Stereochemical Aspects of the Vanadium-catalysed Epoxidation of Conformationally Biased Cyclohex-2-en-1-ols by Alkyl Hydroperoxides

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In the vanadium-catalysed epoxidation of *cis*- and *trans*-5-t-butylcyclohex-2-enol the *trans*-(pseudoaxial) alcohol is epoxidised *ca.* 34 times faster than the *cis*-isomer. A significant competing process is oxidation to αβ-unsaturated ketone, and this becomes the predominant reaction in the case of the *cis*-alcohol.

THE epoxidation of olefins by alkyl hydroperoxides has been shown to be catalysed by transition metal complexes, notably those of molybdenum, tungsten, or vanadium.[1] Apart from the industrial importance of this reaction, an intriguing feature is that although molybdenum catalysts are more efficient than those of vanadium for epoxidation of simple alkenes, vanadium catalysts are particularly effective for allylic alcohols. Thus epoxidation of allylic alcohols by hydroperoxide catalysed by vanadyl acetylacetonate [VO(acac)$_2$] is up to 200 times faster than for the parent olefin (H in place of OH). Furthermore the *cis*-directing effect of a hydroxy-group, observable in suitably constituted allylic alcohols, which is well known for peracid epoxidations, is very much enhanced when the t-butyl hydroperoxide–VO(acac)$_2$ combination is used.[2,3] Thus with cycloalk-2-enols a consistently greater *cis*-stereoselectivity is found for the VO(acac)$_2$-catalysed than for the peracid epoxidation (Table 1). Particularly striking

TABLE 1

Stereochemistry of epoxidation of cyclic allylic alcohols [a]

Substrate	Peracid [b]	Bu^{t}OOH–VO(acac)$_2$
Cyclohex-2-enol	95	99.7
Cyclohept-2-enol	61	99.6
Cyclo-oct-2-enol	0.2	97
Cyclonon-2-enol	0.2	91

[a] Figures are percentage of *cis*-epoxy-alcohol formed.[4]
[b] *m*-Chloroperbenzoic acid–CH$_2$Cl$_2$ at 0 °C.

are the results for the eight- and nine-membered rings where the stereoselectivities for the two methods of epoxidation stand in sharp contrast.[4]

Some years ago we investigated the peracid epoxidation of the conformationally biased 5-t-butylcyclohex-2-enols and showed that the pseudo-equatorial (*cis*-)-alcohol was epoxidised with higher *cis*-stereoselectivity and at a faster rate than the pseudo-axial alcohol.[5] It seemed of interest to study epoxidation of the same alcohols using the Bu^{t}OOH–VO(acac)$_2$ procedure, and this paper describes our results. We find that the pseudo-axial alcohol is epoxidised more rapidly than the pseudo-equatorial and that an important competing reaction is oxidation to the αβ-unsaturated ketone which detracts from the preparative usefulness of the reaction.

RESULTS AND DISCUSSION

The preparation and characterisation of cyclohex-2-enol, the 5-t-butylcyclohex-2-enols, and the related

stereoisomeric epoxy-alcohols has been described in our previous paper.[5]

In the work of Sharpless and Michaelson on VO(acac)$_2$ catalysed epoxidation of cyclohex-2-enol, reaction was only carried out to 5% completion since they were only concerned with a mechanistic study and not with preparative epoxidation. At first our attempts to obtain preparatively useful yields were unsuccessful. However after careful redistillation of t-butyl hydroperoxide a 50% isolated yield of *cis*-2,3-epoxycyclohexanol could be obtained using VO(acac)$_2$ in toluene at 75 °C. The epoxy-alcohol was shown to contain <1% of the *trans*-isomer. A significant by-product was cyclohex-2-enone (11%) which had not previously been reported by earlier workers.

