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Preparation of 'cage molecule' based polyazido core units for dendrimer synthesis

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Abstract—Core molecules based on benzene-, cubane-, and adamantane-polycarboxylates with peripheral polyazido substitution are reported. The first synthesis of 1,3-diazidoacetone and its conversion to the corresponding oxime, DNPH, and 2,2-dinitro derivatives is also reported.

The synthesis of dendritic structures has attracted the continued attention of organic chemists. An ever-growing variety of structural motifs are being incorporated into this fascinating class of molecules that are finding applications in equally diverse areas due to the unique properties exhibited by them.[1] In an ongoing program several novel polyazido compounds have been synthesized as potential energetic materials.[2] This, coupled with our long-term interest in 'cage molecules',[3] presented an opportunity to synthesize a new set of core molecules that have polyazido functionality on the periphery of polyfunctionalized cubane, adamantane, and benzene nuclei. The use of the symmetrically substituted adamantane and cubane skeletons ensures specific spatial disposition of substituents, a concept that has been utilized by Newkome et al.[4] In addition to being readily convertible to an amino group by reduction, the azido group is highly reactive toward acetylenic compounds and nitriles, providing access to triazoles and tetrazoles, respectively. The dipolar cycloaddition reactions of polyazido core molecules synthesized herein will lead to the formation of novel dendrimers incorporating triazole/tetrazole groups.

1,3-Diazido-2-azidomethyl-2-propanol, **1**, and other polyazido compounds were synthesized starting with commercially available methallyl dichloride. Two approaches were used to synthesize **1**. In an initial approach, methallyl dichloride was converted to the corresponding methallyldiazide, **2**, which was subjected to epoxidation with mcpba to obtain 2,2-bis(azidomethyl)oxirane **3**. Ring-opening reaction of **3** with sodium azide produced **1** in good yield. In a more direct approach, methallyl dichloride was converted to the known 2,2-bis(chloromethyl)oxirane **4** by epoxidation with mcpba,[5] which was then treated with 3 equiv of sodium azide to yield **1** as a pale yellow liquid, in what is reminiscent of the click chemistry approach reported by Sharpless and co-workers (Scheme 1).[6]

Methallyl diazide **2** exhibited an interesting dimerization upon standing at room temperature, similar to allyl azide[7a,b] and methallyl azide.[7c] The structure of the novel tricyclic heterocycle **5** was established by NMR spectroscopy and X-ray crystallography. Ozonation of compound **2** in methylene chloride at −78 °C afforded 1,3-diazidoacetone **6**, which was obtained as a clear oil after chromatographic purification and which exhibited satisfactory spectral characteristics. The structure of **6** was further corroborated by X-ray crystallography of its DNPH derivative **7** (Fig. 1). A more direct approach to **6** involved the reaction of 1,3-dichloroacetone with sodium azide in acetone at room temperature. The reaction was complete in 3 h and the product was obtained simply by filtration and removal of the solvent. Upon

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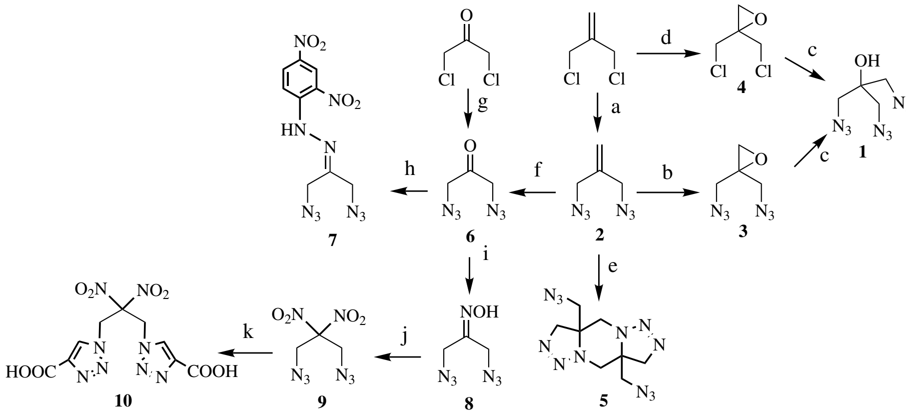


