

UNUSUALLY LARGE KINETIC DEUTERIUM ISOTOPE EFFECTS ON OXIDATION REACTIONS. 1. THE MECHANISM OF HYDROXIDE-CATALYSED PERMANGANATE OXIDATION OF PhCD(CF₃)OH AND PhCD(CH₃)OH IN WATER*

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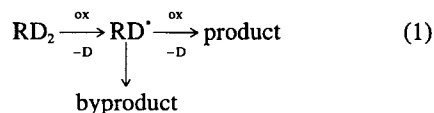
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The oxidation of 1-phenyl-2,2,2-trifluoroethanol (ROH) with potassium permanganate in 0.2 M aqueous sodium hydroxide solution at 25 °C provides 2,2,2-trifluoroacetophenone as the sole product. The reaction rate constant, which was measured under pseudo-first order conditions by following the decrease in substrate concentration as a function of time, was found to be substantially smaller than previously reported. The primary kinetic deuterium isotope effect was measured as $k_2^H/k_2^D = 14.7 \pm 1.0$. A hydrogen-transfer mechanism involving significant tunnelling is proposed. The oxidation of 1-phenylethanol under similar reaction conditions yields acetophenone as the initial product. The kinetic deuterium isotope effect was found to be $k_2^H/k_2^D = 5.2 \pm 0.8$.

INTRODUCTION

Oxidation reactions constitute a large group of reactions with an extensive mechanistic spectrum.¹ Studies of oxidation reaction mechanisms frequently include measurements of kinetic deuterium isotope effects. In principle, there are three plausible rate-limiting transfers which can result in a primary kinetic deuterium isotope effect in these reactions, namely hydride transfer, hydrogen transfer and hydron transfer accompanied by electron transfer. Some of the kinetic deuterium isotope effects reported in the literature for oxidation reactions are unusually large, i.e. they are larger than predicted by 'classical' theory. A large tunnel correction or some type of branched reaction mechanism is required to explain these unusually large kinetic deuterium isotope effects.

For example, the type of branched mechanism shown schematically in the equation



may result in extreme kinetic deuterium isotope effects.² Thus, a normal, substantial kinetic isotope effect on the

first oxidation step to give the intermediate RD*, followed by branching to product and byproduct having different isotope effects, can give rise to an unusually large kinetic deuterium isotope effect on the overall rate of product formation. Moreover, an unusually small kinetic isotope effect on the overall rate of formation of the byproduct is observed under these conditions.² Also, other types of branching may give rise to extreme isotope effects.²

The present study was initiated with the intention of thoroughly investigating the mechanisms of selected oxidation reactions which have been reported to exhibit unusually large kinetic deuterium isotope effects. Are the unusually large isotope effects due to more complex reaction mechanisms such as branching or are they caused by extensive tunnelling? If the cause is tunnelling, what are the factors which favour tunnelling in these cases? It is hoped that these studies will provide new insight into the complex mechanisms of oxidation reactions.

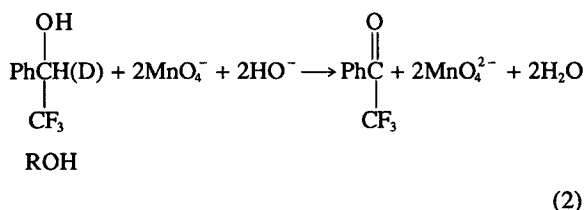
The present paper is the first report from this study. It is a re-examination of the hydroxide-catalysed oxidation of 1-phenyl-2,2,2-trifluoroethanol (ROH) by permanganate ion in water. In previous studies,^{3,4} the reaction was followed by measuring the decrease in

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oxidant concentration with time. A different technique was utilized in the present investigation which allows both the changes in substrate concentration and the product concentration to be monitored during the course of reaction. The same technique has also been used to study the hydroxide-catalysed oxidation of 1-phenylethanol; no previous kinetic study of this reaction seems to have been reported. The mechanistic implications of the results are discussed.

