Synthesis of Cyclopropane Dendrimers

Hye Jung Han and James E. Hanson

Department of Chemistry and Biochemistry
Seton Hall University
South Orange, NJ 07079-2694

Introduction

Dendrimers are highly branched, monodisperse macromolecules that have been the subject of considerable research interest among macromolecular scientists. Since the first controlled syntheses were developed nearly 20 years ago,[1] recent advances have lead to the development of a range of elegant methodologies for the syntheses of finely engineered dendritic structures, which yield many interesting applications, such as dendritic boxes, light harvesting materials, gene therapy and asymmetric catalysts.[2]

Cyclopropane units are a fundamental class of functional group that perform a key structural role in a range of bioactive natural and nonnatural molecules.[3] The challenges posed by the unique cyclopropane arrangement range from fundamental aspects of bonding, through the synthesis of highly strained and stereo-controlled molecules, to an understanding of the mode of action of biologically active cyclopropane derivatives.[4]

In the context of dendrimers, a few examples of branched triangulanes or spiro condensed polycyclopropanes have been synthesized.[5] However, no cyclopropane containing dendrimers have been synthesized. Here we report synthesis of cyclopropane dendrimers which have the cyclopropane unit as a branching point. We would expect the unique structural rigidity and σ-conjugated system would give interesting physical properties. Also, the highly strained and electron deficient tribenzoyl substituted cyclopropane ring should give interesting thermal and photophysical properties.

Experimental

Materials. All reagents were purchased from the Aldrich Chemical Co. and used without further purification. All solvents were dried before use.

Instrumentation. ^{1}H, ^{13}C, COSY and HMQC spectra were obtained on a Varian INOVA-500 spectrometer using 5 mm o.d. tubes. Infrared (IR) spectra were acquired on a MIDAC PRS FT-IR.

Synthesis of Dibenzoyl Ethylene Methyl Ester (G0). The 2,5-bis (tri-n-butylstannyl) furan was prepared as described by Boykin[6] in 80% yield. A mixture of 2,5-bis (tri-n-butylstannyl)furan (15.02 g, 23 mmole, 1 equiv), 4-bromo methylbenzoate (10 g, 46 mmole, 2 equiv) and $Pd(PPh_3)_4$ (1.3 g, 12 mmole, 0.05 equiv) in 300 ml dry dioxane was heated under argon at 100°C for 24 h. The volume of the reaction mixture was reduced under vacuum; 400 ml of $CHCl_3$ and 200 ml of 10% aqueous KF was added and the mixture was stirred for 1 h. The organic layer was separated, dried over magnesium sulfate and the solvent was removed under vacuum. The crude product was chromatographed over neutral alumina (17% ethyl ether in chloroform) to give 5.02g (15 mmole, 65%) of 2,5-bis(4-carbomethoxyphenyl)furan as pale yellow solid. To 4.5g (13 mmole) of 2,5-bis(4-carbomethoxyphenyl)furan in 300 ml chloroform dimethyldioxirane in acetone, which was prepared by literature method[7], was added at room temperature until all the starting material were consumed. The progress of reaction was followed by TLC. Evaporation of solvent gave cis-dibenzoyl ethylene methyl ester (G0) in quantitative yield as pale yellow solid.

Synthesis of G1-OP. The 2.08g (5.9 mmole, 1 equiv.) of dibenzoyl ethylene methyl ester (G0) and sulfonium bromide (3.35g, 6.5 m mole, 1.1 equiv.), which was prepared from 4-hydroxy acetophenone by 3 steps (protection of OH group by tert-butyldiphenylsilyl chloride, bromination by tetrabutylammonium tribromide followed by reaction with dimethyl sulfide) was dissolved in 50 ml dry THF under the argon. The resulting solution was cooled with ice-water and DBU (0.989g, 6.5 mmole, 1.1 equiv.) was added in dropwise. The resultant mixture was cooled to -78°C and stirred for 20 hrs. The reaction mixture was diluted by adding 100 ml of ethyl acetate and then washed with water (3 x 70 ml) and brine (1 x 70 ml). The organic layer was dried over $MgSO_4$, filtered and then removal of the solvent in vacuo gave yellow oily residue. The crude product was purified by flash chromatography using 15% ethyl ether in dichloromethane gave 3g (4.1 mmole, 70%) of cis-G1-OP and 0.6g (0.8 mmole, 15%) of trans-G1-OP as yellow solid.

Synthesis of G1-OH. Cis-G1-OP (2g, 2.7 mmole, 1 equiv.) was dissolved in 50 ml dry THF under the argon. The resulting solution was cooled to -78°C and treated with 8.1 ml (8.1 mmole, 3 equiv.) of tetra-n-butylammonium fluoride (a 1.0 M solution in THF) for 1 h. The reaction mixture was passed through a short silica column and washed with hexane/ethyl acetate 1:2. Removal of the solvent in vacuo gave 1.12g (2.3 mmole, 85%) of cis-G1-OH as white solid. The product was used without further purification.

