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Evidence for cyclodextrin dioxiranes

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Abstract

α-Cyclodextrin, β-cyclodextrin, 2,6-di-*O*-methyl-β-cyclodextrin, methyl-β-cyclodextrin and sucrose have been oxidised by aqueous bromine solution at neutral pH. Both ketone and carboxylic acid containing materials are among the products of the oxidations. For α-cyclodextrin there is clear ^{13}C NMR evidence for the presence of a ketone group and its hydrate form. This together with the continued ability of the product to complex *p*-nitrophenol indicates that the ketone is present at the secondary rim of an intact cyclodextrin ring. A pH dependence for the reaction of bromine with cyclodextrin shows that the maximum rate of bromine loss roughly coincides with the maximum concentration of hypobromous acid, HOBr, indicating that this is the reactive species in these oxidations. The results are consistent with a mechanism involving attack by one of the secondary hydroxyls of cyclodextrin on HOBr, with Br^- leaving to yield an intermediate dehydroxy hydroperoxy cyclodextrin that subsequently decomposes to a keto-cyclodextrin via a Kornblum–De La Mare-type reaction. An alternative pathway prevails when the reaction is carried out under alkaline conditions, where carboxylic acids are the principle products. The keto derivatives produced by bromine oxidation at neutral pH are capable of catalysing the oxidation of *p*-nitrophenol and aryl–alkyl sulfoxides by peroxomono-sulfate in an analogous way to cyclohexanone, which is known to form a dioxirane upon reaction with peroxomonosulfate. It is likely that dioxirane formation is responsible for the observed catalysis in the present case also.

Keywords: Cyclodextrin; Bromine oxidation of cyclodextrin; Ketone; Dioxirane; Phenol oxidation

1. Introduction

We recently decided to extend our work on the affect of cyclodextrin on the peracid–iodide reaction [1] to the analogous bromide oxidation reaction. During preliminary work on this system we were surprised to see that on addition of peroxomonosulfate to a solution containing bromide (50 mM) and α-cyclodextrin (2.4 mM) buffered at pH 7.8, the generated bromine rapidly disappeared, presumably consumed in a reaction with the cyclodextrin. We subsequently learned of several studies on the bromine oxidation of a range of carbohydrates at neutral pH [2], including sucrose [3], methyl α- and β-pyranosides of D-Gal, D-Glc and D-Man [4], α,α- and β,β-trehalose [5], amylopectin [6], and starches [7,8]. In the bromine oxidation of methyl α- and β-pyranosides of D-Gal, D-Glc and D-Man, for example, the secondary

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hydroxyls are oxidised to keto-groups (2-, 3- or 4-uloses). Characterisation was accomplished by using ^{1}H NMR, elemental analysis and GC-MS after first stabilising these sensitive compounds [4,9] by conversion to the corresponding *O*-methyl oxime [4]. A small degree of oxidation of the primary alcohols was also reported, although these are rapidly converted to uronic acids [4].

The bromine oxidation of cyclodextrins should give rise to similar products to that of the methyl pyranosides. We report here on studies of this reaction and the characterisation of the products, which show that a keto-cyclodextrin is indeed produced. In addition to the native cyclodextrins similar studies were carried out on a randomly *O*-methylated β-cyclodextrin and on 2,6-di-*O*-methyl-β-cyclodextrin and sucrose, which is known to form a ketone derivative when subjected to mild oxidation with bromine [3]. 2,6-Di-*O*-Methyl-β-cyclodextrin was used because it has only one hydroxyl group available for reaction with bromine (C-3), allowing us some certainty in the position of any keto-group and also, hopefully, improving the stability of the keto derivative.

The keto-cyclodextrins, like other ketones, are capable of catalysing a number of oxidation reactions of peroxomonosulfate, most probably due to the formation of the more reactive dioxirane intermediate [10]. Preliminary results are presented on the oxidation of a chiral aryl alkyl sulfoxide and an oxidatively inert substituted phenol. The latter oxidation is compared with literature reports of conventional chemical methods for the treatment of high concentration chemical process waste water streams.

2. Results and discussion

General comments on the reaction of bromine with α-cyclodextrin.—Fig. 1 shows the effect of adding α-cyclodextrin to bromine in pH 7.8 phosphate buffer at 25 °C. Over the course of 20 min the absorbance due to the bromine disappeared and a colourless intermediate was formed. Then over the next few hours absorbance bands emerged between 240 and 340 nm. The product of this reaction complexes *p*-nitrophenol (Fig. 2) confirming that the ring integrity of the reacted cyclodextrin is largely maintained. In preparations carried out using the pH-stat, it was observed that the majority of the NaOH was dispensed in the first 30 min in the case of α-cyclodextrin, whereas for the other compounds it was between 2½ and 5 h; this is in general agreement with the time taken for complete bromine loss when the reaction was followed spectrophotometrically. Additionally, it was generally observed that the pH would start to increase at this point, reaching approximately 7.5 to 7.8 before returning to 7.0 (there was no acid dispensing facility on the pH-stat to counter this rise). For samples that were subject to bromide removal, generally only one fraction was eluted from the ion

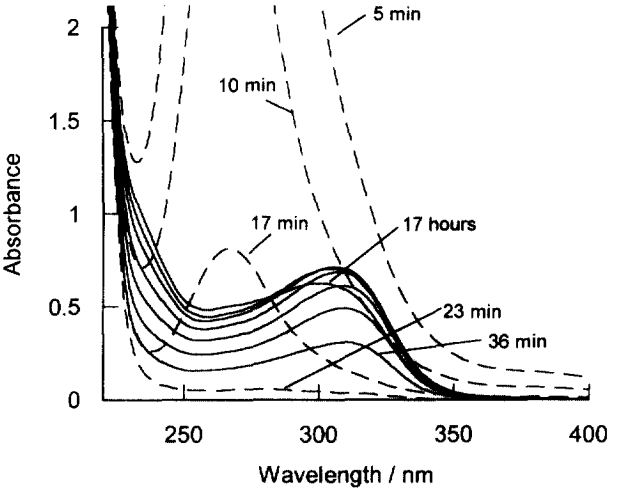


Fig. 1. Sequential spectra for the reaction of 1.8×10^{-3} mol dm^{-3} bromine with 2.2×10^{-3} mol dm^{-3} α-cyclodextrin in pH 7.8 phosphate buffer, ionic strength 0.2 mol dm^{-3} at 25 °C. The dashed and solid lines show, respectively, the decrease in absorbance across the spectrum due to the reaction of bromine, and the subsequent emergence of absorbance bands.

