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International Journal of Mass Spectrometry 221 (2002) 9–19

International Journal of Mass Spectrometry

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Review

Unusually stable magic number clusters of serine with a surprising preference for homochirality

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Received 24 July 2002; accepted 26 August 2002

Abstract

The amino acid serine forms unusually stable octameric clusters upon electrospray ionization of relatively concentrated solutions. A strong preference for homochiral clusters is observed, while mixed clusters of D- and L-serine are significantly underrepresented. The present essay reviews the experimental results as well as the structures suggested so far. Surprisingly, there is good agreement on the experimental facts among different research groups, but a vivid discussion with respect to the octamer structure is going on. In order to provide a firm basis for a discussion of these issues, we briefly address the questions of chiral recognition of amino acids and cluster formation in more general terms. Another important issue in this respect is the generation of zwitterionic amino acids in the gas phase. This paper suggests a new structure that seems to be in good agreement with the experimental evidence gathered so far. The review terminates with some thoughts on the implications of the homochirality of serine octamers for homochirogenesis and the origin of life. (Int J Mass Spectrom 221 (2002) 9–19)
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Keywords: Amino acid clusters; Chirality; Mass spectrometry; Serine octamer

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1. Homochirogenesis! But how did it evolve?

The evolution of life on a prebiotic earth is closely related to the homochirality of natural amino acids and sugars. There still is a debate what existed first, a rudimentary form of life based on biomolecules without clear chiral preferences or an excess of L-amino acids and D-sugars, which allowed life in its present form to evolve. No matter which of these alternatives holds true, the complexity of living organisms as we see them now would be impossible without homochirality. Only a defined chirality can account for the self-assembly of complex structures, for highly selective molecular recognition, and the tremendous amount of information transfer in living species. However, the mechanisms driving homochirogenesis are by no means clear [1,2].

As categorized by Bonner [3], different *biotic* theories exist, which imply that some modern version of the old *vis vitalis* concept could explain nature's preferences for L-amino acids and D-sugars. In terms of modern chemistry, however, they leave the exact mechanisms of symmetry breaking unexplained and

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PII S1387-3806(02)00955-7

ascribe them to a diffuse force immanent in living organisms only—thus, avoiding and hampering an explanation at the molecular level. Other, *abiotic* theories invoke an accidental occurrence of a slight deviation from the racemate, coupled to an autocatalytic process that amplified the major component exponentially. Although such a rationalization is in principle possible, it remains unsatisfactory—in principle, because it implies mere coincidence, but also with respect to more practical issues, since despite all attempts to generate efficient self-replicating systems [4], their number is still limited and the replicators remain rather complex structures. In view of the long time span of the evolution of simple life forms, this argument of course does not rule out theories involving spontaneous statistical fluctuations with subsequent amplification of chirality. Also, the separation of some substances into macroscopic homochiral crystals may circumvent the problems associated with chiral amplification.

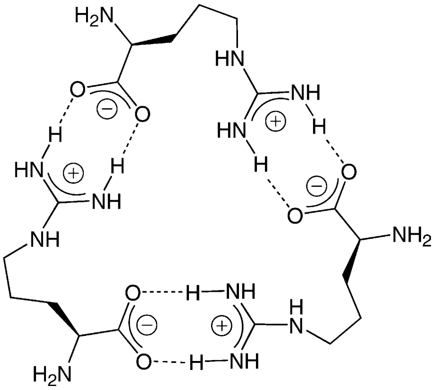
A third family of hypotheses also belongs to the abiotic theories. They are, however, *deterministic* in that they make use of the intrinsic energy difference between enantiomeric molecules resulting from a parity violation in the weak nuclear force [5,6]. Such energy differences are in the range of a few hundred femtoJoules per mole, and thus, are many orders of magnitude smaller than those usually encountered in chemical bonding. Consequently, they rise the problem of how these small energy differences between the left- and right-handed enantiomers provoke homochirality.

To put it briefly, the final answer to the problem of homochirogenesis has not been given yet. But even if it would never be found, all studies in this direction are aiming at the question of the origin of life, a question of utmost fundamental importance for chemistry and biology justifying all the effort invested into this research and rewarding us with lots of highly interesting discoveries to be made on the way.

