were measured at low temperatures (4.2 K or 78 K). The source was kept at room temperature. Spectra were recorded over a velocity range of $\pm$ 25 mm s^{-1} using an NaI(Tl) scintillation counter. Fitting of the spectra was carried out on the basis of the theoretically expected lineshape arising from the allowed transitions between the quadrupolar-split energy levels of the ground state ($I = 5/2$) and the excited state ($I = 7/2$).

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[10] a) The compound crystallizes in the monoclinic space group $P2_1/c$, $a =$ 11.743(2), $b = 11.358(2)$, $c = 30.878(6)$ Å, $\beta = 95.78(3)°$, $V =$ 4097.5(14) Å^3, $Z = 4$, $\rho = 2.117$ mg m^{-1}, $\mu(Mo_{K\alpha}) = 3.99$ mm^{-1}, $F(000) = 2544$. STOE AED-II diffractometer, monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Lorentz, polarization, and absorption corrections; 17068 reflections; range $1.74 \le \theta \le 27.53$; 9436 unique data; 8164 with $I \ge 2\sigma(I)$. Structure solution was performed with SHELXS-97 using direct methods.[10b] Refinement was done against F^2 using SHELXL-97.[10c] All heavy atoms were refined anisotropically. Several C atoms are disordered with occupancies given in parentheses: C6(50%), C6′(50%), C9(60%), C9′(40%), C11(50%), C11′(50%), C13(70%), C13′(30%). The hydrogen atoms were positioned with idealized geometry and refined with fixed isotropic displacement parameters using a riding model. Final reliability values: $R1 = 0.0344$ for all reflections, $wR2 = 0.0682$ for all reflections, goodness-of-fit = 1.058. CCDC-188070 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk); b) G. M. Sheldrick, SHELXS-97, Program for the Solution of Crystal Structures, Universität of Göttingen, Göttingen (Germany), **1997**; c) G. M. Sheldrick, SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen (Germany), **1997**.
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Efficient Solid-Phase Synthesis of a Complex, Branched *N*-Glycan Hexasaccharide: Use of a Novel Linker and Temporary-Protecting-Group Pattern**

Xiangyang Wu, Matthias Grathwohl, and Richard R. Schmidt*

Oligosaccharides are known to be important molecules in various biological processes; therefore, they have gained increasing interest in recent years.[1] However, in contrast to oligopeptides[2] and oligonucleotides[3] which are routinely constructed on automated synthesizers employing standardized building blocks and polymer supports, no generally applied synthetic methodology has yet appeared for the solid-phase synthesis of complex oligosaccharides.[4] Success in this challenging task would provide several advantages over solution-phase techniques: 1) the required standardized building blocks could become commercially available, 2) an excess of building blocks and/or reagents could be used to drive reactions to completion, 3) the synthesis could become much faster, and 4) purification procedures could become simpler.

Another fundamental key issue for solid-phase oligosaccharide synthesis is the availability of a high-yielding and stereoselective glycosylation strategy. Of the various glycosyl donors employed for this purpose,[5–11] *O*-glycosyl trichloroacetimidates[12] are suitable because of their high glycosyl-donor properties in the presence of just catalytic amounts of a (Lewis) acid. In combination with solvent and temperature effects, type of catalyst, protecting-group pattern, and anchimeric assistance these donors also permit the desired control of the stereoselectivity at the anomeric center.[13]

An additional requirement for solid-phase oligosaccharide synthesis is access to branching which is found in many oligosaccharides and glycoconjugates but not in peptides and oligonucleotides. Thus, for chain extension and branching, besides permanently protected functional groups, to be liberated only after completion of the solid-phase oligosaccharide synthesis, a suitable temporary-protecting-group pattern is required. This temporary-protecting-group pattern provides the orthogonality required for branching and should also accommodate the demands of the linker which necessitates an additional temporary functional group.

