Examination and Enhancement of Enantioselective Autoinduction in Cyanohydrin Formation by *Cyclo*[(*R*)-His-(*R*)-Phe]

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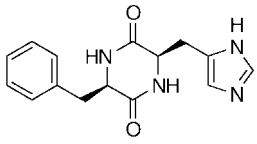
The cyclic dipeptide *cyclo*[(*R*)-His-(*R*)-Phe] (**1**) has been known since 1981 to catalyze the enantioselective formation of cyanohydrins from aldehydes and HCN. Although **1** has proved to be very effective in the production of optically active cyanohydrins, the precise structure of its catalytically active form remains unresolved. The reaction of 3-phenoxybenzaldehyde and HCN in the presence of **1** has also been shown to exhibit enantioselective autocatalysis: the product (*S*)-3-phenoxymandelonitrile reacts with **1** to form a new, more enantioselective catalytic species. It is now demonstrated that this autocatalytic phenomenon is general and that, furthermore, it can be used to improve the enantioselectivity of cyanohydrin formation for several problematic substrates. Upon addition of a small (8 mol %) quantity of (*S*)-mandelonitrile or (*S*)-3-phenoxymandelonitrile to these reactions, the enantioselectivity of cyanohydrin formation was improved by as much as 20% ee. This effect has been ascribed to the formation of a complex between the added (*S*)-cyanohydrin and **1** that exhibits superior enantioselectivity to **1**, either alone or complexed to the cyanohydrins of problematic substrates. A mathematical model has been developed, on the basis of a two-state equilibrium between **1** and a complex of **1** and cyanohydrin and used to explain the enantioselective autoinduction phenomenon in terms of five parameters: rate constants for the production of (*R*)- and (*S*)-cyanohydrin by both **1** and its cyanohydrin complex and an association constant for the formation of a cyanohydrin complex by **1**. Two versions of this model, based on monomeric and dimeric **1**, have been evaluated in light of the available data. Examination of the results reveals that the complexes of **1** and many of the cyanohydrins studied are highly enantioselective catalysts but that the complexes of **1** and cyanohydrins are only weakly associated; moreover, the complexation of **1** with most cyanohydrins leaves the rate of cyanohydrin formation unchanged, though both autocatalysis and enantioselective poisoning have been observed as well.

Introduction

The formation of carbon−carbon bonds by asymmetric, catalytic processes is a central goal of modern organic synthesis. The last 20 years have seen an explosion of research in this area, resulting in the discovery of many outstanding new catalytic species for the enantioselective formation of carbon−carbon bonds.[1] Typically, such catalytic species fall into one of two categories: organotransition metal catalysts and enzymes. One intriguing exception to this categorization is the cyclic dipeptide catalyst *cyclo*[(*R*)-His-(*R*)-Phe] (**1**), shown by Inoue and co-workers in 1981 to effectively catalyze the enantioselective addition of HCN to benzaldehyde in benzene.[2] Subsequent investigations by Inoue[3] and Jackson[4] established that **1** was most effective when the aldehyde substrate was aromatic and the solvent was toluene, in which **1** is a heterogeneous gel. These findings have led to the commercial use of **1** in the synthesis of pyrethroid insecticides.[5]



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The exceptionally high enantioselectivity exhibited by a small molecule catalyst containing no transition metals has prompted a number of researchers to examine the structure and behavior of **1** in attempts to understand its mode of catalysis. North[6] and DeVries[7] have both undertaken detailed NMR and theoretical investigations of the structure of **1** in DMSO solution and the solid state. Though these studies have shed light on the intrinsic conformational preferences of **1**, their relevance to the catalytic species has been limited by the lack of enantioselectivity shown by **1** in those solvents in which it is fully soluble. Thus, at present, no comprehensive model of the catalytic complex exists.

In recent years, our understanding of catalysis by **1** has been further complicated by several remarkable discoveries. First, Inoue,[3e] Jackson,[4b] and workers at

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(6) North, M. *Tetrahedron* **1992**, *48*, 5509−5522.

(7) Callant, D.; Coussens, B.; v. d. Maten, T.; de Vries, J. G.; de Vries, N. K. *Tetrahedron: Asymmetry* **1992**, *3*, 401−414.

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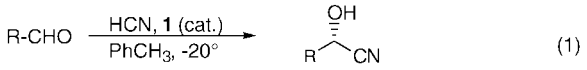
Shell[8] revealed that the method by which **1** was obtained in the solid state affected its catalytic activity: more amorphous solids were more effective and enantioselective catalysts. Second, Danda observed that the gellike state of **1** in toluene solution exhibited thixotropic behavior and that increased enantioselectivity was observed upon increasing stirring rate (and concomitantly decreased viscosity).[9a] In a separate publication, Danda noted that the conversion of 3-phenoxybenzaldehyde (**2b**) to its (*S*)-cyanohydrin (**3b**) catalyzed by **1** (eq 1) exhibited enantioselective autoinduction,[9b] as defined by Alberts and Wynberg.[10] By monitoring the enantiomeric excess



(1)

