Tetrahedron Letters No. 18, pp 1535 - 1538, 1976. Pergamon Press. Printed in Great Britain.

EXCEPTIONAL RANGE OF STEREOSELECTIVITY IN THE HYDROGENATION OF A NEARLY PLANAR CONJUGATED COMPOUND: 3,5-DIMETHYLCYCLOHEX-2-ENONE

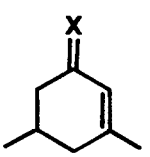
M.J.F. Burman, D. R. Elliott, M. H. Gordon, R. G. Peck and M.J.T. Robinson*

The Dyson Perrins Laboratory, University of Oxford

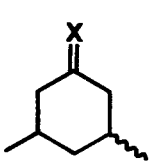
(Received in UK 3 March 1976; accepted for publication 22 March 1976)

Stereoselectivity in the catalytic hydrogenation of an olefin is usually explained by differences in steric hindrance to the two faces of the C-C double bond.[1] We have now found that hydrogenation of a simple, α;β-unsaturated ketone (enone) 1a shows a hundred-fold variation in stereoselectivity with changes in catalyst and conditions, with addition of hydrogen occurring preferentially from the more hindered face of the molecule (Tables). The exceptional stereoselectivity shown by Pd, and earlier work on the hydrogenation of enones,[2-4] has prompted us to begin a study of the hydrogenation of enones and analogous conjugated system with special emphasis on Pd catalysts and our preliminary results indicate the inadequacy of earlier mechanisms, that are in any case partly contradictory.[5] For example, McQuillin, Ord, and Simpson[3] considered that 1,4-addition to 5 was favoured by acid (protonation of the carbonyl oxygen before adsorption) and apparently also by non-polar solvents (in which it was proposed that the oxygen coordinated with the metal, acting as a Lewis acid, leading to an 'uncoupling' of the double bond) and led to 5α-steroids (5α-6: trans-fusion of the A and B rings). In contrast Augustine et al.[4] have suggested that 1,4-addition was favoured by acid, polar aprotic solvents, and the less polar hydroxylic solvents, but not by non-polar nor by very polar hydroxylic solvents and led to cis-decal-2-one (cis-4) from 3!

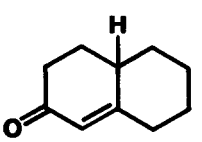
In a preliminary study[6] of the palladium catalysed hydrogenation of three deuteriated enones we have observed cis-1,2-addition of hydrogen (varying from ~80-85% in EtOH—1% HCl to 100±5% in cyclohexane



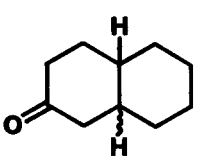
1



2



3



4

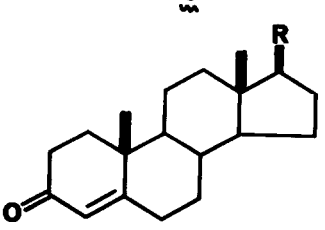
a: X = O

b: X = N.NH.CO.NH$_2$

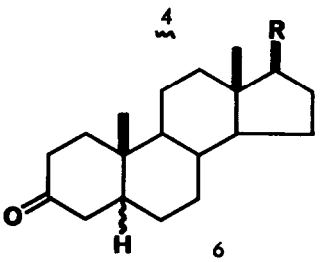
c: X =

d: X = CMe_2

e: X = $\overset{+}{O}H$



5



6

Table 1. Stereoselectivity[a] for hydrogenation of 1a,d,[b] mainly in ethanol, and 1b,c, mainly CF_3CO_2H (data in brackets), 0.5M, at 20°/1 atm, as a function of the catalyst.[c]

Substrate	Catalyst:	5% Pd/C	PtO_2	Raney Ni	Rh/Al_2O_3	Ru	Ir
1a	R[a] =	90 (23)	13[d] (8)[e]	4.9	2.9[d,e]	2.2[d]	1.45[d]
1b[g]		18 (18)	- (3.0)				
1c[g]		- (13)	- (3.4)				
1d		0.6	1.2	2.0	0.77	0.83	0.70

[a] R = [cis-2]/[trans-2] [b] R for reduction of 2,3-double bond only in 1d is given here: an investigation of regio- and stereoselectivity in the hydrogenation of 1d and related dienes will be published elsewhere.[8] [c] See note 9 and Table 2. [d] Hydrogenation was stopped when 60-80% complete to avoid over-reduction to alcohols. [e] Significant over-reduction to alcohols, which were re-oxidised to 2 with Jones' chromic acid, was observed. [f] R reported as 1.3 for ~2M solution in EtOH/H_2O,[10] we have observed R = 1.6 for 2.5M solution in MeOH. [g] 2b,c hydrolysed to 2a for analysis by GLC following hydrogenation; relatively few solvents and catalysts are suitable for these substrates.

and neutral EtOH) in the major stereoisomeric products. As a working hypothesis, therefore, we suppose that direct cis-1,2-addition is the only important mechanism in neutral and weakly acidic media because (a) prior enolisation by acid would have led to loss of deuterium and (b) 1,4-addition followed by ketonisation, in view of the known stereoselectivity in the ketonisation of cyclohexenols,[7] would have given a more or less large amount of trans-1,2-addition overall. These observations are not consistent with the dichotomy of mechanism, 1,2-addition and 1,4-addition followed by ketonisation, previously proposed to explain the effects of change of solvent and acidity on the stereoselectivity of hydrogenation of bicyclic,[4] e.g. 3 and steroid[3] (5) enones over palladium.