Based on our recent studies on new temporary protecting groups,[12,14] new linker types,[14] and the synthesis of branched oligosaccharides,[12e,15] we report herein a novel strategy which

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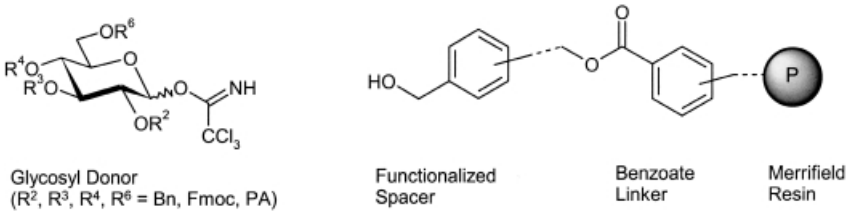
should fulfil the demands of a generally applicable methodology. As shown in Scheme 1, the system comprises:

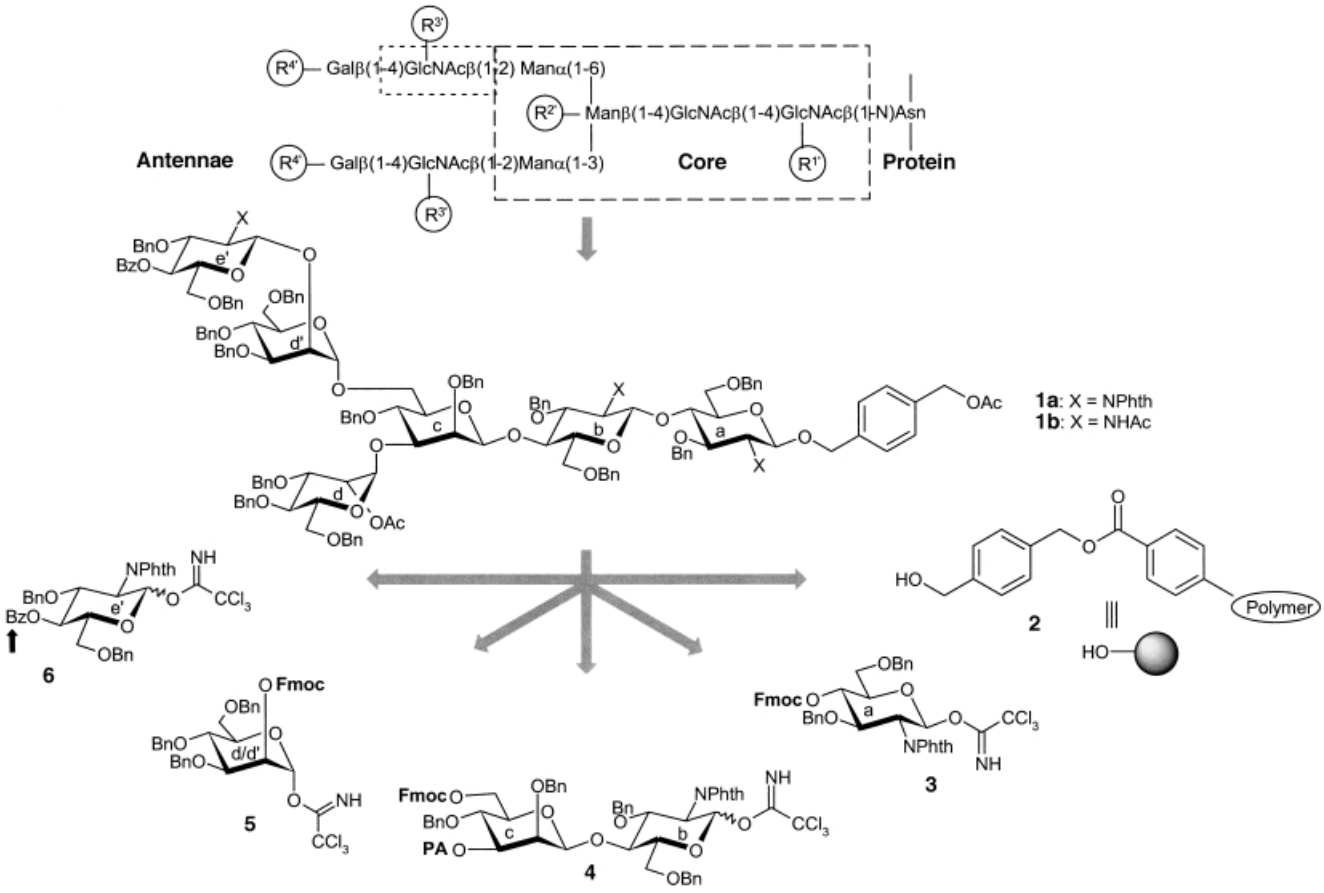
1) a Merrifield-type resin
2) a enzoate ester as the linker because this offers the desired stability towards acid and base and it permits the cleavage of more reactive esters under very mild alcoholysis conditions
3) a benzyl spacer linked to the anomeric center of the sugar residue at the reducing end, thus leading, after final cleavage, to a structurally defined target molecule which can be deprotected under standard hydrogenolysis conditions
4) *O*-glycosyl trichloroacetimidates as glycosyl donors, with the advantages discussed above
5) essentially benzyl for permanent protection of hydroxy groups and phthaloyl, dimethylmaleoyl, or azido for the masking of amino groups
6) 9-fluorenylmethyloxycarbonyl (Fmoc) and/or phenoxyacetyl (PA) groups for temporary protection because these groups permit selective cleavage (with NEt_3 for Fmoc, release of 9-methylenefluorene; with NaOMe (0.5 equiv) or $MeNH_2$ in CH_2Cl_2/MeOH for PA, release of phenoxyacetate) in the presence of the benzoate linker and UV monitoring of the cleavage product
7) NaOMe (four equivalents) in CH_2Cl_2/MeOH for final cleavage of the target molecule from the resin. This simple ester based methodology is very efficient as will be shown below.

