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The Specification of Asymmetric Configuration in Organic Chemistry*

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This paper interprets, modifies, and extends a previous paper[4], which contained a certain proposal concerning the specification of asymmetric configuration, and will be cited in the sequel as Paper 1. The present paper is written in two Parts. In the First Part we explain the background of the proposal, and then illustrate its application to the most important organic type of optical isomerism, that referable to asymmetric atoms in the common sense. In the Second Part, we broaden the treatment sufficiently to permit application to all the more special types of optical isomerism which occur in organic chemistry.

First Part
The Sequence Rule and its Central Field of Application

(1) *Background of the Construction of a System for the Specification of Optical Configurations*

(1.1) *The Requirement of a General and Absolute System.* Systems for the specification of asymmetric configuration in organic chemistry have grown like islands of local government in a large semi-civilized country. For the most part, these local systems of specification, for example, the system of carbohydrate chemistry, work well internally. But such systems leave between them large areas unregulated. They may also grow to overlapping in certain regions, as have the carbohydrate and amino-acid systems; and then they sometimes produce inconsistent regulation. On these practical grounds, a case exists for having available an universal system. Such a system need not be allowed to disturb any local system in an area in which the latter is preserving good order. But a general system could provide for the unregulated areas; and it could be used to circumvent ambiguities caused by the overlapping of local systems.

A reason of principle can be given for having a general system. For the local systems grew up in a time when configurations could not be assigned otherwise than relatively. It has, indeed, been held that all that could be determined, concerning the configuration of an optically active molecule Cjklm, was whether, if the place of j were taken by a, that of k by b, of l by c, and of m by d, the dextro- or laevo-rotatory form would be produced of a selected reference substance Cabcd. But since any group can be replaced by any other by suitable processes, there can be no rational basis for generalizing any arbitrary set of genetic connexions, as of j with a, of k with b, etc. And therefore the type of molecule Cjklm that could be so linked with any one standard Cabcd was effectively limited to members of a series defined by a sufficiency of common features to furnish some unambigous principle of genetic correlation. Such a principle appears if the general molecule Cjklm is allowed to differ from the chosen standard Cabcd with respect to one group only. But as soon as the series is so broadened as to allow for differences in two groups, then alternative genetic connexions become possible, and the correlations of configurations becomes either arbitrary or ambiguous: e.g., one can derive Cabcd from Cablm by replacing l by c, and m by d, or alternatively, l by d and m by c; and thus one isomer Cablm can be converted into either isomer of Cabcd.

This was the situation, the more or less fatalistic acceptance of which has hitherto favoured the development of local systems of configurational specification. But this situation no longer exists: the methods are known by which the structure of an optically active molecule can be so determined as to require its representation, without need or room for convention, by a unique three-dimensional model[5]. We are therefore required to describe such a model uniquely, that is, to specify absolute configuration. Moreover the problem of specification presents itself as a general one: a system of absolute specification should clearly be a general system.

Thus our single problem is the construction of a system of specification that is at once general and absolute. And we have reasons of both convenience and principle for desiring to solve it.

(1.2) *Approach to the Construction of a System.* We have taken it as a fundamental requirement of the system to be set up that it should involve *only a few*

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[4] R. S. CAHN and C. K. INGOLD, J. chem. Soc. 612 (1951).

[5] J. M. BIJVOET, A. F. PEERDEMAN, and A. J. VAN BOMMEL, Nature *168*, 271 (1951); cf. review by WERNER KUHN, Z. Elektrochem. *56*, 506 (1952).

general rules, which can be formulated exactly, and express every arbitrary element that is to be admitted. This requirement indicates the inadvisability of many possible, and some attempted approaches; and it goes far towards defining the desirable method of approach. It leads immediately to three major prohibitions, as follows.

(i) The requirement calls for general rules. It therefore excludes all systems based on genetic assumptions. For, as noted above, no generally applicable rules can possibly be based on genetic relations, which by their nature cannot be rationalized.

(ii) Our requirement calls for a few, exact rules. It therefore excludes the description of molecular models indirectly through projection formulae. For no general system of projection can be framed, which is based on a small number of exact rules: only a great mass of conventions could *perhaps* resolve all the ambiguities which arise when one of the dimensions of matter is discarded. On a long view, we believe that this prohibition is to be welcomed; for projection formulae, from being good servants, tend to become bad masters, by denying us the practice through which we could (very easily at the appropriate age) have learned to think three-dimensionally with a facility which would be convenient to those who have to deal with structure. Projection, though useful for the expression of a finished thought, is inadequate as a vehicle of thought, especially as it often gives so poor a picture of the actual molecular geometry.

