On the Self-replication of Chirality

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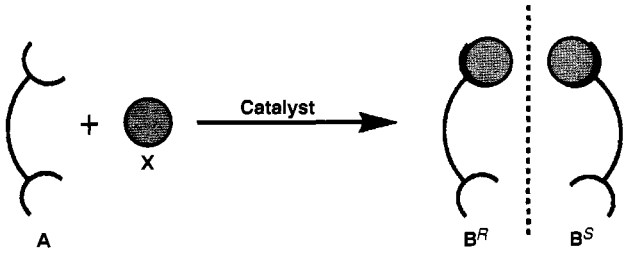
The 'MB_2-catalyst' model, involving two product molecules in an autocatalytic process, is the simplest system that is capable of self-replication to generate optically active products spontaneously.

The origin of the chirality of the building blocks of life is one of the most fundamental questions to have been posed by chemists, and many models have been proposed for the evolution of handedness in biomolecules.[1] For the synthetic organic chemist, two specific questions are particularly pertinent: (i) What is the simplest self-replicating model system that could generate optically active products spontaneously? (ii) What practical features might facilitate the design and identification of such a system? Answers to these two questions are proposed in this paper.

In order to simplify the visualisation of the theoretical analysis, a two-dimensional model is presented in the Schemes. Thus, in Scheme 1, the achiral starting material **A** is converted into $\mathbf{B}^R$ and $\mathbf{B}^S$, which are non-superimposable mirror images of the product **B**. The formation of **B** is *auto-catalytic*, so that **B** (or a complex of **B**) catalyses its own formation from **A**, with replication of **B**'s structure and chirality. Two types of catalyst are considered, the first involving one molecule of **B**, and the second involving two molecules of **B**. The two-dimensional models transpose into three-dimensions without affecting the calculations.

Let us first consider the case where the catalyst contains a single molecule of **B** (*e.g.* the catalyst in Scheme 1 is unimolecular **B**, equivalent to simple replication). For clarity, Table 1 presents the results of a self-replication cycle, assuming the newly generated product **B** does not affect the catalyst until the cycle is complete; this is equivalent to calculating the rate of change of e.e. [*i.e.* d(*e.e.*)/d*t*], and the final e.e. can be readily determined by an iterative process (e.e. = enantiomeric excess). In the results presented in Table 1, the reaction is assumed to proceed with 80% asymmetric induction [*e.g.* 9:1 ratio of enantiomeric products ($\mathbf{B}^R:\mathbf{B}^S$) are formed from homochiral catalyst ($\mathbf{B}^R$)], and the results indicate that, whatever the optical purity of **B** used to initiate the reaction, the e.e of the product continuously decreases towards zero. Perhaps surprisingly, this simple 1:1 self-replication model inevitably leads to racemic product, whatever the enantiomeric excess of the starting catalyst or fidelity of chiral replication.