The two 5-t-butylcyclohex-2-enols were each treated with Bu^{t}OOH–VO(acac)$_2$ under similar conditions. Results obtained are summarised in Table 2 along with

TABLE 2

Bu^{t}OOH–VO(acac)$_2$ Epoxidation of cyclohex-2-enols

| Substrate	Products		Isomeric purity of epoxy-alcohol (% cis)	$\dfrac{k_e(\mathrm{eq})}{k_e(\mathrm{ax})}$	$\dfrac{k_o(\mathrm{ax})}{k_o(\mathrm{eq})}$
	enone (%)	epoxy-alcohol (%)			
Cyclohex-2-enol	11	89	>99		
trans-5-t-Butyl-cyclohex-2-enol(ax)	8 [a]	92 [a]	>99.9	34	0.29
cis-5-t-Butyl-cyclohex-2-enol(eq)	91 [a]	9 [a]	>99		

[a] Assuming g.l.c. response ratio of unity for enone : epoxy-alcohol.

those for cyclohex-2-enol. Also included are estimates of the relative rates of epoxidation to epoxy-alcohol [$k_e(\mathrm{ax})/k_e(\mathrm{eq})$] and of oxidation to enone [$k_o(\mathrm{ax})/k_o(\mathrm{eq})$] obtained from competition studies (see Experimental section).

Highly stereospecific epoxidation *cis* to hydroxyl is found for both allylic alcohols and the pseudo-axial alcohol is epoxidised faster than the pseudo-equatorial by a factor of 34, in contrast to the result, mentioned above, for peracid epoxidation. The competing reaction of oxidation to enone proved serious in the case of the pseudo-equatorial alcohol, and unless a means can be found of obviating this process the synthetic usefulness of the catalysed reaction for such alcohols is clearly limited. Fortunately the two methods of epoxidation of allylic alcohols are conveniently complementary in their stereochemical propensities, and we recommend, on

the basis of our results, that peroxy-acid epoxidation should be used for the preparation of *cis*-epoxy-alcohols from pseudo-equatorial alcohols, and the hydroperoxide–$VO(acac)_2$-catalysed process for pseudo-axial alcohols.

Previous work on the mechanism of transition-metal-catalysed alkyl hydroperoxide epoxidation [6] has culminated in the suggestion that for allylic alcohols an intermediate species is involved in which the oxygen of the alcohol and the oxygen of the hydroperoxide further from the alkyl group are co-ordinated to the metal atom.[7] In our cases the key step in epoxidation would correspond to (1) ⟶ (2). Clearly the steric demands of the transition state would be better satisfied for a pseudo-axial hydroxyl, and our results provide further

(1)   (2)
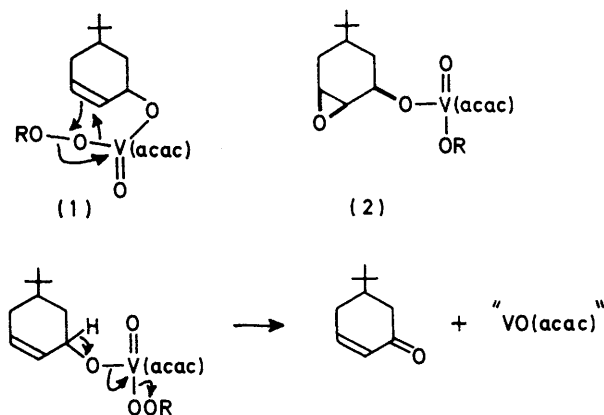
SCHEME

justification for an intracomplex mechanism of this type. A possible route to enone could be by an alternative mode of breakdown of the vanadium(v) complex (see Scheme) followed by re-oxidation of the V^{III} fragment by hyroperoxide. It is known from studies of chromium(vi) oxidation of allylic alcohols that unhindered pseudo-equatorial are oxidised faster than pseudo-axial alcohols,[8] and the rate difference is of the same order of magnitude as that found here.

EXPERIMENTAL

^1H N.m.r. spectra were recorded with a Perkin-Elmer R 24 instrument operating at 60 MHz unless otherwise stated. G.l.c. was carried out using either 15% Apiezon L (column A) or 15% TCEP (column B) as stationary phase.

