

Aspects of Catalysis. Part V.¹ Stereoselectivity in the Transition Metal-catalysed Transfer of Hydrogen to Cyclohexanones

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Substituted cyclohexanones (3- and 4-t-butyl, 2-methyl, and 3,3,5-trimethyl) are reduced to alcohols when heated with propan-2-ol in the presence of metal catalysts prepared by precipitation methods; ruthenium is particularly effective. The stereoselectivity of the reduction depends on the metal used, and on kinetic and equilibrium control during the reaction.

RECENT work shows that substituted cyclohexanones can be reduced either to the more stable equatorial alcohols² or to the less stable axial alcohols³ with a stereoselectivity in each case of more than 95%. The reactions involved proceed in solution and so it was of interest to examine the reduction of the ketones under heterogeneous conditions. Some observations in this area have been reported: for example, the formation of a 45:35:55:65 ratio of axial to equatorial alcohols in the reduction of 4-t-butylcyclohexanone by hydrogen in acetic acid with a platinum catalyst, and the change of this ratio to 78:22 when hydrochloric acid is also present.⁴

Reduction can also be effected in the absence of molecular hydrogen by a Raney nickel-catalysed hydrogen transfer reaction from ethanol (used also as solvent for the ketone). Reduction of cholestanone in this way, with freshly prepared catalyst, gave a 17:83 ratio of axial to equatorial alcohol products (close to the equilibrium ratio of 16:84),⁵ whereas use of old, non-pyrophoric nickel gave a higher proportion of axial alcohol (66:34).⁶ This latter ratio, representing a large degree of kinetic control, moved towards the equilibrium ratio when longer reaction times were employed.⁷

The relative effectiveness of the higher Group VIII transitional elements for catalysing the transfer of hydrogen from a secondary alcohol to a ketone has now been investigated. A preliminary survey indicated (a) that ruthenium, osmium, and iridium are, in general, more active catalysts for the reaction than rhodium, palladium, and platinum, and (b) that propan-2-ol is a better donor than ethanol (Ir present), and a much better donor than cyclohexene or 1-methylpyrrolidine (Os or Ru present). Therefore, the extent and stereoselectivity of reduction of substituted cyclohexanones (especially 4-t-butylcyclohexanone) was studied with propan-2-ol as reductant in the presence of ruthenium, osmium, and iridium. A solution of the ketone in an excess of propan-2-ol was simply heated under reflux with the metal (prepared by precipitation by reduction of a metal salt by aqueous sodium formate).

Ruthenium prepared by keeping the reaction mixture from potassium hexachlororuthenate and sodium formate

¹ Part IV, H. B. Henbest and J. Trocha-Grimshaw, preceding paper.

² E. L. Eliel and M. N. Rerick, *J. Amer. Chem. Soc.*, 1960, **82**, 1367.

³ H. B. Henbest and T. R. B. Mitchell, *J. Chem. Soc. (C)*, 1970, 785.

⁴ E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.*, 1957, **79**, 5992.

⁵ H. R. Nace and G. L. O'Connor, *J. Amer. Chem. Soc.*, 1951, **73**, 2824.

for more than 4 h was immediately effective as a catalyst, but when the metal was collected after 15 min (preparation time) it became active as a catalyst only after an induction period of up to 3 h in boiling propan-2-ol. Reduction was then rapid, being complete in *ca.* 2 h. (Ruthenium shows similar behaviour in catalytic hydrogenations; the induction period is eliminated by first shaking the catalyst and solvent under hydrogen for 1–2 h.)⁸ The same sample of ruthenium was used for seven successive reductions although the rate was slightly less each time.

Induction periods were not encountered when osmium or iridium was used as catalyst but these reductions took longer times to proceed to completion; for example, *ca.* 20 h for the osmium-catalysed reaction.

When ruthenium was used as catalyst the axial-equatorial alcohol product ratio remained constant at *ca.* 65:35 while ketone was present. Continuance of the experiment after reduction of the ketone was complete resulted in the composition of the product alcohol mixture moving towards its equilibrium ratio. Osmium behaved similarly except that the axial-equatorial alcohol ratio was close to 50:50 during the reduction stage. However, with iridium, reduction and equilibration proceeded simultaneously, and the highest axial-equatorial product ratio was present only when a small amount of ketone had reacted.

