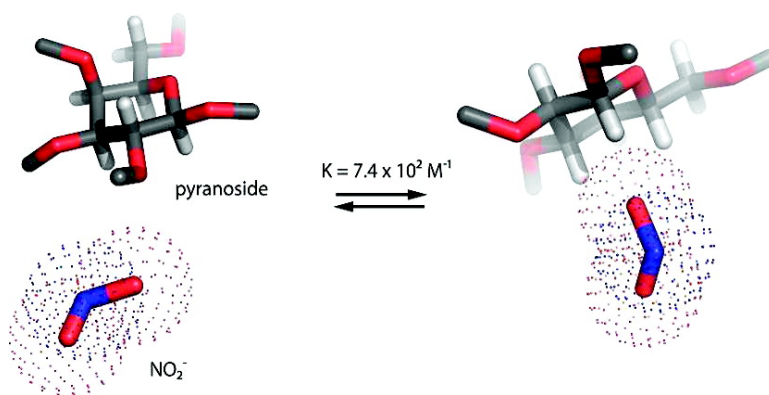


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Supramolecular Control in Carbohydrate Epimerization: Discovery of a New Anion Host–Guest System

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Supramolecular control is an important advancement in modern synthetic chemistry,¹ enabling for example improved selectivities and enhanced reaction rates. Recognition-based proximity effects of participating reactants are generally involved in these systems, positioning the components by templating prior to the reaction sequence. Such means to achieve improved control is perhaps particularly important in carbohydrate synthesis, owing to small differences in reactivity between different positions, and application of supramolecular principles may in this case lead to new and improved reaction routes. For example, the control of substitution reactions could in this case be envisaged, arranging an anionic nucleophile to the electrophilic species. However, other than hydrogen-bond interactions by hydroxyl groups, often taking place in biological systems, anion recognition by carbohydrates has never been reported.

In the present study, we describe the effect of supramolecular control in carbohydrate epimerization based on a new anion-recognition system (Figure 1). The interaction between pyranosides and nitrite thus resulted in dramatic rate control in the inversion reaction, leading to either activation or deactivation effects.

Recently explored in our laboratory,² the Lattrell–Dax (nitrite-mediated) epimerization reaction is an attractive way to generate carbohydrate structures of inverse configuration.³ This substitution reaction proceeds through an unstable nitrite ester intermediate and is preferentially performed in polar aprotic solvents such as acetonitrile or DMF.^{2–4} Nonpolar solvents are mainly chosen when neighboring group participation effects need to be suppressed.⁵

However, more detailed studies of the reaction revealed an unusual solvent effect for certain reactants (Figure 2). For example, when the β -D-galactopyranoside derivative **1a** was tested in the reaction, the reaction rates proved generally higher in more polar solvents, as expected, and the rate increased in the order: $\text{CDCl}_3 < \text{CD}_2\text{Cl}_2 < \text{CD}_3\text{CN} < \text{DMF-}d_7$. However, the results in benzene broke this trend, and although this solvent has the lowest polarity, the reaction proceeded at a faster rate.

To further analyze these results, a series of tests was performed for the epimerization of different methyl D-glycopyranosides. All reactions were performed separately in DMF and toluene at 50 °C, and the reaction times were monitored. The results were in this case very conspicuous: inversion of the 2-position of methyl β -D-galactopyranosides **2a** and **2b** proceeded to >90% conversion in 20–24 h in DMF,⁶ whereas it completely failed in toluene (Table 1). Furthermore, in contrast to the rapid reaction times for the inversion of the 3-position of β -galactosides **1a** in toluene, no reaction occurred for its α -anomer (**3**).

During ¹H NMR studies of these reactions, it was surprisingly found that certain signals were dramatically shifted when nitrite anion was added. More detailed studies were performed, and the 3-OTf derivative **1b** was analyzed in deuterated DMF, acetonitrile, chloroform, and benzene. Interestingly, it was found that the relative shift differences in the absence and presence of nitrite were close



Figure 1. Supramolecular control from carbohydrate-anion recognition.

