

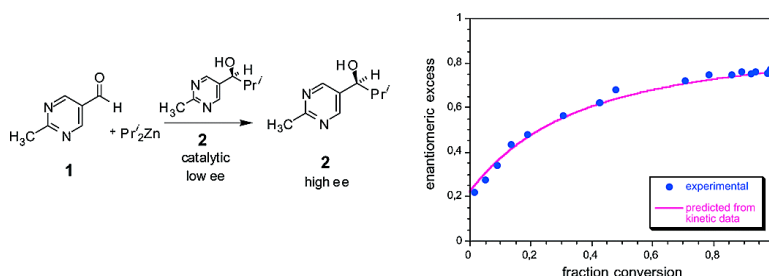
Communication

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## Kinetic Evidence for a Tetrameric Transition State in the Asymmetric Autocatalytic Alkylation of Pyrimidyl Aldehydes<sup>†</sup>

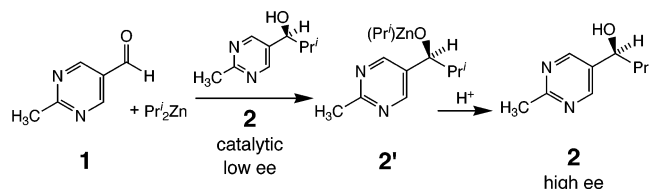
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Autocatalytic reactions have been implicated both in the self-replication of biological molecules<sup>1</sup> and in the amplification of enantiomeric excess of a chiral molecule in the prebiotic environment.<sup>2,3</sup> In a remarkable example related to the latter case, Soai<sup>4,5</sup> has shown that pyrimidyl alcohols such as **2** may serve as both the catalyst and the product in dialkylzinc alkylations of the corresponding pyrimidyl aldehydes (Scheme 1). Alcohols such as **2** in very low enantiomeric excess have been shown to catalyze their own formation in greatly amplified enantiomeric excess.

### Scheme 1



In kinetic studies of the reaction shown in Scheme 1, we<sup>6</sup> showed that the catalytically active species is a dimer formed by combination of two molecules of **2'**, the Zn alkoxide of **2**. Remarkably, and in contrast to examples of significant asymmetric amplification in *catalytic* reactions, we found that in this autocatalytic case there is no stability difference between homochiral and heterochiral dimers. We determined that the origin of the asymmetric amplification rests solely on the relative inactivity of the heterochiral species as a catalyst and not on its higher stability. Achieving high selectivity by capitalizing on stability differences between complex species is a common tool in modern asymmetric catalyst design; however, it is one that is unlikely to have been available to the simple molecules present in the prebiotic world. Thus, amplification without this requirement, as demonstrated by our studies, may provide an important clue toward the understanding of the biochemical origin of homochirality.

In this communication we report kinetic evidence for a tetrameric transition state in the Soai autocatalytic reaction shown in Scheme 1. Our refined kinetic model accurately predicts both the reaction rate and the amplification in enantiomeric excess observed in reactions carried out under a wide range of conditions. These studies reveal the Soai reaction to be an example of true autocatalytic efficiency in a template-directed "minimal system"<sup>7</sup> for self-replication.

Equations 1–3 outline the rate law developed in our previous work.<sup>2</sup> The enantiomers of **2'** combine to form homochiral (**3<sub>RR</sub>** and **3<sub>SS</sub>**) and heterochiral (**3<sub>RS</sub>**) dimers with equal probability ( $K_{\text{eq}} = 4$ , eq 2); however, only the homochiral species are active

catalysts. A proposed model for a macrocyclic dimer structure was given in that work.



$$[\mathbf{3}]_{\text{active}} = ([\mathbf{3}_{RR}] + [\mathbf{3}_{SS}]) \quad K_{\text{eq}} = 4 = \frac{[\mathbf{3}_{RS}]^2}{[\mathbf{3}_{RR}][\mathbf{3}_{SS}]} \quad (2)$$

$$\text{rate} = k[\mathbf{1}][\text{Pr}_2^i\text{Zn}][\mathbf{3}]_{\text{active}} \quad (3)$$

Approximately equimolar ratios of **1** and  $\text{Pr}_2^i\text{Zn}$  were employed in the reactions carried out to develop this kinetic model. Intriguingly, we find in the current work that, for reactions employing  $[\text{Pr}_2^i\text{Zn}]$  and **1** in ratios other than stoichiometric, the reaction rate no longer obeys the rate law given by eq 3.