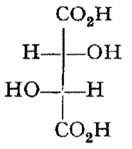
(iii) Our requirement calls for a system which explicitly includes all arbitrary elements in its own rules, and will not admit any arbitrary interference which it cannot control. It therefore precludes the making of configurational specification dependent on systems of nomenclature, or of nomenclatural enumeration; for such systems are essentially arbitrary, and are subject to alternative and changing conventions. Given a particular molecular model, we want its configurational specification to remain unchanged, even if the name of the substance should be rearranged, or the direction of the numbering in the name altered.

As an indication of the practical importance of these three prohibitions, the following illustrations are given of consequences which have arisen from their neglect.

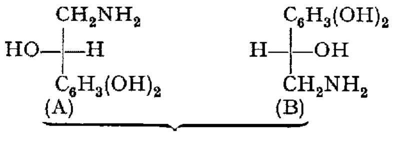
(i*a*) A simple example of the confusion which follows the introduction of genetic assumptions is presented by tartaric acid, form (I) having originally been termed *d* by Fischer, but subsequently L by those chemists who insisted on regarding it as a carbohydrate derivative.

(ii*a*) The difficulties inherent in the development of a system by way of projection formulae are well illustrated in McCasland's proposed system[6]. It involves 62 rules, preceded by 16 definitions. And yet the rules contain inadequately defined terms, whose meaning is nevertheless critical for general application. One such term is "fundamental chain". What, for example, is the "fundamental chain" in pentaerythritol esterified with four acids? The author's claim that "every stereoisomer in each set of stereoisomers has a unique [configurational] prefix" is obviously insubstantial, despite the 62 rules.

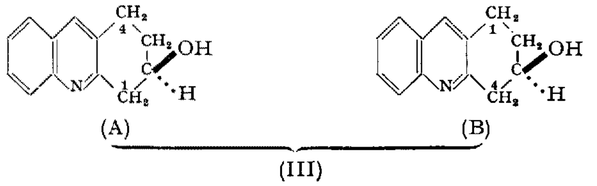
(iii*a*) The duplexity in configurational specification, which results from accepting dependance on nomenclatural convention may also be illustrated by reference to McCasland's system, which ties configurational specification to the direction of enumeration. The following three examples will show how this operates. Dalgliesh's compound (II) is L-3:4:β-trihydroxy-β-phenylethylamine, if named and numbered as in (IIA), but D-2-amino-1-(3:4-dihydroxyphenyl)-ethanol, if named and numbered after (IIB). The acridine derivative (III) is D, if numbered (IIIA) according to Richter and the Chemical Society, but L, if numbered (IIIB) according to the Ring Index. The symbols applying to the methyl*cyclo*hexanediol (IV) are all D or all L, according to whether the methyl group or a hydroxyl group is assigned the number 1.



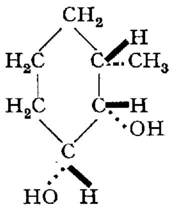
(I)



(II)



(III)



(IV)

This discussion shows that our demand for a system of stereochemical specification, *which shall be carried wholly on the conventions of a few general but definite rules*, practically determines the type of system which must be set up. For reasons which have been indicated under (ii), we have to describe the asymmetry of molecular models, not by way of projection formulae, but directly; and that means that we must order the groups on which asymmetry depends, and describe the *spatial* pattern traced by their sequence. For reasons given under (i) and (iii), we have to order the groups,

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[6] Available as a pamphlet at Chemical Abstracts, Ohio State University, Columbus 10, Ohio, and dated 1953.

not through the mediation of any external correlative, natural or artificial, such as a chemical transformation or a name, but directly by reference to permanent internal characters. It remains only to choose the characters. We have chosen, as chief reference character, the most basic one possible, that of atomic number. Subsidiary reference characters are introduced only as far as is necessary.

This principle, viz., that asymmetric configuration can be specified, by ordering groups on the basis of atomic number, and describing the spatial pattern of the resulting sequence, was the central idea of Paper 1, where it was formulated and illustrated for the class of organic molecules in which dissymmetry depends only on asymmetric atoms.

(1.3) *Development of a General and Absolute System.* In building a system from this starting point, we have attempted to fulfil the following requirements:

(a) The general system should be generally applicable in organic chemistry, and adaptable, as and when required, to inorganic chemistry.

