Highlight Review

Chiral Symmetry Breaking in Chiral Crystallization and Soai Autocatalytic Reaction

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Abstract

Complete chiral crystallization and absolute chiral synthesis are both fascinating phenomena shedding light on the possible origins of homochirality in nature and opening perspectives for efficient preparations of optically pure materials. Originally these two phenomena have been considered mechanistically quite different belonging to the hetero- and homogeneous systems, respectively. However, the results of the active research in both fields undertaken in the last few years suggest that there may be a much closer likeness of the most important mechanistic features of these two phenomena. In the present review, we bring together the latest data on the complete chiral crystallization and absolute chiral synthesis including our own data on the mechanism and spontaneous break of chirality in the Soai asymmetric autocatalysis.

◆ 1. Introduction

There are several important reasons warming the interest for the long-standing problem of spontaneous symmetry breaking in chemical and physical systems. The mystery of homochiral life is frequently referred as the stimulating question. Indeed, the homogeneity in chirality characteristic for the biomolecules has not so far received a clear deterministic explanation, and the physical phenomena or chemical reactions capable to produce enantiomeric excess without initial chiral input are realistic candidates for rationalizing the origin of homochirality in nature.

However, even without the reference to the global problems the experiments leading to optically active materials without clear source of chirality are important and revealing since they provide a breakthrough in our knowledge on the enantioselective reactions, and the mechanism of creating and amplifying of chirality.

Discussion in this area has a noble history originating from the polemics in *Nature* of 1898.[1–7] At that time, only the experiments on the symmetry breaking during the crystallization from solution were known, and the crucial argument of the vitalistically minded Japp was that the symmetry breaking is conceivable in a physical process, but absolutely unimaginable for a chemical reaction.[1,3] This was cleverly questioned by Strong,[6] who actually proposed the first ever model for asymmetric autocatalysis. This model has been criticized by Japp[3] as being purely speculative (probably not so, as we know now), but in any case this was an important apprehension of the possibility for a catalytic reaction to reproduce chirality indefinetly. After almost a century of further speculations, occasional experiments, and discussions[8] the 90-ties brought new experimental discoveries both in chiral crystallization[9] and in asymmetric autocatalytic reactions,[10] that brought to life the extensive experimental and theoretical studies. In this review, it was attempted to summarize the most recent data in these fields with the emphasis on the examples of the spontaneous symmetry breaking, and growing understanding of the resemblance of physical and chemical mechanisms responsible for this phenomenon.

This area is regularly reviewed,[8,11–14] hence the most recent results and further perspectives of the research are mainly highlighted.

◆ 2. Chiral Symmetry Breaking during Crystallization

More than 100 years ago, it has been found that when achiral molecules, e.g. of sodium chlorate, give chiral crystals due to the asymmetry of the crystal space group, the crystallization from solution does not give equal number of L and D crystals.[15] The observed deviations from the mean value were evidently stochastic and followed a typical monomodal probability distribution centered at zero cee (crystal enantiomeric excess).

In 1990, Kondepudi showed, however, that if the solution of sodium chlorate is continuously stirred during the crystallization, the crystals with the over 98% dominance of either L or D form is obtained almost in each experiment. In other words, the probability distribution becomes bimodal with two sharp peaks near -1 and 1 of cee.[9] Similar observations were made for the crystallization of the binaphtyl melt: The monomodal Gaussian distribution of cee observed for non-stirred melt[16,17] is replaced by bimodal one if the melt is stirred, and the cee observed in almost every crystallization is over 80%.[18]

This almost perfect chiral symmetry breaking has been explained in terms of the secondary nucleation theory.[19] This approach suggests that the sense and order of the cee obtained in each particular crystallization experiment are determined by the first crystal which propagates itself initiating the formation of the crystals of the same chirality in the vicinity of its surface. Several experimental observations have been accepted as a support for the secondary nucleation scheme; the most illustrative is the videotaped collision of a $NaClO_3$ crystal and the stir bar followed by the rapid production of the secondary nuclei.[20] Nevertheless, it was realized that the solid–solid contact is not an essential requirement for the secondary nucleation, since it is possible to get high cee of $NaClO_3$ crystals upon seeding with a chiral crystal of $NaBrO_3$ without mechanical stirring, with mass transfer maintained via solution flow.[21]

