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Facile Assembly of Cell Surface Oligosaccharide Mimics by Copolymerization of Carbohydrate Modules**

Kenji Sasaki, Yoshihiro Nishida,* Tomoaki Tsurumi, Hirotaka Uzawa, Hirosato Kondo, and Kazukiyo Kobayashi*

Artificial glycoconjugate polymers (glycopolymers) and other multivalent carbohydrate ligands constitute a new class of biomimetic supramolecules.[1] They have shown many biological applications in, for example, cultivation, tumor diagnosis and detection, and the trapping of viruses and bacterial toxins.[2] Their utility is ascribed mainly to their strong and species-specific interactions with the receptor proteins as a result of multivalent binding and/or carbohydrate cluster effects. Although most of the glycopolymers so far prepared and applied were made up of simple mono- and disaccharides, more intense interest has been directed to glycopolymers carrying cell-surface oligosaccharides such as sialyl Lewis^X (sLe^X)[3] and globosyl oligosaccharides[4] that have potentially greater biological significance. From a practical viewpoint, however, the synthesis and application of these glycoconjugates are seriously restricted by the difficulty in preparing target oligosaccharides in sufficient amounts prior to their incorporation into the multivalent models.

In the course of our synthetic study of glycopolymers carrying the mimics of cell-surface oligosaccharides,[5] we found recently that an acrylamide copolymer carrying α-L-fucopyranoside and 3-sulfo-β-D-galactopyranoside as a side chain shows strong activity in blocking L-selectin/sLe^X tetrasaccharide adhesion.[6] As judged from the observation that none of the acrylamide copolymers carrying only one of the two glycosides showed a notable activity, the observed activity was ascribed to the cooperative binding of the α-L-fucoside and 3-sulfo-β-D-galactoside to L-selectin. This finding indicated the potential utility of the module approach and prompted us to generalize it as a "carbohydrate module method".

For the facile understanding of our "carbohydrate module method", let us assume a model consisting of the binding of a branching pentasaccharide with the receptor protein (Figure 1). In this model the two glycoside residues (A1 and A2) at the nonreducing terminal provide key binding interactions with the receptor protein at the *r*(A1) and *r*(A2) binding sites. Conventional mimic syntheses may target a branching trisaccharide carrying A1, A2, and B residues, thus developing the multivalent model (polymer-(A1 + A2 + B)) in Figure 1b. Our approach targets a copolymer-(A1/A2) species carrying the key interactive sugars (Figure 1c) to circumvent the difficulty in preparing the branching saccharide. The copolymer-(A1/A2) species is assumed to have a certain probability of occupying both of the binding sites and, thus, is expected to show a higher binding activity than the polymers carrying only one of the key sugars (poly-(A1) and poly-(A2)). This situation means that copolymerization of two key interactive sugars (A1 and A2 in the present case) provides a facile way to mimic the biologically active structures of oligosaccharides. The glycopolymers thus derived may show potent biological activity in blocking the binding of the oligosaccharide to receptor proteins.

The present approach involves the following three steps: segmentation of a targeted oligosaccharide into smaller sugars, synthesis of the corresponding glycosylated monomers (defined as "carbohydrate modules" in this study), and the reassembly of oligosaccharide mimics by copolymerization of the modules. Previously, we employed this process for sLe^X tetrasaccharide **1a**, which was segmented into modules of allyl α-L-fucoside and *p*-acrylamidophenyl 3-sulfo-β-D-galactopyranoside to afford the copolymer (**2**) with potent activity in blocking L-selectin/sLe^X binding.[6] In the present study, we took the module approach to 6-sulfo-sialyl Lewis^X (6-sulfo-sLe^X) tetrasaccharide **1b** which has a 6-sulfo-GlcNAc at the reducing residue. The biological significance of **1b** is evident from recent studies[7] in which it was substantiated that the 6-sulfo analogue **1b** is a better ligand than sLe^X (**1a**) for L-selectin. We aimed to not only prepare multivalent 6-sulfo-Le^X mimics but also to investigate the possible role of the 6-sulfo-GlcNAc residue in binding to L-selectin.

