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Platinum(II) and palladium(II) complexes with methyl 3,4-diamino-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside

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To develop new complexes of Pt(II) and Pd(II) that have ligands in a shape complementary to DNA, we designed and synthesized a methyl 3,4-diamino-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside (**V**). This synthetic ligand imitates the shape of daunosamine, a DNA minor groove binding sugar moiety present in the antineoplastic anthracycline antibiotics doxorubicin and daunorubicin. Ligand **V**, was used to form the Pt(II) and Pd(II) chloride complexes $[MCl_2(\mathbf{V})]$ **1**, **2**, **3**, and **4**, which have potential antitumor properties. We characterized these complexes by X-ray diffraction and in solution by ^{1}H-, ^{13}C-, ^{15}N- and ^{195}Pt-NMR. Both Pt(II) and Pd(II) complexes seem to be isostructural, as shown by X-ray diffraction and molecular modeling. The complexes formed dimers in the crystal lattice with short M–M and Cl ··· N(H) hydrogen bonds. Detailed dynamic NMR studies in CD_2Cl_2 and CD_3CN solutions confirm the monomeric structure in both solvents as well as solvation around the metal and intermolecular hydrogen bonding of NH in CD_3CN.

Introduction

The effectiveness of *cis*-diaminodichloroplatinum (*cis*-DDP) and analogous platinum complexes in cancer therapy is limited by their high toxicity[1,2] as well as by the development of drug resistance.[3–7] Numerous laboratories have attempted to use chemical modification to overcome these problems and to increase the effectiveness of platinum-based drugs, and a great many complexes of platinum and other metals (*e.g.*, palladium, ruthenium, and rhodium) with different ligands have been prepared and tested.[8–13]

Among the antineoplastic drugs in common therapeutic use that are known to bind to DNA are the anthracycline antibiotics, exemplified by daunorubicin (DNR) and doxorubicin (DOX).[14,15] Both DNR and DOX contain an identical carbohydrate moiety, a rare amino sugar known as daunosamine. Anthracyclines bind to DNA with their aglycon serving as an intercalator, whereas daunosamine acts as a tiny minor-groove binder. Daunosamine contributes close to 40% to the free energy of DNR binding to DNA.[16,17] Chemical modification of the sugar moiety in DOX has been shown to increase antitumor activity against multidrug-resistant tumors.[15]

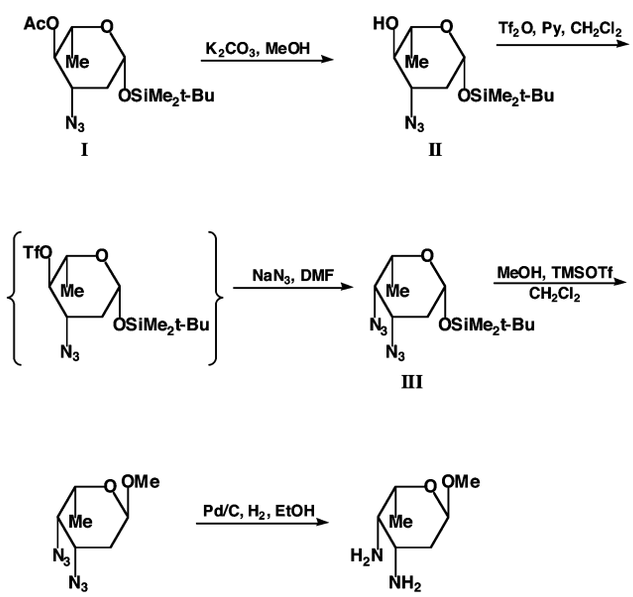
It has already been demonstrated that complexes of Pt with the diamino derivatives of D-glucose, D-mannose, and L-arabinose can be formed and display significant antitumor activity against sarcoma-180 in mice.[18] However, none of these sugars has been shown to bind DNA. The main objective of the study presented here was to prepare a diaminosugar that has a configuration identical to the minor groove binding sugar daunosamine and to use that diaminosugar as a ligand in the formation of Pt(II) and Pd(II) complexes. We describe in detail the synthesis and characterization of methyl 3,4-diamino-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside (**V**), a 4-amino analog of daunosamine, and its complexes with Pt(II) and Pd(II) (**1**, **2**, **3**, and **4**).

Results and discussion

Synthesis

1-*O*-silylated hexopyranose **I**, used as a precursor in the synthesis of the diamino carbohydrate ligand **V**, was prepared in several steps from 3,4-di-*O*-acetyl-L-rhamnal as described previously by Kolar and others.[19] Compound **I** was a useful substrate because of its L-*arabino* configuration, which allowed transformation to the L-*lyxo* series by using nucleophilic substitution at C-4 and inversion of the configuration.

In the first step (see Scheme 1), compound **I** was deacetylated



Scheme 1 Synthesis of methyl 3,4-diamino-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside (**V**).

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at position 4 to the 4-hydroxy compound **II** in 92% yield. The latter was derivatized with trifluoromethanesulfonic anhydride to a 4-*O*-triflate and without any purification used in a nucleophilic substitution reaction with sodium azide to give 3,4-diazido hexopyranose **III** (total yield 72%). Subsequently, to imitate doxorubicin's alpha glycosidic linkage between daunosamine and doxorubicinone, the beta anomer of 1-*O*-silyl ether (**III**) was reacted in the presence of trimethylsilyl trifluoromethanesulfonate with methanol to give the desired methyl alpha glycoside (**IV**), with a yield of 92%. Finally, the azido groups in compound **IV** were reduced by hydrogenation catalyzed by 10% Pd on carbon to produce methyl 3,4-diamino-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside (**V**).

Compound **V**, in the form of either a free amine or its hydrochloride salt, was applied for the synthesis of the Pt(II) complex **1** and the Pd(II) complex **3** (see Fig. 1). These complexes were synthesized by using standard preparative procedures as described elsewhere.[18,20] Aqueous solutions containing equimolar amounts of dipotassium tetrachloride platinum(II) or palladium(II) were reacted with the diamino monosaccharide **V**. The desired complexes **1** and **3** crystallized from the reaction mixture (yields of compounds **1** and **3** were 42.8 and 59.1%, respectively).

