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Study of Interhalogens/Silver Trifluoromethanesulfonate as Promoter Systems for High-Yielding Sialylations

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We have studied interhalogen/silver trifluoromethanesulfonate (IX/AgOTf) promoted glycosylations and found differences in the sensitivity of the formed oxocarbenium ions (e.g. from compounds with or without participating groups) toward halide nucleophiles. These differences can be explained using the HSAB theory. By applying this theory on sialylations, we increased the yield for a model reaction from a highly unpredictable 35-46% using ICl to 74% using IBr. We have also showed that the most prominent role of the silver ions is lowering the concentration of the halide nucleophile rather than activating the interhalogen compound and, by increasing the amount of AgOTf from 1 to 1.5 equiv (with respect to IBr), the yield in the model reaction improved from 74% to 89%. A comparison of two different anomeric leaving groups showed that glycal formation can be minimized using a thiophenyl donor instead of xanthate. By combining these observations, we were able to increase the yield of the model reaction to 97%.

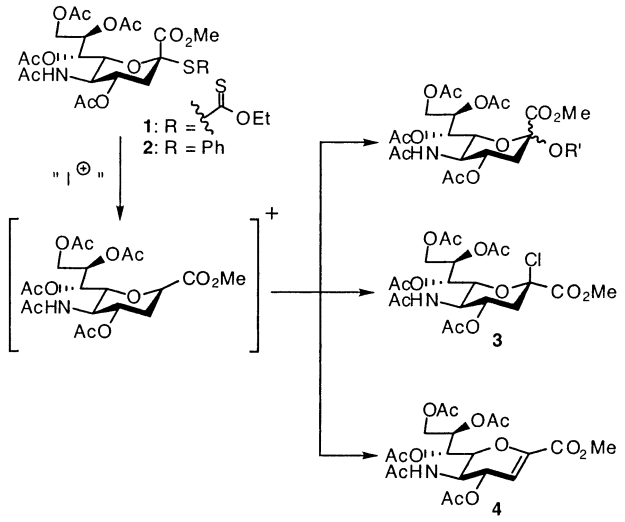
Introduction

The importance of sialic acid containing oligosaccharides and glycoconjugates is reflected in the immense number of different methods for sialylation found in the recent literature.[1] However, despite numerous new methods, no approach has been reported that allows glycosylation of a wide range of acceptors in high yields and stereoselectivities.[1] In a recent paper we presented iodine monochloride/silver trifluoromethanesulfonate (ICl/AgOTf) as a convenient and efficient promoter system for thioglycoside activation,[2] and in a number of glycosylations we demonstrated its capability. ICl/AgOTf, like most promoter systems for thioglycoside activation (e.g. MeSBr/AgOTf or NIS/TfOH),[3] first generates a thiophilic species (i.e. an iodonium ion, "I^+") that activates the sulfur-containing anomeric leaving group to generate an electrophilic oxocarbenium ion (Scheme 1). The ICl/AgOTf system worked well for most glycosylations but gave low yields and unpredictable results upon sialylation (Scheme 2 and Table 1; entry 1). This paper describes mechanistic details and optimization of interhalogen/silver trifluoromethanesulfonate promoted sialylations.

Results and Discussion

To investigate why sialic acid donor **1**[4] performed poorly under ICl/AgOTf promoted conditions,[2] we conducted an NMR experiment which indicated that the donor is activated and consumed within 1 h, forming

SCHEME 1. Activation and Reaction Pathway for Sialic Acid Thio Donors Using ICl/AgOTf



glycoside **6**, sialic acid glycal **4**,[5] and, more surprisingly, sialic acid chloride **3**[5] (Scheme 1).

To examine if sialic acid chloride **3** is a stable byproduct or a slowly reacting intermediate, we synthesized the chloride **3** and subjected it to AgOTf under standard sialylation conditions (Table 1; entries 7 and 8). No disaccharide **6** could be isolated from the reaction mixture; only acceptor **5** and sialic acid chloride **3** together with decomposed donor in the form of sialic acid glycal **4** were recovered.

The formation of the chloride **3**, despite an equimolar amount of silver ions added,[6] indicates that sialylation

(1) Boons, G. J.; Demchenko, A. V. *Chem. Rev.* **2000**, *100*, 4539.
(2) Ercegovic, T.; Meijer, A.; Magnusson G.; Ellervik, U. *Org. Lett.* **2001**, *3*, 913.
(3) (a) Veeneman, G. H.; Van Leeuwen, S. H.; Van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331. (b) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1988**, *177*, C13.
(4) Marra, A.; Sinay, P. *Carbohydr. Res.* **1989**, *187*, 35.
(5) Byramova, N. E.; Tuzikov, A. B.; Bovin, N. V. *Carbohydr. Res.* **1992**, *237*, 161 and references therein.

