Serine Octamer Clusters Direct the Chirality of Peptides Formed in Water Microdroplets

*Brison A. Shira and R. Graham Cooks**

Purdue University, Department of Chemistry, 560 Oval Drive, West Lafayette, IN 47907 USA.

Abstract: The chemistry underlying biological homochirality remains challenging. We propose that non-covalent clusters may have served as the means through which homochiral biochemistry emerged. Serine has long been known to exhibit a chiral preference in clustering to form the octamer; we extend this finding by reporting the effects of a non-zero e.e. in serine on the chiral preference seen in the formation of non-covalent clusters with other amino acids and in the formation of their covalent condensation products, peptides. We show (i) enantiopure serine directs racemic leucine and proline toward enantioselective dipeptide formation in water microdroplets and (ii) likely intermediates are seen as amino acid substitution products into the serine octamer cluster. This work indicates the relevance of microdroplet sprays, such as those found in natural aerosols, to molecular clustering phenomena and to homochirality.

Introduction

Non-covalent chemistry has been somewhat neglected in the study of the origins of homochirality. A range of physical processes has been proposed to explain the enantiomeric excess (e.e.) that has emerged in extant biology[1-3] but we here demonstrate a chemical process, implicating non-covalent

effects, that produces asymmetric bio-oligos. Work studying the gaseous serine octamer (a non-covalent assembly of serine monomers with a pronounced preference for homochirality)[4-8] and microdroplet reactivity, principally within the mass spectrometry community, has identified avenues for the formation of prebiotically significant molecules.[9-14] We thus suggest that chemical processes at the air-water interface and in the gas-phase may explain the asymmetry of biology's polymers.[4, 14]

It is known from MS studies that aqueous microdroplets, which possess large interfacial areas relative to their volumes, enable spontaneous formation of peptides from free amino acids without the use of any coupling reagent.[15,16] Furthermore, microdroplets are known to facilitate molecular clustering, including formation of the serine octamer with its pronounced homochiral preference.[17-19] We here report that enantiopure serine facilitates previously unknown chemistry: an enantioselective, prebiotically plausible route to peptide formation.

Microdroplets—and chemical "microenvironments" more broadly—have long been proposed to feature in prebiotic chemistry.[20,21] Serine's chiral preference as a gas-phase molecular cluster, whether ionized or neutral, whether generated by spraying a solution or sublimation, has been the subject of robust interrogation. Most notably, its octamer exhibits strong homochiral preference which is maintained when it substitutes other biomolecules, namely hexoses or amino acids, for one or two serine units.[17-19,22] More broadly, we show that the serine octamer is a strong case demonstrating the general phenomenon that molecular clusters, held together by ion/dipole forces, represent a medium in which steric effects may amplify the thermochemical gap between enantiomers.[23] In fact, the common methods of separating enantiomers (chromatography, kinetic method, crystallization, *etc*.) all depend on non-covalent interactions exerting asymmetric influence.

The experiments we report show that enantiopure serine directs peptide chirality in the course of peptide bond formation between racemic leucine and proline in water microdroplets. The ProLeu/LeuPro dipeptide formed displays a chiral preference that matches serine's chirality; *i.e.*, microdroplets containing L-Ser preferentially generate L-ProLeu/LeuPro dipeptides, or conversely with D-Ser, D-ProLeu/LeuPro dipeptides are formed. Neither of these experiments utilized chiral agents or catalysts other than the amino acids themselves. The use of non-racemic Ser in the reaction solution is prebiotically plausible because the macroscopic accumulation of local Ser chiral excess has been demonstrated;[22] even if only a microscopic enrichment is conceded, the micrometer scale of the chemistry here reported can be interpreted as a realization of the proposal of microenvironment chiral excess.[21] Thus, we demonstrate the transformation of biological monomers (amino acids) into oligomers (peptides) and propose a model to explain how a matrix containing non-zero e.e. serine directs racemic amino acids to enantioselective oligomerization. We propose non-covalent, microdroplet-based chiral transmission, dependent upon a chiral cluster, the serine octamer; with this species exhibiting enantioselective amino acid substitution and so accounting for the observed asymmetric accumulation in the ProLeu/LeuPro dipeptide.

This suggestion combines the previous finding of the serine octamer's ability to enantioselectively incorporate other amino acids with the observation that these serine-based clusters enantioselectively control peptide bond formation between free amino acids in water. Accepting two known properties of microdroplet sprays (i) they produce the serine octamer with its preference for homochiral assembly and (ii) they promote the condensation reaction of amino acids

into peptides, we proceeded to explore water microdroplets as the medium for asymmetric peptide formation (**Figure 1**).

