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Stochastic Analysis of the Parity-Violating Energy Differences between Enantiomers and Its Implications for the Origin of Biological Chirality

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A stochastic description of a racemic mixture is developed taking into account the slight energy difference between enantiomers originating from parity violation ($\Delta E_{PV} \approx 10^{-13}$ Jmol^{-1}). The system can be described by an asymmetric binomial distribution. A method is developed to calculate the probability of forming the more-stable isomer in excess, which is not significantly larger than 50% under normal conditions. It is concluded that the parity-violating energy difference between enantiomers is very unlikely to be relevant in considerations about the origin of biological chirality.

Introduction

It is now well established that the two enantiomers of a chiral molecule may have slightly different energies because of parity violation in nuclear physics.[1−12] Ab initio methods estimated this parity-violating energy difference, ΔE_{PV}, to be about 10^{-13} Jmol^{-1} for biomolecules like amino acids or carbohydrates.[1−8] For the simplest chiral amino acid, alanine, the naturally occurring L isomer is usually quoted as somewhat more stable.[3−4] It has been suggested that this small excess of the L isomer caused by ΔE_{PV} could have been amplified by chiral autocatalysis and could give rise to the present biological chirality.[9] In this view, sometimes referred to as *de lege* (lawlike) selection,[4] the dominance of L amino acids is a necessary consequnce of the existence of ΔE_{PV}.

Although a lot of experimental[13−17] and theoretical findings[18−25] show that asymmetric autocatalysis is indeed viable and may even lead to absolute asymmetric synthesis,[14,19,23] the possible role of ΔE_{PV} is still contraversial for two reasons. First, recent calculations showed that in some of its possible conformations D-alanine seems to be more stable than L-alanine and the preference may also be influenced by solvent effects.[5−6] Second, the expected excess of the more-stable enantiomer as a consequence of ΔE_{PV} is very low. The stochastic approach, which can interpret absolute asymmetric synthesis readily,[22−23] is used in this paper to show that it is orders of magnitude lower than the natural fluctuations under normal conditions. It will also be demonstrated that the probability of obtaining the more-stable enantiomer in excess in a chemical process is only slightly higher than 50%, which is a stong argument against *de lege* selection in biological chirality. The main text of this paper will only state the relevant equations; the proofs are deposited as Supporting Information.

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Results and Discussion

As noted in the introduction, the total energies of the two different enantiomers of a chiral molecule are slightly different. Therefore, when this chiral molecule is formed from nonchiral starting materials without any external chiral influence, the more-stable enantiomer is somewhat more likely to form. The probability of forming the more-stable enantiomer (L for alanine) is given as $(0.5 + \epsilon)$ in order to give a fully quantitative treatment. The probability of forming the less-stable enantiomer in the same experiment is then obviously $(0.5 - \epsilon)$. The value of ϵ can be calculated from the ΔE_{PV} through thermodynamic considerations:

$$\epsilon = \frac{\Delta E_{PV}}{4RT} \tag{1}$$

If one accepts the estimate of 10^{-13} Jmol^{-1} for ΔE_{PV},[5−6] then eq 1 gives the value of ϵ as 10^{-17} at room temperature.

It has been noted in several different works that a "racemic mixture", if viewed on a molecular rather than bulk level, is not expected to have exactly the same number of enantiomer molecules even if $\epsilon = 0$.[26−29] Actually, an exactly racemic mixture is very unlikely to form and the probability of obtaining a slight excess of either enantiomer is 50−50%. It has also been pointed out that these natural fluctuations are described statistically by a binomial distribution.[26−29] This is also true if $\epsilon > 0$, but the binomial distribution is asymmetric. The probability of getting exactly m molecules of the more-stable enantiomer, $P(m)$, in a system containing a total of N molecules can be given as

$$P(m) = \binom{N}{m}(0.5 + \epsilon)^m(0.5 - \epsilon)^{N-m} \tag{2}$$

This binomial distribution has an expectation of $N \times (0.5 + \epsilon)$ for the number of the more-stable enantiomers, $2\epsilon N$ for the excess of this enantiomer, and a standard deviation of [$N \times$

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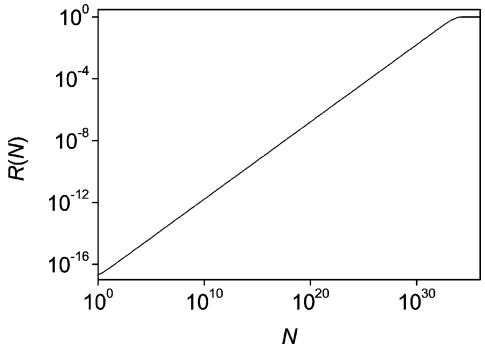

Figure 1. Excess probability of forming the more-stable enantiomer as a function of overall molecule number for $\epsilon = 10^{-17}$.

