Research Article

Dinuclear Copper(I) Thiodiacetate Complex-Mediated Expeditious Synthesis of the Chlorine-Containing Cyclen-Cored 36-Glucose-Coated Glycodendrimer

Anand K. Agrahari,1 Sunil Kumar,1 Anindra Sharma,2 and Vinod K. Tiwari1

1Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India
2Department of Chemistry, A.P.S.M. College-Barauni, LNM University, Darbhanga, India

Correspondence should be addressed to Vinod K. Tiwari; tiwari_chem@yahoo.co.in

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High-sugar-tethered glycodendrimers are a remarkable tool in glycochemistry for the investigation of carbohydrate-protein interaction using its multivalency property. An enthralling double-stage convergent synthetic approach was selected to build a novel class of chlorine-containing glucose-coated dendrimers using an efficient click catalyst ‘dinuclear copper(I) thiodiacetate complex.’ In this context, cyclen core was developed through a divergent approach, while the glucodendron was developed via a convergent approach independently. Both azide-alkyne partners were coupled through a modular copper azide-alkyne cycloaddition (CuAAC) strategy to afford a high yield of the desired 36-glucose-coated glycodendrimer. The synthesized glycodendrimer has been elucidated by NMR, gel permeation chromatography (GPC), and IR spectral analysis.

1. Introduction

Glycodendrimer chemistry is an increasingly important area to overcome the low affinity and specificity of monosaccharide ligands mainly because of its multivalency effect [1–3]. As we know, multivalent carbohydrate-protein interaction regulates numerous biological processes such as cell recognition, cellular adhesion, pathogen invasion, and fertilization [4–8]. The diverse structural diversity of carbohydrates along with their remarkable features such as hydrophilicity, biocompatibility, less toxicity, and superior ADME (absorption, distribution, metabolism, and excretion) properties encouraged the scientist towards the construction of sugar-tethered dendrimers, i.e., glycodendrimers [1, 9, 10]. Glycodendrimers, because of several notable features such as their high number of sugar appendages at the periphery, enhanced monodispersity, and, moreover, the possibility to organize their well-defined size, have been captured over the other class of multivalent glyoclusters [11–16]. Cyclen core is well investigated for its wide application in the field of chemical biology and biomedicine [17]. In recent years, cyclen and related macrocyclic polyamines have been greatly explored as a promising vehicle of radio nuclides in radioimmunotherapy (RIT), single-photon emission computed tomography (SPECT), and positron [18]. The easy N-alkylation of cyclens facilitates significant alteration in the macrocycles for the development of promising hypercore of wide applications [19–21]. Therefore, several chemical ligation tools have been reported for the successful synthesis of glycodendrimer [22–29].

Among the other applied protocols including chemical ligation, Michael addition, and acid-amine coupling, copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, i.e., click chemistry, is one of the most reliable, adaptable, efficient, high-yielding, and proficient tool for an easy access of regioselective glycohybrids, glycoconjugates, and neoglycoconjugates [1, 27, 30]. In most of the cases, clicking of azides and alkynes was executed simply by using the CuSO4/NaAsc catalytic system in the aqueous condition, which is especially favorable in terms of yields and
regioselectivity [30]. However, it has few shortcomings as it requires higher quantity and prolonged time, has insufficient stability, and has the reducing nature of NaAsc that may also facilitate some other unwanted reactions with proteins in biological systems [31]. Thus, there is an increased demand of suitable click catalysts for efficient CuAAC coupling. Towards this end, a number of promising such catalysts such as mono- and dinuclear heteroleptic Cu(I) dithio-PPh3 complexes [32], di- and mononuclear heteroleptic Cu(I) dixanthate/xanthate-phosphine complexes [33], heteroleptic [Cu(PPh3)2(β-oxodithioester)] complexes [34], thio-carboxylate complexes, and cubane-based hydrosulfide complexes of Cu(I) [35] were displayed efficient catalytic activities for the click conjugation with carbohydrates. Among all, a highly stable Cu(I) catalyst [(PPh3)2Cu(μ-tda)] Cu(PPh3)2.6H2O with significant catalytic activity has been copiously exploited for the thriving construction of regioselective 1,4-disubstituted dendritic architectures [36].

As reported in the literature, the chlorine atoms occupy a special position in a variety of potent natural products such as the antibiotics vancomycin, clindamycin, chloramphenicol, and griseofulvin [37, 38]. Thus, this inclusion of chlorine atoms into one or more definite loci of a biologically active scaffold may enhance the inherent biological activity [39]. The chlorinated compounds might increase the lipophilicity of the whole molecule towards lipophilic domains of a protein which prompts an increased local concentration of the said compound near a biological target site. Until now, only a few literature reports are available to develop high-functional chlorine-containing glycodendrimers [40]. The notable lead of such type of glycocluster is the amplified functional chlorine-containing glycodendrimers [40].

