

"Smart Decomposition" of Cyclic Alanine-Alanine Dipeptide by VUV Radiation: A Seed for the Synthesis of Biologically Relevant Species

Dário Barreiro-Lage, Paola Bolognesi,* Jacopo Chiarinelli, Robert Richter, Henning Zettergren, Mark H. Stockett, Laura Carlini, Sergio Diaz-Tendero,* and Lorenzo Avaldi



Cite This: *J. Phys. Chem. Lett.* 2021, 12, 7379–7386



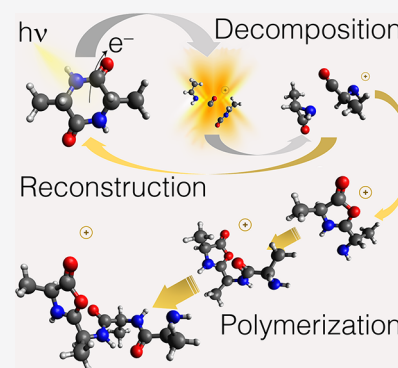
Read Online

ACCESS |

Metrics & More

Article Recommendations

ABSTRACT: A combined experimental and theoretical study shows how the interaction of VUV radiation with cyclo-(alanine-alanine), one of the 2,5-diketopiperazines (DKPs), produces reactive oxazolidinone intermediates. The theoretical simulations reveal that the interaction of these intermediates with other neutral and charged fragments, released in the molecular decomposition, leads either to the reconstruction of the cyclic dipeptide or to the formation of longer linear peptide chains. These results may explain how DKPs could have, on one hand, survived hostile chemical environments and, on the other, provided the seed for amino acid polymerization. Shedding light on the mechanisms of production of such prebiotic building blocks is of paramount importance to understanding the abiotic synthesis of relevant biologically active compounds.



In the early 1950s,¹ it was proven that organic compounds can be synthesized spontaneously from simple inorganic precursors. These findings explained the observation of the large variety of organic matter,^{2–5} including amino acids^{6–8} and even simple peptides,⁹ detected in hostile and abiotic environments as meteorites and carbonaceous chondrites.¹⁰ Since then, many experiments have been performed^{11–14} and theoretical models¹⁵ have been developed in order to understand and reproduce the chemical evolution of biologically relevant compounds under the harsh conditions of, for example, astronomical objects in the interstellar medium: high exposure to VUV light and cosmic rays, low temperatures, and low pressures. Under such conditions, UV photons can ionize and/or excite the molecules and, as a direct consequence, generate highly reactive radical compounds in the interstellar medium.^{16,17}

Beyond the formation of amino acids, the condensation of these elementary units into increasingly complex peptides has been the necessary step in the development and evolution of life. However, peptide bonds are not formed spontaneously. Rather, one of the reactants must be activated, commonly through the carboxylic group.^{18–20} Peptide bond formation is indeed a fundamentally important reaction in organic synthesis and is typically mediated by the so-called coupling reagents.²¹ In abiotic environments, external agents are required in the absence of such activating reactants, and several mechanisms have been envisioned for the abiotic synthesis of proto-peptides, from thermal polymerization and wet–dry cycles to the intervention of condensing agents.^{22,23} The role of the surface-catalyzing

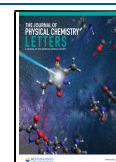
condensation of two amino acids has also been discussed.^{24–28} Charge transfer between the amino acid and the substrate can be responsible for such catalysis. Other potential mechanisms behind the surface-catalyzed reaction imply the formation of a zwitterionic form after proton migration.²⁵ Ultrafast hydrogen migration has also been observed in ionized gas-phase amino acids, both in isolated molecules^{29–31} and in a cluster environment.^{32,33}

The lifetime of individual peptide bonds is in the range of tens or even hundreds of years,³⁴ while their formation depends on the density of activating species and available energy. Thus, at the low concentration of amino acids in the primordial or astronomical environments, reaction rates for peptide formation are likely to be very slow. Activated intermediates such as diketopiperazines (DKPs) and 5(4H)-oxazolones are considered to be among the major cyclic intermediate units that can significantly favor the abiotic formation of peptides.²² 2,5-DKPs, cyclodipeptides obtained by the condensation of two α -amino acids via two peptide bonds and the ejection of two water molecules, are considered to be among the most relevant players in the emergence of life and homochirality.³⁴ Oxazolidinones are another type of heterocyclic organic compound which has had a

