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Rationalization of Anomalous Nonlinear Effects in the Alkylation of Substituted Benzaldehydes

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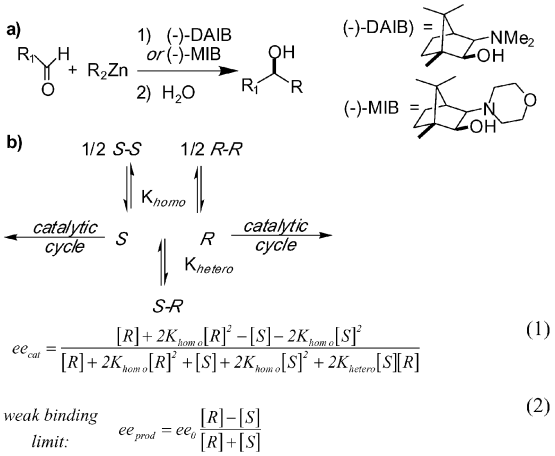
Since Kagan's pioneering studies[1] of nonlinear effects of catalyst enantiopurity on product enantiomeric excess, observations of this phenomenon have become an important diagnostic tool in mechanistic studies of asymmetric reactions.[2] Such an observation is usually taken as an indication that dimeric or higher-order species are formed in the system, either as the catalytic species itself or in equilibrium with monomeric catalysts. Modifications of these models have also been proposed,[2c] and a central theme is the attribution of asymmetric amplification to the presence of a heterochiral dimeric species which is more stable than the homochiral dimer, or less active, or both.

One system which exhibits striking nonlinear effects is the nucleophilic alkylation of carbonyl groups by dialkylzinc reagents using chiral amino alcohol catalysts such as dimethylamino isoborneol (DAIB)[3,4] or its morpholino variant MIB[5,6] (Scheme 1a). Noyori and co-workers have carried out extensive mechanistic investigations of these reactions. They showed that the amino alcohol reacts with the alkylzinc reagent to produce a monomeric tricoordinate Zn catalyst species (Scheme 1b, *R* and *S*) in equilibrium with dimeric complexes (see Supporting Information for proposed structures of *R*−*R*, *S*−*S*, and *S*−*R*) in which the Zn is four-coordinate. Their detailed kinetic model predicts trends in the product enantioselectivity as a function of a range of reaction variables, including K_{hetero}:K_{homo}, and substrate binding strength.

Recently, however, Walsh and co-workers[6] observed that reactions of benzaldehydes with electron-donating substituents on the aromatic ring exhibited a more significant nonlinear effect in these reactions than did electron-withdrawing substituents. These results are in constrast to Noyori's model, and the present paper demonstrates how a modification to the Noyori model can rationalize these observations. This work highlights the substrate-dependence of the catalyst composition and demonstrates that catalytic species must be considered within the context of the particular reaction under study.

The equilibrated catalyst mixture shown in Scheme 1b will exhibit relative proportions of monomeric and dimeric species dictated by the relative magnitudes of the dimerization equilibrium constants K_{homo} and K_{hetero}. The catalyst enantiomeric excess ee_{cat} is defined by the total concentrations of [*R*] and [*S*] ligands added to the system, as given by eq 1. Since only the monomer species act as active catalysts, the product ee for a catalytic reaction using nonenantiopure catalyst, ee_{prod}, is given by eq 2, where ee_0 is the product ee for the enantiopure case (the terminology "weak binding limit" will be discussed below).[7] A nonlinear effect arises because ee_{cat} is not proportional to ee_{prod}.

Scheme 1



$$\text{ee}_{\text{cat}} = \frac{[R] + 2K_{\text{homo}}[R]^2 - [S] - 2K_{\text{homo}}[S]^2}{[R] + 2K_{\text{homo}}[R]^2 + [S] + 2K_{\text{homo}}[S]^2 + 2K_{\text{hetero}}[S][R]} \quad (1)$$

$$\underset{\text{limit:}}{\text{weak binding}}\ \text{ee}_{\text{prod}} = \text{ee}_0\frac{[R] - [S]}{[R] + [S]} \quad (2)$$

A strongly binding substrate added to this equilibrated catalyst mixture may occupy a large fraction of the free catalyst *R* and *S*. Noyori's model predicts that this will result in an adjustment in the relative monomer/dimer concentrations in Scheme 1b, as the reaction network strives to maintain the equilibria dictated by K_{homo} and K_{hetero}. In the limiting case, *all* of the dimer species *R*−*R*, *S*−*S*, and *S*−*R* will be pulled into the catalytic cycle. As a result, the enantiomeric excess of the *active* catalyst will equal the ee of the ligand employed, and no nonlinear effect will be observed.

The Noyori model assumes that the effect of substrate binding is instantaneous: the monomer/dimer system shifts from its original equilibrium composition in the absence of a strong binding substrate to a new equilibrium composition *immediately* upon introduction of the substrate to the system. However, if the system response to the perturbation caused by substrate binding is not timely compared to the rate of reaction, the product ee may reflect a nonequilibrium monomer/dimer partitioning. In cases of significant asymmetric amplification where K_{hetero} is much greater than K_{homo}, it may be suggested that dissociation of the heterochiral dimer occurs very slowly, if at all, over the time scale of the catalytic reaction.

