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Abstract

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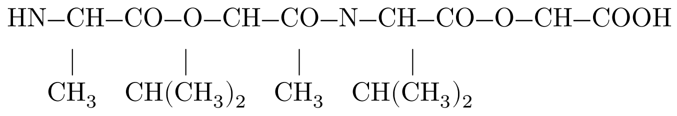
Conformational Factors in the Cyclization of Depsipeptides

In the course of studying the chemistry of natural cyclodepsipeptides ($^{1-3}$), we undertook a detailed investigation of the influence of various factors on the cyclization of linear depsipeptides. Thus, it had previously been established (^{4}) that the doubling of molecules often observed in the cyclization of depsipeptides cannot be explained on the basis of Schwitzer' s concept of the formation of hydrogen-bonded associates (^{5}). From this it was concluded that the behavior of linear depsipeptides during cyclization under conditions of high dilution is determined by other factors, the principal ones being the preferred conformation of the initial depsipeptide (from the standpoint of its spatial proximity to the precyclization transition state) and the degree of strain of the cyclodepsipeptide formed. The purpose of the present work was the experimental verification of this conclusion using cyclotetradepsipeptides as an example.

As the principal objects of the investigation, eight stereoisomeric tetradepsipeptides I-VIII were selected, constructed from regularly alternating residues of N-methylvaline and α-hydroxyisovaleric acid and representing all possible diastereomers of this tetradepsipeptide (with the exception of antipodes). The synthesis of these compounds was carried out on the basis of the general methods for constructing linear depsipeptides developed by us earlier (^{1,6}). Cyclization of tetradepsipeptides I-VIII was carried out by the chloroanhydride method under standard conditions (^{1}); the yields, constants, and analytical data of the cyclodepsipeptides IX-XV obtained are given in Table 1.



$$HN-\underset{\underset{CH_3}{|}}{CH}-CO-O-\underset{\underset{CH(CH_3)_2}{|}}{CH}-CO-N-\underset{\underset{CH_3}{|}}{CH}-CO-O-\underset{\underset{CH(CH_3)_2}{|}}{CH}-COOH$$

(I)	*LDLD*	(V)	*LLDD*
(II)	*LDDD*	(VI)	*DDDL*
(III)	*DDLD*	(VII)	*DLDD*
(IV)	*LDDL*	(VIII)	*DDDD*

$$[-N-CH-CO-[-O-CH-CO-N-CH-CO-]_n-O-CH-CO-\quad]$$

(IX) $n = 1$ (*LDLD*) (XII) $n = 1$ (*LLDD*)
(X) $n = 1$ (*LDDD*) (XIII) $n = 1$ (*DDDL*)
(XI) $n = 1$ (*LDDL*) (XIV) $n = 1$ (*DDDD*)
(XV) $n = 3$ (*DDDDDDDD*)

As can be seen from the data presented, upon cyclization of tetradepsipeptides I-VII the corresponding cyclotetradepsipeptides IX–XIII are formed in fairly high yields (40–75%), and only in the case of compound VIII with the monotonic *DDDD*-configuration is the yield of cyclotetradepsipeptide XIV 8%; moreover, along with it, as a result of doubling, cyclooctadepsipeptide XV is formed in 13% yield. In order to clarify the reasons for such distinctive behavior of the linear tetradepsipeptides studied by us during their cyclization, we carried out a detailed conformational analysis of these compounds, as well as of the corresponding cyclotetradepsipeptides.

Table 1

Yields, constants, and analytical data for cyclodepsipeptides

Compound	Yield, %	M.p., °C	$[\alpha]_D^{20}$ (c in CHCl)	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N
IX	70 (from I)	228–229	+4.8°(0.9)	**					
X	75 (from II)	144	+218°(0.7)	62.11	8.79	6.38	61.94	8.98	6.57
XI	60 (from III)								
XI	70 (from IV)	229–230	0°*	62.19	8.91	6.40	61.94	8.98	6.57
XII	40 (from V)	229–230	0°*	62.01	8.78	6.56	61.94	8.98	6.57
XIII	46 (from VII)	129	+66°(0.4)	61.97	9.03	6.39	61.94	8.98	6.57
XIII	45 (from VI)								

Compound	Yield, %	M.p., °C	$[\alpha]_D^{20}$ (c in CHCl)	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N
XIV	8 (from VIII)	156–158	+61°(1.0)	**					
XV	13 (from VIII)	182–184	+124°(0.75)	**					

* Meso form; a mixed sample of XI and XII has m.p. 208°.
** For analytical data see (4).

First of all it is necessary to note that conformational analysis of linear depsipeptides and peptides is a rather complicated problem, since at present there are no reliable criteria for deciding the question of their preferred conformations, although this problem has been the object of a number of studies[7–9], which have made it possible to draw conclusions about the spatial arrangement of individual portions of the peptide chain. Therefore, in constructing molecular models we proceeded from the following premises. For N-methylamide and ester bonds we accepted, as sufficiently obvious, a planar trans configuration (cf.[10,11]). As for the question of the nature of internal rotation about ordinary $C—C_\alpha$ and $N—C_\alpha$ (or $O—C_\alpha$) bonds, it is expedient to discuss it in greater detail. On the basis of quantitative spectral studies and thermodynamic calculations it had previously been established[12–14] that, in the case of a bond between tetrahedral and trigonal atoms, the most favorable conformations are those in which the double bond eclipses one of the substituents of the adjacent tetrahedral carbon atom. Therefore, taking into account that N—CO and O—CO bonds may be regarded as partially double, one should consider possible the existence of six most favorable and relatively stable conformations XVI—XXI for the $C_{amide}—C_\alpha$ bond and, correspondingly, XXII—XXVII for the $C_{ester}—C_\alpha$ bond.

