Chirality

Meteoritic C^{α}-Methylated α-Amino Acids and the Homochirality of Life: Searching for a Link

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Growing evidence has recently accumulated on the occurrence of chiral, C^{α}-methylated α-amino acids with significant L (*S*) enantiomeric excess (*ee*; up to 15%) in carbonaceous chondritic meteorites.[1–3] The amino acids analyzed to date include isovaline (Iva), C^{α}-methyl norvaline [(αMe)Nva], C^{α}-

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methyl valine [(αMe)Val], C^{α}-methyl isoleucine [(αMe)Ile], and C^{α}-methyl *allo*isoleucine [(αMe)*a*Ile] (Figure 1). In contrast, the α-amino acids lacking the C^{α}-methyl group (including the proteinogenic amino acids) have been found to be racemic within experimental and terrestrial contamination errors.[1–6] As opposed to C^{α}-methylated α-amino acids which are known to resist racemization, proteinogenic amino acids tend to racemize on an evolutionary time scale owing to their weakly acidic C^{α}-hydrogen.[5,7–12] It has been calculated that during just one million years an amount of $\geq 10^{12}$ Kg of organic carbon was delivered by meteorites to the Earth.[1–3] It has been also shown that C^{α}-methylated α-amino acids are generally abundant (10–100 ppm) in meteorites, although the ratios of C^{α}-methylated to C^{α}-nonmethylated α-amino acids (e.g., Iva/Ala) vary significantly (6.8/0.3) between samples. Other potentially chiral organic compounds largely found in meteorites are the α-hydroxy acids. For both classes of compounds (α-amino and α-hydroxy acids) a Strecker-like synthesis from aldehydes and ketones, HCN, water, and ammonia has been proposed.[13] Taken together, these results have suggested that C^{α}-methylated α-amino acids of extraterrestrial origin, delivered by meteorites which heavily bombarded the early Earth, could have been homochirality seeds for life on our planet,[14] which has developed upon proteinogenic amino acids of L-configuration. However, as C^{α}-methylated α-amino acids play a marginal role in contemporary biochemistry, this hypothesis implies that their *ee* values would have been somehow transferred to proteinogenic amino acids.[14] The results reported herein represent an addition to the already postulated mechanisms of chiral transmission between biomolecules, the two most recently published mechanisms involve the stable homochiral Ser octameric cluster[15] and Iva itself[16] as key players. It was also proposed[14] that initially life may have been based on the 3_{10} helix,[17] the typical architecture of peptides rich in C^{α}-methylated α-amino acids,[18,19] rather than on the α helix, the most stable regular secondary structure of proteinogenic amino acids.

Herein we describe the results of a study aimed at determining whether appropriately carboxy-activated, short peptides and long, 3_{10} helical peptides, based on chiral, C^{α}-methylated α-amino acids, can react with proteinogenic amino acids and favor the incorporation in the sequence of one of their enantiomers over the other. Our investigation focused on L-Iva and L-(αMe)Nva, as they are some of the most abundant and frequently analyzed chiral C^{α}-methylated α-amino acids in terms of *ee* value in meteoritic samples,[1–3] and on L-(αMe)Val, as a representative of the highly sterically hindered subclass of β-branched, C^{α}-methylated α-amino acids which also includes L-(αMe)Ile and L-(αMe)*a*Ile.[1–3]

There is a general agreement on the view that some sort of chemical evolution occurred before the onset of life on Earth, this evolution led to the formation of polymers, or at least oligomers, of amino acids. Therefore, we developed a test system based on homochiral homooligomers of Iva, (αMe)Nva, and (αMe)Val (Figure 2). These peptides are acetylated (Ac) at the N-terminus and activated as 5(4*H*)-oxazolones (OXL) at the C-terminus. While *N*-acetylation favors peptide solubilization in organic solvents and prevents reactivity of the α-amino function, the use of OXL is because they are generated to a significant extent from C^{α}-methylated α-amino acid residues by nearly all activation methods used for peptide-bond formation.[20] In particular, oxazolones are easily produced by intramolecular dehydration of C^{α}-methylated peptides with a free carboxy terminus. Thus, oxazolones represent an almost unavoidable entry to prebiotic peptide formation involving C^{α}-methylated α-amino acids. These peptide oxazolones were allowed to react with a large excess (8 equiv) of the racemate of a representative proteinogenic amino acid or its methyl ester (e.g. H-DL-Val-OH or H-DL-Val-OMe). Formation of the two resulting diastereomeric peptides (differing by the chirality of the incorporated,

