



Asymmetric Hydrocyanation of Aldehydes with Cyclo-dipeptides: A New Mechanistic Approach

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Abstract: A new mechanistic suggestion for the asymmetric hydrocyanation reaction of aldehydes with cyclo[-(S)-phenylalanyl-(S)-histidyl] (CPH) as catalyst is presented. Kinetic measurements indicate a second order reaction in the cyclopeptide catalyst. A heterogeneous hydrogen bonded polymer of CPH is considered to be the reactive state of the catalyst where two adjacent imidazole bases function as the reactive sites. This structural proposition is also supported by MNDO calculations performed on a dimer of CPH. Copyright © 1996 Elsevier Science Ltd

Introduction: Hydrocyanation of aldehydes and ketones using HCN as the cyanide anion source is a fundamental reaction in organic chemistry.¹ Cyanohydrins constitute an important class of intermediates in organic synthesis,² some of commercial value. Optically active cyanohydrins and methods for their preparation have lately become a focus of attention due to a recent emerging interest in enantiomerically pure drugs³ and agrochemicals.⁴

A study of the state of the art regarding asymmetric hydrocyanation reaction of aldehydes reveals two leading catalysts: oxynitrilase in enzymatic catalysis⁵, and a group of chiral diketopiperazines (cyclo-dipeptides) derived from optically active amino acids, in chemical catalysis.^{6,7} Both catalysts lead to optically active cyanohydrins with impressive stereoselectivities of ca. 97% ee and high chemical conversions. Of the diketopiperazines, R,R or S,S cyclo[phenylalanylhistidyl] (CPH) is by far the most efficient and studied catalyst, reported both in the open^{6,7,9} and patent literature⁸. The most studied substrates are benzaldehyde and *m*-phenoxybenzaldehyde leading to optically active mandelonitrile and *m*-phenoxybenzaldehyde cyanohydrin respectively.

As pointed out by Inoue,⁹ the discoverer of the cyclo-dipeptide catalysts, the structural simplicity of the CPH molecule vis-a-vis the structural complexity of the oxynitrilase enzymes is striking, considering that the same degree of stereoselectivity was attained by both catalysts in hydrocyanation reactions of aldehydes. The desired configuration of the cyanohydrin may be controlled by selecting the appropriate configuration of the amino acids of the cyclo-dipeptide, or by choosing the appropriate enzyme.⁵ The mechanistic knowledge of catalysis with CPH may bear on the mode of action of the oxynitrilase enzymes, and may lead to the development of structurally similar catalysts for asymmetric addition reactions to carbonyl groups.

Results and discussion: Several research groups have tackled the mechanism of the cyanohydrination reaction with diketopiperazines.^{7,9,10,11,12,13,13a} However, up to now there is no definitive and experimentally supported mechanistic picture. Two experimentally important facts regarding the above reaction have been observed by us and others:

a. The enantioselectivity of the reaction is solvent dependent in the sense that those solvents capable of sustaining the catalyst in a gel form throughout the reaction period give rise to the highest ee. Thus, *enantio-efficient hydrocyanation reactions are heterogeneous in the CPH catalyst.*

b. The mode of preparation of the catalyst is crucial for the conversion and the enantioselectivity of the reaction. Amorphous CPH catalyst, prepared by a variety of methods, has been claimed to be most efficient. Thus low crystallinity of the catalyst is associated with high enantioselectivity.^{6,11} We have now found that it is not only the degrees of crystallinity which effects the hydrocyanation reaction, but most importantly the structure of the solid. Thus, two samples from the same batch of CPH, obtained by methanol precipitation, were dried, one in vacuum at 50 °C, and the other at the critical point of CO₂ (see experimental). It turned out that both had practically identical degree of crystallinity (53%), yet their microscope pictures, presented in Figures 1 (thermal drying) and 2 (CO₂ drying), are strikingly different. Most importantly, the CPH dried thermally was chemically *inert* towards hydrocyanation, while under the same reaction conditions, the one dried with CO₂ generated, at high rate, a cyanohydrin in 96% yield and 97% ee. The above results point toward the nature of the surface area of the solid CPH as the dominant factor in controlling the hydrocyanation reaction of aldehydes. Volume changes during thermal drying bring about the collapse of the gel walls which is prevented by CO₂ critical point drying, the results of which are clearly evident in Figures 1 and 2.