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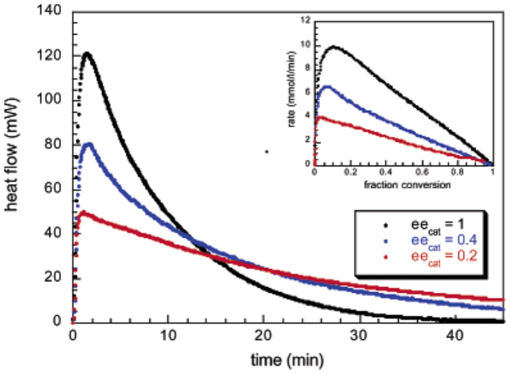

Figure 1. Reaction heat flow vs time for the alkylation of *p*-(trifluoromethyl)benzaldehyde (0.1 M) with Et_2Zn (0.28 M) using 1.9 mol % MIB of varying enantiopurity at 298 K in toluene: black: 100% ee (−)-MIB; blue: 40% ee MIB; red: 20% ee MIB. Inset shows rate vs fraction conversion.

Blackmond recently discussed theoretical models for systems exhibiting nonlinear effects in which the Curtin−Hammett condition for equilibrium exchange between species is not met.[2c] A limiting case of strong substrate binding may be envisioned where *none* of the heterochiral dimer dissociates while *all* of the homochiral dimer enters the catalytic cycle via dissociation to the monomer. In this strong binding limit, the enantiomeric excess of the reaction product for the reaction using any nonenantiopure catalyst mixture will be given by eq 3. Equation 2, which may be considered as giving the product ee for the limit of weak substrate binding, may be compared with eq 3 to reveal that a greater asymmetric amplification will be achieved for the strong binding limit, as was observed in the Walsh study.[6] Reaction rates may also be predicted for the weak and strong binding limits as given by eqs 4 and 5, where r_0 is the rate expected for the enantiopure catalyst $[R]_0$.[7]

$$\text{strong binding limit: } ee_{prod} = ee_0 \frac{([R] + 2K_{homo}[R]^2) - ([S] + 2K_{homo}[S]^2)}{([R] + 2K_{homo}[R]^2) + ([S] + 2K_{homo}[S]^2)} \quad (3)$$

$$\text{strong binding limit: } \frac{r}{r_0} = \frac{([R] + 2K_{homo}[R]^2 + [S] + 2K_{homo}[S]^2)}{([R]_0 + 2K_{homo}[R]_0^2)} \quad (4)$$

$$\text{weak binding limit: } \frac{r}{r_0} = \frac{([R] + [S])}{[R]_0} \quad (5)$$

Thus, experimental rate and ee data may combined to test the predictions of eqs 2−5 for weak and strong substrate binding. Reaction calorimetry[5b,8] was used to measure rates for a series of reactions of substituted benzaldehydes with diethylzinc using the amino alcohol MIB of varying enantiopurity. Figure 1 shows the reaction heat flow curves for the reaction using *p*-(trifluoromethyl)-benzaldehyde for three different ee_{cat}. The inset of the figure shows the data plotted as reaction rate (mM^{-1} min^1) versus fraction conversion, where the slopes of the curves give the relative reaction rates. Product ee's were also measured for these reactions, and both rate and ee were then compared to the kinetic model as given in eqs 2−5 (Figure 2). The experimental data for both rate and ee fall approximately within the boundaries for weak and strong binding limits when the ratio $K_{hetero}/K_{homo} = 30$.

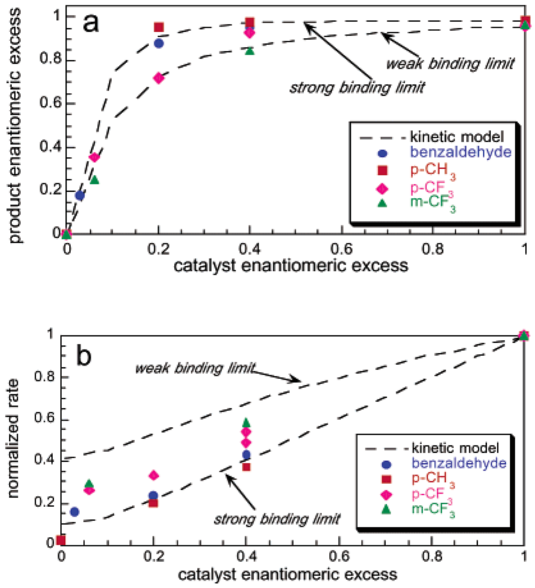

Figure 2. Experimental ee_{prod} (a) and reaction rate (b) data for substituted benzaldehydes. Weak binding limits for ee and rate are given by eqs 2 and 5, respectively. Strong binding limits for ee and rate are given by eqs 3 and 4, respectively. (●) benzaldehyde; (■) *p*-tolualdehyde; (◆) *p*-(trifluoromethyl)benzaldaldehyde; (▲) *m*-(trifluoromethyl)benzaldehyde.

Thus, this model rationalizes the apparently anomalous results observed by Walsh and co-workers through a simple extension of the Noyori model to allow for nonthermodynamically controlled monomer/dimer partitioning. This work also highlights an important point[4c] concerning nonlinear effects in systems exhibiting this type of dynamic monomer/dimer interaction: catalyst composition may be a function of the substrate properties. While in many cases the observation of nonlinear effects in a reaction is used as a diagnostic probe of the reaction mechanism, perturbation of the catalyst by the reaction itself may introduce additional complexity into such a mechanistic tool.

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Supporting Information Available: Details of the model calculations determining the strong and weak binding limits and experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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