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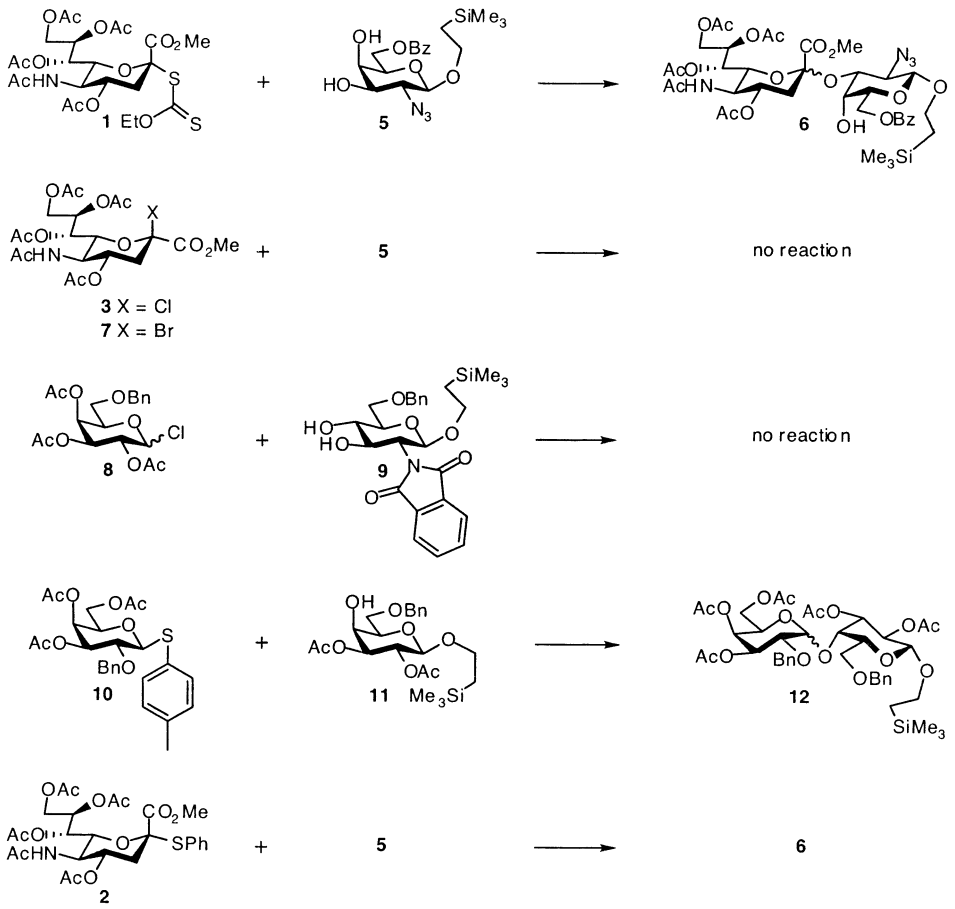
SCHEME 2[a]



[a] Reaction conditions are given in Table 1.

TABLE 1. Reaction Data for Schemes 2 and 3

entry	donor	acceptor	IX	mole ratio[a]	reaction conditions[b]	product[c]	yield (%)
1	**1**[4]	**5**[12]	ICl	1.5:1.0:1.5:1.5	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**6**	35−46
2	**1**	**5**	IBr	1.5:1.0:1.5:1.5	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**6**	74
3	**1**	**5**	I_2	1.5:1.0:1.5:1.5	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**6**	67
4	**1**	**5**	IBr	1.5:1.0:2.0:3.0	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**6**	89
5	**1**	**5**	ICl	1.5:1.0:1.5:−	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**6**	0[d]
6	**1**	**5**	IBr	1.5:1.0:1.5:−	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**6**	0[d]
7	**3**[5]	**5**	ICl	1.5:1.0:1.5:1.5	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h		0
8	**3**	**5**		1.5:1.0:−:1.5	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h		0
9	**7**[5]	**5**		1.5:1.0:−:1.5	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h		0
10	**8**[13]	**9**[14]		1.3:1.0:−:3.0	1:2 MeCN−CH_2Cl_2, −72°C, 1 h		0
11	**10**[15]	**11**[15]	ICl	1.3:1.0:1.3:1.3	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**12**[15]	0[d]
12	**10**	**11**	IBr	1.3:1.0:1.3:1.3	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**12**	35
13	**2**[11]	**5**	ICl	1.5:1.0:1.5:1.5	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**6**	50
14	**2**	**5**	IBr	1.5:1.0:1.5:1.5	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**6**	87
15	**2**	**5**	IBr	1.5:1.0:2.0:3.0	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**6**	97
16	**1**	**13**[25]	IBr	3.0:1.0:3.2:6.0	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**14**	43
17	**1**	**15**[31]	IBr	1.5:1.0:2.0:3.0	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**16**[32]	75
18	**2**	**13**	IBr	3.0:1.0:3.2:6.0	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**14**	44
19	**2**	**15**	IBr	1.5:1.0:2.0:3.0	3:2 MeCN−CH_2Cl_2, −72 °C, 2 h	**16**	88

[a] Donor:acceptor:IX:AgOTf. [b] Solvents and molecular sieves were dried and activated, respectively, using conventional methods. [c] NMR data were in agreement with those reported in the literature. [d] Only trace amounts of disaccharidic product isolated.

