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Stereochemistry of the Enantioselective Reductive Alkylation of Proline with Ketones

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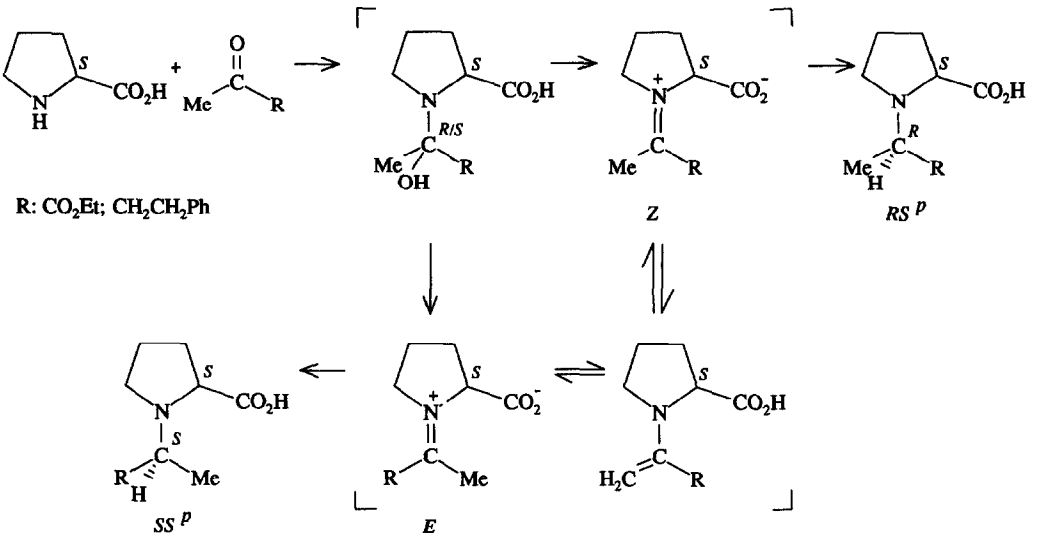
This paper is dedicated to the memory of Günther Snatzke.

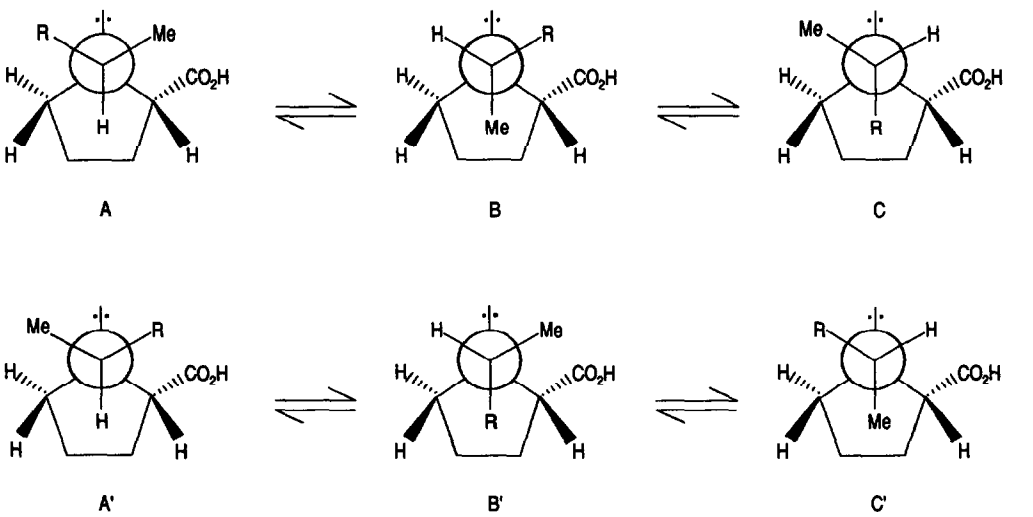
Abstract: Enantioselective heterogeneous catalytic hydrogenation of pyruvic acid ethyl ester and benzylidene-acetone with Pd/C catalyst in the presence of (*S*)-proline was investigated, where the reductive alkylation of proline was observed. The structure of the main products was elucidated by different NMR methods and the configuration and predominant conformation of (-)-(*S*)-1-(1-Ethoxycarbonyl-ethyl)-pyrrolidine-(*S*)-2-carboxylic acid (**1**) was established.

