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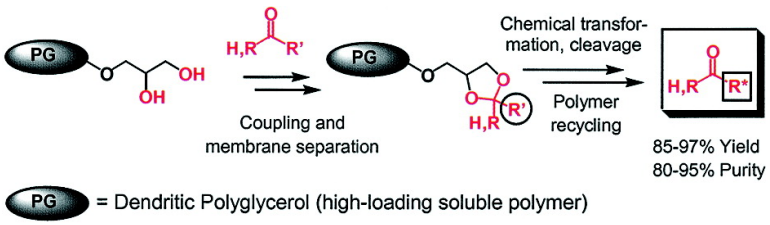

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Articles

Dendritic Aliphatic Polyethers as High-Loading Soluble Supports for Carbonyl Compounds and Parallel Membrane Separation Techniques

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This paper describes the use of dendritic polyglycerol as a new high-loading polymeric support. The soluble polyether skeleton allows the parallel synthesis of small libraries on a large scale (1−5 mmol). Purification of polymer-bound products is easily achieved by a parallel dialysis apparatus, which was developed to separate up to 12 reaction mixtures simultaneously. The terminal 1,2-diol groups of polyglycerol (loading capacity: 4.1 mmol diol/g) can be directly coupled with carbonyl compounds without additional linker groups. At the same time the polyglycerol support acts as a polymeric ketal protecting group. The coupling of the carbonyl compounds occurs in high yields, and effective loading capacities of up to 3.5 mmol of ketone/g can be reached. The obtained polymeric acetals can easily be characterized by standard analytical techniques, such as NMR, IR, UV, and SEC. The versatility of this new polymeric support for solution-phase organic synthesis is demonstrated by two efficient polymer-supported syntheses: nucleophilic substitutions of γ-chloroketones with amines and Suzuki-coupling on *p*-bromobenzaldehyde. The acid-catalyzed acetal cleavage with a solid-phase acidic ion-exchange resin in methanol demonstrates the orthogonal use of these soluble polymeric supports with conventional solid-phase reagents. Cleavage of products occurs in high yields, and almost complete recovery (>95%) of the polyglycerol support has been demonstrated after phase separation or ultrafiltration.

Introduction

In the past few years, soluble high-loading polymers and dendrimers have been introduced by several groups as potential alternatives for solid-phase supports in combinatorial chemistry.[1,2] Although highly successful, solid-phase synthesis exhibits a number of problems due to the heterogeneous nature of the reaction and the low concentration of accessible functional groups (typically ≤1.5 mmol of substrate/g of polymer). To obtain reasonable quantities of final products, substantial substrate loadings (>1.5 mmol/g) are required, which are difficult to achieve for many linker systems on polystyrene beads.[3] In contrast to solid-phase supports, soluble polymeric supports allow simple characterization of the polymer-bound compounds by standard analytical techniques such as NMR, IR, UV, and SEC. Fast and convenient characterization on the polymeric support is a useful tool, especially for multistep reactions.[1]

Similar to solid-phase supports, soluble polymeric supports can be separated from low molecular weight compounds after each reaction step by, for example, ultrafiltration, dialysis, preparative size exclusion chromatography (SEC), or precipitation. Even though the automation of these techniques is not yet as advanced as it is for solid-phase resins, tremendous progress has been made in the past few years. The use of alternative separation techniques for soluble polymeric supports compared to those used for conventional solid-phase supports permits the orthogonal use of both polymeric supports (soluble and solid-phase) in one chemical reaction and subsequent sequential separation.[1,4]

Up to now, the most widely used soluble polymer in organic synthesis is monomethylated poly(ethylene glycol) (typically MPEG 5000).[1,5] Because of the chemical properties of the linear polyether backbone, it is stable toward a broad range of reagents and can easily be precipitated from the reaction mixture with unpolar organic solvents such as diethyl ether. However, linear MPEG 5000 contains only one reactive OH or diol functionality[6] and hence has a rather poor loading capacity (0.2 mmol OH/g). More recently, several higher loading PEG derivatives have been prepared that are also suitable for precipitation. These starlike PEG derivatives[7] or terminally branched PEGs[8] reach loading capacities of up to 1 mmol of OH/g of polymer but require a significant synthetic effort for their preparation. Linear polymers carrying functional groups on every monomer unit, such as poly(vinyl alcohol),[9] polyacrylamides,[10] and ROMP-

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based polymers,[11] have also been used in solution-phase organic synthesis. These high-loading polymeric supports, however, can be problematic in some cases because of their limited solubility and stability, which can be overcome by further double bond functionalization.[12] Also, perfect dendrimers (polyamidoamine, polysilane)[2] and dendritic polyester[13] supports have been introduced for combinatorial synthesis.[1] These soluble polymeric supports have a high theoretical loading capacity; however, the chemical sensitivity of the dendrimer backbones, the rather low molecular weights,[14] and the multistep preparation limit their general use for combinatorial chemistry.

Dendritic aliphatic polyethers (branched analogues of PEG), on the other hand, are chemically stable for many reaction conditions and hence would be useful as polymeric supports in organic synthesis. In addition, the chemical and physical properties of these materials are ideal for solution-phase organic synthesis. Also, the globular shape of dendritic polymers can improve the separation based on membrane techniques (dialysis and ultrafiltration). Aliphatic polyether dendrimers containing terminal 1,3-diol and 1,2-diol units (6 and 7 mmol of OH/g) have recently been prepared using seven- and six-step syntheses, respectively.[15,16] A major limitation for the use of these perfect dendrimer supports in organic synthesis is their tedious multistep preparation and the relatively low molecular weights.