using interhalogens is a more complex reaction than we originally anticipated. We suggest that a polyhalide ion, ICl_2^-, which can be formed from Cl^- reacting with ICl,[7,8] is the actual chloride nucleophile. The ICl_2^-, generated through the dissociation of ICl in MeCN,[9] does not form a precipitate of AgCl when subjected to AgOTf. Instead, UV spectroscopy showed a lowered concentration of ICl_2^-,

(6) Luehrs, D. C.; Iwamoto, R. T.; Kleinberg, J. J. *Inorg. Chem.* **1966**, *5*, 201.
(7) (a) Popov, A. I.; Pflaum, R. T. *J. Am. Chem. Soc.* **1957**, *79*, 570. (b) Faull, H. J. *J. Am. Chem. Soc.* **1934**, *56*, 522.
(8) Popov, A. I.; Swensen, R. F. *J. Am. Chem. Soc.* **1955**, *77*, 3724.
(9) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*; Pergamon Press: Oxford, U.K., 1997; p 824.

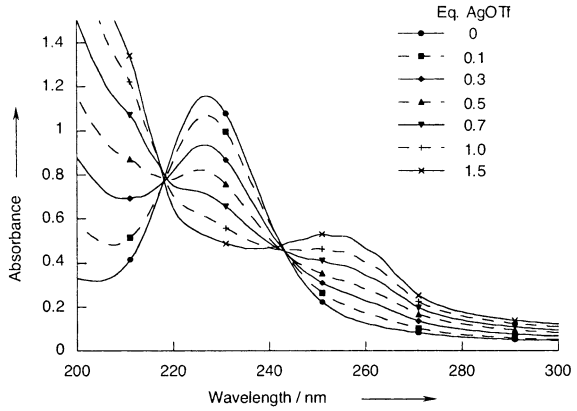


FIGURE 1. Plot showing the absorption spectra of an ICl solution titrated with AgOTf. The absorption maximum at 227 nm is the characteristic peak of ICl_2^-.[8]

indicating the formation of a soluble complex between silver ions and ICl_2^- (Figure 1).

To further demonstrate the nucleophilicity of an ICl solution, we performed a simple NMR experiment where methyl iodide (MeI) and ICl were dissolved in deuterated acetonitrile. Without silver ions present, the formation of methyl chloride is reasonably fast, having second-order reaction kinetics with respect to MeI and ICl (Figure 2a). When 0.5 equiv of AgOTf is added, the reaction slows down and proceeds with more complex reaction kinetics (Figure 2b).

Once we isolated the problem to interfering chloride nucleophiles, we turned our attention to the more intriguing question of why some glycosylations work well whereas sialylations may be inferior, when using ICl/AgOTf.[2]

Since the donors that performed well (i.e. did not form glycosyl chlorides) with the ICl/AgOTf system all carried a participating group and the sialic acid donor **1** did not,[2] we now hypothesized that the interaction of the participating groups with the anomeric position of the donor influenced the reaction outcome. The interaction might result in one of the following scenarios: (i) the glycosyl chloride formed from a donor carrying a participating group is activated under these reaction conditions or (ii) glycosyl donors carrying a participating group are less prone to be transformed into chlorides.

To examine scenario i, i.e., if glycosyl chlorides are reactive intermediates, chloride donor **8**[13] was mixed with AgOTf and acceptor **9**[14] (Table 1; entry 10). The thio equivalent of donor **8** is capable of glycosylating acceptor **9** using ICl/AgOTf at the same temperature.[2] However, no product was obtained, implying that this donor carrying a participating group is not activated under these reaction conditions (−72 °C).[13] Then, to examine whether the absence of participating groups influence the

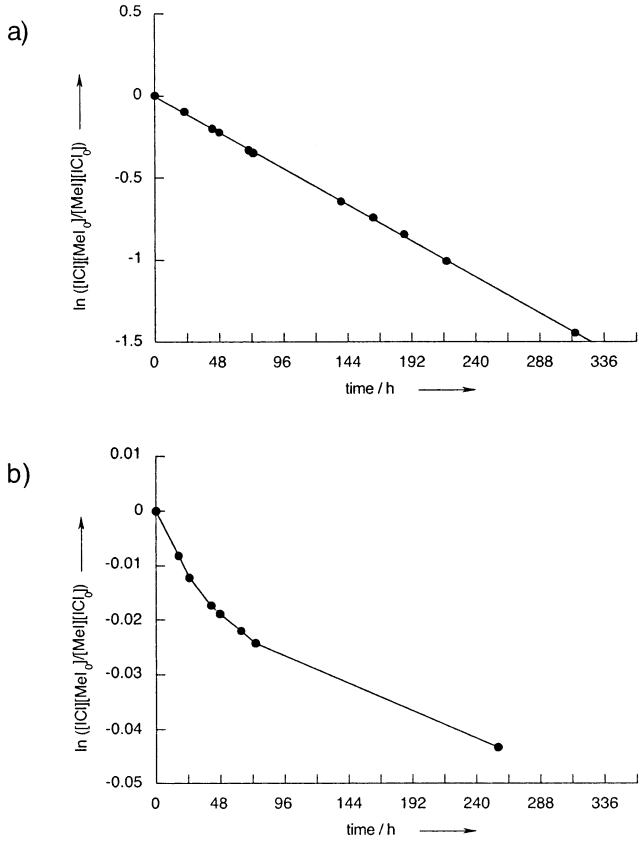


FIGURE 2. (a) Plot showing second-order reaction kinetics for the nucleophilic substitution of MeI using ICl. (b) Plot showing slower rate and more complex reaction kinetics when 0.5 equiv of AgOTf is added.