2a: R=Ph	**3a**: R=Ph
2b: R=3-PhOPh	**3b**: R=3-PhOPh
2c: R=2-naphthyl	**3c**: R=2-naphthyl
2d: R=2-furyl	**3d**: R=2-furyl
2e: R=*t*-Bu	**3e**: R=*t*-Bu
2f: R=*c*-C_6H_{11}	**3f**: R=*c*-C_6H_{11}
2g: R=*i*-Bu	**3g**: R=*i*-Bu
2h: R=*i*-Pr	**3h**: R=*i*-Pr
2i: R=C_5H_{11}	**3i**: R=C_5H_{11}

of the product as a function of time, Danda demonstrated that the reaction grew *more* enantioselective with time, thereby implying that the product cyanohydrin interacts with **1** to form a more enantioselective catalyst. Danda further elaborated this observation by demonstrating that **1**, when mixed with racemic cyanohydrin, preferentially complexes the *S* isomer (the major product) in a 0.8:1 ratio. Addition of the (*S*)-cyanohydrin was shown to eliminate autoinduction in the reaction. These observations have been largely corroborated by the recent study of Shvo, in which autoinduction was also observed in the hydrocyantion of **2b**, and two other hydroxylic species were shown to suppress autoinduction upon their introduction to the reaction.[11]

While these findings have provided valuable information about the nature of the catalytic behavior of **1**, to date no definitive explanation for enantioselectivity exists. Indeed, the recent studies on **1** have raised as many questions as they have answered. For instance, it is unknown whether the autocatalytic behavior of **1** is a general phenomenon or limited only to 3-phenoxybenzaldehyde. Also, it is unknown whether autoinduction results from autocatalysis or from another source. In addition, no structural model currently exists for the catalytic complex. In the present study, the reactions of a number of different aldehydes—both alone and in the presence of external additives—have been examined to shed further light on the complex behavior of **1**.

Results and Discussion

A number of methods for activating **1** as a catalyst have been put forth in the literature, including precipitation from methanol[3e] and methanol−ether,[3e,9b] spray drying,[8] and supercritical CO_2 drying.[11] It has been empirically noted that optimal preparations of **1** are amorphous solids with low melting points.[9e,4b] In our hands, lyophilization of aqueous solutions of **1**[12] was found to produce an amorphous solid with optimal catalytic properties. Moreover, unlike precipitation from solvent mixtures, lyophilization resulted in complete mass recovery of **1**. Hydrocyanation reactions catalyzed by activated **1** were carried out in accord with the procedures of Inoue.[3e] Yields and enantioselectivities were determined by analysis of the crude reaction products. Yields were determined by integration of the ^{1}H NMR spectra, while enantioselectivity was determined by derivatization of cyanohydrin products, either with (−)-menthyl chloroformate[13] or (−)-MTPA.[14] During these experiments, it was found that the data showed considerable variation. To lessen the impact of such variation, all data were collected in duplicate or triplicate.

Is Autoinduction A General Phenomenon?

One limitation of the studies by Danda and Shvo is the number of substrates examined. All the examples of enantioselective autoinduction used 3-phenoxybenzaldehyde as the substrate, leaving open the question of whether such a phenomenon is restricted to this one case or, rather, is a general property of **1**. That question has been tested by studying the conversion of five different aldehydes (**2a**−**e**) to their corresponding cyanohydrins (**3a**−**e**) as a function of time. It was found that much of the variability from run to run could be attributed to variable induction times; this problem was circumvented by considering the enantioselectivity of reaction as a function of conversion. The results of these studies are presented in Figure 1.

In all five cases, the enantioselectivity of reaction was shown to increase with increasing conversion. Thus, the autoinduction observed in the hydrocyanation of 3-phenoxybenzaldehyde (**2b**) was found to be quite general, though the degree of nonlinearity in the curves is highly variable. Nonetheless, from these graphs it would appear that autoinduction is a general property of **1**, thereby implying that most (if not all) cyanohydrins are capable of interacting with **1**—and in so doing, form *more enantioselective* catalysts. The nature of the interaction between cyanohydrin and **1**, and the structure of the complex, remain to be determined.

The Kinetic Consequences of Autoinduction

Two different explanations for these data can be proffered. The complexes formed between **1** and the cyanohydrins (**3**) could be more effective catalysts than uncomplexed **1** (autocatalysis) or the complexes could be made more enantioselective catalysts by suppression of a pathway leading to the undesired isomer, thus slowing the turnover rate (enantioselective poisoning). This latter possibility might be likened to product inhibition in enzymatic systems, though the fact that complexation with **3** *reinforces* the preference for the major isomer argues against such a simple explanation. Though the distinction between the two possibilities would seem to