2. Experimental

2.1. General Experimental Procedure for the Cu(I)-Catalyzed Click Reaction. Polypropargylated terminal alkyne and its counterpart organic azide and catalyst 9 (0.02 equiv. or 2 mol % per propargyl) were stirred in dry CH2Cl2 for 3 h. The completion of the reaction was monitored by TLC; upon completion of the reaction, the solvent was removed under reduced pressure to obtain the crude product. The resulting crude mass was purified using flash column chromatography to afford the targeted glycoconjugates.

2.2. Synthetic Procedure of Methyl 3,4,5-Tris (Propargyloxy) Benzoate (2) [29]. 3,4,5-Tris (propargyloxy) benzoic acid 1 (5.0 g, 32.4 mmol) was dissolved in dry methanol (80 mL); thereafter, the catalytic amount of conc. H2SO4 (1.0 mL) was added dropwise in the cold condition. Furthermore, the reaction was set to reflux for 5 h. After the consumption of the starting material on TLC, the resulting reaction mixture was condensed under in vacuo followed by extraction. Thus, ethyl acetate (100 mL) was added to the obtained crude mass and washed with NaHCO3 solution (2 × 50 mL), dried over anhydrous Na2SO4, filtered, and again evaporated to furnish the targeted scaffold 2 in good yield. The physical data (NMR) of compound 2 were closely matched with the reported literature.

2.3. Synthetic Procedure of Methyl 3,4,5-Tris (Propargyloxy) Benzoate (3) [29]. The said compound was synthesized as reported in the literature. Spectroscopic data were matched with the earlier reported literature.

2.4. Synthetic Procedure for 3,4,5-Tris (Propargyloxy) Phenyl Methanol (4) [40]. To a stirred solution of anhydrous THF (40 mL), LiAlH4 (0.45 g, 11.8 mmol, 1.2 equiv) was added at 0°C followed by portion-wise addition of ester 3 (3.0 g, 10.05 mmol) in a period of 15 min maintaining the said temperature. Then, the reaction was set to stir for 6 h at room temperature until the completion of the reaction (monitored by TLC). The resulting reaction mixture was quenched by 5% aq. NaOH, and then the resulting precipitate was filtered out; the resulting filtrate was extracted with ethyl acetate and washed with water (2 × 20 mL) followed by brine wash. The obtained organic layer was evaporated under reduced pressure, and the resulting crude mass was loaded to column chromatography to furnish the targeted compound 4. Spectroscopic data were matched with the earlier reported literature.

2.5. Synthesis of AB3 Dendritic Monomer (5) [40]. 3,4,5-Tris (propargyloxy) phenyl methanol 3 (2.0 g, 7.39 mmol) was taken in a round bottom flask, and sulfuryl chloride (7.17 mL, 12.0 equiv) was added at 0°C followed by portion-wise addition of ester 3 (3.0 g, 10.05 mmol) in a period of 15 min maintaining the said temperature. Then, the reaction was set to stir for 6 h at room temperature until the completion of the reaction (monitored by TLC). The resulting reaction mixture was quenched by 5% aq. NaOH, and then the resulting precipitate was filtered out; the resulting filtrate was extracted with ethyl acetate and washed with water (2 × 20 mL) followed by brine wash. The obtained organic layer was evaporated under reduced pressure, and the resulting crude mass was loaded to column chromatography to furnish the targeted compound 4. Spectroscopic data were matched with the earlier reported literature.

2.6. Synthesis of 12-Alkynyl-Functionalized Hypercore (7) [40]. 1,3-Dichloro-2-(chloromethyl)-4,5,6-tris (propargyloxy) benzene 5 (187 mg, 0.522 mmol, 4.5 equiv) reacted with macrocycle cyclen unit 6 (20 mg, 0.116 mmol, 1.0 equiv) under the mixture of aqueous 1 M NaOH (15 mL) and CH2CN (15 mL). The reaction was allowed to stir for 12 h at room temperature (the progress of the reaction was monitored by TLC), and then it was extracted with ethyl acetate (2 × 20 mL). The organic layer was collected, dried over Na2SO4, and filtered, and the solvent was evaporated under...
in vacuo (<55°C). The resulted residue was loaded to column chromatography to furnish the desired hypercore 7 in good yield. Yield (111 mg, 66%); $R_f = 0.3$ (25% EtOAc/n-hexane); $^1$H-NMR (500 MHz, CDCl$_3$): $\delta = 4.83$ (d, $J = 2.0$ Hz, 8H, 4×−NCH$_2$Ar), 4.78–4.77 (m, 16H, cyclen-H), 3.64 (s, 8H, OCH$_2$), 2.77 (s, 16H, 8×−OCH$_2$), 2.51–2.49 (m, 12H, acetylenic-H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta = 146.5, 145.0, 132.1, 127.1, 78.2, 78.1, 76.3, 76.2, 61.1, 60.8, 54.9,$ and 50.7 ppm.