Received: June 4, 2021

Accepted: July 14, 2021

Published: July 29, 2021



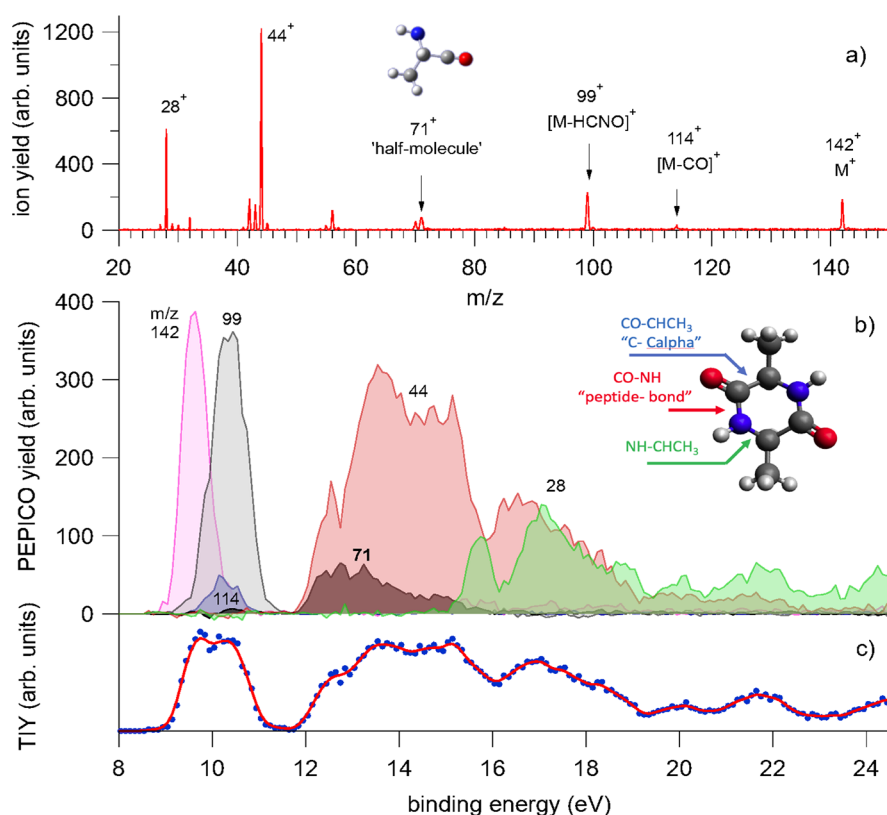


Figure 1. PEPICO spectra and ion yields. (a) Sum of all PEPICO spectra of cAA up to BE 24 eV; all the fragments relevant to this work and the structure of the 71^+ fragment (Figure 2) are indicated. (b) PEPICO breakdown curves of the fragment ions indicated by arrows in panel (a). In the inset, the structure of the cAA molecule and the bond breaks responsible for the ring opening are indicated. (c) Total ion yield (dots) obtained by adding up the breakdown curves for all fragment ions shown in panel (a), apart from fragments 17^+ and 18^+ , clearly assigned to the water, and its three-point smoothing.

role in prebiotic chemistry.^{35,36} The five-membered moiety of these compounds has been found in the structure of biologically active natural products, and their activity is specifically connected to the ring shown in its structure.³⁷ These highly reactive intermediates, also commonly used in modern laboratories for peptide synthesis,³⁸ could also be formed and activated spontaneously without any catalyst or other reactive species, as we show in this work.

In this study, experiments and modeling have been combined to demonstrate that ionization induced by the VUV irradiation of cyclo-dipeptides has the potential to trigger diverse reactive mechanisms. In particular, we show how the degradation of alanine-alanine diketopiperazine (cyclo-(alanine-alanine) or cAA), one among the simplest 2,5-DKPs,³⁹ after photoionization can drive two highly relevant chemical processes: (i) the reconstruction of the dipeptide itself through reactions among some of its decomposition products and (ii) the formation and elongation of a linear peptide via isomerization of the molecular parent ion into oxazolidinones structures. The mechanisms of both processes have been computed. The former explains cAA stability in hostile environments, and the latter provides the seed of an abiotic mechanism for peptide synthesis. These processes require neither a catalyst nor an aqueous environment but only VUV radiation as an activating agent. Thus, they may have played an important role in the early stages of prebiotic chemistry.

In the experiments, performed at the CIPOL beamline⁴⁰ of the Elettra synchrotron radiation facility, we used a monochromatic photon beam of 60 eV energy and an end station where an

electron energy analyzer (VG 220i) is mounted opposite to a time-of-flight (TOF) spectrometer at the magic angle with respect to the polarization vector of the radiation.⁴¹ These two spectrometers can be operated independently to record photoelectron spectra or mass spectra or, in conjunction, to perform photoelectron-photoion coincidence (PEPICO) measurements. The latter have been performed in the binding energy (BE) range from the cAA ionization threshold up to 24 eV. Thanks to the time correlation between the fragment ions and the kinetic energy selected photoelectrons, the PEPICO technique provides the breakdown curves, i.e., the yield of each fragment versus BE and therefore direct information on state-selected molecular fragmentation paths.⁴² The cAA sample ($C_6H_{10}N_2O_2$, see inset in Figure 1) was inserted into a crucible under vacuum and heated to 87 °C to produce an effusive beam. The residual pressure in the chamber with the beam on was 3.4×10^{-7} mbar. The breakdown curves of the ion species that dominate the mass spectrum are reported in Figure 1. These include the parent ion (m/z 142⁺), the fragment ions at m/z 114⁺ and 99⁺ assigned to the CO and HNCN losses, respectively, and the channels at m/z 44⁺, 28⁺, and 71⁺. Clear state selectivity in the molecular fragmentation is observed. Indeed, the parent ion is observed only at BE < 10.5 eV, the 114⁺ and 99⁺ fragments in a well-defined range are centered around 10.3 eV, and other fragments appear at BE > 12 eV. Among them, the 71⁺ fragment, observed as a stable species in the BE region of 12–16 eV, is particularly intriguing and will be the topic of this work because with its mass, which is half of the cAA mass, it is produced in a symmetric breakup of cAA and may be

