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NATURE OF THE CATALYTIC CYCLE IN IRIDIUM-COMPLEX CATALYSED HYDROGENATION OF UNSATURATED ALCOHOLS

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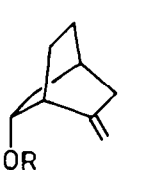
Abstract: The endo face specific reduction of endo-6-methylenebicyclo[2,2,2]octan-2-ol and endo-6-methylbicyclo[2,2,2]-oct-5-en-2-ol with D_2 and iridium catalysts is accompanied by deep-seated isotopic redistribution through an intramolecular mechanism, although only two deuterium atoms are incorporated on average. Individual isotopomers of the product may be identified in the ^{13}C N.m.r. spectrum at 125 MHz, and their ratio is generally consistent with a mechanism in which product is formed by breakdown of an alkyliridium trihydride. Iridium (and rhodium) catalysts part-isomerise the exocyclic olefin to its endocyclic isomer via an Ir-allyl intermediate without incorporation of deuterium. The reduction of 3-methylcyclohex-2-enol is likewise accompanied by considerable scrambling, with isotopic enrichment occurring at C2, C3, C4 and C5 of the product, trans-3-methylcyclohexanol. Deuteration occurs exclusively on the hydroxyl-bearing face of the molecule.

The preceding paper is concerned with hydroxyl-directed hydrogenation of unsaturated bicyclo[2,2,2]octan-2-ols. Catalysis by rhodium complexes was accompanied by olefin isomerisation and the products derived by D_2 addition were readily analysed as a result of the competitive reduction of exo- and endocyclic olefins. Carrying out related reactions with iridium catalysts led to a complex mixture of isotopically labelled products, revealing the reaction mechanism in unexpected detail.

Analysis of results

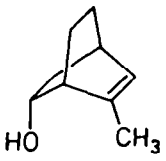
Compound (1) and its endocyclic isomer (2) were prepared as described and reductions carried out by standard methods.[1] Addition of D_2 was carried out in CH_2Cl_2 solution and the product (3) isolated by preparative g.l.c. Analysis by ^1H and ^2H N.m.r. showed that the product from reduction of (1) catalysed by complex (4)[2] bore a superficial resemblance to the Rh^+-catalysed reaction. Approximately 2.0 deuterium atoms were distributed between C5 (endo), C6 (endo) and C9 in the ratio 0.54: 0.66: 0.75. The most striking feature, also quite evident in the ^1H N.m.r. is the incomplete deuteration at C6. This indicates that, unlike the rhodium case, reaction cannot proceed by direct addition of D_2 to compound (1) or to an equilibrating mixture of (1) and (2).

Similar observations were made when addition of D_2 was catalysed by complex (5)[3] and the deuterium distribution to C5 (endo), C6 (endo) and C9 is then 0.66: 0.58: 0.66. The pattern is maintained in reduction of methyl ether (6) with 0.57, 0.70 and 0.74 atoms of deuterium at C5, C6 and C9 respectively. The endocyclic olefin (2) shows less extensive deuterium scrambling but there is still substantial deuteration at C9.



1 R=H

6 R=CH_3



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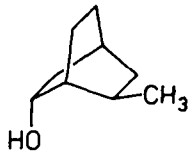

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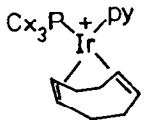

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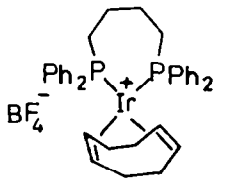


5

The ^{13}C spectrum of compound (3) was instrumental in analysis of the pattern of deuteration. It was assigned by direct comparison with literature chemical shifts[4] for bicyclo[2,2,2]octan-2-ols. In accord with this, samples of (3) produced by D_2 addition with Rh^+ catalysts showed partial deuteration at C5, C6 and C9 consistent only with a mixture of isotopomers A and B (2). With Ir^+ catalysts at least nine products were formed, all of which were identified on the basis of empirically determined isotope shifts (Table 1). The β-shifts are always positive, and in accord with literature values[5] but the γ-shift induced at C6 by deuteration at C9 is to high field by 0.04 p.p.m., and the γ-shift induced at C9 by deuteration at C6 (endo) is to low field by 0.01 p.p.m.[6] In addition, γ-deuteration causes a slight but characteristic broadening through long-range coupling.

	C5	C6	C9
α	0.41	0.43	0.31
β	0.12	0.11,0.09*	0.12
γ	0.04	--	-0.01

* to C9

TABLE 1. Deuterium isotope shifts for the three labelled carbons. Upfield shifts are positive.

