The Mechanism of RuO₄-Mediated Oxidations of Ethers: Isotope Effects, Solvent Effects and Substituent Effects

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The mechanism of the RuO₄-mediated oxidation of ethers to esters has been investigated. Oxidation of cyclopropylmethyl methyl ether gave methyl cyclopropanecarboxylate. No rearranged products were observed. On RuO₄ oxidation of benzyl methyl ether and p-methoxybenzyl methyl ether in CCl₄ with NaIO₄ as stoichiometric oxidant, no chlorinated products were observed. A series of 4-substituted benzyl methyl ethers was oxidized with RuO₄–NaIO₄. A correlation of the rate of the reaction with Hammett σ-values gave a ρ of – 1.7, indicating only a moderate charge separation in the transition state (TS). Benzyl methyl ether (1) was oxidized in a series of acetone–water mixtures. From these experiments, a Grunwald–Winstein m-value of 0.11 was obtained, indicating a non-polar TS for the reaction. PhCHDOCH₃ (2) and PhCD₂OCH₃ (3) were oxidized and two deuterium isotope effects, one of 6.1 ± 0.4 and another of 1.3 ± 0.1 were obtained. If one assumes a one-step reaction mechanism, the value of 1.3 would be a large α-secondary isotope effect, indicating a change in the hybridization of the benzylic carbon during the reaction. α-Methylbenzyl methyl ether (4) was oxidized at a seventh of the rate of 1, despite the fact that 4 would have given a more stable carbocation than 1.
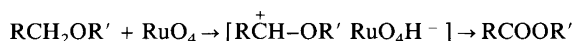
These conflicting pieces of evidence are difficult to rationalise with a hydride or hydrogen abstraction mechanism. Instead it is proposed that the reaction proceeds by either a concerted reaction or by a reversible oxidative addition of the ether to RuO₄ followed by a slow concerted step to give the product.

Oxidation of ethers to esters and lactones can be performed with ozone, chromium(VI) reagents, zinc dichromate, potassium permanganate, zinc permanganate, benzyltriethylammonium permanganate or ruthenium tetraoxide.[1] Of these only the use of chromium(VI) oxidants and RuO₄ are of synthetic importance.[2] The RuO₄ oxidation gives esters or lactones in fair to good yields for methyl or symmetrical ethers, or for ethers with only one primary carbon atom attached to the oxygen atom.[3]

The RuO₄ oxidations of lipophilic organic compounds are usually performed in the Sharpless two-phase solvent system consisting of CCl₄, CH₃CN and H₂O (2:2:3), where RuO₄ is generated from catalytic amounts of hydrated RuO₂ or RuCl₃ and stoichiometric amounts of a primary oxidant, such as NaIO₄.[4] Other solvents can also be used, for instance water together with halogenated hydrocarbons, ethyl acetate, acetonitrile, acetic acid or acetone. We have found water–acetone mixtures useful for the oxidations of saturated hydrocarbons.[5]

Only a limited number of studies of the reaction mechanism of the RuO₄ oxidation of ethers have been reported. Lee and van den Engh proposed a hydride transfer from the substrate to RuO₄ as the rate-determining step for the oxidation of THF,[6] while Balavoine et al. have suggested

an alternative pathway in which coordination of RuO₄ to the substrate was followed by a one-electron transfer.[7] Both pathways would lead to the same intermediate. We have now reinvestigated this reaction.

$$RCH_2OR' + RuO_4 \rightarrow [R\overset{+}{C}H{-}OR' \; RuO_4H^-] \rightarrow RCOOR'$$

$$RCH_2OR' + RuO_4 \rightarrow [RH_2COR']^{\cdot+} + [RuO_4]^{\cdot-} \rightarrow RCOOR'$$

Results

As a model substrate benzyl methyl ether (1) was used. The oxidation of 1 by RuO₄ gave methyl benzoate (71% yield) and benzoic acid (4% yield) at 90% conversion of the ether. A control experiment showed that methyl benzoate was not hydrolysed to benzoic acid and methanol under the reaction conditions applied. Oxidations in CCl₄–CH₃CN–H₂O (the Sharpless system[4]) and in acetone–water (3:1) gave the same product composition. The kinetic investigation showed the disappearance of the substrate to be of first order over four half-lives. The reaction in acetone–water was ca. five times faster than that in the Sharpless system. Analyses by GC and

Table 1. Kinetics of oxidation of benzyl methyl ether (1) by sodium periodate mediated by RuO_4 in acetone–water (3:1). $[ether]_0 = 25$ mM.