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Kinetics of the experimentally observed time evolution has been fitted to the empirical law for the rate of production of the secondary nuclei,[19] the inevitably stochastic nature of the conclusions was probed by computer simulations,[22] and the overall experimental data were thought to be in qualitative agreement with the formal theory of secondary nucleation in an open system.[23–25]

However, in 2004 and 2005, Viedma published the results of the new experiments seriously undermining the validity of the hypothesis of randomly generated "mother crystal" in the chiral symmetry breaking during crystallization.[26,27]

In the first series of experiments,[26] Viedma showed that contrary to the prediction of the secondary nucleation theory, a very fast crystallization from strongly supersaturated solutions leads in fact to the perfect symmetry breaking, producing 100% of crystals of the same handedness from samples of the same solution. The rate of crystallization in Viedma's experiments tremendously differed from that in the previous tests. Thus, normal rate of nucleation maintained for avoiding the primary nucleation effects was of the order 0.2–2 nuclei/min, whereas in each Viedma's experiment 700,000–900,000 crystals with a size of about 20 µm were formed almost instantaneously, all being of the same handedness.[26]

In another set of experiments, a still more striking evinence against the "mother crystal" theory was collected.[27] The 100% symmetry breaking was obtained from the systems initially containing both L and D crystals of $NaClO_3$—either equal amounts or with 5% predominance of either enantiomer if the stirred solutions contained certain amount of small glass balls (3 mm of diameter) that continuously crushed the crystals keeping their maximal size of about 200 µm. The rate of achieving complete chiral breaking was proportional to the quantity of the glass balls and to the speed of rotation. Under the same conditions the systems with initial 5% cee achieved 100% cee of the same sign within 8 h, whereas initially symmetrical mixtures of L and D crystals gave randomly 100% cee of either sign after 24 h. The systems containing no glass balls kept their initial cee's indefinitely, although being stirred.[27]

It is quite evident that the achievement of complete chiral purity in Viedma's experiments cannot be explained by the model of an initial single chiral crystal. Taking into account the intrinsic role of grinding glass balls for the achieving of the symmetry break, Viedma suggests that under these conditions a continuous dissolution–crystallization phenomenon is highly enhanced by the abrasion-grinding process making the system very similar to the homogeneous autocatalytic reaction.[27] The chiral crystalline cell of $NaClO_3$ contains 4 molecules, the individual molecules of any associates of less than 4 molecules are achiral. Thus, as a result of continuous grinding all crystals can be degraded to the achiral state with equal probability. If we look at this process averaged by time from the statistical point of view, we can regard the system as containing only achiral molecular units and some amount of chiral crystals—of the handedness that was present in excess at the beginning of the experiment. Viedma's experiments demonstrate convincingly that this excess, whatever small initially, can be sooner or later bred to 100% cee.

Uwaha has published a mathematical model (applying approach similar to that previously described by Decker, see Ref. 38) adequately describing the Viedma's experiments with minimal reasonable assumptions: The mass-transfer complications common for usual crystallizations are neglected, complete dynamic reversibility is supposed, and for simplicity of equations, a minimal chiral unit is considered to be bimolecular.[28] Solving the corresponding differential Eq 1–5, Uwaha has got for the sample with initial cee 0.5% of the x hand the time evolution curves shown in the Figure 1, where x and y represent quantities of the crystals with opposite chirality, x_u and y_u are the amounts of minimal chiral units, and z represents the concentration of achiral molecules.

