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A Carbohydrate–Anion Recognition System in Aprotic Solvents

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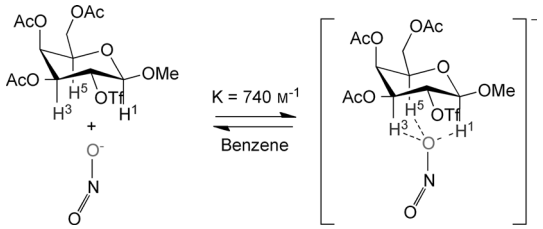
Abstract: A carbohydrate–anion recognition system in nonpolar solvents is reported, in which complexes form at the B-faces of β-D-pyranosides with H1-, H3-, and H5-*cis* patterns similar to carbohydrate–π interactions. The complexation effect was evaluated for a range of carbohydrate structures; it resulted in either 1:1 carbohydrate–anion complexes, or 1:2 complex formation depending on the protection pattern of the carbohydrate. The interaction was also evaluated with different anions and solvents. In both cases it resulted in significant binding differences. The results indicate that complexation originates from van der Waals interactions or weak CH···A$^-$ hydrogen bonds between the binding partners and is related to electron-withdrawing groups of the carbohydrates as well as increased hydrogen-bond-accepting capability of the anions.

Keywords: anions · carbohydrates · molecular recognition · pi interactions · supramolecular chemistry

Introduction

Carbohydrate–aromatic interactions represent a widely investigated research area in biochemistry,[1] in part owing to the fact that carbohydrate–protein recognition plays an important role in many biological processes.[2] This type of interaction is a common feature in the recognition of carbohydrates, and it is dependent on the electronic nature of the aromatic group.[3] The interactions generally occur between the B-face of the carbohydrate,[4] particularly the "three-point landing surface" that consists of the H1, H3, and H5 protons of the pyranosides, and the face of an aromatic side chain.[1c,j,5] However, these interactions are so weak that it is difficult to provide direct evidence showing that they contribute to the driving force of biological processes.

Recently, we discovered a novel carbohydrate–anion recognition mechanism very similar to these systems (Scheme 1).[6] With a similar three-point binding motif as for the carbohydrate–π interactions, this binding occurs between anions and the axial H1, H3, and H5 protons of the carbohydrates. The interaction proved in this case to be fairly strong, and ^{1}H NMR spectroscopic titration clearly indicated that the driving force stems from the contribution of the CH–anion interactions.



Scheme 1. Carbohydrate–anion recognition.[6]

Anion recognition has been reported extensively and is well known to often be strongly affected by solvent effects, as a consequence of the related high free energies of solvation and associated coordinative saturation.[7] Hence, a potential anion receptor must effectively compete with the solvent environment for any anion recognition to take place, which explains the particular appearance of these carbohydrate–anion recognition systems in nonpolar solvents. In the present study, we set out to address these effects, and further examine the novel host–guest interaction discovered with respect to the host structure, anion type, and solvent effects.

The carbohydrate–anion recognition initially came to our attention during investigation of supramolecular control in carbohydrate epimerization.[6] Prompted by the formation of a carbohydrate–nitrite complex, the Lattrell–Dax (nitrite-mediated) epimerization reaction shown in Scheme 2 was either activated or deactivated, depending on whether the nucleophilic reagent attacked from the same or from the opposite direction as the anion binding. For example, when the methyl β-D-galactopyranoside derivatives **1** were tested in

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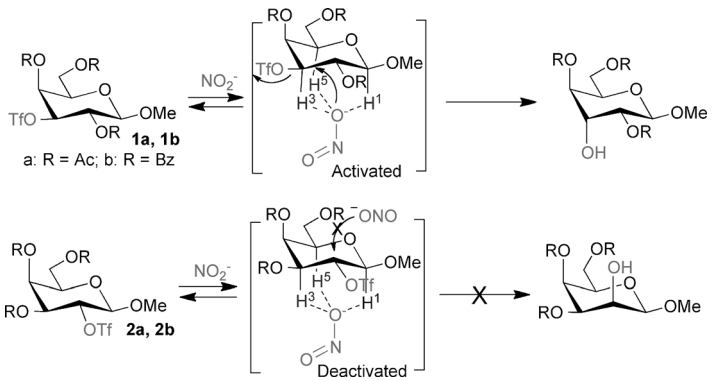


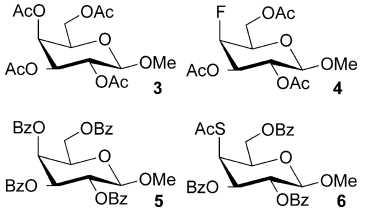
Scheme 2. Supramolecular control from carbohydrate–anion recognition.

this reaction, the rates increased in the order of $CHCl_3 < CH_2Cl_2 < CH_3CN <$ DMF, benzene and toluene. However, although the Lattrell–Dax reaction proceeded very well in CH_3CN and DMF for methyl β-D-galactopyranoside derivatives **2**, it completely failed in benzene and toluene. The formation of the carbohydrate–anion complex was revealed through NMR spectroscopic analyses.[6]

Results and Discussion

As previously demonstrated,[6] the supramolecular carbohydrate–anion recognition effect is likely due to charge/dipole attraction and/or weak hydrogen bonding between the CH 1-, 3-, 5-position three-point binding motif of galactosides and anions. This effect should be general, and the supramolecular carbohydrate/anion recognition could be envisaged to also occur between other carbohydrates with an H1-, H3-, and H5-*cis* pattern and other anions. The effects could furthermore be accentuated by electron-withdrawing groups. To further explore these effects, a series of fully protected glycosides carrying electron-withdrawing groups were evaluated in [D]benzene with a large excess amount of nitrite anions. The results of these tests indeed indicate the interaction between nitrite anions and other carbohydrates that hold the H1-, H3-, and H5-*cis* pattern (Table 1).

