Kurzmitteilung / Short Communication

Evidence for Exchange Processes Associated with the Hydrogenation of Methyl (Z)-α-Acetamidocinnamate by a Silica-Bound Chiral Dirhodium Catalyst

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Mass spectrometric studies show that hydrogen/deuterium exchange processes precede the hydrogenation of the title compound.

In a recent study[1] we have shown that both homogeneous (**1**) and silica-bound (**2**) (+)-dicarbonyl-μ-chloro-[μ-[2-(triethoxysilyl)-ethanethiolato-S,S]bis⟨[5-methyl-2-(1-methylethyl)cyclohexyl]diphenylphosphine⟩dirhodium catalyze the asymmetric hydrogenation of methyl (Z)-α-acetamidocinnamate (**3**). The optical purity of the N-acetylphenylalanine methyl ester (**4**) formed, was found to be up to 98% ee at low conversions, but it dropped gradually when the reduction advanced. Loss in optical purity was also observed upon (i) lowering the hydrogen pressure below 7 atm, (ii) decreasing the catalyst: substrate ratio, and (iii) increasing the reaction temperature.

[(+)-neomenthyl]Ph₂P, Cl, PPh₂[(+)-neomenthyl]

Rh Rh
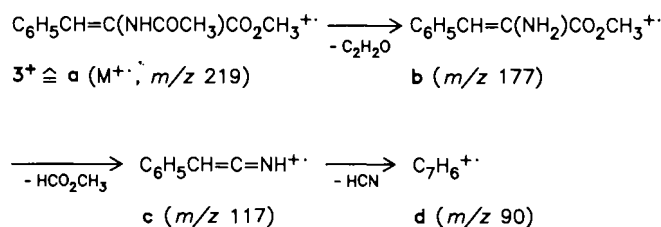
OC, S, CO

CH₂CH₂Si(OEt)₃

1
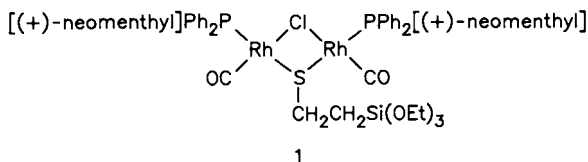
Since the homogeneous dirhodium catalyst decomposes in part during the hydrogenation process, we have initially attributed the diminishing in optical purity to a competing nonasymmetric hydrogenation induced by some of the liberated metallic rhodium. However, as the reduction of **3** by the silicon-bound catalyst (which does *not* deteriorate) was also found to give, with increasing reaction time, increasing amounts of racemic product, we considered hydrogen scrambling at the chiral carbon atom in **4** as an alternative cause for gradual loss in optical activity. Therefore, we decided to investigate the possibility of H/D exchange during the course of the hydrogenation process by using D₂ in CH₃OH or CD₃OD as solvents.

In a series of experiments, 0.42 mmol of **3** in a mixture of either 2.5 ml of CH₃OH and 5.0 ml of C₆H₆, or of 2.5 ml of CD₃OD and 5.0 ml of C₆H₆ was hydrogenated in the presence of 2.21×10^{-2} mmol of *fully activated* **3**[1] at 120°C and 7.14 atm (initial pressure)

of either H₂ or D₂. Mass spectral analyses of the resulting reaction mixtures after 4 and 16 h, revealed that both the product and the recovered starting material had undergone extensive H/D exchange both by D₂ and by the labeled solvent.

The 70-eV EI mass spectrum of the starting material **3** that consisted of peaks at m/z (%) = 219 (6), 177 (60), 176 (7), 118 (13), 117 (100), 116 (21), 91 (17), 90 (26), 89 (23) suggests that the principal fragmentations follow the sequence shown in Scheme 1.
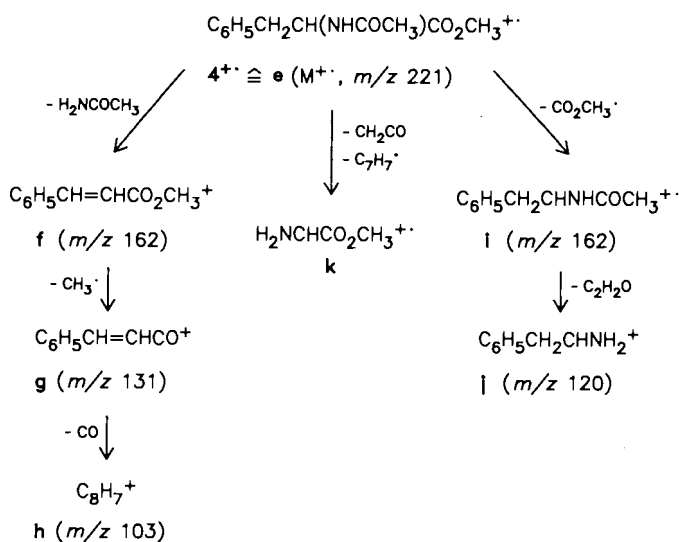
Scheme 1