The heterogeneity of the reaction system impedes experimental mechanism studies. Furthermore, to date no X-ray crystal data for the CPH molecule has been reported, as quality crystals could not be obtained.

Any mechanism study must address the heterogeneity of the catalytic hydrocyanation reaction system. Thus, nmr conformational studies^{12,13a,14} of CPH and related diketopiperazines carried out in homogeneous solutions are interesting but not necessarily relevant to the catalyst structure prevailing in the *heterogeneous* reaction mixture. Theoretical conformational calculations and molecular modelling,^{12,13a,14} although of basic importance, were carried out on an isolated CPH molecule, disregarding the intermolecular effects originating from neighbouring CPH monomers in a polymer (*vide infra*) of the cyclo-dipeptide gel. Therefore, previous structural models describing the spatial ternary interactions cyclodipeptide - aldehyde - HCN toward the formation of a chiral cyanohydrin, and are based on nmr studies and theoretical calculations of the cyclodipeptide *monomer*, are probably inaccurate. This has been recently commented upon by de Vries *et. al.*¹² who carried

out NMR studies of CPH in DMSO solutions as well as molecular computations. It is only very recently that North et. al.^{13b} have measured the solid state NMR spectra of CPH (vide infra).



Figure 1: Cyclo[-(R)-phenylalanyl-(R)-histidyl] dried in vacuum at 50°C

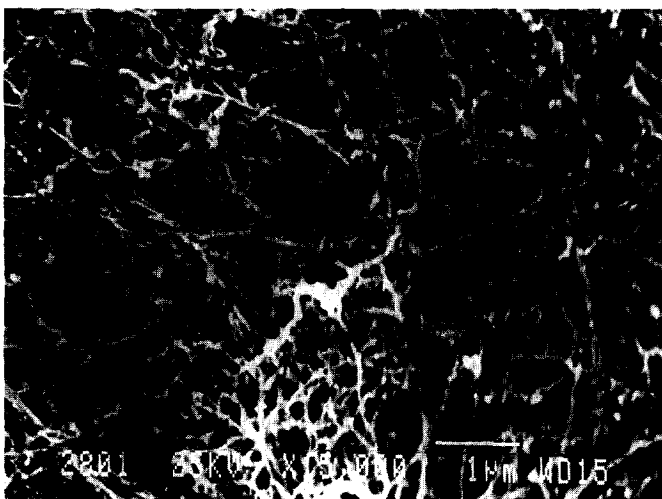
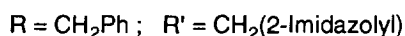
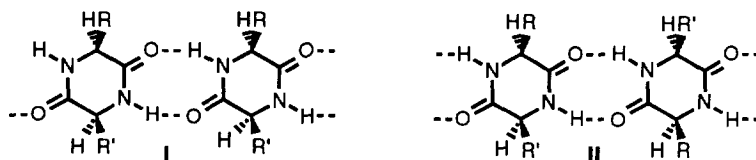


Figure 2: Cyclo[-(R)-phenylalanyl-(R)-histidyl] dried at the critical point of CO₂

The single most unique physical property of diketopiperazines is their propensity to form intermolecular hydrogen bonds.¹⁵ In fact it is this property which

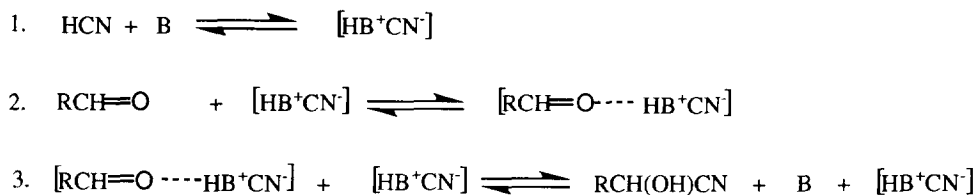
must be responsible for the gel formation, and was not taken into account in the previous mechanism studies. Ultimately, it is the solid state intermolecular hydrogen bonding forces between CPH monomers which will govern the structure of the polymer and consequently the chemical and stereochemical course of the hydrocyanation reaction.