Table 1. Comparison of ^{1}H chemical shifts of several β-D-glycosides before and after addition of nitrite anions (20 equiv) in benzene.



Compound	Δ*H*1	Δ*H*3	Δ*H*5	Compound	Δ*H*1	Δ*H*3	Δ*H*5
1a	0.52	0.68	0.80	**2a**	0.48	0.74	0.47
1b	0.82	1.03	1.14	**2b**	0.78	0.44	0.88
3	0.02	−0.02	0.06	**4**	0.07	0.06	0.1
5	0.24	0.09	0.34	**6**	0.06	0.01	0.05

With acetyl groups (compound **3**), very few changes were recorded for the chemical shift values of H1, H3, and H5, probably indicating very weak supramolecular effects between the carbohydrate and the nitrite anions. However, when one of the acetylated hydroxyl groups was changed to a more electron-withdrawing fluoride or triflate group (compounds **1a**, **2a**, and **4**), relatively larger changes in the chemical shift values of H1, H3, and H5 were recorded likely owing to the stronger supramolecular effect. With benzoyl groups (compound **5**), an intermediate supramolecular effect was observed, and when one of the benzoyl groups was changed to a more electron-withdrawing triflate group (compounds **1b** and **2b**), larger changes in the chemical-shift values of H1, H3, and H5 were again observed. Analogously, when one of the benzoyl groups was instead changed to a less electron-withdrawing thioacetyl group (compound **6**), a much weaker effect was observed. These results indicate that the supramolecular effect is related to electron-withdrawing groups of these carbohydrates.

Carbohydrates with different anions in [D]benzene were also tested. The results of these tests indicate that the stability of the carbohydrate/anion complex is strongly associated with the hydrogen bonding ability of the anions. Compounds **1b** and **2a** were tested in [D]benzene with 10 equivalents of benzoate, chloride, and bromide, respectively (Table 2). The order of the hydrogen-bonding ability of these anions is $BzO^- > Cl^- > Br^-$,[8] and it was found that the chemical shift differences of H1, H3, and H5 produced by these anions followed the same pattern. For the benzoate anions, the protons shifted downfield by $\delta = 1.03$, 0.78, and 1.60 ppm for compound **1b** and by $\delta = 0.50$, 0.63, and 0.47 for compound **2a**. For the chloride anions, the protons in positions 1, 3, and 5 shifted downfield by $\delta = 0.63$, 0.75, and 0.84 ppm for compound **1b** and by $\delta = 0.45$, 0.68, and 0.42 for compound **2a**. For the bromide anions, downfield shifts by $\delta = 0.61$, 0.67, and 0.81 ppm for compound **1b** and by $\delta = 0.40$, 0.63, and 0.37 for compound **2a** were recorded.

Table 2. Relative ^{1}H shifts (Δδ) of derivatives **1b** and **2a** in the presence and absence of different anions in [D]benzene. Tetrabutylammonium (TBA) anion salts (10 equiv) were used throughout.

Compound	Anion	Δ*H*1	Δ*H*2	Δ*H*3	Δ*H*4	Δ*H*5	Δ$H6_a$	Δ$H6_b$
1b	BzO^-	1.03	−0.08	0.78	0.27	1.60	0.21	0.30
1b	Cl^-	0.63	0.04	0.75	0.17	0.84	0.09	0.14
1b	Br^-	0.61	0.03	0.67	0.16	0.81	0.08	0.11
2a	BzO^-	0.50	0.05	0.63	0.37	0.47	0.20	0.12
2a	Cl^-	0.45	0.10	0.68	0.37	0.42	0.14	0.14
2a	Br^-	0.40	0.08	0.63	0.33	0.37	0.11	0.11

Owing to poor solubility, dry tetrabutylammonium fluoride (TBAF) and tetrabutylammonium iodide (TBAI) could not be tested in this case. High concentrations of TBAF also led to complex side reactions, such as acyl group migration and deprotonation. Thus, compound **1b** was tested in [D]benzene with only 0.3 equivalents of TBAF. It was found that the chemical shift difference of F^- shifted downfield by

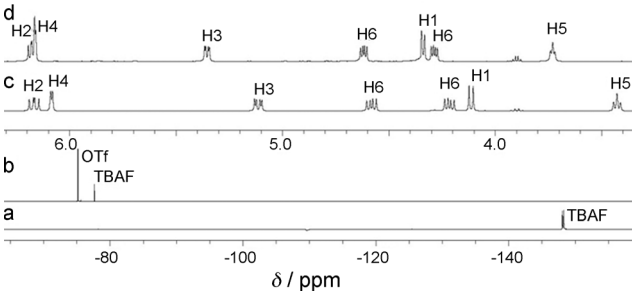
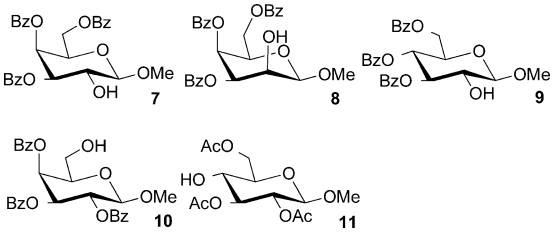


Figure 1. ^{19}F and ^{1}H NMR spectroscopic tests of compound **1b** with TBAF (0.3 equiv). a) ^{19}F NMR spectroscopic test of TBAF. b) ^{19}F NMR spectroscopic test of compound **1b** with TBAF. c) ^{1}H NMR spectroscopic test of compound **1b**. d) ^{1}H NMR spectroscopic test of compound **1b** with TBAF.

