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# Hydrogen peroxide oxidation of palatinose and trehalulose: direct preparation of carboxymethyl α-D-glucopyranoside

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**Abstract**

The direct oxidation of palatinose and trehalulose by hydrogen peroxide in acidic medium provided carboxymethyl α-D-glucopyranoside (α-CMG) in moderate to fair yields in a single step. The effect of catalytic sodium tungstate on the reaction was studied. α-CMG is a versatile synthon able to supply a glucosyl moiety through the acylation of alcohols or amines, via the opening of the δ-lactone obtained by acetylation. 

*Keywords:* palatinose; trehalulose; oxidation; hydrogen peroxide.

As a part of our efforts towards the use of carbohydrates as organic raw materials,[1] and in the context of clean oxidation processes,[2] we were interested in the chemistry of two reducing disaccharides, palatinose and trehalulose, 6-α-D-glucopyranosyl-D-fructofuranose and 1-α-D-glucopyranosyl-D-fructopyranose, respectively, both obtained in one-step from sucrose by bioconversion.[3] The oxidation of palatinose can lead to glucosyl-α-D-arabinonates by air oxidation under basic conditions, or to more carboxylated derivatives under platinum-catalysed oxidation conditions.[4] Further oxidation could offer an access towards other interesting synthons such as carboxymethyl α-D-glucopyranoside (α-CMG), for which there are no straightforward preparative methods available. This compound can be used as a reagent able to supply a carbohydrate entity by reaction of its carboxylic function.[5] On the other hand, polyhydroxycarboxylates derived from carbohydrates can also be seen as potential cation sequestering agents.[6]

Aqueous hydrogen peroxide is a very attractive system for the oxidation of organic compounds taking into account that it is easy to handle, easily available, and that it generates no by-products. In the case of carbohydrates, the outcome of hydrogen peroxide oxidation reactions depends on the occurrence of hemiacetalic centres, the basic or acidic conditions, and the presence of additives such as metal salts. All these aspects have been recently reviewed by

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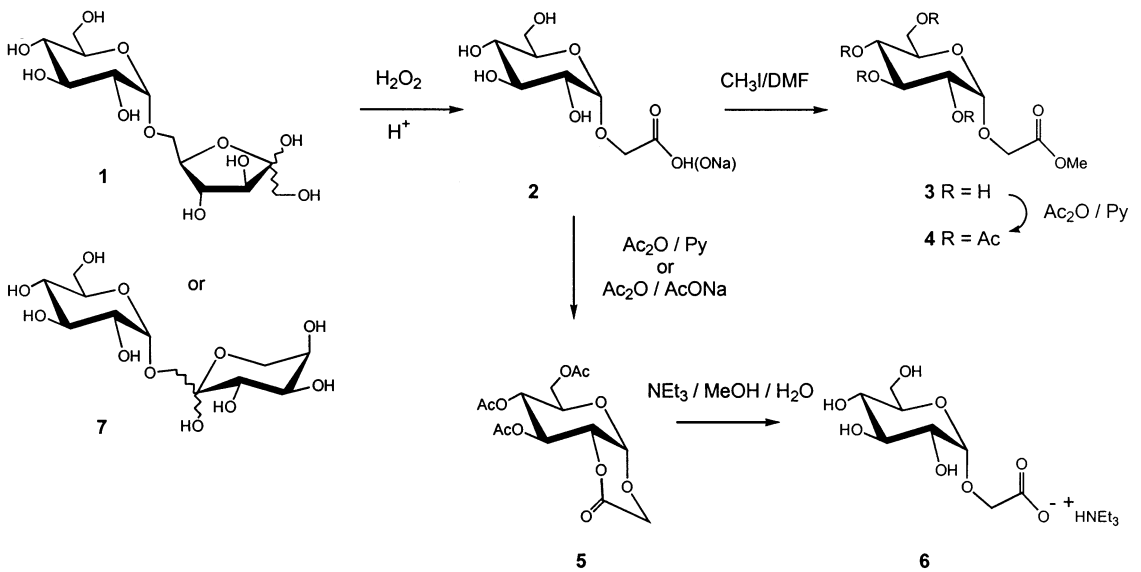
Sheldon et al.[7] Some of these reactions are degradative oxidation-decarboxylation sequences since the immediate products are also oxidisable, leading to short acids as final products.

