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Oxidation of benzyl alcohols by dimethyldioxirane. The question of concerted versus stepwise mechanisms probed by kinetic isotope effects

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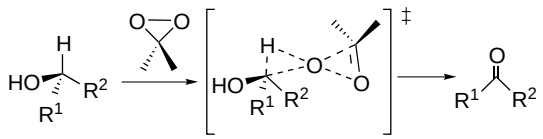
Abstract—The primary and β-secondary kinetic isotope effects in the oxidation of secondary alcohols with dimethyl dioxirane were measured. The substantial primary and the absence of a β-secondary kinetic isotope effect support a concerted mechanism for the title reaction.

Dimethyldioxirane (DMD) and its trifluoromethyl analogue (TFMD) are very potent oxidizing agents.[1] They react stereoselectively under mild conditions with alkenes to produce epoxides with nonactivated hydrocarbons to insert an oxygen atom, whereas with alcohols they afford carbonyl products. Several mechanisms for the oxidation of secondary alcohols by dioxirane have been reported. For example, Curci and co-workers[2] proposed an electrophilic one-step insertion mechanism (Scheme 1) and excluded a radical-chain pathway. Similar conclusions support later studies involving the 'radical clock' test.[3]

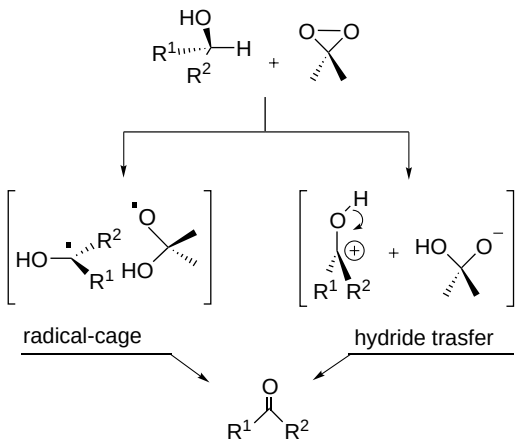
Baumstark and Kovăc, based on results involving Hammett correlations, primary isotope effects and the characterization of a minor product of this reaction, suggested a radical-cage mechanism.[4] However, they stated that a concerted insertion process cannot be excluded. More recently, computational work by Rauk and Shustov suggested[5] that the regioselectivity of the title reaction may be rationalized by a hydride-like transfer mechanism. Both reactive intermediates proposed earlier are shown in Scheme 2.

The controversy in the literature regarding the mechanism of the synthetically useful[6] DMD oxidation of alcohols, as well as our own mechanistic study on the DMD epoxidation of alkenes,[7] prompted us to investigate the nature of the transition state of the title reaction. In this paper we report the primary and, for the first time, the β-secondary isotope effect of the DMD oxidation of alcohols and discuss the mechanism of this reaction.[8]

Phenylethanols **1-d$_0$**, **2-d$_0$** and benzyl alcohol **3-d$_0$**, as well as their deuterated analogues **1-d$_4$**, **2-d$_1$**, **3-d$_2$** and **4-d$_1$** were suitable substrates for the measurement of the



Scheme 1. Concerted mechanism for the DMD oxidation of alcohols.



Scheme 2. Proposed radical and polar intermediates for the DMD oxidation of alcohols.

Keywords: dioxiranes; isotope effects; mechanisms.

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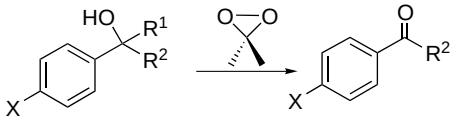
Table 1. Inter- and intramolecular primary isotope effects of DMD oxidation of secondary alcohols **1**, **2**, **3** and **4**



X	R^1	R^2	
H	H	CH_3	**1-d$_0$**
H	D	CD_3	**1-d$_4$**
CF_3	H	CH_3	**2-d$_0$**
CF_3	D	CH_3	**2-d$_1$**
H	H	H	**3-d$_0$**
H	D	D	**3-d$_2$**
H	D	H	**4-d$_1$**

Entry	Substrate	% Conversion	k_H/k_D
1	**1-d$_0$/1-d$_4$**	8	3.6±0.1[a]
		15	3.6±0.1[a]
		32	3.6±0.1[a]
2	**2-d$_0$/2-d$_1$**	20	4.8±0.2[b]
		31	4.8±0.2[b]
3	**3-d$_0$/3-d$_2$**	8	4.5±0.2[b]
		23	4.6±0.2[b]
4	**4-d$_1$**	7	4.4±0.2[b]
		18	4.5±0.2[b]

[a] The values of the isotope effect were determined by GC.
[b] Determined by ^{1}H NMR integration of the appropriate signals.

primary inter- and intramolecular isotope effects (Table 1). Equimolar quantities of protio and deutero substrates were dissolved in acetone as the solvent. Small quantities of DMD in acetone (0.05–0.1 M) were added to the reaction mixture at 0°C. The reaction was monitored by gas chromatography. The inter- (entries 1, 2 and 3) and intramolecular (entry 4) isotope effects were measured by gas chromatography or ^{1}H NMR integrations of the signals of the carbonyl products or the remaining starting alcohols and the k_H/k_D values were calculated[9] according to Eq. (1).† Reactions were run to less than 32% conversion to products. These results are summarized in Table 1.

