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A Mechanistic Model for the Selective Oxidation of 1,4-Diols to γ-Lactols by *o*-Iodoxybenzoic Acid

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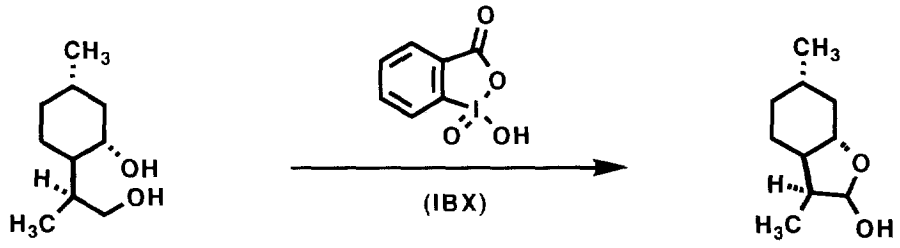
Summary: *The selective oxidation of 1,4-diols to γ-lactols by o-iodoxybenzoic acid occurs by a rate-limiting carbonyl-forming elimination pathway in which the carbinol proton is abstracted internally via a six-atom cyclic arrangement, which explains the observed selectivity.*

We recently described the application of *o*-iodoxybenzoic acid in dimethyl sulfoxide solution[1] to the selective oxidation of a number of 1,4-*bisprimary* and 1,4-*primary-secondary* diols to γ-lactols.[2] For example, diol **1** was converted to γ-lactol **2** in >80% yield.[2] Under the usual reaction conditions for this useful transformation (23 °C for *ca.* 2 h) very little γ-lactone is produced by further oxidation of the product γ-lactol, despite the facility of this oxidation (relative to comparable secondary alcohols) with most oxidants (e.g. Cr (VI), MnO_2 and NBS reagents). We present herein a study of the oxidation of alcohols by *o*-iodoxybenzoic acid (IBX) in dimethyl sulfoxide (DMSO) solution which provides a mechanistic explanation for the observed selectivity.



1 **2**

The first objective of this investigation was the determination of whether the rate-limiting step involves iodic ester formation or carbonyl forming elimination (analogous to the classical findings of F. H. Westheimer on the chromic acid oxidation of alcohols[3]). The rate of oxidation of a simple primary alcohol, 2-phenylethanol, was determined in DMSO-d_6 solution at 23 °C by observation of the ^1H NMR peak due to the carbinol protons (CH_2–O at 3.68 δ) as a function of time. Using six equivalents of IBX good pseudo first order kinetics were observed up to 68% complete reaction, as shown in Figure 1, and a k_1 of 12.7 x 10^{-4} sec^{-1} was calculated. In a parallel experiment with $C_6H_5CH_2CD_2OH$ (following the benzylic CH_2 peak at 2.68 δ) a value k_1 = 2.06 x 10^{-4} sec^{-1} was obtained, leading to a kinetic isotope effect, k_H/k_D, of 6.3. The oxidation of dibenzylcarbinol and its α-deuterio analog also exhibited a primary kinetic isotope effect. It is clear from these experiments that carbonyl forming elimination from an iodic ester derivative is rate limiting.

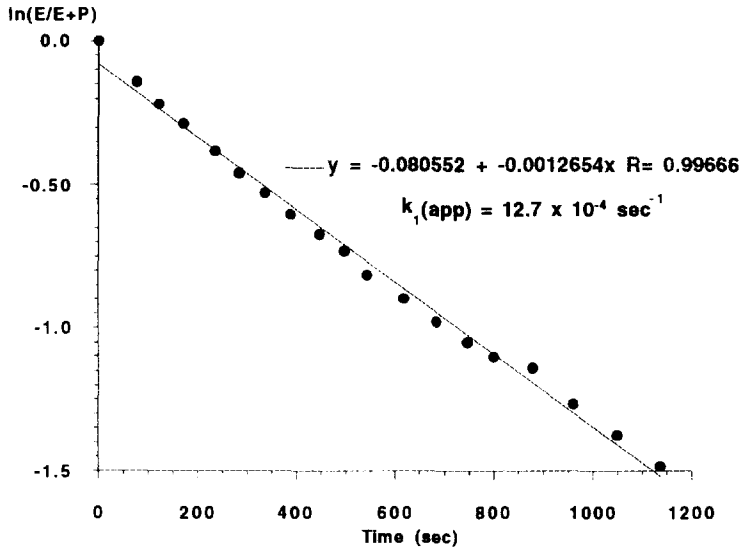
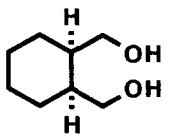


Figure 1. Pseudo first order rate plot of ln(E/E+P) vs time for the oxidation of $C_6H_5CH_2CH_2OH$ with excess IBX at 23 °C in DMSO-d_6; E= educt conc.; P= product conc.

