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Mechanistic study of the Soai autocatalytic reaction informed by kinetic analysis

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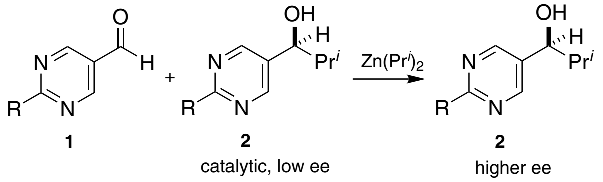
Abstract—Detailed kinetic studies of the Soai reaction affirm the basic mechanistic picture previously developed in kinetic, spectroscopic and molecular modelling studies, and also suggest that refinements to the proposed elementary reaction steps must be considered. The alkanol reaction product is driven strongly and without bias towards the formation of homochiral and heterochiral dimers. The reaction is catalyzed by only the homochiral dimers. Consideration of the kinetic profiles from reactions carried out with different initial dialkylzinc concentrations support a proposal for a tetrameric transition state, but further experimental work is required to delineate the nature of this species. The power of reaction calorimetry as a kinetic tool for discerning subtle effects of the shape of the kinetic profile is highlighted. The importance of combining kinetic evidence with spectroscopic and other characterization tools is emphasized.

1. Introduction

The origin of biological homochirality has intrigued scientists ever since the importance of L-amino acids and D-sugars was first recognized. In a theoretical paper, Frank showed that if one hand of a primitive asymmetric catalyst could act to replicate itself and, at the same time, act to suppress replication of its opposite enantiomer, this would provide a 'simple and sufficient life model' to explain how homochirality could have developed from an initial small imbalance of enantiomers.[1] Experimental confirmation of this theory came with Soai's discovery that the alcohol product of the alkylation of pyrimidyl aldehydes (Scheme 1) catalyzes its own production at a much greater rate than it does the production of its enantiomer.[2]



Scheme 1. Soai autocatalytic reaction.

Blackmond et al. and Brown et al. have carried out extensive studies of the mechanistic aspects of this reaction, both jointly[3] and separately.[4,5] This body of work has led to a coherent mechanistic model of the Soai reaction. A combination of in situ kinetic studies, detailed spectroscopic characterization of the catalyst resting state and molecular modelling of proposed solution species, have elucidated the following important features of this intriguing reaction system: (a) the alkanol product of the reaction is significantly driven towards dimerization; (b) heterochiral and homochiral dimers are formed stochastically, exhibiting approximately equal thermodynamic stability and (c) homochiral dimers are implicated as the active species in autocatalytic reactions in which product enantiomeric excess is amplified.

Subsequent kinetic studies by our group have suggested further complexities in the autocatalytic reaction mechanism outlined by this simple dimer model. Herein we discuss these observations and current mechanistic proposals.

2. Elucidation of the dimer model

2.1. Reaction calorimetry as a kinetic tool

Autocatalytic processes exhibit complex temporal reaction progress profiles, featuring time-dependent product

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selectivities and catalyst concentrations. One key to understanding such systems lies in finding accurate methods for analyzing the progress of these reactions. Mechanistic studies by our group focus on detailed reaction progress kinetic analysis using in situ tools that provide virtually continuous temporal rate profiles.[6] Our experimental technique of choice in many cases is reaction calorimetry.[7] This technique relies on the accurate measurement of the heat evolved or consumed when a chemical transformation occurs in the absence of other thermal effects. The energy characteristic of the transformation—the heat of reaction, ΔH_{rxn}—is a thermodynamic quantity serving as the proportionality constant between the evolved heat and the reaction rate (Eq. 1). The fractional heat evolution yields the fraction conversion of the limiting substrate (Eq. 2).[8]

$$q = \Delta H_{\mathrm{rxn}} \cdot \begin{pmatrix} \text{reaction} \\ \text{volume} \end{pmatrix} \cdot \text{rate} \tag{1}$$

$$\text{fraction conversion} = f(t) = f_{\mathrm{final}} \cdot \frac{\int_0^t q(t)\,\mathrm{d}t}{\int_0^{t(\mathrm{final})} q(t)\,\mathrm{d}t} \tag{2}$$

The primary data in a reaction monitored by reaction calorimetry are obtained as a kinetic profile of heat flow as a function of time. Figure 1a shows this for the Soai reaction carried out using equimolar substrate concentrations and 10 mol % alkanol catalyst present as enantiopure, racemic and 43% ee. These data may be converted to fraction conversion versus time using Eq. 2, as shown in Figure 1b, based on an independently obtained value for the final chemical conversion f_{final}. A third kinetic plot can be obtained by combining the first two plots. By removing time as an explicit variable, we obtained a plot of *normalized rate* (rate(t)/maximum rate) versus fraction conversion as in Figure 1c. Such a plot is called a '*graphical rate equation*'.[6] Normalization of the y-axis allows rapid visual comparison of the inflection points.

