JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Mechanism-Based Chemical Understanding of Chiral Symmetry Breaking in the Soai Reaction. A Combined Probabilistic and Deterministic Description of Chemical Reactions

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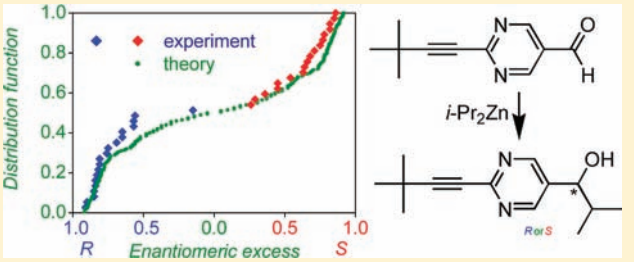
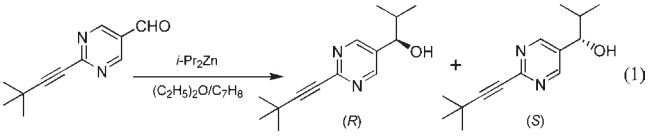
Supporting Information

ABSTRACT: The experimentally observed distribution of enantiomers in the Soai reaction is interpreted in this Article on the basis of a chemical mechanism using a newly developed stochastic kinetic method, accelerated Monte Carlo simulation combined with deterministic continuation and symmetrization. The method is in principle suitable for handling large mechanisms with realistic particle numbers and could be useful for any case where the kinetics of a process shows inherent random fluctuations. The mechanism shows how a slow initial reaction combined with efficient and highly enantioselective autocatalysis can give rise to chiral symmetry breaking under completely nonchiral external conditions.



INTRODUCTION

The Soai reaction has continued to fascinate scientists since the publication of the first report proving strong enantioselective autocatalysis in this system.[1] Following the initial report on asymmetric amplification, a previously unobserved phenomenon termed absolute asymmetric synthesis, which is a form of chiral symmetry breaking resulting in the formation of macroscopically detectable enantiomeric excess (ee) of a chiral product in a chemical reaction under completely nonchiral conditions, was also found in this reaction.[2−5] The chemical reaction is a carbon−carbon bond formation process yielding a chiral alcohol starting from a pyrimidinyl carbaldehyde and a dialkyl zinc compound under strictly air- and water-free conditions:



Studying the mechanism of the Soai reaction and symmetry breaking has drawn a lot of recent scientific attention as it has very important implications for the origin of biological chirality.[6−34] Absolute asymmetric synthesis, as was also shown by another known example featuring chiral octahedral cobalt complexes,[35] is stochastic in nature: the magnitude of produced ee and the identity of excess enantiomer vary unpredictably in any single experiment but obey probabilistic laws for a sufficiently high number of repetitions.[19,36−38] The reported experimental results for the absolute asymmetric synthesis variant of the Soai reaction[3] are shown in Figure 1 using the distribution function, which is understood to be a representation much

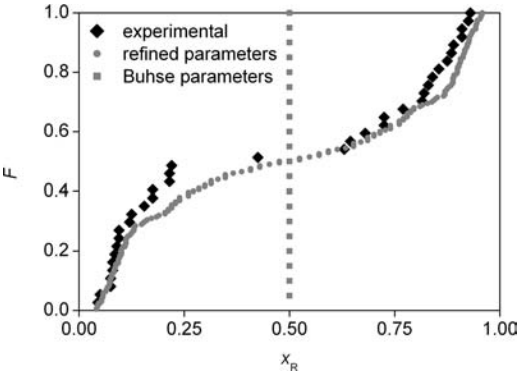


Figure 1. Experimentally observed and theoretically predicted probability distributions of enantiomeric excesses in the Soai reaction. Experimental data from Soai et al.[3]

superior to histograms.[37,38] Such phenomena cannot be interpreted using the usual deterministic approach to chemical kinetics, which never predicts the formation of significant ee from achiral initial conditions.[19,36−38]

The stochastic approach to chemical kinetics has been used in a few initial attempts to interpret the final distribution of enantiomers in the Soai reaction.[19,29,36,37] These mostly used the continuous time discrete state (CDS) approach, the theory of which had been developed earlier.[38−40] The CDS approach is not simply an alternative to usual chemical kinetics, but a much more

Received: August 6, 2011
Published: October 03, 2011

general theory that entirely embodies deterministic kinetics as a limiting case for high particle numbers.[38,41] The initial stochastic attempts were either not based on any chemical mechanisms,[19,29] or the chemical mechanisms involved no intermediates at all.[36,37] The Soai reaction is much more complicated, but CDS stochastic calculations with chemically reasonable amounts of material were not possible primarily because of computational limitations.[38,42] This work reports a new method for the stochastic handling of complex mechanisms, and, as a proof of concept, predictions are calculated for the final distribution of enantiomers based on a chemical mechanism.

