Sugar-Incorporated N-Heterocyclic Carbene Complexes

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Summary: A glucopyranoside-incorporated N-heterocyclic carbene iridium complex was synthesized using an Ag complex as a carbene transfer agent. The catalytic ability of the Ir complex, the structure of which was determined by X-ray crystallography, toward H/D exchange reactions involving 2-propanol and cyclohexanol in D_2O were examined.

Incorporation of saccharide groups into transition-metal complexes gives them advanced properties such as hydrophilicity and molecular recognition. Saccharide-incorporated ligands make their complexes highly soluble in water, and therefore, they can be utilized for applications in water. For example, a ligand prepared by the reaction of 2-quinolinecarboxaldehyde with D-glucosamine has been shown to be useful for the selective detection of Hg^{2+} ions in natural water.[1] In this system, the role of the saccharide is not only to improve the solubility in water but also to interact with Hg^{2+} ions for selective detection. Moreover, water-soluble Rh complexes with saccharide-incorporated ligands are catalysts for enantioselective hydrogenation.[2] These results suggest the possibility of selective interactions between saccharides and other substrates, which can be utilized for catalytic reactions. Furthermore, the interaction between saccharides is important for cell recognition in biological systems,[3] and it has been utilized for anticancer drug delivery.[4] In these systems, saccharide groups have been incorporated into metal complexes via N-, S-, and P-donor linkages.[5]

On the other hand, N-heterocyclic carbene (NHC) complexes have been investigated intensively for their catalytic ability: for example, olefin metathesis,[6] hydrogenation,[7] hydrogen transfer,[8] hydroformylation,[9] and hydrosilylation.[6f,10] The complexes are thought to be alternatives to catalysts containing phosphine ligands, because the NHC ligands containing only C, H, and N atoms are more sustainable and some of them have better catalytic ability than the corresponding phosphine complexes due to better σ-donation. For example, an IrCp* NHC complex has been shown to have better catalytic ability for the H/D exchange reaction involving organic molecules via C−H activation.[11] In addition, NHC ligand precursors with a variety of substituents can be easily prepared.

Inspired by these reports, we decided to examine whether saccharide-incorporated NHC complexes are useful for the development of new catalysts and drugs. Herein, we report the synthesis of a glucopyranoside-substituted NHC precursor and its NHC Ag complexes, which are useful starting materials for transmetalation syntheses of many other transition-metal complexes. We also report the structure and properties of an Ir complex prepared using the Ag complex as a starting material.

A glucopyranoside-incorporated NHC precursor, 1-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)imidazolium bromide (**1HBr**, magiHBr) (Scheme 1), was synthesized by the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide and 1-methylimidazole in acetonitrile. NMR spectra of **1HBr** clearly showed that all four acetyl groups remained. In addition, the spectra suggested that it was a β-anomer due to the neighboring group participation.

One synthetic method for obtaining NHC complexes is transmetalation using Ag NHC complexes, which are well-known to be carbene transfer agents.[12] To establish the general syntheses of a variety of metal complexes of **1**, we prepared Ag complexes to act as starting materials for transmetalation.

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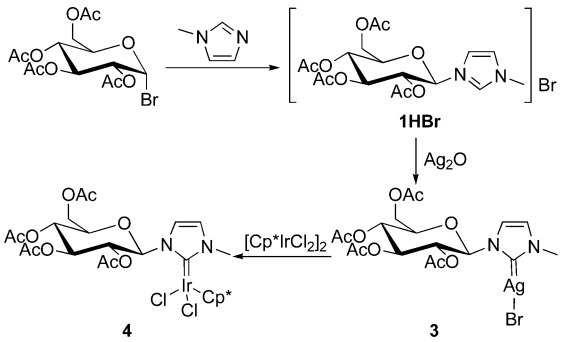
Scheme 1. Preparation of the β-D-Glucopyranoside-Incorporated NHC Precursor and Its NHC Ag and Ir Complexes



The reactions of **1HBr** and Ag_2O were solvent dependent and afforded different silver complexes of **1** in acetone or DMSO. These complexes had different signals in the ^{1}H NMR spectra, and the signal for the proton at the 2-position of the imidazole ring was absent. Only the product from the reaction in DMSO gave a molecular ion peak using electrospray mass spectrometry (ESI-MS), and it was determined to be an ionic complex, $[Ag(magi)_2](AgBr_2)$ (**2**).[13] Another product, which showed no molecular ion peaks in ESI-MS, was determined to be a molecular complex, [AgBr(magi)] (**3**).[14] This solvent dependence was reported for some Ag complexes.[15]

