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Abstract

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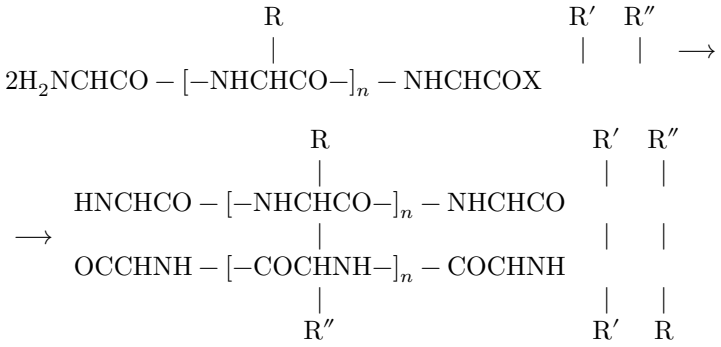
MECHANISM OF DOUBLING IN THE CYCLIZATION OF DEPSIPEPTIDES AND PEPTIDES

The study of cyclic peptides and depsipeptides constitutes one of the current areas of peptide chemistry, since they include a large group of biologically important natural compounds. At present, a number of convenient methods have been developed for the synthesis of cyclopeptides and cyclodepsipeptides, which are usually obtained by constructing the corresponding linear compounds and subsequently cyclizing them under conditions of high dilution, using the customary techniques of peptide chemistry. In this way the synthesis of several natural cyclopeptides and their analogs has been carried out ([1,2]), and a number of natural cyclodepsipeptides has also been obtained ([3–8]).

In the course of these synthetic investigations it was established that one of the characteristic features of the cyclization of many linear peptides is the so-called doubling. This feature consists in the fact that, as a result of cyclization of a linear peptide, a cyclopeptide is formed with twice the number of amino-acid residues, owing to condensation of two molecules of the starting peptide:

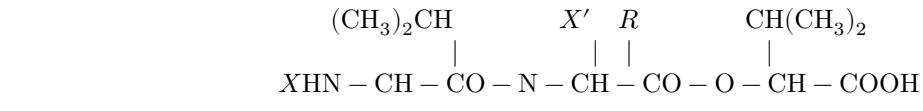


$$X = OR,\ SR \text{ and others.}$$

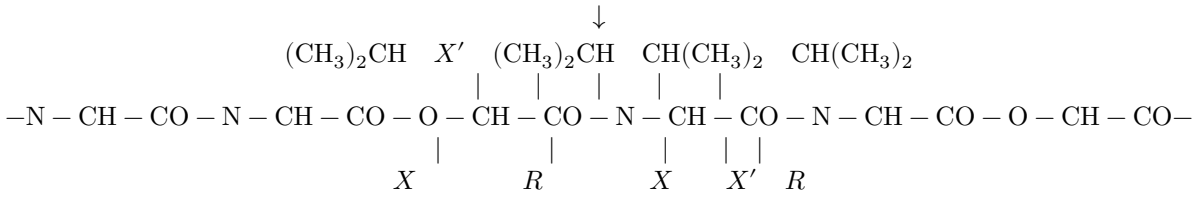
Studying this problem in detail, Schwyzer as early as 1956 came to the conclusion ([9,10]) that the doubling process is preceded by the formation of associates (stabilized by intermolecular hydrogen bonds between NH and CO groups), in

which two molecules of a linear peptide are arranged in the manner of the antiparallel pleated sheet of Pauling–Corey ([11]); the subsequent condensation, accompanied by only slight changes in the spatial arrangement of the reacting groups, leads to a cyclopeptide with an analogous "pleated" conformation. On the basis of this hypothesis Schwyzer also concluded that associates of this kind can form predominantly in those cases in which the linear peptides contain an odd number of amino-acid residues, since under this condition the maximum number of intermolecular hydrogen bonds is realized; hence he drew the conclusion that cyclization of linear tri-, penta-, hepta-, and other odd peptides (in contrast to di-, tetra-, hexa-, and other even peptides) should, as a rule, lead to doubling. This concept received broad recognition and found well-known experimental confirmation ([12–19]).