2.2. Kinetic model: equimolar substrate concentration

The wealth of information contained in these reaction progress profiles enabled us to propose a mechanistic model for the Soai reaction. Figure 1a shows that the maximum rate of the reaction carried out using enantiopure catalyst was double that of the racemic catalyst. Figure 1c shows that the maximum rate was attained at identical fraction conversion for these two reactions, while for the 43% ee catalyst the maximum rate was shifted by ca. 5% towards higher conversion. Note that neither of these features of the data can be easily extracted from the data plotted as fraction conversion versus time in Figure 1b, which represents the most commonly used type of kinetic profile. The importance of this point will be highlighted later.

The simplest model that accounts for these experimental observations dictates that the system consists predominantly of dimers *RR*, *SS*, *RS* formed from the alkanol products as in Eqs. 3–5, giving values of K_{homo} and K_{hetero} that are both very large (Eqs. 6 and 7). These dimers have approximately equal stability ($K_{\mathrm{dimer}} = 4$, Eq. 8).

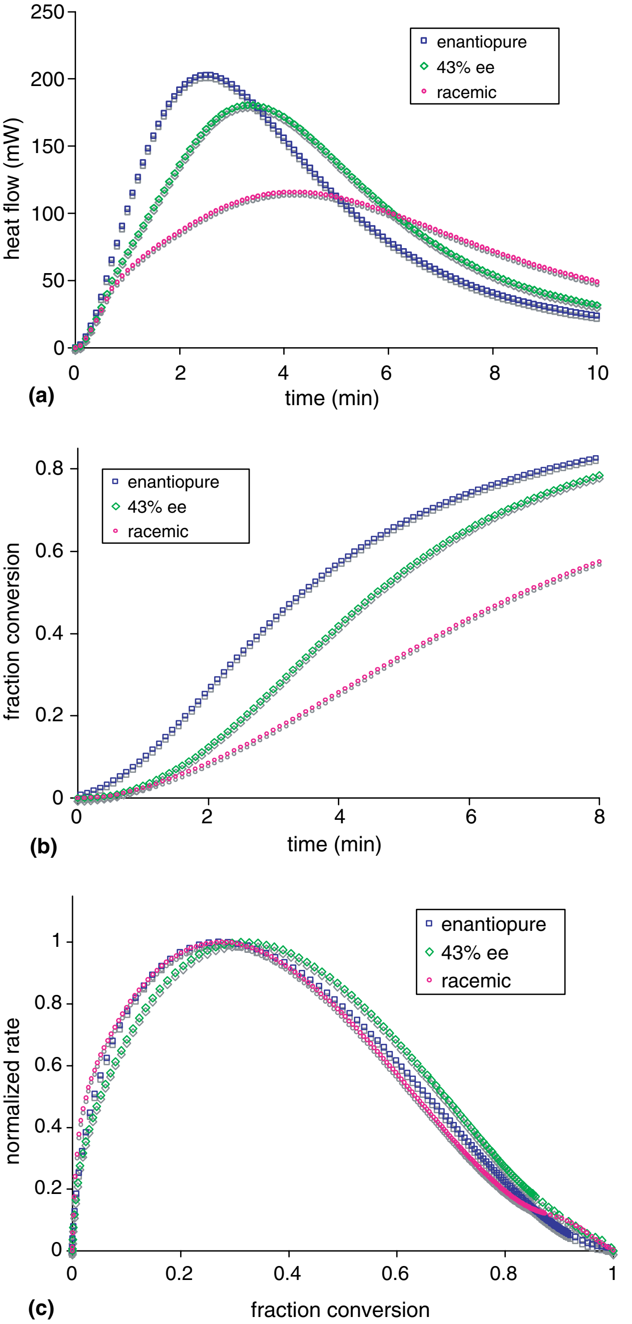

Figure 1. Reaction calorimetric monitoring of the Soai reaction with approximately equimolar [A] (0.18 M) and [Z] (0.20 M) and 10 mol % enantiopure, 43% ee and racemic alkanol **1** as catalyst. (a) Reaction heat flow versus time; (b) fraction conversion versus time; (c) normalized rate versus fraction conversion. Yield was quantitative in all three reactions.

