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Synthesis of a pH-independent bifurcated amphiphile

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Abstract

An efficient synthetic method for preparing bifurcated amphiphiles has been developed such that the functionality for attachment is located at the interface between the lipophilic and hydrophilic side chains. Attachment of the amphiphile to the repeat units of polymeric substrates enables the rapid preparation of amphiphilic homopolymers.

Keywords: Amphiphile; Amphiphilic monomer; Amphiphilic polymer; Amphiphilic homopolymer

The human production and use of amphiphilic compounds dates to prehistory, when triacylglycerides were hydrolyzed in alkaline solution affording soaps to enable the aqueous dispersion of lipids. Since that time, amphiphiles have seen widespread use owing to their unique ability to modulate the surface properties of molecules, particles, or solid surfaces with respect to their environment. Amphiphilic materials also can be used to enhance medical technologies, from their encapsulation of potent but insoluble drugs in micellar carriers to their disruption of fungal cell walls. Much effort has been focused on the synthesis and applications of amphiphilic block copolymers; however, equally promising but relatively underexplored architectures include amphiphilic homopolymers[1] and dendrimers,[2] in which each repeat unit bears both lipophilic and hydrophilic side chains. If amphiphilic homopolymers can organize into discrete nanoscale reverse micelles, they offer promise as carriers to transport polar therapeutics through the lipophilic stratum corneum, thereby enhancing transdermal drug delivery.

The traditional oral route for delivering drugs is incompatible with many therapeutics due to the harshly acidic and enzymatically active gastric environment, therefore, efforts have shifted to investigate technologies that would allow the transdermal administration of these materials. While the lipids within the skin are permeable to small, lipophilic molecules, most therapeutics are required to be hydrophilic to permit their distribution throughout the body via the bloodstream. However, only a handful of therapeutics exhibits the amphiphilic character that affords both permeability through the skin and systemic delivery through the bloodstream. Amphiphilic carriers can be designed to compatibilize polar drugs with the skin lipids to enable their transdermal transport, while allowing their release once they reach the bloodstream.

To probe the efficacy of amphiphilic homopolymers for improving transdermal drug delivery, a broad range of polymer sizes and architectures should be explored. The first step toward this goal is the development of an efficient synthetic method for preparing bifurcated amphiphiles. The amphiphilic unit can then be attached either to the monomer before polymerization or to each repeat unit after polymerization (Scheme 1).

The bifurcated amphiphile **1** was designed so that the hydrophilic and hydrophobic chains had the same proximity to the attachment point. A dodecyl unit was selected as the lipophilic side chain because its length is comparable to the average length of hydrocarbon chains found among the lipids in the dermal extracellular matrix. A triethylene glycol hydrophilic side chain was selected because it

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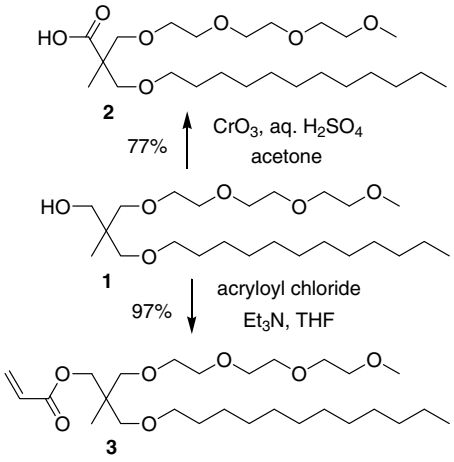
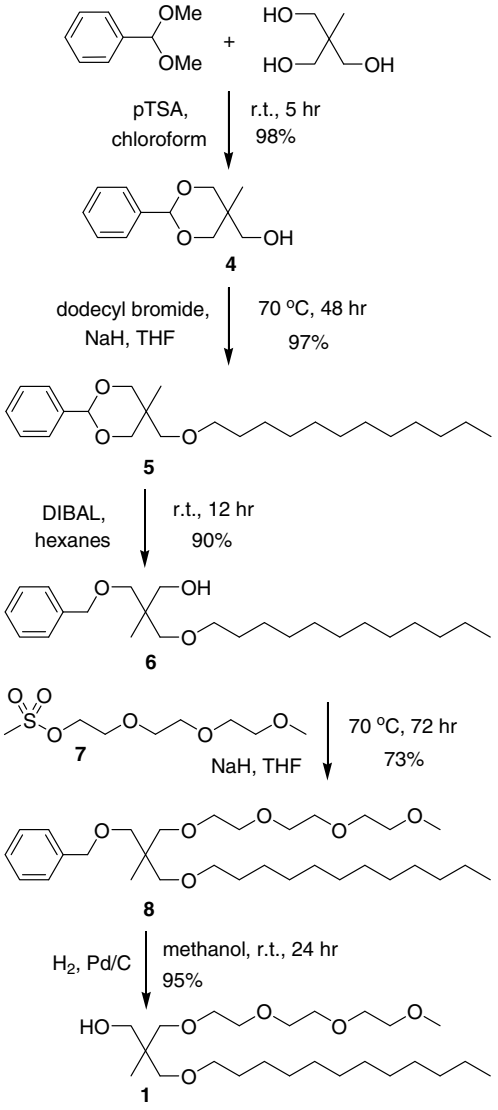


