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Polyurethane Dendrimers via Curtius Reaction

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Abstract: Reaction of 5-(*t*-butyldiphenylsiloxy)propyloxyisophthalic acid with dodecanol and diphenylphosphoryl azide (DPPA) affords the diurethane via Curtius reaction. Removal of the silyl group affords an alcohol which undergoes similar reaction with the isophthalic acid. Iteration of the process affords dendritic wedges through generation four, which can be attached to 1,3,5-benzenetricarboxylic acid in the same fashion. Materials are characterized by NMR and MALDI-TOF mass spectrometry.

Keywords: dendrimers; urethanes

Over the past decade, a number of research groups have reported the synthesis of dendritic polymers of unique chemical and physical properties[1,2]. Most of the syntheses involved the use of ether[2-4], amide[5] ester[6], ethyne[7] and silyloxy[8] linkages. Only a few research groups have reported polyurethane dendritic macromolecules[9], but none of them has reported the synthesis of dendrimers using the polyurethane group as the linking element. We report the synthesis of a monodisperse polyurethane dendrimer using a convergent approach based on the Curtius reaction.

A common method for the preparation of polyurethanes is the reaction of alcohols with isocyanates[10]. In many approaches, the isocyanate monomer is generated by introducing phosgene into the dihydrochloride salt of the amine. Due to the hazard of phosgene, our group avoided using this reagent gas. As an alternative, diphenylphosphorylazide (DPPA) is a useful reagent for conversion of carboxylic acids to urethanes[11-12]. This reagent can be prepared very easily by the reaction of diphenyl chlorophosphate with a slight excess of sodium azide in acetone at room temperature. Employing this strategy, our group succeeded in preparing polyurethane compounds which could be synthesized from an isocyanate formed by a modified

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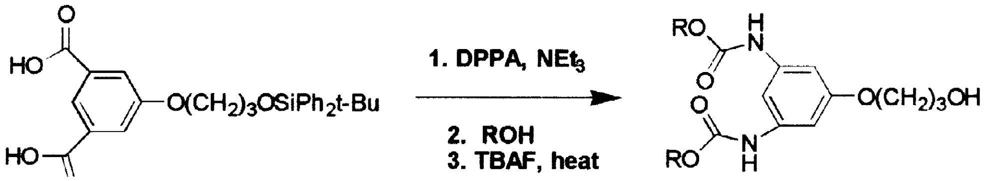
Curtius reaction. The advantages of this strategy are: the reaction proceeds smoothly by simply refluxing the reaction mixture in a one-pot reaction and the byproduct (diphenylphosphoric acid) can be separated from the desired product by column chromatography eluting with the appropriate solvent. In our synthesis, 5-(oxy-propane-*tert*-butyldiphenylsiloxy)isophthalic acid **(1)** was employed as a building block to construct dendritic wedges up to generation four. Our linking compound, **(1)** was prepared in four steps. Fischer esterification of 5-hydroxyisophthalic acid was followed by alkylation with 3-bromo-1-propanol (potassium carbonate/acetone, reflux). Protection of the alcohol with *t*-butyldiphenylsilyl chloride/imidazole (the best protecting group we have found for the long synthesis) followed by saponification afforded the substituted diacid.

With the diacid in hand, the synthesis of dendritic wedges proceeded readily. Reaction of **(1)** with dodecanol and DPPA in benzene (reflux, triethylamine) followed by deprotection (TBAF) afforded the first generation urethane **(2)** in 73% yield. A similar reaction of the first generation alcohol **(2)** with the linking group **(1)** afforded (after deprotection) the second generation alcohol **(3)** in 67% yield. Repetition afforded generation 3 alcohol **(4)** in 57% yield and, yet again, generation four wedge **(5)**. The yield of generation four was limited to 10%, with the first observation of unidentified reaction side products. Products were readily purified by normal phase silica gel chromatography.



(1)

(2) R = $CH_3(CH_2)_{11}$

(3) ROH = (2)

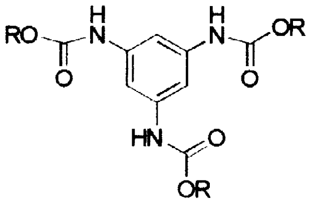
(4) ROH = (3)

(5) ROH = (4)

To complete the convergent synthesis of a monodisperse polyurethane dendrimer, the generation 3 dendritic wedge **(4)** was coupled to 1,3,5- benzenetricarboxylic acid in 40% yield. Use of 3.15 equivalents of the alcohol resulted in isolation of the symmetrical dendrimer **(6)**, which could be easily separated from a small amount of incompletely substituted byproduct.