Table 3. Relative ^{1}H shifts ($\Delta\delta$) of derivatives **7**–**11** in the presence and absence of nitrite anions in [D]benzene.



Compound	$\Delta H1$	$\Delta H2$	$\Delta H3$	$\Delta H4$	$\Delta H5$	$\Delta H6_a$	$\Delta H6_b$
7	0.90	**0.32**	0.46	0.17	0.50	0.1	0.09
8	0.64	**0.36**	0.39	0.06	0.42	0.23	0.34
9	0.70	**0.41**	0.26	0.00	0.36	0.04	0.00
10	0.24	0.00	0.22	0.50	0.35	**0.90**	**1.00**
11	0.40	0.15	0.45	**0.60**	0.90	0.50	0.60

$\delta = 70$ ppm in an ^{19}F NMR spectroscopy test and the chemical shift differences of H1, H3, and H5 shifted downfield by $\delta = 0.23$, 0.26, and 0.31 ppm in an ^{1}H NMR spectroscopy test (Figure 1). These results indicated a strong effect between compound **1b** and fluoride anion.

Partially protected β-D-glycosides with one unprotected hydroxyl group were also tested with nitrite anions in [D]benzene (Table 3). Although a similar supramolecular effect could be observed in these cases, the hydroxyl group affected the results to some extent. It is in this context reported that hydrogen bonding can take place between anions and carbohydrate hydroxyl groups in nonpolar solvents,[8c] an effect that explains the downfield shifts of the 2-OH protons of compounds **7**, **8**, and **9**, the 6-OH proton of compound **10**, and the 4-OH proton of compound **11**, respectively. However, the concurrent dramatic downfield shift of the H1, H3, and H5 signals for all of these compounds can be explained only by the carbohydrate–anion recognition effect reported herein.

This explanation was subsequently supported by ^{1}H NMR spectroscopic titration experiments using compound **7** and tetrabutylammonium nitrite in [D]benzene (Figure 2). Analysis of the results of these experiments indicated a 1:2 carbohydrate/nitrite ratio of the binding partners, in congruence to nitrite binding to the CH 1-, 3-, and 5-position three-point binding motif by means of the CH···A^- effect, and to the hydroxyl group in position 2.

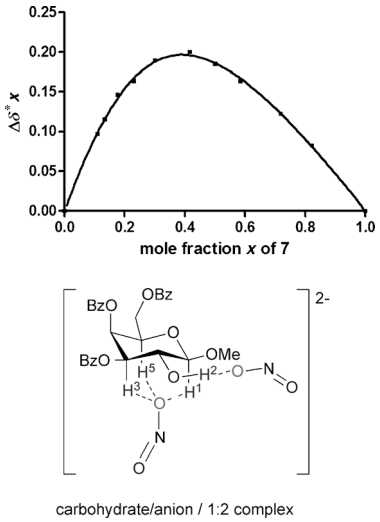
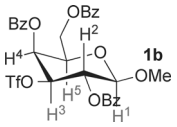


Figure 2. Job plot of compound **7**/nitrite. The maximum value of $\Delta\delta^* x$ is at the 0.333 position on the x axis, which indicates exactly a carbohydrate/anion 1:2 complex.

More interestingly, it seemed that certain solvents also gave rise to the supramolecular effect with carbohydrates holding H1-, H3-, H5-*cis* pattern. Comparison of the ^{1}H-chemical shifts of compound **1b** with and without nitrite anions in deuterated solvents was thus performed (Table 4). It was found that in DMF, acetonitrile, and chloroform, the difference values of the proton shifts were close to negligible. In benzene, the difference values for the chemical shifts

Table 4. Comparison of ^{1}H chemical shifts of intermediate **1b** before and after addition of nitrite anion in various deuterated solvents.



	[D]solvent	H1	H2	H3	H4	H5	$H6_a$	$H6_b$
no nitrite	benzene	4.11	6.16	5.10	6.07	3.42	4.22	4.58
nitrite	benzene	4.93	6.24	6.13	6.34	4.56	4.41	4.69
$\Delta\delta$		**0.82**	**0.08**	**1.03**	**0.27**	**1.14**	**0.19**	**0.11**
no nitrite	$CDCl_3$	4.67	5.74	5.23	6.05	4.22	4.41	4.66
nitrite	$CDCl_3$	4.68	5.63	5.30	5.96	4.26	4.32	4.54
$\Delta\delta$		**0.01**	**−0.09**	**0.07**	**−0.09**	**0.04**	**−0.09**	**−0.12**
no nitrite	CD_3CN	4.85	5.60	5.60	6.04	4.40	4.42	4.55
nitrite	CD_3CN	4.94	5.57	5.78	6.03	4.52	4.41	4.52
$\Delta\delta$		**0.09**	**−0.03**	**0.18**	**−0.01**	**0.12**	**−0.01**	**−0.03**
no nitrite	DMF	5.20	5.82	6.21	6.29	4.85	4.70	4.56
nitrite	DMF	5.25	5.85	6.28	6.32	4.91	4.72	4.60
$\Delta\delta$		**0.05**	**0.03**	**0.07**	**0.03**	**0.06**	**0.02**	**0.04**

of the 2-, 4-, and 6-protons remained small, whereas the shifts for the protons in position 1, 3, and 5 were displaced downfield by $\delta = 0.82$, 1.03, and 1.14 ppm, respectively. Similar effects were observed for compounds **1a**, **2a**, and **2b**, although they were not observed for the 2- or 3-OTf (Tf = trifluoromethanesulfonate) intermediate of α-galactoside. Thus, these results indicate the formation of a carbohydrate–nitrite complex in benzene and provided a clue as to how the reported supramolecular control occurred.[6]