Consequently, it is no surprise, when considerable attention was attracted by a series of recent studies that reported the formation of unusually stable serine octamers with a strong preference for homochirality [7–11]. In the electrospray ionization mass spectra of rather concentrated 0.1 M methanol solutions of serine, the octameric serine cluster appears not only as a signal much more intense than all other clusters [12,13]. It also reveals a pronounced stereochemical preference for the formation of homochiral $(\text{L-Ser})_8\text{H}^+$ and $(\text{D-}[^{13}\text{C}]\text{Ser})_8\text{H}^+$ from a mixture of these two amino acid enantiomers. Instead, their mixed analogs $(\text{L-Ser})_n(\text{D-}[^{13}\text{C}]\text{Ser})_{8-n}\text{H}^+$ ($n = 1$–7) appear with abundances much lower than those calculated from statistics. In order to be able to discuss the implications of these facts, some background information is required. Before we come back to these results and their implications for homochirogenesis, we will briefly summarize some general issues of amino acid structures and chiral recognition of amino acids in the gas phase, followed by a detailed discussion of the serine octamer cluster structure.

2. Amino acid zwitterions in the gas phase?

At their isoelectric points, amino acids exist in solution as zwitterions with a carboxylate and an ammonium group rather than the neutral “amino acid” form. It is important to understand that this preference is mainly due to solvation effects. Polar, protic media such as water or methanol stabilize the charges significantly. In the absence of solvent, e.g., under the environment-free conditions in the high vacuum of a mass spectrometer, no such stabilization exists and the zwitterionic form is significantly destabilized as compared to the corresponding nonionic structure [14,15]. However, a zwitterionic structure can be stabilized even in the gas phase, if an appropriate cation is attached [16–18]. Theoretical calculations suggest that only two water molecules should also be sufficient to stabilize the zwitterion of glycine with respect to the nonionic form [19]. Also, self-solvation in peptides has been shown to provide enough stabilization for salt bridge structures [20]. A special case is arginine with its strongly basic guanidine group in the side chain. Zwitterionic forms of arginine would rather be the result of a proton transfer from the

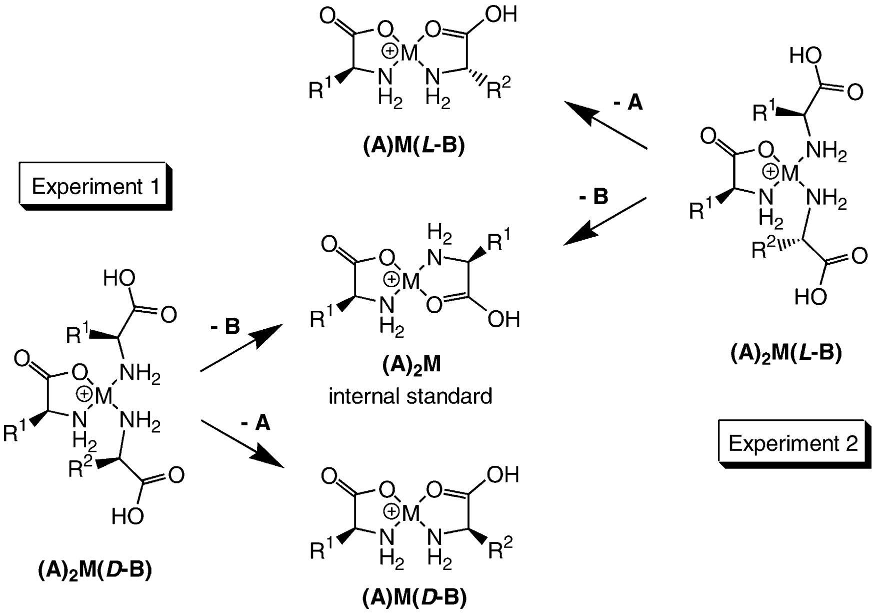


Scheme 1. The cyclic arginine trimer in its zwitterionic form.

carboxylic acid to the guanidine group than to the amine group. Ab initio calculations [21] predict in line with IR spectroscopic experiments [22] neutral arginine to exist in its nonionic form. However, the zwitterionic form is only a few kiloJoules per mole higher in energy and thus, can easily be generated upon metal ion attachment [23] or oligomerization [24,25]. The cyclic arginine trimer (Scheme 1) and other higher clusters with all arginine moieties in the zwitterionic form prove to be exceptionally stable complexes in the gas phase [26–28]. The bottom line of these studies is that isolated amino acid molecules or ions prefer a nonionic structure. However, often not much of a change within the solvation sphere is needed to provide the necessary stabilization through solvation which makes the zwitterionic form energetically favorable. We will see later, why these remarks are important for the case of the serine octamer.