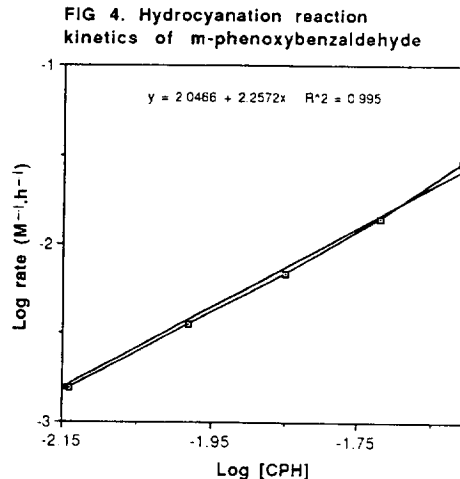
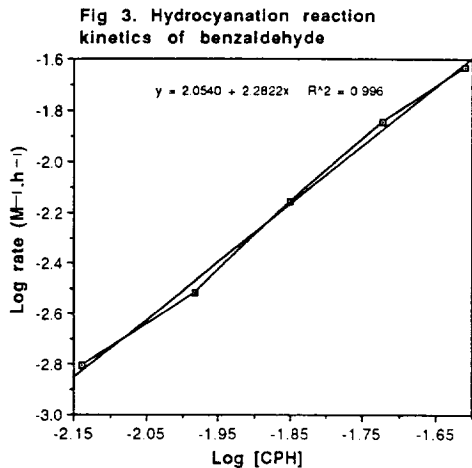
The principal H-bonding of CPH leading to a polymer structure is depicted in structures **I** with head-to-head and **II** with head-to-tail arrangements. There is ample evidence for the above bonding mode in diketopiperazines.¹⁵ The heat of dimerization of δ -valerolactam is -10.3 Kcal/mol, and the free energy, being offset by the negative entropy of dimerization, is -3.6 Kcal/mol.¹⁶ Structures **I** and **II** result from the configuration of the CPH monomer. The R and R' groups in the monomer are necessarily cis (with respect to the ring) because the two amino acids (phenylalanine and histidine) have the same configuration, either R or S.

That molecular aggregation of the catalyst is essential for high stereoselective hydrocyanation reaction is supported by the fact that *no* enantioselectivity was found in a methanol solution, where the CPH used is soluble, and intermolecular H bonds between CPH molecules are probably disrupted by the solvent. Granting that a polymer is the chemically active state of the cyclodipeptide, the question now is how does it function in the hydrocyanation reaction and how does it induce the high enantioselectivity during product formation. The polymeric aggregation suggests a cooperative action of two polymer bound CPH molecules. Indeed it has been known for some time that hydrocyanation reactions catalyzed by organic bases in organic solvents (homogeneous) are second order in the base catalyst. The following bimolecular mechanism had been proposed by Prelog *et. al.*¹⁷ (Scheme I):

SCHEME I



Central to the above scheme is the activation of the carbonyl carbon atom by a [HBCN] ion pair (Eq 2) followed by delivery of a cyanide anion by a different ion pair (Eq 3), thus accounting for a second order reaction in B. Applying this idea to the CPH reaction system, we have carried out kinetic studies of the hydrocyanation reaction in toluene using (S,S)-CPH, which existed as a gel throughout the kinetic study, in order to determine the order of the reaction in the catalyst. Two substrates, benzaldehyde and m-phenoxybenzaldehyde, were studied. The CPH catalyst used was synthesized by a known method⁹ and activated by drying it at the critical point of CO₂ (see experimental section). Initial rates method was used; enantioselectivity >95% was attained under our experimental conditions with both substrates. The results are presented in Figures 3 and 4 with a linear regression curve fitting. The slopes of the two graphs indicate, within experimental error, a *second order* reaction in the charged CPH monomer with both substrates.



