COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Switching extended 1,3-diequatorial and bent 1,3-diaxial states of a disubstituted hinge sugar by ligand exchange reactions on Pt(II)†

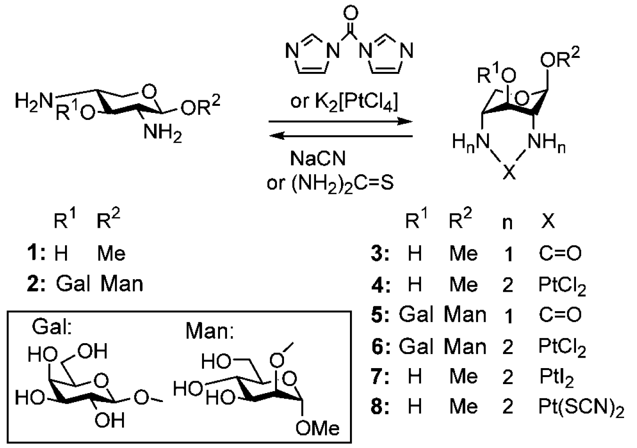
Takuhiro Izumi, Hironobu Hashimoto and Hideya Yuasa*
Department of Life Science, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Nagatsutacho, Midoriku, Yokohama 2268501, Japan. E-mail: hyuasa@bio.titech.ac.jp

Received (in Cambridge, UK) 26th September 2003, Accepted 30th October 2003
First published as an Advance Article on the web 20th November 2003

The bent conformation of a trisaccharide containing 2,4-diaminoxylopyranoside, in which both end sugars are presented in 1,3-diaxial orientation, is fixed by chelation of the diamino groups to Pt(II) and unfixed by a ligand exchange reaction with NaCN or thiourea giving its extended conformation.

Conformationally constrained saccharides can be used as bound-conformation analogs of the oligosaccharides in their receptor proteins[1] or as scaffolds for peptidomimetics.[2] Of particular interest are those having unusual conformations, such as the turn motif in which sugar moieties are attached to both 1,3-diaxial hydroxy groups of a constrained pyranose. However, glycosylation of the both axial hydroxy groups is not an easy task, usually producing a mixture of monoglycosylated products.[3] Furthermore, modification of 1,3-diaxial hydroxy groups with bulky groups may distort the pyranose ring, and hence the 1,3-diaxial orientation.[4] Another approach to the turn motif can be a closing-tongs strategy, in which 1,3-diequatorial substituents are converted to 1,3-diaxial orientation by conformational transition of the six-membered ring. In close relation to this strategy, we reported in the previous paper that the 1,3-diaxial state was only transiently obtained by the addition of mercury or zinc ion to a 1,3-disubstituted-2,4-diaminoxylopyranoside (hinge sugar).[5] Chelation of the diamino groups to those metal ions was an equilibrium process, causing a $^4C_1$–$^1C_4$ conformational exchange concomitant with a flip between 1,3-diequatorial and the 1,3-diaxial states. This paper describes the success of the closing-tongs strategy in obtaining a $^1C_4$-locked hinge sugar with 1,3-diaxially oriented components, and switching between the 1,3-diaxial and 1,3-diequatorial orientations.

To fix the hinge sugar into $^1C_4$ conformation, we first examined an intramolecular covalent cross-linking of the diamino groups of the hinge sugar and its trisaccharide derivative **2** using carbonyldiimidazole. Whereas **1** reacted smoothly (room temperature, 2 h), **2** required harsh conditions (120 °C, 24 h), to yield the cyclic urea derivatives **3** and **5**‡ in 77% and 36% yields, respectively (Scheme 1). The $^1C_4$ conformation of the hinge sugar was confirmed for each product by ^{1}H NMR from the small ^3J values (0–3.8 Hz) and the significant values of ^4J (0.6–1.4 Hz) for H-1 through H-4 and one of two H-5s, whose values are typical for the serial equatorial protons. Compound **3** is quite stable, tolerating 6 M HCl and 10 M NaOH for 24 h at 23 °C. In other words, carbonylation of the hinge sugar turned its extended structure into a bent one, but it could not be unlocked.



	R^1	R^2
1:	H	Me
2:	Gal	Man

	R^1	R^2	n	X
3:	H	Me	1	C=O
4:	H	Me	2	$PtCl_2$
5:	Gal	Man	1	C=O
6:	Gal	Man	2	$PtCl_2$
7:	H	Me	2	PtI_2
8:	H	Me	2	$Pt(SCN)_2$