3. Chiral recognition in amino acid clusters

One of the particular features of the serine octamer is its strong tendency for homochirality. Thus, let us comment briefly on some studies devoted to the determination of the chirality of amino acids in clusters. The proton-bound trimers A_2BH^+ of amino acids A and B form ABH^+ and A_2H^+ fragments upon collisional activation (or metastable decay). With two independent measurements of the fragment ratio $[ABH^+]/[A_2H^+]$ for $A_2(L\text{-}B)H^+$ and $A_2(D\text{-}B)H^+$ using the two different stereoisomers L- and D-B, the differences in binding energies can be determined, since the A_2H^+



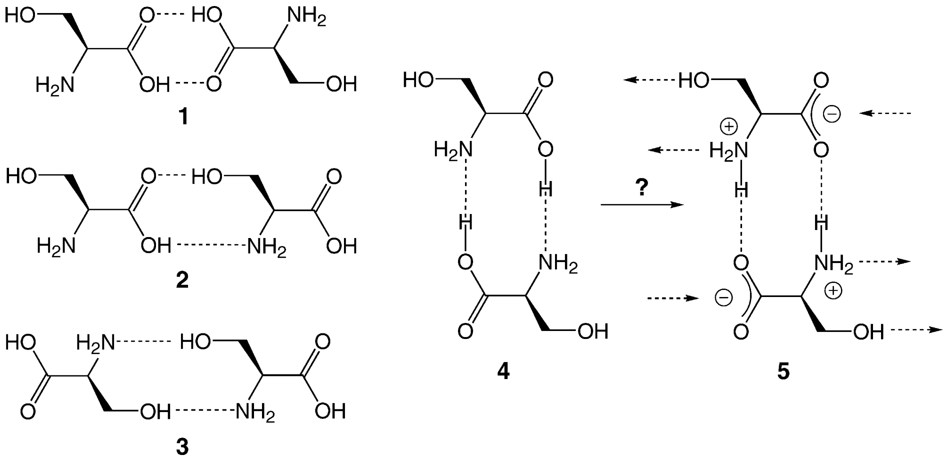
Scheme 2. Fragmentation mechanism of transition metal bound amino acid trimers utilized for the determination of chirality in such clusters.

fragment is the same in both measurements and may serve as an internal standard, while the ABH^+ fragment is homochiral in one and heterochiral in the other [29,30]. Instead of the protonated trimers, transition metal bound clusters can also be used. In a series of elegant studies, Cooks and coworkers demonstrated that the kinetic method is applicable to the amino acid trimers of the transition metals Cu^{2+} [31,32] and Ni^{2+} [33]. Binding of one amino acid in the transition metal ion–amino acid trimer complex is postulated to be bidentate, while the other two bind with the softer, more basic and thus, more favorable amino terminus. The fragmentation products are dimers, in which both amino acids bind in a bidentate fashion (Scheme 2). Interestingly, amino acids as the chiral selectors that contain aromatic side chains enhanced the chiral discrimination, while oxygen donors in the side chains reduced it. This effect was attributed to charge transfer interactions between the aromatic residue and the carboxylate π-system of the other amino acid. Also the possibility of charge-π-interactions was discussed. It is, however, believed to be less important in the examples under study. Whatever the reason, for a practical application of the method it is, thus, important to choose the appropriate chiral selector for optimal results. These studies provide evidence that mass spectrometry—although it gives only the m/z ratio as primary information—is well suited for studying chirality issues in properly chosen amino acid clusters and complexes. It should therefore be applicable to the chirality issues related to the serine octamer as well.

4. The serine octamer: experimental facts

Let us now gather all known experimental results on the serine octamer and see what we can learn from them. As far as experiments have been performed by different groups or different methods, they agree quite well with each other so that no severe dispute exists over the experimental facts.