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(9) (a) Danda, H. *Synlett* **1991**, 263−264. (b) Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740−6741.
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(11) Shvo, Y.; Gal, M.; Becker, Y.; Elgavi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 911−924.
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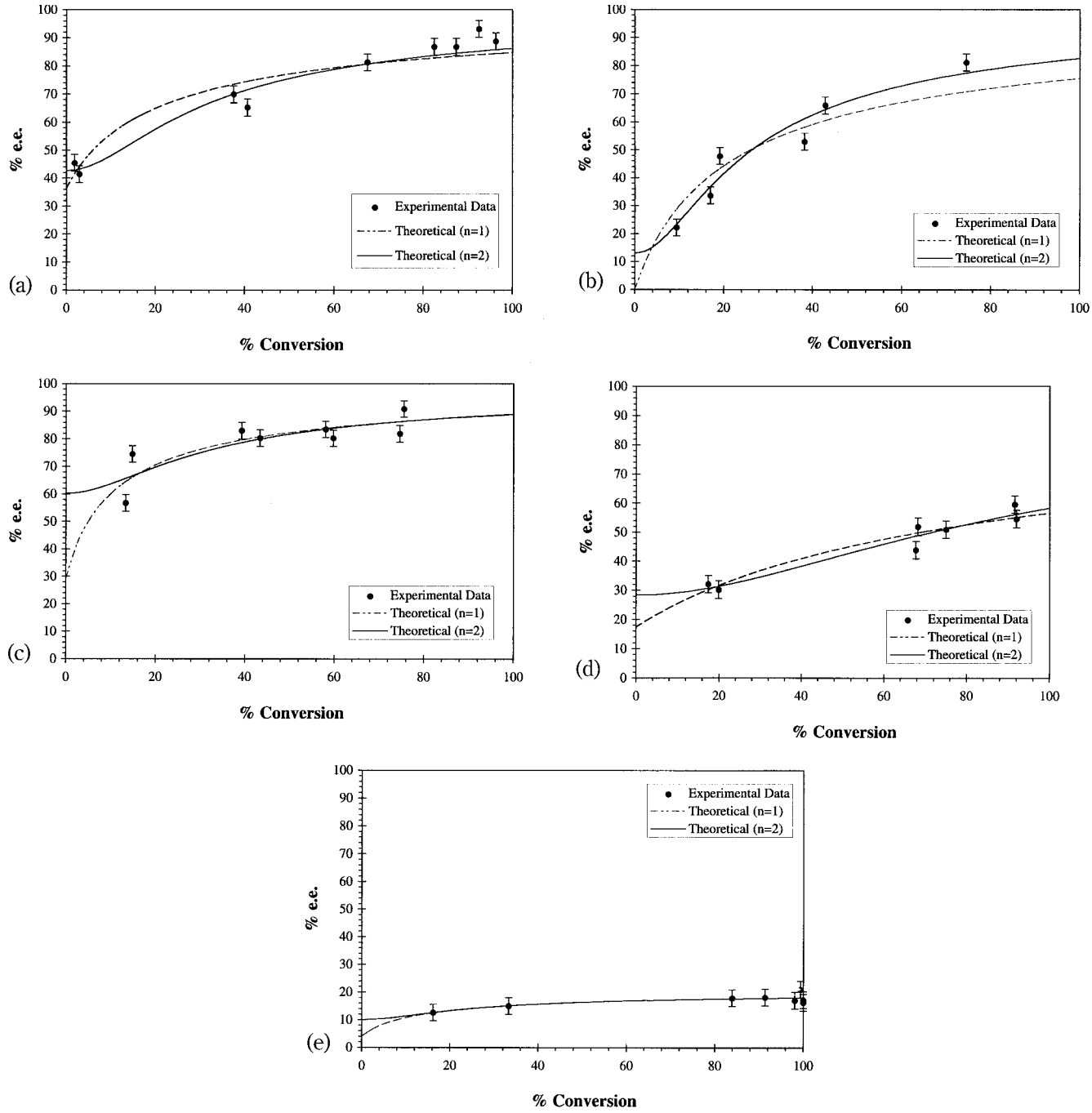


Figure 1. Graphs of enantioselective autoinduction in hydrocyanation reactions catalyzed by **1** using various aldehydes: (a) benzaldehyde (**2a**); (b) 3-phenoxybenzaldehyde (**2b**); (c) 3-naphthaldehyde (**2c**); (d) furfural (**2d**); and (e) pivaldehyde (**2e**).

be a profound one, the net result is identical: increasing enantioselectivity as product formation increases. Therefore, distinguishing between the two cases requires a thorough understanding of the kinetics of the system.

Such an understanding requires in turn the development of a general kinetic model for such an autoinduction process. Because there is no evidence for covalent bonding between **1** and any of the other components, the model must view the interaction of **1** and **3** as a reversible equilibrium. The reaction of HCN and aldehyde in toluene must be considered irreversible, as a catalyst is unable to substantially perturb an equilibrium. Such a model is presented in Scheme 1. In Scheme 1, complexation of **1** and **3** is viewed as a simple two-state equilibrium between **1** and a noncovalent complex **1•3**, both of which catalyze an irreversible reaction of HCN and aldehyde. Although, in principle, the two enantiomeric cyanohydrins $\mathbf{3}_R$ and $\mathbf{3}_S$ could give rise to diastereomeric complexes with **1**, the finding of Danda[9b] that only $\mathbf{3}_S$ complexes **1** leads to the simplifying assumption of only one complex; hence, **1•3** is shown as a single species. No background reaction is included in this model, in accord with the findings of Inoue.[3e] Thus, our kinetic model is completely described by five substrate-dependent parameters: rate constants for the production of each isomer of **3** by **1** and **1•3** (k_{1R}, k_{1S}, k_{13R}, k_{13S}) and an association constant (K_A) for the complexation of **1** by **3**. Using these parameters and the initial concentration of aldehyde ($[\mathbf{2}]_0$), one can express the enantioselectivity of product formation as a function of conversion (χ) (eq 2).[15]

