

Letter

Cyclodextrins in reactions of alcohols with aqueous hypochlorite: catalysts or reactants?

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Abstract

β -Cyclodextrin, a cyclic oligosaccharide/poly alcohol, reacts with aqueous sodium hypochlorite at elevated temperatures, resulting in a drop in the pH of the medium. Hypochlorite-induced oxidations of 1-phenyl-1-propanol or benzyl alcohol in the presence of the cyclic oligosaccharide are enhanced by lowering of pH rather than by inverse phase transfer catalysis. The secondary alcohol is inert in aqueous hypochlorite maintained at high pH, even in presence of the cyclodextrin. More rapid and efficient oxidations may be effected by pH control than by heating and/or addition of β -cyclodextrin. © 1998 Elsevier Science B.V.

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The cyclic oligosaccharide, β -cyclodextrin, has been widely used to promote reactivity as a catalyst [1]. Recent articles in this journal have described enhanced oxidation of alcohols to corresponding aldehyde and ketone products by sodium and calcium hypochlorite in the presence of β -cyclodextrin [2,3]. In each of these cases, enhanced reactivity was attributed to involvement of the β -cyclodextrin functioning as an inverse phase transfer catalyst. However, since the oligosaccharide itself is a poly alcohol, the distinct likelihood exists that the β -cyclodextrin is a reactant in this system. To the extent that the cyclodextrin consumes oxidant

and produces products, the course as well as the kinetics of hypochlorite reactions with simple alcohols as substrates well might be influenced.

A series of reactions has been conducted to identify the key reaction parameters in such reactions. Significantly, the pH of the medium employed has been found to be more crucial than either β -cyclodextrin or elevated temperature in the oxidation of 1-phenyl-1-propanol, **I**, or benzyl alcohol, **II**, with aqueous sodium hypochlorite. Specifically, compound **I** was almost inert to aqueous sodium hypochlorite in the presence of β -cyclodextrin when heated for up to six h, as long as the pH remained elevated. In contrast, these same reactants demonstrated a high degree of reaction at ambient temperature at pH 8.5–9.5 when no β -cyclodextrin was present.

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Table 1

Reactions of aqueous sodium hypochlorite (20 ml, 12%, 0.03 mol) with β -cyclodextrin (β -CD, 0.0003 mol) and/or 1-phenyl-1-propanol (I, 0.005 mol)

Initial pH	Time (h)	Final pH	BCD (yes/no); I used (\pm)	Reaction temperature ($^{\circ}$ C)	Recovered Alcohol (%) (range; average)	Propiophenone, III (%) (range; average)	By-products (%) (range; average)
13.0–13.1 ^a	< 5	12.0–12.4	yes; – (blank)	50			
13.0–13.1 ^a	> 5	6.8–7.0	yes; – (blank)	50			gas evolved ^e
13.0–13.2 ^a	4–5	7.5–8.2	yes; +	50	1–29 ^d ; 17	36–80; 61	2–14; 8
13.4–13.5 ^b	6–6.8	13.3–13.4	yes; +	50	95–97; 96	none	none
8.6–8.9 ^c	0.5–1.5	8.6–9.3	no; +	25	3–8; 4	70–84; 78	trace

^aUnadjusted.

^b10 ml of 5% NaOH added initially.

^cAdjusted initially with 0.1 g of $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$ (buffer) and concentrated HCl.

^dPercent experimental data for five runs.

^eCollected in balloon, yielded ppt. with aqueous $\text{Ba}(\text{OH})_2$.

In 'blank' reactions (no alcohol substrate present), mixtures of β -cyclodextrin heated at 50 $^{\circ}$ C with aqueous hypochlorite exhibited dramatic drops in pH (from pH > 13 to pH 6.8–7) after 4–5 h. Comparable decreases in pH, observed for heated reactions of 1-phenyl-1-propanol with hypochlorite in presence of β -cyclodextrin, required at least 4 h. Only when a pH decrease was observed or induced was compound **I** converted in modest yield to the ketone, **III**. Further, pH of heated substrate/oligosaccharide/hypochlorite systems proved to be difficult to control, dropping sometimes into the acid range of pH < 5. Under these condition, substantial by-product formation occurred. In contrast, at pH 9 and ambient temperature with no cyclodextrin present, good yields of **III** were achieved in relatively short time periods.

