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STEREOCHEMICAL CONTROL BY CARBOXYLATE GROUPS IN HOMOGENEOUS HYDROGENATION

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Summary

The stereochemistry of hydrogenation of a range of unsaturated cyclohexanecarboxylic acids and their esters has been investigated, employing either bis(1,4-diphenylphosphino)butanerhodium or pyridine(tricyclohexylphosphine)iridium based cationic catalysts in CH_2Cl_2. For methyl 3-methylcyclohex-2-enecarboxylate, highly selective reduction to the *trans*-product was achieved in both cases, whereas the isomeric methyl 3-methylenecyclohexanecarboxylate gave appreciable amounts of the *cis*-isomer. A predominance of *trans*-isomer was also achieved in the reduction of methyl 4-methylcyclohex-3-ene carboxylate, in a rather slower reaction. Reductions with D_2 revealed that considerable isomerisation of the olefinic double bond occurred during hydrogenation.

The corresponding unsaturated acids were reduced with moderate to high selectivity but reaction was either very slow, or ceased after a few turnovers. Related cyclohexadienecarboxylates were unreactive to homogeneous hydrogenation with cationic catalysts.

Introduction

In the last three years a number of stereoselective homogeneous hydrogenations have been reported in which a common feature is control of hydrogen delivery to the olefin by a suitably disposed hydroxyl group [1–5]. The first examples involved acyclic allylic and homoallylic alcohols (**1**) and (**2**), both of which reduce to the R^*S^* product with high diastereoselectivity, although in the former case about 20% of isomerisation to saturated ketone (**3**) occurs in a competing side-reaction. The catalyst employed was bicyclo[2.2.1]heptadiene (bis-(1,4-diphenylphosphino)butane)rhodium tetrafluoroborate in CH_2Cl_2 solution and under these conditions the hydroxyl group of the substrate binds to rhodium concomitantly with the olefinic double bond so that the stereochemical outcome depends on the preferred diastereomeric form of the intermediate. It was subsequently shown that 3-methylene-

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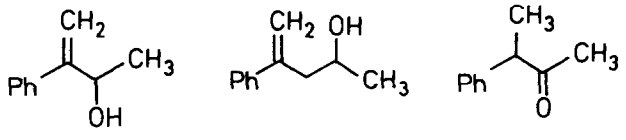
cyclohexanol (**4**) is hydrogenated with high *trans*-selectivity by the same catalyst. Significantly the competing isomerisation involved in reduction of allylic alcohols is pressure-independent, and the scope of reaction is extended by working at high H_2 pressures.

The highly reactive iridium catalysts introduced by Crabtree and Felkin [6] for olefin homogeneous hydrogenation prove to be effective in the stereoselective reduction of cyclic unsaturated alcohols [7,8] with highly variable spatial relationship between olefin and alcohol. In all cases, hydrogen is delivered to the hydroxyl-carrying face of the molecule. For acyclic substrates, iridium catalysts may be less effective than their rhodium counterparts [5] and sensitive to for example, the relative molar concentration of catalyst and substrate.

In principle, other polar functional groups capable of coordination to rhodium or iridium should lead to stereoselective reduction. There is one early example of alkoxide direction of hydrogenation by a neutral chloro-rhodium catalyst (the parent alcohol (**5**) was not hydrogenated selectively) [9]. The only other relevant example is reduction of dehydrovaline (**6**) with HT catalysed by $ClRh(PPh_3)_3$. The high selectivity in tritiated product (i.e. of the chiral methyl group) requires participation either by the amide or carboxyl group, more probably the latter [10]. In view of the dearth of examples, we have begun a survey of the effectiveness of other functional groups in directing the stereochemical course of hydrogenation, and report here the results of experiments with some simple cyclohexane carboxylates.