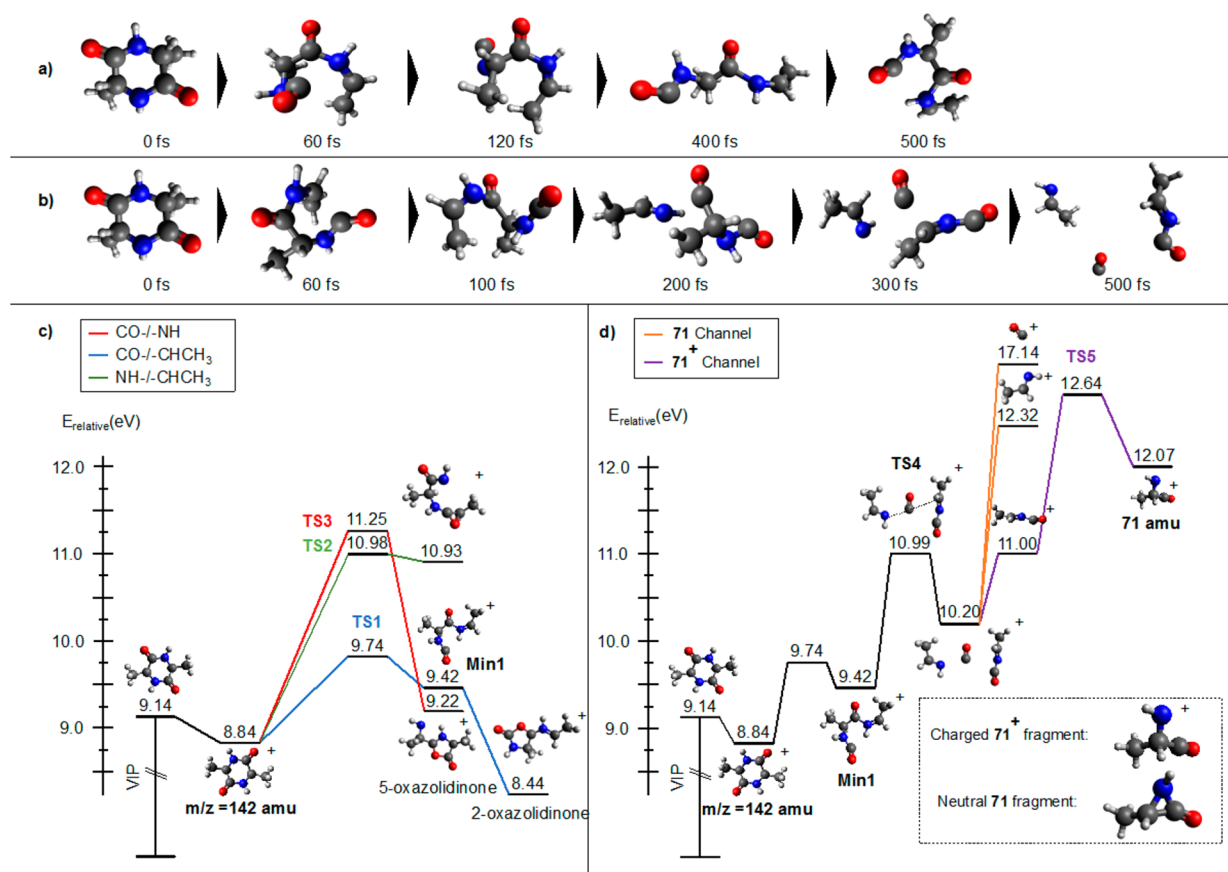


Figure 2. *Ab initio* molecular dynamics and PES exploration. Upper panels: examples of molecular dynamics trajectories leading to (a) the ring opening through the CO–NH bond rupture and (b) the production of a linear 71⁺ fragment. Lower panels: potential energy surface with the critical points (minima and transition states) showing (c) the three possible paths for ring opening to produce oxazolidinone structures and (d) the mechanisms for the production of neutral 71 and cationic 71⁺ fragments. In the potential energy surface, relative energies are given in eV with respect to the neutral cAA structure. Calculations are carried out at the DFT-B3LYP/6-311++G(d,p) level (Computational Details). VIP stands for vertical ionization potential, i.e., the energy required to extract one electron from the neutral molecule at the geometry of the most stable conformer.

related to the [alanine-H-OH]⁺ fragment. The appearance energy of the 71⁺ fragment, well below the second ionization potential of cAA estimated according to empirical rules^{43,44} at about 20 eV, rules out an identification with cAA²⁺. A detailed discussion of all the other observed fragmentation channels will be the subject of a forthcoming publication.

We have performed quantum chemistry calculations to identify the most relevant fragmentation channels and the structure of the produced compounds and to infer the mechanisms behind the experimental observations. Here we use the two-step computational strategy that has recently been implemented to study the fragmentation of ionized glycine and thymidine.^{29,45} First, we performed *ab initio* molecular dynamics (MD) simulations. In order to mimic the experimental conditions, we considered the vertical ionization from the neutral molecule, and with a given amount of excitation energy randomly redistributed among the nuclear degrees of freedom, we let the system evolve by analyzing the most populated channels after 500 fs of propagation. Then, from the most populated channels and taking as reference the experimental observations, we run a second set of calculations exploring the potential energy surface (PES). We located the critical points on the PES, transition states (TS), and local minima, connecting the pathways from the ionized molecule to the charged fragments observed in the experiments. All of the simulations were carried out using the density functional theory (DFT) as

implemented in the Gaussian 16 package⁴⁶ (see Computational Details). This strategy enabled us to unravel the fragmentation pathways and structural rearrangements for all of the main fragments observed in the mass spectra and PEPICO experiments. The upper panels in Figure 2 show examples of the trajectories in the MD simulations leading to the channels studied in this work. The corresponding mechanisms are shown on the PES (lower panels in Figure 2). According to the simulations, the cAA⁺ fragmentation in the near-ionization threshold region is always initiated by a ring opening that preferentially involves the CO–CHCH₃ bond cleavage (blue path, TS1). It may also proceed via the NH–CHCH₃ (green path) or the CO–NH amide (red path) bond breaking through higher-energy transition states TS2 and TS3, respectively. It is noticeable that after the CO–CHCH₃ and amide bond openings, pathways going through the TS1 and TS3 transition states, respectively, the cationic molecule efficiently collapses into stable oxazolidinone structures. The most stable one is found after CO–CHCH₃ bond cleavage through TS1 and leads to the Min1 linear structure, which evolves toward (S)-4,5-disubstituted 2-oxazolidinone (S-ethylideneammonium-4-methyloxazolidin-2-one), about 0.5 eV below the entrance channel. A second oxazolidinone compound is achieved after TS3; it is an (S)-2,4-disubstituted 5-oxazolidinone (2-(1-aminoethyl)-4-methyloxazolidin-5-one; terminal-amino dehydrogenated), in this case ~0.1 eV above the entrance channel.