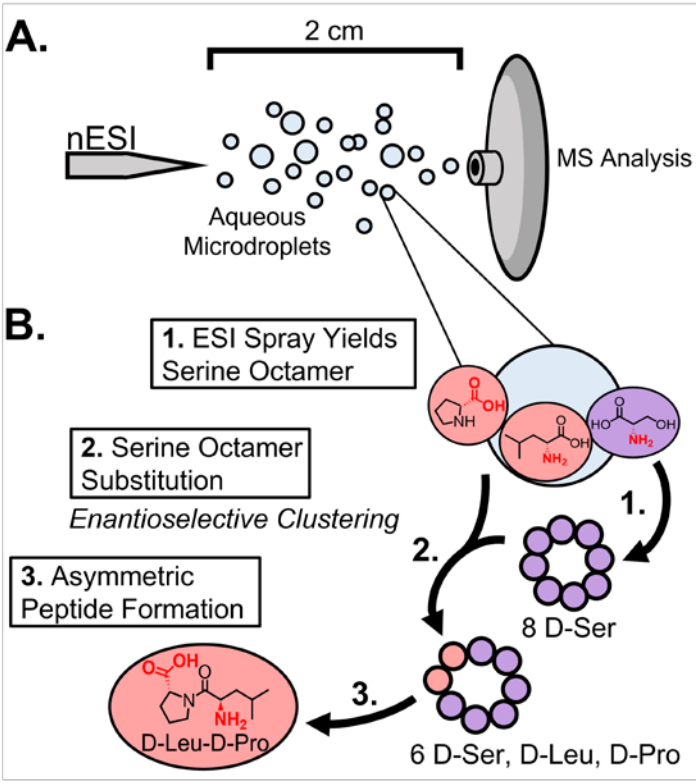
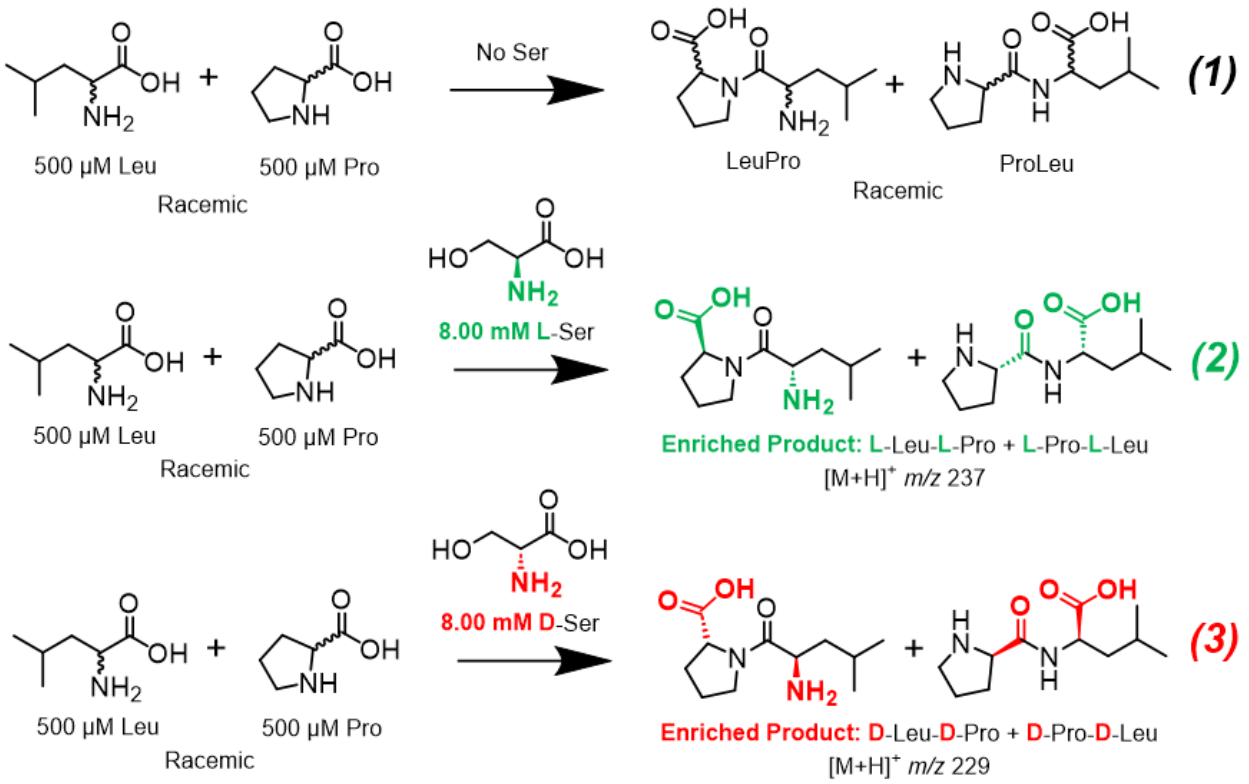


Figure 1. (**A.**) nESI generates aqueous microdroplets containing enantiopure serine and racemic leucine and proline. (**B.**) Flow diagram depicting a model by which molecular clustering drives asymmetric peptide formation from an individual droplet. Each step has literature precedence (homochiral clustering, enantioselective clustering, and peptide formation) but asymmetric peptide synthesis guided by serine is unprecedented and it connects the three steps. Here homochiral D-serine monomers are purple, the other D-amino acids are red, L-amino acids are omitted for clarity. The isomeric peptide D-Pro-D-Leu is not shown.

Methods

We prepared three solutions in LC-MS water (Fisher Scientific, Fair Lawn, NJ USA): **(soln. 1)** 250 μM D-Pro, L-Pro, D-Leu, and L-Leu; **(soln. 2)** 250 μM D-Pro, L-Pro, D-Leu,



Scheme 1. Asymmetric, abiotic microdroplet reactions in sprays analyzed by mass spectrometry.

