

Negatively-Charged Halide Adducts of Homochiral Serine Octamers

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Negatively charged halide adducts of serine octamers, $(\text{Ser}_8+2\text{Cl})^{2-}$ and $(\text{Ser}_8+2\text{Br})^{2-}$, appear as magic number clusters in the negative ion electrospray mass spectra of solutions containing serine and the halide. Like the well-known protonated serine octamer, these negatively charged adducts are formed with homochiral preference and also undergo chiroselective substitution reactions with other amino acids. Tandem mass spectra of negatively charged halide adducts of serine octamers show that these ions also have a characteristic fragmentation signature. The fact that octamers of both polarities display analogous chemical properties suggests that these may be characteristics of the so-far-unknown neutral octamer. If serine played a key role in the origin of homochirality on the primitive earth, it was likely through both the neutral octamer and the ionic adducts. Unlike the octamers, the formation of halide-containing serine cluster ions of particular sizes is unfavorable under the conditions of the experiment. Signals corresponding to the ions $(\text{Ser}_9+2\text{Br})^{2-}$ and $(\text{Ser}_{15}+2\text{Br})^{2-}$ are particularly low in intensity, giving rise to gaps in the distribution of serine/bromide clusters in the negative ion electrospray mass spectra. These cluster sizes are likely to correspond to unstable “anti-magic number” clusters recently reported by Clemmer.

Introduction

The protonated serine octamer, $(\text{Ser}_8+\text{H})^+$,^{1–4} first observed in the positive ion electrospray mass spectra of aqueous solutions of the amino acid serine,^{1–4} represents a most remarkable case of a noncovalently bound magic number cluster. Under select conditions⁵ the protonated octamer is formed almost exclusively compared to clusters of other sizes.⁵ Even more intriguing is the remarkable homochiral preference associated with the formation of the protonated serine octamer.^{5–22} Several studies have sought information on the structure(s) of serine clusters: they include ion mobility cross section measurements,^{4,10,18,21} theoretical calculations,^{2,3,20,21} infrared multiphoton dissociation (IRMPD) spectroscopy,¹⁷ and ion/molecule reactions, such as serine/amine substitution^{14,22} and hydrogen/deuterium exchange experiments.^{8,16,22–24} These studies have provided evidence for two structural types of serine octamers,^{8,16} associated with zwitterionic and non-zwitterionic forms of monomeric serine. However, determination of detailed structures has proven to be a refractory task. These structural issues and the relevance of serine octamers in the origin of homochirality have recently been reviewed.^{14–19}

Various theories have been advanced^{25–31} to explain how life evolved homoenantiomerically, i.e., in such a way as to strongly favor L-amino acids and D-saccharides. One suggestion^{2,3} is that homochiral biomolecules might have emerged as a consequence of chiral choices that involved the formation and dissociation of clusters of free amino acids, among which serine and its octamer are candidates of special interest. Not only does the protonated serine octamer exhibit a preference for homochirality, but it can be generated easily using conditions encountered in the prebiotic environment (e.g., heating serine in air).¹³ It has been proposed^{2,7} that serine was involved in prebiotic mechanisms that (i) accumulated left-handed serine through formation

of homochiral octamers (chiral enrichment)^{12,15} and (ii) transferred the chiral choice to other left-handed amino acids⁷ and right-handed saccharides⁹ through chiroselective substitution reactions in the octamer (chiral transmission).^{7,9} Chiral enrichment in serine has been demonstrated in recent experiments using cycles of formation, isolation, and dissociation of octamers which were initially generated from solutions containing small enantiomeric excess.^{12,15} Chiral transmission has been shown to occur in substitution reactions involving the octamer and other biologically relevant chiral molecules in which the stereochemical choices are those found in life.^{7,9} There is no evidence for a role of serine or its octamer in symmetry breaking,^{32–34} the process that must have occurred along with chiral enrichment and chiral transmission. However, it is known that serine is one of the amino acids that epimerize under relatively mild conditions,^{9,35,36} possibly facilitating symmetry breaking in the presence of an external chiral agent.⁹

Despite the relatively large literature^{1–22} covering gas-phase serine octamers, only positively charged ions have previously been reported. The lack of evidence for the existence of negatively charged octamers has made it difficult to draw connections between the ionic adducts observed in a mass spectrometer and the putative neutral octamer. The negative electrospray ionization mass spectra of serine solutions in aqueous methanol show a different pattern of serine clusters than observed for positive adducts under identical conditions.⁵ Deprotonated octamers, $(\text{Ser}_8-\text{H})^-$, are not favored.⁵ In this paper we report the first observation of negatively charged serine octamers, $(\text{Ser}_8+2\text{Cl})^{2-}$ and $(\text{Ser}_8+2\text{Br})^{2-}$, which are formed from solutions that contain chloride and bromide, respectively, at either neutral or acidic pH. These ions appear as magic number clusters in the negative ion electrospray mass spectra and react in a chirally selective fashion just as does the well-known protonated serine octamer. We propose that the chiroselective chemistry observed for the ionic adducts of serine could represent the behavior of neutral octamers, and this provides

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support for previous claims^{2,7,9,12} that the serine octamer may have played a unique role in the origin and transmission of homochirality in living systems. The observation of serine octamers of both polarities with analogous properties suggests that the charges simply allow the underlying chemistry to be followed by mass spectrometry and that the observed magic number clustering and chiroselective chemistry is intrinsic to the neutral serine octamers.