Previously we have reported on the enantioselective hydrogenation of α,β-unsaturated ketones and pyruvic acid ethyl ester with Pd/C catalyst in the presence of (*S*)-proline as chiral additive.[1-4] We observed that the reductive alkylation of the nitrogen in (*S*)-proline also took place beside the enantioselective hydrogenation of the C=C and carbonyl groups. The addition and condensation products of (*S*)-proline and the ketone were supposed as intermediates: carbinolamine, *Z* and *E* iminium salts and enamine (Scheme 1). There are reports on the use of (*S*)-proline ester derivatives for enantioselective alkylation[5-14], and on the asymmetrical reduction of C=N double bonds in homogeneous phase by sodium (*S*)-prolinate-borane complexes.[15-18] In our present paper the structure elucidation, inclusive configurational and conformational analysis, of some of the products from the above mentioned reductive alkylation will be discussed.

As model compounds the alkylation products (**1**,**2**) of pyruvic acid ethyl ester and benzylidene-acetone were chosen. The enantioselectivity of the reaction was investigated by the NMR spectra of the crude products (Table 1). In the spectra two sets of signals were observed, but the ^{1}H NMR signals of the two diastereoisomers (*SS*-**1**, *RS*-**1** and *SS*-**2**, *RS*-**2**, respectively) were very close to each other. Separation of the signals could be observed only on the methyl and on the protons connected directly to the stereogenic centres. The NMR signals of **2** were broad at ambient temperature because of the hindered rotation of the substituent on the proline N atom. To overcome the unwanted line-broadening the spectra were also measured at 373 K. In the case of **1** and **2** the major diastereomers were isolated by crystallization and investigated. The assignment of the ^{1}H NMR signals (Table 1) was supported by decoupling experiments, while that of the ^{13}C NMR signals (Table 2) was based on the known ^{13}C NMR data of proline.[19] In the case of **1** and **1**·HCl further experiments were needed to distinguish among C-2, NCH, OCH_2, furthermore the two carbonyl and the two methyl carbons, respectively, because of the close chemical shift values. Polarization transfer from NCH proton by the two- dimensional (2D) semiselective INEPT experiment[20]



Scheme 1



1 R: CO_2Et

2 R: CH_2CH_2Ph

Scheme 2. Conformational equilibrium of products with *SS* (A/B/C) and *RS* (A'/B'/C') configuration

optimized for J(C,H)=5 Hz long-range couplings allowed the unambiguous assignment of the carbon signals C-2, Me and CO_2R. In the case of **1**·HCl the one-dimensional (1D) semiselective INEPT[21] (J(C,H)=7 Hz) from Hα-3 led to the differentiation of the nearby CO_2H and CO_2R signals. The same type of measurement starting from Hα-5 gave the assignment of the NCH and C-5 signals.

Table 1. ^1H chemical shifts and diastereomeric ratios (Q)

	1	**1**·HCl	**2**[a]	**2**·HCl[b]
Hα-2	3.57	4.47	3.63	4.45
Hα-3	1.99	2.43	2.0	2.40
Hβ-3	1.77	2.06	2.0	1.75-2.25
Hα-4	1.71	2.06	1.75	1.75-2.25
Hβ-4	1.71	1.88	1.75	1.75-2.25
Hα-5	2.69	3.39	2.89	3.31
Hβ-5	2.96	3.65	3.37	3.58
CO_2H	8.4	9.5	8.2	9.5
Me	1.19	1.52	1.20	1.38
CH	3.63	4.50	3.16	3.58
CH_2	4.07	4.19	1.70 1.94	1.75-2.25
CH_2CH_3	1.18	1.27		
CH_2CH_2Ph			2.64	2.68
H_2-2'			7.21	7.10-7.40
H_2-3'			7.26	7.10-7.40
H-4'			7.16	7.10-7.40
Q	82/18		57/43	