Interestingly, the same effect was found in comparison of the proton chemical shifts in intermediates **1b** and **2b** in the absence of nitrite anions in the various deuterated solvents. The proton shift values in positions 1, 3, and 5 were generally displaced to a lower field with an increase in solvent polarity. For example, for intermediate **1b** (Figure 3), the protons in positions 1, 3, and 5, respectively, shifted from $\delta =$ 4.11, 5.10, and 3.42 ppm in benzene to $\delta = 4.67$, 5.23, and 4.22 ppm in chloroform; $\delta = 4.85$, 5.60, and 4.40 ppm in acetonitrile; $\delta = 4.96$, 6.04, and 4.42 ppm in DMSO; and $\delta =$ 5.20, 6.21, and 4.85 ppm in DMF. The proton shifts in DMSO were very similar to the deshielding results for nitrite in benzene ($\delta = 4.93$, 6.15, and 4.56 ppm), which suggests that the same interaction occurs between intermediate **1b** and DMSO as that between intermediate **1b** and the nitrite anions. However, DMF resulted in higher shift values

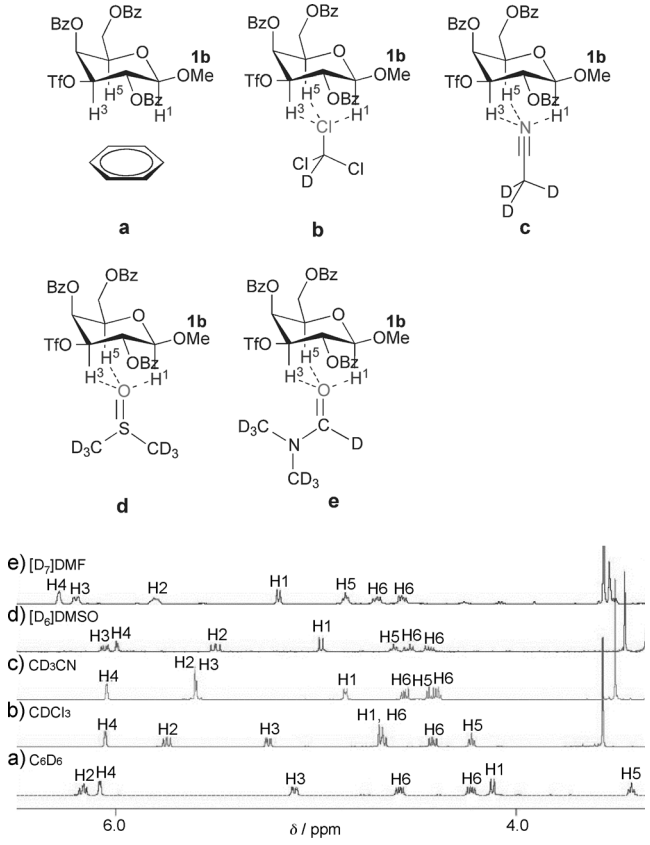


Figure 3. Comparison of ^{1}H chemical shifts of compound **1b** in different deuterated solvents and proposed **1b**/solvent molecule complexes with a) C_6D_6, b) $CDCl_3$, c) CD_3CN, d) [D_6]DMSO, and e) [D_7]DMF.

than did the nitrite anions in benzene. For intermediate **2b**, the protons in positions 1, 3, and 5 shifted from $\delta = 3.96$, 5.53, and 3.47 ppm in benzene to $\delta = 5.30$, 6.10, and 4.85 ppm in DMF, which are slightly higher than the shift values that result from nitrite in benzene ($\delta = 4.74$, 5.97, and 4.35 ppm).

These results indicate that, similar to the nitrite ions, the solvent molecules are also able to interact with the CH 1-, 3-, 5-position three-point binding motif to form van der Waals or hydrogen-bond complexes (Figure 3). It has been shown that carbohydrate/π interactions generally occur between H1, H3, and H5 protons of pyranosides and the benzene ring.[1c,j,5] Thus, it is possible that, in the nonpolar solvent benzene, complex **a** can form between compound **1b** and the benzene molecules by means of CH–π interactions, although this type of interaction may be quite weak (Figure 4). However, owing to the magnetic anisotropy of

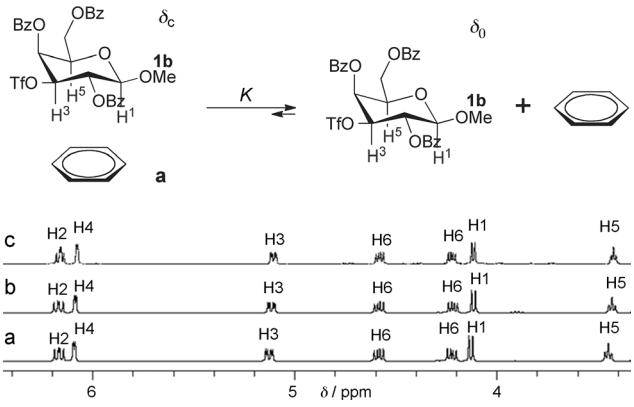
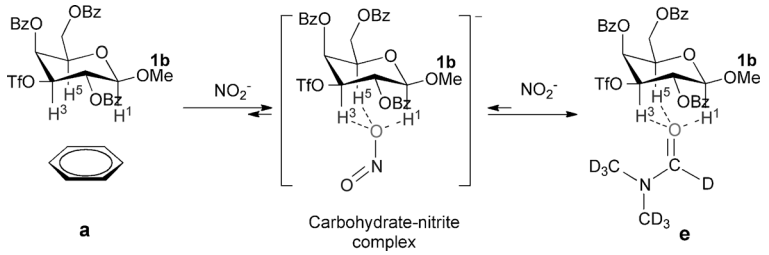


