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A facile and efficient method to fabricate high-resolution immobilized cellulose-based chiral stationary phases via thiol-ene click chemistry

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ABSTRACT

Immobilized chiral stationary phases (CSPs) have attracted much attention because of strong solvent resistance and selection of wide range of eluents. In this work, a facile, efficient and engineering method is developed to fabricate high-resolution immobilized cellulose-based CSPs. A controllable amount of acrylate groups, the key to dominate the immobilization degree, is introduced into cellulose chains to obtain cellulose mixed esters with well-defined structure by homogeneous esterification reaction. Subsequently, via simple, efficient, and highly selective thiol-ene click reaction, cellulose mixed esters were chemically bonded onto thiol-modified silica gel to obtain immobilized cellulose-based CSPs, C-AC5-N95 and C-AC25-N75. Due to the stable "C—S—C" crosslinking bonds, the resultant immobilized CSPs exhibit strong solvent resistance, thus they can be used in a wide range of eluents, including normal-phase non-standard solvents and reversed-phase solvents. They withstand even strong solvents of cellulose derivatives, such as hot pyridine, chloroform, DMF and DMSO. More importantly, the immobilized CSPs C-AC5-N95 displays excellent chiral recognition capability, which is similar with, or even better than, that of coated CSPs.

1. Introduction

Chirality, a ubiquitous feature in living systems, is closely related to human health and daily life. Different optically active enantiomers exhibit different or even opposite biological activities, thus it is of great importance to obtain optically pure enantiomer in pharmaceutical, biological and materials fields. Chromatographic enantioseparations, especially chiral recognition by high-performance liquid chromatography (HPLC) and supercritical fluid chromatography (SFC), are considered as the most efficient tools not only for measuring the enantiomeric excess but also for obtaining optically pure enantiomers on analytical and industrial scales. The key of chromatographic enantioseparation is to develop high-performance chiral stationary phases (CSPs). Because of the excellent chiral separation capability, polysaccharide derivatives are usually used as CSPs to analyze and separate chiral compounds. Nowadays, polysaccharide benzoates and phenylcarbamates are commercially available CSPs which can achieve efficient separation for 90% racemic compounds.[1,2] However, most of CSPs are prepared by physically coating polysaccharide derivatives on a chromatographic support and hence, they show low solvent resistance and narrow range of eluents selection. For expanding the practical application of polysaccharide-based CSPs, an efficient method is to immobilize polysaccharide derivatives onto silica gel and prepare immobilized CSPs by chemical bonding. Immobilized CSPs have attracted much attention, due to their strong solvent resistance and wider use range of eluents. However, chemical immobilization obviously affects the helical structure of polysaccharide derivatives, which is essential to separate enantiomers. Generally, chemical immobilization significantly reduces the chiral recognition capability of CSPs. The higher degree of immobilization, the lower will be the chiral recognition capability. Ikai et al. [3] and Guntari et al. [4] pointed out that when there was only 1–3% immobilization point, the immobilized CSPs with a high enantioseparation capability could be obtained. Therefore, for fabricating high-resolution immobilized CSPs, an ideal immobilization method has to achieve an effective immobilization and govern a suitable degree of immobilization.

Over the past two decades, several immobilization methods for the polysaccharide derivatives have been proposed. (1) Diisocyanate

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method [5,6]: The reagents containing diisocyanate groups are employed as the bifunctional linker to connect the hydroxyl groups of cellulose with the amino groups on the aminopropyl silica gel. (2) Alkoxysilyl groups method [7–13]: Intermolecular polycondensation between trialkoxysilyl groups, which are chemically bond on cellulose, is used to fabricate the commercial immobilized CSPs. (3) Vinyl groups method [14–21]: Radical polymerization is adopted for linking cellulose derivatives bearing vinyl groups with vinyl silica gel. The above three methods are the most commonly used immobilization methods, but they have some fatal drawbacks. The chemical bonding and self-crosslinking reaction of polysaccharide derivatives occur simultaneously, thus the immobilization processes are difficult to control, and the resultant immobilized CSPs exhibit relatively low chiral recognition capabilities due to the existence of self-crosslinking phenomenon. (4) Epoxy groups method [22]: Through a ring-opening addition reaction between epoxysiloxane silica gel and cellulose hydroxyl groups, the immobilized CSPs are obtained. In this method, the used linkage agents contain two different functional groups, so the self-crosslinking reaction between cellulose derivatives is avoided effectively. However, during this process, a cationic BF_3•OEt_2 catalyst, which is extremely sensitive to moisture, is added for catalyzing the epoxy groups; (5) Terminal aldehyde groups method [23,24]: The terminal aldehyde groups of cellulose and amylose chains react with the amino groups of aminopropyl silica gel by catalysts $NaBH_3CN$ and acid. This method ensures that each polymer chain only has one immobilization point and well-defined immobilization position, thus it should be a superior method to fabricate immobilized CSPs. However, the practical application of this method is limited, due to the complicated preparation process and low immobilization efficiency originated from only one immobilization point per one chain. (6) Azido groups method by Staudinger reaction [25,26]: Azido modified cellulose derivatives react with aminopropyl silica gel through Staudinger reaction. (7) Azido groups method by click reaction [27,28]: The efficient and highly selective click reaction between azido groups and unsaturated bonds makes the immobilization easy to control. The introduction of unstable azido groups in methods 6 and 7, however, increases the danger coefficient of the immobilization process. Recently, Han et al. [29] claimed a new immobilization method. They used bromodecanoic acid groups to substitute —NH— groups in cellulose tri(3,5-dimethylphenylcarbamate) by using NaH as a catalyst, and then achieved an efficient immobilization by a condensation reaction between carboxylic acid groups and amino groups on aminopropyl silica gel with *N*-ethyoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) as a catalyst. In addition, for cyclodextrin-type and Pirkle-type CSPs, other immobilization methods have been developed as well [30–37]. However, due to the difficulty in the synthesis of polysaccharide derivatives with controllable structure, it is terribly difficult to handle the number, site and distribution of immobilization points on polysaccharide derivatives. Thus, despite several methods made in this regard, there is still a critical need to develop controllable, simple, safe and highly-selective immobilization methods for achieving appropriate immobilization efficiency, high solvent resistance, high chiral recognition ability, wide practicability and simple processing.