reaction outcome on sugars other than sialic acid, we subjected the sulfide donor **10**[15] to the ICl/AgOTf promoter system. This reaction gave no disaccharidic product but, instead, the corresponding chloride[16] in addition to recovered acceptor **11**[15] (Table 1; entry 11).

In summary, the absence of a participating group makes the activated donor more reactive toward the competing reaction with nucleophilic chloride species, forming a stable sugar halide and thereby lowering the total yield of the reaction.

The explanation for the differences in chloride affinities might be that the oxocarbenium ion formed on activation of the donor without a participating group is a *hard* electrophile (Figure 3a), well-matched to the chloride nucleophile.[17] In comparison, the *softer* acyloxonium ion formed by a participating group (Figure 3b) will interact less with the *hard* chloride nucleophile. The possibility for some delocalization by interaction with the ester functionality (Figure 3c)[18] renders the sialic acid less *hard* than a standard glycoside without a participating group.[19]

The different selectivities of donors with or without participating groups have been noted by others. Fraser-

(10) Boons, G. J. *Carbohydrate Chemistry*; Blackie Academic: London, 1998; p 139.
(11) Kirchner, E.; Thiem, F.; Dernick, R.; Heukeshoven, J.; Thiem, J. *J. Carbohydr. Chem.* **1988**, *7*, 453.
(12) Wilstermann, M.; Kononov, L. O.; Nilsson, U.; Ray, A. K.; Magnusson, G. *J. Am. Chem. Soc.* **1995**, *117*, 4742.
(13) Donor **8** has been used in a glycosylation reaction with AgOTf as promoter, albeit at a higher temperature (−45 °C to room temperature): Pozsgay, V.; Trinh, L.; Shiloach, J.; Robbins, J. B.; Donohue-Rolfe, A.; Calderwood, S. B. *Bioconjugate Chem.* **1996**, *7*, 45.
(14) Ellervik, U.; Magnusson, G. *Carbohydr. Res.* **1996**, *280*, 251.
(15) Wilstermann, M.; Balogh, J.; Magnusson, G. *J. Org. Chem.* **1997**, *62*, 3659.
(16) Kovác, P. *J. Carbohydr. Chem.* **1992**, *11*, 999.
(17) Hevesi, L. *Phosphorus, Sulfur Silicon Relat. Elem.* **2001**, *171*, 55.
(18) Horenstein, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 1101.
(19) Ho, T. *Chem. Rev.* **1975**, *75*, 1.

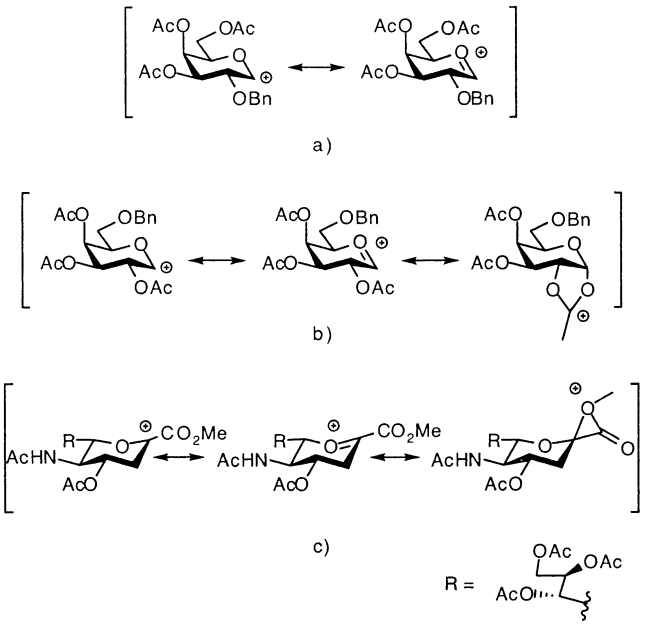


FIGURE 3. (a) Possible stabilization of an activated glycosyl donor by resonance. (b) Possible stabilization of an activated glycosyl donor by resonance and formation of an acyloxonium ion. (c) Possible stabilization of an activated sialic acid donor by resonance and interactions with the ester functionality.