Scheme 1

The greatest advantage of using the closing tongs strategy will be obtained when the closed state can be turned back into its original extended state in response to an external stimulus, by which an allosteric system[6] can be added to mimetic ligands. We thus examined chelation by metal ions to instal a releasable locking system for the bent structure. Among several metal reagents added to a buffered solution (pH 7) of the hinge sugar **1**, $K_2[PtCl_4]$ permitted a slow change in $[\alpha]_D$ from −15° to −51° over 10 h at 30 °C, suggesting irreversible conformation change from $^4C_1$ to $^1C_4$. It was also shown by ^{1}H NMR that signals of the platinum complex **4** having a $^1C_4$ conformation emerged 15 min after Pt(II) addition and predominated after 12 h (46% yield). An ESI-Mass analysis§ confirmed that this compound had a cisplatin structure, in which two chlorine atoms were retained.[7] The trisaccharides **2** also underwent formation of a cisplatin-like structure to yield a bent-locked trisaccharide **6** within 12 h (46% yield). Comparison of ^{1}H NMR between **2** and **6** clearly indicates that only the hinge signals underwent changes in both chemical shifts and coupling constants of the hinge sugar (Fig. 1). The small coupling constants again supported the $^1C_4$ structure of the hinge sugar. Inter-residual NOE cross peaks were observed in NOESY spectrum of the trisaccharide **6** for H-1:H-1′, H-2:H-1′, H-2′:H-1″, and H-3′:H-1″; there were no cross peaks between the reducing and non-reducing ends. This result supports a bent structure as shown in Fig. 2, in which O-5 and O-2″ are in close contact. This close contact might arise from favorable water exclusion by the inter-residual squeezing.

From the time course of the optical rotation, both the carbonylation (k = 1.19×10^{-3} s^{-1}) and Pt(II) complex formation (k = 1.30×10^{-4} s^{-1}) were found to be first order reactions, indicating that the intramolecular N–C and N–metal formations leading to bicyclic structures are rate-determining. These results demonstrate how energy-consuming it is to close the hinge sugar, with a view to the general idea that intramolecular six-membered ring formations are kinetically favored over intermolecular bond formations. However, the use of a carbohydrate derivative to do this difficult task is validated by the fact that 2-deoxystreptamine, (1,3/2,4,6)-4,6-diamino-1,2,3-cyclohexanetetrol, underwent no conformational changes upon addition of Pt(II). Presumably both the anomeric effect, which favors axial over equatorial glycosides, and the absence of substituents on the ring oxygen atom play roles in facilitating the ring flipping.

To unchelate the platinum complex **4**, we undertook some ligand exchange reactions. Treatment of **4** with four equivalents of thiourea (30 °C, 24 h, 80%) or sodium cyanide (30 °C, 2.5 h, 74%) led to a complete ligand exchange, each giving the unchelated compound **1**. However, treatment with KI and KSCN underwent halfway ligand exchanges to give the complexes **7** and **8**, respectively. These ligand reactivities are explainable by the trans effect: the ligand located trans to the leaving group has a powerful effect on the rate of ligand exchange reactions. The order of

---

† Electronic supplementary information (ESI) available: experimental procedures and full characterization of the reported compounds. See http://www.rsc.org/suppdata/cc/b3/b311811h/

DOI: 10.1039/b311811h

This journal is © The Royal Society of Chemistry 2004

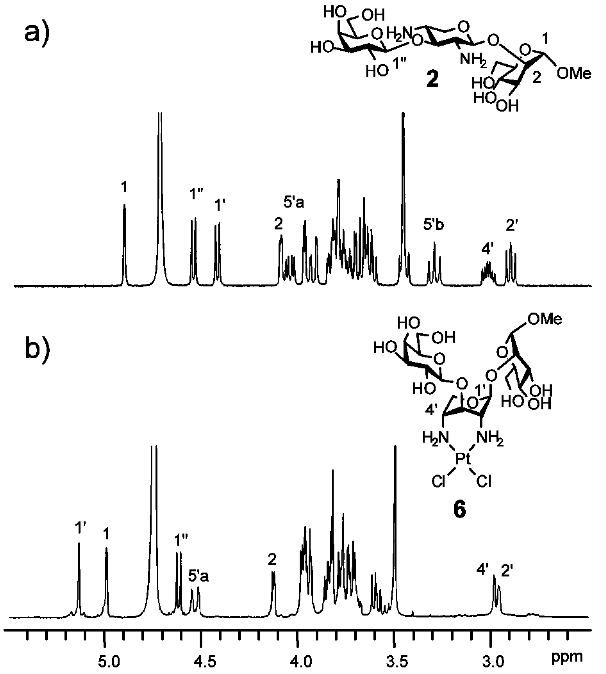


Fig. 1 (a) The extended structure of the trisaccharide, Galβ(1,3)Hinβ-(1,2)ManαOMe (**2**), and its 400 MHz ^{1}H NMR spectrum in D_2O at 30 °C. (b) The bent structure of the trisaccharide, Galβ(1,3)Hin($PtCl_2$)β(1,2)-ManαOMe (**6**), and its 400 MHz ^{1}H NMR spectrum in D_2O at 30 °C. Hin denotes the hinge sugar **1**.