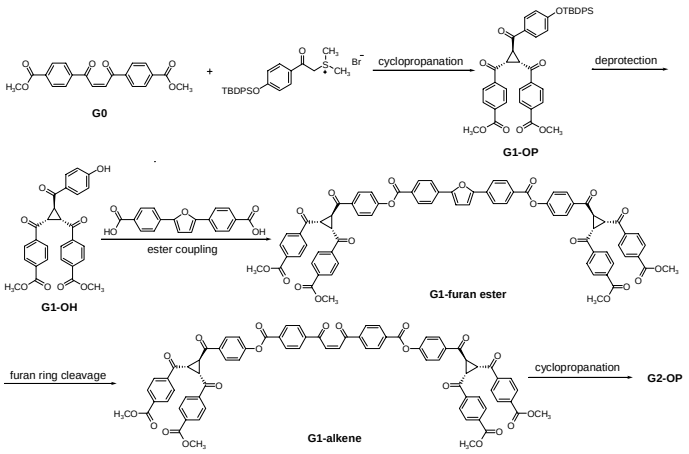
Synthesis of G1-furan ester. The 2,5-bis(4-carboxyphenyl)furan was prepared from 2,5-bis(tri-n-butylstannyl)furan by palladium catalyzed cross coupling reaction with 4-bromobenzonitrile followed by hydrolysis as described by Boykin[8] in 85% yield. The mixture of G1-OH (0.9g, 1.8 mmole, 1 equiv), 2,5-bis(4-carboxyphenyl)furan (0.58g, 1.8 mmole, 1 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.43g, 2.25 mmole, 1.25 equiv), and (dimethylamino)pyridine (DMAP) (0.022g, 0.18 mmole, 0.1 equiv) in 30 ml dry dichloromethane was stirred for 96 h at room temperature under the argon. After addition of water (15 ml) the organic phase was separated, washed with 0.5N-HCl (15 ml x 3), saturated $NaHCO_3$ (15 ml x 3) and water (15 ml x 2). The organic layer was dried over $MgSO_4$, filtered and then removal of the solvent in vacuo gave yellow oily residue. The crude product was purified by flash chromatography using 10% ethyl acetate in dichloromethane gave 0.56g (0.45 mmole, 50%) of G1-furan ester as white solid and unreacted G1-OH (0.4g).

Synthesis of G1-alkene. To 0.4g (0.32 m mole) of G1-furan ester in 50 ml dichloromethane, dimethyldioxirane in acetone was added at room temperature until all the starting material was consumed. The progress of reaction was followed by TLC. Evaporation of solvent gave 0.41g (0.32 m mole) of G1-alkene in quantitative yield as white solid.

Synthesis of G2-OP. The 0.087g (0.17 mmole, 1.1 equiv.) of sulfonium bromide was dissolved in 15 ml dry THF under the argon. The resulting solution was cooled with ice-water. DBU (0.026g, 0.17 mmole, 1.1 equiv.) was added in dropwise and stirred for 30 min. The resultant mixture was cooled to -78°C and G1-alkene (0.2g, 0.15 mmole, 1 equiv.) added. The reaction mixture stirred 24h at -78°C and gradually raised temperature to -20°C during 5 h period. The reaction mixture was diluted by adding 20 ml of ethyl acetate and then washed with water (3 x 20 ml) and brine (1 x 20 ml). The organic layer was dried over $MgSO_4$, filtered and then removal of the solvent in vacuo gave yellow oily residue. The crude product was purified by flash chromatography using dichloromethane/hexane/ethyl acetate 4:3:1 gave mixture of cis- and trans-G2-OP. Recrystallization from ethyl acetate/ethyl ether gave cis-G2-OP (0.12g, 0.07 mmole, 50%) as transparent pale yellow solid and trans-G2-OP (0.06g, 0.04 mmole, 24%) as yellow solid.