$\theta/°C$	$[RuO_4]/mM$	$k_{obs}/10^{-3}\,s^{-1}$	$k_2/M^{-1}\,s^{-1}$	r^2
10	1.44	0.215(2)	0.149	0.9997
	1.44	0.172(3)	0.119	0.9993
15	1.44	0.250(2)	0.173	0.9998
	1.44	0.264(7)	0.183	0.9937
30	1.44	0.668(3)	0.464	0.9997
	1.44	0.622(1)	0.432	0.99995
	1.44	0.599(2)	0.416	0.9990
	1.44	0.674(2)	0.468	0.989
	2.16	1.029(6)	0.476	0.99998
	2.88	1.314(6)	0.456	0.998
45	1.44	1.33(3)	0.924	0.9959
	1.44	1.02(2)	0.709	0.9988

GC–MS showed that no chlorinated products were produced in the CCl_4–CH_3CN–H_2O solvent system (0.1% would have been detected), neither were chlorinated products formed upon oxidation of 4-methoxybenzyl methyl ether in the same system. The kinetic results of the RuO_4 oxidation of benzyl methyl ether over a range of RuO_4 concentrations and temperatures are given in Table 1. The observed first-order rate coefficients, k_{obs} for the disappearance of the ether increased in proportion to $[RuO_4]$. Accordingly, the observed rate coefficients were transformed into second-order rate constants k_2 ($k_2 = k_{obs}/[RuO_4]$). We assumed the RuO_4 concentration to be constant during the reaction. The reoxidation of RuO_2 to RuO_4 has been shown to be rapid on the time-scale of the oxidation reactions.[8] The calculated activation parameters are given in Table 2.

Cyclopropylmethyl methyl ether was oxidized under the same conditions to give a 2:1 mixture of methyl cyclopropanecarboxylate and cyclopropanecarboxylic acid. These were the only products observed by GC analyses and by ^1H NMR of an experiment run in 1:2 mixture of ^2H_2O–($^2H_6$)acetone. No signals from olefinic protons were observed in the spectrum.

Kinetic Deuterium Isotope Effects (KIEs). The KIEs were determined from the oxidations of monodeuteriated (α-$^2H_1$-1) and dideuteriated (α-$^2H_2$-1) benzyl methyl ether (2 and 3). We also oxidized tetrahydrofuran (THF) and ($^2H_8$)THF in acetone–water. The results are given in Table 3. These gave a KIE = 7.0 ± 0.4 for THF–

($^2H_8$)THF. For benzyl methyl ether two KIEs were obtained, one of 6.1 ± 0.4 and a second one of 1.3 ± 0.1. Details of the calculations are given in the Discussion section.

Solvent effects. To obtain quantitative data on the influence of the solvent on the reaction rate, benzyl methyl ether was oxidized in a series of acetone–water mixtures. The rate constants were correlated with the Y-values in the Grunwald–Winstein equation [eqn. (1)].[9] The solvent ionizing power is characterised by Y of the given solvent, while m reflects the substrate's sensitivity to changes in 'ionizing power' of the medium. By definition, $m = 1.0$ for the solvolysis of *tert*-butyl chloride or 1-adamantyl tosylate (limiting S_N1 mechanism). We obtained an m-value of 0.11 ± 0.02 ($r^2 = 0.963$, Table 4) using the Y-values from the solvolysis of 1-adamantyl tosylate.[5]

$$\log(k_{solvent}/k_{acetone-water}) = mY \tag{1}$$

Substituent effects. In order to investigate the influence of the substituents on the rate of reaction, we oxidized a series of p-substituted benzyl methyl ethers to the corresponding esters in acetone–water 3:1. The rate constants (Table 5) were correlated with the Hammett σ-values in the Hammett equation [eqn. (2)].

$$\log(k/k_o) = \rho\sigma \tag{2}$$

A ρ-value of -1.7 ± 0.3 was obtained ($r^2 = 0.915$). A correlation of the data with σ^+ values gave a ρ-value of -1.1 ± 0.2 ($r^2 = 0.865$).

α-Methylbenzyl methyl ether (4) and its 4-substituted derivatives were oxidized to give the corresponding ketones. Reaction rates are given in Table 4. The ether 4 reacted at a seventh of the rate of benzyl methyl ether. Reaction rates were correlated with Hammett σ and σ^+ values (Table 6) to give $\rho = -1.1 \pm 0.1$ ($r^2 = 0.974$) and $\rho^+ = -1.0 \pm 0.2$ ($r^2 = 0.897$). Substances with electron-donating substituents on the aromatic ring (negative σ-values) such as CH_3 and CH_3O, could not be used as substrates. In those cases, the aromatic ring was oxidized at a higher rate than was the benzylic carbon.

