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COMMUNICATION

Syntheses, NMR and XRD studies of carbohydrate-ferrocene conjugates

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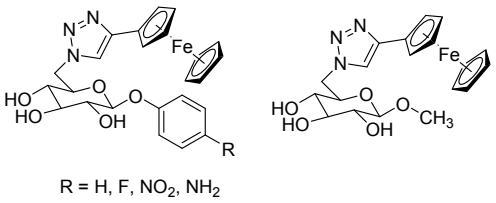
Carbohydrate-ferrocene conjugates were synthesized and showed that the ferrocene entity appeared to be confined to a low volume so that proton NMR spectroscopy revealed 3 to 4 signals for substituted cyclopentadienyl instead of two usually.

Introduction

Ferrocenes are entities that have attracted a lot of interest since their appearance in the middle of the 20th century. They are present in a wide range of applications integrated in miscellaneous structures involving an important investment in the design and the synthesis [1]. Ferrocene has been associated with carbohydrates to target biological activities, [2-4] molecular recognition [5] or as a redox detector. [6] They can be synthesized via side chains containing triazole, amide, carboxylate, boronate [7], thioether moieties [8]. Transacetalisation is another way to link ferrocene and carbohydrate [9]. The structures obtained can be complex and the NMR tool can be very valuable in elucidating certain conformations. [10-11] Studies on the free rotation of cyclopentadienyl rings around the Cp-Fe-cp axis have attracted attention and depending on substitution, eclipsed and staggered conformations are stable. [1] NMR spectroscopic studies usually show that alpha and beta hydrogens are equivalent to two to two and that their chemical shifts depend on the substituent as shown on chalcones linked to ferrocenes. [12] Longitudinal relaxation times on the carbons of substituted cyclopentadienyl have also been measured. Relaxation time is depending on the degree of mobility of the cyclopentadienyl ring, ie faster with bulky substituent. [13] The association of ferrocene with groups such as carbohydrates can lead to conformations in which the hydrogen in alpha position of the substitution becomes magnetically different.[14]



R = H, F, NO_2, NH_2

Figure 1. Substituted carbohydrate-ferrocene conjugates.

In the context of our research work on active antifouling compounds, we have synthesized a series of compounds in which ferrocene was bound to glucose via a triazole link. The substitution on anomeric position was varied to study the influence of substituents on NMR spectroscopic properties and on the solid state organization.

Experimental

Tosyl chloride, sodium azide, ethynylferrocene, sodium ascorbate and $CuSO_4.5H_2O$ were purchased from Aldrich and **1** from Combi-Blocks. **2** was prepared from glucose. [15] **3** and **5** were prepared from **2** using $BF_3.Et_2O$ in DCM under Ar atmosphere. [16] **4** was prepared from **1** using Ag_2CO_3 as catalyst [17] and **6**, **7**, **8** and **9** were obtained using MeONa in methanol. [18] All the compounds obtained have the same spectroscopic characteristics as those obtained in literature. Characterizations of the isolated products were carried out in $CDCl_3$ or $(CD_3)_2SO$ at 25°C. Chemical shifts are reported in ppm relative to the solvent residual value: δ=7.26 ($CDCl_3$), 2.50 ($(CD_3)_2SO$) for ^1H NMR and δ= 77.16 ($CDCl_3$), 39.52 ($(CD_3)_2SO$) for ^{13}C NMR. NMR spectra were recorded on a Bruker Avance 300 (^1H: 300.1 MHz, ^{13}C: 75.7 MHz, T = 300 K). Spectra were referenced against the internal NMR-solvent standard. Chemical shifts were expressed in parts per million (ppm) and were reported as s (singlet), d (doublet), t (triplet), m (multiplet) and coupling constants *J* were given in Hz. Mass

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spectra were recorded under EI mode on a VG-Autospec mass spectrometer. The main peaks are described according to m/z. The peak corresponding to molecular mass is expressed as ($M^{+\bullet}$). Analytical grade solvents were used.

