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NMR MEASUREMENTS AND SEMI-EMPIRICAL CALCULATIONS IN A FIRST APPROACH TO ELUCIDATE THE MECHANISM OF ENANTIOSELECTIVE CYANOHYDRIN FORMATION CATALYSED BY CYCLO-(S)-PHE-(S)-HIS

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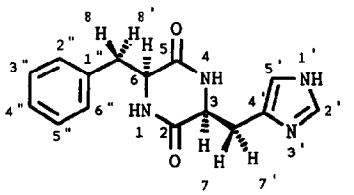
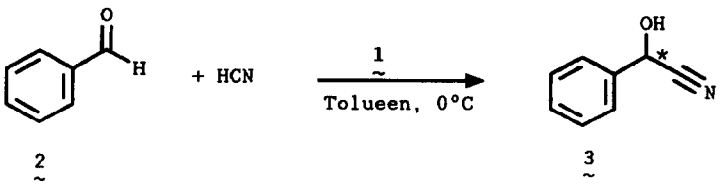
Abstract: A model was proposed for the stereochemical course of the highly enantioselective hydrocyanation of aromatic aldehydes catalysed by cyclo-(S)-Phe-(S)-His (**1**). The conformation populations of **1** were determined by substituting the NMR coupling constants of the relevant protons in the Karplus equations. In addition the relative stabilities of these conformations were calculated using the semi-empirical AM1 and PM3 methods. The nature of the interaction between HCN and the imidazole moiety of **1** was calculated using a model system. No experimental evidence could be obtained for the interaction of benzaldehyde with **1** using NMR or IR.

INTRODUCTION

After the pioneering work by Inoue[1] on the asymmetric hydrocyanation of benzaldehyde catalysed by the cyclic dipeptide cyclo-(S)-Phenylalanyl-(S)-Histidyl **1**, much effort has been put into the synthesis of similar catalysts to broaden the scope of the reaction to other aldehydes, and to further improve the optical purity of the resulting cyanohydrins[2,3]. Also, factors influencing the reaction (Scheme 2) have been investigated, e.g. solvent[4,5], temperature[3,5], and crystallinity of the catalyst[6,7]. Generally, the optical purity of the cyanohydrins (the R-enantiomer is formed) is highest when the reaction proceeds in non-polar solvents at low temperature with a non-crystalline catalyst[5]. Furthermore, the optical purity of the reaction products is usually higher with aromatic aldehydes than with aliphatic aldehydes[5,8], cyclo-(S)-Leucinyl-(S)-Histidyl being a notable exception giving higher and reversed enantioselectivity in the



Scheme 1. Numbering of **1**



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Scheme 2. Hydrocyanation of benzaldehyde

hydrocyanation of aliphatic aldehydes[2]. In contrast, (S)-Phenylglycidyl-(S)-Histidyl shows no enantioselectivity for any aldehyde[3].

To explain the enantioselectivity of the reaction in Scheme 2, two mechanisms have been proposed. Based on molecular models, Jackson et al,[3] suggested a non-folded conformation in which both aromatic rings are situated on one side of the diketopiperazine ring. It was pointed out that this would allow for a simultaneous three point attachment (cyanide associated with imidazole ring, aldehyde carbonyl hydrogen bonded to one of the diketopiperazine ring NH's and aryl-aryl interactions), without going into further details about the exact conformation of the ternary complex. Inoue[5] does present a clear picture of this complex, (see Figure 1), however, some questions can be raised regarding his model.

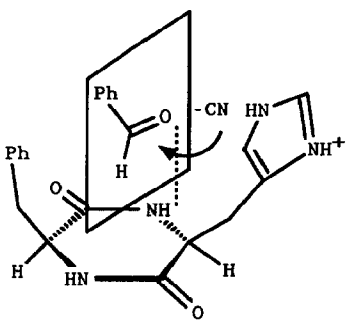

Figure 1. Mechanism according to S. Inoue et al

It would seem that the function of the aromatic ring of phenylalanine is slightly more complicated than a mere blocking of one side of the aldehyde, since cyclo-(S)-Phenylglycidyl-(S)-Histidyl[3] gives rise to completely racemic mandelonitrile **3**. Also, it does not explain why the optical yield is much higher with aromatic aldehydes than with aliphatic aldehydes.

In this paper we describe our attempts at clarifying this picture based upon experimental evidence regarding the structure of the ternary complex, which was obtained by NMR measurements combined with semi-empirical AM1[14] and PM3[15] calculations. It was recently shown for the cinchona and ephedra alkaloids that this approach can give very good results in the prediction of the stereochemical course of a reaction[9].

