Asymmetric autocatalysis: Novel structures, novel mechanism?

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The amplifying asymmetric autocatalysis discovered by Soai and coworkers in 1995 does not fit easily into the extensively investigated framework of organozinc alkylation of aldehydes. In that case the catalyst is a monomeric Zn chelate that functions as both Lewis acid and Lewis base, permitting the simultaneous coordination of both dialkylzinc reagent and aldehyde reactant. By contrast, the Soai reactants are rigid γ-aminoaldehydes that cannot function as mononuclear chelates. Structural and computational evidence for a binuclear resting state is presented, and the energetics of mono-, di-, tri-, and tetrameric species accessible to the reacting system have been computed.

Since the early successes of asymmetric catalysis in hydrogenation and epoxidation, much progress has been made. Despite the recent surge in organocatalysis§ (1), the majority of catalytic reactions in organic chemistry that lead to significant enantiomer excess involve a ligated metal. The ligand plays a critical role in stereoselection by defining the space accessible to reactants and reagents.

The approach that has found most favor in catalyst design is to form a stable chelate at the reactive metal center. This almost invariably involves two distinct heteroatoms bonding to the metal to form a five-, six-, or seven-membered ring. Thousands of enantiomerically pure diphosphines, hundreds of diols or aminoalcohols, and every other conceivable combination of the common heteroatoms has been used. Examples of effective asymmetric induction for almost all of the common catalytic processes of organic synthesis are on hand. Only recently has the predominance of chelating ligands been challenged by carefully designed undentate ligands (2, 3), redeveloping an early strand (4), but this work does not seriously undermine the effectiveness of basic principles of chelate catalyst synthesis. These principles are as follows.

• Identify a metal complex system capable of catalyzing the desired reaction.
• Define a suitable cis-chelating ligand.
• Ensure that the resulting complex is rigid and has an asymmetric distribution of accessible space around the metal.

Every conceivable means of introducing chirality – central, axial and planar – has been used. It has produced catalysts whose function can be understood simply in terms of space-filling: generally speaking, the spatial distribution of the stereochemically defining groups on the ligand is similar in the ground state and transition state. This “rigid scaffold” approach to catalysis provides selectivities based on differential steric repulsion, and attractive catalyst–reactant interactions are relatively rare. This is in contrast to enzymes, where selectivity arises largely through fine-tuning of such attractive forces. In enzymatic mechanisms, the ground and transition states can have very different structures. The inherent flexibility of the peptide permits many different residues, to engage in the stabilization of the substrate, the organization of water molecules, and the orientation of biological reagents (5–8).

Because the stereoselectivities in biology are often exquisite rather than merely very good, it is clear that the chemist still has much to learn.

Nature can utilize more than metal center to enhance the power of a catalyst, or to access pathways that are otherwise impossible (9). By contrast, binuclear chemical catalysis is sporadic (10, 11). General principles that can assist in the design of binuclear catalysts are lacking. This ought to be a challenging area for future research effort; the binuclear assembly can engage functional groups at considerably greater distances than the mononuclear entity and thus have distinct substrate specificity. Because chelation of the reactant is frequently as important an exponent of selectivity as chelation of the ligand, this also impinges on bimolecular catalysis.

