The Origins of the Enantioselection in Asymmetric Catalytic Hydrogenation of Amino-acid Precursors

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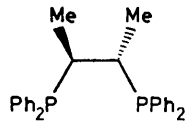
Summary Comparison of c.d. spectra confirms that the isolated diastereomer of the initial catalyst–substrate adduct in the [Rhchiraphos]$^+$-catalysed [chiraphos = (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane] hydrogenation of ethyl (*Z*)-α-acetamidocinnamate is also the major diastereomer in solution; this supports the conclusion that the prevailing chirality of the product has its origins in the minor diastereomer.

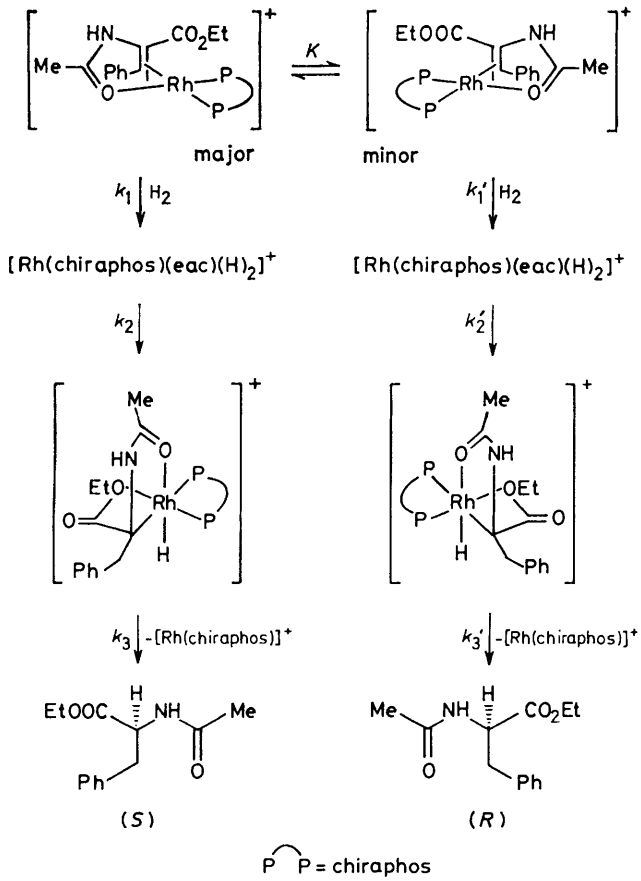
ASYMMETRIC catalytic hydrogenation of amino-acid precursors using soluble cationic chelating chiral diphosphine–rhodium(I) complexes has reached a level of refinement where

the enantioselection rivals that of enzymatic reactions.[1-4] The mechanism of these asymmetric hydrogenations has been recently clarified[5-7] and is depicted in the Scheme using as an example chiraphos (**1**) [chiraphos = (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane] and the amino-acid precursor ethyl (*Z*)-α-acetamidocinnamate (eac).



(1) chiraphos

The structures of the four-co-ordinate diastereomers have been established both in solution[8] and in the solid state[7,9] (Scheme). It is known that the equilibrium (*K*) is rapidly established in the presence of excess of amino-acid precursor substrate.[7] At ambient temperatures the rate-determining step is assumed to be (k_1,k_1') but at low temperatures (k_3,k_3') is rate-determining and the *mono*-hydrido-intermediate has been intercepted and its structure inferred from n.m.r. results[5,6] (Scheme). A four-co-ordinate diastereomer of [Rh(chiraphos)(eac)]ClO_4 has been isolated and its structure determined.[7] The chirality of the olefin–rhodium binding is such that, assuming *cis-endo* hydrogen transfer, the chirality of the ethyl *N*-acetylphenylalaninate product would be (*S*); yet the chirality of the product after actual hydrogenation is not (*S*) but (*R*), and the product is nearly optically pure (*R*). On this basis, together with kinetic data, it was assumed that the *minor* four-co-ordinate diastereomer reacted overwhelmingly faster than the major isomer[7] despite the fact that the minor isomer's proportion was less than 5% at equilibrium.[7] This would represent a velocity difference of at least 1000 in favour of the minor species and the possible reasons for this have been discussed.[4,7] It is clear, however, that these conclusions hinge on the assumption that the major isomer in solution was the one isolated and that this was not a case where the (less soluble) minor isomer was 'milked' out of a solution in which the species were in rapid equilibrium. In order to resolve this issue we require a technique which samples chirality. We have used circular dichroism.