Figure 1 shows the results of four reactions carried out under a range of different substrate ratios (0.1 M **1**, 2–4 equiv of  $\text{Pr}_2^i\text{Zn}$ ) and different initial catalyst enantiomeric excess (10 mol % **2** compared to **1**, initial ee(**2**) = 0.06–0.97). As in our previous studies, reaction calorimetry was used to monitor rate continuously over the course of the reaction. The kinetic model corresponding to eq 3, which gave excellent agreement to the experimental data when the ratio of  $[\text{Pr}_2^i\text{Zn}]:[\mathbf{1}]$  was close to 1:1, is shown in Figure 1 as the dashed lines; clearly, that model does not provide an adequate description of the reaction kinetics at higher  $[\text{Pr}_2^i\text{Zn}]:[\mathbf{1}]$  ratios. Most importantly, the form of the experimental reaction rate profile was not altered by increases in the concentration of  $\text{Pr}_2^i\text{Zn}$  in the manner predicted by eq 3. Instead, the rate profile retains the form expected for the general autocatalytic reaction ( $\mathbf{A} + \mathbf{B} + \mathbf{C} \rightarrow \mathbf{C} + \mathbf{C}$ ) employing *stoichiometric* ratios of **A** and **B**.

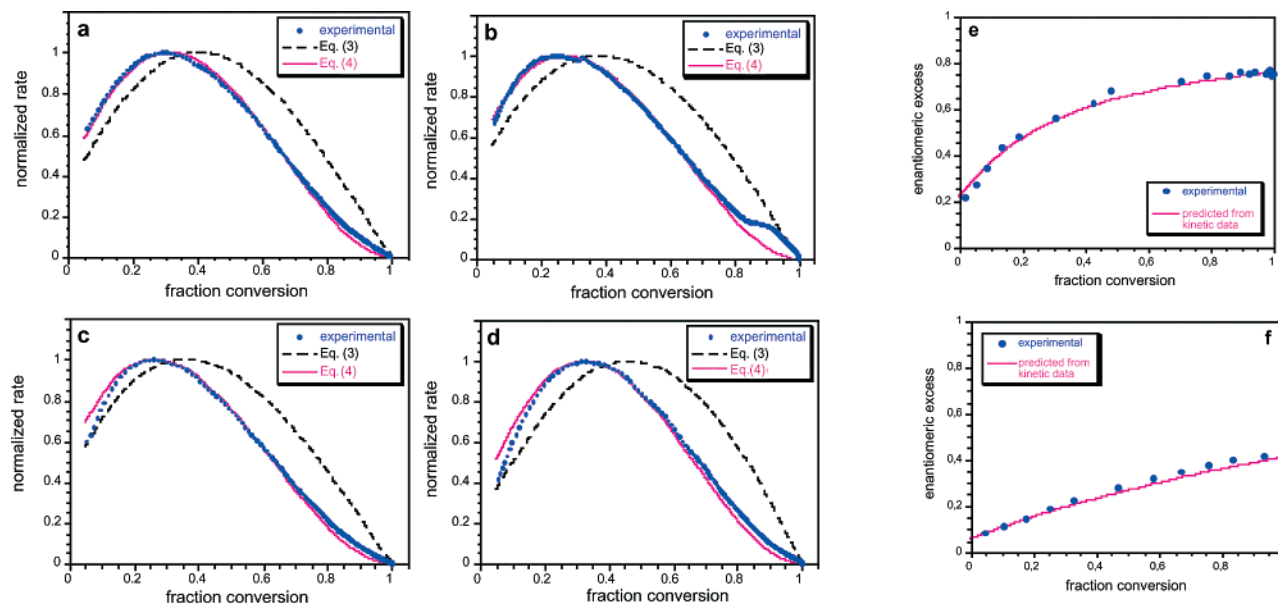
The simplest model which is consistent with both our current and former observations is a rate law which is second order in **1**, as given by eq 4:

$$\text{rate} = k'[\mathbf{1}][\mathbf{1}][\mathbf{3}]_{\text{active}} \quad (4)$$

Remarkably, as shown in Figure 1, eq 4 gives an excellent description of the reaction for a range of  $[\text{Pr}_2^i\text{Zn}]:[\mathbf{1}]$  ratios and different values for the initial enantiomeric excess of **2**. Figure 1 also shows that the amplification of product enantiomeric excess in experiments employing enantioimpure **2** is also accurately predicted by this kinetic model applied to the reaction rate data (eq 5):<sup>8</sup>

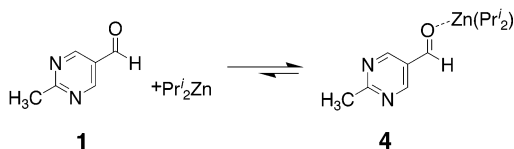
$$ee_{\text{dx}} = ee_0 \frac{[\mathbf{3}_{RR}] - [\mathbf{3}_{SS}]}{[\mathbf{3}_{RR}] + [\mathbf{3}_{SS}]}; \quad ee_{x+\text{dx}} = \frac{ee_x[\mathbf{2}] + ee_{\text{dx}} \frac{\text{dx}}{2} [\mathbf{1}]_0}{[\mathbf{2}] + \frac{\text{dx}}{2} [\mathbf{1}]_0} \quad (5)$$

<sup>†</sup> This work was first described as part of a Woodward Scholar Lecture, October 7, 2002.