1. The serine octamer $(Ser)_8H^+$ is exceptionally stable. It is a magic number cluster with a magic number effect of more than 20 [7]. The magic number effect M can be derived from the relative intensity of the cluster with n components as compared to those of the clusters with $n-1$ and $n+1$ building blocks. It is expressed as $M = 2I_n/(I_{n-1} + I_{n+1})$. The only other cluster of considerable abundance is the dimer $(Ser)_2H^+$. This unexpected stability must be reflected in the structure.
2. Upon collisional activation in an MS/MS experiment, the octamer predominantly fragments into a protonated hexamer and a neutral dimer [7,8]. An MS/MS/MS experiment with the resulting hexamer again reveals a major loss of a dimer rather than any other fragment [7]. Such a dimer pattern is also expressed in the clusters smaller than the octamer. Tetramers and hexamers are more abundant than trimers, pentamers and heptamers [8]. For clusters larger than the octamer, the distribution does not reveal such a pattern. This suggests that the octamer is constructed from dimeric building blocks such as those shown in Scheme 3.
3. Larger clusters have been observed which are built from more than one octamer [8,9]. Besides the protonated octamer $(Ser)_8H^+$, a hexadecamer $(Ser)_{16}(H^+)_2$ and a tetracosamer $(Ser)_{24}(H^+)_3$ (and many other clusters up to 40 serines and even more) exist. Similarly, larger clusters have been observed with sodium ions attached to provide the charge instead of protons. Consequently, one might assume that the octamer is built according to a building principle that is open for extensions.
4. The most spectacular finding is the strong preference for homochirality. Evidence comes from mixtures of L-serine and D-[^{13}C]serine isotopically labeled at the carboxylate [7]. Similar results are obtained, if L-[D_3]serine deuterium labeled at the C–H bonds is mixed with D-serine [8]. Fig. 1 shows the differences between the statistical and the experimentally determined intensity distribution within the observed octameric clusters. We conclude that the structure must provide a reasonable explanation why homochiral octamers are that strongly preferred over mixed ones. One might expect that the OH group of the serine side chain, whose position depends on the stereochemistry



Scheme 3. Different nonionic (**1**–**4**) and zwitterionic dimers (**5**) of serine which may serve as building blocks for the octamer cluster. Likely, **4** easily rearranges to **5** by a coupled double proton transfer, if sufficient stabilization of the charges is provided in the octamer. Upon fragmentation this reaction might well be reversed in the neutral dimeric fragment avoiding an unfavorable neutral fragment. Arrows in structure **5** indicate possible binding sites for vicinal dimers in the octamer.

at the α-C, is strongly involved in stabilizing the structure, which then should be quite regular.

5. The collision cross-sections of the octamer and its larger relatives have been measured by ion mobility experiments. Two values are available for the octamer: 187 Å^2 [8] and 191 Å^2 [9]. Comparison of several structures obtained from calculations with these figures results in the unavoidable conclusion that only zwitterionic structures can be this small, while all nonzwitterionic forms of serine octamers turned out to be much larger. The strong electrostatic forces operating between carboxylates

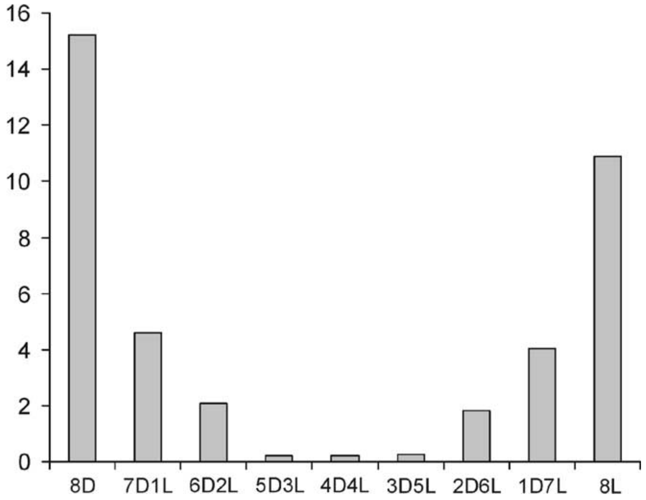
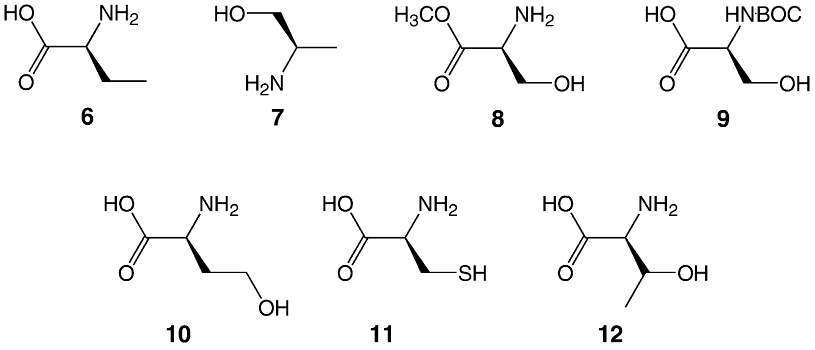


Fig. 1. Differences between the experimental and statistically expected intensities of different serine octamers generated from a 46:54 solution of L-[D$_3$]Ser and D-Ser. Similar results are obtained with mixtures of L-Ser and D-[^{13}C]Ser. Note that factors are shown. That means that the all-D cluster is ca. 15 times more abundant than expected, while the signal for the 4D:4L cluster is 5 times less intense as calculated from statistics. A purely statistical result would rise all columns to unity.