RESULTS

NMR Measurements

When the structure of the ternary complex dipeptide **1** - HCN - benzaldehyde has to be elucidated, three questions must be answered: What is the conformation of the dipeptide (specifically the orientation of the imidazole and phenyl ring), where is HCN (or H^+CN^-) situated, and what is the orientation of benzaldehyde with respect to **1**. In principle these questions can be answered with NMR measurements. However, in this particular case serious difficulties are encountered. It is known that the reaction of benzaldehyde with HCN, catalysed by **1**, gives high e.e.'s only when done in a non-polar solvent (e.g. benzene or toluene). This reaction is heterogeneous since the dipeptide is virtually insoluble in these solvents. It is soluble in polar solvents like DMSO or methanol, but in these cases the enantioselectivity drops to almost zero. Therefore, it is likely that the results obtained in a medium where NMR measurements are possible do not give an accurate picture of the ternary complex. To circumvent this problem we have adopted the following approach. The structure of the dipeptide **1** is characterized in DMSO according to procedures used previously for other cyclic dipeptides. Then, NMR-spectra are obtained in decreasingly polar solvents. The decreased solubility is accompanied by an increased line broadening which eventually prevents the measurements of coupling constants. In pure benzene no spectrum whatsoever could be obtained. It was hoped that a trend could be observed which would allow to make some extrapolation to the structure in benzene. The results of the NMR measurements of **1** in various deuterated solvents (chemical shifts and coupling constants) are listed in Table I.

The assignments were established using decoupling experiments and, in the case of DMSO and C_6D_6, 2D-NMR measurements (COSY and NOESY). A comparison with literature data for other cyclic dipeptides e.g. cyclo-(S)-Trp-(S)-His[10] and cyclo-(S)-(5-MeO)-Trp-(S)-(4-Me)-Tyr[11], shows that there is good agreement, α-protons resonating around 4 ppm, β-protons around 2-3 ppm and the amide-protons (in DMSO) around 8 ppm. Also, as is the case for the other two dipeptides, the diketopiperazine ring of **1** is essentially planar as can be elucidated from $^5J_{H(3)H(6)} = 1.1$ Hz.

The specific assignments for the ß-protons 7, 7', 8 and 8' requires more attention since these have to be specified in the Karplus relation which is used for the conformational analysis. Sheinblatt et al. concluded on the basis of NOE measurements that the high field β-proton of the Trp residue in cyclo-(S)-Trp-(S)-His is H(8'), and that the proton at low field is H(8)[10]. Also, it was argued that $^3J_{H(6)H(8')} > {}^3J_{H(6)H(8)}$. In view of the great similarities in chemical shifts and coupling constants (4.5 and 4.9 versus 4.4 and 4.9 Hz) we adopt the same assignment for the Phe residue of **1**. Note however, that a reversed assignment does not influence the conclusions drawn for the conformation around C(6)-C(8) (vide infra). For the His residue of **1**, we also followed the assignment made by Sheinblatt for the His residue in cyclo-(S)-Trp-(S)-His. The high field proton at δ 1.56 with the large coupling constant ($^3J_{H(3)H(7)} = 9.0$ Hz) is assigned to H(7). As can be seen in Table I, the chemical shifts

Table I. Chemical shifts (PPM) and coupling constants (Hz) for **1**.

Proton	DMSO	MeOH	Acetone	Pyridine	THF	C_6D_6 [c]
1	8.11	-	7.20	9.22	7.56	6.61
3	3.83	4.22	4.10	4.51	3.99	3.98
4	7.79	-	-[a]	9.02	7.10	6.11
6	4.13	4.42	4.30	4.61	4.21	3.94
7	1.56	1.85	1.70	2.29	2.64	2.05
7'	2.55	2.83	-[a]	3.38	2.96	2.85
8	2.85	3.01	3.20	3.21	3.08	2.94
8'	2.80	3.13	-[a]	3.15	3.08	2.70
2'	7.53	7.80	7.70	7.82	7.51	-[a]
1'	11.9	-	11.2	13.0	11.1	-[a]
5'	6.59	6.88	6.59	7.00	6.76	6.75
J_{H6-H8}	4.52	4.51	4.60	3.90	-	4.30
$J_{H6-H8'}$	4.90	5.17	-	-[b]	-	6.60
J_{H3-H7}	9.00	8.75	10.6	-[b]	9.80	8.20
$J_{H3-H7'}$	3.64	3.95	-	-[b]	-[b]	3.90

a. Obscured by other resonances
b. Not obtainable because of line broadening
c. Contained 100 eq. of 3 relative to 1

and coupling constants in other pure solvents are essentially similar.