**Figure 1.** Reaction rate (parts a–d) and enantiomeric excess (parts e–f) as a function of fraction conversion of **1** for the reaction shown in Scheme 1. Blue circles represent experimental data points; lines represent the kinetic models: dashed black lines, eq 3; solid pink lines, eq 4 (for rate, parts a–d) and eq 5 (for ee, parts e–f). Reaction progress was monitored using reaction calorimetry for reactions carried out in toluene at 298 K with  $[1]_0 = 0.1$  M and 10 mol % **2** as catalyst, with varying initial enantiomeric excess of **2** and equivalents  $\text{Pr}_2\text{Zn}$  as noted: (a)  $ee(2)_0 = 0.22$ , 1.8 equiv of  $\text{Pr}_2\text{Zn}$ ; (b)  $ee(2)_0 = 0.06$ , 2.0 equiv of  $\text{Pr}_2\text{Zn}$ . (c)  $ee(2)_0 = 0.97$ , 2.0 equiv of  $\text{Pr}_2\text{Zn}$ . (d)  $ee(2)_0 = 0.22$ , 3.6 equiv of  $\text{Pr}_2\text{Zn}$ . (e)  $ee(2)$  as a function of conversion for the reaction shown in (a). (f)  $ee(2)$  as a function of conversion for the reaction shown in (b).

A plausible chemical rationalization of the absence of  $[\text{Pr}_2\text{Zn}]$  in the rate law in eq 4 proposes the formation of a **1**– $\text{Pr}_2\text{Zn}$  complex prior to the alkyl transfer step, possibly a nascent Zn alkoxide species formed in a Lewis acid–base interaction (eq 6):



For an autocatalytic reaction between two molecules of **4** and the dimeric catalyst  $\mathbf{3}_{\text{active}}$ , the rate is given by eq 7.<sup>9</sup>

$$\text{rate} = k''[\mathbf{4}][\mathbf{4}][\mathbf{3}]_{\text{active}} \quad (7)$$

If the reaction shown in eq 6 is strongly driven toward the product **4**, then we can make the approximation that the concentration of **4** will be given simply by that of the limiting reagent, **1** (saturation kinetics in  $[\text{Pr}_2\text{Zn}]$ ). This substitution affords the rate law of eq 4 accurately describing the experimental data for both stoichiometric and nonstoichiometric ratios of **1** and  $\text{Pr}_2\text{Zn}$ .

The suggestion that two molecules of **4** interact with the dimeric catalyst  $\mathbf{3}_{\text{active}}$  points toward a *tetrameric* transition state. This is in notable contrast to the *trimeric* transition state that the rate expression given in eq 3 suggests.<sup>10</sup>

Tetrameric structures are well-known in reactions of dialkylzinc compounds with amino alcohols. A tetramer arising from the dimeric alkoxide catalyst and two nascent alkoxide monomers bears a resemblance to the “template–template” entities defining the “minimal systems” for self-replication developed by von Kiedrowski<sup>1a–b</sup> and others for nucleic acids,<sup>1a–c</sup> peptides,<sup>1e,f</sup> small organic molecules,<sup>1d</sup> and ribozyme<sup>1g</sup> autocatalytic systems. Failure to sustain autocatalysis has been noted in many of these cases due to self-poisoning by strong binding of the catalyst–product complex or by competition from the uncatalyzed reaction. Our studies

demonstrate that, unlike many of these examples, the Soai reaction is a template-directed self-replicating system which successfully maintains ideal exponential growth kinetics, and therefore high autocatalytic efficiency, over many turnovers. Further studies aimed at elucidating the details of the tetrameric transition state leading to this high autocatalytic efficiency are underway.

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- (8) Equation 5 describes the incremental change in enantiomeric excess,  $ee_{\text{dr}}$ , as a function of an incremental change in conversion,  $dx$  (see ref 6b).
- (9) The model can accommodate assembling the tetramer either in one trimolecular step or, perhaps more likely, in two sequential bimolecular steps with the second being rate-controlling.
- (10) The kinetic equations 3 and 7 suggest that the transition state is assembled from  $\mathbf{3}_{\text{active}}$ , originating from two molecules of the alkoxide **2'** plus (**1** +  $\text{Pr}_2\text{Zn}$ ) (eq 3, hence a trimer), or two molecules of **4** = (**1** +  $\text{Pr}_2\text{Zn}$ ) (eq 7, hence a tetramer).

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