Formation of azide derivatives (10 and **12) (general procedure):** Azide derivative was prepared from alcohol in two steps. To a solution of glucose derivative (10.4 mmol, 1equiv) in pyridine (26 ml), was added tosyl chloride (13.6 mmol, 1.3 equiv) in portions at 0°C. Once the addition is finished, the reaction mixture was stirred at room temperature overnight. Then, the residue was extracted with ethyl acetate and washed with water and brine. The organic solution was dried over $MgSO_4$ and evaporated at reduced pressure. The crude product was purified by flash column chromatography to give the desired product as a brown solid. The tosylated derivative (1.96 mmol, 1equiv) was then directly engaged. It is dissolved in anhydrous DMF (7mL), sodium azide (7.86 mmol, 4equiv) was then added. The solution becomes yellow. The mixture was stirred overnight at 70°C. Once the mixture was cooled to room temperature, the residue was diluted with ethyl acetate and washed several times with brine and dried over $MgSO_4$. The organic phase was filtered and concentrated in vacuo. Purification by column chromatography gave a white compound.

Phenyl 6-azido-6-deoxy-β-D-glucopyranose 10. Yield 68 % (from tosylate derivative). Mp 98-99 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.30 (m, 2H, H-arom), 7.02 (m, 3H, H-arom), 5.42 (d, *J* = 4.8 Hz, 1H, OH), 5.31 (d, *J* = 5.4 Hz, 1H, OH), 5.21 (d, *J* = 4.6 Hz, 1H, OH), 4.95 (d, *J* = 7.4 Hz, 1H, H-1), 3.59 (m, 1H, H-5), 3.45 (m, 2H, H-6 and H-7), 3.28 (m, 2H, H-2 and H-3), 3.15 (s, 1H, H-4). ^{13}C NMR (76 MHz, DMSO) δ = 157.2, 129.4, 122.0, 116.3, 100.2, 76.1, 75.1, 73.2, 70.6, 51.4. IR (cm^{-1}): 2092, 1590, 1491, 1220 and 1064 cm^{-1}.HRMS (FAB neg): calculated for $C_{12}H_{15}N_3O_5$ m/z 280.0933, found 280.0930.

4-fluorophenyl 6-azido-6-deoxy-β-D-glucopyranose 12. Yield 98 % (from tosylate derivative). Mp °C. ^{1}H NMR (499 MHz, DMSO-*d*6) : δ = 7.12 (m, 2H, H-arom), 7.06 (m, 2H, H-arom), 5.42 (d, *J* = 4.7 Hz, 1H, OH), 5.30 (d, *J* = 5.5 Hz, 1H, OH), 5.19 (d, *J* = 4.6 Hz, 1H, OH), 4.91 (d, *J* = 7.2 Hz, 1H, H-1), 3.58 (m, 1H, H-5), 3.44 (m, 2H, H-6 and H-7), 3.27 (m, *2*H, H-2 and H-3), 3.13 (m, 1H, H-4). ^{13}C NMR (76 MHz, DMSO-d6) δ = 157.4 (d, *J* = 237 Hz), 153.5 (d, *J* = 2 Hz), 118.0 (d, *J* = 8 Hz), 115.8 (d, *J* = 23 Hz), 100.8 , 76.0 , 75.1 , 73.1 , 70.6 , 51.4. IR (cm^{-1}): cm^{-1}.HRMS (FAB neg): calculated for C12H13FN3O5 m/z 298.0839, found 298.0837.

Formation of triazole ring (14, 15, 16 and **17) (general procedure):** To a solution of azide glucose (3.8 mmol, 1 equiv) in mixture DMF:H_2O (20 mL, 3:1), ethynylferrocene (4.18 mmol, 1.1eq), sodium ascorbate (3 mmol, 0.8 equiv,) and $CuSO_4.5H_2O$ (1.52 mmol, 0.4eq,) were added at room temperature. The reaction mixture was stirred at room temperature overnight. The mixture was poured into saturated NH_4Cl solution, and then extracted with EtOAc and washed with NaCl. The organic phase was concentrated under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/EtOH, 100:0 to 95:5) to give the desired product.

