LETTER

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Lysine dendrimers based on thiacalix[4]arene core moieties as molecular scaffolds for supramolecular host systems†

Dietmar Appelhans,*[a] Mario Smet,[ab] Galina Khimich,[ac] Hartmut Komber,[a] Dieter Voigt,[a] Pavel Lhoták,[d] Dirk Kuckling[e] and Brigitte Voit[a]

[a] *Leibniz Institute of Polymer Research Dresden, Hohe Str. 6, D-01069 Dresden, Germany. E-mail: applhans@ipfdd.de; Fax: +49 351 4658565; Tel: +49 351 4658353*
[b] *Laboratory for Organic Synthesis, Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Heverlee (Leuven), Belgium*
[c] *Institute of Macromolecular Compounds, Russian Academy of Sciences, Bolshoy pr. 31, 199004 Saint-Petersburg, Russia*
[d] *Department of Organic Chemistry, Institute of Chemical Technology, Technická 5, 166 28 Prague 6 Czech Republic*
[e] *Institute for Macromolecular Chemistry and Textile Chemistry, Dresden University of Technology, Mommsenstr. 4, D-01069 Dresden, Germany*

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Cone-type and spherical lysine dendrimers up to generation 3 based on thiacalix[4]arene core units were successfully prepared and characterized in order to use as molecular scaffolds for supramolecular host systems.

Introduction

Thiacalixarenes, which have recently been prepared as new members of the calixarene family,[1] have become the subject of increasing studies in the field of supramolecular chemistry.[2] The presence of sulfur atom bridges in thiacalix[4]arenes results in potentially useful properties, mostly unknown in the chemistry of classical calixarenes, such as excellent complexation ability toward transition metals in combination with chemical modification (oxidation) of bridge units and different conformational preferences. Compared to calixarenes,[3–8] the application of thiacalix[4]arenes as building blocks, molecular scaffolds, and receptors in dendrimer, supramolecular or polymer chemistry is still rather limited by the absence of generally applicable derivatization methods. Among these, direct modifications of the lower or upper rims are the most frequently described. However, the use of thiacalix[4]arenes for the synthesis of large dendritic molecules[9–11] has not been described so far. Herein, we report on the synthesis and characterization of novel lysine dendrimers up to the 3rd generation using suitable thiacalix[4]arene cores possessing acid[12] or amino surface groups.

Aiming at the decoration of the thiacalix[4]arenes **1**[12] and **7**[12] with different lysine monodendrons, one preliminary goal of this study was to prove the utility of the core moieties **1** and **7** in dendrimer chemistry using the convergent and divergent approaches. The dendrimers **2–4** and **8–10** with the *cone* type or spherical structure, respectively, were synthesized by the synthetic routes A–C as illustrated in Scheme 1.

In order to carry out the conversion steps of the thiacalix[4]-arene possessing *cone* (**1**, **5**, **6**) and 1,3-*alternate* (**7**, **11**, **12**) conformations with different functionalized monodendrons, the corresponding lysine monodendrons up to the 3rd generation with *N*-Boc-protected amino surface groups and acid (HO(O)C-G1 and HO(O)C-G2) and methyl ester (MeO(O)C-G1, MeO(O)C-G2, and MeO(O)C-G3) groups at the focal side were prepared as described by Dykes *et al.*,[13] Davies *et al.*,[14] and Keller *et al.*[15] The subsequent reaction of the lysine monodendrons MeO(O)C-G1, MeO(O)C-G2, and MeO(O)C-G3 with excess 1,2-diaminoethane in methanol led smoothly to the desired *N*-aminoethyl-substituted lysine monodendrons H_2N-G1,[12] H_2N-G2, and H_2N-G3 in quantitative yield (ESI as Fig. S1†).