(b) Its descriptions should in each case refer to a definite molecular model, which, when connected with an individual substance, defines its absolute configuration.

(c) Its descriptions should be sufficiently brief for use in naming stereoisomers.

(d) Descriptions by the general system should be incapable of confusion with those given by any local system of proved and continuing usefulness.

These aims are modified from those which guided Paper 1, first as regards (a), and secondly, with reference to (b), (c), and (d) in combination.

As to (a), Paper 1 showed that a system based on the principles described could be formulated with precision; but it did not claim to demonstrate generality, inasmuch as the discussion was essentially confined to dissymmetry dependent on asymmetric carbon atoms. In this paper, we shall take reducibility to exact formalism as having already been sufficiently illustrated; but we shall go further than before towards showing that the system developed can meet all conceivable demands. In particular, we shall show that it covers all the known types of asymmetry and pseudoasymmetry which lead to stable isomerism in organic chemistry, or, more generally, in structures of atoms of covalency up to 4. In order not to lengthen the paper unduly, we shall stop here, though we could at this time go on to show how conformational differences can be covered, as well as the stereoisomerism of inorganic structures involving atomic covalencies up to 6.

As to what is to be described, and in what terms, (b), (c), and (d) involve changes made advisable by recent experimental advances. When Paper 1 was written, it was impossible to determine absolute configuration; therefore the general system, like any local system, had to specify relative configuration; and therefore the specifying symbols were made to agree as closely as possible with those of local systems. However, the general system was put into a form that looked ahead to its eventual use in specifying absolute configuration, when that should become possible. Now that this has happened in less time than was foreseen, it seems wise, (1) to restrict the general system to the specification of absolute configuration, and (2) to introduce new and distinctive symbols, which shall be understood to denote absolute configuration (proved or presumed), and be allowed no other significance.

(2) *General Procedure for the Specification of Configuration*

(2.1) *Summary of the Method.* The discussion in this paper will be restricted to dissymmetry which is dependent on the spatial arrangement of up to four groups, either about an asymmetric atom, or about some general type of frame. If the system actually contains only three such groups, we can add a fourth, in the form of an imaginary atom of atomic number zero, and thus retain a common procedure based on four groups. This procedure involves three steps:

(A) The four groups are first ordered in a priority sequence, according to a formula known as the *sequence rule*. This rule is divided into several sub-rules, of which one is of central importance, whilst others may have to be brought in, e.g., for the purpose of dealing with some of the more subtle kinds of non-equivalence among groups.

(B) The sequence having been determined, we have to note whether it describes a right- or left-handed pattern on the molecular model, as viewed according to an instruction called the *conversion rule*. Alternatively, a mnemonic can be set up, by which the pattern can be thus classified without the necessity of visualizing the model.

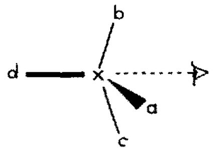
(C) The pattern having been classified as right- or left-handed, we assign to the asymmetric atom or frame an *absolute-configuration label*. We shall use two types of label, according as asymmetry or pseudoasymmetry is being classified.

It is convenient to discuss these steps in backward order.

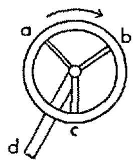
(2.2) *Absolute-configuration Labels.* The suggested indications for asymmetry leading, under the sequence and conversion rules, to a right- and left-handed pattern, are capital italic R and S, respectively, where R derives from the Latin *rectus*, meaning "right", and S from *sinister*. This last word means "left" not only in Latin: it appears with that significance in several modern languages: and, although in English its common meaning is the symbolic derivative, "of evil omen", in a few special uses it retains its original meaning of "left"

For the description of pseudo-asymmetric atoms, it is proposed to employ the corresponding lower-case italic symbols, *r* and *s*.

As to the use of these symbols in the naming of stereoisomers, a further change from Paper 1 is proposed. In that paper, configurational symbols were often mixed with the names of the substances. Thus the configuration assigned to Reichstein's substance K was described by the name *allo*pregnane-3*S*:17*R*:20*R*:21:tetraol, if we translate into absolute-configuration symbols, but otherwise retain the original form of the name. There is a double use of numbers here, which is not conducive to clear thinking. Consider, for example, the number 3: it is 3-C, which is *S*; also, one of the hydroxyl groups is 3-ol; but this 3-OH, though important, is no more important than the 3-H, or than certain other carbon atoms, in determining the classification of 3-C. It is obviously better to use numbers in one way at a time; and this we can do, if we separate completely the configurational description, as a parenthetic prefix, from the name of the substance as this would appear without configurational symbolism. In this new form, the name illustrated becomes (3*S*:17*R*:20*R*)-*allo*pregnane-3:17:20:21-tetraol; and we think that such a repetition of numbers is justified by the increased clarity.