Experimental Section

Negative ion electrospray ionization (ESI) mass spectrometry^{37,38} was used to generate and to study serine/halide clusters. Mass spectra were recorded using a commercial Finnigan LCQ quadrupole ion trap mass spectrometer (Thermo Electron Corp., San Jose, CA). Instrumental conditions were set as follows unless otherwise indicated: heated capillary temperature, 100 °C; spray voltage, 4.5 kV; sheath gas (N_2) flow rate, 50 arb units; auxiliary gas (N_2) flow rate, 10 arb units; sample flow rate, 7.0 μ L/min; electron multiplier voltage, 1.1 kV. All solutions were prepared in 50:50 methanol/water, with a serine concentration of 1×10^{-2} M and halide (F^- , Cl^- , Br^- , or I^-) concentration of 5×10^{-4} M. In the case of chloride and bromide, either the salts NaCl and NaBr or the acids HCl and HBr were used as the sources of Cl^- and Br^- , respectively. Both procedures gave similar results. Peaks corresponding to serine/halide anions have been identified in the mass spectra by (i) mass-to-charge ratio measurements, (ii) tandem mass spectrometry, and (iii) careful examination of the isotopic distributions of chlorine- and bromine-containing ions.

Tandem mass spectrometry experiments were performed by isolating the ions of interest using a notched waveform (25 m/z units in width) to excite and eject undesirable ions. Fragmentation of the isolated precursor ion was subsequently achieved through collision-induced dissociation (CID) with helium buffer gas. Default activation conditions employed a Mathieu parameter $q = 0.250$, used in all MS^2 experiments. The collision energy is expressed in terms of the manufacturer's relative collision energy (%), in which the interval from 0 to 100% corresponds to 0–2.5 V (zero-to-peak) at the secular frequency of the ion of interest.

Results and Discussion

Negatively Charged Serine Octamers. Only positively charged serine octamers have been reported previously,^{1–22} a fact that motivated this work. Thus, in a search for negatively charged octamers we studied the clustering preferences of serine in the presence of halide anions by negative ion electrospray mass spectrometry. Chloride and bromide adducts of the octamer are formed readily with two halogen ions being incorporated into the cluster. A comparison of the positive and negative ion electrospray mass spectra of L-serine in the presence of 5×10^{-4} M HCl is shown in Figure 1. As is the case for the protonated serine octamer, the chloride adduct of the octamer is highly abundant compared to other cluster species. Both spectra show a similar clustering pattern for serine from the monomer through the octamer, with Ser_1 , Ser_2 , and Ser_8 adducts appearing in high abundance, while the clusters Ser_3 through Ser_7 are unfavorable. Note that, in Figure 1b, signals above m/z 500 mainly correspond to multiply charged Ser/Cl^- adducts. Even though simple inspection of the data (see Figure 1) reveals preferential formation of dihalide serine octamers, $(Ser_8+2Cl)^{2-}$, we cannot rule out the existence of the singly charged species, $(Ser_8+Cl)^-$, whose signal would overlap with that of $(Ser_{16}+2Cl)^{2-}$. We focus our attention to the doubly

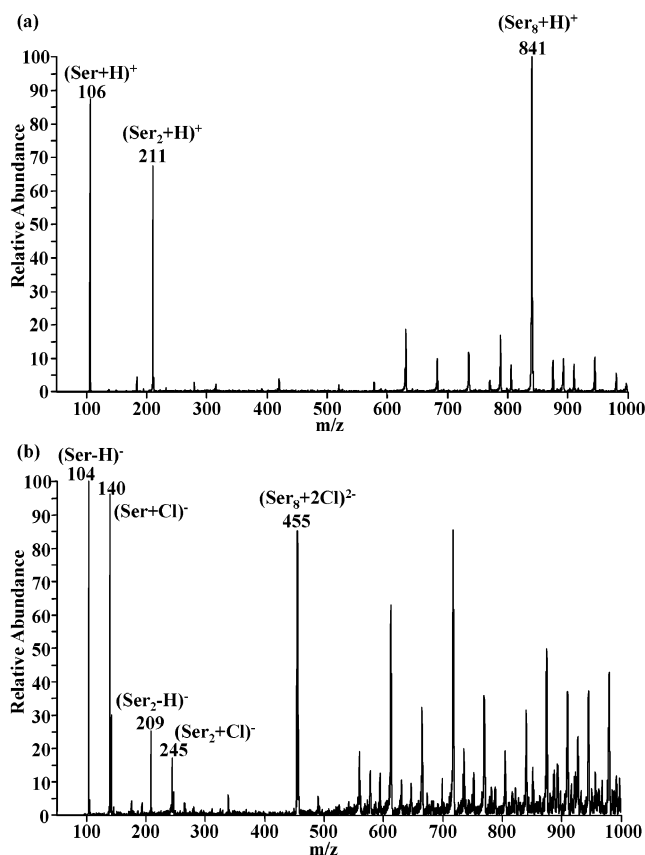


Figure 1. (a) Positive and (b) negative ion ESI mass spectra of a solution containing 1×10^{-2} M L-serine and 5×10^{-4} M HCl. The serine octamer appears as a magic number cluster in both spectra, ionized by attachment of H^+ and Cl^- , respectively.

charged adducts of the octamer, since they give a signal that does not interfere with highly abundant isobaric clusters. For example, the isotope envelope observed centered around mass-to-charge 455 is in good agreement with that expected for $(Ser_8+2Cl)^{2-}$, confirming that the signal mainly corresponds to doubly charged dihalide adducts of the octamer rather than the singly charged isobaric tetramer.

Interesting clustering tendencies have been observed at relatively high m/z values (i.e., m/z 500–2000), especially in the case of solutions containing Br^- . This is discussed in a later section. Negative ion ESI mass spectra of serine in the presence of bromide resulted in the formation of the analogous $(Ser_8+2Br)^{2-}$ adduct ion as a magic number cluster. The general similarity between all three data sets (H^+ , Cl^- , and Br^- adducts) suggests that the negatively charged octamers are structural analogues of the protonated octamers.