Scheme 1. Reagents and conditions: (a) NaN_3/acetone/reflux; (b) mcpba/1,2-dichloroethane, reflux; (c) NaN_3/acetone/H_2O/reflux; (d) Ref. 5; (e) room temperature/several days; (f) 1. O_3/CH_2Cl_2/−78 °C; 2. dimethylsulfide; (g) NaN_3/acetone/room temperature; (h) 2,4-dinitrophenylhydrazine; (i) $NH_2OH{\cdot}HCl$/NaOAc/MeOH; (j) HNO_3/CH_2Cl_2/reflux; (k) propiolic acid/chloroform/reflux, 3 h.

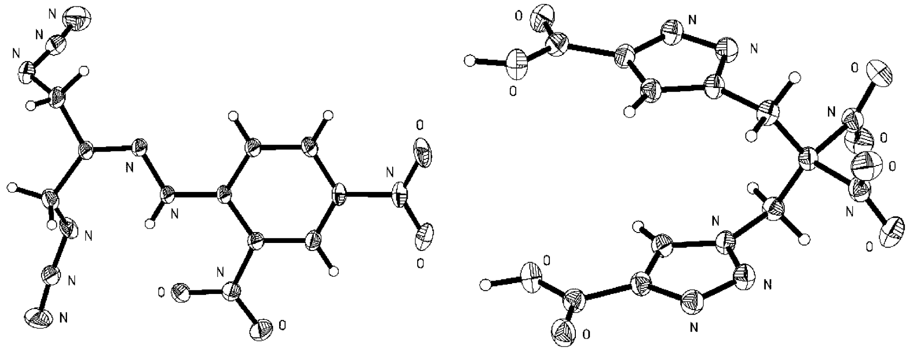
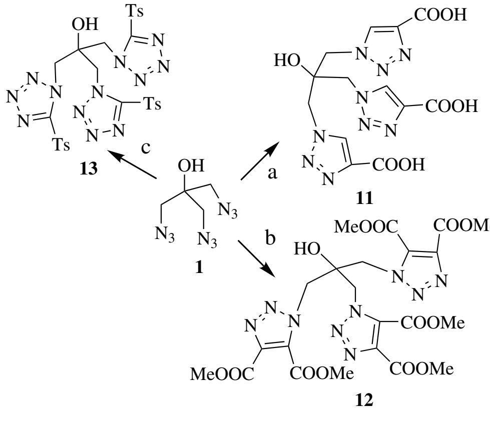


Figure 1. Ortep views of **7** and **10**.

attempted purification, the material detonated subsequent to distillation, and so was used without further purification for subsequent steps. Compound **6** was converted to its oxime **8** by reaction with hydroxylamine hydrochloride in methanol buffered with sodium acetate. Oxidative nitration[8] of **8** with nitric acid in methylene chloride gave 2,2-dinitro-1,3-diazidopropane, **9**, as a colorless oil after chromatographic purification. Compound **9** gave satisfactory NMR spectra. As a further proof of structure, compound **9** was treated with an excess of propiolic acid to obtain the corresponding bis-triazole **10**. The structure of this adduct was established by its NMR spectra and proven unequivocally by X-ray crystallography (Fig. 1).

