CYCLOSTEREOISOMERISM

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ABSTRACT

Cyclostereoisomerism is a new concept in organic stereochemistry in which the stereoisomers constitute an even number of chiral units differing in the sense of ring direction while the chiral framework remaining the same. The different types of cyclostereoisomers have been discussed and illustrated with cyclopolypeptides.

Louis Pasteur (1848), as rightly pointed out by Mislow[1] was the first 'practitioner' in organic stereochemistry which was later placed on solid foundation by van't Hoff and Le Bel (1874) with their structural theory of organic compounds. Subsequent years saw a rapid development in this area which mainly corroborated and put into practice the ideas of these two scientists till 1950 when Barton and Hassel set another landmark in organic stereochemistry with their conformational theory which made it possible to understand the dynamic aspect of molecular geometry and its relation to reaction mechanisms. The modern methods of instrumental analysis particularly nuclear magnetic resonance spectroscopy, and measurements of optical rotatory dispersion and circular dichroism have contributed much towards solving many intricate problems of stereochemistry, and broadened its scope and application. Considerable progress has been made on some selected areas such as asymmetric synthesis, stereodynamics, prostereoisomerism, enzymatic stereospecificity, chemical topology, etc. There have been important changes in the stereochemical nomenclature[2] so that many of the basic concepts can now be defined in more precise terms. Changes have also been suggested at the fundamental level as in the classification and definition of stereoisomers and even in the understanding of asymmetric carbon atom[3] on which the main edifice of organic stereochemistry stands. New types of stereoisomerism have been recognised. One such type is cyclostereoisomerism, first investigated by Prelog and coworkers[4] introducing a new concept in stereochemistry. However, because of the rarity of its occurrence, it is hardly mentioned or referred to in common text-books[5]. The purpose of the present article is to provide an introduction to this novel stereoisomerism.

Cyclic systems containing an equal number of R (rectus) and S (sinister) forms of a particular chiral unit, either as parts of the ring or as side chains can give rise to cyclostereoisomerism provided certain conditions are fulfilled. The number of the chiral units must be even ($2n$) half having R and the other half having S configuration. The achiral chain may be 'nonorienting' i.e. the two directions of the chain are equivalent e.g. $-CH_2-CH_2-$ or 'orienting' i.e. the two directions are nonequivalent e.g. –CO–NH– with either end joined to a chiral centre. Cyclopolypeptides built up of equal number of R and S aminoacids of the same kind (monotonic) satisfy these conditions admirably and are discussed here. Such rings have directional property (clockwise or anticlockwise) depending on the 'orientation' of the peptide linkages and it is the ring direction that distinguishes the cyclostereoisomers from one other. A short-hand notation for a two-unit chain containing one R and one S alanine moiety is shown in figure 1 which is used subsequently for the description of cyclopolypeptides.

The white circle stands for R and the crossed circle for S alanine residue while the arrow(→) pointing to the right and the arrow (←)

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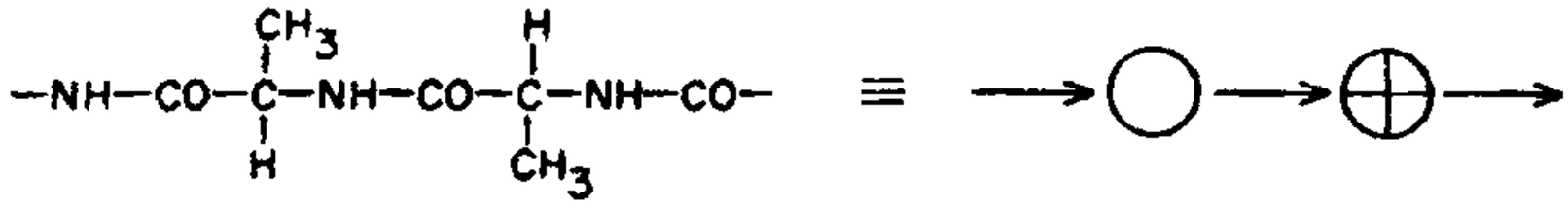

Figure 1.

pointing to the left stand for –NH–CO– and –CO–NH– respectively. The white circle and the crossed circle are mirror images of each other and so are the two arrows.

