The Mechanism of Oxidation of Cyclohexanone under Acid Conditions. Part 4.[1] Primary and Solvent Isotope Effects on Oxidations of Ketones and Enols: an Indirect Determination of the Relative Enol Contents of Isotopically Substituted Ketones in Water and Deuterium Oxide, and of the Solvent Isotope Effects for the Electron Transfer Processes

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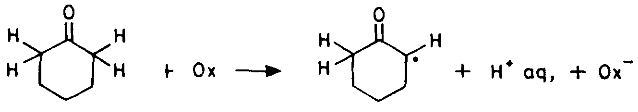
Two non-bonded electron transfer oxidants, trisbipyridylruthenium(III) and hexachloroiridium(IV), are known to abstract an electron from the enol of cyclohexanone, and can be used under conditions where the oxidation step is rate limiting. The solvent and substrate deuterium isotope effects have been studied under these conditions, and they provide evidence which can be used to distinguish between attack on enol and attack directly on the ketone even under circumstances where direct kinetic evidence cannot be used to make this distinction. In these, and similar systems, the apparent existence of a primary isotope effect can be highly misleading if the reagents are not in isotopic equilibrium, since the isotope effects in the enolisation process change the enol content of the solution by a factor of up to 7. The electron transfer step is found to be retarded by deuterium oxide by a factor of *ca.* 1.9.

EARLIER papers on oxidation of cyclohexanone by $IrCl_6^{2-}$ [2] and tris-2,2′-bipyridylruthenium(II) [3] have established that both these reagents attack the enol form, since under conditions of higher oxidant concentration or lower acidity the reactions become zero order in oxidant and approximate to the known rate of acid-catalysed enolisation of the ketone. At higher acidities, or lower oxidant concentrations, the removal of enol is less rapid than its formation, and the reactions become first-order in oxidant and independent of acidity. It is well known that the same phenomenon occurs in the bromination reaction, but as the necessary concentration of bromine is $<10^{-7}$M it is difficult to study the first-order reaction accurately.[4] On the other hand a number of oxidants, *e.g.* chromic acid [5] and vanadium(V),[6] oxidise cyclohexanone at a rate which is under all accessible conditions slower than that of enolisation. It is not however valid to assume that these oxidants attack the enol form, since other one-equivalent oxidants such as Co^{III} [5] are reduced at a rate faster than, and not limited by, the enolisation rate, and so must be attacking the ketone directly. A criterion based on solvent isotope effects was developed to try to decide the mechanism in the ambiguous cases,[5,6] but although it gave useful indications it was not possible to test it rigorously, on a system which was known to involve the enol, but under conditions where the reaction is not limited by the enolisation step. In addition allowances had to be made for solvent isotope effects due to the acid dependence of the oxidation processes, and these allowances tended to obscure the situation. The above mentioned oxidations by iridium(IV) and ruthenium(III) complexes are however not subject to acid catalysis and therefore provide suitable systems in which to determine the isotope effects and test the validity of the solvent isotope effect criterion.

DISCUSSION

There are two situations to consider, and in both the effects of isotopic substitution in substrate and in solvent on the rate of the reaction must be considered.

(1) The ketone is attacked directly by the oxidant (Scheme 1). If the rate-determining step of the oxidation involves fission of a C–H bond, and the hydrogen is transferred to the solvent, it is to be expected that the use of 2,2,6,6-tetradeuteriocyclohexanone will result in a normal primary isotope effect, *i.e.* k_H/k_D *ca.* 5—7 at 25°. This should be effective whether the solvent is H_2O or D_2O. The solvent isotope effect k_{H_2O}/k_{D_2O} should be small, since even if the solvent is acting as a base in helping the proton removal, the base strengths of H_2O and D_2O are known to be virtually identical.[7] Some solvent effect might also be expected to arise from the different solvation requirements of Ox and Ox^-, but in the cases of Ir^{IV} and Ru^{III}, which are large ions, these effects ought not to be large. There may also be some small medium effect on the actual non-bonded electron transfer itself. We can therefore predict that $k_{H_2O}/k_{D_2O} = 1 \pm 0.2$ and $k_{H,H_2O}/k_{D,D_2O}$ may be 4—8.