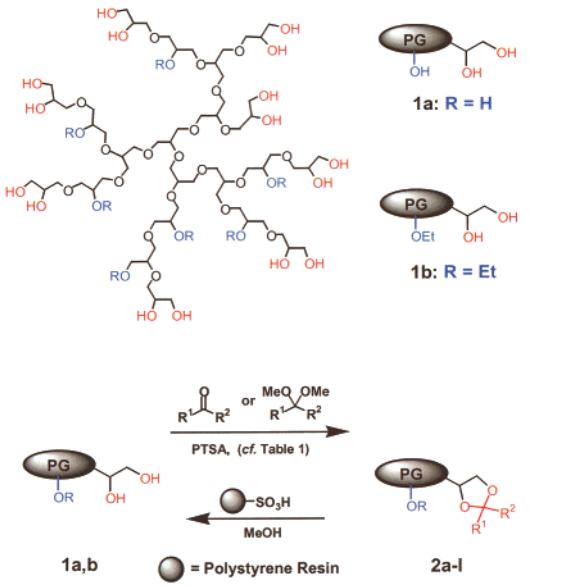
Recently, we have reported the controlled synthesis of well-defined dendritic polyglycerols **1** using racemic or chiral monomers.[17] These aliphatic polyether polyols possess a chemically stable backbone and are conveniently prepared in a one-step synthesis on a kilogram scale.[18] Molecular weights (M_n) up to 30 000 g/mol with narrow polydispersities ($M_w/M_n \leq 1.5$) can be obtained. The dendrimer-like structure of the polyglycerol **1** is characterized by exactly one focal unit (F) with multiple glycerol units randomly incorporated as both: linear (primary, secondary OH) and terminal groups (1,2-diols). The total density of functional groups in polymer **1** is 13.5 mmol of OH/g of polymer, of which approximately 30% (4.1 mmol/g) are terminal 1,2-diols. These terminal diols show excellent accessibility and can be used directly as linker groups to couple aldehydes and ketones onto this polymeric support **1** (Scheme 1). At the same time the diol-functionalized support can act as a polymeric ketal protecting group.[6]

In this paper we present the use of dendritic polyglycerols as soluble high-loading supports for aldehydes and ketones and the separation of polymer-bound compounds by parallel membrane separation techniques. The utility and chemical stability of this dendritic polymer for solution-phase organic synthesis are demonstrated for several functionalized carbonyl compounds and their conversions into aminoketones as well as Suzuki coupling products.

Results and Discussion

1. Properties and Separation of Polyglycerol Supports. 1.1. Chemical Stability. Dendritic polyglycerol **1** consists of an aliphatic polyether backbone, which is stable under many chemical conditions including strong acid (e.g., HCl, PTSA, TFA) and bases (e.g., KOH). Although the oxidative stability of **1** has not yet been fully explored, several oxidants, such as NMO/OsO_4, $NaIO_4$, and CrO_3, do not attack the polyether skeleton but only affect the terminal functional groups. Other reagents such as thionyl chloride, DCC, DEAD, PPh_3, $NaBH_4$, and phosphonic esters have been sucessfully used in combination with polyglycerol **1a**. For the reaction of polyglyerol acetals **2** (R = H) with organometallic reagents, excess reagent is required because of the remaining unfunctionalized core OH groups. To overcome this incompatibility, we have recently developed a method for the selective functionalization of the remaining core OH units with alkyl groups **1b** (R = alkyl).[19] After coupling of carbonyl compounds, the fully functionalized polyglycerol acetals **2** (R = Et) are stable even in the presence of strong bases such as LDA and *n*-BuLi.

Scheme 1. Dendritic Polyglycerol **1a** (PG) and Core-Ethylated PG **1b** as High-Loading Polymeric Support for Carbonyl Compounds[a]



[a] Polyglycerol acetals **2** can be formed under various conditions (cf. Table 1). Acetal cleavage can be achieved with solid-phase acidic ion-exchange resins. The depicted polymer structure **1** represents only one possible isomer and a small part of the polyglycerol (M_n = 7000 g/mol) scaffold.

1.2. Thermal Stability. We have investigated the thermal stability of polyglycerols **1a,b** by thermogravimetric analysis (TGA) in the absence and presence of oxygen. The TGA plots (Figure 1) clearly demonstrate that these materials are stable under thermal conditions up to ca. 300 °C in the absence of oxygen (250 °C with oxygen).