Scheme 1. Target amphiphiles.

provides a pH-independent hydrophilic moiety (as opposed to amines or carboxylic acids) that has an analogous length to the dodecyl chain. Finally, a third functionality was included as a means of attachment to the polymer. Because of the large number of natural and synthetic biocompatible polymers with alcohol functionalities, such as carbohydrates, poly(vinyl alcohol), poly(hydroxyethyl acrylate), and poly(hydroxyethyl methacrylate), the third functionality was converted to carboxylic acid **2** for attachment. This carboxylic acid can be easily attached to the hydroxyl side chains via the conversion of **2** to the acid chloride or through carbodiimide couplings using either *N*,*N*′-dicyclohexylcarbodiimide (DCC) or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide (EDC). In addition, the alcohol of **1** can be esterified with acryloyl chloride to yield the polymerizable amphiphile **3**.

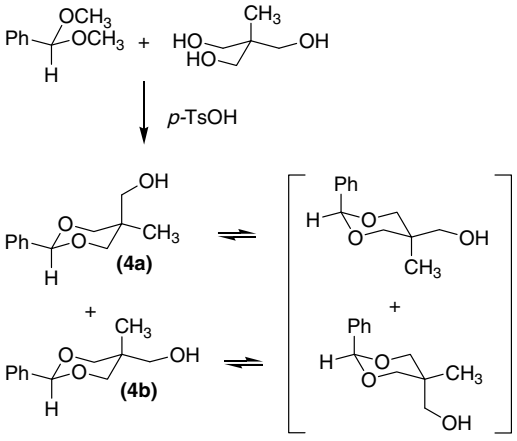
1,1,1-Tris(hydroxymethyl)ethane was selected as the core for our amphiphile largely because of its low cost and commercial availability. To carry out selective functionalizations on each of the three hydroxyl groups, a ketal protecting group was selected to mask two of the alcohols.[3] Ketal protecting groups have seen extensive use for the protection of 1,2- and 1,3-diols for a wide range of applications including the selective modification of carbohydrates,[4] the synthesis of natural products,[5] the production of deep UV photoresists,[6] and the preparation of hydroxylated dendrimers.[7] The benzylidene ketal was chosen specifically because of its unique ability to be partially cleaved, exposing one of the alcohols, and leaving the other one protected as a benzyl ether.[8] This partial deprotection reaction is quite useful for selective functionalization of diols, and has demonstrated high regioselectivity with appropriate substrates.[9] For our synthesis, the benzylidene protecting group enables selective and high yielding modifications of each of the three hydroxyls of 1,1,1-tris(hydroxymethyl)ethane. The protection, selective modification, and deprotection of the hydroxyl groups were carried out over five synthetic steps outlined in Scheme 2 to produce amphiphile **1** in high yields.



Scheme 2. Preparation of bifurcated amphiphile.

Protection of two alcohols of 1,1,1-tris(hydroxymethyl)ethane with the dimethyl acetal of benzaldehyde was achieved by using *p*-toluenesulfonic acid as a catalyst. The substituted 1,3-dioxane product **4** is isolated as a mixture of two isomers in which the phenyl substituent can either be *cis* (**4a**) or *trans* (**4b**) to the hydroxymethyl substitutuent (Scheme 3). Both stereoisomers are expected to exist predominantly in the conformation where the bulky phenyl ring is in the equatorial position due to 1,3-diaxial interactions (**4a** and **4b**).

