poor solubility of zinc triflate in chloroform, 0.5–0.8 mg were first placed into each NMR tube. A 1:2 solution of core **5** and branching unit **18** with a concentration of  $2.06 \cdot 10^{-3}$  M in  $\text{CDCl}_3$  was prepared and the calculated amount needed for the zinc triflate was added to each tube.  $\text{CDCl}_3$  was added, until an overall volume in all tubes of 550  $\mu\text{L}$  was reached. The tubes were placed in a sonication bath for 15 min. All other complexes were formed following this procedure.

**Preparation of the imines, hydrazones, oximes:** For the formation of the imine or imine-like structures, 100  $\mu\text{g}$ –5 mg of the respective  $\text{H}_2\text{N}$  species were dissolved in 100–3000  $\mu\text{L}$   $\text{CDCl}_3$  and the calculated amount of 1 equiv. for every aldehyde group was added.

All  $^1\text{H}$  NMR spectra of the complexes/imines/hydrazones/oximes were measured with 128 scans at 500 or 600 MHz.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Heteroleptic • Monodispers • Orthogonal • Self-assembly • Terpyridine

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