Asymmetric Autocatalysis

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Unraveling the Mechanism of the Soai Asymmetric Autocatalytic Reaction by First-Principles Calculations: Induction and Amplification of Chirality by Self-Assembly of Hexamolecular Complexes

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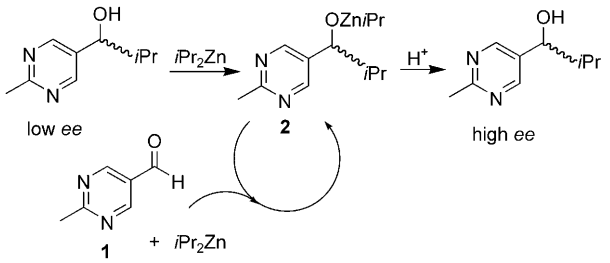
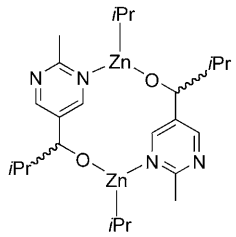
The Soai reaction, that is, the addition of diisopropylzinc to aromatic aldehydes (see Scheme 1 for an example), is the sole



Scheme 1. Chiral amplification by the Soai autocatalytic reaction.

case of amplifying asymmetric autocatalysis reported to date.[1] Its behavior stands out as a paradigm for absolute asymmetric synthesis and the origin of homochirality in nature,[2] yet the underlying mechanism remains elusive, thus prompting us to investigate the reaction by computational methods.[3]

The reaction is confined to the addition of [iPr$_2$Zn] to aromatic aldehydes with at least one pyridinic nitrogen in the γ-position, but the presence of a suitable substituent in the δ-position, such as a methyl or a *tert*-butylethynyl group, is also important to reach the highest levels of chiral amplification. Blackmond and co-workers reported that the rate with the racemic catalyst is approximately half that with the enantiopure catalyst throughout the reaction, and ascribed this fact to the catalytic activity of homochiral dimers which are in statistical equilibrium with an inactive heterochiral dimer.[2e,4] They also found that the reaction rate is second-order in aldehyde, first-order in the active dimers, and independent of the concentration of [iPr$_2$Zn].[4c,d] The initially proposed structure for the dimers, **3**, [4a] was successively refuted in favor of the structure **4**, detected by NMR spectroscopy,[5] although it should be noted that a catalytic intermediate is not necessarily the most abundant species.



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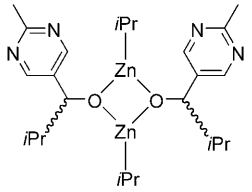

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Since all the structural features noted above are essential for the success of the reaction, a meaningful computational study does require that all of them are retained in the calculations. Owing to the large size of the systems involved, energies of both ground and transition states (TSs) were calculated at the B3LYP/6-31G(d)//HF/3-21G(d) level of theory and corrected for ZPVEs.[6]

At the onset, we made the reasonable working assumption that all the association processes occurring in solution are fast and reversible whereas the transfer of the isopropyl group from zinc to aldehyde is irreversible and rate limiting. The detected rate law indicates that in the TS there are two molecules each of **1** and **2**, but the assumption above implies that at least one molecule of [iPr$_2$Zn] must also be present. The high level of chiral induction detected suggests the fast self-assembly of an ordered complex in which the reactants are held in close proximity before the isopropyl transfer takes place. After several unsuccessful attempts to model a meaningful assembly made of two molecules of **1**, two of **2**, and one of [iPr$_2$Zn], we passed to examine assemblies made of two molecules each of **1**, **2**, and [iPr$_2$Zn]. At this level of complexity, we found an appealing homochiral structure, dubbed **7**-(*R*,*anti*)$_2$, with two symmetrically equivalent sides. For each side, the *anti* notation refers to the orientation of the isopropyl group bound to the *R* carbon relative to the neighbouring [iPr$_2$Zn], as emphasized by the bond torsion in bold in the structure *Anti*.

The structure provides a straightforward explanation not only for the chiral induction but also for the critical role of isopropyl groups and γ-pyridinic nitrogen atoms. Indeed, the *anti* arrangement makes one of the zinc-bound isopropyl groups (that on the right in *Anti*) correctly oriented to attack the *Re* face of the aldehyde so as to reproduce the chirality of the *R* catalyst acting as template. The *syn* orientation, in the front side of the structure dubbed **7**-*R*,*anti*-*R*,*syn*, which is predisposed for isopropyl attack at the "wrong" *Si* face, suffers from steric interactions among the isopropyl groups, as illustrated by the structure *Syn*.