Figure 4. Comparison of ^{1}H-chemical shifts of compound **1b** in C_6D_6 in various concentrations: a) 0.006, b) 0.025, c) 0.066 M.

benzene, protons H1, H3, and H5, may also experience additional magnetic shielding in the complex. On the other hand, the "real" chemical shift (without any shielding effects) of compound **1b** δ_0 should be displaced downfield compared to the "real" chemical shift of complex **a**. Since a low concentration of compound **1b** equates the formation of a large proportion of complex **a** owing to equilibration, the recorded chemical shifts of H1, H3, and H5 in high concentrations of **1b** should become displaced downfield as compared to the recorded chemical shifts at low concentrations of **1b**. The experiments support this (Figure 4), where the recorded chemical shifts of H1, H3, and H5 were $\delta =$ 4.13, 5.13, and 3.45 ppm for a 0.066 M concentration, $\delta =$ 4.12, 5.12, and 3.43 ppm for a 0.025 M concentration, and $\delta =$ 4.11, 5.10, and 3.42 ppm for a 0.006 M concentration respectively, thus indicating the equilibration between compound **1b** and complex **a**.

However, the downfield shifts of protons H1, H3, and H5 of this complex upon addition of certain entities, indicate the dissociation of the carbohydrate/π complex. The carbohydrate/new-entity association energy thus compensates for the carbohydrate/π dissociation energy. By ^{1}H NMR spec-



Scheme 3. Binding competition between the nitrite and solvent molecules.

troscopic titration experiments, the binding constant relative to carbohydrate/π complex can be determined. Thus, after the addition of relatively poorly solvated nitrite anions, the benzene molecule was instantly displaced from complex **a** to form a carbohydrate-nitrite complex (Scheme 3). In the polar solvents chloroform, acetonitrile, DMF, and DMSO, complexes **b**–**e** can form between compound **1b** and the solvent molecules through van der Waals interactions or weak hydrogen bonds. In these cases, the nitrite anions are also more efficiently solvated, resulting in lower concentrations of carbohydrate–nitrite complexes. Thus, these effects for nitrite were found only in the nonpolar solvents toluene and benzene because of binding competition between the nitrite and solvent molecules (Scheme 3).

^{1}H NMR spectroscopic titration experiments using compound **1b** and various solvents in benzene were also performed (Figure 5). The association constant of DMF, DMSO, and acetonitrile amounted to 1.87, 4.01, and 0.67 M, respectively, thus indicating the proposed **1b**/solvent molecule complexes. It also indicated that these complexations were strengthened by the hydrogen-bonding ability of the solvents.

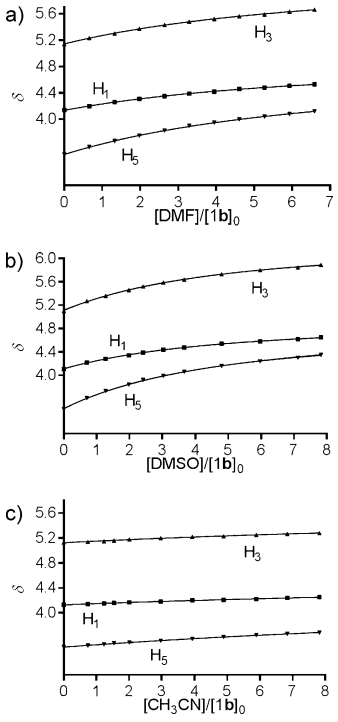


Figure 5. NMR spectroscopic titration for compound **1b** with a) DMF, b) DMSO, and c) acetonitrile in benzene. For DMF, $K = 1.87$ M, $R^2 = 1.000$; for DMSO, $K = 4.01$ M, $R^2 = 1.000$; and for acetonitrile, $K = 0.67$ M, $R^2 = 0.998$.

Conclusion

This study reports the evaluation of a carbohydrate–anion system, in which complexes form between anions and pyranoside B-faces through an H1-, H3-, H5-*cis* pattern. Complexation is likely derived from van der Waals interactions or weak CH···A$^-$ hydrogen bonds between the species, and may be strengthened by electron-withdrawing groups of the carbohydrates and the hydrogen-bonding ability of the anions. This novel host–guest system represents a general effect for pyranoside–anion recognition, which can be applied to a wide range of similar systems.

Experimental Section

General

All commercially available starting materials and solvents were reagent-grade and used without further purification. ^{1}H NMR were recorded with a 400 or 500 MHz or instrument at 298 K in C_6D_6, $CDCl_3$, CD_3CN, [D_6]DMSO and [D_7]DMF using the residual signals from C_6D_6 (^{1}H: $\delta =$ 7.16 ppm), $CHCl_3$ (^{1}H: $\delta = 7.25$ ppm), CD_3CN (^{1}H: $\delta = 1.94$ ppm), [D_6]DMSO (^{1}H: $\delta = 2.50$ ppm) and [D_7]DMF (^{1}H: $\delta = 8.03$ ppm) as internal standards. ^{1}H peak assignments were made by first-order analysis of the spectra, supported by standard ^{1}H,^{1}H correlation spectroscopy (COSY).

