

The results of CD spectroscopy accord well with the amide proton/deuterium exchange NMR measurements performed in $[D_4]$ methanol, where **4** lost its amide signal intensity in 15 minutes, while the amide protons of **5** survived for more than 1 hour. The lower exchange rate for heptamer **5**, together with the IR and CD results, supports the view that the folding occurs in a cooperative manner as the chain length increases.

Herein we have shown that the 1*R*,2*S*-ACPC pentamer and heptamer adopt a self-stabilizing six-strand secondary structure in the solution phase. From earlier results, we know that the model system composed of (1*R*,2*R*)-*trans*-ACPC monomers adopts the highly stable 12-helix conformation^[16] (Figure 6). The change in the relative configuration of the ACPC residues in these models provides an efficient control over the

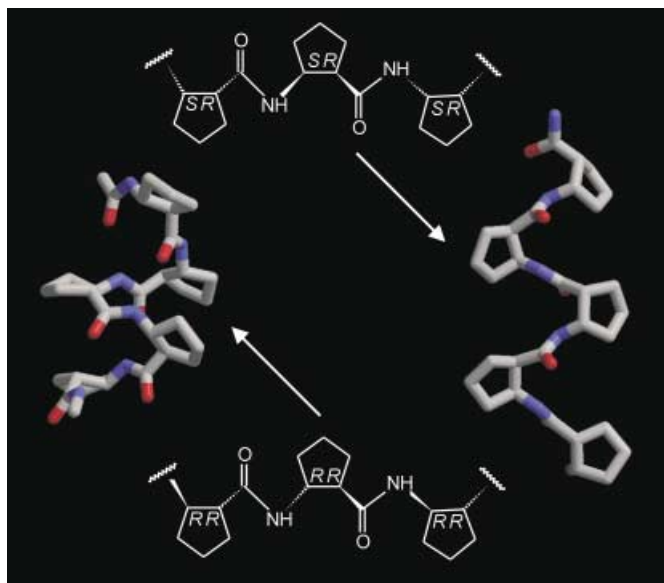


Figure 6. Comparison of the secondary structures induced by the different relative configurations of the ACPC residues.

secondary structures of the helix and strand. The application of the 2-aminocycloalkanecarboxylic acids as a general backbone in the controlled design of β -peptide foldamers is supported by the relatively easy synthetic availability of this family of compounds.^[17] This type of chirality-based selection between regular secondary structures may become a general tool in the design of β -peptide foldamers and may facilitate the construction of stable tertiary structures.

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Chiral Transmission between Amino Acids: Chirally Selective Amino Acid Substitution in the Serine Octamer as a Possible Step in Homochirogenesis**

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Pasteur's discovery^[1] that tartaric acid can occur in two enantiomeric forms raised still unanswered questions^[2–6] concerning the origin of chirality in biological systems (homochirality). Homochirogenesis, the set of events leading to the almost exclusive preference for one enantiomeric form over the other in the suite of biological compounds that make up living organisms, can be considered to have involved three steps: 1) symmetry breaking, 2) chiral enrichment, and 3) chiral transmission.

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Symmetry breaking requires a chemical, physical, or merely statistical process that favors one chiral form over the other. As a case in point, an intrinsic energy difference is predicted between enantiomeric molecules as a result of a parity violation in the weak nuclear force.^[7, 8] Symmetry breaking might also arise in appropriate circumstances from external chiral agents, such as circularly polarized light,^[9–12] vortex motion,^[13] and magnetic forces.^[14, 15] Chiral enrichment, the second step, involves the build-up of large enantiomeric excesses in biologically relevant compounds. Mechanisms that have been considered include chirally directed (“majority rules”^[16]) polymerization, polycondensation in particular cases (such as leucine) where the chirally pure polymer has significantly enhanced stability,^[17] autocatalytical processes including those catalyzed by enantiomorphous crystal faces such as that of quartz,^[18] asymmetric synthesis,^[19] and self-replication by such biomolecules as peptides.^[20] We hypothesize that chiral accumulation occurred in one or just a few compounds during terrestrial homochirogenesis, thus underlining the importance of the third step of the overall process, chiral transmission—the transfer of chirality from one molecule (or molecular assembly) to another. We consider here the transfer of chirality from serine, a presumed primitive amino acid, to other biomolecules. Serine attracts attention because it is known that molecular clusters with strong chiral preferences^[21–23] can be extracted from aqueous solutions by electrospray ionization mass spectrometry (ESI-MS). We now report that chiral transmission from serine to other amino acids occurs under these same conditions. The formation of clusters presumably occurs during the evaporation of highly concentrated microdroplets.