This is an important new finding in relation to the mechanism of the CPH induced hydrocyanation reaction, since it now allows the application of the Prelog mechanism¹⁷ (Scheme I) to the heterogeneous gel-CPH catalysis.

Armed with the two facts - polymer heterogeneous catalyst and a second order reaction in the catalyst - we assert that two *different* imidazole bases bound to a diketopiperazine polymer grid must participate in the hydrocyanation reaction of aldehydes. It is proposed that within the polymer array, one imidazole - HCN ion pair coordinates an aldehyde molecule via a charge-dipole interaction, while an adjacent imidazole - HCN ion pair delivers the cyanide anion. In fact, the polymer may now be considered mostly as a poly-ion pair type polymer. It stands to reason that the two imidazole bases involved are situated on adjacent H-bonded diketopiperazine rings. However, the situation may be far more complex as the two imidazole bases may also be associated with two different closely situated polymer units.

There is no doubt that the reaction system is heterogeneous (physical observation), and when homogeneous (in methanol) it fails enantioselectively. Nevertheless, a question may still be raised as to the nature of the catalytic active species - a polymer, oligomer or dimer, the latter two being perhaps partially soluble in the reaction solution. In Danda's recent work¹⁸ as well as in our experiments (*vide infra*), an increase of the enantioselectivity with time during hydrocyanation reaction with optically active CPH was observed. This may mean that "structural defects" in the polymeric gel are being self repaired by an autoinduction process. An insight into this repairing process has been provided by Danda¹⁸ whereby the asymmetric induction was eliminated (i.e. no change in % ee with time) when a small quantity of the optically active cyanohydrin product was present at the start of the hydrocyanation reaction, while the presence of the opposite cyanohydrin enantiomer did not affect the reaction at all.

In fact a similar phenomena were previously reported in a US. Patent¹⁹, whereby the addition of a small quantity of various alcohols, including the cyanohydrin product, was found to reduce the induction period of the reaction and improve the enantiomeric selectivity.

Suspecting that above effects may perhaps be due to the fact that, being an alcohol, the cyanohydrin product may affect in some way the hydrogen bonding of the polymeric gel, we have further pursued this point. The results of experiments A-D, carried out under reaction conditions very similar to those of Danda's,¹⁸ are listed in Table I. Experiment A (standard conditions) clearly demonstrates ee autoinduction similar to that observed by Danda. The small increase in the initial ee level is attributed to the different modes of catalysts preparation, but the fact that autoinduction is being observed with two different preparations of the catalyst is significant. In experiments B and C, 4.4 and 1.5 mmol respectively of hydroxyacetonitrile, an achiral cyanohydrin, were added at the outset of the reaction. No autoinduction is evident. In experiment D, 1.5 mmol of methanol was added and again no auto induction is detected. Thus, it may be concluded that the "repairing agent" must not necessarily be chiral, but may also be an alcohol and perhaps must be a protic compound, such as for example, the cyanohydrin product. However it is not clear why the addition of a cyanohydrin having a configuration opposite to that of the incipient product does not affect the autoinduction. Nevertheless, our experimental evidences as well as those mentioned in the US. patent support the above hypothesis.