First trials, using the convergent route A, focused on the conversion of BOP-activated[16] di- and tetraacid **1** and **7** with H_2N-G1, H_2N-G2, and H_2N-G3 to result in the desired dendrimers. After work up and final column chromatography, all dendrimers **2–4**, **8**, and **9** were isolated in high yields. The new lysine dendrimers were characterized by means of ^{1}H NMR, ^{13}C NMR, IR, SEC, and MALDI-TOF-MS.[17]

Lysine dendrimer **10**, however, was not obtained by the convergent route A, and thus we explored the conversion of 1st and 2nd generation lysine dendrimers possessing amino surface groups with acid-functionalized lysine monodendrons HO(O)C-G1 and HO(O)C-G2 to realize preferentially the dendrimers **4** and **10** using the divergent/convergent routes B and C. The required amino-functionalized precursors **5**, **6**, **11**, and **12** were isolated in quantitative yield by the conversion of **2**, **3**, **8**, and **9** with trifluoroacetic acid in dichloromethane. Thus, the *cone* type generation 3 lysine dendrimer **4** was obtained, but in lower yields (69% and 60% for synthetic route B and C, respectively) compared to the synthetic route A (82% yield). The lysine dendrimer **10**, however, was only accessible, and then in low yield (23%), by the conversion of **12** with BOP-activated lysine monodendron HO(O)C-G1 (synthetic route C). The 1,3-*alternate* generation 3 lysine dendrimer **10** was characterized by ^{1}H NMR, ^{13}C NMR, IR, SEC, and MALDI-TOF-MS. Principally, the suitability of **11** as a building block/molecular scaffold *via* synthetic route B was proven. Hence, the conversion of the octaamino-functionalized **11** with the smaller monodendron HO(O)C-G1 was feasible to isolate **9** in slightly higher yield (75%) compared to the synthetic route A.

† Electronic supplementary information (ESI) available: Synthesis and characterization of **2–6** and **8–12** including figures for NMR, SEC, and MALDI-TOF-MS results. See http://dx.doi.org/10.1039/b509655c

