

Toward Novel Polyacetals by Transacetalation Techniques: Dendrimeric Diacetals

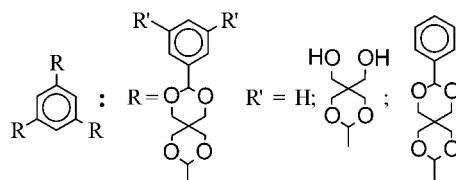
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ABSTRACT



A new approach to polyacetal systems using sequential transacetalation and protection–deprotection techniques was developed for the preparation of macromolecular polyacetals and applied to secure new dendrimers with 2,4,8,10-tetraoxaspiro[5,5]undecane dendrons from pentaerythritol and polyaldehydes. These novel dendrimers, featuring a 1,3,5-benzene-tricarbaldehyde core, viz., the dodecaol (18) and its hexaacetal (19), were prepared, and molecular modeling revealed peculiar dendron convergent structures above the core, due to intramolecular π -stacking interactions, reinforced by H-bonding of multifunctional termini.

Dendrimers¹ are subject of intense attention recently because of their peculiar structural and physical properties and the anticipated potentialities arising from their shape and ease of functionalization. Since the initial reports on cascade systems by Vögtle et al.^{1a} in 1978 and despite the impressive diversity to date, to the best of our knowledge there are no examples of polyacetal dendrimers. Such dendrimers may feature functional end-groups and serve as good ligands and, significantly, may undergo judicious hydrolysis to effectively “unzip” the dendrimer to polyfunctional macromolecules or degrade it altogether.

In the context of our recent studies of novel diacetal and diaminal systems² and their podand and macrocyclic versions prone to binding cations and other electron-accepting molecules, we have set out to investigate polymeric and

dendrimeric diacetal systems. The scientific significance of polymers and dendrimers containing such lone-pair abundant cores consists of their anticipated propensity for guest inclusion, self-assembly, and channel formation and is enhanced by their hydrolytic (controllable) degradability to fragments and eventually back to their starting materials for possible recycling. Their potential applications lie in the much sought field of environment- and bio-friendly plastic materials for medical and agricultural purposes. We report now our first results in the series.

The starting materials for the planned polyacetal systems were di-, tri-, and tetraaldehydes on one hand and tetraols of the bis(1,3-diol) type on the other hand. Here we report on the basic tetraol, pentaerythritol (**1**, which had been used before in a number of diacetal polymers),³ with the aromatic 1,3,5-benzenetricarbaldehyde.

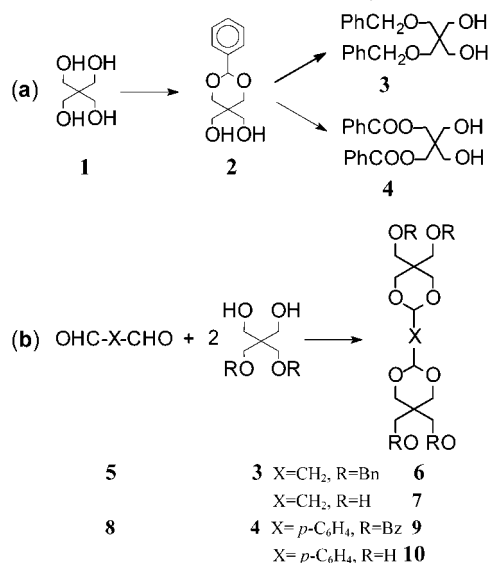
(1) (a) Vögtle, F.; Buhleier, F.; Wehner, W. *Synthesis* **1978**, 155. (b) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, 29, 138. (c) Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* **1995**, 132, 875. (d) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules: Concepts, Synthesis and Perspectives*; Wiley-VCH: Weinheim, 1996. (e) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, 97, 1681. (f) Hecht, S.; Frechet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, 40, 74. (g) Vögtle, F.; Gestermann, S.; Hesse, R.; Schwier, H.; Windisch, B. *Prog. Polym. Sci.* **2000**, 25, 987.