RESULTS

The reaction of 1-phenyl-2,2,2-trifluoroethanol (ROH) with potassium permanganate in 0.2 M aqueous sodium hydroxide solution at 25 °C provides 2,2,2-trifluoroacetophenone as the sole product [equation (2)]:



In water, this product is rapidly converted to the hydrated form $\text{PhC}(\text{CF}_3)(\text{OH})_2$.⁵ The kinetics of the reaction were studied by a sampling-quench, high-performance liquid chromatography procedure. Thus, the decrease in concentration of substrate ROH (actually the sum of $[\text{ROH}]$ and $[\text{RO}^-]$) and the increase in product concentration were followed as functions of time. The reaction was of pseudo-first order type since the concentration of permanganate ion was much larger than the concentration of substrate, $[\text{MnO}_4^-]_0 \gg 20 \times [\text{ROH}]_0$. The reaction requires 2 mol of permanganate per mole of product [equation (2)].⁴

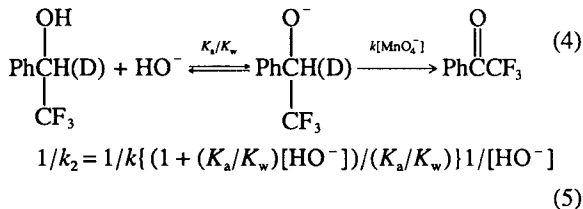
The reaction follows the rate law of equation (3):

$$\begin{aligned} \text{Rate} &= k_{\text{obs}}([\text{ROH}] + [\text{RO}^-]) = k_2[\text{MnO}_4^-]([\text{ROH}] + [\text{RO}^-]) \\ &= k_3[\text{HO}^-][\text{MnO}_4^-]([\text{ROH}] + [\text{RO}^-]) \end{aligned} \quad (3)$$

The rate constant k_{obs} was measured at constant pH. The results are presented in Table 1 and confirm that the reaction is first order in oxidant. The reaction is also first order in substrate. This was checked by using a much higher concentration of deuteriated substrate (Table 1).

Stewart and van der Linden⁴ have studied the effect of hydroxide concentration on the observed rate constants. In dilute hydroxide ion solution, the observed pseudo-second-order rate constant (k_2) for the oxidation of the alcohol increases in an approximately linear manner with increasing hydroxide ion concentration. In more concentrated solutions of hydroxide ion, the rate-constant increase levels off to a nearly constant value.

This can be attributed to the conversion of the alcohol to the alkoxide anion with the dissociation constant K_a ; the latter undergoes oxidation:



A plot of $1/k_2$ against $1/[\text{HO}^-]$ according to equation (5), employing previously published data,⁴ gives the second-order rate constant for oxidation of the alkoxide anion, $k \approx 8.7 \text{ M}^{-1} \text{ s}^{-1}$, from the ordinate intercept and $K_w/(K_a k) = 1/k_3$ as the slope (Figure 1), which gives $k_3 \approx 580 \text{ M}^{-2} \text{ s}^{-1}$ and $\text{p}K_a = 12.2$ based on $K_w = 10^{-14}$. The same treatment of the data for the deuteriated substrate (Figure 2) gives $k_3^D \approx 30 \text{ M}^{-2} \text{ s}^{-1}$, $k^D \approx 0.52 \text{ M}^{-1} \text{ s}^{-1}$ and $\text{p}K_a^D = 12.2$. A value of $\text{p}K_a = 11.9$ has been measured by spectrophotometry.⁵

The oxidation of the alkoxide anion follows the rate laws

$$\begin{aligned} \text{Rate} &= k[\text{MnO}_4^-][\text{RO}^-] + k(K_a/K_w)[\text{HO}^-][\text{MnO}_4^-][\text{ROH}] \\ &= k \{ (K_a/K_w) / (1 + (K_a/K_w)[\text{HO}^-]) \} \\ &\quad \times [\text{HO}^-][\text{MnO}_4^-]([\text{ROH}] + [\text{RO}^-]) \end{aligned} \quad (6)$$

Thus $k_{\text{obs}} = k_2[\text{MnO}_4^-]$ and

$$k_2 = k \{ (K_a/K_w) / (1 + (K_a/K_w)[\text{HO}^-]) \} [\text{HO}^-] \quad (7)$$

$$k_3 = k \{ (K_a/K_w) / (1 + (K_a/K_w)[\text{HO}^-]) \} \quad (8)$$

Addition of sodium acetate has no effect on the reaction rate (Table 1).