Discussion

Reaction products. Balavoine *et al.* oxidized 4-methoxybenzyl methyl ether with $RuCl_3\cdot3H_2O$–NaOCl in CH_2Cl_2–H_2O under phase-transfer catalysis conditions

Table 2. Activation parameters for RuO_4 oxidation of saturated hydrocarbons and ethers in acetone–water (3:1). $[RuO_4] = 1.44$ mM for ethers, $[RuO_4] = 2.88$ mM for saturated hydrocarbons, $[substrate]_0 = 25$ mM.

Substrate	$\log a$	$\Delta H^{\ddagger}/kcal\,mol^{-1}$	n	r^2	$\Delta S^{\ddagger}/cal\,K^{-1}\,mol^{-1}$	$\theta/°C$ (average)
Adamantane	8.9(2)	14.0(3)	6	0.9973	−20(1)	27.4
cis-Decalin	7.5(5)	12.3(7)	6	0.9985	−26(2)	27.4
Benzyl methyl ether	3.5(1)	8.7(2)	8	0.9990	−44.6(7)	25.0

Table 3. Kinetics for oxidation of deuteriated benzyl methyl ether and tetrahydrofuran by $NaIO_4$ mediated by RuO_4 in acetone–water (3:1) at 30 °C, $[ether]_0 = 25$ mM, $[RuO_4] = 1.44$ mM.

Substrate	$k_{obs}/10^{-3}$ s^{-1}	k_2/M^{-1} s^{-1}	r^2
2 [a]	0.289(2)	0.201	0.994
	0.298(1)	0.207	0.978
	0.313(2)	0.218	0.994
3	0.0774(2)	0.0537	0.998
	0.0796(8)	0.0553	0.953
	0.084(9)	0.0587	0.963
THF	0.214(6)	0.148	0.996
	0.222(5)	0.154	0.997
$(^2H_8)$THF	0.030(1)	0.0209	0.987
	0.032(4)	0.0225	0.887

[a] Uncorrected values. Correction for 5.4% **1** gives $k_{obs} = 0.299$.

and obtained chlorinated products (ca. 5%) in addition to methyl 4-methoxybenzoate and 4-methoxybenzoic acid. From these results, they proposed a one-electron transfer mechanism for the reaction. However, chlorinated products are often obtained as by-products with NaOCl as the stoichiometric oxidant.[10] Because of this, we oxidized 4-methoxybenzyl methyl ether with RuO_4 in CCl_4–CH_3CN–H_2O but with $NaIO_4$ as the stoichiometric oxidant. We assumed that CCl_4 would be a better chlorine source than CH_2Cl_2 as all radical reactions with the solvent would result in chlorinated products. By this procedure, no chlorinated products were obtained. The chlorinated products obtained by Balavoine were therefore probably artifacts from the reaction of NaOCl and should not be considered as evidence for a reaction via single-electron intermediates.

The oxidation of cyclopropylmethyl methyl ether produced no rearranged products, only methyl cyclopropanecarboxylate and cyclopropanecarboxylic acid. Cyclopropylmethyl radicals rearrange to olefinic products at a rate of ca. 10^8 s^{-1}.[11] If the oxidation proceeded by a radical pathway, the radicals formed would have to recombine in a solvent cage at a rate faster than 10^8 s^{-1}. A reaction by a radical pathway and with a recombination rate grater than 10^8 s^{-1} can therefore not be excluded from these results.

Table 4. Rate of reaction of benzyl methyl ether (**1**) in acetone–water at 30 °C, $[ether]_0 = 25$ mM, $[RuO_4] = 1.44$ mM.

Vol% H_2O	Y_{Tos}	$k_{obs}/10^{-1}$ s^{-1} [a]	n
20	−0.94	0.63(7)	2
25	−0.50	0.65(3)	6
30	0.07	0.7(1)	3
40	0.66	0.9(1)	4

[a] Average value of n runs.

Table 5. Kinetics for oxidation of 4-substituted benzyl methyl ethers in acetone–water (3:1) at 30 °C. $[RuO_4] = 1.44$ mM, $[ether]_0 = 25$ mM.

