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Note

NMR evidence for the participation of triflated ionic liquids in glycosylation reaction mechanisms

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Abstract—A systematic low-temperature NMR study of a glycosylation reaction was performed in the presence of different ionic liquids and acidic catalysts. The influence of the triflate anion derived from [emim][OTf] on the stereochemistry of the glycosylation products was evaluated.

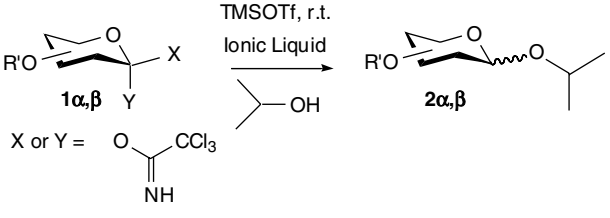
Keywords: Ionic liquids; Glycosylation; Low-temperature NMR

The growing awareness of the multiple biological functions of carbohydrates over the past 30 years[1] has stimulated the development of numerous glycosylation protocols.[2] However, influencing the reaction course towards a unique anomeric product still often requires a demanding effort in regulating coupling conditions and protecting group pattern,[3] because these reactions proceed through many possible intermediates, the most common one being an oxocarbenium ion.[4]

We recently described the effectiveness and scope of a glycosylation reaction using trichloroacetimidate donors in ionic liquids (ILs).[5] The reaction conditions were mild and the ILs could be recycled while retaining the catalytic properties of the Lewis acid. Interestingly, when performed in [emim][OTf] with trichloroacetimidates bearing non-participating groups on O-2, the reaction afforded glycoside products without the need for an acidic catalyst. Moreover, the β-glycoside was obtained as the major product, even in the absence of the anchimeric assistance of the protecting group on O-2.

We have subsequently performed a systematic study on 2,3,4,6-tetra-*O*-benzyl glucose trichloroacetimidates **1α,β**, which contain a non-participating group on O-2, by comparing their glycosylation properties in a classical solvent (dichloromethane) and ILs composed of both a coordinating and a non-coordinating anion (Scheme 1 and Table 1).[6] Our results, supported by low-temperature ^{1}H NMR experiments, assessed the influence of [emim][OTf] on the stereochemical outcome of the reaction through the formation of a transient α-glycosyl triflate, which shields the α-face of the oxonium ion and biases the attack of the acceptor from the β-face.

Very little is known about the influence of ILs in reaction mechanisms and only few papers have appeared in the literature describing investigations of reaction mechanisms in ILs, and in particular by NMR spectroscopy.[7]



Scheme 1. Glycosylation of isopropanol with α- and β-trichloroacetimidates.

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Table 1. Glycosylation of isopropanol with α- and β-2,3,4,6-tetra-*O*-benzyl glucopyranose trichloroacetimidates **1** in different solvents[a]

Entry	Donor	Solvent	Product	Yield (%)	α/β Ratio[b]
1	**1α**	CH_2Cl_2	**2α,β**	85	16/84
2		[emim][OTf]		67	16/84
3		[emim][OTf][c]		79	15/85
4		CH_2Cl_2/ [emim][OTf] 1:1		65	25/75
5		[bmim][PF_6]		98	18/82
6	**1β**	CH_2Cl_2	**2α,β**	86	70/30
7		[emim][OTf]		Quant.	45/55
8		[emim][OTf][c]		85	20/80
9		CH_2Cl_2/ [emim][OTf] 1:1		72	54/46
10		[bmim][PF_6]		98	76/24

[a] All reactions were carried out with 20 equiv of isopropanol, 0.01 equiv of TMSOTf in 0.5 mL of solvent at room temperature.
[b] Determined by NMR spectroscopy.
[c] Reaction performed without Lewis acid catalysis.