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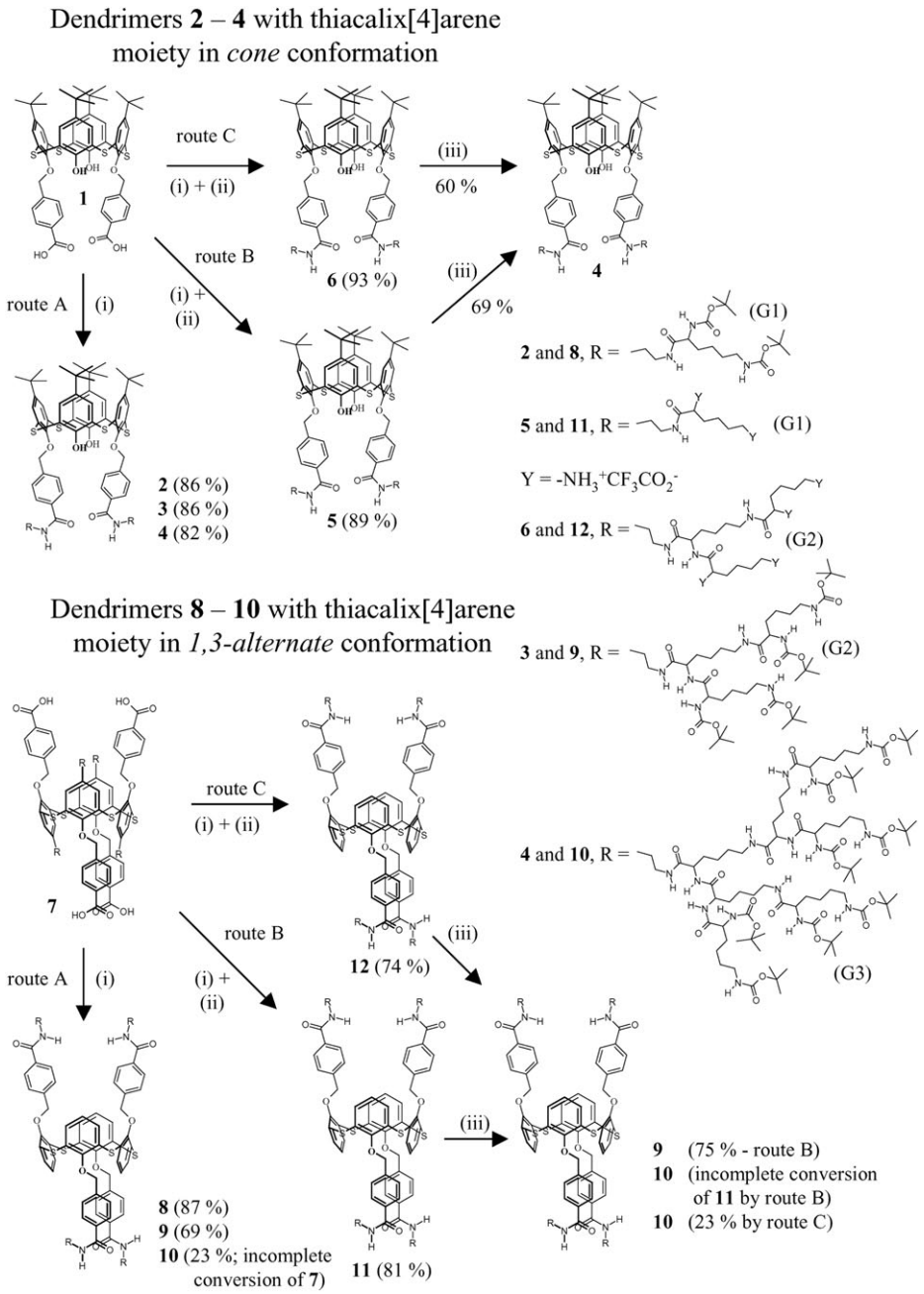

Scheme 1 Synthesis of lysine dendrimers with a thiacalix[4]arene moiety as core unit. *Reaction conditions*: (i) H_2N-G1, H_2N-G2 or H_2N-G3–BOP–DIEA in DCM or DMF, overnight, rt; (ii) TFA–DCM (1 : 1), rt, several h; (iii) HO(O)C-G1 or HO(O)C-G2–BOP–DIEA in DCM or DMF, overnight, rt.

An important point of the structural characterization of the lysine dendrimers **2–4** and **8–10** is to prove that all acid groups of **1** and **7** were converted into the corresponding aromatic amide group during the reaction of **1** and **7** with the *N*-aminoethyl-substituted lysine monodendrons. This aromatic amide group is the critical linkage group between the thiacalix[4]arene moiety and the lysine monodendrons. Besides the ^{1}H NMR signal of the aromatic NH-amide group at about 8.5 ppm, the ^{13}C NMR signal for the carbonyl carbon of the aromatic amide group was also observed at 166 ppm for all dendrimers (as an example ^{13}C NMR spectra of **2–4** are presented in the ESI as Fig. S2).

The ^{1}H NMR signal intensities and the absence of signals due to unreacted functional groups of the thiacalix[4]arenes gave an additional indication of the complete conversion of the acid groups in dendrimers **2–4**, **8**, and **9** using synthetic route A. Incomplete conversion of carboxylic groups results in two ^{1}H NMR signals at 5.2 ppm for the benzylic CH_2-group as demonstrated for dendrimer **10** obtained *via* synthetic route A (Fig. 1). The successful synthesis of **10** by synthetic route C was revealed by the presence of only one signal for the benzylic CH_2-groups in the ^{1}H NMR spectrum (Fig. 1). The structural imperfection of **10** obtained by route A was further confirmed by its ^{13}C NMR spectrum which reveals the presence of two carbonyl carbon atoms on the aromatic group (ESI Fig. S3). Results from SEC (ESI Figs. S4 and S5) and MALDI-TOF-MS (Fig. 2 and ESI Fig. S6a–S6e and Table S1) prove the presence of the desired lysine dendrimers.

