Preliminary Communication

The oxidation of secondary alcohols by dimethyldioxirane: re-examination of kinetic isotope effects

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Abstract

The kinetic isotope effects for the oxidation of a series of deuterated isopropanols and α-trideuteromethyl benzyl alcohol by dimethyldioxirane (**1**) to the corresponding ketones were determined in dried acetone at 23°C. A primary kinetic isotope effect (PKIE) of 5.2 for the oxidation of isopropyl-2-d alcohol by **1** was obtained. The SKIEs for oxidation of α-trideuteromethyl benzyl alcohol and isopropyl-1,1,1,3,3,3-d_6 alcohol were found to be 1.07 and 0.98, respectively. Oxidation of isopropanol-d by **1** yielded a k_{OH}/k_{OD} value of 1.12, which is similar to that previously reported for α-methylbenzyl alcohol-d. Both normal and inverse secondary kinetic isotope effect (SKIEs) are observed. Mechanistically, the results indicate that the process is more complex than the previously proposed models.

Keywords: dimethyldioxirane; isotope effects; secondary alcohol oxidation.

Introduction

Dimethyldioxirane (**1**) has been shown to be an extremely versatile oxygen-atom transfer reagent for the oxidation of a wide range of substrates under mild conditions (for selected reviews, see Curci, 1990; Adam et al., 1992; Adam and Hadjiarapoglou, 1993; Curci et al., 1995; Adam and Zhao, 2006). In addition, oxidations by **1** can be carried out conveniently either *in situ* (Corey and Ward, 1986; Adam et al.,

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1991; Denmark and Wu, 1998; Frohn et al., 1998) or in an isolated solution (Murray and Jeyaraman, 1985; Baumstark and McCloskey, 1987). The epoxidation of alkenes and heteroatom oxidation by isolated solutions of **1** in acetone have been extensively investigated (Murray and Jeyaraman, 1985; Baumstark and McCloskey, 1987; Baumstark and Vasquez, 1988; Winkeljohn et al., 2004, 2007). Dioxiranes can also insert oxygen into unactivated CH bonds of alkanes (Murray et al., 1986). However, this important reaction generally requires a dioxirane more reactive than dimethyldioxirane to be of utility (Kuck et al., 1994; D'Accolti et al., 2003). The oxidation of secondary alcohols by dimethyldioxirane, **1**, to ketones can be achieved in high yield under mild conditions and with convenient reaction times (Kovac and Baumstark, 1994; Cunningham et al., 1998; Baumstark, 1999). Two mechanistic extremes have been proposed for secondary alcohol oxidation by **1**: a) concerted insertion (Mello et al., 1991; Angelis et al., 2001) and b) direct radical-cage processes (Kovac and Baumstark, 1994). Computational model studies (Shustov and Rank, 1998; Freccero et al., 2001) on dioxirane oxyfunctionalization of C-H bonds have been carried out and seem to support a stepwise process. Reported kinetic isotopic studies have come to differing conclusions concerning the secondary alcohol oxidation process: the initial study (Kovac and Baumstark, 1994) favored a radical-cage process while a subsequent study (Angelis et al., 2001) supported a concerted mechanism. We report here a re-examination of the kinetic isotope effects for the oxidation of selected secondary alcohols by dimethyldioxirane.

Results and discussion

The reaction of dimethyldioxirane (**1**, in excess) with 2-propanol (**2**), isopropyl-2-d alcohol (**3**), isopropyl-1,1,1,3,3,3-d_6 alcohol (**4**), 2-propanol-d (**5**), α-methyl benzyl alcohol (**6**), and α-trideuteromethyl benzyl alcohol (**7**) (Rxn 1) produced the corresponding ketones in excellent yields. The products were characterized (where possible) by gas chromatograhy/mass spectrometry (GC/MS) data and by comparison of spectra properties with those of authentic samples. The reaction was of the second order overall, first order in both dioxirane and alcohol. Pseudo-first order kinetic studies were carried out in dried acetone with at least a 10-fold excess of the secondary alcohol at 23.0±0.3°C employing ultraviolet methodology. For all cases excellent pseudo-first order plots were obtained (r values were greater than 0.99). Reproducibility between the kinetics runs of the k_2 values was excellent,

Table 1 Kinetic isotope effects for the reaction of secondary alcohols **2–7** with **1** at 23°C in dried acetone.