RESULTS AND DISCUSSION

The stochastic kinetic method developed in this work has four cornerstones: the use of Monte Carlo simulations, accelerating them by the CDS analogue of the pre-equilibrium approximation, deterministic continuation, and symmetrization. These aspects will be explained in some detail, and a code written in Matlab[43] is deposited in the Supporting Information.

The chemical mechanism developed in this work for the Soai reaction is a modified version of the model published by Buhse,[8] which also served as a basis for a deterministic study about oscillatory symmetry breaking.[23] Models have already been developed for the Soai reaction that may be more satisfactory in some respect,[12,13,17,33] but there is no general agreement in this matter. The essence of our model (Table 1) is the initial formation of the chiral zinc alcoholate COZn from the reactants carbaldehyde CHO and dialkyl zinc Zn, with the later intervention of dimolecular and trimolecular species $(COZn)_2$ and $(COZn)_2$−CHO, which open an enantioselective pathway of the formation of COZn (notations are the same as in ref 8). The full mechanism contains 10 species and 18 elementary reactions.

Monte Carlo simulations are used in many fields of science, but rarely in chemical kinetics.[44−46] In this method, the probabilities of all elementary reactions are calculated from the rate equation, and a random number is generated to decide which of these reaction steps occurs next, and than the procedure is repeated. The initial "coin tossing" character of the Soai reaction has been demonstrated by empirical calculations.[24] The random number generator of the software Matlab has been carefully tested in this work (Figures S1 and S2 in the Supporting Information), because any error in this would cause a major flaw in the simulations.

Initial Monte Carlo simulations were extremely slow and could only be used for up to dozens of product molecules. Testing the algorithm (Table S1 in the Supporting Information) revealed that more than 99% of steps taken were forward and backward steps in the dimerization, which has the chemical implication that this reaction can be treated as a fast equilibrium. The problem was solved by developing a stochastic equivalent of the pre-equilibrium approach. Instead of using the molecule numbers for COZn and $(COZn)_2$ separately, they were combined into a single variable:

$$m = COZn + 2 \times (COZn)_2 \quad (2)$$

Here, $COZn$ and $(COZn)_2$ in italics mean molecule numbers for species COZn and $(COZn)_2$, respectively, whereas m is their sum weighted by the number of zinc atoms present. When calculating the probabilities of individual reaction steps in the simulation, $COZn$ and $(COZn)_2$ were obtained as the

Table 1. Elementary Reactions, Rate Constants, and Parameter Values in the Proposed Mechanism[a]

reaction	rate constant
CHO + Zn → (*R*)-COZn	k_1
CHO + Zn → (*S*)-COZn	k_1
(*R*)-COZn + (*R*)-COZn → (*R*)(*R*)-$(COZn)_2$	k_2
(*R*)(*R*)-$(COZn)_2$ → (*R*)-COZn + (*R*)-COZn	k_{-2}
(*S*)-COZn + (*S*)-COZn → (*S*)(*S*)-$(COZn)_2$	k_2
(*S*)(*S*)-$(COZn)_2$ → (*S*)-COZn + (*S*)-COZn	k_{-2}
(*R*)-COZn + (*S*)-COZn → (*R*)(*S*)-$(COZn)_2$	$\alpha \times k_2$
(*R*)(*S*)-$(COZn)_2$ → (*R*)-COZn + (*S*)-COZn	k_{-2}
(*R*)(*R*)-$(COZn)_2$ + CHO → (*R*)(*R*)-$(COZn)_2$ − CHO	k_3
(*R*)(*R*)-$(COZn)_2$ − CHO → (*R*)(*R*)-$(COZn)_2$ + CHO	k_{-3}
(*S*)(*S*)-$(COZn)_2$ + CHO → (*S*)(*S*)-$(COZn)_2$ − CHO	k_3
(*S*)(*S*)-$(COZn)_2$ − CHO → (*S*)(*S*)-$(COZn)_2$ + CHO	k_{-3}
(*R*)(*S*)-$(COZn)_2$ + CHO → (*R*)(*S*)-$(COZn)_2$ − CHO	k_3
(*R*)(*S*)-$(COZn)_2$ − CHO → (*R*)(*S*)-$(COZn)_2$ + CHO	k_{-3}
(*R*)(*R*)-$(COZn)_2$ − CHO + Zn → (*R*)(*R*)-$(COZn)_2$ + (*R*)-COZn	k_4
(*S*)(*S*)-$(COZn)_2$ − CHO + Zn → (*S*)(*S*)-$(COZn)_2$ + (*S*)-COZn	k_4
(*R*)(*S*)-$(COZn)_2$ − CHO + Zn → (*R*)(*S*)-$(COZn)_2$ + (*S*)-COZn	k_4
(*R*)(*S*)-$(COZn)_2$ − CHO + Zn → (*R*)(*S*)-$(COZn)_2$ + (*R*)-COZn	k_4