SCHEME. An outline of the mechanism of asymmetric catalytic hydrogenation of eac using chiraphos–rhodium(I) species.

The Figure shows the absorption and c.d. spectra of [Rh(chiraphos)(eac)]ClO_4 in methanol solution containing a 12-fold excess of eac and in the solid state dispersed as a 1% KBr disc.† It will be noted that the absorption spectra are similar and that the c.d. spectra show the same sign

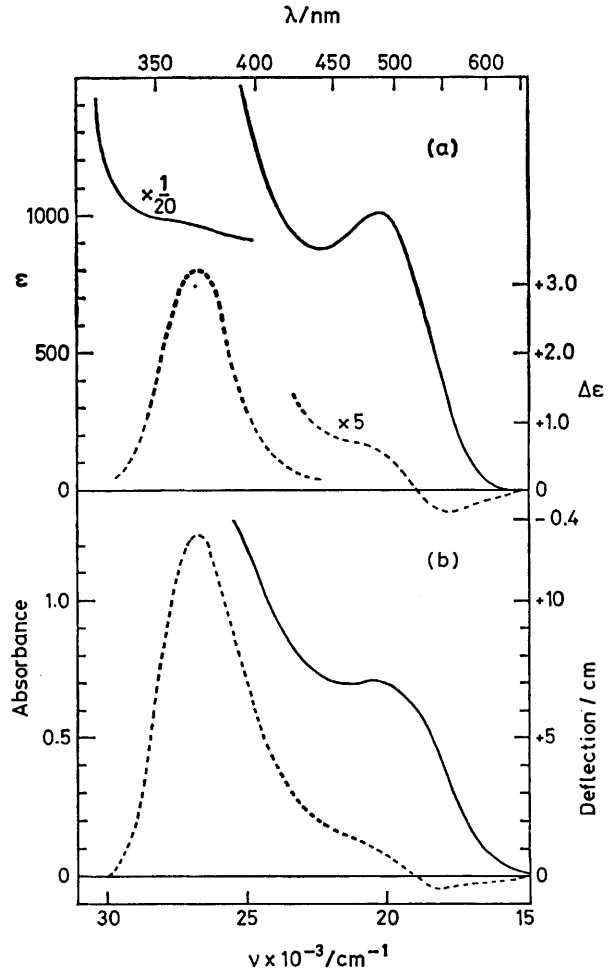


FIGURE. The absorption (——) and c.d. (– – – –) spectra of [Rh(chiraphos)(eac)]ClO_4 (a) in methanol solution and (b) as a 1% dispersion in a KBr disc.

† For techniques in the preparation of KBr discs for c.d., B. Bosnich and J. M. Harrowfield, *J. Am. Chem. Soc.*, 1972, **94**, 3425.

pattern in both media. Moreover, the relative intensities of the c.d. bands for the two spectra are also similar. We therefore conclude that the solid and solution state spectra refer to the same diastereomer.

Because the equilibration is rapid in the presence of excess of substrate and because the equilibrium (K, Scheme) favours the major isomer to the extent of $> 95\%$,[7] the solution c.d. spectrum represents almost exclusively that of the major diastereomer. For completeness of the argument, we should point out that the c.d. spectrum consists of two, probably additive, parts:[10] the contribution due to chiraphos co-ordination and that due to the chiral co-ordination of eac. The only circumstance which would affect our conclusion would be if the c.d. contribution of eac co-ordination were so small compared with that of co-ordinated chiraphos that the c.d. spectra would be insensitive to the chirality of eac co-ordination. We consider this highly unlikely because we have found with other comparable systems that the chirality of the amino-acid substrate co-ordination has a marked effect on both magnitude and sign patterns of the c.d. spectrum.[4]

This and the other accumulated evidence[5–7] strongly support the conclusion that catalytic asymmetric hydrogenation of amino-acid precursors using chiral chelating diphosphines proceeds mainly *via* the minor four-co-ordinate diastereomer. Such a conclusion has broad implications in the design of systems for asymmetric synthesis[4,7] and elicits caution in drawing conclusions about optical yields from diastereomeric equilibria.

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