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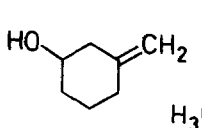

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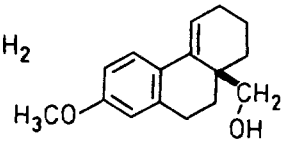

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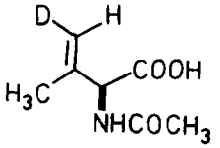

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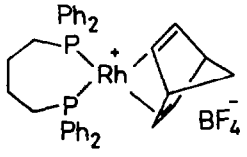

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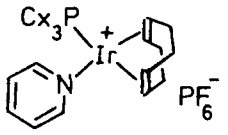

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Results and discussion

(a) Stereoselective reductions

Reductions were carried out either with rhodium complex (**7**) or iridium complex

TABLE 1

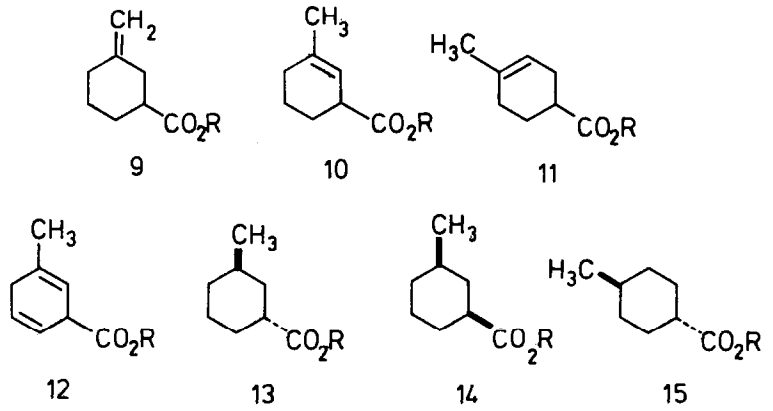
STEREOCHEMICAL COURSE OF HYDROGENATION REACTIONS

Substrate	Catalyst	% *trans*-product	Turnovers/time [a]
9a	7	90.4	15/17 h
9a	8	81.4	C/10 min
9a	Pd/C (THF)	21	
10a	7	96.9	> 40/22 h
10a	8	99.9	C/10 min
11a	7	88.0	< 5/22 h
11a	8	89.2	C/15 min
11a	Pd/C (THF)	72	
9b	7	50	< 5/15 h
9b	8	88.3	C/6 h

[a] C symbolises complete reaction under the conditions described in the Experimental section.

(**8**) at ambient temperature and pressure, normally in CH_2Cl_2. Unless otherwise stated, olefinic starting materials (**9–12**) were prepared by literature methods, or straightforward variations thereon, as described in the Experimental section.

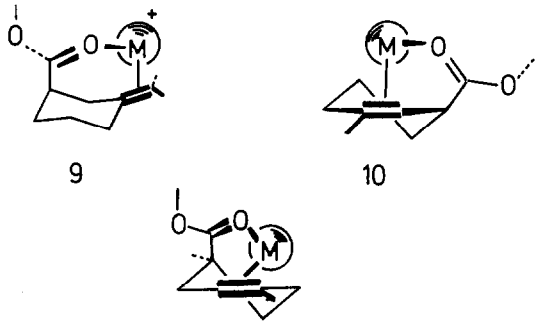
The first experiments were carried out with methyl 3-methylenecarboxylate (**9a**) (Table 1). With the rhodium catalyst, reduction is moderately selective towards formation of the *trans*-isomer (**13a**) but it is slow and incomplete. In contrast, the iridium catalyst gives complete reduction but with lowered selectivity. This indicates that the carbomethoxy group is rather less effective in coordinating to the metal than is hydroxyl since the latter gives very high stereoselectivity at the analogous site, in **4**. The hydroxyolefin metal complex is a 5-ring chelate and thus favoured. By comparison, the carbalkoxyolefin complex is a 6-ring chelate (Scheme 1) and thus intrinsically of lower stability. This permits a substantial portion of the reduction to occur via intermediates lacking carboxyl participation and leading to *cis*-product. The selectivities quoted in Table 1 represent maximum values (vide infra).



a R = CH_3 b R = H

By contrast, reduction of the endocyclic olefin (**10a**) proceeded to completion with high *trans* selectivity, using either catalyst. Clearly the endocyclic double bond is better disposed for carboxylate participation during the catalytic cycle. Whilst we

did not make accurate rate measurements it was very apparent that the iridium catalyst (which gives the higher proportion of *trans*-product) was more active. Hydrogenation of its isomer (**11a**) where the new epimeric centre formed is one bond more remote from the carbomethoxy group, occurs more slowly, and the selectivity is lower although still in excess of 90% towards (**15a**) i.e. *trans*-preference. Successful participation of the carbomethoxy group in the reduction of **11a** requires that it adopt a pseudo-axial conformation (Scheme 1) with the possibility of unfavourable MeO–C–C–H eclipsing interactions.