and L-Leu with 8.00 mM L-Ser; **(soln. 3)** 250 µM D-Pro, L-Pro, D-Leu, and L-Leu with 8.00 mM D-Ser. D-Pro, D-Leu, and D- and L-Ser were not heavy isotope labeled (D-Ser, D-Pro, D-Leu, Fisher Scientific, Hampton, NH USA, and L-Ser, Millipore Sigma, St. Louis, MO USA), while L-Pro was labeled $^{13}C_5$, 99%; ^{15}N, 99%, and L-Leu was labeled $^{13}C_2$, 99% (Cambridge Isotope Labs, Tewksbury, MA USA). Each solution (**Scheme 1**) was subject to the same positive ion mode mass spectrometry (MS) experiment, using a Thermo TSQ Quantum Access MAX triple quadrupole instrument. ProLeu and LeuPro standards obtained from Millipore Sigma, St. Louis, MO USA. Each solution was loaded (in 2.0 µL aliquots) into pulled borosilicate capillary nano-electrospray ionization (nESI) emitters with 5 µm inner tip diameter and positioned 2 cm from the MS inlet (capillaries and P97 puller, Sutter Instrument, Novato, CA USA); each measurement was repeated 4 times over multiple days between which the instrument was cleaned. Tandem MS analysis gives

a targeted measure of relative ion abundance, even of trace species, and is a standard method of peptide analysis.[24,25]

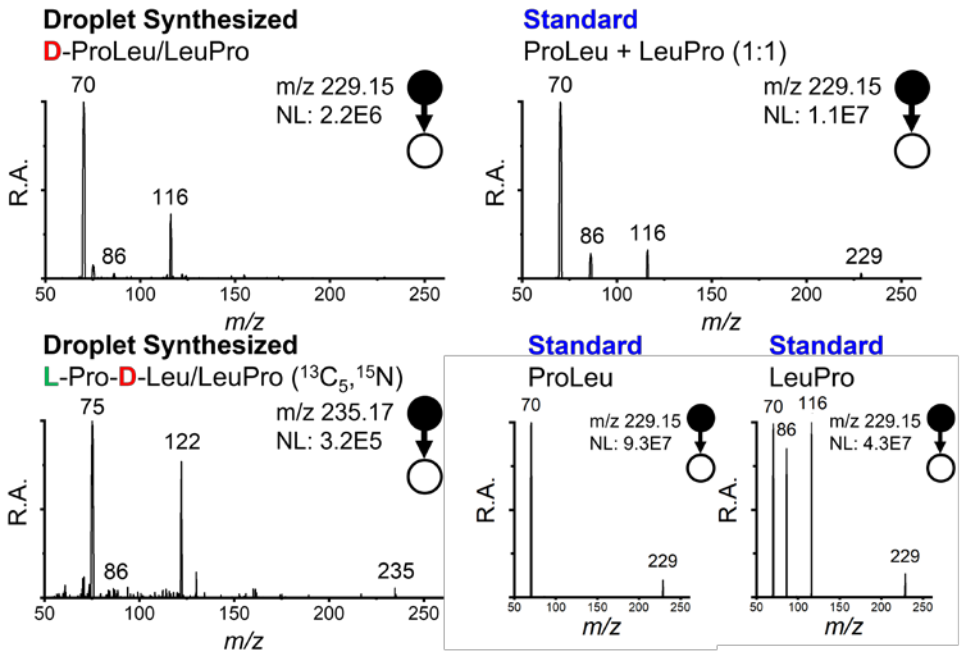


Figure 2. Left: Illustrative normalized positive ion MS/MS data. Sequence ion fragments corresponding to Pro (*m/z* 116/122, D- and L-, respectively) and the immonium fragment ions (*m/z* 70/75 for D- and L-Pro, and 86/87 for D- and L-Leu) appear in MS/MS and were used for quantitation. Note the chemical noise at ~5% relative abundance (R.A.) which necessitates the added specificity of tandem MS for quantitation as opposed to the simpler measurement of $[M+H]^+$ peak height. NL is normalization level, the arbitrary units of the most intense peak in a spectrum. Right: Comparison of standard ProLeu/LeuPro dipeptide spectra. The fact that identical product ions are generated confirms the ProLeu/LeuPro assignment and the relative intensities suggest a preference for the LeuPro sequence in microdroplets.

Operational parameters of our method are included in **Supplementary Information 1** (**S1**), but generally we select dipeptide molecular ions by their *m/z*, fragment them and compare the abundance of the fragment ions corresponding to peptide sequence fragments and immonium ions.

