Homochirality

DOI: 10.1002/anie.200804566

"If Pigs Could Fly" Chemistry: A Tutorial on the Principle of Microscopic Reversibility**

*Donna G. Blackmond**

autocatalysis · chirality · microscopic reversibility · non-equilibrium processes · reversible reactions

In memory of Leslie E. Orgel and Jeremy R. Knowles

A recent essay in this journal by Hoffmann, Schleyer, and Schaefer III commented on what the authors called a "tense and fruitful balance between theory and synthesis in chemistry," in the context of computational approaches to predicting molecules.[1] A similar kind of tension may be found in many other areas of chemistry, as, for example, in research concerning the origin of life: the "geneticists" largely believe in the RNA world, whereas the "metabolists" believe that complex transformations characteristic of enzymes might have occurred prior to the evolution of informational molecules.[2]

A thread connecting these examples is the conspicuous absence in both cases of experimental scientific evidence to back up the stated hypothesis—and for good reason: we can't know the properties of molecules that have not yet been synthesized, and we can't travel back in time to monitor the prebiotic broth. In the former example, the authors of reference [1] make a considered appeal for circumspection in describing calculations so that the synthetic search for these molecules will be fueled by well-informed predictions. In the latter example, the late Leslie Orgel, who sat in the geneticists' camp, made his own understated appeal for scientific rigor in origin-of-life research with his comment that "scenarios that are dependent on 'if pigs could fly' hypothetical chemistry are unlikely to help."[2,3]

A central concern in both of these examples is how we deal with a quantitative result obtained from computation or theory that does not enjoy the benefit of experimental verification. This essay explores this concern further in the context of current origin-of-life research focused on developing models for the evolution of biological homochirality (a term used to refer to a group or molecules that possess the same sense of chirality). I share the sentiment of Hoffmann et al. that the reporting of non-experimentally corroborated conclusions carries with it a special responsibility, and I hope that this essay will serve to endorse their suggestion that simple common sense can be a practical aid. On top of that, I would emphasize that our first responsibility is to remain rigorously true to the fundamental chemical principles upon which both experimental and computational research must be based.

Several recent studies modeling the evolution of homochirality have failed this test, specifically with regards to the dictates and implications of the principle of microscopic reversibility.[4] Remembered by many chemists as a rather esoteric topic from undergraduate physical chemistry lectures, microscopic reversibility (and its companion, the detailed balance) turns out to be an eminently common-sense principle. This essay aims to show that it is straightforward to understand and apply, and should be neglected or misinterpreted only at great peril, lest the lure of perpetual motion machines and free lunches tempt us away from our responsibility to scientific rigor in trying to understand the mystery of life's origin.

Models for Homochirality

The molecular asymmetry inherent in biological processes has intrigued scientists for more than a century. Even outside the scientific community, the concept of chirality fascinates, as when Alice famously wondered whether Kitty would be able to drink the milk in the world found through the looking-glass.[5] How life based on strictly L-amino acids and D-sugars could have developed from a presumably racemic prebiotic broth has been a rich topic of scientific discussion. Initiated with theoretical ideas developed by Frank[6] and by Calvin[7] in the 1950s, the field has accelerated in the past two decades to include striking experimental findings based on both physical phase behavior[8–11] and chemical reactions.[12,13] Indeed, it was recently remarked that we are now "spoilt for choice"[14] in possibilities for how our present biological reality may have come about.

Models for the evolution of homochirality based on autocatalytic reactions have received significant attention. Characterized as "far-from-equilibrium", these reaction networks are most often modeled under conditions where it is assumed that the reverse reactions are too slow on a practical time scale to be included. Recently, however, the question has been raised of how reversibility may contribute to the generation of predominantly one enantiomer in autocatalytic reactions where the L or

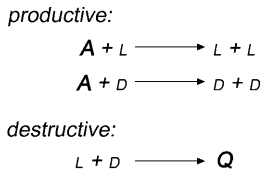
[*] Prof. D. G. Blackmond
Department of Chemistry and
Department of Chemical
Engineering & Chemical Technology
Imperial College
London SW7 2AZ (UK)
Fax: (+44) 7594-5804
E-mail: d.blackmond@imperial.ac.uk

[**] Stimulating discussions with John M. Brown, Gerald F. Joyce, Richard M. Kellogg, John S. Bradley, Alan Armstrong, Roald Hoffmann, and Dilip K. Kondepudi are gratefully acknowledged. D.G.B. is the recipient of a Royal Society Wolfson Research Merit Award.