The C6 signal is best resolved and may be analysed quantitatively (Figure 1) on the assumption that all isotopomers are equally relaxed[7] so that signal areas represent a true measure of relative proportions. The results are internally consistent (see footnotes to Table 2) and give a predicted deuterium distribution which is consistent with that observed in the ^2H N.m.r. spectrum. Furthermore the results agree well with limited mass spectrometric data (Table 3) providing us with sufficient confidence to attempt a quantitative interpretation. One important feature is the presence of d_0 and d_4-isotopomers in small amounts. The latter implies the presence of CHD_2-components and these are confirmed by the observation of a weak pentuplet in the expected position at C9, consistent with J, and a weak peak as part of C6 with an upfield shift of (2β + β') corresponding to I.

The endocyclic olefin (2) on deuterium reduction gave rise to a very much simpler product distribution in which the main component B is derived by direct addition. A smaller quantity of isomer A is present along with other d_1, d_2 and d_3 species (Table 2). As will be seen, the results are entirely consistent with those obtained in the reduction of compound (1) with D_2.

Control experiments

The reduction of exocyclic alcohol (1) was carried out with a deficiency of D_2. The components were separated by preparative g.l.c. into starting material, endocyclic isomer (2) and product (3). The first two compounds were shown to be completely lacking in deuterium enrichment by ^1H and ^2H N.m.r. spectroscopy, whereas the product (3) had substantially similar isotopic distribution to that observed under standard conditions. A similar result was obtained when compound (1) was reduced with $Rhdppb^+$ and a deficiency of D_2, in that recovered starting material and its endocyclic isomer had not incorporated isotope. These results demand that isomerisation occurs by an allyl-hydride mechanism (Figure 2) rather than addition-elimination, which would have led to deuterium incorporation in the methyl-group. Catalysed isomerisations by the allylmetal hydride route are known[8] but they are rarer than the addition-elimination process under the conditions of homogeneous hydrogenation.[9]

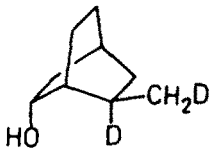
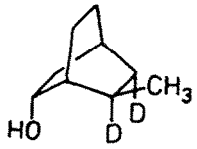
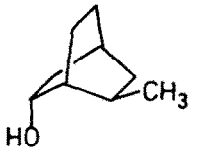
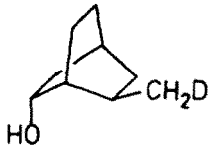
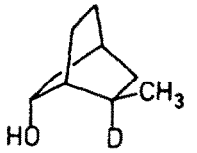
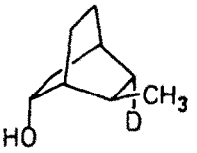
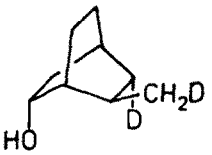
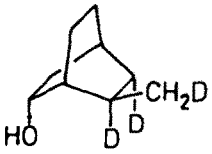
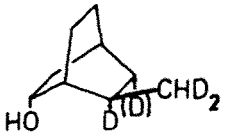
Compound		Reduction	% C5	δ C5	δ C6	CH_3
	A	I	26			
		II	28	0.15	0.52	0.43
		III	13			
	B	I	74			
		II	9	0.53	0.55	0.09
		III	57			
	C	II	2	0.0	0.0	0.0
		III	-			
	D	II	5	0.04	0.09	0.31
		III	-			
	E	II	13	0.12	0.43	0.12
		III	13			
	F	II	6	0.41	0.11	-0.01
		III	2			
	G	II	19	0.44	0.20	0.30
		III	2			
	H	II	16	0.57	0.63	0.42
		III	15			
	I (J)	II	~2 (2)		0.29	

Table 2 Isotopomer ratios produced in deuterium reductions. Chemical shifts are upfield from the fully protiated compound [C5 35.49, C6 21.98, C9 20.19 p.p.m.] and agree with predicted values (Table 1) within 1 Hz. Analysis of C6 and C9 was consistent with the data above but in the first case only the protonated carbon signals were analysed [C:D:F:G = 6:14:22:57] and in the second case overlaps hindered full signal analysis [(F+C) : (B+E) : (D+G) : (A+H) = 9:22:24:42]. Procedures: (I), $Rhdppb^+$, compound (1); (II); catalyst (4) compound (1); (III), catalyst (4), compound (2). All analyses were carried out by direct weighing of scale-expanded traces.

