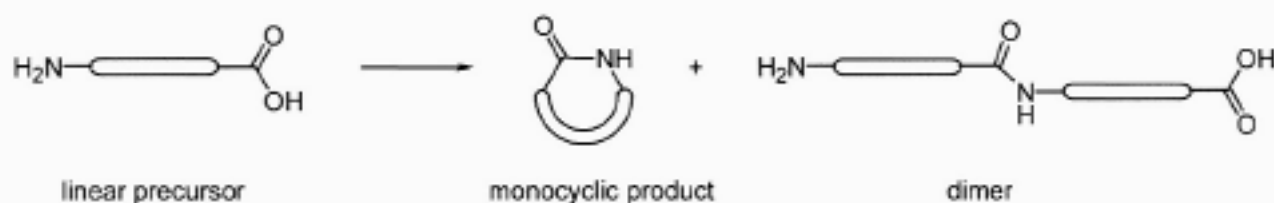


Summary

**Core-functionalised carbosilane dendrimers as
lactamisation tools**

The ring-closure of medium-sized lactams (7-15 membered ring) is still a great challenge for organic chemists. These heterocyclic compounds have a high potential in drug discovery, materials and catalysis research. Backbone cyclisation of a linear peptide precursor to furnish the desired monocyclic product is often in competition with the intermolecular process that leads to the formation of (cyclic) dimers and (cyclic) oligomers (Scheme 1).



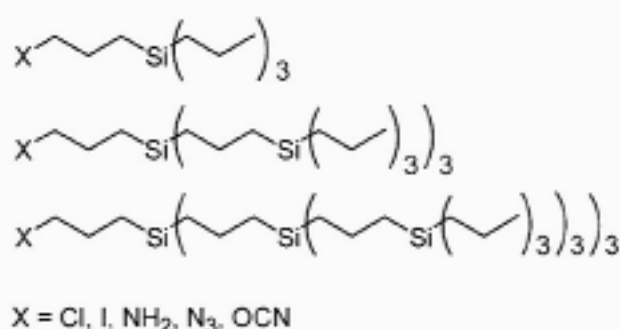
Scheme 1. Cyclisation to obtain the desired monocyclic product is in competition with the formation of dimers.

A dendrimer is a highly branched macromolecule with an internal cavity which is isolated from the bulk solution due to steric shielding by the dendrimeric branches. Therefore, a functional group in the dendrimeric core is located in a specific site isolated nanoenvironment. As a consequence, such a functional group can display special properties. Various core functionalised dendrimers have been synthesised and explored in detail.

This research aims to explore the site isolation effect in carbosilane dendrimers as a new tool for the ring-closure *via* amide bond formation of medium-sized lactams. We anticipated that a coupling reagent embedded in the dendrimeric structure could function as a unique tool to facilitate difficult cyclisation reactions by suppressing intermolecular processes.