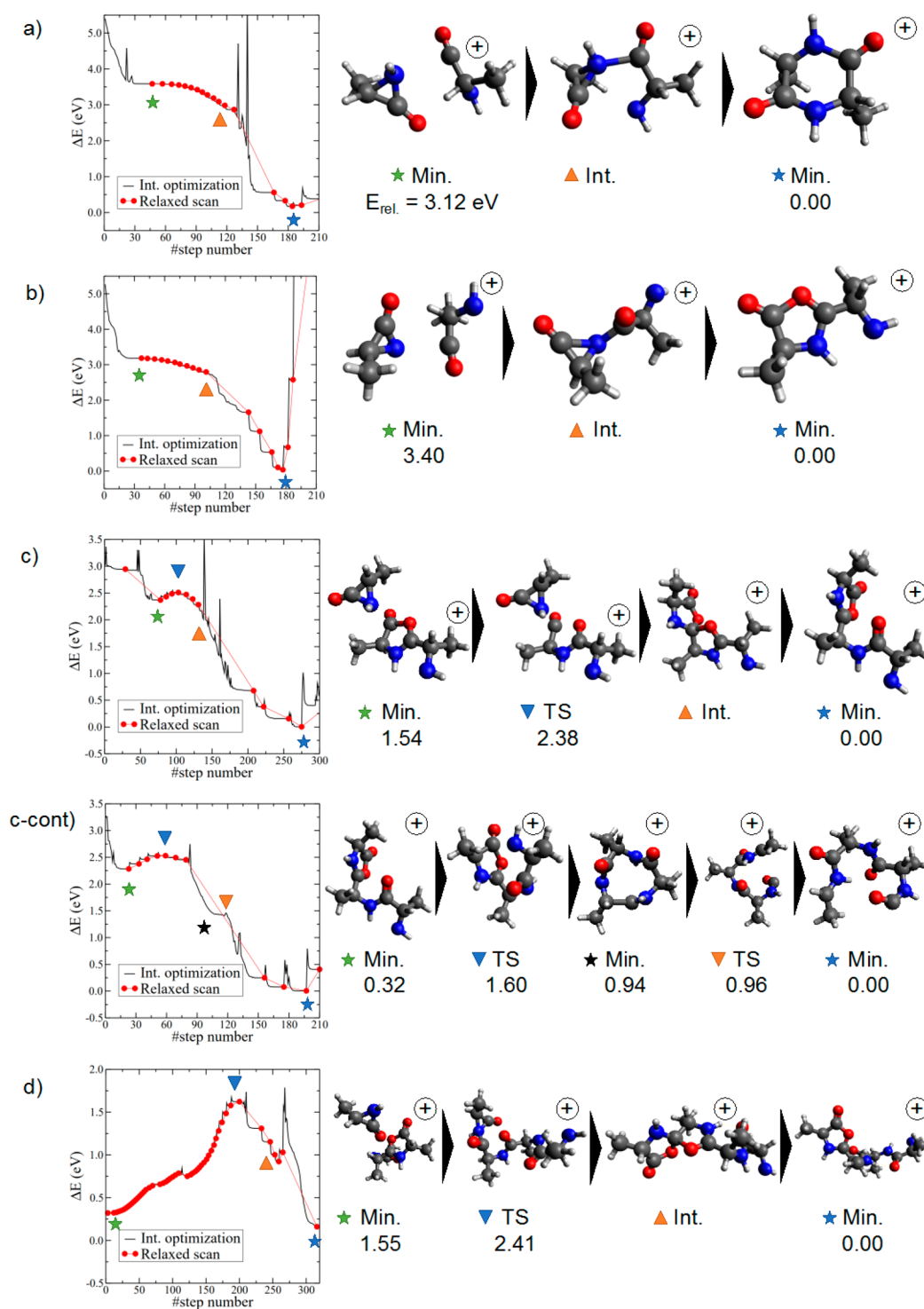


Figure 3. Relaxed scans and critical points on the reactivity of neutral 71 and 71⁺ fragments. Left column: relative energies in eV with respect to the final product in the bond distance scan. The black line shows all the intermediate steps, and red points refer to the optimized structures for a given bond distance. Left column: critical points in the mechanisms (intermediate, transition states, and final products). Symbols relate the corresponding points in the scan used as a reference to obtain the final structure. Relative energies are given in eV with respect to the final product in each mechanism: (a) neutral 71 and cationic 71⁺ fragments producing cAA⁺; (b) neutral 71 and cationic 71⁺ fragments producing cationic 5-oxazolidinone⁺; (c) neutral 71 fragment and cationic 5-oxazolidinone⁺ leading to a peptide chain linked to the 5-oxazolidinone⁺; (c-cont) evolution of the previous structure leading to a cationic tripeptide⁺; and (d) reaction of the product obtained in (c) with a neutral 71 fragment leading to a dipeptide chain linked to the 5-oxazolidinone⁺.

Taking the lower-energy path initiated at the CO–CHCH₃ bond break (blue path, TS1), we followed the evolution of linear structure Min1 toward the production of the neutral and charged fragments with 71 amu (Figure 2d). In this case, passing

through TS4 (located at 10.99 eV with respect to the neutral cAA), a weakly bound three-fragment structure [CO⋯C₂NH₅⋯C₃H₅NO]⁺ is formed. This structure can further evolve, leading to three-body fragmentation where the charge can be hosted in

any of the three produced fragments. The lowest-energy process corresponds to the formation of $\text{C}_3\text{H}_5\text{NO}^+$ (m/z 71⁺). Figure 2b reports an example of the MD simulations showing also the direct production of the cationic 71⁺ fragment, supporting the validity of the proposed path. This fragment, which indeed corresponds to “half” of the molecule, has enough energy to overtake the TSS barrier and can rearrange into an amino acid-like structure, where the canonical alanine ion has lost the hydroxyl group from the carboxylic end and a hydrogen atom from the amino side. In a simplified picture, this amino acid-like structure is the core of the amino acid in a peptide chain, after peptide bond formation and water release. It is interesting to observe that in the PEPICO spectrum (Figure 1b) the 71⁺ fragment appears very close to the calculated energy of 12.07 eV above the neutral cAA. The other two paths lead to the charge located in the smaller fragments and a neutral structure (also with 71 amu), which is stabilized in a three-membered cyclic substructure (panel in Figure 2d). Fragment 71⁺ is a chiral molecule, and in Figure 2, the “sinister” S enantiomer is shown. Nevertheless, TSS may lead to both S and R fragments. Because the same amount of energy is required to arrive at any of these enantiomers, there is no mechanistic proof to explain an enantiomeric excess. Since only L peptides are obtained in living organisms, from now on we will perform our simulations with the S enantiomer.

The main question we would like to address is whether these peculiar features, i.e., (i) the cationic oxazolidinones generated by the molecular rearrangement of the cAA^+ parent ion (Figure 2c) and (ii) the amino acid-like structure and rearrangements of their neutral and charged fragments (71 and 71⁺ in Figure 2d), have the potential to support the formation of cyclic or linear peptides. For this purpose, we investigated the reactivity between the neutral 71 and cationic 71⁺ fragments as well as the subsequent addition of a neutral 71 fragment to cationic oxazolidinones. The results are represented in Figure 3. The strategy followed in this further study is similar to the previous one. In this case, we explored the PES through relaxed scans, where the distance between the atoms forming the new bond is shortened while the rest of the structure is allowed to relax into the configuration of minimum energy. The results are the energy profiles shown in the left column of Figure 3. Then, starting from the most relevant structures of the scans, we computed intermediates, transition states, and final products on the PES. These species are shown on the right-hand side of the figure. We started by inducing reactivity between the neutral 71 and cationic 71⁺ products. Two possible paths were obtained: the first one (Figure 3a) corresponds to the stabilization on the original cAA^+ structure, and in the second one (Figure 3b), the observed reactivity produces the same 5-oxazolidinone obtained after ring opening via the CO–NH bond cleavage of the original cAA^+ . With the addition of a further neutral 71 fragment, this molecule evolves toward a new 5-oxazolidinone with a peptide chain as the final product (Figure 3c). As shown in Figure 3c, this molecule may evolve, after overtaking two transition states, in a linear tripeptide. If, instead of letting the system evolve, we study the reactivity of the peptide-chain-substituted oxazolidinone obtained in Figure 3c with another neutral 71 fragment, we end up with a new oxazolidinone holding a longer peptide chain. All of these mechanisms share a common structure, that of the neutral 71 fragment, which is polarized and electrostatically attracted by a cationic reagent as an anchoring point. They further confirm the potential of the observed photoionization products of cAA to react, creating long peptide

chains. The seed for the polymerization of the peptide chain is the cationic 5-oxazolidinone, which is also present as a photoionization product in the one-step isomerization process (TS3 in Figure 2). Interestingly, the processes shown in Figure 3 are energetically quite favorable, with small (or negligible) barriers that, once overtaken, lead to the final product. Thus, the formation of oxazolidinones and fragments 71 and 71⁺ after the VUV irradiation of cAA is the key step in the subsequent polymerization reactions.