Using complex **3** as a carbene transfer agent, an Ir complex of **1**, $[IrCp^*Cl_2(magi)]$ ($Cp^* = \eta^5$-C_5Me_5) (**4**),[16] was synthesized by the reaction of $[IrCp^*Cl_2]_2$[17] with **3**. Single crystals of **4** suitable for X-ray analysis were obtained by slow diffusion of Et_2O into a CH_2Cl_2 solution.[18] There were crystallographically

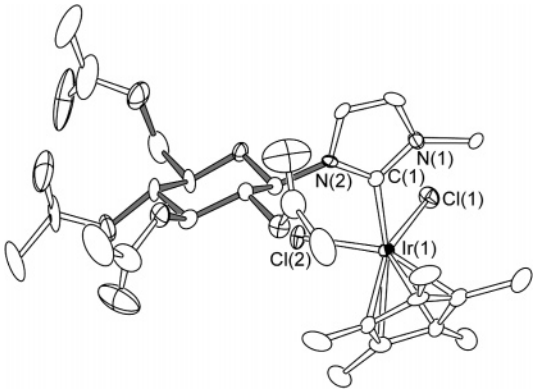


Figure 1. ORTEP drawing of **4** (thermal ellipsoids set at 30% probability). Hydrogen atoms are omitted for clarity.

two independent molecules (**4a** and **4b**) in the asymmetric unit, and only one of them is shown in Figure 1, because both molecules have almost the same structure. In **4**, all four protecting acetyl groups remained, and the NHC ligand was a β-linked product. In both of the molecules, each IrCp* unit was located on the sterically less hindered α-face of the glucopyranoside group in the crystal. This conformation was maintained in chloroform, which was confirmed through the NOESY spectrum of **4** in $CDCl_3$. NOE correlations were observed for the methyl protons of Cp* with the C1 and C5 protons in the α-face of the glucopyranoside group and one of the imidazolylidene protons with the C2 proton on the β-face. The coordination geometry and bond parameters of the Ir center were similar to those found in $[IrCp^*Cl_2$(1-benzyl-3-methylimidazol-

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(13) Synthesis of **2**: Ag_2O (23 mg, 0.10 mmol) was added to a solution of **1HBr** (100 mg, 0.20 mmol) in DMSO (2 mL). After it was stirred for 4 h, the mixture was filtered through Celite. The filtrate was poured into water to afford a white precipitate of the complex, which was collected by filtration and dried under vacuum. Because the complex slowly decomposed during purification, satisfactory elemental analysis data could not be obtained. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (d, 2H, 4-imidazolylidene), 7.50 (d, 2H, 5-imidazolylidene), 6.10 (d, 2H, 1-glucose), 5.55 (t, 2H, 3-glucose), 5.48 (t, 2H, 2-glucose), 5.22 (t, 2H, 4-glucose), 4.37 (m, 2H, 5-glucose), 4.32 (d, 4H, 6-glucose), 3.82 (s, 6H, CH_3 N), 2.04 (s, 6H, CH_3 AcO), 2.02 (s, 6H, CH_3 AcO), 1.98 (s, 6H, CH_3 AcO), 1.88 (s, 6H, CH_3 AcO). ^{13}C NMR (400 MHz, DMSO-d_6): δ 180.86 (2-imidazolylidene), 170.5 (C═O), 170.0 (C═O), 169.9 (C═O), 169.1 (C═O), 124.2 (4-imidazolylidene), 119.9 (5-imidazolylidene), 86.0 (1-glucose), 73.5 (5-glucose), 72.3 (3-glucose), 71.3 (2-glucose), 68.1 (4-glucose), 62.4 (6-glucose), 39.0 (CH_3 N), 21.0 (CH_3 AcO), 20.9 (CH_3 AcO), 20.7 (CH_3 AcO), 20.6 (CH_3 AcO). ESI-MS: *m*/*z* 413 ($[M - AgBr_2]^+$).