Unfortunately, there is no clear trend in the coupling constants going towards decreasingly polar solvents, making it impossible to predict the conformation of **1** in non polar solvents. Therefore, a different approach was adopted. It is mentioned in ref. 4 that in the course of the reaction of benzaldehyde with HCN in benzene (or toluene), the originally heterogeneous reaction mixture turns to a homogeneous gel, and that in fact **1** is soluble in a mixture of mandelonitrile (**3**) and benzene. Indeed, we found that an NMR spectrum of the dipeptide can be obtained under these conditions. The minimal concentration of **3** necessary for obtaining a well-resolved spectrum was approximately 50 mg in 0.4 ml C_6D_6, which is a hundred-fold excess compared to the dipeptide. In our experience this is the best approximation of the dipeptide structure in benzene that can be obtained with solution NMR measurements. Addition of a tenfold excess of HCN (relative to **1**) did not change the coupling constants appreciably (neither in THF nor in Benzene/**3**). The results of the NMR measurements under these conditions are also listed in Table I.

With the coupling constants $^3J_{H(6)H(8)}$, $^3J_{H(6)H(8')}$, $^3J_{H(3)H(7)}$ and $^3J_{H(3)H(7')}$ available in DMSO and benzene/**3**, the conformations around C(6)-C(8) and C(3)-C(7) can be obtained with the Karplus equations.

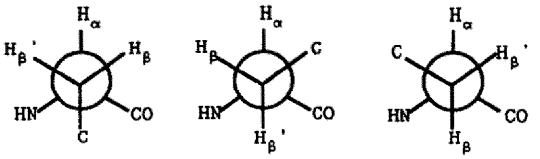

Figure 2. Rotamers for the C_α -C_β bond.

Usually a three rotamer model is used (see figure 2), and the fractional distribution among the rotamers is calculated
To calculate these rotamer distributions we have used the following equations that were previously established for cyclo-(S)-Trp-(S)-His[10].

$$^3J_{\alpha\beta} = 2.6\ g^+ + 2.4\ t + 12.1\ g^-$$
$$^3J_{\alpha\beta'} = 5.2\ g^+ + 12.4\ t + 2.7\ g^-$$

When the coupling constants from Table I are substituted the rotamer distributions listed in Table II are obtained.

As can be seen in Table II there is a drastic change in the rotamer distribution when the solvent is changed from DMSO to benzene/**3**. Especially the contribution of the g^+ conformation of C(6)-C(8) (phenyl ring oriented above the diketopiperazine ring) diminishes from 0.77 to 0.56. On raising the temperature, these values shift towards a more random distribution, as expected. It should be mentioned here that the outcome for the g^+ population is independent of the assignment for H(8) and H(8'). A reversal of the assignment only approximately reverses the values for t and g^-. The actual absolute values for the rotamer populations can of course be slightly different, depending on the coefficients chosen for the

Table II. Rotamer population distribution for **1** around C(6)-C(8) and C(3)-C(7) in DMSO and benzene/**3**

	C(6)-C(8) (Phe)				C(3)-C(7) (His)			
	DMSO		Benzene/**3**		DMSO		Benzene/**3**	
	294°K	353°K[a]	294°K	353°K[b]	294°K	353°K	294°K	353°K
g^+	0.77	-	0.56	0.47	0.31	0.26	0.39	0.37
t	0.03	-	0.26	0.30	0.02	0.05	0.02	0.09
g^-	0.20	-	0.18	0.23	0.67	0.69	0.59	0.54

(a) $^3J_{H(3)H(7)}$ = 9.2 Hz, $^3J_{H(3)H(7')}$ = 3.8 Hz. $^3J_{H(6)H(8)}$ and $^3J_{H(6)H(8')}$ could not be obtained due to chemical shift equivalency of H(8) and H(8').
(b) $^3J_{H(6)H(8)}$ = 4.7 Hz, $^3J_{H(6)H(8')}$ = 6.8 Hz, $^3J_{H(3)H(7)}$ = 7.7 Hz and $^3J_{H(3)H(7')}$ = 4.5 Hz

Karplus equations. However, the difference between two sets of rotamer populations for different solvents will not be affected much. Therefore, there seems to be a clear difference in conformation in polar and non polar solvents for **1**.

IR Measurements

The high enantioselectivity in the formation of **3** (see scheme 2) can only be rationalised on the assumption of at least two interactions between benzaldehyde and **1**. These could take the form of a hydrogen bond, stacking or steric hindrance. We have attempted to collect experimental evidence for the existence of such interactions. Because it was not to be expected that stacking and hydrogen bonding were observable in the presence of a large excess of **3** in benzene, we have not attempted to do NMR measurements, but have used IR measurements instead.