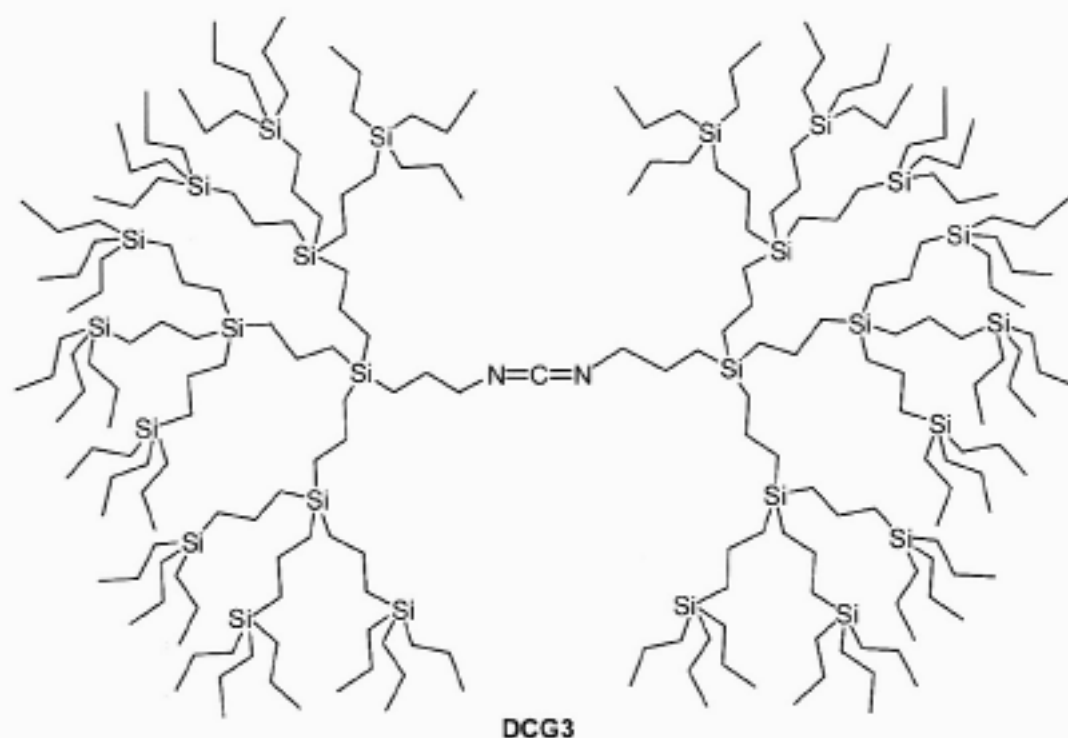
Chapter 1 offers a general introduction and it is divided into three parts. In the first part an overview of the most common synthetic and biochemical methodologies to achieve ring-closure of peptides is presented. An outline of the applications of core functionalised dendrimers, in particular in the field of homogeneous catalysis, is given in the second part. The third part describes a brief historical account about carbosilane dendrimers.

In **Chapter 2** an efficient synthesis of three generations of carbosilane dendrons is presented. The focal points of these dendrons were efficiently transformed into a diverse set of functional groups (Scheme 2).



Scheme 2. Focal point functionalised three branched carbosilane dendrons.

Carbodiimides are popular reagents used in peptide bond formation. The synthesis of three different generations of dendrimeric carbodiimides **DCG1**, **DCG2** and **DCG3**, starting from the dendron building blocks, is described in **Chapter 3**. **DCG1** and **DCG2** could be obtained via dehydration of the corresponding urea. This procedure was unsuccessful for **DCG3**, hence a different strategic route was designed in this case. The use of the Staudinger reaction, starting from focal point azide and isocyanate functionalised dendrons, gave smooth access to **DCG3** (Scheme 3). Furthermore, this approach enables the synthesis of non-symmetrical dendrimeric carbodiimides.



