Ruthenium-catalysed C–H Bond Activation. Evidence for a Concerted Mechanism in Oxyfunctionalization of Cyclic Saturated Hydrocarbons

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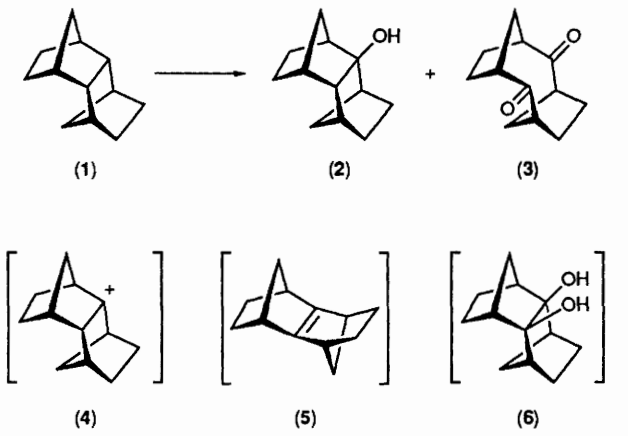
Oxidation of bridged polycyclic alkanes with *in situ* generated RuO_4 occurs by a concerted mechanism involving interaction of the highly electrophilic oxoruthenium species with tertiary unhindered C–H bonds.

We have recently reported that tertiary hydroxylation of saturated bridged bicyclic and tricyclic alkanes can be achieved efficiently using ruthenium tetraoxide generated *in situ*.[1] These reactions were carried out with catalytic amounts of $RuCl_3$, and stoichiometric quantities of $NaIO_4$ in a CCl_4–MeCN–H_2O solvent mixture, and usually take place under mild conditions between room temperature and 70 °C.† We report here evidence which favours a concerted mechanism involving the interaction of a tertiary C–H bond with a highly electrophilic oxoruthenium species. This is in contrast with previously reported results favouring a carbonium ion intermediate resulting from hydride abstraction.[2] The absence of bridgehead hydroxylation,[1,2] the preferential hydroxylation of tertiary bridgehead carbon atoms rather than the secondary atoms in adamantane, and kinetic data[2] have been taken as support for carbonium ion intermediates. This appeared unlikely to us, as we observed[1] neither Wagner–Meerwein rearrangement products[3] nor oxidation derivatives thereof. Furthermore DMDN (**1**)‡ is hydroxylated to yield the tertiary alcohol (**2**) accompanied by the diketone (**3**). If a carbonium ion had been involved in the formation of (**2**) it would have readily rearranged to 2-cyclopentenylnorbornane[5] (a rearrangement which occurs even at −25 °C).

It is, therefore, unlikely that the diketone (**3**) has compound (**5**) as the precursor as the latter could only have been formed *via* (**4**). Consequently it is much more reasonable to assume that further hydroxylation of (**2**) gives rise to the formation of the *cis*-glycol (**6**) which is then readily cleaved to give the diketone (**3**) by sodium periodate. Indeed the isolated alcohol (**2**) is oxidized to (**3**) under the same conditions.

† As emphasized in Table 1, lowering the temperature from 70 to 25 °C does not change the outcome of the reaction but only slows its rate. We have shown that RuO_4 is indeed the active oxidizing species by carrying out experiments under stoichiometric conditions: A. Tenaglia and B. Waegell unpublished results.

‡ DMDN = 1,2,3,4,4a,5,6,7,8,8a-decahydro-1,4-*exo,endo*-5,8-dimethanonaphthalene. It is obtained by hydrogenation of the Diels–Alder adduct between norbornene and cyclopentadiene. For the stereochemistry of the Diels–Alder adduct see ref. 4.



