Comment on "Enantiomer Resolution by Pressure Increase: Inferences from Experimental and Topological Results for the Binary Enantiomer System (R)- and (S)-Mandelic Acid"

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I read with interest the recent article by Rietveld et al. on the possibility of racemic compound-to-conglomerate conversion, and hence spontaneous resolution, under pressure.[1] While I agree with their conclusions and the fact that this is possibly the first detailed study that assesses the stability of mandelic acid racemates as a function of pressure and temperature, I would like to offer a series of comments and reflections. They should be of further benefit to the readership and serve in addition for clarification and amplification regarding the effect of pressure on stereoisomers.

It is known that pressure may even affect the conformational energies of rotational isomers,[2] as well as the stereotacticity during polymerization reactions catalyzed by racemic metal complexes.[3] The main effects of pressure rely on changes in intermolecular interactions, including hydrogen bonding, bond distortion, strain, and crystal packing. Such effects have been studied in some chiral molecules, notably a few proteinogenic amino acids, for which compression is accompanied by phase transitions due to shorter and stronger intermolecular contacts or formation of a more stable conformation.[4] In this context, the preparation of high-pressure polymorphs, even though known for a long time, represents an emerging field en route to new pharmaceuticals and materials. High-pressure crystallization from solution often leads to metastable polymorphs, which are more affected by kinetic than thermodynamic parameters such as the rates of compression/decompression.[5] Enantioenrichment of L-mandelic acid from scalemic mixtures can actually be achieved by high-pressure crystallization in water; the solubility decreases on increasing the pressure and L/D compositions move to the racemic compound.[6]

Given the importance of amino acids as sources of primeval chirality, one would have expected a considerable literature under high pressure in an attempt to mimic geological conditions. This is certainly the case, although amino acids are quite reluctant to pressure and compression modifies slightly the structural arrangement of the typical hydrogen-bonded head-to-tail chains linking zwitterionic molecules.[4,5] As a result, polymorphic transitions occur at relatively high pressures. A well-studied case is glycine with transformations occurring for β- and γ-polymorphs in a wide range of GPa's.[7] Glycine is of course achiral, but some crystalline polymorphs (e.g., α-glycine) are decorated by enantiotopic faces, which have been employed for resolution of other proteinogenic amino acids via enantioselective occlusion at the air−water interface.[8] α-Glycine is remarkably robust and does not undergo any phase transition even at pressures above 20 GPa.[9] For alanine, the ambient-pressure crystalline phase (β-form) is also stable at high pressures and only undergoes a reversible change to an amorphous phase above 15 GPa.[10]

Since an increase in pressure may lead to structures with higher density and smaller voids relative to ambient pressure conditions, the empirical Wallach rule stating that racemic compounds are more densely packed than their enantiomer constituents has been frequently invoked.[11] As a result, there remains the widespread assumption that heterochiral associations are more stable and slightly denser than homochiral packings, which would also account for the prevalence of racemic compounds over conglomerates. However, density does not necessarily reflect the thermodynamic stability,[12−14] and a reassessment of the Wallach rule shows that the examples are nearly equally divided between those in which the racemic compound is denser than the enantiomer and those in which the opposite trend occurs. Therefore, the existence of a given racemate would rather reflect either kinetic factors during nucleation and growth or simply a more favorable packing.[12] The effects of pressure on racemic crystals[15] are still relatively unexplored and further studies will be needed to correlate the transition to conglomerate phases with structural or packing modifications. In a recent example, aimed to increase the density under pressure and validate Wallach's rule, the crystallization of racemic *trans*-1,2-diaminocyclohexane, a useful ligand in catalysis, has been explored. Notably, this substance crystallizes as a conglomerate up to 2 GPa, as it occurs at ambient pressure due to a favorable crystal packing.[16] Amino acids often exhibit particular behaviors associated with their hydrogen bonding contacts in the zwitterionic structures. Homochiral L-serine and DL-serine show similar compressibilities up to 5 GPa. *Rac*-serine remains stable in its ambient-pressure phase up to nearly 9 GPa.[5]

Finally, important arguments that should be quoted are related to Monte Carlo simulations for the direct calculation of excess volumes in fluid mixtures, which depend on both attractive interactions and molecular shape.[17,18] Such results show that weakly positive excess volumes will occur at high pressures, thus making the spontaneous separation of enantiomers possible. An analysis of the stability condition in terms of the dimensionless excess volume integral suggests that the racemic mixture becomes unstable at pressures above 1 GPa and room temperature.[17] Racemic mixtures of larger molecules