The transmission of chirality from serine to other amino acids occurs by substitution of the amino acids in the recently discovered homochiral serine octamer.^[21–23] Addition of cysteine to a solution of serine followed by electrospray ionization of the mixture yields the homochiral octamer and the products in which substitution of one or two cysteine molecules of matching chirality into the cluster has occurred. In contrast, cysteine alone forms a singly protonated, hexameric magic number cluster, without regard to chiral composition. All the other amino acids investigated (aspartic acid, asparagine, leucine, and methionine) are also incorporated into the serine octamer (by either mono- or disubstitution) provided they have the same chirality as serine; much less incorporation of the wrong enantiomer was observed. The net result is the transmission of the chiral choice made in the serine octamer to the amino acid that is substituted into the cluster. We argue that this chirally selective incorporation represents a method of chiral transmission and that it might have had a role in this phenomenon as it occurred on the primitive earth. At the very least, this case represents a striking display of homochiral selectivity in an elementary biomolecule of great importance.

The positive-ion ESI mass spectrum of cysteine, chosen since it is the sulfur analogue of serine, exhibits a magic number cluster m/z 727 (corresponding to the singly charged hexamer and doubly charged dodecamer). Figure 1a shows the ESI mass spectrum of a 0.01M solution of L-Cys; note that only the singly charged monomer, dimer, and hexamer are

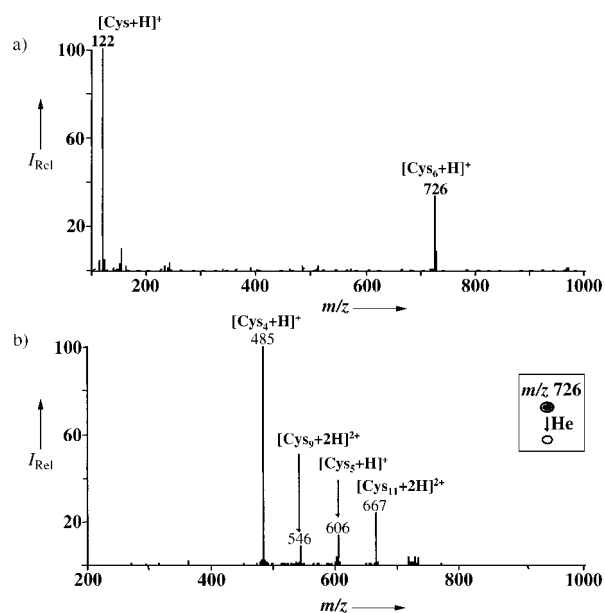


Figure 1. a) The positive-ion ESI mass spectrum of a 0.01M solution of L-cysteine in aqueous methanol. b) Tandem mass spectrum showing products of the collision-induced dissociation of $[Cys_6+H]^+$ m/z 727.

sufficiently stable to be isolated using an isolation window of $m/z = 20$. A series of D:L mixtures (100:0, 80:20, 50:50, 20:80, 0:100) showed absolute and relative ion abundances that were reproducible within $\pm 5\%$ in their mass spectra as well as in their tandem (MS^2) spectra when examining the products of collision-induced dissociation of the m/z 727 ion, the protonated hexamer. These observations indicate that, unlike the case of serine, there is no chiral preference for clustering. Collision-induced dissociation (CID) of the hexamer (Figure 1b) yielded both singly and doubly charged fragments, an indication of the presence of the doubly charged dodecamer.^[24]

Ab initio calculations were performed using the GAMESS program^[25] at the Hartree–Fock (HF) level using the 6-31G double-zeta basis set. The calculated geometries were assembled using the Spartan program. The maximum and root-mean square gradient values for the octamers were set to 0.0003 and 0.0001, respectively. For all the other calculated systems, the default values were used (0.0001 and 0.00003). The final structures were checked using the MOLDEN program.^[26] The electronic energies associated with each optimized structure are reported in Table 1. Ab initio calculations on the Cys hexamer show the lowest energy structure to be a trimer of neutral dimers (Figure 2). The hexamer is composed of three Cys dimers, bound to each other by hydrogen bonding through the amino groups. Note that the

Table 1. Electronic energies obtained using Hartree–Fock level calculations.