The procedure was used to reduce other substituted cyclohexanones (3-t-butyl, 3,3,5-trimethyl, and 2-methyl); the order of effectiveness of the catalysts continued to be Ru(active form) > Os > Ir. With 4-t-butylcyclohexanone and iridium, equilibration of the product alcohols began when the ketone was still present, but this did not occur until after complete reduction of the ketone when ruthenium and osmium were used. 3-t-Butylcyclohexanone and the 3,3,5-trimethyl ketone were readily reduced but the reaction of 2-methylcyclohexanone was slower, indicating steric hindrance. In all the reactions axial alcohols were formed in proportions greater than the equilibrium value.

Dried propan-2-ol was used in the foregoing work but, in contrast with the reactions catalysed by the soluble iridium-sulphoxide complexes,⁹ ethers were not produced

⁶ C. Djerassi, A. J. Manson, and M. Gorman, *J. Amer. Chem. Soc.*, 1955, **77**, 4925.

⁷ E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, 1965, **87**, 5031.

⁸ L. M. Berkwitz and P. N. Rylander, *J. Org. Chem.*, 1959, **24**, 708.

⁹ Part III, Y. M. Y. Haddad, H. B. Henbest, J. Husbands, T. R. B. Mitchell, and J. Trocha-Grimshaw, *J.C.S. Perkin I*, 1974, 596.

to any appreciable extent. However, up to 25% of ether (1-isopropoxy-4-t-butylcyclohexane) was formed when 4-t-butylcyclohexanone was reduced by propan-2-ol in the presence of platinum black and hydrochloric acid.

We also studied the effectiveness, as hydrogen transfer catalysts, of the materials obtained by reducing Group VIII salts with sodium borohydride; these materials act as catalysts for the reduction of organic compounds by molecular hydrogen.¹⁰ The products from all six of the higher metals (Ru, Rh, Pd, Os, Ir, and Pt) were effective catalysts for the reduction of 4-t-butylcyclohexanone by propan-2-ol, the axial-equatorial product ratios ranging from 72:28 (Pt) to 23:77 (Ir)—but equilibration may have occurred in the latter process as in the earlier described reactions involving iridium.

Sodium formate does not reduce bivalent iron, cobalt, and nickel salts in water, but black precipitates are obtained when sodium borohydride is used. The cobalt produced was active for hydrogen transfer and gave a high proportion, *ca.* 85%, of axial alcohol. The nickel product gave the alcohols in their equilibrium ratio, but iron was inactive.

Some metal oxides were briefly investigated. Higher temperatures were required (*e.g.* 200° in cyclopentanol) before hydrogen transfer occurred. Copper(II) oxide and copper chromite were active under these conditions, but alumina and zinc oxide were not effective.

EXPERIMENTAL

(A) Dependence of the Extent and Stereoselectivity of Reduction of Various Ketones on Three Metal Catalysts (Ru, Os, and Ir) and on the Reaction Time

The reactions described in this section were carried out under standard conditions: reflux condenser; heating bath containing boiling propan-1-ol; propan-2-ol (reaction solvent) previously dried over barium oxide and distilled.

Reduction of 4-t-Butylcyclohexanone.—(a) *Ruthenium.* The catalyst was made by adding a solution of sodium formate (0.82 g) in water (20 ml) at 80° to a solution of potassium hexachlororuthenate (0.79 g) in water (160 ml) at 80°. The metal precipitated immediately but the mixture was kept at 80° for 4 h to obtain an immediately effective catalyst (see later). The black precipitate was filtered off and dried (290 mg) in a vacuum desiccator.

A solution of 4-t-butylcyclohexanone (25 mg) in propan-2-ol (3 ml) containing ruthenium black (12 mg) was heated under reflux. Samples (0.3 ml) were withdrawn and analysed by g.l.c. (7% polyphenyl ether on Celite at 97°) (see Table 1). When the mixture in the preparation of the

TABLE 1

Time (h)	1	2	4	8	24
Reduction (%)	93	97	100	100	100
Ratio of axial to equatorial alcohol product	65:35	62:38	62:38	54:46	34:66

catalyst was kept at 80° for only 15–30 min, the reduction of the ketone did not begin until after 3 h, and was not complete until after *ca.* 5 h.