(14) Synthesis of **3**: Ag_2O (116 mg, 0.50 mmol) was added to a solution of **1HBr** (100 mg, 0.20 mmol) in acetone (2 mL). After it was stirred for 2 h, the mixture was filtered through Celite to give a pale yellow filtrate, which was dried under reduced pressure to afford a light yellow material. Anal. Calcd for $C_{18}H_{24}N_2AgBrO_9$: C, 36.02; H, 4.03; N, 4.67. Found: C, 36.09; H, 3.99; N, 4.48. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, 1H, 4-imidazolylidene), 7.03 (d, 1H, 5-imidazolylidene), 5.76 (d, 1H, 1-glucose), 5.40 (t, 1H, glucose), 5.27 (t, 1H, glucose), 5.22 (t, 1H, glucose), 4.31 (dd, 2H, 6-glucose), 4.16 (dd, 1H, glucose), 3.86 (s, 3H, CH_3 N), 2.10 (s, 3H, CH_3 AcO), 2.08 (s, 3H, CH_3 AcO), 2.01 (s, 3H, CH_3 AcO), 1.96 (s, 3H, CH_3 AcO). ^{13}C NMR (400 MHz, $CDCl_3$): δ 184.13 (2-imidazolylidene), 170.3 (C═O), 169.41 (C═O), 169.37 (C═O), 169.1 (C═O), 122.7 (4-imidazolylidene), 118.1 (5-imidazolylidene), 86.5 (1-glucose), 74.2 (5-glucose), 72.6 (3-glucose), 70.7 (2-glucose), 67.6 (4-glucose), 61.4 (6-glucose), 38.9 (CH_3 N), 20.53 (CH_3 AcO), 20.42 (CH_3 AcO), 20.36 (CH_3 AcO), 20.29 (CH_3 AcO).

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(16) Synthesis of **4**. Method A: Ag_2O (23 mg, 0.10 mmol) was added to a solution of **1HBr** (98 mg, 0.20 mmol) in acetone (2 mL), and the mixture was stirred at room temperature for 1 h. After removal of the insoluble solids by filtration using Celite, the solvent was removed under reduced pressure to give **3**. A solution of $[IrCp^*Cl_2]_2$ (80 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) was added to **3**. After the mixture was stirred for 18 h, insoluble solids were filtered off to give a yellow filtrate, from which the solvent was removed under reduced pressure to afford yellow microcrystals of **4** (yield: 45 mg, 0.055 mmol, 55%). Method B: Ag_2O (58 mg, 0.25 mmol) was added to a solution of **1HBr** (250 mg, 0.51 mmol) in CH_2Cl_2 (5 mL). After the mixture was stirred for 1 h at room temperature, $[IrCp^*Cl_2]_2$ (200 mg, 0.25 mmol) was added to the reaction mixture and the mixture was stirred for a further 17 h. Insoluble solids were filtered off through Celite, and then the solvent was removed under reduced pressure to give a yellow oily product. The oily product was redissolved in a small amount of CH_2Cl_2, and Et_2O was added to the solution to afford a yellow powder of **4** (yield: 328 mg, 0.41 mmol, 81%). Recrystallization from a solution in a 9:1 mixture of CH_2Cl_2 and acetone (2 mL) by slow diffusion of Et_2O gave yellow crystals of **4** (yield: 236 mg, 0.29 mmol, 58%). Anal. Calcd for $C_{28}H_{39}Cl_2IrN_2O_9$: C, 41.48; H, 4.85; N, 3.46. Found: C, 41.08; H, 4.74; N, 3.23. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18 (s, 1H, 4-imidazolylidene), 6.98 (s, 1H, 5-imidazolylidene), 6.15 (d, 1H, 1-glucose), 5.55 (t, 1H, 2-glucose), 5.25 (m, 2H, 4- and 5-glucose), 4.34 (m, 2H, 3-glucose, 6-glucose), 4.14 (dd, 1H, 6-glucose), 3.99 (s, 3H, CH_3 N), 2.09 (s, 3H, CH_3 AcO), 2.05 (s, 3H, CH_3 AcO), 2.02 (s, 3H, CH_3 AcO), 1.91 (s, 3H, CH_3 AcO), 1.67 (s, 15H, Cp*). ^{13}C NMR (600 MHz, $CDCl_3$): δ 170.9 (C═O), 170.0 (C═O), 169.5 (C═O), 168.5 (C═O), 160.1 (2-imidazolylidene), 124.1 (4-imidazolylidene), 119.2 (5-imidazolylidene), 89.3 ($C_5(CH_3)_5$), 84.5 (1-glucose), 74.1 (5-glucose), 74.0 (3-glucose), 70.1 (2-glucose), 68.0 (4-glucose), 61.4 (6-glucose), 39.0 (CH_3 N), 20.9 (CH_3 AcO), 20.59 (CH_3 AcO), 20.55 (CH_3 AcO), 20.50 (CH_3 AcO), 9.1 ($C_5(CH_3)$). ESI-MS: *m*/*z* 775 ($[M - Cl]^+$), 755 ($[M - Cl - AcO + Na]^+$), 733 ($[M - Cl - AcO + H]^+$), 697 ($[M - 2Cl - AcO]^+$).