D catalyst molecules are also the reaction product (enantiomeric excess, $ee = |(L-D)/(L+D)|$). It is here that the great culture clash with the principle of microscopic reversibility unfolds. But before going into that, it is useful to introduce the kinetic models for the evolution of homochirality that lie at the heart of the whole discussion.

Autocatalysis: The Models

One of the most prominent approaches to discussion of the evolution of homochirality is based on Frank's classic theoretical paper from 1953 on asymmetric autocatalysis.[6] His simple thesis was that if one "hand" of a chiral molecule can replicate itself while devising a way to suppress the synthesis of its opposite "hand", over time the system will inexorably become enriched in this "hand" of the molecule. Scheme 1

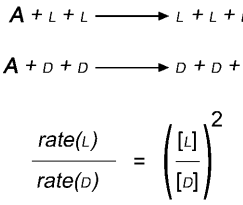


Scheme 1. Mutual antagonism model[6] for the autocatalytic production of enantiomers and destruction by means of a 1:1 quenching reaction.

illustrates one simple system treated by Frank. A prochiral reactant **A** reacts with either an L or a D enantiomer as a catalyst to produce another L or D enantiomer and regenerate itself at the same time. Direct reaction between an L and a D enantiomer produces an inactive product **Q** by the destructive reaction shown in Scheme 1, thus preventing any further productive autocatalytic turnover from these particular L and D molecules.

Frank showed that if the initial concentrations of L and D enantiomers are unequal—even by just a little bit—then with continued reaction turnover, the concentration of the major enantiomer will increase at the expense of that of the minor enantiomer. The "siphoning off" of a 1:1 proportion of the enantiomers ultimately captures *all* of the minor enantiomer, leaving behind only the major enantiomer and the inactive destruction product **Q**.

A related autocatalytic reaction network shown in Scheme 2 also accomplishes amplification of *ee*, but in this case without invoking a quenching reaction.[15] Because these productive reactions are second order in catalyst concentration, the rate of formation of enantiomers is proportional to the square of their concentration ratio. This nonlinearity between the rate and concentration ratios results in amplification of the major enantiomer when an initial imbalance between L and D exists.



Scheme 2. Nonlinear autocatalysis model for the evolution of homochirality.[15]

Autocatalysis: The "Catch"

Simulations of the reactions for the models of Scheme 1 and 2 may be carried out under conditions where reactant **A** is mixed in solution with a catalytic amount of a nearly 1:1 mixture of L and D molecules, as in a laboratory reaction vial or in an isolated prebiotic pool (a system closed to mass flow but open to energy transfer). Figure 1 confirms that both autocatalytic networks exhibit amplification of catalyst *ee* over time. However, each case exhibits important limitations. For the model in Scheme 1, enantioenrichment is complete, but overall yield of the major enantiomer may be low. For the model in Scheme 2, the yield may be high but the enantioenrichment will not be complete.

These limitations derive from a feature common to both models: when the initial difference between the concentrations of L and D enantiomers is very small, production starts out at a similar rate for the major and minor enantiomers, meaning that a lot of the "wrong" enantiomer is created at the beginning of the reaction. Each model employs its own approach to deal with this problem. In Scheme 1, destruction of the minor enantiomer by the quenching reaction can be completely effective over time, leading to homochirality, but it necessarily destroys an equal amount of the major enantiomer, leading to low yield. In Scheme 2, the nonlinear competition between the two reactions means that production of the major enantiomer eventually pulls ahead, but the ultimate level of enantioenrichment is capped because the minor enantiomer remains in the system. The more turnovers, the higher the ultimate enantioenrichment, but there are practical limits to this approach in a closed reaction system.

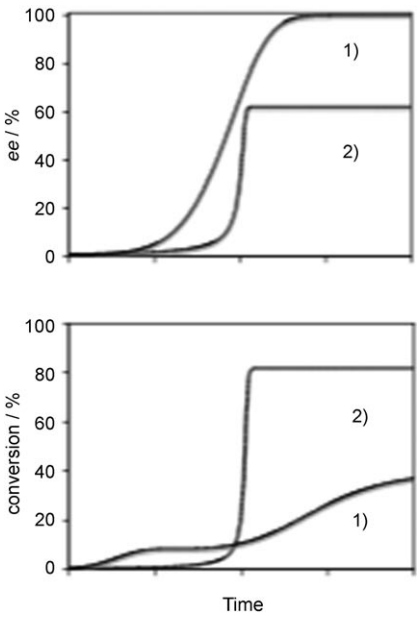


Figure 1. Simulation results showing evolution of catalyst enantiomeric excess (top) and conversion of **A** to the major enantiomer (bottom) for the autocatalytic reaction networks from 1) Scheme 1 and 2) Scheme 2. In both cases the starting conditions are 1 mol% initial catalyst concentration at 1% *ee*.

