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Green and sustainable route to carbohydrate vinyl ethers for accessing bio-inspired materials with a unique microspherical morphology

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Abstract

Synthesizing chemicals and materials based on renewable sources is one of the main tasks of modern science. Carbohydrates represent excellent renewable natural raw materials, that are eco-friendly inexpensive and biologically compatible. Herein, we developed a green vinylation procedure for carbohydrates using readily available calcium carbide. Various carbohydrates were utilized as starting materials resulting in mono-, di- and tetra-vinyl ethers in high to excellent yields (81-92 %). The synthesized bio-based vinyl ethers were utilized as monomers in free radical and cationic polymerizations. A unique combination of smooth surface and intrinsic microcompartments was achieved in the synthesized materials. Two types of bio-based materials were prepared involving microspheres and "Swiss cheese" polymers. Scanning electron microscopy with built-in ion beam cutting was applied to reveal the spatial hierarchical structures in three-dimensional space.

Keywords: biomass; carbohydrates; calcium carbide; vinylation; bio-based materials.



Introduction

Bio-inspired materials have found numerous applications in regenerative medicine, biochemistry, organic framework preparation, soft robotics, and nano and polymer science.^{1,2,3,4,5,6,7} This field is rapidly developing with several breakthrough opportunities in modern science and technology.

Natural carbohydrates represent an excellent class of compounds for the development of bioinspired materials.⁸ The tunable nature of carbohydrates makes it possible to protect their hydroxyl groups to facilitate hydrophobic properties. The ability to control the hydrophobic properties is important for numerous practical applications and for increasing the stability of carbohydrates against degradation.⁹

For accessing sustainable products, it is important to develop synthetic routes based on starting materials from renewable sources. Moreover, it is important to maintain green chemistry procedures which avoid toxic chemicals and minimize the amount of organic waste when processing biomass-deriver raw materials. Challenged with these requirements, in the present study, we have developed bio-inspirer materials based on sustainable biomass (Scheme 1). The carbohydrates from biomass can be easil protected to obtain the required number of hydroxyl-groups (Scheme 1, route a). Sustainable vinylation was carried out using calcium carbide (Scheme 1, route b), which reacts *in situ* with protected carbohydrates and produces vinyl monomers (Scheme 1, route c). Vinyl monomers can be efficiently converted to polymeric materials (Scheme 1, route d).

It is important to mention that virtually all kinds of carbon can be used to prepare calciun carbide.¹⁰ Renewable sources of carbon, carbon obtained from waste processing, carbon-containing feedstocks and natural carbon can be transformed into calcium carbide with very good efficiency.¹ Applying CaC₂ is one of the best approaches for the incorporation of vinyl functional groups into organi compounds.¹¹ From an environmental viewpoint, it is a clean process since calcium salts can be regenerated and reused (Scheme 1, route *e*). Overall, the polymeric materials developed here are accessible only when using renewable natural resources (carbohydrates and carbon) as raw starting materials.



Scheme 1. Sustainable route to the bioinspired carbohydrate polymers proposed in the present study.

The key step is to develop a rapid and green methodology for the one-pot reaction of CaC_2 with carbohydrates (Scheme 1, route *c*). It is important to carry out the reaction in a one-pot manner instead of using dangerous and highly flammable acetylene gas.^{12,13} In the present work, we report a green route for 2

the vinylation of carbohydrates with calcium carbide, synthesis of vinyl ethers of natural carbohydrates and preparation of the corresponding polymeric material (Scheme 1).

Results and discussion

Carbohydrates contain several OH groups; however, only certain OH groups should be vinylated, while the other OH groups should be protected to maintain the hydrophobic properties. We protected four OH groups with isopropylidene protecting groups to obtain a pure monovinylated product while avoiding a mixture of vinyl ethers. To demonstrate the applicability of the method, we have also vinylated two and four OH groups (divinyl and tetravinyl products were isolated in their pure form).