In the course of the synthesis of cyclodepsipeptides we also encountered a doubling reaction. Thus, upon cyclization of tridepsipeptide (I) by the acid chloride method, the corresponding cyclohexadepsipeptide (VII) was obtained as the sole reaction product.



I.(DDL), $X = X' = H$, $R =$ iso-Bu; IV.(LLD), $X = H$, $X' = Me$, $R =$ sec-Bu;
II.(LLL), $X = X' = Me$, $R =$ iso-Bu; V.(DLL), $X = H$, $X' = Me$, $R =$ iso-Bu;
III.(DLD), $X = H$, $X' = Me$, $R =$ sec-Bu; VI.(LLL), $X = H$, $X' = Me$, $R =$ iso-Bu.



VII.$(DDLDDL)$, $X = X' = H$, $R =$ iso-Bu; X.$(LLDLLD)$, $X = H$, $X' = Me$, $R =$ sec-Bu;
VIII.$(LLLLLL)$, $X = X' = Me$, $R =$ iso-Bu; XI.$(DLLDLL)$, $X = H$, $X' = Me$, $R =$ iso-Bu;
IX.$(DLDDLD)$, $X = H$, $X' = Me$, $R =$ sec-Bu; XII.$(LLLLLL)$, $X = H$, $X' = Me$, $R =$ iso-Bu.

Since depsipeptides are very close to peptides, owing to the fact that the ester group, in its spatial characteristics, models the amide group well ([20]), it seemed natural to us to assume that the concept proposed by Schwyzer is also valid for depsipeptides. However, further studies showed that this is not the case. Thus, for example, it turned out that tridepsipeptides (II)–(VI), which are not capable of giving hydrogen-bonded associates because of the presence of N-methyl groups, nevertheless upon cyclization form doubling products (VIII)–(XII) in yields close to or exceeding the yield of cyclohexadepsipeptide (VII), which contains no N-methyl groups (see Table 1).

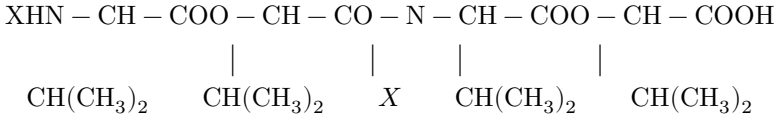
Table 1

Yields, constants, and analytical data of cyclodepsipeptides*

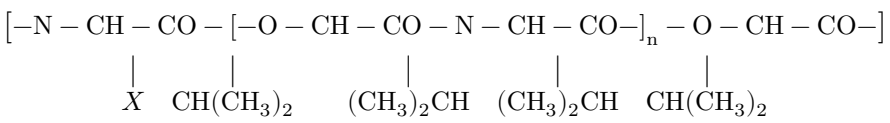
Compound	Empirical formula	Yield, %	m.p., °C	$[\alpha]_D^{25}$	C (in $CHCl_3$), %	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N
VII	$C_{32}H_{56}N_4O_8$	32	295 – 297	+112°	0.9	61.66	9.05	8.92	61.51	9.03	8.97
VIII	$C_{36}H_{64}N_4O_8$	21	oil	−156°	1.1	63.80	9.29	7.98	63.50	9.47	8.23
IX	$C_{34}H_{60}N_4O_8$	29	215 – 216	+71°	1.7	62.77	9.44	8.52	62.55	9.26	8.58
X	$C_{34}H_{60}N_4O_8$	28	222 – 223	−179°	3.1	62.67	9.25	8.50	62.55	9.26	8.58
XI	$C_{34}H_{60}N_4O_8$	33	245 – 246	−5.8°	1.6	62.47	9.44	8.71	62.55	9.26	8.58
XII	$C_{34}H_{60}N_4O_8$	11	237 – 238	−268°	1.4	62.49	9.25	8.53	62.55	9.26	8.58
XVIII	$C_{22}H_{38}N_2O_6$	8	156 – 158	+61°	1.0	62.21	9.01	6.50	61.94	8.98	6.57
XIX	$C_{20}H_{34}N_2O_6$	6	319 – 320	−51°	0.5	60.33	8.70	7.00	60.28	8.60	7.03
XX	$C_{22}H_{38}N_2O_6$	7	228 – 229	+4.8°	2.0	62.04	8.98	6.46	61.94	8.98	6.57
XXII	$C_{44}H_{76}N_4O_{12}$	4	182 – 184	+124°	0.8	62.12	8.82	6.39	61.94	8.98	6.57
XXIII	$C_{40}H_{68}N_4O_{12}$	9	270 – 272	+28°	1.3	60.42	8.62	7.04	60.28	8.60	7.03
XXIV	$C_{40}H_{102}N_6O_{18}$	8	232 – 233	+41°	0.9	60.49	8.59	7.12	60.28	8.60	7.03