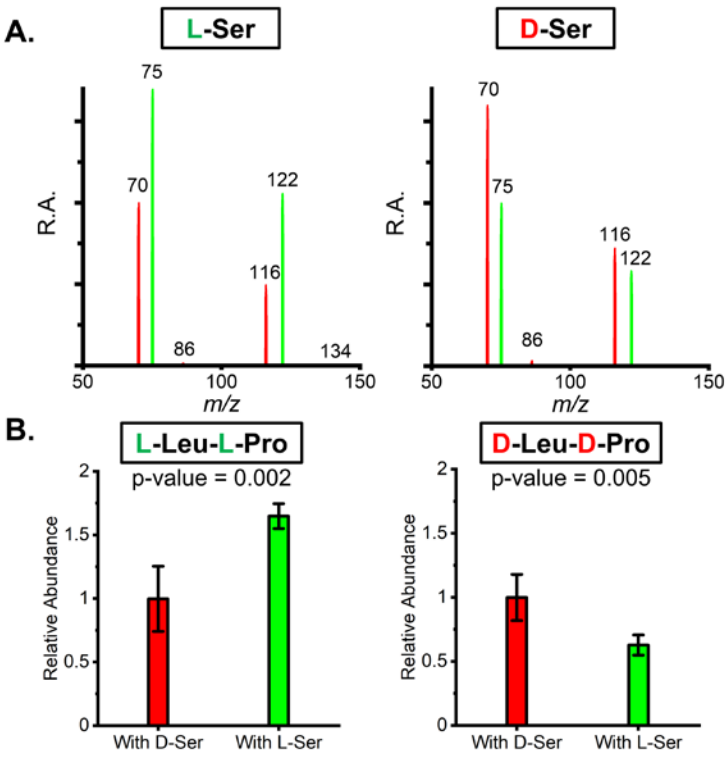


Figure 3. (**A.**) Tandem MS quantitation data constructed from individual precursor/product ion transitions showing the average relative abundance of L-ProLeu/LeuPro and D-ProLeu/LeuPro fragment ions. Signals were recorded for the fragmentation of *m/z* 237 to 75, 87, 122, 134 and *m/z* 229 to 70, 86, 116, 132. When L-Ser was included in the solution (left), L-ProLeu/LeuPro fragments were observed at higher intensity, when D-Ser was included (right), the inverse was observed. (**B.**) Relative abundance of the observed homochiral dipeptides L-ProLeu/LeuPro (left) and D-ProLeu/LeuPro (right) scaled to the average abundance observed in the No Ser (**soln. 1**) case, not pictured. For each experiment, n = 4 and error bars indicate ± 1 sample standard deviation. The green and red bars (**soln. 2** and **soln. 3**) indicate increased production of homochiral peptide, as controlled by the chirality of the accompanying serine.

To validate our analysis, a qualifier scan was used to positively identify the D-ProLeu/LeuPro $[M+H]^+$ at *m/z* 229 before data collection (**Figure 2**). Comparing these microdroplet synthesized spectra to the MS/MS fragmentation of commercial standards confirmed the peak assignments.

High resolution MS analysis confirmed the molecular formula assignments of precursor and product ions (**S2**). The relative abundance of the dipeptide products was calculated by scaling the abundance of heavy isotope L-dipeptide signals to those of the D-dipeptide and comparing to the no serine case. Relative abundances presented in **Figure 3** reflect the average ratio observed over 4 trials and the error bars indicate ± 1 sample standard deviation.

Results and Discussion

Our results demonstrate enantioselective peptide formation and the role of serine in this selection. **Soln. 2**, which has L-Ser, shows 1.7 ± 0.4 times more L-ProLeu/LeuPro product relative to **soln. 3**, while **soln. 3** shows 1.6 ± 0.4 times more D- ProLeu/LeuPro than **soln. 2**. The chiral preferences of the D- *vs.* L-Ser case satisfy one tailed t-tests past the 99% confidence level (p-values in **Figure 3**, **S3**). Furthermore, under the same conditions that generated the peptide, these solutions exhibited the serine octamer cluster ion and its enantioselective incorporation of leucine and proline monomers.

The enantioselectivity favoring the homochiral cluster of 6 Ser, 1 Leu, and 1 Pro compared to the heterochiral cluster matches the enantioselectivity observed in peptide formation. Thus, in the clusters generated from **soln. 2**, a 2:1 ratio of homochiral to heterochiral substitution was observed, favoring the incorporation of L-Leu and L-Pro. In the clusters generated from **soln. 3**, a 3:2 ratio was observed, favoring the substitution of D-Leu and D-Pro (**S4**). This finding offers mechanistic support for our model of non-covalent chiral transmission, suggesting that the clusters are reaction intermediates which yield the peptides.

Octamer substitution is suggested to be the locus for enantioselection: peptide formation is enantioselective because it follows the chiral preference observed during hybrid cluster formation.

Directly supporting this suggestion, peaks at *m/z* 859 and 867 corresponding to six Ser monomers clustered with a protonated ProLeu/LeuPro dipeptide were observed to accompany the amino acid substituted serine clusters. These findings, taken together with the quantitation of homochiral peptide products, are summarized in **Figure 4**.

Peptide products containing serine were not detected, and diproline and dileucine products were detected only at low levels from sprayed **solns. 1, 2,** and **3**, without apparent enantioselectivity (**S5**). We speculate that there are characteristics of Leu and Pro that make them particularly susceptible to asymmetric microdroplet peptide formation; namely, Leu's R-group is electron donating and stabilizes the intermediate during nucleophilic attack, while Pro has been shown to efficiently incorporate in condensations;[26] the steric bulk of the R-groups in Pro and Leu likely increase their susceptibility to enantioselective peptide bond formation. Evidence that the effect measured by tandem MS is not due to isotopic substitution is found in the reversal seen between the L-Ser and D-Ser data: similar chiral excess in the ProLeu/LeuPro product was measured when the ProLeu/LeuPro was or was not isotopically labeled. Nevertheless, we supported our findings further with a control experiment where isotopically labeled L-Leu was not used (**S6**).

These experiments were designed to simulate prebiotic chemistry. It is probable that water, Leu, Pro, and Ser were available on the early earth and elsewhere in the solar system.[27-31] If so, it seems certain that these compounds would be found in prebiotic Earth's microdroplets, whether sea sprays, clouds, or fog, or any other abiotic aerosol.[20] That serine, in particular, could have been present in elevated e.e. is supported by the results of past experiments that demonstrate monomeric enantioenrichment, without any additional chiral actor.[22,32] Further, enantioenrichment has been anticipated at the "microenvironment" scale and our work is an empirical realization of this concept.[21] Crystallization,[33-37] mineral mediated processes,[38] polarized light,[39] meteoric

seeding,[40,41] and most recently, chirality-induced spin selectivity[42,43] provide additional pathways to monomeric chiral excess—such as in the serine non-zero e.e. that we presupposed in our study.