Stimson et al. have performed conformational studies of small oligopeptides[12]. They used several techniques to establish the presence of intramolecular hydrogen bonds between amides. In DMSO, hydrogen bonding gave rise to IR bands at 1650 cm^{-1}, near the band at 1685 cm^{-1} of non-hydrogen bonded amides. In CD_2Cl_2 these values were 1635 and 1672 cm^{-1} respectively. The NH band around 3300 cm^{-1} showed similar differences.

For benzaldehyde in cyclohexane we found the C=O stretch band at 1712 cm^{-1}. Upon addition of **1** (maximum two equivalents relative to benzaldehyde) the largest shift we observed was 4 cm^{-1} to 1716 cm^{-1}. Also, no shift was observed in the NH band of **1**. Thus no experimental evidence for hydrogen bonding could be obtained. Measurements in benzene and DMSO gave similar results.

Theoretical Calculations

Conformational energy analysis of 1

In order to gain more insight regarding the structure of **1** in non polar media, theoretical calculations were carried out with the MOPAC 6.0 package[13], using the AM1[14] and PM3[15] methods. They involved a full optimization of the molecular geometry in the space of cartesian coordinates until the norm of the gradient dropped below 0.1 kcal/radian or 0.1 kcal/Ångstrom. As starting values for the dihedral angles χ_1^1 = N(4)-C(3)-C(7)-C(4') and χ_2^1 = N(1)-C(6)-C(8)-C(1") we choose 60°, 180° and -60° corresponding to the staggered conformations g^+, t and g^-. For the dihedral angles χ_1^2 = C(3)-C(7)-C(4')-C(5') and χ_2^2 = C(6)-C(8)-C(1")-C(2") the values 90° and 270° were taken. Obviously, the conformation with χ_2^2 = 90° is energetically equivalent with the conformation in which χ_2^2 = 270°. Such an equivalency does not hold for the imidazole ring and following Sheinblatt[10] we will denote the conformations with χ_1^2 = 90° by A and the conformation with χ_1^2 = 270° by B. For each combination of χ_1^1 and χ_2^1, the imidazole group has been put in the A as well as in the B orientation. As such, a total of 18 conformations have been calculated. The results of these calculations are listed in Tables III and IV.

Table III. Total and relative heats of formation (kcal/mol) for the different conformers of cyclo-(S)-Phe-(S)-His calculated at the AM1 level[a].

Conformation (His, Phe)	χ_1^1	χ_1^2	χ_2^1	χ_2^2	H[b]	ΔH^b	H[c]	ΔH^c
(g^+A, g^+)	57.2	109.2	51.5	89.4	4.5	5.3	4.7	5.3
(g^+B, g^+)(*)	56.4	-104.5	46.9	85.5	0.7	1.5	1.2	1.8
(tA, g^+)(*)	-136.7	120.8	58.8	91.2	0.8	1.6	1.0	1.6
(tB, g^+)	-	-	-	-		--->	(tA, g+)	
(g^-A, g^+)	-62.0	88.7	57.9	90.1	2.2	3.0	2.4	3.0
(g^-B, g^+)	-56.2	-95.3	60.3	95.2	2.4	3.2	2.5	3.1
(g^+A, t)	48.7	110.3	-156.9	62.8	5.7	6.5	5.9	6.5
(g^+B, t)(*)	58.8	-104.1	-134.3	100.2	2.1	2.9	2.3	2.9
(tA, t)(*)	-167.0	74.9	-168.0	78.7	2.4	3.2	2.5	3.1
(tB, t)	-	-	-	-		--->	(tA, t)	
(g^-A, t)	-	-	-	-		--->	(g^-A, g^-)	
(g^-B, t)	-	-	-	-		--->	(g^-B, g^-)	
(g^+A, g^-)	56.9	113.1	-61.8	95.4	1.7	2.5	1.9	2.5
(g^+B, g^-)(*)	59.7	-103.9	-60.6	97.4	-0.2	0.6	0.1	0.7
(tA, g^-)(*)	-139.0	125.3	-63.5	90.7	-0.8	0.0	-0.6	0.0
(tB, g^-)	-	-	-	-		--->	(tA, g^-)	
(g^-A, g^-)	-62.7	87.9	-62.3	91.9	0.7	1.5	0.9	1.5
(g^-B, g^-)	-58.4	-102.6	-62.9	89.7	0.6	1.4	0.8	1.4

(a) See text for definition of dihedral angles. The conformations indicated by a (*) possess an intramolecular hydrogen bond between the NH proton of the imidazole ring and one of the C=O groups of the diketo-piperazine ring.

(b) Without molecular mechanics correction for the HNCO barrier.

(c) With molecular mechanics correction for the HNCO barrier.

