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Preliminary communication

Utilization of functionalized polymers in synthesis: immobilization of carbohydrates as acetals, and some chemical transformations*

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Over the past few years, a large number of compounds, ranging from macromolecules to small-sized molecules, have individually been covalently attached to water-insoluble polymers[1]. Although these immobilized substrates have mainly been exploited in biologically oriented problems[1,2], the potential utility of the technique in synthetic organic chemistry has been demonstrated by Merrifield[3] in his ingenious, solid-phase, peptide synthesis, and, among others, by Letsinger[4], Khorana[5], Calvin[6], and their respective co-workers in polynucleotide synthesis. Inspired by this work, several groups[7,8] have endeavored to effect saccharide syntheses on solid supports[9], and have, indeed, attained the primary objective of disaccharide synthesis.

We now describe another facet of the concept and use of solid-phase polymer chemistry, as exemplified by the covalent attachment of various carbohydrates in the form of benzylidene acetals to a Merrifield type of resin in which the chloromethylene groups have been replaced‡ by aldehyde groups[7].

In a typical experiment§, a suspension of polymer B (0.5 g) and an excess§§ of methyl 2-(benzyloxycarbonylamino)-2-deoxy-α-D-glucopyranoside[11] (1) (0.657 g) in 1,4-dioxane (25 ml) containing *p*-toluenesulfonic acid monohydrate (49 mg) was boiled overnight in a Soxhlet apparatus, with continuous removal of water by means

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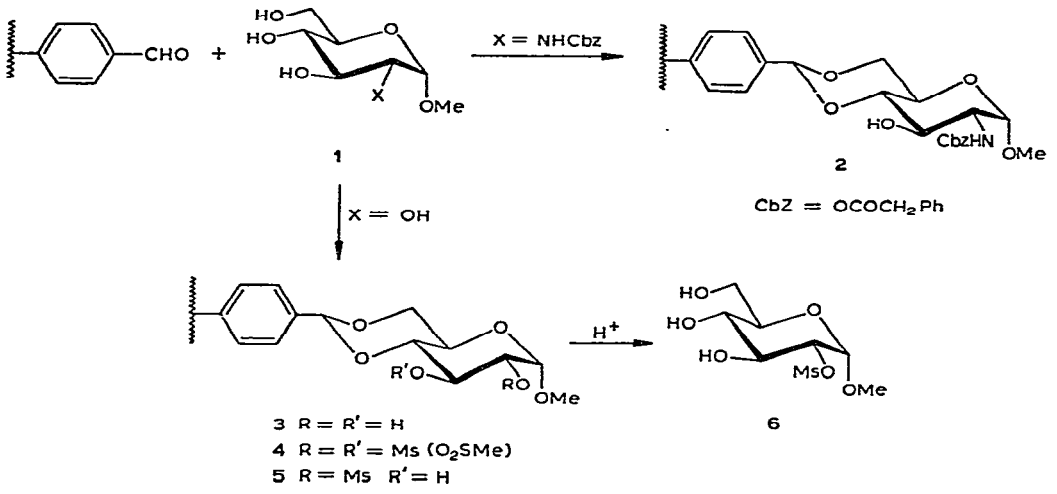
‡Two types of polymers, oxidized with Me_2SO–$NaHCO_3$ according to Frechet and Schuerch[7], have been used in this work. The polymer originating from a (chloromethyl)ated resin containing 0.75–1 meq of chlorine/g of resin (Pierce Chemical Co., lot 24610, 1% cross-linked) is designated polymer A. That originating from a resin containing 2.2 meq of chlorine/g of resin (Schwarz-Mann, lot Y2216, 2% cross-linked) is designated polymer B.

§For an elegant use of the technique in the preparation of a polymer-bound catalyst, see ref. 10.

§§The presence of an excess of the substrate is not mandatory, but it ensures maximum attachment.

of 3A molecular sieves (see Scheme 1). The suspension was cooled, pyridine (2 ml) was added, the suspension was filtered, and the solid was washed successively with 1,4-dioxane, *N*,*N*-dimethylformamide, water, and ethanol, and dried to constant



Scheme 1.

weight, to give 0.7–0.8 g (80–90%) of the polymer acetal (**2**). Its infrared spectrum (KBr) showed the virtual disappearance of the carbonyl stretching band at $\sim 1690\ cm^{-1}$ of the original polymer. For the regeneration of the substrate, a suspension of **2** (0.48 g) in methanol (8 ml) containing 1% of acetyl chloride* was stirred at room temperature, and the release of **1** was monitored by t.l.c. After 10–15 h, the polymer was filtered off, and washed with methanol, and the filtrate was treated with IR-45 (OH^-) ion-exchange resin, and processed as usual, to give a chromatographically homogeneous syrup that crystallized (69%), m.p. and mixed m.p. 154–155°, $[\alpha]_D^{25}$ +91.1° (*c* 1, MeOH); authentic **1** had m.p. 155–157°, $[\alpha]_D^{25}$ +89.2° (*c* 0.96, MeOH). The recovered resin exhibited an intense carbonyl band, indicating the restoration of the aldehyde group. By the same technique, but using polymer A, methyl α-D-glucopyranoside and methyl α-D-galactopyranoside were immobilized as their respective 4,6-*O*-benzylidene acetals (80–90% yields), and subsequently released from the solid supports by use of 80% acetic acid for 4.5 h at 95°.