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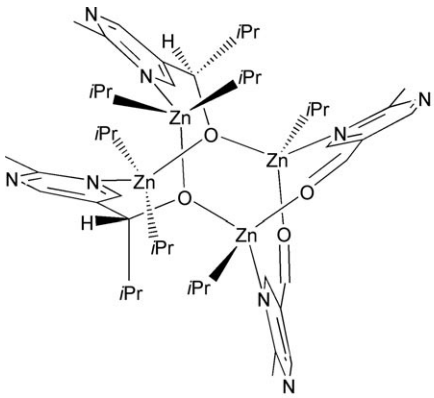
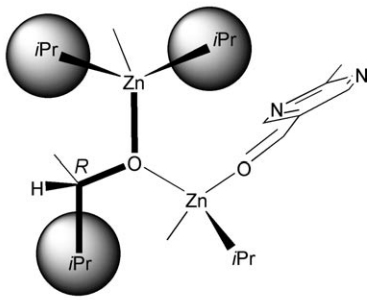
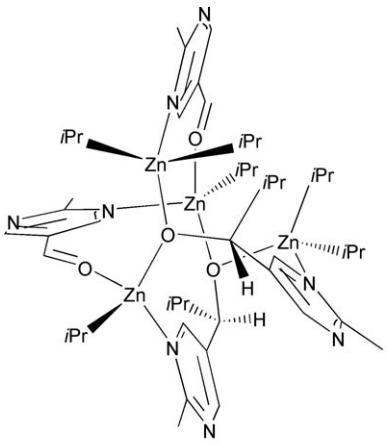


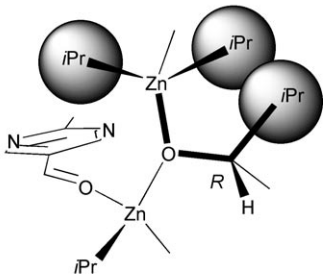
7-R_2



Anti



7-*R,anti-R,syn*



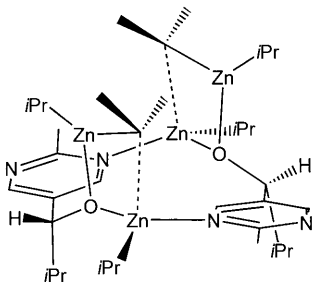
Syn

This explanation is confirmed by calculations showing that **7**-(*R*,*anti*)$_2$ is 4.6 kcal mol^{-1} more stable than **7**-*R*,*anti-R*,*syn*. Even more important is the fact that the *anti* arrangement smoothly evolves toward the corresponding TS, whereas we were unable to locate the TS structure from the severely distorted *syn* arrangement. While the role of the γ-pyridinic nitrogen atoms is essential for the self-assembly process, the steric hindrance of the isopropyl groups is critical for addressing the assembly toward an *anti*, *anti* arrangement: a smaller group would fail to reach this goal whereas a larger group would introduce so much strain to destabilize even the less crowded *anti*, *anti* assemblies.

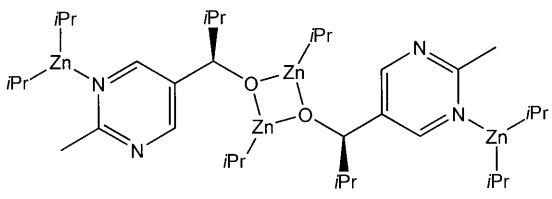
Owing to the above considerations, only assemblies with the *anti*, *anti* arrangement are considered in the following; in particular we studied the reaction paths of the homochiral **7**-(*R*,*anti*)$_2$ and the heterochiral **7**-*R*,*anti-S*,*anti* whose structure can be simply obtained from that of **7**-*R*,*anti-R*,*syn* by inverting the configuration of the *R* carbon involved in the *syn* arrangement. Inspection of the structure reveals that **7**-*R*,*anti-S*,*anti* is not a *meso* form because of a chiral axis of *P* configuration passing through the two alkoxylic oxygen atoms. Accordingly it should be indicated more properly as **7**-*R*,*anti-S*,*anti-P*. From hereon, the assemblies **7**-(*R*,*anti*)$_2$ and **7**-*R*,*anti-S*,*anti-P* will be referred to simply as **7**-R_2 and **7**-*RSP*, respectively.