The following procedures did not transform the less immediately active catalyst into a more rapidly active form: heating the ruthenium (12 mg) with (a) t-butyl-

cyclohexanone (25 mg) at 82° for 1 h, (b) propan-2-ol (3 ml) at 82° for 3 h, or (c) ketone (25 mg), propan-2-ol (3 ml), and dimethyl sulphoxide (20 mg) for 1 h.

(b) *Osmium.* Sodium formate (0.68 g) in water (20 ml) at 80° was added to potassium hexachloro-osmate (0.80 g) in water (160 ml) at 80°, and the mixture was kept at 90° for 4 h. Filtration and drying as before gave osmium black (330 mg).

A solution of 4-t-butylcyclohexanone (175 mg) in propan-2-ol (21 ml) containing catalyst (84 mg) was heated under reflux. Samples (0.5 ml) were withdrawn for analysis (Table 2). The catalyst from this experiment was filtered

TABLE 2

Time (h)	1	4	6	11	22	43
Reduction (%)	33	75	90	94	100	100
Ratio of axial to equatorial alcohol product	52:48	50:50	52:48	51:49	53:47	45:55

off and added to 4-t-butylcyclohexanone (55 mg) in propan-2-ol (5 ml) containing dimethyl sulphoxide (15 mg). After being heated under reflux for 20 h, the mixture contained ketone (22%) and 4-t-butylcyclohexanols (78%); axial:equatorial ratio 62:38).

(c) *Iridium.* Sodium formate (1.4 g) in water (40 ml) at 80° was added to potassium hexachloroiridite (1.4 g) in water (150 ml) at 85°, and the mixture was kept at 90° for 9 h. Filtration and drying gave the catalyst (443 mg).

The procedure described for osmium was used to reduce the ketone (Table 3).

TABLE 3

Time (h)	1	4	6	10	21	90
Reduction (%)	19	45	59	72	80	90
Ratio of axial to equatorial alcohol product	64:36	50:50	46:54	44:56	41:59	38:62

Reduction of 3-t-Butylcyclohexanone.—Each of the three metals (30 mg; as prepared above) was added to the ketone (100 mg) in propan-2-ol (7 ml) and the mixture was heated under reflux. Samples (0.5 ml) were withdrawn and analysed by g.l.c. (7% polyphenyl ether on Celite at 97°) (Table 4).

TABLE 4

Ruthenium						
Time (h)	1	4	29	57	117	
Reduction (%)	50	90	98	100	100	
Ratio of axial to equatorial alcohol	64:36	66:34	57:43	50:50	24:76	
Osmium						
Time (h)	1	2	4	7	22	
Reduction (%)	28	46	57	71	95	
Ratio of axial to equatorial alcohol	45:55	48:52	50:50	49:51	50:50	
Iridium						
Time (h)	1	4	31	47	118	
Reduction (%)	17	40	72	75	83	
Ratio of axial to equatorial alcohol	68:32	60:40	56:44	50:50	48:52	

Reduction of 3,3,5-Trimethylcyclohexanone.—The same procedure was adopted as for the foregoing ketone (except that 72° was used for g.l.c. analysis); see Table 5 for results.

¹⁰ H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, 1962, **84**, 1493, 2827.

Reduction of 2-Methylcyclohexanone.—The foregoing procedure was used (except that g.l.c. analyses were performed with 11% glycerol on Celite at 50°); for results see Table 6.

TABLE 5

Ruthenium					
Time (h)	0.75	2	5.5	23	24
Reduction (%)	20	63	99	100	100
Ratio of axial to equatorial alcohol	74 : 26	79 : 21	76 : 24	48 : 52	45 : 55
Osmium					
Time (h)	1	3	7	72	
Reduction (%)	12	30	65	100	
Ratio of axial to equatorial alcohol	66 : 34	67 : 33	64 : 36	56 : 44	
Iridium					
Time (h)	1	3.5	7.5	24	
Reduction (%)	13	31	49	67	
Ratio of axial to equatorial alcohol	91 : 9	92 : 8	89 : 11	92 : 8	

4-t-Butylcyclohexanone, Platinum, and Acid.—A solution of the ketone (71 mg) in propan-2-ol (10 ml) containing hydrochloric acid (0.1 ml) was heated under reflux for 44 h. The ketone was converted into a *ca.* 75 : 25 mixture of 4-t-butylcyclohexanols and the related isopropyl ethers. The axial-equatorial composition of the alcohol was 90 : 10.