Formation of serine/halide clusters was attempted for each of the common anions of group VII (fluoride, chloride, bromide, and iodide). Adducts of serine clusters with fluoride and iodide were either observed in very low yield or not detected; thus these halides are not considered further in this study.

Chiral Effects. The chiral selectivity associated with the formation of protonated serine octamers^{1–4,20–22} as well as their chiroselective reactions with other amino acids^{5,7} appear to be intrinsic chemical characteristics of the octamer system. This is indicated by the fact that analogous chiral effects are also associated with the formation of negatively charged adducts of serine octamers. Figure 2 shows the signal intensity of $(Ser_8+2Cl)^{2-}$ ions as a function of the enantiomeric composition of the serine solution. As expected for a cluster ion that exhibits homochiral preference, the signal intensity is lowest for racemic

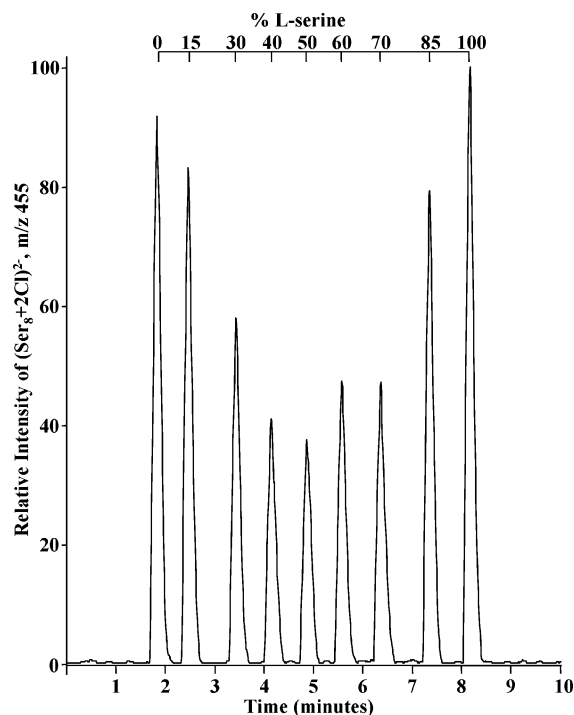
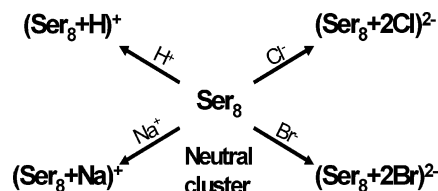


Figure 2. Chiral effects associated with the formation of $(\text{Ser}_8+2\text{Cl})^{2-}$ clusters. The data show the signal intensity of $(\text{Ser}_8+2\text{Cl})^{2-}$, m/z 455, as a function of time, as serine samples containing different enantiomeric compositions are sequentially introduced into the mass spectrometer by loop injection. The total serine and HCl concentrations were kept constant at 1×10^{-2} M and 5×10^{-4} M, respectively.

solutions. This behavior is similar to the homochiral preference exhibited by the protonated serine octamer.² Isotopic labeling experiments, using mixtures of 2,3,3- d_3 -L-serine (108 Da)/D-serine (105 Da) and 2,3,3- d_3 -L-serine/L-serine (reference), also showed strong chiral effects. The charge state of the clusters of interest (-2), together with the low resolution of the quadrupole ion trap mass analyzer, limits the quality of the data, thus making necessary the analysis of homochiral solutions to generate reference spectra. For example, the negative ESI mass spectra of solutions containing 10^{-2} M 2,3,3- d_3 -L-serine, 10^{-2} M L-serine, and 5×10^{-4} M Cl^- (reference experiment) resulted in a statistical distribution of serine octamers from

SCHEME 1: Dihalide Adducts of the Serine Octamer Show Similar Chemical Behavior to the Well Known Positively Charged Octamers^a



^a It is proposed that the chiroselective formation and substitution reactions observed for all these ions could reflect the behavior of the as-yet-unknown neutral serine octamer.

$(\text{L-Ser}_8+2\text{Cl})^{2-}$ at m/z 455 to $(2,3,3\text{-}d_3\text{-L-Ser}_8+2\text{Cl})^{2-}$ at m/z 467. By contrast, racemic solutions containing 2,3,3- d_3 -L-serine, D-serine, and chloride showed that homochiral clusters are favored when compared to the reference experiment. This is also accompanied by a drop in the signal intensity of the entire isotopic distribution.

Once the chiral preference of $(\text{Ser}_8+2\text{Cl})^{2-}$ and $(\text{Ser}_8+2\text{Br})^{2-}$ ions had been demonstrated, attempts to transfer the chiral choices of these octamers to other amino acids were carried out. This included evaluating the chiral selectivity of substitution reactions where serine molecules in negatively charged octamers are replaced by other amino acids such as threonine and cysteine. The experiment is done by electrospraying a mixture of serine and the reactant amino acid. Figure 3 shows typical mass spectra for the serine/threonine substitution reaction in the $(\text{Ser}_8+2\text{Cl})^{2-}$ cluster.³⁹ As is the case for the protonated octamers,⁷ the amino acid substitution reaction occurs chiroselectively. Positively charged sodiated serine octamers, $(\text{Ser}_8+\text{Na})^+$, have also been observed as magic number clusters and are known to behave similarly to protonated octamers.^{6,40} The fact that each of these species undergoes chiroselective substitution reactions with other amino acids suggests that the underlying chemical properties are those of the neutral serine octamers. The attachment of the cations H^+ and Na^+ or the anions Cl^- and Br^- to neutral serine octamers allows the underlying chemistry to be followed by mass spectrometry (see Scheme 1).

