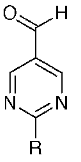
Zinc Autocatalysts

Solution Structure and Reagent Binding of the Zinc Alkoxide Catalyst in the Soai Asymmetric Autocatalytic Reaction**

Ilya D. Gridnev, Jörg M. Serafimov, and John M. Brown**

The remarkable zinc alkylation reactions discovered and developed by Soai and co-workers remain the sole example of amplifying asymmetric autocatalysis, even after more than seven years.[1,2] The phenomenon is confined to rigid γ-aminoaldehydes, especially **1**, and uniquely limited to diisopropylzinc. An O-Zn-N monomeric chelate structure, common to all such structurally characterized catalysts for asymmetric zinc alkylation reactions, cannot operate in this case.[3] The efficiency of the autocatalysis experiment is affected by substituents at the 2-position of the pyrimidine ring, with alkynyl groups being optimum.[4] Understanding the structural and mechanistic principles of this reaction will permit the rational development of new examples of autocatalysis and a better understanding of spontaneous asymmetric synthesis in this system.[5]

In earlier joint work we demonstrated that the resting state is a dimeric zinc alkoxide, which is active only in its homochiral form.[6] Initial NMR spectroscopy experiments in C_7D_8 revealed the dynamic nature of the system. More easily interpretable spectra were obtained from **2a** and **2b** with $i\mathrm{Pr}_2\mathrm{Zn}$ in $[\mathrm{D}_8]$THF or $[\mathrm{D}_7]$DMF, the solutions being more stable in $[\mathrm{D}_8]$THF. In solution in THF, however, turnover is slow and amplifying autocatalysis does not occur, which is in keeping with the inhibiting effect of this strongly Lewis basic solvent.[7] The statistical distribution between homo- and heterochiral associates of **3a** or **3b** was verified in $[\mathrm{D}_8]$THF (Figure 1). A further key observation made from the ^{1}H NMR spectra defines the structure in solution. For enantiomerically pure **3b**, four distinct doublets are observed for the isopropyl methyl groups, indicating that both $\mathrm{ZnOCHCH}\mathit{Me}_2$ and $\mathrm{ZnCH}\mathit{Me}_2$ are diastereotopic (Figure 1a). For racemic **3b**, which contains equal proportions of the homo- and heterochiral dimers, three additional doublets arising from methyl groups are seen (Figure 1b), with the $\mathrm{ZnCH}\mathit{Me}_2$ pair now isochronous in all ^{1}H and ^{13}C NMR spectra over a wide temperature range (Figure 1). This result demonstrates that the heterochiral form has a symmetry plane that encompasses C-Zn····Zn-C. The results also fit uniquely with the structures of the homochiral and heterochiral dimers being (*R*,*R*)-**4b** and (*R*,*S*)-**4b**. These diastereomeric structures have been verified by B3LYP DFT calculations on model compounds with a full 6-31G* basis set and shown to be comparable in enthalpy,[8] whereas the previously postulated macrocyclic structure **5** has been shown to be significantly less favorable (Figure 2).[9] A third possible dimeric structural type **6** of permissible symmetry is ruled out by the ^{1}H NMR spectra of a solution of (*R*)-**2b** in C_7D_8 treated with 0.5 equivalents of $i\mathrm{Pr}_2\mathrm{Zn}$ which indicate an equal mixture of (*R*,*R*)-**4b** and (*R*)-**2b**. There is good precedent for the postulated $\{\mathrm{ZnO}\}_2$ square dimer form.[10]



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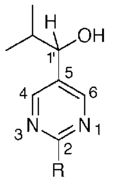

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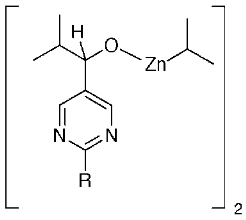