The protection of D-(-)-fructose (**1a**) and synthesis of **2a** was carried out using an acetone/H₂SO system according to the standard procedure¹⁴ (see the experimental part). To study the vinylation process, we used a model reaction of protected D-(-)-fructose with calcium carbide under basic conditions (Scheme 2). Acetylene was generated *in situ* upon the reaction of CaC₂ with water. The base was required to facilitate nucleophilic addition of the hydroxyl group to the triple bond of acetylene. The optimization of the reaction conditions for the vinylation of the protected D-(-)-fructose with CaC₂ i summarized in Table 1.



Scheme 2. Synthesis of the vinyl ethers of carbohydrates using calcium carbide.

Table 1. Optimization of the reaction conditions for the vinylation of the protected D-(-)-fructose (see Scheme 2 for the reaction).^{*a*}

Entry	Solvent	System	CaC ₂ : H ₂ O ratio	Yield ^{<i>b</i>} , (%)
1	DMF	KOH/KF	1:4	NR
2	Dioxane	KOH/KF	1:4	NR
3	Toluene	KOH/KF	1:4	NR
4	THF	KOH/KF	1:4	NR
5	DMSO	KOH/KF	1:4	92
6	DMSO	KOH/KF	1:2	63
7	DMSO ^c	KOH/KF	1:0	NR

8	DMSO	-	1:4	Traces
9	DMSO	K_2CO_3	1:4	Traces
10	DMSO	Et₃N	1:4	NR

^a Reaction conditions for the vinylation: substrate (1 mmol), CaC₂ (6 mmol), base (1.1 mmol), solvent (5 mL), and additive (4 mmol). ^b Isolated yield. ^c Anhydrous DMSO.

The experiments in different solvents showed that DMSO is the solvent of choice for carrying out vinylation with calcium carbide (entries 1-5; Table 1). An optimal $CaC_2 : H_2O$ ratio of 1 : 4 was utilized decreasing the amount of water lowered the yield, and without added water, the reaction did not proceed (entries 5-7; Table 1). Using a base was important for promoting the reaction (entries 5, 8), and a combination of KOH and KF improved the performance (entries 5, 9, 10; Table 1). Thus, a one-pc procedure was developed to perform vinylation under simple conditions in excellent yield (92 %). The vinylation reaction was carried using only simple inorganic compounds (CaC₂, KOH and KF), which readily simplified the isolation and purification of the synthesized organic product **3a**. The isopropylident protecting group was stable under the studied experimental conditions. It should be emphasized tha granulated calcium carbide from commercial sources may release varying amounts of acetylene (i.e typically around 75%).¹⁵ The exact amount of acetylene may be measured by volumetric analysis in eacl particular batch, however a more flexible solution is to apply an excess of CaC₂. This will also account fo plausible traces of water, which may be available in the system.

Using the optimized conditions, we synthesized a series of vinylated carbohydrates (Table 2) Different procedures were utilized for the vinylation of carbohydrates bearing both even and odd number of hydroxyl groups. Carbohydrates with an odd number of hydroxyl groups (fructose, galactose, glucose and sorbose) were protected using isopropylidene protecting groups, leaving one –OH group for the reaction with acetylene (entries 1-5; Table 2). Carbohydrates with an even number of hydroxyl group: (arabinose, lyxose, and ribose) were protected using isopropylidene and a methyl protecting group in order to leave a single –OH group for the reaction with acetylene (entries 6-8; Table 2). At the end of the reaction, the final products (2a - 2h) were isolated after extraction with hexane. Products 2a - 2h were synthesized in excellent yields of 81 - 92 %.