Tandem Mass Spectra. Further attempts to characterize the chloride and bromide adducts of serine octamers and to compare them to the well-known protonated octamer employed tandem

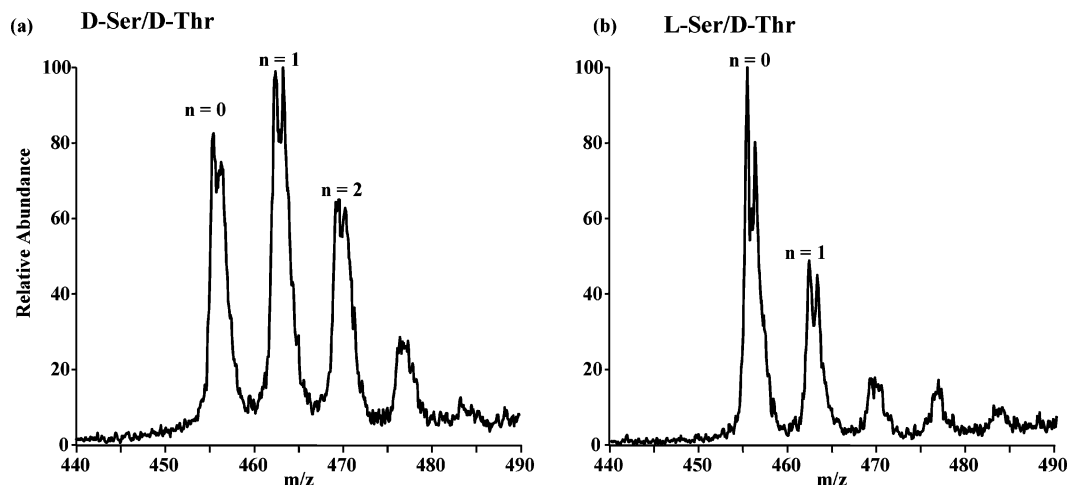


Figure 3. Example of chiroselective substitution reactions: electrospray mass spectra of serine/threonine mixtures in the presence of 5×10^{-4} M Cl^- . Spectra of solutions containing (a) 1×10^{-2} M D-serine and 2.5×10^{-3} M D-threonine and (b) 1×10^{-2} M D-serine and 2.5×10^{-3} M L-threonine, where n corresponds to the number of serine molecules replaced by threonine in the cluster. As in the case of protonated serine octamers, other amino acids can replace serine in negatively charged chloride adducts of the octamers. Homochiral substitution reactions to form the homochiral products (L/L and D/D) are favored over heterochiral (L/D) substitutions.

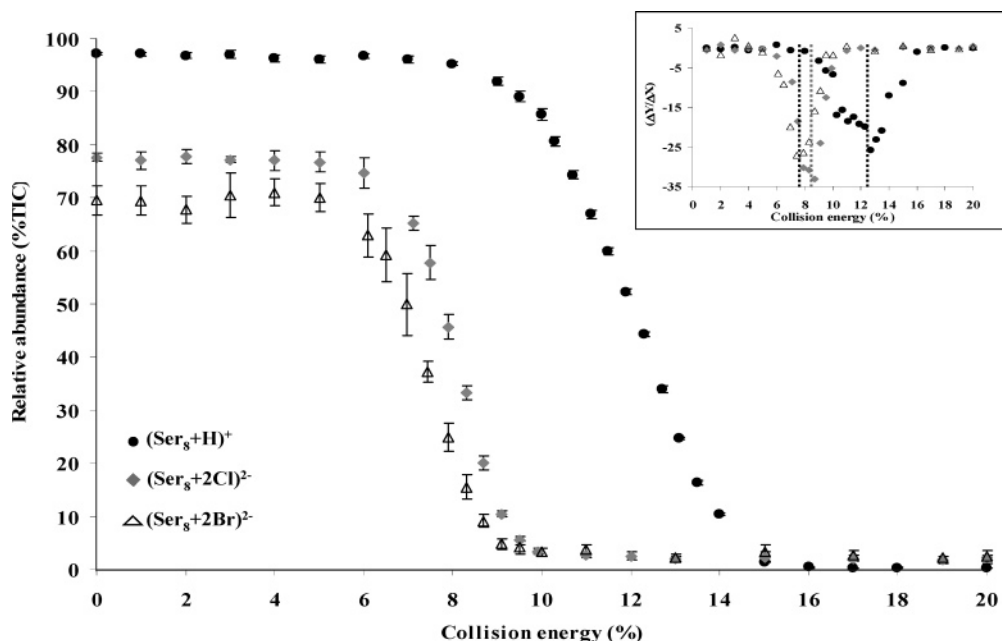


Figure 4. Relative abundance of $(\text{Ser}_8+\text{H})^+$, $(\text{Ser}_8+2\text{Cl})^{2-}$, and $(\text{Ser}_8+2\text{Br})^{2-}$ plotted as a function of collision energy. The data were recorded separately for the three systems under identical conditions, in which the ion trap injection time was set at 300 ms. The abundance (Y-axis) is shown as a percentage of the total ion current. Error bars represent 1σ in each direction. The maximum total ion current obtained (relative collision energy of 0%) was $1.2 \times 10^{+8}$, $9.6 \times 10^{+6}$, and $2.0 \times 10^{+6}$ for $(\text{Ser}_8+\text{H})^+$, $(\text{Ser}_8+2\text{Cl})^{2-}$, and $(\text{Ser}_8+2\text{Br})^{2-}$, respectively. The inset shows the first derivative of each data set, revealing inflection points that occur at nominal collision energies of approximately 12.4%, 8.5%, and 7.6% for $(\text{Ser}_8+\text{H})^+$, $(\text{Ser}_8+2\text{Cl})^{2-}$, and $(\text{Ser}_8+2\text{Br})^{2-}$, respectively.