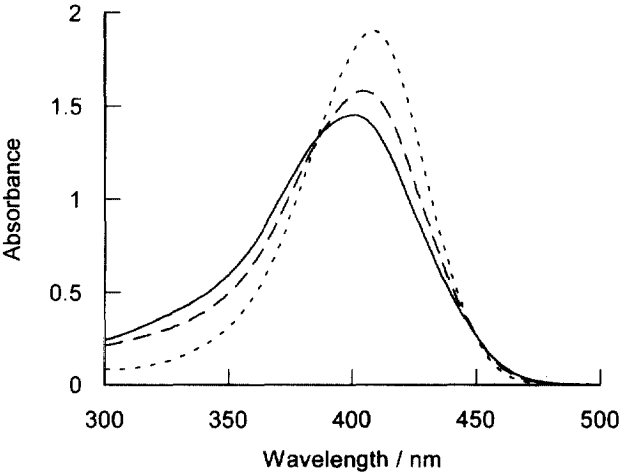


Fig. 2. Spectrum of 1.0×10^{-4} mol dm^{-3} *p*-nitrophenol in pH 7.8 phosphate buffer, ionic strength 0.2 mol dm^{-3}, 25 °C, solid line; and in the presence of: 0.01 mol dm^{-3} α-cyclodextrin, dotted line; and 3.8×10^{-4} mol dm^{-3} of the ketone containing product, dashed line.

exchange column, however when α-cyclodextrin (2.4 mM) was reacted with a 10-fold excess of bromine at least three fractions were eluted from the column. This, together with the observation that none of the three fractions were able to bind *p*-nitrophenol suggests that the cyclodextrin ring is broken up under these conditions producing charged ring fragments (presumably carboxylic acid containing [11]). When 2,6-di-*O*-methyl-β-cyclodextrin was oxidised under similar conditions only one fraction was obtained, although significantly reduced *p*-nitrophenol complexation was observed compared to the parent compound. A general characterisation of the main products of these reactions was accomplished using ^{13}C NMR spectroscopy, as detailed in the next section. We did not, however, attempt to characterise the colourless intermediate of this reaction although there is literature evidence to suggest that it may be a dehydroxy hydroperoxy cyclodextrin and this is discussed later [12].

^{13}C NMR characterisation of bromine oxidation products of cyclodextrin.—A general characterisation of the bromine oxidation products of α- and β-cyclodextrin and 2,6-di-*O*-methyl-β-cyclodextrin was accomplished using ^{13}C NMR spectroscopy. This confirmed that significant amounts of ketone and carboxylic acid were present in the oxidation products of α-cyclodextrin (Fig. 3). No ketone resonance could be observed for either β-cyclodextrin or 2,6-di-*O*-methyl-β-cyclodextrin, though there were strong carboxylic acid resonances. The ketone carbonyl carbon signals were identified by comparison with published values for bromine oxidation products of methyl α-D-glucopyranoside in which the secondary hydroxyls at either the C-2 or C-4 are oxidised to give the keto-derivatives **1** and **2**, respectively [4]. Comparisons were also made with data published for the corresponding 3-ulose **3** [4], and with the bromine oxidation products of potato starch [11] and dextran **4**, which is an α-(1→6) linked D-glucan [13]. Table 1 summarises the literature δ values and those obtained for bromine oxidation products of cyclodextrins. In addition to the ketone and carboxylic acid shifts Table 1 lists the shifts for ketone hydrates, $>C(OH)_2$, which exist in equilibrium with the keto forms in aqueous solution [14,15]. Compounds **1** and **2** for

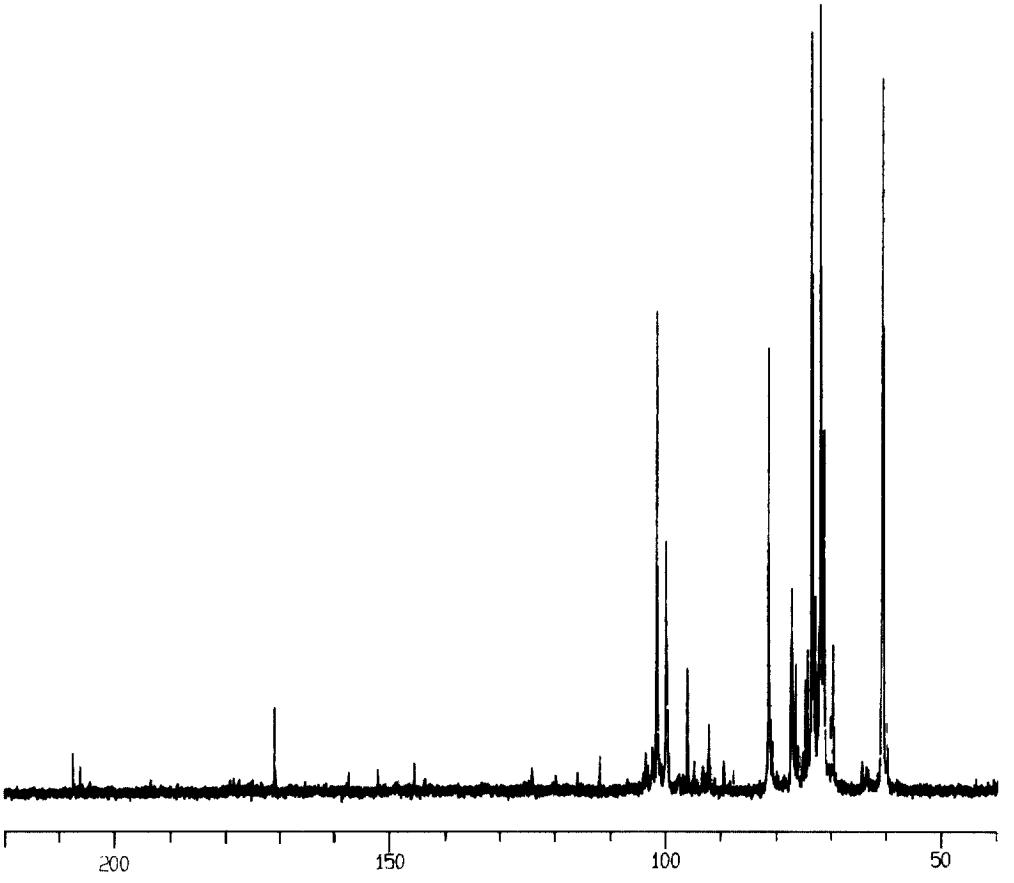


Fig. 3. Fully decoupled ^{13}C NMR spectrum of keto-α-cyclodextrin in H_2O at 67.8 MHz.

Table 1
Comparison of literature ^{13}C NMR data with the main ^{13}C NMR resonances obtained for the bromine oxidation, at neutral pH, of native and substituted cyclodextrins, dextran and potato starch

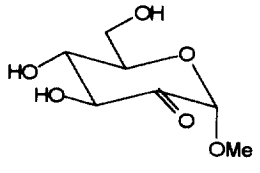
Compound	Chemical shifts (ppm)			Reference
	>C=O	-COOH	$>C(OH)_2$	
Bromine oxidation products of:				
α-cyclodextrin	208.8 206.8	171.6	93.0 95.6	This work
β-cyclodextrin	—	176.0 171.1	92.6 93.7 95.3 96.4 97.4 98.1	This work
2,6-*O*-methyl-β-cyclodextrin	—	162.4	—	This work
Potato Starch	206.4	94.4		[11]
Dextran **4**	204.2 207.2	174.0 176.3 176.7 176.8	95.4 93.4 93.8	[13]
Other compounds:				
1	—	n/a[a]	93.4	[13]
2	204.9	n/a	94.1	[13]
3	207.2	n/a	—	[13]
D-xylo-hexos-5-ulose(5-keto-glucose)	211.1	n/a	—	[16]
Keto-β-cyclodextrin	—	n/a	98.7	[18]

[a]Not applicable.

example exist almost exclusively as the hydrate and keto form, respectively, whereas for **3** there are significant proportions of both forms [13].