$(0.5 + \epsilon) \times (0.5 - \epsilon)]^{0.5}$. It is seen that for 1 mol of chiral molecules ($N = 6 \times 10^{23}$) the expected excess (6×10^6) is much smaller than the standard deviation (1.9×10^{11}), which describes average fluctuations. This fact suggests that the probability of obtaining the more-stable enantiomer in excess (Q) cannot be much larger than 50%.

To calculate exact values of Q, first the excess probability of forming the more-stable enantiomer, $R(N)$, is defined. $R(N)$ can be calculated by adding the probabilities of all cases in eq 2, which feature an excess of the more-stable enantiomer, and subtracting the probabilities of all cases where the less-stable enantiomer is formed in excess:

$$R(N) = \sum_{i=0}^{l} [P(N - i) - P(i)] \tag{3}$$

Here l is defined as $N = 2l + 1$ for odd values of N, and $N = 2l + 2$ for even values of N.

The value of $Q(N)$ can thus be written as

$$Q(N) = 0.5 + 0.5 \times R(N) \tag{4}$$

Numerical calculation of $R(N)$ using eqs 2 and 3 directly is not possible. Meaningful values can only be obtained after further mathematical considerations. It can be shown that the value of $R(N)$ for an even N is the same as the value of $R(N)$ for the preceding odd N.

$$R(2l + 2) = R(2l + 1) \tag{5}$$

Furthermore, mathematical induction can be used to show that the following equation holds for any odd values of N:

$$R(2l + 1) = \sum_{i=0}^{l} (-1)^i \epsilon^{2i+1} \frac{2^{2i-2l+1}(2l + 1)!}{(2i + 1)l!i!(l - i)!} \tag{6}$$

Values of $R(N)$ calculated using eq 6 are plotted as a function of N in Figure 1 for the special case $\epsilon = 10^{-17}$, which was obtained earlier from the present best estimate of ΔE_{PV}.[3−6] Both axes are shown on logarithmic scales.

Table 1 gives some values of N corresponding to Q values of 50.1%, 50.5%, 51%, 55%, 60%, and 75%. Figure 1 also shows that the double logarithmic plot is linear with a slope of 0.5 until very high values of N are reached. This can also be confirmed by mathematical approximations that give the following simplified equation for not very high values of N:

$$R(N) \cong 4\epsilon\sqrt{\frac{N}{2\pi}} \tag{7}$$

TABLE 1: Probabilities of Forming the More-Stable Enantiomer in Excess for $\epsilon = 10^{-17}$.

Q	R	N
50.1%	0.002	1.6×10^{28}
50.5%	0.01	3.9×10^{29}
51%	0.02	1.6×10^{30}
55%	0.1	3.9×10^{31}
60%	0.2	1.6×10^{32}
75%	0.5	1.1×10^{33}

The results reported in this paper clearly show that the probability of forming the more-stable enantiomer in excess is hardly higher than 50% even if the parity-violating energy difference is taken into account. This probability is still only 50.6% when 1 Mmol ($= 10^6$ mol) of chiral molecules is considered and is substantially lower for lower amounts of substance. A quantity of 1 Mmol (8.9×10^4 kg for alanine) is quite high for usual observations, but perhaps not very high on a global scale. However, even if the emergence of biological chirality is assumed to be a global event, then it should also be kept in mind that forming a substantial enantiomeric excess through chiral autocatalysis requires most of the products to be formed in the autocatalytic pathway. The mechanism amplifies small differences that may be present at low conversions (tyipically lower than 0.01%) in a reaction.[19−23] The probability of forming the more-stable enantiomer in an initial excess and amplifying it is only negligibly higher than the same probability for the less-stable enantiomer even if ΔE_{PV} is taken into account. This is in agreement with the fact that known experimental examples of absolute asymmetric synthesis[13,14,17] do not show a preference for any of the enantiomers for the chiral molecule formed.[23]

Although numerous quantum chemical calculations of ΔE_{PV} for biologically important molecules have been reported in equilibrium,[1−8] very little is known for transition states leading to these products. These transition states might even be nonchiral. In this case, the formation rate of the two enantiomers would be the same, the rate of the reverse reaction would be influenced only, and ΔE_{PV} could only play a role if reverse reactions are important. It is more likely that the transition state is chiral in such a reaction. It does not seem unreasonable to assume that ΔE_{PV} for the transition state would be similar in magnitude to those estimated for stable molecules, and the statistical arguments reported here remain unchanged.