* The synthesis of the starting linear depsipeptides was carried out on the basis of previously developed general methods ([32]); cyclization of the linear peptides was carried out under the standard conditions of the acid chloride method (Et_3N in C_6H_6) (cf. [4]).

Moreover, we have shown that doubling also occurs upon cyclization of a number of tetradepsipeptides. Thus, it was recently described ([21]) that, upon cyclization in benzene of tetradepsipeptide (XIII), which contains no N-methyl groups, cyclotetradepsipeptide (XVII) is formed in 18% yield and the corresponding cyclooctadepsipeptide (XXI) in 8% yield. It was further found that cyclization of tetradepsipeptide (XV) in benzene is accompanied not only by doubling but also by tripling: along with cyclotetradepsipeptide (XIX), we isolated cyclooctadepsipeptide (XXIII) and cyclododecadepsipeptide (XXIV) in yields of 6, 19, and 8%, respectively. Significantly, carrying out the cyclization in tetrahydrofuran, which sharply reduces the probability of formation of intermolecular hydrogen bonds ([22,23]), led only to some change in the ratio of yields of the same cyclodepdepsipeptides (26, 18, and 9%), but it did not inhibit the process of doubling (tripling). In the case of tetradepsipeptides, doubling sometimes also occurs during the cyclization of N-methylated compounds; for example, from tetradepsipeptide (XIV) there are formed cyclotetradepsipeptide (XVIII) and cyclooctadepsipeptide (XXII). The behavior of the linear tetradepsipeptides considered during their cyclization also contradicts Schwyzer' s concept and, in particular, his oddness principle. Thus, on the basis of the experimental data presented above, one may conclude that this concept is completely inapplicable to depsipeptides.



XIII. $(DDDD)$, $X = \mathrm{H}$; XV. $(LDLD)$, $X = \mathrm{H}$;
XIV. $(DDDD)$, $X = \mathrm{Me}$; XVI. $(LDLD)$, $X = \mathrm{Me}$.



XVII. $n = 1$ $(DDDD)$, $X = \mathrm{H}$; XXI. $n = 3$ $(DDDDDDDD)$, $X = \mathrm{H}$;
XVIII. $n = 1$ $(DDDD)$, $X = \mathrm{Me}$; XXII. $n = 3$ $(DDDDDDDD)$, $X = \mathrm{Me}$;
XIX. $n = 1$ $(LDLD)$, $X = \mathrm{H}$; XXIII. $n = 3$ $(LDLDLDLD)$, $X = \mathrm{H}$;
XX. $n = 1$ $(LDLD)$, $X = \mathrm{Me}$; XXIV. $n = 5$ $(LDLDLDLDLDLD)$, $X = \mathrm{H}$.