Before considering the evolution of the complexes **7**-R_2 and **7**-*RSP* towards the products, let us take one step back along the reaction coordinate and consider their formation from reactants. The detected zero-order kinetics in [*i*Pr$_2$Zn] suggests that either the aldehyde or the dimeric catalyst is saturated by [*i*Pr$_2$Zn]. Accordingly, we examined the possible structures resulting from the binding of one molecule of [*i*Pr$_2$Zn] to **1**, and two molecules of [*i*Pr$_2$Zn] to the homochiral and heterochiral forms of both **3** and **4**. The most stable structures of the adducts involve binding of [*i*Pr$_2$Zn] to the nitrogen of **1**, *anti* to the carbonyl oxygen (binding energy (BE) = −5.9 kcal mol^{-1}); binding of two molecules of [*i*Pr$_2$Zn] to the oxygen atoms of **3** and forming isopropyl bridges with adjacent zinc atoms as illustrated in structure **5**-R_2 (average BE per [*i*Pr$_2$Zn] = −10.3 kcal mol^{-1}); binding of two [*i*Pr$_2$Zn] to the nitrogen atoms of **4** as illustrated in the structure **6**-R_2 (average BE per [*i*Pr$_2$Zn] = −7.5 kcal mol^{-1}). The results indicate that [*i*Pr$_2$Zn] preferentially binds to the dimers rather than to the aldehyde, in agreement with NMR spectroscopic binding studies in solution.[5]

The energies of homochiral and heterochiral dimers, **5**-R_2 and **5**-*RS*, are very similar (ΔE = 0.3 kcal mol^{-1}), as well as those of **6**-R_2 and **6**-*RS* (ΔE = −0.03 kcal mol^{-1}), thus homochiral dimers are virtually in statistical equilibrium with the corresponding heterochiral one. Although dimers of the type **6** are about 4 kcal mol^{-1} more stable than dimers of the type **5**, the type



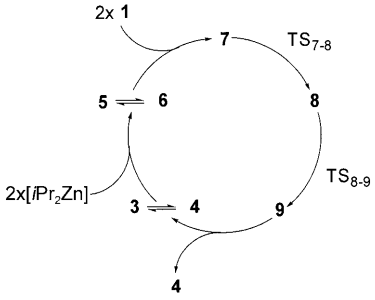
5-R_2



6-R_2

5 dimers structurally appear as more likely precursors of the TSs, as they resemble the corresponding assemblies **7**. Then the question may arise: "What is the actual structure of the zinc-saturated catalyst?" As pointed out by Hammett for an analogous case, as long as the equilibrium between dimers **5** and **6** is fast, "the question is irrelevant to any presently observable phenomena".[7]

To make the remaining discussion easier to follow, the complete catalytic cycle, characterizing both the homochiral and heterochiral paths, is anticipated in Scheme 2. Note that all the steps are reversible apart from those indicated by the corresponding TSs above the arrows.

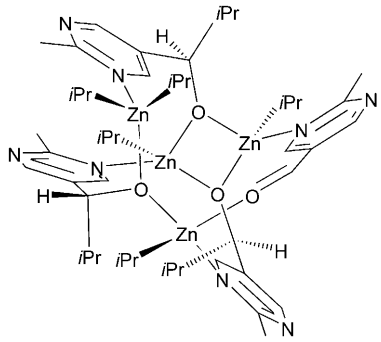


Scheme 2. Catalytic cycle for the Soai reaction.

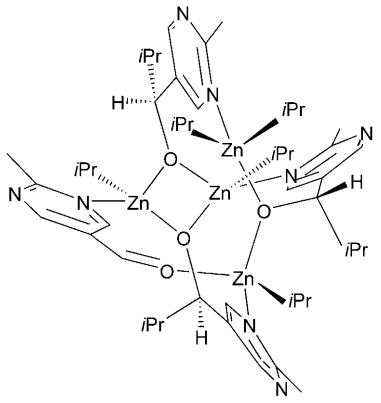
TSs for the isopropyl transfer occurring at one of the sides of the assemblies **7** (TS_{7-8}) and yielding **8**-R_3 from **7**-R_2, and either **8**-R_2S or its enantiomer **8**-RS_2 from **7**-*RSP* were successfully located. All the TSs have a rather early structure with little elongation of the Zn–C bond relative to the *i*Pr group that is being transferred (from 2.06 Å to 2.20–2.23 Å). Owing to the presence of the chiral axis in **7**-*RSP*, the TSs leading to the enantiomeric **8**-R_2S and **8**-RS_2 are diastereomeric, the former being lower in energy by as much as 6.2 kcal mol^{-1}. Accordingly it can be concluded that **7**-*RSP* virtually yields **8**-R_2S only.[8] Most interestingly, the TS leading to **8**-R_3 is 2.9 kcal mol^{-1} lower in energy than that leading to **8**-R_2S. Considering that the corresponding reactants, that is, the aldehyde and either the homochiral or heterochiral zinc-saturated catalyst, have practically the same energy, the homochiral catalyst is 135-times more efficient at 25 °C than the heterochiral catalyst, in perfect agreement with the proposal of Blackmond, Brown, and co-workers, that the active catalyst is constituted by homochiral dimers, which are in statistical equilibrium with the inactive heterochiral dimer.[4a]