1.3. Solubility and Compatibility. Despite their lower degree of branching, dendritic polymers behave in many aspects like perfect dendrimers. Low glass transition and high solubility in many organic solvents are the characteristics of this class of materials. In contrast to the linear poly(vinyl alcohol), polyglycerol **1a** is soluble even at high concentrations in a variety of polar solvents (protic and aprotic) such as DMF, DMA, DMSO, NMP, MeOH, pyridine, and water. Polyglycerol acetals **2**, on the other hand, are soluble in all kinds of organic solvents, even relatively unpolar solvents such as toluene and halogenated alkanes. A very poor solubility, however, is observed in pure alkanes such as hexane. For better compatibility and higher solubility in

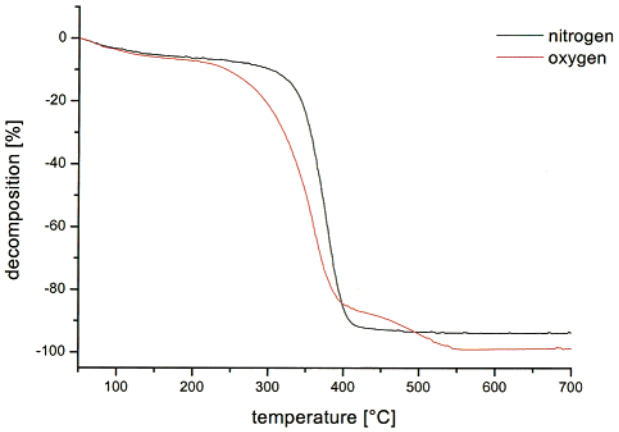


Figure 1. Thermogravimetric analysis (TGA) of polyglycerol **1b** under nitrogen and oxygen atmosphere with decomposition starting at 284 and 237 °C, respectively.

unpolar solvents, core-alkylated polyglycerols **1b** can be used.[19] For example, the core-ethylated polyglycerol **1b** has a similar high loading capacity (3.5 vs 4.1 mmol/g) for polyglycerol **1a** and is readily soluble in unpolar solvents such as toluene and dichloromethane.

1.4. Optimal Molecular Weights of Polyglycerol Supports. Although polyglycerols can be prepared with molecular weights up to 30 000 g/mol, it is known for many polymer analogue reactions that their yields are dependent on the molecular weight of the polymer. For polyglycerols **1** we have observed incomplete conversions, e.g., acetalization and alkylation at molecular weights higher than 15 000 g/mol. Therefore, molecular weights between 5000 and 10 000 are most suitable for polymer-supported synthesis and still allow the easy separation of the polymer from low molecular weight compounds by membrane separation techniques (see below).

In the present work we used polyglycerol **1a** with a molecular weight (M_n) of 7000 ($M_w/M_n = 1.5$) containing approximately 30 terminal 1,2-diol units per molecule. This dendrimer-like macromolecule was prepared on a large scale[18] by anionic ring-opening multibranching polymerization of glycidol using bis(2,3-dihydroxypropyl)stearylamine as the core unit.[17b]

1.5. Separation of Polyglycerol Supports from Low Molecular Weight Compounds. Several separation techniques (ultrafiltration, dialysis, SEC, precipitation, and phase separation) have been reported for soluble polymeric supports.[1a] We have tested all these techniques for the separation of polyglycerol supports **1** from low molecular weight compounds. It appears that only dialysis and ultrafiltration (see Experimental Section) are useful for the separation of polyglycerol derivatives on a large scale (0.5−3 g). Since these separation techniques up to now were not used in combinatorial synthesis, we have developed a parallel dialysis unit. Currently, this apparatus (Figure 2) can purify up to 12 samples (ca. 1−5 mmol of compound) simultaneously. It can be operated in many organic solvents, e.g., chloroform, MeOH, THF, and toluene if a solvent-resistant membrane is used (see Experimental Section). To the precision of ^{1}H NMR spectroscopy (98%), we could not detect any cross-contamination when using the parallel dialysis apparatus

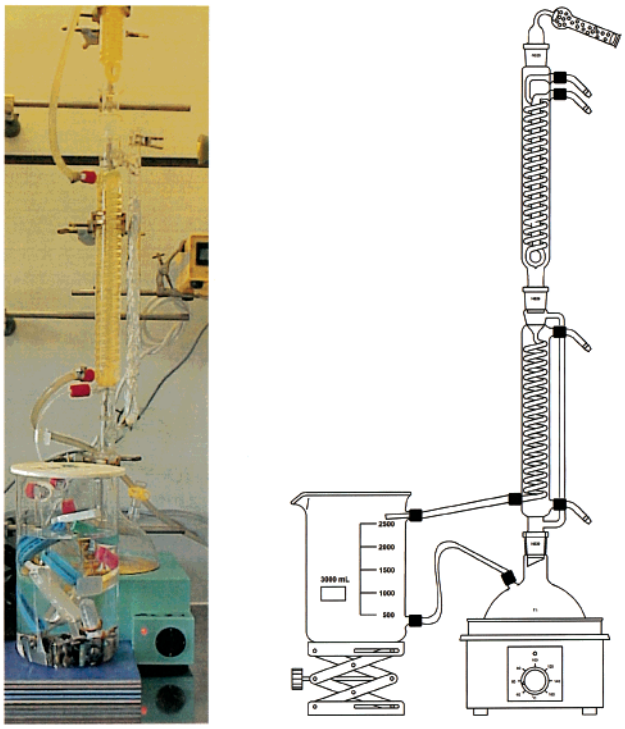


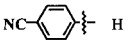
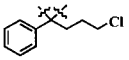
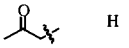
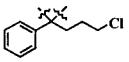
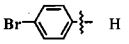
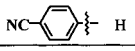
Figure 2. Parallel dialysis apparatus as a new separation tool for soluble polymeric supports.

(Figure 2). Typical separation times are 12−36 h, depending on the amount of low molecular weight impurities. A much faster separation technique, which can be used especially in the final separation after cleavage of the product, is ultrafiltration. Commercial systems (see Experimental Section) are readily available, and parallelization is in progress. In contrast to dialysis, separation times can be reduced to 1−5 h for about 10−50 mL of sample volume.