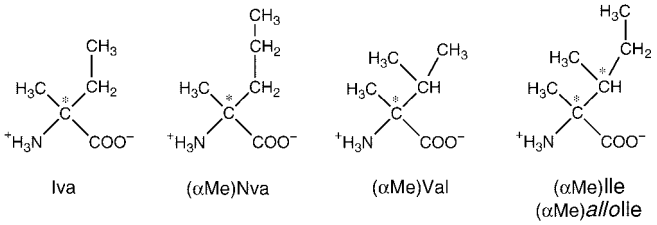

Figure 1. C^{α}-Methylated α-amino acids found in significant L enantiomeric excess in the Murchison and Murray meteorites. Chiral carbon atoms are starred.

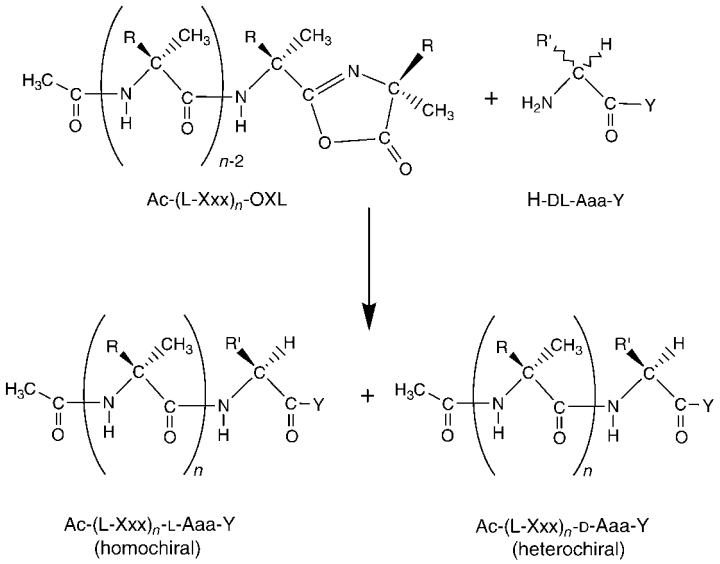

Figure 2. The test system developed for this study. Xxx represents a C^{α}-methylated α-amino acid (R = ethyl: Iva; *n*-propyl: (αMe)Nva; *iso*-propyl: (αMe)Val), while Aaa is a proteinogenic amino acid, either in its free form (Y = OH) or protected as the methyl ester (Y = OCH_3). The H-DL-Aaa-Y:Ac-(L-Xxx)$_n$-OXL molar ratio (in acetonitrile or acetonitrile–water mixtures) was 8:1, large enough to ensure thermodynamic rather than kinetic control of the stereochemical outcome of the reaction.

C-terminal proteinogenic amino acid) was quantified chromatographically.

Initial experiments were performed in acetonitrile (a good solvent for reaction and HPLC analysis of terminally blocked peptides) with dipeptide oxazolones carrying one C^{α}-methylated L-residue at the C-terminus and the achiral α-aminoisobutyric acid (Aib, or C^{α}-methyl alanine), which is abundant in chondritic meteorites,[21] at the penultimate position. Homochiral tripeptides are preferentially formed. Diastereoselection is temperature independent, and is comparable for L-Iva and L-(αMe)Nva while it is significantly higher for L-(αMe)Val (Table 1). By shifting the chiral residue to the penultimate position [for example, Ac-L-(αMe)Val-Aib-OXL] diastereoselection is completely suppressed (data not shown). These results would suggest that the chiral residue within the oxazolone ring is the only one involved in the stereoselection process. However, the related homodipeptide oxazolones behave differently (Table 1). The homochiral diastereoselectivities are temperature dependent and significantly lower than those obtained with the corresponding Ac-Aib-L-Xxx-OXLs, particularly at 30 °C and for the L-(αMe)Val oxazolone, thus pointing to a role of the penultimate residue as well in the diastereoselection process. These results can be explained on the basis of the reactant-like nature of the transition state of the step leading to peptide-bond formation through oxazolones,[22] and of the likely occurrence of multiple conformers, differently populated at different temperatures, for the homodipeptide oxazolones. This occurrence of multiple conformers is particularly relevant for the relatively large temperature effect observed for the L-Iva homodipeptide oxazolone. Indeed, two independent molecules are present in the X-ray diffraction structure of Ac-(L-Iva)$_2$-OXL,[23] differing by the signs of the φ,ψ backbone torsion angles at the penultimate residue.