We describe the obtention of α-CMG (**2**) from palatinose (**1**) or trehalulose (**7**) in one-step using hydrogen peroxide. We also studied the effect of the presence of sodium tungstate, known to promote the oxidative cleavage of glycols when used in combination with hydrogen peroxide, via peroxotungstate species, in a very clean and efficient manner which was developed by Venturello and Ricci,[8] and more recently by Noyori et al. who applied it to a straightforward synthesis of adipic acid.[9] Applied to starch and maltodextrins, erythronic acid-terminated oligoglucosides were obtained.[10]

The reaction of palatinose with excess hydrogen peroxide either in acidic conditions (pH 2) at 80°C or in basic conditions at room temperature provided essentially one product having a carbohydrate skeleton, identified as carboxymethyl α-D-glucopyranoside (**2**, α-CMG) (Scheme 1). This compound could be isolated by silica gel chromatography, but was fully characterised after chemical derivatisation as its methyl ester **3** upon treatment with methyl iodide in DMF and subsequent peracetylation to the tetraacetyl derivative **4**. On another hand, treatment of the carboxylate **2** ($Ac_2O$, py or AcONa) led to the triacetyl lactone **5** which was quantitatively converted into the triethylammonium salt **6** ($NEt_3$, MeOH, $H_2O$).[11,12] One-dimensional ($^1H$ and $^{13}C$) and two-dimensional NMR spectroscopic analyses of all these compounds were consistent with the presence of the α-carboxymethyl linkage. Long distance C–H correlations (HMBC) were observed between H-7ab and C-1 and between H-7ab and C=O. The pure triethyl ammonium salt was used for establishing two analytical procedures necessary for the optimisation of the reaction, based on the direct assay by ion-exchange analytical chromotography (Carbopac, Dionex) or using gas chromatography after persilylation (py-TMSCl-HMDS, 9/3/1 vol, ultrasound bath, 30 min, phenyl β-D-glucopyranoside as internal standard). All new compounds gave satisfactory analytical data.




Scheme 1.

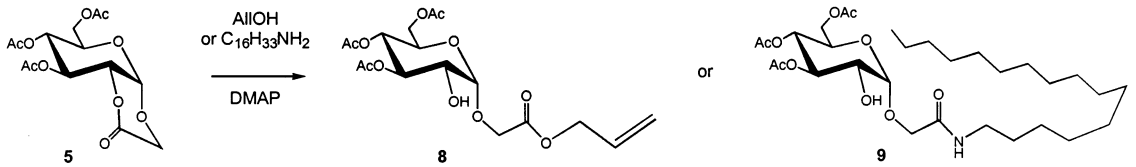
The rates of formation of α-CMG and the yields depended strongly on the pH (Table 1). Under basic conditions at room temperature (or under conditions used by Isbel et al. for the oxidation of dissaccharides leading to similar compounds such as β-CMG or the α-galacto derivative from melibiose and gentiobiose),[13] a very slow formation of α-CMG was observed, with yields below 15%, although palatinose was fully consumed. The same observation was made with sodium peroxide as oxidant. In both cases, a complex mixture of products was obtained as seen by NMR spectroscopy. However, under acidic catalysis and at higher temperature, we could increase the yield up to 35%. Increasing the pH from 2 to 5 led to a slower reaction and lower yields, showing that the issue was not only to prevent acidic hydrolysis of the product. At pH 4, an interesting effect of the presence of sodium tungstate was observed, as the yield was increased to 38% compared to 23% without tungstate (Table 1).[14] This effect might be due to the cleavage of the C-3–C-4 bond of the fructofuranose moiety, thus pushing the reaction two steps ahead compared to the sequential degradation mechanism. Increasing the tungstate amount did not improve the process. Under the more acidic conditions (pH 2), which are described to be the best conditions in the Venturello–Ricci–Noyori method, there is no advantage in using the tungstate. Decreasing the amount of hydrogen peroxide to the stoichiometric amount necessary to oxidise only the fructose moiety of the substrate led to only slightly lower yields of α-CMG (**2**) showing that the intermediate compounds are more easily oxidised than palatinose itself. The reaction rate was increased in this case because of higher concentrations, the reaction volume being mostly that of the hydrogen peroxide aqueous solution. Starting from trehalulose (**7**), the same product was obtained in 42% yield at pH 2 and 40% at pH 4 with tungstate ions (47 and 59% based on starting material recovery, respectively), in a slower conversion rate compared to palatinose, but with a faster α-CMG formation rate. Even though the yields are moderate because of a slow further oxidation, α-CMG is obtained in a very straightforward manner in comparison with the methods described in the literature requiring several steps from glucose[15] or very low yielding and not selective at the anomeric center by direct reaction of glucose with glycolic acid.[16]