Phase separation is another simple and fast method for the separation of unpolar compounds from polyglycerol **1a** after final cleavage of the products (see below) and has been used previously in parallel synthesis.[20] Also, removal of the soluble polymeric support **1a,b** after the final cleavage step by a small silica cartridge is possible with polyglycerol supports.[21]

2. Coupling and Cleavage of Carbonyl Compounds. 2.1. Coupling of Carbonyl Compounds onto Polyglycerol Supports. The reversible coupling of aldehydes and ketones onto the polyglycerol support **1** is performed by selective acetal formation on the terminal 1,2-diols, and effective loadings (total loading after coupling of substrate) up to 3.5 mmol/g can be achieved. By use of standard Dean−Stark conditions in toluene with a catalytic amount of *p*-toluenesulfonic acid, the polymer-supported acetals **2a**−**c** can be isolated in high yields after purification by dialysis (Scheme 1, Table 1). The formation of the polyglycerol acetals **2** from ketones and aldehydes occurs smoothly when the carbonyl compounds have a higher boiling point than toluene and are chemically stable under the conditions used. However, the substrates acetaldehyde, acetone, chlorobutyrophenone, and 4-cyanobenzaldehyde did not give acceptable yields under these reaction conditions. In these cases, the reaction of **1** with the corresponding dimethyl acetals[22] yielded the poly-

Table 1. Formation of Polyglycerol Acetals **2a**−**l** from Ketones and Aldehydes (Methods A and A′) and of Dimethyl Acetals (Method B) from Dendritic Polyglycerols **1a**,**b**

Acetal	Polymer	R^1	R^2	Method	Time [h]	Yield[a] [%]
2a	**1a**	-$(CH_2)_5$-		A	18	87
2b	**1a**	C_5H_{11}	CH_3	A	18	99
2c	**1a**	Phenyl	H	A	18	quant.
2d	**1a**	CH_3	H	B	3	93
2e	**1a**	CH_3	CH_3	B	3	quant.
2f	**1a**	C_5H_{11}	C_5H_{11}	B	3	quant.
2g	**1a**		H	B	3	95
2h	**1a**			B	3	96
2i	**1a**		H	B	3	95
2j	**1b**			A′	8	98
2k	**1b**		H	A′	8	89
2l	**1b**		H	A′	18	97

[a] Isolated yields after dialysis.

glycerol acetals **2d**−**i** under mild conditions with significantly shorter reaction times. For example, the formation of the acetylethyl acetal **2i** from polyglycerol **1a** and acetylacetaldehyde dimethyl acetal was complete after only 30 min at ambient temperature using ultrasonication. These mild conditions are similar for all other dimethyl acetal substrates and result in high conversions (>95%) of the terminal 1,2-diols, as determined by ^{13}C NMR spectroscopy. After concentration and dialysis, the corresponding acetals **2d**−**i** were isolated in high yields (Table 1).

For many functional carbonyl compounds the respective dimethyl acetals are not commercially available, and the direct conversion of polyglycerol **1a** is slow or does not occur at all. In these cases we have used a core-alkylated polyglycerol **1b**,[19] which gave the corresponding acetals **2j**−**l** in significantly shorter reaction times using Dean−Stark conditions. The reaction of the core-ethylated polyglycerol **1b** with the γ-chlorobutyrophenone (**2j**) and *p*-bromobenzaldehyde (**2k**) is quite remarkable because they did not react with the unfunctionalized polyglycerol **1a** at all and the use of their dimethyl acetals is rather complicated. For example, in the case of **2h**, similar high yields were obtained; however, the effective loading capacity was slightly lower (approximately 2 mmol/g) because of the core-alkylation.

Another advantage of soluble polymeric supports is the direct characterization of the chemical transformation on the support by standard analytical techniques. Because of the high loading capacity of polyglyerols **1** and the high concentration of polymer-supported compounds, fast detection by standard solution NMR is possible. In addition, the polyether scaffold **1a** exhibits only few signals in a very narrow region and allows a simple characterization of many chemical transformations. For example, in the ^{13}C NMR spectra of the acetals **2** (e.g., cyclohexylidene acetal **2a**, Figure 3), the chemical shifts of the carbon atoms of the terminal glycerol units (T′) changed significantly compared to the terminal units (T) in polyglycerol **1a**. The complete conversion of the terminal 1,2-diols was confirmed, while the rest of the dendritic scaffold remained unaffected (Figure 3). The presence of intense peaks at 25, 26, 36, 38, and 111 ppm clearly indicated the formation of the cyclohexylidene acetal **2a**.