An alternative explanation of the observed enantioselection relates to the phase behavior of serine. Considering literature showing enantioenrichment of serine during crystallization, dissolution, and sublimation,[22,32] it could be suggested that the microdroplet spray and desolvation processes of nESI involve two separate phase transitions: (i) serine crystallization as solvent evaporates and (ii) sublimation or nebulization to give gaseous serine. In this case, it would be possible for crystallization to "stack the deck" by sequestering all of the minor enantiomer in the thermodynamically favored conglomerate crystal, while the excess of the major enantiomer remained in solution prior to nebulization or as the solid sublimes to form non-racemic gas phase serine. Recent computational efforts, however, suggest that serine does not proceed through a crystalline intermediate in the course of nESI and octamer formation.[19] Rather, analytes escaping bulk solution and entering the interfacial regions of the microdroplets where peptide condensation is proposed to occur and where clusters—such as the octamer—may exist between the gas and solvated phases would explain the enantioselectivity observed in dipeptide formation.[18, 10] At present, the best evidence available—the direct observation of serine octamers corresponding to putative reaction intermediates—suggests the direct involvement of the octamer cluster in the observed enantioselection.

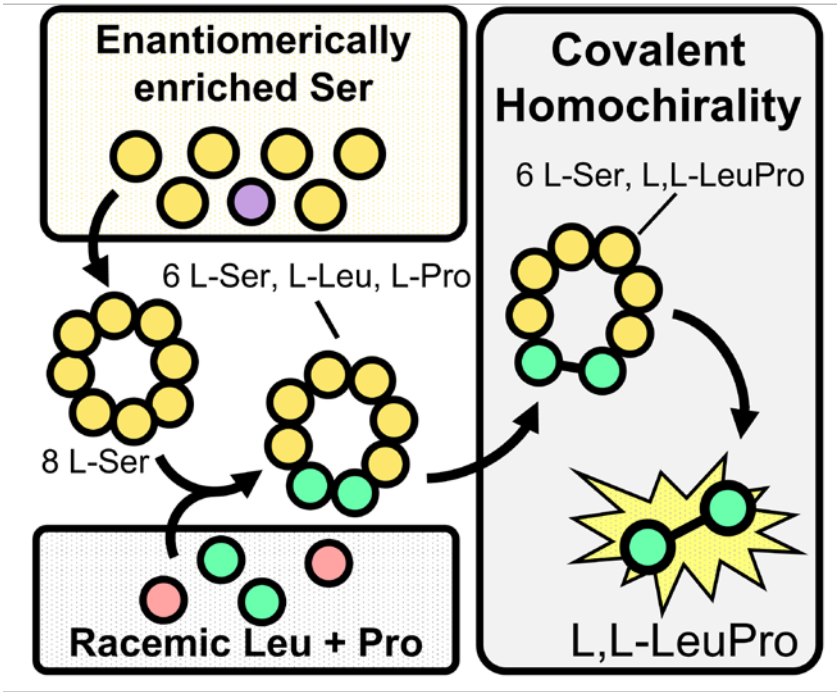


Figure 4. Summary of the chemistry observed: non-covalent octamers formed from enantiomerically enriched serine favor homochirality in their substitution of Leu and Pro for Ser, thereby enantioselectively extracting monomers from the Leu and Pro racemate, directing the accumulation of covalently bound homochiral dipeptides. Here, yellow circles represent L-Ser monomers, red represents D-amino acids, green represents L-amino acids.

Thus, in summary, our experiment models a situation in which serine has acquired a non-zero e.e., and then dissolves along with other amino acids present in racemic form, and this solution is dispersed as microdroplets. Our empirical results indicate that the chiral selection observed in the serine octamer is closely linked to that peptide formed in microdroplets. Our experiment extends prior demonstrations of prebiotically plausible enantioselective bond formation at the monomer level to the cluster level.[4] Though we showed enantioselectivity with enantiopure serine, there is no reason to expect that a lesser e.e. would not generate an intermediate effect with less (but not zero) enantioselectivity in peptide products. We have experimentally implicated non-covalent, steric effects, which others[44,45] have theorized might underpin molecular selection during chemical

evolution. The chiral transmission described herein enables monomeric excess to accumulate in covalent oligomers, priming evolution for homochirogenesis (see **S7**).

Conclusion

Despite the early discovery of chirality,[46] the literature lacks consensus to explain homochirality's origin. In large part, this is attributable to the fact that there is no fundamental difference between D- and L-biomolecules and "mirror life" is apparently possible.[47] In fact, some D-amino acids are found in biology.[48] The physical explanation for an inherent, albeit slight, symmetry breaking has been proposed in the molecular parity violation energy,[49,50] which explains the initial non-zero e.e. from which monomer level enrichment could occur. Thus, we surmise that biological asymmetry must have its basis in chemical reactivity in evolution's earliest stages; we then presuppose the presence of amino acids and proceed to demonstrate a mechanism which enables chiral transmission with *enantioenrichment accumulating in oligomers from racemic monomers.* We argue that because our system accumulates chirality in oligomers, it represents a form of chiral amplification, wherein an initial asymmetry propagates, as in the classic Frank autocatalysis mechanism (though some might hesitate to call microdroplet chemistry "catalysis").[51-53]

This study connects the accumulation of enantioenriched monomers, such as amino acids, to asymmetric bond formation in oligomers without the influence of chiral surfaces or external electromagnetic fields. We have elucidated a chemistry in which chiral recognition may occur outside the condensed phase (through microdroplet-formed serine octamer) and demonstrated that this process correlates with asymmetric dipeptide formation. We have uncovered the control of peptide chirality *via* chiral serine in microdroplet chemistry: symmetry breaking during bio-

oligomer formation involving only biological monomers; this is hitherto unknown but significant chemistry.