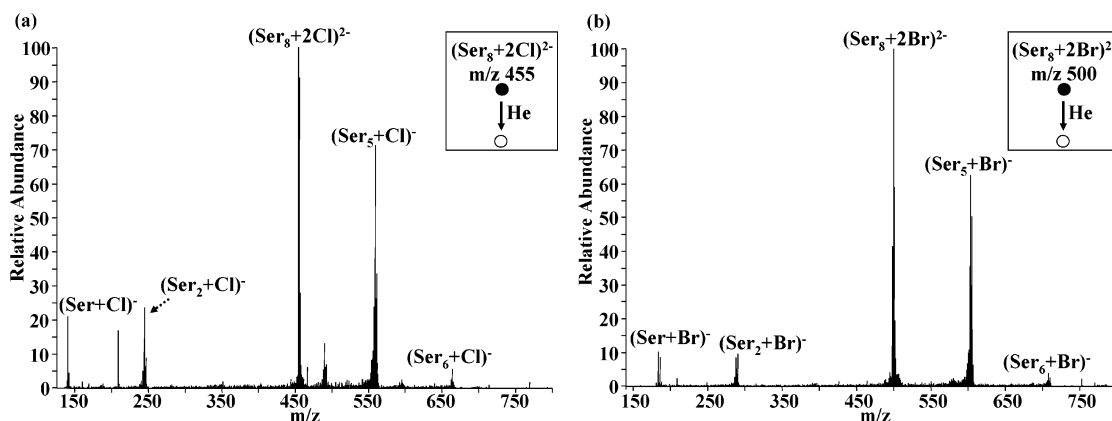


Figure 5. Tandem mass spectra of (a) $(\text{Ser}_8+2\text{Cl})^{2-}$ and (b) $(\text{Ser}_8+2\text{Br})^{2-}$ recorded at the inflection point of the fragmentation plots (Figure 4) corresponding to relative collision energies of 8.5% and 7.6%, respectively.

mass spectrometry. The ions $(\text{Ser}_8+\text{H})^+$, $(\text{Ser}_8+2\text{Cl})^{2-}$, and $(\text{Ser}_8+2\text{Br})^{2-}$ have been isolated, activated, and dissociated in the quadrupole ion trap. In three independent experiments, performed under identical conditions, the signal intensity of the octameric adducts was followed as a function of collision energy. The results are compared in Figure 4, which shows how fragmentation products are generated upon excitation of the ions through collisions with the helium buffer gas. The data reveal that the protonated serine octamer is relatively more stable than the halide adducts (e.g., it requires a higher energy input to cause dissociation). Note also that a significant number of $(\text{Ser}_8+2\text{Cl})^{2-}$ and $(\text{Ser}_8+2\text{Br})^{2-}$ ions undergo dissociation during the isolation step in the ion trap. Repulsion between the two negative charges within the relatively small cluster could contribute to the unimolecular dissociation reaction of $(\text{Ser}_8+2\text{Cl})^{2-}$ and $(\text{Ser}_8+2\text{Br})^{2-}$, especially since doubly charged fragment ions are not observed in the tandem mass spectra (see Figure 5). In addition, chloride and bromide may weaken Ser-Ser interactions in the cluster through their steric demands. Upon closer examination of the data shown in Figure 4, the $(\text{Ser}_8+2\text{Br})^{2-}$ cluster is seen to

undergo dissociation more readily than the chloride analogue. For example, the first derivative of the data (Figure 4 inset) reveals that the inflection points in the fragmentation plots of $(\text{Ser}_8+2\text{Cl})^{2-}$ and $(\text{Ser}_8+2\text{Br})^{2-}$ occur at collision energies (in arbitrary units) of 8.5% and 7.6%, respectively. The small energy difference in the dissociation plots suggests that both clusters are structurally similar and the difference is attributed to the size of the anions; larger steric effects are expected in the dibromide serine octamer. Under identical conditions, the analogous $\text{Ser}_8/\text{iodide}$ adduct was not observed, suggesting even greater destabilization due to larger steric demands.

Tandem mass spectra (Figure 5) showed comparable dissociation patterns for $(\text{Ser}_8+2\text{Cl})^{2-}$ and $(\text{Ser}_8+2\text{Br})^{2-}$, again suggesting that they are analogous cluster ions. The fragment ions $(\text{Ser}_2+\text{X})^-$ and $(\text{Ser}_5+\text{X})^-$, where $\text{X} = \text{Cl}, \text{Br}$, are preferentially formed upon dissociation of the negatively charged octamers. The distinctive fragmentation patterns of these anions contrast with the sequential loss of single amino acid units expected for aggregates formed without a preferred structure.