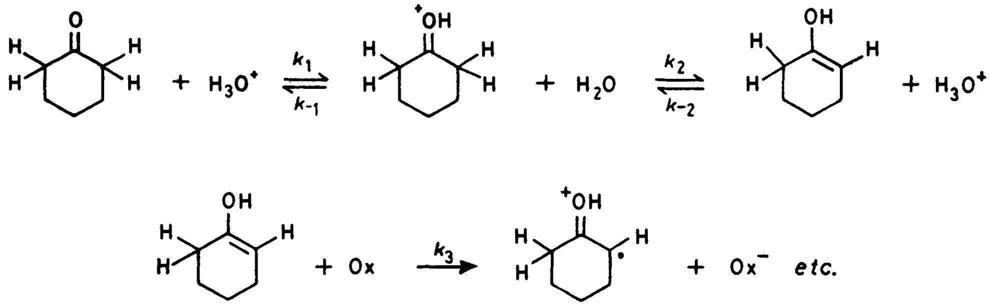
SCHEME 1

(2) The enol is formed by an acid-catalysed pre-equilibrium and then attacked (Scheme 2). When the ketone is dissolved in water the reactions k_1, k_2, k_{-1}, and k_{-2} occur until the equilibrium concentration of enol is formed. In view of the enol content equilibrium constant (at most 4×10^{-6} and probably 2.3×10^{-7}) [4] and the rate of enolisation (3×10^{-4} l mol^{-1} s^{-1}) [1] the equilibrium enol concentration in 1M-acid should be reached in a few hundredths of a second. However, the same enolisation rate constant shows that only *ca.* 1/3 of the molecules will have actually undergone enolisation even after 15 min, and this is consistent with the observed relatively slow rate of isotope exchange with the solvent. Hence when an isotopically non-equilibrated system is set up (*i.e.* tetradeuterioketone in water or protioketone in D_2O) a ‘ sort of pseudo-equilibrium ’ [8] is set up in which an enol content is established which is not

necessarily that which will eventually be found in the final isotopically equilibrated system. Attempts have been made [9] to measure the pseudo-equilibrium and equilibrium enol contents by the direct bromination method [4] under these conditions, but the level is so small that we have not been able to achieve sufficient accuracy to determine the differences in enol content with any confidence. However the reaction k_3 provides a kinetic method of analysis, though it also introduces the uncertainty that the isotope effects in the step k_3 are not known. However this step is known to be a rapid non-bonded electron transfer. It must essentially involve the π orbital of the enol system which is orthogonal to the σ-H–O bond, and therefore it will not show a primary hydrogen isotope effect. Secondary effects due to solvation of the initially formed cation are likely to be comparable to those in the similar formation of a protonated keto-group in the bromine or mercury(II) oxidations of an alcohol or ether,[10] since the charge is less localised in the present system so we can assume that $k_{3(\mathrm{H_2O})}/k_{3(\mathrm{D_2O})} \sim 1.5$, and this value probably encompasses the other solvent effects on electron transfer mentioned in section (1). Oxidation of a phenol by iridate(IV) has given a value of 1.7.[10] Similarly $k_{3(\mathrm{H})}/k_{3(\mathrm{D})}$ should be unity since the carbon carrying the H(D) atom does not even change its hybridisation. The various possible combinations of isotopic substitution must now be considered. They will each have a different effect on the observed overall rate constant k, which can be seen to be the result of the effects on the individual constants which make it up [equation (1)]. Ketone

$$k = k_1/k_{-1} \times k_2/k_{-2} \times k_3 \qquad (1)$$

deuteriation is represented by the subscript D, and solvent change by the subscript D_2O; all values quoted are for 25°.