(2) (a) Grabarnik, M.; Lemcoff, N. G.; Madar, R.; Abramson, S.; Weinman, S.; Fuchs, B. *J. Org. Chem.* **2000**, 65, 1636. (b) Star, A.; Goldberg, I.; Lemcoff, N. G.; Fuchs, B. *Eur. J. Org. Chem.* **1999**, 2033, 3. (c) Star, A.; Lemcoff, N. G.; Goldberg, I.; Fuchs, B. *Tetrahedron Lett.* **1997**, 3573. (d) Frische, K.; Greenwald, M.; Ashkenazi, E.; Lemcoff, N. G.; Abramson, S.; Golender, L.; Fuchs, B. *Tetrahedron Lett.* **1995**, 36, 9193.

The critical step in the growing process of a polyacetal dendrimer is the creation of a new acetal moiety (2nd generation and up) without destroying the existing ones in the previous generations and formation of complex mixtures of products due to erratic transacetalation processes instead of the expected selectively consecutive acetalation. To overcome this dilemma, we had to devise an effective procedure consisting of a sequential series of selective transacetalation steps, i.e., transacetalation of a less stable acyclic acetal so that the new generation could be generated without harming the existing cyclic acetal.

A series of model acetalation studies on aromatic dialdehydes with pentaerythritol (to be reported in due course) indicated that the first acetalation step is usually faster than the second one, apparently because of the second (e.g., *para*) carbaldehyde function, which destabilizes the carbocation intermediate, as happens in the hydrolysis process as well.⁴ The subsequent acetalation of the monoacetal is less efficient, since there is actually a second weak EDG (acetal) function in the, e.g., *para* position to the aldehyde. Hence, protection/deprotection techniques were devised, using half-protected pentaerythritol (Scheme 1a) viz., the known monobenzal-

Scheme 1. Preparation of (a) Monoprotected Pentaerythritols (3, 4) and (b) Terminal Bis(1,3-diol) Systems (7, 10)



pentaerythritol (2),^{5a} the dibenzyl ether (3),^{5b} and the dibenzoate (4).⁶ The transacetalation processes were generally catalyzed by pyridinium *p*-tosylate (PPTS).

These enabled us to secure from malonaldehyde (5) the diacetal (6) and from terephthalaldehyde (8) its diacetal (9)

(3) (a) Cohen, S.; Lavin, E. *J. Appl. Polym. Sci.* **1962**, 23, 503. (b) Bailey, W.; Volpe, A. *J. Polym. Sci. A-1* **1970**, 8, 2109. (c) Zalar, F. V. *Macromolecules* **1972**, 5, 539. (d) Solich, J. M.; Barth, M. *Polish J. Appl. Chem.* **1995**, 2, 249. (e) Makhseed, S.; McKeown, N. B. *Chem Commun.* **1999**, 255.

(4) (a) Fife, T.; Jao, L. *J. Org. Chem.* **1965**, 39, 1492. (b) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, 74, 581.

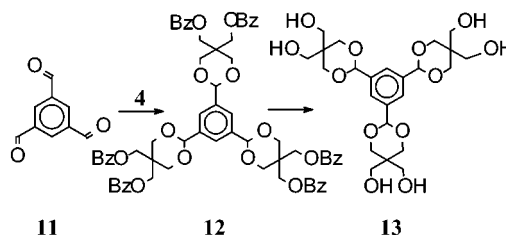
(5) (a) Issidorides, C. H.; Gulen, R. *Org. Synth.* **1958**, 38, 65. (b) Weber, E. *J. Org. Chem.* **1982**, 47, 3478.

(6) Orthner, L.; Freyss, G. *Liebigs Ann.* **1930**, 484, 131.

(Scheme 1b). These diacetals were subsequently deprotected to the tetraols 7 and 10, respectively, which are viable bis-(1,3-diol) units, for further acetalation processes. Since the benzyl protecting group in the aromatic acetal could not be removed selectively without harming the benzylidene unit,⁷ the benzoyl protecting groups (R = Bz) was used instead.