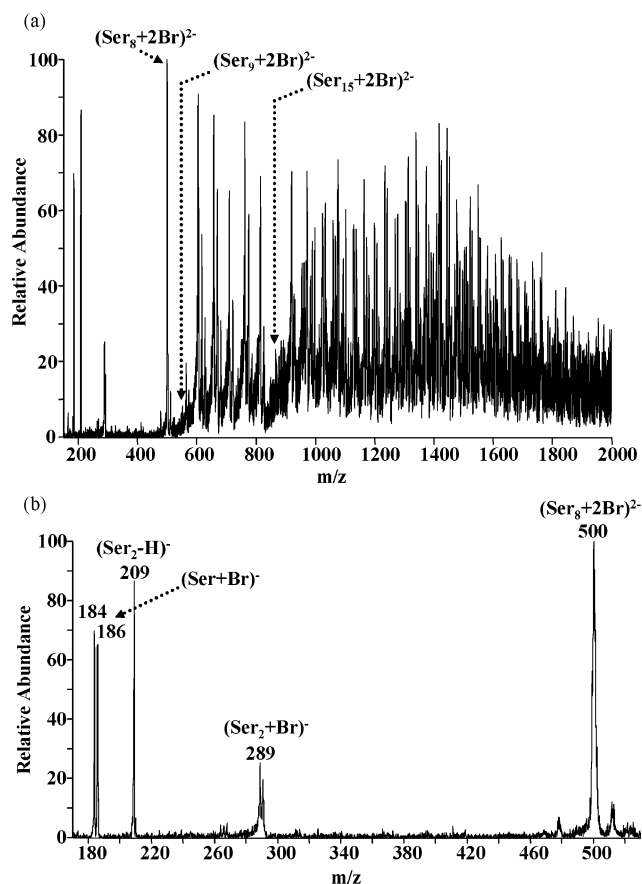


Figure 6. (a) Typical negative ion electrospray mass spectrum of a solution containing 1×10^{-2} M L-serine and 5×10^{-4} M NaBr. (b) Expanded region of the spectrum showing clusters containing 1, 2, and 8 serines.

Other Serine/Halide Clusters. Many other interesting features have been observed in the mass spectra of serine/halide mixtures as evidenced in Figure 6 which shows representative negative ion ESI mass spectra of a solution containing 1×10^{-2} M L-serine and 5×10^{-4} M NaBr. These data resemble those recorded for serine in the positive ion mode¹⁰ using a home-built hybrid ion mobility/time-of-flight mass spectrometer,⁴¹ which also showed abundant clusters covering a wide range of sizes. Under the particularly mild conditions of the ion mobility experiment, very large protonated aggregates containing over 600 serine units were observed.¹⁰ Crystal-like gas-phase growth was suggested to be responsible for the formation of these cluster ions. Even though the overlapping distributions of charge states greatly complicate the mass spectra, large serine/ Br^- aggregates can also be seen in Figure 6. For example, quadruply charged clusters containing more than 70 serine units and up to four bromides can be identified by their unique mass-to-charge ratios.

The fact that the presence of halides favors the formation of highly abundant adducts, many of which are larger in size than the octamer, allows the study of clusters otherwise not observed in the quadrupole ion trap instrument. Tandem mass spectrometry has been employed to evaluate the fragmentation pattern of selected serine/halide clusters. A group of aggregates that showed a peculiar fragmentation signature are the doubly charged 10-mers, $(\text{Ser}_{10}+\text{Cl})^{2-}$ and $(\text{Ser}_{10}+2\text{Br})^{2-}$. It has been reported that, under particular conditions, doubly protonated 10-mers of serine can be formed¹¹ and that these ions exhibit a heterochiral rather than a homochiral preference.¹¹ Note that very mild conditions are needed in order to generate $(\text{Ser}_{10}+2\text{H})^{2+}$ ions,¹¹ which in many other electrospray mass spectrometry

experiments^{2,3,21} either are not observed or are formed in very low abundance. The negatively charged analogues of these ions, $(\text{L-Ser}_{10}+2\text{Cl})^{2-}$ and $(\text{L-Ser}_{10}+2\text{Br})^{2-}$, mainly dissociate by the loss of a neutral serine dimer to form doubly charged dichloride and dibromide serine octamers, respectively. This confirms the remarkable stability of the octamer. It also provides a perhaps speculative explanation for previous observations of heterochiral preference in serine decamers. Such a preference for heterochirality can arise if the doubly charged 10-mers are derivatives of the less stable *heterochiral* octamers, which under particular conditions could undergo a nonchiroselective addition reaction with smaller serine units to form a presumably more stable decameric cluster.

Another feature of the data is the near absence of particular clusters that belong to the -2 charge state distribution. This includes the cluster ions $(\text{Ser}_9+2\text{Br})^{2-}$ and $(\text{Ser}_{15}+2\text{Br})^{2-}$, the formation of which appears to be highly unfavorable under the conditions of the experiment (see Figure 6). The absence of certain cluster sizes is common; however, the extent to which this occurs in the negative ESI mass spectra of Ser/ Br^- -containing solutions is remarkable. Similar clustering signatures have been observed in other systems where particular cluster sizes appear with considerably lower abundance. For example, this has been seen in positive electrospray mass spectra of sodium chloride clusters⁴² as well as amino acids.¹⁸ This phenomenon is typically associated with cluster sizes that correspond to unstable structures and therefore are the opposite of magic numbers ("anti-magic numbers", in recent terminology^{18,43,44}).

Conclusions

Negatively charged dihalide adducts of serine octamers, $(\text{Ser}_8+2\text{Cl})^{2-}$ and $(\text{Ser}_8+2\text{Br})^{2-}$, are observed as magic number clusters in the negative ion electrospray mass spectra of solutions containing serine and halides. As in the case of the well-known protonated serine octamers, these ions are formed with homochiral preference and share other unique properties of the $(\text{Ser}_8+\text{H})^+$ ions.

The discovery of negatively charged halide adducts of homochiral serine octamers connects the chemistry of the ionic species of both polarities, the cations $(\text{Ser}_8+\text{H})^+$ and $(\text{Ser}_8+\text{Na})^+$ and the anions $(\text{Ser}_8+2\text{Cl})^{2-}$ and $(\text{Ser}_8+2\text{Br})^{2-}$, and points to their distinctive properties as being characteristics of the still-undiscovered neutral serine octamer. The attachment of the cations H^+ and Na^+ or the anions Cl^- and Br^- to neutral serine octamers seems to simply allow the underlying chemistry to be followed by mass spectrometry.