Alkanol products *R* and *S* are formed from aldehyde A and dialkylzinc Z with dimers *RR* and *SS* as catalysts (Eqs. 9 and 10), while the heterochiral species *RS* is inactive. Kinetic modelling of the reaction rate data shown in Figure 1 provided quantitative support for this model, as is shown in Figure 2a. Further confirmation comes from the models's accurate prediction of the evolution of enantiomeric excess (Eq. 11) for reactions initiated with alkanol catalyst at different ee, a prediction based solely on the heat flow data.

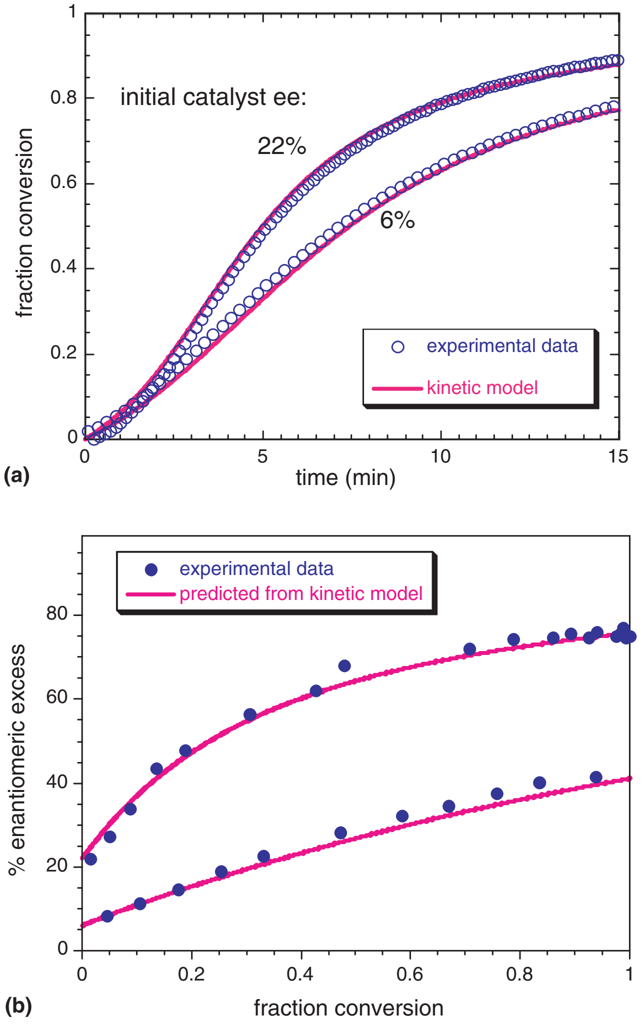

Figure 2. Comparison of experimental kinetic data and dimer model calculations for reactions at 22% and 6% initial catalyst enantiomeric excess. (a) Kinetic data and dimer model fit to Eqs. 3–10; (b) alkanol enantiomeric excess predicted from the kinetic data and Eq. 11 compared to that measured by HPLC. Initial concentrations are $[A] = 0.2$ M; $[Z] = 0.4$ M; catalyst 10 mol %. The yield was quantitative in both reactions.

$$R + R \overset{K_{\text{homo}}}{\leftrightarrows} RR \tag{3}$$

$$S + S \overset{K_{\text{homo}}}{\leftrightarrows} SS \tag{4}$$

$$R + S \overset{K_{\text{hetero}}}{\leftrightarrows} SR \tag{5}$$

$$K_{\text{homo}} = \frac{[RR]}{[R]^2} = \frac{[SS]}{[S]^2} \tag{6}$$

$$K_{\text{hetero}} = \frac{[SR]}{[R]\cdot[S]} \tag{7}$$

$$K_{\text{dimer}} = 4 = \left(\frac{K_{\text{hetero}}}{K_{\text{homo}}}\right)^2 = \frac{[SR]^2}{[RR]\cdot[SS]} \tag{8}$$