$$C_6H_5CH=C(NHCOCH_3)CO_2CH_3^{+\cdot} \xrightarrow{-C_2H_2O} C_6H_5CH=C(NH_2)CO_2CH_3^{+\cdot}$$

3⁺ ≙ **a** (M⁺·, m/z 219)　　　　　**b** (m/z 177)

$$\xrightarrow{-HCO_2CH_3} C_6H_5CH=C=NH^{+\cdot} \xrightarrow{-HCN} C_7H_6^{+\cdot}$$

c (m/z 117)　　　　　　**d** (m/z 90)

The corresponding spectrum of **4**, m/z (%) = 221 (1), 162 (78), 161 (18), 131 (36), 120 (55), 119 (11), 103 (35), 102 (16), 91 (52), 88 (100), is also in line with well-known mass spectrometric fragmentation patterns, and the major fragmentations of **4**⁺· are those given in Scheme 2. In addition, both **3**⁺· and **4**⁺· were found to form the C₇H₇⁺ ion (**l**) by several different fragmentation routes.

In light of the fragmentation processes of **3**⁺·, the mass spectral data of recovered starting material from four hydrogenation and deuteration reactions (I−IV) were analyzed. Table 1 summarizes the data for **3** after treatment with (I) H₂/CH₃OH, (II) D₂/CH₃OH, (III) H₂/CD₃OD, and (IV) D₂/CD₃OD for 4 h. The figures permit the following conclusions to be drawn: (i) Both D₂ and CD₃OD induce fast H/D exchange at the amido nitrogen. Hence, the high intensity of a-, b- and c-type fragments in experiments II−IV. By comparison of the spectra taken after 4 and after 16 h, it was noticed that this kind of H/D exchange is more pronounced by CD₃OD than by the hydrogenation agent. We assume that D₂ and CH₃OH form initially deuterated methanol[2], which in turn, causes fast NH→ND exchange. (ii) Both the deuterated reagent and the solvent induce a second H/D exchange in which the vinylic hydrogen is affected[3]. This exchange proved to be considerably slower than

Scheme 2

$$C_6H_5CH_2CH(NHCOCH_3)CO_2CH_3^{+\cdot}$$

$$4^{+\cdot} \triangleq \ominus (M^{+\cdot}, m/z \ 221)$$

$- H_2NCOCH_3$

$- CH_2CO$
$- C_7H_7^{\cdot}$

$- CO_2CH_3^{\cdot}$

$C_6H_5CH=CHCO_2CH_3^+$

f (m/z 162)

$H_2NCHCO_2CH_3^{+\cdot}$

k

$C_6H_5CH_2CHNHCOCH_3^{+\cdot}$

l (m/z 162)

$- CH_3^{\cdot}$

$C_6H_5CH=CHCO^+$

g (m/z 131)

$- C_2H_2O$

$C_6H_5CH_2CHNH_2^+$

i (m/z 120)

$- CO$

$C_8H_7^+$

h (m/z 103)

that on the amido nitrogen. Thus, in experiment III the m/z values of the nitrogen-containing fragments **a**, **b**, and **c** (but *not* the nitrogen-free ions **d** and **l**) were found to increase by one unit after a reaction period of 4 h and by two units after 16 h. The relative intensities of fragments $m/z = 218 - 221$ that were 8, 82, 10, and 0% in the 4-h spectrum changed to 0, 22, 66, 24, and 10% after 16 h. Likewise, the CI spectrum of **3** which consists mainly of three peaks at $m/z = 219, 220, 221$ contained a peak at $m/z = 222$ in the 16-h experiment. The assignment of the second H/D exchange to the vinylic hydrogen is based on the increase of the relative intensities of ions **d** and **l**; the relative intensities of signals at $m/z = 89, 90, 91$, and 92 which were 30, 38, 30, and 0% after 4 h became 25, 33, 29, and 13% after 16 h. (iii) Transesterification takes