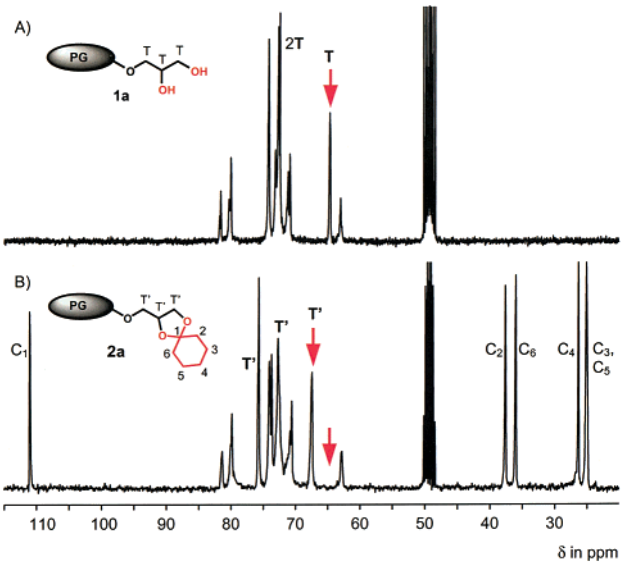


Figure 3. ^{13}C NMR spectra (75.5 MHz, [D_4]-methanol) of (A) polyglycerol **1a** (PG) and (B) polyglycerol cyclohexylidene acetal **2a**. For the assignment of the glycerol signals, see ref 26.

2.2. Cleavage of Carbonyl Compounds from the Polyglycerol Supports. The acetal cleavage can be performed either with aqueous TFA or with a solid-phase acidic ion-exchange resin (such as DOWEX-50). The latter clearly demonstrates the orthogonal use of two types of polymeric supports (soluble and solid-phase) in *one* reaction mixture.[4] For the recovery of the carbonyl compound and the recycling of the polyglycerol, we used two simple workup protocols: ultrafiltration and phase separation (water/chloroform). The latter can only be applied when a relatively unpolar carbonyl compound was cleaved from the polyglycerol support. On the basis of the polar nature of the polymeric support **1a** and the hydrophobic character of the many carbonyl compounds, separation in a water/chloroform mixture was possible in many cases. This technique allows the almost quantitative recovery of the carbonyl compound and the polyglycerol **1a**. In the case of more polar carbonyl compounds, e.g., **4a**,**b** (see below), we have used ultrafiltration through a cellulose membrane for the separation of the carbonyl compounds from the polymeric support.

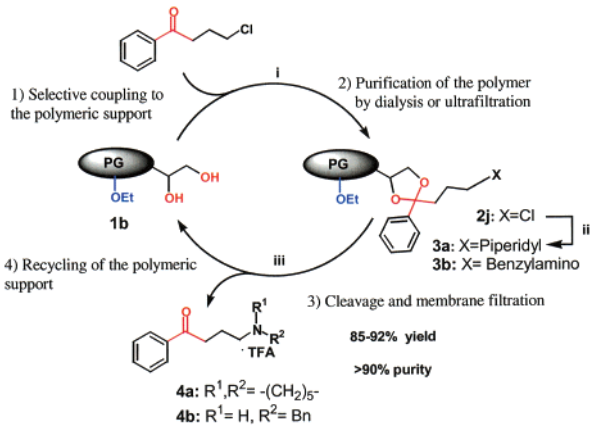
Although some groups have previously used orthogonal polymers (soluble and solid-phase) in one reaction vessel,[4] it is not obvious how these macromolecules would interact and whether there is a size limit for soluble polymers. We

have therefore studied the acetal cleavage by ion-exchange resins as a function of the degree of cross-linkage. While cleavage of acetal occurred with a 2% divinylbenzene cross-linked PS resin (DOWEX-50 and Lewatit K1131), 7 h quantitatively, only a trace (<1%) of cleaved acetal could be observed with an 8% cross-linked acidic ion-exchange resin (Lewatit SP112). It appears that the degree of cross-linking in the ion-exchange resin clearly affects the conversion of the acetal cleavage reaction. For higher molecular weight soluble polymers, this can be a limiting factor.

3. Chemical Modifications on Polyglycerol Supports. To demonstrate the utility of this homogeneous polymeric support **1** for liquid-phase organic synthesis, we performed nucleophilic substitution reactions on the polymer-bound acetal **2j** and a Suzuki cross-coupling reaction on the polymer-bound aromatic halide **2k**. In addition, various techniques for the acetal cleavage, the simple isolation of the products, and the recycling of the support were investigated.

3.1. Synthesis of Aminoketones on Polyglycerol Supports. 4-Amino alcohols derived from 4-aminobutyrophenones are of pharmaceutical interest because of their antiarrhythmic activity.[23] The reaction of 4-chlorobutyrophenone with amines has been reported to occur in modest yields, and protection of the carbonyl functionality was necessary to achieve regioselective transformations.[23] In the case of the polymer-supported chlorobutyrophenone **2j**, we obtained the corresponding amino acetals **3a** and **3b** in high yields (92% and 85%, respectively) after dialysis (Scheme 2). In this case aqueous TFA was used for the acetal

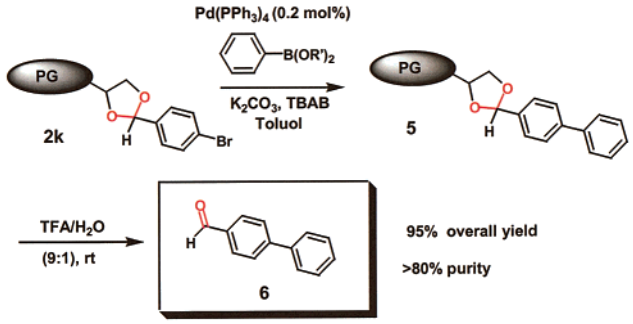
Scheme 2. Use of Polyglycerol **1** (PG) as a Recyclable Polymeric Support for Carbonyl Compounds in the Synthesis of Aminoketones **4a**,**b**[a]



