A Simple and Highly Selective Biomimetic Oxidation of Alcohols and Epoxides with *N*-Bromosuccinimide in the Presence of β-Cyclodextrin in Water†

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Abstract: A simple, mild and highly efficient biomimetic oxidation of various alcohols and epoxides with *N*-bromosuccinimide (NBS) catalyzed by β-cyclodextrin in water has been developed. A series of alcohols and epoxides were oxidized selectively at room temperature in excellent yields. This method is a direct one-pot synthesis under mild conditions using water as solvent and has many advantages over the existing methodologies.

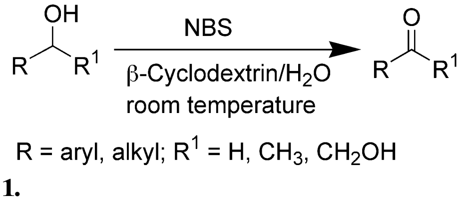
Keywords: alcohols; biomimetic; *N*-bromosuccinimide; β-cyclodextrin; epoxides; oxidation; water

Introduction

There is an ever-increasing demand to develop sophisticated target systems involving selective synthetic methodologies to discriminate various functional groups. Amongst them, oxidation of alcohols occupies the prime place especially to attain selectivity between 1,2-diols and controlled oxidation of various alcohols to aldehydes without any overoxidation. Numerous methods have been developed which still have some limitations. Amongst them, stoichiometric oxidants such as manganese dioxide,[1] hypervalent iodine,[2] activated dimethyl sulfoxides,[3] chromium(VI)-based oxidants,[4] etc. were the most commonly used. Although these methods are being used in various types of organic syntheses, the heavy metal oxidants, apart from being expensive, form toxic wastes, whereas activated dimethyl sulfoxide gives rise to awfully smelling dimethyl sulfide. Regarding hypervalent iodine, oxidants such as IBX are either explosive on impact or on heating to more than 200 °C. Another most conventional industrial oxidant,[5] nitric acid, though cheap unavoidably forms various nitrogen oxides. However, even catalytic oxidations have some limitations such as pH of the medium, controlled temperature, hazardous reagents and solvents, formation of side products etc.[6,7] The *N*-bromosuccinimide (NBS) oxidations of alcohols reported are usually carried out using either anhydrous solvents or in acidic or basic media at varied temperatures. The selectivities observed were also not encouraging in some cases.[8] Oxidation of various alcohols still remains the most problematic process. Thus there is still demand for clean and safe oxidation procedures.

Green chemistry is becoming a central issue in both academic and industrial research in the 21st century.[10] Industrial chemistry is not sustainable without this approach. Thus the development of environmentally benign and clean synthetic procedures is the goal of present day researchers. Every reaction should proceed with a high atom-economy,[11] thereby minimizing the cost of waste disposal. Thus there is need for developing clean oxidation reactions in water without the use of any harmful organic solvents because water is a safe, economical and environmentally benign solvent.[12] In our efforts to develop biomimetic approaches for chemical reactions involving cyclodextrins in water,[13] we report herein for the first time the highly selective oxidation of a variety of alcohols, diols and epoxides as their β-cyclodextrin complexes with *N*-bromosuccinimide in water without the presence of any acidic or basic catalyst (Schemes 1 and 2).

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host-guest complexes by non-covalent bonding as seen in enzymes. Complexation depends on the size, shape and hydrophobicity of



R = aryl, alkyl; R^1 = H, CH_3, CH_2OH

Scheme 1.

