

Autocatalytic oxidations of primary hydroxyl groups of cellulose in phosphoric acid with halogen oxides

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Abstract

Selective oxidation of the primary hydroxyl groups in cellulose has been achieved in phosphoric acid with: (i) sodium bromate, (ii) sodium chlorate, and (iii) sodium chlorite as stoichiometric oxidants in the presence of catalytic amounts of sodium bromide and chloride. With these reaction systems, where the oxidising oxyhalogen species are formed in situ, the primary alcohol groups could be completely (>90%) oxidised to carboxylic acids. Ring cleavage also occurred, especially with chlorate. The carbonyl groups formed by oxidation of secondary hydroxyl groups were subsequently reduced with sodium borohydride. This oxidation–reduction sequence of secondary alcohol groups gave epimerisation. Polymer degradation differed markedly. Using water soluble pullulan with $\langle M_w \rangle \sim 170$ kg/mol as a probe for degradation, bromate yielded a polymer with $\langle M_w \rangle \sim 70$ kg/mol while chlorate and chlorite yielded highly degraded polyuronates of $\langle M_w \rangle \sim 10$ kg/mol. A common mechanism for the oxidation of primary hydroxyls is suggested to account for the selectivity observed. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: Cellulose; Selective oxidation; Primary alcohol; Autocatalytic; Halate

1. Introduction

The selective oxidation of primary hydroxyl groups in carbohydrates is an important chemical modification which, due to the similarity of primary and secondary alcohol groups, cannot be accomplished with most of the oxidants in common use [1]. Recently, a highly efficient catalytic method has been introduced for the regioselective oxidation of primary alcohol groups of water soluble polysaccharides [2]. So far, the only method known for the oxidation of primary alcohols of cellulose and other insoluble polysaccharides has

been the oxidation with nitrogen oxides [3–6]. Heterogeneous oxidation of cellulose with nitrogen tetroxide yields principally 6-carboxycellulose [3], a polysaccharide commercially available as a wound healing agent to prevent post-surgical adhesions [7]. Since cellulose dissolves in 85% phosphoric acid with limited hydrolysis its *homogeneous* oxidation can be carried out generating the nitrogen oxides in situ by adding a stoichiometric amount of sodium nitrite at ambient temperature [4,5] or, better, by adding a stoichiometric amount of sodium nitrate with a catalytic amount of sodium nitrite at 4 °C [6]. In both cases, the oxidation is

not completely selective and a reduction step with sodium borohydride is necessary to reduce the ketones (10–20%) formed by oxidation of secondary alcohol groups. This method yields complete (>95%) conversion of cellulose primary alcohols to carboxylic groups.

Oxidation of polymeric glucans with halogens and oxyhalogen species has been extensively studied. Thus, cellulose treated with aqueous hypochlorite yields a highly degraded product oxidised at random [8], whereas the oxidation of soluble polymeric glucans (starch, inulin) with hypochlorite at pH 7 [9] and with hypobromite [10] at pH 10 yields the 2,3-dicarboxy-glucans. Interestingly, hypochlorous acid at pH 4 preferentially oxidises the primary hydroxyl groups of starch yielding a polymer containing both 6-aldehydoglucose and glucuronic acid residues [11]. Although this latter result has been known for more than 40 years, no reasons have been suggested to explain the selectivity observed. This is regrettable, since natural polyuronates such as pectins or alginates have commercial applications due to valuable properties like gel forming ability at low concentration and high metal sequestering capacity [12], and new methods for the conversion of cheap and readily available polysaccharides into polyuronates could be of commercial interest. In this work, we have applied the halide catalysed oxidations in 85% phosphoric acid with sodium bromate, sodium chlorate and sodium chlorite to the glucans cellulose and pullulan (a linear polysaccharide consisting of the repeating trimer [\rightarrow 6)- α -D-Glcp-(1 \rightarrow 4)- α -D-Glcp-(1 \rightarrow 4)- α -D-Glcp-(1 \rightarrow)]). The use of water soluble pullulan allowed us to determine the extent of polymer degradation. We compare these oxidations with previous results involving sodium nitrate [6]. The oxidations were followed by a reduction step with sodium borohydride. A reaction mechanism for the oxidation of the primary hydroxyls is suggested.