Vanadyl-catalysed Epoxidation of Cyclohex-2-enol with t-Butyl Hydroperoxide.—Cyclohex-2-enol (5 g) was dissolved in dry toluene (25 ml). t-Butyl hydroperoxide (4.6 g; dried over $MgSO_4$ and redistilled; b.p. 36—40 °C at 19 mmHg; 96% pure by iodometric titration) and vanadyl acetylacetonate (0.1 g, 0.012 mol. equiv.) were added and the solution was maintained at 75 °C for 5 h. G.l.c. (column A) showed that <10% of starting material remained and that *cis*-2,3-epoxycyclohexanol (89%) and cyclohex-2-enone (11%) were present. No *trans*-epoxy-alcohol could be detected. The solution was extracted with water (4 × 25 ml), after which no epoxy-alcohol was present in the organic phase (g.l.c.). Brine (30 ml) was added to the aqueous phase which was extracted with chloroform (10 × 50 ml). Evaporation followed by distillation gave *cis*-2,3-epoxy-

cyclohexanol (2.9 g, 50%), b.p. 86.5—88 °C at 10 mmHg (lit.,[5] 100—102 °C at 13 mmHg), identified by comparison with an authentic sample.

The same product distribution was obtained by carrying out the reaction at 20 °C. In this case, 90% of starting material was consumed after 5 days.

In a further experiment, direct distillation of crude product from the reaction mixture (carried out at 75 °C) gave a 40% yield of epoxy-alcohol contaminated with cyclohex-2-enone (8%).

Vanadyl-catalysed Epoxidation of trans-5-*t-Butylcyclohex-2-enol with t-Butyl Hydroperoxide.*—*trans*-5-t-Butylcyclohex-2-enol (0.29 g), t-butyl hydroperoxide (0.175 g), and vanadyl acetylacetonate (0.01 g) were dissolved in dry toluene and maintained at 75 °C for 2 h by which time the reaction was complete (g.l.c., column A). The epoxy-alcohol produced was >99.9% *cis*-2,3-epoxy-*trans*-5-t-butyl-cyclohexanol, but contained 5-t-butylcyclohex-2-enone (8% assuming a response ratio of unity). Evaporation of solvent and distillation gave the *cis*-2,3-epoxy-*trans*-5-t-butyl-cyclohexanol b.p. 71—73 °C at 0.6 mmHg (lit.,[5] 71—73 °C at 0.05 mmHg). The identity of the product was confirmed by comparison of i.r. and n.m.r. data with those of an authentic specimen.[5]

Epoxidation of cis-5-*t-Butylcyclohex*-2-*enol.*—*cis*-5-t-Butylcyclohex-2-enol (37.5 mg), t-butyl hydroperoxide (22.5 mg), and vanadyl acetylacetonate (1.6 mg) in dry toluene (1 ml) were maintained at 75 °C for 2 h by which time >90% of the starting material had been consumed (g.l.c., column A). The product contained *cis*-2,3-epoxy-*cis*-5-t-butylcyclohexanol (9%) and 5-t-butylcyclohex-2-enone (91%) assuming a response ratio of unity. The isomeric purity of the epoxy-alcohol was >99% as judged by g.l.c. comparison with mixtures of authentic samples.

In a control experiment using similar conditions, but omitting the vanadium catalyst, no starting material had been consumed after 6 h.

Competitive Reaction of cis- *and* trans-5-*t-Butylcyclohex-2-enols with t-Butyl Hydroperoxide.*—A mixture of *cis*- and *trans*-5-t-butylcyclohex-2-enols (25 mg of each) and vanadyl acetylacetonate (3 mg, 0.05 mol. equiv.) were dissolved in dry toluene (5 ml) and heated to 75 °C. Tetrahydronaphthalene (15 mg) was added as a g.l.c. standard. t-Butyl hydroperoxide (35 mg) was added to the stirred solution and portions were removed at regular intervals over 80 min. The portions were quenched by cooling and diluting with ether and were analysed by g.l.c. (column B). From a plot of concentration against time, initial rates of disappearance of each allylic alcohol were estimated from gradients at t 0, giving a value k_{trans}/k_{cis} of 3.26 (3.38 in a duplicate run). The relative rate constants quoted in Table 2 were derived on the basis that $k_{trans}/k_{cis} = (k_e + k_o)_{trans}/(k_e + k_o)_{cis}$, where k_e and k_o represent rate constants for epoxidation and oxidation (to enone) respectively, and that $(k_e/k_e + k_o)_{trans}$, *i.e.* the fraction of *trans*-allylic alcohol giving epoxide, $=0.92$ while $(k_e/k_e + k_o)_{cis} = 0.09$. This treatment obviously assumes the same order with respect to vanadyl acetylacetonate and t-butyl hydroperoxide for the epoxidation and oxidation reactions.

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