Table 2. Low-temperature NMR experiments[a]

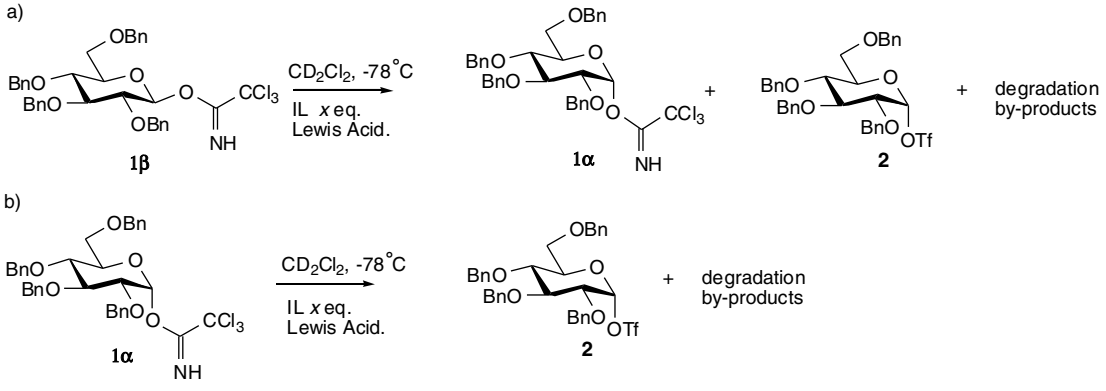
Exp. #	Donor	Ionic liquid (equiv)[b]	Lewis acid (equiv)[c]
1a	**1α**	[emim][OTf] (1.0)	TMSOTf (0.01)
1b	**1β**	[emim][OTf] (0.6)	TMSOTf (0.01)
2a	**1α**	[bmim][PF_6] (1.8)	TMSOTf (0.03)
2b	**1β**	[bmim][PF_6] (1.6)	TMSOTf (up to 0.26)
3a	**1α**	—	TMSOTf (0.2)
3b	**1β**	—	TMSOTf (0.1)
4a	**1α**	[emim][OTf] (1.6)	$BF_3{\cdot}Et_2O$ (0.45)
4b	**1β**	[emim][OTf] (1.4)	$BF_3{\cdot}Et_2O$ (0.45)

[a] In a typical experiment, the donor was dissolved in CD_2Cl_2 in an NMR tube together with the IL (except entries 3a and 3b) and cooled to −78 °C. The Lewis acid was subsequently added at the same temperature and the NMR spectra were recorded at regular time intervals.
[b] The exact amount of the IL was ascertained through integration of the signals of the H-2 of the IL and of the N*H* of the donor before addition of the Lewis acid.
[c] The exact amount of Lewis acid was determined through the integration of $Si(CH_3)_3$ signal for TMSOTf and of $(CH_3CH_2)_2O$ signal for $BF_3{\cdot}Et_2O$.

Therefore, we describe here a more detailed study on the possible intermediates generated upon acidic activation of glycosyl donors **1α,β** in the solvents reported in Table 1, using low-temperature NMR spectroscopy.

The ^1H NMR experiments were performed as outlined in Scheme 2 and Table 2. Donor **1α** or **1β** was dissolved in CD_2Cl_2 together with the IL (except Experiments 3a and 3b) and the sample was cooled to −78 °C. The exact amount of the IL was calculated by integration of NH of the donor and H-2 of the IL. The acidic catalyst was subsequently added at the same temperature and the NMR spectra were recorded at regular time intervals. Experiment 1b revealed that **1β** (H-1, doublet at 5.74 ppm, $J = 7.4$ Hz; NH, singlet at 8.83 ppm) was converted within 30 min to glucosyl imidate **1α** (H-1, broad doublet at 6.40 ppm, $J = 3.4$ Hz; NH, singlet at 8.71 ppm) and to the α-glucosyl triflate, whose chemical shift (a doublet at δ 6.16 ppm with $J = 2.9$ Hz) was consistent with the data reported in the literature (Fig. 1a and b).[8] No peak corresponding to the β-glucosyl triflate was detected during the experiment. The peaks corresponding to **1α** and to the α-glucosyl triflate disappeared after 40 and 100 min, respectively, affording degradation by-products. The same experiment was performed with donor **1α** (Table 2, Experiment 1a), which, on the contrary, gave a sluggish reaction. The H-1 peak intensity decreased slowly and only a small amount of the α-triflate was generated.