Table 1
Formation of α-CMG (**2**) by oxidation of palatinose (**1**) or trehalulose (**7**)[14]

| Substrate | pH | $Na_2WO_4$ (equiv.) | $H_2O_2$ (equiv.) | $T$ (°C) | $t$ (h) | **2** (%) |
|---|---|---|---|---|---|---|
| **2** | 13 | | 36 | 20 | 2 | 15 |
| **2** | 2 | | 9.8 | 80 | 12 | 30 |
| **2** | 2 | | 19.6 | 80 | 10 | 36 |
| **2** | 3 | | 19.6 | 80 | 12 | 32 |
| **2** | 4 | | 19.6 | 80 | 14 | 23 |
| **2** | 2 | 0.24 | 19.6 | 80 | 8 | 31 |
| **2** | 4 | 0.12 | 19.6 | 80 | 25 | 38 |
| **2** | 4 | 0.24 | 19.6 | 80 | 20 | 38 |
| **2** | 4 | 0.48 | 19.6 | 80 | 17 | 35 |
| **7** | 2 | | 19.6 | 80 | 8 | 42 (*47*)[a] |
| **7** | 4 | 0.24 | 19.6 | 80 | 20 | 40 (*59*)[a] |

[a] In brackets are given the yields based on starting material conversion.

Having α-CMG in hands, acetylation easily afforded the lactone **5** (H-2 and H-7ab correlated with C=O), as in the case of the carboxymethyl-β-lactoside.[17] This lactone was used as a reagent able to supply a carbohydrate entity, a useful process for either providing chirality, water-solubility or more specific properties due to its carbohydrate nature.[18] Reaction of **5** with alcohols (e.g. allyl alcohol) or amines (e.g. hexadecylamine) under basic conditions led to the corresponding ester **8** (88%) and amide **9**[19] (76%) of 3,4,6-tri-*O*-acetyl-α-CMG, having a free OH-2 (Scheme 2).




Scheme 2.

In conclusion, we have shown that carboxymethyl α-D-glucoside can be obtained in one single step in moderate yields from palatinose or trehalulose with hydrogen peroxide under acidic conditions. The best conditions are pH 4 in the presence of catalytic amounts of sodium tungstate (interesting in the case of substrates which would exhibit lower stability) or pH 2 without any other catalyst. The lactone obtained quantitatively by acetylation of α-CMG can be opened by nucleophiles (alcohols, amines) to provide the corresponding glucosyloxycarbonylated derivatives.

The scope of the use of this lactone as an acylating agent able to supply a carbohydrate moiety with respect to other alcohols and amines is currently in progress in our laboratory.

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## References

1. Gagnaire, J.; Toraman, G.; Descotes, G.; Bouchu, A.; Queneau, Y. *Tetrahedron Lett*. **1999**, *40*, 2757–2760; Potier, P.; Maccario, V.; Giudicelli, M.-B.; Queneau, Y.; Dangles, O. *Tetrahedron Lett*. **1999**, *40*, 3387–3390; Porwanski, S.; Salanski, P.; Descotes, G.; Bouchu, A.; Queneau, Y. *Synthesis* **2000**, 525–528.
2. Brochette-Lemoine, S.; Trombotto, S.; Joannard, D.; Descotes, G.; Bouchu, A.; Queneau, Y. *Ultrasonics Sonochem*. in press; Lemoine, S.; Thomazeau, C.; Joannard, D.; Trombotto, S.; Descotes, G.; Bouchu, A.; Queneau, Y. *Carbohydr. Res*. **2000**, *326*, 176–184.
3. Schiweck, H.; Munir, M. K.; Rapp, M.; Schneider, B.; Vogel, M. In *Carbohydrates as Organic Raw Materials*; Lichtenthaler, F. W., Ed.; VCH: Weinheim, 1991; pp. 57–94; Nagai, Y.; Sugitani, T.; Tsuyuki, K. *Biosci. Biotech. Biochem*. **1994**, *58*, 1789–1793.
4. Kunz, M. In *Carbohydrates as Organic Raw Materials*; Lichtenthaler, F. W., Ed.; VCH: Weinheim, 1991; pp. 127–153; Lichtenthaler, F. W.; Klimesch, R. G. DE 3248404, US 4618675 (*Chem. Abs*. **1985**, *115*, 7034x); Röger, H.; Puke, H.; Kunz, M. *Zuckerindustrie* **1990**, *115*, 174–181.