The primary intermolecular isotope effect, k_H/k_D, which is the result of an intermolecular isotopic competition between **2-d$_0$** and **2-d$_1$**, is proportional to the ratio of protio/deutero carbonyl products.

$$\frac{k_H}{k_D}=\frac{\log[1-H_r/H_t]}{\log[1-D_r/D_t]} \quad (1)$$

In entry 1, the advantage of the **1-d$_4$** analogue instead of **1-d$_1$** for the intermolecular competition between **1-d$_0$** versus **1-d$_4$** is that both the ratio of the oxidation products acetophenone-d_0/acetophenone-d_3, as well as the ratio of the remaining benzylic alcohols **1-d$_0$/1-d$_4$** may be accurately determined by the areas under their well-separated capillary column GC signals‡ (Fig. 1). In this case, a small β-secondary IE could contribute to the total measured isotope effect; however, as shall be discussed later, the negligible β-secondary isotope effect influences little, if at all, the total value of the primary isotope effect. The GC retention times of the products and starting materials matched those of the authentic samples, as confirmed by control experiments.

The substantial kinetic and product isotope effects in the inter- and intramolecular competition (Table 1) support a concerted one-step reaction, i.e. TS_I in Scheme 3, with C–H(D) bond breaking in the rate-determining step. These results are consistent with previous findings[1] and support a one-step mechanism for

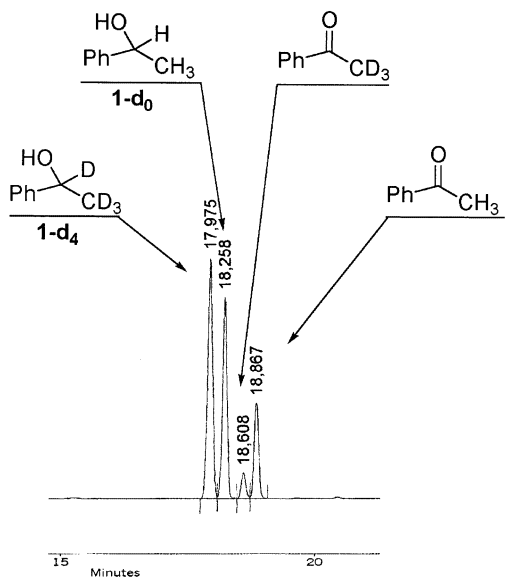
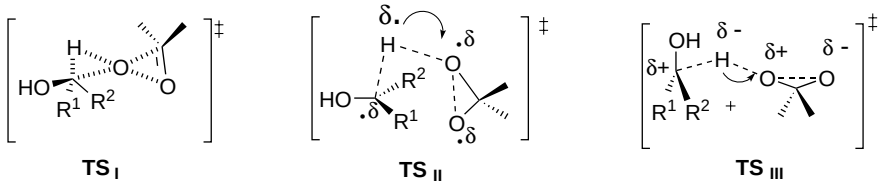


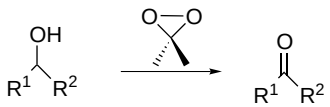
Figure 1. Primary isotope effect measurements of **1-d$_0$** versus **1-d$_4$** determined by the areas under the product signals on a 60 m GC (5% phenyl methylpolysiloxane) capillary column.

† For example, H_r and D_r are the amounts of products **1-d$_0$** and **1-d$_4$**, H_t and D_t are the initial amounts of **1-d$_0$** and **1-d$_4$**.
‡ The GC response factors for the deuterated and the nondeuterated substances were measured against methyl benzoate as internal standard; the relative response factors were in the range of 1.00–1.02.



Scheme 3. Proposed concerted, diradical- and dipolar-type transition states for the DMD oxidation of alcohols.