The oligosaccharide sequence was divided into Lewis^X (Le^X), sLe^X, and 6-sulfo-GlcNAc to investigate key epitopes for L-selectin. To construct the library of Le^X, sLe^X, and 6-

[*] Dr. Y. Nishida, Prof. Dr. K. Kobayashi, K. Sasaki, T. Tsurumi
Department of Molecular Design and Engineering
Graduate School of Engineering
Nagoya University
Chikusa-ku, Nagoya 464–8603 (Japan)
Fax: (+81) 52–789–2528
E-mail: nishida@mol.nagoya-u.ac.jp
kobayash@mol.nagoya-u.ac.jp
Dr. H. Uzawa
National Institute of Advanced Industrial Science and Technology (AIST) (Japan)
Dr. H. Kondo
Research & Development Division
Nippon Organon K. K. (Japan)

[**] Part of this research is supported by grants from the Japanese Ministry of Education and Science (K.K. and Y.N). We thank the Japan Society for the Promotion of Science Research for a research fellowship for young scientists (K.S.).

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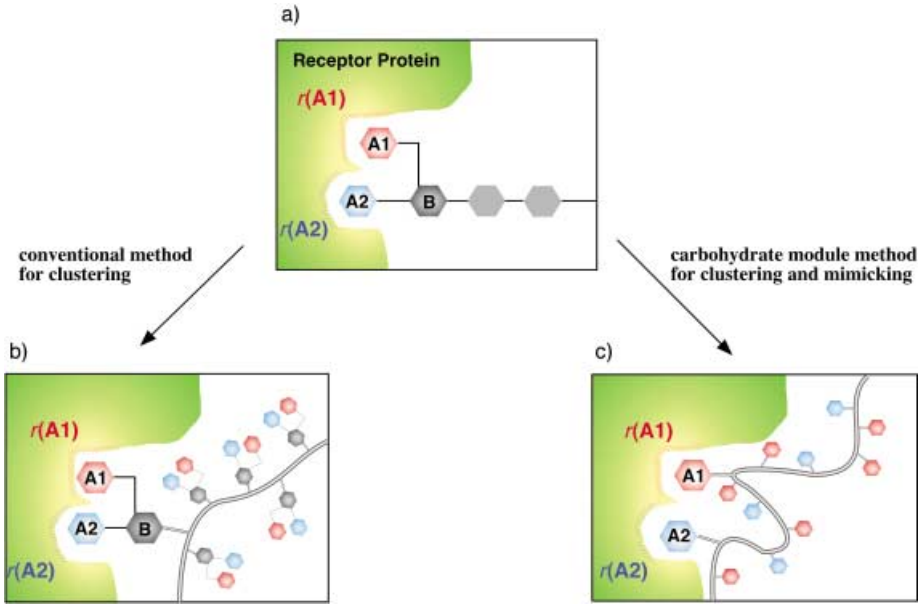
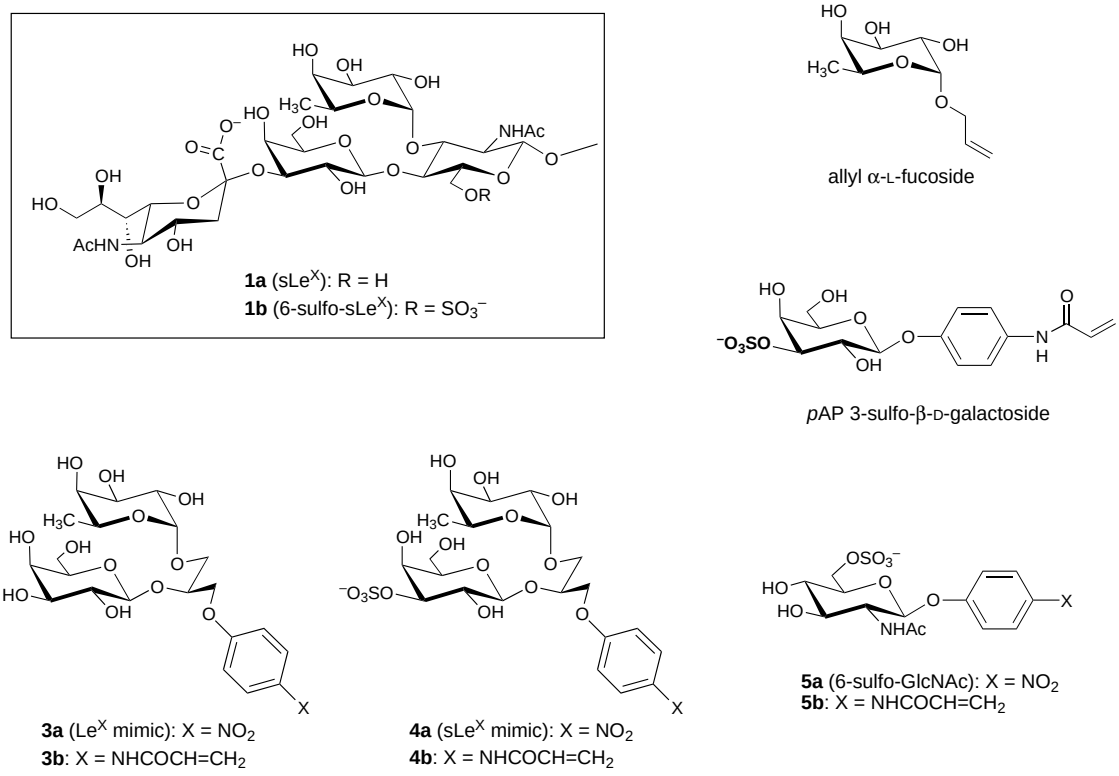