Reid reported a glycosylation reaction where the prescence or absence of a participating group on the donor controlled the regioselectivity. The selectivity could not be explained by purely steric factors. Instead, a model describing the electronic properties of the carbocations (depicted as *Diffuse* and *Compact*) was used to explain the reaction outcome.[20]

One way to minimize the unwanted interactions would be to change the promoter system to IBr or I_2/AgOTf, thus changing the nucleophilic species from chloride to the *softer* bromide or iodide, which would interact less with the electrophile.

Indeed, glycosylation of acceptor **11** with the *hard* donor **10**, using the *softer* promoter system IBr/AgOTf, this time yielded disaccharide **12** (Table 1; entry 12).[21] Sialylation of acceptor **5** with donor **1** using IBr/AgOTf produced **6** in the improved yield of 74% (Table 1; entry 2), whereas I_2/AgOTf gave a somewhat lower yield of 67% (Table 1; entry 3) together with unactivated donor, indicating the low reactivity of molecular iodine. These results are in full agreement with the reactivity order of the interhalogens that has been thoroughly investigated by Field and established as ICl > IBr > I_2.[22] To prove that the increased yield in the IBr promoted reaction is not due to the transformation of sialic acid bromide **7**[5] to disaccharide **6** by the action of silver ions,[23] bromide **7** was synthesized and mixed with AgOTf and acceptor **5** at −72 °C (Table 1; entry 9). No product **6** was formed; i.e., the increased yield is due to less interaction between the bromide ion and the carbocation.

To investigate the role of silver ions, we found ICl so reactive that it can partly activate the sialic acid donor **1** under our sialylation conditions even without silver present (Table 1; entry 5).[24] However, only traces of disaccharidic product were detected, with sialic acid glycal **4** and chloride **3** as major products, indicating the importance of silver ions in lowering the concentration of competing chloride nucleophiles. IBr is also capable of activating xanthate donor **1** under the same conditions, but less donor is consumed after the same reaction time (Table 1; entry 6). Molecular iodine is too unreactive and not capable of activating all donor **1** even with silver present (Table 1; entry 3).

Logically, an increase of the silver ion concentration would lower the amount of the halide nucleophile and thereby increase the yield of the sialylation. Indeed, when the amount of AgOTf is increased from 1 to 1.5 equiv (with respect to IBr), the yield in the model reaction improved from 74% to 89% (Table 1; entry 4) without even trace amounts of sialic acid bromide **7**.[25]

In addition to formation of sialic acid halides, sialic acid glycal **4** is also formed as a byproduct in the reaction. To evaluate the importance of the leaving group on the formation of different byproducts, and to confirm its redundancy in the interaction between interhalogen nucleophiles and activated sialic acid species, we subjected sialic acid thiophenyl donor **2**[11] to IX/AgOTf conditions (Table 1; entries 13 and 14). The xanthate donor **1** is usually considered as a more powerful donor in sialylations,[26] but to our surprise we obtained better yields using the thiophenyl donor: 50% vs 35−46% using ICl and 87% vs 74% using IBr.

To learn more about the reactions, we perfomed a study of the reaction kinetics. Small-scale reactions were conducted and stopped at different times (using cyclohexene and diisopropylamine) and then analyzed by NMR. Interestingly, the xanthate donor seems to follow a faster initial reaction rate than the thiophenyl donor. After 1 min 50% of the xanthate donor is consumed, compared to 15% of the thiophenyl donor (Figure 4). However, while the thiophenyl donor is consumed in about 10 min, the activation of the xanthate donor slows down and trace amounts of unreacted donor can be isolated even after 1 h.[27] We therefore speculate that the higher yield using the thiophenyl donor compared to the xanthate donor is due to the different rates of consumption (i.e. formation of reactive species). The fast initial activation of the xanthate donor gives rise to a higher

(20) (a) Anilkumar, G.; Nair, L. G.; Fraser-Reid, B. *Org. Lett.* **2000**, *17*, 2587. (b) Fraser-Reid, B.; Lopez, J. C.; Radhakrishnan, K. V.; Mach, M.; Schlueter, U.; Gomez, A. M.; Uriel, C. *J. Am. Chem. Soc.* **2002**, *124*, 3198.

(21) The yield has increased from 0% (ICl) to 35% (IBr) but is still modest. We wish to point out that the reaction conditions are not optimized but chosen for best comparison with other glycosylations reported in this paper.

(22) Cura, P.; Aloui, M.; Kartha, K. P. R.; Field, R. A. *Synlett* **2000**, *9*, 1279.

(23) Paulsen, H.; Von Deessen, U. *Carbohydr. Res.* **1988**, *175*, 283.

(24) Field has successfully used the interhalogens as promoters without the aid of AgOTf. However these glycosylation reactions were carried out at higher temperatures (−10 °C): (a) Kartha, K. P. R.; Field, R. A. *Tetrahedron Lett.* **1997**, *38*, 8233. (b) Kartha, K. P. R.; Aloui, M.; Field, R. A. *Tetrahedron Lett.* **1996**, *37*, 5175.