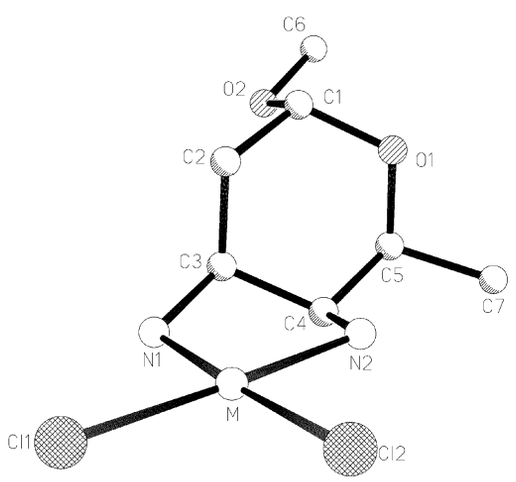

Fig. 1 Schematic molecular structure of *cis*-[Pt(II)Cl_2(**V**)] and *cis*-[Pd(II)Cl_2(**V**)] complexes. The model presented is based on the X-ray geometry of the monomer of a platinum complex, with hydrogen atoms minimized in electrostatic force fields from Molecular Simulations, Inc., and the geometry of heavy atoms being maintained from X-ray coordinates of complex **2**. The respective dihedral angles for hydrogen atoms on 1-N (H^c, H^t–N–C–H^3) are 37.3 and −87.0°, and on 2-N (H^c, H^t–N–C–H^4) they are 47.6 and 164.9°.

To obtain crystals suitable for further X-ray diffraction analysis, complexes **1** and **3** were recrystallized from ethanol, resulting in the formation of complexes **2** and **4**, respectively. In the course of the structural investigations, we found that complexes **2** and **4** were isostructural with complexes **1** and **3**.

Solid state structures

Crystallographic data of complexes **2**, **3**, and **4**, with the structure refinement details, are given in Table 3 (see Experimental). The main interatomic distances and angles are presented in Table 1. The investigated complexes **2**, **3**, and **4** formed isostructural complexes with pyranose rings of $^1C_4$ conformation. Two chlorine ligands and the nitrogen atoms from the diaminosugar ligand **V** formed a planar, square complex, whereas the pyranose rings were nearly perpendicular to the coordination plane (Fig. 2). The amino groups on 3-C and 4-C were equatorial and axial, respectively, with respect to the hexopyranose ring. The molecules interacted in the crystal lattice so as to allow formation of the dimers with short M ··· M and

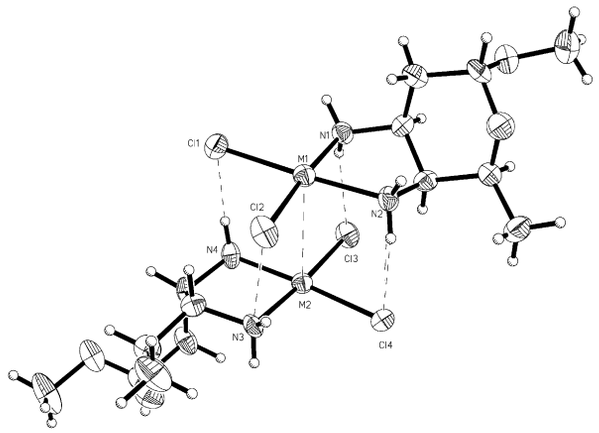

Fig. 2 The general mode of dimerization of complexes **2**, **3**, and **4**. The figure shows the X-ray structure of complex **2**.

Cl ··· N(H) contacts (Fig. 2 and Table 1). Such hydrogen-bonded molecular pairs, with a distance between the square planes of about 3.3 Å, correspond well to those for the *cis*-diaminodichloroplatinum(II) complexes.[21,22] The short Pt ··· Pt distance has also been found in the molecular structure of other diaminoligands[23] but until now it has not been established for the diaminosugar complex.[10,11] The water molecules in the crystal lattice of complex **3** formed chain-type structures bridging the dimers (Fig. 3), whereas the ethanol molecule in complexes **2** and **4** filled the space between two pairs of dimers, revealing a slightly different pattern of interactions (Fig. 4). Consequently, the dimers of complex **3** crystallized with two water molecules, and the dimers of complexes **2** and **4** each crystallized with one ethanol molecule.

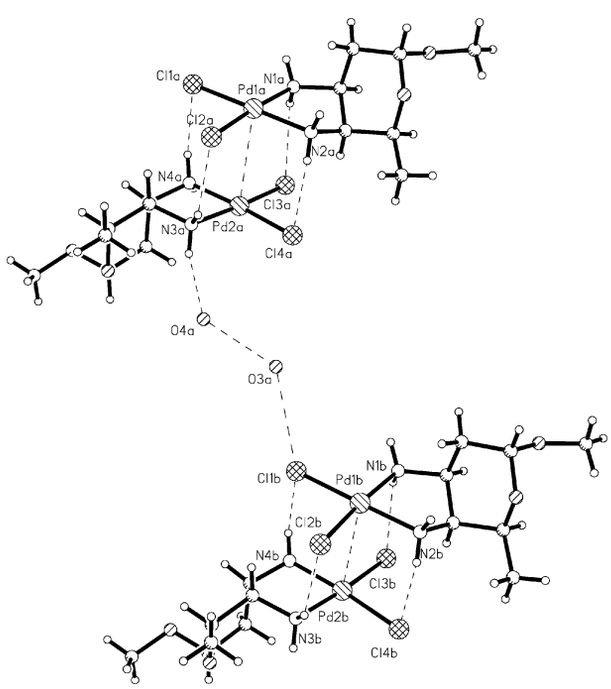

Fig. 3 The crystal structure of complex **3**. The intermolecular N ··· H_2O, H_2O ··· H_2O and H_2O ··· Cl hydrogen bonds are indicated by broken lines.