Figure 1. Concept of the carbohydrate module approach for the mimic synthesis of oligosaccharides. a) A targeting branching trisaccharide carrying A1, A2, and B residues to bind to the receptor protein. b) The conventional multivalent model. c) The copolymer-(A1/A2) species carrying the key interactive sugars prepared on the basis of our concept of "carbohydrate module method".

sulfo-Le^X mimics, *p*-*N*-acrylamidophenyl (*p*AP) glycosides **3b** and **4b** were designed as simple Le^X and sLe^X modules, respectively (Scheme 1). They were prepared from allyl α-L-fucopyranoside as depicted in Scheme 2. The diastereomeric mixture **15** (50% *de*) could be resolved by either fractional crystallization or reversed-phase HPLC column chromatography to afford single isomers **3b** and **4b** (>95% *de* by ^{1}H NMR analysis). The *R* configuration of the acyclic moiety corresponds to the absolute stereochemistry along the C-3, C-4, and C-5 bonds of the GlcNAc residue in sLe^X **1a**. Another key module **5b** (*p*AP 6-sulfo-β-D-GlcNAc) was prepared from *p*-nitrophenyl (*p*NP) β-D-GlcNAc with a sulfur trioxide/trimethylamine complex.[8] Each of these 6-sulfo-sLe^X modules **3b**–**5b** was copolymerized with acrylamide to give a series of acrylamide copolymers **6**–**8**. Moreover, copolymerization of **4b** and **5b** in the presence of acrylamide gave a terpolymer **9** (Scheme 3).[9]

An enzyme-linked immunosorbent assay (ELISA) was performed in microtiter plates (96 wells, PROBIND) coated with sLe^X pentaceramides as reported previously.[10] Both the polymeric **6**–**9** and monomeric ligands **3a**–**5a** were assayed in the same way to evaluate the effect of multivalent binding on their ability to block L-selectin. The results summarized in Table 1 indicate that none of the monomeric glycosides possesses notable activity (IC_{50} > 50 μM), while most of the polymers, except for Le^X mimic **6**, possess potent activity. The strong multivalent binding effect thus observed suggests the



Scheme 1. Segmentation of sialyl Le^X **1a** and 6-sulfo-sLe^X tetrasaccharides **1b** into key carbohydrate modules.