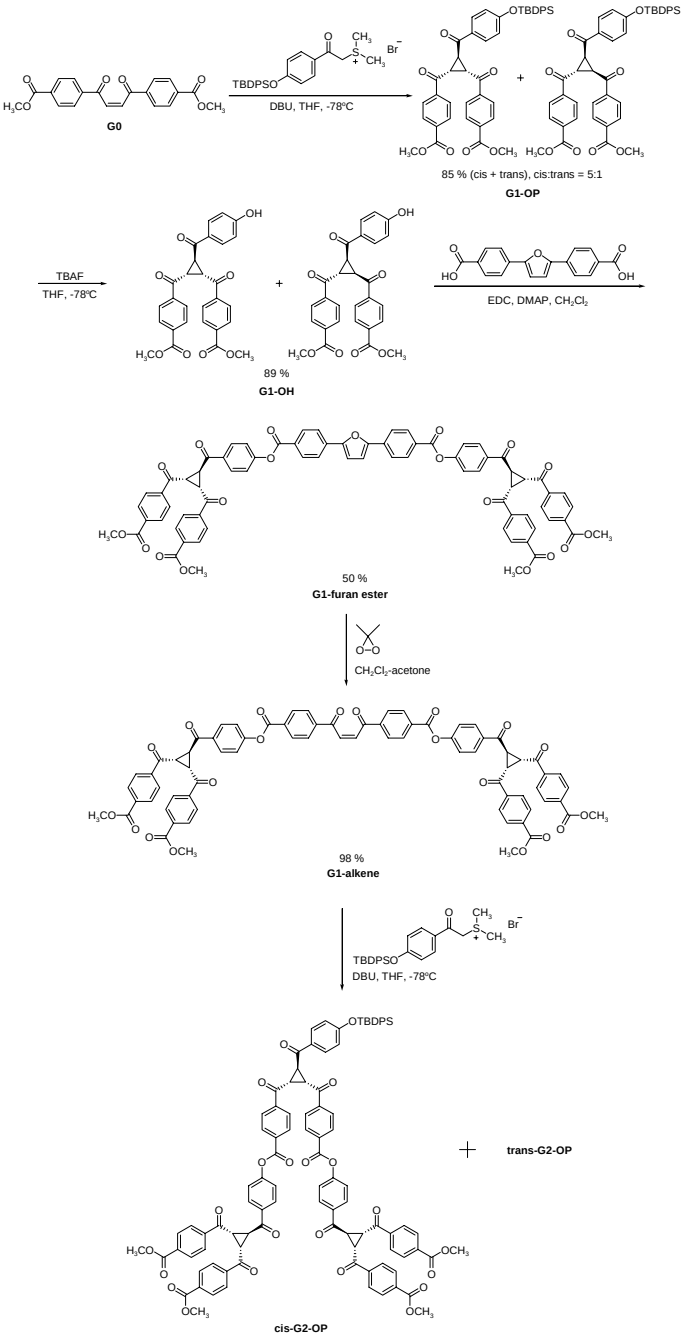
Result and Discussion

We have developed a synthesis of cyclopropane dendrimers. This synthesis is based on a convergent approach and includes four steps per generation: 1) the cyclopropanation of a sulfonium bromide with dibenzoyl ethylene methyl ester (G0) to give a tert-butyldiphenylsilyl terminated monodendron (G1-OP); 2) deprotection of the tert-butyldiphenylsilyl group to give an alcohol terminated monodendron (G1-OH); 3) coupling of G1-OH to 2,5-bis(4-carboxyphenyl)furan to give G1-furan ester: 4) furan ring cleavage to give the G1-alkene, which is then ready for cyclopropanation to G2.



Scheme 1. Synthetic strategy for cyclopropane dendrimers.

The key feature of this synthesis is the stereocontrolled cyclopropanation of the electron deficient dibenzoyl ethylene (Scheme 2). The reaction of dibenzoyl ethylene methyl ester (G0) with sulfonium ylid generated *in situ* by treatment of sulfonium bromide with DBU gives high yield (85%) and good diastereoselectivity, with cis to trans ratio of 5:1. Deprotection of the TBDPS protecting group by TBAF at room temperature causes scrambling of the stereochemistry. But deprotection reaction at -78°C with TBAF cleanly cleaves the TBDPS group without scrambling of stereochemistry to gave G1-OH. Coupling reaction of G1-OH with 2,5-bis(4-carboxyphenyl)furan by EDC and catalytic amount of DMAP gives G1-furan ester at moderate 50% yield. Furan ring cleavage with dimethyldioxirane gives G1-alkene in quantitative yield. Another cyclopropanation with G1-alkene gives G2-OP.



Scheme 2. Synthesis of G2-OP.

Conclusions

We have synthesized cyclopropane dendrimers up to generation 2. Synthesis of higher generations, characterization (SEC, DSC, TGA, MALDI), NMR diffusion and complexation studies are currently under way. Details about the synthesis, characterization and NMR study will be published elsewhere.[9]

References

(1) *Dendrimers and other Dendritic Polymers*; Fréchet, J. M.; Tomalia, D. A. Eds.: John Wiley & Sons, Ltd.: West Sussex 2001.
(2) *Dendrimers and Dendrons*: Newkome, G. R.; Moorefield, C. N.; Vögtle, F. Eds.: Wiley-VCH: Weinheim 2001.
(3) Papageorgiou, C. D.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 828.
(4) Faust, R. *Angew. Chem. Int. Ed*. **2001**, *40*, 2251.
(5) de Meijere, A.; Kozhushkov, S. I. *Chem. Rev*. **2000**, *100*, 93.
(6) Kumar, A.; Stephens, C. E.; Boykin, D. W. *Heterocycl. Commun*. **1999**, *5*, 301.
(7) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem*. **1987**, *52*, 2800.
(8) Boykin, D. W.; Kumar, A.; Xiao, G.; Wilson, W. D.; Bender, B. C.; McCurdy, D. R.; Hall, J. E.; Tidwell, R. R. *J. Med. Chem*. **1998**, *41*, 124.
(9) Han, H. J.; Hanson, J. E. in preparation.