Calculated structure	Electronic energies (Hartree)
$[L-Ser_8+H]^+$	– 3172.87005
$[L-Ser_7+L-Cys+H]^+$	– 3495.52063
$[L-Ser_7+D-Cys+H]^+$	– 3495.51662
$[Cys_2+H]^+$	– 1438.40273
$[Ser+Cys]$	– 1115.75135

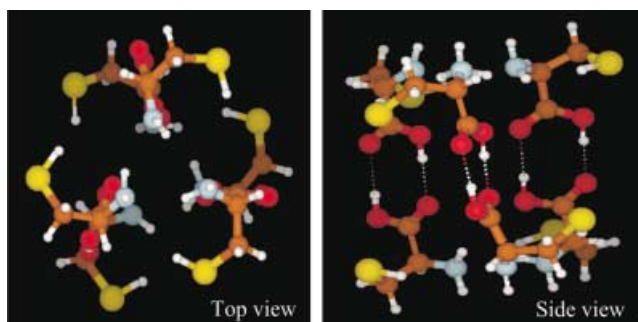


Figure 2. The calculated structure of the cysteine hexamer shown to be assembled from three Cys dimers bound together by interactions between the amino groups.

weak hydrogen-bonding character of the SH group of cysteine, unlike the strong hydrogen-bonding character provided by the OH group in serine, rationalizes the diminished abundance of the cluster and the lack of chiral dependence.

The characteristic homochiral clustering of serine is observed in the mixed clusters generated from a mixture of cysteine and serine. The mass spectrum of a mixture of 0.01M solutions each of L-Ser and L-Cys (Figure 3a) shows the

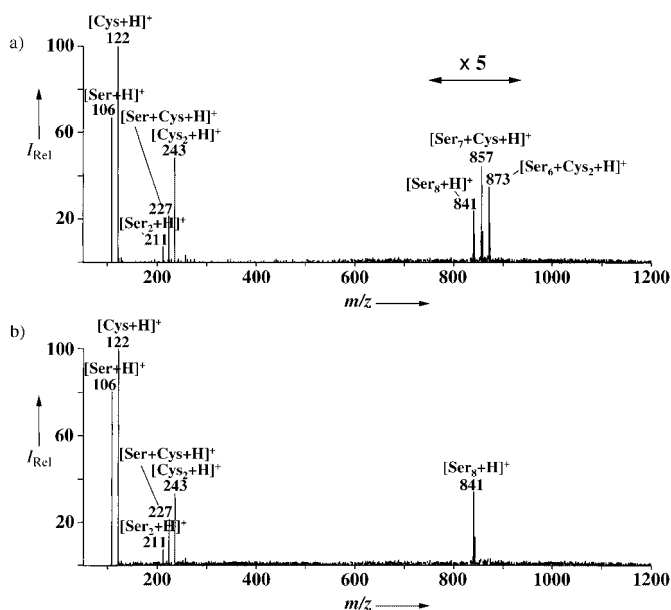


Figure 3. a) ESI mass spectrum of a mixture of L-serine (0.01M) and L-cysteine (0.01M) showing the formation of singly and doubly substituted serine octamers. b) ESI mass spectrum of a mixture of L-serine (0.01M) and D-cysteine (0.01M) showing the lack of formation of mixed octamers.

formation of the singly and doubly substituted serine octamers.^[27] A series of Ser:Cys mixtures (100:1, 20:1, 10:1, 4:1, 1:1, 1:4, 1:10, 1:20, 1:100) demonstrates that a maximum of two serine molecules can be substituted by cysteine. The resulting structure has been calculated at the HF/6-31G level and the results indicate that one serine residue in each of the two faces of the serine octamer is replaced by cysteine and results in destabilization of the octamer by 0.5 kcal mol⁻¹. The octamer ions [Ser₈+H]⁺, [Ser₆+Cys₂+H]⁺, and [Ser₇+Cys+H]⁺ fragment by preferential loss of neutral serine dimers.

The mass spectrum of a 0.01M solution of D-Ser mixed with a 0.01M solution of L-Cys (Figure 3b) stands in dramatic contrast to that of the homochiral mixture. The serine octamer is observed in approximately its original abundance, but few substituted octamers are generated.^[28] The contrast between the two mass spectra clearly indicates that the chirality of cysteine plays a critical role in its incorporation into the serine octamer. Ab initio calculations reveal a destabilization energy of 2.5 kcal mol⁻¹ associated with the incorporation of the wrong enantiomer. By contrast, the cost in terms of energy of incorporating the “wrong” amino acid but with the “right” chirality is only 0.5 kcal mol⁻¹ per incorporation!