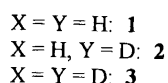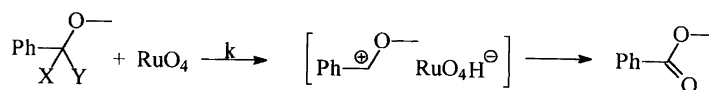| Substituent	$k_{obs}/10^{-3}$ s^{-1}	r^2	σ	σ^+
OCH_3 [a]	0.96(3)	0.999	−0.27	−0.78
H [b]	0.65(3)		0	0
Cl	0.146(8)	0.976	0.23	0.15
	0.121(4)	0.989		
Br	0.56(5)	0.955	0.23	0.11
	0.28(2)	0.975		
CN	0.059(5)	0.930	0.66	0.66
	0.04(1)	0.460		

[a] $[RuO_4] = 0.72$ mM. [b] Average from Table 1.

The carboxylic acids produced in the oxidations might have been formed by hydrolysis of the intermediates in Scheme 2 to the corresponding aldehydes followed by oxidation to the carboxylic acids. Balavoine *et al.* have proposed the direct formation of the aldehyde from the intermediate by expulsion of a methoxide ion.[7]

Kinetic isotope effects (KIEs). Lee and van den Engh oxidized THF and $(^2H_8)$THF, with stoichiometric amounts of RuO_4 in aqueous perchloric acid solutions and obtained a KIE of 1.4. They concluded that this was a small primary isotope effect rather than a very large secondary one, and proposed a mechanism with hydride abstraction as the rate-determining step.[6] We obtained a KIE of 7.0 oxidizing the same compounds with RuO_4 in a one-phase system of acetone–water. The different reaction systems may be the reason for these different results.

If we assume that the first step in the reaction is rate determining, for instance a hydride abstraction mechanism as shown in Scheme 1, we obtain eqns. (3)–(5), where the subscript denotes the atom left on the benzylic carbon and the superscript the one removed.

Table 6. Kinetics for oxidation of 4-substituted α-methylbenzyl methyl ether (**4**) in acetone–water (3:1) at 30 °C. $[RuO_4] = 1.44$ mM, $[ether]_0 = 25$ mM.

Substituent	$k_{obs}/10^{-4}$ s^{-1}	r^2	σ	σ^+
H	0.85(1)	0.9967	0	0
	0.87(2)	0.9942		
NO_2	0.112(4)	0.9918	0.78	0.79
	0.105(3)	0.9959		
Cl	0.362(5)	0.9969	0.23	0.11
	0.367(8)	0.9989		
Br	0.334(6)	0.9979	0.23	0.15
	0.399(5)	0.9992		

X = Y = H: **1**
X = H, Y = D: **2**
X = Y = D: **3**

Scheme 1.

$$k_{obs}(1) = 2k_H^H \tag{3}$$

$$k_{obs}(2) = k_H^D + k_D^D \tag{4}$$

$$k_{obs}(3) = 2k_B^D \tag{5}$$

If it is assumed that identical primary and secondary KIEs operate in the reactions of both monodeuteriated (**2**) and dideuteriated (**3**) methyl benzyl ether, we obtain eqns. (6) and (7) where KIE_{prim} is the primary kinetic isotope effect and KIE_{sec} the secondary one.

$$k_{obs}(1)/k_{obs}(3) = KIE_{prim} \cdot KIE_{sec} \tag{6}$$

$$2[k_{obs}(2)/k_{obs}(1)] = 1/KIE_{prim} + 1/KIE_{sec} \tag{7}$$

These equations then give $KIE_{prim} = 6.1 \pm 0.4$ and $KIE_{sec} = 1.3 \pm 0.1$. The primary kinetic isotope effect indicates the abstraction of a hydrogen species in the rate-determining step. The secondary one is rather large and indicates a close to sp^2 hybridised TS.

Streitwieser *et al.* have explained the α-secondary KIE by the effect of the D–H substitution on the out-of-plane bending vibration. Thus, the change from sp^3 hybridization at the α-carbon in the reactant to sp^2 hybridization in the intermediate (carbocation or radical) would give approximately $k_H/k_D = 1.4$ at 298 K if the transition state was close to the sp^2 hybridised product. This corresponds to the frequency difference with an aldehydic C–H bond as the model for the C–H bond in a carbocation. The KIE would be smaller with an earlier TS.[12] Observed α-secondary KIEs for reactions via carbocations range from 1.09 to 1.25. Values larger than 1.25 are uncommon.[13] For the formation of alkyl radicals by the decomposition of the corresponding azo compounds, an α-secondary KIE of 1.13 per deuterium atom was observed.[14] The main contribution to α-secondary KIEs stem from the geometrical structure of the reaction TS, but other factors may contribute as well, mainly through the weakening/strengthening of the C–H bond (inductive effects, leaving group, nucleophile, etc.). Saunders argues that tunnelling may contribute to the α-secondary isotope effects.[15] As the KIE dependence on temperature was not investigated no conclusions can be made on this point. However, the combination of a large primary and a large α-secondary KIE supports a mechanism in which a hydrogen species is abstracted with a substantial change in the bending force constants at the isotopic centre from the ground state to the transition state, e.g., by the formation of a carbocation or radical in the rate-determining step.