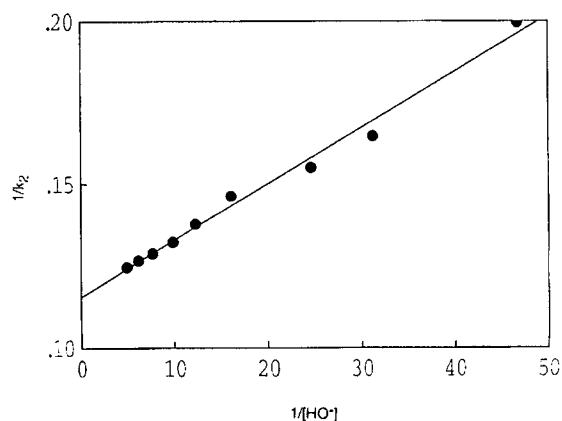


Figure 1. Dependence of the pseudo second-order rate constant for reaction of $\text{PhCH}(\text{CF}_3)\text{OH}$ on the hydroxide ion concentration. Data from Ref. 4

Table 1. Rate constants and isotope effects for the oxidation of 1-phenyl-2,2,2-trifluoroethanol (ROH)^a and 1-phenylethanol^b by KMnO₄ in aqueous sodium hydroxide^b at 25 °C

Compound	[KMnO ₄] (μM)	10 ⁶ k _{obs} ^H (s ⁻¹)	10 ⁶ k _{obs} ^D (s ⁻¹)	k ₂ ^H (M ⁻¹ s ⁻¹)	k ₂ ^D (M ⁻¹ s ⁻¹)	k ₂ ^H /k ₂ ^D
1-Phenyl-2,2,2-trifluoroethanol	504	1583	108.0	3.14	0.214	14.7 ± 1.0 ^c
	3030		643		0.212	
	4040		874		0.216	
	4040		886 ^d		0.213 ^d	
	4040		887 ^e			
1-Phenylethanol	1020 ^f			7.5 ^f	0.47 ^f	16.0 ^f
	1410	1461		1.04		5.2 ± 0.8 ^c
	1410		281		0.199	
	2020	~61 ^g		0.03 ^g		

^a Substrate concentration 26 μM.

^b [NaOH] = 0.2 M.

^c Maximum error including maximum systematic errors and random errors.

^d Substrate concentration 204 μM.

^e Sodium acetate added, [NaOAc] = 0.2 M.

^f Data of Stewart and van der Linden,⁴ obtained under pseudo-second-order rate conditions at 25.2 °C by following the decrease in oxidant by iodometric titration; substrate concentration was 510 μM.

^g Without addition of sodium hydroxide.

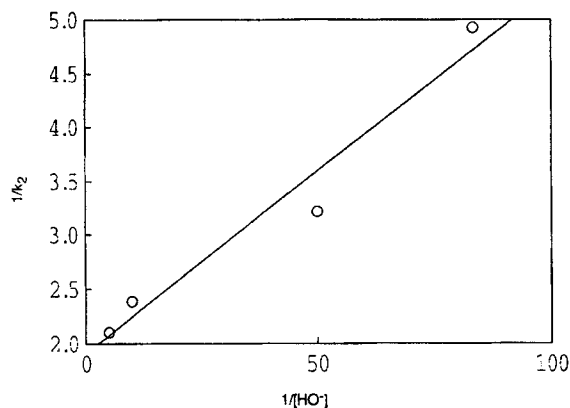
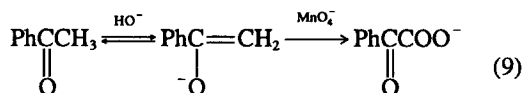


Figure 2. Dependence of the pseudo second-order rate constant for reaction of PhCD(CF₃)OH on the hydroxide ion concentration. Data from Ref. 4

The reaction of 1-phenylethanol with potassium permanganate in 0.2 M aqueous sodium hydroxide solution at 25 °C provides acetophenone as the initial product. This reaction is analogous to that of ROH [equation (2)]. However, the acetophenone is not stable under these conditions but is rapidly oxidized further to benzoylformic acid in basic solution,¹ which requires six more equivalents of permanganate ion:



For this reason, the reaction solution was made more concentrated in KMnO₄ to maintain pseudo-first-order behaviour. A maximum concentration of a few per cent

of acetophenone is achieved after a short reaction time. The reaction was studied by the same method as described above for the trifluoro analogue. The reaction conditions and rate data are presented in Table 1. The reaction in neutral solution is about 30 times slower. The acetophenone product is stable under these conditions.

DISCUSSION

The measured rate constants for the trifluoro alcohol ROH are lower than those reported under second-order conditions by Stewart and van der Linden:⁴ 2.4 times for k₂^H and 2.2 times faster for k₂^D (Table 1). The explanation of these differences, which are much larger than expected from the temperature difference of 0.2 °C (Table 1), is not known but is probably attributable to differing experimental techniques. Kinetic studies under second-order conditions using an iodometric procedure require knowledge of the exact stoichiometry of the reactions involved, which can be a source of error. A larger, but presumably not significantly larger, kinetic deuterium isotope effect was measured previously: k₂^H/k₂^D = 16.0, compared with 14.7 ± 1.0 measured in this study. The large isotope effect is presumably not caused by a type of reaction branching,² since the reaction does not yield a detectable amount of byproduct.