2. Results and discussion

Oxidations.—Under the homogeneous acidic conditions provided by dissolving cellulose in phosphoric acid, the complete (>90%) oxidation of cellulose primary hydroxyls is achieved using sodium chlorate and bromate with, respectively, a catalytic amount of sodium chloride and bromide. Moreover, in contrast to the limited (0.1–1%)

oxidation reported for the oxidation of cellulose primary hydroxyls with an acidified (pH 5) solution of sodium chlorite [13], we found that the oxidation of cellulose dissolved in 85% phosphoric acid with sodium chlorite and a catalytic amount of sodium chloride yields a polymer with a degree of oxidation at C-6 of about 95%. In the case of bromate oxidation, it was observed that the use of 80% phosphoric acid led to higher yields and degree of oxidation whereas chlorate oxidation was best carried out in 85% phosphoric acid. Results for cellulose are presented in Table 1.

The ^{13}C NMR spectra of the oxidised–reduced polymers obtained with bromate and chlorite (4 °C, 24 h) are shown in Figs 1 and 2. The lack of signals at 61–62 ppm and the signals at 176 ppm indicate that primary alcohol groups are completely oxidised to yield carboxylic acids. However, the oxidations are not completely selective. In the spectra, *two* anomeric carbon peaks were observed at 103 and 105 ppm and two peaks appear at 176 ppm. The ^1H spectra (not shown) indicate that ring cleavage between C-2 and C-3 occurs to different extent [14]. Hence, ring cleavage was more pronounced using chlorate and chlorite (30%) than using bromate (20%).

As discussed previously in the nitrate oxidation [6], a reduction step was carried out under alkaline conditions with an excess of sodium borohydride to reduce the carbonyl functionalities formed by the oxidation of secondary hydroxyl groups. The 3-hydroxybiphenyl assay for uronic acids [15] showed absorbances of the order of 20% higher after the reduction. Yields were lower than the yield (90%) of nitrate oxidation [6]. Thus, yields were of the order of 60% using the halates and of 80% using chlorite.

Table 1
Degree of oxidation with cellulose as the substrate^a

Oxidant	DO ^b (%)	Yield ^c (%)
NaBrO ₃	96	85
NaClO ₃	90	55
NaClO ₂	95	60

^a Conditions: 1.0 g cellulose in 30 mL 85% H₃PO₄ with (i) 0.80 mol halate/mol AGU, and (ii) 1.2 mol chlorite/mol AGU. With bromate, 80% H₃PO₄ was used. Oxidation time 24 h.

^b Degree of oxidation of the products after reduction with NaBH₄ as measured with the 3-hydroxybiphenyl assay for uronic acids.

^c Yield as calculated with the monomer molar masses depending on the DO.