The ^{13}C NMR data are qualitative and therefore ketone resonances are likely to be significantly under-represented, which may also explain the difficulties in observing these signals for β-cyclodextrin, which is expected to undergo a similar transformation to that seen for α-cyclodextrin. Nevertheless, a series of weak signals were observed between δ 92.6 and δ 98.1 for the bromine oxidation product of β-cyclodextrin, which is the region in which resonances for the ketone hydrate would be expected [17]. Two of these resonances coincide with the much stronger ketone hydrate resonances observed for α-cyclodextrin, and the resonance observed at δ 98.1 is in agreement with that observed by Czarnik et al. for a keto-β-cyclodextrin [18]. For 2,6-di-*O*-methyl-β-cyclodextrin, a very weak ^{13}C spectrum was obtained in which no ketone carbonyl carbons or the corresponding ketone hydrates could be detected, though there was a significant carboxylic acid resonance. Nevertheless, the accelerative effect of this compound on sulfoxide oxidation, as reported later, indicates the presence of some ketone groups.

Effect of pH.—Bromine speciation is dependent on pH, as shown by the distribution diagram (Fig. 4) and, consequently, pH should be expected to have a significant effect on its reactivity. Fig. 4 has been calculated by obtaining a solution to the system of eqs (1)–(3), for which it was necessary to assume the presence of an excess of bromide. Values of 2×10^{-9} mol dm^{-3}, 16.85 dm^3 mol^{-1} and



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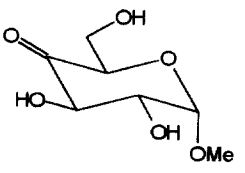

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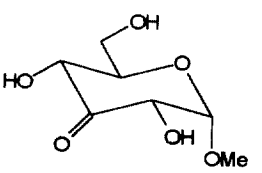

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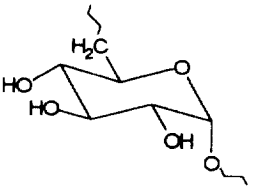

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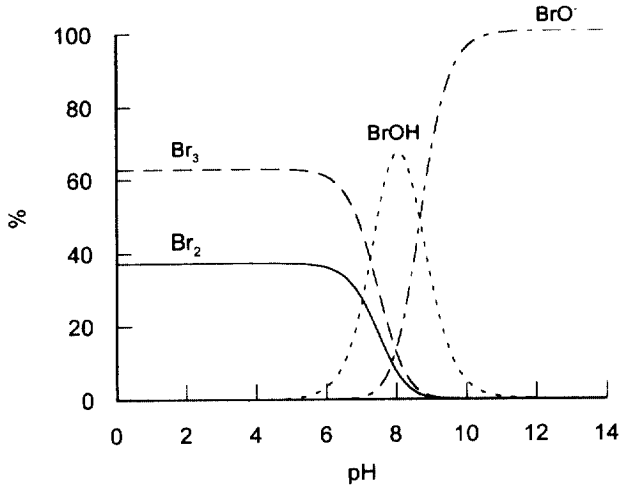


Fig. 4. Composition of an aqueous bromine solution as a function of pH, where the total bromine concentration is 0.5×10^{-4} mol dm^{-3} and there is an excess of bromide (0.1 mol dm^{-3}).

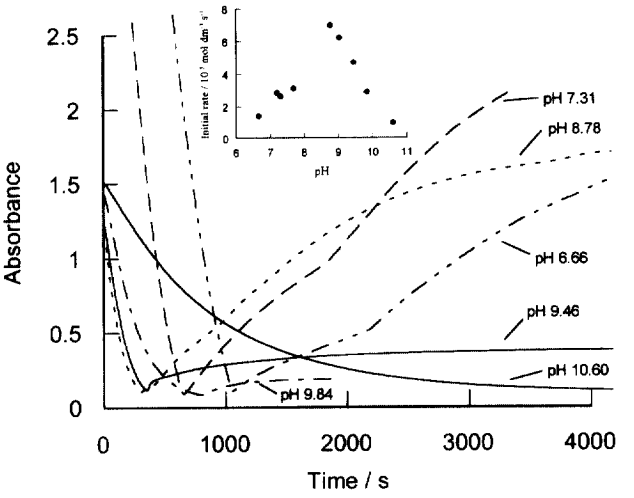


Fig. 5. Effect of pH on absorbance changes at 350 nm during the initial and subsequent stages of the reaction between 10.32×10^{-3} mol dm^{-3} bromine and 3.33×10^{-3} mol dm^{-3} α-cyclodextrin. Buffers were phosphate or carbonate, ionic strength 0.2 mol dm^{-3}, 25 °C. The inset shows the effect of pH on the initial rate of bromine loss, conditions as for the main figure.

9×10^{-9} mol^2 dm^{-6}, were used for K_a, K_{Br3} and K_h, respectively [19,20].

$$K_a = \frac{[BrO^-]\cdot[H^+]}{[HOBr]} \quad (1)$$

$$K_{Br} = \frac{[Br_3^-]}{[Br_2]\cdot[Br^-]} \quad (2)$$

$$K_h = \frac{[HOBr]\cdot[H^+]\cdot[Br^-]}{[Br_2]} \quad (3)$$

The initial rate of bromine loss upon its reaction with α-cyclodextrin, and the extent to which absorbance bands emerge was significantly affected by pH as shown in Fig. 5. When the reaction was carried out above pH 9 there was minimal emergence of the absorbance bands and this is most likely due to a pathway whereby dicarboxylic acids are formed rather than ketone groups. The ^{13}C NMR studies detailed in Table 1 show that significant amounts of carboxylic acid are formed during the bromine oxidation of cyclodextrin and, moreover, that the proportion increases if the reaction is carried out at pH 8.5 compared to pH 7.0 (results not shown). Literature studies on the bromine oxidation of a variety of carbohydrate substrates also report significant carboxylic acid formation at high pH and this reaction has been used in the production of calcium-chelating polycarboxylate derivatives of inulin [21], linear dextrins [22] and starch [23]. In these reactions a hypochlorite/bromide system was used whereby there was rapid Br^-/OCl^- interconversion to the proposed reactive species, HOBr and BrO^-.

A further significant finding is the observation that if the bromine oxidation reaction was carried out at pH 7.2 and the solution subsequently raised to pH 10.8 then a rapid and substantial increase in absorbance was observed (Fig. 6). This is very different from the behaviour observed when the reaction was carried out entirely at high pH (Fig. 5).