6-Deoxy-6-(4-ferrocenyl-1*H*-1,2,3-triazol-1-yl)-1-phenyl-β-D-glucopyranose 14 Yield: 17 %. Mp: 166-167 °C. ^{1}H NMR (300MHz, DMSO-d_6): δ = 7.95 (s, *1*H, triazole-H), 7.12 (dd, *J* = 7.4 and *J* = 8.4 Hz, 2H, Ar-H), 6.91 (t*, J = 7.4 Hz,* 1H, Ar-H), 6.76 (dd, J = 1.0 and J = 8.4 Hz, 2H, Ar-H), 5.53 (d, *J = 5.4 Hz*, 1H, OH), 5.41 (d, *J = 5.0Hz*, 1H, OH), 5.27 (d, *J = 4.9 Hz*, 1H, OH), 4.82 (d, *J = 7.6 Hz*, 1H, H-1), 4.76 (d, *J = 2.1 and J = 14.3 Hz*, 1H,), 4.68 (m, 1H, Cp-H), 4.55 (m, 1H, Cp-H), 4.41 (dd, J = 9.0 and *J* = 14.3 Hz, 1H, CH_2), 4.29 (m, 2H, Cp-H), 3.99 (s, 5H, Cp-H), 3.86 (m, 1H, CH), 3.30 (m, 2H, CH), 3.15 (m, 1H). ^{13}C NMR (76 MHz, DMSO): δ = 157.1, 145.0, 129.2, 121.9, 121.5, 116.2, 100.3, 76.1, 74.3, 73.1, 71.3, 69.2, 69.2, 68.1, 66.4, 66.3, 50.9. IR (cm^{-1}): 3292, 1232, 1108 and 1026. HRMS (EI) calculated for $C_{24}H_{25}FeN_3O_5$ m/z 491.1144; found 491.1137.

6-Deoxy-6-(4-ferrocenyl-1*H*-1,2,3-triazol-1-yl)-1-(4-nitrophenyl)-β-D-glucopyranose 15 Yield: 69%. Mp 187.2°C-201°C. ^{1}H NMR (300MHz, DMSO-d_6): δ = 7.99 (d, *J = 9.3Hz*, 2H, Ar-H), 7.90 (s, 1H, Ar-H), 6.92 (d*, J=9.3Hz*, 2H, Ar-H), 5.61 (d, *J = 5.4Hz*, 1H, OH), 5.57 (d, *J = 4.9Hz*, 1H, OH), 5.37 (d, *J = 4.9Hz*, 1H, OH), 5.10 (d, *J = 7.5Hz*, 1H, H-1), 4.78 (dd, *J= 2.1 Hz*, *J = 14.3Hz*, 1H, H-6), 4.68-4.66 (m, 1H, Cp-H), 4.47-4.46 (m, 1H, Cp-H), 4.38 (m, 1H, H-6), 4.28 (m, 1H, Cp-H), 4.23 (m, 1H, Cp-H), 3.96 (m, 1H, H-5), 3.95 (s, 5H, Cp-H), 3.33 (m, 2H, H-2 and H-3), 3.22-3.18 (m, 1H, H-4). ^{13}C NMR (300MHz, DMSO-d_6): δ = 161.9, 145, 141.6, 125.5, 121.8, 116.4, 99.3, 76, 75.9, 74.4, 72.9, 71.3, 69.1, 68.2, 68.1, 66.3, 50.9. IR (cm^{-1}): 3533, 3117, 2881, 1657, 1591, 1513, 1493, 1342, 1244, 1062. HRMS (FAB+) calculated for $C_{24}H_{24}FeN_4O_7$ m/z 536.0994; found 536.0993.

6-Deoxy-6-(4-ferrocenyl-1*H*-1,2,3-triazol-1-yl)-1-(4-fluorophenyl)-β-D-glucopyranose 16 Yield: 55%. Mp 209-211°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (s, 1H, triazole-H), 6.90 (m, 2H, H-arom), 6.78 (m, 2H, H-arom), 5.53 (d, *J* = 5.4 Hz, 1H, OH), 5.42 (d, *J* = 5.0 Hz, 1H, OH), 5.28 (d, *J* = 4.9 Hz, 1H, OH), 4.76 (m, 2H, H-1 and H-6), 4.68 (m, 1H; Cp-H), 4.57 (m, 1H, Cp-H), 4.41 (m, 1H, H-6), 4.30 (m, 2H, Cp-H), 3.98 (s, 5H, Cp-H), 3.83 (m, 1H, H-5), 3.25 (m, 1H, H-3), 3.16 (m, 2H, H-2 and H-4). ^{13}C NMR (76 MHz, DMSO) δ = 157.2 (d, *J* = 237 Hz), 153.3 (d, *J* = 2 Hz), 153.3, 145.0, 121.7, 117.9, 117.8, 115.8, 115.5, 100.8, 76.1, 76.1, 74.3, 73.1, 71.3, 69.2, 68.2, 68.2, 66.3, 66.3, 50.9. IR (cm^{-1}): 3297, 1506, 1169, 1106 and 1033. HRMS (FAB+) calculated for $C_{24}H_{24}FFeN_3O_5$ m/z 509.1049; found 509.1046.