SCHEME 1. Orientation of carboxylate groups in directed hydrogenation of **9a**, **10a** and **11a**.

(b) Deuterium addition

Isomerisation is an important competitive reaction in the directed hydrogenation of allylic and homoallylic alcohols [1,4,11], and addition of D_2 has helped to highlight important mechanistic details, [11]. In the present case compound **10a** was reduced with D_2 in CH_2Cl_2, employing the Ir catalyst, and the product then isolated by preparative GLC. The ^{13}C NMR spectrum [12] showed that deuterium was distributed between three sites in the product C(2), C(3), C(4), but not the methyl group (Fig. 1). Only those hydrogens *syn* to the carbomethoxyl group were part replaced by deuterium, as evidenced by the ^2H NMR spectrum, assigned by direct comparison with the standard ^1H NMR*. By itself, this experiment does not distinguish between isomerisations by addition-elimination of Ir–D [13] or by a π-allyliridium hydride mechanism [14]. The fact that only two deuterium atoms are incorporated on average in the product strongly suggests that isomerisation and reduction occur without release of substrate from the catalyst. In related reactions, [11] the possibility of isomerisation catalysed by metallic iridium has been ruled out.

When the exocyclic olefin **9a** was reduced with D_2 under similar conditions, it gave a product containing 20% of *cis*-isomer (**14a**) (which was not separated from *trans*-isomer by preparative GLC under our conditions). The ^{13}C and ^2H NMR indicated a substantial proportion of deuterium incorporation in the methyl group, demonstrating that at least part of the reduction occurs without isomerisation.

* The latter was in turn fully assigned by ^{13}C–^1H correlation spectroscopy.

Widespread deuteration of the ring, with C(2) and C(4) carrying similar relative proportions of deuterium to those observed in the reduction of **10a**, indicates that the selective reduction pathway may be common to both isomers (Fig. 2).

In summary, we believe that formal double-bond migration occurs with exceptional ease under the conditions of directed hydrogenation. This has obvious synthetic implications including a limitation to selective isotope incorporation and the possibility of isomerisation to stable non-reducible species in competition with hydrogenation.

(c) Other hydrogenations

It was found (Table 1) that the acids **9b–11b** were, with one exception, incom-