The rate constant k₂ is a product of the rate constant k for the oxidation step and a factor (f) which is a function of the acidity of the substrate and the hydroxide concentration [equation (7)]. However, the pK_a of the protium substrate ROH is, within experimental error, the same as the pK_a of the deuterium substrate.⁴ Accordingly, the isotope effect ratio f^H/f^D should be very close to unity at [HO⁻] = 0.2 M, inferring that the measured isotope effect on k₂ is equal to the isotope effect on the oxidation rate

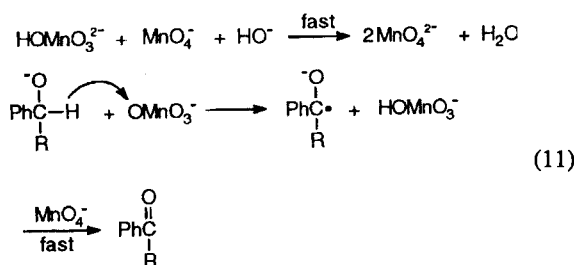
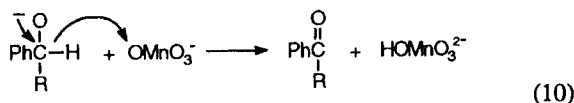
constant k for the alkoxide ion, i.e. $k_2^H/k_2^D = k^H/k^D$. A difference in pK_a of $pK_a^D - pK_a^H = 0.1$ corresponds to $f^H/f^D = 1.02$, i.e. k_2^H/k_2^D is 2% larger than k^H/k^D .

The isotope effect ratio f^H/f^D is presumably larger for the 1-phenylethanol reaction owing to a larger pK_a of 1-phenylethanol (which could be estimated as 15.5)⁶ and to a presumably larger difference in pK_a of labelled and unlabelled alcohol than for the trifluoro analogues. The assumption of a pK_a difference for 1-phenylethanol of $pK_a^D - pK_a^H = 0.1$ corresponds to $f^H/f^D = 1.26$ at 0.2 M hydroxide concentration, i.e. the measured isotope effect of $k_2^H/k_2^D = 5.2$ is 26% larger than the oxidation isotope effect k^H/k^D . Accordingly, the isotope effect k^H/k^D for the oxidation of the anion of 1-phenylethanol could be as small as about 4.

The difference between the pK_a value of 12.2 and the estimated pK_a of 15.5 for 1-phenylethanol⁶ indicates that the three fluoro substituents in the methyl group stabilize the alkoxide anion by *ca* 3.2 pK_a units, i.e. about 4.4 kcal mol⁻¹ (1 kcal = 4.184 kJ).

The large isotope effects measured for the two alcohols show that the rate-limiting steps must involve transfer of hydrogen, either as a hydron, a hydrogen atom or a hydride anion. The experimental results also clearly show that the alkoxide ion RO⁻, and not the alcohol ROH, is the species which undergoes oxidation [Figure 1 and equation (4)]. Thus, the termolecular processes discussed previously,^{4,7} such as a mechanism involving concerted abstraction of the hydron by hydroxide ion and electron transfer to permanganate ion or a mechanism in which hydroxide ion attacks the central carbon as a nucleophile coupled with hydride transfer to the permanganate ion, can be ruled out.

The simplest oxidation mechanism consistent with the results of Table 1 is a direct hydride transfer from the alkoxide anion to the oxidant in a single-step process [equation (10)]. An alternative is a two-step mechanism [equation (11)] in which hydrogen transfer occurs in the first step to give the radical anion. In the subsequent step, an electron is rapidly transferred to a second permanganate ion. The mechanisms require two moles of permanganate ion for the oxidation process.



Different sensitivities to ring substituents are expected for the two mechanistic alternatives. Electron-donating groups should accelerate the reaction if the hydride-transfer mechanism prevails, but hydrogen transfer should show relatively small substituent effects. Stewart and van der Linden⁴ measured very small rate effects of substituents in the aromatic ring of ArCH(CF₃)OH and the results should therefore exclude the hydride-transfer mechanism for ROH. Thus, the reaction should follow the hydrogen-transfer mechanism shown in equation (11).

It has been suggested that the oxidation of alcohols may follow both mechanisms.⁸ Easily oxidized compounds may react by the hydride transfer mechanism [equation (10)] but more unreactive substrates may undergo hydrogen transfer [equation (11)]. However, no supporting indications seem to have been reported.