Scheme 1

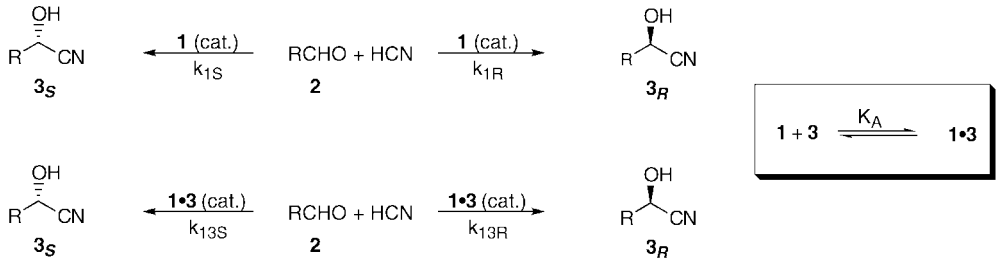


Table 1. Rate and Association Constants from Analysis of Enantioselectivity Data Using Eqs 2 and 3

aldehyde	eq	ee_1,[a] %	$ee_{1•3}$,[a] %	k_{rel}[a]	K_A (M^{-1})
2a	2	37	100	1.0	9.9
2a	3	43	100	1.0	5.8
2b	2	0.0	100	1.0	9.7
2b	3	13	100	1.0	7.2
2c	2	29	100	6.4	2.9
2c	3	60	98	8.5	1.9
2d	2	17	100	1.0	2.2
2d	3	28	100	1.0	1.8
2e	2	4.0	21	0.56	27
2e	3	10	20	0.95	7.2

[a]Defined in ref 16.

An additional complication has been raised by Shvo.[11] Examination of the consumption of HCN by potentiometric titration gave a second-order rate dependence on **1**, leading to the conclusion that two molecules of **1** are involved in the transition state. Although Shvo interpreted this finding in terms of catalysis by a polymer, taking these findings along with Danda's observation of thixotropy leads to an alternate conclusion that the catalytic species may be a *dimer* of **1**. Such a hypothesis can be incorporated into our kinetic model and results in an alternate expression for enantioselectivity as a function of conversion (eq 3).

Nonlinear curve-fitting of these two equations to the data produces the curves shown in Figure 1. As can be seen, both functional forms can be fit to the data within error limits of the experimental values. Thus, no direct conclusions can be drawn as to the aggregation state of **1** in the catalytic complex. Nonetheless, the parameters derived from the fits provide useful insight into the interactions responsible for effective catalysis. Since the enantiomeric excess of a kinetic process can be defined in terms of the rates of production of major and minor isomers, the data obtained from the fitted curves can be expressed in the form of four parameters: the enantioselectivity of uncomplexed **1** (ee_1), that of the complex **1•3** ($ee_{1•3}$), the autocatalytic rate acceleration (k_{rel}),[16] and the association constant K_A. These parameters, obtained from the rate constants that are obtained in turn from both eqs 2 and 3, are provided in Table 1.

Several interesting implications for the behavior of **1** emerge from consideration of the data in Table 1. First, the binding of the cyanohydrins to **1**, though weak, is quite variable from cyanohydrin to cyanohydrin. The poorest complexation is seen with **3c** and **3d**, when the benzene ring of **3a** has been replaced by a 3-naphthyl or 2-furyl substituent, respectively; on the other hand, the tightest complexation may occur with **3e**, with a *tert*-butyl side chain derived from pivaldehyde. Thus, a simple steric explanation is unlikely to explain the degree of association of cyanohydrins with **1**.

Examination of the autocatalytic rate acceleration k_{rel} demonstrates that there is no consistent deviation in rate attendant upon formation of the complex **1•3**. Rather, in three of the cases (**2a,b,d**) there is no significant rate change; hydrocyanation of naphthaldehyde (**2c**) does exhibit autocatalytic behavior, whereas eq 2 implies that the cyanohydrin **3e** actually poisons **1**! Thus, it appears that the enhancement of enantioselectivity attendant upon complexation of **1** is independent of the rate of catalysis and should therefore be viewed as an independent phenomenon.

The enantioselectivities of the two catalytic species, **1** and **1•3**, also bear scrutiny. With all the aromatic aldehydes (**2a**−**d**), the model for autoinduction suggests that the complexes **1•3a**−**d** are *wholly enantioselective*, regardless of the model used; in contrast, pivaldehyde remains a poor substrate even after formation of the complex **1•3e**. Because uncomplexed **1** exhibits no worse enantioselectivity for hydrocyanation of pivaldehyde than, e.g., 3-phenoxybenzaldehyde (**2b**), one is forced to conclude that the problem is more likely to lie with the complex **1•3e** than with the aldehyde itself.