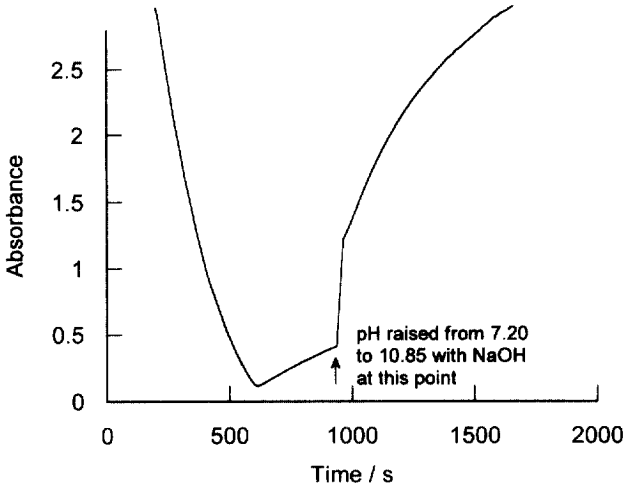


Fig. 6. Effect of raising the pH to 10.85, using NaOH, in a solution containing 3.33×10^{-3} mol dm^{-3} α-cyclodextrin that had previously reacted with 10.32×10^{-3} mol dm^{-3} bromine in pH 7.20 phosphate buffer, ionic strength 0.2 mol dm^{-3}, 25 °C.

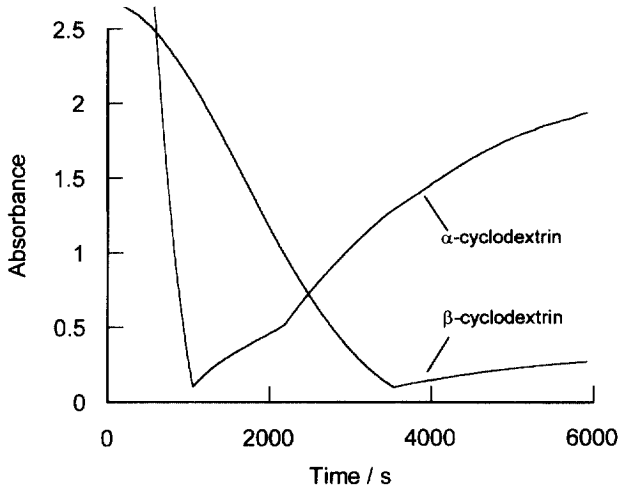


Fig. 7. Comparison of the relative reactivities of α-and β-cyclodextrin (3.33×10^{-3} mol dm^{-3}) towards bromine (10.32×10^{-3} mol dm^{-3}) in a pH 6.66 phosphate buffer, ionic strength 0.2 mol dm^{-3}, 25 °C.

The inset to Fig. 5 shows a bell-shaped curve for the effect of pH on the initial rates of bromine consumption. The maximum rate appears to occur at about pH 8.7, however it is difficult to definitely state whether the maximum actually coincides with the pKa of BrOH (8.69 [24]) or the maximum BrOH concentration (~ pH 7.9 [25]) because of the possibility of buffer effects [26]; the change over to carbonate from phosphate buffer occurred at approximately the point where the maximum initial rate was observed.

Effect of ring size of the cyclodextrin on the rate of reaction.—Absorbance traces for the reaction of α- and β-cyclodextrin with bromine at pH 6.7 are shown in Fig. 7. The emergence of absorbance bands due to the keto-cyclodextrin clearly begins significantly earlier for α-cyclodextrin compared to β-cyclodextrin. It is possible that this is due to a size factor whereby the reactive bromine species binds strongly with α-cyclodextrin but less so with β-cyclodextrin, which because of proximity effects leads to a much faster rate with α-cyclodextrin. As far as we are aware there are no published stability constants for BrOH or BrO^- with cyclodextrins. Whilst different binding affinities of hypobromous acid with the cyclodextrins may be an obvious explanation, another plausible reason concerns the hydrogen bonding interactions between hydroxyls at the secondary rim. The relatively low solubilities of native cyclodextrins have been attributed to hydrogen bonding between the hydroxyls, resulting in reduced interaction with the bulk solvent [27]. β-Cyclodextrin is considerably less soluble than α-cyclodextrin, possibly implying greater hydrogen bonded interactions. It follows that this may well affect the extent of reaction of hypobromous acid with the hydroxyl groups. The fact that the β-cyclodextrin derivatives that we have looked at also react slowly with bromine does not necessarily detract from the latter argument since although solubility is greatly increased as a result of the derivatisations disrupting the hydrogen bonded structure, there are less reactive sites.

Mechanisms.—It is clear from the pH dependence that there are two separate pathways for the initial oxidation step of cyclodextrins by bromine; one occurring at neutral pH, where ketones are significant products, and the other taking place under alkaline conditions where carboxylic acids are largely produced. Additionally, the intermediate formed when the oxidation takes place under neutral conditions subsequently decomposes in either neutral or alkaline conditions as demonstrated by Fig. 6.

Whilst there have been a number of studies carried out on the bromine oxidation of secondary alcohols over the past three decades, many involving carbohydrates, there is still no general consensus on the role of the main bromine species in these reactions over the full pH range. Palou, has recently reviewed the mechanism of bromine oxidations of a range of organic molecules, including secondary alcohols, however the author mainly concentrates on reactions involving Br_2 [25]. The most widely accepted mechanism for this species, which predominates at pH's below 6, involves rate limiting hydride transfer from the carbon to Br_2 followed by a rapid proton removal step to yield the ketone (Scheme 1) [25,28,29]. The effect of electron withdrawing or donating groups on the rate of bromine oxidation of a range of secondary alcohols supports this view [30]. Alternative

Scheme 1.

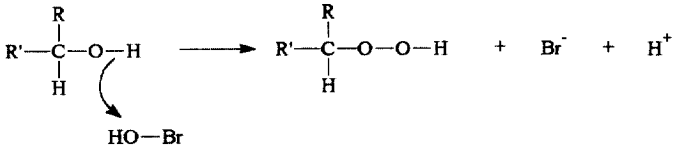
mechanisms at low pH involve the formation of a hypobromite ester by direct attack of the bromine on the hydroxyl together with proton abstraction from the carbon [31]. In studies conducted at pHs above 6, where hypobromous acid and hypobromite predominate, mechanisms involving hydride transfer to Br_2 are still often referred to, despite observed rate dependencies on HOBr concentration [4]. Doane and Whistler [6], and more recently, Besumer and Van Bekkum [21–23] have suggested the involvement of both HOBr and BrO^- in the oxidation of a range of polysaccharides, in which carbonyl groups and carboxylic acids were the main products, with the latter increasing in proportion at high pHs. However, no clear mechanisms were postulated for the involvement of these species.