General NMR Spectroscopic Analysis Experiments

Carbohydrates (1–3 mg) and TBA salts of the anions (10–20 equiv) were dissolved in deuterated solvents (0.5 mL). The proton shifts were recorded, and the proton peak assignments were made by first-order analysis of the spectra, supported by standard ^{1}H,^{1}H COSY.

Binding Analysis[9]

Compound **7** (2.5 mg) and different amounts of TBA nitrite were dissolved in deuterated benzene (0.5 mL). The proton shifts were recorded, and the proton peak assignments were made by first-order analysis of the spectra, supported by standard ^{1}H,^{1}H COSY.

*Methyl-2,4,6-tri-O-acetyl-3-O-triflate-β-d-galactoside (**1a**)*

The compound was acquired by triflation[10] of methyl 2,4,6-tri-*O*-acetyl-β-D-galactoside.[11] ^{1}H NMR (C_6D_6, 500 MHz): $\delta = 5.67$ (dd, J(H2,H1) = 8.7 Hz, J(H2,H3) = 10.0 Hz, 1H; H2), 5.52 (d, J(H4,H3) = 3.5 Hz, 1H; H4), 4.75 (dd, J(H3,H2) = 10.0 Hz, J(H3,H4) = 3.5 Hz, 1H; H3), 4.08 (dd, J($H6_a$,H5) = 7.0 Hz, J($H6_a$,$H6_b$) = 11.2 Hz, 1H; $H6_a$), 4.00 (dd, J-($H6_b$,H5) = 6.5 Hz, J($H6_b$,$H6_a$) = 11.2 Hz, 1H; $H6_b$), 3.87 (d, J(H1,H2) = 8.7 Hz, 1H; H1), 3.16 (s, 3H; OMe), 3.04–3.08 (m, 1H; H5), 1.79 (s, 3H; OAc), 1.64 (s, 3H; OAc), 1.41 ppm (s, 3H; OAc).

*Methyl-2,4,6-tri-O-benzoyl-3-O-triflate-β-D-galactoside (**1b**)*

The compound was acquired by triflation[10] of methyl 2,4,6-tri-*O*-benzoyl-β-D-galactoside.[11] ^{1}H NMR (C_6D_6, 500 MHz): δ = 8.01–8.18 (m, 6H; OBz), 6.81–7.14 (m, 9H; OBz), 6.16 (dd, *J*(H2,H1) = 7.8 Hz, *J*(H2,H3) = 10.3 Hz, 1H; H2), 6.07 (d, *J*(H4,H3) = 3.5 Hz, 1H; H4), 5.10 (dd, *J*(H3,H2) = 10.0 Hz, *J*(H3,H4) = 3.5 Hz, 1H; H3), 4.58 (dd, *J*($H6_a$,H5) = 6.8 Hz, *J*($H6_a$,$H6_b$) = 11.2 Hz, 1H; $H6_a$), 4.22 (dd, *J*($H6_b$,H5) = 6.2 Hz, *J*($H6_b$,$H6_a$) = 11.2 Hz, 1H; $H6_b$), 4.11 (d, *J*(H1,H2) = 7.8 Hz, 1H; H1), 3.42 (t, *J*(H5,H6) = 6.8 Hz, 1H; H5), 3.20 ppm (s, 3H; OMe).

*Methyl-3,4,6-tri-O-acetyl-2-O-triflate-β-D-galactoside (**2a**)*

The compound was acquired by triflation[10] of methyl 3,4,6-tri-*O*-acetyl-β-D-galactoside.[11] ^{1}H NMR (C_6D_6, 500 MHz): δ = 5.37 (d, *J*(H4,H3) = 3.5 Hz, 1H; H4), 5.00 (dd, *J*(H3,H2) = 10.5 Hz, *J*(H3,H4) = 3.5 Hz, 1H; H3), 4.93 (dd, *J*(H2,H1) = 7.6 Hz, *J*(H2,H3) = 10.5 Hz, 1H; H2), 3.94–4.03 (m, 2H; H6), 3.79 (d, *J*(H1,H2) = 7.6 Hz, 1H; H1), 3.3 (t, *J*(H5,H6) = 6.8 Hz, 1H; H5), 3.21 (s, 3H; OMe), 1.78 (s, 3H; OAc), 1.65 (s, 3H; OAc), 1.55 ppm (s, 3H; OAc).

*Methyl-3,4,6-tri-O-benzoyl-2-O-triflate-β-D-galactoside (**2b**)*

The compound was acquired by general triflation[10] of methyl 3,4,6-tri-*O*-benzoyl-β-D-galactoside.[11] ^{1}H NMR (C_6D_6, 500 MHz): δ = 7.93–8.16 (m, 6H; OBz), 6.80–7.14 (m, 9H; OBz), 6.07 (d, *J*(H4,H3) = 3.5 Hz, 1H; H4), 5.53 (dd, *J*(H3,H2) = 10.3 Hz, *J*(H3,H4) = 3.5 Hz, 1H; H3), 5.42 (dd, *J*(H2,H1) = 7.7 Hz, *J*(H2,H3) = 10.3 Hz, 1H; H2), 4.58 (dd, *J*($H6_a$,H5) = 6.8 Hz, *J*($H6_a$,$H6_b$) = 11.3 Hz, 1H; $H6_a$), 4.14 (dd, *J*($H6_b$,H5) = 6.5 Hz, *J*($H6_b$,$H6_a$) = 11.3 Hz, 1H; $H6_b$), 3.96 (d, *J*(H1,H2) = 7.7 Hz, 1H; H1), 3.47 (t, *J*(H5,H6) = 6.5 Hz, 1H; H5), 3.22 ppm (s, 3H; OMe).