[a] measured at 373 K
[b] at 250 MHz

Table 2. ^{13}C chemical shifts

	1	**1**·HCl	**2**[a]	**2**·HCl[b]
C-2	60.9	65.0	63.4	62.3
C-3	29.9	28.6	23.0	21.9
C-5	50.3	52.8	50.0	50.9
CO_2H	176.4	169.7	173.6	169.2
CH_3	15.6	13.3	15.5	14.8
CH	57.9	60.5	56.7	58.9
CO_2	173.1	168.3	-	-
CH_2	59.9	61.8	33.9	31.9
CH_2CH_3	14.0	13.4	-	-
CH_2CH_2Ph	-	-	31.2	31.0
C-1'	-	-	141.2	140.7
C-2'	-	-	127.7	127.8[c]
C-3'	-	-	127.7	127.9[c]
C-4'	-	-	125.2	125.6

[a] measured at 373 K
[b] at 250 MHz
[c] tentative assignment

To elucidate the stereochemistry of **1** and **2** we had to establish only the configuration of the new stereogenic centre (NCH), because the C-2 of (*S*)-proline was not involved in the reaction. We have also studied the conformational equilibria of compounds **1** and **2**, considering the different envelope and twist forms of the five-membered ring and the three favourable rotamers about the N-CH(Me)(R) bond (Scheme 2).

The 400 MHz spectrum of **1** can be considered as first ordered, thus J(H-2, Hα-3)=9.2 Hz and J(H-2, Hβ-3)=3.1 Hz. (In our discussion we use the α/β nomenclature to distinguish between the position of the ring protons, therefore the protons on the same side as H-2 were indicated as α. The spatial position of the hydrogen atoms was proved by 1D NOE measurements, see Table 3.)

Table 3. Results of ^{1}H NOE difference experiments

1

Hα-2	: Hα-3 (4.8%); Hα-5 (1%); CH_3 (5.2%)
Hα-5	: Hα-2 (1.1%); Hα-3 (1.1%); Hα-4 (4.8%); Hβ-5 (24.4%); NCH (2.0%)
Hβ-5	: Hβ-4 (2.0); Hα-5 (10.5%); CH_3 (1.5%); NCH (1.3%)
CH_3	: Hα-2 (3.8%); Hα-5 (2.4%); NCH (5.6%)
NCH	: Hα-5 (1.8%); Hβ-5 (2.2%); CH_3 (7.8%)

1·HCl

Hα–5	: Hα-3 (1.3%); Hα-4 (3.8%); Hβ-4 (1%); Hβ-5 (14.1%); NCH (3.4%); CH_3 (3.4%)
Hβ–5	: Hα-4 (2.9%); Hβ-4 (3.5%); Hα-5 (14.4%); CH_3 (2.4%)
CH_3	: Hα-2 (7.6%); Hα-5 (6.5%); Hβ-5 (3.4%); NCH (10%)

2[a]

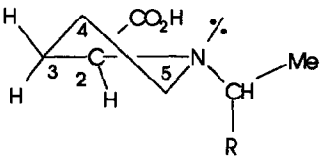
Hα-2	: Hα-3 (5.6%); $NCHCH_2$ (2.6%); NCH (1.8%);.CH_3 (2.2%)
CH_3	: Hα-2 (2.8%); Hα-5 (2.0%); Hβ-5 (1%); NCH (4.9%);CH_2CH_2Ph (2.0%); $NCHCH_2$ (2.2%)

[a] measured at 373 K

Utilizing the modified Karplus relationship, taking also into account the electronegativity of the atoms, the above discussed coupling constants indicate dihedral angles of about 10° (H-2, Hα-3) and 250° (H-2, Hβ-3).[22] These data refer to a predominant twist conformer of proline in which N-(C-2)-(C-3) are in one plane, while C-4 above and C-5 below this plane (Scheme 3).