Conclusions

In summary, it seems to be highly unlikely that biological chirality was determined through *de lege* selection by the intrinsic parity-violating energy difference between enantiomers. This conclusion is based on the present best estimate of this energy difference obtained in quantum chemical calculations but does not change even if ΔE_{PV} is 3−4 orders of magnitude higher, does not depend on quantum mechanical calculations, and is independent of further possible improvements in such calculations. If there are no important and yet unknown selection processes, then the present experimental and theoretical data suggest that the biological chirality was determined by random choice.

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Supporting Information Available: Proofs and derivations for equations appearing in the manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Mason, S. F.; Tranter, G. E. *J. Chem. Soc., Chem. Commun.* **1983**, 117−119.

(2) Tranter, G. E. *Nature* **1985**, *318*, 172−173.

(3) Buschman, H.; Thede, R.; Heller, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4033−4036.

(4) Quack, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4619−4630.

(5) Berger, R.; Quack, M. *ChemPhysChem* **2000**, *1*, 57−60.

(6) Laerdahl, J. K.; Wesendrup, R.; Schwerdtfeger, P. *ChemPhysChem* **2000**, *1*, 60−62.

(7) Laerdahl, J. K.; Schwerdtfeger, P.; Quiney, H. M. *Phys. Rev. Lett.* **2000**, *84*, 3811−3814.

(8) Szabó-Nagy, A.; Keszthelyi, L. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 4252−4255.

(9) Yamagata, Y. *J. Theor. Biol.* **1966**, *11*, 495−498.

(10) Wesendrup, R.; Laerdahl, J. K.; Compton, R. N.; Schwerdtfeger, P. *J. Phys. Chem. A* **2003**, *107*, 6668−6673.

(11) Keszthelyi, L. *Quart. Rev. Biophys.* **1995**, *28*, 473−507.

(12) Pályi, G.; Micskei, K.; Bencze, L.; Zucchi, C. *Magy. Kem. Lapja* **2003**, *58*, 218−223.

(13) Asakura, K.; Ikumo, A.; Kurihara, K.; Osanai, S.; Kondepudi, D. K. *J. Phys. Chem. A* **2000**, *104*, 2689−2694.

(14) Soai, K.; Sato, I.; Shibata, T.; Komiya, S.; Hayashi, M.; Matsueda, Y.; Imamura, H.; Hayase, T.; Morioka, H.; Tabira, H.; Yamamoto, J.; Kowata, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 185−188.

(15) Soai, K.; Shibata, T.; Sato, I. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1063−1073.

(16) Kawasaki, T.; Suzuki, K.; Hatase, K.; Otsuka, M.; Koshima, H.; Soai, K. *Chem. Commun.* **2006**, 1869−1871.

(17) Kawasaki, T.; Suzuki, K.; Shimizu, M.; Ishikawa, K.; Soai, K. *Chirality* **2006**, *18*, 479−482.

(18) Kondepudi, D. K.; Asakura, K. *Acc. Chem. Res.* **2001**, *34*, 946−954.

(19) Mislow, K. *Coll. Czech. Chem. Commun.* **2003**, *68*, 849−864.

(20) Blackmond, D. G. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5732−5736.

(21) Rivera Islas, J.; Lavabre, D.; Grevy, J. M.; Lamoneda, R. H.; Rojas Cabrera, H.; Micheau, J. C.; Buhse, T. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *103*, 13743−13748.

(22) Lente, G. *J. Phys. Chem. A* **2004**, *108*, 9475−9478.

(23) Lente, G. *J. Phys. Chem A* **2005**, *109*, 11058−11063.

(24) Micskei, K.; Póta, G.; Caglioti, L.; Pályi, G. *J. Phys. Chem. A* **2006**, *110*, 5982−5984.

(25) Klussmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H., Jr.; Urvish Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621−623.

(26) Ishida, K. *J. Phys. Chem.* **1968**, *72*, 92−96.

(27) Gridnev, I. D.; Serafimov, J. M.; Quiney, H.; Brown, J. M. *Org. Biomol. Chem.* **2003**, *1*, 3811−3819.

(28) Pályi, G.; Micskei, K.; Zékány, L.; Zucchi, C.; Caglioti, L. *Magy. Kem. Lapja* **2005**, *60*, 17−24.

(29) Caglioti, L.; Hajdu, C.; Holczknecht, O.; Zékány, L.; Zucchi, C.; Micskei, K.; Pályi, G. *Viva Origino* **2006**, *34*, 62−80.