ASSOCIATED CONTENT

Supporting Information. **S1**: Operational parameters used in tandem MS analysis; **S2**: High resolution MS (HRMS) analysis of ProLeu/LeuPro; **S3**: Hypothesis testing and error analysis; **S4**. Serine octamer observed in experimental conditions of peptide formation; **S5**: Relative abundance of diproline and dileucine formed from solutions 1-3; **S6**: Results of experiments without isotopically labeled Leu; **S7**: Suggestion as to how monomeric excess accumulated in oligomers and primed homochirogenesis.

AUTHOR INFORMATION

Corresponding Author

*__R. Graham Cooks__ — Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, United States; orcid.org/0000-0002-9581-9603; Email: cooks@purdue.edu

Author

Brison A. Shira — Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, United States; orcid.org/0000-0002-5250-5882; Email: bshira@purdue.edu

Author Contributions

The manuscript was written through contributions of all authors.

Funding Sources

We acknowledge financial support from the Multi-University Research Initiative of the Air Force Office of Scientific Research (FA9550-21-1-0170) via Stanford University (sub-award 62741613-204669).

ACKNOWLEDGMENT

We gratefully acknowledge discussions with Dylan T. Holden, Myles Q. Edwards, Lingqi Qiu, Nicolás M. Morato, and Christopher Welch. We acknowledge the Purdue Research Infrastructure facility for high resolution MS.

ABBREVIATIONS

Leu, leucine; Pro, proline; Ser, serine; e.e., enantiomeric excess; LC-MS water, water for use in liquid chromatography-mass spectrometry (the standard analytical grade); MS, mass spectrometry; MnESI, nano-electrospray ionization; [M+H]+, protonated molecule; *m/z*, mass to charge ratio; ppm (mass error), parts per million; MS/MS, tandem mass spectrometry; R.A., relative abundance; NL, normalization level; soln., solution.

REFERENCES

1. Blackmond, D. The Origin of Biological Homochirality. *Cold Spring Harb. Perspect. biol.*, **2019**; Vol. 1.
2. Sallembien, Q.; Bouteiller, L.; Crassous, J.; Raynal, M. Possible chemical and physical scenarios towards biological homochirality. *Chem. Soc. Rev.* **2022**, *51* (9), 3436-3476.
3. Weller, M. G. The Mystery of Homochirality on Earth. *Life* **2024**, *14* (3), 341.
4. Cooks, R. G.; Zhang, D.; Koch, K. J.; Gozzo, F. C.; Eberlin, M. N. Chiroselective Self-Directed Octamerization of Serine: Implications for Homochirogenesis. *Anal. Chem.* **2001**, *73* (15), 3646-3655.
5. Julian, R. R.; Hodyss, R.; Kinnear, B.; Jarrold, M. F.; Beauchamp, J. L. Nanocrystalline Aggregation of Serine Detected by Electrospray Ionization Mass Spectrometry: Origin of the Stable Homochiral Gas-Phase Serine Octamer. *J. Phys. Chem. B.* **2002**, *106* (6), 1219-1228.
6. Nanita, S. C.; Takats, Z.; Cooks, R. G.; Myung, S.; Clemmer, D. E. Chiral enrichment of serine via formation, dissociation, and soft-landing of octameric cluster ions. *J. Am. Soc. Mass Spectrom.* **2004**, *15* (9), 1360-1365.
7. Seo, J.; Warnke, S.; Pagel, K.; Bowers, M. T.; von Helden, G. Infrared spectrum and structure of the homochiral serine octamer–dichloride complex. *Nat. Chem.* **2017**, *9* (12), 1263-1268.

