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ASYMMETRIC HYDROGENATION OF β-METHYLCINNAMATES OF PHENYLALKYLMETHANOLS. CATALYST-PHENYL GROUPS INTERACTIONS IN THE PREFERRED ADSORPTION CONFORMATION

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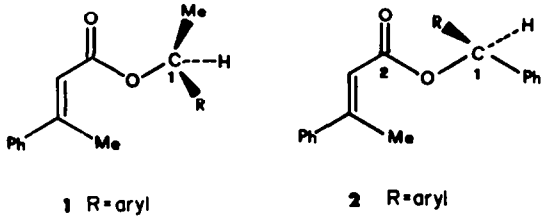
Abstract—The β-methylcinnamates of four *S*-alkylphenylmethanols have been hydrogenated on Pt catalyst. The observed asymmetric inductions suggest that simultaneous bonded interactions of both the phenyl groups with the catalyst in the transition states do not occur.

The role of the chiral centre in the asymmetric catalytic hydrogenation of β-methylcinnamates was studied by Prelog in 1959:[2] the esters of optically active methyl-*t*-butylmethanol and of four methylarylmethanols were hydrogenated and the results rationalised by assuming a selective attack of the molecule from the least-hindered side of the adsorption conformation **1**. According to this hypothesis, the most favourable transition state **1a**, which incorporates the catalyst, results from a minimization of all the steric interferences within the molecule and between the catalyst and the molecule. This model is an extension of the Prelog rule for asymmetric syntheses from α-ketoesters and represents a useful tool for predicting the steric course of the hydrogenation of α,β-unsaturated esters of optically active alcohols.



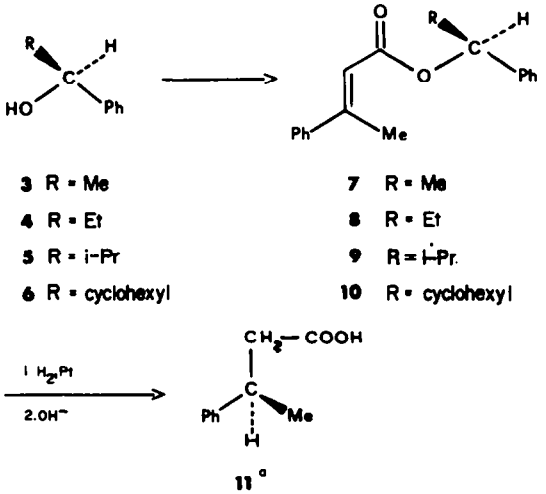
1 R = aryl **2** R = aryl

Fig. 1. Adsorption conformations assumed in the transition states **1a** and **2a**.

Whilst the Prelog model applied to α-ketoesters has been widely studied, also from a theoretical point of view, its application to asymmetric hydrogenation has not been used for further mechanistic studies.

It is now well established that the steric course of catalytic hydrogenation can be strongly influenced by bonded interactions with the catalyst surface due to the presence of polar and/or aromatic groups.[3] The directing effect of the phenyl group has recently been shown to control the mode of adsorption of the molecule in the hydrogenation of 2-benzylidenecycloalkanols.[4]

On the basis of these data, it seemed interesting to see if the transition state **2a**, derived from the adsorption conformation **2**, also intervenes in the asymmetric hydrogenation of β-methylcinnamates. This model cannot be excluded *a priori* since, like **1a**, it allows a correct prediction of the steric course of the reaction. Furthermore, the transition state **2a**, derived from **1a** by a rotation of 30° about the C_1–O bond, has the aromatic group in the same plane as the cinnamic moiety, parallel to the surface of the catalyst. In this situation the alkyl group is further removed from the carbonyl oxygen and the alkyl-C_1 and O–C_2 σ bonds are completely staggered. Both these circumstances should supply extra stabilization through a release of steric and torsional strain. Moreover, the C_1 phenyl, parallel to the catalyst surface, could further improve the stability of **2a** through bonded interaction with an appropriate site on the catalyst. To check this suggestion, catalytic hydrogenation of β-methylcinnamates of the *S*-phenylalkylmethanols **3**–**6** has been carried out and optical yields have been determined.



3 R = Me **7** R = Me
4 R = Et **8** R = Et
5 R = i-Pr **9** R = i-Pr
6 R = cyclohexyl **10** R = cyclohexyl

11[a]

[a]Configuration of the prevailing enantiomer.

Scheme 1.