Entry	Starting material	Protected carbohydrate	Vinylated product and isolated yield
1	OH OH OH 1a D-(-)-Fructose		0,, 0 0,, 0 0,
2	OH OH OH 1a D-(-)-Fructose	оч оч о о о о о о о о о о о о о о о о о	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
3	CH ₂ OH OH OH OH OH Ic D-(+)-Galactose		3c, 91%
4	CH ₂ OH OH OH OH OH OH OH OH OH OH OH OH		0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
5	OH HO OH 1e L-(-)-Sorbose		0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
6	OH OH OH If L-(+)-Arabinose	O O O O O O O O O O O O O O O O O O O	O,,OMe O O 3f, 86%
7	OH OH 1g D-(-)-Lyxose	HO ^{IIIII} O 2g	3g, 82%

Table 2. Vinylation of different carbohydrates using the developed procedure with CaC₂.^a



^a Reaction conditions: protected carbohydrate (1 mmol), CaC₂ (6 mmol), H₂O (24 mmol), DMSO (5 mL), KOH (1.1 mmol), KF (4 mmol), 130 °C, and 3 h.

To assess the possibility of double vinylation, the developed procedure was applied to 1,2 isopropylidene- α -L-xylofuranose (**2i**). In this carbohydrate, two hydroxyl groups were protected in the forn of monoacetonide, and two hydroxyl groups were available for the reaction (Scheme 3). The one-pc transformation with calcium carbide in the presence of KF/KOH led to double vinylation with an exceller isolated yield of 75 % divinyl ether **3i**.



Scheme 3. Double vinylation of protected xylose using calcium carbide.

The developed vinylation reaction involving calcium carbide proceeded efficiently for the studied substrates. In all the studied cases, isopropylidene protective groups were found to be completely stable (130 °C, 3 h). Important for practical applications, we also monitored the stability of the benzylidene protecting groups under these reaction conditions. The reliable performance of the protective groups was completely consistent with previous investigations.¹⁶ Methyl 4,6-*O*-benzylidene- α -D-glucopyranoside (2) was obtained from methyl- α -D-glucopyranoside (1) and was utilized as a starting material (Scheme 4) Double vinylation was successfully carried out in the developed system, and product 3j was isolated in 74 % yield. After extraction with hexane, only the completely vinylated product was soluble in the organi phase. The presence of a single –OH group caused the sugars to remain in the DMSO/KOH phase. This is a crucial advantage of this synthetic procedure; independent of the number of hydroxyl group presented in the starting sugar, only the final vinylated products are isolated. The vinylated product extracted with hexane were usually of sufficient purity, but when required, further purification was carried out using distillation under vacuum.



Scheme 4. Double vinylation of methyl-4,6-*O*-benzylidene- α -D-glucopyranoside (**2j**) using calcium carbide.

The possibility of multiple vinylations was an interesting option to explore. Using methyl *a*-D-glucopyranoside (**1k**), one-pot tetravinylation was carried out in the presence of KF (Scheme 3). Minor amounts of incompletely vinylated sugars were also present in the reaction mixture at the end of the reaction (i.e., mono-, bis- and tris-vinylated compounds). Nevertheless, pure product **3k** was isolated in 75 % yield using the same simple separation procedure. The yield of the product was significantly lower in the presence of KOH due to side-reactions causing product degradation. The yield was improved by using a larger excess of KF in the absence of KOH. Most likely, on one hand the bases facilitate the addition reaction and improve the product yield. On the other hand, the base additives may initiate polymerization. Therefore, the optimal amounts of KOH and KF should be determined for a particula carbohydrate substrate.



Scheme 5. Quadruple vinylation of methyl α -D-glucopyranoside with calcium carbide.

To demonstrate synthetic utility of the reaction we have carried out the vinylation on a large scale and isolated 3.5 g of **3a** in 88 % yield under the same optimized conditions (Table 1, entry 5). The reaction may be performed in a suitable sealed flask or small autoclave. Acetylene has a good solubility in DMSO and it was readily consumed during the reaction.