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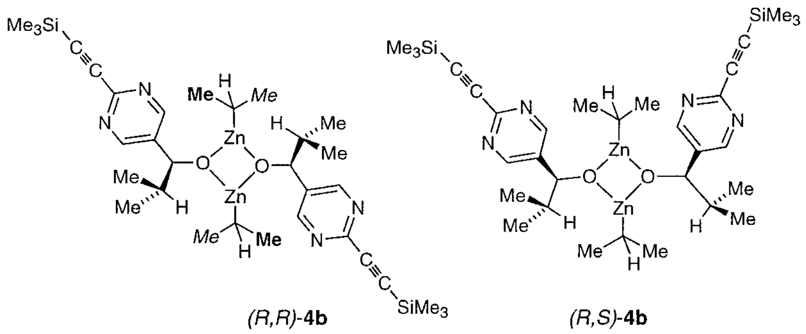
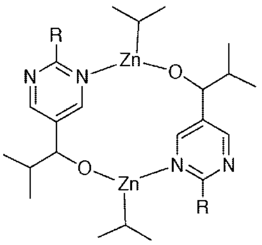
a R = Me, **b** R = C≡CSiMe$_3$, **c** R = Ph



(*R*,*R*)-**4b** (*R*,*S*)-**4b**



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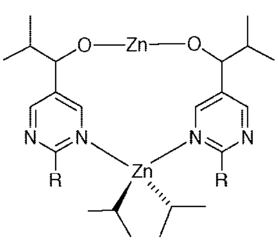

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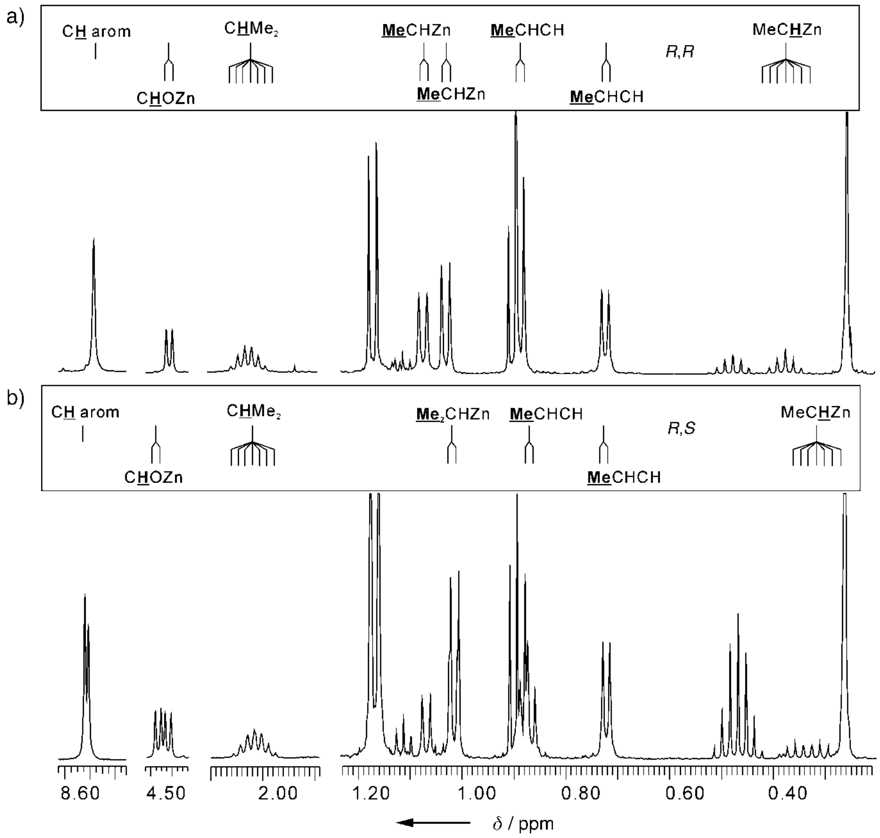


Figure 1. ^{1}H NMR spectra of a) (*R,R*)-**3b** and b) (*R,S*)-**3b** in [D$_8$]THF at ambient temperature, 500 MHz. In the 1.5 to 0.5 ppm region, the upper trace of the homochiral dimmer shows both pairs of magnetically inequivalent CHMe$_2$ groups. The lower trace (a 1:1 equilibrium mixture of homo- and heterochiral dimers) additionally shows the equivalent ZnCHMe$_2$ at 1.02 ppm (overlapping) and inequivalent CHCHMe$_2$ groups at $\delta = 0.88$ and 0.72 ppm (overlapping). Co-produced propane is at $\delta = 0.90$ ppm.