Autocatalysis: A Second Chance?

Recent papers have offered suggestions for how to beat these limitations inherent in closed-system autocatalysis as described by Scheme 1 and Scheme 2. If only a way could be found to *recycle* the wrong enantiomer of the catalyst produced early on in the process, turn it back into fresh reactant, and reconvert it to product; this would provide a chance to correct the mistakes made previously.

And the second time around the autocatalytic reaction will be more selective because the reaction vial now contains catalyst at amplified *ee*.

The nature of the "second chance" given to these autocatalysts differs in the two models. For the model in Scheme 1, Tsogoeva, Mauksch, and co-workers[16] reasoned that instead of combining L and D enantiomers in a quenching reaction to form inactive **Q**, one might imagine combining them to reconstruct our prochiral reactant **A**, as in Equation (1).

$$\text{L} + \text{D} \rightarrow \mathbf{A} + \mathbf{A} \qquad (1)$$

For the model in Scheme 2, Saito and Hyuga[17] reasoned that the L and D products could revert back to reactant **A** according to the simple decomposition reactions shown in Equations (2a) and (2b).

$$\text{L} \rightarrow \mathbf{A} \qquad (2a)$$

$$\text{D} \rightarrow \mathbf{A} \qquad (2b)$$

Simulations of the extended reaction networks formed by including the elementary rate Equations (1) and (2a)/(2b) in the reaction networks of Scheme 1 and 2, respectively, reveal that indeed the limitations outlined above disappear under these recycling conditions, and a homochiral state with high yield is obtained in both cases.

Although the form of the recycling differs in the two cases above, the idea of retracing our steps back to reactant **A** is key to both. Except that in neither case were these steps retraced *exactly*. And this is where the problems start. The principle of microscopic reversibility sets the rules for our route back to reactant. Let's review that principle and then discuss it in the context of these examples to answer the question: have we obeyed the rules?

Microscopic Reversibility

This is what the IUPAC Compendium of Chemical Terminology has to say: *"The principle of microscopic reversibility at equilibrium states that, in a system at equilibrium, any molecular process and the reverse of that process occur, on the average, at the same rate."*[18a]

The Compendium goes on to say that microscopic reversibility should be considered as synonymous with the concept of "detailed balance": *"Accordingly, the reaction path in the reverse direction must in every detail be the reverse of the reaction path in the forward direction (provided always that the system is at equilibrium)."*[18b]

The implications of this principle may be considered equally in terms of free energy diagrams or in terms of elementary rate equations and rate constants.

Free energy considerations. The statement of detailed balance given above also derives necessarily from transition state theory. For any elementary reaction, on average, the activated state must be the same in both directions. If the easiest pathway from one side of a mountain to the other is to skirt along its base, then the easiest way back won't involve climbing to the summit, which would require a lot more work. This idea is shown schematically in Figure 2 and is true whether or not the system has attained equilibrium. Even under far-from-equilibrium conditions, where for example the forward reaction occurs much more often than the reverse reaction, the higher energy reverse pathway will not be taken.

Relations between rate constants. Onsager[19] thought about the concept of microscopic reversibility in terms of rate constants in a network of elementary reactions. In his classic discussion of a "triangle reaction" (Scheme 3), he developed the reciprocal relationship between the rate constants that is given in Equation (3).

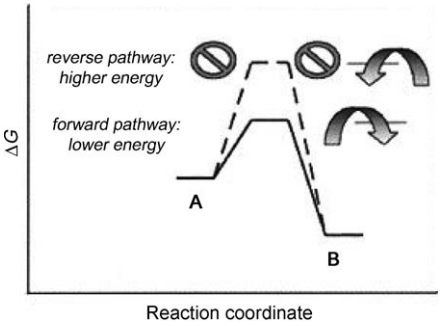
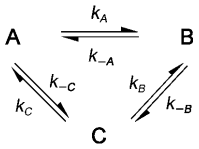


Figure 2. Schematic energy diagram for a reversible reaction. The lower energy pathway from **A** to **B** will also be that taken from **B** back to **A**. The higher energy pathway will not be taken.