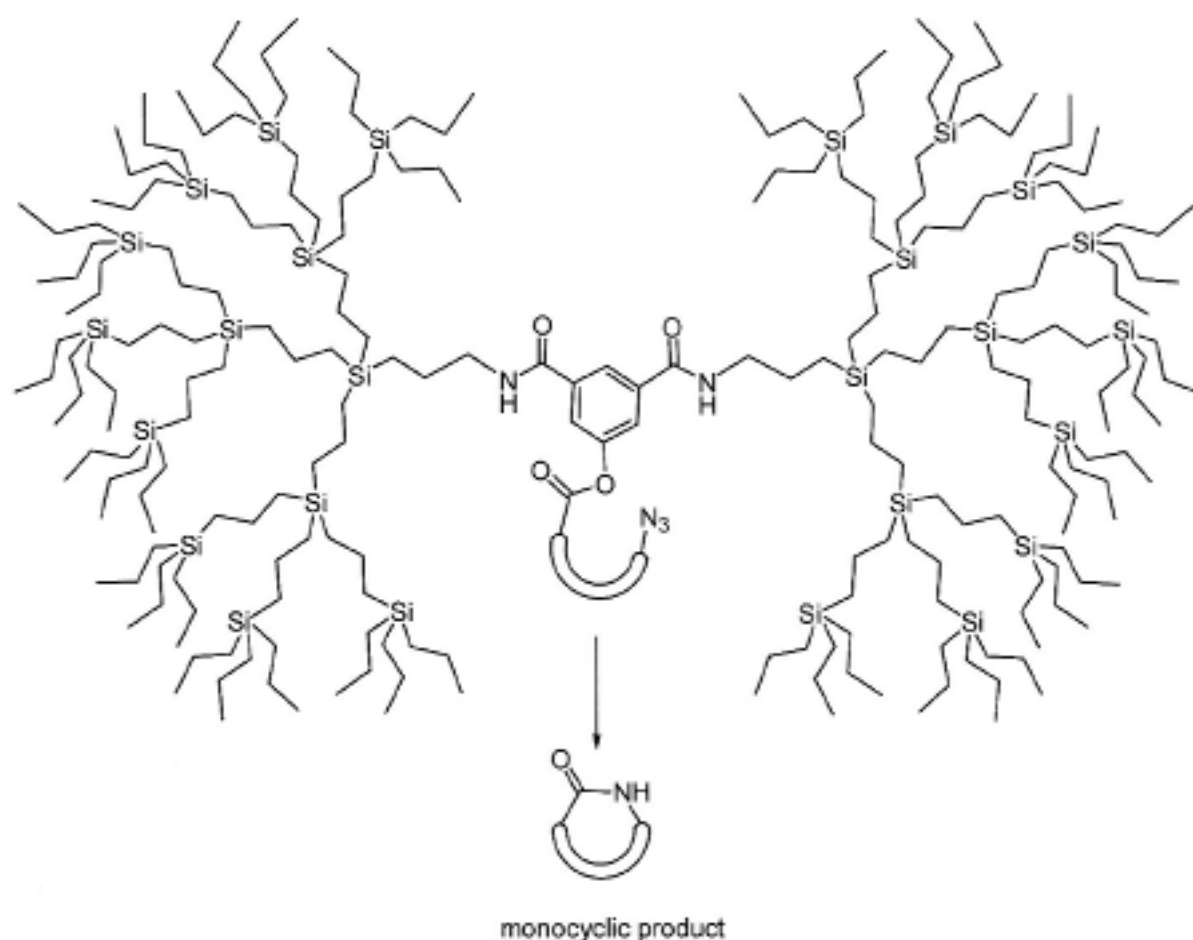
Scheme 3. Third generation dendrimeric carbodiimide.

The hydrogen bonding properties of the dendrimeric ureas have been studied (by ^1H NMR and FT-IR) providing insight into core-core interactions and hence into the extent of the site isolation of the core. With the first, and to a minor extent, with the second generation dendrimeric ureas, aggregate formation by intermolecular hydrogen bonding was observed.

In contrast, no hydrogen bonding was observed for the third generation thus indicating that the core is site-isolated.

In **Chapter 4** the dendrimeric carbodiimides were used to mediate the intramolecular amide bond formation to obtain 7-membered lactams. However, comparing the results of different generations **DCG1**, **DCG2**, **DCG3** and commercial dicyclohexylcarbodiimide no clear trend could be observed. We attribute this lack of dendrimeric effect to the complex mechanism of the carbodiimide mediated coupling in which several "dendrimer free" pathways play a role.

Chapter 5 is focussed on the synthesis of recyclable dendrimeric peptide coupling reagents that could give a controllable cyclisation reaction. Initially, the synthesis of a dendrimeric 4-dimethylaminopyridine (DMAP) analogue was attempted. The developed route was successful only for the first generation dendrimeric DMAP analogue. By having recognised the synthetic difficulties attending the syntheses of DMAP derivatives we decided to switch to the synthesis of dendrimeric phenol derivatives. A convergent three step route efficiently gave three different generations dendrimeric phenols. The compounds were investigated in their capability of facilitating cyclisations of α -Cbz ϵ -azide lysine and of azido dipeptides made of α - and β -amino acids (Scheme 4).



Scheme 4. Cyclisation of the dendrimeric ester linear precursor.

The extent of the site isolation effect was explored by conducting the cyclisation reactions at different concentrations. A minor concentration dependency of the cyclisation yield for the reactions mediated by the third generation dendrimeric phenol indicates that the linear precursor attached at its core is indeed encapsulated and that intermolecular processes are to a certain extent suppressed.