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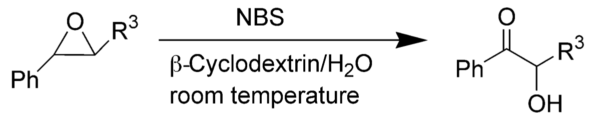

R^3 = CH$_2$OH, CH$_2$OTBDMS, COOMe, COOEt

Scheme 2.

the guest molecule. Thus, mimicking biochemical selectivity, which is due to orientation of the substrate by complex formation positioning only a certain region for favorable attack, will be superior to chemical selectivity, which involves random attack due to intrinsic reactivity of the substrate at different regions. These attractive features of cyclodextrins in the biomimetic modeling of chemical reactions prompted us to investigate a variety of oxidations using the substrate-β-cyclodextrin complexes with NBS in water. The complexes were formed with β-cyclodextrin since it is easily accessible and least expensive among the cyclodextrins.

Results and Discussion

In general, the reaction was carried out by the *in situ* formation of the β-cyclodextrin complex of the substrate in water followed by the addition of NBS and stirring at room temperature to give the corresponding carbonyl compounds in impressive yields (Table 1). The reaction goes smoothly at room temperature without the formation of any side products or rearrangements. No overoxidation to acids was observed in the case of aldehyde products (Entries 1–8, Table 1). This methodology is also compatible to the presence of other functionalities such as methoxy, nitro, and amino, hydroxy, methylenedioxy and alkene double bonds. These reactions are highly selective for vicinal diols in oxidizing only the secondary hydroxy group α to the benzene ring (Entries 18–20, Table 1). In the case of various types of epoxides (Entries 21–24, Table 1), α-hydroxyketones were the only products obtained in excellent yields keeping intact the functionalities such as primary OH, TBDMS, OMe and OEt. These cyclodextrin-mediated, water-based reactions proceed under mild conditions and are also useful from the point of view of not having to handle flammable and anhydrous organic solvents and toxic reagents. Although inclusion complexation takes place *in situ* during the reaction, the complexes have been isolated and characterized by powder X-ray[14] and ^{1}H NMR studies.[15] All the compounds were characterized by mass, ^{1}H NMR, IR and by comparison with known compounds.[16] In these reactions succinimide was obtained as the by-product. This has been recycled to NBS as described in the experimental section. Cyclodextrin has also been recovered and reused. In the case of epoxycinnamyl alcohol (Entry 21) also the product obtained in dichloromethane (in the absence of β-CD) was only the aldehyde by the oxidation of the primary alcohol retaining the oxirane as observed by Mukaiyama et al.,[7] whereas in the presence of β-CD in water the α-hydroxyketone was obtained as the product. When a catalytic amount of cyclodextrin (0.1 mmol per 1 mmol of substrate) was used the reaction with alcohols did not go to completion and the product formation was only to the extent of 40–50% under the reported reaction conditions. In the case of epoxycinnamyl alcohol only the primary alcohol was oxidized giving epoxycinnamyl aldehyde.

The mechanism of oxidation has been postulated as follows. The fact that these reactions do not take place in the absence of cyclodextrin in water and that the starting substrate was intact indicates the essential role of cyclodextrin. Here the role of cyclodextrin appears to be to form an inclusion complex of alcohol/epoxide from the secondary side with the attack of NBS from the primary side of CD enabling the reaction to proceed (Figure 1). The evidence for this mechanistic approach was deduced from ^{1}H NMR spectroscopy. These studies were carried out with 4-methoxybenzyl alcohol as a

Table 1. Oxidation of alcohols and epoxides with NBS in presence of β–CD in water.

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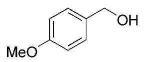
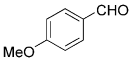
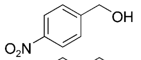
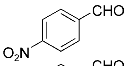
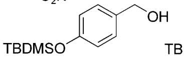
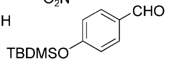
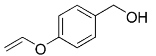
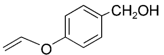
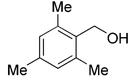
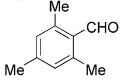
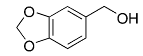
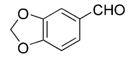
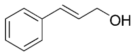
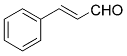
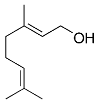
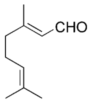
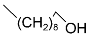
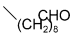
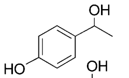
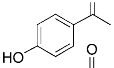
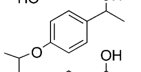
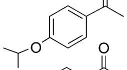
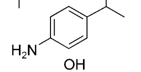
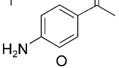
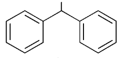
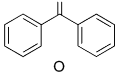
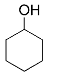
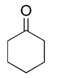
1			8	98
2			8	92
3			8	96
4			8	95
5			8	96
6			8	94
7			8	94
8			8	92
9			8	88
10			10	95
11			10	96
12			10	95
13			10	96
14			12	92