Solution structures

All of the compounds studied here had a dimeric structure in the solid state. Complex **1** crystallized from H_2O was not investigated by X-ray crystallography, but the MS spectra for complexes **1** and **3** showed molecular peaks for monomers. The crystals containing water in the crystal lattice were chosen

Table 1 Selected geometric parameters (Å,°) for compounds $[Pt(C_7H_{16}N_2O_2)Cl_2]_2 \cdot C_2H_5OH$ (**2**), $[Pd(C_7H_{16}N_2O_2)Cl_2]_2 \cdot C_2H_5OH$ (**4**) and $[Pd(C_7H_{16}N_2O_2)Cl_2] \cdot H_2O$ (**3**)

	2 Molecule		**4** Molecule		**3** Molecule	
Complex	A	B	A	B	A	B
Pt(1)–Cl(1)	2.307(3)	2.309(3)	—	—	—	—
Pt(1)–Cl(2)	2.300(3)	2.299(3)	—	—	—	—
Pt(1)–N(1)	2.047(8)	2.017(8)	—	—	—	—
Pt(1)–N(2)	2.029(9)	2.028(9)	—	—	—	—
Pd(1)–Cl(1)	—	—	2.281(5)	2.266(5)	2.305(3)	2.311(3)
Pd(1)–Cl(2)	—	—	2.286(5)	2.285(5)	2.306(3)	2.309(3)
Pd(1)–N(1)	—	—	1.986(16)	1.923(15)	2.024(8)	2.027(9)
Pd(1)–N(2)	—	—	1.936(15)	2.041(16)	2.056(9)	2.055(9)
O(1)–C(1)	1.437(15)	1.438(15)	1.47(3)	1.37(2)	1.435(13)	1.424(14
O(1)–C(5)	1.426(13)	1.434(14)	1.38(2)	1.53(2)	1.433(12)	1.429(15)
C(1)–C(2)	1.497(15)	1.498(16)	1.51(3)	1.47(4)	1.521(15)	1.497(15)
C(2)–C(3)	1.488(15)	1.514(16)	1.54(3)	1.56(3)	1.502(16)	1.519(15)
C(3)–C(4)	1.512(14)	1.511(13)	1.50(2)	1.43(3)	1.526(14)	1.507(15)
C(4)–C(5)	1.518(14)	1.525(15)	1.49(3)	1.49(3)	1.539(15)	1.539(15)
C(5)–C(7)	1.533(17)	1.521(16)	1.45(5)	1.54(4)	1.506(15)	1.513(17)
C(1)–O(2)	1.380(15)	1.394(16)	1.29(2)	1.48(3)	1.367(15)	1.397(13)
O(2)–C(6)	1.415(15)	1.441(15)	1.45(3)	1.44(5)	1.434(17)	1.444(13)
Cl(1)–Pt–Cl(2)	93.15(11)	93.04(11)	—	—	—	—
Cl(1)–Pt–N(1)	91.8(3)	92.0(3)	—	—	—	—
Cl(2)–Pt–N(2)	91.7(3)	91.8(3)	—	—	—	—
N(1)–Pt–N(2)	83.3(4)	83.1(4)	—	—	—	—
Cl(1)–Pd–Cl(2)	—	—	92.9(2)	93.6(3)	93.42(13)	95.19(11)
Cl(1)–Pd–N(1)	—	—	89.1(5)	90.7(8)	91.4(3)	90.3(3)
Cl(2)–Pd–N(2)	—	—	92.1(4)	91.6(7)	91.232)	91.5(3)
N(1)–Pd–N(2)	—	—	86.0(6)	84.1(9)	83.9(3)	83.0(4)
Pt–N(1)–C(4)	110.0(6)	110.7(6)	—	—	—	—
Pt–N(2)–C(3)	108.6(6)	109.9(6)				
Pd–N(1)–C(4)	—	—	111.0(12)	102.5(12)	108.6(6)	108.8(6)
Pd–N(2)–C(3)	—	—	108.2(10)	115.6(14)	110.0(6)	110.4(7)
N(1) ··· Cl(3)	3.128(5)		3.273(5)		3.192(5)	
N(2) ··· Cl(4)	3.117(5)		3.228(5)		3.273(5)	
N(3) ··· Cl(2)	3.322(5)		3.241(5)		3.328(5)	
N(4) ··· Cl(1)	3.282(5)		3.275(5)		3.245(4)	
Pt(A) ··· Pt(B)	3.282(2)		—		—	
Pd(A) ··· Pd(B)	—		3.237(3)		3.331(2)	

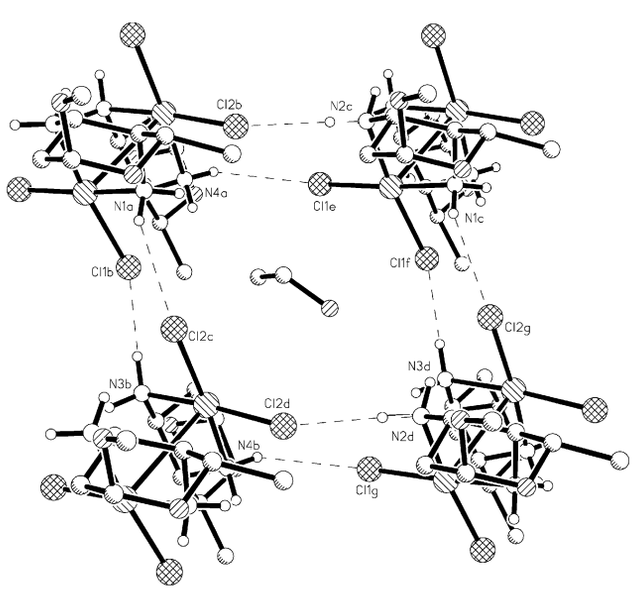

Fig. 4 The crystal structure of complex **4** showing the packing of solvent molecules.

for studies in solution. Their solubility in organic solvents without electron-donating groups was very low, *ca.* 0.1 mM L^{-1}. Dissolving complex **3** in CD_2Cl_2 did not produce large changes in chemical shifts in infinite time; the crystalline water appeared at 1.5 ppm, a chemical shift characteristic of molecular water dispersed in an organic phase. In contrast, dissolving complex **1** in CD_2Cl_2 solution enabled water to be seen as a broad signal at 7.15 ppm, most probably hydrogen-bonded to a solute molecule.