Scheme 3. Onsager's "triangle reaction" network showing the reciprocal relations between the rate constants.[19]

$$\left(\frac{k_{\mathbf{A}}}{k_{-\mathbf{A}}}\right)\left(\frac{k_{\mathbf{B}}}{k_{-\mathbf{B}}}\right)\left(\frac{k_{\mathbf{C}}}{k_{-\mathbf{C}}}\right) = 1 \qquad (3)$$

Notice that Equation (3) contains only rate constants and no concentration terms. This highlights an important point. This relationship was developed by considering the system at equilibrium, where microscopic reversibility and the detailed balance must hold. However, Equation (3) clearly holds whether the system is near or far from equilibrium, because rate constants are just that: *constant*, at a given temperature, regardless of the extent of reaction progress or the position with respect to the equilibrium condition at that temperature. It is called the "principle of microscopic reversibility at equilibrium", but clearly its power to help us assess the viability of reaction networks extends far beyond the equilibrium condition. It permits the derivation of an expression for any of these rate constants in terms of the others, as for example for $k_{-\mathbf{C}}$ in Equation (4). This relationship holds fast even when the system operates away from equilibrium.

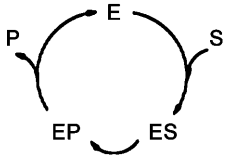
$$k_{-\mathbf{C}} = k_{\mathbf{C}}\left(\frac{k_{\mathbf{A}}}{k_{-\mathbf{A}}}\right)\left(\frac{k_{\mathbf{B}}}{k_{-\mathbf{B}}}\right) \qquad (4)$$

Equation (4) shows that it isn't up to us to decide arbitrarily whether the rate of reforming **C** from **A** is small compared to other rates in the network, even under conditions far away from equilibrium; the degree to which this reaction contributes to the overall network is dictated by this relationship between the rate constants in the network, which in turn is governed by the principle of microscopic reversibility at equilibrium.

Another critical point to note concerning this triangle reaction network is that the reverse rate constants are

related to each other in an inverse manner: if the reactions for producing **B** from **A** and **C** from **B** are driven strongly forward, then the reaction from **C** to **A** will be driven in the opposite direction.

Any catalytic cycle is in fact a recycle system similar to Onsager's triangle. Any productive catalytic cycle (i.e., one that is making a net amount of product at a given time) by definition is operating out of equilibrium and does not follow detailed balance. Consider the simple enzyme cycle of Scheme 4



Scheme 4. Simple catalytic cycle for conversion of substrate **S** to product **P** by binding to catalyst **E** to form intermediates **ES** and **EP**.

obeying Michaelis–Menten kinetics. The catalyst is regenerated in the final step, which is not the reverse of the first step in the cycle, in which substrate reacts with the catalyst. Does this square with what we've learned about microscopic reversibility? The answer is yes, and the procedure is the same as before: we examine the system at equilibrium, where no net **P** is produced and no net **S** is consumed, considering all steps in the network with reversible arrows (written in linear fashion as Equation (5)), in order to determine the

$$\mathbf{E} + \mathbf{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{ES} \underset{k_{-\mathbf{S}}}{\overset{k_{\mathbf{S}}}{\rightleftharpoons}} \mathbf{EP} \underset{k_{-\mathbf{P}}}{\overset{k_{\mathbf{P}}}{\rightleftharpoons}} \mathbf{E} + \mathbf{P} \qquad (5)$$

relationships between the rate constants, which is given in Equation (6).

$$k_{-\mathbf{P}} = k_{\mathbf{P}} \left(\frac{k_1}{k_{-1}} \right) \left(\frac{k_{\mathbf{S}}}{k_{-\mathbf{S}}} \right) \frac{[\mathbf{S}]_{eq}}{[\mathbf{P}]_{eq}} \qquad (6)$$

If $[\mathbf{P}]_{eq}$ is very large compared to $[\mathbf{S}]_{eq}$, $k_{-\mathbf{P}}$ will tend toward zero; cases where the catalyst cycle is driven far towards product thus allow us to neglect $k_{-\mathbf{P}}$. The observed values for rate constants in such a catalytic cycle operating away from equilibrium are in fact a consequence of the detailed balance found at equilibrium. It is interesting to note, however, that the maximum efficiency of a catalytic cycle will be reached when the system remains close to equilibrium, as shown theoretically as well as experimentally by Knowles and Albery for the triosephosphate isomerase system, an enzyme that has evolved to near-perfect efficiency.[20]