Improving Enantioselectivity through Exploitation of Autoinduction

One implication of the previous conclusion is that replacement of **1•3e** with a more functional complex might substantially improve the enantioselectivity of forming the cyanohydrin **3e**. More generally, the possibility exists that the reactions of more problematic substrates can be made more enantioselective by addition

$$\%ee(\chi) = 100\left\{\frac{k_{13S}+k_{13R}}{k_{13R}+k_{13S}} + \frac{(k_{1S}-k_{1R})(k_{13R}+k_{13S})-(k_{1R}+k_{1S})(k_{13S}-k_{13R})}{(k_{13S}+k_{13R})^2 K_A[\mathbf{2}]_0\chi}\ln\left[1+\frac{k_{13R}+k_{13S}}{k_{1R}+k_{1S}}[\mathbf{2}]_0 K_A\chi\right]\right\} \quad (2)$$

$$\%ee(\chi) + 100\left\{\frac{k_{13S}-k_{13R}}{k_{13R}+k_{13S}} + \frac{(k_{1S}-k_{1R})(k_{13R}+k_{13S})-(k_{1R}+k_{1S})(k_{13S}-k_{13R})}{(k_{13S}+k_{13R})^{3/2}\sqrt{k_{1R}+k_{1S}}K_A[\mathbf{2}]_0\chi}\tan^{-1}\left[\sqrt{\frac{k_{13R}+k_{13S}}{k_{1S}+k_{1R}}}K_A[\mathbf{2}]_0\chi\right]\right\} \quad (3)$$

Table 2. Effect of Added Cyanohydrins on the Enantioselectivity of Catalysis by 1

entry	aldehyde	additive	time, h	yield,[a] %	ee,[a,b] %	Δee,[c] %
1	**2b**	none	4	92	85	
2		**3a**	4	94[d]	87[d]	+2
3		**3b**	4	87[d]	89[d]	+4
4	**2c**	none	1.5	67	73	
5		**3a**	1.5	95	88	+15
6		**3b**	1.5	93	88	+15
7	**2d**	none	7	92[e]	53[e]	
8		**3a**	7	95	81	+28
9		**3b**	7	94	80	+27
10	**2e**	none	4	100	21[f]	
11		**3a**	4	100	24[f]	+3
12		**3b**	4	100	32[f]	+11
13	**2f**	none	2.5	96	42[g]	
14		**3a**	2.5	100	61[g]	+19
15		**3b**	2.5	100	67[g]	+25
16	**2g**	none	5	95	23[g]	
17		**3a**	5	96	30[g]	+6
18		**3b**	5	98	28[g]	+4
19	**2h**	none	5	100	26[f]	
20		**3a**	5	100	46[f]	+20
21		**3b**	5	100	48[f]	+22
22	**2i**	none	8	100	40[g]	
23		**3a**	8	100	44[g]	+4
24		**3b**	8	100	55[g]	+15

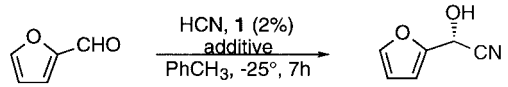
[a]Based on the average of two trials unless otherwise noted. [b]Determined by ^{1}H NMR of (−)-menthyl chloroformate derivatives unless otherwise noted. [c]Defined as the difference in % ee between seeded and unseeded reactions. [d]The average of three trials. [e] The average of six trials. [f]Determined by ^{1}H NMR of (−)-MTPA derivatives. [g]Determined by ^{19}F NMR of (−)-MTPA derivatives.

of a cyanohydrin known to form a highly enantioselective complex with **1**, in this case either **3a** or **3b**. Such a possibility was explored with seven different substrates (**2c**−**i**, Table 2). In all cases, an increase in enantioselectivity was observed, in some cases by over 20% ee! This finding not only reinforces the conclusions from the kinetic analysis but also illustrates a method for improving the enantioselectivity of problematic substrates.

The results obtained using 3-phenoxybenzaldehyde as a substrate (Table 2, entries 1−3) also served to validate our kinetic model. Using the kinetic parameters and binding constant from Table 1, the effect of addition of 8 mol % product to the reaction mixture can be predicted: application of both eqs 2 and 3 predicts an increase of 1% in the enantiomeric excess of the product formed at completion. In the event, an increase of 4% was observed, within experimental error of the prediction.

Having established that addition of an exogenous cyanohydrin can markedly improve the enantioselectivity of catalysis by **1**, we next sought to examine the generality of the interaction by introducing other hydroxylic compounds into a reaction catalyzed by **1**. Such an investigation was suggested by the work of Shvo[11] and Dong,[17] in which alcohols other than cyanohydrins were shown to eliminate enantioselective autoinduction. Whereas those groups examined the reactions of 3-phenoxybenzaldehyde (**2b**), our study used the reaction of furfural (**2d**); this change was made in response to the dramatic improvement in enantioselectivity observed when cyanohydrins were added to the reactions of **2d** (Table 2, entries 7−9).