Preliminary complexation studies on **2** and **3** with Zn(II), Cu(II), and Ag(I) indicated in most cases no formation of neutral complexes in contrast to the unmodified tetra(*p-tert*-butyl)tetrathiacalix[4]arenetetraol and the methyl ester of compound **1** obtained from liquid–liquid extraction experiments.[18] Therefore, compounds **2** and **3** may act as heteroditopic

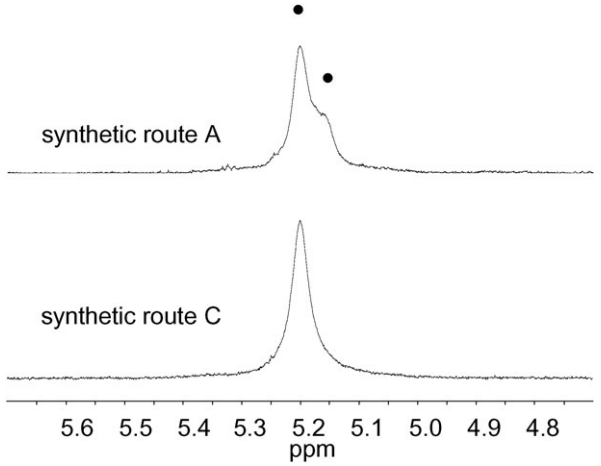

Fig. 1 Comparison of the ^{1}H NMR spectra for the lysine dendrimer **10** presenting the signals for the benzylic CH_2-group at 5.2 ppm as indicator for incompletely (two signals (●) for synthetic route A; top spectrum) and completely (one signal for synthetic route C; bottom spectrum) converted acid groups.

receptors. This fact has to be proven by additional extraction experiments to fully explain the influence of the substitution pattern of the lower rim on the complexation behavior of different thiacalix[4]arene derivatives. Also, theoretical calculations on the Zn(II) and Cu(II) complexation of parent thiacalix[4]arene and the methyl ester of **1** were done to obtain a deeper insight into the complexation ability of the disubstituted lower rim for the development of suitable supramolecular hosts/receptors with thiacalix[4]arene moieties.[19]

In conclusion, we have described the suitability of thiacalix[4]arene derivatives with acid and amino surface groups as dendritic cores for the realization of novel lysine dendrimers up to the 3rd generation. Especially, the *cone* and 1,3-*alternate* thiacalix[4]arenes with amino surface groups were found useful as potential building blocks and molecular scaffolds in dendrimer chemistry. Future investigation of the acid- and amino-functionalized molecular scaffolds will focus on the development of supramolecular receptors with different complexing features.

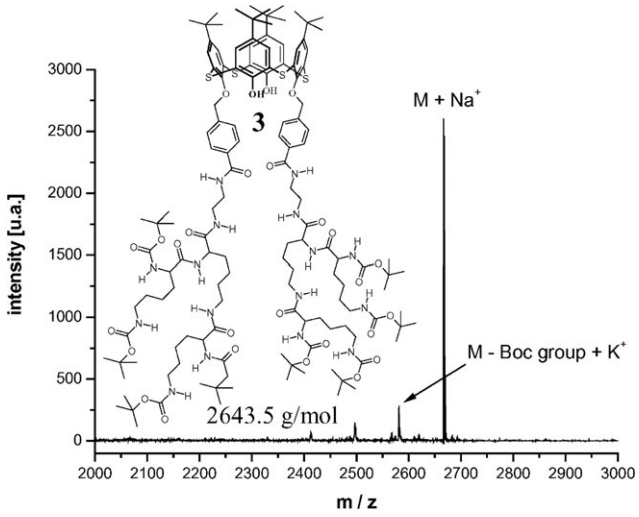

Fig. 2 MALDI-TOF-MS spectrum of **3**—detection of desired molar mass (2643.5 g mol^{-1}) of **3** assigned as M + Na^+. Additional mass peaks result from loss of Boc protecting groups.