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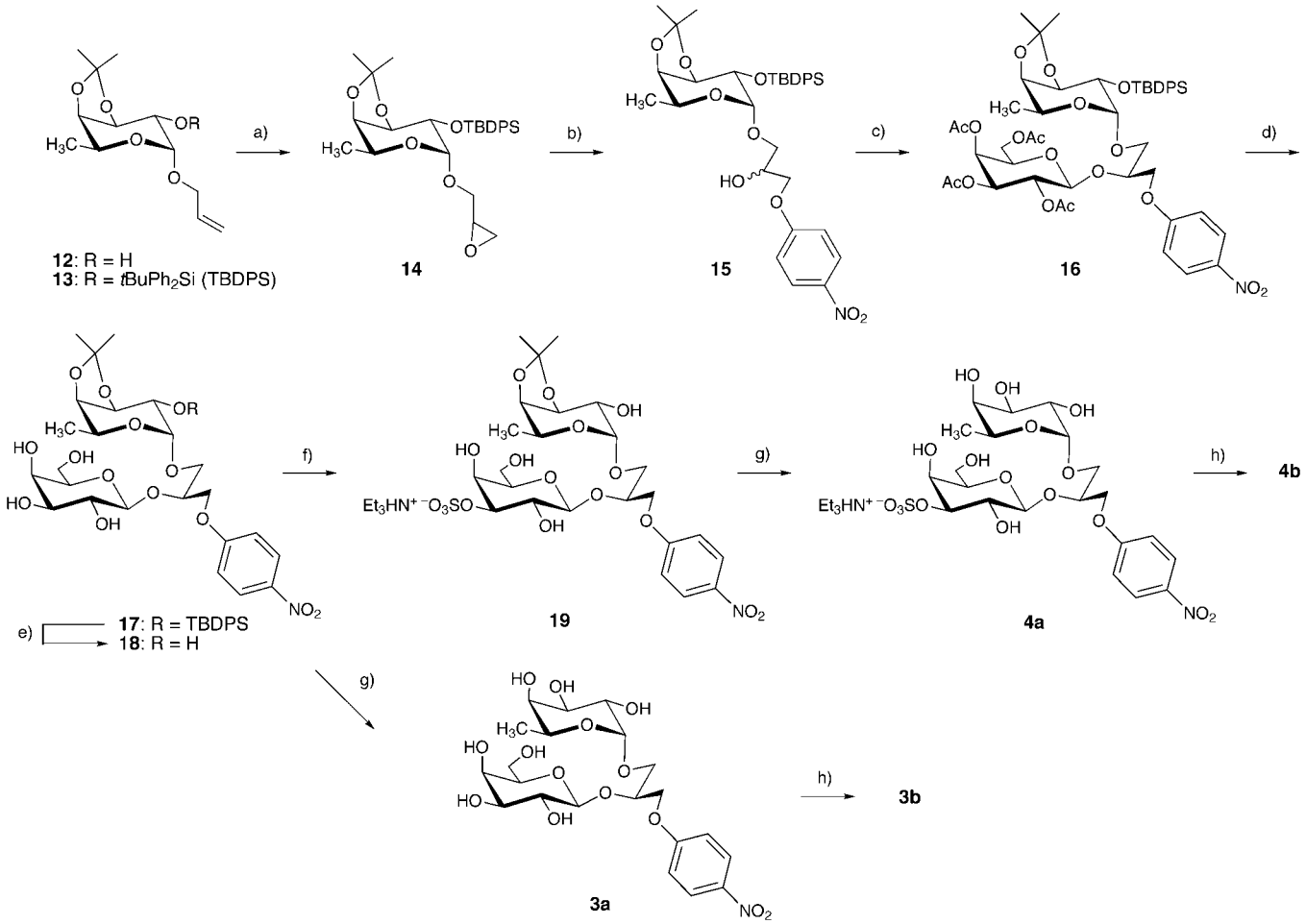