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(18) Crystal data for **4**: $C_{28}H_{39}Cl_2IrN_2O_9$, M_r = 810.75, size 0.20 × 0.05 × 0.05 mm, monoclinic, space group $P2_1$, a = 13.962(3) Å, b = 14.058(2) Å, c = 17.559(3) Å, β = 98.762(4)°, $F(000)$ = 1616, V = 3406.3(10) Å^3, T = 193(1) K, Z = 4, D_{calcd} = 1.581 Mg/m^3, μ = 4.1364 mm^{-1}, refinement method full-matrix least squares on F^2, R1 = 0.0557 (observed data with $I > 2\sigma(I)$), wR2 = 0.0934, GOF = 1.021, Flack parameter 0.016(7).

Table 1. Comparison of Bond Lengths (Å) and Angles (deg) of 4 and Other IrCp*NHC Complexes

	4a	**4b**	[Ir-BM][a]	[Ir-Me_4][b]
Ir−C(NHC)	2.054(7)	2.042(8)	2.061(5)	2.044(4)
Ir−Cl	2.426(2)	2.421(2)	2.4150(11)	2.415(1)
	2.431(2)	2.446(2)	2.4256(11)	2.425(1)
Ir−C(Cp*)	2.117(11)−2.232(9)	2.129(10)−2.215(10)	2.148(4)−2.227(5)	2.150(4)−2.257(4)
Cl−Ir−C	85.63(7)	85.30(8)	86.32(4)	85.73(5)
Cl−Ir−Cl	91.5(2)	92.0(2)	91.54(13)	89.8(1)
	93.0(2)	92.5(2)	93.36(13)	92.0(1)
C═C(NHC)	1.287(14)	1.335(15)	1.318(7)	1.333(7)
N−C−N	103.8(6)	103.3(7)	104.4(4)	104.2(4)

[a] [Ir-BM] = [IrCp*Cl_2(1-benzyl-3-methylimidazol-2-ylidene)].[11] [b] [Ir-Me_4] = [IrCp*Cl_2(1,3,4,5-tetramethylimidaol-2-ylidene)].[19]

2-ylidene)][11] and [IrCp*Cl_2(1,3,4,5-tetramethylimidazol-2-ylidene)],[19] as shown in Table 1.

The above results suggest that the properties of the metal center and the NHC ligand, including the strength of σ-donation, do not change after incorporation of the glucopyranoside into the NHC unit; thus, **4** is expected to have the catalytic abilities of other Ir complexes. The catalytic ability of **4** toward H/D exchange reactions was briefly examined for 2-propanol and cyclohexanol in D_2O in the presence of AgOTf. Only the signal of the methyne proton of 2-propanol became smaller after heating at 100 °C for 3 h in a sealed NMR tube, and the signal ratio of methyl and methyne protons was 130:1. In the reaction with cyclohexanol, the ipso proton was completely exchanged under the same reaction conditions, while the other protons were partially exchanged.

In the ESI mass spectrum of **4** in methanol, there were intense signals for the $[M - 2Cl - AcO]^+$ ions and smaller peaks for the $[M - Cl]^+$ and $[M - Cl - AcO]^+$ ions, indicating that partial deprotection of the acetyl groups occurred in methanol. On the other hand, no fragmentation between the C1 anomeric carbon and imidazolylidene nitrogen atoms was observed, implying that the glucopyranoside-incorporated NHC system has the same stability as other NHC systems. This was also supported by X-ray crystallography, which showed no significant difference in the C−N(imidazolylidene) bond lengths of **4** (1.425(11)−1.472(15) Å) and other IrCp* NHC complexes (1.444(6)−1.460(6) Å).[11,19]

In conclusion, we have developed a general synthesis for a saccharide-incorporated NHC ligand precursor and its NHC complexes by preparing a glucopyranoside-incorporated N-heterocyclic carbene precursor and the first examples of saccharide-incorporated NHC transition-metal complexes. The Ag complexes should be useful as starting materials for the syntheses of other metal complexes by transmetalation, and one of them was used to prepare an Ir complex. The X-ray structure of the Ir complex had almost the same coordination geometry as other Ir NHC complexes. Because many kinds of bromosaccharides are available, our method can be used to synthesize other metal complexes having NHC ligands with a variety of saccharides. Saccharide-incorporated NHC ligands should make it possible to develop new drugs and novel catalysts for syntheses in water. Detailed studies of the catalytic ability of the Ir complex and the syntheses of other transition-metal complexes using the Ag complexes as a carbene transfer agent are currently in progress.

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Supporting Information Available: Text, figures, and a CIF file giving the crystal structure and NOESY spectrum of [IrCp*Cl_2(magi)], synthesis and characterization details for **1HBr**, and ^{1}H NMR spectra for catalytic H/D exchange reactions. This material is available free of charge via the Internet at http://pubs.acs.org. Alternatively, the file CCDC 626629 contains the supplementary crystallographic data for compound **4**. This can be downloaded free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Centre, 12 Union Road, Cambridge CB21EZ, U.K.; fax (+44) 1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

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