Our investigation of the diastereoselection by the homochiral, homopeptide oxazolones was extended to the pentamer level for L-Iva and L-(αMe)Nva, and to the octamer for L-(αMe)Val (Table 1). For the L-Iva series preferential incorporation of the homochiral proteinogenic amino acid is observed. Diastereoselectivity tends to level off at the tetramer/pentamer level. In the L-(αMe)Nva series the L-selectivity decreases slightly but steadily with increasing peptide length, tending to a preference for the heterochiral peptide at the pentamer level. For the L-(αMe)Val series reversal of diastereoselection from L to D is found at the trimer level, all longer oligomers giving large heterochiral diastereoselectivities. Along this series the largest variation is observed from trimer to tetramer.

These results led us to the hypothesis that the C^{α}-methylated residue within the oxazolone ring and the preceding one have opposite effects on diastereoselection. More specifically, the chiral, C^{α}-methylated residue within the oxazolone ring seems to favor the incorporation of the proteinogenic amino acid of the same chirality, whereas the preceding residue appears to preferentially induce formation of the heterochiral peptide. On this basis, a peptide oxazolone in which the penultimate and the C-terminal residues are of opposite chirality (e.g. L–D) should show an increased selectivity (compared to the L–L sequence) for the D-isomer of the proteinogenic amino acid. Indeed, the reaction of Ac-[L-(αMe)Val]$_2$-D-(αMe)Val-OXL with H-DL-Val-OMe in acetonitrile at 80 °C gave a D-selectivity of 42 % (not listed in Table 1), significantly higher than the value of 14 % obtained for the corresponding all-L trimer. The inversion of chirality at the C-terminal residue in the N-terminal acetylated (αMe)Val tetramer led to a variation of the D-selectivity in the same direction as in the above experiment with the trimer, but of much lower magnitude, from 47 % for Ac-[L-(αMe)Val]$_4$-OXL to 50 % for Ac-[L-(αMe)Val]$_3$-D-(αMe)Val-OXL (the latter is not listed in Table 1). However, we already noted for the all-L (αMe)Val series a sharp increase in heterochiral diastereoselectivity as the result of main-chain elongation from trimer to tetramer, which suggests the contribution of a conformational effect which may take place at the level of the tetramer.

N-terminal-acylated homotripeptides from Iva, (αMe)Nva, and (αMe)Val fold into β turns,[24] stabilized by an intramolecular hydrogen bond between the NH group of the third residue and the carbonyl oxygen of the acyl group. Consecutive β turns are formed by the higher homologues, giving rise to 3_{10} helices.[19,25,26] The L configurations of (αMe)Nva and (αMe)Val promote the onset of turns and helices with a largely predominant right-handed screw sense. For Iva, the amino acid of this family with the smallest difference in length between the two side chains, the relationship between residue chirality and helical screw

Table 1: Chirality of the incorporated proteinogenic amino acids in the reaction products Ac-Aib-Xxx-D,L-Val-OMe or Ac-(Xxx)$_n$-D,L-Val-OMe from the peptide oxazolones Ac-Aib-Xxx-OXL or Ac-(Xxx)$_n$-OXL and H-DL-Val-OMe in acetonitrile solution at 80 °C (or 30 °C, in parentheses).[a]