Mass spectrometry is a very sensitive analytical technique, and typical electrospray ionization efficiencies for relatively small systems are low, often $<1\%$. This suggests that the neutral species could be orders of magnitude more abundant than the ionic adducts detected in the mass spectrometer. Consequently, the probable existence of very abundant homochiral neutral octamers of serine strengthens the hypothesis^{2,7,9,12} that serine played a role in prebiotic mechanisms that led to the homochirality of life, although much remains to be done to further test it. Specifically, the processes that we now suggest to have involved to *neutral* serine⁴⁵ are (i) chiral enrichment of serine through the formation, dissociation, and re-formation of the octamer and (ii) transmission of chirality from serine to other amino acids.

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References and Notes

- (1) Zhang, D.; Koch, K. J.; Tao, W. A.; Cooks, R. G. Clustering of Amino Acids in the Gas Phase by Electrospray Ionization Mass Spectrometry. 48th ASMS Conference on Mass Spectrometry and Allied Topics, Long Beach, CA, 2000.
- (2) 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*, 3646.
- (3) Hodyss, R.; Julian, R. R.; Beauchamp, J. L. Spontaneous Chiral Separation in Noncovalent Molecular Clusters. *Chirality* **2001**, *13*, 703.
- (4) Counterman, A. E.; Clemmer, D. E. Magic Number Clusters of Serine in the Gas Phase. *J. Phys. Chem. B* **2001**, *105*, 8092.
- (5) Takats, Z.; Nanita, S. C.; Cooks, R. G.; Schlosser, G.; Vekey, K. Amino Acid Clusters Formed by Sonic Spray Ionization. *Anal. Chem.* **2003**, *75*, 1514.
- (6) Koch, K. J.; Gozzo, F. C.; Zhang, D.; Eberlin, M. N.; Cooks, R. G. Serine Octamer Metaclusters: Formation, Structure Elucidation and Implications for Homochiral Polymerization. *Chem. Commun.* **2001**, 1854.
- (7) Koch, K. J.; Gozzo, F. C.; Nanita, S. C.; Takats, Z.; Eberlin, M. N.; Cooks, R. G. Chiral Transmission between Amino Acids: Chirally-Selective Amino Acid Substitution in the Serine Octamer as a Possible Step in Homochirogenesis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1721.
- (8) Takats, Z.; Nanita, S. C.; Schlosser, G.; Vekey, K.; Cooks, R. G. Atmospheric Pressure Gas-Phase H/D Exchange of Serine Octamers. *Anal. Chem.* **2003**, *75*, 6147.
- (9) Takats, Z.; Nanita, S. C.; Cooks, R. G. Serine Octamer Reactions: Indicators of Prebiotic Relevance. *Angew. Chem., Int. Ed.* **2003**, *42*, 3521.
- (10) Myung, S.; Julian, R. R.; Nanita, S. C.; Cooks, R. G.; Clemmer, D. E. Formation of Nanometer-Scale Serine Clusters by Sonic Spray. *J. Phys. Chem. B* **2004**, *108*, 6105.
- (11) Julian, R. R.; Myung, S.; Clemmer, D. E. Spontaneous Anti-Resolution in Heterochiral Clusters of Serine. *J. Am. Chem. Soc.* **2004**, *126*, 4110.
- (12) Nanita, S. C.; Takats, Z.; Myung, S.; Clemmer, D. E.; Cooks, R. G. Chiral Enrichment of Serine via Formation, Dissociation and Soft-Landing of Octameric Cluster Ions. *J. Am. Soc. Mass Spectrom.* **2004**, *15*, 1360.
- (13) Takats, Z.; Cooks, R. G. Thermal Formation of Serine Octamer Ions. *Chem. Commun.* **2004**, 444.
- (14) O'Hair, R. A. J.; Gronert, S.; Fagin, A. Ion-Molecule Reactions of the Protonated Serine Octamer: Implications on the Emergence of Homochirality. 52nd ASMS Conference on Mass Spectrometry and Allied Topics, Nashville, TN, 2004.
- (15) Nanita, S. C.; Takats, Z.; Cooks, R. G. Homochiral Clusters of Serine Studied by Ion Soft-Landing: Implications for the Origin of Homochirality. 52nd ASMS Conference on Mass Spectrometry and Allied Topics, Nashville, TN, 2004.
- (16) Mazurek, U.; Reuben, B. G.; McFarland, M. A.; Marshall, A. G.; Lifshitz, C. Elucidating Structures of Protonated Amino Acid Clusters from H/D Exchange Experiments: The Protonated Serine Octamer. 52nd ASMS Conference on Mass Spectrometry and Allied Topics, Nashville, TN, 2004.
- (17) Hwang, H. Y.; Lin, C.; Oh, H.; Breuker, K.; Carpenter, B. K.; McLafferty, F. W. Chiral Differentiation and Structural Characterization of Proton Bound Amino Acid Multimers Using IR Photodissociation Spectroscopy with Fourier Transform Mass Spectrometry. 52nd ASMS Conference on Mass Spectrometry and Allied Topics, Nashville, TN, 2004.
- (18) Julian, R. R.; Myung, S.; Clemmer, D. E. Chiral Selectivity in the Formation of Noncovalent Clusters of Amino Acids. 52nd ASMS Conference on Mass Spectrometry and Allied Topics, Nashville, TN, 2004.
- (19) Hvelplund, P.; Rangama, J.; Liu, B.; Nielsen, A. B.; Nielsen, S. B.; Tomita, S. Collision Induced Dissociation of Multiply Charged Serine Clusters. 52nd ASMS Conference on Mass Spectrometry and Allied Topics, Nashville, TN, 2004.