(V)



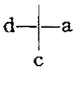
(VI)

With the specific indications of the typography, as well as the brackets, and, in practically all real cases, the context, there seems to be no chance that the stereochemical symbol *S* could be mistaken to mean sulphur-bound. This would be nearly as difficult as to mistake D-glucose as meaning a deuterated form of that sugar.

(2.3) *The Conversion Rule.* The four groups in an assemblage Xabcd having been ordered in the priority a, b, c, d, the conversion rule states that their spatial pattern shall be described as right- or left-handed according as the sequence a → b → c traces a right- or left-handed turn, when viewed from an external point on the side remote from d. A right-handed arrangement is shown at (V).

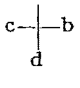
Motorists will often have before them a model which may facilitate the application of this rule. The groups a, b, c are placed at the ends of the spokes of the steering wheel, and group d at the foot of the steering column. A right- or left-handed sequence a → b → c on the wheel represents a right- or left-handed arrangement in the molecular model. A right-handed arrangement is shown at (VI).

It may be convenient on some occasions to read absolute configurations from Fischer projections without first decoding the latter. This can be done by a mnemonic, based on the principle that one exchange of a pair of groups inverts configuration, and therefore an even number of such exchanges does not change configuration. An even number of exchanges may nevertheless change the projection, because a single form, e.g., *R*, of Xabcd has 12 equivalent Fischer projections, and its enantiomer another 12.



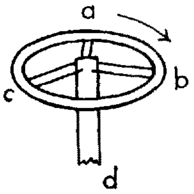
$$\begin{array}{c} \mathrm{b} \\ \mathrm{d}-\!\!\!+\!\!\!-\mathrm{a} \\ \mathrm{c} \end{array}$$

(VII)

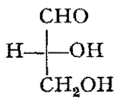


$$\begin{array}{c} \mathrm{a} \\ \mathrm{c}-\!\!\!+\!\!\!-\mathrm{b} \\ \mathrm{d} \end{array}$$

(VIII)



(IX)



$$\begin{array}{c} \mathrm{CHO} \\ \mathrm{H}-\!\!\!+\!\!\!-\mathrm{OH} \\ \mathrm{CH_2OH} \end{array}$$

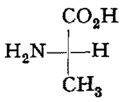
(X)

The mnemonic is this: *Transform the given Fischer projection by an even number of exchanges of pairs of groups, so that* d *occupies the bottom position, and, on the transformed projection, read the pattern* a → b → c *as R or S.* If d is already at the bottom in the given projection, no exchange is needed, and our instruction still covers the case, because zero is an even number. If d is not already at the bottom, then two exchanges are the fewest that can place it there without alteration in the configuration represented. Thus, if the given projection is (VII), we must exchange c with d, in order to bring d to the bottom, and then, without further disturbing d, we have to exchange any available pair of groups, say, a with b. Thus we obtain the equivalent projection (VIII), in which the pattern a → b → c is evidently *R*. The correctness of the procedure of reading the pattern *directly on the projection* can be seen by superposing the latter on the steering-wheel model (IX).

The usual projection of D-glyceraldehyde, which is also (*R*)-glyceraldehyde, is (X). The sequence-rule order of the groups is OH, CHO, CH_2OH, H. Therefore the projection is in the same form as (VII), which, as we have seen, represents an (*R*)-form.

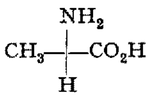
It is essential to the Fischer system of projection that groups projected to left and right are nearer the observer than groups projected in the top and bottom positions. That is the reason why we can superpose the Fischer projection (VIII) directly on the steering-wheel model (IX). It is therefore important for the application of our mnemonic, not to mistake for Fischer projections the superficially similar, but actually irregular, projections, which are sometimes seen. For example, the projection (XI) is the usual Fischer projection for L-alanine, which is also (*S*)-alanine. But in order to save space, such diagrams are sometimes turned through a right angle as at (XII). Clearly,

(XII) is not a Fischer projection, because it breaks the Fischer convention. The simplest way of dealing with an irregular projection, such as (XII), is to re-convert it into a Fischer projection, such as (XI), by a suitable rotation, before applying the mnemonic.