Vinyl ethers are well known as excellent monomer that easily undergo polymerization using ioni or free radical initiators.^{17,18} To address this possibility, we used 2,3:4,5-di-*O*-isopropylidene- β -D fructopyranose (**3a**) as a monomer using both free radical and cationic polymerization mechanism (Scheme 6). The free radical polymerization of **3a** in the presence of AIBN (2 mol%) and DMF yielded a well-defined oligomer (**4a**) as a gum (Scheme 5). Cationic polymerization with boron trifluoride etherated under an inert atmosphere yielded crystalline solid **5a** (Scheme 6). Reprecipitation from a methanol/hexane mixture resulted in pure polymeric materials, which were characterized by NMF spectroscopy and size exclusion chromatography (SEC). The values of M_{n,SEC} = 3500 and 8500 [g/moi] were obtained for **4a** and **5a**, respectively (Scheme 6).

Achieving higher molecular weights and accessing large polymers is a well-developed area for vinyl ethers.¹⁹ This topic was not addressed in the present study since we were interested in tuning the morphology of soft and soluble polymeric materials using dissolution/precipitation procedures. Polymers with high molecular weights typically possess poor solubility and are not suitable for the liquid-phase-

controlled design of flexible morphologies. In the present case, polymers with medium molecular weights were synthesized and exhibited controlled solubility in commonly used solvents (toluene and methanol).











С



d



Figure 1. Electron microscopy images of the polymeric materials with a microspherical morphology (a, b) and fused hierarchical morphology (c, d) and the intrinsic structure found in the cut of the fused hierarchical material. Scale bars: 10 μm (a, c), 1 μm (*b*, *d*, *e*), and 200 nm (*f*).

As determined experimentally, the synthesized polymers with medium molecular weights enable the possibility of designing unique morphologies upon precipitation from solution and the controller removal of the solvent. The morphology of the isolated polymeric materials was characterized using scanning electron microscopy (SEM). A simple procedure involving the dissolution of the polymer in toluene, followed by reprecipitation with hexane and drying under vacuum generated a microspherica morphology (Figure 1a and 1b). Excellent shape uniformity and a relatively narrow size distribution (1 - : μ m) were revealed in the SEM study. By changing the reprecipitation and drying conditions, it was possible to induce fusion of the microspheres into hierarchical 3D structures with smooth outer surface (Figure 1c and 1d). Mechanical cutting of the hierarchical material revealed a number of cavities inside the polymer (Figure 1e and 1f). The cavities possessed spherical shapes with diameters of 0.2 – 2 μ n (Figure 1e and 1f).

To examine the intrinsic organization of the cavities, spatially controlled cutting with a focused ion beam was carried out inside the electron microscope (Figure 2). The focused ion beam removes this layers slice-by-slice from the selected area of the material. Indeed, the intrinsic organization of the studied material showed the presence of boundaries between the cavities and the absence of networking connections between them (Figure 2; see also the video in the Supporting Information).



Figure 2. SEM images of polymer **5a** after cutting with a focused ion beam. In the first and last images, the purple rectangles show the examined area. The yellow and red arrows show changes in the surface after each cutting; the green arrows indicate the existing boundaries of the cavities.

Thus, the arrangement of the microspherical outer morphologies (Figure 1a and 1b) of the individual particles and the incorporation of spherical cavities inside the hierarchical fused materia (Figure 1c – 1f) were observed. The prepared morphologies are applied for encapsulation and controlled release applications. Typically, rather complicated experimental protocols are utilized to prepare sucl materials. In contrast, in the present study a straightforward and simple procedure was developed using biobased monomeric building blocks. Innovative materials containing natural carbohydrate units have been successfully utilized in a number of important applications including access to glycoconjugates, drug delivery, and biocompatible materials, among many others.²⁰