Scheme 4. Control compounds and homologues of serine: 2-aminobutyric acid (**6**), 2-aminopropanol (**7**), serine methyl ester (**8**), BOC protected serine (**9**), homoserine (**10**), cysteine (**11**), and threonine (**12**).

and ammonium groups provide the driving force leading to very compact structures. Although there might be some uncertainty here, the arrival time distribution have been reported to suggests that only one structure is realized, ruling out the simultaneous presence of different noninterconverting conformers.

6. Control compounds (Scheme 4) such as 2-aminobutyric acid (**6**, OH group replaced by CH_3), 2-aminopropanol (**7**, no carboxyl group), serine methyl ester (**8**, carboxyl group blocked), or BOC protected serine (**9**, amino group blocked) do not form similarly stable octamers [7,8]. This indicates that all functional groups of serine are involved in binding. One might of course argue that these derivatives do just not fit sterically into the octamer structure, and thus, this argument should be taken as support, but not as strong evidence.
7. Instead, homoserine (**10**) forms doubly charged octamers and 6:2 mixtures of serine and homoserine yield clusters in which one or two serine molecules can be exchanged against a homoserine. Similar results were obtained with cysteine (**11**) and several other amino acids [11]. Serine can also be substituted with threonine (**12**) carrying an additional side chain methyl group; singly and doubly protonated octameric clusters are formed, where the singly charged ones reveal a distribution close to statistical expectation [8]. It seems, however, that the stability of these clusters is somewhat reduced [7]. Thus, any structure for the serine octamer should be able to incorporate homoserine, cysteine, and threonine at least to some extent.

5. The search for a structure

In the literature, several different structural alternatives for the serine octamer have been discussed [7–11]. The first issue of debate is the zwitterionic nature of the octameric cluster. Cooks and his coworkers argue that the zwitterionic dimer of serine would be energetically less favorable in the gas phase as compared to nonionic structures by ca. 150 kJ/mol, and thus, also suggest a structure for the octamer, which contains eight neutral serines in a cyclic array of carboxylic acid dimers **1**. This dimer indeed has been calculated to be the most stable complex among structures **1**–**3** (Scheme 3) [7]. In this structure, two sets of four serines each are connected with each other by four acid–acid contacts as realized in **1**. As the authors state themselves, this structural assignment is problematic, because in methanolic (or aqueous) solution, zwitterions are favored over nonionic structures and it is not clear how the rearrangement into the nonionic form upon electrospray ionization should occur. However, the unfavorable zwitterionic dimers do not at all rule out the existence of zwitterionic octamers.

This argument would definitively be severe, if the octamer were assembled from dimers in the gas phase, because in this case, the dimers were to be generated first and energetically more favorable structures would then be favored. However, if the octamer is formed in solution and then electrosprayed or formed in the nanodroplets during the ESI process, the stability of the dimers is not necessarily important. Much more important is the question whether the whole octamer could be favorable in a zwitterionic structure. We have discussed earlier that minor changes of the solvation sphere around an amino acid in the gas phase might significantly favor the zwitterionic structure and an octamer definitively is a good candidate for such a self-solvating structure. Consequently, we cannot easily rule out zwitterionic structures. Another difficulty associated with the geometry suggested by Cooks and coworkers is the transmission of chiral information from one tetrameric half of the complex to the other one. In other words, the two homochiral $(L\text{-Ser})_8H^+$ and $(D\text{-Ser})_8H^+$ clusters would be expected to be accompanied by a $(L\text{-Ser})_4(D\text{-Ser})_4H^+$ cluster formed through replacing half of the octamer with the other enantiomers. A four-point contact between these two halves is thus not sufficient to explain the preference for $(L\text{-Ser})_8H^+$ and $(D\text{-Ser})_8H^+$ over the mixed $(L\text{-Ser})_4(D\text{-Ser})_4H^+$ cluster.