Scheme 2. Synthesis of Le^X module **3b** and sLe^X module **4a**. a) mCPBA, CH_2Cl_2, −40 °C→RT, 17 h (89 %); b) sodium *p*-nitrophenoxide, DMF, 70 °C, 13 h (50 % yield, 80 % *de* crystallized); c) *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)trichloroacetimidate,[16] TMSOTf, 4Å-MS, CH_2Cl_2, −40 °C→RT, 1 h; d) NaOMe, MeOH, 2 h (40 % over two steps from **15**); e) TBAF, THF, 24 h (90 %); f) Bu_2SnO, benzene, reflux, 5 h, then $Me_3N{\cdot}SO_3$, Et_3N, DMF, 40 °C, 2 h (76 %); g) TFA, MeOH, H_2O, 1 h (99 %); h) 1. H_2, $Pd(OH)_2$/C, MeOH, 1 h; 2. acryloyl chloride, Et_3N, THF, CH_2Cl_2, 2 h, then Dowex (Na^+ form) (63 % for **4b**, 75 % for **3b** over two steps, 95 % *de* for **4b**, 99.5 % *de* for **3b**). mCPBA = *meta*-chloroperoxybenzoic acid, TMSOTf = trimethylsilyl trifluoromethanesulfonate, MS = molecular sieves, TBAF = terabutylammonium fluoride, TFA = trifluoroacetic acid.

presence of multiple carbohydrate binding sites in L-selectin. The poor activity of **6** indicates that the nonspecific binding of the polyacrylamide backbone is negligibly small. Moreover, it is also clear that the 3′-sulfate group in the sLe^X mimic **7**, which serves as a substitute for 3′-silalic acid, plays a major role in the binding to L-selectin.

Roy et al. had previously prepared an acrylamide copolymer carrying the 3′-sulfo-Le^X trisaccharide to prove its ability to block L- and E-selectins at micromolar concentrations.[3a] Our polyvalent 3′-sulfo-Le^X **7** could also show comparable binding to L-selectin (6 μM), even though the mimic has a much simpler and acyclic skeleton that allows facile preparation. Moreover, comparison of the blocking activity of **7** and **2** provides a useful measure to assess the efficiency of our previous copolymerization approach since the activity of **7** (which serves as a typical model of polymer-(A1 + A2 + B) in Figure 1b) could represent the maximal activity of **2** (which serves as a model of copolymer-(A1/A2) in Figure 1c) if L-selectin possesses binding sites specific for the sLe^X structure. The blocking activity of **7** was approximately 2.5 fold stronger than **2**. The enhanced activity could support the presence of sLe^X binding site in L-selectin, and the level of incorporation could substantiate the efficiency of our module approach. Moreover, the terpolymer **9** carrying both the sLe^X and 6-sulfo-GlcNAc modules showed much higher activity than **7**. This observation indicates the major role of the 6-sulfo-GlcNAc residue in the adhesion to L-selectin and suggests the presence of another binding site for 6-sulfo-Glc residue. The potent activity, which seems to be the strongest of the L-selectin blockers so far reported,[11] supports the utility of the carbohydrate module method as a tool to assemble oligosaccharide mimics of high biological significance.

To our surprise 6-sulfo-GlcNAc copolymer **8** was found to show potent activity that was comparable to that of the terpolymer **9**. The possibility of there being nonsepecific interactions observed between P-selectin and polyanions such as fucoidin[12] and ion-exchange resins[13] is ruled out in the case of E- and L-selectins.[6] Moreover, as judged from our preceding results which showed that neither of the copolymers **10** and **11** carrying respective 3- and 6-sulfo-β-D-galactopyranoside showed such potent activity (Table 1),[6] it is clear that the 6-sulfo-GlcNAc residue provides a key and