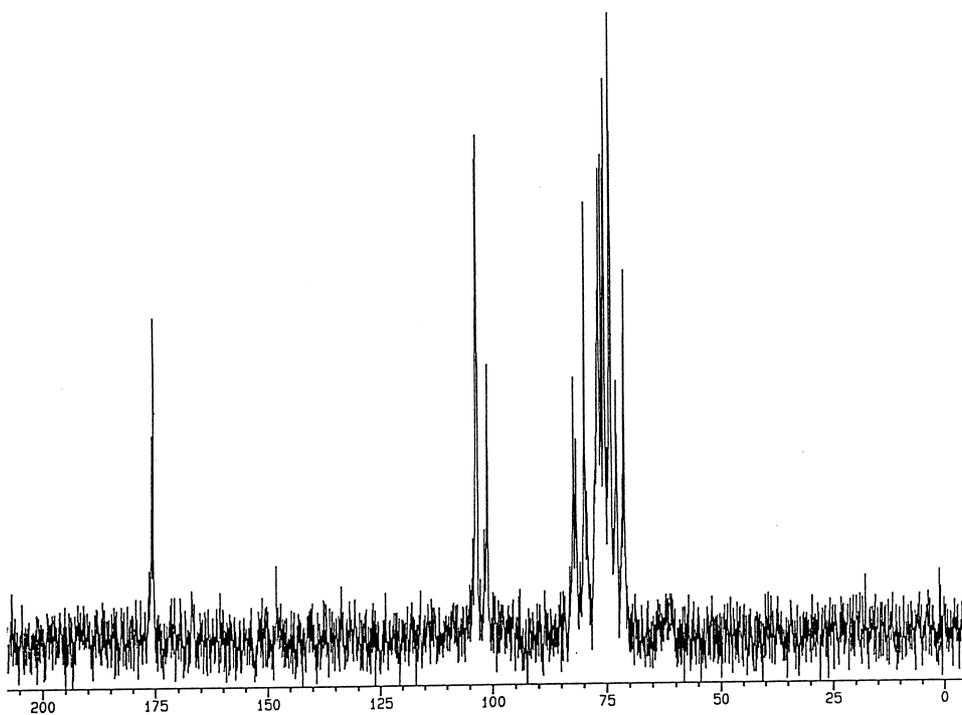


Fig. 1. ^{13}C NMR spectrum of oxidised cellulose obtained with sodium bromate after the reduction with sodium borohydride. Reaction conditions were as described in Section 3.

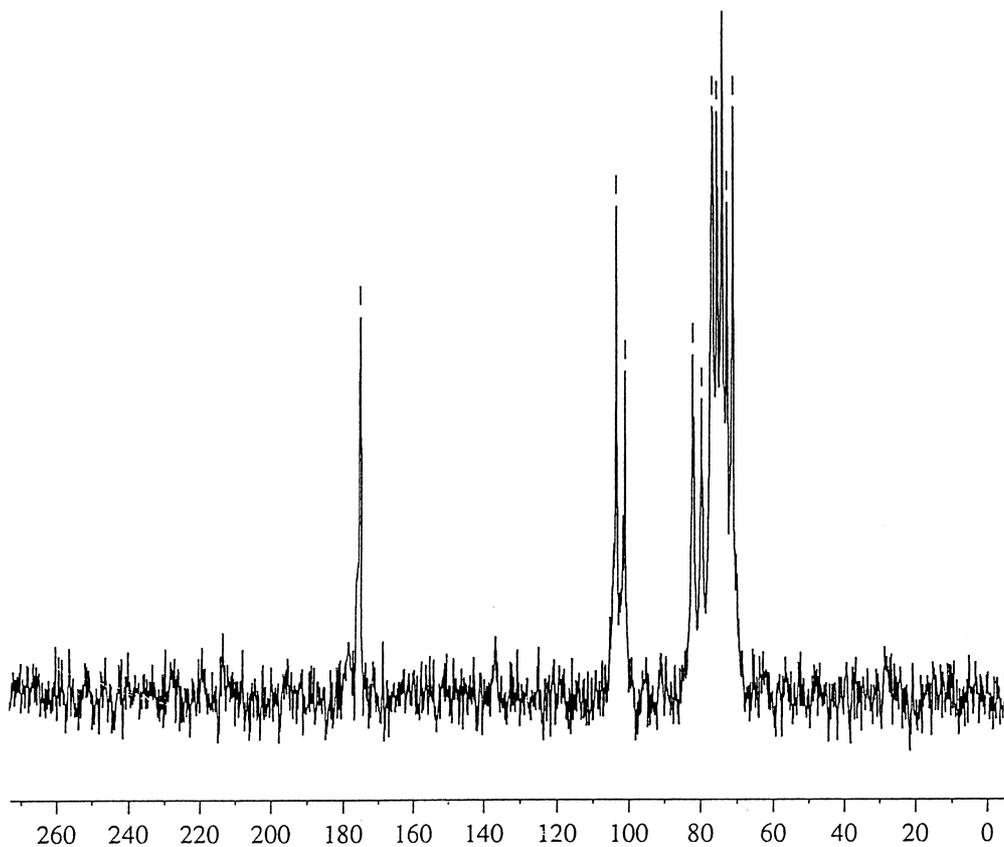


Fig. 2. ^{13}C NMR spectrum of oxidised cellulose obtained with sodium chlorite after the reduction with sodium borohydride. Reaction conditions were as described in Section 3.