Table 3. Effect of Added Hydroxylic Compounds on the Enantioselective Hydrocyanation of Furfural (2d)



2d **3d**

entry	additive	amt,mol %	yield,[a] %	ee,[a,b] %	Δee,[c], %
1	none		92[d]	53[d]	
2	**3a**	8	95	81	+28
3	(*R*)-**3a**	8	78	50	−3
4	**3b**	8	94	80	+27
5	**3d**	8	87	75	+22
6	**3d**	20	91	70	+17
7	**3d**	80	66	28	−25
8	**3e**	8	77	55	+2
9	**4**	8	83	73	+20
10	MeOH	8	94	57	+4
11	MeOH	20	85	58	+5
12	(*S*)-**5**	8	94	72	+19
13	(*R*)-**5**	8	86	58	+5

[a]The average of two trials unless otherwise noted. [b]Determined by ^{1}H NMR of (−)-menthyl chloroformate derivatives. [c]Defined as the difference in ee between seeded and unseeded reactions. [d]The average of six trials.

Our results largely bear out the findings of previous researchers (Table 3). Whereas addition of (*S*)-mandelonitrile (**3a**) produced a substantial improvement in enantioselectivity (Table 3, entry 2), addition of its enantiomer (*R*)-mandelonitrile (Table 3, entry 3) produced no observable change in enantioselectivity. These results are in accord with Danda's findings on the hydrocyanation of 3-phenoxybenzaldehyde (vide supra). A comparison of four different cyanohydrins, **3a,b,d,e**, as seeding agents demonstrated that while the three aromatic cyanohydrins exhibited similar improvements in enantioselectivity (Table 3, entries 2, 4, and 5), the aliphatic cyanohydrin **3e** afforded no significant increase (Table 3, entry 8). In addition, while addition of the furfural-derived cyanohydrin **3d** produced an improvement in enantioselectivity, the observed increase was not as great as those observed with **3a,b**. Addition of increasing amounts of **3d** (Table 3, entries 6 and 7) did not produce a concomitant increase in enantioselectivity. Indeed, when sufficient cyanohydrin was added, a *decrease* in enantioselectivity was noted (Table 3, entry 7). Such a finding reinforces the conclusions of DeVries,[7] who found that solubilization of **1** by addition of mandelonitrile resulted in loss of enantioselectivity, perhaps by disruption of hydrogen bonding in the catalytic complex.

The dramatic difference in effect observed between (*S*)- and (*R*)-mandelonitrile prompted us to examine the addition of the achiral cyanohydrin of acetone (**4**) to the reaction of furfural (Table 3, entry 9). In marked contrast to (*R*)-mandelonitrile, **4** proved to effectively improve the enantioselectivity of cyanohydrin formation. Thus, it would appear that the chirality of, e.g., **3a** is not an essential factor in its ability to improve the enantioselectivity of hydrocyanation, though differences between the enantiomers of chiral cyanohydrins are pronounced. Another test was conducted where methanol was examined for its ability to improve enantioselectivity. Shvo had reported[9] that addition of methanol eliminated autoinduction in the hydrocyanation of 3-phenoxyben-

(15) Derivations of eqs 2 and 3 and the solution for parameters k_{1R}, k_{1S}, k_{13R}, k_{13}, and K_A are given in the Supporting Information.

(16) The parameters ee_1, ee_{13}, and k_{rel} are defined as the ratios $(k_{1S} - k_{1R})/(k_{1R} + k_{1S})$, $(k_{13S} - k_{13R})/(k_{13R} + k_{13S})$, and $(k_{13R} + k_{13S})/(k_{1R} + k_{1S})$, respectively; the parameter ee_1 reflects the enantioselectivity exhibited by uncomplexed **1**, ee_{13} reflects that of the complex **1**•**3**, and k_{rel} quantifies the catalytic advantage (or disadvantage) conveyed to **1** upon complexation by **3**.

(17) Dong, W.; Friend, P. S. *U.S. Pat.* 4,611,076, 1986.

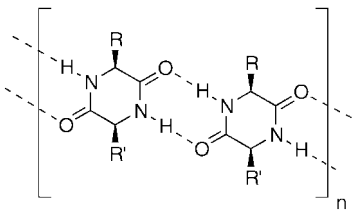


Figure 2. Structure of chiral diketopiperazine polymers in the solid state (from ref 17).

zaldehyde. In our experiments, addition of methanol (Table 3, entries 10 and 11) resulted in only a modest increase in enantioselectivity. In another experiment, the chiral secondary alcohol 1-phenyl-1-ethanol (**5**) was examined in both enantiomeric forms. When the *S* isomer was added (Table 3, entry 12), an improvement in enantioselectivity comparable to those produced by cyanohydrins was observed; conversely, when the *R* isomer was added (Table 3, entry 13), it was no more effective than methanol at improving the enantioselectivity. Thus, it appears that the nitrile functionality of cyanohydrins is not essential to their interaction with **1**, but that the chirality of an added hydroxylic species is the most critical factor leading to enhancement of enantioselectivity.

Probing the Aggregation State of the Catalytic Complex

The most intractable problem surrounding the catalytic behavior of **1** is the aggregation state of the true catalytic species. Although Inoue's original model of the catalytic complex invoked a monomer of **1**, multiple inconsistencies of this model (vide supra) with experimental findings force us to abandon it. Questions about the aggregation state of **1** are brought to the fore by several recent findings. First, the thixotropic behavior of **1** in toluene[9a] is consistent with mechanical disruption of a polymer, suggesting that **1** is polymeric in solution; it is reasonable to believe that **1** forms a hydrogen-bonded polymer in which the s-cis lactams of **1** form eight-membered, hydrogen-bonded rings such as are seen in the solid state (Figure 2).[18] The improvement of enantioselectivity at high stirring rates, however, suggests that either efficient transport is needed for high enantioselectivity or that the most enantioselective catalyst is *not a polymer but a lower oligomer*.