Since the presence of NH protons lying close to metal cannot be established from X-ray crystallography, the geometry was derived from molecular modeling using X-ray coordinates for C, N, O, and Pt atoms with minimization of all proton positions. This model for complex **1** is shown in Fig. 1. Fig. 5 shows the part of the ^1H NMR spectrum indicating the shape of respective NH resonances and their assignments in complex **3**. The assignments were the same as those in complex **1**. The NH protons were labeled *cis* or *trans* with regard to their spatial arrangement to 3-H or 4-H ring protons. Thus according to the Karplus potential curve, one can expect small vicinal coupling constants for *cis*-labeled NHs on both nitrogen atoms and nearly nulled spin–spin coupling for N^1H^t, characterized by a −87° dihedral angle, and a large coupling for N^2H^t with a large dihedral angle. Given the broadening of the NH resonances and uncertainty in measurements of these vicinal coupling constants, we did not attempt to cite them explicitly; nevertheless, the shape of the discussed NH signals was helpful in assignments.

The chemical shifts of the NH protons were the most characteristic and diagnostic feature of both complexes with regard to their structure in solution. The NH resonances appeared at four distinct chemical shifts (see Fig. 5) assigned by GCOSY (gradient COSY) and $^1H/^{15}N$ GHSQC (gradient HSQC) experiments to 1-N and 2-N atoms. Several features influenced

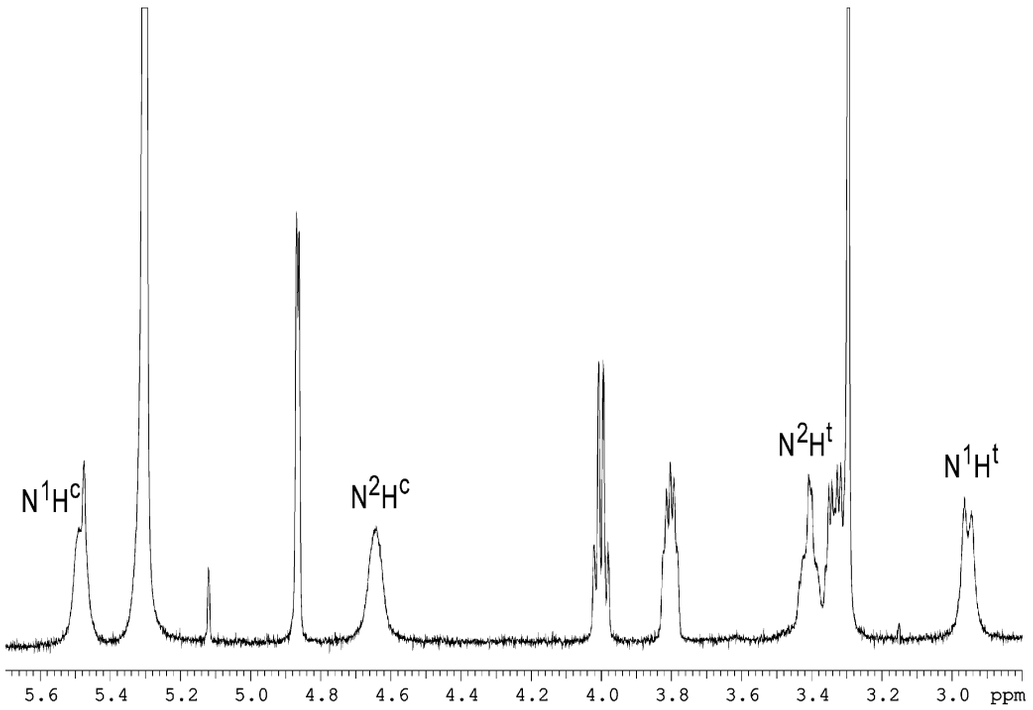

Fig. 5 A part of the NMR spectrum of complex **3** in CD_2Cl_2 showing the shape of the NH resonances used for stereochemical assignments in both complexes (see Fig. 1). The spectrum was taken at 30 °C, referenced to an internal solvent signal of 5.31 ppm.

the NH chemical shifts of NH protons in the studied complexes, the first being the spatial placement of a given proton with respect to the coordination bond N–M. Usually the proton that lies in or close to the five-membered plane containing the metal had the smaller chemical shift than the one placed outside this plane. The second feature was the exchange with H_2O, bulk or molecular, present in molar excess in studied solvents; efficient exchange on raising the temperature resulted in a low-frequency shift in the NH proton. The third influence was the presence of a hydrogen bond of an NH proton to a solvent or an intramolecular acceptor, such as chlorine atoms.

Bearing these factors in mind, we examined the complexes under study in CD_2Cl_2 in the temperature range from 0 to 30 °C and in CD_3CN in the temperature range from 5 to 60 °C.

Solvent and temperature dependence of the NH chemical shifts are described in Table 2. The stereochemical assignment of NH protons on each nitrogen atom was accomplished by a $^1H/^{13}C$ GHMBC (gradient HMBC) experiment linking geminal protons on each nitrogen atom and by considering the shape of each resonance to be dependent on the mutual scalar geminal coupling and vicinal coupling to ring 3-H or 4-H protons.

There was no apparent temperature shift for NH resonances for either complex dissolved in CD_2Cl_2 and cooled to 0 °C. This, together with the fact that the chemical shifts were infinitely stable after the crystals were dissolved, indicated that the ligands in the complex were not fluxional in that solvent. Thus, this solvent is the best one with which to study the structure of a parent complex in solution.

On the other hand, dissolving the crystals in neat CD_3CN and immediately cooling the solution to 5 °C showed a small but definite negative temperature dependence, *i.e.*, a high-frequency shift of NH resonances in both complexes when the temperature was decreased. The temperature dependence of the NH resonances within the studied range for both complexes is given in Table 2.

We also studied the complexes by electrospray MS and ^2H and ^{195}Pt NMR. The parent peak of m/z^+ 432.1, observed in the spectrum of complex **1**, corresponds to the ion in which one chlorine atom had been displaced by the CH_3CN ligand. We also examined the ^{195}Pt spectrum of that sample, which showed signal at −2256 ppm, which is shifted by 40 ppm to lower frequency from the position in CD_2Cl_2 solution. Careful analysis of the ^2H spectra of both complexes in CD_3CN did not reveal the presence of any other CD_3CN signal, except that of bulk solvent. The presence of other signals might indicate the chloride ligand exchange observed in the electrospray MS experiment; however, the MS experiment was performed at high temperature in the presence of a high electrostatic field.