When the total number of alanine residues ($2n$) is two, only one arrangement is possible (R and S doubly linked through peptide chains) which is achiral since it contains an inversion centre (equivalent to an S_2 axis). When $2n$ is four, two cyclic arrangements are possible as shown in figure 2. The structure (I) with consecutive R and S has an inversion centre (S_2) and the structure (II) with alternate R and S has an S_4 axis* which may be seen in the detailed structure (Ia) and (IIa) respectively. Each of them is thus a single nonresolvable compound and the two are diastereoisomerically related.

When $2n$ is six, three different cyclic arrangements are possible. One in which three R and three S units are placed consecutively (structure not shown) has an inversion centre (S_2) similar to the structure (I) and so exists in a single meso form. The second one (III) (figure 3) with R and S placed alternately is also a meso-compound since it contains a S_6

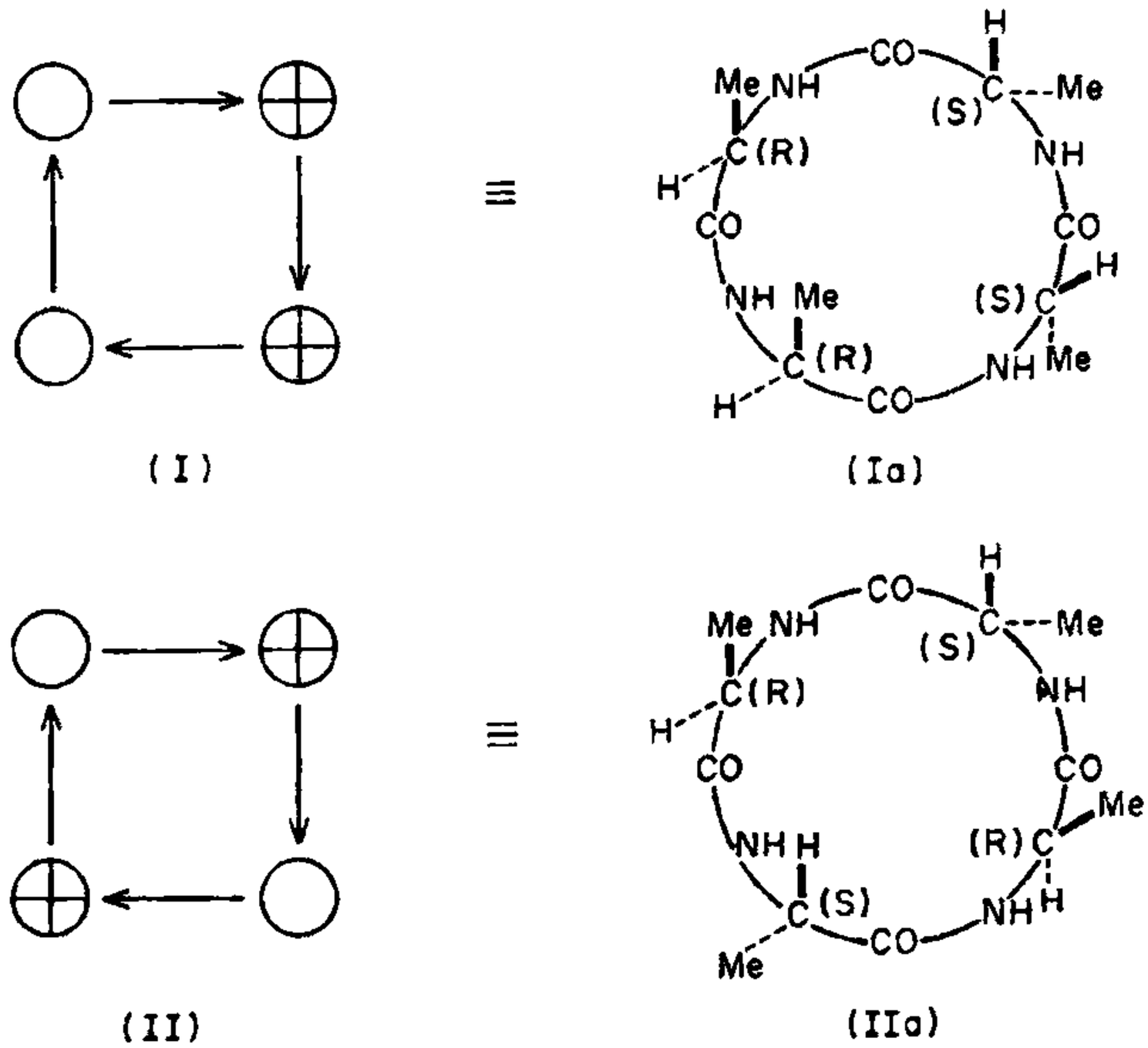

Figure 2.