Reduction of Cholestan-3-one (Dr. Y. M. Y. HADDAD).—(a) A solution of the ketone (650 mg) in propan-2-ol (80 ml)

TABLE 6

Ruthenium		
Time (h)	2	24 ^a
Ratio of axial to equatorial alcohol	51 : 49	50 : 50
Osmium		
Time (h)	70 ^b	
Ratio of axial to equatorial alcohol	63 : 37	
Iridium		
Time (h)	16	70 ^c
Ratio of axial to equatorial alcohol	64 : 36	61 : 39

^a Reduction 58% complete. ^b Reduction 30% complete. ^c Reduction 28% complete.

with ruthenium black (70 mg) was heated under reflux for 60 h. Chromatography of the product over deactivated alumina (65 g) afforded cholestan-3 α -ol (176 mg) and cholestan-3 β -ol (470 mg).

(b) A similar experiment, for 22 h, with ketone (340 mg), propan-2-ol (25 ml), and iridium black (160 mg) gave unchanged ketone (198 mg), cholestan-3 α -ol (47 mg), and cholestan-3 β -ol (94 mg). When dimethyl sulphoxide (2 ml) was also present no reduction occurred.

(B) *Experiments with Metal Borides and Oxides*

4-t-Butylcyclohexanone and Metal Borides.—The metal salt (0.5 mmol) in water (10 ml) was added to a stirred solution of sodium borohydride (0.5 g) in water (40 ml). Black, finely divided solids rapidly separated, which were filtered off and dried.

Each solid was added to a solution of the ketone (100 mg) in propan-2-ol (10 ml), which was then heated under reflux. The results (Table 7) are presented with reference to the positions of the metals in the Periodic Table. The figures refer to: reaction time; % reduction of ketone; axial-equatorial alcohol ratio.

TABLE 7

{Fe (from FeCl ₂) {72 h; 0; —	{Co (from CoCl ₂) {70 h; 56; 85 : 15	{Ni (from NiCl ₂) {42 h; 100; 20 : 80
{Ru (from K ₂ RuCl ₆) {96 h; 80; 49 : 51	{Rh (from K ₂ RhCl ₆) {40 h; 47; 67 : 33	{Pd (from K ₂ PdCl ₆) {91 h; 90; 30 : 70
{Os (from K ₂ OsCl ₆) {75 h; 63; 50 : 50	{Ir (from K ₂ IrCl ₆) {72 h; 98; 23 : 77	{Pt (from K ₂ PtCl ₆) {48 h; 64; 72 : 28

The palladium experiment was repeated, for 4 days, with dioxan in place of propan-2-ol. Most (*ca.* 98%) of the ketone was not reduced.

Palladium-boride supported on charcoal. This material was made by performing the boride preparation in the presence of charcoal (1 g). The product was added to the ketone (1 g) in propan-2-ol (20 ml) and the mixture heated under reflux for 6 h. G.l.c. analysis gave (in order of elution): 1-isopropoxy-4-t-butylcyclohexanes (2%), *cis*- and *trans*-4-t-butylcyclohexanols (15 + 7%), two unidentified products (*ca.* 20%), and *p*-t-butylphenol (55%). This last compound was isolated *via* extraction with aqueous sodium hydroxide and identified (g.l.c. and i.r. spectrum) by comparison with an authentic sample.

4-t-Butylcyclohexanone and Metal Oxides.—The ketone (50 mg) in the solvent (5 ml) was heated with the potential catalyst (50 mg). Reactions in cyclopentanol at 200° were carried out in a Carius oven.

(a) *Copper chromite.* The ketone was completely reduced in cyclopentanol at 200° in 24 h, the axial-equatorial product ratio being 27 : 73. At 140° in 48 h reduction was 91% complete, and the alcohol ratio was 73 : 27. The ketone was not appreciably reduced in either boiling propan-2-ol or cyclohexene (80 h).

(b) *Copper(II) oxide.* The ketone was 97% reduced in cyclopentanol at 200° during 24 h, the alcohol ratio being 67 : 33.

(c) *Aluminium oxide or zinc oxide.* Only a trace of the ketone was reduced in cyclopentanol at 200° during 24 h.

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