Preliminary data have been obtained for the formation of singly and doubly substituted serine octamers with a set of amino acids, including aspartic acid, asparagine, leucine, methionine, and phenylalanine, selected as representative of amino acids with acidic, amide, aliphatic, aromatic, and sulfur-containing side chains. When examined in the presence of serine, up to two amino acids with the correct chirality are incorporated into the serine octamer in each case. Figure 4a shows that one or two asparagine molecules of the correct

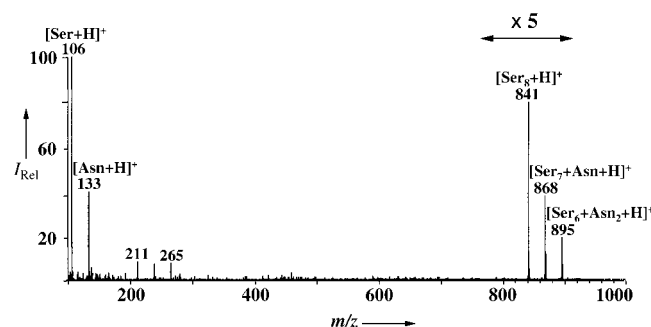


Figure 4. ESI mass spectrum of a mixture of L-serine (0.01M) and L-asparagine (0.01M) showing the formation of singly and doubly substituted serine octamers.

chirality are readily incorporated into the serine octamer; the following data, given as the relative abundance ratios (serine octamer):(singly substituted serine octamer):(doubly substituted serine octamer), summarize the relative extent of formation of the various substituted L-serine clusters: L-Asp (6:2:1), L-Asn (4:2:1), L-Leu (3:4:3), L-Met (1:2:1), L-Phe (2:1:1). Octamer substitution appears to be a function of the size and functional groups of the amino acid side chain. The absence of incorporation of the wrong enantiomer (Figure 4b) clearly shows the effects of chirality in the asparagine case. Chiral transmission from serine to the other amino acids—through their incorporation into the homochiral octameric cluster—represents a novel possibility for the transmission of chirality between amino acids. Chiral transmission is clearly demonstrated by the fact that cysteine itself clusters in a chirally independent fashion, but in the presence of serine one enantiomer is strongly favored for substitution into the homochiral cluster. The possible role of this process in primitive earth is the subject of ongoing enquiry.^[29]

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- [27] In this experiment, the cysteine solution was injected into a flowing stream of the serine solution. The degree of incorporation is always limited to two molecules but relative abundances are strongly dependent on the ESI operating conditions.
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Hydrogen-Bonded Helices in Crystals with Prescribed Organization**

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Self-assembled molecular helices are ubiquitous in nature and can be found in many biologically important macromolecules. It is therefore not surprising that chemists have made significant efforts to introduce helicity in many artificial systems.^[1] The inherent chirality present in such spiral structures is generally associated with enantioselectivity^[2] or interesting optoelectronic properties.^[3] Theoretical^[4] and experimental^[5] studies have indicated that helical supramolecular networks can affect chiral ordering in crystal lattices.

Molecular helicity can be programmed by judicious selection of elements that are encoded with structural and conformational information designed to enforce intramolecular self-organization in a spiral arrangement. Examples such as helicenes,^[6] poly(*m*-phenylene),^[7] polyheterocyclic strands,^[8] *m*-phenylacetylene oligomers,^[9] β -peptides,^[10] polyisocyanates,^[11] and oligoarylamides^[12] elegantly illustrate this concept. The generation of supramolecular helices requires an additional design element, namely, a reliable noncovalent motif that can provide the desired connectivity of the building blocks in a predictable manner. Hydrogen bonds,^[13] metal coordination,^[14] and π – π stacking interactions^[15] are often utilized in this regard. These design strategies, however, are generally limited to one dimension, coinciding with the helix direction, while the assembly and structure along the remaining two crystal dimensions are difficult to control. The rational construction of new materials with tailored functions and properties, however, requires control of crystal architecture in all three dimensions. Here we report the formation of hydrogen-bonded helices with predictable three-dimensional (3D) organization in the solid state. This study represents a key first step towards the rational design of crystalline, hydrogen-bonded chiral networks with potential applications in enantioselective separation.^[16]

We are actively involved in the design of molecular crystals based on the self-assembly of complementary guanidinium and organosulfonate ions, which typically crystallize in a quasihexagonal hydrogen-bonded network (Figure 1a).^[17] These 2D layers can be described as consisting of 1D ribbons along a_1 . The S...S distance along this axis is nominally identical for all these compounds (7.5 ± 0.2 Å). The ribbons themselves aggregate by hydrogen bonding along the orthogonal direction b_1 . The magnitude of b_1 can vary significantly (7.3 – 13 Å) as a result of puckering of the sheet about the hydrogen bonds that connect the ribbons.

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