Compound number	Structure	k_2/M/s	Kinetic isotope effect
2	$CH_3CHOHCH_3$	$1.62\pm0.01\times10^{-2}$	$k_H/k_D=5.2\pm0.1$
3	$CH_3CDOHCH_3$	$0.31\pm0.01\times10^{-2}$	
4	$CD_3CHOHCD_3$	$1.67\pm0.01\times10^{-2}$	$k_{CH3}/k_{CD3}=0.98\pm0.01$
5	$CH_3CHODCH_3$	$1.46\pm0.01\times10^{-2}$	$k_{OH}/k_{OD}=1.12\pm0.01$
6	$PhCHOHCH_3$	$2.17\pm0.06\times10^{-2}$	$k_{CH3}/k_{CD3}=1.07\pm0.05$
7	$PhCHOHCD_3$	$2.02\pm0.02\times10^{-2}$	

Table 2 Summary of PKIE data for the oxidation of secondary alcohols by **1**.

Entry	Alcohol/deuterated alcohol	Method (T)	k_H/k_D	Reference/Comment
1	$CH_3CHOHCH_3/CH_3CDOHCH_3$	Kinetics (23°C)	5.23	Current results
2	$PhCHOHCH_3/PhCDOHCH_3$	Kinetics (25°C)	3.55	(Kovac and Baumstark, 1994)
3	$PhCHOHCD_3/PhCDOHCD_3$	GC (0°C)	3.6	(Angelis et al., 2001); SKIE effects included
4	$CF_3ArCHOHCH_3/CF_3ArCDOHCH_3$	NMR (0°C)	4.8	(Angelis et al., 2001)
5	$PhCH_2OH/PhCD_2OH$	NMR (0°C)	4.6	(Angelis et al., 2001); SKIE effect included
6	$PhCH_2OH/PhCHDOH$	NMR (0°C)	4.5	(Angelis et al., 2001); SKIE effect included

NMR, nuclear magnetic resonance spectroscopy.

generally 1–2%. Second-order rate constants (k_2 values) obtained with a 10-fold excess of dioxirane yielded data consistent with those with excess alcohol but with a larger error range. The primary kinetic isotope effect (PKIE) results for the oxidation of isopropanol (**2/3**) was found to be 5.2. The overall secondary kinetic isotope effect for the double CD_3 formal substitution (**2/4**) was found to be inverse, while that
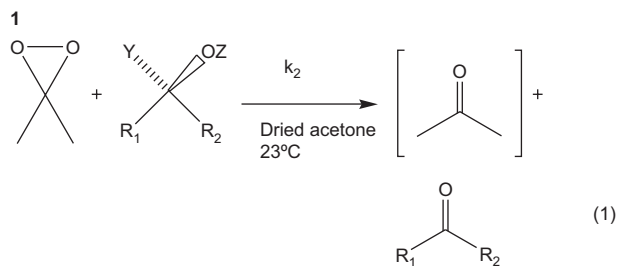
2 $R_1=R_2=Me, Y=Z=H$
3 $R_1=R_2=Me, Y=D, Z=H$
4 $R_1=R_2=CD_3, Y=Z=H$
5 $R_1=R_2=Me, Y=H, Z=D$
6 $R_1=Ph, R_2=Me, Y=Z=H$
7 $R_1=Ph, R_2=CD_3, Y=Z=H$

for single CD_3 formal substitution (**6/7**) was found to be normal. The secondary kinetic isotope effect for deuteration of the alcohol proton on isopropanol (**2/5**) was normal: 1.12. The results for compounds **2-7** are summarized in Table 1.

The current PKIE of 5.2 for oxidation of the secondary aliphatic alcohol **3** to a ketone is in good agreement with those in the literature. The published data for the oxidation of various

secondary alcohols by dioxirane **1** fall in the range of 3.6 to 4.6. Clearly, all the data are consistent with breaking the secondary C-H of the alcohol in the rate-determining step (rds) of rxn 1. The current and published PKIE results for secondary alcohol oxidation by **1** are summarized in Table 2.

Differentiation between the proposed mechanistic extremes (concerted-direct insertion vs. radical-cage models) is focused on expectations of the secondary kinetic isotope effects (SKIE) for each process. Scheme 1 shows the expected transition states for the extremes. An inverse SKIE would be expected for the concerted route and a normal value for the other. The current and previous SKIE results for the oxidation of secondary alcohols by **1** are summarized in Table 3.