This latter supposition is also supported by Shvo's observation that hydrocyanation of 3-phenoxybenzaldehyde is second-order with respect to the concentration of **1**.[11] Although Shvo has argued that such kinetics are consistent with catalysis by two histidine residues on a polymer of **1**, it can also be argued that they support a *dimeric* structure for the catalytic form of **1**. Such a view has several attractive features, not least of which are structural simplicity and consistency with Prelog's mechanistic work on catalysis of cyanohydrin formation.[19] Indeed, our kinetic analysis of autoinduction in the reactions of **1** (vide supra) demonstrates that a dimer is entirely consistent with the available data, although a monomeric catalyst cannot be easily excluded either.

Upon close examination, however, the reactions of pivaldehyde (**2e**) provide distinction between the two kinetic models. Whereas eq 2 predicts that pivaldehyde cyanohydrin (**3e**) binds **1** tighter than any other cyanohydrin studied, eq 3 predicts binding comparable to that of the aromatic cyanohydrins **3a**,**b**. Thus, eq 2 implies that **3e** should be capable of poisoning the reaction of, e.g., **2b** with **1** while eq 3 implies the opposite; likewise, eq 3 implies that addition of **3a** or **3b** should improve the enantioselectivity of hydrocyanation of pivaldehyde (**2e**) when catalyzed by **1** while eq 2 suggests the opposite. These contrasting predictions were examined experimentally (Table 2, entries 11 and 12; Table 3, entry 8), and in both cases, the predictions of eq 3 were borne out. Thus, on the basis of these data, one must conclude that the dimeric model for **1** is in better accord with experiment than a monomeric model.

Conclusions

It has been demonstrated that autoinduction in the reactions of **1** is a general phenomenon, applicable to a variety of different aldehydes. Furthermore, such behavior is explainable by reversible, noncovalent complexation between **1** and the product cyanohydrins **3**. Examination of the individual rate constants shows that while the complexed catalyst **1•3** is more enantioselective than **1** alone, it is rarely a more effective catalyst as judged by rate acceleration. Additionally, examination of the hydrocyanation of an aliphatic aldehyde—pivaldehyde—suggests that poor substrates are those aldehydes whose cyanohydrins cannot form a highly enantioselective complex with **1**; consequently, their enantioselectivity can be substantially improved by the addition of a chiral, aryl cyanohydrin or secondary alcohol. Such an improvement in enantioselectivity was also shown to result exclusively from addition of the *S* isomers; when the enantiomeric *R* isomers were added, no improvement in enantioselectivity was seen.

While both monomeric and dimeric complexes of **1** are largely consistent with the data, the ability of cyanohydrins **3a**,**b** to improve the enantioselective hydrocyanation of pivaldehyde strongly supports the dimeric model. Equally important, one need not invoke a polymer of **1** to explain these results. Owing to the complexity of developing a kinetic model for catalysis by a polymer of **1**, it is difficult to conclusively exclude that possibility; rather, one can say that a dimer of **1** is wholly concordant with known experiments. Further experiments are underway to investigate in detail the structure of the complex **1•3**.

Experimental Section

General Procedures. All reactions were performed in glassware dried by flame or in an oven, and perfomed under a positive pressure of nitrogen gas. All aldehydes were distilled and stored under nitrogen prior to use. Diethyl ether was distilled from sodium benzophenone ketyl and toluene from calcium hydride. All other reagents were used as received without further purification. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer and ^{19}F NMR were recorded on a General Electric QE-300 (282 MHz).

Activation of *cyclo*[(*R*)-His-(*R*)-Phe] (1). A solution of *cyclo*[(*R*)-His-(*R*)-Phe] in deionized water (250 mg in 250 mL) was stirred at room temperature for 72 h to completely dissolve **1**. The solution was then frozen and lyophilized, yielding >99% recovery of a flocculant white solid.

Preparation of HCN. Concentrated H_2SO_4 (50 mL) was added dropwise via additon funnel to an aqueous solution of

(18) MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383.
(19) Prelog, V.; Wilhelm, M. *Helv. Chem. Acta* **1954**, *192*, 1634.

NaCN (5 M, 200 mL) in a three-neck round-bottom flask connected, by tubing, to a gas washing flask containing anhydrous $CaCl_2$ and a coldfinger condenser cooled to −78 °C. Anhydrous HCN was collected as a solid on the surface of the condenser and once HCN evolution was complete, allowed to slowly warm to 5 °C and collected in a receiving flask containing anhydrous $CaCl_2$ at −78 °C. The HCN (20 mL, 0.5 mol) was stored as a solid at −78 °C until needed, at which point it was warmed to 0° and transferred via chilled syringe. CAUTION: HYDROGEN CYANIDE IS EXTREMELY TOXIC! EITHER INHALATION OF HCN VAPOR OR SKIN CONTACT WITH THE LIQUID CAN CAUSE DEATH. EXTREME CAUTION SHOULD BE TAKEN WHEN PREPARING, STORING, AND USING HCN.[20]