Table 2. β-Secondary kinetic isotope effects



R^1	R^2	
Ph	CH_3	**1-d$_0$**
Ph	CD_3	**1-d$_3$**
$PhCH_2$	CH_3	**6-d$_0$**
$PhCD_2$	CD_3	**6-d$_5$**

Entry	Substrate	% Conversion	k_H/k_D[a]
1	**1-d$_0$/1-d$_3$**	6	1.00±0.02
		11	0.99±0.02
		18	1.01±0.02
		32	0.98±0.02
2	**6-d$_0$/6-d$_5$**	4	0.98±0.02
		8	0.99±0.02
		17	1.01±0.02
		35	0.98±0.02

[a] The values of the isotope effects were determined by GC analysis of the product or the remaining starting alcohol signals; each value is the average of three consecutive measurements; the error was ±2%.

the DMD oxidation of secondary alcohols or hydrocarbons.[1]

However, these and previous[2,4] results on primary isotope effects cannot exclude the intervention of a diradical or dipolar intermediates with CH(D) bond breaking in the transition states TS_{II} and TS_{III}, as shown in Scheme 3.

To probe the mechanism further and obtain information on the formation of diradical or dipolar intermediates, we measured the β-secondary intermolecular isotope effects of this DMD-alcohol oxidation. For this purpose, 1-phenylethanol (**1-d$_0$**) and 1-phenyl-2-propanol (**6-d$_0$**) with their deuterated analogues 1-phenylethanol-2,2,2-d_3 (**1-d$_3$**) and 1-phenyl-2-propanol-2,2,3,3,3-d_5 (**6-d$_5$**) were prepared. The k_H/k_D values for the intermolecular secondary isotope effect were obtained from the equimolar competition of **1-d$_0$** versus **1-d$_3$** and **6-d$_0$** versus **6-d$_5$** by DMD. The experimental and analytical conditions were similar to those described here for the measurements of the primary isotope effect; again the product ratio is proportional to the k_H/k_D isotope effect. Analogously, the β-secondary IE (k_H/k_D) was determined from the area of the appropriate capillary column GC signals of the carbonyl products; these results are summarized in Table 2.

A typical capillary column gas chromatographic analysis of the unreacted 1-phenyl-2-propanols **6-d$_0$** and **6-d$_5$** and their carbonyl products, after oxidation, are shown in Fig. 2. The small inverse isotope effects found in the intermolecular competition between **1-d$_0$** and **1-d$_3$**, as well as in **6-d$_0$** and **6-d$_5$**, exclude the formation of a

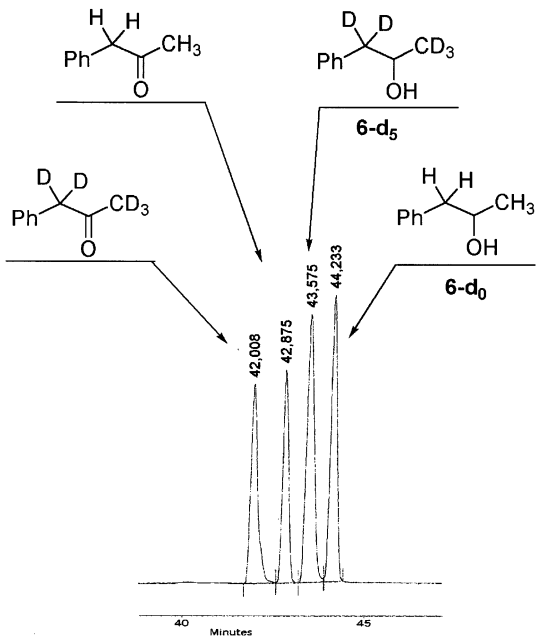


Figure 2. GC capillary column (5% phenyl methylpolysiloxane) determination of the β-secondary isotope effects by the areas under the appropriate product or the remaining alcohol signals.

diradical- or dipolar-type transition state TS_{II} and TS_{III}, as shown in Scheme 3.

In the transition states TS_{II} and TS_{III}, the hyperconjugative effect of the five hydrogen atoms in **6-d$_0$** versus the five deuterium atoms in **6-d$_5$** are expected to give a substantial normal secondary IE ($k_H/k_D \approx 1.03$–1.1 per deuterium atom), as found in the oxidation of propanol by organo ruthenium(III) complexes[10] and in the dipolar cycloadditions of TCNE to 2,4-dimethylhexadiene.[11]

The results are consistent with a concerted mechanism, as shown in TS_I (Scheme 3). In the nonpolar transition state TS_I, the steric interactions in going from a less crowded ground state to a more crowded transition state would lead to a small inverse secondary IE, as found. This inverse β-secondary isotope effect is comparable to previously calculated[12] or measured ones for other reactions,[13] which were taken as support for a concerted mechanism.

The small amount of α-hydroxy acetophenone (2–3%), which was observed previously[4] in the DMD oxidation of 1-phenylethanol and confirmed by us, may be formed by a minor radical-chain process, which is irrelevant to the major concerted oxidation mechanism. Thus, in conclusion, the present isotope effects (primary and β-secondary), when taken in conjunction, exclude the formation of any diradical- or dipolar-type intermediate and suggest a concerted transition state for the DMD oxidation of alcohols.

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