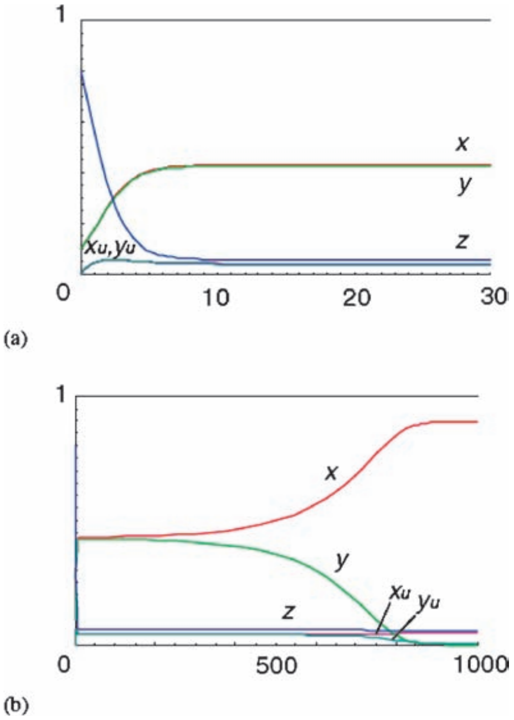

Figure 1. Time evolution for $x(0) = 0.101$, $y(0) = 0.100$, and $x_u(0) = y_u = 0$. (a) Initial rapid change and (b) slow relaxation to equilibrium.

It is important to note that, according to the properties of the real system, there is no direct or concealed preference for formation of either L or D form of the crystal in this model. The differential equations use the same rate constants for describing the formation of both enantiomeric crystals. Therefore, the chiral symmetry breaking in terms of this model is not a stochastic effect, but the inevitable outcome for any system capable to produce chiral crystals from achiral units if the complete reversibility is secured and mass-transfer problems are eliminated. And the Viedma experiments demonstrate quite convincingly that this is very probably the case.

3. Spontaneous Symmetry Breaking in Soai Autocatalytic Reaction

3.1. Experimental Evidence

In 1995, Soai et al. reported the first example of asymmetric autocatalytic reaction (Scheme 1).[10] Pyrimidyl alcohol (**2a**) acted as a chiral catalyst for its own formation in the reaction of corresponding aldehyde (**1a**) with diisopropylzinc. Moreover, the amplification of ee was observed in this reaction: loading **2a**

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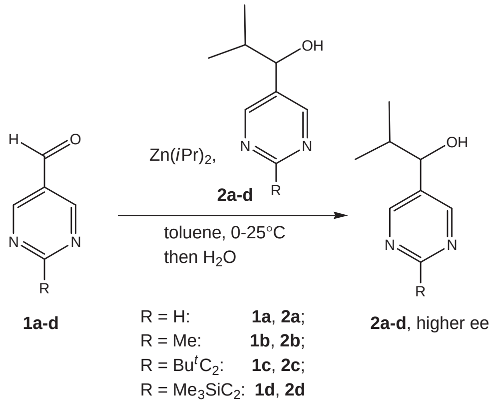


Scheme 1. Soai autocatalytic reaction.

with low ee as a catalyst, one gets the same compound with significantly higher ee as a reaction product. Further experiments showed that one does not even need **2** itself in the beginning of the reaction; a large variety of chiral initiators, including chiral crystals or trace amounts of enantiomerically pure substances can induce the initial chirality that can be later amplified in successive runs of the autocatalytic reaction.[11]

The spontaneous symmetry breaking in Soai reaction was first reported as a Japanese patent in 1997.[29] This patent described experiments in which the reaction of **1a** with diisopropylzinc without any discrete chiral additives produced a small enantiomeric excess of either *S* or *R* enantiomer of the corresponding alcohol **2a** detectable after three amplification cycles.[29]

When Singleton and Vo repeated these experiments in 2002 (using **1b**) in a more systematic way, they observed only 10 *R* outcomes in 48 trials. Such non-symmetric distribution of the sense of the chiral symmetry breaking led the authors to a conclusion that no absolute asymmetric synthesis takes place, but the symmetry breaking is induced by unknown chiral impurities.[30]

However, Soai reported in early 2003 a stochastic distribution of the chirality outcomes (19 times formation of *S* and 18 times of *R* enantiomer of **2c**), for the reaction carried out in a mixture of toluene and diethyl ether, thus demonstrating that the spontaneous symmetry breaking in his reaction can actually take place.[31] It was also shown that the catalyst **2c** with ee as low as 0.00005% can breed its own chirality to more than 99.5% ee.[32]