One of the most difficult tasks constitutes the synthesis of complex type N-glycans[16] which consist of a branched core pentasaccharide having different antennae-like sugar side chains (Scheme 2, R^1–R^4 = H or sugar residues).

Therefore, the efficiency of our strategy was investigated with the synthesis of hexasaccharide **1a** comprising the core pentasaccharide and one GlcNAc residue. Retrosynthetic analysis considering the strategy discussed above leads to the spacer-linker-polymer support **2** containing the previously employed benzene-1,4-dimethanol unit[17] as the spacer and to glycosyl donors **3**–**6**. Hence, for the selective attachment of different antennae at the 2-*O* position of Man residues d and d′, orthogonal protection of Man residue c is required,



Scheme 1. Solid-phase synthesis based on different esters (Fmoc and PA) for both temporary protection and linkage to the solid support, benzyl groups for permanent protection and as spacer to the anomeric center (see text for full details).



Scheme 2. General structure of complex type N-glycans and retrosynthetic analysis of core hexasaccharide **1** for the synthesis on solid phase; Phth = phthaloyl

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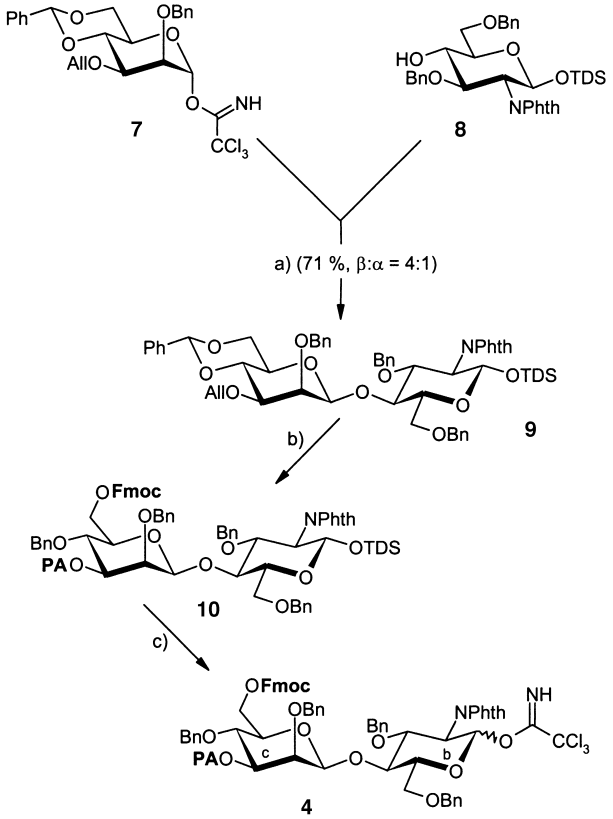
as exhibited by building block **4**. Because of the lack of a highly β-selective mannosyl donor,[18,19] the required Manβ(1-4)GlcN disaccharide donor **4** had to be prepared independently (Scheme 3).



Scheme 3. Synthesis of the required Manβ(1-4)GlcN building block **4** having orthogonal temporary protecting groups. a) TMSOTf, CH_2Cl_2, −50 °C; b) 1. *trans*-[$Pd(NH_3)_2Cl_2$], *t*BuOH (68 %); 2. PACl, py (88 %); 3. BH_3·THF, Bu_2BOTf (79 %); 4. FmocCl, py (68 %); c) 1. HF·py, THF (65 %); 2. CCl_3-CN, NaH (78 %); py = pyridine, TDS = thexyldimethylsily; All = allyl.

The synthesis is based on a recently reported direct β-selective mannosylation procedure with **7**[18] as donor and **8**[20] as acceptor furnishing the desired β-disaccharide **9** in good yield (β:α = 4:1, 71 %). For the introduction of the temporary protecting groups first the allyl protecting group was removed under Pd catalysis with *tert*-butanol as the nucleophile[21] and phenoxyacetylation was performed; then, reductive opening of the 4c,6c-*O*-benzylidene group with borane in the presence of dibutylborane triflate[22] afforded the desired 6c-O-unprotected intermediate which on treatment with Fmoc-Cl in pyridine gave disaccharide **10** with the two orthogonal temporary protecting groups. Removal of the *O*-silyl group with HF·pyridine and then reaction with trichloroacetonitrile in the presence of sodium hydride as base furnished the desired glycosyl donor **4** without affecting the temporary protecting groups; even the base-sensitive Fmoc group was retained. Building blocks **3**, **5**, and **6** are readily available following previously reported procedures.[12a,23]

For the solid-phase oligosaccharide synthesis commercially available Merrifield resin containing benzoic acid groups was selected. As spacer and linker to the benzoyl group 1,4-bis(hydroxymethyl)benzene[17] was chosen; after monotritylation, reaction with the acid chloride of the solid support in pyridine in the presence of 4-dimethylaminopyridine (DMAP), then capping of excess acid chloride with methanol in pyridine, and finally detritylation with trifluoroacetic acid in CH_2Cl_2 afforded polymer **2** (Scheme 4). The loading could be easily determined by the amount of trityl cation released; 0.146 mmol g^{-1} of dry resin led to good results; higher loadings diminished the overall yields of the oligosaccharide synthesis.

Reaction of polymer **2** as acceptor with glycosyl donor **3** in CH_2Cl_2 at −40 °C in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst (0.2 equivalents) afforded cleanly the desired glycosylated polymer. This reaction was monitored by analytical cleavage with NaOMe (4 equivalents) in CH_2Cl_2:MeOH (8:1) furnishing 4-hydroxymethylbenzyl glycoside **11** (R = H; see Experimental Section). Alternatively, reaction of **11** (R = Fmoc)[23] with the Merrifield resin in the presence of diisopropyl carbodiimide and DMAP in CH_2Cl_2 afforded the same polymer.