It seems reasonable that in the case of cyclodextrins, and most probably for other carbohydrates also, the mechanism at neutral pH could involve direct attack of the secondary hydroxyl on HOBr, with Br^- then leaving to yield a hydroperoxy cyclodextrin; this would correspond to the colourless intermediate that we observe (Scheme 2). We have no experimental evidence for the nature of this intermediate but it has recently been reported that β-cyclodextrin can react with hydrogen peroxide to yield a dehydroxy hydroperoxy cyclodextrin (8.8 mM cyclodextrin, 30% H_2O_2, 60 °C for 3 days) [12]. This species decomposes with a half-life of about 3 h at pH 8.5, which is similar to the decomposition of the intermediate that we observe. The authors suggest that hydrogen bonding between the secondary hydroxyls of the cyclodextrin activates one of these with respect to nucleophilic attack on the hydrogen peroxide. A similar attack on BrOH would be facilitated by the better leaving group ability of bromide compared with hydroxide. It was suggested by Czarnik et al. that the dehydroxy hydroperoxy β-cyclodextrin decomposes to a dialdehyde [12], however the evidence is not conclusive and it is plausible that a ketone is formed, as is observed for the decomposition of the intermediate in the present work. The Kornblum–De La Mare reaction gives a precedent for the conversion of β-hydroxy hydroperoxides to ketones, and whilst our case is not strictly analogous because of the absence of a neighbouring aromatic group, it is still a reasonable mechanism (Scheme 3) [32]. This is particularly so in the light of the enhanced decomposition of the intermediate upon raising the pH (Fig. 6).

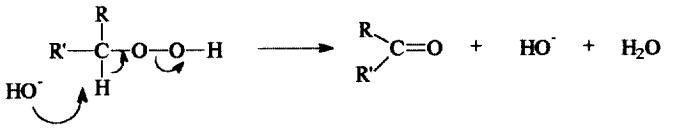
It is still necessary in this mechanism for the carbon hydrogen to be removed (as a proton) and so there is still consistency with the arguments of Theander et al. who have produced ^1H NMR evidence which shows that the position at which the keto groups are formed in the bromine oxidation of carbohydrates is significantly affected by steric factors [3,4]. Thus, for methyl-α-D-Glc, virtually no oxidation takes place at the C-3 position for which the axial hydrogen in a syn diaxial relationship with the bulky *O*-methyl group at the C1 position and, consequently, only 2-uloses and 4-uloses are formed [4]. It is uncertain whether the same steric factors would be important in the case of cyclodextrins.

The mechanism involved when the bromine oxidation takes place entirely under alkaline conditions, and for which carboxylic acids are significant products, is unclear although the participation of a dehydroxy hydroperoxy intermediate is unlikely.

Substrate oxidation.—There is clear confirmation from ^{13}C NMR spectroscopy that keto-cyclodextrins are among the products obtained from the bromine oxidation of cyclodextrins. At neutral pH



Scheme 2.



Scheme 3.

ketones such as acetone and cyclohexanone can catalyse the decomposition of peroxomonosulfate and enhance the rate of many oxidation reactions of peroxomonosulfate and it was these original observations which led Montgomery to propose the formation of dioxiranes, generated in situ from the ketone and peroxomonosulfate [33]. Edwards continued this work producing strong evidence from ^{18}O labelling experiments for the presence of dioxiranes and also showing that dioxiranes are powerful oxidising agents [34]. In view of this it is reasonable to expect the keto-cyclodextrins to perform similar catalysis via the formation of a transient cyclodextrin dioxirane species. The possibility of a dioxirane moiety attached to a chiral cyclodextrin cavity raises interesting implications for both catalysis and chiral oxidations.

We have looked at the effects of peroxomonosulfate/ketone systems on the decomposition of peroxomonosulfate, the oxidation of aryl alkyl sulfoxides to the corresponding sulfones and the oxidation of *p*-nitrophenol. Fig. 8 shows a comparison of absorbance changes for the oxidation of (S)-(-)-methyl-*p*-tolyl sulfoxide in the presence of peroxomonosulfate alone, peroxomonosulfate/cyclohexanone and peroxomonosulfate/keto-(α-cyclodextrin. There is a modest two-fold increase in the initial rate of oxygen transfer for the latter system, which is comparable to the cyclohexanone system once relative concentrations are accounted for. Table 2 summarises the effect of a range of ketones on sulfoxide oxidation by peroxomonosulfate. The observation of a reduced catalytic effect of keto-α-cyclodextrin on the oxidation of 4-bromophenyl methyl sulfoxide compared to (S)-(-)-methyl-*p*-tolyl sulfoxide, where the former would be expected to form the stronger inclusion complex, and both would be expected to bind in an orientation where the sulfoxide group is at the secondary hydroxyl rim [35], suggests that the cyclodextrin dioxirane reacts principally with unbound sulfoxides. An increased catalytic effect might have been expected for the oxidation of the stronger binding bromophenyl methyl sulfoxide if the converse were true. It is possible, however, that the orientation of sulfoxides within the cyclodextrin cavity is unsuitable for interaction with a proximal dioxirane moiety. Other classes of substrates may show different effects. For the *O*-methylated cyclodextrins there are contrasting effects, with keto-methyl-β-cyclodextrin actually showing rate inhibition whereas the keto derivative of 2,6-di-*O*-methyl-β-cyclodextrin is reasonably effective. It is noteworthy that the keto-sucrose derivative proves to be even more effective than keto-α-cyclodextrin.

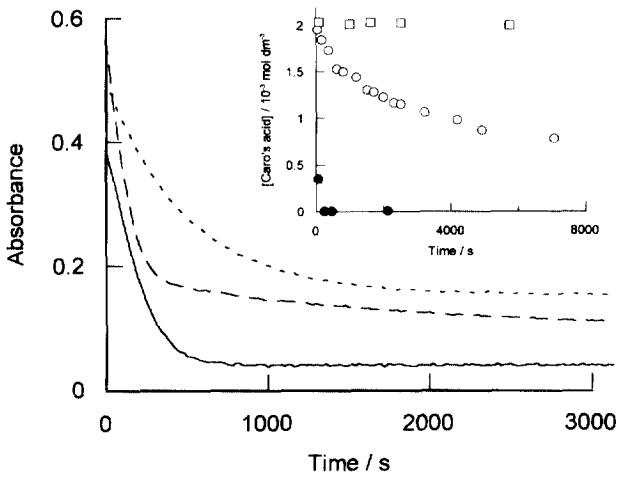


Fig. 8. Catalytic effect of keto-α-cyclodextrin on the oxidation of (S)-(-)-methyl-*p*-tolyl sulfoxide and on the decomposition of peroxomonosulfate. The main figure shows the reaction of 4.25×10^{-3} mol dm^{-3} peroxomonosulfate with 0.109×10^{-3} mol dm^{-3} (S)-(-)-methyl *p*-tolyl sulfoxide in the presence of 3×10^{-3} mol dm^{-3} keto-α-cyclodextrin, solid line; 8×10^{-3} mol dm^{-3} cyclohexanone, dashed line; and buffer alone, dotted line. The reactions were carried out in pH 7.6 phosphate buffer, ionic strength 0.2 mol dm^{-3}, 25 °C. Absorbance changes were followed at 244 nm and were corrected for the background change in absorbance due to the keto-α-cyclodextrin or cyclohexanone. The inset shows the effect of keto-α-cyclodextrin on the decomposition of 1.92×10^{-3} mol dm^{-3} peroxomonosulfate in pH 7.6 phosphate buffer, where the symbols represent: peroxomonosulfate/phosphate buffer alone, open squares; 12×10^{-3} mol dm^{-3} keto-α-cyclodextrin, filled circles; 0.75×10^{-3} mol dm^{-3} keto-α-cyclodextrin, open circles. All solutions contained 2×10^{-5} mol dm^{-3} EDTA.