*Because of the ring direction, these cyclostereoisomers cannot have mirror plane.

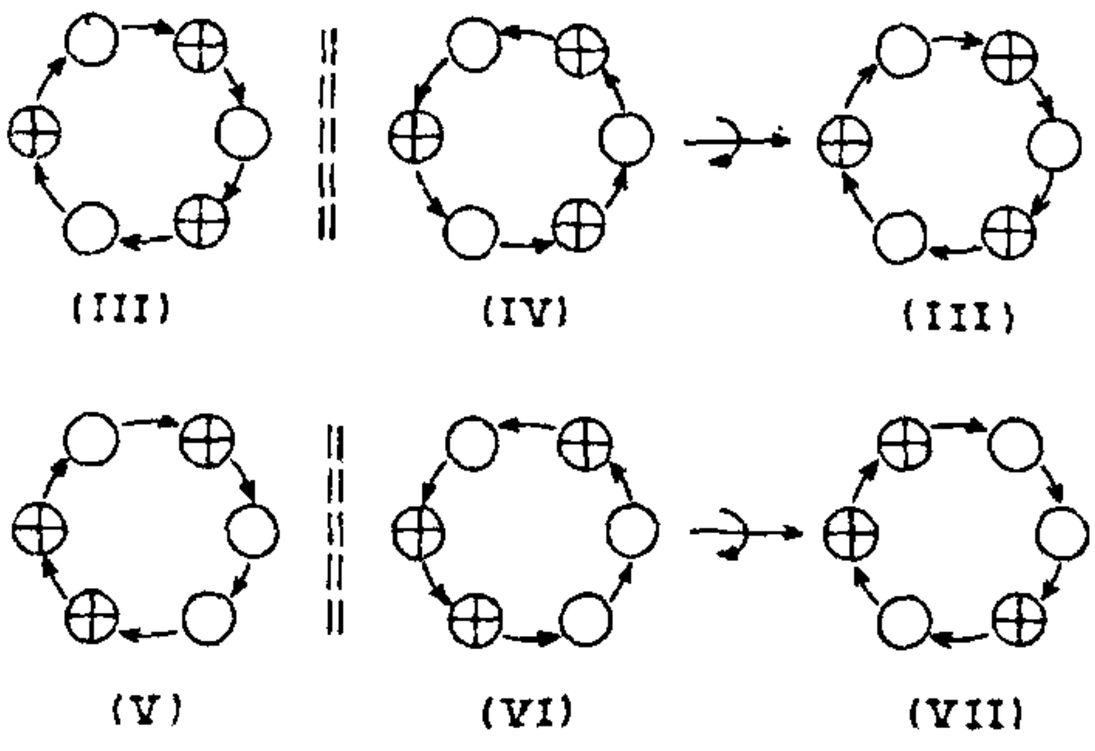

Figure 3. Cycloenantiomerism.

axis. Its mirror image (IV) seemingly different in ring direction can be made superimposable with the original by rotating the structure through 180° around the horizontal axis. The third arrangement (V) does not have any alternating axis of symmetry and is truly chiral belonging to point group C_1. Its mirror image (VI) has all the R and S units arranged in exactly the same way as in the original (V) but the ring direction is opposite. Thus the two cyclopeptides (V) and (VI) are related in a way that (i) they are *mirror images* of each other, (ii) have identical *chiral frameworks*, (iii) but have different *ring directions*. Such stereoisomers are called *cycloenantiomers* and the isomerism is known as *cycloenantiomerism*. Like true enantiomers, they possess identical properties and differ only in optical rotation which is equal but opposite for the two isomers. Thus cyclohexaalanine (V) with a clockwise ring direction has an $\propto_D^{23°}$ of $-25.5°$ while its cycloenantiomer (VI) has an $\propto_D^{23°}$ of $+22.2°$ (the small difference being due to imperfect purification). At first sight, it might seem odd that the cyclostereoisomers should have any optical rotation at all since there are as many R units as S in the ring cancelling each other's effect. However, the ring direction also contributes to the dissymmetry of the molecules and has its own inherent rotation. It may be noticed that a 180° rotation of VI around the horizontal axis leads to the structure (VII) which has the same ring direction as V but the chiral framework turns out to be nonsuperimposable.