The optically active alcohols **3–6** were prepared by known methods.[5–10] The optical purities based upon maximum literature rotations are shown in Table 1. To detect any accidental, large deviation of these values from the true enantiomeric purities, ^{1}H NMR spectra of the resolved alcohols in the presence of Eu(tfc)$_3$ as chiral shift reagent[11] were determined. Pseudocontact shift differences ($\Delta\Delta\delta$) in the range 0.35–0.73 ppm were regularly observed for the enantiotopic α-protons of partially resolved alcohols. The results obtained by this method are substantially in accordance with the optical purities reported in Table 1.

The β-methylcinnamates **7–10** were hydrogenated in acetic acid with PtO_2 as catalyst, always adopting the same experimental conditions as used by Prelog.[2] Reactions were interrupted when an equivalent amount of hydrogen was consumed, although slowing down of the hydrogen up-take was not observed at this point. This indicates that undesired reduction of the aromatics and/or hydrogenolysis of benzylic C–O bonds take place concurrently. Apart from the reduction of the aromatics, the reaction mixtures were expected to contain the saturated esters together with some starting material, β-methylcinnamic acid and β-phenylbutyric acid.† After removal of these acids by alkaline extraction, the esters were saponified to give β-phenylbutyric acid, β-methylcinnamic acid and β-cyclohexylbutyric acid. These impurities could not be easily removed by distillation. Distilled materials were however used to determine the optical activities. The results, corrected for the optical purities of the starting alcohols (Table 1) are reported in Table 2, together with the composition of the samples as evaluated by careful integration of appropriate ^{1}H NMR signals. 3-Phenyl-3-butenoic acid (formed by thermal isomerization of β-methylcinnamic acid) was found as an impurity only at this stage.

As shown in Table 2, asymmetric induction decreases on changing the alkyl group from methyl to cyclohexyl. While this result is in accordance with the proposal of Prelog, the opposite trend is required for the transition state **2a**: increase of alkyl bulkiness indeed causes no significant destabilization of the preferred conformations (**2**) and further enhances steric hindrance at the most-hindered side. Furthermore, were both the transition states **1a** and **2a** operating simultaneously, a residual asymmetric induction, attributable only to **2a**, would have been observed, even when the alkyl group approaches the same size as the phenyl. Since asymmetric

†β-Phenylbutyric acid can result from hydrogenolysis of β-methylcinnamates followed by hydrogenation of β-methylcinnamic acid, thus escaping asymmetric induction. However, negligible hydrogenolysis is suggested by nearly quantitative recovery of the neutral products.

Table 1. Optical purity of the alkylphenylmethanols

Alcohol	Maximum value(deg) reported	Observed(deg)	Optical purity,[a] %
3[b]	$[\alpha]^{21}_D$ -43.5[c]	$[\alpha]^{22}_D$ -43.41[d]	99.8
4[e]	$[\alpha]^{22}_D$ -28.1[e]	$[\alpha]^{22}_D$ -26.77[d]	95.3
5[f]	α^{23}_D -20.23[g]	α^{23}_D -20.82[d,h]	100
6[i]	$[\alpha]^{22}_D$ -31.80[i]	$[\alpha]^{22}_D$ -32.03[j]	100

[a] 100 x $[\alpha]_D$ obsd / $[\alpha]_D$ max. [b] See ref 5. [c] See ref 6. [d] Neat. [e] See ref 7. [f] See ref 8. [g] See ref 9. [h] 1 dm tube. [i] See ref 10. [j] c 3.7, cyclohexane.

Table 2. Asymmetric hydrogenation of β-methylcinnamates

Ester	Acidic products %				$[\alpha]^{25}_D$, deg[a]	Optical yield,[b] %
	Ph-CH(Me)-CH_2-COOH	C_6H_{11}-CH(Me)-CH_2-COOH	Ph-C(Me)=CH-COOH	Ph-C(CH_2)-CH_2-COOH		
7	77.6	5.2	13.0	4.1	-5.62 ± 0.37	9.87
8	78.7	5.4	12.4	3.5	-4.18 ± 0.37	7.70
9	78.3	6.0	12.5	3.2	-0.55 ± 0.37	0.96
10	78.6	6.2	12.0	3.2	-0.37 ± 0.37	0.65

[a] Benzene solutions of the mixtures (7 g per 100 ml) were used. $[\alpha]_D$ are referred to the real concentrations of β-phenylbutyric acid. [b] 100 x $[\alpha]_D$ obsd / $[\alpha]_D$ max; $[\alpha]_D$ max -57° (c 9.8, C_6H_6) [cf. H. Rupe, Justus Liebigs Ann. Chem., 369, 325 (1909)].

induction approximates zero for compounds **9** and **10**, the contribution of **2a** transition states and the directing effect of the C_1 phenyl group in the hydrogenation of β-methylcinnamates, is clearly negligible.