Using the said approach, the reaction of 3 mol of dibenzoylpentaerythritol (4) with 1,3,5-benzenetricarb aldehyde (11)⁸ (Scheme 2) provided the protected aromatic

Scheme 2. First Generation Dendrimer Cores (12, 13) Derived from 1,3,5-Benzenetricarb aldehyde (11)



dendrimer (12), which could be completely deprotected by ammonolysis in methanol to afford the hexaol-terminated quasi-first generation dendrimer (13) (95%). The only difference in the acetalation reaction conditions was the use of *p*-toluene sulfonic acid (PTSA) as the catalyst instead of PPTS, which was (curiously) ineffective in this case.

The challenge of making now the next generation without harming the precursor core, i.e., to introduce a new acetal into a molecule that already has one, was a cardinal point in this investigation, in view of potentially spurious transacetalation and hydrolysis processes. Indeed, the PPTS-catalyzed reaction between terephthalaldehyde and monobenzal-pentaerythritol (2) afforded a mixture of transacetalation products. The average length of the oligomer obtained by reaction in refluxing benzene after 2.5 h is about $n = 3$ as assessed by NMR. In a similar reaction of the hexaol (13) and the electron-poor *p*-nitrobenzaldehyde in refluxing toluene, the latter completely sequestered the pentaerythritol molecules from 13, giving bis(*p*-nitro benzylidene) pentaerythritol diacetal (14) as the sole product of complete transacetalation.

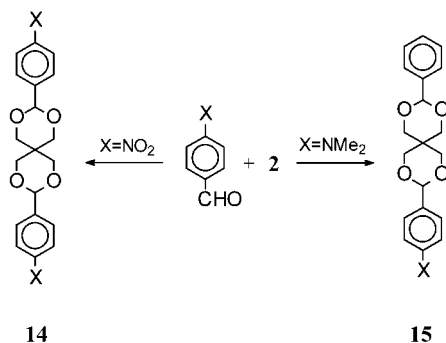
These results conform with early observations on acetal/diacetal formation,⁹ which have been largely ignored in current synthesis. In a cursory scrutiny of the PTSA-catalyzed reactions of 2 and two different (EWG and EDG) *p*-substituted benzaldehydes (Scheme 3), the electron-poor *p*-nitrobenzaldehyde in refluxing toluene gave bis(*p*-nitrobenzylidene) pentaerythritol diacetal (14) as the sole product, i.e., complete transacetalation took place. At the same time, in the reaction of the electron-rich *p*-dimethylaminobenzal-

(7) Bieg, T.; Szeja, W. *Synthesis* **1985**, 76.

(8) Höberg, H.; Wennerström, O. *Acta Chem. Scand. B* **1982**, 36, 661.

(9) (a) Bograchov, E. *J. Am. Chem. Soc.* **1950**, 72, 2268. (b) Marrian, S. F. *Chem. Rev.* **1948**, 48, 149. (c) Tanasescu, I.; Iliescu, I. *Bull. Soc. Chim. Fr.* **1938**, 5, 1446. (d) Fairbourne, A.; Woodley, J. W. *J. Chem. Soc.* **1926**, 3240.

Scheme 3. Acetalation/Transacetalation Modes of Monobenzal Pentaerythritol (**2**)

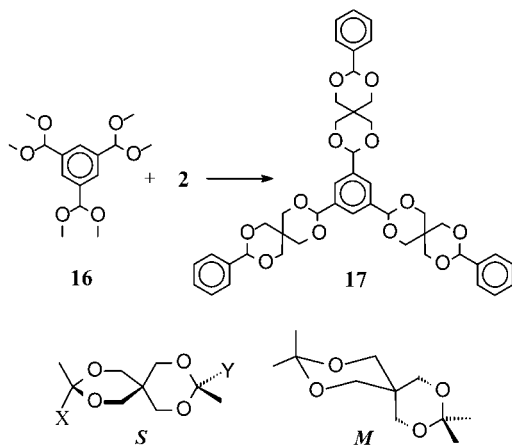


dehyde and **2**, no transacetalation occurred and the mixed acetal (**15**) was exclusively isolated.^{9d} In a compelling subsequent action, the reaction of the hexaol (**13**) with *p*-dimethylamino benzaldehyde provided the expected tris-(*p*-dimethyl aminobenzal) triacetal (vide infra).