Because the AM1 and PM3 methods underestimate the HNCO barrier, the MOPAC 6.0 package allows a molecular mechanics correction to be applied which increases the barrier (e.g. to 14 kcal/mole in N-methyl acetamide). A test of the relevance of this correction at the AM1 level revealed no change in the relative energies of the conformers, as can be seen in Table III. Therefore, the PM3 calculations were only performed without the molecular mechanics correction.

A further inspection of Table III shows that both theoretical methods agree in predicting that the phenyl group prefers to adopt the g^- conformation. As far as the preference for g^+ or t is concerned, the AM1 method appears to predict the g^+ conformation to have the lowest energy but at the PM3 level the energy differences are very small, except when the imidazole ring adopts the g^- conformation. In this latter case, the PM3 results agree with the AM1 data. Apparently, the calculated relative energies for the rotamers around the C(6)-C(8) bond differ from the

Table IV. Total and relative heats of formation (kcal/mol) for the different conformers of cyclo-(S)-Phenylalanyl-(S)-Histidyl calculated at the PM3 level[a].

Conformation (His, Phe)	χ_1^1	χ_1^2	χ_2^1	χ_2^2	H[b]	ΔH[b]
(g^+A, g^+)	60.3	90.1	46.9	85.1	-21.5	7.0
(g^+B, g^+)(*)	58.1	-92.7	45.1	83.2	-24.6	3.9
(tA, g^+)(*)	-138.5	107.9	64.5	92.7	-25.6	2.9
(tB, g^+)	-175.4	-143.2	60.8	89.4	-23.8	4.7
(g^-A, g^+)	-67.0	89.3	59.1	86.8	-26.1	2.4
(g^-B, g^+)	-57.6	-56.9	64.6	89.2	-25.5	3.0
(g^+A, t)	55.3	37.0	-161.2	67.1	-21.8	6.7
(g^+B, t)(*)	55.9	-92.9	-144.7	79.0	-24.3	4.2
(tA, t)(*)	-138.9	111.8	-136.8	85.2	-25.4	3.1
(tB, t)	-	-	-	-	---> (g^-B, t)	
(g^-A, t)	-77.0	82.0	-161.3	70.9	-23.8	4.7
(g^-B, t)	-67.7	-60.2	-162.7	70.1	-23.8	4.7
(g^+A, g^-)	59.8	81.1	-63.4	106.4	-25.6	2.9
(g^+B, g^-)(*)	57.1	-92.7	-67.8	104.9	-25.8	2.7
(tA, g^-)(*)	-143.1	113.7	-67.0	107.5	-28.3	0.3
(tB, g^-)	177.1	-131.7	-55.2	107.1	-25.8	2.7
(g^-A, g^-)	-63.9	85.8	-65.3	107.9	-28.5	0.0
(g^-B, g^-)	-62.4	-61.4	-63.2	106.5	-28.0	0.5

(a) See text for definiton of dihedral angles. The conformations indicated by a (*) possess an intramolecular hydrogen bond between the NH proton of the imidazole ring and one of the C = O groups of the diketopiperazine ring.
(b) Without molecular mechanics correction for the HNCO barrier.

experimental ones (Table II). This will be addressed in the Discussion.

With respect to the imidazole ring, Table III indicates that the relative energies at the AM1 level are completely determined by the possibility of forming an intramolecular hydrogen bond between H(1') and one of the carbonyl groups of the diketopiperazine ring. Indeed, for a given orientation of the phenyl group, the tA and g^+B conformation possess a lower energy than any of the other structures. On the other hand, Table IV shows that this is no longer the case when the PM3 parametrisation is used. As a matter of fact, when the phenyl ring adopts the g^+ or g^- conformation, the g^- orientation of the imidazole ring is preferred. This PM3 result is in agreement with the experimental NMR data.

The interaction of HCN with 1

Another question that has been addressed from a theoretical point of view, is the preferred orientation of the HCN molecule with respect to **1**. It is commonly accepted that hydrogen cyanide interacts with the

Table V: Heats of formation and interaction energies (kcal/mol) for the HCN/4-methylimidazole complexes of Figure 3.

Structure	H	ΔH
a	70.8	-2.5
b	85.0	11.7
c	62.1	-11.2
d	68.0	-5.3
e	63.3	-10.0
f	61.1	-12.2
g	62.8	-10.5
h	67.7	-5.6
i	64.1	-9.2
j	60.0	-13.3
k	67.8	-5.5
l	66.1	-7.2
m	62.6	-10.7
n	63.9	-9.4
o	65.4	-7.9
p	142.0	68.7

imidazolyl moiety of the histidine residue either as a molecule or dissociated as H^+CN^-.[3,5] Therefore, we considered it a valid simplification to represent the cyclic dipeptide **1** by a smaller molecule, namely 4-methylimidazole. Calculations were performed for several addition products of HCN and 4-methyl imidazole as well as for different complexes of these molecules and their ionic forms. All these calculations were performed with the MOPAC 6.0 package[13] at the AM1 level[14] and involved a full optimization of the molecular geometries until the norm of the gradient was less than 0.1 kcal/radian or 0.1 kcal/Å. Figure 3 shows the resulting energy minima.