Our own experiments published later in the same year showed almost statistical distribution of *S* and *R* products (**2d**) in 20 experiments carried out in a single day using toluene as a solvent.[33] Moreover, generation of ee as high as 84% (*R*) in the single run without any chiral input has been observed in one of the NMR experiments, whereas 90% ee (*S*) was observed in one of single-run experiments in diethyl ether.[33] In a preparative scale experiment (carried out with the purpose to prepare a stock of racemic catalyst actually) around 200 mg of **2d** was obtained with 52% ee (*R*).[33] A normal autocatalytic reaction leading to such outcome would require about 20 mg of **2d** with approximately 20% ee carefully loaded prior to the addition of the aldehyde.[34] The probability of overlooking such an "impurity" is negligible. Truly stochastic nature of the Soai autocatalytic reaction is also seen in the dependence of the ee observed in the catalyzed reactions of **1d** with diisopropylzinc on concentration of the catalyst with 99% ee (Figure 2).[33] Whereas the uncatalyzed reaction ($x = 0$ points) gives almost equal numbers of *R* and *S* outcomes, and the relatively high catalyst loadings (10^{-2} to 10^{-4} mol) give reproductively the product with ee close to 100%, the micromolar catalyst loading gives a broad distribution of the observed ee's values, but the sense of enantioselection is always the same as in the used catalyst.

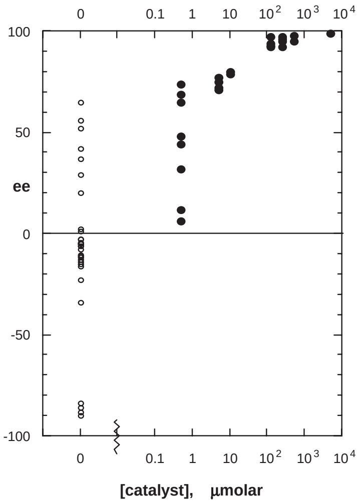


Figure 2. Dependence of the ee on catalyst concentration for the reaction between **1d** (0.025 M) and $Zn(iPr)_2$ (0.0425 M) in toluene (4 mL) at 273 K in the presence of 0.002 to 20 mol % catalyst (*R*)-**2d**. The $x = 0$ points refer to reactions without added catalyst.

Singleton and Vo in their second approach to the problem were also able to observe a random distribution of *S* and *R* products in the reactions of **1** (R = Me) with diisopropylzinc in pure diethyl ester.[35] They also showed that if only about 60,000 molecules of *R* product are used to initiate the reaction, the *R* product is repeatedly produced.[35]

Thus, at least in the present moment, there is a consensus among researches on the origin of the apparent "spontaneous symmetry breaking" in the Soai autocatalytic reaction. Tiny natural imbalance of enantiomers is being enhanced in the course of autocatalytic reaction. This point of view has also obtained an enthusiastic and well-documented support in the review of Mislow[8] which was published even before the most conclusive evidence was disclosed. Accepting this as an established experimental fact, we now turn to the mechanistic approaches for the explanation of the amplifying autocatalysis.

3.2. *Theoretical Models*

The first reliable experimental example of the symmetry breaking in a chemical reaction was found almost 100 years after the seminal experiments with chiral crystallization.[29] Such a delay reflects the complexity of the chemical systems compared to the physical ones. Greater structural flexibility, occurrence of side reactions, solvent effects, etc. seriously affect the thermodynamic properties of the chemical systems and can easily conceal the experimentally detectable results of the symmetry breaking.

Hence, it is quite understandable that the theoretic studies on the possibilities of spontaneous symmetry breaking in chemical reactions appeared before the actual experimental observation of the phenomenon

As it was mentioned in the introduction, the first consideration on the capability of an autocatalytic reaction to reproduce chirality has been published quite early,[6] however, this study did not take into account the inevitable competition between two enantiomers simultaneously present in the reaction mixture. Frank analyzed the system containing both enantiomers, but finished with not much less speculative suggestion of a chemical substance "that is a catalyst for its own production and an anti-catalyst for the production of its own enantiomer."[36] The idea of the importance of autocatalytic scheme for the possibility of autoamplification was further developed by Calvin,[37] Goldanskii and Kuz'min,[38] and clearly stated by Kagan[39] who argued that autocatalysis coupled with a positive non-linear effect (either via reservoir mechanism or due to the higher order kinetic law) can be a sufficient requirement for the possibility of asymmetric amplification.