The above results bring forth two possibilities: a. Protic compounds bring about the partial breaking down of the cyclo-dipeptide polymer structure resulting in oligomers (or dimers), which are partially soluble in the reaction medium, and are in fact the true catalytic species. This hypothesis may apparently be supported by the finding that the hydrocyanation reaction mixture exhibits thixotropy¹¹, which may be associated with polymer degradation.

b. The protic additive ruptures *discrete* hydrogen bonds in the cyclo-dipeptide polymer, thereby modifying its secondary structure but preserving the gross polymeric structure. Such structural alteration may also bring about thixotropy, as claimed for instance in the case of gelatin²⁰. Granting such a behavior, it must be the heterogeneous cyclo-dipeptide polymer which functions as the true hydrocyanation catalyst.

Table I. The Effect of Additives on the Enantioselectivity of the Hydrocyanation Reaction of *m*-Phenoxybenzaldehyde with (S,S)-CPH^a.

method	time (h)	conv (%)	ee (%) ^b
A	0.5	33	74
	1	72	78
	2	87	89
	4	93	92
B	0.5	39	84
	4.4 mmol	1	57
	hydroxyaceto	2	67
	-	4	77
C	0.5	35	89
	1.5 mmol	1	58
	hydroxyaceto	2	71
	-	4	82
D	0.5	36	92
	1.5 mmol	1	61
	methanol	2	70
	-	4	81

^a For reaction conditions see Experimental section.

^b The product is (R)-*m*-phenoxy benzaldehydecyanohydrin.

It is noted that thixotropy affects the enantioselectivity but not the rate of the hydrocyanation reaction.¹¹ Should degradation products of the polymer be the true catalytic species, then rate enhancement would also be anticipated. Therefore, the picture that emerges is that the cyclo-dipeptide gel polymer is the indeed the catalytic species; small quantities of alcohol or other protic compounds effect the secondary structure of the gel, most probably by selective disruption of hydrogen bonds which in turn results in improved enantioselectivity of the hydrocyanation reaction. Excessive quantities of the protic solvent diminish the enantioselectivity (compare methods B and C, Table I, and the lack of ee in pure methanol), probably

by extensive degradation of the polymeric gel via disruption of the hydrogen bonds responsible for maintaining the backbone structure of the polymer.

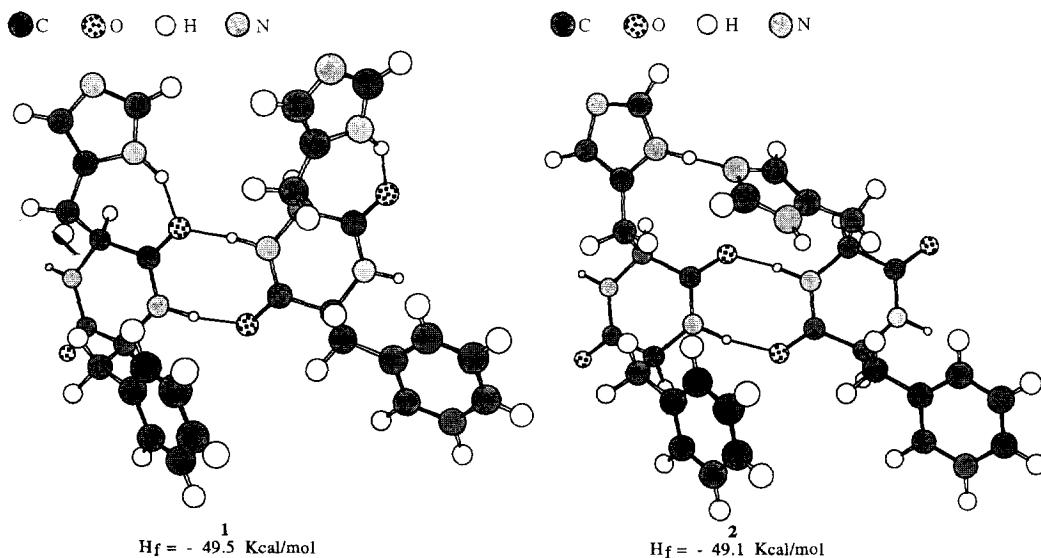
The idea of CPH polymerization was briefly studied by computational optimization using MNDO/H-90, a calculation method developed by Goldblum²¹ for the treatment of hydrogen bonding. It must be stressed that the structural computations were carried out on the neutral dipeptide. We have no information regarding the structure and conformation of the protonated dipeptide which most probably differ from the ones described here. Furthermore, in order to simplify the calculations, only a dimer unit was used as a model for the extended polycyclo-dipeptide.