Chain extension on the solid-phase followed a convenient, standardized procedure. Treatment of the polymer, to which the Fmoc containing glucosamine residue was linked, with NEt_3 in CH_2Cl_2 (1:8) to remove the Fmoc group, then, after washing with CH_2Cl_2:THF (1:1), glycosylation with donor **4** in CH_2Cl_2 at −20 °C in the presence of TMSOTf (0.35 equivalents) as catalyst led to the desired trisaccharide as shown by monitoring the reaction by the cleavage of glycoside **12** from small resin samples (see Experimental Section). After washing with CH_2Cl_2/THF and repetition of the same procedure with donors **5** and **6**, tetrasaccharide **13** and pentasaccharide **14** were obtained. Because the antenna was to be terminated with building block **6**, a benzoyl group was selected as protecting group for the 4-hydroxy group. Thus, the selective removal of the PA protecting group at 3c-O with NaOMe (0.5 equivalents) in CH_2Cl_2:MeOH (8:1) could be performed without release of other groups. Then washing with CH_2Cl_2/MeOH and CH_2Cl_2/THF and glycosylation with donor **5** furnished the desired hexasaccharide on the polymer which was ready for further chain extension. Preparative cleavage under the conditions of analytical cleavage and then O-acetylation with acetic anhydride furnished after chromatography pure target molecule **1a** as ascertained by the NMR spectroscopy data (see Experimental Section). The total yield was 19 % over eleven steps which is an average yield of 86 % per step. Cleavage of the *N*-phthaloyl groups under standard conditions[24] and then N,O-acetylation afforded **1b**; the physical data of **1b**[23] are also in accordance with the assigned structure.

In conclusion, a highly efficient solid-phase synthesis of a branched N-glycan oligosaccharide containing the core structure could be performed, which in terms of time and yield is superior to a solution-phase approach. The novel linker and temporary-protecting-group pattern containing different types of ester linkages offers the advantage of releasing (after cleavage) from the polymer support a benzyl aglycon moiety, which can be removed by hydrogenolysis. The simplicity and efficiency of the chain-extension procedure and of the final removal of the target molecule from the solid support should