The extent of polymer degradation was examined using pullulan as substrate. Since pullulan is water soluble, this allows the comparison of the molar mass of the oxidised–reduced pullulans with that of the parent polymer [6]. The molar mass distribution was determined by size exclusion chromatography (SEC) with on-line multi-angle laser light scattering (MALLS) detection. In Fig. 3 the molecular weight plots of pullulan and oxidised–reduced pullulans obtained using chlorate, bromate and nitrate are shown. Starting from pullulan of $\langle M_w \rangle \sim 170$ kg/mol, chlorate or chlorite yielded highly degraded polymers of $\langle M_w \rangle \sim 10$ kg/mol while bromate yielded a polymer of molar mass 70 kg/mol closer to that (96 kg/mol) promoted by nitrate [6].

Mechanism.—Chlorous acid oxidises sugars only slowly whereas chloric and bromic acid do not oxidise either aldoses or ketoses [16]. However, acidic bromate [17] and chlorite [18] are well known as efficient oxidants of several organic substrates including alcohols. These are autocatalytic reactions in which a small amount of bromide or chloride is added to bromate or chlorite to reduce the induction time analogous to autocatalytic nitrate oxidations in which a small amount of sodium nitrite is used. Autocatalytic acidic nitrate and bromate oxidations are known to show important similarities [19].

In accordance with their autocatalytic nature [20], the present oxidations originate fast propagating waves. This became evident when performing the reactions in a Petri dish without stirring. When

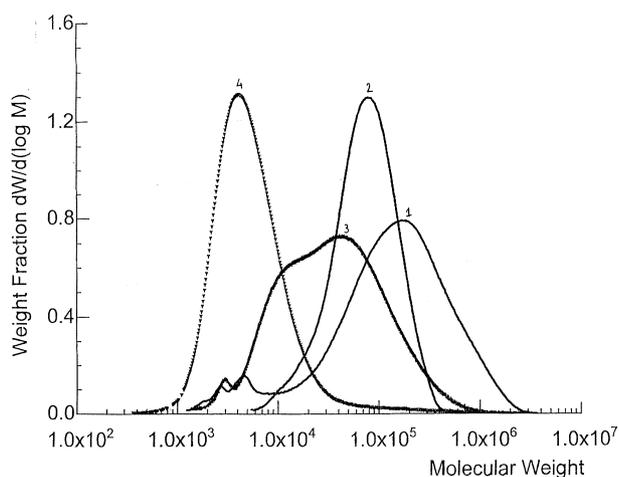
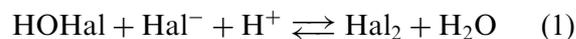


Fig. 3. Differential molecular weight plots of pullulan (1) and oxidised–reduced pullulans as obtained by SEC–MALLS. Oxidant: 2, NaNO₃; 3, NaBrO₃; 4, NaClO₃.

a drop of concentrated solution of the stoichiometric oxidants was added to a solution of cellulose in 85% phosphoric acid containing dissolved sodium halogenides, suddenly yellow (chlorate and chlorite) or red (bromate) reaction fronts developed which rapidly reached the sides of the Petri dish.