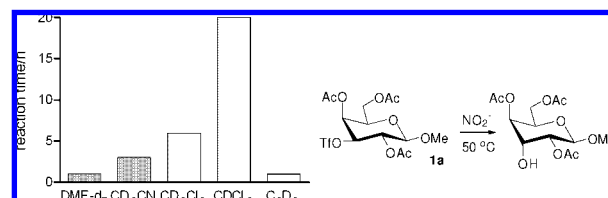


Figure 2. Solvent effects in the Lattrell–Dax epimerization reaction.

to negligible in DMF, acetonitrile, and chloroform, whereas pronounced differences were recorded in benzene (Table 2). The signals for the protons in the 1-, 3-, and 5-positions were in this case shifted downfield by 0.82, 1.03, and 1.14 ppm, respectively, while the shifts of the 2-, 4-, and 6-protons remained largely constant. Similar effects were also recorded for the 2-OTf derivative **2b**, where the 1-, 3-, and 5-protons were deshielded by 0.78, 0.44, and 0.88 ppm, respectively, in benzene, and the relative shifts of the 2-, 4-, and 6-protons were close to zero. In DMF, no deshielding could be seen. Furthermore, in contrast to the results for the β -anomer, no effects were observed for the α -form (**3**) of the 3-OTf derivative.

All these results point to a supramolecular control effect. The carbohydrate structures present polar binding regions in their favored conformations, accentuated by electron-withdrawing protecting/leaving groups. Negatively charged species can thus interact with these structures, forming relatively strong molecular complexes. The nitrite ion can in this case be accommodated at the center of the pyranoside B-face to produce an anion-carbohydrate

Table 1. Comparison of Nitrite-Mediated Inversion in DMF and Toluene

reactant	DMF		toluene	
	time (h)	convn (%)	time (h)	convn (%)
1a	1	87	1	89
1b	2	92	2	90
2a	20	94	24	0
2b	24	95	20	0
3	72	61	72	0

Table 2. Relative ^1H Shifts ($\Delta\delta$) of Derivatives **1b**, **2b**, and **3** in the Presence and Absence of Nitrite Anion in *d*-Benzene

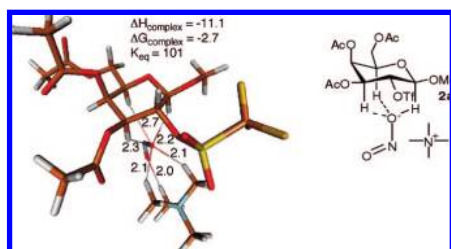
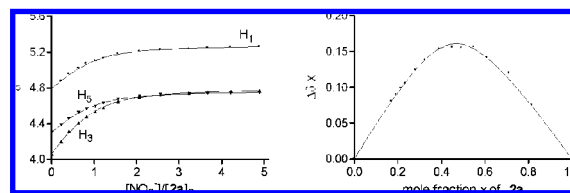
	H1	H2	H3	H4	H5	H6 _a	H6 _b
1b	0.82	0.08	1.03	0.27	1.14	0.19	0.11
2b	0.78	0.04	0.44	0.13	0.88	0.12	0.09
3	0.00	-0.02	0.00	0.00	0.06	0.00	0.00

complex, apparently reinforced by weak CH–O bonds, resulting in a 1-, 3-, 5-hydrogen deshielding effect. This also explains why the effect was only found in nonpolar solvents, since competition in better solvating media hampers the binding effect.

This model is further corroborated by the experimental results obtained from the Lattrell–Dax reaction. Especially for the inversion of the β -galacto-type 3-position in nonpolar solvents, an improved formation of this anion-carbohydrate complex controls the overall rate leading to accelerated reaction compared to more polar solvents. Although the host–guest complex is also formed between nitrite and derivatives **2a** and **2b**, the outcome is unproductive since the inversion path of the reaction originates from the A-face.

To further support the host–guest model, a quantum chemical study was performed. All structures were optimized at the B3LYP/6–31G(d) level using the Gaussian 03 program,⁷ and vibrational analysis was performed at the same level of theory. Single-point energies in toluene were obtained at the B2PLYP/aug-cc-pVDZ level with the COSMO solvation model, employing the ORCA program suite.⁸ Compound **2a** and tetramethylammonium nitrite were chosen as the model, and the binding mode and the association constant of the host–guest system were calculated (Figure 3). The binding constant could in this case be estimated to $1.0 \times 10^2/\text{M}$, and the guest nitrite anion was found to be situated slightly closer to the 1- and 3-hydrogens than to the 5-hydrogen at the carbohydrate B-face.