Experimental study carried by Brown and Blackmond showed that the main kinetic features of the Soai autocatalytic reaction are described by accepting a model of homochiral dimeric catalyst, its heterochiral counterpart being inactive.[40] An essentially similar conclusion concerning the involvement of a homochiral dimer catalyst was subsequently reached by Soai.[41,42] Later Buono and Blackmond suggested that even higher order kinetic law may apply in Soai reaction.[43,44]

Although no definite conclusion could be driven from the extensive study of the precipitation phenomena in the Soai reaction, since the effects (difference of ee between the solution and the solid state) are not too pronounced and strongly depend on the nature of solvent,[45] the possibility of the involvement of highly aggregated species brings the absolute asymmetric synthesis in this reaction somewhat closer to the symmetry break during crystallization discussed in the first chapter of this account. Indeed, Saito and Hyuga showed recently that, similarly to the crystallization case,[27] it is possible to build a model allowing to achieve perfect homochirality in an autocatalytic reaction.[46] It was shown that in a close conserved system (instead of the Frank's open flow system) the second-order autocatalytic reaction accompanied by a slower back reaction can lead to the appearance of the chiral steady-states.[46] Similar conclusions have been made independently for a more sophisticated analysis referring to the reversible polymerization of amino acids.[47]

So far the Soai reaction has been considered as irreversible. However, it is not impossible that at certain reaction conditions (e.g. low temperature, particular concentration range) it can operate as a reversible transformation. In this case, the abnormally high ee's obtained in a single run[33] (see previous section) may arise from this kind of amplification regime. Interestingly, when we were following by NMR the progress of the reaction of **1d** with $Zn(iPr)_2$ without catalyst, we have often observed the raise of the concentration of **1d** at different stages of the reaction (Figure 3).[33]

In the bottom trace of the Figure 3 one can clearly see a completely unexpected raise of the aldehyde concentration (one fourth of the whole concentration) followed by more or less typical autocatalytic kinetic curve. One possible explanation might be the initial formation of a dynamic complex not seen in the NMR slowly releasing aldehyde, but the reversibility of the reaction at the early stage of this experiment cannot be excluded. Also worth noting are the apparent oscillations of the aldehyde concentration clearly seen at the upper trace (e.g. in the 6000–8000 s region or 12000–15000 s region). On the whole, those two kinetic curves demonstrate the plethora of possible kinetic regimes for the alkylation of pyrimidyl aldehyde with diisopropylzinc, as well as randomness in the ee generation: the alcohol obtained from the experiment corresponding to the bottom trace was of 6% ee (*R*), whereas the upper trace experiment did not produce any measurable ee.

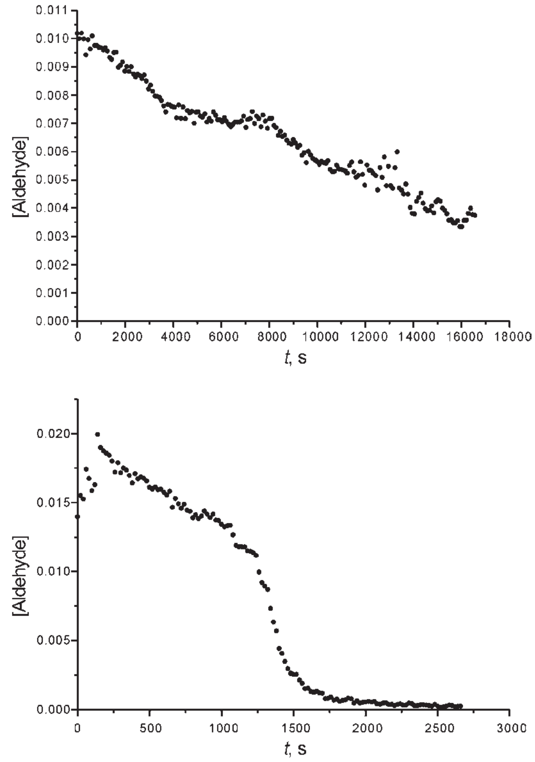
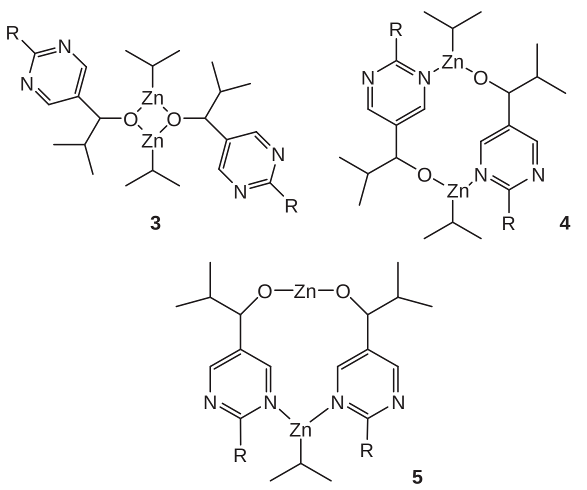