In structures **a** and **b** there is a hydrogen bond between HCN and one of the nitrogen atoms of the imidazole, structure **p** is a complex between CN^- and the protonated form of 4-methyl imidazole and all other structures are the result of an addition reaction between HCN and 4-methyl imidazole. Table V lists the corresponding heats of formation and the calculated interaction energies. The latter are defined by

$$\Delta H = H(\text{calculated minimum}) - H(HCN) - H(\text{4-methylimidazole})$$

As such, a positive ΔH value indicates that the complex has a lower stability than the separated moieties, while a negative ΔH value stands for a higher stability.

DISCUSSION

From the NMR data in Table II it can be concluded that six conformations of **1** are possible (disregarding for a moment the variation in χ_1[2]). Since the simultaneous presence of the phenyl and imidazole rings above the diketopiperazine ring is unlikely because of steric hindrance, five conformations seem to be prevailing (see Figure 4), with **1A** as the dominant one.

Going from polar to non polar solvents there is a shift towards an increasing population of conformations **1D** and **1E**, i.e. the phenyl ring turns away from the diketopiperazine ring and this position is occupied increasingly by the imidazole ring. Note that **1D** and **1E** show some resemblance with the transition states, proposed by Inoue[5] and Jackson[3] respectively.

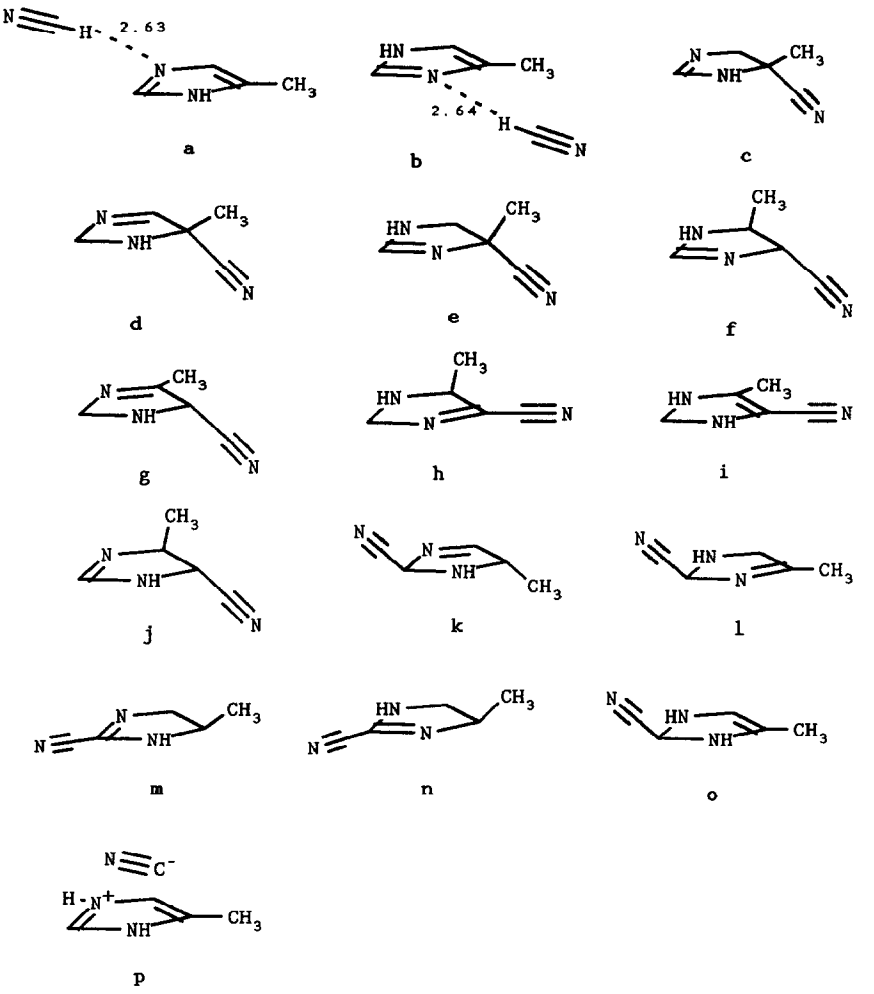

Figure 3. Possible interactions of HCN with 4-methyl imidazole determined by AM1 calculations

A comparison of the NMR structures with the conformations produced by the AM1 and PM3 calculations shows a remarkable difference. For the orientation around the C(6)-C(8) bond, both semi-empirical methods predict the g^- form as the most stable rotamer, whereas the NMR populations indicate the g^+ form to have the lowest energy. A CNDO study on cyclo-Pro-Phe also failed to reproduce the experimental g^+ preference of the phenyl group[16]. On the other hand, MO-PCILO and molecular mechanics calculations on a number of cyclic dipeptides were successful in predicting the side chain conformational preference[17,18].