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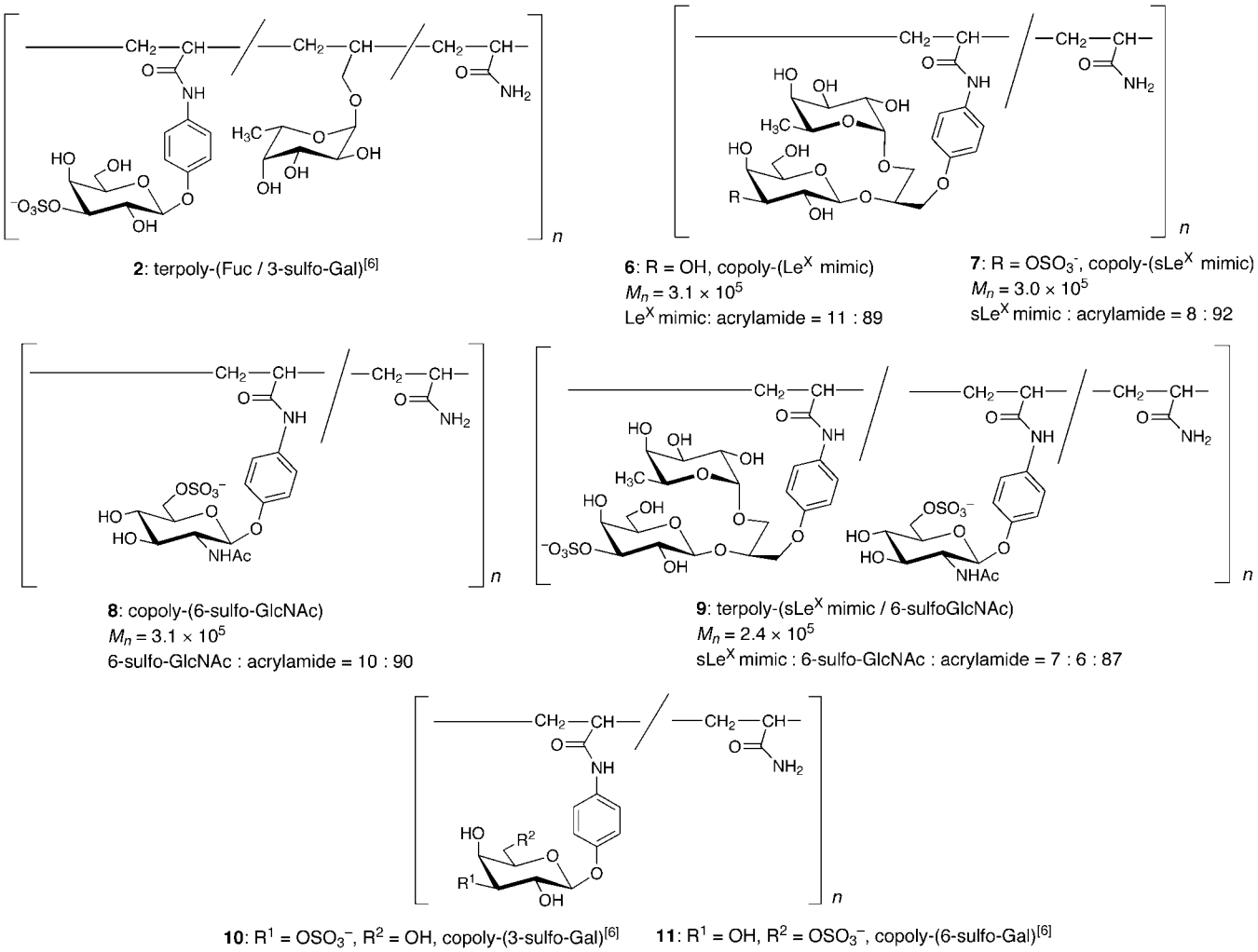

Scheme 3. Structures of polyvalent Le^X **6**, 3′-sulfo-Le^X **7**, 6-sulfo-GlcNAc **8**, 3′,6-disulfo sLe^X mimics **9**.

Table 1. Activity of monomeric and polymeric ligands to block L-selectin/sLe^X binding.