6-Deoxy-6-(4-ferrocenyl-1*H*-1,2,3-triazol-1-yl)-1methyl-β-D-glucopyranose 17 Yield: . Mp. 219-220°C. ^{1}H NMR (300MHz, DMSO-d_6): δ = 8.12 (s, 1H, H-triazole), 5.38 (d, 1H, *J* = 5.8 Hz, OH), 4.94 (d, 1H, *J* = 5.0 Hz, OH), 4.83 (d, 1H, *J* = 6.4 Hz, OH), 4.73 (m, 2H, H-Cp), 4.71 (dd, 1H*, J = 2.1 Hz and J = 14.1 Hz*, H-6'), 4.54 (d, 1H, *J* = 3.6 Hz, H-1), 4.38 (dd, 1H, *J = 8.7 Hz and J = 14.1 Hz*, H-6), 4.29 (m, 2H, Cp-H), 4.00 (s, 5H, Cp-H), 3.72 (m, 1H, H-5), 3.41 (m, 1H, H-3), 3.22 (m, 1H, H-2), 3.02 (m, 4H; CH_3 and H-4). ^{13}C NMR (76 MHz, DMSO-d_6) δ = 145.1, 121.3, 99.7, 76.1, 73.1, 71.8, 71.7, 70.6, 69.2, 68.3, 66.5, 54.1, 21.0. IR (cm^{-1}) : 3329.3, 2898.6-2864.1, 1629.13, 1509.5, 1221.8, 1064.6. HRMS calculated for $C_{19}H_{23}FeN_3O_5$ m/z 429.0987 ; found 429.0988.

6-Deoxy-6-(4-ferrocenyl-1*H*-1,2,3-triazol-1-yl)-1-(4-aminoophenyl)-β-D-glucopyranose 18 To a solution of **15** (900