Figure 3. Progress of the reaction between aldehyde **1d** and $Zn(iPr)_2$ in C_7D_8 at 273 K. Product formation was monitored by integration of the ^1H NMR signal of aromatic protons of aldehyde against the signals of residual aromatic protons in the 4.5 ppm region. Starting concentrations: (up) 0.01 M **1d**, 0.02 M [Zn]; 300 4 K point spectra were taken at 60 s intervals. (bottom) 0.02 M **1d**, 0.04 M [Zn]; 140 4 K point spectra were taken at 20 s intervals.

4. Structure of catalyst in Soai reaction

Theoretical and kinetic analysis of the Soai reaction suggest several possible schemes for the realization of amplifying autocatalysis, but one cannot succeed in further understanding the phenomenon without structural information. It was quite easy to exclude the possibility of the reservoir mechanism[39] of the chiral amplification on the dimerization stage (preferential binding of minor enantiomer into heterochiral dimers) since the NMR spectra of alcoholate clearly demonstrated statistical distribution of diastereomeric dimers.[40,48] However, one cannot be sure that the chiral amplification is not based on a reservoir mechanism at the higher association level (some oligomeric heterochiral species being more stable than the homochiral ones).

There are three possible structural types of dimers (Scheme 2) and although originally the macrocyclic structure **4** was suggested,[40] both the symmetry of the ^1H NMR spectra[48] and the computational results[49] unequivocally point on the



Scheme 2. Possible dimeric structures of the pyrimidyl alcoholates.[48]

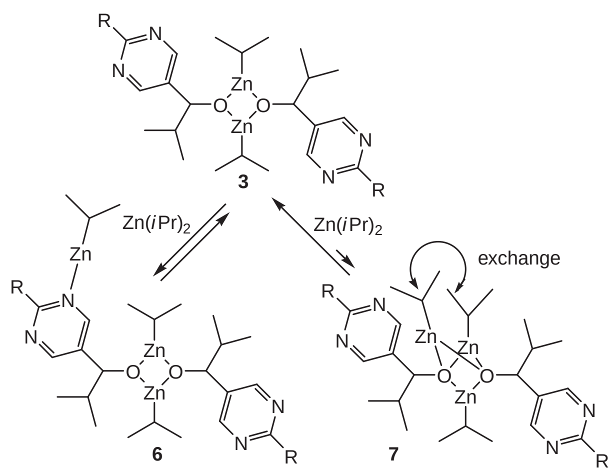
square dimer structure **3** as the main component of the alcoholate solution either in toluene or in THF.

However, the statistical mixture[50] of homo- and heterochiral square dimers **3** is by no way the only component of the alcoholate solution. The dimers are involved in the large number of dynamic processes, the most important ones include dissociation to the monomer, association either with monomer or with another molecule of dimer to produce higher oligomers and the coordination of the excessive diisopropylzinc.[48]

Variable temperature NMR study of the dissociation of dimers in toluene was used to estimate that the half-life of an individual dimer molecule with respect to $R \rightleftharpoons S$ exchange is about 15 s at 293 K.[48] This value gives good reasons to believe that it is a dimer molecule that acts in fact as a catalyst in the Soai reaction.