(e.g., polymers) can have larger absolute excess volumes and would be unstable at lower pressures.[18]

Although the above remarks arise from a thermodynamic analysis, one might wonder if pressure alone is a sufficient condition to induce absolute enantioselectivity. The answer is obviously no. Local temperature and pressure are time-even scalars; however, the associated gradients ∇T and ∇P are time-even polar vectors and could be components of a falsely chiral influence capable of contributing to deracemization under kinetic conditions.[19]

Before concluding, a corollary in pressure-induced transformations is that both the equilibrium state and the conversion kinetics need to be taken into account. There is no question of dominance between thermodynamics and kinetics; while the former determines the hierarchy of phase stability, the latter determines how quickly the most stable phase will be attained.[20]

Summing up, both the recent study by Rietveld and associates and the preceding analysis clearly indicate that pressure should seriously be regarded as an environmentally plausible physical influence for chirogenesis. Its effects could have taken place at great depths on early Earth, where racemic mixtures are unstable and any minute enantiomeric imbalance would experience further amplification.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Rietveld, I. B.; Barrio, M.; Tamarit, J.-L.; Do, B.; Céolin, R. *J. Phys. Chem. B* **2011**, *115*, 14698−14703.

(2) (a) Taniguchi, Y. *J. Mol. Struct.* **1985**, *126*, 241−250. (b) Chandler, D. *Faraday Discuss. Chem. Soc.* **1978**, *66*, 184−190.

(3) Volkis, V.; Shmulinson, M.; Averbuj, C.; Lisovskii, A.; Edelmann, F. T.; Eisen, M. S. *Organometallics* **1998**, *17*, 3155−3157.

(4) Moggach, S. A.; Parsons, S.; Wood, P. A. *Crystallogr. Rev.* **2008**, *14*, 143−184.

(5) Boldyreva, E. V. *Acta Crystallogr.* **2008**, *A64*, 218−231.

(6) Nishiguchi, N.; Moritoki, M.; Shinohara, T.; Toyokura, K. In *Separation and Purification by Crystallization*; Botsaris, G. D., Toyokura, K., Eds.; ACS Symposium Series, Vol. 667; American Chemical Society: Washington, DC, 1997; pp 73−82.

(7) Dawson, A.; Allan, D. R.; Belmonte, S. A.; Clark, S. J.; David, W. I. F.; McGregor, P. A.; Parsons, S.; Pulham, C. R.; Sawyer, L. *Cryst. Growth Des.* **2005**, *5*, 1415−1427.

(8) Weissbuch, I.; Addadi, L.; Leiserowitz, L.; Lahav, M. *J. Am. Chem. Soc.* **1988**, *110*, 561−567.

(9) Murli, C.; Sharma, S. M.; Karmakar, S.; Sikka, S. K. *Phys. B* **2003**, *339*, 23−30.

(10) Funnell, N. P.; Marshall, W. G.; Parsons, S. *CrystEngComm* **2011**, *13*, 5841−5848.

(11) Wallach, O. *Justus Liebigs Ann. Chem.* **1895**, *286*, 90−118.

(12) Brock, C. P.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811−9820.

(13) Eliel, E. L.; Wilen, S. H. *Sterochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Chapter 6, pp 165−167.

(14) Jeong, K. S.; Kim, D. E.; Lee, E.; Jhon, Y. H.; Han, H.; Kim, J.; Jeong, N. *Tetrahedron: Asymmetry* **2009**, *20*, 1736−1741.

(15) The term racemic crystal often appears in the literature (such as that mentioned through this article), although when one hears this term either racemate phase comes to mind. Strictly, the term racemic crystal should only be applied to crystals whose space groups include improper symmetry elements. A racemic compound can eventually crystallize in a chiral space group and can also occur in chiral and achiral polymorphs. For an illuminating comment, see ref 12, p 9811, footnote (4).

(16) Cao, W.; Katrusiak, A. *CrystEngComm* **2011**, *13*, 6742−6746.

(17) Deiters, U. K. *Fluid Phase Equilib.* **2001**, *182*, 17−26.

(18) Kenney, J. F.; Deiters, U. K. *Phys. Chem. Chem. Phys.* **2000**, *2*, 3163−3174.

(19) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Barron, L. D. *Chem. Rev.* **1998**, *98*, 2391−2404.

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