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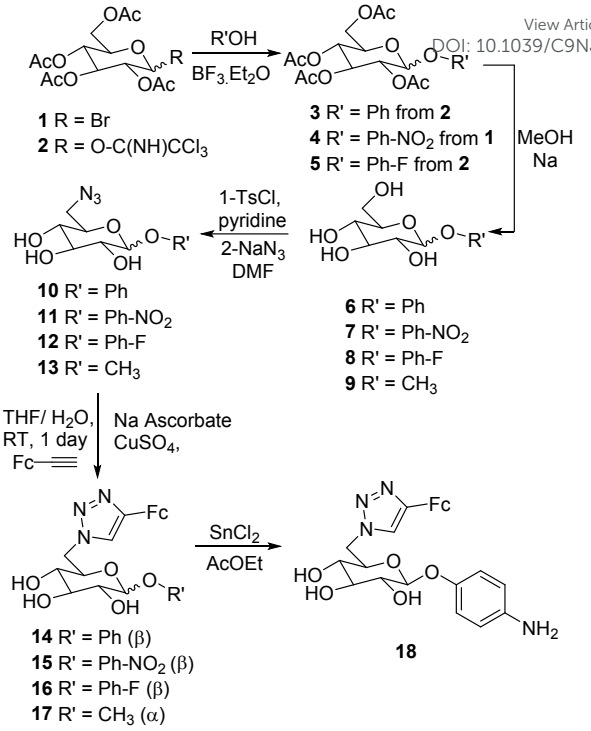
mg, 1.67 mmol) in ethyl acetate (40 ml) was added $SnCl_2.2H_2O$ (1.89 g, 5eq, 8.39 mmol) at room temperature. The reaction mixture was stirred overnight at reflux (80°C). Once the reaction was completed, the mixture was cooled to room temperature. The mixture was poured into saturated aqueous $NaHCO_3$. A white precipitate was formed and filtered. Then, the reaction mixture was extracted with ethyl acetate, washed with water and NaCl. Then, the organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/EtOH, 100:0 to 90:10) to afford the final compound as an orange-yellow solid. Yield: 40 %. Mp: 203-204°C. ^{1}H NMR (300MHz, DMSO-d_6): δ = 7.95 (s,1H, Ar-H), 6.56 (d, *J = 8.7Hz*, 2H, Ar-H), 6.38 (d, *J = 8.8Hz*, 2H, Ar-H), 5.47 (d, *J = 5.5 Hz*, 1H, OH), 5.33 (d, *J = 5.0 Hz*, 1H, OH), 5.21 (d, *J = 5 Hz*, 1H, OH), 4.76 (dd, *J = 2.4Hz, J = 14.5 Hz*, 1H, H-6), 4.71 (s, 2H, NH_2), 4.67 (m, 1H, Cp-H), 4.62 (m, 1H, Cp-H), 4.55 (d, *J = 7.7 Hz*, 1H, H-1), 4.40 (dd, *J = 8.8 Hz* , *J = 14.3 Hz* , 1H, H-6), 4.29 (m, 2H, Cp-H), 4.00 (s, 5H, Cp-H), 3.71 (dt, *J = 1.9 Hz*, *J = 9.2 Hz*, 1H, H-5), 3.28 (m, 1H, H-3), 3.14 (m, 2H, H-2 and H-4). ^{13}C NMR (300MHz, DMSO-d_6): δ = 148.4, 145.1, 143.8, 121.5, 117.9, 114.4, 102.3, 76.1, 76.0, 74.3, 73.2, 71.3, 69.3, 68.2, 68.1, 66.5, 66.4, 50.9. IR (cm^{-1}): 3329, 2898, 1629, 1509, 1221, 1064. HRMS (EI) calculated for $C_{24}H_{26}FeN_4O_5$ m/z 506.1253; Found 506.1258.

Results and Discussion

Different carbohydrates substituted ferrocene have been synthesized in 5 or 6 steps using classical pathways for these kinds of syntheses (Figure 1). **3** and **5** were obtained by glycosylation using Schmidt acceptor **2,** and **4** was obtained from the bromoglucose **1**. After deprotection, primary alcohol (**6**-**9**) was transformed in two steps in azide group (**10**-**13**) to introduce ferrocene by cycloaddition (**14**-**17**). **15**-**17** were obtained in modest yields. Nitro group was then reduced using tin chloride to afford the amino group (**18**) (Scheme 1).

Complete NMR study was done on each compound and all the signals have been attributed. Usually on a monosubstituted ferrocene, proton NMR shows three different chemical shifts, one for proton of the free cyclopentadienyl and two other ones for α and β protons of the substituted cyclopentadienyl. In the series of molecules we have synthesized, we can observe up to 5 different signals for the monosubstituted ferrocene. In the literature, this behaviour is not mentioned, however we have pointed out in at least one paper that clicked ferrocenes on acetylated glucose or mannose showed that the two alpha protons of ferrocene were magnetically different [14]. No supplementary studies can explain this behaviour. By comparing compound **17** with the other derivatives, only three signals correspond to ferrocene, indicating that the alpha (H8 and H11) and beta (H9 and H10) protons of substituted ferrocene are equivalent to two to two, and the third signal (H12) corresponds to the five protons of the free cyclopentadienyl (Table 1). A simple methoxy in anomeric position does not influence the NMR shift of ferrocene protons. When the carbohydrate is functionalized by different aryls, it seems that the environment of ferrocene changes. It results in a splitting of the alpha signals and even a splitting of the beta signals for compound **15** (Figure 2).