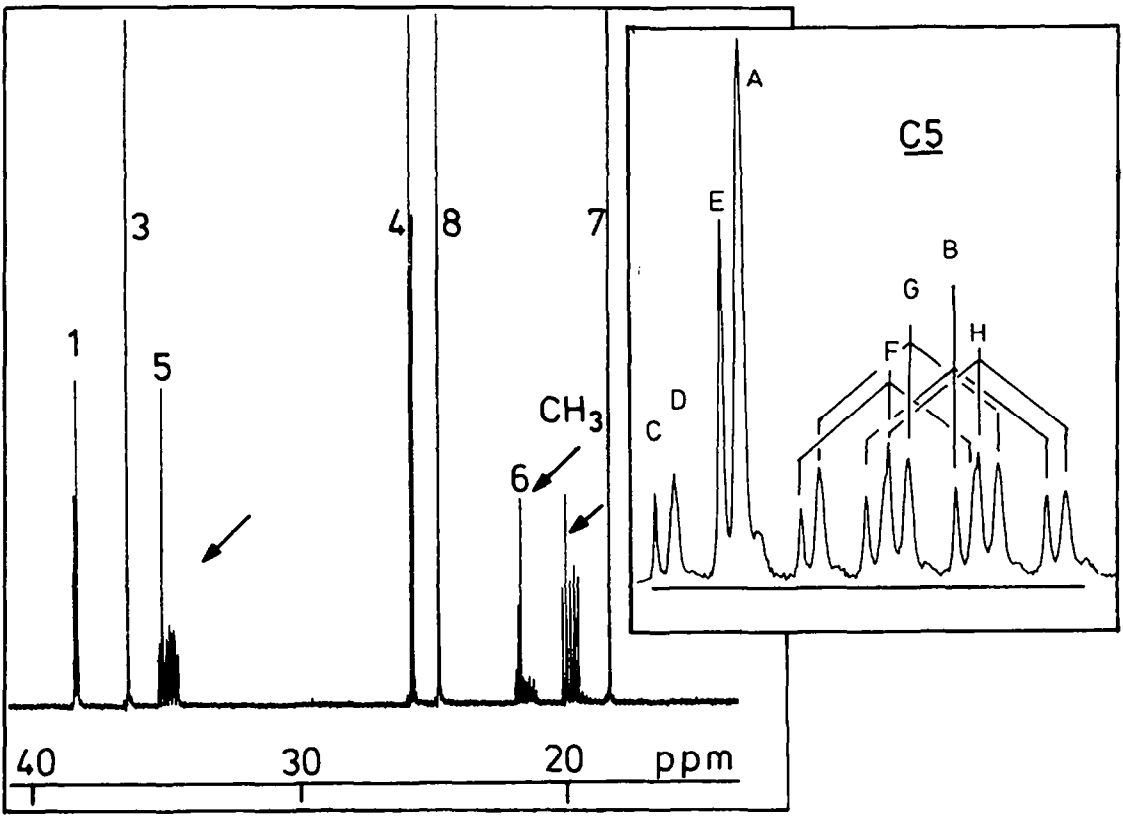
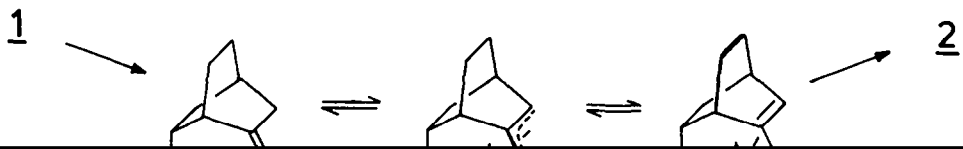


Figure 1 ^{13}C N.m.r. spectrum at 125.7 MHz of the reduction product (3) employing catalyst (4) and D_2 in CH_2Cl_2. C2 is off-scale at 70.0 p.p.m.