On the contrary, there are some convincing arguments in favor of ionic structures that may also help to resolve the latter issue: first of all, their generation from solution, in which the amino acids exist as zwitterions, would be easily explained. Then, the low collisional cross-sections of ca. 190 $Å^2$ points to a rather compact structure. All nonionic geometries minimized at different levels of theory so far have much larger calculated cross-sections. Counterman and Clemmer [9] suggested one cluster conformation, whose cross-section is close to the experimental one. However, several serine OH groups are not involved in any interaction within the cluster so that it is likely difficult to explain the strong stereochemical preference. Another zwitterionic structure has been reported by Beauchamp and coworkers [8]. The eight serine molecules are arranged in a “flattened cube”-like fashion with one serine in each corner of the cube. It is based on dimer **5** (Scheme 3), and thus, provides an eight-point contact between the upper and lower tetrameric halves of the octamer. Such an arrangement provides a directionality along the seam of electrostatic interactions in the center of the octamer and thus, may circumvent the problems associated with the 4L/4D clusters, although the Beauchamp group reported that such structures are close in energy to the homochiral clusters [8]. In their structure, the serine OH groups however, back-bond to the carboxylate groups of the same molecule, so that it is not quite clear, why according to the control compounds, e.g., **6** (Scheme 4), the hydroxyl group is necessary for the formation of homochiral clusters. Nevertheless, it explains most of the experimental results and is the best candidate suggested so far.

The major conclusion from these considerations is that most of the structures presented in the literature so far are not fully satisfying and do not agree well with all experimental results. This is even more surprising, since so much undisputed structure-relevant data has been accumulated so far. We would therefore like to take the liberty to suggest a structural alternative here, which we believe to be in line with the experiments (Fig. 2). Our structure has been found as the lowest energy conformer in a 3000 step Monte Carlo conformational search performed with the Amber* force field implemented in MacroModel 7.0.[2] It is based on zwitterionic dimers **5** and is closely related to the “flattened cube” as discussed earlier. The central core is zwitterionic in nature and strong attractive electrostatic forces hold the eight amino acids tightly together (Fig. 2, center). A total of more than 30 hydrogen bonds is formed, which probably do not contribute much to the overall binding energy, but are responsible for the positioning the eight serine molecules. This is due to the directionality of a hydrogen bond, while electrostatic forces just depend on the charge–charge distance. Thus, while the charge–charge interactions

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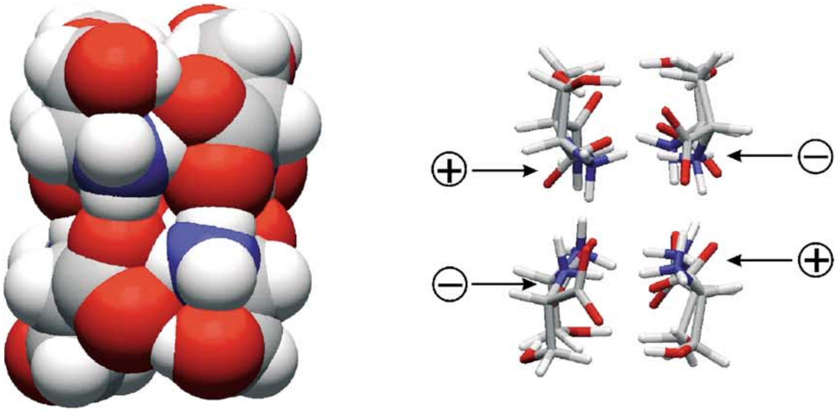
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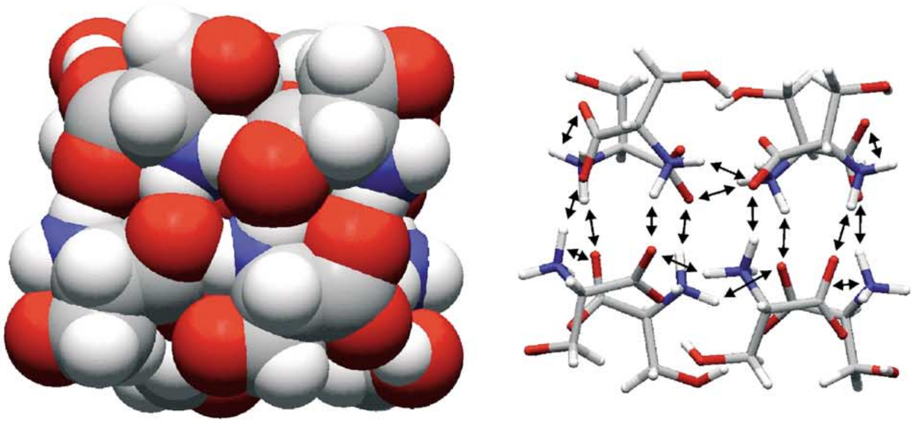