Background: Catalytic Asymmetric Alkylation with Organozinc Complexes

The alkylation of carbonyl compounds, especially aldehydes, with dialkylzinc reagents fails completely in the absence of a ligand but is made into an effective asymmetric synthetic procedure by the addition of small quantities of a β-aminoalcohol (12). The mechanism of reaction and the origin of enantioselectivity are well understood. The amino-alcohol undergoes a simple protolytic reaction with the dialkylzinc and forms a chelate complex that has a propensity to dimerize (Fig. 1). The dimeric resting state needs to dissociate...
because only the monomer is reactive in catalysis. The catalytic monomer functions by acting as a template both for the carbonyl compound through zinc coordination, and the dialkylzinc through oxygen coordination. After the critical bond making step the new alkoxide dissociates and is removed from the reacting system by oligomerization. By working with scalemic amino-alcohol, it is observed that the enantiomeric purity of the product is substantially higher than the enantiomeric purity of the catalyst. The reason for this is well understood; the catalyst dimer acts as a reservoir from which the reactive monomer is liberated. When the heterochiral (racemic) dimer is more tightly bound than the homochiral dimer, the reservoir will have a higher proportion of the less dominant enantiomer than the remaining pool of monomer. Hence, the enantiomer excess (ee) of the available catalyst is enhanced, often strikingly so. A catalyst with 10% ee can give rise to a product with >90% ee (13–15). The reaction remains the classic example of an amplifying nonlinear effect. As Kagan realized, amplification when selective association of monomeric species is absent requires that the active catalyst is a dimer or oligomer (16–18).

**The Pathway to Autocatalysis**

The catalyst above is a β-aminoalcohol that becomes a zinc alkoxide on activation by R₂Zn, and the product is also a zinc alkoxide. This triggered consideration of the possibility of autocatalysis, first demonstrated by Soai in the alkylation of simple pyridinals (19). But when autocatalysis is accompanied by an amplifying nonlinear effect, the consequence is remarkable. An initial catalyst with a very small ee can form product with high ee; extrapolating backwards, measurable chirality in product can be created from undetectable levels of enantiomeric purity. His ensuing work was spectacularly successful in realizing this, but the structural requirements he discovered were remarkable. Instead of encouraging chelation, the reactants precluded it. The rigid geometric relationship between the amine and aldehyde, together with the demonstration that the catalytic reaction is specific to self-reproduction, indicates that both functionalities must be intimately involved in autocatalysis (20–24). The work frequently involves multistage reactions in which the enantiomer excess ratchets upwards in each step (Fig. 2).

This brilliant demonstration of a novel stereochemical phenomenon was unaccompanied by insights into its mechanism, providing the cue for our own involvement 4 years later. Although Soai’s autocatalysis involved only iPr₂Zn, and the described mechanistic work on asymmetric alkylation only Me₂Zn or Et₂Zn, a common transition-state structure was assumed at the outset. As an initial foray, a comparison of the NMR spectroscopic properties of racemic and enantiomerically pure zinc alkoxides derived from the simple pyrimidinal A was planned. Blackmond’s interest in a calorimetric approach to the kinetics of autocatalysis led to a fruitful collaboration on the problem. Analysis of the results derived by microcalorimetry revealed that the relative ac-

**Fig. 2.** The basis of Soai’s amplifying asymmetric autocatalysis.

**Fig. 3.** The successive binding of dimethylzinc, alkylation, and further binding of dimethylzinc starting with aldehyde A. Energies are quoted in kcal mol⁻¹.
tivity of racemic and enantiomerically pure Zn alkoxide catalysts remained constant throughout the course of autocatalysis, with the latter about twice as reactive as the former. Plots of normalized rate vs. fraction conversion were superimposable. In the scalemic case, the activity of the catalyst increased over time as a consequence of amplifying autocatalysis. These observations are consistent with a dimeric resting state that does not discriminate between homochiral and heterochiral forms. The observed amplification requires that only the homochiral complex is the active catalyst, directly or indirectly (25).

Questions immediately arise as to the structure of the catalytic resting state; NMR provided the answers. The first experiments were carried out in THF, which does not encourage autocatalysis but permitted us to demonstrate that the same conclusions applied in toluene, whose basic entity is the square dimer, but in rapid reversible equilibrium with other associated species (26).

Computation to Reveal Accessible Organozinc Structures

The purpose of computational work was to define feasible oligomeric structures accessible to autocatalysis. To limit computer time, much was based on Me2Zn and 2-methylpyrimidin-5-yl. Calculations were carried out by using DFT at the B3LYP function level with a 6–31G* basis set for all atoms. In many cases the conclusions were verified through further calculations on iPr2Zn-derived species, including the 2-TMSalkynyl compounds used in the NMR studies.