The temperature dependence of the NH resonances indicates the formation of hydrogen bonds, either within the molecule of the complex, as in the dimers in the crystal state, or between the complex and the solvent. Although neither possibility can be ruled out, the latter possibility is more probable in view of the fact that in the CD_2Cl_2 solution, much smaller temperature dependence of the NHs was observed.

Table 2 Solvent and temperature dependence of NH chemical shifts, δ (ppm) and $\Delta\delta$ (ppb K^{-1}), respectively, in **1** and **3**[a]

			1-N		2-N	
Complex	Solvent		*cis*	*trans*	*cis*	*trans*
1	CD_2Cl_2	δ	5.81	3.42	5.00	3.71
		$\Delta\delta$	1.4	−1.6	0.7	−1.0
	CD_3CN	δ[b]	4.60	3.90	4.37	3.90
		$\Delta\delta$	−1.7	−1.7	−1.6	−1.7
3	CD_2Cl_2	δ	5.51	2.97	4.66	3.43
		$\Delta\delta$	1.3	1.0	0.4	0.9
	CD_3CN	δ	4.24	3.28	3.91	3.54
		$\Delta\delta$	−3.3	−2.5	−2.4	−2.8

[a] Chemical shifts are cited at 30 °C; temperature change for CD_2Cl_2 solutions was 30 °C and 55 °C for CD_3CN solutions. In addition, within 24 hours, we observed the temperature-related irreversible shift of a few Hz in one of the 3-H, 4-H resonances, which persisted over time in CD_3CN. However, the temperature study of NH resonances, performed immediately after dissolving and after 24 hours, showed the same temperature dependence in both complexes as the fresh solutions after dissolving. The minor change observed thus could be derived from acidity or other impurities in the solvent. [b] Much broader signals than in the CD_2Cl_2 solution did not permit observation of the signal shape; thus, the assignment was assumed to be the same as in the CD_2Cl_2 solution.

The nature of the solvent plays a crucial role in setting the NH chemical shift pattern. In contrast to CD_2Cl_2, CD_3CN can form a solvation shell around platinum, forming fifth or sixth coordination as well as forming hydrogen bonds to NH protons. Also taking into account the diamagnetic susceptibility anisotropy of this solvent molecule, the solvation resulted, on average, in a low-frequency shift of all NHs, as compared with CD_2Cl_2. This solvation finds confirmation in two facts. The ^{195}Pt resonance moved upfield 40 ppm when the solvent was changed from CD_2Cl_2 to CD_3CN, which may indicate an increase in electron density around metal induced by acetonitrile solvation. Second, lowering the temperature of the CD_3CN solution resulted in a noticeable high-frequency shift for all NHs in both complexes **1** and **3**. In CD_2Cl_2 the temperature shift was negligible and could not be accounted for by any specific interaction. Interestingly, the Pt(II) complex **1** was apparently much less sensitive to the temperature changes than was the Pd(II) complex **3**.

The ^{15}N chemical shifts are the most sensitive probe for uncovering the complexation of the metals.[24] The nitrogen atoms N1 and N2 resonated at lower frequencies for the Pt(II) complex than for the Pd(II) complexes. However, comparison of the absolute ^{15}N chemical shifts for both metals cannot be directly discussed, as the phenomenon of complexation shifts is complex and depends among other things on the neighbor anisotropy term, which is vastly different for both nuclei.

Experimental

Synthesis

3-Azido-1-*O*-*tert*-butyl(dimethyl)silyl-2,3,6-trideoxy-β-L-*arabino*-hexopyranose (II). 4-*O*-Acetyl-3-azido-1-*O*-*tert*-butyl-(dimethyl)silyl-2,3,6-trideoxy-β-L-*arabino*-hexopyranose (**I**) (1 mmol, 0.33 g) was dissolved in methanol (10 mL). Potassium carbonate (1 g) was added, and the reaction mixture was stirred at room temperature until substrate disappeared. Progress of the reaction was monitored by TLC using a 4 : 1 mixture of hexane–ethyl acetate. Inorganic salts were filtered off from the reaction mixture and the filtrate was diluted with water (10 mL) and extracted with hexane (3 × 15 mL). Combined hexane extracts were washed with water until neutral pH was reached and then dried over sodium sulfate. Sodium sulfate was removed and solvents evaporated under vacuum to give a crude product that was purified by column chromatography (silica gel 60, Merck) using first hexane and then hexane–ethyl acetate (98 : 2 and then 95 : 5) as eluent. Purification resulted in pure product **II** (yield: 263.4 mg, 91.5%). Anal. found: C, 50.20; H, 8.78; N, 14.54. $C_{12}H_{25}N_3O_3Si$ requires C, 50.14; H, 8.77; N, 14.62%. δ_H (300 MHz, solvent $CDCl_3$, standard $SiMe_4$) 4.83 (1 H, dd, *J* 9.3, 2.0 Hz, H-1), 3.42 (1 H, ddd, *J* 4.8, 12.6, 9.6 Hz, H-3), 3.35 (1 H, q, *J* 6.1 Hz, H-5), 3.17 (1 H, td, *J* 3.6, 9.6 Hz, H-4), 2.30 (1 H, d, 4-OH), 2.21 (1 H, ddd, *J* 12.6, 4.8, 2 Hz, H-2e), 1.68 (1 H, ddd, *J* 12.6, 12.6, 9.3 Hz, H-2a), 1.34 (3 H, d, *J* 6.1 Hz, H-6), 0.92 (9 H, s, *t*-BuSi), 0.14 (3 H, s, Me_2Si), 0.13 (3 H, s, Me_2Si).