In typical experiments, 1-phenyl-1-propanol (5.0 mmol) was stirred magnetically with 20 ml of 12% (w/w) aqueous sodium hypochlorite (30 mmol) ¹. For heated experiments, a 48–50 $^{\circ}$ C constant temperature bath was employed, and reactions at ambient temperature were typically

at 24–26 $^{\circ}$ C. The initial pH was > 12 for media before β -cyclodextrin (0.25–0.26 mmol) was added. In such reactions, a slight drop in pH was noted before a mixture was heated. After cooling, the pH was determined for reaction mixtures, and the aqueous solution was extracted twice with 20 ml portions of dichloromethane. Chlorobenzene in concentration equal to substrate was added to the extract as a standard. An aliquot was washed with aqueous, acidified 5% potassium iodide ² and analyzed by capillary gas chromatography. The results were compared and correlated with a standard mixture containing the chlorobenzene, the substrate and propiophenone (1-phenyl-1-propanone). Gas chromatography/mass spectrometry indicated the presence of chlorinated ketone by-products in reactions using the catalyst. In selected experiments, initial pH values were modified by addition of aqueous sodium hydroxide or a buffer with hydrochloric acid as shown in Table 1 (results comparable to those in Table 1 were observed when commercial

¹ Obtained from Spectrum Quality Product, Gardena, CA. Different bottles of such material, as obtained, exhibited pH as low as 11 and high as over 13. Heated reactions conducted with lower pH material proceeded more quickly, and results were less reproducible.

² Gas chromatographic analysis showed no substantial difference when the potassium iodide treatment was omitted in the studies described herein. However, experience with other hypochlorite oxidations leads us to suggest that the potassium iodide work-up generally is a good idea prior to chromatographic analysis (personal communication with W.H. Hendrickson).

bleach, 'Clorox,' 5.25% sodium hypochlorite, was employed).

Oxidation reactions of benzyl alcohol (**II**) yielded substantial benzoic acid, regardless of conditions employed. In 5-h reactions at 50°C with β -cyclodextrin in 12% hypochlorite, only 5–12% conversion to benzaldehyde was observed, whereas 30–56% of **II** was converted to benzoic acid, and 1–14% starting material was recovered. Initially, the reaction exhibited pH 13 and dropped to ending pH 6.1–7.8 (analysis was accomplished by gas chromatography first of dichloromethane extracts and, after destruction of residual hypochlorite with sodium bisulfite, of diethyl ether extracts). In heated reactions maintained at pH > 13 with added 5% NaOH, benzoic acid also was the major product. At pH 9 with no β -cyclodextrin present, compound **II** was consumed completely in one h in an exothermic reaction and largely converted to compounds soluble in dilute sodium hydroxide, including benzoic acid and chlorinated benzoic acids. No benzaldehyde was found under these conditions.

These results strongly indicate that β -cyclodextrin enhances the reactivity of sodium hypochlorite by serving as a reactant, not as a catalyst. Reaction of the oligosaccharide with hypochlorite results in a drop in pH, even when no substrate is present. When a substrate alcohol is present, its oxidation is promoted by the drop of pH in to an active range, resulting from β -cyclodextrin reaction with hypochlorite. Elevated temperatures, catalyst, and long reaction periods are not required at lower pH, but pH is a crucial control parameter for completion of reactions and control of competing and subsequent processes that generate by-products.

Facile hypohalite reactions of polysaccharides are known [4], and pH sensitivity of

hypochlorite-induced reactions generally is well established [5,6]. It will likely be difficult to discern the degree that cyclodextrins actually catalyze any hypochlorite-induced oxidation of organic substrates, including alcohols, due to competition with reaction of the oligosaccharide itself. Studies in such systems must involve determination of stability of potential catalysts as well as careful monitoring and control of reaction parameters, such as pH, to distinguish clearly the factors impacting reactivity.

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