Conformations XVI—XXVII

(XVI) (XVII) (XVIII) (XIX) (XX) (XXI)

(XXII) (XXIII) (XXIV) (XXV) (XXVI) (XXVII)

According to the data of a number of authors' works devoted to the study of rotation about the $C—C_\alpha$ bond[8,9,15], of the 12 conformations XVI—XXVII, 6 should be more preferable, namely XIX—XXI for the $C_{amide}—C_\alpha$ bond and XXV—XXVII for the $C_{ester}—C_\alpha$ bond. In turn, among the 3 most probable orientations XIX—XXI for the $C_{amide}—C_\alpha$ bond, the preferred conformation is XXI, in which—

substituents possessing large volume (R and NMe) or like polarity are farthest removed from one another. An analogous picture is also obtained when considering conformations XXV–XXVII for the $C_{ester} - C_\alpha$ bond, although here it is more difficult to choose between the orientations XXV and XXVII. However, taking into account the data of Mizushima ([8]), conformation XXVII should be the more stable one.

With regard to the barriers to rotation about the $N - C_\alpha$ (or $O - C_\alpha$) bonds, at present there are no experimental data. However, proceeding from the considerations set forth above, in the case of the $N - C_\alpha$ bond we regard conformations XXVIII–XXX as relatively more favorable (because of the partial double-bond character of the $OC - N$ bond). Of these rotational isomers, isomer XXVIII, destabilized by repulsion of the CO groups, may be disregarded, and preference should be given to conformation XXIX, where the $N - CO$ bond screens the least bulky substituent; this conclusion is confirmed by analysis of molecular models.

Schematic conformations XXVIII-XXXIII

In the case of the $O - C_\alpha$ bond (isomers XXXI–XXXIII), for the same reason we consider conformation XXXII to be more favorable; however, here it is difficult to choose between this conformation and orientations differing from the latter by a rotation of 60° about the $O - C_\alpha$ bond, since the oxygen atom is not trigonal. It should be noted, however, that mutual interconversion of these close conformations leads only to a slight change in the shape of the depsipeptide chain.

Consideration, on the basis of the principles set forth above, of molecular models of tetradepsipeptides I–VIII showed that the linear tetradepsipeptide (I) has a folded conformation and the smallest distance between the ends of the chain in comparison with the other seven tetradepsipeptides, whereas tetradepsipeptide VIII has an extended chain form with the terminal groups farthest apart; this conclusion is directly reflected in the tendency of tetradepsipeptides I and VIII toward cyclization (see Table 1). As for tetradepsipeptides II–VII, they all have a folded chain form, more or less close to the conformation of depsipeptide I, and, like the latter, display a sufficiently high tendency toward cyclization. In turn, the sharp difference in the behavior of these linear depsipeptides during cyclization may serve as direct confirmation of the existence in them of preferred conformations of the indicated type, clearly realized on molecular models.

In this connection it is necessary to note that, in the case of linear peptides and depsipeptides, an extended chain form is characteristic exclusively of compounds with a monotonic (entirely *L* or *D*) configuration (naturally, in the absence of intramolecular hydrogen bonds or other interactions), whereas changing the configuration of any amino-acid (or hydroxy-acid) residue to the opposite one leads to twisting of the chain. This conclusion,

agrees with data obtained in the physicochemical study of *LL*- and *LD*-diastereomeric peptides ([16–18]), as well as with Kenner' s studies ([9,19]) on the cyclization of a series of stereoisomeric pentapeptides in comparison with the values of the dielectric increments of these compounds (although such comparisons are not always legitimate).

In considering the results of cyclization of linear depsipeptides, it is necessary, along with conformational analysis of the latter, to take into account the degree of strain of the cyclodepsipeptide being formed. In particular, cyclization of the most diverse tripeptides and tridepsipeptides leads, as a rule, to cyclohexapeptides and cyclohexadepsipeptides ([4,5]) because of the high strain of the nine-membered ring with three cis-amide (ester-amide) bonds ([20,21]). Cyclotetrapeptides and, especially, cyclotetradepsipeptides IX–XIV are already less strained. Nevertheless, these compounds possess very rigid conformations, which hinder the possibility of conformational transitions, and therefore even small changes in the spatial arrangement of atoms and groups have a pronounced effect on the stability (and, consequently, on the realizability) of the corresponding ring. In this respect, 12-membered cyclotetrapeptides and cyclotetradepsipeptides (analogously to medium-sized carbon rings) are very successful objects, making it possible to study in detail the influence of even slight spatial factors.

The conformational analysis of cyclotetradepsipeptides IX–XIV carried out by us showed that, relatively speaking, the most favorable conformations, both from the standpoint of the spatial arrangement of the isopropyl and N-methyl groups and from the standpoint of internal rotation about the ordinary $C{-}C_\alpha$-, $N{-}C_\alpha$-, and $O{-}C_\alpha$-bonds, may be possessed by compounds IX–XII. Less energetically favorable is the conformation of cyclotetradepsipeptide XIII (three isopropyl and two N-methyl groups on one side of the ring), and, finally, the conformation of cyclotetradepsipeptide XIV is very unfavorable, when all the isopropyl and N-methyl groups are located on one side of the ring, and all the CO groups on the other. These conclusions are well confirmed by the experimental data (see Table 1).

It follows from the foregoing that, in the cyclization of linear depsipeptides and peptides, the conformation of the starting compound and the strain of the ring being formed play the decisive role. On the other hand, cyclization carried out under standard conditions provides simple and reliable information about the preferred conformational states of a linear chain.

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