Computational and experimental models of thermal cycling to break chiral symmetry

Dante M. Lepore*; Carl Barratt and Pauline M. Schwartz**
DML, PMS - Department of Chemistry and Chemical Engineering, Tagliatela College of Engineering, University of New Haven, West Haven, CT, USA 06516.
CB - Department of Mechanical, Civil and Environmental Engineering, Tagliatela College of Engineering, University of New Haven, West Haven, CT, USA 06516.

Abstract:
Computational modeling of reaction systems can provide a strong foundation for experimental investigations. In this investigation, we first propose a unique theoretical system for breaking chiral symmetry that utilizes thermal cycling to amplify a small initial asymmetry. Unlike models in the literature, no autocatalytic reactions were needed for homochirality in this model to emerge. Following from the theoretical model, experiments were designed with thermal cycling of NaClO$_3$ solutions in DMSO. NaClO$_3$ is not optically active in solution, but crystallizes into two optically active forms; under typical crystallization conditions, both forms arise in roughly equal amounts. With thermal cycling, however, one of the two optically active forms predominates. We hope to extend this experimental model to biologically important reactions to learn if thermal cycling played a role in chiral symmetry breaking in pre-biotic chemistry.

Introduction:
The emergence of chiral selectivity in biological molecules such as amino acids (L) and sugars (D) has long been a topic of interest in the scientific community (1). The fact that traditional synthesis of such compounds yields racemic mixtures (equal amounts of both forms) and not an excess of one enantiomer begs the question as to how such an enantiomeric excess (ee) could arise to provide the foundation for life on the planet. The famous Frank model suggests that an asymmetric autocatalytic system, in which one species acts as a catalyst for itself and an inhibitor for formation of its enantiomer, would be sensitive enough for a small initial imbalance between the two enantiomers to drive the reaction system to chiral symmetry breaking (1). This model has gained a great deal of attention and has since been demonstrated experimentally via the Soai reaction (2).

One of the goals of this project was to create a computational chemical model, which would amplify a small asymmetry (such as in the Frank model), but do so via thermal cycling. Thermal cycling has been shown in previous computational studies to yield counter-intuitive results that were not observed at any individual temperature (3,4). Here we investigate the effect of thermal cycling on reaction systems in order to drive chiral symmetry breaking.

Also, we investigated the crystallization of NaClO$_3$ as a possible process that might achieve chiral resolution via thermal cycling. Despite NaClO$_3$ not being chiral itself, it solidifies into two different optically active crystal forms. NaClO$_3$ also possesses a quality referred to as chiral amnesia (5), meaning that when in solution, the NaClO$_3$ molecules lose their distinct optical activity that they possessed in crystal form, thus providing a mechanism for rapid racemization. Experiments have shown that racemic mixtures of NaClO$_3$ can break chiral symmetry via stirring, boiling, or aerosol solutions (6,7,8). Based on the results from our computational model, we employed thermal cycling conditions in an attempt to achieve similar results. Applications of such a mechanism could inspire new and creative approaches to prebiotic synthesis reactions to break chiral symmetry.

Results: Computations Models
Kintecus 3.96, a powerful Arrhenius-based program was used to develop possible reaction schemes and calculate concentrations of theoretical chemical components over time (9). A reaction scheme was designed in which a racemic mixture of R and S exist and have the potential to racemize (Fig 1a and 1b). Also a catalytic surface, C, can bind with an enantiomer (equally with R and S), and the resulting product catalyzes racemization to favor production of the bound enantiomer. At a high temperature however, the catalytic surface becomes inactivated and any bound enantiomers are released back into solution. The only asymmetry in this model is a small difference (less than 1.5%) in the rate of decomposition between the two different enantiomer-catalytic surface species. It is also interesting that this model does not possess an
autocatalytic reaction, thus deviating from the Frank model (1).

The reaction was simulated for 10,000 seconds at 300K and 400K (initial conditions listed in Table 1): no significant enantiomeric excess was achieved at either fixed temperature (Fig. 2b). However, by simply changing the parameters to cycle back and forth between either temperature (60 seconds at 300K and 15 seconds a 400K) chiral symmetry breaking is achieved (Fig 2). Due to the nature of the reaction, each cycle is able to ensure that more of the Cs complex remains (as compared to the Cr complex) after the high temperature beings to inactive the catalytic surface. Thus, the racemization at the low temperature increasingly shifts the production of S at the expense of R; however, this is
still a very small change in ee after one cycle, but there is amplification with thermal cycling giving rise to an enantiomeric excess over time with multiple cycles.