The energy difference between the two TSs is responsible for the chiral amplification in the Soai reaction. Inspection of the molecular models suggests an important role, in this respect, of the substituent in the 2-position of the pyrimidine ring (the δ-substituent). Steric interactions between this group and the zinc-bound isopropyl groups may have the beneficial effect of increasing the differential strain energy of the two TSs.

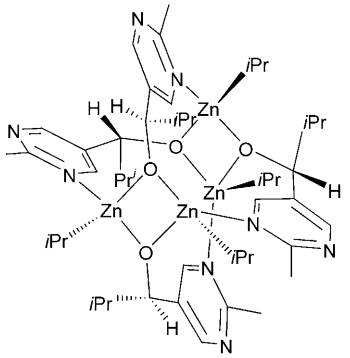
The intermediate assemblies **8**-R_3 and **8**-R_2S, once formed, behave as short-lived intermediates, rapidly reacting to yield the tetramers **9**-R_4 and **9**-R_2S_2, respectively.[9] This phenom-



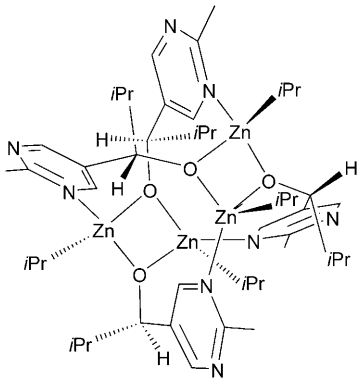
8-R_3



8-R_2S



9-R_4



9-R_2S_2

enon was verified by evaluating the barrier leading to the corresponding TSs, whose structure is also of the early type. The possibility that the assemblies **8**-R_3 and **8**-R_2S can directly form from the reactants is ruled out on the basis of the evident second-order dependency of the rate on aldehyde concentration,[4c] and on the basis that trimers, in contrast to dimers, were not detected in solution.[5]

The tetramers **9**-R_4 and **9**-R_2S_2 successively undergo a rapid and reversible dissociation to yield two molecules of the corresponding dimer, thus beginning a new catalytic cycle.

Relative energies for all the species appearing in the homochiral "all *R*" and heterochiral "*RSP*" catalytic cycles are reported in Table 1. Of course for each of these cycles there is an enantiomeric counterpart, namely the homochiral "all *S*" and the heterochiral "*RSM*" catalytic cycles. All these cycles are chemically connected through any of the possible equilibria involving enantiomeric exchange, for example, **4**-R_2 + **4**-S_2 ⇄ 2 × **4**-*RS*. Note that the heterochiral cycles are in fact unproductive with respect to the homochiral ones because of the higher energy of their rate-limiting TSs. Accordingly their role is just to drain coupled *RS* enantiomers so as to increase the activity of the dominant homochiral cycle, thus leading to chiral amplification.

Table 1: Relative energies[a] of the species characterizing the homochiral and heterochiral catalytic cycles.

Homochiral Cycle		Heterochiral Cycle	
Structure	E[b]	Structure	E[b]
3-R_2 + 2 × [iPr$_2$Zn] + 2 × **1**	24.7	**3**-*RS* + 2 × [iPr$_2$Zn] + 2 × **1**	21.8
4-R_2 + 2 × [iPr$_2$Zn] + 2 × **1**	15.0	**4**-*RS* + 2 × [iPr$_2$Zn] + 2 × **1**	14.8
5-R_2 + 2 × **1**	4.1	**5**-*RS* + 2 × **1**	4.4
6-R_2 + 2 × **1**	0.0	**6**-*RS* + 2 × **1**	−0.03
7-R_2	19.8	**7**-*RSP*	23.8
$TS_{7R2\text{-}8R3}$	26.9	$TS_{7RSP\text{-}8R2S}$	29.8
8-R_3	−32.1	**8**-R_2S	−29.8
$TS_{8R3\text{-}9R4}$	−25.4	$TS_{8R2S\text{-}9R2S2}$	−27.2
9-R_4	−92.8	**9**-R_2S_2	−87.8
2 × **4**-R_2	−75.8	2 × **4**-*RS*	−76.2