5. Bandai, T.; Okumoto, H.; Hara, K.; Mikuni, K.; Hara, K.; Hamada, H. JP 09227584 (*Chem. Abstr.* **1997**, *127*, 248356).
6. Besemer, A. C.; van Bekkum, H. In *Carbohydrates as Organic Raw Materials III*; van Bekkum, H.; Röper, H.; Voragen, A. G. J., Ed.; VCH: Weinheim, 1996; pp. 273–293. Nieuwenhuizen, M. S.; Kieboom, A. P. G.; van Bekkum, H. *J. Amer. Oil Chem. Soc.* **1983**, *60*, 44–48.
7. Arts, S. J. H. F.; Mombarg, E. J. M.; van Bekkum, H.; Sheldon, R. A. *Synthesis* **1997**, 597–613.
8. Venturello, C.; Ricci, M. *J. Org. Chem.* **1986**, *51*, 1599–1602.
9. Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386–12387; Sato, K.; Aoki, M.; Noyori, R. *Science* **1998**, *281*, 1646–1647.
10. Floor, M.; Schenk, K. M.; Kieboom, A. P. G.; van Bekkum, H. *Starch* **1989**, *41*, 303–309.
11. Triacetyl lactone (**5**): $[\alpha]_D^{20}$+141 (*c* 1, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm) 5.53 (t, 1H, $J_{2,3}=J_{3,4}=9.6$ Hz, H-3), 5.32 (d, 1H, $J_{1,2}=3.0$ Hz, H-1), 5.04 (t, 1H, $J_{4,5}=9.8$ Hz, H-4), 4.66 (d, 1H, $J_{7a,b}=17.7$ Hz, H-7a), 4.48 (d, 1H, H-7b), 4.40 (dd, 1H, H-2), 4.3–4.2 (m, 2H, H-5, H-6a), 4.08 (m, 1H, H-6b), 2.06, 2.05, 2.01 (3 s, 9H, 3AcO); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ (ppm) 170.9, 170.4, 169.8 (3AcO), 163.7 (CO), 91.5 (C-1), 76.3 (C-2), 71.9 (C-3), 70.5 (C-5), 67.3 (C-4), 64.9 (C-7), 61.7 (C-6), 21.1, 20.9 (3AcO); anal. calcd for $C_{14}H_{18}O_{10}$: C, 48.5; H, 5.2; found: C, 48.3; H, 5.0; MS (FAB+) *m*/*z* 331.1 $[M-CH_3]^+$.
12. Triethylammonium α-CMG (**6**): $[\alpha]_D^{20}$+116 (*c* 1, MeOH); $^1$H NMR ($D_2O$, 300 MHz) $\delta$ (ppm) 4.93 (d, 1H, $J_{1,2}=3.7$ Hz, H-1), 4.13 (d, 1H, $J_{7a,b}=15.4$ Hz; H-7a), 3.93 (d, 1H, H-7b), 3.9–3.6 (m, 4H, H-3, H-5, H-6), 3.52 (dd, 1H, $J_{2,3}=9.6$ Hz, H-2), 3.40 (t, 1H, $J_{3,4}=9.5$ Hz, H-4), 3.19 (q, 6H, $CH_2$), 1.27 (t, 9H, $CH_3$); $^{13}$C NMR ($D_2O$, 7.5 MHz) $\delta$ (ppm) 179.9 (COO), 101.0 (C-1), 75.9 (C-3), 74.7 (C-5), 74.3 (C-2), 72.3 (C-4), 69.6 (C-7), 63.2 (C-6), 49.4 ($CH_2$), 10.9 ($CH_3$); anal. calcd for $C_{14}H_{29}O_{18}N+1.3H_2O$: C, 46.3; H, 8.8; N, 3.9; found: C, 46.3; H, 8.7; N, 3.8; HRMS (FAB+) *m*/*z* calcd for $C_{14}H_{30}O_8N$ $[MH]^+$ 340.1971, found 340.1966.
13. Isbel, H. S.; Frush, H. L. *Carbohydr. Res.* **1987**, *161*, 181–193.
