Evidence that a dioxirane is not responsible for alkene epoxidation in a ketone–Oxone® system

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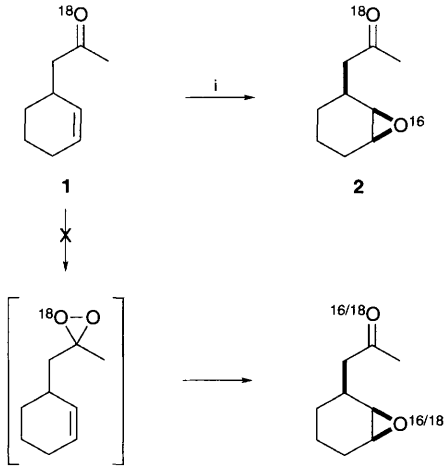
An ^{18}O labelling study shows that a dioxirane intermediate is probably not responsible for alkene epoxidation in a ketone-accelerated Oxone® epoxidation system.

The epoxidation of alkenes using Oxone® (active constituent $KHSO_5$) in a biphasic solvent system gives very poor conversion, but is catalysed by ketones.[1,2] In the absence of an alkene, the presence of a ketone accelerates the decomposition of $KHSO_5$ into sulfate ion and O_2, and experiments using ^{18}O labelled $KHSO_5$ have provided strong evidence that a dioxirane intermediate is involved.[3] Moreover, distillation of certain dioxiranes from the reaction mixture as dilute solutions in their parent ketone has allowed spectroscopic characterisation of these cyclic peroxides.[4] Since these isolated dioxirane solutions have been shown to be powerful reagents for alkene epoxidation, it has been not unreasonably assumed that dioxiranes are responsible for the epoxidation in the biphasic Oxone®–ketone system. Here we present experiments using an ^{18}O labelled ketone that suggest that this may not necessarily be the case.

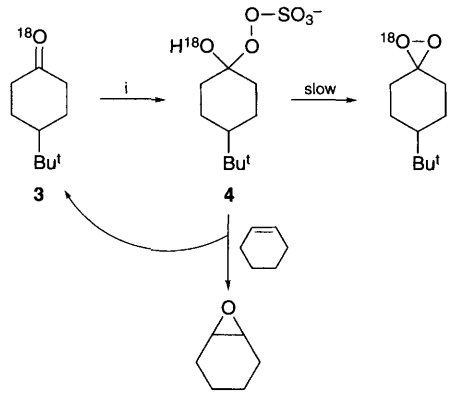
As part of our investigations into intramolecular dioxirane epoxidation reactions,[5] we recently developed conditions for the epoxidation of ketone **1** with the biphasic Oxone® system which afford only the *syn*-isomer **2** (Scheme 1).[6] Given that intermolecular epoxidation of **1** with dimethyldioxirane affords a mixture of *syn*- and *anti*-isomers,[5] and given also the known acceleration of Oxone® epoxidations by ketones,[1,2] we believed this reaction to be an example of intramolecular dioxirane epoxidation. As indicated in Scheme 1, a dioxirane intermediate in this process would require transfer of ^{18}O label from the carbonyl to the epoxide. Assuming that addition of $KHSO_5$ to the carbonyl group is non-stereoselective, a dioxirane intermediate would result in 50% label incorporation into the epoxide, providing that either of the diastereotopic oxygen atoms is geometrically capable of being transferred to the alkene. However, when ^{18}O labelled **1** was subjected to the reaction conditions, no such label transfer was observed by ^{13}C NMR or MS fragment analysis.

A problem inherent in this intramolecular epoxidation study is that it is not possible to measure directly the rate of background epoxidation of the alkene in the absence of ketone, and so it cannot be proven that the ketone is accelerating the epoxidation. We therefore decided to repeat the labelling study with an intermolecular system similar to those studied by other workers.[1,2] We chose to use 4-*tert*-butylcyclohexanone **3** in order to avoid problems with purification and isolation, particularly due to volatility, during the incorporation of ^{18}O label. Acid-catalysed hydrolysis of the dimethyl ketal of **3** in $H_2{}^{18}O$ (Aldrich, 95 atom% ^{18}O) resulted in *ca.* 50% label incorporation (by MS and ^{13}C NMR[7] analysis). Epoxidation was performed using a modification of the conditions reported by Curci[1] where pH was controlled using aqueous sodium bicarbonate buffer.[8]‡ The reaction was monitored by GC–MS. In the epoxidation of cyclohexene in the absence of ketone, the reaction was found to be 2% complete after 5 h. Under the same conditions, in the presence of 1 equiv. of labelled (50%) ketone **3**, the reaction was found to be 15% complete after the same time.§ This represents an acceleration of *ca.* 7 times over the background rate. However, GC–MS analysis showed no transfer of the ^{18}O label to the epoxide; importantly, there was also no loss of ^{18}O from the ketone carbonyl. A dioxirane is therefore probably not involved in this ketone-accelerated epoxidation.¶