8. Scutelnic, V.; Perez, M. A. S.; Marianski, M.; Warnke, S.; Gregor, A.; Rothlisberger, U.; Bowers, M. T.; Baldauf, C.; von Helden, G.; Rizzo, T. R.; et al. The Structure of the Protonated Serine Octamer. *J. Am. Chem. Soc.* **2018**, *140* (24), 7554-7560.
9. Nam, I.; Lee, J. K.; Nam, H. G.; Zare, R. N. Abiotic production of sugar phosphates and uridine ribonucleoside in aqueous microdroplets. *Proc. Nat. Acad. Sci.* **2017**, *114* (47), 12396-12400.
10. Mondal, S.; Acharya, S.; Biswas, R.; Bagchi, B.; Zare, R. N. Enhancement of reaction rate in small-sized droplets: A combined analytical and simulation study. *J. Chem. Phys.* **2018**, *148* (24).
11. Hao, H.; Leven, I.; Head-Gordon, T. Can electric fields drive chemistry for an aqueous microdroplet? *Nat. Commun.* **2022**, *13* (1), 280.
12. Lee, J. K.; Banerjee, S.; Nam, H. G.; Zare, R. N. Acceleration of reaction in charged microdroplets. *Q. Rev. Biophys*. **2015**, *48* (4), 437-444.
13. Vannoy, K. J.; Edwards, M. Q.; Renault, C.; Dick, J. E. An Electrochemical Perspective on Reaction Acceleration in Microdroplets. *Annu. Rev. Anal. Chem.* **2024**, *17*, 149-171.
14. Wei, W.; Chu, F.; Chen, G.; Zhou, S.; Sun, C.; Feng, H; Pan, Y. Prebiotic Formation of Peptides Through Bubbling and Arc Plasma. *Chem. Eur. J.* **2024**, *30*, e202401809.
15. Holden, D. T.; Morato, N. M.; Cooks, R. G. Aqueous microdroplets enable abiotic synthesis and chain extension of unique peptide isomers from free amino acids. *Proc. Nat. Acad. Sci.* **2022**, *119* (42).
16. Qiu, L.; Cooks, R. G. Oxazolone mediated peptide chain extension and homochirality in microdroplets. *Proc. Nat. Acad. Sci.* **2024**, *121* (2).
17. Nihamkin, M.; Kaiser, A.; Nemtsov, I.; Martini, P.; Scheier, P.; Mastai, Y.; Toker, Y. Chiral recognition via abundances of mixed chiral clusters. *Int. J. Mass Spectrom.* **2019**, *446*, 116215.
18. Jordan, J. S.; Williams, E. R. Effects of Electrospray Droplet Size on Analyte Aggregation: Evidence for Serine Octamer in Solution. *Anal. Chem.* **2021**, *93* (3), 1725-1731.
19. Alinezhad, V; Ng, Y. K.; Konermann, L. Uncovering the Pathway of Serine Octamer Magic Number Cluster Formation during Electrospray Ionization: Experiments and Simulations. *J. Am. Chem. Soc.* **2024**, *146*, 26726–26742.
20. H. Tervahattu, A. F. Tuck, V. Vaida, Chemistry in prebiotic aerosols: A mechanism for the origin of life in *Origins*, J. Seckbach, Ed.; Springer Dordrecht, 2004; pp 153–165.
21. Welch, C. J. Formation of highly enantioenriched microenvironments by stochastic sorting of conglomerate crystals: A plausible mechanism for generation of enantioenrichment on the prebiotic earth. *Chirality*, **2001**, *13*, 425-427.
22. Chen, R.; Wei, Z.; Cooks, R. G. Collection and Characterization by Mass Spectrometry of the Neutral Serine Octamer Generated upon Sublimation. *Anal. Chem.* **2021**, *93* (2), 1092-1099.
23. Atlasevich, N.; Holliday, A. E.; Valentine, S. J.; Clemmer, D. E. Collisional Activation of [14Pro+2H]2+ Clusters: Chiral Dependence of Evaporation and Fission Processes. *Phys. Chem. B.* **2012**, *116* (26), 7644-7651.
24. Manicke, N. E.; Yank, Q.; Wang, H; Oradu, S.; Ouyang, Z.; Cooks, R. G. Assessment of paper spray ionization for quantitation of pharmaceuticals in blood spots. *Int. J. Mass Spectrom.* **2011**, *300*, 123-129.
25. Hunt, D. F.; Yates, J. R.; Shabanowitz, J.; Winston, S.; Hauer, C. R. Protein sequencing by tandem mass spectrometry. *Proc. Nat. Acad. Sci.* **1986**, *83* (17), 6233-6237.
26. Ervin, J. N.; Bouza, M.; Fernandez, F. M.; Forsythe, J. G. Proline behavior in model prebiotic peptides formed by wet-dry cycling. *ACS Earth Space Chem.* **2020**, *4* (8), 1349-1359.