$$\mathrm{A} + \mathrm{Z} + RR \overset{k_{\text{cat}}}{\rightarrow} RR + R \tag{9}$$

$$\mathrm{A} + \mathrm{Z} + SS \overset{k_{\text{cat}}}{\rightarrow} SS + S \tag{10}$$

$$\text{ee}_{\text{prod}} = \frac{[RR] - [SS]}{[RR] + [SS] + [SR]} \tag{11}$$

2.3. Spectroscopic corroboration of the kinetic model

The stochastic distribution of dimer species predicted by the kinetic model was verified experimentally by ^{1}H NMR spectroscopic characterization of solutions of enantiopure and racemic alkanols.[3,5] Solutions of enantiopure alkanol revealed only homochiral dimer species. Racemic mixtures revealed heterochiral and homochiral dimers present in a 52:48 ratio, within experimental error of the 50:50 ratio predicted by the kinetic model with $K_{\text{dimer}} = 4$. The veracity of a model developed from kinetic investigations alone requires confirmation from other methods, since a unique fit to a single mechanism is unlikely. Spectroscopic and structural identification of species predicted by a kinetic model can add significant weight to a mechanistic proposal and may help to eliminate possibilities. In particular, the critical observations that dimer species dominate and are formed in a stochastic distribution must be taken into account in any mechanistic treatment of this reaction. This important point has been neglected in several recent studies of the Soai reaction that proposed alternative mechanisms based on kinetic modelling alone.[9–11]

2.4. Implications of the shape of the kinetic profile

Further information may be extracted from these autocatalytic reaction data, when they are plotted in the form of the 'graphical rate equation' in Figure 1c. An autocatalytic reaction between two substrates A and Z can exhibit two theoretical limiting kinetic profiles depending on the relative initial concentrations of the two substrates. Written in terms of fraction conversion, the rate expression for the case of equimolar $[A]_0$ and $[Z]_0$ is given by Eq. 12, which is overall third-order kinetics (second order in substrate conversion, *f*, and first order in [cat]). Eq. 13 shows the rate expression for the case where the concentration of Z is large enough to give pseudo-zero-order kinetics in [Z], reducing the global kinetics to overall second order. Figure 3 shows how the shape of the kinetic profile changes from one limiting case to the other. The inflection point—the value of conversion where the rising reaction rate changes

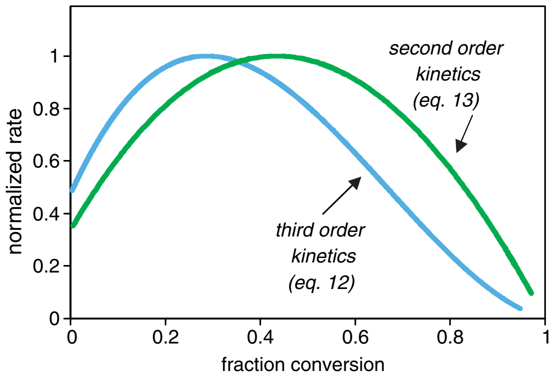

Figure 3. Comparison of theoretical autocatalytic kinetic profiles for an autocatalytic reaction (A + Z + cat) with 1 mol % initial catalyst concentration under the limiting cases of equimolar substrate concentrations (0.1 M, Eq. 12) and an initial 10-fold excess in [Z] (pseudo-zero-order kinetics in [Z], Eq. 13).

to a falling rate—shifts to higher conversion as the initial concentration $[Z]_0$ increases. When the reaction becomes pseudo-zero order in [Z], the rate exhibits overall second-order kinetics and the shape shifts towards a symmetric parabola. The shape of the rate profile and the position of the rate maximum also depend on the initial catalyst concentration, shifting to higher conversion at lower initial catalyst concentration.

$$[Z]_0 = [A]_0: \quad \text{rate} = k \cdot [A]_0 \cdot [Z]_0 \cdot (1-f)^2 \cdot [\text{cat}] \tag{12}$$

$$[Z]_0 \gg [A]_0: \quad \text{rate} = k \cdot [A]_0 \cdot [Z]_0 \cdot (1-f) \cdot [\text{cat}] \tag{13}$$

The curves in Figure 1c clearly indicate overall third-order kinetics, as was confirmed by the model fit in Figure 2a to the third-order rate equations 9 and 10.