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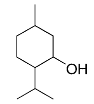
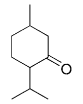
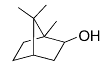
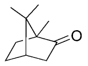
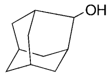
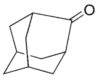
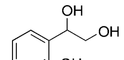
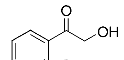
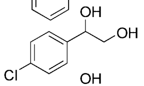
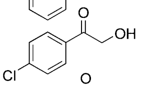
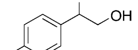
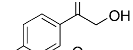
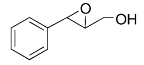
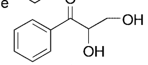
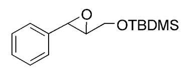
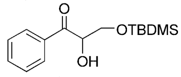
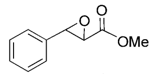
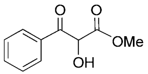
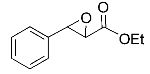
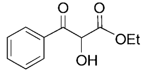
15			12	89
16			12	88
17			12	92
18			10	96
19			10	95
20			10	96
21			24	88
22			24	90
23			24	89
24			24	89

[a] All products were identified by IR, NMR, and mass spectroscopy.
[b] Yields of solated products.

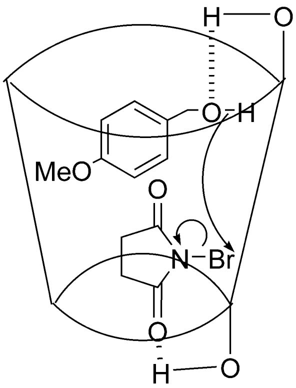


Figure 1.

representative example. A comparison of the ^{1}H NMR spectra (D_2O) of β-cyclodextrin, β-cyclodextrin-alcohol and freeze-dried reaction mixtures at 5 h and 8 h was undertaken. It can be seen from Figure 2 that there is a clear upfield shift of the H3 (0.03) and H5 protons (0.04) in the β-CD-alcohol complex (Figure 2B) The shift of these protons of cyclodextrin in the cyclodextrin-alcohol complex (Figure 2B) as compared to cyclodextrin (Figure 2A) indicates the formation of inclusion complex.[15] However, it can be observed from the spectra of the reaction mixtures at 5 h and 8 h (Figures 2C and 2D) that in these complexes, apart from retention of the