27. Kvenvolden, K.; Lawless, J.; Pering, K.; Peterson, E.; Flores, J.; Ponnamperuma, C.; Kaplan, I. R.; Moore, C. Evidence for Extraterrestrial Amino-acids and Hydrocarbons in the Murchison Meteorite. *Nature* **1970**, *228* (5275), 923-926.
28. Zaia, D. A. M.; Zaia, C. T. B. V.; De Santana, H. Which Amino Acids Should Be Used in Prebiotic Chemistry Studies? *Orig. Life Evol. Biosph.* **2008**, *38* (6), 469-488.
29. Kaiser, R. I.; Stockton, A. M.; Kim, Y. S.; Jensen, E. C.; Mathies, R. A. On the Formation of Dipeptides in Interstellar Model Ices. *Astrophys J* **2013**, *765*, 111.
30. Frenkel-Pinter, M.; Jacobson, K. C.; Eskew-Martin, J.; Forsythe, J. G.; Grover, M. A.; Williams, L. D.; Hud, N. V. Differential Oligomerization of Alpha versus Beta Amino Acids and Hydroxy Acids in Abiotic Proto-Peptide Synthesis Reactions. *Life* **2022**, *12* (2), 265.
31. Ghosh, J.; Methikkalam, R. R. J.; Bhuin, R. G.; Ragupathy, G.; Choudhary, N.; Kumar, R.; Pradeep, T. Clathrate hydrates in interstellar environment. *Proc. Nat. Acad. Sci.* **2019**, 116 (5), 1526-1531.
32. Zhang, H.; Wei, Z.; Jiang, J.; Cooks, R.G. Nebulization Prior to Isolation, Ionization, and Dissociation of the Neutral Serine Octamer Allows its Characterization. *Angew. Chem. Int. Ed.* **2018**, *57* (52), 17141-17145.
33. Cintas, P. Chirality of Living Systems: A Helping Hand from Crystals and Oligopeptides. *Angew. Chem., Int. Ed.* **2002**, *41* (7), 1139-1145.
34. Kawasaki, T.; Sasagawa, T.; Shiozawa, K.; Uchida, M.; Suzuki, K.; Soai, K. Enantioselective Synthesis Induced by Chiral Crystal Composed of dl-Serine in Conjunction with Asymmetric Autocatalysis. *Org. Lett.* **2011**, *13* (9), 2361-2363.
35. Noorduin, W. L.; Meekes, H.; van Enckevort, W. J. P.; Millemaggi, A.; Leeman, M.; Kaptein, B.; Kellogg, R. M.; Vlieg, E. Complete Deracemization by Attrition-Enhanced Ostwald Ripening Elucidated. *Angew. Chem., Int. Ed.* **2008**, *47* (34), 6445-6447.
36. Steendam, R. R. E.; Verkade, J. M. M.; van Benthem, T. J. B.; Meekes, H.; van Enckevort, W. J. P.; Raap, J.; Rutjes, F. P. J. T.; Vlieg, E. Emergence of single-molecular chirality from achiral reactants. *Nat.Commun.* **2014**, *5* (1), 5543.
37. Viedma, C.; McBride, J. M.; Kahr, B.; Cintas, P. Enantiomer-specific oriented attachment: formation of macroscopic homochiral crystal aggregates from a racemic system. *Angew. Chem. Int. Ed.* **2013**, *52* (40), 10545-10548.
38. Fraser, D. G.; Fitz, D.; Jakschitz, T.; Rode, B. M. Selective adsorption and chiral amplification of amino acids in vermiculite clay-implications for the origin of biochirality. *Phys. Chem. Chem. Phys.* **2011**, *13* (3), 831-838.
39. Mishima, K.; Kaji, D.; Fujiki, M.; Imai, Y. Remarkable Effects of External Magnetic Field on Circularly Polarized Luminescence of EuIII(hfa)3 with Phosphine Chirality. *ChemPhysChem* **2021**, *22* (17), 1727-1727.
40. Pizzarello, S.; Huang, Y.; Alexandre, M. R. Molecular asymmetry in extraterrestrial chemistry: Insights from a pristine meteorite. *Proc. Nat. Acad. Sci.* **2008**, *105* (10), 3700-3704.
41. Myrgorodska, I.; Meinert, C.; Martins, Z.; Le Sergeant d'Hendecourt, L.; Meierhenrich, U. J. Molecular Chirality in Meteorites and Interstellar Ices, and the Chirality Experiment on Board the ESA Cometary Rosetta Mission. *Angew. Chem., Int. Ed.* **2015**, *54* (5), 1402-1412.
42. Ozturk, S. F.; Liu, Z.; Sutherland, J. D.; Sasselov, D. D. Origin of biological homochirality by crystallization of an RNA precursor on a magnetic surface. *Sci. Adv.* **2023**, *9* (23).
43. Ozturk, S. F.; Sasselov, D. D. On the origins of life's homochirality: Inducing enantiomeric excess with spin-polarized electrons. *Proc. Nat. Acad. Sci.* **2022**, *119* (28).

44. Schuster, G. B.; Hud, N. V.; Alenaizan, A. Structural and Thermodynamic Control of Supramolecular Polymers and DNA Assemblies with Cyanuric Acid: Influence of Substituents and Intermolecular Interactions. *Phys. Chem. B.* **2022** *126* (50), 10758-10767.
45. Zepik, H.; Shavit, E.; Tang, M.; Jensen, T; Kjaer, K.; Bolbach, G.; Leiserowitz, L.; Weissbuch, I.; Lahav, M. Chiral Amplification of Oligopeptides in Two-Dimensional Crystalline Self-Assemblies on Water. *Science* **2002**, *295*,1266-1269.
46. Pasteur, L. Sur les relations qui peuvent exister entre la forme crystalline, la composition chimique et le sens de la polarization rotatoire. *Annales Chimie Phys.* **1848**, *24*, 442-459.
47. Xu, Y; Zhu, T.F. Mirror-image T7 transcription of chirally inverted ribosomal and functional RNAs. *Science* **2022**, *378* (6618), 405-412.
48. Armstrong, D. W.; Berthod, A. Occurrence of D-amino acids in natural products. *Nat. Prod. Bioprospect.* **2023**, *13* (1).
49. Aucar, J. J.; Stroppa, A.; Aucar, G. A. A Relationship between the Molecular Parity-Violation Energy and the Electronic Chirality Measure. *J. Phys. Chem. Lett.* **2024**, *15* (1), 234-240.
50. Quack, M.; Seyfang, G.; Wichmann, G. Perspectives on parity violation in chiral molecules: theory, spectroscopic experiment and biomolecular homochirality. *Chem. Sci.* **2022**, *13* (36), 10598-1064.
51. Frank, F. C. On spontaneous asymmetric synthesis. *Biochim Biophys Acta* **1953**, *11*, 459-463.
52. Matsumoto, A.; Ozaki, H.; Tsuchiya, S.; Asahi, T.; Lahav, M.; Kawasaki, T.; Soai, K. Achiral amino acid glycine acts as an origin of homochirality in asymmetric autocatalysis. *Org. Biomol. Chem.* **2019**, *17* (17), 4200-4203.
53. Soai, K.; Shibata, T.; Morioka, H.; Choji, K. Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule. *Nature* **1995**, *378* (6559), 767-768.

SYNOPSIS

In water microdroplets, the serine octamer transmits chirality to racemic amino acids by substitution, resulting in enantioselective dipeptide formation.

TOC Figure