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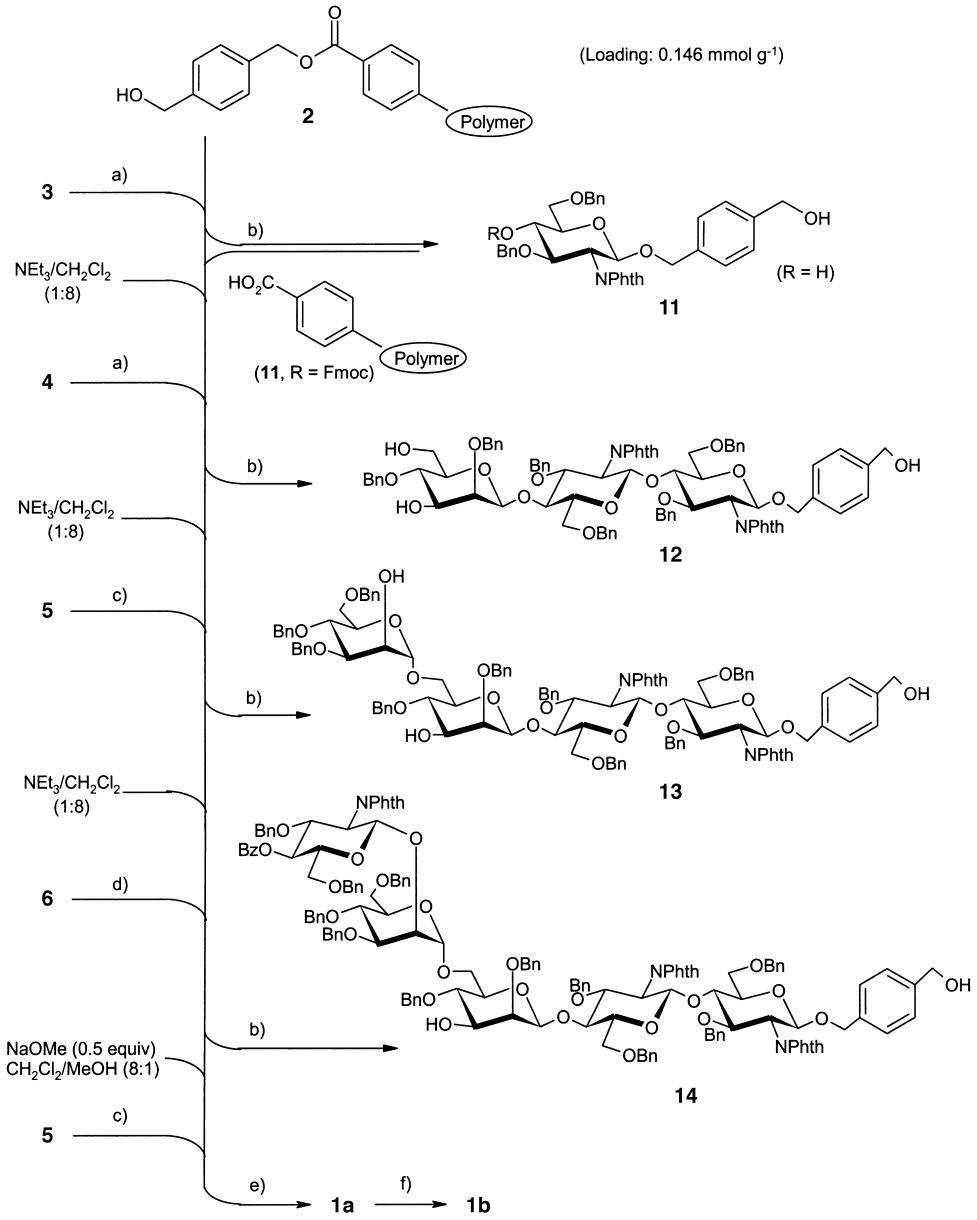

Scheme 4. Synthesis of target molecule **1** on a functionalized solid support **2** with **3**–**6** as glycosyl donors. a) TMSOTf, CH_2Cl_2; b) NaOMe (4 equiv), CH_2Cl_2:MeOH (8:1); c) TMSOTf, CH_2Cl_2:Et_2O (4:1), −20 °C; d) TMSOTf, CH_2Cl_2:MeCN (4:1), −40 °C; e) 1. NaOMe, MeOH (4 equiv); 2. Ac_2O; py; f) 1. $H_2NCH_2CH_2NH_2$, BuOH; 2. Ac_2O, py.

provide also a basis for the development of a generally applicable automated synthesis of oligosaccharides having different glycosidic linkages.

Experimental Section

General procedure for glycosylation: Dry acceptor-loaded resin was directly swollen in a CH_2Cl_2 solution (15 mL g^{-1} resin) containing donor (3 equiv). The resulting suspension was cooled under argon to −20 °C and shaken for 10 min. A solution of a freshly prepared 0.5 M TMSOTf solution in CH_2Cl_2 (0.3 equiv) was added, and shaking was continued for 1 h. The resin was collected by filtration, washed alternately with THF (3 × 15 mL g^{-1} resin) and CH_2Cl_2 (3 × 15 mL g^{-1}) and dried under high vacuum.