The conformational structures of two CPH *monomers*, the 1H and 3H imidazole ring tautomers, were first computed. The 1H tautomers (H-bond between diketopiperazine NH and imidazole N3) was found to be more stable than 3H tautomer (H-bond between imidazol N3H and diketopiperazine CO) by 1.3 Kcal/mole, in contrast to the findings of North.¹³ The latter conformation was found to be similar to that calculated by de Vries¹² using PM3 method.

Next, several hydrogen bonded *dimers* were examined. Central to our computations are the prevailing diketopiperazine - diketopiperazine hydrogen bonds as in **I** and **II**, with calculated distances (N)H---O=C in the range of 1.5 - 1.6 Å. Then the relative stability of **I** vs. **II** and 1H vs. 3H imidazol ring tautomers (in dimers) were examined. In each such minimum energy search, selected conformations of the imidazol and benzyl groups were subjected to optimization by the MNDO-H/90 program.

The dimer structures **1** and **2**, differing by 0.4 Kcal/mol, were found to have the lowest calculated energy from six different calculated structures. The following features are noteworthy:

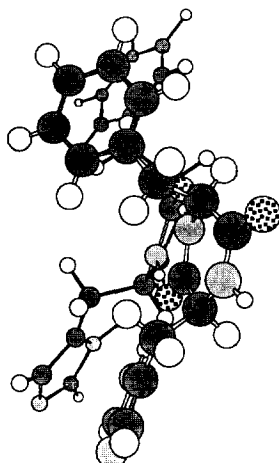
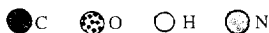
- a. Both dimers, **1** and **2**, are the 3H imidazole ring tautomers, in contrast to the situation in the monomers (1H more stable than 3H).
- b. Both dimers possess a head-to-head arrangement of the diketopiperazine rings as in **I**, which were found to be more stable by 2-3 Kcal/mol then the head-to-tail arrangement (**II**).
- c. In **1**, the 3H atoms of the imidazole rings are hydrogen bonded to their respective diketopiperazine carbonyls (1.6Å) bringing the number of hydrogen bonds per dimer to four. Only minor conformational changes can be detected in the individual monomers constituting the CPH dimer **1**, relative to the corresponding free monomer.
- d. In **2**, the two imidazol rings are engaged in hydrogen bonding (NH---N, 1.5Å). This structure was found to lie only 0.4 Kcal/mol higher than **1**, indicating a comparable stability.
- e. The dimerization of two monomers was found to be associated with stabilization energy of ca. 11 Kcal/mol.



f. Both the liquid and solid^{13b} states ¹H-NMR spectra of CPH exhibit a high field signal which was assigned to one β -proton of the histidine residue. The shielding of this proton was claimed to originate from the phenyl ring that is folded over the diketopiperazine ring. Neither structure **1** nor **2** have a folded phenyl ring but both show that one histidine β -proton resides over the diketopiperazine ring, more specifically in the back space of the carbonyl group. We suggest that this proton may be shielded due to the anisotropy of the carbonyl group. A local Cartesian coordinate system was constructed where the midpoint of the C=O bond was placed along the X axis at (0,0,0). From geometrical calculations, and the knowledge of all bond distances and angles from the MNDO computations, the coordinate points of the above β -proton was calculated as: -1.344(x), 0.723(y), 2.72(z). From the long range shielding effects diagrams of a carbonyl²², a shielding of 0.1 ppm was measured for the said proton. Regardless of the accuracy of these calculations, it is obvious that the above proton is located in the shielding region of the carbonyl group in structure **1** as well as the structure proposed by North et. al.,^{13b} and its effect on the chemical shift of the histidine β -proton should also be considered.

