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Long-Lived Glycosyl-Chromium(III) Complex Intermediates in Aqueous Medium. Preparation of Pyranoid Glycals.

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Abstract: Acetylated glycosyl-chromium(III)L (L=EDTA, NTA, IDA) complex intermediates (1) were detected in aqueous medium, with half-life-times of 30-300 minutes. The decay of these intermediates led to glycals (7-9) of high purity in preparatively usable 70-90% yields.

Generation of a carbanionic centre at the anomeric position of carbohydrate derivatives can be useful for the preparation of glycals[1] by an $E1_{cb}$ type elimination of the C-2 substituent on the one hand, and for the synthesis of various C-glycosyl compounds[2] by trapping the carbanionic intermediates with C-electrophiles on the other.

Most known methods for glycosyl carbanion formation[2] require (in most cases strongly) basic reagents and, consequently, base-stable protecting groups and strictly anhydrous medium. Reductive elimination from the C1-C2 centres with zinc can be performed in aqueous acetic acid (the classical Fischer-Zach method[3] for the synthesis of acylated glycals). C-Elongations[4,5] at the anomeric centre have been made with zinc in the presence of relatively labile acyl protecting groups under anhydrous conditions. Most recently the use of lanthanide reagents such as $CeCl_3$[5] and especially SmI_2[6] mediating the formation of nucleophilic anomeric centres under neutral conditions has been reported. With suitably designed substrates the latter results in formation of glycals, a fact which is considered to be an evidence for a glycosyl-SmI_2 intermediate. Mechanistically[7] these reactions most probably proceed according to equations (1) and (2) (R=alkyl, glycosyl, X=Br, Cl, $ArSO_2$; $M=Sm^{2+}$).

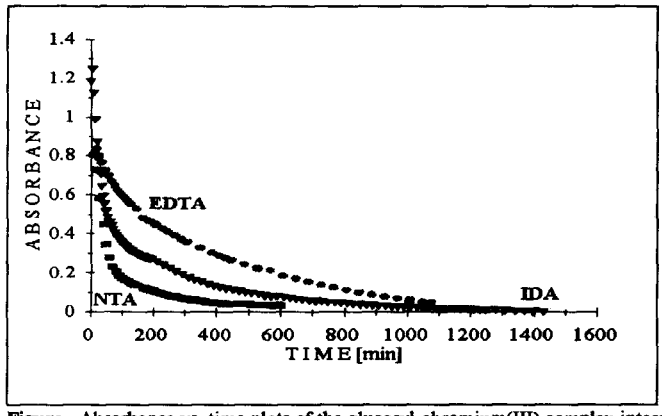
$$R\text{-}X + M^{n+} \rightarrow R^{\bullet} + M^{(n+1)+} + X^{-} \quad (1)$$

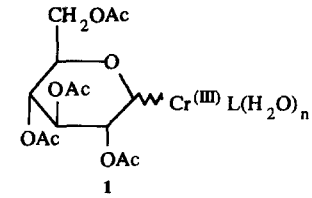
$$R^{\bullet} + M^{n+} \rightarrow R\text{-}M^{(n+1)+} \quad (2)$$

Similar reductions of alkyl halides by low-valent transition metal ions such as chromium(II), vanadium(II), titanium(III) ($M=Cr^{2+}$, V^{2+}, Ti^{3+}) are also known[8,9].

The importance of chromium(II) compounds in organic synthesis and their most wide-spread applications[10] including C-C bond formations[11] in aprotic medium were discussed in detail. Glycals have also been made by using chromium(II)acetate in *anhydrous* DMF in the presence of 1,2-diamino-ethane[12]. Kochi and coworkers revealed[13] the synthetic possibilities of this metal ion and its 1,2-diamino-ethane complexes with organic halides in aqueous medium via organochromium(III) complex intermediates. Mechanistic investigations are also in progress[14].