Solvent effects. The change from the non-polar CCl_4–CH_3CN solvent system to the polar acetone–water gave only a fivefold increase in the rate of reaction. This did not indicate a very polar TS. To obtain more information on this point $PhCH_2OCH_3$ was oxidized in different acetone–water mixtures. The obtained *m* value from the Grunwald–Winstein equation, 0.11, was in the lower range of those of typical S_N2 reactions.[16] We have already discussed the objections to the use of the Grunwald–Winstein equation for this type of reaction.[5] However, it is difficult to fit these results with a very polar TS, for instance one for the carbocation formation in Scheme 1.

Substituents effects. The results from the investigation of substituent effects indicated a rather low degree of charge separation in the TS, $\rho = -1.7$. Acid-catalysed hydrolysis of acetals is believed to proceed by a rate-determining formation of the cation intermediate **5**.

$$ArCH(OCH_3)_2 + H_2O/H^+ \rightarrow ArCH = \overset{+}{O}CH_3 \rightarrow ArCHO$$

$$\mathbf{5}$$
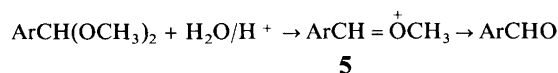
The formation of **5** would be analogous to the formation of a cation intermediate in the ether oxidation.

$$ArCH_2OCH_3 + RuO_4 \rightarrow [ArCH = \overset{+}{O}CH_3 \; RuO_4H^-]$$
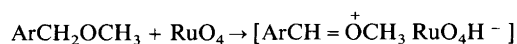
For the acetal hydrolysis, a Hammett plot gave $\rho = -3.3$,[17] considerably larger than the one we found for the ether oxidation (-1.7). This indicates that the charge separation in the TS of the RuO_4 oxidation of the benzyl methyl ethers was not large and that a cation or an ion pair is not an intermediate.

This was also indicated by the oxidation of $ArCH(CH_3)OCH_3$ (**4**). The introduction of an α-methyl group should have facilitated a reaction via a carbocation intermediate. However, **4** was oxidized at a seventh of the rate of benzyl methyl ether. These results are in accordance with the results of Salomon *et al.* They observed at least a 5 to 1 preference for oxidation at a methylene position in competition with a methine on RuO_4 oxidation of ethers.[18]

On oxidation of a series of compounds **4** substituted in

the phenyl ring $\rho = -1.1$ was found, again indicating only a moderate charge separation. Earlier investigations have shown that RuO$_4$-oxidations are strongly affected by steric hindrance.[18-20] For saturated hydrocarbons the preference of oxidation is $CH > CH_2 \gg CH_3$. For ethers, this preference is $CH_2 > CH > > CH_3$ as indicated both by our results and those reported by Gore.[3]

The results from the study of the influence of substituents, both on the phenyl ring and on the α-carbon therefore indicate that the energy of the TS is not greatly influenced by electronic factors but rather by steric ones.

Activation parameters. The activation parameters for the RuO$_4$ oxidation of benzyl methyl ether showed a low activation enthalpy (8.7 kcal mol^{-1}) and a large negative entropy of activation (-44.6 cal K^{-1} mol^{-1}). For comparison, these are given together with those for the RuO$_4$ oxidation of adamantane and *cis*-decalin in Table 2. The large negative entropy of activation for the ether oxidation strongly suggests a highly ordered TS. It is more negative than the one observed for the hydride transfer from isobutane to *tert*-butyl cation ($E_a = 3.6$ kcal mol^{-1}, $\Delta S^{\pm} = -27$ cal K^{-1} mol^{-1}).[21] It is also more negative than the ones for the oxidations of adamantane and *cis*-decalin in CCl$_4$–CH$_3$CN (-20 and -26 cal K^{-1} mol^{-1}, respectively). For the oxidation of benzyl methyl ether we therefore have a more ordered TS than for these two types of reaction.

Mechanism. We have presented the following evidence.

1. The rate of reaction is only marginally sensitive to the polarity of the medium.

2. The rate of reaction is only moderately sensitive to the substituents on the benzene ring.

3. The reaction is kinetically first order in both substrate and RuO$_4$, with a small enthalpy of activation and a large negative entropy of activation.

4. Chlorine is not abstracted from carbon tetrachloride by intermediates in the reaction, and oxidation of cyclopropylmethyl methyl ether produced no rearranged products.