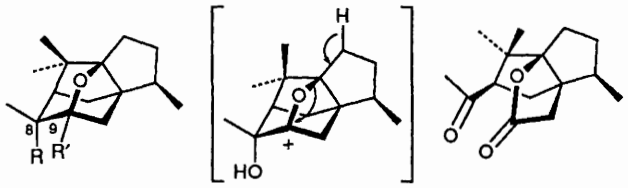
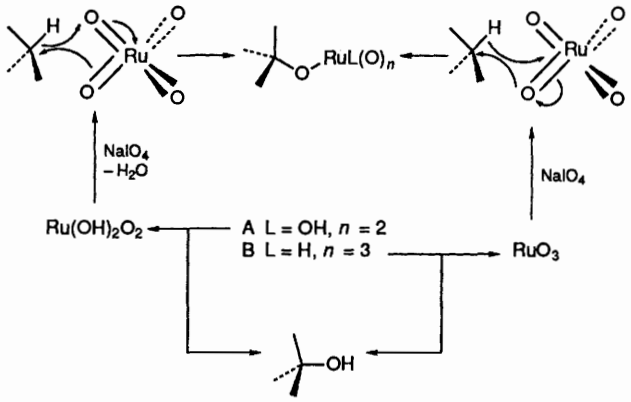


Table 1. Influence of conditions on the oxidation of DMDN (1) by RuO_4.[a]

		Isolated yield (%)	
T/°C	t/day	(2)	(3)
70	1	73	13
25	11	72	13
25	8[b]	25	—
60	6[c]	—	35

[a] See ref. 1. [b] Triethylbenzylammonium chloride was used as phase-transfer catalyst. [c] Excess of sodium periodate was used; molar ratio (1) : $NaIO_4$: $RuCl_3$, 1 : 8.2 : 0.02.

Moreover it is interesting to consider the reactivity of neoisocedranol oxide[8] (7) featuring two vicinal unhindered tertiary C–H bonds (at C-8 and C-9) which are likely to be hydroxylated. That α to the oxygen atom of the tetrahydrofuran ring (C-9–H) should be the most reactive, since such rings are readily oxidized to corresponding lactones.[6] The latter process involves a stabilized carbonium ion intermediate[7] similar to (**10**). If such a carbonium ion had been involved, the initial hydroxylation would have occurred on C-9, thus leading to a fragmentation reaction[8] as a consequence. However, hydroxylation occurs first on the somewhat less hindered C-8–H bond to give the alcohol (**8**) (60%) and keto-lactone (**11**) (25%). This cleavage product (**11**) is most likely formed *via* the intermediate *cis*-glycol (**9**), and can also be obtained directly from neoisocedranol oxide (**7**) in 75% isolated yield by using a large excess of reoxidizing $NaIO_4$ [14 equiv. with respect to (**7**)]. It can also be obtained by oxidation of the isolated alcohol (**8**) under the same conditions.



Scheme 1. Mechanistic pathways for RuO_4 oxidation of C–H bonds.

All these observations are more consistent with a concerted oxidation mechanism§ than with the formation of a carbonium ion as previously postulated.[2] However it is possible to reconcile our results with those of Bakke and Lundquist by considering that the reaction occurs[9] on a polarized $C^{\delta+}$–$H^{\delta-}$ bond where the polarization is induced by the approach of the very electrophilic ruthenium tetraoxide.

At this stage, it is difficult to decide whether an alkoxyhydroxo-oxoruthenium **A** (L = OH) or alkoxyhydrido-oxoruthenium species **B** (L = H) is involved as a key intermediate (Scheme 1). The former would be more stable, but would require a hydrolysis step, whereas the latter, although less stable, would readily undergo reductive elimination to yield directly the hydroxylation product. Both intermediates would explain the easy formation of a *cis*-α-glycol when two *cis*-tertiary C–H bonds are available as in the formation of (**6**) or (**9**).

We are now attempting to elucidate the intimate nature of the organometallic intermediates involved in these oxidization reaction.

We thank Drs. Delavarenne and Grosius for stimulating discussions and Orkem/Norsolor for financial support (to E. T.).

Received, 15th December 1989;¶ Com. 9/05337I

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§ In answer to a referee's comment it is interesting to point out that the mixture of epicedrane (8α-H) and cedrane (8β-H) (obtained by catalytic hydrogenation of cedrene) is hydroxylated exclusively into epicedrol (8α-OH), whereas the cedrane remains unchanged.

¶ Received in revised form 29th May 1990.