General deprotection procedure: Fmoc-cleavage was performed on solid phase according to the procedure previously described.[12b] For PA deprotection dry resin was swollen in CH_2Cl_2 (10 mL g^{-1} resin) and the resulting suspension was shaken under argon for 10 min. A solution of MeONa in MeOH (0.5 equiv; 10 % of the total volume) was added and the resulting mixture was shaken for 10 min, then the resin was collected by filtration and the procedure repeated until the UV spot of the washing solution completely disappeared. Finally, the resin was washed alternately with THF (3 × 15 mL g^{-1} resin) and CH_2Cl_2 (3 × 15 mL g^{-1} resin) and dried under high vacuum.

Cleavage of the products was performed according to the procedure previously described.[12b]

MALDI MS: **11** *m/z* 632.2 [*M*+Na$^+$]; $C_{36}H_{35}NO_8$ (609.67); **12** *m/z* 1446.8 [*M*+Na$^+$]; $C_{84}H_{82}N_2O_{19}$ (1423.55); **13** *m/z* 1880.6 [*M*+Na$^+$]; $C_{111}H_{110}N_2O_{24}$ (1856.06); **14** *m/z* 2454.7 [*M*+Na$^+$]; $C_{146}H_{139}N_3O_{31}$ (2431.67).

1a: MALDI MS: *m/z* 2970.6 [*M*+Na$^+$]; $C_{177}H_{171}N_3O_{38}$ (2948.25); ^{1}H NMR (600 MHz, $CDCl_3$): sugar residue a: $\delta = 4.91$ (d, $^3J_{1,2} = 8.5$ Hz, 1 H, 1-H), 4.15 (2-H) 4.07 (3-H), 4.17 (4-H), 3.24 (5-H), 3.37 (6-H), 3.37 ppm (6-H); sugar residue b: $\delta = 5.20$ (d, $^3J_{1,2} = 8.2$ Hz, 1 H, 1-H), 4.15 (2-H), 4.19 (3-H), 4.00 (4-H), 3.18 (5-H), 3.37 ppm (2 6-H); sugar residue c: $\delta = 4.61$ Hz (dd, $^3J_{1,2} < 1.0$ Hz, 1 H, 1-H), 3.86 (2-H), 3.6 (3-H), 3.84 (4-H), 3.1 (5-H), 3.68, 3.60 ppm (2 6-H); sugar residue d: $\delta = 5.12$ (dd, $^3J_{1,2} <$ 1.0 Hz, 1 H, 1-H) 5.48 (2-H), 3.96 (3-H), 3.82 (4-H), 3.92 (5-H), 3.69 ppm (2 6-H); sugar residue d′: $\delta = 4.49$ (dd, $^3J_{1,2} < 1.0$ Hz, 1 H, 1-H), 4.01 (2-H), 3.69 (3-H), 3.42 (4-H), 3.31 (5-H), 3.17, 2.81 ppm (2 6-H); sugar residue e′: $\delta =$ 4.98 (1-H), 4.34 (2-H), 4.28 (3-H), 5.35 (t, $^3J = 9.4$ Hz, 1 H, 4-H), 3.04 (5-H), 3.42 ppm (2 6-H); ^{13}C NMR (150.9 MHz, $CDCl_3$): sugar residue a: $\delta = 97.1$ (C-1), 56.7 (C-2), 76.3 (C-3), 75.5 (C-4), 74.5 ppm (C-5); sugar residue b: $\delta = 96.7$ (C-1), 55.6 (C-2), 76.8 (C-3), 90.3 (C-4), 74.8 ppm (C-5); sugar residue c: $\delta = 102.4$ (C-1), 77.9 (C-2), 80.9 (C-3), 74.1 (C-4, C-5), 68.9 ppm (C-6); sugar residue d: $\delta =$ 99.5 (C-1), 68.5 (C-2), 78.1 (C-3), 72.4 (C-4), 67 ppm (C-5); sugar residue d′: $\delta = 97.0$ (C-1), 73 (C-2), 76.8 (C-3), 74 (C-4), 72.2 (C-5), 69.6 ppm (C-6); sugar residue e′: $\delta = 97.0$ (C-1), 55.1 (C-2), 76.6 (C-3), 72.7 (C-4), 72.8 (C-5), 69.7 ppm (C-6).