2.7. Synthetic Protocol of 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl Azide (8) [16]. Compound 8 was synthesized as reported in the literature, and the spectral data were well elucidated.

2.8. Synthesis of Catalyst [(PPh$_3$)$_2$Cu(μ-tda)Cu(PPh$_3$)$_2$]$\cdot$6H$_2$O (9) [36]. The catalyst was synthesized as earlier reported in the literature, and spectral data were closely matched with the reference sample.

2.9. Synthesis of the Chlorine-Functionalized Glucodendron (10). Compound 1,3-dichloro-2-(chloromethyl)-4,5,6-tris(propargyloxy) benzene 5 (0.1 g, 0.279 mmol) reacted with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide 8 (417 mg, 1.11 mmol, 4.0 equiv.) using catalyst 9 (24.6 mg, 0.06 equiv.) under dry CH$_2$Cl$_2$ solvent according to the general procedure. The obtained crude mass was subjected to flash column chromatography (SiO$_2$) to form chlorine-functionalized glycoconjugate 10 in good yield. Yield (346 mg, 84%).
2.10 Synthesis of the Azide-Functionalized Glucodendron (11).

Glycoconjugated dendron 10 (0.3 g, 0.203 mmol) was dissolved in DMF, then sodium azide (52 mg, 0.812 mmol, 0.4 equiv.) was administered in argon ambient, and the reaction was continuously stirred for 12 h at 70 °C. The reaction mixture was evaporated under reduced pressure, and the obtained crude mass was extracted with ethyl acetate (2 × 20 mL), cleaned with brine solution (2 × 15 mL), and dried over anhydrous sodium sulphate. The organics were collected and concentrated; the resulting residue was loaded to column chromatography to furnish the targeted azide-functionalized dendritic wedge 11 in excellent yield. Yield (295 mg, 98%); $R_f = 0.4$ (55% ethyl acetate/n-hexane); $^1H$ NMR (500 MHz, CDCl$_3$): $\delta$ = 8.30 (s, 1H, triazolyl-H), 8.22 (s, 2H, triazolyl-H), 6.07 (d, $J = 9.5$ Hz, 2H, $H_1$), 5.97 (d, $J = 9.5$ Hz, 1H, $H_1$), 5.60–5.53 (m, 3H, $H_3$), 5.46–5.30 (m, 11H, $H_3$, $-CH_2$Ar), 4.53–4.47 (m, 2H, $H_2$), 4.29–4.26 (m, 3H, $H_2$, $-CH_2$Ar), 4.69–4.68 (m, 2H, $H_2$, $H_4$), 4.27–4.24 (m, 1H, $H_1$), 2.07–2.03 (m, 20H, 0.4 equiv.), 1.95 (s, 6H, $-COCH_3$), 1.86 (s, 3H, $-COCH_3$), 1.83 (s, 6H, $-COCH_3$), $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ = 170.5, 170.0, 170.4, 169.9, 169.4, 169.5, 169.4, 168.9, 168.7, 147.0, 146.9, 143.9, 143.4, 130.0, 126.1, 122.8, 122.7, 85.6, 85.5, 75.0, 74.8, 72.8, 72.7, 70.2, 70.1, 67.7, 67.6, 65.4, 61.6, 41.3, 20.7, 20.4, 20.1, and 20.0 ppm. IR (KBr): $\nu_{max}$ 3473.73, 2958.25, 1755.58, 1647.97 cm$^{-1}$. HRMS: m/z $C_{30}H_{69}Cl_3N_9O_{29}$ +; calculated = 1476.3211; found = 1476.3215 (M + H)$^+$. 