A second question we should address, related to the elusive problem of the homochirality in life, is whether both reactants and products are conserved stereochemically pure throughout the entire reaction. Compounds very similar to the oxazolidinones found in this work, such as 5(4H)-oxazolone, have been widely used in peptide synthesis.^{47,48} However, they have been traditionally considered to be side products to be avoided during peptide synthesis since they can lead to the loss of optical activity from stereochemically pure reactants due to a tautomerization process.⁴⁹ Interestingly, in the case of ionized 5-oxazolidinones, the tautomerization transition state (calculated at the same level of theory) shows an energy barrier of 3.28 eV according to our calculations, while the formation of the first intermolecular minimum in Figure 3c between the oxazolidinone and the neutral 71 fragment is a favorable barrierless process. Therefore, if both reactants are stereochemically pure, then the proposed mechanism upholds this property and during polymerization acts as “asymmetric seeds” producing nonracemic peptide mixtures. To eventually explain the homochirality in nature, further studies on the possible energy difference in the paths leading to the different enantiomers are required, as slight energy differences due to symmetry violation may favor a mechanism toward enantiomeric excess.^{50–52} In this context, it has been shown that polarized VUV light could induce an enantiomeric excess in gas-phase amino acids.^{53–60}

Peptide bond formation in the gas phase is attracting more and more interest. Indeed, it has been recently investigated in the collision-induced dissociation (CID) of (i) molecular clusters formed by tryptophan or serine molecules inside charged helium droplets⁶¹ and (ii) protonated serine–serine dipeptides⁶² as well as in the interaction of energetic highly charged ions with neutral clusters of β -alanine.³² In this work, we demonstrate that the VUV ionization of simple DKP molecules triggers a complementary route, with the formation of 5-oxazolidinone and reactive species (71 and 71⁺) as prebiotic building blocks.⁶³ The interaction between them easily promotes the formation of peptide chains with the oxazolidinone as the elongation seed.

In summary, this work demonstrates how a cyclic dipeptide such as cAA could have been a suitable oligomer to survive rather hostile environments, where molecules are constantly exposed to radiation. The key mechanism we propose here relies on the formation of neutral and charged fragments in the peculiar amino acid-like structure of [alanine-H-OH], which is the core of the amino acid in a peptide sequence. We demonstrate via molecular dynamics simulations and potential energy surface exploration that these fragments, experimentally observed in the molecular BE region 12–16 eV after cAA exposition to VUV photons, have the potential to easily polymerize in both cyclic and linear structures, ready for peptide elongation. The smart decomposition of this cyclic dipeptide is based on the power of amino acid-like produced fragments to recycle themselves into cyclic-dipeptide structures or to provide the seed for linear polymerization. These prebiotically plausible

pathways for peptide formation may have played a role in the early stages of the chemical evolution of life.

The generality of the processes shown here for other amino acids and mixtures of different amino acids and their possible contribution to explain the homochirality displayed by nature are still open questions, which deserve to be further investigated in the future.

Computational Details: *Ab initio* molecular dynamics (AIMD) simulations on ionized and excited cyclic-alanine-alanine (cAA) were carried out by using the optimized geometry of the neutral molecule as the initial structure. This approach relies on a sudden ionization of the neutral cAA in a Franck–Condon way, leading, in this case, to the singly charged amino acid. To mimic the experimental conditions, we have introduced a certain amount of excitation internal energy (E_{exc}) randomly redistributed among the nuclear degrees of freedom. Typical values of internal energy of $E_{\text{exc}} = 10$ and 20 eV were used to consider the excited states prepared upon ionization. With these values, we are covering a sufficiently large energy range as observed in the PEPICO spectra, thus allowing us to identify the experimentally observed fragments. Notice that we are assuming a fast relaxation of the energy after the ionization of inner orbitals into nuclear degrees of freedom, i.e., with dynamics occurring in the electronic ground state with the energy excess transferred into vibrational modes. The *ab initio* molecular dynamics calculations were performed using the atom-centered density matrix propagation (ADMP) method. Trajectories have been carried out in the framework of the density functional theory (DFT) by using the B3LYP functional in combination with the 6-31++G(d,p) basis set. These simulations were performed with a time step of $\Delta t = 0.1$ fs, a fictitious mass of $\mu = 0.1$ au, and a maximum propagation time of $t_{\text{max}} = 500$ fs. For each value of excitation energy, 100 trajectories have been carried out. For the further exploration of the potential energy surface (PES) via simulations carried out to study the radiolysis mechanisms, we used the DFT-B3LYP/6-311++G(d,p) level of theory. Relaxed scans were computed at the same level of theory to obtain the energy barriers of the reported polymerization mechanisms and the final structure of the products. All of the simulations were performed using the Gaussian 16 program.⁴⁶

AUTHOR INFORMATION

Corresponding Authors

Paola Bolognesi – Institute of Structure of Matter-CNR (ISM-CNR), 00015 Monterotondo, Italy; orcid.org/0000-0002-6543-6628; Email: paola.bolognesi@cnr.it

Sergio Diaz-Tendero – Departamento de Química, Universidad Autónoma de Madrid, 28049 Madrid, Spain; Condensed Matter Physics Center (IFIMAC) and Institute for Advanced Research in Chemical Science (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain; orcid.org/0000-0001-6253-6343; Email: sergio.diaztendero@uam.es

Authors

Dário Barreiro-Lage – Departamento de Química, Universidad Autónoma de Madrid, 28049 Madrid, Spain