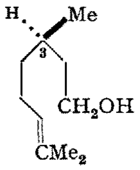
$$\begin{array}{ccc} & CO_2H & \\ H_2N & - & H \\ & CH_3 & \end{array}$$

(XI)

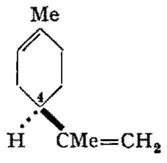


$$\begin{array}{ccc} & NH_2 & \\ CH_3 & - & CO_2H \\ & H & \end{array}$$

(XII)



(XIII)



(XIV)

Many molecules are not customarily or conveniently represented by projections; but they can still be classified by the use of the steering-wheel model. Thus formula (XIII) for (+)-citronellol is seen to represent (*R*)-citronellol, because, with 3-H placed down the steering column, the groups around the wheel, in sequence-rule order, are

$$CH_2CH_2OH,\ CH_2CH_2CH{=}CMe_2,\ CH_3.$$

Again, formula (XIV) for (+)-limonene represents (*R*)-limonene, because, when 4-H is placed down the steering column, the groups on the wheel, in order, are

$$CMe{=}CH_2,\ CH_2CH{=}C<,\ CH_2CH_2-.$$

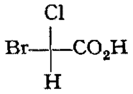
(2.4) *The Sequence Rule: Basic Idea with Examples.* The central part of the sequence rule prescribes that groups about an asymmetric atom shall be arranged in order of decreasing atomic number of the atoms by which they are bound to it[7]; and that if the relative priority of two groups cannot be thus decided, it shall be determined by a similar comparison of the atomic numbers of the next atoms in the groups, or, if this fails, of the next: so one works outwards, always first towards atoms of higher atomic number, and from atoms of higher atomic number, where there is any choice, until a decision is obtained. Octet valency structures, unique, or most stable, or, if there is still a choice, to give most rapid ordering, are assumed; and when a double or triple bond is encountered, the atom at its more remote end is regarded as duplicated or triplicated; moreover, octet-forming atoms are considered to be 4-co-ordinated, by the imaginary attachment to them as far as necessary, of atoms of atomic number zero. This procedure, which, as was shown in Paper 1, is completely unambiguous, will enable four, or indeed any required number of constitutionally different groups to be arranged in order. Some examples, involving asymmetric carbon and nitrogen atoms, Cabcd, and Nabc, will now be given.

The simplest case may be exemplified by bromochloroacetic acid (XV). Priority of the groups (a, b, c, d) is here determined simply by the atomic numbers as Br, Cl, C (of CO_2H), H. Hence, by the conversion rule (or by use of the steering-wheel model) formula (XV) represents an (*R*)-form.

More usually in organic chemistry, at least two groups are bound to the asymmetric atom by carbon atoms. It is then necessary to work outwards from these carbon atoms in order to determine priorities. Some examples of this situation follow.

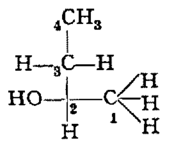
In (−)-butan-2-ol (XVI), the O atom has highest priority and the 2-H atom the lowest. It remains to order C_1 and C_3. But C_3 is bound to (C_4, H, H) and C_1 to (H, H, H): and therefore C_3 has the higher priority. Hence the complete order is OH, Et, Me, H; and, by the conversion rule, the represented form is (*R*)-butan-2-ol.

In dextrorotatory amyl alcohol (XVII), the 2-H atom takes last place, and ethyl precedes methyl as before. It remains to place the hydroxymethyl group. But its carbon carries (O, H, H), whilst the corresponding carbon of ethyl carries (C, H, H); and therefore hydroxymethyl precedes ethyl. It follows that the complete order is CH_2OH, Et, Me, H; and that the molecule formulated is (*R*)-2-methylbutan-1-ol.



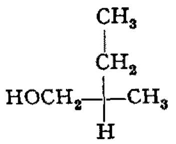
$$\begin{array}{ccc} & Cl & \\ Br & - & CO_2H \\ & H & \end{array}$$

(XV)



$$\begin{array}{ccc} & {}_4CH_3 & \\ & H-{}_3C-H & \\ & | & \\ HO & -_2- & {}_1C\begin{smallmatrix}H\\H\\H\end{smallmatrix} \\ & H & \end{array}$$

(XVI)



$$\begin{array}{ccc} & CH_3 & \\ & CH_2 & \\ HOCH_2 & - & CH_3 \\ & H & \end{array}$$

(XVII)

This simple principle suffices for the classification of many more complex examples. As mentioned above, the sequence of groups about C_3 in citronellol (XIII, p. 85) is CH_2CH_2OH, $CH_2CH_2CH{=}CMe_2$, CH_3, H. The reasons are just as for the amyl alcohol, except that we have to work outwards by yet one more carbon atom in order to arrange the first two groups: $\cdot CH_2CH_2O$ precedes $\cdot CH_2CH_2C$. Citronellal and some related compounds have already been formulated according to the sequence rule (but using the earlier symbols D and L)[8].