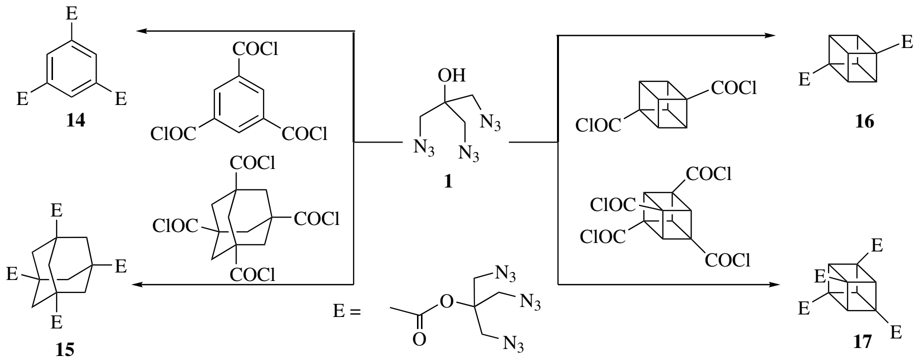
The propensity of the reaction of multiple azido groups with representative acetylenic and nitrile compounds was investigated as shown in Scheme 2. The reaction of **1** with propiolic acid was best carried out in chloroform as the product **11** precipitated out of solution and was obtained by simple filtration, and purified by recrystallization from water. The reaction of **1** with dimethyl acetylenedicarboxylate also proceeded smoothly to provide the tris(triazole dicarboxylate) **12**.

The reaction of *p*-toluenesulfonyl cyanide with **1** was carried out in a sealed tube following the conditions reported by Sharpless and Demko.[9] The tris(tetrazole) **13** was obtained in a pure form by chromatography. The structures of the cycloaddition products were established by NMR spectroscopy, and for **12** and **13**, further corroborated by X-ray crystallography.



Scheme 2. Reagents and conditions: (a) propiolic acid/$CHCl_3$/reflux; (b) dimethyl acetylenedicarboxylate/$CHCl_3$/reflux; (c) tosyl cyanide/sealed tube.

Encouraged by the facile reactions of **1** with acetylenic and nitrile dipolarophiles, core units based on **1** were synthesized as shown in Scheme 3.



Scheme 3.

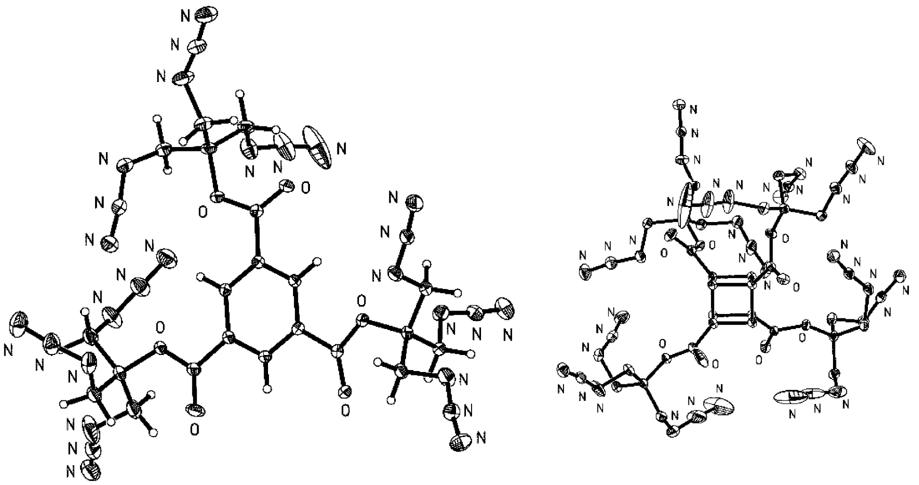


Figure 2. A drawing of molecules **14** and **17** as they occur in their crystals at 21 and −170 °C, respectively, showing the thermal displacement ellipsoids. All hydrogen atoms in **17** were removed for clarity.

The reaction of **1** with commercially available 1,3,5-benzenetricarbonyl chloride in refluxing pyridine provided the triester **14**,[10] which was purified by chromatography. However, the reaction of **1** with 1,3,5,7-adamantanetetracarbonyl chloride,[11] 1,4-cubanedicarbonyl chloride, and 1,3,5,7-cubanetetracarbonyl chloride[12] under similar conditions failed to provide the expected products. These reactions were carried out successfully by first converting **1** to the corresponding sodium salt with sodium hydride and then treating with the carbonyl chlorides in refluxing THF for an extended period of time. The esters **15**, **16**, and **17** were isolated in a pure form by chromatography. The structures of the esters were established by NMR spectroscopy, and for **14**, **16**, and **17** corroborated by X-ray crystallography (Fig. 2 depicts the structures of two of these molecules).

