Insensitivity to Conformational Changes in Potassium Bromate Oxidation of Steroidal Alcohols & Sterically Hindered 2-Adamantanol, Dicyclohexymethanol & Borneol

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The kinetics of potassium bromate oxidation of the title steroidal and highly hindered alcohols in the presence of Hg(OAc)\textsubscript{2} proceed at comparable rates, in contrast to Cr(VI) oxidation. Unlike Cr(VI) oxidations, α-C-H bond cleavage does not occur in a slow step in the title oxidation reactions and hence it is not subjected to steric influences of conformers.

A wide variation of reactivity-dependence on the ring size exists in the oxidation of cyclanols by Br\textsubscript{3}, Cr(VI) oxide\textsuperscript{3,4}, Ce(IV)\textsuperscript{5} and several other oxidants, but potassium bromate\textsuperscript{6} oxidation of cyclanols is insensitive to the size of the ring, probably due to the bromate-ester formation being the rate-determining step. As the C-H bond cleavage in a secondary alcohol is susceptible to electronic and steric influences, we have investigated for the first time Br(V) oxidation of certain steroidal alcohols such as 3α-hydroxy-5β-pregn-20-one, 3β-hydroxy-5β-pregn-20-one, 3α-hydroxy-5α-androst-17-one and sterically hindered alcohols such as dicyclohexymethanol, 2-adamantan-2-one and borneol.

Materials and Methods

The organic compounds used in the present work were of reagent grade (Aldrich) and were used after ascertaining their purity. Potassium bromate, perchloric acid, acetic acid, mercuric acetate and other compounds were of reagent grade (BDH).

The kinetics were followed by estimating the unreacted Br(V) at various time intervals by an iodometric procedure\textsuperscript{7}.

Stoichiometry and product analyses

Nearly 2 mol of Br(V) are consumed by 1 mol of cyclohexanol or isopropanol indicating bromination/oxidation of the product, ketone, by the reactive intermediate, Br(III) or Br(I). One of the products of the reaction in the case of cyclohexanol has been separated by TLC and identified as 2-bromocyclohexanone (yield 40\% m.p. 105°). Under the same conditions 2 mol of Br(V) are consumed by 1 mol of cyclohexanone yielding 2-bromocyclohexanone in ~40\% yield. As Br(V) did not oxidise camphor, the products, isolated in the Br(V) reaction with borneol were 3-bromocamphor (yield 60\% m.p. 178°). In contrast to this, 1 mol of Br(V) consumes 3 mol of adamantanol to give adamantanone, m.p. 256°, in 95\% yield, the IR spectrum of which compares favourably with that reported in literature. This implies that further bromination oxidation of adamantanone is difficult because both the α-C-H bonds are at the bridge-heads. This in a way suggests that bromination of ketone by intermediate species, probably Br(I), precedes oxidation of ketone by Br(III) or Br(V) and whenever the α-position has a -CH\textsubscript{2} group, probably dibromination occurs before the ring-opening of the ketone. As such a reaction is not possible in adamantanone the net consumption of Br(V) is less.

Results and Discussion

Table 1 summarises the kinetic and thermodynamic data for Br(V) oxidation of certain secondary alcohols in 50\% v/v aq. HOAc in the presence of 0.20 mol dm\textsuperscript{-3} HClO\textsubscript{4} and 0.062 mol dm\textsuperscript{-3} mercuric acetate which complexes\textsuperscript{7} Br\textsuperscript{-} (one of the products of the reaction) preventing \textit{in situ} formation of Br\textsubscript{2}. The reaction exhibits total second order kinetics, first order with respect to each reactant as shown by the linear plot of logarithm of unreacted [Br(V)] versus time. Bromate oxidation of 3α-hydroxy-5α-androst-17-one, in 50\% v/v aq. acetic acid in the presence of 0.062 mol dm\textsuperscript{-3} Hg(OAc)\textsubscript{2} at 55 ± 0.2° C at a constant ionic strength of 1.00 mol dm\textsuperscript{-3} is an acid-catalysed one. The rate increases proportionally with increase in [HClO\textsubscript{4}] in the range of 0.20 mol dm\textsuperscript{-3} to 0.80 mol dm\textsuperscript{-3}. The first order dependence in [H\textsuperscript{+}] is suggestive of HBrO\textsubscript{3} as the reactive species under the reaction condition. The rate expression for an acid-catalysed reaction is given by Eq.(1)

\[
\frac{-d[Br(V)]}{dt} = k_{obs} [Br(V)] [alcohol] [H\textsuperscript{+}] \quad (1)
\]
### Table 1 — Second Order Rate Constants for Potassium Bromate Oxidation of Secondary Alcohols