Ligands	Carbohydrate modules	Activity (IC_{50}) [μM][a]
Monomeric		
3a	Le^X (α-L-Fuc + Gal)	> 50
4a	3′-sulfo-Le^X (α-L-Fuc + 3-sulfo-Gal)	> 50
5a	6-sulfo-GlcNAc	> 50
Polymeric		
2	α-L-Fuc/3-sulfo-Gal (1/2)	15[6]
6	Le^X (α-L-Fuc + Gal)	> 50
7	3′-sulfo-Le^X (α-L-Fuc + 3-sulfo-Gal)	6
8	6-sulfo-GlcNAc	3
9	3′-sulfo-Le^X/6-sulfo-GlcNAc (1/1)	3
10	3-sulfo-Gal	> 50[6]
11	6-sulfo-Gal	> 50[6]

[a] IC_{50} values are given per glycoside unit.

species-specific interaction with L-selectin. This finding, which suggests the high biological significance of polyvalent 6-sulfo-GlcNAc **8**, may lead to the mass production of sugar-based medicinal agents through the abundant resources of chitin/chitosans. Moreover, the strong activity of **8** provides a significant insight into the carbohydrate recognition of L-selectin, although the precise mechanism awaits further synthetic and biological studies.

In conclusion, we have proposed a carbohydrate module method as a facile approach to assemble the biologically active structure of cell-surface oligosaccharides. This approach has enabled us to prepare glycopolymers that show potent activity in blocking L-selectin/sLe^X binding, in which a glycopolymer carrying a 6-sulfo-GlcNAc cluster was found to serve as one of the most promising agents. This finding supports recent studies[7,14] on the biological role of 6-sulfo-sLe^X tetrasaccharides and GlcNAc-6-*O*-sulfotransferases. Just recently, Patel and Lindhorst reported their module approach for the synthesis of oligosaccharide mimics.[15] Although their approach is based on the assembly of different sugar epitopes on dendric glycoconjugates and may be discriminated in principle from ours, these approaches will provide a promising pathway to construct artificial glycoconjugates with high biological potential.

Received: May 16, 2002
Revised: September 9, 2002 [Z19315]

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[9] For the synthetic procedure for the preparation of these glycopolymers, see ref. [6]. Selected data for copolymer **6**, **7**, **8**, and terpolymer **9** are as follows: **6**: $M_n = 3.1 \times 10^5$, $M_w/M_n = 1.86$ (size-exclusion chromatography (SEC) in phosphate buffer saline (pH 7.4), calibrated with pullulans); ^{1}H NMR (500 MHz, D_2O, 60 °C): $\delta = 7.36$ (brs, 2H, aromatic-H), 7.06 (brs, 2H; aromatic-H), 4.91 (brs, 1H; Fuc H-1), 4.61 (brd, 1H, $J = 8.5$ Hz; Gal H-1), 4.40–3.53 (brm, 15H), 2.40–2.17 (brm, C*H*CH$_2$), 1.79–1.45 (brm, CHC*H*$_2$), 1.11 ppm (brs, 1H; Fuc H-6); (Le^X:acrylamide = 11:89). **7**: $M_n = 3.0 \times 10^5$, $M_w/M_n = 1.87$ (SEC in phosphate buffer saline (pH 7.4), calibrated with pullulans); ^{1}H NMR (500 MHz, D_2O, 60 °C): $\delta = 7.56$ (brs, 2H, aromatic-H), 7.25 (brs, 2H, aromatic-H), 5.11 (brs, 1H, Fuc H-1), 4.91 (brd, 1H, $J = 7.0$ Hz, Gal H-1), 4.50–3.84 (brm, 15H), 2.60–2.30 (brm, C*H*CH$_2$), 2.00–1.75 (brm, CHC*H*$_2$), 1.32 ppm (brd, 1H, $J = 6.5$ Hz, Fuc H-6); (3′-sulfo-Le^X:acrylamide = 8:92). **8**: $M_n = 3.1 \times 10^5$, $M_w/M_n = 1.74$ (SEC in phosphate buffer saline (pH 7.4), calibrated with pullulans); ^{1}H NMR (500 MHz, D_2O, 60 °C): $\delta = 7.60$ (brs, 2H, aromatic-H), 7.27 (brs, 2H, aromatic-H), 5.32 (brs, 1H, GlcNAc H-1), 4.57 (brs, 1H), 4.42 (brs, 1H), 4.19 (brs, 1H), 4.00 (brs, 1H), 3.85 (brm, 1H), 3.78 (brm, 1H), 2.52–2.22 (brm, C*H*CH$_2$), 2.10 (brs, 3H, COCH$_3$), 2.00–1.75 (brm, CHC*H*$_2$); (6-sulfo-GlcNAc:acrylamide = 10:90). **9**: $M_n = 2.4 \times 10^5$, $M_w/M_n = 1.77$ (SEC analysis in phosphate buffer saline (pH 7.4), calibrated with pullulans); ^{1}H NMR (500 MHz, D_2O, 60 °C): $\delta = 7.58$ (brm, 4H, aromatic-H), 7.23 (brm, 4H, aromatic-H), 5.32 (brs, 1H, GlcNAc H-1), 5.11 (brs, 1H, Fuc H-1), 4.90 (brs, 1H, Gal H-1), 4.60–3.78 (brm, 22H), 2.60–2.30 (brm, C*H*CH$_2$), 2.20 (brs, 3H COCH$_3$), 2.12–1.75 (brm, CH-C*H*$_2$-), 1.29 ppm (brs, 1H, Fuc H-6); (3′-sulfo-Le^X: 6-sulfo-GlcNAc:acrylamide = 7:6:87).
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Attachment of Molecules at a Molecular Printboard by Multiple Host–Guest Interactions**