In a subsequent experiment, an IL with a non-coordinating anion was used, under similar conditions (0.03 equiv of TMSOTf, Experiments 2a,b). In this way, we hoped to detect any alternative intermediate that could explain the inversion of the anomeric configuration in the products observed in this IL (Table 1, entries 5 and 10). Under these conditions, the reaction of donor **1α**, as well as of donor **1β**, was very slow and no formation of the anomeric triflate was detected, not even after 150 min. This is in line with a mechanism where the direct attack of the acceptor on trichloroacetimidate affords the glycoside product with the opposite anomeric configuration.



Scheme 2. Low-temperature NMR experiments.

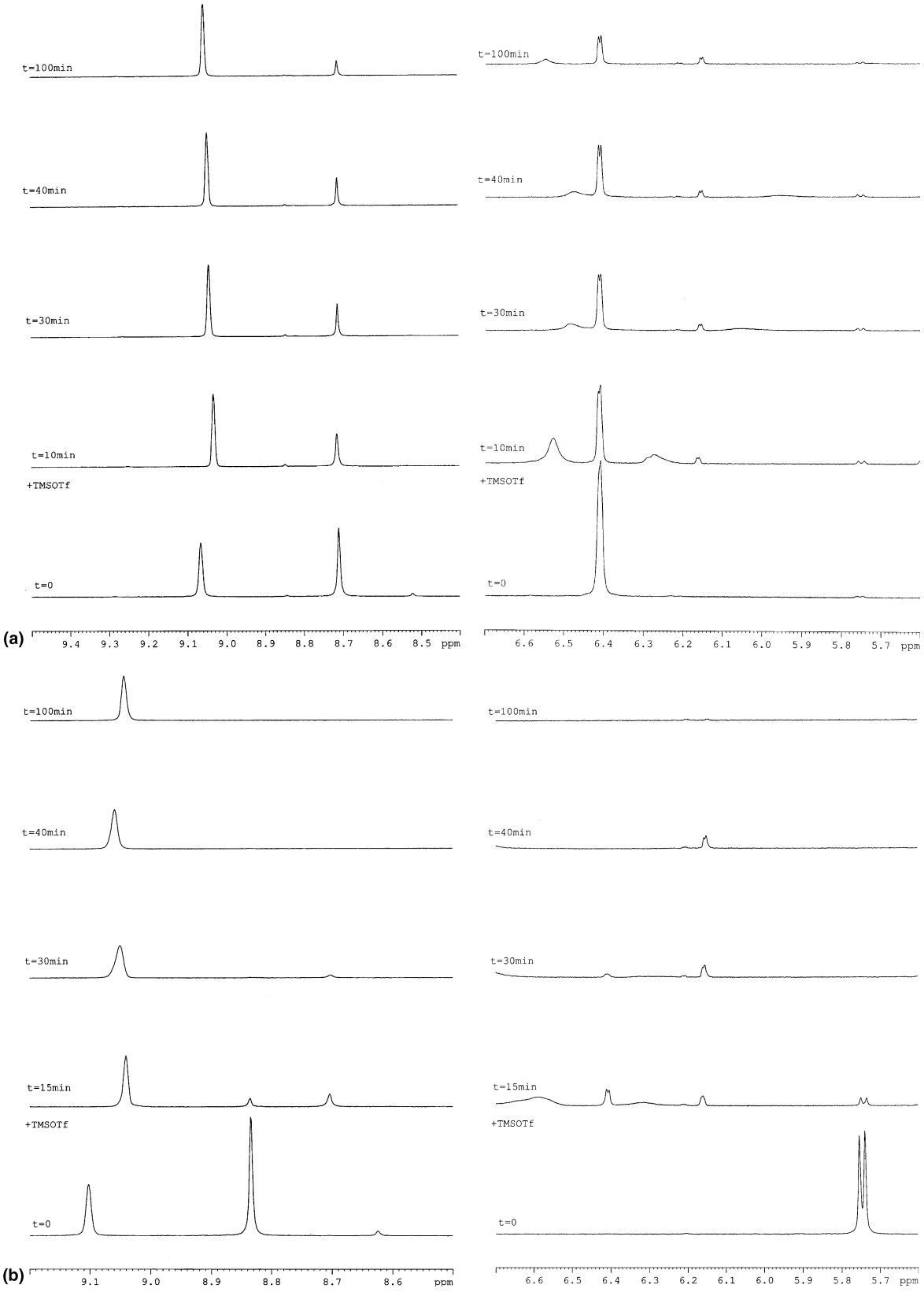


Figure 1. Partial ^{1}H NMR spectrum from Experiments 1 (Table 2). (a) Experiment 1a: The singlet at 9.06 ppm corresponds to the H-2 proton of [emim][OTf], whose chemical shift slightly varies in the presence of the Lewis acid. The singlet at 8.71 ppm corresponds to the NH proton of **1α**; the signal at 6.40 ppm (a singlet that is resolved to a doublet during the course of the experiment, $J = 3.4$ Hz) is the anomeric proton of **1α**; the doublet at 6.16 ppm ($J = 2.9$ Hz) corresponds to the anomeric proton of α-triflate **2**. (b) Experiment 1b: The singlet at 8.83 ppm corresponds to the NH of **1β**; the doublet at 5.74 ppm ($J = 7.4$ Hz) corresponds to the anomeric proton of **1β**.

Nevertheless, when the amount of the Lewis acid was raised to 0.26 equiv (Experiment 2b), compound **1β** quickly anomerized to **1α**, and was then converted to the α-glucosyl triflate, which was stable up to 6 h under these conditions. This behaviour raised a critical issue because a relatively low amount of TMSOTf (0.2 equiv) was sufficient to induce the formation of an anomeric triflate, the α-triflate observed in Experiment 1 could derive from both the [emim][OTf] and from the Lewis acid. Experiments 3, performed without the addition of IL but using 0.1 equiv of TMSOTf, supported this hypothesis. In fact, under these conditions, both the donors formed the α-triflate after 3 min. Donor **1β** also displayed the concomitant anomerization to its α-anomer.