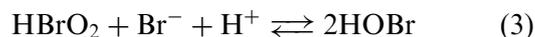
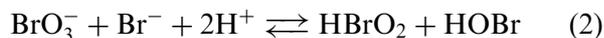
An important difference between cellulose oxidation with nitrate and the oxidations with halates here described lies in the role of the Cl⁻ and Br⁻ produced in the latter reactions as compared to the role of NO produced in the nitrate oxidation. Thus, while NO is known to be inactive toward further oxidation, bromide and chloride produced in the acidic halogenate oxidations catalyse the formation of the active oxidants molecular bromine or chlorine:



Surprisingly, however, it has been reported that bromine and chlorine bubbled into a cellulose solution in 85% phosphoric acid at ambient temperature do oxidise and degrade the polysaccharide to a very limited extent even after 40 h [21].

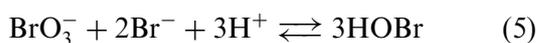
It is known that chlorine oxyacids are stronger oxidants than the corresponding bromine species. Thus, in acidic solution both chlorate and chlorite are stronger oxidants than bromate [22]. This might explain the enhanced polymer degradation observed using chlorate and chlorite compared to that observed using bromate. A similar finding has been reported for the alkaline hypohalite oxidation of starch in which the use of hypobromite in place of hypochlorite reduces polymer degradation [10].

According to extensive studies carried out to elucidate the mechanism of acidic bromate oxidations in the presence of bromide, several oxybromo species are present in the reaction mixture and the reactions generating important oxybromo species are the following [23]:



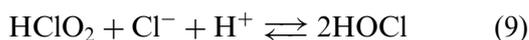
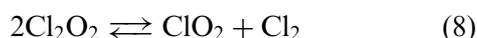
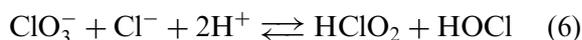
Bromous acid disproportionates rapidly (eq (4), $k = 4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ [18]). At high bromate and acid

concentration and in the presence of sufficient bromide, a rapid equilibrium is established between bromate and hypobromous acid through eq (2) and (3):



Under these conditions, oxidation by hypobromous acid predominates and autocatalysis is observed with a number of organic substrates [24]. Hypobromous acid oxidises the substrate and is reduced to bromide which in its turn promotes bromate decomposition (feedback). The only role for bromate is to reoxidise the bromide formed in the oxidative step.

Acidic chlorate oxidations are also carried out with a small amount of chloride. According to the reaction conditions (pH, chloride concentration) different equilibria predominate [25]:



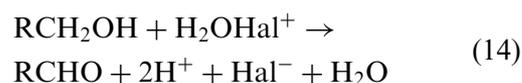
In a previous paper, the autocatalysis observed in the nitrate oxidation of cellulose was explained by the following reactions [6]:



According to this scheme, NO^+ is the actual oxidant of primary alcohols and the only role for nitric acid is to reoxidise the NO formed in the reaction mixture.

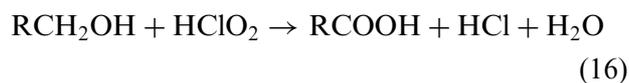
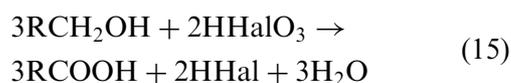
Analogies between hypochlorous and nitrous acid chemistry have been reported. For instance,

acidic chlorinations and N-nitrosations have been ascribed to the conversion of HO–NO and HO–Cl to H_2ONO^+ and H_2OCl^+ species with subsequent attack on the substrates by the ions formed [26]. Furthermore, oxidations of primary [27] and secondary alcohols [28] in acidic medium with *N*-bromoacetamide and *N*-bromosuccinimide have been ascribed to the oxidative attack of H_2OBr^+ . On the basis of the analogies discussed above, we propose that, under our reaction conditions, the oxidation of primary alcohol groups in cellulose with bromate, chlorate and chlorite should be attributed to the oxidative attack on primary hydroxyls by (protonated) hypobromous and hypochlorous acid (Hal = Br, Cl):



While the oxidation of cellulose primary hydroxyls with an acidified (pH 5) aqueous solution of sodium chlorite does not proceed in yield more than 1% [13], carrying out the reaction in the strongly acidic medium provided by 85% phosphoric acid in the presence of added chloride, the formation of (protonated) hypochlorous acid is enhanced [eq (9)] and we observed complete oxidation of primary hydroxyls to carboxylic acids.