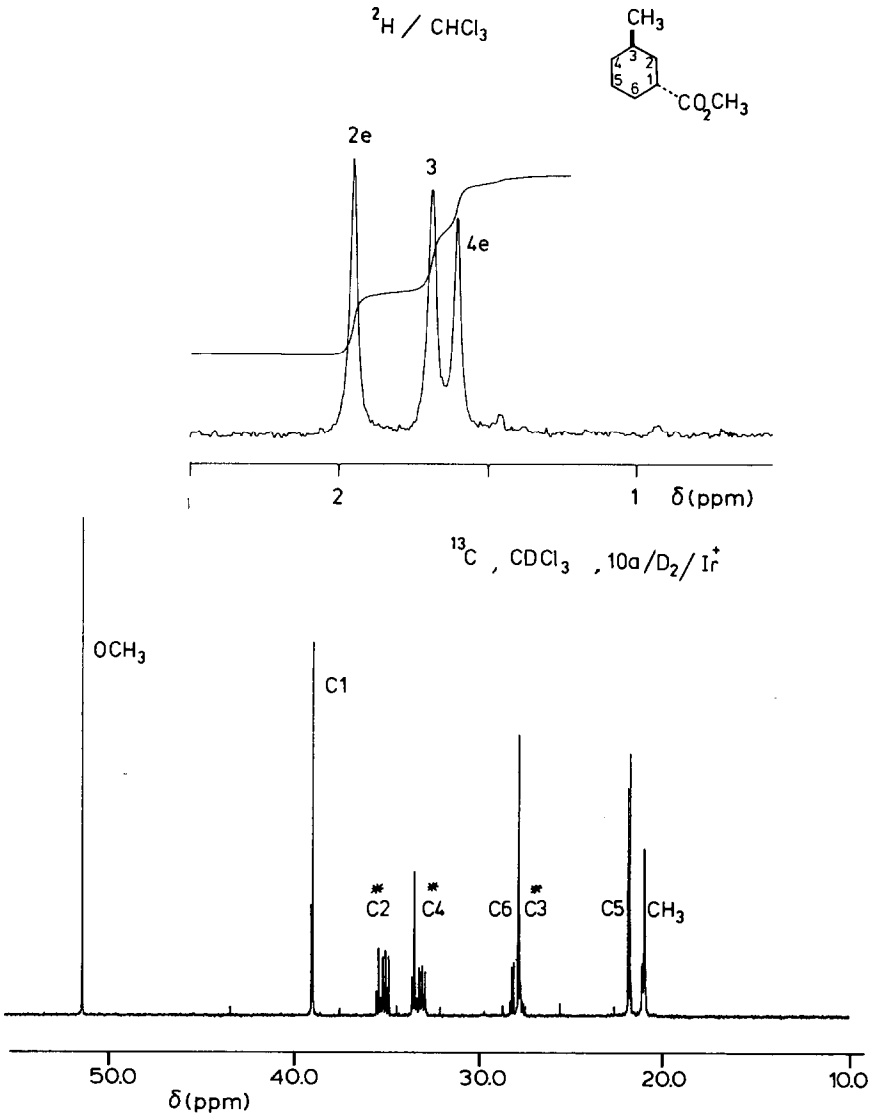


Fig. 1. ^2H and ^{13}C NMR spectra from the reduction of **10a** with D_2, iridium catalyst.