1b: MALDI MS: *m/z* 2706.3 [*M*+Na$^+$]; $C_{159}H_{171}N_3O_{35}$ (2684.1); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 4.62$ (1a-H), 4.36 (1b-H), 4.56 (1c-H), 5.16 (1d-H), 4.80 (1d′-H), 5.00 ppm (1e′-H); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 99.8$ (C-1a), 100.3 (C-1b), 101.7 (C-1c), 99.7 (C-1d), 98.7 (C-1d′), 97.8 ppm (C-1e′).

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First Direct Observation of the Two Distinct Steps in an S_N1 Reaction**

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The differentiation of bimolecular (S_N2) and unimolecular nucleophilic substitutions (S_N1) by Ingold and co-workers marks the beginning of the mechanistic period of organic chemistry.[1] Since then, countless investigations on the rates and products of S_N1 reactions have been performed. A considerable part of our knowledge of the relationships between structure and reactivity of carbocations (R^+), the intermediates of these reactions, has been derived from solvolysis studies[2–5] [Eq. (1)].

$$R{-}Cl \overset{\text{slow}}{\rightleftharpoons} R^+ + Cl^- \xrightarrow[\text{fast}]{\text{SolvOH}} R{-}OSolv + HCl \qquad (1)$$

The discovery by Olah and co-workers that many types of carbocations exist as long-lived species in superacidic solutions, media of low nucleophilicity, allowed the direct observation of carbocations by spectroscopic methods.[6,7]

In recent years, much information on the rates of the reactions of carbocations with nucleophiles,[8,9] including solvents (SolvOH) of S_N1 reactions,[10,11] became available. In agreement with earlier conclusions from solvolysis studies,[12,13] the rates of decay of laser-flash photolytically generated carbocations in 2,2,2-trifluoroethanol (TFE) revealed this alcohol as a weakly nucleophilic solvent.[10] Accordingly, we have now found a first-order rate constant of $12.7 \pm 0.4\ s^{-1}$ for the decay of bis(4-methoxyphenyl)carbenium tetrafluoroborate (**1**-BF_4) in TFE/acetonitrile (91:9 (v/v)) at 20 °C, corresponding to a half-life of 55 ms (Table 1, entry 1). This rate constant is only slightly reduced in the presence of tetra-*n*-butylammonium chloride (nBu_4NCl) (Table 1, entry 2) and remains almost constant as the TFE/CH_3CN ratio is reduced from 91:9 to 20:80 (Table 1, entries 3–5). Entries 6 and 7 in Table 1 indicate that the presence of 0.5 M $NaClO_4$ or $LiClO_4$ does not affect the rate of the reaction of $\mathbf{1}^+$ with TFE.[14]

The ethanolysis rate constant of chlorobis(4-methoxyphenyl)methane (**1**-Cl), that is the rate of the S_N1 reaction in ethanol, has previously been determined as $k = 57\ s^{-1}$ at 25 °C, a million times higher than the ethanolysis rate constant of the parent chlorodiphenylmethane ($5.34 \times 10^{-5}\ s^{-1}$).[15] Since chlorodiphenylmethane, on the other hand, was reported to undergo solvolysis in TFE/water (97:3 (w/w)) with $k = 1.05\ s^{-1}$,[16] we extrapolated an S_N1 reactivity of **1**-Cl in TFE/water (97:3 (w/w)) of $57\ s^{-1} \times (1.05/5.34 \times 10^{-5}) = 1.1 \times 10^6\ s^{-1}$.

The ionization of **1**-Cl in TFE was thus expected to be 10^5 times faster than the reaction of $\mathbf{1}^+$ with this solvent. Since

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