SCHEME 2

(a) *Deuteriated Ketone in Light Water:* $k_{\mathrm{H,H_2O}}/k_{\mathrm{D,H_2O}}$ (*Non-equilibrium Primary Effect*).—The value of $(k_1k_2/k_{-1})_{\mathrm{H}}/(k_1k_2/k_{-1})_{\mathrm{D}}$ is known, since it is the primary isotope effect observed in the normal zero-order acid-catalysed bromination, and it has a value of 5.6,[1,11] though measurements of the C–H (C–T) isotope effect (which are not subject to isotope titration errors) enable us to calculate a value of 6.7 in agreement with measurements on acetone.[12] There is no reason to expect k_1/k_{-1} to change significantly with isotopic substitution, so this arises from the primary isotope effect, and possibly some secondary effect, on k_2. The value of $(k_{-2})_{\mathrm{H}}/(k_{-2})_{\mathrm{D}}$ should be close to 1 since the atom transferred in both cases is protium, and only the secondary effect of sp^2–sp^3 rehybridisation of the C–D bond is effective. Literature values for addition to other double bonds suggest a value of 0.8 for this, though values of 0.9 have been observed in some systems,[13] and Toullec argues that the values should be between 0.9 and 1.0, since the effect of the rate of formation of a hydroxycarbonium ion should be considerably smaller than the known effect (0.77) on the stability of a true carbonium ion. Hence equation (2) applies. Since the last term in the above expression

$$\frac{k_{\mathrm{H,H_2O}}}{k_{\mathrm{D,H_2O}}} = \left(\frac{k_1k_2}{k_{-1}}\right)_{\mathrm{H}} \Big/ \left(\frac{k_1k_2}{k_{-1}}\right)_{\mathrm{D}} \times \frac{(k_{-2})_{\mathrm{D}}}{(k_{-2})_{\mathrm{H}}} \times \frac{(k_3)_{\mathrm{H}}}{(k_3)_{\mathrm{D}}} = 6.7 \times 1/0.95 \times 1 = 7.0 \qquad (2)$$

is unity this ratio is also the ratio of the 'pseudo-equilibrium' enol contents of the two systems. It is clear that an apparent primary isotope effect does not prove that the appropriate C–H (C–D) bond is broken in the rate-determining step in systems where an isotopic pseudo-equilibrium is set up.

(b) *Protio-ketone in Heavy Water:* $(k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}})$ (*Non-equilibrium Solvent Effect*).—It is well known that heavy water increases the extent of protonation (deuteriation) of weak bases [14] by a factor of *ca.* 2.0, and there is also an effect on k_2 due to the differences in basicity of H_2O and D_2O. This is consistent with the observed value, determined for acetone [12] $[(k_1k_2/k_{-1})_{\mathrm{H_2O}}/(k_1k_2/k_{-1})_{\mathrm{D_2O}} = 0.53 \pm 0.3]$. The same authors, by studying the diffusion-controlled addition of bromine and iodine to the enol, find $(k_{-2})_{\mathrm{H_2O}}/(k_{-2})_{\mathrm{D_2O}} = 3.7$, close to the theoretical maximum.[14] This gives a pseudo-equilibrium enol content ratio $(k_1k_2/k_{-1}k_{-2})_{\mathrm{H_2O}}/(k_1k_2/k_{-1}k_{-2})_{\mathrm{D_2O}} = 0.53/3.7 = 0.143$, *i.e.* there is 7.0 times more enol present in heavy water. If the mole-fraction of deuterium in the heavy water is <100%, the experimental data on bromination enable us to make a correction, since values are tabulated (k_{II} in ref. 12) for the variation of this ratio with mol fraction of D_2O.

Using this value, and the value of 1.5 suggested above for $k_{3(\mathrm{H_2O})}/k_{3(\mathrm{D_2O})}$ we arrive at $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}}$ *ca.* 0.21, *i.e.* k should be *ca.* 4.6 times larger in heavy water. It can be seen that as a result of using the above data, a rather higher value of the enol content in heavy water is obtained than was estimated previously,[5,6] when the only data available were based on the protonation of the much more basic anion of a β-diketone,[7] but that the present data are also in good agreement with calculations based on a value for $k_{-2(\mathrm{H_2O})}/k_{-2(\mathrm{D_2O})}$ derived from studies in the protonation of enol ethers.[15]