[a] B3LYP/6-31G(d)//HF/3-21G(d) electronic energies + ZPVEs, relative to the reactants (**6**-R_2 + 2 × **1**); [b] E [kcal mol^{-1}]

In summary, for the first time a mechanism has been proposed for the Soai reaction, which is detailed at the molecular level and supported by calculations based on first principles. The mechanism not only provides a rationale for both the detected chiral induction and amplification, but also sheds light on the puzzling roles played by isopropyl groups, γ-pyridinic nitrogen atoms, and the δ-substituent. The mechanism has been evaluated in the gas phase with a basis set of limited extension. Future work is directed toward investigating the mechanism at a higher level of theory and assessing its scope in solution. Nevertheless, the valuable insights these discoveries provide should stimulate further advancements in the field of asymmetric autocatalysis.

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[1] a) K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767 – 768; b) K. Soai, T. Shibata, I. Sato, *Acc. Chem. Res.* **2000**, *33*, 382 – 390; c) K. Soai, T. Kawasaki, *Chirality* **2006**, *18*, 469 – 478; d) K. Soai, T. Kawasaki, I. Sato in *New Frontiers in Asymmetric Catalysis* (Eds.: K. Mikami, M. Lautens), Wiley-Interscience, Hoboken, **2007**, pp. 259 – 274.

[2] a) D. A. Singleton, L. K. Vo, *J. Am. Chem. Soc.* **2002**, *124*, 10010 – 10011; b) K. Soai, I. Sato, T. Shibata, S. Komiya, M. Hayashi, Y. Matsueda, H. Imamura, T. Hayase, H. Morioka, H. Tabira, J. Yamamoto, Y. Kowata, *Tetrahedron: Asymmetry* **2003**, *14*, 185 – 188; c) I. D. Gridnev, J. M. Serafimov, H. Quiney, J. M. Brown, *Org. Biomol. Chem.* **2003**, *1*, 3811 – 3819; d) K. Mislow, *Collect. Czech. Chem. Commun.* **2003**, *68*, 849 – 864; e) D. G. Blackmond, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5732 – 5736; f) B. Barabas, L. Caglioti, C. Zucchi, M. Maioli, E. Gál, K. Micskei, G. Pályi, *J. Phys. Chem. B* **2007**, *111*, 11506 – 11510.

[3] Previous computational studies of the Soai reaction were mainly focused on oligomeric structures of the product catalyst: a) I. D. Gridnev, J. M. Brown, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5727 – 5731; b) J. Klankermayer, I. D. Gridnev, J. M. Brown, *Chem. Commun.* **2007**, 3151 – 3153.

[4] a) D. G. Blackmond, C. R. McMillan, S. Ramdeehul, A. Schorm, J. M. Brown, *J. Am. Chem. Soc.* **2001**, *123*, 10103 – 10104; b) D. G. Blackmond, *Adv. Synth. Catal.* **2002**, *344*, 156 – 158; c) F. G. Buono, D. G. Blackmond, *J. Am. Chem. Soc.* **2003**, *125*, 8978 – 8979; d) D. G. Blackmond, *Tetrahedron: Asymmetry* **2006**, *17*, 584 – 589.

[5] I. D. Gridnev, J. M. Serafimov, J. M. Brown, *Angew. Chem.* **2004**, *116*, 4992 – 4995; *Angew. Chem. Int. Ed.* **2004**, *43*, 4884 – 4887.

[6] a) This approach is considered the best trade-off for large systems, since energies computed with the B3LYP functional are surprisingly insensitive to the geometry optimization level. J. B. Foresman, Æ. Frisch, *Exploring Chemistry with Electronic Structure Methods*, *2nd ed.*, Gaussian Inc., Pittsburgh, **1996**, pp. 146 – 150; b) HF/3-21G(d) frequencies were scaled by the factor 0.9207. A. P. Scott, L. Radom, *J. Phys. Chem.* **1996**, *100*, 16502 – 16513; c) Computational details, optimized geometries, and energies are reported in Supporting Information.

[7] L. P. Hammett, *Physical Organic Chemistry*, *2nd ed.*, McGraw-Hill, New York, **1970**, pp. 117 – 119.

[8] The enantiomer of **7**-*RSP*, **7**-*RSM* (where *M* denotes the axial chirality opposite to *P*) will give exclusively **8**-RS_2.

[9] In principle the assemblies **8**-R_3 and **8**-R_2S could also rapidly dissociate to give the corresponding reactant molecules. Although this possibility seems unlikely, the overall rate of reaction would be in this case just half that of the case being considered.