To gain definitive evidence that the triflate anion of [emim][OTf] was able to provide the anomeric α-triflate, in Experiments 4 boron trifluoride–diethyl ether complex ($BF_3{\cdot}Et_2O$) was used as the promoter. As this Lewis acid is weaker than TMSOTf, more equivalents were added to the mixture (0.45 equiv). After the addition of $BF_3{\cdot}Et_2O$, ^1H and ^{19}F NMR spectra were recorded at regular time intervals. Donor **1α** was completely converted within 30 min to the anomeric α-triflate, which was stable up to 2 h (Fig. 2a). Donor **1β**, in turn, epimerized to the α-donor and was partially transformed into the α-glucosyl triflate before degradation (Fig. 2b). ^{19}F NMR spectroscopy (Fig. 3a and b) revealed a peak at δ −77.9 ppm that appeared in both the experiments, in agreement with the formation of the anomeric α-triflate observed in the ^1H NMR spectra. The chemical shift of this peak is consistent with the values corresponding to an anomeric triflate reported in the literature by Lowary and co-workers.[8b]

Taken together, our results support a direct participation of the anion of [emim][OTf] in the glycosylation reaction by the formation of a transient α-glycosyl triflate, which biases the attack of the glycosyl acceptor from the β-face. On the other hand, in the presence of [bmim][PF_6] no transient species was detected by NMR experiments. Therefore, in the glycosylation reaction this IL displays a behaviour similar to classical non-coordinating solvents, where the direct attack of the acceptor to the donor is favoured, providing a product with the opposite configuration.

ILs can be therefore considered as 'designer solvents'[9] for glycosylation reactions, as they can act during the course of the reaction by modulating the stereoselectivity of the products. This method provides a new way to simplify the construction of oligosaccharides without the use of complex protecting group patterns. Further