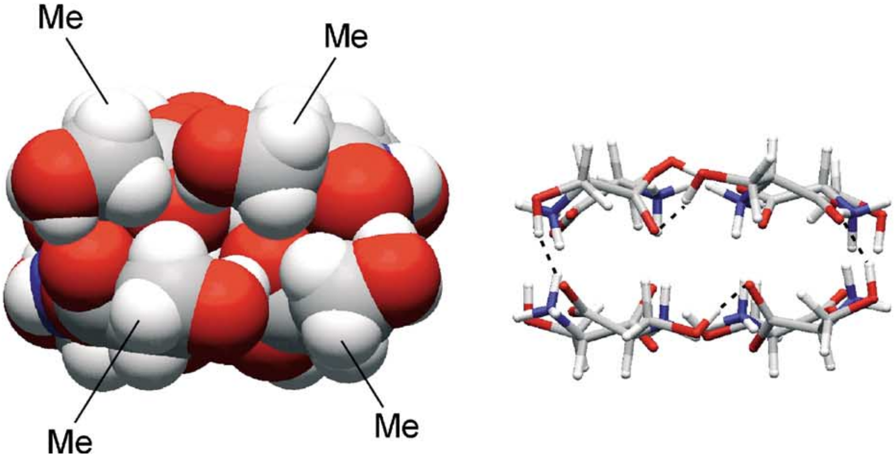
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provide most of the binding energy, the hydrogen bonds keep the cluster in shape.

The chiral preference is easily explained by the O–H · · · O hydrogen bonds between the side chain OH groups and the carboxylate of the next serine (Fig. 2, bottom). In this respect, our structure differs from the flattened cube discussed by Beauchamp and coworkers [8]. Incorporation of one D-serine in an L-serine octamer would require to break one of these hydrogen bonds and thus, disfavors the cluster—and so forth for higher D-serine contents. Also, the alternating pattern of carboxylates and ammonium groups around the core together with the arrangement of the two serines in the dimer subunits **5** is an eight-point rather than a four-point contact surface. As discussed earlier, it provides a defined directionality around the seam of alternating ammonium and carboxylate groups and thus, requires *all eight* of the serines to have the same configuration at the α-position. The calculated collisional cross-sections are in good agreement with the experimental values of 187 and 191 Å^2. Using the exact-hard-spheres-scattering-model we obtain a value of 191 Å^2, with a trajectory calculation, a value of 183 Å^2 is calculated.

Some high-level calculations were performed with the serine monomer and octamer with the Turbomole package [34]. We employed the density functional GGA level of theory (DFT) with the S-VWN + Becke–Perdew parameterization (BP-86) [35,36] and the SV(P) split valence basis set included in the Turbomole package [34]. All geometries were fully optimized without any symmetry constraints. The zwitterionic serine monomer is less favorable than its nonionic counterpart by 128 kJ/mol. For eight serine molecules, this would result in a destabilization of 1024 kJ/mol. Instead, the zwitterionic octamer is calculated to be more stable by 1018 kJ/mol relative to eight separated neutral serine molecules. Seemingly, the solvation of charges within the octamer stabilizes the assembly by ca. 2000 kJ/mol relative to eight separate zwitterionic serine molecules. We also performed geometry optimizations at the DFT level with the structures proposed by Beauchamp and coworkers [8] and Counterman and Clemmer [9] as starting points. Both the overall neutral clusters and the singly protonated octamers have been considered. Among the neutral structures, that of Beauchamp et al. is the energetically most favorable lying 10 kJ/mol below that suggested in this article. For the protonated structures the difference is 15 kJ/mol. For a cluster as large as that under study, this difference is probably within the error of the method and one can say that both structures are at least very similar in energy. The neutral analogue obtained from the structure suggested by Clemmer and Counterman is higher in energy by ca. 164 kJ/mol. Of course, the problem of the possible existence of 4L/4D octamers close in energy remains also for the structure suggested here.