place as evidenced in the experiment using CD₃OD. The [M + 1]⁺ signal of **3** in the CI spectrum ($m/z = 220$) expanded in experiments III and IV to a series of peaks with masses as high as $m/z = 225$ (owing to one N*D*, one C_6H_5CD, and three CD_3 deuterium atoms). Proof for the transesterification was obtained by the change in the relative intensities of the ester-containing fragment ion **b**. These CD_3-containing peaks were found to be more intense in the 16- than in the 4-h spectrum, although even after the longer reaction period the abundances of the highest masses were still quite low. The highest degree of deuterium labeling of the recovered starting material was recorded in experiment IV in which both the hydrogenation agent and the solvent were fully deuterated.

Table 2 summarizes the mass spectral data for **4** formed in the different experiments during 4-h reaction periods. The data indicate that the same hydrogen atoms that were exchanged in the recovered starting material **3** were also labeled in the product. However, additional H/D exchange, in particular at the benzylic position takes place during the hydrogenation process. Thus, e.g., the $C_7H_7^+$ ion region from experiments III and IV was found to incorporate up to two deuterium atoms. Consequently, the spectrum of the product formed in experiment II gave evidence for the formation of the tetradeuterated compound $C_6H_5CD_2CD(NDCOCH_3)COOCH_3$, and the data for experiments III and IV indicate the accumulation of the analogous trideuteriomethyl ester $C_6H_5CD_2(NDCOCH_3)$-$COOCD_3$.

In contrast to **3**, for which significant differences have been observed between the spectra after 4 and 16 h, only minor time-dependent changes were noticed in the corresponding spectra of **4**. This suggests that the exchange reaction in the product is relatively fast and does not necessarily require initial H/D exchange in the starting material.

Deuterium/hydrogen exchange during metal-catalyzed deuteration of carbon = carbon bonds was often found to take place at a stage where the olefin is attached to the metal by a π bond and one hydrogen and one deuterium atom are coordinated as hydride and

Table 1. Mass spectral data for recovered methyl (Z)-α-acetamidocinnamate from hydrogenation reactions using **2** as a catalyst[a]

Experiment	Hydrogenation system	70-eV EI spectrum[b]: m/z (%)				CI spectrum[c]: m/z (%)
		a-type ions	**b**-type ions	**c**-type ions	**d**- and **l**-type ions	
I	H₂, CH₃OH/C₆H₆	218 (11)	176 (8)	116 (16)	89 (31)	219 (4)
		219 (86)	177 (92)	117 (71)	90 (36)	220 (96)
		220 (3)		118 (10)	91 (23)	
				119 (3)		
II	D₂, CH₃OH/C₆H₆	218 (8)	176 (8)	116 (11)	89 (30)	219 (5)
		219 (82)	177 (84)	117 (58)	90 (39)	220 (86)
		220 (10)	178 (12)	118 (23)	91 (31)	221 (9)
				119 (4)		
				120 (4)		
III	H₂, CD₃OD/C₆H₆	218 (5)	176 (6)	116 (7)	89 (23)	219 (3)
		219 (19)	177 (4)	117 (32)	90 (29)	220 (38)
		220 (62)	178 (43)	118 (39)	91 (31)	221 (33)
		221 (13)	179 (8)	119 (11)	92 (17)	222 (7)
		222 (1)	180 (3)	120 (6)		223 (8)
				121 (5)		224 (8)
						225 (3)
IV	D₂, CD₃OD/C₆H₆	218 (3)	176 (2)	116 (5)	89 (15)	220 (11)
		219 (22)	177 (21)	117 (24)	90 (32)	221 (73)
		220 (59)	178 (62)	118 (50)	91 (33)	222 (10)
		221 (14)	179 (10)	119 (15)	92 (20)	223 (2)
		222 (2)	180 (5)	120 (3)		224 (2)

[a] The reaction mixtures were separated and analyzed with the aid of a GC/MS system composed of a Varian 3700 GC and a Varian MAT 44 mass spectrometer. The GC was equipped with a CP Sil 5 capillary column (Chromopack) operated between 100 and 310°C (temperature increase 25°C/min). — [b] The data given are corrected for natural ¹³C contributions and expressed in percent of the sum of the individual ion-type intensities. — [c] Reagent gas isobutane.