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>$10^2 k_2 \text{(dm}^3 \text{mol}^{-1} \text{s}^{-1})$</th>
<th>$E_a$ (kJ mol$^{-1}$)</th>
<th>$\Delta H^\ddagger$ (kJ mol$^{-1}$)</th>
<th>$\Delta S^\ddagger$ (J K$^{-1}$ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45°C</td>
<td>55°C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclohexanol$^b$</td>
<td>2.2</td>
<td>3.4</td>
<td>44.2</td>
<td>41.6</td>
</tr>
<tr>
<td>Cyclohexenol</td>
<td>2.7</td>
<td>4.5</td>
<td>44</td>
<td>41.4</td>
</tr>
<tr>
<td>Cyclohexadecan</td>
<td>1.48</td>
<td>3.3</td>
<td>64.2</td>
<td>61.6</td>
</tr>
<tr>
<td>Dicyclohexylmethanol</td>
<td>2.6</td>
<td>10.2</td>
<td>123.2</td>
<td>120</td>
</tr>
<tr>
<td>2-Propanol</td>
<td>0.81</td>
<td>1.20</td>
<td>33.9</td>
<td>31.3</td>
</tr>
<tr>
<td>2-Propanol-a-d</td>
<td>0.82</td>
<td>1.26</td>
<td>36.5</td>
<td>33.9</td>
</tr>
<tr>
<td>Benzhydrol</td>
<td>1.37</td>
<td>2.5</td>
<td>48.6</td>
<td>46</td>
</tr>
<tr>
<td>Borneol$^b$</td>
<td>2.9</td>
<td>9.5</td>
<td>99.6</td>
<td>97</td>
</tr>
<tr>
<td>2-Adamantanol</td>
<td>2.0</td>
<td>5.3</td>
<td>74.3</td>
<td>71.6</td>
</tr>
<tr>
<td>3α-Hydroxy-5α-androstan-17-one</td>
<td>2.4</td>
<td>5.9</td>
<td>80.6</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3α-Hydroxy-5β-pregnan-20-one</td>
<td>2.5</td>
<td>5.8</td>
<td>67</td>
<td>64.4</td>
</tr>
<tr>
<td>3β-Hydroxy-5β-pregnan-20-one</td>
<td>2.1</td>
<td>5.8</td>
<td>79</td>
<td>76.3</td>
</tr>
</tbody>
</table>

$^a$All these reactions were carried out with [alcohol] = 5.0 x 10$^{-3}$ mol dm$^{-3}$, [BrO$_3$]$^- = 5.0 x 10^{-4}$ mol dm$^{-3}$ and [HClO$_4$] = 0.20 mol dm$^{-3}$.

$^b$Under the same conditions $k_2 = 22 x 10^{-2}$ dm$^3$ mol$^{-1}$ s$^{-1}$ at 55°C for Br(V) oxidation of cyclohexanone.

$^c$Camphor does not consume Br(V) under the same conditions and hence it, probably, undergoes bromination by intermediate, Br(I) forming 3-bromocamphor.

$^d$The specific rate in 0.20 mol dm$^{-3}$ HClO$_4$ at an ionic strength of 1.00 mol dm$^{-3}$.

$^e$The specific rate in 0.40 mol dm$^{-3}$ HClO$_4$ at an ionic strength of 1.00 mol dm$^{-3}$.

$^f$The specific rate in 0.80 mol dm$^{-3}$ HClO$_4$ at an ionic strength of 1.00 mol dm$^{-3}$.