[a] n_0 (CHO) = 0.10 mmol; n_0 (Zn) = 0.20 mmol; V = 0.90 cm^3; $\alpha = 1.0 \times 10^{-5}$; $k_1 = 7.0 \times 10^{-18}$ M^{-1} s^{-1}; k_2 = 800 M^{-1} s^{-1}; k_{-2} = 110 s^{-1}; k_3 = 100 M^{-1} s^{-1}; k_{-3} = 100 s^{-1}; $k_4 = 8.0 \times 10^5$ M^{-1} s^{-1}.

equilibrium expectations of species number using the following formulas:

$$(COZn)_2 = \frac{\sum_{i=0}^{\lfloor m/2 \rfloor} i \frac{m!}{(m-2i)!i!2^i}\left(\frac{k_2}{k_{-2}N_A V}\right)^i}{\sum_{i=0}^{\lfloor m/2 \rfloor} \frac{m!}{(m-2i)!i!2^i}\left(\frac{k_2}{k_{-2}N_A V}\right)^i}$$

$$COZn = m - 2 \times (COZn)_2 \quad (3)$$

Here, ! denotes factorial, $\lfloor m/2 \rfloor$ denotes the floor function of $m/2$ (the largest integer less than or equal to $m/2$), N_A is Avogadro's constant, and V is the volume of the system. An equivalent formula was published for the stochastic description of the 2A ⇌ B equilibrium,[47] but it is also readily derived using the concept of partition functions from statistical thermodynamics (notes in the Supporting Information). With this acceleration, the Monte Carlo simulation could be carried out up to 10 000 product molecules.

Simulations up to 10^{19} molecules (0.1 mmol) were still unviable, and a technique termed deterministic continuation was developed to solve this problem. The Monte Carlo simulations up to 10 000 molecules were followed by calculations based on the usual differential equations of deterministic kinetics. The molecule numbers for the intermediates $(COZn)_2$ and $(COZn)_2$−CHO were always orders of magnitude lower than for CHO, Zn, and COZn. Therefore, the steady-state assumption for these two intermediates could be used as the essential concept behind the

steady-state approach is that the (absolute) rate of concentration change for minor species is much lower than for the major species.[48] In addition, the deterministic differential equations were not integrated as a function of time, but using the concentration of CHO as the independent variable. The following asymmetry function (ω) was introduced:

$$\omega = \frac{\dfrac{d[(R)\text{-COZn}]}{dt}}{\dfrac{d[(S)\text{-COZn}]}{dt}} = \frac{k_1 + k_2k_3k_4\dfrac{[(R)\text{-COZn}]^2 + \alpha[(R)\text{-COZn}][(S)\text{-COZn}]}{k_{-2}(k_{-3} + k_4[\text{Zn}])}}{k_1 + k_2k_3k_4\dfrac{[(S)\text{-COZn}]^2 + \alpha[(R)\text{-COZn}][(S)\text{-COZn}]}{k_{-2}(k_{-3} + k_4[\text{Zn}])}} \quad (4)$$