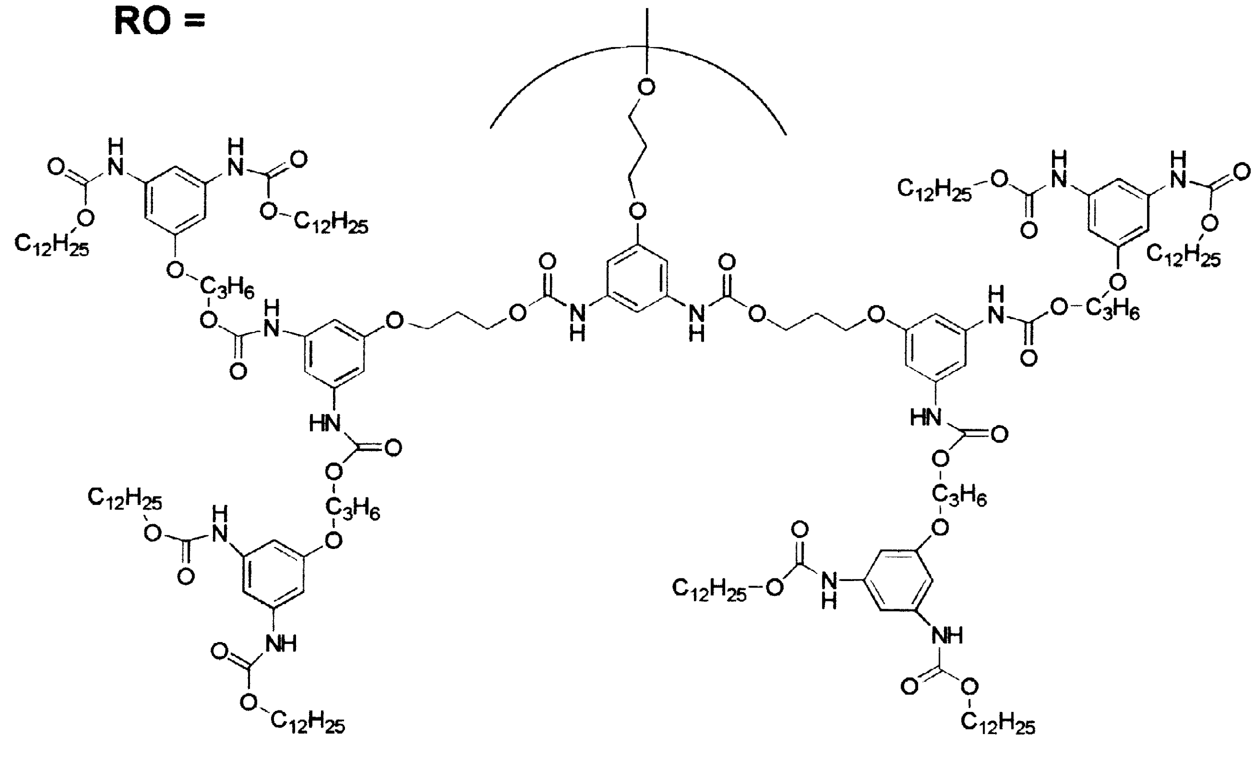
While the isolated compounds exhibited HNMR and CNMR spectra consistent with the structures proposed, the fastest and most efficient way to confirm the identity and purity of the compounds isolated was MALDI-TOF mass spectrometry. While the NMR spectra of the succeeding generations were difficult to distinguish, it was possible to use MALDI techniques to determine the completion of the reaction and to search for defects in each generation. For all of the dendritic molecules reported herein, the yields are of material homogeneous by this technique, exhibiting peaks only for the molecular species (M + Na and M + K). Such spectra allowed us to arrive at ideal conditions for deprotection of the alcohol, which was sluggish at the focal point in higher generations and allowed selection of the ideal tethering linkages. Substantial side reactions were observed when an undecyl group was used as the tether and decomposition was observed with no tether (as would be expected for diaryl urethanes). The molecular weights of the compounds reported herein are: 606, 1446, 3126 and 6497 for wedges **2**, **3**, **4** and **5** respectively. Dendrimer **6** was measured at 9588.

Work is proceeding on the preparation of polyurethane dendrimers with charged peripheries and on non-symmetrical species. Solubility characteristics and behavior as thin films will be investigated.



(6)

RO =



General procedure for urethane formation:

Into a round-bottomed flask was added 5-(*tert*-butyldimethylsiloxy)-isophthalic acid (1 equiv), triethylamine(4 equiv), diphenylphosphoryl azide (DPPA) (4 equiv), and benzene (20 ml/g of isophthalic acid). The reaction mixture was refluxed for 45 min. Alcohol (2.1 equiv) and benzene(5 ml/g of alcohol) were added to the mixture, which was refluxed for an additional 17 h. The reaction mixture was cooled. The solvent was removed under reduced pressure and the crude residue was redissolved in ethyl acetate, washed with water, separated, dried with magnesium sulfate, and evaporated. Without any further purification, the crude oil was subjected to the deprotection reaction. The crude mixture was redissolved in THF, and 1.0 M solution of tetra-n-butylammonium fluoride (3.775 equiv) was added (THF:TBAF=1:1 v/v). The reaction mixture was stirred under nitrogen at 40C for 20 h. After complete deprotection (verified by TLC and/or MALDI), the crude mixture was purified by column chromatography eluting with the gradient range from 70%CH_2Cl_2:hexane and gradually increasing to 30%EtOAc:CH_2Cl_2.

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