A series of relative rates of oxidation was measured for a group of relevant substrates using ^1H NMR spectroscopy to monitor oxidation reactions in DMSO-d_6 at 23 °C. In this way the relative rates of oxidation were determined for **3**, **4** and **5** = 40 : 4 : 1. On the basis of these data the mechanism shown in Scheme 1 for the oxidation of **3** to **5** seems plausible.



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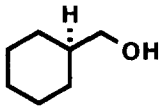

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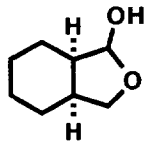
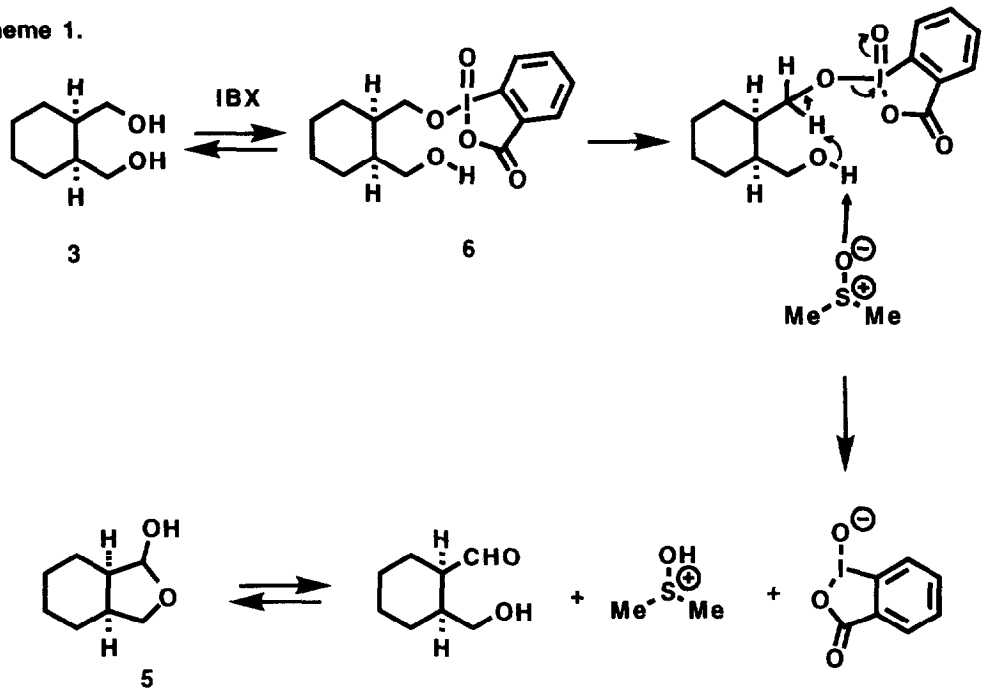


5

The first step is *non*-rate limiting and probably reversible formation of iodic ester **6**. The following step, irreversible, rate-limiting carbonyl-forming elimination, is proposed to be assisted by the other hydroxyl group of the 1,4-diol acting as a base because of proximity (6-membered cyclic structure for internal proton abstraction) and also enhanced basicity due to hydrogen bonding to dimethyl sulfoxide. Thus dimethyl sulfoxide serves not only as a good solvent for IBX (which is insoluble in solvents such as CH_2Cl_2 or $CHCl_3$), but also as a catalytic base. The internal pathway for the proton abstraction-elimination step explains the ten-fold faster rate of oxidation of diol **3** relative to mono alcohol **4**. In addition, the forty-fold faster rate of oxidation of diol **3** as compared to the product γ-lactol **5** makes the lack of further conversion of lactol **5** to the corresponding lactone (under conditions of minimal reaction time) readily understandable.

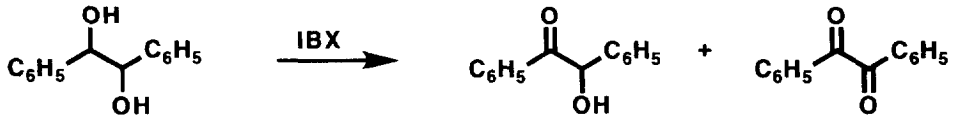
Scheme 1.