5. Both a primary and a secondary KIE were observed.

The first three points indicate a reaction with only a moderate charge separation in the TS and the fourth that

radicals, if present as intermediates would have a lifetime of less than ca. 10^{-8} s. A carbocation or radical intermediate would therefore have to be present in a tight ion or radical pair with a partial covalent bond in the TS for its formation. In the TS for the formation of such a pair, the benzylic carbon would not be close to sp^2 hybridized and one would not expect such a large (1.3) secondary KIE as the one we observed. It is therefore difficult to accommodate the evidence in points 1–5 above with a reaction *via* either a carbocation or a radical intermediate. We will therefore discuss two other mechanisms together with points 1–5. One is a concerted reaction, the other a two-step mechanism involving a pre-equilibrium (Scheme 2).

In the concerted reaction, the TS (6) would be similar to those of some aliphatic electrophilic substitution reactions (S$_E$2) which involve a front-side attack of the electrophile on the reactive centre.[22] In one such reaction, acidic decomposition of (di-*n*-octyl)mercury, an α secondary KIE was observed, 1.10 per deuterium atom.[23] The data in points 1–5 might therefore fit such a reaction mechanism. In a concerted reaction there would be no or only a limited charge separation in the TS (points 1, 2). The TS would be highly ordered as indicated by the large negative entropy of activation (point 3). Both a primary and a secondary KIE would be observed (point 5), although the secondary KIE observed by us is larger than the one observed for the S$_E$2 reaction cited above (1.3 vs. 1.1). Finally, the concerted reaction mechanism would not give rise to rearranged products (point 4).

However, the results may also be explained by a two-step reaction consisting of a pre-equilibrium followed by a rate-determining step (route b, Scheme 2).
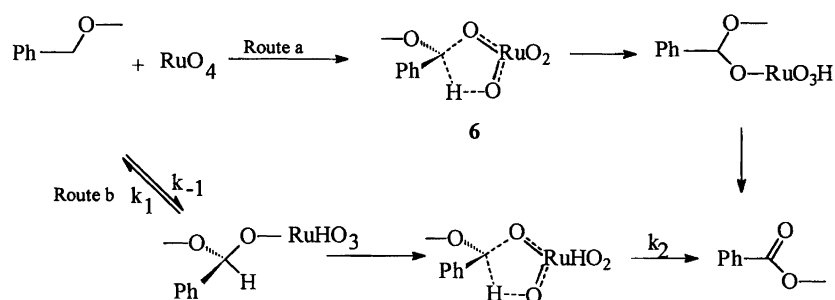
For **1**, **2**, and **3** we obtain eqns. (8)–(10).

$$k_{obs}(1) = 2(k_1^H \cdot k_2^H)/(k_{-1}^H + k_2^H) \tag{8}$$

$$k_{obs}(2) = k_1^H \cdot k_2^D/(k_{-1}^H + k_2^D) + k_1^D \cdot k_2^H/(k_{-1}^D + k_2^H) \tag{9}$$

$$k_{obs}(3) = 2(K_1^D \cdot k_2^D)/(k_{-1}^D + k_2^D) \tag{10}$$

If $k_2^H \ll k_{-1}^H$, $k_2^H \ll k_{-1}^D$, $k_2^D \ll k_{-1}^H$ and $k_2^D \ll k_1^D$, then eqns. (11)–(13) hold, where the subscripts denote the atom removed and the subscript the rate constants in Scheme 2.

Scheme 2.

$$k_{obs}(1) = 2K^H k_2^H \tag{11}$$

$$k_{obs}(2) = K^H k_2^D + K^D k_2^H \tag{12}$$

$$k_{obs}(3) = 2K^D k_2^D \tag{13}$$

From these equations one obtains the two deuterium isotope effects, 6.1 ± 0.4 and 1.3 ± 0.1. The smallest one would presumably apply to the pre-equilibrium and the larger to the second, rate-determining step. This scheme, with a reversible oxidative addition of the ether to RuO_4 followed by a second step with a concerted mechanism also appears to be in accordance with the observations: there need not be a large charge separation in the TS of any of the steps, in accordance with points 1 and 2 above. The concerted second step explains the large negative $\Delta S^{\ddagger}$ (point 3) and the rather large 'secondary' KIE (point 4) is an equilibrium isotope effect of the pre-equilibrium (Scheme 2). This mechanism would also explain the lack of rearrangement during the reaction (point 5).