In the present work, we developed a simple, efficient, controllable and safe immobilization method. As shown in Scheme 1, via a homogeneous esterification reaction in 1-allyl-3-methylimidazolium chloride (AmimCl), a controllable amount of acrylate groups was introduced into cellulose chains to obtain cellulose mixed esters with well-defined structure. Subsequently, taking advantage of the facile, engineering and highly-selective "thiol-ene" click reaction, the above cellulose mixed esters were chemically bonded onto thiol-modified silica gel, consequently high-resolution immobilized cellulose-based CSPs were fabricated effectively.

2. Experimental section

2.1. Materials

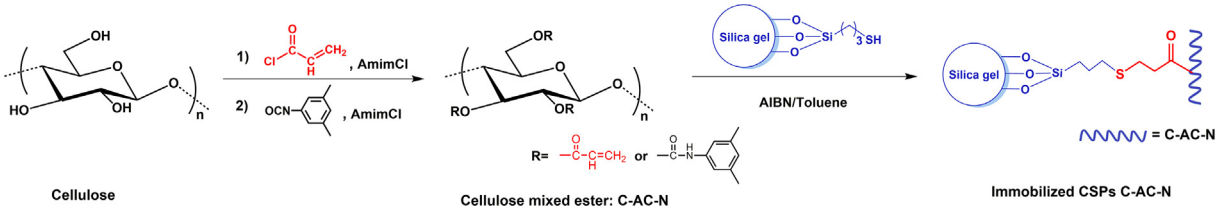
Microcrystalline cellulose (MCC, Vivapur 101) was purchased from Beijing Fengli Jingqiu Commerce and Trade Co., Ltd. The viscosity-average degree of polymerization (DP) of MCC measured using an Ubbelohde viscometer in cupriethylenediamine hydroxide solution (CUEN) was 220. MCC was dried in vacuum at 80 °C for 24 h prior to use. AmimCl was synthesized according to our previous work.[38] Porous sphere silica gel with a mean particle size of 5.8 μm and a mean pore diameter of 26 nm was obtained from Beijing Greenherbs Science and Technology Development Company. 3,5-Dimethylphenyl isocyanate, acryloyl chloride, 3-aminopropyltriethoxysilane and γ-mercaptopropyltrimethoxysilane were received from J&K Scientific Ltd. All other chemicals were supplied by Beijing Chemical Reagent Company, China. All the reagents were of analytical grade. The eight racemates: (1) 2-phenylcyclohexanone, (2) Tröger's base, (3) DL-*sec*-phenethyl alcohol, (4) flavanone, (5) 1-(2-naphthyl)-ethanol, (6) benzoin, (7) cobalt (III) acetylacetonate and (8) 2-phenyl-1-propanol were purchased from Sigma Aldrich. DL-α-Tocopherol and 2,2,2-trifluoro-1-(9-anthryl)-ethanol were received from TCI.

2.2. Synthesis of cellulose acrylate 3,5-dimethylphenylcarbamates (C-AC-N)

Dried MCC (1.0 g, 6.17 mmol) was added into AmimCl (24.0 g) to yield 4.0 wt% cellulose/AmimCl solution by mechanically stirring at 80 °C for 1.5 h. Then, at 50 °C, pyridine (0.73 g, 9.23 mmol) and acryloyl chloride (0.28 g, 3.09 mmol) were successively added into the cellulose/AmimCl solution. After 1.5 h, the reaction system was heated to 80 °C, and excess 3,5-dimenthylphenyl isocyanate (8.63 g, 58.6 mmol) was added to substitute the residual hydroxyl groups of cellulose. The resultant products were isolated as methanol-insoluble fractions, filtered and washed three times with methanol. They were redissolved in DMSO, precipitated again and thoroughly washed with methanol. Finally, the product C-AC5-N95 was dried under vacuum at 60 °C. During the synthesis of C-AC25-N75, acryloyl chloride of 1.40 g (15.5 mmol) was added into cellulose/AmimCl solution in the first step, then 3,5-dimenthylphenyl isocyanate of 6.80 g (46.2 mmol) was used in the second step. During the synthesis of C-AC0-N100, only 3,5-dimenthylphenyl isocyanate of 9.00 g (61.2 mmol) was added into cellulose/AmimCl solution at 80 °C for 3 h.

2.3. Preparation of γ-mercaptopropyl silica gel (γ-MPS)

Pure silica gel (12 g) was placed in a 250 mL flask and dried in



Scheme 1. Synthesis route of immobilized cellulose-based CSPs.