1 R = Br
2 R = O-C(NH)CCl$_3$

3 R' = Ph from **2**
4 R' = Ph-NO$_2$ from **1**
5 R' = Ph-F from **2**

6 R' = Ph
7 R' = Ph-NO$_2$
8 R' = Ph-F
9 R' = CH$_3$

10 R' = Ph
11 R' = Ph-NO$_2$
12 R' = Ph-F
13 R' = CH$_3$

14 R' = Ph (β)
15 R' = Ph-NO$_2$ (β)
16 R' = Ph-F (β)
17 R' = CH$_3$ (α)

18

Scheme 1 Syntheses of the different ferrocene-carbohydrate conjugates

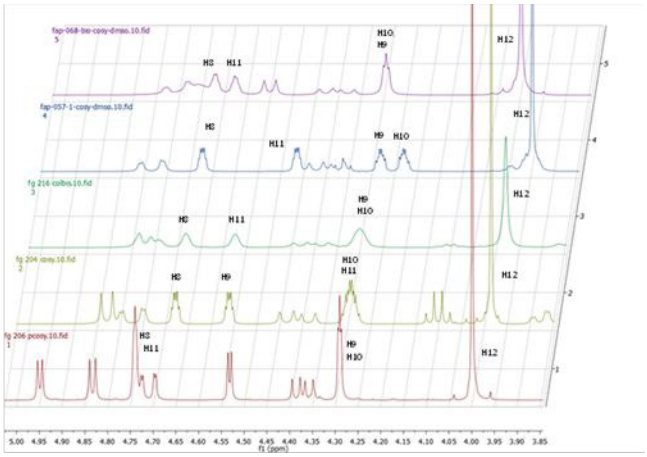
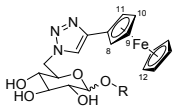


Fig. 2 Zoom on ferrocene ^{1}H NMR signals of **15**.

As it can be seen on figure 2, shift of the proton NMR of the free cyclopentadienyl is not really influenced by the rest of the molecule, whereas, for the substituted cyclopentadienyl, α protons are separated from 0.1 to 0.2 ppm. H assignments were confirmed by 2D NMR experiments. For compounds **14**, **16**, **17** and **18**, four ^{1}H NMR signals are present in the spectra and correspond to H-8, H-11, H-12 and H-9 with H-10 under the same signal. Since, the environment around the ferrocene seems to influence the chemical shift of the protons, other NMR experiments were performed on the different carbohydrates. First, a test with a temperature increase on compound **15** in DMSO *d6* was realized to see if the alpha and beta hydrogens could become equivalent. When the temperature is increased, a decrease of the difference in chemical displacement between the two alpha protons and the two beta

protons was observed passing from 0.2 to 0.13 ppm difference for alpha protons

Table 1. ^{1}H NMR chemical shifts of ferrocene in compounds **15**-**18**



Compound	δ_{H8}	δ_{H9}	δ_{H10}	δ_{H11}	δ_{H12}
14(R =Ph)	4.68	4.29	4.29	4.57	3.98
15(R = $PhNO_2$)	4.67	4.28	4.22	4.47	3.95
16(R = PhF)	4.68	4.30	4.29	4.57	3.98
17(R = CH_3)	4.75	4.30	4.30	4.75	4.00
18(R =$PhNH_2$)	4.67	4.29	4.29	4.62	4.00

and 0.06 to 0.03 ppm for beta protons (Figure 3). However, at 120 °C, no coalescence was obtained. A similar experiment has been realized with compound **18**. β protons are magnetically equivalent at room temperature whereas α protons show different chemical shifts. When the temperature is raised during the NMR experience, the chemical shifts of the two alpha protons remain identical, indicating that the adopted configuration seems blocked. Thus, another experiment was performed lowering the temperature to -40°C. We would like to see if the β signals (H-9 and H10) were able to separate, however we just pointed out an NMR shift without any separation of the signals. These experiments were realized in deuterated methanol, DMSO being solid at this temperature.