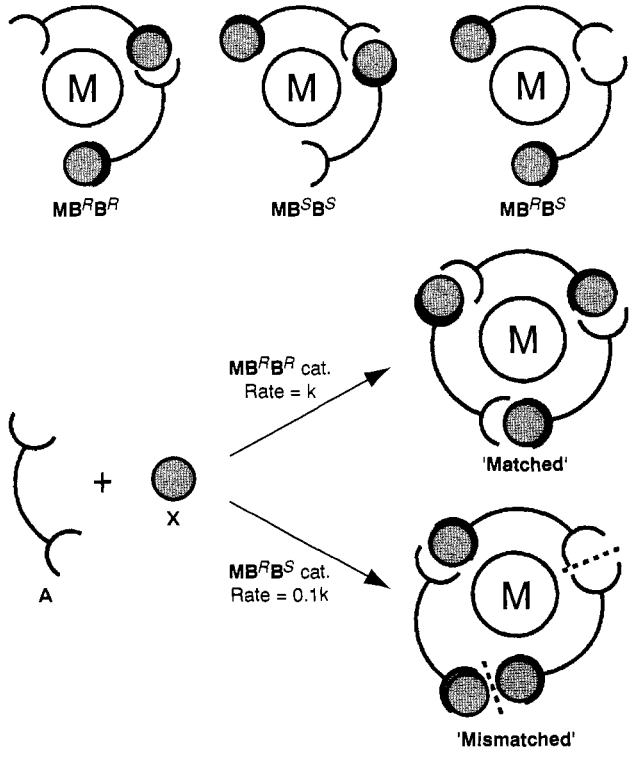
What happens if the catalyst contains two molecules of the product **B**? This situation is illustrated in Scheme 2, in which the conversion of **A** into **B** is catalysed by complexes containing two molecules of **B** ($\mathbf{MB}^R\mathbf{B}^R$, $\mathbf{MB}^R\mathbf{B}^S$, or $\mathbf{MB}^S\mathbf{B}^S$); in this example, the catalyst has been organised around a central moiety **M**, although this plays no part in the analysis. The results of the calculations presented in Table 2 are based on the following definitions and assumptions: (*a*) the chiral replicator is labelled **B**, and *R* or *S* superscripts identify the enantiomeric form ($\mathbf{B}^R$ or $\mathbf{B}^S$); (*b*) the enantiomers $\mathbf{B}^R$ and $\mathbf{B}^S$ cannot interconvert; (*c*) the molecules self-replicate using an achiral building block **A** which becomes bonded to **X**; (*d*) the active catalyst is an $\mathbf{MB}_2$ complex; (*e*) $\mathbf{MB}^R\mathbf{B}^R$, $\mathbf{MB}^R\mathbf{B}^S$, and $\mathbf{MB}^S\mathbf{B}^S$ are isoenergetic;[2] (*f*) the catalytic activity of the [$\mathbf{MB}^R\mathbf{B}^R$] or [$\mathbf{MB}^S\mathbf{B}^S$] catalysts are 10 times higher than that of the diastereoisomeric [$\mathbf{MB}^R\mathbf{B}^S$] catalyst; (*g*) the fidelity of self-replication of chirality corresponds to asymmetric induction of 80%, so [$\mathbf{MB}^R\mathbf{B}^R$] catalyses conversion of **A** → **B** in an enantiomeric ratio of $\mathbf{B}^R:\mathbf{B}^S$ = 90:10; (*h*) conversion of **A** → **B** is negligible in the absence of $\mathbf{MB}_2$ catalyst; (*i*) product inhibition is not a problem (*i.e.* $\mathbf{MB}_3$ dissociates); (*j*) the results of self-replication cycles in Table 2 assume the newly generated product **B** does not affect the catalyst until the cycle is complete.



Scheme 1 Two-dimensional model for **A** → **B**, where **B** is a chiral product, $\mathbf{B}^R/\mathbf{B}^S$. For simple self-replication, the catalyst is **B**.

Table 1 The result of a single cycle of self-replication of **B** catalysed by **B** (see Scheme 1) with various starting e.e.s, assuming chirality reproduced with 90% fidelity

Starting ratio *R*/*S*	Replication	Product ratio *R*/*S*
100 *R* 0 *S*	90 *R* + 10 *S* 0 *R* + 0 *S*	90 *R* 10 *S*
90 *R* 10 *S*	81 *R* + 9 *S* 9 *S* + 1 *R*	82 *R* 8 *S*
60 *R* 40 *S*	54 *R* + 6 *S* 36 *S* + 4 *R*	58 *R* 42 *S*



Scheme 2 The asymmetric self-replication system analysed in Table 2, depicting $\mathbf{MB}_2$ catalysts; the dotted lines indicate unfavourable interactions that might reduce the catalytic activity for a 'mismatched' reaction

Let us now explore the result of such a system undergoing self-replication of 100 molecules of **B**. When the initial e.e. of **B** is 90%, the optical purity drops after a single cycle. However, starting with **B** of 60% e.e., a replication cycle leads to **B** *of increased optical purity*. By an iterative process, it can be shown that the e.e. approaches 74.6% asymptotically, as demonstrated by the maintenance of optical purity when **B** of this e.e. undergoes a replication cycle (Table 2). Whatever the optical purity of the initial catalyst, *the system is spontaneously asymmetric*, and will generate an optically active product of known enantiomeric excess.