	Exocyclic alcohol (1) catalyst (4)	Exocyclic alcohol (1) Ir dppb$^+$	Exocyclic ether (6) catalyst (4)
d_0	1.5	9.5	0
d_1	17.5	23.6	17.4
d_2	56.1	40.3	61.0
d_3	20.9	23.3	20.0
d_4	4.0	3.3	1.6

Table 3 Deuterium distribution in reduction products analysed by mass spectrometry (CI,NH_3). Data are standardised by comparison with the mass spectra of undeuterated samples, in the mass range 138–144



Deuteriation of the O-H group in compound (1), and then reduction catalysed by complex (4) with H_2 did not lead to detectable C-D incorporation in the product. This demonstrates that exchange reactions between metal-bound O-H and Ir-D do not occur. Finally, the reduction product (3) was stirred for a protracted period with D_2 and catalyst (4) in CH_2Cl_2, without detectable deuterium incorporation. This means that all deuterium uptake is associated with the reduction process, and not with a subsequent C-H activation.[10]

The reaction mechanism

Any attempt to establish the catalytic cycle for iridium-catalysed directed hydrogenations must provide an explanation for the distribution of deuterium observed in reduction II (Table 2). This requires compatibility with the following specific features:

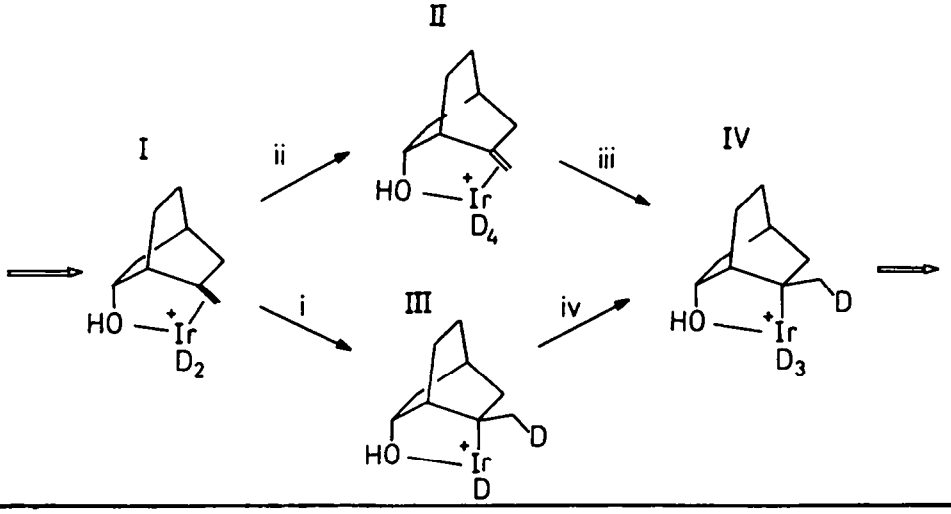
a) The average incorporation of deuterium is 2.0 within experimental error;
b) Deuterium appears only at C5, C6 and C9, being exclusively endo at the former two sites;
c) Comparable amounts of d_1- and d_3-isotopomers are produced along with a much smaller proportion of d_0- and d_4-isotopomers;
d) The CH_3-group (C9) contains 0.7 deuteriums, notwithstanding the absence of major exchange processes involving this centre, so that only a very small proportion of CHD_2-containing isotopomers is observed;
e) A very characteristic distribution of d_2-isotopomers (A > G >> B) and of d_1-isotopomers (E > D ∿ F) is obtained.

Since the experimental conditions are such that deuterium is present in substantial excess over the substrate, observation (a) requires that once deuterium has been transferred to the coordinated olefin, reaction proceeds irreversibly. This implies that the catalytic cycle proposed by Crabtree and co-workers[2] for hydrogenation with catalyst (4) cannot operate in the present case, since it offers no provision for production of d_1 and d_3-isotopomers in an irreversible process. Modification by an intermolecular exchange pathway at the alkyliridium hydride stage (i.e. Ir-D in one molecule with H5 endo in another) is conceivable. It is difficult to see how this is compatible with the small proportion of isotopomer D in the product, and with the substantial deficiency of deuterium in the C9 methyl group.

Allyliridium intermediates are implicated in the isomerisation of starting material at low concentrations of H_2 or D_2 (vide supra, Figure 2).The reduction cycle could in principle occur via deuterium addition to this intermediate,[11] together with some further unspecified exchange process. Any such mechanism predicts that the d_2-isotopomers A B and G will be present in comparable proportions, as will the d_1 isotopomers D, E and F, barring further constraints. This is not in accord with the experimental results.

Attention was then directed to addition-elimination mechanisms for the exchange process.For an irreversible catalytic cycle (i.e, no release of part-deuterated olefin) it is necessary to postulate that iridium-bound deuterium, part-exchanged with hydrogen at C5 endo, is carried forward from one catalytic cycle to the next. This feature is essential to explain the presence of d_0-d_4 isotopomers without invoking intermolecular exchange. Possible pathways were considered in more detail, according to Figure 3. There are two routes which differ in the timing of the hydrogen (deuterium) addition step indicated by (I → II → IV) and (I → III → IV) with the possibility of isotope exchange with H5 endo at one or more intermediate stages.