Jacopo Chiarinelli – Institute of Structure of Matter-CNR (ISM-CNR), 00015 Monterotondo, Italy

Robert Richter – Elettra Sincrotrone Trieste, 34149 Basovizza, Trieste, Italy; orcid.org/0000-0001-8585-626X

Henning Zettergren – Department of Physics, Stockholm University, Se-10691 Stockholm, Sweden

Mark H. Stockett – Department of Physics, Stockholm University, Se-10691 Stockholm, Sweden; orcid.org/0000-0003-4603-5172

Laura Carlini – Institute of Structure of Matter-CNR (ISM-CNR), 00015 Monterotondo, Italy

Lorenzo Avaldi – Institute of Structure of Matter-CNR (ISM-CNR), 00015 Monterotondo, Italy; orcid.org/0000-0002-2990-7330

Complete contact information is available at:
<https://pubs.acs.org/10.1021/acs.jpclett.1c01788>

Author Contributions

D.B.-L. carried out the simulations and analyzed the theoretical results. P.B., J.C., R.R., H.Z., M.H.S., L.C., and L.A. performed the experiments. P.B. and J.C. analyzed the data. P.B., S.D.-T., D.B.-L., and L.A. conceived the project and prepared the original draft of the manuscript. All authors thoroughly reviewed the manuscript and contributed to the final version, suggesting comments for the presentation and discussion of the results.

Funding

This article is based upon work from COST action CA18212 - Molecular Dynamics in the GAS phase (MD-GAS), supported by COST (European Cooperation in Science and Technology). The authors acknowledge the generous allocation of computer time at the Centro de Computación Científica at the Universidad Autónoma de Madrid (CCC-UAM). This work was partially supported by MICINN (Spanish Ministry of Science and Innovation) project PID2019-110091GB-I00, the “María de Maeztu” (CEX2018-000805-M) Program for Centers of Excellence in R&D, MAECI Italy-Sweden project “Novel molecular tools for the exploration of the nanoworld”, and PRIN 20173B72NB project “Predicting and controlling the fate of biomolecules driven by extreme-ultraviolet radiation”. D.B.-L. acknowledges the FPI grant associated with MICINN project CTQ2016-76061-P. H.Z. acknowledges the Swedish Research Council for the individual project grant with contract no. 2020-03437.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Prof. Silvia Cabrera for the critical reading of the manuscript.

REFERENCES

- (1) Miller, S. L. A Production of Amino Acids under Possible Primitive Earth Conditions. *Science* **1953**, *117* (3046), 528–529.
- (2) Schmitt-Kopplin, P.; Gabelica, Z.; Gougeon, R. D.; Fekete, A.; Kanawati, B.; Harir, M.; Gebefuegi, I.; Eckel, G.; Hertkorn, N. High Molecular Diversity of Extraterrestrial Organic Matter in Murchison Meteorite Revealed 40 Years after Its Fall. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107* (7), 2763–2768.
- (3) Botta, O.; Bada, J. L. Extraterrestrial Organic Compounds in Meteorites. *Surv. Geophys.* **2002**, *23* (5), 411–467.
- (4) Tielens, A. G. G. M. The Molecular Universe. *Rev. Mod. Phys.* **2013**, *85* (3), 1021–1081.
- (5) McGuire, B. A. 2018 Census of Interstellar, Circumstellar, Extragalactic, Protoplanetary Disk, and Exoplanetary Molecules. *arXiv* **2018**, 239, 17.
- (6) Hughes, A. B. Amino Acids, Peptides and Proteins in Organic Chemistry. *Origins and Synthesis of Amino Acids*; Wiley-VCH Verlag GmbH & Co. KGaA, 2009; Vol. 1.
- (7) Elsila, J. E.; Aponte, J. C.; Blackmond, D. G.; Burton, A. S.; Dworkin, J. P.; Glavin, D. P. Meteoritic Amino Acids: Diversity in

Compositions Reflects Parent Body Histories. *ACS Cent. Sci.* **2016**, *2* (6), 370–379.

(8) Glavin, D. P.; Callahan, M. P.; Dworkin, J. P.; Elsila, J. E. The Effects of Parent Body Processes on Amino Acids in Carbonaceous Chondrites. *Meteorit. Planet. Sci.* **2010**, *45* (12), 1948–1972.

(9) Shimoyama, A.; Ogasawara, R. Dipeptides and Diketopiperazines in the Yamato-791198 and Murchison Carbonaceous Chondrites. *Origins Life Evol. Biospheres* **2002**, *32* (2), 165–179.

(10) Burton, A. S.; Stern, J. C.; Elsila, J. E.; Glavin, D. P.; Dworkin, J. P. Understanding Prebiotic Chemistry through the Analysis of Extraterrestrial Amino Acids and Nucleobases in Meteorites. *Chem. Soc. Rev.* **2012**, *41* (16), 5459–5472.

(11) Rode, B. M. Peptides and the Origin of Life. *Peptides* **1999**, *20* (6), 773–786.

(12) 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* (2), 111.

(13) Öberg, K. I. Photochemistry and Astrochemistry: Photochemical Pathways to Interstellar Complex Organic Molecules. *Chem. Rev.* **2016**, *116* (17), 9631–9663.

(14) Bernstein, M. P.; Dworkin, J. P.; Sandford, S. A.; Cooper, G. W.; Allamandola, L. J. Racemic Amino Acids from the Ultraviolet Photolysis of Interstellar Ice Analogues. *Nature* **2002**, *416* (6879), 401–403.

(15) Zamirri, L.; Ugliengo, P.; Ceccarelli, C.; Rimola, A. Quantum Mechanical Investigations on the Formation of Complex Organic Molecules on Interstellar Ice Mantles. Review and Perspectives. *ACS Earth Space Chem.* **2019**, *3* (8), 1499–1523.

(16) Tielens, A. G. G. M. The Molecular Universe. *Rev. Mod. Phys.* **2013**, *85* (3), 1021.

(17) van Dishoeck, E. F. Astrochemistry of Dust, Ice and Gas: Introduction and Overview. *Faraday Discuss.* **2014**, *168*, 9.

(18) Martínez-Bachs, B.; Rimola, A. Prebiotic Peptide Bond Formation Through Amino Acid Phosphorylation. Insights from Quantum Chemical Simulations. *Life* **2019**, *9* (3), 75.

(19) Gindulyte, A.; Bashan, A.; Agmon, I.; Massa, L.; Yonath, A.; Karle, J. The Transition State for Formation of the Peptide Bond in the Ribosome. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103* (36), 13327–13332.