Monomeric Species. It was desirable to probe ZnMe2 binding to the aldehyde but Zn alkoxide monomer D (Fig. 3). All of the basic sites associate with the zinc reagent. In complexation to the aldehyde, N-coordination is significantly preferred over O-coordination. The minimized structures are unremarkable aside from the O-alkoxide complex E, a bridging agostic alkyl, which is favored over the alternative N-coordinated structure.

Dimeric Species. Two distinct low-energy dimer structures are revealed, the square dimer G being preferred over the macrocyclic form H by several kcal-mol⁻¹ (1 cal = 4.18 J). Its homochiral and heterochiral forms are close in enthalpy. This is not surprising because the stereogenic centers of the alkoxide are not affected by dimerization, and steric differences seem negligible. Assuming the reliability of these calculations in the real experimental world, it is reasonable evidence that the macrocyclic dimer is not the true catalyst, and indeed no evidence for this or related structures has ever been obtained from extensive NMR studies. The pattern of binding of ZnMe2 to Zn alkoxide dimers follows the monomer precedent. The lowest-energy state in O-coordination of the Zn alkyl to the Zn alkoxide is a C-bridging structure, J. Again, this is lower in energy than the N-Zn coordinated isomer I (Fig. 4). In accord, NMR shows rapid migration of isopropyl groups between the distinct Zn environments in a mixture of Zn alkoxide dimer and ZnR₂ reagent in toluene.

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\text{Zn-Zn} = 7.5 \text{ Å} \quad \text{Zn-Zn} = 5 \text{ Å}
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Fig. 4. The two low-energy dimer structures, and the two types of zinc alkyl binding to the square dimer G. Energies are quoted relative to the summed energies of [2 aldehyde plus 2 or 3 molecules of ZnMe₂].

Fig. 5. Intrazinc distances in the transoid (0° dihedral angle as defined) and cisoid Zn complexes (180° dihedral angle as defined).
overall computed gas-phase enthalpy of reaction (Zn alkyl plus aldehyde to Zn dimer) is 47.7 kcal/mol, compared to the experimental value of 40.2 kcal/mol in toluene (27). The enthalpy of alkylation is comparable to the enthalpy of dimerization of the resulting Zn alkoxide.

Association between an aldehyde and Zn alkyl has a defined geometry, supported by numerous crystal structures of Lewis acid-aldehyde complexes in which the dihedral angle H—C═O—M is close to 0° (28, 29). In the autocatalytic case, the pyrimidine nitrogen must also be associated with a different Zn site with a defined geometry enforced by the N lone-pair vector. With these constraints, the distance between the two Zn atoms is simply measured and is in the region of 7.5 Å. If this “standard model” is followed, it limits the possible transition-state structures that can be derived from accessible Zn alkoxide dimers. Alternatively, the less favorable syn-conformer of the aldehyde Zn complex could be involved, although this has never been invoked previously in explanations of the Lewis acid catalyzed reactions of aldehydes (Fig. 5).

Trimeric Species. The initial product of the reaction aldehyde plus dimeric catalyst plus zinc alkyl is a trimer. The bidentate O, N-system allows three structurally distinct types of trimer, and two were examined; the 18-membered macrocyclic trimer, which is remote from the dimeric ground state, was not scrutinized in detail. The simple [Zn-O]2 structure may exist in monocyclic or bicyclic forms K or L; the latter is substantially more stable and can be regarded as the first step in building a polymeric [Zn-O]n ladder. Of course, neither structure involves binding of the pyrimidine nitrogen to zinc. The macrobicyclic isomer M, in which the pyrimidine is actively engaged, is within 1 kcal-mol⁻¹ of bicyclic form. Indeed, a further association between the free pyrimidine and Zn in this macrocyclic form gives a macrotricyclic structure N, the most stable trimeric species found (Fig. 6). The bicyclic isomer L concludes a conceptually simple pathway from dimeric catalyst to product, but the pyrimidine nitrogens are not coordinated to zinc. Problems remain, however, in defining the precise reaction pathway, because further Zn-N association involving the reactant N and catalyst Zn is required to create the bifunctional array needed for enantioselectivity and substrate specificity.