The following examples demonstrate the variety of substrates that can be covalently attached to polymers A or B, and they illustrate some reactions of preparative significance that can be performed with the immobilized substrates.

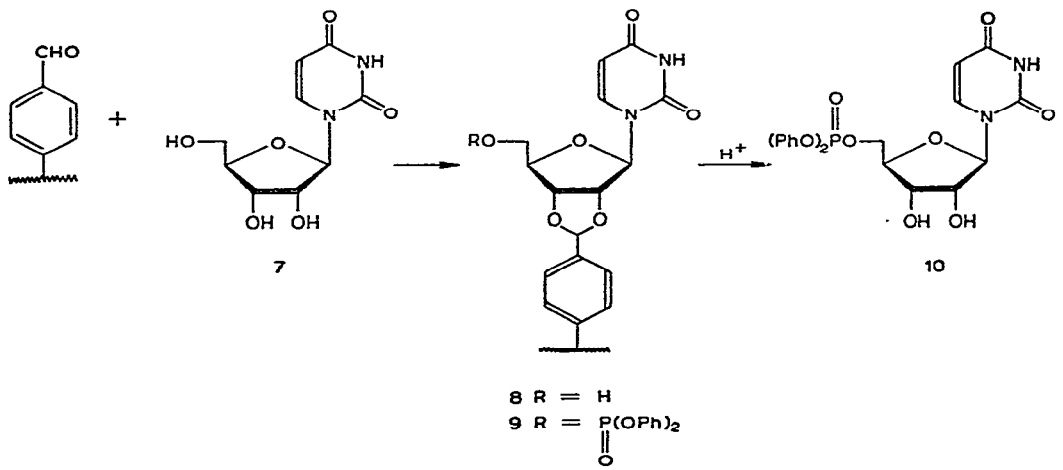
Acylation. — Di- and mono-methanesulfonylation of the acetal **3** was performed in the usual way, to give the methanesulfonylated acetals **4** and **5** in high yield (see Scheme 1). The mono-esterified acetal **5**, obtained by sulfonylation at 0° showed

*For easily anomerizable glycosides, other conditions of acid treatment could be explored.

ν_{max} 1160 and 1345 cm^{-1} (SO_2 stretching); when treated with 1% methanolic hydrogen chloride for 3 h at 25°, it gave methyl 2-*O*-(methylsulfonyl)-α-D-glucopyranoside (**6**) as a syrup (39–42%), $[\alpha]_D^{25}$ +64.5° (*c* 1.3, MeOH); n.m.r. data [60 MHz, $(CD_3)_2CO$]: δ 4.8 (d, $J_{1,2}$ 3 Hz, H-1), 4.28 (dd, $J_{2,1}$ 3 Hz, $J_{2,3}$ 9 Hz, H-2), 3.35 (s, OCH_3), and 3.10 p.p.m. (s, CH_3SO_2); identical with an authentic sample prepared from the corresponding acetal[12]. Similar acylations (acetylation, benzoylation) were performed with the immobilized acetal **3** and with the D-*galacto* analog.

Nucleophilic displacement. — Methyl β-D-ribofuranoside[13], immobilized as the 2,3-*O*-benzylidene acetal on polymer B (87%) was methanesulfonylated for 18 h at 25°, and the acylated acetal (55%) was treated with an excess of sodium azide in *N*,*N*-dimethylformamide for 6 h at 85° to give the azido acetal. When this was treated with 1% methanolic hydrogen chloride for 5 h at 25° and the suspension filtered, methyl 5-azido-5-deoxy-β-D-ribofuranoside was isolated from the filtrate, and characterized as the crystalline di-*p*-toluenesulfonate, m.p. and mixed m.p. 120–121°, lit.[14] m.p. 122–123°.

Phosphorylation. — Uridine (**7**) as its 2,3-*O*-benzylidene acetal was immobilized in the usual way (polymer A or B, 60%) (see Scheme 2). Treatment of **8** with MeOH–HCl released uridine (detected chromatographically) without noticeable degradation.



Scheme 2.

Phosphorylation of the polymer-bound nucleoside (**8**) with $(PhO)_2POCl$–pyridine for 2 h at 37° (ref. 15) gave the phosphoric ester **9**, which, when treated with MeOH–HCl, gave crystalline uridine 5′-diphenylphosphate (**10**), m.p. 114–115°, identical by mixed m.p. and n.m.r. spectrum with an authentic sample prepared from uridine. The overall yield for attachment, phosphorylation, and detachment from the polymer was 15–20%. Although these yields have not yet been optimized, it is clear that the immobilization of nucleosides as their 2′,3′-acetals on water-insoluble polymers, and

the possibility of effecting acylation reactions at O-5′, paves the way to other interesting transformations. Previously, nucleosides have been immobilized *via* ester, mixed ester, and ether formation with functionalized polymers[1,4–6].

Finally, the interesting possibility of utilizing polymer-bound carbohydrate acetals as substrates for saccharide synthesis has not eluded us. Preliminary experiments directed toward achieving this objective indicate that glycosidation does indeed take place.

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