These occurrences provide, in fact, the answer to our quest for asymmetric diacetals of pentaerythritol, and such 2,4,8,10-tetraoxaspiro[5,5]undecane systems are bound to be of interest for a variety of reasons, including charge-transfer studies in corresponding large macromolecules.

All in all, EDG-substituted benzaldehydes do not cause transacetalation of benzyldenepentaerythritols, while EWG substituted ones do. A further transacetalation model reaction was carried out between **2** and 1,3,5-benzenetricarbaldehyde hexamethylacetal (**16**). The expected product (**17**, 70%) was obtained, establishing that transacetalation reactions of the hydrolytically less stable acyclic acetals⁴ takes place readily to form the favored cyclic acetals (Scheme 4). Systems of

Scheme 4. 2,4,8,10-Tetraoxaspiro[5,5]undecane Dendrimer (**17**); Synthesis and Stereochemical Features



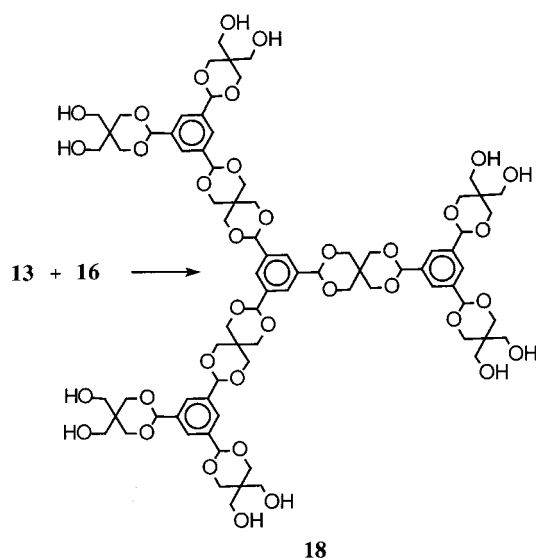
type **17** are stereochemically both complex and interesting, because of the 2,4,8,10-tetraoxaspiro[5,5]undecane unit. This molecular moiety has both axial and helical elements of

chirality,¹⁰ the former being configurationally and the latter conformationally defined (Scheme 4, bottom).

Since the bulky 3,9-substituents must be exclusively equatorial (except in the higher energy twist-boat forms), only *S,M/R,P* configurations are likely to be formed in the acetalation process and 3/4 of the possible diastereomeric forms can be discounted. Thus, **17** with its three spiroun-decane units is bound to have two diastereomers (*S,M;S,M;S,M* and *S,M;S,M;R,P* and their enantiomers). Notably, neither NMR nor HPLC techniques indicated more than one symmetric diastereomeric product (vide infra).

By the same token, a transacetalation reaction of the hexamethylacetal (**16**) (PTSA, DMF, 60 °C, 4 h) with excess hexaol (**13**) afforded (Scheme 5) the desired, sparsely soluble

Scheme 5. Synthesis of the Dodecaol Dendrimer (**18**)



dendrimer (**18**) (HPLC-SEC, NMR, and MALDI-MS) in fair yield (57%), featuring 12 terminal hydroxyl groups prone for further derivation. This also provided some proof of viability of our approach to late cyclic acetals by transacetalation without disrupting the earlier acetals in the molecule.

To probe the structural and stereochemical features of **18**, a simulated annealing calculation was performed, using Insight II.¹¹ After analyzing 2000 conformations of each, no significant energy differences were found between the two diastereomers. The models (Figure 1) depict the general structure of the lowest energy conformations of both compounds, which show very similar features: the three dendronic sidearms are extended in the same direction above the central benzene core, evidently as a result of efficient

(10) (a) Grosu, I.; Mager, S.; Ple, G. *J. Chem. Soc., Perkin Trans. 2* **1995**, 7, 1351. (b) Grosu, I.; Mager, S.; Ple, G.; Horn, M. *J. Chem. Soc., Chem. Comm.* **1995**, 167. (c) Grosu, I.; Mager, S.; Ple, G.; Martinez, R. *Chirality* **1996**, 8, 311.