It must be noted that there are instances in which the rule of microscopic reversibility is known to break down. A reaction that is initiated by photochemical activation is one case: the activated species may decay along a different pathway under these circumstances. The presence of a strong external magnetic field or the influence of Coriolis forces will also result in situations where microscopic reversibility may be violated. But, as pointed out by Onsager, these represent "exceptional cases which can readily be recognized and sorted out".[19] Common sense tells us, for example, that we won't typically encounter such exceptions in thermally driven reactions we carry out routinely in the laboratory.

Let's summarize the main points contained in the principle of microscopic reversibility:

- Whether a reaction network operates near or far from its equilibrium condition, all elementary reactions must proceed in the reverse direction by the same transition state as in the forward direction. Thus the pathway for the entire network of elementary reactions must be identical in the forward and reverse directions.
- Whether a reaction network operates near or far from its equilibrium condition, this condition fixes the values of the forward and reverse rate constants at a given temperature. Thus the equilibrium condition must be considered when an evaluation is made of the plausibility of neglecting some reaction steps when a system operates under non-equilibrium conditions.
- In a recycle system, where the product of one reaction is the reactant for another, all of the rate constants in the network will not be independent of one another. The relationship between the rate constants in any recycle network will be determined by Onsager's reciprocal relations.

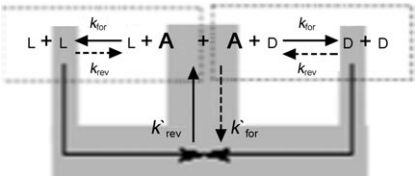
Recycle Models Revisited

In light of this review of the fundamental concepts associated with the priniciple of microscopic reversibility, let's now look back at the models that have been proposed for extending the autocatalytic reaction networks of Scheme 1 and Scheme 2 to include cases where the "wrong" product is recycled back to reactant.

We have just seen that even if the recycle reaction models operate under "far-from-equilibrium" conditions, this doesn't let us off the hook concerning the dictates of the principle of microscopic reversibility. Most importantly for our discussion, the principle says that we cannot arbitrarily decide where to use forward arrows and where to use backwards arrows; we must follow the dictates of the equilibrium condition to determine this. Let's turn back to the models of Scheme 1 and 2 and see whether the recent attempts to recycle these autocatalytic reactions have obeyed the rules.[21]

Recycling in the model of Scheme 1. We discussed earlier how simulations combining the irreversible autocatalytic reactions of Scheme 1 and the irreversible recycle reaction of Equation (1) led to the observation of asymmetric amplification.[16a] The full reaction model is shown in Scheme 5. The rate constants shown with dashed arrows were set equal to zero ($k_{rev} = k'_{for} = 0$) in the simulations that were carried out in support of the recycle model. Our task is to determine whether the principle of microscopic reversibility allows this.

The reaction network in Scheme 5 may be considered as a variation of Onsager's triangle. A critical feature



Scheme 5. Autocatalytic reaction network extended from the model in Scheme 1 to include recycling as in Ref. [16]. Dashed boxes show the productive autocatalytic reactions of Scheme 1; gray area shows recycle reaction L + D → **A** + **A** as in Equation (1), which is employed in place of the destructive reaction L + D → **Q** of Scheme 1.

contained in both is that elementary rate steps connect the reactant **A** to products L and D, and products L and D back to reactant **A** in a cyclic manner. This means that we need to consider the equilibrium condition, including *all* the forward and reverse arrows for *all* of the reactions in Scheme 5, in order to determine the reciprocal relations between the rate constants. What we find when we do this is the relationship between k_{rev} and k'_{for} shown in Equation (7).[21c]

$$k'_{for} = k'_{rev}\left(\frac{k_{for}}{k_{rev}}\right)^2 \quad (7)$$

This analysis reveals that the two rate constants arbitrarily set equal to zero in reference [16a]are in fact related as the *inverse square* of one another! That means when we set k_{rev} to a very small number, say $10^{-6}\,M^{-1}s^{-1}$, the value of k'_{for} becomes $10^{12}\,M^{-1}s^{-1}$, a very large number indeed.[22] Clearly the principle of microscopic reversibility will not allow us to set both constants equal to zero simultaneously, even in a reaction carried out under far-from-equilibrium conditions. When rate constants chosen in accordance with Equation (7) are used in simulations of the network in Scheme 5, an inexorable erosion, rather than amplification, of catalyst enantiomeric excess is observed.[21c] The recycling model based on Scheme 5 violates the principle of microscopic reversibility and therefore does not represent a physically and chemically realistic reaction network.