This result can be explained assuming that the mode of adsorption is entirely controlled by the cinnamic moiety, whose affinity for the catalyst exceeds that of isolated aromatic or ethylenic groups.[12] In this situation the C_1 phenyl group cannot find an appropriate site of the catalyst for simultaneous bonded interaction. As a consequence, powerful directing effects of the phenyl group appear to be confined to the hydrogenation of unsaturated groups conjugated with the aromatic.[4]

EXPERIMENTAL

General. All m.ps. are uncorrected. The ^{1}H NMR spectra were obtained on a Varian EM-390 spectrometer. Optical rotations were determined with a Schmidt & Haensch 16065 polarimeter.

Eu(tfc)$_3$ Shift Experiments. Eu(tfc)$_3$ was obtained from E. Merck, Darmstadt. NMR samples were prepared according to the following procedure: 0.5 ml of a 0.42 M solution of Eu(tfc)$_3$ in CCl_4 were syringed into a 5-mm NMR tube containing 0.27 mmol of alcohol. 1% TMS was used as internal standard. The following values of δ and ΔΔδ (in parenthesis) were observed for the α-protons: **3**, 14.34(0.37); **4**, 12.95(0.35); **5**, 11.01(0.55); **6**, 11.56(0.73). No overlapping of the α H signals was found for alcohols **3**, **4** and **6**. Slight overlapping with the lower-field aromatic protons was observed for alcohol **5**. However, the spectrum of partly active **5** in the presence of Eu(tfc)$_3$ shows different shifts (S, 3.48 δ; R, 3.61 δ) for the corresponding higher-field methyl group of the enantiomers. This nonequivalence can be advantageously used for direct determination of the enantiomeric composition in this case.

Preparation of β-methylcinnamates **7–10**. *General procedure.* To a stirred solution of the alcohol (10 mmol) and pyridine (11 mmol) in dry benzene (15 ml), β-methylcinnamoyl chloride (11 mmol) in dry benzene (10 ml) was added over 30 min at 0°. After standing for 15 h at 0°, the mixture was diluted with ether and washed with 2 N HCl, 2 N aqueous Na_2CO_3 and water. Drying (Na_2SO_4) and evaporation of the solvents gave the crude esters which were chromatographed on neutral alumina (100 g; activity grade III) using hexane as the eluent. Overall yields of the purified esters ranged from 50 to 70%. IR and ^{1}H NMR spectra are in accordance with the structures. The following specific rotations were observed: **7**, $[\alpha]_D^{25}$ + 57.7°; **8**, $[\alpha]_D^{25}$ + 52.2°; **9**, $[\alpha]_D^{25}$ + 67.1°; **10**, $[\alpha]_D^{25}$ + 47.1°.

Catalytic hydrogenation of β-methylcinnamates **7–10** *and recovery of β-phenylbutyric acid. General procedure.* The reaction was carried out in a 50 ml hydrogenation flask at 28° and atmospheric pressure. PtO_2 (Fluka; 41 mg) and 15 ml of acetic acid (Merck, 96%) were stirred for 10 min under a hydrogen atmosphere. A solution of the ester (1.63 mmol) in acetic acid (5 ml) was added and the hydrogenation was continued until 40.3 ml of hydrogen were consumed. The time required for the hydrogen up-take ranged from 13 to 15 min. A solution of methionine (5 mg) in acetic acid (1 ml) was immediately added to inactivate the catalyst. The mixture was filtered and diluted with 30 ml of ether. 4 N NaOH (about 90 ml) was slowly added to the stirred solution maintaining the temperature below 10°. The alkaline aqueous solution was extracted with ether (2 × 30 ml). After washing with 1 N NaOH (20 ml) and brine (2 × 20 ml), the organic phases were collected, dried (Na_2SO_4) and evaporated.

The crude saturated ester, obtained in essentially quantitative yield, was hydrolyzed by heating at reflux for 1 h with 7% methanolic KOH (8 ml). The solvent was removed *in vacuo* and the residue was dissolved in H_2O (12 ml). The aqueous solution was extracted with ether (2 × 20 ml) and the organic phases were washed with 2 N NaOH (12 ml). The combined alkaline solutions were acidified at 0° with HCl and extracted with ether (2 × 20 ml). The organic extracts, washed with water (20 ml), were collected, dried (Na_2SO_4) and evaporated to give an oily residue. Samples used for ^{1}H NMR and $[\alpha]_D$ determinations were obtained by distillation at 25 mm (155° oil bath). The weight of the distilled materials ranged from 200 to 215 mg.

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