Figure 3 Exchange pathways



Deuterium distribution in the product was simulated for a number of possible mechanisms making the simplifying assumptions that both kinetic and equilibrium isotope effects can be ignored and that the $-CH_3$ group does not participate in the exchange process. The method is exemplified by that pathway in which isotope exchange occurs only at the iridium alkyl-deuteride stage (III, Figure 3). Intermediates I, III and IV are considered in all relevant isotopomeric forms and the partitioning between them in steps (i) and (iv) carried out. For example, the $IrHD$ analogue of I will partition equally between two isotopomers of III containing respectively $DIrCCH_3$ and $HIrCCH_2D$. The first of these will then give rise to IV with equal proportions of D_3IrCCH_3[H5 endo] and HD_2IrCCH_3[D5 endo] as a result of the exchange process. A simple iterative computer program was set up (see Experimental) which calculates the distribution of isotopomers in the product. Values were recorded after iteration for 20 cycles, after which the distribution did not change significantly.

It happens that this particular mechanism does not give a product distribution close to experiment, and neither does one where exchange occurs exclusively at stage II (Table 4). A closer, but still inaccurate simulation was obtained by permitting complete exchange with H5 endo both at stage III and stage IV. Further improvement was attained by assuming complete exchange at stage III and 50% exchange at stage IV. At this point all the main features of the isotopomer distribution had been simulated and in view of the many approximations in the model, further refinement was not attempted. The main shortcomings are in underestimating the proportions of 1,3-dideuterated isotopomer G and trideuterated isotopomer H. The former discrepancy can be accommodated by assuming some exchange at stage I, via an allyliridium hydride. The latter is most easily explained by involving some CH_2D IrD exchange at stage III or IV, which is in accord with the presence of small quantities of $-CHD_2$ isotopomers and the mass-spectral observation of d_4-containing species.

When similar procedures were carried out for the (I → II → IV) pathway with isotopic exchange permitted at stage I or stage II, comparable quantities of the d_2-isotopomers A, B and G were computed, since an intermediate with allylic symmetry would need to be involved.

Exchange Mechanism	A	B	C	D	E	F	G	H
III	43.4	6.7	0	6.6	10.1	3.3	9.9	20.0
II	15.6	15.6	1.2	4.4	12.1	4.4	23.2	23.5
I	19.3	19.3	0.7	6.6	6.7	6.6	19.2	21.4
III + IV	19.0	14.9	0.9	4.6	8.8	8.8	18.9	24.0
III + 0.5 IV	31.0	10.2	0.5	6.0	10.3	5.3	14.2	22.5
observed	28	9	2	5	13	6	19	16

Table 4. Computed values for isotopomer distribution based on different exchange models.

The most novel feature of the resulting mechanism (Figure 4) is that reductive elimination does not proceed directly from the first-formed alkyl III, but rather after a second addition step. There is independent evidence to suggest that iridium alkyls are rather stable, particularly when the metal-carbon bond is part of a heteroatom-stabilised chelate ring. To account for the observed deuterium distribution the iridium trihydride must undergo partial exchange with H5 endo; this requires partial dissociation (-OH or pyridine ??) to create a 16-electron intermediate capable of reversible β-hydrogen transfer.