*Methyl-2,3,4,6-tetra-O-acetyl-β-D-galactoside (**3**)*

The compound was acquired by the general acetylation procedure using acetic anhydride/pyridine. ^{1}H NMR (C_6D_6, 500 MHz): δ = 5.68 (dd, *J*(H2,H1) = 7.9 Hz, *J*(H2,H3) = 10.3 Hz, 1H; H2), 5.55 (d, *J*(H3,H4) = 3.7 Hz, 1H; H4), 4.83 (dd, *J*(H3,H2) = 10.3 Hz, *J*(H3,H4) = 3.7 Hz, 1H; H3), 4.10 (dd, *J*($H6_a$,H5) = 6.8 Hz, *J*($H6_a$,$H6_b$) = 11.3 Hz, 1H; $H6_a$), 4.02 (dd, *J*($H6_b$,H5) = 6.8 Hz, *J*($H6_b$,$H6_a$) = 11.3 Hz, 1H; $H6_b$), 3.94 (d, *J*(H1,H2) = 7.9 Hz, 1H; H1), 3.18 (s, 3H; OMe), 3.14–3.19 (m, 1H; H5), 1.79 (s, 3H; OAc), 1.65 (s, 3H; OAc), 1.42 ppm (s, 6H; 2XOAc).

*Methyl-2,3,6-tri-O-acetyl-4-fluoride-β-D-galactoside (**4**)*

The compound was synthesized using methods found in the literature.[11,12] ^{1}H NMR (C_6D_6, 500 MHz): δ = 5.73 (dd, *J*(H2,H1) = 9.0 Hz, *J*(H2,H3) = 10.0 Hz, 1H; H2), 4.96 (dd, 1H; *J*(H3,H2) = 10.0 Hz, *J*(H3,F4) = 30 Hz, H3), 4.58 (d, *J*(H4,F4) = 52.8 Hz, 1H; H4), 4.33 (dd, *J*($H6_a$,H5) = 6.7 Hz, *J*($H6_a$,$H6_b$) = 11.2 Hz, 1H; $H6_a$), 4.08–4.15 (dd, 1H; $H6_b$), 4.11 (d, *J*(H1,H2) = 9.0 Hz, 1H; H1), 3.21 (s, 3H; OMe), 3.12–3.22 (m, 1H; H5), 1.71 (s, 3H; OAc), 1.63 (s, 3H; OAc), 1.59 ppm (s, 3H; OAc).

*Methyl-2,3,4,6-tetra-O-benzoyl-β-D-galactoside (**5**)*

The compound was acquired by the general benzoylation procedure using benzoyl chloride/pyridine. ^{1}H NMR (C_6D_6, 500 MHz): δ = 7.96–8.24 (m, 8H; OBz), 6.68–7.13 (m, 12H; OBz), 6.33 (dd, *J*(H2,H1) = 8.0 Hz, *J*(H2,H3) = 10.4 Hz, 1H; H2), 6.20 (d, *J*(H4,H3) = 3.5 Hz, 1H; H4), 5.75 (dd, *J*(H3,H2) = 10.4 Hz, *J*(H3,H4) = 3.5 Hz, 1H; H3), 4.73 (dd, *J*($H6_a$,H5) = 6.6 Hz, *J*($H6_a$,$H6_b$) = 10.2 Hz, 1H; $H6_a$), 4.38 (d, *J*(H1,H2) = 8.0 Hz, 1H; H1), 4.31 (dd, *J*($H6_b$,H5) = 6.6 Hz, *J*($H6_b$,$H6_a$) = 11.3 Hz, 1H; $H6_b$), 3.73 (t, *J*(H5,H6) = 6.6 Hz, 1H; H5), 3.25 (s, 3H; OMe), 1.57 ppm (s, 3H; OAc).

*Methyl-2,3,6-tri-O-benzoyl-4-S-acetyl-β-D-galactoside (**6**)*

The compound was synthesized using methods found in the literature.[11,12] ^{1}H NMR (C_6D_6, 500 MHz): δ = 8.07–8.27 (m, 6H; OBz), 6.84–7.13 (m, 9H; OBz), 5.98 (dd, *J*(H2,H1) = 7.8 Hz, *J*(H2,H3) = 10.0 Hz, 1H; H2), 5.79 (dd, *J*(H3,H2) = 10.0 Hz, *J*(H3,H4) = 4.5 Hz, 1H; H3), 4.86 (d, *J*(H4,H3) = 4.5 Hz, 1H; H4), 4.74 (dd, *J*($H6_a$,H5) = 7.0 Hz, *J*($H6_a$,$H6_b$) = 11.3 Hz, 1H; $H6_a$), 4.35 (dd, *J*($H6_b$,H5) = 5.8 Hz, *J*($H6_b$,$H6_a$) = 11.3 Hz, 1H; $H6_b$), 4.29 (d, *J*(H1,H2) = 7.8 Hz, 1H; H1), 3.79–3.86 (m, 1H; H5), 3.18 (s, 3H; OMe), 1.57 ppm (s, 3H; SAc).