1-*O*-*tert*-Butyl(dimethyl)silyl-3,4-diazido-2,3,4,6-tetradeoxy-β-L-*lyxo*-hexopyranose (III). A solution of trifluoromethanesulfonic anhydride (3.86 mmol, 0.65 mL) in dichloromethane (3 mL) was added dropwise to the previously prepared solution of 3-azido-1-*O*-*tert*-butyl(dimethyl)silyl-2,3,6-trideoxy-β-L-*arabino*-hexopyranose (**II**) (1 mmol, 0.287 g) and pyridine (0.65 mL; 7.4 mmol) in dichloromethane (72 mL), which had been cooled to −40 °C. The reaction mixture was stirred and the temperature allowed to rise to 0 °C. Progress of the reaction was monitored by TLC using an 8 : 1 mixture of hexane–ethyl acetate. After substrate **II** disappeared, the reaction mixture was washed with a 10% solution of sodium acetate in water (4 × 25 mL) and then dried over sodium sulfate for 1 h. The drying agent was filtered off and solvents were evaporated under reduced pressure. Then toluene was added and the solution was evaporated again, and this procedure was repeated two additional times. Without further purification, the remaining oil of 4-*O*-triflate was dissolved in dimethylformamide (2 mL), and sodium azide (4.7 mmol, 0.308 g) was added. The reaction mixture was stirred at room temperature overnight and progress of the reaction was monitored by TLC using an 8 : 1 mixture of hexane–ethyl acetate. Then, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). Combined extracts were washed three times with water and dried over sodium sulfate. Drying agent was filtered off, the filtrate was evaporated under reduced pressure, and the crude product obtained was purified by column chromatography (silica gel 60, Merck) using hexane and hexane–ethyl acetate (98 : 2), as eluents, to give 1-*O*-*tert*-butyl(dimethyl)silyl-3,4-diazido-2,3,4,6-tetradeoxy-β-L-*lyxo*-hexopyranose (**III**) (yield 225.9 mg, 72.3%). Anal. found: C, 46.22; H, 7.76; N, 26.78. $C_{12}H_{24}N_6O_2Si$ requires C, 46.13; H, 7.74; N, 26.90%. δ_H (300 MHz, solvent $CDCl_3$, standard $SiMe_4$): 4.74 (1 H, dd, *J* 8.9, 2.5 Hz, H-1), 3.62–3.55 (2 H, m, 3-H, H-5), 3.45 (1 H, d, *J* 6.3 Hz, H-4), 2.00 (1 H, dddd, *J* 11.5, 3.9, 2.4, 1.1 Hz, H-2e), 1.89 (1 H, ddd, *J* 11.5, 8.9, 2.5 Hz, H-2a), 1.36 (1 H, d, *J* 6.4 Hz, H-6), 0.91 (9 H, s, t-BuSi), 0.12, (3 H, s, Me_2Si), 0.10 (3 H, s, Me_2Si).

Methyl 3,4-diazido-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside (IV). 1-*O*-*tert*-Butyl(dimethyl)silyl-3,4-diazido-2,3,4,6-tetradeoxy-β-L-*lyxo*-hexopyranose (**III**) (1 mmol, 0.312 g) and methanol (0.125 mL; 3 mmol) were dissolved in dichloromethane (5 mL). Then 4 Å molecular sieves (0.5 g) were added and the reaction mixture was stirred at room temperature for 2 h. After that period, the reaction mixture was cooled to −20 °C, and trimethylsilyl trifluoromethanesulfonate (0.444 g, 2 mmol) was added and the mixture was stirred at −20 °C for 10 min. The reaction was monitored by TLC using an 8 : 1 mixture of hexane–ethyl acetate. After the reaction was completed, the molecular sieves were filtered off, and the filtrate was diluted with dichloromethane (20 mL) and then washed with saturated sodium bicarbonate followed by water until neutral pH was reached, and then dried over sodium sulfate. Filtration and evaporation of solvents gave a crude product that after column chromatography gave pure methyl 3,4-diazido-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside (**IV**) (yield: 0.206 g, 92.4%). Anal. found: C, 39.86; H, 5.81; N, 39.88. $C_7H_{12}N_6O_2$ requires C, 39.62; H, 5.70; N, 39.60%. δ_H (300 MHz, solvent $CDCl_3$, standard $SiMe_4$): 4.81 (1 H, d, *J* 3.5 Hz, H-1), 3.99–3.87 (2 H, m, H-3, H-5), 3.52 (1 H, bs, H-4), 3.32 (3 H, s, OMe), 2.03 (1 H, ddd, *J* 12.8, 12.8, 3.6 Hz, H-2a), 1.98 (1 H, ddd, *J* 12.8, 4.8, 1.3 Hz, H-2e), 1.30 (3 H, d, *J* 6.5 Hz, H-6).

Methyl 3,4-diamino-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside (V). Methyl 3,4-diazido-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside (**IV**) (1 mmol, 0.212 g) was dissolved in ethyl alcohol (10 mL), after which 10% Pd/C (15 mg) was added and the mixture was hydrogenated using a Paar apparatus at 50 psi. After 2 h, the reaction was completed as evidenced by TLC (with an 8 : 1 mixture of hexane–ethyl acetate for substrate and 85 : 13 : 2 chloroform–methanol–2 N NH_3 in methanol for product) and the reaction mixture was filtered through Celite. The filtrate was evaporated under reduced pressure, and the crude product was purified by column chromatography (silica gel 60, Merck) using first chloroform and then a mixture of chloroform–methanol (95 : 5 and 90 : 10) as eluents (yield: 0.139 g, 87%). Anal. found: C, 52.30; H, 10.21; N, 17.61. $C_7H_{16}N_2O_2$ requires C, 52.48; H, 10.07; N, 17.49%. δ_H (300 MHz, solvent $CDCl_3$, standard $SiMe_4$): 4.69 (1 H, d, *J* 3.7 Hz, H-1), 3.92 (1 H, qr, *J* 6.5 Hz, H-5), 3.31 (3 H, s, OMe), 3.18 (1 H, ddd, *J* 12.3, 8.3, 4.1 Hz, H-3), 2.59 (1 H, d, *J* 3.1 Hz, H-4), 1.65 (1 H, dd, *J* 13.5, 4.7 Hz, H-2e), 1.55 (1 H, ddd, *J* 12.8, 3.7 Hz, H-2a), 1.19 (3 H, d, *J* 6.5 Hz, H-6).