It has been shown that, in acidic autocatalytic bromate [18] and chlorite [29] oxidations, the oxidising oxyhalogen species are reduced to halides. Thus, the stoichiometries of the overall primary alcohol oxidation reactions are given by



The fact that HOCl buffered at pH 4 oxidises starch preferentially at C-6 [11] is in accordance with the formation of H_2OCl^+ and its subsequent oxidative attack on the oxygen of starch primary alcohol groups. In the case of cellulose oxidation in phosphoric acid, the selectivity observed with nitrate, bromate and chlorate indicates that a radical (monoelectronic) reaction mechanism is unlikely. In general, such a mechanism involves either the

non-selective attack on the glucose units as proposed for the heterogeneous oxidation of cellulose with hypochlorite [8] or the oxidation of secondary alcohol groups in the homogeneous conversions of soluble polysaccharide [10].

3. Experimental

Materials.—Pullulan was obtained from Haya-shibara (Yokohama, Japan), and microcrystalline cellulose (DS-0) from Fluka (Buchs, Switzerland). All chemicals were analytical grade commercial products and were used without prior purification.

Oxidation methods.—Halate oxidations were performed adding an excess of NaBrO₃ or NaClO₃ [0.80 mol halate/mol primary hydroxyl, 0.66 mol halate/mol primary hydroxyl according to eq (15)] to the cellulose soln containing dissolved NaBrO₃ or NaClO₃, respectively. Similarly, the oxidation of cellulose with NaClO₂ at 4 °C was performed adding a modest excess of NaClO₂ (1.2 mol/mol primary hydroxyl) with a catalytic amount of NaCl. The degree of oxidation (DO) of the products was measured after a NaBH₄ reduction by the colorimetric 3-hydroxybiphenyl assay for uronic acids. The polysaccharide (cellulose: 1 g, pullulan: 5.0 g) was dissolved in H₃PO₄ (30 mL, 85% w/w for NaClO₃ and 80% for NaBrO₃) until a clear, viscous soln was obtained (6 h, 4 °C). After about 6 h slowly stirring, a viscous soln was obtained and sodium halide was added (NaBr 0.20 g, NaCl 0.15 g). After a further 30 min stirring, the sodium halate was added. After 24 h, the oxidised polymer was precipitated in a fumehood with cold EtOH (20 °C, 200 mL) under vigorous stirring with a spatula. During this action, toxic halogen oxides were released. The precipitate was filtered and washed several times with aq EtOH (80% v/v) and dissolved in cold water (200–400 mL). The solution was neutralised with Na₂CO₃ and excess NaBH₄ (0.3 g/g polymer) was rapidly added. After stirring overnight at room temperature, the pH was brought to 5–6 by adding glacial acetic acid. The product was purified and isolated by extensive dialysis, ultrafiltration and freeze drying. The same procedure was followed with NaClO₂ as stoichiometric oxidant by slowly adding the excess of NaClO₂ given above (beware that during this addition, explosive ClO₂ was immediately released) to the polysaccharide solution containing dissolved NaCl (0.10 g).

SEC–MALLS.—Pullulan samples were dissolved in 0.1 M aq NaNO₃ solns and fractionated with three PW TSK columns (G6000PW–G500PW–G300PW, Toyo Soda) in series. Absolute molar masses were determined on-line with a DAWN-DSP-F (Wyatt Technology Co.) MALLS detector. An interferometric refractive index detector (Optilab) was used as the concentration detector. The refractive index increment was measured with the Optilab refractometer.

NMR analysis.—The ¹³C NMR spectra were recorded on Bruker spectrometers operating at a proton NMR frequency of 400 MHz. The oxidised–reduced products were dissolved in D₂O.