If, however, one takes into account a number of recently published experimental data, then Schwyzer' s concept gives rise to serious objections also with respect to cyclopeptides. Thus, Klotz and Franzen ([22, 23]), in studying the stability of interpeptide hydrogen bonds in solution, established that in aqueous and alcoholic peptide solutions intermolecular association is practically absent; it was

also shown that hydrogen bonds of the NH···.OC type are very weak even in such solvents as, for example, dioxane and tetrahydrofuran. If one considers the conditions under which cyclization of peptides is accompanied by doubling, it is easy to see that the latter takes place even in such polar media as water ([12], [18], [19]), methyl alcohol ([17], [30]), pyridine (at 90-95°) ([13], [14]), and dimethylformamide ([24]). These data argue against the formation of hydrogen-bonded associates in solutions of low-molecular peptides. On the other hand, the oddness principle is not always observed in the cyclization of peptides. Thus, for example, Kenner ([19], [25]) and Brockmann ([26]), in the cyclization of pentapeptides, obtained cyclopenta-, and not cyclodecapeptides, as the main reaction products.

The data set forth make it possible to conclude that the mechanism of the doubling reaction, in all probability, is fundamentally different from that proposed by Schwyzer. In our opinion, the principal competing process accompanying the cyclization of a peptide (depsipeptide) is linear polycondensation, leading to the successive formation of poly-mer homologs of increasing degree of polymerization*.

$$\begin{array}{ccccc} \mathrm{H-[NHCHCO]_n-Y} & \longrightarrow & \mathrm{H-[NHCHCO]_{2n}-Y} & \longrightarrow & \\ \Big| & & \Big| & & \\ R & & R & & \\ \longrightarrow \ \mathrm{H-[NHCHCO]_{3n}-Y} & \longrightarrow \cdots \longrightarrow & \mathrm{H-[NHCHCO]_{xn}-Y} & & \\ \Big| & & \Big| & & \\ R & & R & & \end{array}$$

However, since cyclization is carried out under conditions of high dilution, the initial and the formed linear peptides, possessing reactive terminal groups, undergo intramolecular

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* Usually, during the cyclization of peptides and depsipeptides, high-molecular polymers are formed, lowering the yield of low-molecular cyclic compounds.

condensation into the corresponding cyclopeptides. The ratio of these processes (polycondensation and cyclization) is determined chiefly by the extent to which the most stable conformation of the given linear peptide is close to the conformation of the corresponding cyclopeptide (more precisely, of the transition state) and, on the other hand, by how energetically favorable (in particular, with respect to Baeyer and Pitzer strain) the conformation of the cyclopeptide being formed is. Indeed, owing to the great strain of the nine-membered peptide ring ([19], [27], [28]), cyclotripetides are usually not formed at all upon cyclization of tripeptides, and the main reaction products are cyclohexapeptides ([12-14]), linear hexapeptides ([18]), and diketopiperazines ([18], [29]). Conversely, upon cyclization of hexapeptides, cyclohexapeptides are formed predominantly ([13], [14], [30]), because the 18-membered peptide ring has an energetically favorable conformation

([31]). Exactly the same picture is observed, according to our data (see above, and also ([5], [7], [8])), in the cyclization of tri- and hexadepsipeptides. On the other hand, the influence of the conformation of the initial or intermediate linear peptides (depsipeptides) on the nature and yield of the cyclization products has also found direct confirmation in the experimental data obtained by us. Since the conformation of a linear peptide or depsipeptide is largely determined by the configuration of the amino-acid (or hydroxy-acid) residues comprising it, we investigated the cyclization of two tetradepsipeptides (XIV) and (XVI), differing only in configuration, and showed that in the case of compound (XIV) (*DDDD* configuration) 8% of cyclotetra- (XVIII) and 13% of cyclooctadepsipeptide (XXII) are formed, whereas in the case of the stereoisomeric tetradepsipeptide (XVI) (*LDLD* configuration) exclusively cyclotetradepsipeptide (XX) is formed in 70% yield. A detailed conformational analysis of the problem considered and a more thorough experimental study of it are the subject of our further investigations.