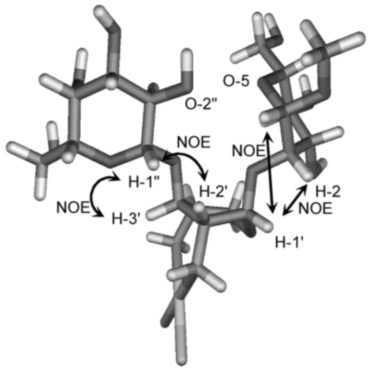


Fig. 2 Observed NOEs and predicted conformation of trisaccharide–Pt(II) complex **6**.

enhancement is CN^- > $(H_2N)CS$ > NCS^- > I^- > Cl^-.[8] Substitution of the chlorine atoms of **4** with strongly enhancing ligands, such as CN^- or $(H_2N)CS$ facilitated a further substitution of the amino groups with the excess ligands. Thus, the bent trisaccharide **6** was unchelated with sodium cyanide (30 °C, 4 h, 81%) to obtain the extended trisaccharide **2**.

In conclusion, we demonstrate here a novel carbohydrate-based turn motif, in which two sugar components can be presented in the crowded 1,3-diaxial orientation and the addition of an external stimulus recover the extended 1,3-diequatorial orientation. This system can be regarded as a molecular machine, because it can do work through repeated closing and opening by cycling between addition of the fuel Pt(II) and its subsequent removal with the 'fuel release' ligand.[6] Moreover, the tongs-like motion of the hinge sugar would be used to construct a variety of molecular devices.

This work was supported by the Grant of the 21st Century COE Program and a Grant-in-Aid for Scientific Research (No. 13680668) from Japanese Ministry of Education, Culture, Sports, Science and Technology. We thank Professor Yasuhiro Kajihara for the ^{1}H NMR analysis of compounds **5** and **6**.

Notes and references

‡ *Selected data for* **5**: ^{1}H NMR (D_2O) δ 5.05 (s, 1H, H-1′), 5.01 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1), 4.71 (d, 1H, $J_{1'',2''}$ = 7.6 Hz, H-1″), 4.47–4.52 (m, 2H, H-3′, 5a′), 4.14 (dd, 1H, $J_{2,3}$ = 3.7 Hz, H-2), 4.05 (dd, 1H, J = 0.6, 3.4 Hz, H-4″), 4.01 (dd, 1H, $J_{5,6a}$ = 2.1, $J_{6a,6b}$ = 12.2 Hz, H-6a), 3.96 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 3.91 (dd, 1H, $J_{5,6b}$ = 5.8 Hz, H-6b), 3.72–3.88 (m, 7H, H-4, 2′, 4′, 3″, 5″, 6a″, 6b″), 3.69 (dd, 1H, $J_{2'',3''}$ = 9.9 Hz, H-2″), 3.64 (bd, 1H, $J_{5a',5b'}$ = 11.6 Hz, H-5b′), 3.53 (s, 3H, OMe). ESI-HRMS calcd 513.1932 (M + H); Found 513.1931.

§ *ESI-Mass of* **4**: *m/z* = 469.0, 468.0, 467.0, 466.0, 465.0. The shape of comb-like signals was consistent with the calculated one based on the natural abundance of ^{35}Cl, ^{37}Cl, ^{194}Pt, ^{195}Pt, ^{196}Pt.

1 H. Yuasa and H. Hashimoto, *Trends Glycosci. Glycotechnol.*, 2001, **13**, 31–55; S. K. Das, J.-M. Mallet, J. Esnault, P.-A. Driguez, P. Duchaussoy, P. Sizun, J.-P. Hérault, J.-M. Herbert, M. Petitou and P. Sinaÿ, *Angew. Chem. Int. Ed.*, 2001, **40**, 1670–1673.
2 F. Peri, L. Cipolla, B. La Ferla, E. Forni, E. Caneva, L. De Gioia and F. Nicotra, *ACS Symp. Ser.*, 2003, **841**, 141–156; P. V. Murphy, J. L. O'Brien, L. J. Gorey-Feret and A. B. Smith III, *Tetrahedron*, 2003, **59**, 2259–2271; S. A. W. Gruner, E. Locardi, E. Lohof and H. Kessler, *Chem. Rev.*, 2002, **102**, 491–514.
3 P. Uhlmann and A. Vasella, *Helv. Chim. Acta*, 1992, **75**, 1979–1994.
4 M.-L. Crublet, I. Pouny, C. Delaude and C. Lavaud, *J. Nat. Prod.*, 2002, **65**, 1560–1567; D. Dai and O. R. Martin, *J. Org. Chem.*, 1998, **63**, 7628–7633; N. Sakairi, M. Hayashida, A. Amano and H. Kuzuhara, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1301–1313.
5 H. Yuasa and H. Hashimoto, *J. Am. Chem. Soc.*, 1999, **121**, 5089–5090.
6 V. Balzani, M. Venturi and A. Credi, in *Molecular Devices and Machines.*, VCH, Weinheim, 2003; V. Balzani, A. Credi, F. M. Raymo and J. F. Stoddart, *Angew. Chem. Int. Ed.*, 2000, **39**, 3348–3391.
7 E. R. Jamieson and S. J. Lippard, *Chem. Rev.*, 1999, **99**, 2467–2498.
8 R. B. Jordan, in *Reaction Mechanisms of Inorganic and Organometallic Systems, second edition*, Oxford University Press, New York, 1998, Chapter 3.