14. Typical procedure: a solution of palatinose (3.4 g, 10 mmol), hydrogen peroxide 30% (w/w) (22.3 g, 196 mmol), eventually sodium tungstate (792 mg, 2.4 mmol) and phosphoric acid 85% (w/w) (138 mg, 1.2 mmol) were adjusted at pH 2–4 by addition of 1 M HCl or 1 M NaOH. After 20 h at 80°C, excess oxidant, if present, was quenched with aqueous sodium sulfite and the medium was adjusted at pH 9 (1 M NaOH). The mixture was then freeze-dried, and the α-CMG was purified by silica gel chromatography (AcOEt–MeOH–$H_2O$, 6:3:2 v/v) or directly submitted to peracetylation.
15. For a selective access to the β-anomer, see Ref. 13 and: Fischer, E.; Helfreich, B. *Justus Liebigs Ann. Chem.* **1911**, *383*, 68–91; Timmel, T. E. *Can. J. Chem.* **1964**, *42*, 1456–1472; Binder, W. H.; Schmid, W. *Monatsch. Chem.* **1995**, *126*, 923–931; Lockhoff, O. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3436–3439.
16. Petersson, G.; Pettersson, S.; Samuelson, O. *Sv. Papperstidn.* **1969**, *72*, 222–225 (*Chem. Abstr.* **1969**, *71*, 23035v).
17. Dean, B.; Oguchi, H.; Cai, S.; Otsuji, E.; Tashiro, K.; Hakomori, S. I.; Toyokuni, T. *Carbohydr. Res.* **1993**, *245*, 175–192.
18. Nicolaou, K. C.; Trujillo, J. I.; Chibale, K. *Tetrahedron* **1997**, *53*, 8751–8778.
19. Amide (**9**): $[\alpha]_D^{20}$+87 (*c* 0.5, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$(ppm) 7.11 (t, 1H, $J=5.3$ Hz, NH), 5.23 (t, 1H, $J_{2,3}=J_{3,4}=9.6$ Hz, H-3), 5.00 (t, 1H, $J_{4,5}=9.8$ Hz, H-4), 4.88 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.25 (dd, 1H, $J_{6a,5}=4.7$ Hz, $J_{6a,6b}=12.4$ Hz, H-6a), 4.18 (d, 1H, $J_{7a,b}=15.8$ Hz, H-7a), 4.04 (d, 1H, H-7b), 4.1–3.9 (m, 2H, H-5, H-6b), 3.79 (dd, 1H, H-2), 3.24 (m, 2H, $CH_2N$), 2.64 (m, 1H, 2-OH), 2.07, 2.05, 2.01 (3 s, 9H, 3AcO), 1.48 (m, 2H, $CH_2$), 1.22 (m, 26 H, 13 $CH_2$), 0.84 (t, 3 H, $J=7.0$ Hz, $CH_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ (ppm) 171.8, 170.6, 169.5, 168.6 (3AcO, CO), 98.9 (C-1), 73.7 (C-3), 70.6 (C-2), 68.0 (C-5), 67.7 (C-4), 67.2 (C-7), 61.7 (C-6), 39.2, 31.9, 29.7, 29.3, 26.9, 22.6 (13$CH_2$), 20.8, 20.7, 20.6 (3AcO), 14.1 ($CH_3$); anal. calcd for $C_{30}H_{53}O_{10}N$: C, 61.3; H, 9.1; N, 2.4; found: C, 61.5; H, 9.1; N, 2.4; MS (FAB+) *m*/*z* 594.5 $[MLi]^+$.