(c) *Deuterio-ketone in Deuterium Oxide:* $(k_{\mathrm{H,H_2O}}/k_{\mathrm{D,D_2O}})$-(*Equilibrium Isotope Effect*).—The effects of substrate and solvent isotopic substitution should be superimposable,[12] so the enol content ratio should be 7.0 × 0.143 = 1.00 ± 0.06 times greater in protio- than in deuterio-systems. It is reassuring that this is close to unity since this equilibrium is now complete. Similar equilibrium constants have been determined in β-diketones, and their values attributed to hydrogen-bonding differences,[16] but the precise values have no direct relevance to the present system.

The overall rate of the oxidation process is still affected by isotope effects in k_3, so $k_{\mathrm{H,H_2O}}/k_{\mathrm{D,D_2O}} = 1.5$—1.7 may well be observed. Assuming that the enol content ratio is exactly unity this provides a direct measure of the solvent isotope effect on k_3.

Determination of $k_{\mathrm{H}}/k_{\mathrm{D}}$ could be made in either solvent, or $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}}$ with either ketone, but we have determined rates in all four situations in order to test the theory and provide a check on the consistency of the data. In a situation where the mechanism is not known a value of $k_{\mathrm{H}}/k_{\mathrm{D}}$ lower than expected would be an argument that enolisation is not involved, and a value of $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}}$ significantly different from that expected purely as a result of any solvent isotope effects in k_3 (including those arising from any acid catalysis of the oxidation), would be an argument against direct attack.

TABLE 1

Oxidation of cyclohexanone by $\mathrm{IrCl_6}^{2-}$: $[\mathrm{H^+}]$ 1.12—1.19M; $[\mathrm{ClO_4}^-]$ 1.8M; temperature 22.05 ± 0.05°; $[\mathrm{Ir^{IV}}]$ 2.86—2.96 × 10^4M

10^2 [ketone] M	Isotope	Solvent	$10^4k'/\mathrm{s^{-1}}$	No. of runs	$10^2k''/$ l mol^{-1} s^{-1}
1.144	H	H_2O	2.205 ± 0.051	4	1.927 ± 0.05
1.152	H	H_2O	2.188 ± 0.050	4	1.899 ± 0.05
1.258	H	H_2O	2.272 ± 0.015	4	1.806 ± 0.02
1.684	H	D_2O	7.722 ± 0.073	4	4.585 ± 0.04
1.931	H	D_2O	8.71 ± 0.027	4	4.511 ± 0.02
1.881	H	D_2O	8.252 ± 0.076	4	4.387 ± 0.04
2.054	H	D_2O	9.37 ± 0.107	4	4.561 ± 0.05
2.414	H	D_2O	10.88 ± 0.039	4	4.507 ± 0.02
2.041	H	D_2O	9 247 ± 0.117	4	4.531 ± 0.05
1.549	D	H_2O	0.453 ± 0.014	4	0.292 ± 0.01
1.072	D	H_2O	0.3385 ± 0.002	4	0.316 ± 0.002
1.065	D	H_2O	0.365 ± 0.005	4	0.343 ± 0.005
0.986	D	H_2O	0.307 ± 0.004	4	0.311 ± 0.004
2.060	D	H_2O	0.614 ± 0.006	4	0.298 ± 0.003
1.516	D	H_2O	0.451 ± 0.016	4	0.297 ± 0.01
0.896	D	H_2O	0.2805 ± 0.0015	4	0.313 ± 0.002
1.021	D	H_2O	0.306 ± 0.003	4	0.300 ± 0.003
1.157	D	H_2O	0.3537 ± 0.001	4	0.306 ± 0.001
1.312	D	H_2O	0.4055 ± 0.0016	4	0.309 ± 0.001
1.344	D	H_2O	0.406 ± 0.009	4	0.302 ± 0.01
1.174	D	H_2O	0.3465 ± 0.007	4	0.295 ± 0.01
1.432	D	H_2O	0.436 ± 0.006	4	0.304 ± 0.004
1.391	D	H_2O	0.3715 ± 0.003	4	0.276 ± 0.002
1.310	D	H_2O	0.398 ± 0.001	4	0.304 ± 0.001
1.512	D	D_2O	1.23 ± 0.02	4	0.813 ± 0.016
1.512	D *	D_2O	1.026 ± 0.028	13	0.679 ± 0.018

* See Experimental section.