Why is an unusually large isotope effect measured for ROH? A maximum loss of zero-point energy of stretching and bending vibrations in the transition state may account, at most, for an isotope effect of about 12.⁹ Hence, the result of the present study should require tunnelling. Substantial tunnelling seems reasonable owing to the following. An electron-withdrawing group such as trifluoromethyl retards the oxidation of alkoxide anions.⁸ The oxidations of PhCH(CH₃)OH and (Ph)₂CHOH are slower and exhibit normal isotope effects of $k^H/k^D = 5.2$ (Table 1) and $k^H/k^D = 6.6$,¹⁰ respectively. This rise in the potential energy barrier owing to the decreased reactivity of the alkoxide ion may facilitate tunnelling. Similarly, the kinetic deuterium isotope effect for Cr^{VII} oxidation of substituted 2,2,2-trifluoroethanols in a HClO₄-HOAc mixture, which is mechanistically of another type, has been found to increase with decreasing reactivity of the substrate.¹¹ Accordingly, the isotope effect for the oxidation of ROH was measured as $k^H/k^D = 8.5$, but the 3,5-dinitro-substituted compound shows an unusually large isotope effect of 13 at 25 °C.

The previously measured activation parameters for ROH,⁴ $\Delta H_D^\ddagger - \Delta H_H^\ddagger = 2.2$ kcal mol⁻¹ and $\Delta S_D^\ddagger - \Delta S_H^\ddagger = 1.9$ cal mol⁻¹ K⁻¹, support the conclusion that tunnelling is significant in the oxidation of ROH by permanganate. However, anomalous activation energy dependences are not alone conclusive evidence for tunnelling, since complex reactions can, under certain conditions, show anomalous temperature dependences in addition to extreme kinetic deuterium isotope effects.^{2,12}

Lewis and Robinson¹³ measured a tritium isotope effect of $k^H/k^T = 57$ for the oxidation of ROH using an insufficient amount of permanganate. This is in fair agreement with the measured kinetic deuterium isotope effect since the Swain equation, $k^H/k^T = (k^H/k^D)^{1.442}$, yields $k^H/k^T = 14.7^{1.442} = 48$.

In summary, a hydrogen-transfer mechanism [equation (11)] is suggested for the oxidation of ROH.

The unusually large deuterium isotope effect is consistent with a substantial amount of tunnelling, and it does not seem possible to rationalize the results with a more complex reaction mechanism such as reaction branching.

EXPERIMENTAL

General. The ^1H NMR analyses were performed with a Varian XL 300 spectrometer. The high-performance liquid chromatography (HPLC) analyses were carried out with a Hewlett-Packard 1090 liquid chromatograph equipped with a diode-array detector on a C_8 or a C_{18} (100×3 mm i.d.) reversed-phase column. The mobile phase was a solution of acetonitrile in water. The reactions were studied at constant temperature in a HETO 01 PT 623 thermostat bath.

Materials. Acetonitrile (Riedel-de Haën) was of HPLC grade and was used without further purification. 1-Phenyl-2,2,2-trifluoroethanol (ROH) and 2,2,2-trifluoroacetophenone, purchased from Aldrich, and acetophenone (Fluka, p.a.) were used without further purification. The substrate 1-phenylethanol (EGA, 97–100%) was purified by distillation. The deuterated substrates were prepared from 2,2,2-trifluoroacetophenone and acetophenone, respectively, by reduction with LiAlD_4 (Ciba, 99% ^2H) by a standard method and purified by distillation. The deuterium content in the 1-position was found to be 98.8 ± 1.0 atom% ^2H and 99.1 ± 1.0 atom% ^2H , respectively, as measured by ^1H NMR.

Kinetics and product studies. The reactions were run in a V-shaped reaction vessel. Substrate and sodium hydroxide solutions were placed in one of the shanks and potassium permanganate solution in the other. After thermostating for 30 min, the reaction was initiated by fast mixing of the two solutions. At appropriate intervals, aliquots were quenched by mixing with a small amount of 1 M HCl and analysed on the HPLC apparatus. The rate constants for the disappearance of

the substrate were calculated from plots of area of substrate peak versus time by means of a non-linear least-squares regression computer program. Very good pseudo-first-order behaviour was seen for all of the reactions studied. The alkoxide anion was found to be stable in 0.2 M NaOH for at least 1 week.

The estimated errors are considered as maximum errors derived from maximum systematic errors and random errors.

ACKNOWLEDGEMENT

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