Recycling in the model of Scheme 2. When the autocatalytic reactions of Scheme 2 are coupled with the proposed recycle reactions of Equations (2a) and (2b), simulations showed asymmetric amplification leading to homochirality.[17] However, all of these reactions were treated with forward arrows only. We may carry out the same treatment as above, using microscopic reversibility and the equilibrium condition to determine the relationships between the forwards and reverse rate constants. A similar result is found: the "missing" rate constants are inversely related to one another in this case, and they simply can't all be neglected simultaneously.[21a]

In this example, it is instructive to view the violation of the principle of microscopic reversibility from the perspective of the energy diagram as well as from the perspective of the rate constant. What the authors of reference [17] chose as the "recycle" reactions of Equations (2a) and (2b) are in fact the *uncatalyzed* complement to the autocatalytic reaction network of Scheme 2. This recycling network proposes that the forward path takes the lower energy autocatalytic reaction coordinate, but the return path takes the higher energy uncatalyzed route (Figure 3).

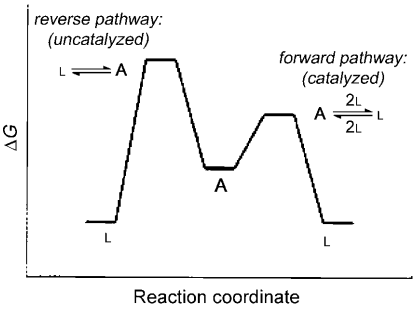


Figure 3. Energy diagram describing the recycle reaction model of Ref. [17], which combines the autocatalytic reactions of Scheme 2 with the recycle reactions of Equations (2a) and (2b). The recycle model asserts that the reaction proceeds in the forward direction by the autocatalytic pathway and in the reverse direction by the uncatalyzed pathway. Illustrated here for the L enantiomer only.

When rate constants for *both* directions in *both* the autocatalytic and noncatalytic pathways are determined in accordance with the principle of microscopic reversibility, simulations show that the fully reversible reaction system for Scheme 2 proceeds inexorably towards the racemic state.[21a] Attempting to attain a homochiral state by recycling the autocatalytic reaction back by its uncatalyzed route clearly breaks the rules.

Recycling Models: The Verdict

The models for asymmetric amplification presented in Scheme 1 and Scheme 2 (without adding in the proposed recycling reactions) satisfy the dictates of microscopic reversibility as long as these reactions are driven strongly forward. This analysis shows that when new reactions are introduced to the network, care must be taken so that modeling in such networks is developed in accordance with the principle of microscopic reversibility. Neither of the recycle models considered here passes this test.

Common Sense, Please

Faced with these cold hard facts derived from the correct application of the principle of microscopic reversibility, the recycle models proposed above might be expected to make a quiet exit from the stage of origin-of-life research. However, the recycling concept has found new life with further proposals for how such networks may get around these awkward truths. Suggestions for why conclusions based on modeling that violates the principle of microscopic reversibility might nevertheless be valid have included the following:[23]

- Negative concentrations of reactants
- Matter–antimatter asymmetry in the universe
- Local nonconservation of microscopic reversibility
- Breakdown of microscopic reversibility under far-from-equilibrium conditions
- Effect of Coriolis forces
- Influence of a charge-parity violating force
- "Stronger" physical conservation laws
- "Strong" autocatalysis under high reactant concentrations
- A distribution between "stored" and fully dissipated energy
- Path-dependent energy levels for molecules