Asymmetric Addition of Hydrogen Cyanide to Aldehydes. Autoinduction Study. Dry toluene (3 mL) was added to solid **1** (17.1 mg, 0.06 mmol) under nitrogen and stirred at room temperature for 45 min. To this solution was added **2** (3.0 mmol) and the resulting mixture cooled to −25 °C. HCN (0.300 mL, 7.5 mmol) was then added to the mixture via precooled syringe and the stirring rate increased. Aliquots of the reaction (0.250 mL) were withdrawn at periodic intervals and quenched in 0.1 N methanolic HCl (0.100 mL). The quenched aliquot was extracted with ether (4 mL) and water (4 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to leave a crude oil that was characterized by ^{1}H NMR. **3a** δ 7.65−7.40 (m, 5 H), 5.54 (s, 1 H), 3.25 (br s, 1 H); **3b** δ 7.62−6.99 (m, 9 H), 5.50 (s, 1 H), 3.0 (br s, 1 H); **3c** δ 8.03 (s, 1 H), 7.95−7.85 (m, 3 H), 7.63−7.52 (m, 3 H), 5.72 (s, 1 H), 2.75 (br s, 1 H); **3d** δ 7.48 (d, J = 1.8 Hz, 1 H), 6.64−6.59 (m, 1 H), 6.43 (dd, J = 1.8, 1.5 Hz, 1 H), 5.56 (s, 1 H), 3.45 (br s, 1 H); **3e** δ 2.36 (s, 1 H), 1.07 (s, 9 H); **3f** δ 4.28 (d, J = 6.2 Hz, 1 H), 2.46 (br s, 1 H), 1.91−1.67 (m, 6 H), 1.38−1.03 (m, 5 H); **3g** δ 4.50 (t, J = 7.3 Hz, 1 H), 1.93−1.69 (m, 3 H), 0.98 (d, J = 6.3 Hz, 6 H); **3h** δ 4.29 (d, J = 5.9 Hz, 1 H), 2.45 (br s, 1 H), 2.06 (dq, J = 6.8, 6.0 Hz, 1 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.08 (d, J = 6.8 Hz, 3 H); **3i** δ 4.48 (t, J = 6.7 Hz, 1 H), 2.85 (br s, 1 H), 1.91−1.79 (m, 2 H), 1.55−1.30 (m, 6 H), 0.91 (t, J = 6.6 Hz, 3 H).

Asymmetric Addition of Hydrogen Cyanide to Aldehydes. Seeding Experiments. Dry toluene (1 mL) was added to **1** (5.7 mg, 0.02 mmol) and **3** (0.08 mmol) under nitrogen and stirred at room temperature for 45 min. To this solution was added **2** (1.0 mmol) and the resulting mixture cooled to −25 °C. HCN (0.100 mL, 2.5 mmol) was then added to the mixture via precooled syringe and the stirring rate increased. At completion, the reaction was quenched by addition of 0.1 N methanolic HCl (0.250 mL). The reaction mixture was extracted with ether (7 mL) and water (7 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to leave a crude oil that was characterized by ^{1}H NMR.

Determination of Optical Purity of Cyanohydrins. Method A (for 3a−d). (1*R*,2*S*,5*R*)-(−)-Menthyl chloroformate (0.025 mL, 0.012 mmol) was added to a solution of crude cyanohydrin (**3**, 0.057 mmol) in toluene (0.5 mL). Pyridine (0.015 mL, 0.019 mmol) was added and the reaction stirred at room temperature for 12 h. The mixture was concentrated in vacuo and analyzed by ^{1}H NMR. The diastereomeric excess was determined by ^{1}H NMR analysis of methine signals near δ 6, corresponding to the methine proton α to the cyano group of each diastereomer of the cyanohydrin menthyl carbonate. ^{1}H NMR ($CDCl_3$): **3a** δ 6.28 (major, s), 6.25 (minor, s); **3b** δ 6.21 (major, s), 6.19 (minor, s); **3c** δ 6.40 (major, s), 6.38 (minor, s); **3d** δ 6.35 (major, s), 6.34 (minor, s).

Method B (for 3e−i). To a small sample of **3** (35 μmol) were added $CDCl_3$ (0.300 mL) and 4-(dimethylamino)pyridine (2 mg, 16 mmol) followed by (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(−)-MTPA-Cl, (0.008 mL, 6.2 μmol)]. The reaction was continued for 6 h under nitrogen in an NMR tube. The diastereomeric excess of the corresponding MTPA ester was determined by ^{1}H or ^{19}F NMR. ^{1}H NMR ($CDCl_3$): **3e** δ 5.15 (major, s), 5.11 (minor, s); **3h** δ 5.31 (major, d, J = 5.9 Hz), 5.28 (minor, d, J = 5.7 Hz). ^{19}F NMR ($CDCl_3$): **3f** δ −70.54 (major, s), −70.85 (minor, s); **3g** δ −70.56 (major, s), −70.84 (minor, s); **3i** δ −70.62 (major, s), −70.86 (minor, s).

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Supporting Information Available: Derivations of kinetic expressions and first derivative curves (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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