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Reactivity of per-*O*-acetylated 1-thioglycosides and glycosyl sulfones towards chromium(II) complexes in aqueous medium

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Abstract—Anomeric carbon–sulfur bonds in 1-thioglycosides and glycosyl sulfones can be cleaved by chromium(II) complexes in water–DMF medium. Anomeric radicals as well as sugar–chromium(III) complex intermediates can be generated in these reactions, leading in some cases, to the exclusive formation of the corresponding glycals.

The chemistry of the anomeric centre of carbohydrate derivatives is characterized by the electrophilic nature of this carbon.[1] Umpolung of this reaction centre can be achieved by the generation of glycosyl radicals[2] or –anions,[3] and such transformations have also been intensively investigated leading to elegant synthetic methodologies and significant achievements in synthetic carbohydrate and natural product chemistry.

With increasing social concerns towards pollution of the environment, the quest for carrying out chemical transformations under environmentally benign conditions has been continuously growing. Among others, water or aqueous conditions have been proposed for a large array of organic reactions.[4] However, most 'classical' methods used for the generation of glycosyl anions[3] are incompatible with aqueous and even protic conditions.

Some years ago, we demonstrated that glycosyl-chromium(III) species were remarkably stable under aqueous conditions.[5a] This method could be elaborated for the preparation of pyranoid glycals from per-*O*-acylated glycosyl chlorides or bromides in water–DMF solvent mixture,[5b] and the transformation could also be performed in water.[5c] Nevertheless, the sensitivity of these substrates towards hydrolysis as well as nucleophilic substitution and elimination proved a disadvantage of these reactions leading to the appearance of several by-products. Therefore, hydrolytically more stable monosaccharide derivatives were sought to achieve higher selectivity under aqueous conditions. In this initial letter, we disclose our initial results on the investigation of the reactions between thioglycosides/glycosyl sulfones and chromium(II) complexes in water–DMF.

While the use of Cr(II) species for the reductive transformation of several functional groups (e.g., halogenides, carbonyl and epoxides) under aprotic conditions[6] has become a very useful and popular synthetic method, to the best of our knowledge, no chromium based reagents have been applied as yet for the cleavage of C–S bonds. Several thioglycosides/glycosyl sulfones were applied in reactions with SmI_2 to achieve the generation of glycosyl radicals and/or –anions.[3,7]

The thioglycosides and glycosyl sulfones studied in this work are collected in Table 1. The most reactive $[Cr^{II}(EDTA)]^{2-}$ complex was used[9] for testing the reactions with derivatives **1**–**11** (Table 2). The formation of glycals **12**–**15** (Scheme 1) was an indication of the

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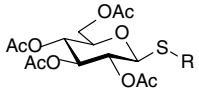
Table 1. The substrates investigated

		R[a]
1		
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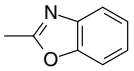
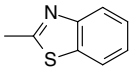
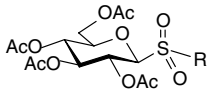
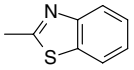
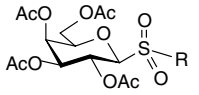
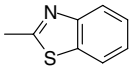
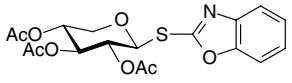
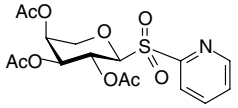
3		
4		
5		
6		
7		
8		
9		
10		
11		

[a] References: **1**,[8a] **2**,[8b] **3**,[8c] **4**,[8c,e] **5**,[8f] **6**,[8g] **8**–**11**.[8h]

efficient formation of a glycosyl-chromium(III) intermediate.[5a] Phenyl thioglucoside **1** was not reactive (entry 1) at the optimal pH for the formation of the $[Cr^{II}(EDTA)]^{2-}$ complex.[10] The reactions of 2-pyridyl thioglucoside **2** exhibited an interesting pH dependence, showing the highest reactivity under significantly acidic conditions (entries 2–5). Since the concentration of the reactive complex is essentially the same in the pH range investigated,[11] the differences must be due to protonation of the pyridine ring. If unprotonated, this substituent has little potency for promoting the transformation by stabilizing the postulated radical–anion intermediate, but with a positive charge this capacity seems sufficient for the reaction to occur. From the thioglucosides, 2-benzoxazolyl derivative **3** showed much higher reactivity as compared to its 2-benzothiazolyl counterpart **4** (entries 6–8), whilst the reaction of **10** corroborated this finding (entry 14). In the glucosyl-sulfone series the phenyl derivative **5** was again unreactive (entry 9), while 2-pyridyl and 2-benzothiazolyl compounds **6** and **7**, respectively, exhibited high reactivities (entries 10 and 11). Similarly, the D-galactosyl (**8**, **9**) and D-arabinosyl (**11**) derivatives (entries 12, 13, and 15) also showed good reactivity.