[a] (i) PTSA, toluene, reflux, $-H_2O$; (ii) amine, NaI, reflux; (iii) TFA/water (9:1), 20 °C.

cleavage. After concentration, the products were separated by ultrafiltration from the polymer support in methanol. In the case of the polymer-bound acetal **3a**,[23a] the 371 mg of the desired 4-piperidinoketone **4a** (>90% purity according to ^{1}H NMR) and 128 mg of the polyglycerol **1b** were obtained after concentration. This corresponds to an effective loading of 2.2 mmol of ketone/g. Despite this high loading capacity, only traces of an intramolecular coupling product could be detected after cleavage in the case of acetal **3b**.[24] Therefore, it might be feasible to use dendritic polyglycerols

Scheme 3. Polyglycerol-Supported Suzuki Coupling for the Synthesis of Biphenylaldehyde **6**



with an even higher loading capacity (7 mmol of diol/g) for these reactions.[16]

3.2. Suzuki Cross-Coupling on Polyglycerol Supports. Suzuki cross-coupling reactions have been investigated by several groups on solid-phase supports.[25] A limiting factor, however, is the large amount of palladium catalyst (typically 5−20 mol %) required for these heterogeneous reactions. For soluble polymers, only recently, a perfect silane dendrimer has been used for this reaction type allowing homogeneous catalysis conditions.[2b] However, in this case a total of 250 mol %(!) of palladium catalyst was used. A smaller amount of the expensive Pd catalyst in these homogeneous reactions would simplify the workup protocol and reduce costs. We therefore studied the Pd-catalyzed Suzuki coupling of polyglycerol-supported *p*-bromo benzacetal **2k** with phenylboronic acid (Scheme 3). It appears that already very low catalyst concentrations (0.2−0.5 mol %) result in the polymer-supported coupling product. The polymer-supported biphenyl **5** was purified by ultrafiltration and then cleaved in a mixture of TFA/water (9:1) to afford the biphenylaldehyde **6** in high yield (95%) and purity (>80%).

Conclusions

In summary, we have demonstrated the use of dendritic polyglycerol (PG) as a new soluble polymeric support for carbonyl compounds and the parallel isolation of these soluble polymeric materials by parallel membrane separation techniques. High loading, short reaction times, and the simple separation of the reaction products are the characteristics of this dendritic polyether. The access to large quantities of these well-defined polyglycerols and the chemical stability of the scaffold, in addition to the multiple possibilities for functionalization, render them ideal candidates for new soluble polymeric supports in organic synthesis. In addition, high retentions (>95%) of the polymer supports were observed in parallel dialysis and ultrafiltration, qualifying these dendritic polyglycerols as suitable materials for membrane separation techniques. The separation techniques used in this work are certainly not suitable for high throughput, but they allow the preparation of small libraries (10−100 compounds) on a large scale (1−5 mmol of compound). In this ongoing project we are currently investigating the use of polyglycerol supports in various other applications, e.g., as support for reagents and catalysts. Also, different linker functionalities such as aldehydes, alkenes, amines, and

carboxylates are accessible on polyglycerol supports,[1a,26] and their chemistry will be presented in due course.

Experimental Section

Materials. Polyglycerol **1a** (M_n = 7000, M_n/M_w = 1.5) was prepared as described previously, using bis(2,3-dihydroxypropyl)stearylamine as initiator.[17b] The selective functionalization of the core OH units with alkyl groups to yield core-ethylated polyglycerols **1b** (R = Et) was performed as reported previously.[19] All aldehydes and ketones, dimethyl acetals, *p*-toluenesulfonic acid (PTSA), benzylamine, piperidine, Dowex 50, Lewatit, and tetrabutylammonium bromide (TBAB) were purchased from Fluka/Aldrich. $Pd(PPh_3)_4$ and all solvents (analytical grade) were purchased from Merck. Reagents and solvents were used without any further purification.

Instrumentation. ^{1}H NMR and ^{13}C NMR spectra were recorded in [D_4]-methanol for polar polyglycerol derivatives and [D_1]-chloroform for modified polyglycerols and cleaved products at concentrations of 100 mg/mL on a Bruker ARX 300 spectrometer operating at 300 and 75.4 MHz, respectively. For the characterization and description of the polyglycerol backbone L, D, T are used for linear, dendritic, and terminal units, respectively.[17] L_{13} and L_{14} describe the two different connectivities of linear glycerol units: primary/secondary and primary/primary ether linkage, respectively.[26]

Dialysis (benzoylated cellulose tubing, Sigma, MWCO 1000) was performed in a 3 L beaker with a continuous recycling of the solvent (Figure 2). This reduced purification times to about 12−36 h. For ultrafiltration we used a commercially available solvent-resistant stirred pressure cell (Millipore, 6 bar, 47 mm) in combination with solvent-resistant membranes (Koch, MPF50). Typical separation times were 1.5 h per 20 mL.