Peptide oxazolone	*X* [%]	Peptide oxazolone	*X* [%]	Peptide oxazolone	*X* [%]
Ac-Aib-L-Iva-OXL	+25 (+25)	Ac-Aib-L-(αMe)Nva-OXL	+23 (+23)	Ac-Aib-L-(αMe)Val-OXL	+45 (+45)
Ac-(L-Iva)$_2$-OXL	+17 (−3)	Ac-[L-(αMe)Nva]$_2$-OXL	+16 (+13)	Ac-[L-(αMe)Val]$_2$-OXL	+12 (+7)
Ac-(L-Iva)$_3$-OXL	+12	Ac-[L-(αMe)Nva]$_3$-OXL	+10	Ac-[L-(αMe)Val]$_3$-OXL	−14
Ac-(L-Iva)$_4$-OXL	+20	Ac-[L-(αMe)Nva]$_4$-OXL	+8	Ac-[L-(αMe)Val]$_4$-OXL	−47
Ac-(L-Iva)$_5$-OXL	+22	Ac-[L-(αMe)Nva]$_5$-OXL	−3	Ac-[L-(αMe)Val]$_5$-OXL	−44
				Ac-[L-(αMe)Val]$_6$-OXL	−54
				Ac-[L-(αMe)Val]$_7$-OXL	−58
				Ac-[L-(αMe)Val]$_8$-OXL	−56

[a] Xxx = L-Iva, L-(αMe)Nva, L-(αMe)Val; the *X* values (defined as % L − % D, where L and D refer to the chirality of the incorporated proteinogenic amino acid) were determined by HPLC. For the assignment of the eluted peaks each diastereomer was prepared separately and used as a standard. The reported *X* values are the average of three independent experiments. Reproducibility is within 2 %.

sense is somewhat ambiguous.[19,26,27] In an *N*-acylated peptide oxazolone, with the C-terminal residue lacking the hydrogen-bonding donor NH group, the minimal main-chain length required for the formation of a single β turn is four residues.[28] Peptide oxazolones based on C^{α}-methylated residues and longer than tetramers are expected to fold into 3_{10} helices. Indeed, we show herein that in the crystal state the octameric oxazolone Z-[L-(αMe)Val]$_8$-OXL (Z, benzyloxycarbonyl) is folded into a right-handed 3_{10} helical conformation (Figure 3). The three-dimensional structural results reported herein, along with the conformational preferences of C^{α}-methylated peptides[17–19,25–27] (discussed above), support Bada's hypothesis[14] that if these peptides had some role during the origin of biological stereochemistry, then initially life may, at least in part, have been based on a different polypeptide architecture (the 3_{10} helix, instead of the classical α helix promoted by the proteinogenic C^{α}-hydrogen amino acids).

Overall, peptide oxazolones with a longer main-chain length and a bulky side chain (for example, as in L-(αMe)Val) preferentially incorporate a proteinogenic amino acid of the chirality opposite to that of the C^{α}-methylated residues, whereas a shorter main chain and a less bulky side chain in the peptide oxazolone (for example, as in L-Iva) direct the stereoselection towards the proteinogenic amino acid of the same chirality, but with lower efficiency. Such a bimodal distribution of diastereoselectivity is substantially retained in acetonitrile–water mixtures, as indicated by reactions of selected peptide oxazolones with either H-DL-Val-OMe or the racemates of the free amino acids Val, Phe, and Leu (Table 2), the free amino acids being prebiotically more relevant than their methyl esters. Thus, the stereochemical implications of our results are not hampered by addition of water (up to 70%) to the reaction medium. Water, either in bulk or at the interface with organic layers, lipid vesicles, or mineral surfaces, is included in all current models of prebiotic chemical evolution on Earth.[29–32] Acetonitrile itself may be not fully devoid of prebiotic relevance, as its occurrence in comets has been reported.[33]