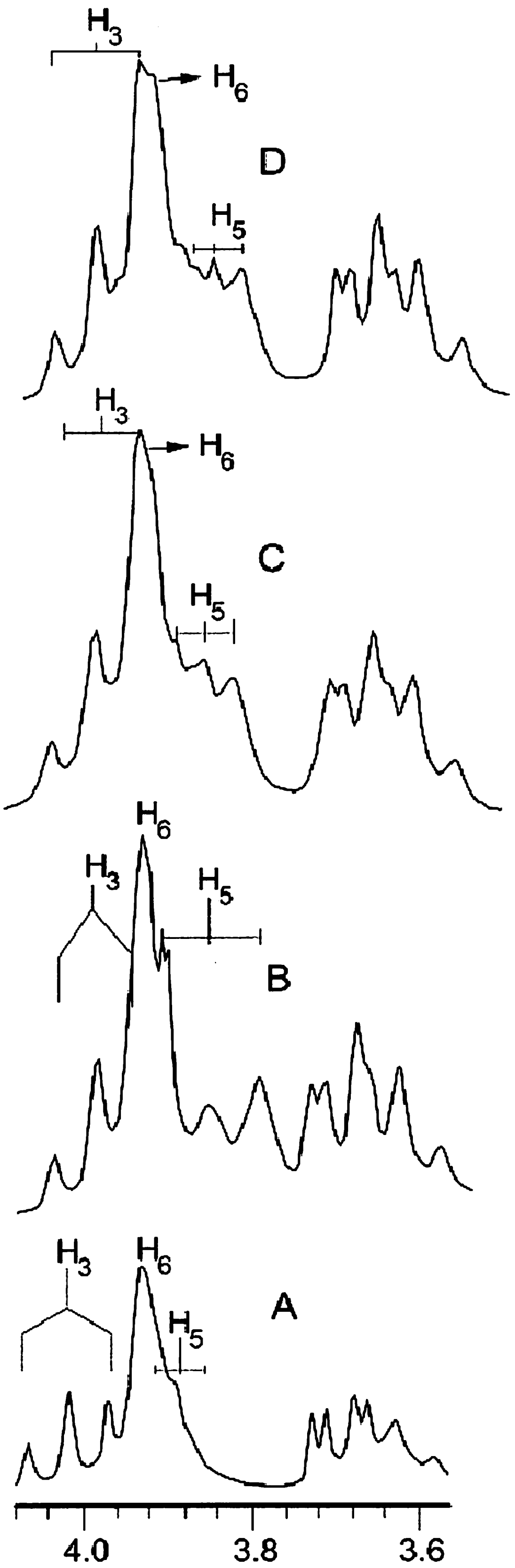


Figure 2. ^{1}H NMR spectra: A: β-CD; B: β-CD-alcohol complex; C: 5-h reaction mixture; D: 8-h reaction mixture.

upfield character of H3 and H5 protons, there is also an upfield shift of the H6 proton (i.e., 0.02 ppm at 5 h 0.025 ppm at 8 h, respectively). This indicates the complexation of NBS from the primary side of CD. From these ^{1}H NMR studies it could be seen that while the alcohol is still being retained in the cavity, NBS complexes from the primary side (Figure 1) for the reaction to proceed further. Thus, it can be seen that the reaction takes place through supramolecular catalysis.

Conclusion

In conclusion, we have presented an elegant and simple methodology for the oxidation of a variety of alcohols and epoxides using NBS in the presence of β-cyclodextrin with water as the solvent under supramolecular catalysis. This approach may be considered as environmentally benign with high potential for various applications.

Experimental Section

General Information

All reactions were carried out without any special precautions in an atmosphere of air. Chemicals and solvents were purchased from Fluka and S. D. Fine Chemicals and used as received. ^{1}H NMR spectra were obtained on a Gemini-200 or 300 MHz spectrometer. IR spectra were recorded on a Nicolet FT-IR spectrometer. Mass spectra were observed on V. G. Auto Spectrometer.

General Procedure

β-Cyclodextrin (1 mmol) was dissolved in water (15 mL) at 60 °C, the substrate (1 mmol) dissolved in methanol/acetone (1 mL) was added slowly with stirring and cooled to room temperature. Then 1 mmol of NBS was added and stirring at room temperature was continued until the reaction was complete (Table 1). The mixture was extracted with ethyl acetate and the extract filtered. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to get the product. The products obtained, although seen as single compounds by TLC, were further purified by passage over a column of silica gel.

The aqueous layer was cooled to 5 °C to recover CD by filtration. To the filtrate which contains succinimide and HBr was added $NaBrO_3$ and concentrated H_2SO_4 as already reported[17] and stirred for 30 min. Then, it was extracted with ethyl acetate and the solvent was removed under vacuum to regenerate NBS in an isolated yield of 75–80%.

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References and Notes

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