In general, the current and published isotope effect data are in good agreement, except for the SKIE effect measured for α-trideuteromethyl benzyl alcohol oxidation. Entries 4 and 5 appear to be contradictory, but the discrepancy may be due to
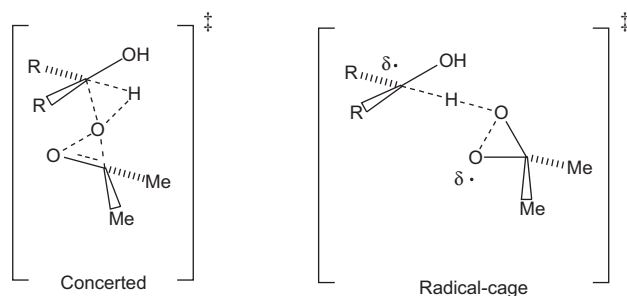

Scheme 1 Expected transition states for rds for concerted and radical-cage mechanisms of secondary alcohol oxidation by **1**.

Table 3 Summary of 'secondary' kinetic isotope effect data for oxidation of secondary alcohols by **1**.

Entry	Alcohol/deuterated alcohol	Method (T)	Isotope effect
1	$CH_3CHOHCH_3$/$CH_3CHODCH_3$	Kinetics (23°C)	k_{OH}/k_{OD}=1.12±0.02
2	$PhCHOHCH_3$/$PhCHODCH_3$	Kinetics (25°C)	k_{OH}/k_{OD}=1.09±0.06 (Kovac, 1994)
3	$CH_3CHOHCH_3$/$CD_3CHOHCD_3$	Kinetics (23°C)	k_{CH3}/k_{CD3}=0.98±0.01
4	$PhCHOHCH_3$/$PhCHOHCD_3$	Kinetics (23°C)	k_{CH3}/k_{CD3}=1.07±0.04
5	$PhCHOHCH_3$/$PhCHOHCD_3$	GC (0°C)[a]	k_{CH3}/k_{CD3}=0.98±0.02 to 1.01±0.02 (Angelis et al., 2001)
6	$PhCH_2CHOHCH_3$/$PhCD_2CHOHCD_3$	GC (0°C)[a]	k_{H5}/k_{D5}=0.98±0.02 to 1.01±0.02 (Angelis et al., 2001)

[a]Via product studies.
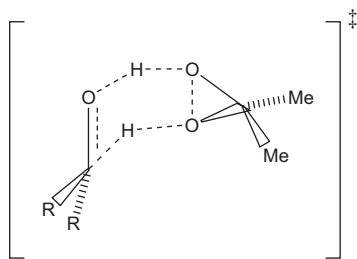
Scheme 2 Proposed multi-centered transition state for the concerted oxidation of secondary alcohols by **1**.

assumptions in the data handling. Entry 4 is based on kinetics measuring the overall disappearance of dioxirane during the reaction. On the other hand, entry 5 is based on product studies. The authors verify that α-hydroxy acetophenone is a minor product. They conclude that it is formed by a minor radical-chain process (irrelevant to the observed mechanism and thus excluded). This assumption affects the calculation of the secondary isotope effects. In effect, the conversion of the alcohol would appear to be reflected in the lower observed yield of acetophenone relative to that of acetophenone-2,2,2-d_3. The outcome of the assumption results in calculated secondary isotope effects for entry 5, Table 3 that would be inverse rather than normal.

The 'absence' of a β secondary isotope result in Angelis et al. (2001) was taken to support a concerted mechanism for reaction 1. The observed effects were interpreted not to be consistent with the earlier proposed caged-radical process. Clearly, the situation is complex with both normal and inverse secondary isotope observed depending on structure. The k_{OH}/k_{OD} results may offer a key insight since the values are significantly larger than expected for a simple secondary effect. Furthermore, secondary isotope effects for deuteration on one or both of the R groups yield normal or inverse effects, respectively. The suggested mechanistic extremes do not predict the observed outcomes. We propose that a novel concerted process in which both the secondary C-H and the O-H hydrogen atoms are abstracted in a multi-centered transition state (Scheme 2) could account for all the KIE data.

In this interpretation, the observed k_{OH}/k_{OD} result would be considered a small primary effect due to the geometry of that abstraction. The complex secondary effects noted for deuteration on the R groups would be due to the positioning of the dioxirane in the transition state. Of course, an explanation in which a caged-radical with a strong hydrogen-bonding component cannot be excluded. Computational modeling studies will need to be carried out to evaluate this novel process.

Acknowledgements

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