In this letter we report on the *application of chromium(II) complex reagents*[15] *to glycosyl halides* and the existence of long-lived glycosyl-chromium(III) complex intermediates *in aqueous medium.*



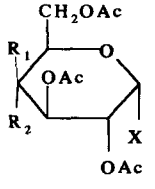


1

L: ethylenediamine-tetraacetate (EDTA)
nitrilotriacetate (NTA)
iminodiacetate (IDA)

Figure. Absorbance vs. time plots of the glucosyl-chromium(III) complex intermediates **1** recorded in 1 cm cell at 320 nm. $[Cr^{2+}]$=5mM, [glucosyl chloride]=0.5mM, [EDTA]=7.4mM, [NTA]=15mM, [IDA]=49mM; pH 6.6, 6.0, 6.5 respectively; solvent H_2O:DMF=1:1; t=25°C; I=0.1 M KCl.

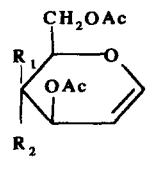
The formation of the carbon-metal bond at the anomeric centre was monitored by spectrophotometry. Thus, UV-VIS spectra in the reaction of chromium(II)L complexes (for (L) see Figure) with glucosyl chloride **2** in H_2O-DMF were recorded[16]. Absorption band characteristic for C-Cr(III)L bonds were observed in the 320-360 nm region as documented in the literature[17]. Since esters are not to be expected to react with the chromium(II) species under the given conditions[18] this can only be explained by the formation of C1-Cr(III)L complex compounds **1**[19]. The kinetic curves (Figure) show considerable stability for the observed intermediates. The half-life-times are between 30 and 300 minutes depending on the ligands applied[20].



2-6

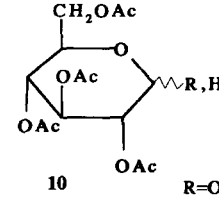
$Cr^{II}L$
4< pH<7
room temp.
one or two phases
aqueous medium

L=IDA,NTA,EDTA



7-9

		R_1	R_2	X
2	7	H	OAc	Cl
3	7	H	OAc	Br
4	8	OAc	H	Cl
5	8	OAc	H	Br
6	9	H	Ac,βDglu	Br



10 R=OH
11 R=H

The fate of the intermediates could be followed by preparative work up of similarly composed reaction mixtures[21]. This gave tri-*O*-acetyl-D-glucal (**7**) either from chloride **2** or bromide **3** in certain cases in very good yields (Table) thereby providing a further proof for the intermediacy of **1**. This transformation could also be performed in two phase systems like H_2O/EtOAc or H_2O/Et_2O thereby simplifying the work-up[22] (Table).

The coordinating ligands obviously play very important roles in these reactions. First, they strongly affect the stability of the organometallic intermediate. Second, their presence facilitates the formation of the carbon-metal bond, since the reactivity of the Cr(II)L mono-complexes increases depending on L in the following order: H_2O (no reaction) <<< malonate (MAL) < glycinate (GLY) < IDA < NTA < EDTA. In other terms this means a *possibility for tuning the electrontransfer ability of the metal ion by a simple additive* in order to meet the requirements of a particular reaction or substrate.

This is well reflected in the glucal forming reactions where the $[Cr^{II}(EDTA)]^{2-}$ and $[Cr^{II}(NTA)]^{-}$ complexes gave high yields of **7** from both **2** and **3**. The raw-products from these reactions were of very high

purity since by-products could be detected neither by ^{1}H NMR nor TLC. The more reactive **3** gave **7** of similar purity also with other ligands (Table). The reactions of the less reactive **2** carried out with IDA, GLY and MAL ligands showed a more complex picture on the TLC. Among the by-products the hydrolysis product **10** of the starting halide could be detected, but **11** was not observed by ^{1}H NMR.

The $[Cr^{II}(EDTA)]^{2-}$ complex gave also excellent yields and purity for the glycals **8** (87% from **4** in H_2O, 98% from **5**) and **9** (95 % from **6**) in H_2O/EtOAc two phase reaction system[23].