Results: Experimental Crystallizations with Sodium Chlorate
Sufficient sodium chlorate (3 grams) (Fisher Scientific) was added to 5mL of dimethyl sulfoxide (DMSO) so that solid NaClO$_3$ remained and was at equilibrium with NaClO$_3$ in solution. The initial
solutions used were basically racemic, and three reaction conditions were employed:

1. Constant room temperature with stirring
2. Thermal cycling between 70 °C for 10 minutes and room temperature (28°C) for 30 minutes
3. Thermal cycling (as above) and stirring

Previous experiments conducted by Viedma et al. show that stirring solutions of NaClO₃ was sufficient agitation to bring about just one type of the optically active crystal (6). DMSO was chosen as a solvent for these experiments because of future aspirations to use NaClO₃ solutions to drive the pro-chiral organic reactions to breaking symmetry.

To quantify the enantiomeric excess of the resulting crystal formations of NaClO₃, a polarizing light microscope was employed. When the polarizer and analyzer are set to be about 87 degrees apart, then the two different NaClO₃ crystals can be visualized as either dark or light. Thus it follows when the polarizer and analyzer are roughly 93 degrees apart, the previous dark crystals have now become the light crystals and vice versa (Fig 3 a,b).

Various samples throughout the stirring and thermal cycling solutions were taken and the number of each optically active crystal recorded to determine percent enantiomeric excess (%ee). Our experiments agreed with the Viedma crystallizations (Fig 4a), in that simple stirring achieved an enantiomeric excess of one form of crystal over time. However, the thermal cycling solutions were able to achieve an ee much more quickly than just stirring (Fig 4b). Combining both thermal cycling and stirring proved to be even more efficient. Overall, a significant increase in ee was achieved by thermal cycling. Further experiments with NaClO₃ crystals with more cycles (10 cycles of heating and cooling) and stirring showed Oswald ripening as a possible mechanism for chiral resolution (Fig 5).

**Discussion**

*Computational models:*

Thermal cycling has been previously shown to yield counter-intuitive results of relatively simple reaction systems (3,4). Here, we were able to design a reaction system that was unable to produce an enantiomeric excess at any fixed temperature, but broke chiral symmetry if thermal cycling conditions were employed. It is conceivable that such thermal cycling conditions could have naturally existed on a prebiotic earth setting, such as a simple night and day cycle or even underwater thermal vents (11).

*Experimental Crystallizations:*

The theoretical model inspired the NaClO₃ crystallization experiments so that thermal cycling could be experimentally established as a condition that can in fact be manipulated to produce an enantiomeric excess. Indeed, thermal cycling was found to be even more efficient in producing an enantiomeric excess than stirring, but a combination of both was even more efficient than any single condition. Oswald ripening was observed after 10 cycles, and therefore suggests a mechanism behind this chiral amplification. Thus, thermal cycling has been shown experimentally as a mechanism to produced chiral symmetry breaking.
Future Plans:
Having preliminary data that supports thermal cycling as a means of obtaining homochirality, more tests will be conducted to definitely conclude that thermal cycling can give rise to one form of NaClO₃. Once established, a prochiral organic reaction will be performed in the presence of just one type of the NaClO₃ crystal, in hope that it will provide a catalytic surface to select one of the enantiomers (12). If thermal cycling can break chiral symmetry during the syntheses of an asymmetric molecule, then such a mechanism might explain the synthesis of L-amino acids under prebiotic conditions. The role of thermal cycling may have theoretical and practical implications for achieving homochirality in chemical and biological systems.

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Biography:
Dante Lepore is a senior at the University of New Haven in pursuit of a degree in Forensic Science and Biochemistry. He has been actively involved in a research with Dr. Schwartz and Dr. Barratt for the past year and has hopes of attending graduate school for a PhD in Biochemistry. He is also the academic peer mentor of New Hall, a forensic LLC tutor, and an avid hiker.

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