Conclusions

To summarize, we have developed a green route for the one-pot vinylation of carbohydrate: using easily available calcium carbide. The developed procedure involved only inexpensive inorganic compounds (KF, KOH and CaC₂) and did not include toxic or environmentally unfriendly components. The straightforward synthetic procedure was combined with efficient separation: simple extraction with hexane resulted in the isolation of pure vinylated products. Further purification was performed using vacuum distillation (chromatography and the excessive use of solvents was completely avoided). This synthetic transformation was universally applied to prepare a number of mono-vinylated carbohydrates in excellent yields (82 - 92 %) and bis- and tetra-vinylated carbohydrates in high yields (75 %). The polymerization reactions were studied using free radical and cationic conditions using a synthesized carbohydrate vinyl monomer. Polymers with suitable molecular weights exhibited medium-dependent solubility and flexible access to the unique morphologies demanded by practical applications. The synthesized materials were characterized using electron microscopy, and the intrinsic organization was studied using a focused ion beam technique.

Using the developed methodology, the vinyl ethers of carbohydrates and their corresponding polymeric materials were obtained from renewable resources (biomass and carbon). Sustainably sourced starting materials were combined with atom-economic vinylation (i.e., the addition reaction of a hydroxyl group to the triple bond of acetylene is atom-economic and does not produce waste). Overall, a cost-efficient and environmentally friendly procedure was developed.

Experimental section

General. The chemicals were obtained from commercial sources (Acros Organics and Sigma Aldrich) and tested with NMR and GC before use. Calcium carbide was utilized in the granulated form.¹ AIBN was recrystallized from dry methanol twice and dried under vacuum overnight. Boron trifluoride etherate was redistilled prior to use. Deuterated NMR solvents (CDCl₃ and acetone) were purchased from Cambridge Isotope Laboratories. In some cases, deuterated chloroform was purified from traces of acie through aluminum oxide, molecular sieves and Ag foil, since synthesized vinyl ethers may underge hydrolysis in the presence of acidic impurities.

NMR spectra of the complexes were recorded using a Bruker Avance DRX 400 spectrometer a 298 K. The ¹H and ¹³C NMR chemical shifts were reported in ppm vs. SiMe₄ and were determined b referencing the peaks to the residual solvent peaks. HRMS (ESI) was performed using a Bruke microTOF. Size exclusion chromatography (SEC) was carried out using a Shimadzu LC-20AD modula system equipped with a TSkgel G5000HHR column (7.8 mm × 300 mm) and an RID-10A differentia refractive index detector. The average molar mass (\overline{Mn}_{SEC}) and molar mass distribution ($\overline{Mw} / \overline{Mn}$ values were determined using SEC in THF at 30 °C (flow rate = 1.0 mL·min⁻¹) vs. polystyrene standards The unit calibration was conducted using commercially available narrow molecular-weight-distribution polystyrene standards (0.5-1000 kDa, Polymer Laboratories). The chromatograms were processed using Shimadzu LCsolution software. The polymer samples were initially filtered through a PTFE filter (0.45 µm 13 mm, Macherey-Nagel) and dissolved in THF (2 mg·mL⁻¹).

The investigations of the polymer materials were carried out using low-voltage scanning electrol microscopy (LV-SEM) through a double-beam FIP-REM Zeiss Auriga station. The accelerating voltage c the electron column was 1 kV, and the beam current was 300 pA. The pressure in the chamber was approximately 3.10⁻⁶ mbar. To obtain the images, a secondary electron emission signal was recorded using an Everhart-Torley detector. To reduce the noise of the image, row averaging was used. The polymer particles were cut by etching with a focused beam of gallium ions using a double-beam FIP-REM Zeiss Auriga station. The accelerating voltage of the ion column was 30 kV, and the beam current was 600 pA.

All manipulations with vinyl ethers were performed under a purified argon atmosphere using standard Schlenk techniques. Synthetic transformations were carried out using a suitable sealed vessel or autoclave, compatible with some internal pressure, which may develop due to reaction of calcium carbide with water.

Experimental procedure for the monovinylation of the protected carbohydrates.