Jurriaan Huskens,* Menno A. Deij, and David N. Reinhoudt*

Dedicated to Professor Manfred T. Reetz on the occasion of his 60th birthday

The exact positioning of molecules on surfaces has become essential for the development of molecular electronics[1] and biochip applications,[2] as well as for conducting single molecule experiments. Commonly, one of two possible routes is followed, either by chemically reacting molecules to surfaces or to anchoring molecules present at a surface, or by physisorption, that is, the use of nonspecific physical interactions between molecule and surface, and between molecules themselves. Covalent chemical modification usually requires synthetic effort, is hard to control at surfaces, and does not allow either self-correction or (intentional) desorption. Physisorption does allow self-correction, which is common for all self-assembly processes, but the thermodynamic and kinetic parameters governing adsorption and desorption are difficult to control. Moreover, neighboring molecule–molecule interactions are usually needed for obtaining stable and ordered layers, thus the formation of densely packed layers is a prerequisite.[3]

Supramolecular interactions serve as an intermediate case with the possibility of employing advantages from both routes. Supramolecular interactions, such as those observed in host–guest complexes, are specific and directional, and a wealth of information is usually available on their binding strengths and kinetics. The application of molecules that allow the formation of multiple supramolecular interactions provides a tool to tune adsorption and desorption process parameters because thermodynamics and kinetics are, in principle, straightforwardly related to the number of interactions, and the strength and kinetics of an individual interaction.

It is therefore our goal to apply host surfaces as "molecular printboards" at which multivalent guest molecules can be positioned. Prerequisites will need to be identified to reach thermodynamically and/or kinetically stable assemblies that can be employed in nanotechnology. It is envisaged that one can control adsorption and desorption by environmental stimuli, for example, by competition with another host in solution. Herein we address the thermodynamic and kinetic

[*] Dr. ir. J. Huskens, Prof. dr. ir. D. N. Reinhoudt, Ir. M. A. Deij
University of Twente, MESA$^+$ Research Institute
Laboratory of Supramolecular Chemistry and Technology
P.O. Box 217, 7500 AE Enschede (The Netherlands)
Fax: (+31) 53-489-4645
E-mail: smct@ct.utwente.nl

[**] Dr. Maurice Baars and Prof. Dr. Bert Meijer (TUE) are gratefully acknowledged for supplying the adamantyl-terminated dendrimers. Frank Geurts (Akzo Nobel, Arnhem) is acknowledged for performing the XPS measurements, and Paul Koster for assistance with the grazing-angle FTIR measurements. Szczepan Zapotoczny is acknowledged for performing the AFM measurements. The Dutch Technology Foundation STW is gratefully acknowledged for funding the Simon Stevin Award project on Nanolithography.

  0044-8249/02/11423-4647 $ 20.00+.50/0