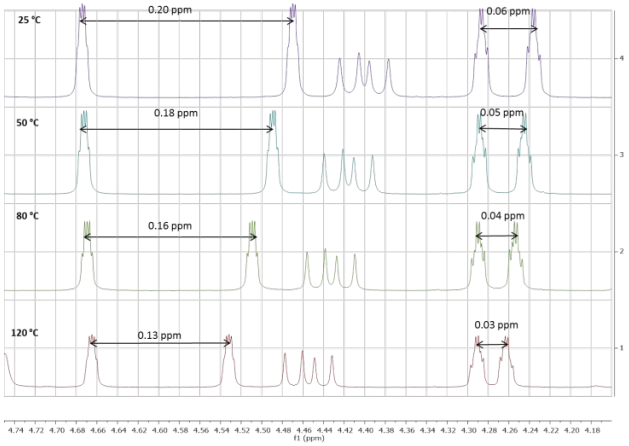


Fig. 3 Temperature effect on ^{1}H NMR signals of ferrocene in **15**

Measurement of longitudinal relaxation times for **15** demonstrates that T1 H_8 and T1 H_{11} are slightly different whereas T1 H_9 and T1 H_{10} are identical (Table 2). In comparison with **17**, the T1 of the different protons are closer. Thus, even if the gap between the relaxation time of the protons is not so significant, it means that the environment around the protons is not exactly the same. Results for the other compounds (**14**, **16** and **18**) show a similar behavior than **15**.

Table 2. Longitudinal relaxation times of ferrocene protons for compounds **14** to **18**.

Compound	T1(s) H_8	T1(s) H_9	T1(s) H_{10}	T1(s) H_{11}
14(R =Ph)	2.6	2.3	2.3	2.4
15(R = $PhNO_2$)	2.5	2.25	2.25	2.4
16(R = PhF)	2.2	2.0	2.0	2.2
17(R = CH_3)	2.3	2.2	2.2	2.3
18(R =$PhNH_2$)	2.0	2.0	2.0	2.1

In order to understand these differences, crystals were obtained for each compound to see the organization of the molecules. Although the results obtained by X-ray diffraction correspond to a solid phase, these informations are very instructive about the folding of molecules in solution and is a valuable tool for the proton NMR interpretation.

In the solid state, the compound **17**, having the simplest NMR system, has a very simple stack governed by a network of hydrogen bonds between OH of carbohydrates. Consequently, ferrocenes are organized in columns (see SI). Thus, methoxy has little influence on stacking whereas the other compounds have complicated X-ray structures due to the anomeric position substitution. The molecules form a U due to the substitutions of carbohydrates in positions 1 and 6. The spatial arrangement will depend on the substitution of phenyl. Indeed, when an amine (compound **18**) is present in para position of the anomeric part, it will participate in hydrogen bonding networks. The amine nitrogen is bound to an adjacent carbohydrate via a N-H bond while the two amine hydrogens are engaged in weak bonds with the oxygen of two other adjacent carbohydrates. The ferrocene is oriented outside of the U shape of the molecule, therefore far from the amine. The behaviour of compounds **14**, **15** and **16** is different. The ferrocene will be positioned inside the U. The nitro group points towards the ferrocene forming a U rather flat, while with the amino group the U is rather helical (Figure 4).

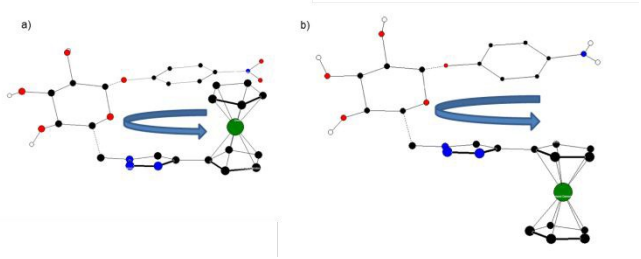


Fig. 4. Molecular representations of a) **15** and b) **18**.

Conclusions

We have synthesized a series of carbohydrate ferrocene conjugates varying the nature of the group in anomeric position. We pointed out that ^{1}H NMR of carbohydrate derivatives could lead to a splitting of signals of the ferrocene protons. Molecules presenting aryl in anomeric position are folded in U shape with the ferrocene that could be positioned inside the U or outside the U if H-bond exists. The molecular representation shows an environment around ferrocene protons that is different if the rotation between ferrocene and triazole is prevented, this would explain the different chemical shifts of ferrocene protons.

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Conflicts of interest

There are no conflicts to declare.

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Notes and references

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Carbohydrate-ferrocene conjugates show a splitting of all the ^{1}H NMR signals of the substituted cyclopentadienyl. XRD of crystals seems to indicate that R group could be responsible of the splitting of the NMR signals.