(25) We have been unable to isolate sialic acid bromide **7** due to its instability and subsequent decomposition to glycal **4**. However, we have been able to isolate the ethyl sialoside formed from the reaction between sialic acid bromide **7** and EtOH from the purification system at workup.[33]

(26) (a) Birberg, W.; Lönn, H. *Tetrahedron Lett.* **1991**, *32*, 7453. (b) Marra, A.; Sinaÿ, P. *Carbohydr. Res.* **1990**, *195*, 303.

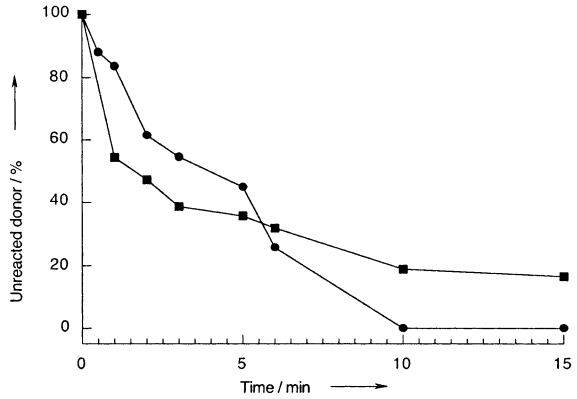


FIGURE 4. Plot showing the amount of unreacted donor left in the reaction mixture as a function of time: (−■−) xanthate donor **1**; (−●−) thiophenyl donor **2**.

concentration of oxocarbenium ions, which we believe explains the higher proportion of sialic acid glycal using this donor.

As a final experiment, we subjected the thiophenyl donor to the higher silver ion concentrations and, indeed, increased the yield of the model reaction from 89% to 97% (Table 1; entry 15).

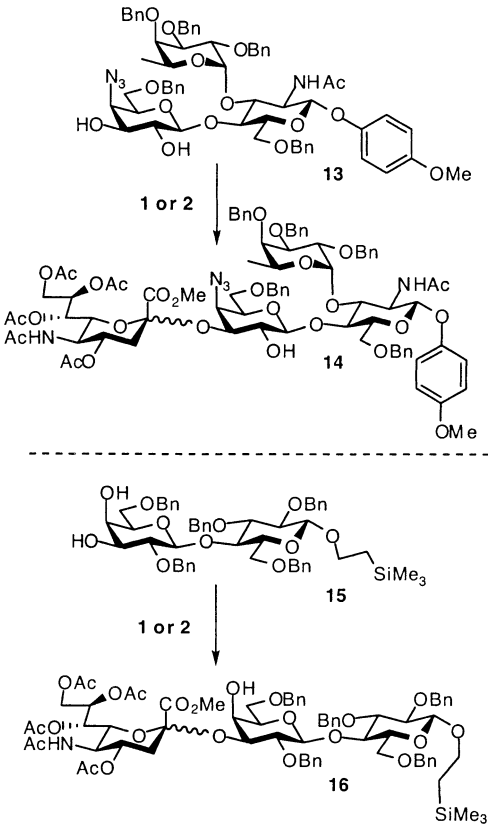
Two more acceptors were sialylated in order to prove the usefulness of the new promoter system. The challenging acceptor **13**[31] was sialylated using 3 equiv of donor **1** or **2** in excellent yields of 43% and 44%, respectively, with an α:*β*:lactone ratio of 66:17:17 (Scheme 3 and Table 1; entries 16 and 18). Prior attempts to sialylate acceptor **13** with donor **1** using MeSBr/AgOTf gave no product.[31] The lactose acceptor **15**[32] was sialylated in 75% and 88% yields (α:*β* 95:5) using 1.5 equiv of xanthate donor **1** or thiophenyl donor **2** (Table 1; entries 17 and 19).[30]

Conclusion

To summarize, we have investigated interhalogen/silver trifluoromethanesulfonate (IX/AgOTf) promoted sialylation reactions. We conclude that formation of sialic acid halide and sialic acid glycal are the two major causes for low yields in the reaction.

We have shown that the interactions of oxocarbenium ions, formed from different carbohydrate donors, with

SCHEME 3[a]



[a] Reaction conditions are given in Table 1.

nucleophilic halide species in the glycosylation reaction follow the predictions of the HSAB theory,[19] which isessentially a new concept in synthetic carbohydrate chemistry.

The halide formation can be minimized by using IBr instead of ICl, and we present IBr/AgOTf as a convenient and efficient promoter system for high-yielding sialylation reactions. Our investigations, which include some mechanistic details of the reaction, have also shown that the most prominent role of the silver ions is lowering the concentration of halide nucleophile rather than activating the interhalogen compound. This opens the door to future investigations using other halophiles.

Formation of sialic acid glycal can be minimized by using a thiophenyl donor with a slower initial reaction rate than the corresponding xanthate donor. By a combination of these findings, we were able to increase the yield of the model reaction from 46% to 97%.