In the context of interpretation of the results of observed catalysis it is important to note that peroxomonosulfate has negligible affinity for α-cyclodextrin [36] and that this is almost certainly the case for the keto-α-cyclodextrin derivatives also. The observed rate enhancements are not, therefore, due to the peroxide activation effects of cyclodextrin that were observed for perbenzoic acids and long chain alkyl peracids [37].

The keto-α-cyclodextrin was also effective in the decomposition of peroxomonosulfate, as shown in the inset to Fig. 8, although this decomposition coincides with a significant and permanent loss in absorbance over the wavelength range associated with the keto-cyclodextrin. Thus, in contrast to dioxiranes generated from acetone and cyclohexanone [10], minimal re-generation of the keto-cyclodextrin was achieved during reaction with peroxomonosulfate.

Table 2
Effect of cyclohexanone and ketone containing products of the bromine oxidation of α-cyclodextrin (α-CD), 2,6-di-*O*-methyl-β-cyclodextrin (2,6-DM-β-CD), methyl-β-cyclodextrin (M-β-CD) and sucrose on initial rate for the oxidation of aryl methyl sulfoxides by peroxomonosulfate (PMS)

Ketone or ketone containing products of bromine oxidation	Substrate (S)	$[S]_o/10^{-3}$ mol dm^{-3}	Buffer[a]	$[PMS]/10^{-3}$ mol dm^{-3}	[Ketone] $/10^{-3}$ mol dm^{-3}	Initial rate $/10^{-7}$ mol dm^{-3} s^{-1}	Acceleration of initial rate
Cyclohexanone	(S)-(-)-Methyl-*p*-tolyl sulfoxide	0.109	pH 7.8, I = 0.52 M	5.13	0.00	2.89 ± 0.08	—
					2.00	4.30 ± 0.13	1.49
		0.109	pH 7.6, I = 0.2 M	4.38	0.00	2.20 ± 0.06	—
					8.00	7.00 ± 0.19	3.12
	4-Bromophenyl methyl sulfoxide	0.100	pH 7.8, I = 0.52 M	5.13	0.00	3.76 ± 0.10	—
					2.00	4.67 ± 0.13	1.24
α-CD	(S)-(-)-Methyl-*p*-tolyl sulfoxide	0.109	pH 7.6, I = 0.2 M	4.25	0.00	2.04 ± 0.04	
					3.30	3.78 ± 0.04	1.85
					6.50	2.86 ± 0.05	1.40
	4-Bromophenyl methyl sulfoxide	0.100	pH 7.6, I = 0.2 M	4.25	0.00	2.23 ± 0.03	—
					1.63	2.73 ± 0.09	1.22
					3.26	2.91 ± 0.04	1.30
2,6-DM-β-CD	(S)-(-)-Methyl-*p*-tolyl sulfoxide	0.109	pH 7.6, I = 0.2 M	4.44	0.00	1.76 ± 0.04	—
					5.20	3.67 ± 0.15	2.09
					10.4	5.07 ± 0.26	2.88
2,6-DM-β-CD[b]	(S)-(-)-Methyl-*p*-tolyl sulfoxide	0.109	pH 7.6, I = 0.2 M	4.57	0.00	1.78 ± 0.02	—
					1.06	3.04 ± 0.08	1.71
M-β-CD	(S)-(-)-Methyl-*p*-tolyl sulfoxide	0.109	pH 7.6, I = 0.2 M	4.38	0.00	2.20 ± 0.35	—
					3.58	1.95 ± 0.06	0.88
					7.16	2.72 ± 0.06	1.23
	4-Bromophenyl methyl sulfoxide	0.100	pH 7.6, I = 0.2 M	4.25	0.00	2.19 ± 0.04	—
					3.58	1.98 ± 0.04	0.90
					7.16	1.54 ± 0.14	0.70
Sucrose	(S)-(-)-Methyl-*p*-tolyl sulfoxide	0.109	pH 7.6, I = 0.2 M	4.38	0.00	2.24 ± 0.09	—
					3.14	4.49 ± 0.13	2.00
					6.28	5.72 ± 0.15	2.55
	4-Bromophenyl methyl sulfoxide	0.100	pH 7.6, I = 0.2 M	4.25	0.00	2.20 ± 0.04	—
					3.14	3.18 ± 0.18	1.44
					6.28	3.90 ± 0.19	1.77

[a]Phosphate.
[b]Second batch, made with a 10-fold excess of bromine.

When the peroxomonosulfate/keto-α-cyclodextrin system was applied to *p*-nitrophenol oxidation, as shown in Fig. 9, the observed catalytic effect was greater than for sulfoxide oxidation. Again the involvement of dioxirane intermediates, generated from the keto-derivatives, is an explanation for the observed accelerative effects. The oxidation of phenols by chemical methods has been widely investigated for the treatment of waste water streams originating from chemical processes where the concentration of organics is often high enough to be toxic to conventional biological treatment processes. Methods employed for phenol degradation include wet air oxidation [38], photocatalysis using TiO_2 [39], and supercritical water systems [40]. Peroxyacids such as peroxomonosulfate react slowly with *p*-nitrophenol as shown in Fig. 9, however in the presence of keto-α-cyclodextrin and the keto-sucrose, the acceleration of *p*-nitrophenol decomposition was comparable to that seen for cyclohexanone yet with significantly lower concentrations. Non-derivatised α-cyclodextrin inhibits *p*-nitrophenol oxidation. No attempt to identify the products of *p*-nitrophenol oxidation was made. This would have been a significant study in its own right and the oxidation of phenols by a variety of oxidants, including dioxiranes [41,42], has been widely reported in the literature [43]. In the case of phenol oxidation by dioxiranes the authors did not analyse the products of the oxidation of mono-substituted phenols due to the complexity of the product mixture and, instead, oxidation was carried out on hindered phenols such as 2,6-di-*tert*-butyl phenol where the product mix was more manageable [42]. The generally accepted mechanism for the initial step in the oxidation of phenols, including that by dioxiranes, is a single electron transfer from the phenol to the oxidant yielding a phenoxy radical which can then react further to form a complex mixture of products including catechols, hydroxyquinones, quinones, diphenyls and other polymeric compounds [43]. Additionally, the hydroxylated compounds and benzoquinones can undergo further oxidation in which there is ring cleavage, yielding muconic and 2,5-dioxo-3-hexenedioc acids and subsequent products [41,44]. It is reasonable to assume that similar product mixtures result from the oxidation of *p*-nitrophenol by the keto-sugar peroxomonosulfate systems.