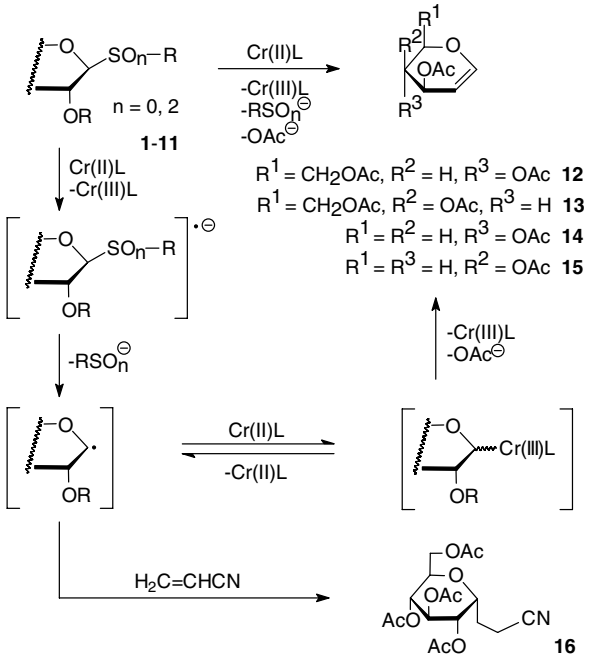
Table 2. Reduction of the C1–S bonds by the $[Cr^{II}(EDTA)]^{2-}$ complex

Entry	Substrate	pH	Reaction time (h)	Product[b]	Conversion[c] (%)
1	**1**	6	48	**12**	N.r.
2	**2**	9	18	**12**	N.r.
3	**2**	6	18	**12**	N.r.
4	**2**	5	18	**12**	17
5	**2**	4	18	**12**	>95
6	**3**	6	36	**12**	>95
7	**4**	6	36	**12**	15
8	**4**	6	2[a] + 34	**12**	17
9	**5**	6	48	**12**	N.r.
10	**6**	6	5	**12**	>95
11	**7**	6	5	**12**	>95
12	**8**	6	36	**13**	>95
13	**9**	6	36	**13**	>95
14	**10**	6	36	**14**	82
15	**11**	6	36	**15**	80

[a] $T = 60$ °C.

[b] 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**12**), 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (**13**), 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-pent-1-enitol (**14**), 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-pent-1-enitol (**15**).

[c] Calculated from the ^{1}H NMR spectra.



Scheme 1.

The reactivity of the Cr(II) ion can be carefully regulated by the coordinated ligand;[5a,b] therefore, the two highly reactive sugar derivatives **3** and **7** were subjected to reactions with less reactive chromium(II) complexes (Table 3). With $[Cr^{II}(OAc)_2]$ (entries 1 and 2), the starting materials were recovered (>90%). On increasing the reactivity with ligands[5b] (MAL < GLY < IDA < NTA < EDTA), the formation of the corresponding glycal **12** could be detected (entries 3–10). Complete conversions were reached when the $[Cr^{II}(EDTA)]^{2-}$ complex was used (entries 11 and 12). In comparison with **3**, reduction of **7** with the less reactive $[Cr^{II}(MAL)]$,

Table 3. Reduction of C1–S bonds by chromium(II) complexes

Entry	Complex $Cr^{II}L$[a]	Substrate	pH[b]	Conversion[c,d] (%)
1	$[Cr^{II}(OAc)_2]$	**3**	6.5	N.r.
2		**7**	6.5	N.r.
3	$[Cr^{II}(MAL)]$	**3**	4.0	33
4		**7**	4.0	>95
5	$[Cr^{II}(GLY)]^+$	**3**	6.0	92
6		**7**	6.0	>95
7	$[Cr^{II}(IDA)]$	**3**	6.0	91
8		**7**	6.0	>95
9	$[Cr^{II}(NTA)]^-$	**3**	6.5	73
10		**7**	6.5	>95
11	$[Cr^{II}(EDTA)]^{2-}$	**3**	6.5	>90
12		**7**	6.5	>95

[a] L: malonic acid (MAL); glycine (GLY); iminodiacetic acid (IDA); nitrilotriacetic acid (NTA); ethylenediaminetetra-acetic acid (EDTA).
[b] Reaction time was 18 h in all reactions.
[c] Calculated from the ^1H NMR spectra.
[d] Product: 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**12**).

$[Cr^{II}(GLY)]^+$, $[Cr^{II}(IDA)]$, and $[Cr^{II}(NTA)]^-$ complexes was also suitable, indicating that the 2-benzothiazolyl sulfonyl moiety makes cleavage of the C–S bond especially easy. (Unfortunately, all efforts so far made towards the preparation of the sulfonyl counterpart of **3** failed because of the extreme lability of that compound.)