Formation of Polyglycerol Acetals. Method A: Polyglycerol Cyclohexylidene Acetal (2a). A mixture of 1.0 g of polyglycerol **1a** (4.1 mmol of terminal 1,2-diols) and 0.1 g of *p*-toluenesulfonic acid (PTSA) in 50 mL of toluene was refluxed for 18 h under Dean−Stark conditions. Within ca. 5 h a homogeneous reaction mixture was observed. The reaction mixture was extracted three times with a concentrated aqueous Na_2CO_3 solution, and the organic phase was dried ($MgSO_4$) and concentrated to obtain 1.5 g of a yellow oil. Dialysis was carried out on the crude product (benzoylated cellulose tubing, Sigma, MWCO 1000). After evaporation of the solvent, 1.17 g (87%) of a pale-yellow oil was obtained. ^{1}H NMR (300 MHz, [D_4]-methanol): δ 4.21 (m, C*H*OCH$_2$O), 3.98 (t, CHOC*H*$_2$O), 3.75 (m, CHOC*H*$_2$O), 3.23−3.55 (m, C*H*, C*H*$_2$, polyether backbone), 1.65 (m, C*H*$_2$, ketal), 1.40 (m, C*H*$_2$, ketal). ^{13}C NMR (75.5 MHz, [D_4]-methanol): δ 111.0 (C_1), 81.2 (L_{13}), 79.9 (D), 75.8 (T), 74.0, 73.8 ($2L_{14}$, T), 72.7 (2D), 70.9 (L_{13}, L_{14}), 67.6 (T), 63.0 (L_{13}), 38.0 (C_2), 36.1 (C_6), 26.4 (C_4), 25.2 (C_3, C_5).

Method B: Polyglycerol 6-Undecanylidene Acetal (2f). A mixture of 1.0 g of polyglycerol **1a** (4.1 mmol of terminal 1,2-diols) and 0.1 g of *p*-toluenesulfonic acid (PTSA) in 5 mL of 6-undecanon dimethyl acetal was agitated in an ultrasonic bath (Sonorex RK255H) at 20 °C. Within 15 min a homogeneous reaction mixture was observed. After 3 h, 100 μL of piperidine was added and all volatile compounds were removed in vacuo to obtain 1.9 g of a colorless oil. Dialysis was carried out on the crude product. Upon evaporation of the solvent, 1.70 g (100%) of a colorless oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20 (m, C*H*OCH$_2$O), 4.00 (t, CHOC*H*$_2$O), 3.85 (m, CHOC*H*$_2$O), 3.25−3.75 (m, C*H*, C*H*$_2$, polyether backbone), 1.82 (m, core-OH), 1.51 (m, COC*H*$_2$, ketal), 1.25 (m, C*H*$_2$, ketal), 0.82 (m, C*H*$_3$, ketal). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 110.6 (acetal C_q), 81.7, 80.4, 80.1, 76.5, 76.3, 74.3, 73.7, 72.7, 71.1, 70.8, 67.9, 63.0 (polyether backbone), 31.0, 27.5 (ketal CH_2), 26.0 (ketal CH_3).

Method A′: Polyglycerol *p*-Brombenzacetal (2k). A mixture of 0.29 g of polyglycerol **1b** (1.0 mmol of terminal 1,2-diols), 0.57 g (3.0 mmol) of *p*-brombenzaldehyde, and 0.07 g of *p*-toluenesulfonic acid (PTSA) in 20 mL of toluene was refluxed for 18 h under Dean−Stark conditions. Within 1 h a homogeneous reaction mixture was observed. The reaction mixture was extracted three times with a concentrated aqueous Na_2CO_3 solution, and the organic phase was dried ($MgSO_4$) and concentrated to obtain 0.43 g of a viscose yellow oil. Dialysis was carried out on the crude product in chloroform. After evaporation of the solvent, 0.38 g (89%) of a yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18−7.28 (m, aromatic), 5.80 (s, OC*H*C$_6$H$_4$Br), 5.66 (s, OC*H*C$_6$H$_4$Br), 4.29 (m, C*H*OCH$_2$O), 4.02 (t, CHOC*H*$_2$O), 3.73 (m, CHOC*H*$_2$O), 3.23−3.53 (m, C*H*, C*H*$_2$, polyether backbone), 0.90−1.20 (m, core-OCH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9 (C_1, aromatic), 129.8 (C_3, C_5, aromatic), 128.2 (C_6, aromatic), 127.8 (C_2, aromatic), 123.2 (C_4, aromatic), 103.6 (O*C*C$_6$H$_4$Br), 103.0 (O*C*C$_6$H$_4$Br), 78.6, 75.0, 72.0, 71.4, 67.5, 66.6, 65.8 (polyether backbone), 14.7 (core-OCH$_2$*C*H$_3$, ketal).

Orthogonal Acetal Cleavage and Recycling of Polyglycerol by Phase Separation. To a solution of 500 mg of polyglycerol 6-undecanylidene acetal (**2f**) in 5 mL of methanol, 500 mg of strongly acidic ion-exchange resin (Dowex-50, Fluka) was added. After the mixture was stirred for 15 h at 50 °C, the solid phase was removed by filtration and 20 mL of a water/chloroform mixture (1:1) was added. The two phases were separated, and the aqueous phase was extracted again with 10 mL of chloroform. Concentration of both phases yielded the following: (aqueous phase) 280 mg (94%) of pure polyglycerol **1**, as determined by ^{1}H NMR spectroscopy; (organic phase) 196 mg (97%) of 6-undecanone, as determined by ^{1}H NMR spectroscopy.