$[Pt(C_7H_{16}N_2O_2)Cl_2]\cdot H_2O$ (1). Dipotassium tetrachloroplatinate (0.5 mmol, 207.5 mg) was dissolved in 1 mL of water and 0.5 mmol (116.6 mg) of methyl 3,4-diamino-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside (**V**) dihydrochloride and 1 mmol of sodium carbonate (286.2 mg of the $Na_2CO_3\cdot 10H_2O$) were added. The solution was stirred until a yellow precipitate appeared. The mixture was placed in a refrigerator for 2 days, after which yellow crystals were collected by filtration. The filtrate was passed through Sephadex G-10 gel. The yellow fraction of the filtrate was concentrated and an additional portion of the precipitate was obtained. The combined crystalline fractions were washed consecutively with small amounts of ethanol and diethyl ether, dried under vacuum, and recrystallized from hot water. Yield: 95.0 mg (0.214 mmol) (42.8%). Anal. found: C, 19.0; H, 4.5; N, 6.2; Cl, 16.6; Pt, 43.9. $PtCl_2C_7H_{18}N_2O_3$ requires C, 18.9; H, 4.1; N, 6.3; Cl, 16.0; Pt, 43.9%. δ_H (500 MHz; solvent CD_2Cl_2; standard internal CD_2Cl_2 at 5.32) 1.18 (3 H, d, *J* 6.8 Hz, H-6), 1.98 (1 H, ddd, *J* 13.4, 5.5, 1.0 Hz, H-2e), 2.63 (1 H, ddd, *J* 13.4, 12.5, 3.7 Hz, H-2a), 3.32 (3 H, s, O–CH_3), 3.35 (1 H, m, H-3), 3.43 (1 H, bd, *J* 8.6 Hz, NH), 3.72 (1 H, bt, NH), 3.86 (1 H, m, H-4), 4.17 (1 H, qd, *J* 6.8, 1.6 Hz, H-5), 4.87 (1 H, d, *J* 3.7 Hz, H-1), 5.0 (1 H, bs, NH), 5.8 (1 H, bs, NH), 7.10 (2 H, bs, H_2O). δ_C (125.7 MHz; solvent CD_2Cl_2; standard internal CD_2Cl_2 at 53.8) 16.6 (C-6), 30.2 (C-2), 55.9 (C-3), 55.4 (OCH_3), 60.4 (C-4), 60.7 (C-5), 97.6 (C-1). $\delta_{^{15}N}$ (50.7 MHz; solvent CD_2Cl_2; standard external CD_3NO_2) −375.4 (1-N), −393.7 (2-N). $\delta_{^{195}Pt}$ (107.16 MHz; standard external K_2PtCl_6) −2216 in CD_2Cl_2; −2256 in CD_3CN. ES-MS (CH_3CN + HCO_2H); *m*/*z* 432.1 ($M - Cl + CH_3CN)^+$.

$[Pt(C_7H_{16}N_2O_2)Cl_2]\cdot C_2H_5OH$ (2). To obtain crystals suitable for X-ray analysis, a part of complex **1** was recrystallized from ethanol, resulting in the formation of complex **2**.

$[Pd(C_7H_{16}N_2O_2)Cl_2]\cdot H_2O$ (3). To a saturated aqueous solution of dipotassium tetrachloropalladate (containing 163.2 mg of the salt, 0.5 mmol), an equimolar amount of the diamino sugar (80.1 mg) was added, and the solution was stirred (0.5 h) and then refrigerated for 24 h. Yellow crystalline precipitate was separated by filtration on Sephadex G-10 gel, washed with a small amount of ethanol and ether, dried under vacuum, and then recrystallized from hot water. Yield: 105 mg (59.1%). Anal. found: C, 23.9; H, 5.6; N, 7.6; Cl, 19.2; Pd, 33.1. $PdCl_2$-$C_7H_{18}N_2O_3$ requires C, 23.7; H, 5.1; N; 7.9; Cl, 19.9; Pd, 29.9%. δ_H (500 MHz; solvent CD_2Cl_2; standard internal CD_2Cl_2 at 5.32) 1.16 (3 H, d, *J* 6.8 Hz, H-6), 2.00 (1 H, dd, *J* 13.5, 5.5 Hz, H-2e), 2.61(1 H, ddd, *J* 13.5, 13.2, 4.0 Hz, H-2a), 2.96 (1 H, bd, *J* 10.9 Hz, NH), 3.32 (3 H, s, OCH_3), 3.35 (1 H, m, H-3), 3.42 (1 H, bt, NH), 3.82 (1 H, m, H-4), 4.02 (1 H, q, *J* 6.8 Hz, H-5), 4.66 (1 H, bs, NH), 4.89 (1 H, d, *J* 4.0 Hz, H-1), 5.49 (1 H, bs, NH). δ_C (125.7 MHz; solvent CD_2Cl_2; standard internal CD_2Cl_2 at 53.8) 16.5 (C-6), 31.2 (C-2), 54.9 (C-3), 55.4 (OCH_3), 58.8 (C-4), 61.2(C-5), 97.7 (C-1). $\delta_{^{15}N}$ (50.7 MHz; solvent CD_2Cl_2; standard external CD_3NO_2) −362.5 (1-N), −379.9 (2-N). ES-MS (CH_3CN + HCO_2H); *m*/*z* 344 ($M - Cl + CH_3CN)^+$.

$[Pd(C_7H_{16}N_2O_2)C1_2]\cdot C_2H_5OH$ (4). Crystals suitable for X-ray diffraction analysis of complex **4** were obtained by recrystallization of complex **3** from ethanol.

Acquisition of NMR data

The NMR spectra were run on a Varian INOVA spectrometer at 500 MHz for ^1H resonances. A standard single-pulse experiment was used to acquire the ^1H spectrum using a 5000 Hz spectral window, 30° pulse width, and 1 s delay between pulses. The FIDs were acquired using 16k data points and were processed without zero-filling or apposition functions.

Spectral assignment was aided by GCOSY[25] showing the scalar coupling interactions required to link the 3-H and 4-H hexopyranose protons to hydrogens on the 1-N and 2-N nitrogen atoms.

The States-TPPI phase-sensitive gradient-selected ^1H-^{13}C HSQC[26] (heteronuclear single quantum coherence) NMR spectra were obtained with a spectral width of 5000 Hz, 2048 points in the ^1H dimension and 15000 Hz, 256 increments in the ^{13}C dimension; 192 transients per t_1 increment, with a relaxation delay of 1 s and $^1J(C,H)$ = 140 Hz. The data were linearly predicted to 1024 points and zero-filled to 2048 points in F_1 before Fourier transformation. Carbon resonances were assigned by means of correlations found in a 2-D GHSQC experiment using known proton assignments.