Our calculations were intended to support the kinetic results and the experimental observation that during the reaction the catalyst is in a state of gel, and provide a logical structural model. Secondary structural features associated with hydrogen bonding involving the imidazol N-H were revealed; possibly they may have stereochemical implications in the hydrocyanation reaction. In the transition state for hydrocyanation, the aldehyde must be bound to two imidazol fragments of the polymer. Structure **3** is a side view of the dimer **1** which in a polymer will generate a channel, flanked by a hydrophobic wall (phenyls) and a polar basic wall

(imidazoles). Upon protonation of the imidazole ring by HCN the latter becomes essentially an ion pair wall which will interact with the oxygen atom of the incoming aldehyde.



3 (side view of 1)

In the absence of additional evidence it is unreasonable to speculate further on the structural features associated with the enantioselectivity of the hydrocyanation reaction within the proposed polymeric array. In particular, it is not clear where the cyanide ions are located. Nevertheless, the structural models previously proposed by others must be reconsidered since they do not conform to our kinetic results and to the Prelog mechanism of hydrocyanation. Extensive molecular computation with possible docking of the aldehyde substrate onto a more extensive array of H-bonded CPH monomers may shed light on this interesting stereochemical problem.

Evidence for the crucial importance of intermolecular hydrogen bonding of CPH molecules in the generation of high ee in the hydrocyanation reaction can be found in the work of Jackson *et al.*²³ Both polystyrene and polysiloxane attached cyclodipeptide gave low ee (10%), while 78% ee was attained with the free peptide. Obviously, the larger spacing of the attached cyclodipeptides monomers in these systems obstructs intermolecular hydrogen bonding.

Experimental

General. Optical rotation was measured on Perkin-Elmer Polarimeter Model 241. Crystallinity measurements of CPH samples were carried out with an electronic microscope, Rigaku Geiger Flex, ModelD-Max-IIC. automatic diffractometer, $\text{CuK}\alpha$; 45KV; 30 mA. 2θ : 5-60°; 2°/min; $\text{K}\alpha_2$ stripping. Microscope pictures of CPH samples were taken with a Jeol Scanning Microscope, 840A, Japan.

cyclo[-(S)-phenylalanyl-(S)-histidyl]

The above compound was prepared according to Tanaka et. al.⁹ It was dried using two methods:

1) A methanol solution of the peptide, obtained from the last synthesis step,⁶ was slowly evaporated in vacuum at 30 °C to a point of a clear gel, which is then transferred in a basket to a critical point drier chamber (Polaron E 3000). The chamber is cooled to 0 °C and filled with liquid CO₂ (P = 50 - 60 ATM). The liquid CO₂ is drained down to the level of the solid to be dried, and the chamber is refilled with CO₂. This operation is repeated 4 times during ca. 2h at 0 - 10 °C. Finally, the chamber temperature is raised to 40 °C during 20 min., the pressure is controlled at 78 - 82 atm by a partial slow release of the gas. After the above temperature has been reached, the gas is vented off during ca. 20 minutes while keeping the temperature at 40 °C. A porous, voluminous white solid is obtained, $[\alpha]_D = -67.2$ (c 0.05 AcOH).

2) The gel obtained above after evaporation of the methanol, as described in 1, was oven dried at 50 °C to a constant weight. The resulting material had an optical rotation identical with that obtained by method 1.

Kinetic measurements

Benzaldehyde²⁴ - Each kinetic run was performed with a toluene solution (35 mL) of benzaldehyde (1.53 M), HCN (1.74M) and (S,S)-CPH (55 - 220 mg) dried at the critical point of CO₂ as described above in method 1. The clear gel was stirred at 0° C, and samples (3.0 mL) were periodically withdrawn into ether (45 mL) for analyses.