Encouraged by these results, we reverted to NMR analyses in toluene. Solutions of zinc alkoxides in C_7D_8 have a tendency to precipitate,[11] which is alleviated by the addition of excess *i*Pr$_2$Zn. The general features of the NMR spectra in [D$_8$]THF are reproduced in toluene, whilst reagent binding is more pronounced (see below). Specifically, the distinct resonance signals of the diastereotopic *i*PrCH and *i*PrZn methyl groups are observed in the homochiral form, and the signal for the *i*PrCH methyl groups is also observed in the heterochiral form, whereas the signal for the *i*PrZn methyl groups is broadened at ambient temperature. The proportions of homo- and heterochiral forms in the racemate are again quite comparable in C_7D_8. The indicated structure is supported by numerous NOESY spectra; the absence of close contact between the 2-H atom of the phenyl substituent and the *i*PrCH or *i*PrZn moieties of **3c** in both C_7D_8 and C_4D_8O is especially telling. For dimer **4a** prepared from aldehyde **1a** without added catalyst **2a,** two broadened singlets of similar intensity were observed at 298 K in the 8.5 ppm region, corresponding to the homo- and heterochiral forms (52:48). On increasing the temperature these broaden and then coalesce at 348 K. Line-shape analysis of the aryl protons over the range 313–353 K and extrapolation of the slope of ln*k*(exchange) to ambient temperature indicates that the half-life of an individual dimer molecule with respect to *R*↔*S* exchange is in the region of 15 s at 293 K.[12]

In a dilute solution (ca. 0.04 M) of (*R*,*R*)-**4b**, prepared from the alcohol by reaction with a modest excess of zinc reagent (0.08 M) in C_7D_8, all the ^{1}H NMR signals associated with the pyrimidine entity broaden markedly on cooling. The oligomeric species formed at low temperature must have low symmetry, and distinct environments for the pyrimidine nitrogen atoms of individual rings, since 4-H and 6-H are inequivalent.[13] The broad ^{1}H NMR signals observed for alkoxide **4b** in the ArH region under static conditions (that is, the probe is not spun) at 273 K is identical to that which develops when the autocatalytic reaction between aldehyde **1b** and *i*Pr$_2$Zn is followed in situ.

The magnetic equivalence of the two aryl hydrogen atoms in the ambient-temperature ^{1}H NMR spectrum of all the mixtures of reactant **1** or alkoxide **4** with added *i*Pr$_2$Zn requires that any N-association is dynamic. To investigate this further, the synthesis of ^{15}N-labeled pyrimidinal **1d** was carried out (Scheme 1).[14] Association of reactant **1d** with varying *i*Pr$_2$Zn concentration was conveniently studied at 213 K by ^{13}C, ^{1}H, and ^{15}N NMR spectroscopy, the latter by means of heteronuclear multiple-bond correlation (HMBC) spectra; at this temperature the aldehyde reacted only slowly with *i*Pr$_2$Zn. These spectra consistently demonstrate binding to *i*Pr$_2$Zn by N coordination. The association constant of 5.8 M^{-1} derived from the ^{1}H NMR spectra is fully consistent with the value of 5.6 M^{-1} obtained by analysis of ^{15}N chemical shift data, in which shielding of up to 15.5 ppm is observed at high zinc concentration.[15] The alkynyl ^{13}C NMR chemical shifts are also markedly affected by zinc binding; increased zinc alkyl concentration causes shielding of C1′, and deshielding of C2′ as well as deshielding of C4. The results all demonstrate rapidly reversible association of *i*Pr$_2$Zn with a pyrimidine nitrogen atom of **1d** without evident involvement of the carbonyl group.[16]

Synthesis of labeled enantiomerically pure alcohol **2d** (Scheme 1) from aldehyde **1d** enabled further zinc-binding studies. Informative ^{15}N HMBC spectra were only obtained at 308 K in C_7D_8 for the zinc alkoxide dimer **4d**, and the progressive shielding of the ^{15}N signal with increasing *i*Pr$_2$Zn concentration indicated association. A quantitative assay was obtained from the substantial ^{13}C chemical shift change of the alkynyl carbon atom signals of alkoxide **4b** on addition of *i*Pr$_2$Zn, and were interpreted as being the result of N coordination. The association constant is 4.6 M^{-1}. Similar