Conclusion. The results from the investigation of the influence of the medium and of the substituents on the RuO_4-mediated oxidations of benzyl methyl ethers together with the observed KIEs cannot be explained by either a hydride-abstraction reaction mechanism or one by a hydrogen-atom abstraction. Instead we propose that the reaction proceeds either by a concerted reaction similar to an S_E2 reaction or by a reversible oxidative addition of the ether to RuO_4 followed by a slow second step with a concerted mechanism to give the product ester.

Experimental

General. The NMR spectra were recorded on a JEOL JNM-EX400 FT NMR SYSTEM using TMS as an internal standard. MS spectra were recorded on an AEI MS 902 instrument operating at 50 eV EI, 150°C. The GC–MS were obtained on a Fisions instrument TRIO 1000 GC-MS system equipped with a 25 m BP-1 fused silica capillary column.

Materials. The benzyl ethers were prepared from the corresponding benzyl alcohols. The procedure given for preparation of 4-bromobenzyl methyl ether was followed for all ethers except for 4-cyanobenzyl methyl ether which was prepared from 4-cyanobenzyl bromide. The α-methylbenzyl alcohols which were not commercially available were prepared by $NaBH_4$ reduction from the corresponding acetophenones. The procedure given for 4-chloro-α-methylbenzyl alcohol was used for all 4-substituted-α-methylbenzyl alcohols. The products of the reactions were identified by comparison with authentic substances or by standard spectroscopic and chromatographic methods.

4-Bromobenzyl methyl ether. To 4-bromobenzyl alcohol (3.74 g, 20 mmol) in anhydrous THF (40 ml), cooled to 0°C was added methyl iodide (2.84 g, 20 mmol) followed by sodium hydride (20% oil, 1.75 g, 56 mmol). The cooling bath was removed and the mixture was stirred at room temperature until the reaction was complete (1–2 h). The reaction was stopped by addition of saturated ammonium chloride solution (2 ml). The reaction mixture was poured into water (15 ml) and ether (30 ml) and the layers separated. The aqueous phase was extracted with ether (2×30 ml) and the combined organic extracts washed with saturated sodium chloride solution (4×15 ml) before being dried over $MgSO_4$ and evaporated. The crude oil was distilled under reduced pressure to give pure 4-bromobenzyl methyl ether ($>99\%$ by GC, 1.9 g, 12 mmol, 61% yield).

4-Cyanobenzyl methyl ether. A solution of the 4-methoxybenzyl bromide (3.9 g, 20 mmol) in methanol (150 ml) was added dropwise to a solution of MeONa (from Na, 0.46 g, 20 mmol) in methanol (5 ml) and stirred overnight. The solution was concentrated, poured into water (75 ml) and extracted with ether (2×75 ml). The combined organic layers were washed with water (50 ml) and saturated aqueous NaCl solution (3×15 ml) and then dried over $MgSO_4$. Distillation under reduced pressure gave the pure product ($>99\%$ by GC, 1.17 g, 12 mmol, 58% yield).

α-Methylbenzyl alcohols. To 4-chloroacetophenone (7.73 g, 50 mmol) in ethanol (100 ml) was added $NaBH_4$ (2.25 g, 60 mmol) in small portions over 5 min at 0°C. After being stirred at room temperature for 1 h, the mixture was added to water (75 ml) and heated to boiling for 1 min. It was then cooled and extracted with ether (2×100 ml), dried over $MgSO_4$ and evaporated to give the product (99% by GC, 6.9 g, 44 mmol, 88% yield) which was methylated without further purification.

Benzyl methyl ether (**1**) was prepared using the same procedure as described for 4-bromobenzyl methyl ether. ^1H NMR (400 MHz, $CDCl_3$): δ 3.38 (3 H, s), 4.46 (2 H, s) 7.34 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 58.1, 74.7, 127.65, 127.7, 128.4, 138.2. MS [EI 50 eV: m/z (% rel. int.)]: 123 (31, $M+1$), 122 (100, M), 121 (62, $M-1$), 114 (21), 110 (19), 109 (24), 107 (19), 97 (18), 95 (13), 93 (24), 92 (28), 91 (81), 85 (19), 83 (37), 82 (21), 81 (28), 79 (24), 77 (47), 71 (42).