Association of the starting aldehyde **1d** and the alcoholate **3d** with $Zn(iPr)_2$ was quantitatively studied by multinuclear NMR.[48] The similar values of the association constant for **1d** and $Zn(iPr)_2$ at 213 K (when the reaction is very slow) derived from the ^1H NMR ($5.8\,M^{-1}$) and ^{15}N NMR ($5.6\,M^{-1}$) together with marked dependence of the $\delta^{13}C$ of the alkynyl carbons on the $Zn(iPr)_2$ concentration are in accord with rapidly reversible association of diisopropylzinc with a pyrimidine nitrogen atom of the aldehyde without evident involvement of the carbonyl group. For the alcoholate **3** ($R = Me_3SiC{\equiv}C$–) the binding constant with $Zn(iPr)_2$ was found to be $4.6\,M^{-1}$ at 308 K (in C_7D_8) and also interpreted as almost pure N coordination.[48] Nevertheless, a weak O coordination can also take place that is manifested in the rapid exchange between zinc-bound isopropyl groups in the reagent and dimer (Scheme 3) characterized by EXSY NMR. The reaction occurs with comparable facility for both homo- and heterochiral dimers; most probably through the bridged Zn–O complex **7** structure of which was located computationally.[48]

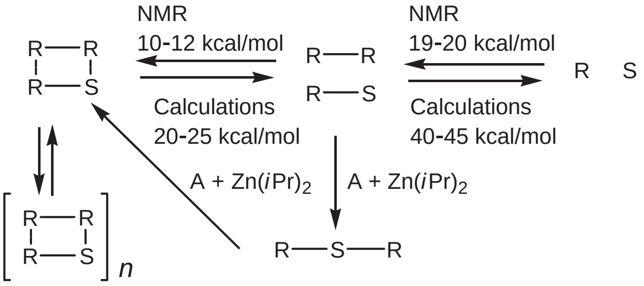
Although the further association of the dimers is quite evident from the NMR spectra of the alcoholate solution taken below the ambient temperature,[48] the complexity of these equilibria did not allow so far a definite interpretation. The problem was therefore approached computationally, and the structures of all topologically possible associates up to tetramers (with Me groups on Zn instead of *i*-Pr) were optimized on the B3LYP/6-31G* level of theory.[49]



Scheme 3. Complexation of the dimer **3** with excessive diisopropylzinc.[48]

Two important conclusions follow from this theoretical study. First, any higher oligomer is constructed from the structural units that can be described either as square dimer **3** or macrocyclic dimer **4**. Since a self-replicating reaction of an *n*-mer must first produce an $(n + 1)$-mer, the new "dimeric" unit created in this event might be capable to act itself as a catalytically active center giving rise to an $(n + 2)$-mer, etc. (Scheme 4). Whether these $(n + x)$-mers would or not dissociate prior to the next alkylation event catalyzed by the same oligomeric molecule will be mostly determined by thermodynamics of these associates, but is also expected to be quite sensitive to the mass-transfer conditions, and can vary from experiment to experiment. This approach makes the Soai reaction formally similar to the formation of the chiral crystals from an achiral solution suggesting that there might be a common principle behind these two phenomena.

Another conclusion is that the O–Zn–N binding via the macrocyclic way evidently disfavored on the dimer stage (**3** is about $10\,kcal\,mol^{-1}$ more stable than **4**) becomes of the same strength with O–Zn–O binding in tetramers.[49] Since the Soai reaction is extremely sensitive to the structure of a substrate and works only with rigid pyrimidynic γ-aminoalcohols, the macrocyclic type of association can be crucial for the formation of a transition state.[49]



Scheme 4. Summary of the results of NMR and computational studies. A is an aldehyde molecule, *R* and *S*—two enantiomers of monomer alcoholate. As could be expected, the gas-phase computations overestimate the coordination energy, nevertheless the main trends in association of zinc alcoholates are correctly reproduced.

◆ Conclusion

We are now witnessing dramatic developments in the understanding of the ways how the optically active compounds can be spontaneously produced from achiral environment. In this highlight, the most recent data on the spontaneous symmetry breaking in chiral crystallization and on Soai autocatalytic reaction which so far remains the only example of a chemical process amplifying chirality are summarized. The last findings indicate that these two symmetry breaking phenomena may be quite close from the mechanistic point of view: In both cases, the amplification of a small initial disballance seems to be achived on a supramolecular level via subtle interplay of kinetic and thermodynamic parameters. However, the structural factors important for the possibility of spontaneous symmetry breaking are not yet completely understood. In the case of chiral crystallization, it is not clear what makes the achiral molecules joining the growing chiral crystal in a stereospecific way instead of producing a racemic crystal. In the same fashion, what particular structural factor is responsible for the higher reactivity of homochiral catalysts compared to the heterochiral ones; this remains a challenging problem for further research.

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