It is known that nitrogen inversion in five-membered rings is a low energy process, thus we have to consider the conformers arising in this way, too. If the substituent at nitrogen is in a β position, the CO_2H and the substituent of nitrogen in the predominant conformer of proline stay in a *syn* arrangement yielding a very unfavourable steric interaction. Furthermore the CH and CH_3 protons of the N-substituent would stay

close to Hβ-4, which is not supported by the NOE measurements. Accordingly, it is possible to consider only the conformer with α substituent at the nitrogen (as depicted on Schemes 2 and 3.).



Scheme 3

The stereochemistry of **1** was established by information obtained from vicinal J(C,H) couplings and NOE difference measurements. The long-range couplings of the NCH proton were measured by 2D semiselective INEPT experiment and among them the ^3J(HC,C-2)=5.0 Hz and ^3J(HC,C-5)=2.4 Hz proved to be crucial. The vicinal couplings in a H-C-N-C moiety give also a Karplus-type relationship between the coupling constant and the dihedral angle, though the current values are dependent on the substituents connected.

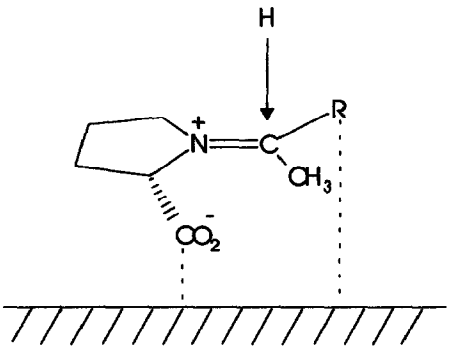
For a 180° dihedral angle 5-6 Hz couplings were found in analogous compounds[23] thus the ^3J(C,H) data discussed above prove the predominance of a conformer, in which the NCH proton and C-2 are in an antiperiplanar arrangement. This corresponds in the case of *SS* configuration to conformation B, in *RS* to B'. The methyl protons gave with Hα-2 and Hα-5 considerable NOE enhancement, proving that in the preferred conformer the methyl group is close to both protons. This steric proximity is only fullfield by configuration *SS* in conformer B. The results of the NOE experiments show that the two other conformers of *SS* can also take part in the conformational equilibrium (e.g. the presence of conformer C is proved by the intensity enhancement on Me peak by irradiating Hβ-5), but a semiquantitative description of the A/B/C conformational equilibrium is still not possible because of the absence of suitable ^3J(C,H) reference data. Though in **1**·HCl the separation of the ^1H signals of proline was better, than in **1**, the chemical shift difference between Hα-2 and NCH signals decreased to 0.03 ppm, thus in this case the selective measurement of the corresponding ^3J(C,H) couplings was not possible.

The observed ratios of the measured 1D NOE values were similar to that of **1**-base, which indicated that the conformational conditions of the *SS* diastereomer do not change significantly with the salt-formation.

In the 400 MHz NMR spectrum of **2** the splittings on Hα-2 signal (8.5 and 4.4 Hz, respectively) do not give the coupling constants directly because of the strong coupling of the ring protons of the proline. Thus it can only be supposed that the conformation of the proline ring is similar to that of **1**. The 1D NOE data show the existence of the conformers B/C of configuration *SS*, [see the NOE values proving the spatial closeness of Hα-2 and R (NCHC$\underline{H}_2$) or that of Hα-2 and the Me group]. Irradiating the methyl protons the measured twofold intensity enhancement on Hα-5 compared to Hβ-5 refers to the predominant occurrence of conformer B. Supposing an *RS* configuration the conformers A'/C' are favoured with C' probably in

excess. Due to the five vicinal coupling partners of NCH its ^1H signal is rather broad therefore it is not surprising that the 2D semiselective INEPT measurement starting from this proton was unsuccessful. Thereby the absolute configuration at NCH could not be revealed on the basis of available data. Investigating **2**·HCl we obtained similar NMR spectra, but here the ^1H signals of NCH and Hβ-5 were completely overlapped.