According to molecular modeling, the exchange of serine against homoserine, cysteine, or threonine leaves the cluster entirely intact. Homoserine with its longer side chain is capable of hydrogen bonding to the next carboxylate. The reduced stability may be attributed either to steric effects that disfavor the cluster or to the need to fix additional degrees of freedom within the longer side chain which is expected to be entropically less favorable. Threonine bears a second center of chirality in the side chain. The natural amino acid carries the methyl group in the outwards position as indicated in Fig. 2. Consequently, they

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Fig. 2. A new “flattened cube” structure for the serine octamer based on a 3000 step Monte Carlo structure search performed with the MacroModel program package (see footnote 2). Top: front view in CPK (left) and stick representations (right). Plus and minus signs indicate sticky ends through which the octamer might form larger hexadecameric and tetracosameric clusters. Center: side view presenting the carboxylate–ammonium salt bridges between different serine molecules. Arrows indicate attractive electrostatic forces between carboxylates and ammonium groups in vicinal serines. Bottom: top view showing the regular pattern of the CH_2OH side chains which mediate chiral recognition. Dotted lines indicate serine–carboxylate hydrogen bonds connecting the four top serines. A similar arrangement is realized for the other four serines. The “Me” labels indicate positions in which the methyl groups are located in the threonine octamer. Note that the structure represents the unprotonated cluster. There are enough polar sites at its surface to attach a proton in the gas phase.

do not hamper octamer formation. Cysteine smoothly replaces serine due to the close analogy in their structures. The only differences are a smaller HSC angle in cysteine and probably weaker S–H···O hydrogen bonds. Similarly, other amino acids may replace serine without destruction of the cluster.

6. Implications for homochirogenesis

Now back to the starting point! Does the formation of homochiral serine clusters have any implications on homochirogenesis at all? To say it right at the beginning: the homochirality of the serine octamer does not offer any explanation for the symmetry breaking step. The L-serine octamer is of course as stable as the D-serine octamer (except for the small energy differences resulting from parity violation, if it indeed exists). As a consequence, we will not learn from the octamer how nature got stuck with L-amino acids and D-sugars instead of their mirror images, if not by coincidence. However, homochirogenesis requires more than the symmetry breaking step. There must be chiral enrichment, i.e., the amplification of chiral information, in order to spread it around the whole prebiotic earth. As a third step, one should find a mechanism for transmission of chirality from one molecule to the other. In other words, if the phenomenon of symmetry breaking remained restricted to a certain molecule, the world as a whole would by and large be racemic.

The serine octamer might contribute in different ways to the latter two steps of homochirogenesis. It might help to amplify chirality, if for example incomplete clusters attached a precursor molecule which then reacts to yield another serine with the same chirality in order to complete the cluster. In this respect, the serine clusters would act as templates for the generation of new, enantiopure serine. Furthermore, one might imagine that small clusters may favor the nucleation of homochiral crystals. Several substances are known which crystallize in a homochiral way even from a racemate. Also, autocatalytic processes are known which generate a large amount of crystals of one enantiomers, while the other one remains in the mother liquor. This effect has been observed, when the growing crystals were broken into small particles by mechanic stress. New seeding crystallites are then produced which again attach other molecules with the same stereochemistry. As a third effect, homochiral octamers may play an important role in the formation of homochiral peptides, if, by any reactant, the formation of peptide bonds could be mediated within the cluster [8]. Finally, the existence of mixed homochiral clusters of serine with other amino acids provides a mechanistic basis for the transfer of chirality from serine to other amino acids and thus, may help to explain, why all natural amino acids exist in the same stereochemical L-configuration [11]. Most of these considerations necessarily remain speculative for the time being, but they offer a new “noncovalent” view on homochirogenesis and open the field for new approaches to this problem. New mechanisms for chiral amplification and transmission come into play, when noncovalently bound aggregates are considered.

One problem remains to be discussed. If the serine octamer is to have any implication for homochirogenesis, it must have existed on prebiotic earth, that means without the help of mass spectrometers and electrospray ionization processes. Consequently, the question arises, if it might exist in solution, and if so, under which conditions. Solvation of ammonium groups and carboxylates in water can be expected to be very strong, even stronger than the electrostatic forces holding together the octamer. Thus, in a diluted solution one may well find monomeric species only. That means that the octamers seen in the ESI-MS experiment are likely formed during the electrospray process [8]. If they are to play any role for homochirogenesis, one needs to find conditions appropriate for octamer formation. This might well happen in areas which are flooded from time to time and then get into contact with the prehistoric oceans, but afterwards dry out so that during this process, highly concentrated and probably also acidic solutions of prebiotic material are formed. These are likely prone to reactions such as, for example, the formation of small peptides and other biomolecules.

Acknowledgements

We are grateful to Prof. J.L. Beauchamp, Ryan Julian, and Prof. D.E. Clemmer for intense, fruitful discussions and communicating detailed structural parameters which we could use to perform some comparative calculations as discussed earlier. We thank Prof. R.G. Cooks for providing us with reprints/preprints of material otherwise difficult to access for us. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie (Liebig fellowship for C.A.S.) is acknowledged.

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