Ring structures may be dissected in order to exhibit what is bound to an asymmetric atom by each of its four bonds. Thus in (−)-car-3-ene (XVIII), atom 1, as the dissection (XIX) shows, carries quaternary C_7, tertiary C_6, secondary C_2, and H. This is the priority order; and the pattern 7 → 6 → 2, as seen on the side remote from the H atom, i.e., from above the formula, determines that the configuration of C_1 is *S*. Similarly, for atom 6, as dissection (XX) shows, the groups in

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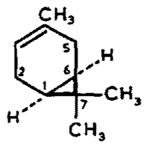
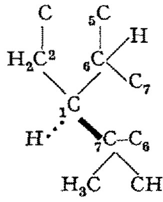
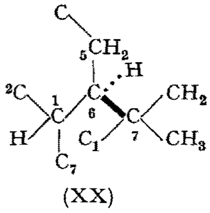
[7] Essentially the same rule, giving all the same configurational assignments, would result if we should require the groups to be arranged in a sequence of increasing atomic numbers. Only in order to avoid duplicated or alternative descriptions in the working out of examples, do we choose here always to work with a particular one of the two completely equivalent methods; and arbitrarily we select that which uses the sequence of decreasing atomic numbers. However, no convention on the point is necessary (or needs to be remembered): either procedure, consistently applied, will give the same answers.

[8] B. Riniker, D. Arigoni, and O. Jeger, Helv. chim. Acta *37*, 546 (1954).

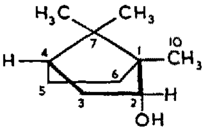
sequence are C_7, C_1, C_5, H; and the pattern 7 → 1 → 5, viewed from above, shows that the configuration of C_6 is *R*. Hence this carene is (1*S*:6*R*)-car-3-ene.

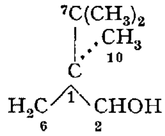

(XVIII)

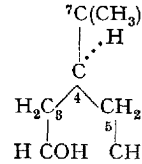

(XIX)

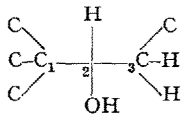

(XX)

It has been mentioned that, in working outwards along groups in order to determine their priorities, one follows the routes of highest atomic numbers. This may be exemplified by an analysis of (−)-borneol, represented by (XXI). Bound to C_1 (dissection XXII) we have quaternary C_7, secondary but OH-substituted C_2, secondary C_6, and primary C_{10}. It is to be noted that secondary but substituted C_2(O, C, H) has priority over quaternary C_7(C, C, C), because, by following the route of highest atomic numbers, priorities are determined by the difference appearing earliest among corresponding atoms in these parentheses, i.e., by the difference in the first atoms, O and C. The complete sequence is thus C_2, C_7, C_6, C_{10}; and, as (XXII) shows, the pattern 2 → 7 → 6 is *S*.


(XXI)


(C_1 seen from C_4)
(XXII)

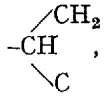

(C_4 seen from C_1)
(XXIII)


(C_2 seen form C_5)
(XXIV)

Bound to C_4 (dissection XXIII) are quaternary C_7, two secondary groups C_3 and C_5, and H. Here the quaternary group C_7(C, C, C) precedes either secondary, e.g., C_3(C, H, H), as is again determined by the earliest difference, that between atoms second in these parentheses. But, in order to obtain a distinction between the secondary groups C_3(C, H, H) and C_5(C, H, H), we have to work one more atom along either, thus finding that $CH_2CH(OH)$– precedes CH_2CH_2–, i.e., that C_3 precedes C_5. The complete order is therefore C_7, C_3, C_5, H; and as (XXIII) shows the pattern 7 → 3 → 5 is *S*. For C_2, the sequence is OH, quaternary C_1, secondary C_3, H; and the arrangement of these groups is *R* (dissection XXIV). So (−)-borneol is the (1*S*:2*R*:4*S*)-compound.

The procedures illustrated suffice without elaboration for the analysis of many more complicated ring compounds than those so far mentioned, e.g., the *allo*-pregnanetetraol discussed in Paper 1.