2.11 Synthetic Procedure for Chlorine-Containing 36-Glucose-Coated Glycodendrimer (12). Glycoconjugate dendron 11 (229 mg, 150 µmol, 15 equiv.) was grafted over hypercore 37 (20 mg, 10.2 µmol) using catalyst 9 (5 mg, 0.24 equiv.) according to the general procedure for the Cu(I)-catalyzed click reaction as described earlier to generate glycodendrimer 12 in moderate yield. Yield (53%); $R_f = 0.50$ (10% MeOH/CH$_2$Cl$_2$); $^1H$ NMR (500 MHz, CDCl$_3$): $\delta$ = 8.39–8.21 (m, 40H, triazolyl-H), 8.02–8.00 (8H, triazolyl-H), 6.12–5.97 (m, 24H), 5.66–5.57 (m, 36H), 5.42–5.29 (m, 84H), 5.09 (d, $J = 4.0$ Hz, 24H), 4.89–4.71 (m, 84H), 4.29–4.10 (m, 72H), 3.89–3.82 (m, 48H), 3.57 (s, 8H), 2.63 (s, 16H, $-COCH_3$), 2.08–1.97 (m, 216H, $-COCH_3$), 1.91–1.86 (m, 216H, $-COCH_3$); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ = 170.5, 170.0, 169.6, 169.4, 168.9, 168.7, 147.3, 147.1, 146.9, 146.6, 146.4, 143.7, 143.2, 139.1, 137.0, 128.2, 127.2, 127.1, 127.0, 126.5, 126.4, 124.7, 123.4, 123.2, 123.0, 122.8, 114.0, 103.7, 85.6, 75.0, 74.8, 72.9, 72.7, 70.1, 67.7, 67.6, 66.8, 65.9, 65.0, 61.6, 61.3, 61.2, 60.9, 50.3, 49.5, 48.4, 20.6, 20.5, and 20.1 ppm. IR (KBr): $\nu_{max}$ 3444.07, 2924.30, 2853.33, 1754.51, 1638.87 cm$^{-1}$.

3. Results and Discussion

To emphasize the importance of multivalent properties for carbohydrate-lectin interaction, we have designed and developed the cyclen-cored 36-glucose-coated (G$_1$ generation) glycodendrimer using regioselective triazole-forming CuAAC reaction. An aromatic ‘aglycone,’ i.e., tripropargylxy benzoate, was taken as the AB$_3$ monomer for the construction of the dendritic wedge of choice of interest. To build the G$_1$-generation cyclen-based glucose-coated dendrimer, a recent double-stage convergent way was embraced which encapsulates both paths, convergent and divergent [43]. Thus, our synthesis of the desired hypercore started with the commercially available gallic acid 1. It was esterified using H$_2$SO$_4$ in methanol to form scaffold 2, followed by propargylation, which led to the formation of compound 3. Subsequently, compound 3 on treatment with lithium aluminium hydride (LAH) in anhydrous THF yielded the corresponding alcohol functionality 4 (Scheme 1). As reported in the literature, chlorine-containing motifs have a family of compounds of promising potential in the medicinal field. Thus, this research encouraged us to develop a novel chlorine-containing glycodendrimer with increased biological importance in the field of pharmaceuticals [44]. Moreover, scaffold 4 was treated with sulphuryl chloride (SO$_2$Cl$_2$) to furnish AB$_3$ monomer 5 (Scheme 1). After the complete elucidation of the developed AB$_3$ monomer 5, it reacted with cyclic azamacrocycle 6 to construct core 7 (Scheme 1). The obtained hypercore 7 was characterized by its spectral studies.

On the contrary, clickable 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide 8 was synthesized from the corresponding D-glucose. For this, D-glucose was acetylated using acetic anhydride in the presence of iodine as a catalyst followed by treatment with HBr (33%) in acetic acid [45]. Then, the addition of Na$_2$N$_3$ in DMF leads to the formation of azido sugar [16]. After chromatographic refining, the developed azido derivative was well characterized by NMR in the available experimental literature. Once the synthesis of the end groups “2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide” and AB$_3$ monomer was accomplished, we next focused towards the regioselective CuAAC click conjugation of azido-appended end group 8 with alkynylated monomer 9. Therefore, we have optimized the dendron synthesis using different catalytic conditions, i.e., entries 1–4, as depicted in Table 1, in which, first of all, azide 8 was clicked with AB$_3$ monomer 5 under CuSO$_4$.5H$_2$O/NaAsc in THF/H$_2$O (1:1), reaction was completed in 12 h at room temperature, and the reaction yield was 80% (Table 1, entry 1). However, when the reaction was performed by using the stable catalyst dendrimer
Cu(I) catalyst [(PPh₃)₂Cu(μ-tda)Cu(PPh₃)₂].₆H₂O (tda = thiodiacetate anion) 9 [36], the reaction was completed in 3 h, and yield was found to be 84% (Table 1, entry 4). In this way, the best catalyst, i.e., catalyst 9, displayed remarkable catalytic advantage in terms of stability, high yield, ligand-free, base-free, and short reaction time for the CuAAC reaction. Therefore, the optimized catalyst 9 was implemented for the development of chlorine-functionalized dendritic wedge 10 along with glycodendrimer 12.