The ^1H–^{15}N g-HSQC spectra were recorded with a spectral width of 5000 Hz, 2048 points in the ^1H dimension and 2500 Hz, 46 increments in the ^{15}N dimension; 2048 transients were recorded for each increment, with a relaxation delay of 1 s and $^1J(N,H)$ = 75 Hz.

The ^{195}Pt NMR spectra were obtained using a single-pulse experiment with the standard acquisition parameters.

Molecular modeling

Positions of all protons were minimized by using ESFF force field (Molecular Simulations, Inc.) and ESFF-derived charges. During the minimization, the X-ray derived positions of all heavy atoms were fixed. The calculations were carried out on a Silicon Graphics O2 workstation using the Discover-3 module from the software package INSIGHT II, version 2000 (Molecular Simulations, Inc.).

Crystal structure determination

Determination of the crystal structures of the title compounds was performed on a KUMA KM4CCD κ-axis diffractometer applying graphite-monochromated Mo-Kα radiation. Crystal data are given in Table 3. The species were positioned at 62 mm from the KM4CCD camera; 920 frames for complexes **2** and **4**, 1152 frames for complex **3**, were measured at 0.8° (complexes **2**, **4** and **3**) intervals with a counting time of 30 s (complexes **2**, **4** and **3**). The data were also corrected for Lorentz and polarization effects, and analytical absorption correction (complex **2**) was applied.[27] Data reduction and analysis were carried out using the KUMA Diffraction (Wroclaw) programs. The structures were solved by direct methods[28] and refined using the SHELXL computer program.[29] The refinement was based on F^2 for all reflections, except for those with the strongly negative F^2 values. Weighted *R* factors, *wR*, and all goodness-of-fit *S* values are based on the F^2 parameters. Conventional *R* factors are based on *F* with *F* set to zero for negative F^2. The $F_o^2 > 2s(F_o^2)$ criterion was used only for calculation of the *R* factors and is not relevant to choice of reflections for the refinement. The *R* factors based on F^2 were about twice as large as those based on *F*. All hydrogen atoms placed in the calculated positions and their thermal parameters were refined isotropically. Scattering factors were taken from the literature (Tables 6.1.1.4 and 4.2.4.2. in ref. 30).

The X-ray measurements were undertaken in the Crystallography Unit of the Physical Chemistry Lab. at the Chemistry Department of the University of Warsaw.

CCDC reference numbers 161953 (**2**), 161954 (**4**) and 161955 (**3**).

See http://www.rsc.org/suppdata/dt/b2/b212681h/ for crystallographic data in CIF or other electronic format.

Conclusions

Our approach to developing metal complexes that have more selective anticancer properties was based on the presumption that a metal complexed with ligands that can bind to specific sequences of DNA will induce more selective DNA damage.

Table 3 Crystal data and structure refinement for $[Pt(C_7H_{16}N_2O_2)Cl_2]_2 \cdot C_2H_5OH$ (**2**), $[Pd(C_7H_{16}N_2O_2)Cl_2]_2 \cdot C_2H_5OH$ (**4**) and $[Pd(C_7H_{16}N_2O_2)Cl_2]_2 \cdot H_2O$ (**3**)

Complex	**2**	**4**	**3**
Empirical formula	$C_{16}H_{38}Cl_4N_4O_5Pt_2$	$C_{16}H_{38}Cl_4N_4O_5Pd_2$	$C_{14}H_{36}Cl_4N_4O_6Pd_2$
Formula weight	898.48	721.10	711.06
Temperature/K	293(2)	293(2)	293(2)
Wavelength/Å	0.71073	0.71073	0.71073
Crystal system	Orthorhombic[a]	Orthorhombic[a]	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12$
a/Å	7.823(2)	7.714(2)	12.345(2)
b/Å	7.827(2)	7.718(2)	28.136(6)
c/Å	43.999(9)	43.528(9)	7.734(2)
Volume/Å^3	2694.1(11)	2591.5(11)	2686.3(10)
Z	4	4	4
Absorption coefficient/mm^{-1}	10.803	1.834	1.770
F(000)	1704	1448	1424
Crystal size/mm	0.1 × 0.1 × 0.05	0.1 × 0.1 × 0.05	0.15 × 0.15 × 0.08
Reflections collected/unique	17915/6468 [*R*(int) = 0.0973]	14285/54500 [*R*(int) = 0.0977]	17973/6426 [*R*(int) = 0.0766]
Refinement method	Full-matrix least-squares on F^2		
Data/restraints/parameters	6468/0/307	4500/0/302	6426/0/304
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0423, *wR*2 = 0.1052	*R*1 = 0.0630, *wR*2 = 0.1745	*R*1 = 0.0740, *wR*2 = 0.1932
R indices (all data)	*R*1 = 0.0446, *wR*2 = 0.1035	*R*1 = 0.0621, *wR*2 = 0.1735	*R*1 = 0.0928, *wR*2 = 0.2114

[a] Refined in the tetragonal *P*4(3)2(1)2 space group appeared to be unsuccesful.

Here, we prepared a novel sugar-based ligand, methyl 3,4-diamino-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside (**V**), a potential DNA minor groove binder, and demonstrated that it easily formed complexes with Pt(II) and Pd(II). Detailed studies of Pt(II) and Pd(II) complexes in the solid state and in solution demonstrated that in the solid state the complexes are dimeric, regardless of the crystallization solvent used, and that different crystalline solvents can be established in various crystals. Common to all complexes were the short N ··· Cl distances between both atoms originating from complementary molecules in the dimer. This finding could be taken as an indication of N–H ··· Cl hydrogen bonds. In the solvents studied, the complexes were stable with respect to ligand exchange. The temperature shifts studied seem to indicate possible solvation of the metals and formation of weak hydrogen bonds in CD_3CN, whereas no specific interaction of solutes with CD_2Cl_2 could be established for either complex.

Evaluation of the antitumor activity of Pt(II) and Pd(II) complexes with methyl 3,4-diamino-α-L-*lyxo*-hexopyranoside and their DNA binding properties are in progress.

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