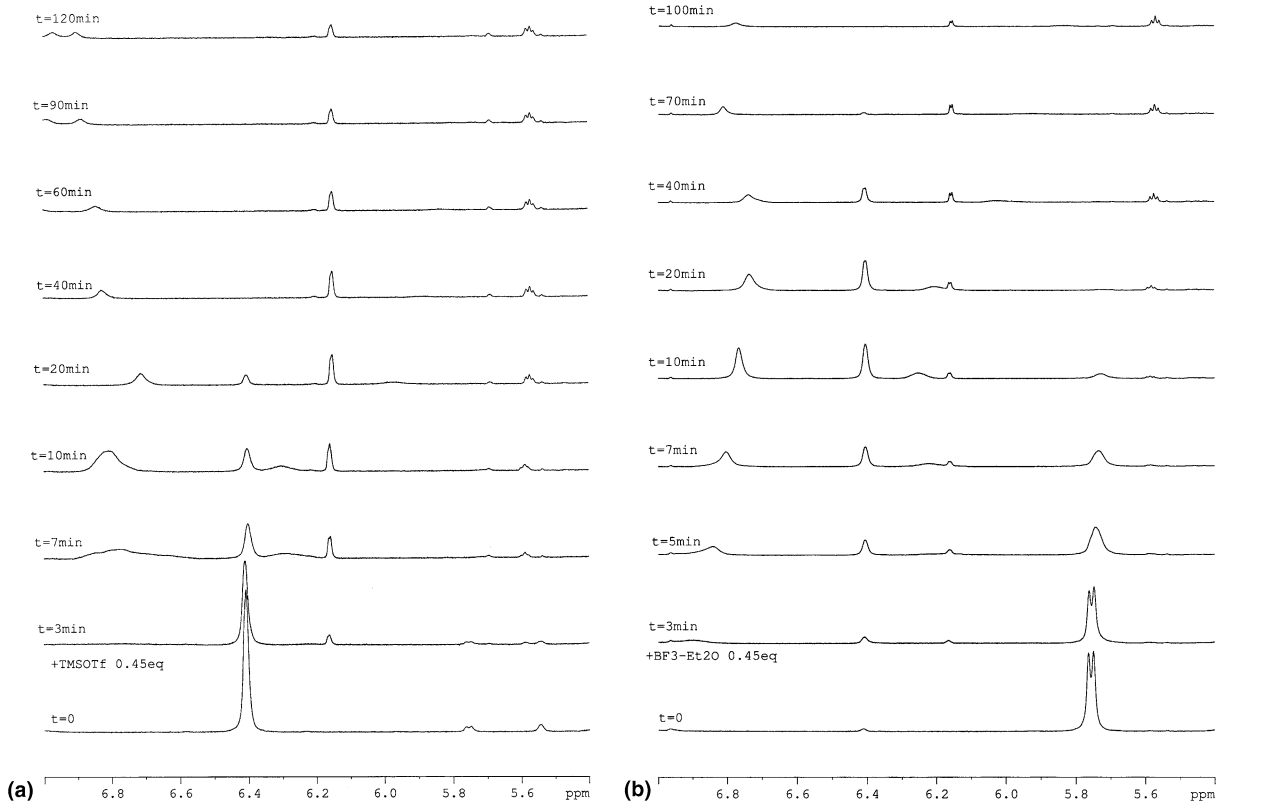


Figure 2. Partial ^1H NMR spectrum of Experiment 4 (Table 2). (a) Experiment 4a: The broad singlet at 6.40 ppm is the anomeric proton of **1α**; the peak at 6.16 ppm, which in this experiment appears as a broad singlet, corresponds to the anomeric proton of α-triflate **2**. (b) Experiment 4b: The doublet at 5.74 ppm, ($J = 7.4$ Hz) corresponds to the anomeric proton of **1β**; the anomeric proton of α-triflate **2** appears as a doublet at 6.16 ppm ($J = 2.9$ Hz).