For cyclo-Phe-His, the discrepancy between the theoretical preference and the experimental results may be due to the fact that the former

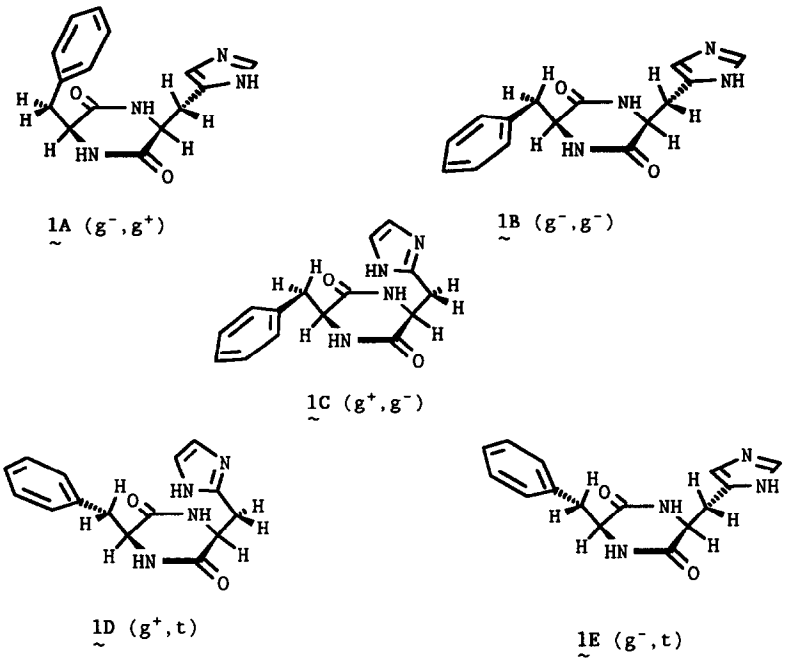

Figure 4. Preferred conformations of **1** in solution

refers to an isolated molecule in the gas phase, whereas the latter were obtained in solution. Moreover, although the C_6D_6/**3** mixture has a lower polarity than DMSO, it is definitely not a non polar medium. It is interesting in this respect to recall the preferred conformation of the phenyl group in cyclo-(S)-Pro-(S)-Phe[19,20]. In polar solvents, this conformation appears to be g^+ but in chloroform the g^- rotamer is found to predominate, which is in agreement with our theoretical calculations. It was suggested that the preference for g^- might be due to an induced polarisation of the electronegative aromatic ring by the proximate electropositive amide hydrogen[20]. Obviously, such a polarisation should affect the atomic charges. However, the results of a Mulliken population analysis reveal that the charge distribution of the phenyl group and the atomic charge of the amide hydrogen are essentially the same in the different rotamers. Apparently, the induced polarisation of the phenyl ring is negligible in this particular case. Alternatively, the preference for the g^- conformation might be explained by considering the interactions between the amide hydrogen H(1) and the protons on C(8). Inspection of molecular models reveals that the distance between H(1) and H(8)/H(8') is largest when the benzyl substituent is in the g^- conformation.

Irrespective of the nature of the differences in conformational preferences of the phenyl group predicted by NMR and calculations, it can be concluded that **1A-C** (figure 4) are among the four energetically most favourable conformations, at least as calculated at the PM3 level. Since,

going from polar to non polar solvents, there is a shift for the Phe moiety away from g^+, and for His towards g^+, we decided to use **1D** (g^+,t) as the most likely candidate structure for **1** as a catalyst.

What remains to be established in order to propose a 'pre-transition state' model is the position of HCN and benzaldehyde. Since it proved difficult to obtain experimental evidence regarding this, we had to rely on semi-empirical calculations. Because a base is necessary for HCN in order to react with benzaldehyde, the location of HCN near the imidazole ring is an obvious choice[3,5]. Of the structures in Figure 3 the addition products are considered unlikely because the addition of HCN to the imidazole would result in the disappearance of the imidazole C-H resonance and an appearance of new NMR-signals at higher field from the formed imidazoline protons. In contrast, we observed a downfield shift of approximately 0.2 ppm for H(5'). This leaves structure **a**, the association complex of HCN with imidazole, as the best alternative to make predictions about the position of HCN in the 'pre-transition state'.