It has been mentioned that when, on working outwards through a group for the purpose of assigning its priority, a double bond is encountered, the atom at its further end is considered to be duplicated. Thus $-CH{=}CH_2$ counts as



$$-CH\begin{matrix}\diagup CH_2\\ \diagdown C\end{matrix},$$

and therefore takes priority over $-CH_2-CH_3$, or indeed over any higher primary alkyl group, such as

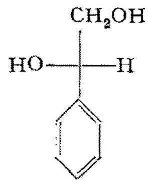
$$-CH_2CH(CH_3)_2,$$

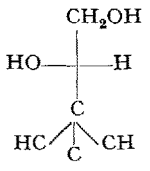
through not over a real secondary group, such as

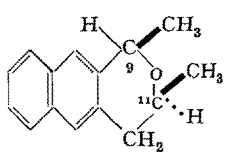
$$-CH(CH_3)_2 \text{ or } -CH<[CH_2]_5.$$

For many ethylenic compounds, this will make no difference to the analysis leading to their stereochemical classification, as, indeed, it does not in the already treated examples, citronellol and car-3-ene. But for some other ethylenic compounds, it determines classification. Such a case is limonene, the (+)-form of which is represented by (XIV) on p. 85. Just as $CH{=}CH_2$ precedes CH_2CH_3, so also $CH_2CH{=}C$ precedes CH_2CH_2C. Thus, the sequence of the groups about C_4 is $CMe{=}CH_2$, $CH_2CH{=}C$, CH_2CH_2C, H; and formula (XIV) represents the (*R*)-form.

The use of valency structures, and the duplication procedure, jointly determine that an aryl carbon is to be treated as carrying three carbon atoms. Thus the first carbon of a simple phenyl group would count as ·C(CH, CH, C). (+)-Phenylethane-1:2-diol has the configuration (XXV); and it has been classified[9] by the sequence rule as having the (*S*)-configuration, analysis being according to (XXVI). Natural (+)-eleutherin has configuration (XXVII), and has likewise been classified[10], in accordance with dissection (XXVIII), as the (9*R*:11*S*)-form. Its three stereoisomers have been assigned as having the (9*R*:11*R*)-, (9*S*:11*R*)-, and (9*S*:11*S*)-configuration.


(XXV)


(XXVI)


(XXVII)

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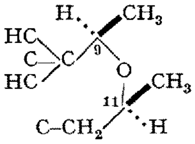
[9] V. PRELOG, M. WILHELM, and D. BRUCE BRIGHT, Helv. chim. Acta *37*, 221 (1954).

[10] H. SCHMID and A. EBNÖTHER, Helv. chim. Acta *34*, 1043 (1951).

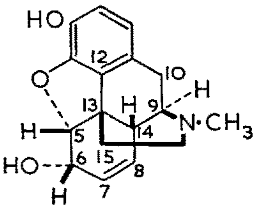


(XXVIII)

The duplication procedure in its application to the aryl group plays no important part in these particular assignments, but in other cases it is essential for a complete stereochemical specification. Such a case is natural (–)-morphine, R. K. Bentley and H. M. E. Cardwell's configuration for which[11] is shown at (XXIX). There are five asymmetric atoms, and the analysis is as follows:

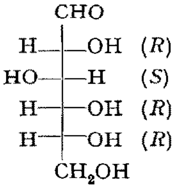
C_5	Sequence:	O, C_6(O, C, H), C_{13}(C, C, C), H
	Conversion:	O → 6 → 13 (from below) = *R*
C_6	Sequence:	O, C_5(O, C, H), C_7(C, C, H), H
	Conversion:	O → 5 → 7 (from below) = *S*
C_9	Sequence:	N, C_{14}(C, C, H), C_{10}(C, H, H), H
	Conversion:	N → 14 → 10 (from above) = *R*
C_{13}	Sequence:	C_5(O, C, H), C_{12}(C, C, C), C_{14}(C, C, H), C_{15}(C, H, H)
	Conversion:	5 → 12 → 14 (from below) = *S*
C_{14}	Sequence:	C_9(N, C, H), C_{13}(C, C, C), C_8(C, C, H), H
	Conversion:	9 → 13 → 8 (from below) = *R*.

Natural morphine is therefore the (5*R*:6*S*:9*R*:13*S*:14*R*)-form. The duplications here are among the atoms carried by C_7 in the sequence for C_6, among those carried by C_{12} in the sequence for C_{13}, and among those borne by C_8 in the sequence for C_{14}. Of these duplications, the first and third do not affect the specification, but the second is essential to it.