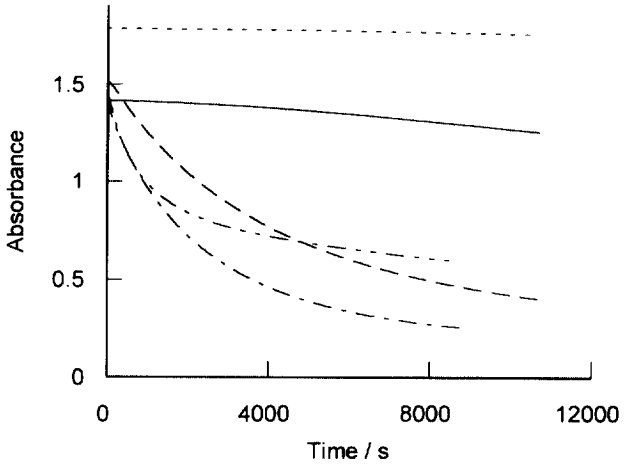


Fig. 9. Absorbance changes at 400 nm for the reaction of 1.0×10^{-4} mol dm^{-3} *p*-nitrophenol and 1.9×10^{-3} mol dm^{-3} peroxomonosulfate in pH 7.8 phosphate buffer, ionic strength 0.2 mol dm^{-3}, 25 °C, solid line; and in the presence of 0.01 mol dm^{-3} α-cyclodextrin, dotted line; 3.8×10^{-3} mol dm^{-3} keto-α-cyclodextrin, dashed line; 7.8×10^{-3} mol dm^{-3} keto-sucrose, dot-dot-dashed line; and 5×10^{-3} mol dm^{-3} cyclohexanone, dot-dashed line.

3. Summary

We have described a convenient method whereby ketone groups can be introduced onto the secondary hydroxyl rim of cyclodextrins using aqueous bromine solution at neutral pH. The ketone-derivatised cyclodextrins and an analogous sucrose derivative are capable of catalysing the peroxomonosulfate oxidation of sulfoxides and phenols, with the formation of a dioxirane intermediate being the most likely explanation for the observed catalysis. Preliminary results indicate, however, that it is the unbound form of the substrate that is oxidised. Additionally, these compounds are unstable and are subject to oxidation by peroxomonosulfate. Nevertheless, there remains a wide range of possible avenues for future research on these compounds. For example, we have only looked at a limited number of substrates and it may well be the case that different substrates form inclusion compounds where the reactive substrate group is in a more favourable orientation with respect to the dioxirane moiety, allowing oxidation of bound substrate. Enantioselective oxidations could be carried out in this way.

We have extended this work to look at the formation of keto-derivatised hydroxypropyl cyclodextrins where the hydroxyls of the isopropyl derivative are available to react with bromine in addition to secondary hydroxyls of the cyclodextrin.

The preparation of these compounds and their affect on a variety of oxidation reactions will be described in a subsequent paper.

4. Experimental

Materials.—2,6-di-*O*-Methyl-β-cyclodextrin was obtained from Cyclodextrin Technology Development Inc., FL and was 99% pure. All other materials were obtained from Aldrich and were the best available grades. Methyl-β-cyclodextrin, which was obtained from Aldrich, is a randomly *O*-methylated derivative with an average of 1.8 methyl groups per glucose residue. Bromine solutions were prepared in distilled water and standardised iodometrically.

Preparation of keto-derivatised cyclodextrins and sucrose.—These materials were prepared by reacting approximately 30×10^{-3} mol dm^{-3} bromine solution with 18×10^{-3} mol dm^{-3} cyclodextrin or sucrose, whilst maintaining the pH at 7.0 using a pH-stat dispensing 0.5 mol dm^{-3} NaOH. The reaction was carried out for approximately 24 h during which time approximately 12 mL NaOH was added. The reaction was started by adding the bromine solution to cyclodextrin or sucrose in powder form. After completion of the reaction, bromide, a product of the oxidation, was removed from the solution in order to prevent interference with subsequent kinetic experiments involving the keto-sugars and peroxomonosulfate. This was accomplished by passing the solution through an Amberlite IRA-743 ion exchange resin. The resin had previously been equilibrated in 2 mol dm^{-3} $NaNO_3$ in order remove chloride ions, which can react with peroxides, that were originally present as the exchange ion. The resin was then washed several times in distilled water before packing in an 80 mL glass column. The bromide concentration at the column outlet was monitored by reacting residual bromide with 10×10^{-3} mol dm^{-3} peroxomonosulfate in weak sufuric acid and measuring the absorbance due to bromine at 398 nm for which the molar absorbtivity is 86 dm^3 mol^{-1} cm^{-1}. Over 99.9% removal efficiency was achieved using the column with a residence time of 15 min. It should be noted that the bromide concentration was evaluated at low pH where the bromine oxidation of cyclodextrin and sucrose is very slow. The fraction containing the oxidised compound was monitored at the peak absorbance (typically 280 to 320 nnm) using a HP-8450 diode array spectrophotometer with a flow cell connected to the column outlet. No further purification was carried out. Variations to the above procedure involved changes to the concentrations of reactants and are as reported in the text. In particular, several experiments were conducted in which the bromine oxidation was carried out in buffer in order to monitor the UV/vis spectral changes during the oxidation. Carbonate and phosphate buffers were used in these cases and the reaction was followed on a Pharmacia Biotech Ultraspec 2000 Spectrophotometer.

^{13}C NMR.—Spectra were obtained in distilled water at pH 6.5–7.5 in 5 mm o.d. sample tubes using a JEOL EX 270 MHz NMR spectrometer at an operating frequency of 67.8 MHz. Sodium acetate (δ 182.61 in H_2O [45]) was used as an internal standard. The solutions containing the bromine oxidation products were reduced down to one tenth of their original volume using a vacuum oven at 40 °C, giving solutions ca. 160–180 mM in oxidised cyclodextrin. Nevertheless, typical acquisitions required between 30,000 to 50,000 scans in order to see detail in the carbonyl region. No bromide removal was carried out when the oxidised cyclodextrins were prepared purely for NMR analysis. The pH of the solutions was approximately 6.5 to 7.5 and so the standard exists predominantly in the anionic form for which complexation with cyclodextrin is negligible [36].