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References

- [1] A.E.J. de Nooy, A.C. Besemer, and H. van Bekkum, *Synthesis*, (1996) 1153–1174.
- [2] A.E.J. de Nooy, A.C. Besemer, and H. van Bekkum, *Carbohydr. Res.*, 269 (1995) 89–98.
- [3] E.C. Yackel and W.O. Kenyon, *J. Am. Chem. Soc.*, 64 (1942) 121–127.
- [4] T.J. Painter, *Carbohydr. Res.*, 55 (1977) 95–103.
- [5] T.J. Painter, A. Cesaro, F. Delben, and S. Paoletti, *Carbohydr. Res.*, 140 (1985) 61–68.
- [6] A.E.J. de Nooy, M. Pagliaro, H. van Bekkum, and A.C. Besemer, *Carbohydr. Res.*, 304 (1997) 117–123.
- [7] S.D. Dimitrijevič, M. Tatarko, R.W. Gracy, C.B. Linsky, and C. Olsen, *Carbohydr. Res.*, 195 (1990) 247–256.
- [8] J.A. Epstein and M. Lewin, *J. Polym. Sci.*, 58 (1962) 991–1008.
- [9] R.L. Whistler, E.G. Linke, and S. Kazeniak, *J. Am. Chem. Soc.*, 78 (1956) 4704–4709.
- [10] A.C. Besemer and H. van Bekkum, *Starch*, 46 (1994) 95–101.
- [11] M.E. Mckillican and C.B. Purves, *Can. J. Chem.*, 32 (1954) 312–321.

- [12] R.L. Whistler and J.N. BeMiller (Eds.), *Industrial Gums*, Academic Press, San Diego, 1993.
- [13] J.A. Smelstorius, *Holzforschung*, 26 (1972) 93–96.
- [14] R. Andersson, J. Hoffman, N. Nahar, and E. Scholander, *Carbohydr. Res.*, 206 (1990) 340–346.
- [15] N. Blumenkrantz and G. Asboe-Hansen, *Anal. Biochem.*, 54 (1973) 484–489.
- [16] J.W. Green, in W. Pigman and D. Norton (Eds.), *The Carbohydrates*, 2nd ed., Vol. IB, Academic Press, New York, 1980, pp 1106–1120.
- [17] J.C. Sullivan and R.C. Thomson, *Inorg. Chem.*, 18 (1979) 2375–2384.
- [18] P. De Kepper, K. Kustin, and I.R. Epstein, *J. Am. Chem. Soc.*, 103 (1981) 2133–2138.
- [19] G. Bazsa and I.R. Epstein, *Comments Inorg. Chem.*, 5 (1986) 57–87.
- [20] I.R. Epstein, K. Kustin, P. De Kepper, and M. Orban, *Sci. Am.*, March (1983) 96–108.
- [21] K. Garves, *Holzforschung*, 47 (1993) 149–154.
- [22] F.A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, 5th ed., Wiley, New York, 1988, p 564.
- [23] S.B. Jonnalagadda, N.M. Munkombwe, P. Hensman, and T. Mushinga, *Int. J. Chem. Kinet.*, 23 (1991) 113–125.
- [24] G.K. Muthakia and S.B. Jonnalagadda, *J. Phys. Chem.*, 93 (1989) 4751–4757.
- [25] C.F.A. Filgueiras, *J. Chem. Ed.*, 69 (1992) 276–277.
- [26] C.G. Swain and D.R. Crist, *J. Am. Chem. Soc.*, 94 (1972) 3195–3200.
- [27] J. Muhherjee and K.K. Banerji, *J. Org. Chem.*, 46 (1981) 2323–2326.
- [28] N. Venkatasubramanian and V. Thiagarajan, *Can. J. Chem.*, 47 (1969) 694–697.
- [29] I. Nagypal, G. Bazsa, and I.R. Epstein, *J. Phys. Chem.*, 108 (1986) 3635–3641.