First, 1.0 mmol of a carbohydrate, 1.1 mmol of KOH, 4.0 mmol of KF and 6.0 mmol of powdered calcium carbide were added to an 18 mL glass tube followed by the addition of 5 mL of DMSO. After adding water (24.0 mmol), the tube was sealed, and the mixture was stirred at 130 °C for 3 hours. After completion, the reaction mixture was extracted with hexane (6 x 5 mL), and the collected hexani solutions were passed through a 2 cm thick celite pad. After solvent removal under a reduced pressure further purification was not required in most cases, and the desired products were obtained with sufficier purity.

Experimental procedure for the divinylation of the protected carbohydrates.

First, 1.0 mmol of a carbohydrate, 2.2 mmol of KOH, 6.0 mmol of KF and 8.0 mmol of powdered calcium carbide were added to an 18 mL glass tube, followed by the addition of 5 mL of DMSO. Afte adding water (32.0 mmol), the tube was sealed, and the mixture was stirred at 130 °C for 3 hours. Afte completion, the reaction mixture was extracted with hexane (6 x 5 mL), and the collected hexand solutions were passed through a 2 cm thick celite pad. After solvent removal under a reduced pressure further purification was not required in most cases, and the desired products were obtained with sufficien purity.

Experimental procedure for the tetravinylation of the methyl α -D-glucopyranoside.

First, 1.0 mmol of a carbohydrate, 17.0 mmol of KF and 8.0 mmol of powdered calcium carbide were added to a 25 mL glass tube, followed by the addition of 10 mL of DMSO. After adding water (32.0 mmol), the tube was sealed, and the mixture was stirred at 130 °C for 3 hours. After completion, the reaction mixture was extracted with diethyl ether (3 x 10 mL). After solvent removal under a reduced pressure, the crude product was dissolved in hexane (20 mL) and passed through a 3 cm thick aluminun oxide pad. After solvent removal under a reduced pressure, the residue was recrystallized from hexane a -18 °C to obtain colorless crystals.

Purification of the vinyl ethers.

The vinyl ethers can be further purified using distillation under vacuum over calcium hydride.

Experimental procedure for the radical polymerization of 2,3:4,5-di-O-isopropylidene-1-Ovinyl-β-D-fructopyranose (3a).

First, 400 mg (1.4 mmol) of **3a** and 5 mg (0.03 mmol) of AIBN were added to an 8 mL glass tube containing 22 mg of dry and degassed DMF. The tube was sealed, and the reaction was performed with stirring under an inert atmosphere at 70 °C for 48 hours. Then, the reaction mixture was precipitated in methanol (3 mL), and the residue was washed with hexane (3 x 3 mL). The crude product was dissolved in DMF (3 mL) and again precipitated in methanol (5 mL). After the residue was washed with hexane (3 x

3 mL), the work up procedure was repeated twice. The residue was dried under a reduced pressure for two days at 40 °C to obtain a colorless gum (200 mg, 0.7 mmol, 50% yield, $M_{n,SEC}$ = 3500 [g/mol], \mathcal{D} = 1.73).

Experimental procedure for the cationic polymerization of 2,3:4,5-di-O-isopropylidene-1-Ovinyl-β-D-fructopyranose (3a).

First, 400 mg (1.4 mmol) of **3a** was placed into a Schlenk tube under an inert atmosphere at 0 °C. Then, 1 mL of degassed dry toluene was injected into the tube. After three degassing cycles, a toluene solution of boron trifluoride diethyl etherate (2 mol %) was injected into the tube under stirring. After 12 hours, the toluene solution was poured into methanol. The white solid was collected through a filter washed with hexane, dissolved in chloroform and precipitated in methanol again. The powder was dried under a reduced pressure for two days at 40 °C (160 mg, 40% yield, $M_{n,SEC}$ = 8500 [g/mol], \mathcal{D} = 1.84).

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