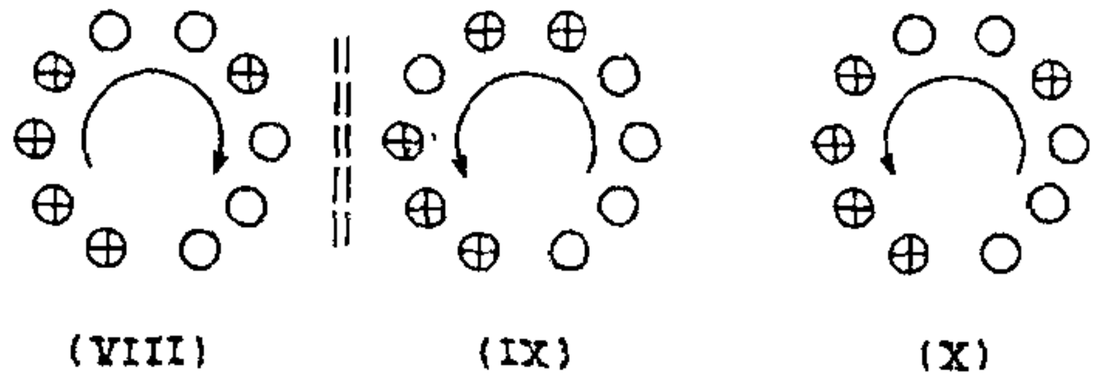

Figure 4. Cyclodiastereoisomerism.

As the value of $2n$ increases, the number of stereoisomers also increases and when $2n$ is ten, there occur four meso forms, six pairs of cycloenantiomers, and five pairs of enantiomers (a total of 26 stereoisomers). The structures (VIII) and (IX) represent an enantiomeric pair (figure 4) (the dotted vertical lines stand for mirrors). The structure (X) represents a member of another enantiomeric pair (the antipode is not shown). Inspection of the two structures (VIII) and (X) reveals that the chiral framework in each is the same but the ring directions are different. They are not, however, mirror images of each other and so cannot be cycloenantiomers. Instead they are called *cyclodiastereoisomers* and possess different properties like normal diastereoisomers despite the fact that they have superimposable chiral framework. The enantiomer of X is in turn cyclodiastereoisomeric with IX.

Characterization of pairs of cyclostereoisomers is thus made on the basis of *three* criteria, namely, the identity or nonidentity of the chiral framework, the ring direction, and the mirror image relationship as summarized in table 1.

Table 1 *Characterization of cyclostereoisomers*

Stereoisomers	Chiral framework	Ring direction	Mirror image relation	Example
Enantiomers	Different	Opposite	Yes	VIII & IX
Cycloenantiomers	Same	Opposite	Yes	V & VI
Cyclodiastereoisomers	Same	Opposite	No	VIII & X