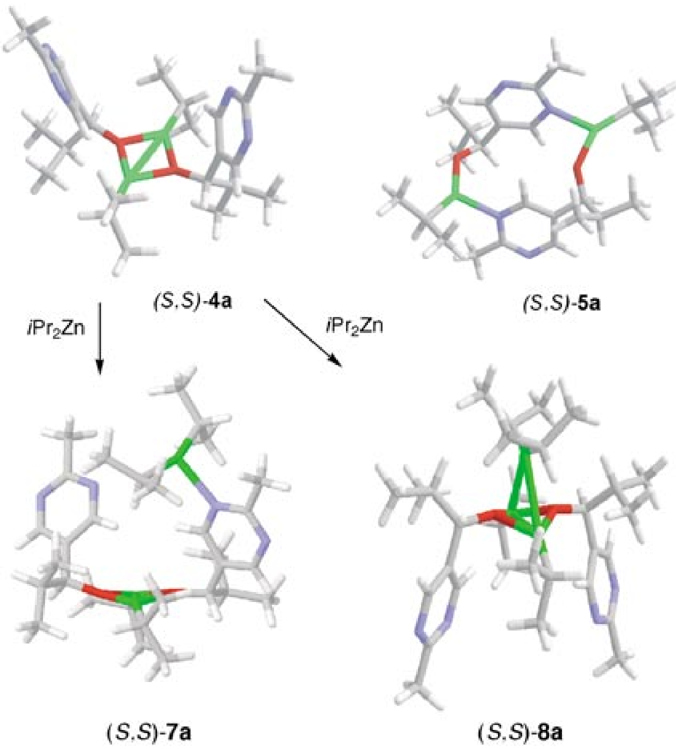
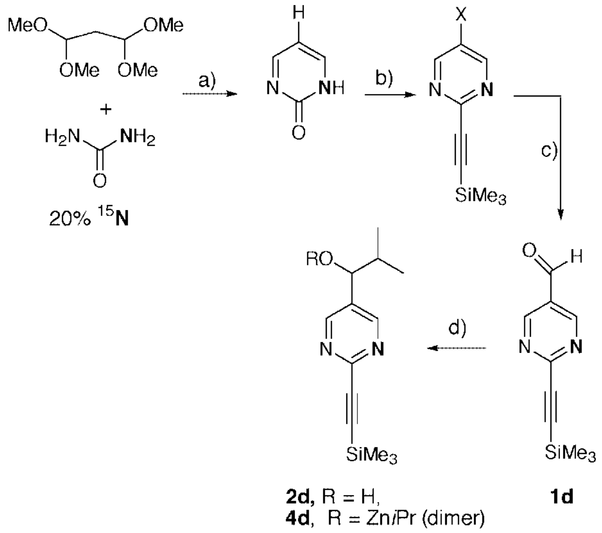


Figure 2. DFT minimized structures of square dimer **4a** and macrocyclic dimer **5a**. For formation of **4a** from monomer, $\Delta H_0 = -38.4$ kcal mol^{-1}, and correspondingly for **5a**, $\Delta H_0 = -29.7$ kcal mol^{-1}. $i\mathrm{Pr_2Zn}$-bound minimized structures **7a** and **8a**, respectively, have binding enthalpies of -10.2 (N–Zn) and -6.5 kcal mol^{-1} (O–Zn–O′).



Scheme 1. The synthesis of ^{15}N-labeled pyrimidines. a) reference [3a], b–d) references [3b,c].

changes were seen in [D$_8$]THF, but in this solvent the association constant is only 0.4 M^{-1}. THF does not function as a solvent for amplifying autocatalysis and the lower association constant probably reflects solvent coordination to zinc.[17]

Allowing for the substantial temperature difference, these results indicate that the zinc alkoxide dimer **4** binds more strongly than the aldehyde **1** to $i\mathrm{Pr_2Zn}$, and that both involve predominant N coordination. Both the C*H* and C*H*$_3$ resonance signals of the $i\mathrm{Pr_2Zn}$ are shielded to an extent that depends on the degree of complexation. Under turnover conditions at 0 °C, these resonance signals change in a manner that indicates increased zinc complexation ($\delta_{\mathrm{CH}} = 0.670$ ppm, $\delta_{\mathrm{CH_3}} = 1.274$ ppm at 25 % reaction, $\delta_{\mathrm{CH}} = 0.704$ ppm, $\delta_{\mathrm{CH_3}} = 1.294$ ppm at 80 %). More intriguingly, the alkoxide dimer acts as a chiral shift reagent towards $i\mathrm{Pr_2Zn}$ with clear temperature-dependent separation of the diastereotopic ZnCHMeMe′ groups of the reagent (Figure 3).