Deuterium labeling experiments are not practicable in alkaline or strongly acid solutions and at present there is no direct evidence concerning the mechanism in the former. We have found, however, that as the acidity is raised from the dilute acids, in which cis-1,2-addition predominates and marked changes of stereoselectivity are found,[3,4] to very high acidities (up to 64% sulphuric acid: Table 2) at which 1a will be substantially protonated the stereoselectivity decreases. There is no clear evidence, therefore, that the

Table 2. Stereoselectivity for hydrogenation of 1a (0.5M) over Pd/C as a function of solvent

Solvent:	MeOH	EtOH	iPrOH	t-BuOH	Me_2CO	Et_2O	MeOH 1% H_2SO_4	H_2O[b]	20% H_2SO_4	54% H_2SO_4	64% H_2SO_4	CF_3CO_2H
R[a]	120	90	76	62	66	38	150	47	58	47	35	23

[a] R = [cis-2a]/[trans-2a]. Data within each group of six solvents were determined using a single batch of catalyst in the same apparatus by the same experimenter. [b] 0.125M.

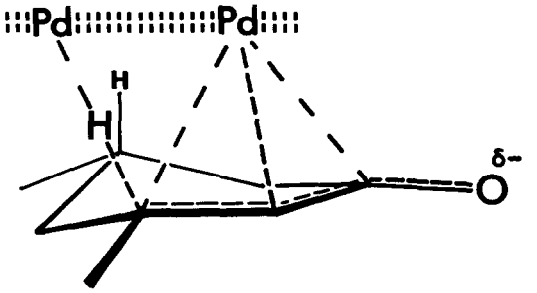


Figure. Suggested transition state for the Pd-catalysed hydrogenation of 1a to cis-2a: the formation of trans-2a may involve either an axial 5-methyl group or a less favourable relationship between the ring atoms and the metal.

protonated enone 1e is the substrate at low acidities, as has been assumed, and is hydrogenated with very high stereoselectivity, whether by 1,2- or 1,4-addition.

The part played by the carbonyl group in 1a is indicated by the considerable stereoselectivity shown in the hydrogenation of the analogues 1b and 1c, but not 1d,[8] over Pd/C. This suggests that the polar carbonyl group, like the polar C=N in 1b and $C=\overset{+}{N}$ in 1c, acts as a Lewis acidic centre[11] giving a more or less fully formed π-allylic complex with Pd, the exact extent of bonding between Pd and C-1 depending on the polarity of the C=X bond, sometimes augmented by hydrogen bonding when X = O, while the non-polar bond in 1d is ineffective.

We suggest that the catalytic hydrogenation of enones over Pd catalysts takes place through predominant cis-1,2-addition in which the product determining transition complex (see Fig.) involves hydrogenolysis of a C-3 metal bond in a chemisorbed molecule in which strong metal-carbon bonding to C-2 and C-3 is supplemented by Pd bonding to C-1 in the C=O, with the ring in a chair-like rather than a boat-like conformation[12] with the 5-methyl group equatorial. The minor product trans-2a may then arise from the chair-like complex with a hindered axial 5-methyl or from a boat-like complex with an unhindered 5-methyl group. For metals such as Ir, Rh, and Ru with little tendency to form π-allyl complexes there will be little bonding to C-1 and low stereoselectivity is to be expected for any one of several product determining steps: it is notable, however, that hydrogenation from the more hindered side of the molecule is always favoured.

REFERENCES AND NOTES

1 See, e.g. S. Siegel, Adv.Catalysis 16, 123 (1966).

2 A. L. Wilds, J. A. Johnson and R. E. Sutton, J.Am.Chem.Soc. 72, 552 (1950).

3 F. J. McQuillin, W. O. Ord and P. L. Simpson, J.Chem.Soc. 5996 (1963).

4 R. L. Augustine, D. C. Migliorini, R. E. Foscante, C. S. Sodano and M. J. Sisbarro, J.Org.Chem. 34, 1075 (1969) and earlier papers in the series.

5 The large effects of changes of catalyst and conditions on the stereoselectivities of hydrogenation are often strikingly different for apparently similar enones such as 3 and 5. This indicates that such stereoselectivities are determined by two (or more) structural factors that respond very differently to such changes: existing mechanisms[3,4] do not account for such differences.

6 We intend to extend the labeling experiments to other catalysts, solvents and conditions, as well as to the isolation of both diastereomeric products whenever possible, before publishing a detailed account.

7 E. J. Corey and R. A. Sneen, J.Am.Chem.Soc. 78, 6269 (1956); G. B. Trimitsis and E. M. Van Dam, J.C.S. Chem.Comm. 610 (1975).

8 M. H. Gordon, R. G. Peck and M.J.T. Robinson, in preparation.

9 R varies with concentration of substrate, amount and origin of catalyst, and solvent: these difficulties are particularly severe for 1a in alcohols over Pd/C (see Table 2) but do not affect conclusions drawn from the very wide spread of stereoselectivities.

10 E. L. Eliel and F. J. Biros, J.Am.Chem.Soc. 88, 3334 (1966).

11 Contrast with the earlier suggestion[3] that >CO acts as a Lewis base in non-polar solvents.

12 The observed stereoselectivity (R up to 150, equivalent to $\delta\Delta G^{\ddagger} \simeq 12$ kJ mol^{-1}) implies that chair-like or boat-like character is well developed in the product-determining transition states, which must have ring conformations very different from that of the substrate 1a, in which all the ring C atoms except C-5 are expected to be coplanar.[13]

13 S. A. Manley and J. K. Tyler, J.Chem.Soc.(D) 382 (1970).