Tetrameric Species. Further possibilities arise at the tetramer level, considering structures based on the square dimer as template. Note here the recent claim that asymmetric autocatalysis involves a tetrameric transition state, with two aldehydes and two dialkylzincs associated to the Zn alkoxide dimer (30). At this level of structural complexity, some simplification is needed. Only the basic ring connectivities are shown in Fig. 7, with the full structures based on square or macrocyclic subunits indicated in Fig. 3. There are four distinct ways in which tetrameric
structures can be directly assembled either from a dimer and two monomers, or a pair of dimers. Of course the [Zn-O]₄ cubic structure O is well preceded (31–34) and is stable. The stepladder isomer P, which lacks one pair of Zn-O associations compared to the cube, is less stable by 19 kcal mol⁻¹. There are two further tetramers that may be constructed from square dimers, the first by pairwise N-Zn binding to form a bridging macrocycle Q. This isomer is 15 kcal mol⁻¹ less stable than the cube. Taking the process involved in its construction further by making first one and then both remaining N-Zn links ultimately produces a barrel-like structure of C₂ symmetry R. The computed −Δ_H of this structure is within 1 kcal mol⁻¹ of the cube. This structure cannot escape from severe transannular interactions, however, with two H–H contacts below 2 Å. If this is reflected in the “real-world” molecule, it will at the very least inhibit the final N-Zn closure and promote formation of the unsymmetrical three-stave barrel S, which is, however, computed to be 5.6 kcal mol⁻¹ less stable. Consideration of these structures permits speculation on the autocatalysis pathway and possible transition states. The one shown is based on a trimeric catalyst that has the macrobicyclic structure M, and leads to the barrel R.

Gas-phase calculations refer to a desolvated state likely to exaggerate the importance of coordination and thus underestimate the significance of steric repulsion. It is notable that the low-temperature ¹H NMR of the Zn alkoxide in toluene provides evidence for a highly dynamic and unsymmetrical tetrameric species, formed by further association of the dimers. That is not consistent if the predominant product of association is the cubic tetramer but would be more consistent with an open barrel form S (Fig. 7).

Conclusions

The NMR experiments indicate a ground-state structure lacking the N-Zn binding that bifunctional autocatalysis requires. Computation reveals stable trimeric and tetrameric structures incorporating this crucial feature, which are therefore candidates for the initial product that must exist immediately after alkyl delivery. This is generally true, because a self-replicating catalytic reaction of an n-mer must first produce an (n + 1)-mer. No significant difference between homo- and heterochiral aggregates was observed, so that the high stereoselectivity observed in autocatalysis is not revealed in the ground states of reactants, catalyst, or probable initial products. Minor differences were observed between the preferred structures of some Me₂Zn- and iPr₂Zn-derived intermediates, but the basic conclusions are unaltered. Because asymmetric autocatalysis works only with iPr₂Zn and not for a range of closely related zinc reagents, it indicates a finely tuned blend of reactivity and steric effects (35). A diverse range of structures is energetically accessible at this limited level of association, contrasting with the simplicity of the chelate monomer involved in conventional zinc asymmetric alkylations. This enhances the challenge associated with understanding bi- and multimetallic catalysts, and increases the complexity of structural and mechanistic analysis immensely. At the trimer and tetramer levels, but not at the dimer level, structures incorporating the required macrocyclic entity are of encouragingly low energy. As a corollary, the synthesis of ligands for which bi- or oligometallic coordination is enforced will prove to be a fertile territory for future exploration in asymmetric catalysis. Attempting such syntheses is not an area for the timid, because as yet there is no clear compass to guide navigation.