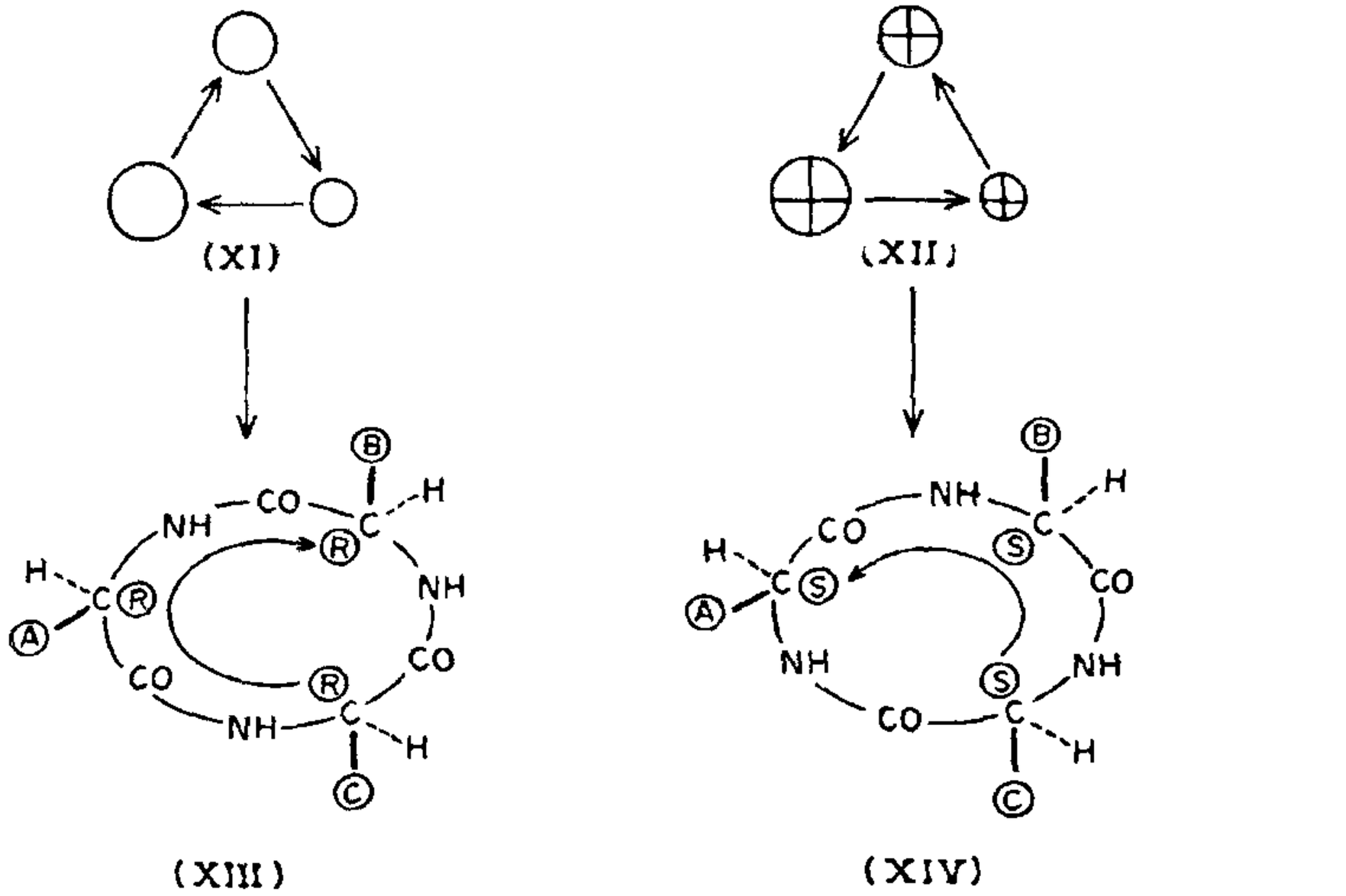

Figure 5. Retro-enantioisomerism.

Since the ring direction can be changed by rotating a structure around the horizontal axis, it is advisable to decide on the nature of cyclostereoisomerism first by keeping the ring directions of any two molecules opposite and then by applying the other two criteria. Any pair of compounds which are neither enantiomers, cycloenantiomers, nor cyclodiastereoisomers are diastereoisomers by default e.g. IX and X.

Yet another interesting type of cyclostereoisomerism is encountered in cyclopolypeptides and analogues consisting of two or more *different* chiral centres. If the configuration of each chiral unit and the ring direction are both reversed for a structure, a new structure results which is essentially a constitutional isomer of the original since the sequence C_1–NH–CO–C_2 has now been replaced by the sequence C_1–CO–NH–C_2, C_1 and C_2 representing two different chiral centres. Two such tripeptides (XI) and (XII) are shown in figure 5. The different circles refer to different aminoacid residues. Such pairs of compounds are called *retro-enantio-isomers*. They are of biological interest because one can effectively replace the other in a biological (enzymatic) reaction. This is due to the fact that both of them have the same relative disposition of the side chains and the same conformation of the peptide chain which will be clear from the two structures (XIII) and (XIV). Thus the antimicrobial activities of enniatin, an antibiotic cyclohexapeptide are almost identical with those of its retro-enantio-isomer[5,6]

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