The stereoselectivities for the ICl-, IBr-, and I_2-promoted sialylations of acceptor **5** (α:*β* 8:1) were virtually identical (Table 1; entries 1−4 and 13−15), and the α/*β* selectivity for the sialylation of lactose acceptor **15** using IBr as promoter (Table 1; entries 17 and 19) is comparable to published results, using PhSCl/AgOTf as promoter.[30] This suggests that the choice of leaving group and thiophilic species in the promoter system is of minor importance for the stereochemical outcome of the glycosylation.[34]

(27) We have been able to isolate dixantogen[28] (the disulfide of ethyl xanthate) and phenyl disulfide[29] in the respective donor reaction mixtures. The isolation of disulfides indicates that an electrophilic sulfur species is present in the reaction mixture.[30] We postulate that the species responsible is the sulfenyl iodide formed from the reaction between iodonium ion (from IX/AgOTf) and thio donor.[3a] Thus, the role of the sulfur leaving group is not only to be reactive enough to be activated by the thiophilic species but also to form a "second" thiophilic species in the reaction mixture. These findings might explain the different consumption patterns of the xanthate and thiophenyl donor seen in Figure 4. Further investigations regarding the kinetics of iodonium-promoted activation of thioglycosides are in progress.

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(30) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702.

(31) Ellervik, U.; Grundberg, H.; Magnusson, G. *J. Org. Chem.* **1998**, *63*, 9323.

(32) Jansson, K.; Ahlfors, S.; Frejd, T.; Kihlberg, J.; Magnusson, G. *J. Org. Chem.* **1988**, *53*, 5629.

(33) van der Vleugel, D. J. M.; van Heeswijk, W. A. R.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1982**, *102*, 121.

Experimental Section

NMR spectra were recorded at 300 or 400 MHz. ^{1}H NMR spectra were assigned using 2D methods (COSY, HETCOR, long-range HETCOR). Chemical shifts are given in ppm downfield from the signal for Me_4Si, with reference to residual $CHCl_3$. Reactions were monitored by TLC using alumina plates coated with silica gel 60 F254 (Merck) and visualized either by using UV light or by charring with H_3PO_4 (aqueous 5% dip solution). Preparative chromatography was performed with Amicon silica gel (35−70 μm, 60 Å). MeCN and CH_2Cl_2 used in glycosylation reactions were stirred overnight with CaH_2 and distilled immediately before use. ICl and IBr are commercially available as 1 M solutions in CH_2Cl_2. The I_2 solution was prepared as follows: molecular iodine was purified by sublimation and dissolved in CH_2Cl_2 and MeCN (2:3). Due to low solubility the concentration was about 0.2 M. Additional purifications of reaction mixtures were performed on a Sephadex LC-20 column (diameter 1.5 cm, height 1 m) using 1:1 CH_2Cl_2−MeOH as the mobile phase.

Precipitation Experiments. To a solution of 26 mg of AgOTf in 2 mL of MeCN was added 0.10 mL of ICl at room temperature. AgCl precipitation occurred only when a Lewis base such as pyridine or xanthate donor **1** was added. The experiment was repeated using MeCN−CH_2Cl_2 (3:2) both at room temperature and at −72 °C, with similar results.

Titration Experiments. A 1 mL amount of a 0.1 mM solution of ICl in MeCN was titrated with a 10 mM solution of AgOTf in MeCN. Spectroscopic data were obtained using a Varian Cary 300 Bio UV−vis spectrophotometer.

NMR Experiments. All spectroscopic data were obtained using a Bruker DRX300 spectrometer at 300 MHz. We chose to plot the ICl concentration (calculated from $[ICl]_0$ and Δ[MeCl]), which is directly proportional to the ICl_2^- concentration.

Figure 2a: to 0.7 mL of CD_3CN in an NMR tube was added 4 μL of MeI and 0.13 mL of ICl. Figure 2b: to 0.5 mL of CD_3CN and 12.8 mg of AgOTf in an NMR tube, protected from light, was added 5 μL of MeI and 0.10 mL of ICl.

Representative Procedure for the Sialylation Reactions. To a stirred solution of **5** (50 mg, 0.122 mmol), **1** (109 mg, 0.183 mmol), and powdered activated molecular sieves (3A, 150 mg) was added CH_2Cl_2 (1.6 mL) and a solution of AgOTf (94 mg, 0.367 mmol) in MeCN (2.4 mL). The reaction mixture was cooled to −72 °C under an argon atmosphere, and a solution of IBr (1.0 M in CH_2Cl_2, 0.244 mL, 0.244 mmol) was added dropwise after 15 min. The reaction mixture was stirred for 2 h at −72 °C, and then diisopropylamine (0.20 mL, 1.4 mmol) was added and stirring was continued for another 20 min. The reaction mixture was then filtered (SiO_2, 25:1−10:1 toluene−EtOH) and concentrated under reduced pressure. The residue was purified on Sephadex (LH-20, 1:1 CH_2Cl_2−MeOH) to give **6** (96 mg, 89%, 8:1 α:β). Compound **6** was acetylated using standard conditions; the product obtained is identical with that reported in the literature.[12]

Reaction Kinetics. The reactions were carried out as described in the general procedures, with the following alterations: the reactions were carried out in 5 mL test tubes on a small scale (0.75 mL of solvent). The IBr solution was added in a single portion in order to simplify the time measuerement. The reaction was quenched by addition of a CH_2Cl_2−cyclohexene−diisopropylamine (2:1:1) solution at −72 °C and then immediately filtered (SiO_2) and concentrated. The residue was dissolved in CH_2Cl_2 and the solution was washed twice with acidified water (H_2SO_4, pH 2) and once with water and then concentrated.