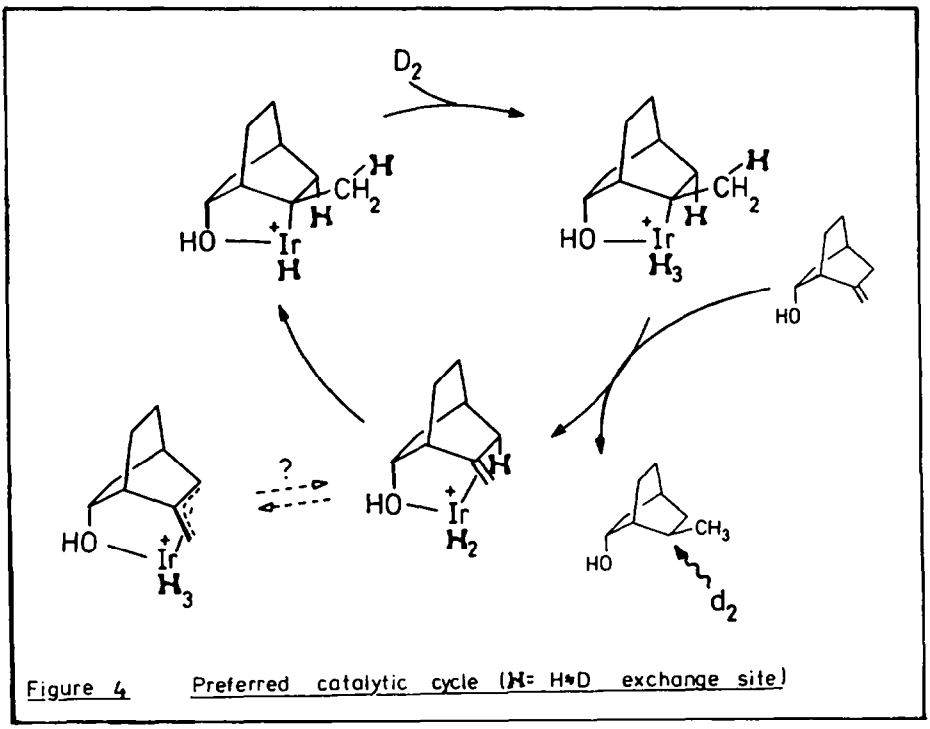


Figure 4 Preferred catalytic cycle (H= H⇌D exchange site)

Any mechanism based solely on the distribution of isotopomers in deuterated product must be tentative. Further work is necessary to test it, including both the identification of intermediates and definition of their reactivity under catalytic conditions. Nevertheless it is given weight by recent work of Crabtree and Lavin[13] in which it is shown that a stable chelated alkyliridium hydride reacts further with hydrogen, displacing a bound water molecule. The resulting $\eta^1\eta^2$-alkyltrihydride is in dynamic equilibrium with a trihydride of more conventional structure. Further, Gilbert and Bergman have isolated iridium trihydride cations,[14] in which unusually strong H····H interaction occurs. Other possibilities for the catalytic cycle of directed hydrogenation must remain open for the present, such as involvement of a binuclear species which remained intact during the catalytic cycle. Iridium (I) dimers have been implicated in the deactivation of catalyst (4) and are easily formed.[15] One analogy for our proposal is in hydrogenation with $ClHRu(PPh_3)_3$, where the catalytic cycle is sustained by a Ru-H species.[16]

Face - selectivity of isomerisation

The generality of isomerisation accompanying directed hydrogenation was demonstrated by reduction of 3-methylcyclohex-2-enol to trans-3-methylcyclohexanol with catalyst (4); this reaction has already been shown to proceed with high stereoselectivity.[17] Deuterium incorporation at C2, C3, C4 and to a smaller extent at C5 (but not the methyl-group) was demonstrated, and the complexity of the ^{13}C N.m.r. spectrum again indicated that a mixture of isotopomers had been formed. A complete analysis of the ^1H N.m.r. spectrum was then carried out by $^{13}C/^1H$ J correlation[18] (Figure 6). This clearly demonstrated that deuterium was only incorporated on the hydroxyl-bearing face of the molecule.

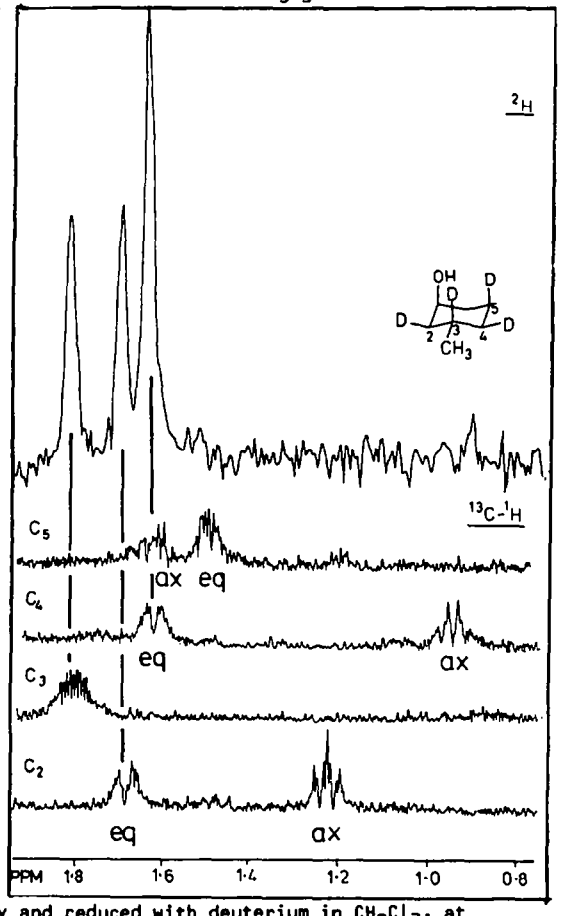


Figure 5 ^2H spectrum of deuterated trans-3-methylcyclohexanol from reduction superimposed on ^1H cross-sections of C_2, C_3, C_4 and C_5 from the $^{13}C/^1H$ shift correlation spectrum of undeuterated product.