Monodeuteriated benzyl methyl ether (**2**). To benzaldehyde, washed with $NaHCO_3$ solution and distilled (1.38 g, 13 mmol) in anhydrous THF (600 ml) was added NaB^2H_4 (Aldrich, 98 atom% ^2H, 0.50 g, 13 mmol) at 0°C. ^2H_2O (11 ml) was added after the reaction had been stirred at room temperature for 7 h. The mixture was stirred for 1 h, then most of the solvent was removed on a rotary evaporator and water added (150 ml). The aqueous phase was extracted with ether (3×100 ml). The

combined organic phases were washed with H_2O (3 × 25 ml) and saturated NaCl solution (25 ml), dried (MgSO₄) and the ether evaporated off. The crude oil was distilled under reduced pressure to give monodeuteriated benzyl alcohol (>99% by GC, 1.19 g, 11 mmol, 84% yield). This was methylated using the same procedure as described above to give monodeuteriated benzyl methyl ether (95% α-²H₁, 5.4% α-²H₀ by ¹H NMR spectroscopy, see below). ¹H NMR (400 MHz, CDCl₃): δ 3.38 (3 H, s), 4.44 (1 H, t, J 1.7 Hz), 4.46 (0.114 H, s) 7.34 (5 H, m). ¹³C NMR (100 MHz, CDCl₃): δ 58.0, 74.3 (t, J 20 Hz), 127.7, 127.8, 128.4, 138.1. MS [EI 50 eV: m/z (% rel. int.)]: 124 (0.3, M + 1), 123 (3, M), 122 (1), 111 (1), 109 (1), 108 (1), 106 (1), 105 (1), 101 (4), 99 (1), 98 (3), 97 (1), 96 (1), 94 (2), 92 (4), 59 (10), 58 (17), 44 (100).

Dideuteriated benzyl methyl ether (**3**). To freshly distilled methyl benzoate (1.37 g, 10.1 mmol) in anhydrous ether (10 ml) was added LiAl²H₄ (Janssen, 98 atom % ²H, 0.25 g, 6 mmol) at −78°C. The reaction was stirred at room temperature for 10 h after which water (0.15 ml) was added. After 15 min aqueous sodium hydroxide (15%, 0.15 ml) was added. After 10 min, more water (0.3 ml) was added. The mixture was stirred for 1 h, filtered, dried (Na₂SO₄) and the ether evaporated off to give dideuteriated benzyl alcohol (98% by GC, 1.03 g, 9.4 mmol, 94% yield). The product was methylated without further purification using the same procedure as described above. ¹H NMR (400 MHz, CDCl₃): δ 3.38 (3 H, s), 7.34 (5 H, m). ¹³C NMR (100 MHz, CDCl₃): δ 58.0, 74 (m), 127.7, 127.8, 128.4, 138.1. MS [EI 50 eV: m/z (% rel. int.)]: 125 (29), 124 (27, M), 123 (23), 112 (12), 111 (43), 109 (20, M − CH₃), 97 (42), 96 (31), 95 (48), 85 (32), 83 (59), 81 (38), 71 (81), 70 (39), 69 (79), 57 (100), 55 (91).

Cyclopropylmethyl methyl ether was prepared from cyclopropylmethanol using the procedure of Dauben *et al.*[24] A mixture of cyclopropylmethyl methyl ether and diethyl ether was obtained (2:3 by ¹H NMR spectroscopy). This mixture was oxidized with RuO₄ in (²H₆)acetone and ²H₂O (2:1). After 2 h the mixture was filtered and analysed by ¹H NMR spectroscopy, which showed the products to be methyl cyclopropanecarboxylate–cyclopropane-carboxylic acid 2:1. Analysis by GC showed only methyl cyclopropanecarboxylate.

Kinetic experiments. The methods used for the kinetic investigations and the analysis have been reported.[5] The experiments with THF were performed slightly differently. THF was dried over LiAlH₄, distilled and stored over activated molecular sieves (4 Å) in a vial with a septum. (²H₈)THF (IC Chemikalien, 99.5 atom% ²H) was stored in the same way. The substrate (1 mmol) was withdrawn with a syringe. The syringe was weighed before and after addition of the substrate to a solution of the internal standard (1 mmol butyl acetate) in a portion of the acetone.

For all the oxidations, the reactions were initiated by the addition of the substrate solution to the yellow solution of RuO₄ in acetone–water. Samples of the reaction mixtures (0.40 ml) were withdrawn via pipette at intervals and quenched in ether (3 ml) with Na₂SO₄ (3 g). This procedure led to the conversion of RuO₄ into the insoluble dioxide. The solution was filtered and analysed by GC (capillary column, Chrompack 9000, CPSil5CB, 25 m × 0.32 mm; temperature programme 35°C × 3 min, then 10°C min⁻¹ to 250°C). For the runs with monodeuteriated benzyl methyl ether (**2**), the results were corrected for the initial presence of 5.4% non-deuteriated ether (**1**). The rate constant k_{obs} (**1**) was used for this correction.

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