Table 2. Mass spectral data for N-acetylphenylalanine formed by hydrogenation and deuteration of 3 using catalyst 2[a]

Experi-ment	Hydrogenation system	e-type ions	f- and i-type ions	70-eV EI spectrum[b]: m/z (%) g-type ions	h-type ions	j-type ions	k- and l-type ions	CI spectrum[d]: m/z (%)
I	H_2, CH_3OH/C_6H_6	220 (11) 221 (81) 222 (8)	161 (19) 162 (81)	130 (17) 131 (83)	102 (31) 103 (69)	117 (6) 118 (8) 119 (14) 120 (72)	87 (6) 88 (55) 89 (0) 90 (5) 91 (30) 92 (4)	221 (4) 222 (96)
II	D_2, CH_3OH/C_6H_6	220 (5) 221 (21) 222 (47) 223 (16) 224 (4) 225 (5)	161 (11) 162 (51) 163 (30) 164 (8)	130 (11) 131 (53) 132 (29) 133 (7)	102 (15) 103 (35) 104 (41) 105 (9)	117 (4) 118 (6) 119 (10) 120 (31) 121 (38) 122 (11)	87 (4) 88 (61) 89 (32) 90 (10) 91 (11) 92 (15) 93 (2)	221 (1.5) 222 (35) 223 (38) 224 (23) 225 (4) 226 (0.5)
III	H_2, CD_3OD/C_6H_6	221 (11) 222 (31) 223 (39) 224 (9) 225 (10) c)	161 (6) 162 (32) 163 (50) 164 (12) c)	130 (6) 131 (32) 132 (52) 133 (10)	102 (12) 103 (33) 104 (43) 105 (12)	117 (3) 118 (6) 119 (9) 120 (21) 121 (36) 122 (21) 123 (4)	87 (3) 88 (24) 89 (32) 90 (9) 91 (10) 92 (13) 93 (7) 94 (2)	222 (14) 223 (33) 224 (32) 225 (16) 226 (3) 227 (2)
IV	D_2, CD_3OD/C_6H_6	222 (6) 223 (32) 224 (47) 225 (15) c)	161 (2) 162 (10) 163 (36) 164 (49) 165 (2) 166 (1)	131 (9) 132 (33) 133 (57)	103 (17) 104 (37) 105 (46)	118 (3) 119 (5) 120 (6) 121 (11) 122 (28) 123 (39) 124 (8)	88 (6) 89 (33) 90 (35) 91 (1) 92 (12) 93 (10) 94 (3)	223 (4) 224 (28) 225 (43) 226 (18) 227 (6) 228 (1)

[a] Spectra recorded as specified in Table 1. — [b] See footnote[b] in Table 1. — [c] Owing to too low abundances the data for the higher peaks are not given. — [d] Reagent gas isobutane.

deuteride, respectively[4,5]. Thus, in the absence of severe steric effects the hydride or deuteride may be reversibly transferred to either site of the coordinated olefinic carbon atoms. Since the olefinic atoms in 3 become the benzylic and the chiral carbon atoms in 4, we assume that H/D exchange at the α position (with respect to the phenyl moiety) is associated also with hydrogen scrambling at the β position (although not necessarily to the same extent). Since under our experimental conditions the *isolated* product 4 does not undergo dehydrogenation by the dirhodium catalyst 2, the hydrogen exchange at the α and β carbon atoms could occur only prior to the final stage of the hydrogenation process.

Unfortunately, however, mass spectral analysis cannot provide an unambiguous proof for direct hydrogen scrambling at the chiral carbon atom. The only weak support for the operation of such a process is the appearance of small peaks (<1% relative intensity) at $m/z = 102$ and 131 in the spectrum of 4 obtained in experiment IV after 16 h. These peaks correspond to deuterium-free k − 1 and h − 1 fragments which could have been formed only by complete exchange of all the deuterium atoms, including that at the β position, by H_2, HD, or CD_3OH that had been generated by the initial H/D exchange processes.

CAS Registry Numbers

3: 60676-51-9 / 4: 62436-70-8 / $C_6H_5CD_2CD(NDCOCH_3)COO$-$CH_3$: 121314-62-3

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[4] See, e. g., G. C. Bond, P. B. Wells, *Adv. Catal.* **15** (1964) 92.
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[141/89]