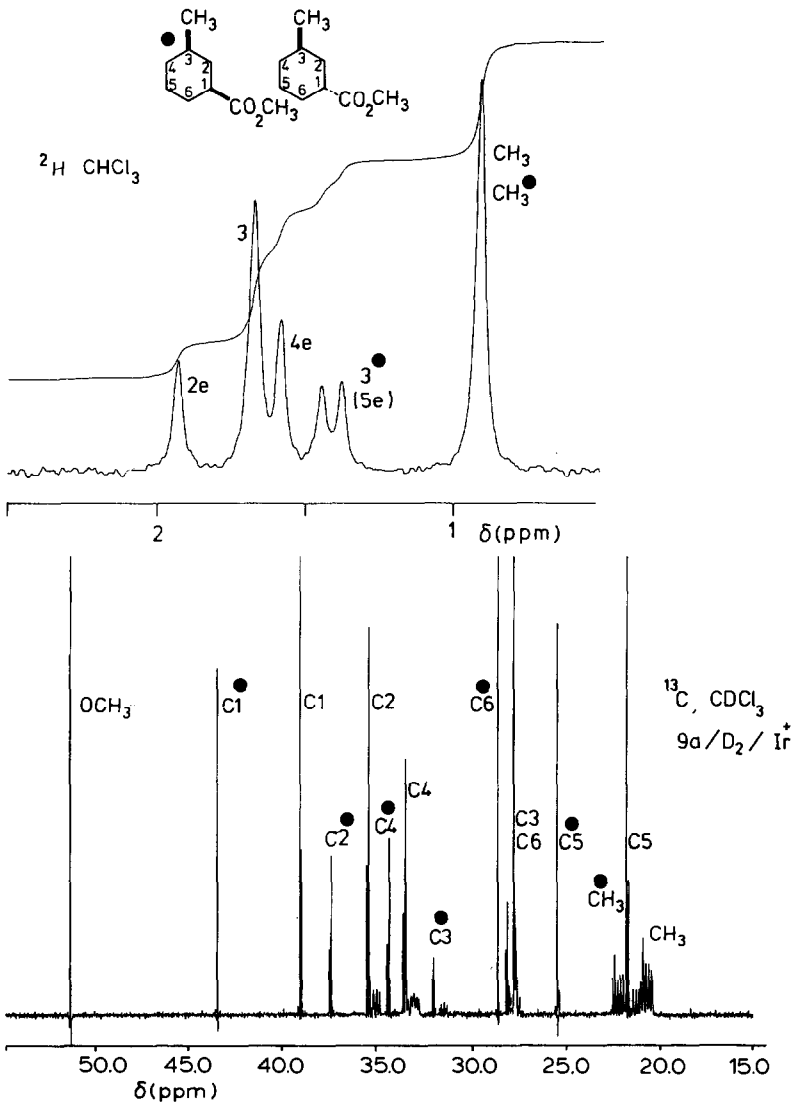


Fig. 2. ^{2}H and ^{13}C NMR spectra from the reduction of **9a** with D_2, iridium catalyst.

pletely reduced under the standard reaction conditions. This implies formation of carboxylate complexes [15] which inhibit further reaction. More surprisingly, the related cyclohexadienecarboxylates (**12a**) were hydrogenated very slowly, and reaction ceased after a few turnovers for both acids and esters. This is in contrast to the highly selective hydrogenation of the disubstituted double bond in **12a** when catalysed by Wilkinson's catalyst [16].

Experimental

All solvents were freshly distilled before use according to standard procedures. NMR spectra were recorded either on a Bruker WH 300 (^{1}H, 300 MHz; ^{2}H, 46.07

MHz) or a Bruker AM 500 (^{13}C 125.78 MHz) and chemical shifts are measured in ppm downfield from TMS. Infra-red spectra were recorded on a Pye-Unicam SP3-200 spectrophotometer. Catalysts were prepared by standard literature procedure [2,17].

Hydrogenation procedures

Reductions were carried out in Schlenk tubes equipped with magnetic follower and connected to a standard vacuum line. The solvent was thoroughly deoxygenated by three freeze-thaw cycles. Typically the respective concentrations of catalyst and substrate were 0.004 *M* and 0.2 *M*. Rhodium-complex catalysed reductions were carried out in the presence of a trace of mercury [4] to nullify any effect of traces of colloidal metal. With minor modifications, the following procedure exemplifies the method:

A sample of CH_2Cl_2 (2 ml) degassed as described was introduced by syringe into a Schlenk tube containing methyl 3-methylenecyclohex-2-enecarboxylate (50 mg, 0.33 mmol). The solution was frozen, cyclooctadiene pyridinetricyclohexylphosphineiridium hexafluorophosphate (5 mg, 5.5 μmol) then added under a stream of Ar, and H_2 then introduced by three cycles of evacuation and refilling. When the solution reached room temperature, stirring was commenced. The pressure of hydrogen was maintained just above ambient by permitting a slow stream to pass through a mercury bubbler. Samples were removed from the reaction mixture at intervals by syringe, diluted with ether (10/1) and analysed by GLC (3% OV-225 on Gas-Chrom Q, 1.5 m × 3 mm, 30 ml m^{-1} N_2) at 80°C. When reaction was complete as judged by loss of starting material (t_r 19.1 min) and formation of saturated products (*cis*, t_r 12.4 min, *trans* t_r 10.8 min), isolation was effected by preparative GLC on OV 225.