(20) Fiser, B.; Jójárt, B.; Szóri, M.; Lendvay, G.; Csizmadia, I. G.; Viskolcz, B. Glutathione as a Prebiotic Answer to α -Peptide Based Life. *J. Phys. Chem. B* **2015**, *119* (10), 3940–3947.

(21) Valeur, E.; Bradley, M. Amide Bond Formation: Beyond the Myth of Coupling Reagents. *Chem. Soc. Rev.* **2009**, *38* (2), 606–631.

(22) Pascal, R.; Boiteau, L.; Commeyras, A. From the Prebiotic Synthesis of α -Amino Acids towards a Primitive Translation Apparatus for the Synthesis of Peptides. *Top. Curr. Chem.* **2005**, *259*, 69–122.

(23) Frenkel-Pinter, M.; Samanta, M.; Ashkenasy, G.; Leman, L. J. Prebiotic Peptides: Molecular Hubs in the Origin of Life. *Chem. Rev.* **2020**, *120* (11), 4707–4765.

(24) Lahav, N.; White, D.; Chang, S. Peptide Formation in the Prebiotic Era: Thermal Condensation of Glycine in Fluctuating Clay Environments. *Science* **1978**, *201* (4350), 67.

(25) Lambert, J.-F.; Jaber, M.; Georgelin, T.; Stieven, L. A Comparative Study of the Catalysis of Peptide Bond Formation by Oxide Surfaces. *Phys. Chem. Chem. Phys.* **2013**, *15* (32), 13371.

(26) de Castro Silva, F.; Lima, L. C. B.; Silva-Filho, E. C.; Fonseca, M. G.; Lambert, J.-F.; Jaber, M. A Comparative Study of Alanine Adsorption and Condensation to Peptides in Two Clay Minerals. *Appl. Clay Sci.* **2020**, *192*, 105617.

(27) Bedoin, L.; Alves, S.; Lambert, J.-F. Origins of Life and Molecular Information: Selectivity in Mineral Surface-Induced Prebiotic Amino Acid Polymerization. *ACS Earth Space Chem.* **2020**, *4* (10), 1802.

(28) Bujdak, J.; Slosiarikova, H.; Texler, N.; Schwendinger, M.; Rode, B. M. On the Possible Role of Montmorillonites in Prebiotic Peptide Formation. *Monatsh. Chem.* **1994**, *125* (10), 1033.

(29) MacLott, S.; Piekarski, D. G.; Domaracka, A.; Méry, A.; Vizcaino, V.; Adoui, L.; Martín, F.; Alcamí, M.; Huber, B. A.; Rousseau, P.; Díaz-Tendero, S. Dynamics of Glycine Dications in the Gas Phase: Ultrafast

Intramolecular Hydrogen Migration versus Coulomb Repulsion. *J. Phys. Chem. Lett.* **2013**, *4* (22), 3903–3909.

(30) Piekarski, D. G.; Delaunay, R.; Maclot, S.; Adoui, L.; Martín, F.; Alcamí, M.; Huber, B. A.; Rousseau, P.; Domaracka, A.; Díaz-Tendero, S. Unusual Hydroxyl Migration in the Fragmentation of β -Alanine Dication in the Gas Phase. *Phys. Chem. Chem. Phys.* **2015**, *17* (26), 16767–16778.

(31) Castrovilli, M. C.; Trabattini, A.; Bolognesi, P.; O’Keeffe, P.; Avaldi, L.; Nisoli, M.; Calegari, F.; Cireasa, R. Ultrafast Hydrogen Migration in Photoionized Glycine. *J. Phys. Chem. Lett.* **2018**, *9* (20), 6012.

(32) Rousseau, P.; Piekarski, D. G.; Capron, M.; Domaracka, A.; Adoui, L.; Martín, F.; Alcamí, M.; Díaz-Tendero, S.; Huber, B. A. Polypeptide Formation in Clusters of β -Alanine Amino Acids by Single Ion Impact. *Nat. Commun.* **2020**, *11* (1), 3818.

(33) Oostenrijk, B.; Barreiro, D.; Walsh, N.; Sankari, A.; Månsson, E. P.; Maclot, S.; Sorensen, S. L.; Díaz-Tendero, S.; Gisselbrecht, M. Fission of Charged Nano-Hydrated Ammonia Clusters-Microscopic Insights into the Nucleation Processes. *Phys. Chem. Chem. Phys.* **2019**, *21* (46), 25749.

(34) Danger, G.; Plasson, R.; Pascal, R. Pathways for the Formation and Evolution of Peptides in Prebiotic Environments. *Chem. Soc. Rev.* **2012**, *41* (16), 5416–5429.

(35) Biscans, A. Exploring the Emergence of RNA Nucleosides and Nucleotides on the Early Earth. *Life* **2018**, *8* (4), 57.

(36) Powner, M. W.; Anastasi, C.; Crowe, M. A.; Parkes, A. L.; Raftery, J.; Sutherland, J. D. On the Prebiotic Synthesis of Ribonucleotides: Photoanomerisation of Cytosine Nucleosides and Nucleotides Revisited. *ChemBioChem* **2007**, *8* (10), 1170–1179.

(37) Zappia, G.; Menendez, P.; Delle Monache, G.; Misiti, D.; Nevola, L.; Botta, B. The Contribution of Oxazolidinone Frame to The Biological Activity of Pharmaceutical Drugs and Natural Products. *Mini-Rev. Med. Chem.* **2007**, *7* (4), 389–409.

(38) Ohta, Y.; Itoh, S.; Shigenaga, A.; Shintaku, S.; Fujii, N.; Otaka, A. Cysteine-Derived S-Protected Oxazolidinones: Potential Chemical Devices for the Preparation of Peptide Thioesters. *Org. Lett.* **2006**, *8* (3), 467–470.

(39) Borthwick, A. D. 2,5-Diketopiperazines: Synthesis, Reactions, Medicinal Chemistry, and Bioactive Natural Products. *Chem. Rev.* **2012**, *112* (7), 3641–3716.

(40) Derossi, A.; Lama, F.; Piacentini, M.; Prosperi, T.; Zema, N. High Flux and High Resolution Beamline for Elliptically Polarized Radiation in the Vacuum Ultraviolet and Soft X-Ray Regions. *Rev. Sci. Instrum.* **1995**, *66* (2), 1718–1720.