Table. Preparation of tri-*O*-acetyl-D-glucal[23] (**7**) from halides **2** or **3**.

Medium	Ligand	pH	Yield from **2** (%)	Yield from **3** (%)
H_2O/DMF	EDTA	5.0	79	87
	NTA	6.0	73	71
	IDA	5.9	58*	77
	GLY	6.6	77*	89
	MAL	5.7	77*	89
	H_2O	5.0	no reaction	no reaction
H_2O/Et_2O	EDTA	4.0	80	90
	NTA	6.0	78	79
	IDA	6.2	84*	87
H_2O/EtOAc	EDTA	4.0	-	91
	NTA	6.2	-	91
	IDA	5.8	-	76

* Hydrolysis product **10** was detected by TLC and ^{1}H NMR.

In summary, we have demonstrated at first the existence of glycosyl-chromium(III) complex compounds. The unusually slow decay of these intermediates even if in aqueous medium leads to glycal formation in very good yields using $[Cr^{II}(EDTA)]^{2-}$ and $[Cr^{II}(NTA)]^{-}$ complexes. Preparation of other glycosyl-Cr(III) complexes and their properties concerning the reaction mechanism and especially possibilities of carbon-carbon bond formations are currently being investigated.

Acknowledgment

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16. Preparation of solutions used for spectrophotometric investigations (concentrations are indicated in the Figure's caption): The ligand was dissolved in water while the peracetylated glucosyl chloride **2** in DMF. The solutions were deoxygenated with argon and then placed into a quartz tandem cell separately. The cell was sealed by silicon rubber caps and flushed with argon using hypodermic needles as inlet and outlet. A known volume from the chromium(II) chloride stock solution[15] was added through a hypodermic needle. The cell was then closed under a small overpressure of argon and after shaking was put into the spectrophotometer.
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19. To the best of our knowledge no direct evidence for the existence of glycosyl-metal intermediates is known in the literature.
20. The evaluation of the kinetic curves under the applied pseudo-first order conditions are complicated. The results of these investigations will be published elsewhere.
21. Typical procedure for the reaction of glycosyl-halides with chromium(II)complexes in homogenous medium: $Na_2EDTA{\cdot}2H_2O$ (1.3g, 3.5 mmoles) was dissolved in 40 cm^3 water at room temperature. DMF (35 cm^3) was then added and the magnetically stirred solution was deoxygenated by bubbling with argon for 15 minutes. $[Cr(OAc)_2\ H_2O]_2$ (0.6g, 1.5 mmoles, 3.0 mmol Cr(II)) was added in one portion under argon, and the colour of the solution turned immediately blue indicating the formation of the reactive complex $[Cr^{II}(EDTA)]^{2-}$. The pH of the solution was between 4 and 5. Glucosyl chloride **2** (0.5g, 1.3 mmoles) was dissolved in DMF (5 cm^3) and the solution was deoxygenated with argon. This was added in one portion to the solution of the complex and the colour of the mixture began to turn to deep-violet. The reaction vessel was than stoppered under a slight overpressure of argon, and stirring was continued for 18 hours. The mixture was saturated with NH_4Cl and extracted with ether (5x), the ethereal phase was washed with water (3x), than dried with Na_2SO_4. The solvent was evaporated under diminished pressure to give **7** as a syrup, which crystallized on standing.
22. Typical procedure for the reaction of glycosyl-halides with chromium(II)complexes in two phases medium: The solution of the $[Cr^{II}(EDTA)]^{2-}$ complex was prepared as above. Glucosyl chloride **2** (0.5g, 1.3 mmoles) was dissolved in diethyl-ether (30 cm^3), the solution was deoxygenated by argon and then added to the complex. Intensive stirring was continued for 18 hours, then the two phases were separated, the aqueous phase was saturated with NH_4Cl and extracted with ether (3x). The ether phase was dried (Na_2SO_4) and after removal of the solvent gave **7**.
23. The isolated products had physical and NMR characteristics identical with those of authentic samples.

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