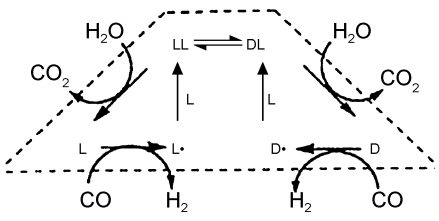
These suggestions appear to be vying for status as what Onsager would call "exceptional cases," which, as he says, should be easily sorted out based on our laboratory experience. This is problematic, however, because none of these recycle models for evolution of homochirality has yet been found to have an experimental counterpart. Lack of experimental corroboration leaves the stage open for fertile and imaginative hypotheses, but it also should remind us of the special responsibility in reporting such results discussed by Hoffmann et al., as well as of Orgel's admonish-

ment concerning "hypothetical chemistry".[2] The analysis presented here is clear: models based on hypothetical reactions with no experimental corroboration have been shown to be in violation of a fundamental chemical principle; exceptional explanations have been invoked, again without experimental grounding, to defend these models and the implications contained in their results. How does this exercise contribute to our basic understanding? Does it aid in designing new experiments? Does it provide enlightenment about basic principles? Here I would simply appeal to common sense to lay to rest at least the more fanciful of the proposals on the above list.

Opening Up the System

Reactions that occur in a closed system such as a reaction vial in the laboratory or in a stagnant prebiotic pool (neglecting evaporation) have been the focus of these models for homochirality. Plasson et al. have looked at recycling reaction networks in an open system that uses chemical energy as a driving force.[24] They considered Onsager-like triangle networks comprising enantiomer activation, dimerization, and dissociation connected by an epimerization reaction. They showed that the cycles could be made to run unidirectionally if powered by the chemical potential of mass flow across the system boundaries (Scheme 6). The reverse reactions mandated by the principle of microscopic reversibility for the closed system within the dashed lines are overwhelmed by mass action. Given an initial imbalance in D and L enantiomers and appropriately adjusted rate constants, one cycle can be enriched at the expense of the other, allowing the establishment of a nonracemic steady state. Enantioenrichment remains viable as long as the chemical energy source is not turned off. Chemical potential drives metabolic reactions in a net forward direction, and this concept applied to the amplification of enantiomeric excess has been termed "protometabolic"[24b] by these authors. While this model is loosely based on an experimental reaction network of CO-driven dipeptide formation studied by Wächtershäuser et al.,[25] it is nevertheless sobering to note that an erosion, not an enhancement, of *ee* was observed experimentally in that system.

Opening up the system and allowing chemical potential to drive reactions has also been suggested by these same authors as a means of rehabilitating the discredited recycling models for the evolution of homochirality that were discussed here. For example, Plasson suggests that the conflict presented in the energy diagram of Figure 3 may be resolved by invoking an "implicit" chemical energy source to drive the uncatalyzed reaction in reverse, as depicted in Figure 4. However, such a reaction would need to be selective enough to operate preferentially on the uncatalyzed reaction and not on the autocatalytic reaction. Both this unidentified chemical energy source reacting across the system boundaries and the closed-system autocatalytic reactions remain hypothetical. Common sense should guide the search for experimental systems exhibiting such behavior; to date the balance between experiment and prediction has been more tense than fruitful.



Scheme 6. Open system with unidirectional cycles driven by a chemical energy source crossing the system boundaries, in this case the water–gas shift reaction.[24] Redrawn from Ref. [21c].

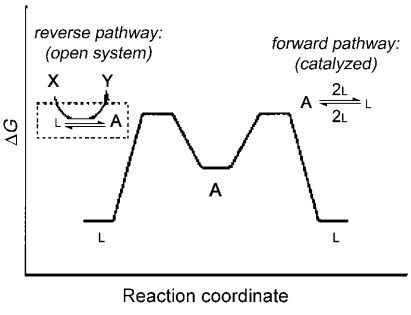


Figure 4. Energy diagram describing a recycle reaction model combining the closed-system autocatalytic reactions of Scheme 2 with an "implicit" open system reaction to drive the uncatalyzed reverse reaction.

Conclusions

The principle of microscopic reversibility at equilibrium is seen to be a powerful tool that sets the rules for how complex reaction networks operate even when far removed from the equilibrium condition. Research aimed at modeling how the homochirality of biological molecules may have evolved in the prebiotic world faces a special challenge in proposing hypothetical reaction networks that cannot come under the scrutiny of experimental evaluation. The fundamental rules for the pathways of such reactions must guide us if the models are to have chemical and physical meaning. As the Cheshire cat said to Alice: "If you don't know where you are going, any road will take you there."