This asymmetry function basically gives the ratio of the formation rates for the two enantiomers of the final product and can be derived using the steady-state approach for intermediates $(COZn)_2$ and $(COZn)_2$−CHO (see the Supporting Information for the detailed derivation). Only the concentrations of reactants and products appear in this ω function, and using it provides a simplified way to state the differential equations following from the deterministic approach, which are shown in eqs 5−7. This set of equations was integrated numerically by a fourth-order Runge−Kutta method[49] using the results obtained in the Monte Carlo simulations as initial conditions.

$$\frac{d[(R)\text{-COZn}]}{d[\text{CHO}]} = -\frac{\omega}{1+\omega} \quad (5)$$

$$\frac{d[(S)\text{-COZn}]}{d[\text{CHO}]} = -\frac{1}{1+\omega} \quad (6)$$

$$\frac{d[\text{Zn}]}{d[\text{CHO}]} = 1 \quad (7)$$

It was supposed that the mechanism shown in Table 1 could interpret the experimentally observed distribution under the actual conditions they were measured[3] with a suitable parameter set. To facilitate the search, a technique called symmetrization was also introduced. Symmetry ensures the same ee must be formed with the same probability for both *R* and *S* enantiomers.[19,37] The Monte Carlo simulation converges toward this symmetry in a probabilistic fashion after a high number of repetitions (convergence is roughly proportional to the square root of the number of repetitions done). We have found a method to force this symmetry into the calculation results: whenever a particular repetition gave a certain final ee value, this was interpreted as two different repetitions giving the same ee values, one favoring the *R*, the other the *S* enantiomer (see Figure S4 in the Supporting Information for further explanation). This technique made sure that the predicted final distribution shows the required symmetry independently of the number of repetitions carried out.

Parameters shown in the last row of Table 1 provided an excellent interpretation of the experimental results[3] as shown in Figure 1 (average deviation, 4.3%; correlation coefficient, R^2 = 0.9692; a correlation plot is given in Figure S4 in the Supporting Information). A less favored, histogram-style graph based on the same data is shown in Figure S5 in the Supporting Information.

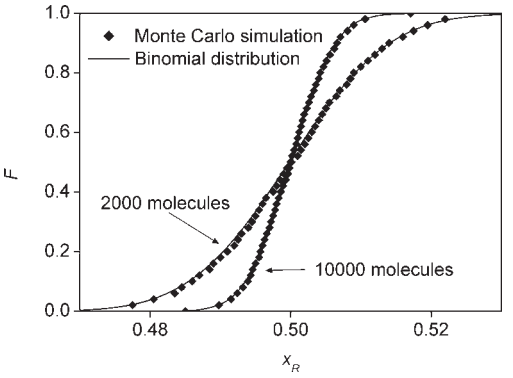


Figure 2. Theoretically predicted distribution of enantiomers in the Soai reaction until the formation of 2000 or 10 000 molecules. Number of repetitions: 1000. Both calculated distributions are indistinguishable from a symmetric binomial distribution. x_R: molar fraction of the *R* enantiomer (=0.5 + 0.5 × ee).

It is noted that rate constant k_1 has a very low value and k_4 is large so that a slow direct pathway could give a larger relative role to the autocatalytic pathway. The small value of α implies highly enantioselective autocatalysis. A full optimization for all six parameters was not viable as the model proved to be heavily overparametrized relative to the available experimental data; that is, many different combinations of parameters could yield a similarly good fit. Further model refinement is only possible with new experimental data such as extensive kinetic measurements. Monte Carlo simulations have shown that the distribution of enantiomers for the first 2000 and 10 000 molecules is identical to the binomial distribution, which is expected for simple racemization[50,51] (Figure 2). This fact implies that the autocatalytic pathways are not yet dominant at these low molecule numbers. This is understandable as the autocatalytic pathway involves dimerization of the product molecule, which is an unlikely event at the very beginning of the overall reaction.

CONCLUSION

Accelerated Monte Carlo simulation combined with deterministic continuation and symmetrization is able to handle large chemical mechanisms within stochastic kinetics. The utility of the method was demonstrated by predicting the enantiomer distribution based on an 18-step model of the Soai reaction and finding a parameter set, which interprets experimental data. The method opens the way to validate any future models of absolute asymmetric synthesis by direct comparisons of model predictions with measured data.

ASSOCIATED CONTENT

Supporting Information. Additional tables, figures, derivations referred to in the text, and Matlab code used in the calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was supported by the TÁMOP 4.2.1/B-09/1/KONV-2010-0007 project, which is cofinanced by the European Union and the European Social Fund.

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