We suggest that radical formation is the first step in C–S bond breaking (Scheme 1) with the cleavage of a sulfide or sulfinate from the possible intermediate radical anion. The structure of the aglycon (R) has a strong bearing on the electron acceptor capacity of the substrates. The 2-benzoxazolyl moiety was found to be the most effective for thioglycosides and the 2-benzothiazolyl moiety for glycosyl sulfones. The radical may equilibrate with a glycosyl-Cr(III) intermediate which then decomposes to give glycals **12**–**15**.

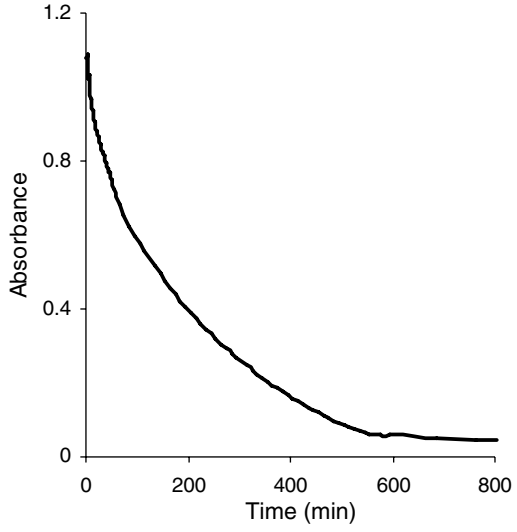


Figure 1. Typical kinetic curve[5a] recorded at 320 nm demonstrating elimination of the organochromium(III) intermediate in the reaction of $[Cr^{II}(EDTA)]^{2-}$ and **7** ($[Cr^{II}] = 5$ mM, $[EDTA] = 7.4$ mM, $[7] = 0.5$ mM, pH = 5, $H_2O/DMF = 1/1$, t = 25 °C in 1.00 cm cell).

The UV–visible spectra (Fig. 1) show the decomposition of the organometallic bond resulting in the elimination product.

In order to test the hypothesis of the intermediate radical (Scheme 1), the reaction of **7** was performed in the presence of acrylonitrile.[12] Analysis of the reaction mixture indicated the formation of *C*-glucosyl derivative **16**[13] as a product of radical coupling.

In this work, we have demonstrated that hydrolytically stable anomeric C–S bonds can be cleaved by chromium(II) complexes to produce a glycosyl radical suitable for coupling as well as a C(1)–Cr(III) organometallic bond featuring a carbanionic anomeric centre.

Acknowledgements

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9. *Typical procedure for the preparation of glycals:* EDTA (1.265 g, 3.4 mmol, 6 equiv) was dissolved in a mixture of water (30 ml) and DMF (30 ml), and stirred under argon.

A calculated amount of an aq KOH solution (2.4446 M, 1.25 ml) was added to this solution to obtain pH ~ 6. After the solution had cleared (30 min), [$Cr(CH_3COO)_2 \cdot H_2O$] (0.540 g, 2.83 mmol, 5 equiv) was added in one portion. Formation of the complex was indicated by a change of colour. The solution of thioglycoside **3** (0.273 g, 0.56 mmol, 1 equiv) in DMF (5 ml) was added to the mixture and stirred at room temperature for 18 h. (For glycosyl-sulfones the reaction time was 5 h.)

Work-up for thioglycosides: Saturated NH_4Cl solution (50 ml) was added to the reaction mixture. This solution was extracted with ether (6 × 20 ml), the organic layer was washed with water (4 × 10 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure. The resulting residue was examined by TLC (eluent: ether/hexane = 6/4) and ^1H NMR. The products had NMR characteristics identical with those of authentic samples.

Work-up for glycosyl-sulfones: Saturated NH_4Cl solution (50 ml) was added to the reaction mixture. This solution was extracted with chloroform (6 × 20 ml), the organic layer was washed with water (4 × 10 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure. The resulting residue was examined by TLC (eluent: ether/hexane = 6/4) and ^1H NMR.

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11. The experimental conditions for pH dependence measurements were the same as above[9] except for the amounts of KOH, which were: 6.25–4.0–2.0–0 ml (entries 2–5, Table 2), and the amount of the ligand EDTA was 8.15 mmol (3.035 g) in all cases.
12. *Typical procedure for generation of the C(1)–C bond:* $[Cr^{II}(EDTA)]^{2-}$ complex was generated in situ in H_2O/DMF = 1/1 as above. A solution of glycosyl-sulfone (0.265 g, 0.56 mmol, 1 equiv), in DMF (5 ml) was added to the mixture. After 15 min, acrylonitrile (2 ml, 0.03 mol, 60 equiv) was added to the reaction mixture in one portion. The reaction was stirred at room temperature for 18 h followed by work-up a similar described above. The resulting residue was examined by TLC (eluent: ether/hexane = 6/4) and ^1H NMR, which show the presence of **16**[13] in ~40% yield.
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