Analysis: After keeping the sample for 2h in an ice bath, the solvent and excess HCN were evaporated in vacuum, and approximately 0.5 g of the residue was accurately weighed and treated with 25 mL of a base solution (60 mL of 2N sodium hydroxide and 50 mL 25% NH₃ solution). The mixture was stirred at room temperature for 30 min. Distilled water (30 mL) were added, and the resulting cyanide solution was titrated potentiometrically with 0.1 or 0.01N AgNO₃ solution.²⁵ Only the linear portions of the individual kinetic traces were used for the kinetic data plot presented in Fig 3.

The enantioselectivity of the reaction was checked at maximum conversion by evaporating the solvent of the reaction mixture, then adding ether, filtering the catalyst, and evaporating the resulting solution to a constant weight.

The optical rotation of this sample has been determined, and the ee was calculated taking into account the concentration of the cyanohydrin in the sample, previously determined at the same point of time, and using $[\alpha]_D = (+) 43.75$ (benzene) for (R)-(+)-mandelonitrile.¹⁰

Note: A very good agreement was obtained when the enantiomeric excesses of several samples of medium and high conversions were determined using Mosher's

reagent and ^{19}F -NMR, and compared to the results obtained by the above described method.

m-phenozybenzaldehyde - Each kinetic run was performed with a toluene solution (35 mL) of m-phenozybenzaldehyde (0.954 M) and HCN (1.93M) and (S,S)-CPH (55 - 220 mg) dried as described above. The reaction conditions as well as the analytical procedure described for benzaldehyde were followed. The results are presented in Figure 4.

The enantioselectivity at maximum conversion had been determined as described above, using $[\alpha]_{\text{D}} = (+) 24.8$ (chloroform) for (R)-(+)-m-phenoxybenzaldehyde cyanohydrin.²⁶

(R)-(+)-m-phenozybenzaldehyde cyanohydrin - cyclo[-(S)-phenylalanyl-(S) histidyl], dried by CO₂ critical point method (see above, method 1), (172 mg; 0.6 mmol) was suspended in a stirred solution of m-phenoxybenzaldehyde (8.0 g; 0.04 mol) in toluene (40 mL). The mixture was cooled in an ice bath, then charged with HCN(l) (3.0 mL; 0.08 mol) and stirred for 7 hrs. The reaction mixture turned into a transparent gel which persisted throughout the reaction period. The reaction was quenched with HCl (1M; 5 mL), the organic phase separated and washed with water (3x30 mL), dried over sodium sulfate, and evaporated under reduced pressure at 45 °C to a constant weight. There was obtained an oil, 8.72 g (96%); $[\alpha]_{\text{D}} = (+) 24.1$, ee (calcd.) = 97.2%.

The above reaction was repeated using cyclo[-(S)-phenylalanyl-(S)-histidyl] dried thermally (see above, method 2). The catalyst persisted as an amorphous solid. No m-phenoxybenzaldehyde cyanohydrin could be detected.

Experiments A-D Table 1; Method A. Cyclo[-(S)-phenylalanyl-(S)-histidyl] (dried by method 1), (313 mg; 1.10 mmol) was suspended in a stirred solution of m-phenoxybenzaldehyde (9.91 g; 50 mmol) in toluene (40 mL). The mixture was cooled in an ice bath, then charged with HCN(l) (3.9 mL; 100 mmol) and stirred at 5 °C. Samples were withdrawn on the time intervals specified in Table 1, and analyzed for the reaction conversion and ee as described above in the kinetic experiment with benzaldehyde.

Methods B and C. Identical with method A but, for Method B (250 mg; 4.4 mmol) and for Method C (85 mg; 1.5 mmol) of hydroxyacetonitrile were added prior to the addition of HCN. The samples were analyzed as above, but the ratios m-phenoxybenzaldehyde cyanohydrin : hydroxyacetonitrile were determined by ^1H -NMR analyses (these values are required for calculation of the reactions' conversion).

Method D. Identical with method A, but methanol, (48 mg; 1.5 mmol) was added prior to the addition of HCN.

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