TABLE 2

Oxidation of cyclohexanone by $\mathrm{Ru(bipy)_3}^{3+}$: $[\mathrm{H^+}]$ 1.0M; $[\mathrm{ClO_4}^-]$ 1.0M; temperature 22 °C; $[\mathrm{Ru^{III}}]$ 2.5 × 10^{-6}M; [ketone] 1.1 × 10^{-4}M

Isotope	Solvent	$10^4k_{\mathrm{obs}}/\mathrm{s^{-1}}$	$k'/$l mol^{-1} s^{-1}
H	H_2O	38.5	35
H	D_2O	88	80
D	H_2O	6.7	6.0
D	D_2O	17	15.4
D *	D_2O	15.1	14

* See Experimental section.

RESULTS

Table 1 and the Experimental section show that for hexachloroiridate $k_{\mathrm{H}}/k_{\mathrm{D}}$ is 6.9 and $k_{\mathrm{D_2O}}/k_{\mathrm{H_2O}}$ *ca.* 3.7 after correction to 100% isotopic substitution of both ketone and solvent. This is entirely consistent with the predicted values for attack on the enol and shows that the retardation of the electron transfer by heavy water is by a factor of 1.9. This value is comparable with that observed in phenol oxidation, although, since it involves corrections for incomplete isotopic replacement of both ketone and solvent, it is unlikely to be more accurate than ±0.1. It is clear that a value of this magnitude does not require the postulation of the simultaneous breaking of the enol O–H (O–D) bond, but can be accounted for purely by solvation effects. The value of $k_{\mathrm{D_2O}}/k_{\mathrm{H_2O}}$ is clearly larger than that predicted in the earlier work,[6] and therefore confirms that the newer values deduced from more recent literature data are more satisfactory. The value of $k_{\mathrm{H}}/k_{\mathrm{D}}$ might well be taken for a primary isotope effect in the electron transfer step were it not for this analysis and the other evidence from kinetic data and solvent isotope effects; it is clear that there is no primary isotope effect involved in the electron transfer step. Table 2 shows that for $\mathrm{Ru(bipy)_3}^{3+}$ $k_{\mathrm{H}}/k_{\mathrm{D}} = 6.5$ (after correction), which again does not distinguish between attack on ketone or on enol, but $k_{\mathrm{D_2O}}/k_{\mathrm{H_2O}} = 3.6$, closely similar to the value for $\mathrm{IrCl_6}^{2-}$. This observation is in full agreement with the kinetic evidence that the enol is the substrate in a very fast electron-transfer process, and the value for $k_{\mathrm{H(H_2O)}}/k_{\mathrm{D(D_2O)}}$ (1.9) again gives the solvent isotope effect on this step.