3. Kinetic studies: non-equimolar concentrations

Our initial kinetic studies on the Soai reaction were carried out using equimolar aldehyde and dialkylzinc substrate concentrations. We next undertook further studies to expand the range of conditions investigated. Figure 4 shows experimental results for fraction conversion versus time in reactions carried out using 2 and 4 equiv of Z. The inset to the figure shows that the kinetic model derived in Eqs. 3–11 predicts that the reaction rate should be sensitive to increasing [Z].

The phenomenon of zero-order kinetics in a substrate, such as that observed in the reactions shown in Figure 4, is most often be rationalized under ‘pseudo-zero-order’ conditions, as in Eq. 13, or under conditions of ‘saturation kinetics’, where very strong binding of Z to the catalyst causes the system to be impervious to changes in [Z]. In either case, the overall observed autocatalytic reaction order is predicted to decrease form third order, as in Eq. 12, to second order, as in Eq. 13, along with a shift in the shape of the kinetic profile towards a parabolic profile with rate maximum approaching 50% conversion.

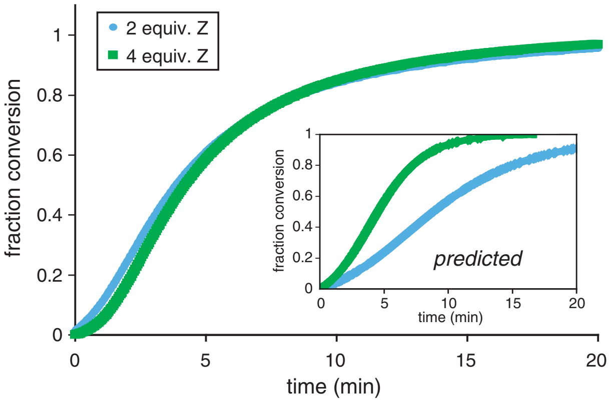

Figure 4. Experimental kinetic profiles for the Soai reaction with 10 mol % catalyst and either 2 or 4 equiv of $(i\text{-Pr})_2Zn$ (Z). Inset: predicted rate profiles for the reaction according to the kinetic model of Eqs. 3–11 developed for equimolar A and Z concentrations. 10 mol % catalyst; [A] = 0.1 M. Yield was quantitative in both reactions.

Intriguingly, we found that the rate maxima for the data in Figure 4 did not show such a shift towards higher conversion as [Z] increased; the data clearly continue to exhibit the profile of an overall *third-order* autocatalytic reaction. This is shown in Figure 5 where the data for reactions in Figure 4 carried out using 2 and 4 equiv show *identical profiles* when plotted as the ‘graphical rate equation’ of normalized rate versus fraction conversion. Figure 6 confirms that our experimental data show no shift in the inflection point conversion for reactions using up to 7.4 equiv Z compared to the significant theoretically predicted upward shift of nearly a factor of two.

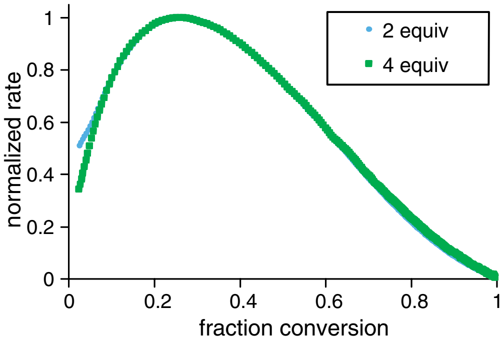

Figure 5. Experimental kinetic profiles for the Soai reaction of Figure 4 at 2 and 4 equiv Z, plotted as the graphical rate equation of normalized rate versus fraction conversion.

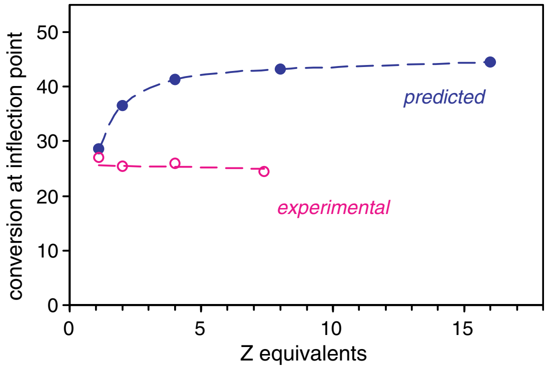

Figure 6. Predicted values for conversion at the rate inflection point as a function of the number of Z equivalents according to the dimer model of Eqs. 3–11 (filled blue circles). Experimental values given as open magenta circles.