Received: September 16, 2008
Published online: December 30, 2008

[1] R. Hoffmann, P. v. R. Schleyer, H. F. Schaefer III, *Angew. Chem.* **2008**, *120*, 7276; *Angew. Chem. Int. Ed.* **2008**, *47*, 7164.
[2] L. E. Orgel, *PLoS Biol.* **2008**, *6*, e18.
[3] One of the most popular, if not the original, versions of this adage comes from *Alice's Adventures in Wonderland* by Lewis Carroll: "'I've a right to think,' said Alice sharply, for she was beginning to feel a little worried. 'Just about as much right,' said the Duchess, 'as pigs have to fly'".
[4] a) R. C. Tolman, *Proc. Natl. Acad. Sci. USA* **1925**, *11*, 436; b) R. C. Tolman, *The Principles of Statistical Mechanics*, Oxford University Press, London, **1938**.
[5] *Through the Looking-glass, and What Alice Found There*, Lewis Carroll, Digital Scanning Inc, **2007**.
[6] F. C. Frank, *Biochim. Biophys. Acta* **1953**, *11*, 459.
[7] M. Calvin, *Molecular Evolution*, Oxford Univ. Press, Oxford, UK, **1969**.
[8] D. K. Kondepudi, *Science* **1990**, *250*, 975.
[9] C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065504.
[10] a) W. L. Noorduin, T. Izumi, A. Millemaggi, M. Leeman, H. Meekes, W. J. P. Van Enckevort, R. M. Kellogg, B. Kaptein, E. Vlieg, D. G. Blackmond, *J. Am. Chem. Soc.* **2008**, *130*, 1158; b) C. Viedma, J. E. Ortiz, T. de Torres, T. Izumi, D. G. Blackmond, *J. Am. Chem. Soc.* **2008**, *130*, 15274.
[11] a) M. Klussmann, H. Iwamura, S. P. Mathew, D. H. Wells, Jr., U. Pandya, A. Armstrong, D. G. Blackmond, *Nature* **2006**, *441*, 621; b) M. Klussmann,

A. J. P. White, A. Armstrong, D. G. Blackmond, *Angew. Chem.* **2006**, *118*, 8153; *Angew. Chem. Int. Ed.* **2006**, *45*, 7985.
[12] K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767.
[13] D. G. Blackmond, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5732.
[14] "Giving Life a Hand" in *Chemistry World*, by Phillip Ball, March 20, **2007**.
[15] a) P. Decker, *J. Mol. Evol.* **1974**, *4*, 49; b) D. K. Kondepudi, G. W. Nelson, *Phys. A* **1984**, *125*, 465.
[16] a) M. Mauksch, S. B. Tsogoeva, S. Wei, I. M. Martynova, *Chirality* **2007**, *19*, 816; b) M. Mauksch, S. B. Tsogoeva, *ChemPhysChem* **2008**, *9*, 2359.
[17] a) Y. Saito, H. Hyuga, *J. Phys. Soc. Jpn.* **2004**, *73*, 33; b) Y. Saito, H. Hyuga, *J. Phys. Soc. Jpn.* **2004**, *73*, 1685.
[18] a) V. Gold, K. L. Loening, A. D. McNaught, P. Shemi, *IUPAC Compendium of Chemical Terminology*, Blackwell Science Oxford, 2nd ed., **1997**; b) V. Gold, K. L. Loening, A. D. McNaught, P. Shemi, *IUPAC Compendium of Chemical Terminology*, Blackwell Science Oxford, 2nd ed., **1997**.
[19] L. Onsager, *Phys. Rev.* **1931**, *37*, 405.
[20] J. R. Knowles, W. J. Albery, *Acc. Chem. Res.* **1977**, *10*, 105.
[21] a) D. G. Blackmond, O. K. Matar, *J. Phys. Chem. B* **2008**, *112*, 5098; b) D. G. Blackmond, *J. Phys. Chem. B* **2008**, *112*, 9553; c) D. G. Blackmond, *Chirality*, **2008**, DOI: 10.1002/chir.20592.
[22] These values are obtained for the missing constants k'_{for} and k_{rev} using $k_{for} = k'_{rev} = 0$ as assigned in Ref. [16a].
[23] All of the proposals in this list were suggested in Ref. [16b].
[24] a) R. Plasson, H. Bersini, A. Commeyras, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 16733; b) R. Plasson, D. K. Kondepudi, H. Bersini, K. Asakura, *Chirality* **2007**, *19*, 589; c) R. Plasson, *J. Phys. Chem. B* **2008**, *112*, 9550.
[25] a) C. Huber, W. Eisenreich, S. Hecht, G. Wächtershäuser, *Science* **2003**, *301*, 938; b) C. Huber, G. Wächtershäuser, *Science* **1998**, *281*, 670.