Comparing the CD spectra of **1**, **1**·HCl, **2** and **2**·HCl we found a negative Cotton-effect at about 220 nm in each case, which refers to the identical configuration of **1** and **2**.



Scheme 4

According to the results of the stereochemical investigations and the found high enantioselectivity we propose the following mechanism for the asymmetric hydrogenation. Proline and the carbonyl compound form an intermediate adduct which turns into an iminium salt by eliminating water. Due to the steric interaction between the CO_2H and CO_2Et the *E* isomer of the iminium salt is favourable, and adsorbs on the surface of the catalyst as shown on Scheme 4. In this position the activated atomic hydrogen can only attack from the opposite side to the catalyst resulting in the new centre of chirality with configuration *S*.

Experimental

(-)-(S)-1-(1-Ethoxycarbonyl-ethyl)-pyrrolidine-(S)-2-carboxylic acid (**1**); m.p. oil, $[\alpha]_D^{20} = -41.2$ (c=1, ethanol), CD λ_{max}=221 nm, $\Delta\varepsilon$=-0.67

(-)-(S)-1-(1-Ethoxycarbonyl-ethyl)-pyrrolidine-(S)-2-carboxylic acid hydrogen chloride (**1**·HCl); yield 45%, m.p. 144-146 °C, $[\alpha]_D^{20} = -33.7$ (c=1, ethanol), CD λ_{max}=222 nm, $\Delta\varepsilon$=-0.08 (Found: C, 47.62 H, 7.32 N, 5.41. Calc. for $C_{10}H_{17}NO_4$·HCl: C, 47.72 H, 7.21 N, 5.57%.)

(-)-1-(1-Methyl-3-phenyl-propyl)-pyrrolidine-(S)-2-carboxylic acid (**2**); m.p. oil, $[\alpha]_D^{20} = -39.6$ (c=1, ethanol)

(-)-1-(1-Methyl-3-phenyl-propyl)-pyrrolidine-(S)-2-carboxylic acid hydrogen chloride (**2**·HCl); yield 32%, m.p. 120-122 °C, $[\alpha]_D^{20} = -46.3$ (c=1, ethanol), CD λ_{max}=215 nm, $\Delta\varepsilon$=-0.39 (Found: C, 63.39 H, 7.92 N, 4.81%. Calc. for $C_{15}H_{21}NO_2$·HCl: C, 63.48 H, 7.81 N, 4.94%.)

Hydrogenations were carried out in a stirred autoclave under 8-10 bar hydrogen pressure and at room temperature in a methanolic solution, at 1:1 (*S*)-proline/ketone molar ratio using 10 % Pd on carbon catalyst.[24] Besides the alkylated prolines (approx. 50 % yield) ethyl-lactate, saturated ketone and (*S*)-proline could be recovered from the reaction mixture. The alkylated prolines were separated and investigated in the form of base or salt. The salts were recrystallized from *iso*-propanol. The NMR spectra were obtained on Bruker AM-400 and AC-250 spectrometers in DMSO-d_6. Chemical shifts are given on the δ scale. In the 1D measurements 64K data points were used for FID. For homonuclear NOE experiments a delay time of 7 s was applied. NOE difference and 2D carbon-proton correlated experiments were run using the Bruker software package. In the 2D experiments 1K x 1K data matrices were transformed. In the case of the 2D semiselective INEPT measurements the data matrices were 1K x 64 data points, and the spectral width in the F1 (proton) dimension was 16 Hz. Selected traces were zero-filled to give a final digital resolution of 0.06 Hz. Shifted sine-bell multiplication in F2 (carbon) and Gaussian multiplication in F1 dimension was applied, before doing the Fourier transformations. CD spectra were recorded in ethanol with a Jobin-Yvon-ISA Dichrographe Mark III connected on-line to a PDP-8e computer. All melting points are uncorrected.

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