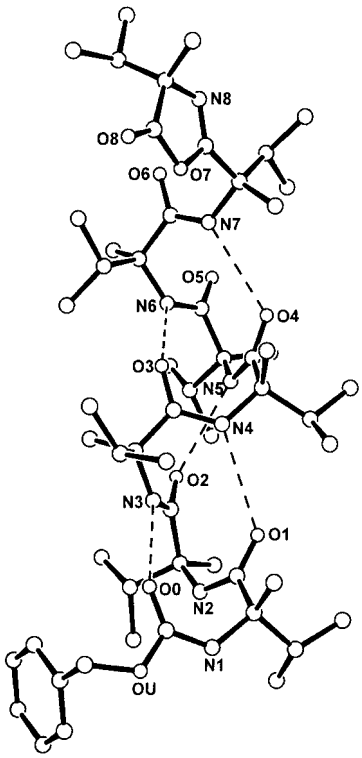

Figure 3. X-ray diffraction structure of Z-[L-(αMe)Val]$_8$-OXL. Only oxygen and nitrogen atoms are labeled. The five intramolecular C=O···H–N hydrogen bonds are indicated by dashed lines. The right-handed 3_{10} helix encompasses amino acid residues 1–6. The seventh residue, external to the helix, adopts a conformation with a screw sense opposite to that of the preceding residues. As a result, the oxazolone ring (N8,07,08) protrudes out of the helical envelope. Residue 8 is part of the oxazolone ring. The normal to the average plane of the oxazolone ring is nearly perpendicular to the helix axis.

Table 2: Chirality of the incorporated proteinogenic amino acids in the reaction products of selected *N*-acetylated, C^{α}-methylated peptide 5(4*H*)-oxazolones with racemic proteinogenic amino acids or their methyl esters (H-DL-Aaa-Y) in H_2O/CH_3CN solution.[a]

Peptide oxazolone	H-DL-Aaa-Y	*X* [%]	Solvent	*T* [°C]
Ac-Aib-L-(αMe)Val-OXL	H-DL-Val-OMe	+30	30% H_2O/CH_3CN	50
Ac-[L-(αMe)Val]$_5$-OXL	H-DL-Val-OMe	−40	30% H_2O/CH_3CN	50
Ac-[L-(αMe)Val]$_5$-OXL	H-DL-Val-OMe	−40	70% H_2O/CH_3CN	80
Ac-Aib-L-(αMe)Val-OXL	H-DL-Val-OH	+7	50% H_2O/CH_3CN	80
Ac-[L-(αMe)Val]$_5$-OXL	H-DL-Val-OH	−33	50% H_2O/CH_3CN	80
Ac-[L-(αMe)Val]$_5$-OXL	H-DL-Phe-OH	−16	50% H_2O/CH_3CN	80
Ac-[L-(αMe)Val]$_5$-OXL	H-DL-Leu-OH	−42	50% H_2O/CH_3CN	80

[a] Y = OH, OMe; the *X* values are defined as % L − % D, where L and D refer to the chirality of the incorporated proteinogenic amino acid.

Prebiotic chemical evolution towards the emergence of peptides is thought to have occurred through a combination of cycles of peptide-bond formation and hydrolysis. A peptide bond between two C^{α}-methylated α-amino acid residues is sterically better protected from hydrolytic cleavage than a bond between a C^{α}-methylated and a proteinogenic amino acid residue. Thus, it is likely that the proteinogenic amino acids incorporated at the C-terminus of C^{α}-methylated peptide chains might have been subsequently released through hydrolysis to a greater extent than those released by the hydrolytic degradation of the fully C^{α}-methylated peptide chains. This process would seem to leave the racemic state of the prebiotic soup unaffected. However, significant epimerization can be expected to occur in between incorporation and release of the proteinogenic amino acids, as a proteinogenic amino acid C-terminal to a peptide chain, upon activation, may undergo cyclization to oxazolone, thus becoming highly prone to racemization.[34] Therefore, the chiral imbalance generated in the prebiotic soup of proteinogenic amino acids by their stereoselective incorporation into the C^{α}-methylated peptides can be retained to an extent which is directly proportional to the occurrence of oxazolone-mediated racemization of the pro-

teinogenic amino acids prior to their cleavage from the C^{α}-methylated peptide chain. Such a process could have been repeated in cycles, with C^{α}-methylated peptides providing a stable source of chiral bias. In the long run, the overall result would have been the enrichment of the primordial soup in proteinogenic amino acids of the chirality opposite to that preferentially incorporated by the C^{α}-methylated peptide chains. If the D-incorporation prevailed, then through amplification mechanisms[35–40] the L-homochirality of life could have emerged.

In summary, our experimental results indicate the possibility that the proteinogenic amino acid homochirality on Earth may have originated from meteoritic C^{α}-methylated α-amino acids and that the 3_{10} helical structure may have played a significant role in this process, although concurrent or alternative pathways[40–42] leading to the same final scenario are not excluded by the present results.

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