In order to achieve the first-generation glucodendron, i.e., chlorine-functionalized dendritic wedge 10, AB₃ monomer 5 was coupled with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide 8 by means of catalyst 9 in anhydrous DCM. Moreover, dendritic unit 10 was altered into

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**Table 1: Optimization of catalysts for the synthesis of the glucodendron.**

| Entry | Catalytic condition | Temp (°C) | Yield (%) | Time (h) |
|-------|---------------------|-----------|-----------|----------|
| 1     | CuSO₄.5H₂O/NaAsc, THF/H₂O (1:1) | 55        | 80        | 12       |
| 2     | CuSO₄.5H₂O/NaAsc, DCM/H₂O (1:1) | rt        | 75        | 12       |
| 3     | CuI/DIPEA, DCM⁹ | rt        | 72        | 12       |
| 4     | [(PPh₃)₂Cu(μ-tda)Cu(PPh₃)₂].₆H₂O (9), DCM⁹/DIPEA | rt        | 84        | 3        |

*Yield reported after column chromatography (SiO₂). ⁹Reaction under the anhydrous condition.
its required azide-functionalized dendritic moiety 11. Furthermore, this transformation (from chloro to azido) was confirmed by its IR spectra (∼2104.96 cm⁻¹) (Figure 2), whereas in ¹³C-NMR, the downfield shifting was noticed during conversion from -CH₂Cl (δ 41.3 ppm) to -CH₂N₃ (δ 49.6 ppm) for scaffold 11, which clearly indicated the unambiguous formation of azide-functionalized dendron 11 (Figure 3).

Finally, azide-functionalized glucodendron 11 was amalgamated with hypercore 7 using dinuclear copper(I) thiodiacetate catalyst 9 in anhydrous DCM to afford 36-glucose-coated glycodendrimer 12 in moderate yield (Figure 1). For instance, the reaction was completed on TLC, while after column chromatography, only 53% yield was achieved. Furthermore, the synthesized glycodendrimer was well characterized by its spectroscopic studies. In IR spectra, there was no
vibrating band of azide and alkyne which indicated the complete absence of free alkyne and azide functionality in the constructed glycodendrimers (Figure 2). Furthermore, the developed glycodendrimer was well characterized and studied by its comparative $^1$H-NMR and $^{13}$C-NMR (Figures 3 and 4).

In the $^1$H-NMR spectra of compound 12, the disappearance of acetylenic-H peak at 2.5 ppm of the core and the appearance of triazolyl peaks at 8.39–8.00 clearly depict the formation of the desired glycodendrimer, whereas the peak pattern of the dendron and core can also be seen in the spectra of Figure 3, which substantiate the generation of glycodendrimer 12.

Apart from this, the disappearance of acetylenic carbon peaks at 78.2, 78.1, 76.3, and 76.2 ppm of the core and the appearance of the triazolyl carbon peak in the glycodendrimer 12 NMR support its formation, while the cyclen (-CH$_2$) peak of the core at 50.3 ppm can also be seen in $^{13}$C-NMR of compound 12, which established the formation of glycodendrimer 12 (Figure 4).

The low polydispersity index (PDI = 1.11) obtained through gel permeation chromatography (GPC) has displayed the thorough molecular structure of the glycodendrimer (Figure 5). We also evaluated the retention time (14.41 min) for glycodendrimer 12.
Figure 4: $^{13}$C-NMR spectra of core 7, dendritic wedge 11, and chlorine-containing glycodendrimer 12.

Figure 5: SEC diagram of the constructed glycodendrimer 12.
4. Conclusion

The work presented here involved the synthesis of glycodendrimers of high-glucose tethers with low generation using the copper catalyst. In this regard, a hypercore having 12-alkynyl functionality derived from the cyclen unit was constructed. Thereafter, glycodendrons were grafted over the hypercore to generate a giant chlorine-containing 36-peripheral glucosylated glycodendrimer of G1 generation. Furthermore, the constructed glycodendrimers were well characterized by their NMR, HRMS, and IR spectral data. Moreover, the size-exclusion chromatogram has displayed the high monodispersity of the achieved glycodendrimer.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors’ Contributions

AKA synthesized and performed the most of the writing part and prepared the original draft. SK performed the synthesis of starting material. AS performed data analysis. VKT and prepared the original draft. SK performed the synthesis and performed the most of the writing part.

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