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REFERENCES CITED

[1] R. Schwyzer, Rec. Chem. Progr., **20**, 146 (1959).
[2] K. Vogler, R. O. Studer, P. Lanz, W. Lergier, E. Boehni, Experientia, **17**, 223 (1961).
[3] H. Brockmann, H. Lackner, Naturwiss., **47**, 230 (1960).
[4] M. M. Shemyakin, Yu. A. Ovchinnikov et al., Tetrahedron, **19**, 995 (1963).
[5] M. M. Shemyakin, Yu. A. Ovchinnikov et al., Izv. AN SSSR, OKhN, **1963**, 579.
[6] Pl. A. Plattner, K. Vogler, R. O. Studer, P. Quitt, W. Keller-Schierlein, Experientia, **19**, 71 (1963).
[7] M. M. Shemyakin, Yu. A. Ovchinnikov et al., Izv. AN SSSR, OKhN, **1963**, 1148.
[8] Yu. A. Ovchinnikov, A. A. Kiryushkin et al., Izv. AN SSSR, OKhN, **1963**, 770.
[9] R. Schwyzer, B. Iselin, W. Rittel, P. Sieber, Helv. chim. acta, **39**, 872 (1956).
[10] R. Schwyzer, CIBA-Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity, **1958**, 171.
[11] L. Pauling, R. B. Corey, Proc. Nat. Acad. Sci. (USA), **39**, 253 (1953).
[12] J. C. Sheehan, M. Goodman, W. L. Richardson, J. Am. Chem. Soc., **77**, 6391 (1955).
[13] R. Schwyzer, P. Sieber, Helv. chim. acta, **41**, 2190 (1958).
[14] R. Schwyzer, B. Gorup, Helv. chim. acta, **41**, 2199 (1958).
[15] R. Schwyzer, P. Sieber, Helv. chim. acta, **41**, 2186 (1958).
[16] R. Schwyzer, Aung Tun-Kyi, Helv. chim. acta, **45**, 859 (1962).
[17] H. Brockmann, M. Springorum, Naturwiss., **49**, 514 (1962).

[18] J. C. Sheehan, D. N. McGregor, J. Am. Chem. Soc., **84**, 3000 (1962).
[19] G. W. Kenner, P. J. Thomson, J. M. Turner, J. Chem. Soc., **1958**, 4148.
[20] J. M. O' Gorman, W. Shand, V. Shemaker, J. Am. Chem. Soc., **72**, 4222 (1950).
[21] M. M. Shemyakin, E. I. Vinogradova et al., Tetrahedron Letters, **1963**, 351.
[22] I. M. Klotz, J. S. Franzen, J. Am. Chem. Soc., **82**, 5241 (1960).
[23] I. M. Klotz, J. S. Franzen, J. Am. Chem. Soc., **84**, 3461 (1962).
[24] M. Rothe, Angew. Chem., **74**, 725 (1962).
[25] P. M. Hardy, G. W. Kenner, R. C. Sheppard, Tetrahedron, **19**, 95 (1963).
[26] H. Brockmann, V. Graef, Naturwiss., **49**, 540 (1962).
[27] J. T. Edward, Research, **85**, 38 (1955).
[28] L. Pauling, R. B. Corey, Proc. Nat. Acad. Sci. (USA), **38**, 86 (1952).
[29] P. W. G. Smith, J. Chem. Soc., **1957**, 3985.
[30] Th. Wieland, K. W. Ohly, Ann., **605**, 179 (1957).
[31] J. Dale, J. Chem. Soc., **1963**, 93.
[32] M. M. Shemyakin, E. I. Vinogradova et al., DAN, **140**, 387 (1961).

Note: Figure translations are in progress. See original paper for figures.