Finally, to complete the 'pre-transition state model', the location of benzaldehyde must be estimated. Preferably, benzaldehyde must have two interactions with **1** to ensure high enantioselectivity. Since the possible interactions of benzaldehyde are very limited, we assume that hydrogen bond formation with the aldehyde carbonyl must be involved, as is done in the literature[3,5]. In view of the great influence that the phenylalanine moiety has on the enantioselectivity, we believe that the other interaction must be stacking, rather than a steric interaction. This is also in accordance with a higher enantioselectivity for aromatic aldehydes compared to aliphatic aldehydes with **1** as catalyst. Recently, a theoretical study about the nature of aromatic-aromatic stacking interactions has been published[21]. Monte Carlo simulations of the benzene dimers in water, chloroform and benzene showed that the energetically preferred interaction is the so called T structure stacking (aromatic rings oriented orthogonal) rather than face-to-face stacking.

All the previously mentioned structural requirements were combined in a molecular modelling study to see whether it is possible to position **1**, HCN and benzaldehyde at reasonable distances from each other, and also in the correct stereochemical configuration. The result is shown in Figure 5. Thus, for benzaldehyde and the phenyl ring of **1**, the separation between the ring centres is ca. 5.5 Å, the distance between the aldehyde carbonyl and the amide proton is reasonable for a hydrogen bond (2.15 Å), HCN is within 2.6 Å of the imidazole nitrogen, and also within 2.7 Å of the aldehyde group where the actual reaction must take place. Note that this model will result in formation of (R)-benzaldehyde cyanohydrin as required.

Even though we were not able to produce other models that fulfil all the requirements starting with conformations **1A-E**, we are aware that this doesn't necessarily make our solution correct. One point that has not been addressed in this paper is the heterogeneous nature of the catalyst. Researchers at Shell found that the degree of amorphousness of the catalyst has a profound influence both on enantioselectivity and reaction rate[6]. This suggests that the reaction takes place at the surface of

larger particles. It is known from X-ray studies[22,23] that many diketopiperazines can form linear polymeric structures (ribbons), through hydrogen bond formation on each side between the amide groups of the diketopiperazine ring with its two neighbours. One would expect the conformation of the side chains in this polymeric structure to be dramatically different from those in the monomer.

Several other questions remain to be verified experimentally e.g.

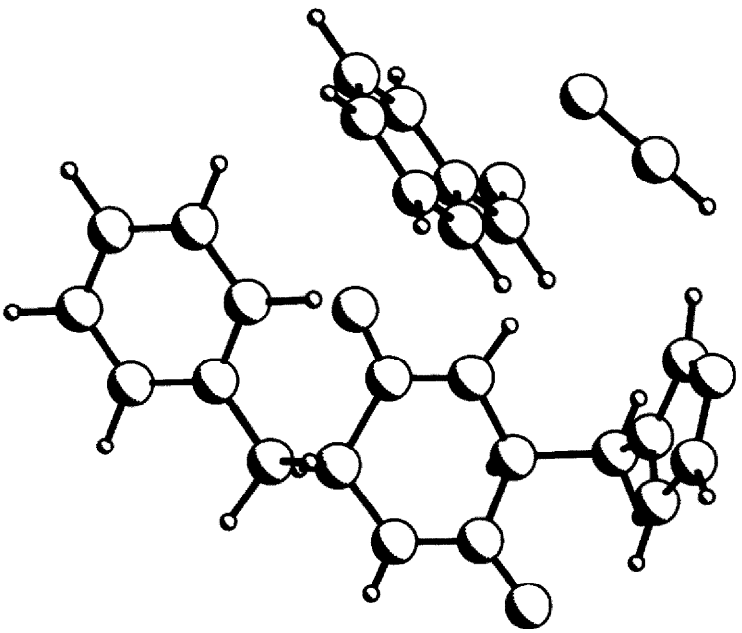

Figure 5. Proposed orientation of **1**, HCN and benzaldehyde prior to the formation of **3**

whether the position of benzaldehyde and of HCN is as assumed in Figure 5. A possible solution to this problem of measuring the presumed proximity of molecules in a gel phase might be provided by the strongly improved solid state NMR techniques. Nowadays, it is possible to measure distances in the range of 5Å with rotational resonance[24] and ^{1}H spin diffusion techniques[25], even though this might require the selective isotopic labelling of the molecules involved.

In conclusion, we have attempted to collect some experimental evidence to clarify the high enantioselectivity in the cyanohydrination of aromatic aldehydes catalysed by **1**. Combined with semi-empirical calculations, this

has led to a model which positions the molecules involved within reasonable distance from each other. Even though not all questions are answered satisfactorily, we hope that these results will contribute to a better understanding of the function of **1** in the hydrocyanation, and may stimulate further research in this area.

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