The newer values do not invalidate any of the conclusions drawn in earlier work; in particular the data for oxidation by vanadium(V), cobalt(III), and cerium(IV) by a co-ordination route [6] are even further from what would now be expected for an enolisation route. There is now independent evidence that chromium(VI) attacks the enols,[17] so we can re-examine whether the data in ref. 5 agree with the present analysis. The observed solvent effects ($k_{\mathrm{D_2O}}/k_{\mathrm{H_2O}}$) were 3.8 in H_2SO_4 (95% D), 4.3 in $HClO_4$ (95% D), and 5.2 in toluenesulphonic acid (99% D) giving 4.9, 5.6, and 5.9 respectively when corrected to 100% D_2O. The calculated value for this ratio is the enol content ratio divided by any direct solvent isotope effect on the oxidation step. However the oxidation step is also acid catalysed, and so is accelerated in D_2O. If the acceleration is by a factor of 1.6, since $\mathrm{HCrO_4}^-$ is a relatively weak base [14] and retardation due to the direct solvent isotope effect is 1.9, comparable to that of the other oxidants, we get a predicted value of $k_{\mathrm{D_2O}}/k_{\mathrm{H_2O}} = 7.0 \times 1/1.9 \times 1.6 = 5.9$ in agreement with observation. For the possibility where attack might be directly on the ketone, k_{D_2O}/k_{H_2O} was predicted to be 2.0—2.5.[5] This was obtained by taking a maximum value for the acid catalysis effect and totally neglecting any other effect which might reduce it, and so is the maximum possible. It is clearly significantly different from the observed value, and confirms that the solvent isotope effect also provides useful mechanistic information in this system even though the mechanism of the attack on the enol may be very different. The reported values of k_H/k_D are less than in the present work, but the values for Cr^{VI} oxidation (4.0, 5.5) are uncorrected for incomplete isotopic substitution, and will also be lower because of the higher temperature (50°) used. A similar analysis can be made of the data on oxidation by ferriin. Originally studies of the air-free system indicated that the enol might not be involved,[18] but this conclusion can be discarded, in the light of evidence that the reaction in the presence of air can be limited by the enolisation rate,[19] and the realisation that the data on the ill-behaved air-free system are probably unreliable. The observed isotope effect, measured in the presence of air of $k_H/k_D = 6.3$ (before correction) is reasonable for the enol route. The solvent isotope effect has also been found to be 2.7 (*i.e.* presumably $k_{H,D_2O}/k_{H,H_2O}$) but as the isotopic purity of the solvent was not reported it is not possible to correct this to 100%. However this is close to the values obtained in the present systems before this correction is applied and this suggests that the situation is identical.

We can therefore conclude that the analysis of the change of enol content under conditions of isotopic non-equilibrium is in agreement with independent kinetic evidence whenever this is available, that the value of the non-equilibrium solvent isotope effect provides a valid criterion as to whether or not the enol is attacked by the oxidant, that the value of the equilibrium isotope effect is relevant to the mechanism of the oxidation step, whether or not the enol is the true substrate, and that the non-equilibrium primary isotope effect is only relevant to the mechanism of the oxidation step when it is significantly different from that due to enolisation or when other evidence shows that the enol is not involved.

EXPERIMENTAL

Materials.—2,2,6,6-Tetradeuteriocyclohexanone was preprepared by repeated isotope exchange of cyclohexanone with 99.8% deuterium oxide (Prochem), using the morpholine enamine route.[20] Rather more than the theoretical number of exchanges proved necessary before adequate incorporation was achieved. The final product showed no n.m.r. absorption due to a α-H atoms, or other impurities, and the protons appeared as a single sharp line at τ 8.2. The relative intensities of the $M(102)$ and $M - 1$ peaks in the mass spectrum showed that it was 97 atom % deuteriated (*i.e.* only 12.5% of the molecules were $C_6H_7D_3O$). The preparation of other materials has been described previously.[2,3]

Kinetics.—Solutions in heavy water contained 92 atom % D, since the acid component was contributed by the dilution of 72% perchloric acid (AnalaR). Sodium perchlorate was used to maintain the ionic strength; it was recrystallised then dried at 190° for at least three days before use. Solutions of oxidant in acid were degassed by repeated freeze–thaw cycles in a vacuum line. Solutions of ketone were made up by dissolution of weighed amounts of ketone in previously degassed water or D_2O. This was carried out in a dry-box under nitrogen, and if the ketone was not in isotopic equilibrium with the solvent only enough solution was made up at a time to carry out four concurrent reactions. Aliquots of oxidant and substrate solutions were pipetted into 1 cm path-length cuvettes which were stoppered, shaken, removed from the dry-box, and transferred to the thermostatted cell holder of an SP 1700 spectrophotometer as soon as possible, usually within 5—10 min of dissolving the ketone. The reactions were carried out at room temperature to avoid the need for long periods of temperature equilibration. The reactions were followed at 480 nm, the optical density being automatically printed out on a teletype at regular intervals. The infinity value was simulated by the addition of a trace of ascorbic acid. A first-order rate constant was fitted to the data from each run by a linear least squares computer program, and the mean value for each batch of ketone solution is recorded in Table 1. Correlation coefficients were in almost all runs better than 0.999. Data for the first 1—2 half lives were used in all cases except that of deuterio-ketone in (light) water, when the first 30—60 min were used corresponding to *ca.* 1/6 life. Attempts to use the Guggenheim method of fitting the first-order constant were very unsuccessful, giving different values and poor correlation coefficients, when the ketone and solvent were not in isotopic equilibrium. This is not surprising since the graphs could be seen to deviate from first order in the manner expected.