Reactions involving the keto-derivatives.—Oxidations of S-(-)-methyl-*p*-tolyl sulfoxide, 4-bromophenyl methyl sulfoxide and *p*-nitrophenol were carried out in phosphate buffer at pH 7.6 and ionic strength 0.2 mol dm^{-3}. The substrate and peroxomonosulfate concentrations are given in the results tables. The reactions were carried out at 25 °C and followed at 244 and 250 nm for (S)-(-)-methyl-*p*-tolyl sulfoxide and 4-bromophenyl methyl sulfoxide, respectively, and at 400 nm for *p*-nitrophenol on a Pharmacia Biotech Ultraspec 2000 spectrophotometer with thermostatted cell-holder. In the case of the sulfoxides, which absorb in a similar region to the keto-derivatives, it was necessary to run a blank in which no substrate was present. This was subtracted from the corresponding run with substrate present in order to account for the decrease in absorbance due to the keto-derivatives as they react with peroxomonosulfate. Confirmation that the sulfoxides were oxidised to sulfones in all cases was obtained by comparing the

product spectra with spectra for the corresponding sulfones [35]. We did not attempt to identify the products of *p*-nitrophenol oxidation for the reasons given in the results section. Initial rates were calculated for the sulfoxide oxidation experiments using the initial 200 s of data where the plot was linear. Peroxomonosulfate concentrations for the oxidation experiments were standardised iodometrically using a thiosulfate titration. The change in peroxomonosulfate concentration during reaction with the derivatised α-cyclodextrin was monitored using a standard spectrophotometric iodometric technique.

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References

[1] D.M. Davies, G.A. Garner, and J.R. Savage, *J. Chem, Soc., Perkin Trans. 2*, (1994) 1531.
[2] O. Theander, in W. Pigman and D. Horton (Eds.), *The Carbohydrates*, 2nd ed., Vol. 1B, Academic Press, New York, 1989.
[3] R. Andersson, O. Larm, E. Scholander, and O. Theander, *Carbohydr. Res.*, 78 (1980) 257.
[4] O. Larm, E. Scholander, and O. Theander, *Carbohydr. Res.*, 49 (1976) 69.
[5] E. Scholander, *Carbohydr. Res.*, 73 (1979) 302.
[6] W.M. Doane and R.L. Whistler, *Starch*, (1964) 177.
[7] I. Ziderman and J. Bel-Ache, *Carbohydr. Res.*, 27 (1973) 341.
[8] L.J. Torneport, B.A-C. Salomonsson, and O. Theander, *Starch*, 42 (1990) 413.
[9] O. Theander, *Ad. Carb. Chem.*, 17 (1962) 223.
[10] For reviews of dioxirane chemistry see: (a) W.A. Adam, R. Curci, and J.O. Edwards, *Acc. Chem. Res.*, 22 (1989) 205; (b) R.W. Murray, *Chem. Rev.*, 89 (1989) 1187.
[11] A.-C.B. Salomonsson, R.E. Anderson, L.J. Torneport, and O. Theander, *Carbohydr. Res.*, 217 (1991) 221.
[12] K.A. Martin, M.A. Mortellaro, R.W. Sweger, L.E. Fikes, D.T. Winn, S. Clary, M.P. Johnson, and A.W. Czarnik, *J. Am. Chem. Soc.*, 117 (1995) 10443.
[13] O. Larm, K. Larsson, E. Scholander, B. Meyer, and J. Thiem, *Carbohydr. Res.*, 91 (1981) 13.
[14] J. Kozlowski and P. Zuman, *Bioelectrochem. and Bioenergetics*, 28 (1992) 43.
[15] H-J. Buschman, H.-H. Füldner, and W. Knoche., *Ber. Bunsenges. Phys. Chem.*, 85 (1980) 41.
[16] J.M. Riordan, Philip E. Morris, and D.E. Kiely, *J. Carbohydrate Chemistry*, 12 (1993) 865.
[17] N.E. Mackenzie, P.G. Malthouse, and A.I. Scott, *Science*, 225 (1984) 883.
[18] M.A. Mortellaro, S. Hong, D.T. Winn, and A.W. Czarnik, *Bioorg. Med. Chem. Lett.*, 4 (1994) 2041.
[19] O.S. Tee and J.M. Bennett, *J. Am. Chem. Soc.*, 110 (1988) 269.
[20] O.S. Tee and B.C. Javed, *J. Chem. Soc., Perkin Trans. 2*, (1994) 23.
[21] A.C. Besemer and H. van Bekkum, *Recuil des Travaux Chimiques des Pays-Bas*, 113 (1994) 399.
[22] A.C. Besemer and H. van Bekkum, *Starch*, 46 (1994) 101.
[23] A.C. Besemer and H. van Bekkum, *Starch*, 46 (1994) 95.
[24] D.R. Lide (Ed.), *CRC Handbook of Chemistry and Physics*, 73rd ed., CRC Press, Boca Raton, FL, 1992.
[25] J. Palou, *Chemical Society Reviews*, (1994) 357.
[26] D.M. Davies and P. Jones, *J. Society of Dyers and Colourists*, 98 (1983) 17.
[27] M.L. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer Verlag, Berlin, 1978.
[28] C.G. Swain, R.A. Wiles, and R.F.W. Bader, *J. Am. Chem. Soc.*, 83 (1961) 1945.
[29] I.R.L. Barker, W.G. Overend, and C.W. Rees, *J. Chem. Soc.*, (1964) 3263.
[30] N. Venkatasubramian and V. Thiagarajan, *Tetrahedron Lett.*, (1968) 1711.
[31] N.C. Deno and N.H. Potter, *J. Am. Chem. Soc.*, 89 (1967) 3555.
[32] R. Hiatt in D. Swern (Ed.), *Organic Peroxides*, Vol 2., Wiley Interscience, New York, 1971.
[33] R.E. Montgomery, *J. Am. Chem. Soc.*, 96 (1974) 7820.
[34] J.O. Edwards, R.H. Pater, R. Curci, and F. Di Furia, Photochem. Photobiol., 30 (1979) 63.
[35] D.M. Davies and M.E. Deary, *J. Chem. Soc., Perkin Trans. 2*, (1995) 1287.
[36] D.M. Davies and M.E. Deary, *J. Chem. Soc., Perkin Trans. 2*, (1996) 2415.
[37] D.M. Davies and M.E. Deary, *J. Chem. Soc., Perkin Trans. 2*, (1996) 2423.
[38] J.E. Sawicki and B. Casas, *Environ. Progress*, 12 (1993) 275.
[39] M.S. Dieckmann and K.A. Gray, *Water Research*, 30 (1996) 1169.
[40] C.J. Martino and P.E. Savage, *Ind. Eng. Chem. Res.*, 36 (1997) 1385.

[41] A. Altamura, C. Fusco, L. D'Accolti, R. Mello, T. Prencipe, and R. Curci, *Tetrahedron Lett.*, 32 (1991) 5445.
[42] J.K. Crandall, M. Zucco, R.S. Kirsch, and D.M. Coppert, *Tetrahedron Lett.*, 32 (1991) 5441.
[43] M. Lj. Mihailovic and Z. Cekovic, in S. Patai (Ed.), *The Chemistry of Functional Groups, Hydroxyl Group*, Wiley, New York, 1971.
[44] A. Pintar and J. Levec, *Chem. Eng. Sci.*, 49 (1994) 4391.
[45] D.L. Rabenstein and T.L. Sayer, *J. Magnetic Resonance*, 24 (1976) 27.