Experimental

Samples were prepared as described previously and reduced with deuterium in CH_2Cl_2, at ca. 50:1 molar ratio substrate:catalyst. In a typical procedure alcohol (1) (0.015 gm., 0.11 Moles) and catalyst precursor (4) (0.002 gm, 0.25 Moles) were dissolved in CH_2Cl_2(1 ml.) under argon in a Schlenk tube, degassed thoroughly and the atmosphere replaced by deuterium. The frozen sample was allowed to thaw, when the orange solution immediately decolorised. Further warming to room temperature with agitation (Fison's "Whirlimix") led to the inception of a light yellow colour, characteristic of the completion of reaction. The sample was then

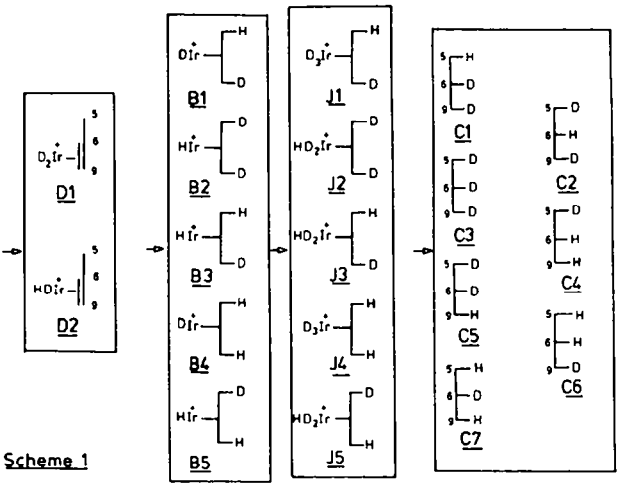
filtered through silica gel to remove catalyst and isolated by preparative g.l.c. (15% PEG.20M, 4.5m., 180°). N.m.r. spectra were recorded under standard conditions in $CDCl_3$ solution, ^1H and ^2H on a Bruker WH-300 spectrometer and ^{13}C on a Bruker AM-500 spectrometer. Mass spectra were recorded on a VG Micromass instrument in CI mode (NH_3) and were duly corrected by comparison with a standard sample.

Computed simulation of deuterium distribution

The procedure is illustrated for a mechanism in which the catalytic flux (I → III → IV) occurs with exchange in intermediate III (Figure 3). The cycle proceeds through a series of intermediates Dn (iridium dihydride adduct of olefin ≡ I) to Bn (alkyliridium hydride ≡ III) to Jn (alkyliridium trihydride ≡ IV) to product Cn. Each isotopomer is specified (D1 → Dn, etc.) and the progression from one stage to the next carried out in accord with Scheme 1. Note that in this particular case it is unnecessary to include intermediate Jn in the computation since there is no exchange process at that level. It is presumed that at step B full exchange occurs between H5 endo and Ir-D. The program commences with the proportion of B1 set at 100 and all other species at 0.00001 (to avoid multiplication by zero). A simple iterative routine is then carried out, and the proportions of each product isotopomer Cn determined after 20 cycles - with no change in the fifth significant figure after a further cycle. The iterative section of the program is as follows:

```
1  FOR Z = 1 TO 20 STEP 1
2  C1 = B1+.67*B3
3  C2 = .33*B2
4  C3 = .67*B2
5  C4 = .33*B5
6  C5 = .67*B5
7  C6 = .33*B3
8  C7 = B4
9  D1 = B1+B2+.33*(B3+B4+B5)
10 D2 = .67*(B3+B4+B5)
11 B1 = .5*D1
12 B2 = .5*D1
13 B3 = .5*D2
14 B4 = .25*D2
15 B5 = .25*D2
```

Similar procedures were carried out for all the pathways indicated in Table 4. In the example shown, the catalytic cycle requires only IrD_2 and IrHD carriers but when exchange at stage IV is involved then IrH_2 carriers must be included. Only in the latter case are d_0-products formed.