The oxidation of 1,3-diols to mono carbonyl product appears to be somewhat less selective than that of 1,4-diols, as might be expected on the basis of the mechanism outlined above (5-membered transition state for internal proton abstraction). Thus, an experiment on the oxidation of diol **7** by 1 equiv of IBX in DMSO-d_6 at 23 °C which was monitored by ^{1}H NMR spectroscopy showed the presence of **7**, **8** and **9** in the ratio of 1 : 8 : 1 towards the end of the reaction.

7 **8** **9**

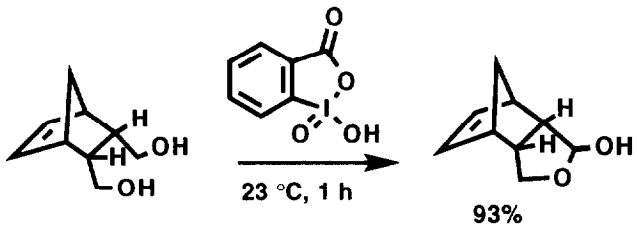
Furthermore, the rate of oxidation of **7** was only *ca.* 3-4 times that of the model mono alcohol neopentyl alcohol. Finally, there is evidently little, if any, special acceleration of the oxidation of 1,2-diols as is apparent from the following preparative experiment:



41% 24%

During the course of this study we observed that IBX, which is quite insoluble in most solvents other than DMSO, can be dissolved in acetone containing 8 equiv of DMSO at 23 °C and that this mixture is effective in the

selective oxidation of 1,4-diols to γ-lactols. The use of this medium is more economical and leads to simplified isolation and higher yields of γ-lactol product. This improved process is illustrated by the following example.



A mixture of dimethyl sulfoxide (0.27 mL), acetone (1.0 mL) and *o*-iodoxybenzoic acid (0.109 g, 0.389 mmol) was stirred for 1 h and the resulting solution was treated with *endo-bis*-2,3-hydroxymethylbicyclo[2.2.1]hept-5-ene (0.050 g, 0.324 mmol). After stirring for 1 h at 23 °C the reaction mixture was quenched with water (2 mL) and filtered. The filtrate was extracted three times with methylene chloride and the extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was flash chromatographed on a silica gel column (EtOAc–hexanes 1 : 4) to afford 0.046 g (93%) of γ-lactol as a colorless oil: R_f 0.21 (50% EtOAc–hexanes); 400-MHz ^{1}H NMR ($CDCl_3$) δ 6.19 (dd, J = 5.6, 2.9 Hz, 1 H), 6.07 (dd, J = 5.6, 2.8 Hz, 1 H), 4.98 (d, J = 2.2 Hz, 1 H), 3.97 (dd, J = 8.8, 7.6 Hz, 1 H), 3.45 (dd, J = 9.0, 2.0 Hz, 1 H), 3.01-2.84 (m, 4 H), 2.69 (s, 1 H), 1.44 (d, J = 8.2 Hz, 1 H), 1.35 (d, J = 8.2 Hz, 1 H); 100-MHz ^{13}C NMR ($CDCl_3$) δ 134.7, 134.5, 100.4, 69.4, 55.5, 51.9, 45.9, 45.8, 44.9; IR (neat) cm^{-1} 3390, 2903, 2871, 1252, 1088, 1044, 992; mass spectrum (EI) *m/z* (rel intensity) 152 (100), 135 (55), 105 (65); exact mass calcd for $C_9H_{12}O_2$ 152.0837, found 152.0840.

In summary, the remarkably selective oxidation of 1,4-diols to γ-lactols can be understood as a consequence of accelerated oxidation of 1,4-diols because of assistance in the transition state for carbonyl-forming elimination by internal proton abstraction (6-membered ring) and also a somewhat faster rate of oxidation for primary alcohols as compared to secondary alcohols or lactols.[4]

References and Notes:

1. (a) Frigerio, M.; Santagostino, M. *Tetrahedron Letters* **1994**, *35*, 8019. (b) *o*-Iodoxybenzoic acid is readily prepared by oxidation of *o*-iodobenzoic acid with potassium bromate. See, Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277 and *J. Org. Chem.* **1983**, *48*, 4155.
2. Corey, E. J.; Palani, A. *Tetrahedron Letters* **1995**, *36*, 3485.
3. Westheimer, F. H. *Chem. Rev.* **1949**, *45*, 419; *Chem. Rev.* **1961**, *61*, 265.
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