*Methyl-3,4,6-tri-O-benzoyl-β-D-galactoside (**7**)*

The compound was synthesized by organotin multiple benzoylation.[13] ^{1}H NMR (C_6D_6, 500 MHz): δ = 7.87–8.15 (m, 6H; OBz), 6.82–7.14 (m, 9H; OBz), 5.91 (d, *J*(H4,H3) = 3.5 Hz, 1H; H4), 5.33 (m, *J*(H3,H2) = 10.1 Hz, *J*(H3,H4) = 3.5 Hz, 1H; H3), 4.61 (dd, *J*($H6_a$,H5) = 7.0 Hz, *J*($H6_a$,$H6_b$) = 11.3 Hz, 1H; $H6_a$), 4.18 (dd, *J*($H6_b$,H5) = 6.6 Hz, *J*($H6_b$,$H6_a$) = 11.3 Hz, 1H; $H6_b$), 4.02–4.10 (m; 1H, H2), 3.92 (d, *J*(H1,H2) = 7.6 Hz, 1H; H1), 3.49 (t, *J*(H5,H6) = 7.0 Hz, 1H; H5), 3.29 (s, 3H; OMe), 1.92 ppm (s, 1H; OH).

*Methyl-3,4,6-tri-O-benzoyl-β-D-taloside (**8**)*

The compound was acquired by inversion of compound **7**.[13] ^{1}H NMR (C_6D_6, 500 MHz): δ = 8.01–8.15 (m, 6H; OBz), 6.87–7.17 (m, 9H; OBz), 5.84 (d, *J*(H4,H3) = 3.5 Hz, 1H; H4), 4.93 (t, *J*(H2,H3), *J*(H3,H4) = 3.5 Hz, 1H; H3), 4.77 (dd, *J*($H6_a$,H5) = 7.3 Hz, *J*($H6_a$,$H6_b$) = 11.4 Hz, 1H; $H6_a$), 4.62 (dd, *J*($H6_b$,H5) = 5.2 Hz, *J*($H6_b$,$H6_a$) = 11.4 Hz, 1H; $H6_b$), 3.96 (d, *J*(H2,OH) = 12.0 Hz, 1H; H2), 3.84 (s, 1H; H1), 3.35–3.40 (m, 1H; H5), 3.18 (s, 3H; OMe), 2.92 ppm (d, *J*(OH,H2) = 12.0 Hz, 1H; OH).

*Methyl-3,4,6-tri-O-benzoyl-β-D-glucoside (**9**)*

The compound was synthesized by organotin multiple benzoylation.[13] ^{1}H NMR (C_6D_6, 500 MHz): δ = 7.94–8.14 (m, 6H; OBz), 6.84–7.14 (m, 9H; OBz), 5.62–5.72 (m, 2H; H3, H4), 4.54 (dd, *J*($H6_a$,H5) = 3.2 Hz, *J*($H6_a$,$H6_b$) = 12.0 Hz, 1H; $H6_a$), 4.34 (dd, *J*($H6_b$,H5) = 6.0 Hz, *J*($H6_b$,$H6_a$) = 12.0 Hz, 1H; $H6_b$), 3.91 (d, *J*(H1,H2) = 7.4 Hz, 1H; H1), 3.60 (b, 1H; H2), 3.46 (b, 1H; H5), 3.24 ppm (s, 3H; OMe).

*Methyl-2,3,4-tri-O-benzoyl-β-D-galactoside (**10**)*

The compound was acquired by removing the 6-TIPS (triisopropylsilyl) group of methyl 2,3,4-tri-*O*-benzoyl-6-O-triisopropylsilyl-β-D-galactoside, which was synthesized using methods found in the literature.[10a,13] ^{1}H NMR (C_6D_6, 500 MHz): δ = 8.00–8.16 (m, 6H; OBz), 6.70–7.01 (m, 9H; OBz), 6.30 (dd, *J*(H2,H1) = 8.0 Hz, *J*(H2,H3) = 10.5 Hz, 1H; H2), 5.97 (d, *J*(H4,H3) = 3.5 Hz, 1H; H4), 5.68 (dd, *J*(H3,H2) = 10.5 Hz, *J*(H3,H4) = 3.5 Hz, 1H; H3), 4.37 (d, *J*(H1,H2) = 8.0 Hz, 1H; H1), 3.67 (dd, *J*($H6_a$,H5) = 6.0 Hz, *J*($H6_a$,$H6_b$) = 10.3 Hz, 1H; $H6_a$), 3.44–3.53 (m, 2H; H5, $H6_b$), 3.24 ppm (s, 3H; OMe).

*Methyl-2,3,6-tri-O-acetyl-β-D-glucoside (**11**)*

The compound was synthesized by organotin multiple acetylation.[13] ^{1}H NMR (C_6D_6, 500 MHz): δ = 5.26 (dd, *J*(H2,H1) = 8.0 Hz, *J*(H2,H3) = 9.2 Hz, 1H; H2), 5.21 (t, *J*(H3,H2) = 9.2 Hz, 1H; H3), 4.32 (dd, *J*($H6_a$,H5) = 4.3 Hz, *J*($H6_a$,$H6_b$) = 12.0 Hz, 1H; $H6_a$), 4.11–4.20 (dd, 1H; $H6_b$), 4.14 (d, 1H; *J*(H1,H2) = 8.0 Hz, H1), 3.40–3.50 (b, 1H; H4), 3.21 (s, 3H; OMe), 2.99–3.08 (m, 1H; H5), 1.74 (s, 3H; OAc), 1.73 (s, 3H; OAc), 1.60 ppm (s, 3H; OAc).

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