Thus, paradoxidically, even as the reaction carried out at higher equivalents of Z appears to lose its dependence on [Z], at the same time the reaction profile does not show the expected decrease in overall reaction order that should accompany such a limiting case. This paradox can be rationalized by suggesting that instead of a dependence on both [A] and [Z], the reaction rate law in fact exhibits a *second-order dependence* on aldehyde concentration, as give by Eq. 14. Under the equimolar conditions employed in our initial studies, this rate law is identical to that shown in Eq. 12 with $[A]_0 = [Z]_0$.

$$\text{rate} = k \cdot [A]_0^2 \cdot (1 - f)^2 \cdot [\text{cat}] \qquad (14)$$

3.1. Tetramer model

Eq. 14 provides a means to rationalize the mathematical form of the kinetic profiles obtained under reaction conditions where [Z] is in excess, and experimental rate data were shown to give an excellent fit to Eq. 14.[4b] However, our aim is to understand the experimental result from a chemical and physical perspective. What mechanistic meaning can we ascribe to the autocatalytic Soai reaction exhibiting overall third-order kinetics, resulting from second-order kinetics in the prochiral aldehyde and first-order kinetics in the dimeric homochiral catalyst? Such a rate law implies that two aldehyde molecules are involved in the transition state along with the homochiral dimeric catalyst. Considering that the dimer catalyst is formed from two alkanol products that themselves originated from the reaction between Z and A, the observed kinetics point towards a tetrameric 'four A' model for the transition state: two A molecules that may be thought of as nascent product alkanols and two A molecules derived from alkanol products that have combined to form the dimeric catalyst.

3.2. Nature of the reactive components

What sort of species might we envisage assembling with the homochiral dimer into such a tetrameric transition state? The first proposal we entertained was a Lewis-acid adduct between aldehyde C=O and dialkylzinc (species 'AZ').[4b] The observed kinetics could be rationalized if such an interaction was driven strongly towards the AZ adduct such that its concentration dominated over that of the free aldehyde as the limiting substrate. The observed kinetics could be rationalized if two such AZ species 'docked' with the catalyst dimer in a way that the second binding event was rate limiting. However, NMR studies by Brown et al.[5b] indicated that the A–Z binding is not strong enough to give the overall zero-order kinetics in Z required to produce the observed kinetic profiles. Such a proposal cannot be considered viable in light of the spectroscopic evidence.

Other mechanistic clues arise from the NMR studies of Brown and co-workers. They observed that significant interaction occurs between Z and the catalyst dimer species, possibly between zinc and the pyrimidyl nitrogen atoms. A model in which two aldehyde molecules bind successively to a Z-saturated dimer catalyst could be invoked to rationalize the observed kinetic behaviour. Sequential aldehyde binding, with the second binding event being rate limiting, could account for stereoselective production of two new alkanol species that then undergo rapid and stochastic formation of dimers. Further kinetic and spectroscopic investigations are required to test this and any other potential mechanistic hypotheses. Any such tetramer model faces significant steric requirements that must be rationalized.[12] As was pointed out by Brown,[5b] any proposed mechanism must be able to account for all of the kinetic, spectroscopic and structural evidence assembled for this intriguing reaction system.

4. Conclusions

Detailed kinetic studies of the Soai reaction affirm the basic mechanistic picture previously developed in kinetic, spectroscopic and molecular modelling studies, but suggest refinements to the proposed elementary reaction steps must be considered. The reaction is catalyzed by homochiral dimers of the product alkanol, which is driven strongly and without bias towards formation of homochiral and heterochiral dimers. Consideration of the kinetic profiles from reactions carried out with different initial dialkylzinc concentrations tentatively support a proposal for a tetrameric transition state, but further experimental work is required to delineate the nature of this species. The power of reaction calorimetry as a kinetic tool for discerning subtle effects of the shape of the kinetic profile is highlighted. The importance of combining kinetic evidence with spectroscopic and other characterization tools is emphasized.

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