(11) *Insight II 98 program package*; Molecular Simulations Inc.: San Diego, CA. The simulated annealing was run on the Discover 3 module using the CFF98 force field and the Decipher module.

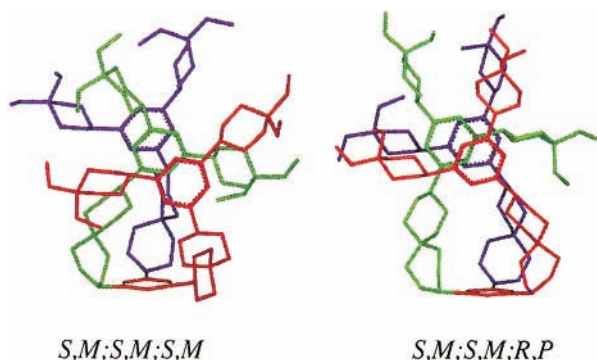


Figure 1. Models (stick rendering) of the dendrimer **18** in its two diastereomeric forms as obtained by molecular mechanics and dynamics (see text). Hydrogens are omitted for clarity.¹¹

π -stacking of the three aromatic rings and to O–H \cdots O H-bonds. The latter is one of the most interesting features of this type of dendrimers, in the context of further ramification and inclusion studies.

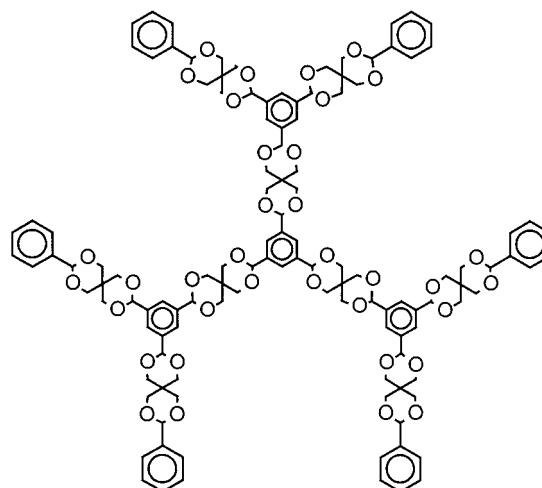
The computational models support the conjecture that even though diastereomers may be obtained, they are too similar to be readily discerned, mainly because of sporadic twist-boat forms within the structures; this point is now being given further attention.

The dodecaol dendrimer was readily derivatized with acetate protecting groups and the peracetylated compound (NMR, MALDI-MS) is soluble in less polar organic solvents. The decisive proof of validity of our approach lies, however, in the possibility to continue the acetalation or transacetalation on the dodecaol (**18**).

This was realized in the reaction of **18** with benzaldehyde dimethylacetal, which gave the quasi-2nd generation dendrimer (**19**) (83%), with similar unidirectional π -stacked dendrons.

In conclusion, the significance of this letter lies in two messages that it carries: (i) A general methodology was made available to prepare polyacetal macromolecular systems using protection–deprotection techniques and properly planned sequential transacetalation reactions, to enable building new

Scheme 6. Second Generation Dendrimer (**19**)



19

acetal functions in molecules already containing ones. (ii) Using these techniques, dendrimers (**18**, **19**) were obtained from the trialdehyde **11** with pentaerythritol, having 2,4,8,-10-tetraoxaspiro[5,5]undecane cores and functional or protected termini. Molecular mechanics and modeling calculations showed the dendrimers (**18**, **19**) to adopt a peculiar dendron convergent structure, mainly because of intramolecular π -stacking interactions and reinforced by H-bonding in the case of polyhydroxy termini. Other extended systems and related aliphatic dendrimers were made by similar techniques, to be described in the full account.¹²

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(12) Fully supporting preparative procedures and experimental data are available on request from the authors by e-mail or fax (+972-3-640 9293).