(41) Plekan, O.; Coreno, M.; Feyer, V.; Moise, A.; Richter, R.; Simone, M. de.; Sankari, R.; Prince, K. C. Electronic State Resolved PEPICO Spectroscopy of Pyrimidine. *Phys. Scr.* **2008**, *78* (5), 058105.

(42) Bolognesi, P.; Kettunen, J. A.; Cartoni, A.; Richter, R.; Tosic, S.; Maclot, S.; Rousseau, P.; Delaunay, R.; Avaldi, L. Site- and State-Selected Photofragmentation of 2Br-Pyrimidine. *Phys. Chem. Chem. Phys.* **2015**, *17* (37), 24063–24069.

(43) Tsai, B. P.; Eland, J. H. D. Mass Spectra and Doubly Charged Ions in Photoionization at 30.4 Nm and 58.4 Nm. *Int. J. Mass Spectrom. Ion Phys.* **1980**, *36* (2), 143–165.

(44) Molloy, R. D.; Danielsson, A.; Karlsson, L.; Eland, J. H. D. Double Photoionisation Spectra of Small Molecules and a New Empirical Rule for Double Ionisation Energies. *Chem. Phys.* **2007**, *335* (1), 49–54.

(45) Maclot, S.; Delaunay, R.; Piekarski, D. G.; Domaracka, A.; Huber, B. A.; Adoui, L.; Martín, F.; Alcamí, M.; Avaldi, L.; Bolognesi, P.; Díaz-Tendero, S.; Rousseau, P. Determination of Energy-Transfer Distributions in Ionizing Ion–Molecule Collisions. *Phys. Rev. Lett.* **2016**, *117* (7), 073201.

(46) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. a.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. a.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, a. v.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. v.; Izmaylov, a. F.; Sonnenberg, J. L.; Williams; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe,

D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, revision C.01; Gaussian, Inc.: Wallin, 2016.

(47) Goodman, M.; McGahren, W. J. Mechanistic Studies of Peptide Oxazolone Racemization. *Tetrahedron* **1967**, 23 (5), 2031.

(48) de Castro, P. P.; Carpanez, A. G.; Amarante, G. W. Azlactone Reaction Developments. *Chem. - Eur. J.* **2016**, 22 (30), 10294.

(49) Weygand, F.; Prox, A.; Schmidhammer, L.; König, W. Gas Chromatographic Investigation of Racemization during Peptide Synthesis. *Angew. Chem., Int. Ed. Engl.* **1963**, 2 (4), 183.

(50) Quack, M. How Important Is Parity Violation for Molecular and Biomolecular Chirality? *Angew. Chem., Int. Ed.* **2002**, 41 (24), 4618–4630.

(51) Takahashi, J. I.; Kobayashi, K. Origin of Terrestrial Bioorganic Homochirality and Symmetry Breaking in the Universe. *Symmetry* **2019**, 11 (7), 919.

(52) Fehre, K.; Eckart, S.; Kunitski, M.; Pitzer, M.; Zeller, S.; Janke, C.; Trabert, D.; Rist, J.; Weller, M.; Hartung, A.; Schmidt, L. P. H.; Jahnke, T.; Berger, R.; Dörner, R.; Schöffler, M. S. Enantioselective Fragmentation of an Achiral Molecule in a Strong Laser Field. *Sci. Adv.* **2019**, 5 (3), eaau7923.

(53) Modica, P.; Meinert, C.; de Marcellus, P.; Nahon, L.; Meierhenrich, U. J.; d'Hendecourt, L. L. S. Enantiomeric Excesses Induced in Amino Acids by Ultraviolet Circularly Polarized Light Irradiation of Extraterrestrial Ice Analogs: A Possible Source of Asymmetry for Prebiotic Chemistry. *Astrophys. J.* **2014**, 788 (1), 79.

(54) Nuevo, M.; Meierhenrich, U. J.; Muñoz Caro, G. M.; Dartois, E.; d'Hendecourt, L.; Deboffle, D.; Auger, G.; Blanot, D.; Bredehöft, J.-H.; Nahon, L. The Effects of Circularly Polarized Light on Amino Acid Enantiomers Produced by the UV Irradiation of Interstellar Ice Analogs. *Astron. Astrophys.* **2006**, 457 (3), 741.

(55) Takano, Y.; Takahashi, J.; Kaneko, T.; Marumo, K.; Kobayashi, K. Asymmetric Synthesis of Amino Acid Precursors in Interstellar Complex Organics by Circularly Polarized Light. *Earth Planet. Sci. Lett.* **2007**, 254 (1–2), 106.

(56) Meierhenrich, U. J. Amino Acids and the Asymmetry of Life. *Eur. Rev.* **2013**, 21 (2), 190.

(57) Hashim, P. K.; Tamaoki, N. Enantioselective Photochromism under Circularly Polarized Light. *ChemPhotoChem.* **2019**, 3 (6), 347.

(58) Potapov, A.; McCoustra, M. Physics and Chemistry on the Surface of Cosmic Dust Grains: A Laboratory View. *Int. Rev. Phys. Chem.* **2021**, 40 (2), 299.

(59) Sandford, S. A.; Nuevo, M.; Bera, P. P.; Lee, T. J. Prebiotic Astrochemistry and the Formation of Molecules of Astrobiological Interest in Interstellar Clouds and Protostellar Disks. *Chem. Rev.* **2020**, 120 (11), 4616.

(60) Muñoz Caro, G. M.; Ciaravella, A.; Jiménez-Escobar, A.; Cecchi-Pestellini, C.; González-Díaz, C.; Chen, Y.-J. X-Ray versus Ultraviolet Irradiation of Astrophysical Ice Analogs Leading to Formation of Complex Organic Molecules. *ACS Earth Space Chem.* **2019**, 3 (10), 2138.

(61) Tiefenthaler, L.; Kočišek, J.; Scheier, P. Cluster Ion Polymerization of Serine and Tryptophan, the Water Loss Channel. *Eur. Phys. J. D* **2020**, 74 (5), 85.

(62) Nihamkin, M.; Isaak, A.; Albeck, A.; Mastai, Y.; Toker, Y. Gas Phase Bond Formation in Dipeptide Clusters. *J. Phys. Chem. Lett.* **2020**, 11 (23), 10100–10105.

(63) Kitadai, N.; Maruyama, S. Origins of Building Blocks of Life: A Review. *Geosci. Front.* **2018**, 9 (4), 1117–1153.