The amount of unreacted donor was determined from the NMR spectra of the reaction mixtures, with the TMS signal from the acceptor/products serving as an internal standard.

Synthesis of 4-Methoxyphenyl (Methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosyl)onate)-(1→3)-(4-azido-6-*O*-benzyl-4-deoxy-β-D-galactopyranosyl)-(1→4)-[2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl]-(1→3)-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside) (14). Compound **14** was synthesized according to the representative procedure using the molar ratios given in Table 1. Compound **14** was obtained in 43% and 44% yields as a 66:17:17 mixture of the α and β diastereomers together with lactonized product. Unfortunately the β and lactonized products were inseparable and no characterization (and subsequently the anomeric configuration of the lactone product was not determined) except HRMS was possible. The α product, however, was obtained as a pure sample and was characterized as follows.

14-α: $[\alpha]^{20}_D = -34.0°$ (*c* 0.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.15−7.40 (m, 25 H), 6.70−6.92 (m, 4 H), 5.95 (d, 1 H, J = 7.6 Hz), 5.40−5.47 (m, 1 H), 5.30−5.34 (m, 2 H), 5.20 (d, 1 H, J = 9.7 Hz), 5.13 (d, 1 H, J = 3.5 Hz), 4.94−5.01 (m, 1 H), 4.95, 4.63 (ABq, 1 H each, J = 11.6 Hz), 4.87, 4.69 (ABq, 1 H each, J = 11.8 Hz), 4.70−4.75 (m, 2 H), 4.58 (d, 1 H, J = 7.6 Hz), 4.45−4.53 (m, 2 H), 4.35−4.46 (m, 2 H), 4.35−4.40 (m, 1 H), 4.29 (t, 1 H, J = 8.0 Hz), 4.25 (dd, 1 H, J = 12.6, 2.7 Hz), 4.17 (dd, 1 H, J = 10.7, 1.8 Hz), 3.85−4.15 (m, 7 H), 3.66−3.80 (m, 5 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.51−3.60 (m, 4 H), 3.11 (s, 1 H), 2.70 (dd, 1 H, J = 13.2, 4.6 Hz), 2.06−2.14 (m, 1 H), 2.10, 2.10, 2.03, 1.97, 1.90, 1.71 (s, 3 H each), 1.11 (d, 3 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 171.30, 170.91, 170.71, 170.54, 170.39, 170.23, 168.55 (C-1‴, $J_{C-1''':H-3'''ax}$ = 6.9 Hz), 155.56, 151.87, 139.21, 139.15, 139.13, 139.01, 138.19, 128.96, 128.87, 128.83, 128.74, 128.61, 128.57, 128.40, 128.29, 128.22, 127.97, 127.91, 127.69, 127.66, 127.62, 119.16, 114.80, 101.82, 99.60, 98.33, 97.91, 75.32, 75.11, 74.57, 74.36, 74.28, 73.77, 73.25, 73.16, 72.95, 71.21, 70.51, 69.26, 68.77, 68.56, 68.27, 67.37, 67.17, 62.61, 60.95, 56.05, 53.52, 50.06, 38.05, 23.73, 23.63, 21.57, 21.28, 21.24, 21.18, 21.11, 17.11; HRMS calcd for $C_{82}H_{97}N_5O_{27}$Na (M + Na) 1606.6269, found 1606.6274.

14-β: HRMS calcd for $C_{82}H_{97}N_5O_{27}$Na (M + Na) 1606.6269, found 1606.6274.

14-lactone: HRMS calcd for $C_{81}H_{93}N_5O_{26}$Na (M + Na) 1574.6006, found 1574.6058.

Methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-β-D-galacto-2-nonulopyranosyl)onate Bromide (7). An anomeric mixture of methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-D-glycero-D-galacto-2-nonulopyranosonate (120 mg, 0.225 mmol) was dissolved in HOAc (2 mL); Ac_2O (1 mL) was added, followed by HBr−HOAc (2 mL, 30% w/v). The mixture was stirred at room temperature for 1.5 h and then lyophilized to remove solvent and excess HBr. The yellowish residue was filtered on a Sephadex LC-20 column (diameter 1.5 cm, height 10 cm) using acetone as the mobile phase and then concentrated without heating to yield a transparent oil consisting of bromide **7** and glycal **4** (3:2). Due to the instability of bromide **7** (eliminates to glycal **4** upon storage and handling) the mixture was used immediately in sialylation reactions.

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Supporting Information Available: NMR spectrum of compound **14**-α. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) The counterion (in this case the triflate ion) is capable of influencing the stereochemical outcome, as shown by Crich: Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291.