In view of the explosive nature of the azido compounds, ^{1}H and ^{13}C NMR data were used for characterization,[13] and the structural assignments further established by X-ray crystallography when possible.[14]

Further elaboration of the core molecules **14**–**17** by reduction, as well as reaction with alkynes and nitriles is underway to prepare dendrimers with triazole- and tetrazole-containing units and will be reported in due course.

In conclusion, a series of core units based on benzene, cubane and adamantane nuclei, peripherally substituted by polyazido groups, and model reactions of the polyazido system with alkynes and nitriles have been demonstrated, paving the way for the preparation of dendrimers incorporating triazole and tetrazole units.

CAUTION: All azido compounds should be considered dangerous and proper precautions should be taken in handling and storage of these molecules.

Acknowledgements

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13. Selected spectral data: **1**. ^{1}H NMR ($CDCl_3$) δ 2.80 (s, br, 1H), 3.40 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 54.53, 74.40; **2**. ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 4H), 5.29 (s, 2H); **3**. ^{1}H NMR ($CDCl_3$) δ 2.88 (s, 2H), 3.50 (AB quartet $J_{AB} = 13.3$ Hz, 4H); **5**. ^{1} H NMR ($CDCl_3$): δ 3.29 (AB, $J_{AB} = 14.9$ Hz, 2H), 4.10, (AB, $J_{AB} = 14.9$ Hz, 2H); 3.54 (AB, $J_{AB} = 12.8$ Hz, 2H, 3.60 (AB, $J_{AB} = 12.8$ Hz, 2H); 4.02 (AB, $J_{AB} = 16.6$ Hz, 2H), 4.22 (AB, $J_{AB} = 16.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 43.99, 50.95, 61.00, 72.83; **6**. ^{1}H NMR ($CDCl_3$): δ 4.07 (s, 4H); **7**. ^{1}H NMR ($CDCl_3$): δ 4.15 (s, 2H), 4.33 (s, 2H), 7.98 (d, 1H), 8.39 (d, 1H), 9.16 (s, 1H); ^{13}C NMR ($CDCl_3$): 47.76, 54.79, 116.53, 123.20, 130.20, 130.62, 139.23, 144.57, 145.80; **8**. ^{1}H NMR ($CDCl_3$): δ 3.99 (s, 2H), 4.27 (s, 2H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 45.31, 51.06, 151.93; **9**. ^{1}H NMR ($CDCl_3$): δ 4.70 (s, 4H); ^{13}C NMR ($CDCl_3$): δ 50.73, 115.14; **10**. ^{1}H NMR (DMSO-d_6): δ 5.98 (s, 4H), 8.70 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 50.67, 116.12, 132.45, 140.79, 162.04; **11**. ^{1}H NMR (DMSO-d_6) δ 4.57 (s, 6H), 6.10 (s, 1H), 8.55 (s, 3H), 13.5 (br, 3H); ^{13} C NMR (DMSO-d_6) δ 53.45, 71.40, 131.30, 131.91, 162.00; **12**. ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 9H), 3.97 (s, 9H), 4.87 (s, 1H), 4.97 (s, 6H); **13**. ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 9H), 5.23 (s, 6H), 7.43 and 7.91 (AB quartet, $J_{AB} = 6$ Hz, 12H); **14**. ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 6H), 8.8 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 51.25, 84.08, 130.98, 135.52, 163.53; **15**. ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 12H), 3.8 (s, 24H); **16**. ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 12H), 4.30 (s, 6H); **17**. ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 24H), 4.79 (s, 4H).
14. Crystallographic data for the structures reported in this paper (compounds **5**, **7**, **10**, **12**, **13**, **14**, **16**, and **17**) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 224943-224945 and 226518-22. Copies can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [e-mail: deposit@ccdc.cam.ac.uk].