Corrections for incomplete isotopic labelling. From Table 1, as it stands, we can obtain the following figures, k_{H,H_2O} 1.87 ± 0.05, k_{H,D_2O} 4.514 ± 0.06, k_{D,H_2O} 0.304 ± 0.004, and k_{D,D_2O} 0.813 ± 0.016 l mol^{-1} s^{-1}, *i.e.* $k_{H,H_2O}/k_{D,H_2O} = 6.17 \pm 0.45$, $k_{H,D_2O}/k_{D,D_2O} = 5.55 \pm 0.18$, $k_{H,D_2O}/k_{H,H_2O} = 2.40 \pm 0.10$, and $k_{D,D_2O}/k_{D,H_2O} = 2.67 \pm 0.17$. Correction for the solvent, which is only 92% D_2O, can be made from the data in ref. 12. By graphical interpolation the solvent isotope effect should be underestimated in this solution by a factor of 1.45.

Applying corrections for 100% labelling of solvent we get k_{H,H_2O} 1.87, k_{H,D_2O} $4.514 \times 1.45 = 6.55$, k_{D,H_2O} 0.304, and k_{D,D_2O} $0.813 \times 1.45 = 1.18$, and hence $k_{H,H_2O}/k_{D,H_2O} = 6.15$, $k_{H,D_2O}/k_{D,D_2O} = 5.55$, *i.e.* $k_H/k_D = 5.9$ and $k_{H,D_2O}/k_{H,H_2O} = 3.48$, $k_{D,D_2O}/k_{D,H_2O} = 3.88$, *i.e.* $k_{D_2O}/k_{H_2O} = 3.7$.

Similarly from the data in Table 2 we get, with the solvent corrections, k_{H,H_2O} 35, k_{H,D_2O} $8.0 \times 1.45 = 115$, k_{D,D_2O} 6.0, and k_{D,D_2O} $15.4 \times 1.45 = 22$, and hence $k_{H,H_2O}/k_{D,H_2O} = 5.8$, $k_{H,D_2O}/k_{D,H_2O} = 5.16$, *i.e.* $k_H/k_D = 5.5$ and $k_{H,D_2O}/k_{H,H_2O} = 3.5$, $k_{D,D_2O}/k_{D,H_2O} = 3.7$, *i.e.* $k_{D_2O}/k_{H_2O} = 3.6$.

The asterisked runs in Tables 1 and 2 are for the same batch of ketone solutions as the previous ones, but which have stood for 24—36 h. While we would normally prefer to take the older solution values as more valid (since isotopic equilibrium should then be complete), we are discouraged by the facts that (a) the 20% drift is in the direction opposite to that expected (since, at first, the solvent is less completely deuteriated than the ketone), and (b) the final value would need a larger correction for departure from 100% deuteriation of the ketone. As it is likely that solutions of ketone in acid are not indefinitely stable, and as all the other measurements on labelled systems were taken, of necessity, as soon as possible after mixing, we have not used the asterisked values. The same phenomenon was observed when ruthenium(III) was used, though the effect is smaller.

With both oxidants one would anticipate that 3% of H remaining in the deuteriated ketone would result in an acceleration of *ca.* 18%, *i.e.* that the k_H/k_D values should be increased by this percentage, giving 6.9 for $IrCl_6^{2-}$, and 6.5 for Ru^{III} when fully corrected for incomplete isotopic substitution and these values have been used in the discussion.

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