Experimental

General

All substances (1,2-diaminoethane, L-lysine monohydrochloride, di-*tert*-butyl dicarbonate, triethylamine, diisopropylethylamine, dimethylformamide, dichloromethane,) were used as purchased from Aldrich, Acros, or Fluka. DIEA (diisopropylethylamine), BOP (benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate), DCM (dichloromethane), TFA (trifluoroacetic acid), DMAc (dimethylacetamide) and DMF (dimethylformamide) were used as abbreviations. Abbreviations for NMR spectroscopy are s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). All reactions were carried out under Ar or N_2 atmosphere.

Measurements

The NMR spectroscopic experiments were performed in 5 mm od sample tubes with a Bruker DRX 500 NMR spectrometer at 500.13 MHz for ^{1}H NMR spectra and at 125.75 MHz for ^{13}C NMR spectra. DMSO-d_6 or $CDCl_3$ were used as solvent for the NMR experiments. For internal calibration the solvent peaks of DMSO-d_6 and $CDCl_3$, respectively, were used: δ (^{13}C) = 39.6 or 77.0 ppm; δ (^{1}H) = 2.50 or 7.26 ppm. The signal assignment was done by ^{1}H–^{1}H COSY, ^{1}H–^{1}H NOESY, ^{1}H–^{1}H TOCSY, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC 2D NMR experiments using the standard pulse sequences provided by Bruker. Because of overlapping signals in the ^{1}H NMR spectrum, no defined integration of some NMR signals obtained from the higher generations was possible. But a clear signal assignment could be carried out by a combination of 1D and 2D NMR experiments.

The IR investigations were carried out with a Bruker IFS66 spectrometer equipped with a heatable Golden Gate Diamond ATR-Unit (SPECAC). 100 scans for one spectrum were added at a spectral resolution of 4 cm^{-1}.

The SEC measurements were performed with a modular chromatographic equipment, Agilent Series 1100, containing an HPLC-pump, refractive index detector and autosampler (Agilent, Germany) at ambient temperature. The column set, containing PL OligoPore (Polymer Laboratories, United Kingdom), was used. The injection volume was 20 µl. The sample concentration was c = 3 g l^{-1}. The flow rate was 1 ml min^{-1}. The experiments were carried out with a mixture of dimethylacetamide–water (98 : 2 v/v) containing LiCl 3 g l^{-1} as eluent. The molar masses were calculated using a calibration curve obtained from poly(2-vinylpyridine) standards (Polymer Standard Service, Mainz, Germany).

The MALDI-TOF-MS experiments were performed on a biflex IV system (Bruker Daltonics) with delayed extraction option. Desorption/ionisation was performed by a pulsed N_2 laser. The mass spectra were obtained from 19 kV acceleration voltage in the reflection mode. The matrix was 2,5-dihydroxybenzoic acid (DHB) using sodium triflate as cationizing agent. All solutions have been prepared with a concentration of approx. 10 g l^{-1} in a 5 : 1 mixture (matrix and sample) of DMAc. The 1 : 5 mixture of sample and matrix was dried on the sample holder. The measurements were carried out with positive polarity. Significant assignments of the important mass peaks were done, but not to mass peaks, which are obviously decomposed fragments, obtained from decomposed fragments (ESI Fig. S6a–S6e). Also traces of K^+ in dendrimers sometimes observed in the mass spectra were caused by the work up procedures.

Synthesis

Compounds **1** and **7** were synthesized according to the literature.[12] Detailed synthetic procedures and characterization data for compounds **2–6** and **8–12** are provided as ESI.†

Acknowledgements

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