Scheme 1

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References

1. J.M. Brown and S.A. Hall, preceding paper.
2. R.H. Crabtree, H. Felkin and G.E. Morris, J.Organometal Chem., 141, (1977) 205; R.H. Crabtree, P.C. Demou, D. Eden, J.M. Mihelcic, C.A. Parnell, J.M. Quirk and G.E. Morris, J.Am.Chem.Soc., 104, (1982) 6994, and intervening papers.
3. D.A. Evans and M.M. Morrisey, Tetrahedron Letters, 4637, (1984).
4. J.B. Stothers and C.J. Tan, Canad.J.Chem., 54, 917, (1976), P.J. Garratt and R. Riguera, J.Org.Chem., 465; 41, (1976); S.Berger, J.Org.Chem., 43, 209, (1978); S.F. Nelsen and G.R. Weisman, J.Amer.Chem.Soc., 98, 1842 (1976); E. Wenkert, D.W. Cochran, H.E. Gottlieb, E.W. Hagaman, R.B. Filho, F.J.L. Abreu Matos and M.I.L.M. Madruga, Helv.Chim.Acta, 59, 2437, (1976).
5. P.E. Hansen, Annual Reps in NMR Sepctroscopy 15, 105, (1983).
6. R. Aydin and H. Günther, J.Amer.Chem.Soc., 103, 1301 (1981); D.G. Morris and A.M. Murray, J.Chem.Soc. Perkin II, 1579 (1976).
7. In ^{13}C spectra the peak heights of secondary and teriary carbons in undeuterated compound (3) were comparable in intensity. Comparison with molecules of similar structure [J.R. Lyerla, Jr, and G.C. Levy, "Topics in Carbon-13 N.m.r. spectroscopy" Chapter 3. G.C. Levy, Ed., Wiley-Interscience, New York 1974] suggests that $-CH_2$ sites in compound (3) will have T_1 values of ca. 2.5 s., and -CH or CHD sites will have T_1 values of Ca. 5s. Spectra were recorded with a flip angle of 45° and a relaxation delay of 1.6 s. (parameters chosen to ensure adequate signal to noise at the sample concentrations available) so that CHD signals may be less completely relaxed than CH_2 signals. The discrepancy is likely to be small, since the proportions of deuteration at C5, C6 and C9 estimated from the ^{13}C spectrum are 0.52:0.68:0.72 in close agreement with the proportions calculated from the ^{2}H N.m.r. spectrum. Since a 20% error in measuring signal areas of CHD isotopomers relative to CH_2 isotopomers would change the recorded proportions by less than 2%, no further correction was attempted.
8. K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori and S. Otsuka, J.Am.Chem.Soc., 106, 5208 (1984).
9. R.R. Schrock and J.A. Osborn, J.Am.Chem.Soc., 98, 2134 (1976).
10. R.H. Crabtree, M.F. Mellea, J.M. Mihelcic and J.M. Quirk, J.Am.Chem.Soc., 104, 107, (1982); H. Felkin, T. Fillebeen-Khan, Y. Gault, R. Holmes-Smith and J. Zakrazewski, Tetrahedron Letters 1279, (1984).
11. W.D. McGhee and R.G. Bergman, J.Am.Chem.Soc., 107, 3388, (1985).
12. N.W. Alcock, J.M. Brown, A.E. Derome and A.R. Lucy, J.Chem.Soc.Chem.Commun., 575 (1985); M. Basato, B. Longato, F. Morandini and S. Bresadola, Inorg.Chem., 23, 3972, (1984).
13. H.H. Wang and L.H. Pignolet, Inorg.Chem., 19, 1470, (1980); R.H. Crabtree, Acc.Chem.Res., 12, 331, (1979); R. Bau, R.G. Teller, S.W. Kirtley and T.F. Koetzle ibid, 12, 176, (1979).
14. F.H. Jardine, Prog.Inorg.Chem., 31, 265, (1984).
15. R.H. Crabtree and M. Lavin, J.Chem.Soc.Chem.Commun., 794, (1985).
16. T.M. Gilbert and R.G. Bergman J.Am.Chem.Soc., 107, 3502, (1985).
17. G. Stork and D.E. Kahne, J.Am.Chem.Soc., 105, 1072 (1983).
18. G. Bodenhausen and R. Freeman, J.Am.Chem.Soc., 100, 320 (1978); R. Freeman and G.A. Morris, J.Chem.Soc.Chem.Commun., 684 (1978); R. Benn and H . Günther, Angew.Chem. Int.Ed., 22, 350 (1983).