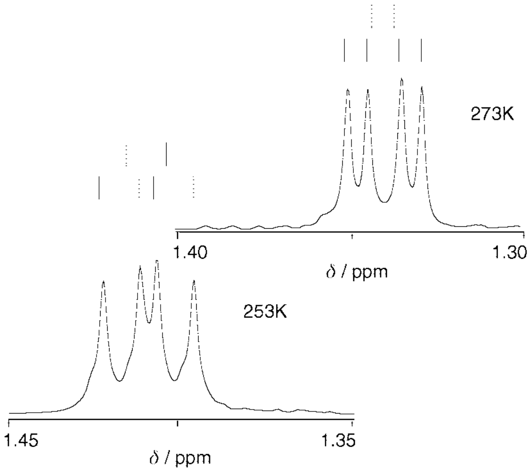


Figure 3. Detail of the ^{1}H NMR spectrum of zinc alkoxide **3b** (0.08 M) in $\mathrm{C_7D_8}$ showing the $\mathrm{CH_3}$ resonance signal of excess $i\mathrm{Pr_2Zn}$ (0.04 M), shifted from its normal position of $\delta = 1.20$ ppm (at 273 K in the absence of **3b**).

In the presence of excess $i\mathrm{Pr_2Zn}$ the EXSY spectrum of alkoxide dimer **4b** in both THF and toluene shows rapid exchange between zinc-bound isopropyl groups in the reagent and dimer. The reaction occurs for both racemic and homochiral dimers with comparable facility. In toluene the rate increases with increasing $i\mathrm{Pr_2Zn}$ concentration, but in THF saturation occurs above 0.2 M reagent. This observation is consistent with the trigonal, coordinatively unsaturated zinc sites proposed in structure **4b**. In THF, desolvation may be necessary before the formally trigonally coordinated zinc site is exposed to the reagent.[17] The proposed pathway is supported by computational studies on the $i\mathrm{Pr_2Zn}$ complexes of **4a** (Figure 2). Of the two defined energy minima, the bridged (O-ZnR$_2$-O) structure **8a** is favorably disposed for alkyl exchange. The nitrogen-bonded isomer **7a** is somewhat more stable.

What is the relevance of these studies to autocatalysis? We postulate a $\{\mathrm{Zn{-}O}\}_2$ square structure for the resting state, which has a significant affinity for the complexation of $i\mathrm{Pr_2Zn}$. Under typical autocatalytic turnover conditions (0 °C–25 °C, 0.05–0.2 M $i\mathrm{Pr_2Zn}$),[1b] both the dimer and its zinc-association complex are present. Any mechanism that seeks to explain the reaction is required to take this into account. The aesthetically appealing possibility of a tetrameric transition state is encompassed by these studies, but the strong aldehyde–ZnR$_2$ binding postulated in the model proposed by Buono and Blackmond,[18] remains unsupported by in situ observations.

Experimental Section

1d: The ^{15}N labeled 2-hydroxypyrimidine hydrochloride was prepared in 77% yield by condensation of ^{15}N-urea (10%, Aldrich) with 1,1,3,3-tetramethoxypropane.[14] Further steps paralleled those for the unlabeled compound (see Scheme 1).

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[18] F. Buono, D. G. Blackmond, *J. Am. Chem. Soc.* **2003**, *125*, 8978–8979. This recent publication from Buono and Blackmond raised the intriguing possibility that the limiting transition state for autocatalysis is tetrameric. To interpret the kinetics at high [Zn]/[A], (A = aldehyde) it was suggested that strong binding of iPr$_2$Zn to the required aldehyde, 2-methylpyrimidine-5-aldehyde, might occur to produce a single coherent entity. NMR spectroscopic examination of the aldehyde/iPr$_2$Zn system in C_7D_8 at 298 K does show minor upfield movement of ^{1}H and ^{13}C resonances of the aldehyde in both the spectra at high zinc concentration. The association is weak, as exemplified by the ^{13}C shift change for C4 in **1** ($\delta = -2.59$ ppm at 0.33 M [Zn], 213 K) with that in 2-methylpyrimidine-5-aldehyde ($\delta = -0.34$ ppm at 1.21 M [Zn], 298 K). Other changes are also in line with weak association.