Synthesis of Aminoketones on Polyglycerol Supports. Reaction of Polyglycerol-Supported γ-Chlorbutyrophenone 2j with Amines. The preparation of γ-piperidylbutyrophenone is representative of the nucleophilic substitution on the polymeric support. A solution of 1.0 g (2.4 mmol) of polyglycerol-supported γ-chlorbutyrophenone (**2j**) and 1.2 g (8.0 mmol) of sodium iodide in 12.0 mL of piperidine was heated to 120 °C. After the mixture was stirred for 24 h at this temperature, the solution was filtered and excess piperidine removed in vaccuo. The product was dialyzed in chloroform for over 48 h to obtain 1.03 g (92%) of supported γ-piperidylpropiophenone **3a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10−7.45 (m, aromatic), 4.29 (m, C*H*OCH$_2$O), 4.10 (m,

CHOCH_2O), 4.02 (m, CHOCH_2O), 3.13−3.93 (m, CH, CH_2, polyether backbone), 2.40 (m, NCH_2), 1.80, 1.65, 1.40 (m, CH_2), 1.15 (m, core CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1 (C_1, aromatic), 128.3 (C_3, C_5, aromatic), 125.7 (C_2, C_4, aromatic), 111.0 (OCC$_6$H$_5$), 72.5, 71.6, 66.9, 65.7 (polyether backbone), 58.0 (core OCH_2CH$_3$), 54.3 (NCH_2), 36.2, 27.3, 25.1, 24.3, 20.1 (CH_2), 14.7 (core CH_3).

Cleavage of the γ-Piperidylbutyrophenone 4a. A solution of 0.5 g of supported γ-piperidylpropiophenone **3a** in 5 mL of TFA/water (9:1) was stirred at 25 °C. After 18 h the solvent was removed in vaccuo and the crude product was purified by ultrafiltration (regenerated cellulose membrane, MILLIPORE, MWCO 1000) in methanol. After concentration, 371 mg of **4a** as a pale-yellow oil (filtrate) and 128 mg of a polyglycerol residue were obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.40 (s, 1 H, NH^+), 7.36−7.53 (m, 5 H, aromatic), 3.74 (m, 2 H, CO−CH_2−CH$_2$), 3.13−3.18 (m, 4 H CH_2 piperdine), 2.68−2.71 (m, 2 H, CH_2−NH$^+$), 1.36−1.45 (m, 6 H, CH_2 piperdine), 1.18 (s, 2 H, COCH$_2$−CH_2−CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0 (C═O), 136.1 (C_1, aromatic), 133.5 (C_4, aromatic), 128.7 (C_2, C_6, aromatic), 128.1 (C_3, C_5, aromatic), 56.8 (CH$_2$−CH$_2$−NH$^+$), 53.6 (piperidine), 35.3 (CO−CH$_2$−CH$_2$), 22.7 (piperidine), 21.8 (piperidine), 18.1 (COCH$_2$−CH$_2$−CH$_2$). MS (CI, NH_3), m/z: 232 (100) [M + H]$^+$.

Polyglycerol-Supported Suzuki Cross-Coupling Reaction 5. To a solution of 0.21 g of polyglycerol acetal **2k** (0.84 mmol of supported *p*-brombenzaldehyde) in 10 mL of DMF, 0.14 g of phenylboronic ester (0.93 mmol), 0.37 g of K_2CO_3 (2.3 mmol), 0.34 g of TBAB (1.0 mmol), and 4.7 mg of Pd(PPh$_3$)$_4$ (0.52 mol %) were added under an argon atmosphere. The reaction mixture was heated to 90 °C for 18 h, then cooled to room temperature, filtered, and concentrated. Dialysis in chloroform was carried out on the crude product. After evaporation of the solvent, 300 mg (ca. 105%) of the polymer-supported biphenyl **5** (containing TBAB salts) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24−7.59 (m, aromatic), 5.71 (s, OCHC$_6$H$_4$Br), 5.66 (s, OCHC$_6$H$_4$Br), 4.29 (m, CHOCH$_2$O), 4.16 (m, CHOCH_2O), 3.87 (m, CHOCH_2O), 3.22−3.49 (m, CH, CH_2, polyether backbone), 1.10 (core-OCH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5 (C_4, aromatic), 140.3 (C_7, aromatic), 136.7 (C_1, aromatic), 128.6 (C_9, C_{11}, aromatic), 127.3 (C_3, C_5, aromatic), 126.9 (C_8, C_{12}, aromatic), 103.8 (OCC$_6$H$_4$−C$_6$H$_5$), 103.2 (OCC$_6$H$_4$−C$_6$H$_5$), 78.5, 75.0, 72.0, 71.6, 67.5, 66.5, 65.6 (polyether backbone), 13.6 (core-OCH$_2$$CH_3$).

Cleavage of the Biphenyl-4-carbaldehyde (6). A solution of 285 mg of supported biphenyl acetal **5** in 10 mL of TFA/water (9:1) was stirred at 25 °C. After 3 h the solvent was removed and the crude product again was dissolved in toluene and filtered through a short silica cartridge (3 cm) to remove polymer, catalyst, and salts. The concentration of the organic phase gave 153 mg (95%) of the desired biphenyl-4-carbaldehyde (ca. 80% purity according to ^{1}H NMR), and the aqueous phase contained 132 mg of polyglycerol **1b** after concentration. All NMR spectroscopic data were in agreement with those reported.[27]

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Supporting Information Available. ^{1}H NMR and MS spectra of compounds **2**−**6** described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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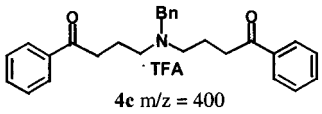

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