A possible explanation for the lack of label transfer is that the tetrahedral species **4**, resulting from addition of HSO_5^- to the carbonyl group, is capable of alkene epoxidation (Scheme 2). Ring closure of **4** is likely to be the rate determining step in dioxirane formation. It is therefore possible that in the presence of an alkene, epoxidation by **4** is faster than ring closure to the dioxirane. This scenario explains both our labelling experiments and the earlier evidence for the involvement of dioxiranes in the decomposition of $KHSO_5$. There is precedent for epoxidation by species similar to **4** in the work of Rebek[9] on α-hydroxyperoxides, and in the α-silyloxyperoxide epoxidation



Scheme 1 *Reagents and conditions:* i, Oxone®. Bu_4NHSO_4, $(EDTA)Na_2$, 1 mol dm^{-3} aqueous $NaHCO_3$, CH_2Cl_2, 0 °C to room temp.



Scheme 2 *Reagents and conditions:* i, Oxone®. Bu_4NHSO_4, $(EDTA)Na_2$, 1 mol dm^{-3} aqueous $NaHCO_3$, CH_2Cl_2, 0 °C

studied by Saito.[10] We have also proposed such an intermediate as a possible epoxidising species in ketone-directed peracid epoxidation.[5]

In conclusion, we have shown that a dioxirane is not the species responsible for the observed acceleration in the biphasic ketone–Oxone® epoxidation of alkenes, at least for ketone **3** under these conditions. This important observation may stimulate further kinetic and mechanistic studies of this oxidation system, as well as theoretical calculations on the ability of species such as **4** to effect alkene epoxidation. Our results are also of importance from a synthetic viewpoint since it is crucial in the development of chiral ketones for catalytic asymmetric epoxidation and in the design of probes of transition state stereoelectronics that the nature of the oxidising species is well understood.

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Footnotes

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‡ We find that these conditions give similar results to those of Curci[1] for the epoxidation of cyclohexene with Oxone®–acetone and are experimentally much simpler. A solution of Oxone® (3.68 g, 12 mmol of $KHSO_5$) in distilled water (30 ml), with (EDTA)Na_2 (20 mg), was added in one portion to a biphasic solution of cyclohexene (0.52 ml, 5 mmol), tetrabutylammonium hydrogensulfate (400 mg, 1 mmol) and 4-*tert*-butylcyclohexanone (770 mg, 5 mmol) in CH_2Cl_2 (50 ml) and 1 mol dm^{-3} aqueous $NaHCO_3$ (17 ml) at 0 °C. Initial pH: 8.40, pH after Oxone® addition: 7.25. The reaction was stirred at 0 °C and followed at intervals by GC–MS (Fisons MD-800; DD-1 25 m × 0.25 mm column, film thickness 0.25 μm; 10 min at 30 °C, ramp at 20 °C min^{-1} to 150 °C, held at 150 °C for 30 min. Retention times: cyclohexene, 2.17 min; cyclohexene oxide, 7.42 min; ketone **3**, 15.77 min).

§ While this conversion may appear low, it should be noted that Curci[1] uses a large excess of acetone (10 equiv.) in his two-phase epoxidation studies. Denmark[2] has reported 50% conversion after 24 hours for epoxidation of *E*-6-benzyloxyhex-2-ene with Oxone® and 1 equiv. of acetone under rigorous pH control (pH stat).

¶ As a referee has pointed out, the possibility exists that addition to the carbonyl group of 4-*tert*-butylcyclohexanone occurs with high stereoselectivity, leading to a dioxirane with the ^{18}O predominantly in either the axial or the equatorial position. Lack of label transfer, as is observed, would then require that one of the two oxygens is transferred selectively to the alkene, which seems unlikely. Any primary kinetic isotope effect is likely to be small; k_{16O}/k_{18O} has been calculated as 1.073 for cleavage of a hypothetical C–O molecule at 25 °C, but observed values have been considerably lower.[11]

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