Although many explanations have been offered for the origin of handedness in biomolecules, the '$\mathbf{MB_2}$-catalyst' model described above is the simplest system that is capable of self-replication to generate optically active products spontaneously. It is noteworthy that, in a detailed analysis of the efficiency of chiral catalysts in asymmetric synthesis, Kagan pointed out that the e.e. of a chiral product could be higher than that of the chirally inducing additive, but only if a complex of at least two chiral additive molecules are present in the active catalyst.[3]

Table 2 The result of a single cycle of self-replication of **B** catalysed by $\mathbf{MB_2}$ (see Scheme 2) with various starting e.e.s, assuming chirality reproduced with 90% fidelity

Starting ratio *R*/*S*	Ratio of catalysts	Replication	Product ratio *R*/*S*	Product % ratio *R*/*S*
90 *R*	81 *RR*	72.9 *R* + 8.1 *S*	73.9 *R*	88.2 *R*
	18 *RS*	0.9 *R* + 0.9 *S*		
10 *S*	1 *SS*	0.9 *S* + 0.1 *R*	9.9 *S*	11.8 *S*
80 *R*	64 *RR*	57.6 *R* + 6.4 *S*	59.6 *R*	83.7 *R*
	32 *RS*	1.6 *R* + 1.6 *S*		
20 *S*	4 *SS*	3.6 *S* + 0.4 *R*	11.6 *S*	16.3 *S*
87.3 *R*	76.21 *RR*	68.59 *R* + 7.62 *S*	69.86 *R*	87.3 *R*
	22.17 *RS*	1.11 *R* + 1.11 *S*		
12.7 *S*	1.61 *SS*	1.45 *S* + 0.16 *R*	10.18 *S*	12.7 *S*

Moreover, several papers have reported autocatalytic systems in which chirality is self-replicated, but reductions in the optical purity of the products/catalysts were always observed.[4]

So how might an asymmetric self-replication system be developed? If the chiral 'replicator' **B** were a bidentate ligand capable of participating in octahedral coordination to a transition metal cation **M**, then it might be possible to design an $\mathbf{MB_2}$ complex that would fulfil the criteria above, and act as a Lewis acid catalyst for the asymmetric self-replication of **B** from an achiral precursor **A**. To identify a successful reaction, the e.e. of the initiating catalyst should be low, so that the telltale enhancement in optical purity might be observed in a system that exhibits only modest asymmetry. An attractive feature of such a system is that it might reasonably have been formed under prebiotic conditions. And whilst the origin of biomolecular asymmetry will probably never be proven, the '$\mathbf{MB_2}$-catalyst' model is both pleasingly simple, and provides adequate guidelines for such systems to be designed and tested.

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References

1 Leading reviews include: L. D. Barron, *Chem. Soc. Rev.*, 1986, **15**, 189; L. D. Barron, in *New Developments in Molecular Chirality*, ed. P. G. Mezey, Kluwer, Dordrecht, 1991, pp. 1–55; S. F. Mason, *Ciba Found. Symp.*, 1991, **162**, 3; S. F. Mason, *Chirality*, 1991, **3**, 223; A. Salam, *J. Mol. Evol.*, 1991, **33**, 105; W. A. Bonner, *Origins Life Evol. Biosphere*, 1991, **21**, 59, 407; W. A. Bonner, *Origins Life Evol. Biosphere*, 1994, **24**, 63.

2 See M. Terada, K. Mikami and T. Nakai, *J. Chem. Soc., Chem. Commun.*, 1990, 1623.

3 D. Guillaneux, S.-H. Zhao, O. Samuel, D. Rainford and H. B. Kagan, *J. Am. Chem. Soc.*, 1994, **116**, 9430,.

4 For example: A. H. Alberts and H. Wynberg, *J. Am. Chem. Soc.*, 1989, **111**, 7265; K. Soai, S. Niwa and H. Hori, *J. Chem. Soc., Chem. Commun.*, 1990, 982.