The calculation predictions were subsequently supported by ^1H NMR titration experiments using compound **2a** and tetrabutylammonium nitrite in *d*-benzene (Figure 4). The association constant amounted to $7.4 \times 10^2/\text{M}$, and Job's analysis indicated a 1:1 ratio of the binding partners. The 1-, and 3-hydrogens were notably more deshielded than the 5-proton, suggesting that the nitrite anion is located closer to these in the complex. In principle, these results are compliant with the well-known carbohydrate-aromatic interactions often found in carbohydrate-binding proteins,⁹ where recent

**Figure 3.** Quantum chemical model of the nitrite-compound **2a** complex. Energies have been calculated for 298 K and 1 M and are given in kcal/mol. Bond lengths are given in angström (Å).**Figure 4.** NMR titration and Job's plot for compound **2a** with tetrabutylammonium nitrite in benzene. $K = 7.4 \times 10^2/\text{M}$, $R^2 = 0.9996$.

results suggest a “three point landing surface” via a CH 1-, 3-, 5- π interaction.^{9d,e} Consequently, the anion recognition effect presented here may have unknown implications in biological recognition. Ongoing studies with anions other than nitrite show similar results, suggesting a general recognition effect.

In conclusion, we have identified a new supramolecular anion-recognition system, which also exerts pronounced effects in carbohydrate synthesis. The effect proved sensitive to the carbohydrate structure, requiring a H1-, H3-, H5-cis pattern for efficient complexation. Given these constraints, we believe that this is a general effect for pyranoside-anion recognition, applicable to a wider range of similar systems.

Acknowledgment. This study was supported by the Swedish Research Council and the Royal Institute of Technology.

Supporting Information Available: ^1H shifts of derivatives **1b**, **2b**, and **3** in DMF and benzene. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (a) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; Wiley-VCH: Weinheim, Germany, 1995. (b) Lehn, J.-M. *Science* **2002**, *295*, 2400–2403. (c) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2383–2426. (d) Fyfe, M. C. T.; Stoddart, J. F. *Acc. Chem. Res.* **1997**, *30*, 393–401. (e) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37–44.
- (a) Dong, H.; Pei, Z. C.; Ramström, O. *J. Org. Chem.* **2006**, *71*, 3306–3309. (b) Dong, H.; Pei, Z. C.; Angelin, M.; Byström, S.; Ramström, O. *J. Org. Chem.* **2007**, *72*, 3694–701. (c) Dong, H.; Pei, Z. C.; Ramström, O. *Chem. Commun.* **2008**, 1359–1361.
- (a) Albert, R.; Dax, K.; Link, R. W.; Stutz, A. E. *Carbohydr. Res.* **1983**, *118*, C5–C6. (b) Lattrell, R.; Lohaus, G. *Justus Liebigs Ann. Chem.* **1974**, 901–920.
- (a) Liakatos, A.; Kiefel, M. J.; von Itzstein, M. *Org. Lett.* **2003**, *5*, 4365–4368. (b) Trost, B. M.; Yang, H. B.; Probst, G. D. *J. Am. Chem. Soc.* **2004**, *126*, 48–49.
- (a) Rich, J. R.; Szpacenko, A.; Palcic, M. M.; Bundle, D. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 613–615. (b) Rich, J. R.; Bundle, D. R. *Org. Lett.* **2004**, *6*, 897–900. (c) Pei, Z. C.; Dong, H.; Ramström, O. *J. Org. Chem.* **2005**, *70*, 6952–6955.
- Mixtures were produced in the reactions due to remote group participation between the 2- and 4-positions (see ref 2b).
- Frisch, M. J. et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.
- Neese, F.; Schwabe, T.; Grimme, S. *J. Chem. Phys.* **2007**, *126*, 124115.
- (a) Mazik, M.; Cavga, H.; Jones, P. G. *J. Am. Chem. Soc.* **2005**, *127*, 9045–9052. (b) Klein, E.; Crump, M. P.; Davis, A. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 298–302. (c) Terraneo, G.; Potenza, D.; Canales, A.; Jiménez-Barbero, J.; Baldrige, K. K.; Bernardi, A. *J. Am. Chem. Soc.* **2007**, *129*, 2890–2900. (d) Screen, J.; Stanca-Kaposta, E. C.; Gamblin, D. P.; Liu, B.; Macleod, N. A.; Snoek, L. C.; Davis, B. G.; Simons, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3644–3648. (e) Stanca-Kaposta, E. C.; Gamblin, D. P.; Screen, J.; Liu, B.; Snoek, L. C.; Davis, B. G.; Simons, J. P. *Phys. Chem. Chem. Phys.* **2007**, *9*, 4444–4451.

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