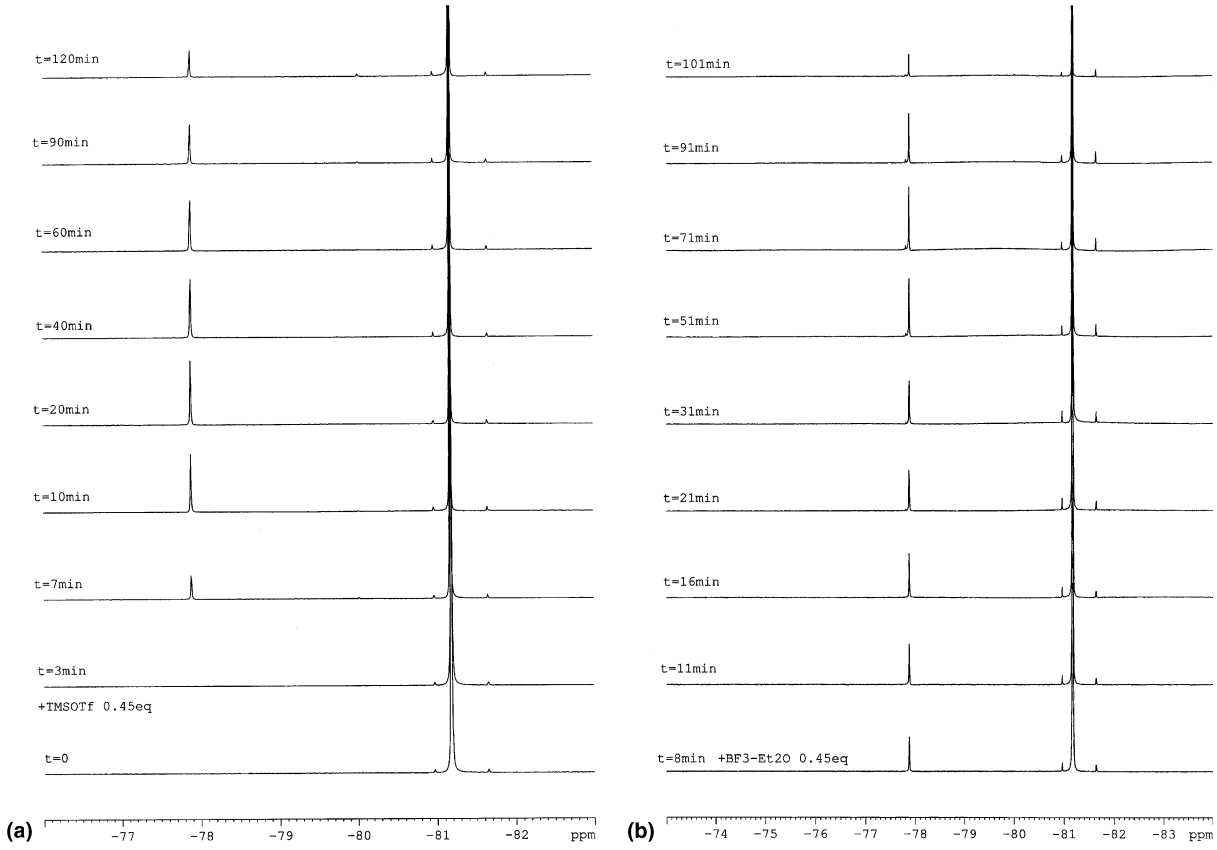


Figure 3. Partial ^{19}F NMR spectrum of Experiments 4a (a) and 4b (b) (Table 2). The singlet at −77.9 ppm corresponds to the anomeric α-triflate; the singlet at −81.2 ppm corresponds to the triflate of [emim][OTf].

studies on the influence of differently coordinating ionic liquids in glycosylation reactions are under investigation and the results of these studies will be reported in due course.

1. Experimental

1.1. General methods

^{1}H NMR and ^{19}F NMR experiments were performed using a 500 MHz *Bruker Avance* spectrometer, equipped with a 5 mm QNP probe (^{13}C, ^{13}P, $^{19}F/^{1}H$ coils) and with an N_2 evaporator cooling system unit (able to work down to −150 °C), which was used for experiments acquired at low temperature.

1.2. Representative experiment

Glucosyl imidate **1** (1 equiv) was dissolved in CD_2Cl_2 in a 5 mm NMR tube in the presence of the ionic liquid (equivalents according to Table 2, calculated by integration of the NH of the donor and the H-2 of the IL) and the sample was cooled to −78 °C. The mixture was stable at these conditions and therefore the shimming of the sample (lock on the ^{2}H nuclei of CD_2Cl_2 solvent) and the acquisition of the first ^{1}H or ^{19}F spectrum (labelled with $t = 0$) was performed. The donor was activated by addition of the Lewis acid (equivalents according to Table 2) at −78 °C. A second spectrum was acquired after the necessary manipulation and lock stabilization time ($t = 5$ min). ^{1}H and ^{19}F experiments (35 min each) were subsequently acquired at regular time intervals until the no changes were evident in the spectrum.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.02.021.

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