It is noteworthy that cyclohexanol, cyclohexenol and cyclohexadecanol are oxidised by Br(V) at rates unexpected according to $I$-strain concept, unlike in the oxidation of cyclopentanes and cycloalkanols by Cr(VI) oxide. Surprisingly cyclohexanone gets oxidised and brominated by Br(V) at a faster rate compared to cyclohexanol yielding 2-bromocyclohexanone as one of the products. The reactivity of Br(V) with dicyclohexylmethanol also seems to be comparable with that of cyclohexanol at 45°C though dicyclohexylmethanol is sterically more crowded than cyclohexanol. However, if the C-H bond cleavage were to occur in a slow step, as it results in change in hybridization from $sp^3$ to $sp^2$, rate enhancement should have been observed as in Cr(VI) oxidation$^a$ reactions. Dicyclohexylmethanol being aliphatic analogue of benzhydrol, rate enhancing influences of phenyl rings should be absent and it should be as reactive as propan-2-ol. But for the marginal reduced reactivity of propan-2-ol, there is no marked difference in the specific rates of Br(V) oxidation of these alcohols. Further the C-H bond cleavage in the slow step of oxidation of compounds like borneol with an axial -OH is expected to have (i) enhancing relief of strain from the axial interaction with H, due to the change in hybridization from $sp^3$ to $sp^2$ and (ii) a rate-retarding steric strain between the $\alpha$-C-H and bridgehead gem-dimethyl groups. Even such primary steric influences do not seem to alter the rate of Br(V) oxidation at 45°C. 2-Adamantanol with -OH group essentially equatorial, but quasi-axial with respect to one of the ring systems, reacts with Br(V) in no way different from cyclohexanol, indicating insensitivity of Br(V) oxidation to conformational changes. Had the C-H bond cleavage in 2-adamantanol been involved in the slow step as in Cr(VI)$^{10}$, there would have been at least a five-fold increase in the rate.

Surprisingly the reactivity of even 3α-hydroxy-5α-androstan-17-one with more stable A/B trans fusion does not differ much from that of 3α-hydroxy-5β-pregnan-20-one and the specific rate of Br(V) oxidation of 3β-hydroxy-5β-pregnan-20-one with an axial -OH group is close to that of its conformers. Thus there is little selectivity in Br(V) oxidation of conformational epimers. Added to this 2-propanol-$\alpha$-d gets oxidised by Br(V) at a rate almost similar to that of propan-2-ol, pointing to the non-participation of $\alpha$-C-H bond in the rate-determining step.
observations are in favour of the bromate forming an ester with the alcohol in a slow step which does not involve $\alpha$-C-H bond followed by decomposition of bromate-ester in a fast step, with $\alpha$-C-H bond cleavage not subjected to any steric influence of conformers (see Scheme 1).

\[ \begin{array}{c}
\text{H} \\
\text{C} \\
\text{OH} \\
\xrightarrow{\text{slow}} \\
\text{0} \\
\text{O} \\
\text{BrO}_2 \\
\xrightarrow{\text{fast}} \\
\text{H}_2\text{O} \\
\text{Br}^+ \\
\text{h} \\
\end{array} \]

\[ \begin{array}{c}
\text{Br}^{(III)} \\
\text{Br}^{(V)} \\
\text{Br}^{(II)} \\
\xrightarrow{\text{C} = \text{O}} \\
\text{BrO} \\
\end{array} \]

Scheme 1

Similar kinetic results about the insensitivity of reaction rates to structure in Br(V) oxidation of alcohols have been reported by earlier workers\textsuperscript{11}. This is in agreement with the observation that inorganic esterification of this type are not susceptible to structural variation in alcohol moiety\textsuperscript{12}. In contrast since Cr(VI) oxidation of alcohols, though presumed to proceed via a preformed chromate-ester, involves the cleavage of $\alpha$-C-H bond in the slow step, these reactions are susceptible to steric influences of conformers. The present oxidation reactions exhibit Arrhenius dependence suggesting that these are simple bimolecular reactions and the entropies of activation evaluated for dicyclohexylmethanol and borneol are positive, indicating greater disorder in the transition state.

References
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7 Natarajan R & Venkatasubramanian N. Int J chem Kinet, 8 (1979) 205.