- (20) Schalley, C. A.; Weis, P. Unusually Stable Magic Number Clusters of Serine with a Surprising Preference for Homochirality. *Int. J. Mass Spectrom.* **2002**, *221*, 9.
- (21) Julian, R. R.; Hodyss, R.; Kinnear, B.; Jarrold, M.; 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*, 1219.
- (22) Gronert, S.; O'Hair, R. A. J.; Fagin, A. E. Ion/Molecule Reactions of the Protonated Serine Octamer. *Chem. Commun.* **2004**, 1944.
- (23) Ustyuzhanin, P.; Ustyuzhanin, J.; Lifshitz, C. An Electrospray Ionization-Flow Tube Study of H/D Exchange in Protonated Serine. *Int. J. Mass Spectrom.* **2003**, *223-224*, 491.
- (24) Geller, O.; Lifshitz, C. An Electrospray Ionization-Flow Tube Study of H/D Exchange in the Protonated Serine Dimer and Protonated Serine Dipeptide. *Int. J. Mass Spectrom.* **2003**, *227*, 77.
- (25) Green, M. M.; Selinger, J. V. Cosmic Chirality. *Science* **1998**, *282*, 880.
- (26) Berger, R.; Quack, M.; Tschumper, G. S. Electroweak Quantum Chemistry for Possible Precursor Molecules in the Evolution of Biomolecular Homochirality. *Helv. Chim. Acta* **2000**, *83*, 1919.
- (27) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. Chiral Autocatalysis: Where Stereochemistry Meets the Origin of Life. *Chem. Commun.* **2000**, 887.
- (28) Hazen, R. M.; Filley, T. R.; Goodfriend, G. A. Selective Adsorption of L- and D-Amino Acids on Calcite: Implications for Biochemical Homochirality. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 5487.
- (29) Cintas, P. Chirality of Living Systems: A Helping Hand from Crystals and Oligopeptides. *Angew. Chem., Int. Ed.* **2002**, *41*, 1139.
- (30) Jorissen, A.; Cerf, C. Asymmetric Photoreactions as the Origin of Biomolecular Homochirality: A Critical Review. *Orig. Life Evol. Biosph.* **2002**, *32*, 129.
- (31) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. Amplification of Enantiomeric Excess in a Proline-Mediated Reaction. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317.
- (32) Bakasov, A.; Ha, T. K.; Quack, M. Ab Initio Calculation of Molecular Energies Including Parity Violating Interactions. *J. Chem. Phys.* **1998**, *109*, 7263.
- (33) Ribo, R. M.; Crusats, J.; Sagues, F.; Claret, J.; Rubires, R. Chiral Sign Induction by Vortices During the Formation of Mesophases in Stirred Solutions. *Science* **2001**, *292*, 2063.
- (34) Rikken, G. L. J. A.; Raupach, E. Enantioselective Magnetochiral Photochemistry. *Nature* **2000**, *405*, 932.
- (35) Schwass, D. E.; Finley, J. W. Heat and Alkaline Damage to Proteins: Racemization and Lysinoalanine Formation. *J. Agric. Food Chem.* **1984**, *32*, 1377.
- (36) Nouadje, G.; Nertz, M.; Courderc, F. Study of the Racemization of L-Serine by Cyclodextrin-Modified Micellar Electrokinetic Chromatography and Laser-Induced Fluorescence Detection. *J. Chromatogr. A* **1995**, *716*, 331.
- (37) Fenn, J. B.; Mann, M.; Meng, C. K.; Wong, S. F.; Whitehouse, C. M. Electrospray Ionization for Mass-Spectrometry of Large Biomolecules. *Science* **1989**, *246*, 64.
- (38) Fenn, J. B. Electrospray Wings for Molecular Elephants (Nobel Lecture). *Angew. Chem., Int. Ed.* **2003**, *42*, 3871.
- (39) Substitution reactions with cysteine also showed a homochiral preference.
- (40) Kunitamura, M.; Sakamoto, S.; Yamaguchi, K. Alkali Metal-Mediated Proline Aggregation in Solution Observed by Coldspray Ionization Mass Spectrometry. *Org. Lett.* **2002**, *4*, 347.
- (41) Myung, S.; Lee, Y. J.; Moon, M. H.; Taraszka, J.; Sowell, R.; Koeniger, S.; Hilderbrand, A. E.; Valentine, S. J.; Cherbas, L.; Cherbas, P.; Kaufman, T. C.; Miller, D. F.; Mechref, Y.; Novotny, M. V.; Ewing, M. A.; Sporleder, C. R.; Clemmer, D. E. Development of High-Sensitivity Ion Trap Ion Mobility Spectrometry Time-of-Flight Techniques: A High-Throughput Nano-LC-IMS-TOF Separation of Peptides Arising from a Drosophila Protein Extract. *Anal. Chem.* **2003**, *75*, 5137.
- (42) Zhang, D.; Cooks, R. G. Doubly-Charged Cluster Ions, [(NaCl)_m-(Na)₂]²⁺: Magic Numbers, Dissociation, and Structure. *Int. J. Mass Spectrom.* **2000**, *195/196*, 667.
- (43) Julian, R. R.; Myung, S.; Clemmer, D. E. Chiral Selectivity in the Formation of Noncovalent Clusters of Amino Acids. 36th Central Regional Meeting of the American Chemical Society, Indianapolis, IN, 2004.
- (44) Julian, R. R.; Myung, S.; Clemmer, D. E. Do Homochiral Aggregates Have an Entropic Advantage? *J. Phys. Chem. B* **2005**, *109*, 440.
- (45) A reviewer has emphasized that the experiments described here, while they may be suggestive of a role of neutral serine octamers in chiral transmission, provide no direct evidence for this. We agree and one objective of this study is to stimulate work on the neutral octamer.