Preparation of starting materials

*Methyl 3-methylenecyclohexanecarboxylate (**9a**)*

A solution of butyllithium in hexane (11.6 ml, 1.44 *M*, 17 mmol) was added by syringe to a suspension of methyltriphenylphosphonium bromide (7.05 g, 19.7 mmol) in dry Et_2O (45 ml) stirred under Ar at 0°C. After 5 min, a solution of methyl 3-oxocyclohexanecarboxylate [18] (2.52 g, 16.3 mmol) in Et_2O (8 ml) was added, causing decolorisation. The mixture was shaken thoroughly, dimethylsulphoxide (5 ml) was added, and the mixture shaken again. After dilution with water (100 ml) and extraction with Et_2O (3 × 20 ml) the organic layer was washed with water (20 ml) and triturated with petrol, the ensuing precipitate of $OPPh_3$ being removed by filtration. Removal of solvent in vacuo and distillation of the residue gave methyl 3-methylenecyclohexanecarboxylate (1.13 g, 45%, b.p. 20°C (bath)/0.2 mmHg). NMR (300 MHz, $CDCl_3$); δ 4.68 (2H, s), 3.67 (3H, s), 2.49 (1H, br), 2.39 (1H, tt, *J* 11, 4 Hz), 2.26 (1H, br), 2.19 (1H, br, *J* 11 Hz), 1.96 (2H, m), 1.55 (1H, dq, *J* 12.5, 4 Hz), 1.38 (1H, tq, *J* 12.5, 4 Hz) ppm. IR (Film); ν_{max} 3080m, 1720s, 1640m cm^{-1}. MS (CI, NH_3); *m/z* 154 (3, M^+), 95(100), 122(18), 94(59).

*3-Methylenecyclohexanecarboxylic acid (**9b**)*

A stirred suspension of methyl 3-methylenecyclohexanecarboxylate (285 mg, 1.85 mmol) in 5 *M* aqueous KOH 25 ml was heated under reflux until it became

homogeneous (ca. 1.5 h). The cooled solution was extracted with ether (3 × 1.5 ml) and dichloromethane (2 ml) was added. After acidification with hydrochloric acid and extraction with dichloromethane (3 × 2 ml), the extract was dried and solvent removed in vacuo.

The resulting oil (82%) was distilled in vacuo to yield 3-methylenecyclohexanecarboxylic acid, as a white solid, m.p. 58°C, (204 mg, 79%). Found: C, 68.44; H, 8.55. $C_8H_{12}O_2$ calcd.: C, 68.53; H, 8.63. NMR (300 MHz, $CDCl_3$); δ 4.71 (2H, brs); 2.54 (1H, br), 2.44 (1H, tt), 2.27 (1H, br, dt), 2.22 (1H, t), 2.00 (2H, br, dt), 1.87 (1H, m), 1.59 (1H, dq), 1.38 (1H, tq) ppm. IR($CHCl_3$); ν_{max} 1695vs, 1645m, 1290m cm^{-1} MS(EI); m/z 140(5, M^+), 95(100), 122(16).

*Methyl 3-methylcyclohex-2-enecarboxylate (**10a**)* was prepared as described [19] and purified by preparative GLC (OV 225; 200°C, 4.5 m). NMR: (300 MHz, $CDCl_3$) δ 5.46 (1H, br, m) 3.68 (3H, s) 3.07 (1H, br, m), 2.0–1.5 (6H, m), 1.68 (3H, s) ppm. Likewise *3-methylcyclohex-2-enecarboxylic acid (**10b**)*, purified by distillation (b.p. 110–115°C/0.1 mmHg; Lit. [20] 123°C/7 mmHg. NMR (300 MHz, $CDCl_3$) 5.50 (1H, m) 3.13 (1H, m) 2.0–1.5 (6H, m), 1.71 (3H, s) ppm.

*Methyl 4-methylcyclohex-3-enecarboxylate (**11a**)* was prepared by Diels–Alder reaction between methyl acrylate and isoprene [21] in $CHCl_3$ on a 0.25 mol scale in the presence of 20 mol% $TiCl_4$ over 3 h at room temperature, in 99% crude yield and high regioselectivity. A portion was purified by distillation, (b.p. 90–95°C/30 mmHg; Lit. [21] 83–86°C/13 mmHg) NMR (300 MHz, $CDCl_3$): 5.36 (1H, brs) 3.67 (3H, s) 2.48 (1H, m) 2.20 (2H, m) 1.98 (3H, m) 1.7–1.5 (1H, m) 1.64 (3H, s) ppm. Hydrolysis (KOH, MeOH) gave *4-methylcyclohex-3-enecarboxylic acid (**11b**)* m.p. 98–99°C (Lit. [22] 99°C) NMR (300 MHz, $CDCl_3$ 5.38 (1H, br m) 2.54 (1H, brm) 2.25 (2H, brm) 2.02 (3H, br m) 1.8–1.6 (2H, m) 1.66 (3H, s) ppm.

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