As both isomers were predicted to have similar, but not identical, kinetic and thermodynamic parameters for formation, a mixture of products was expected.[3] Well resolved differences in their ^{1}H NMR spectra, particularly of the acetal hydrogen (5.42 ppm for cis vs 5.39 ppm for trans) and the methyl hydrogens (0.80 ppm for cis vs 1.31 ppm for trans), enabled the product ratios to be easily determined using ^{1}H NMR. NMR integration studies confirm that the polarity of the reaction solvent significantly



Scheme 3. Diastereomeric products (and conformers) of the acid catalyzed benzylidene protection of two of the three alcohols of 1,1,1-tris(hydroxymethyl)ethane.

affects the ratio of isomers. When acetone is used as the solvent, the cis isomer is favored 3 to 1 over the trans isomer. Only negligible changes in product ratio were observed when the reaction temperatures were varied from −70 to 56 °C using acetone solvent. However, polar, hydrogen-bonding solvents, such as acetonitrile, reduced the cis/trans ratio to 2:1 while less polar solvents, such as chloroform, increased the ratio to 5:1. It is presumed that the preference toward the cis isomer in non-polar solvents results from hydrogen bonding between the hydroxyl group and the two oxygens of the dioxane ring. The stereochemistry was confirmed by the isolation of the major isomer (**4a**) by column chromatography, followed by X-ray crystallographic characterization (Fig. 1) and was in agreement with previously reported studies.[3] Because the stereochemistry was not a critical factor in our studies, the synthesis was continued with the sample as a mixture of isomers.

Next, the primary alcohol of **4** was converted to the alkyl ether **5**, via a Williamson ether coupling. Sodium hydride was used to generate the alkoxide, which carried out a nucleophilic substitution of the bromide of 1-bromododecane. Higher yields were obtained when the reaction mixture was heated to 70 °C, but an excess of 1-bromodecane was required, presumably a result of the competing elimination reaction.

Reduction of benzylidene protected diol **5**, with diisobutylaluminumhydride (DIBAL) yielded compound **6**, with one unprotected alcohol and a benzyl ether.[9] Because the cleavage of the 1,3-dioxane ring is not stereoselective, the product was obtained as a racemic mixture of *R* and *S* isomers. Without further purification, the unmasked alcohol of **6** was functionalized with a hydrophilic triethylene glycol chain via a second Williamson ether coupling. The mesylate-functionalized triethyleneglycol monomethylether **7** was prepared[10] from the addition of methylsulfonyl chloride to triethyleneglycol monomethylether and reacted with the alkoxide of **6** to yield the benzyl protected amphiphile **8**. The remaining benzyl ether was removed by palladium catalyzed hydrogenation to afford the desired amphiphile **1**, in nearly quantitative yields. The racemic product was isolated from the metal catalyst by simple filtration over Celite.

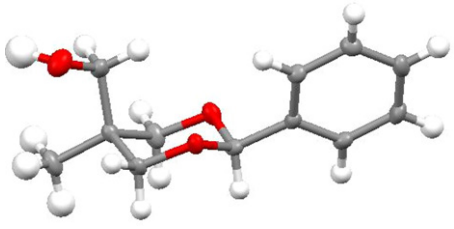


Fig. 1. Crystal structure of the major isomer **4a** from the benzylidene protection reaction.

Several methods of oxidizing the primary alcohol to a carboxylic acid were attempted. Use of potassium permanganate as the oxidant caused degradation of the starting material, while use of TEMPO as the oxidant with a phosphate buffer[11] failed to oxidize the alcohol in sufficient yields. However, an excess of Jones reagent (2.67 M) in acetone achieved a clean oxidation of the primary alcohol to carboxylic acid **2** without significant degradation of the molecule. This reaction was easily monitored by the disappearance of the starting material by TLC and the appearance of the ^{13}C NMR carbonyl signal of the carboxylic acid at 178 ppm. Partial oxidation to the aldehyde was not observed as long as an excess of Jones reagent was used. The amphiphilic carboxylic acid **2** could be isolated by a series of extractions in a 77% yield.

The amphiphilic monomer **3** was prepared by the reaction of the primary alcohol **1** with acryloyl chloride. Triethylamine was added to the tetrahydrofuran solvent to quench the hydrochloric acid produced as a bi-product of the esterification reaction. The product was purified by flash chromatography in a 97% yield and the attachment of the acrylate group confirmed by the presence of the distinct vinyl resonances in the ^{1}H NMR.

In summary, we have developed an efficient synthesis for the preparation of a bifurcated amphiphile. Amphiphile **1** could be obtained in a 60% overall yield from the starting material with only two chromatographic purifications. Amphiphilic homopolymers can be prepared readily by either attachment of this molecule to a monomer before polymerization (compound **3**) or the attachment of an activated ester (compound **2**) after polymerization. The latter has been demonstrated with polymers bearing alcohols on each repeat unit, and is expected to be equally effective for amine bearing polymers. Both pre- and post-polymerization attachment approaches are being fully investigated in our labs, and more complicated polymer architectures, such as cyclic and star polymers will be explored in the near future.

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Supplementary data

An experimental section with full synthetic procedures, characterization data, and NMR spectra of the cis and trans isomers of compound **4** is provided in supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.132.

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