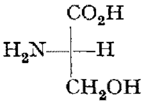


(XXIX)

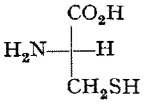
(XXIX)



(XXX)

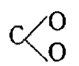


(XXXI)



(XXXII)

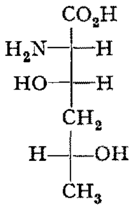
The atom-duplication procedure as applied to carbonyl involves treating C=O as



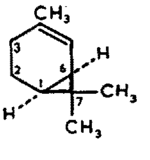
so that CHO counts as C(O, O, H) and CO_2H as C(OH, O, O). Thus is determined the order of the groups CHO and $CH_2 \cdot OH$ of glyceraldehyde, the full sequence for which is OH, CHO, CH_2OH, H; and so D-glyceraldehyde becomes (*R*)-glyceraldehyde (X, p. 84). Other carbohydrates can be treated similarly: D-glucose has the absolute-configuration symbols shown at (XXX).

L-Serine is equally (*S*)-serine (XXXI). The relative and absolute configurational symbols of many amino-acids similarly correspond; but this is not the universal rule, and L-cysteine, which is (*R*)-cysteine (XXXII), is a notable exception.

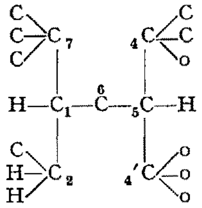
As remarked earlier, the carbohydrates and the amino-acids are fields which have their own, internally satisfactory systems for the specification of configuration. Ambiguities arise only round the peripheries of these domains, or where they overlap. Here our universal system could help, since it has no ambiguities deriving from questions of range or from rival desired correlations. Thus the still disputed symbolism for dextrorotatory tartaric acid (I, p. 82) could be resolved by naming it (*RR*)-tartaric acid. The aminohydroxy-acid (XXXIII) could conveniently be described as the (2*S*:3*S*:5*R*)-form. Again, a satisfactory internal scheme of configurational notation has been devised for the basic ring-system of the steroids. But the present universal scheme could still resolve the ambiguities, which appear around the junctions with that ring-system, of furan and pyran attachments, and arise from the use there of conflicting sets of symbols.



(XXXIII)



(XXXIV)



(XXXV)

It is a part of our procedure that all octet-forming atoms, i.e., all atoms but hydrogen, are imagined to be 4-co-ordinated by the addition as necessary of phantom atoms of atomic number zero. Such imaginary additions very often have no effect on the stereochemical specification of asymmetric carbon atoms, and that is why they have not been mentioned in the preceding examples. However, the phantom atoms are occasionally required in order to provide the contrast of atomic numbers needed to complete a specification. As an example, we may take (–)-car-4-ene (XXXIV). Its configuration at C_1 is *S*, just as for the already considered (–)-car-3-ene. But the determination of its configuration at C_6 requires our full procedure, without abbreviation. Of the groups about C_6, the first in sequence is obviously quaternary C_7, and the last is the H atom. The two "tertiary" groups C_1(C_7, C_2, H) and C_5(C_4, C_4', H) remain to be ordered. Of the attachments to C_5, the atom C_4 is considered to be duplicated in C_4';

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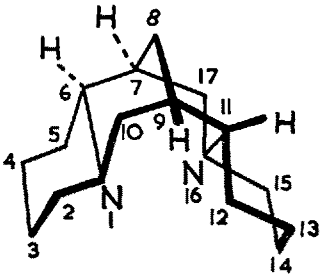
[11] We are grateful for this information before its publication [J. chem. Soc. 3252 (1955); *cf.* M. Mackay and D. C. Hodgkin, J. chem. Soc. 3261 (1955)].

and now, in order to conserve 4-co-ordination, C_4 must be supplied with one phantom atom and C_4' with three (all marked o in the dissection XXXV). The ordering of C_1 and C_5 depends on that of the first in sequence of their attachments, viz., C_7 and C_4; and this order is determinate, in that, apart from balancing groups, C_7 carries C, whilst C_4 carries o: these carried atoms provide the required distinction in atomic number. Thus C_1 precedes C_5. The pattern 7 → 1 → 5, from above, is *R*; and therefore (XXXIV) represents (1*S*:6*R*)-car-4-ene.



(XXXVI)

The imaginary atom of atomic number zero plays an essential part in the procedure for specifying the configuration of tercovalent nitrogen. For the phantom atom, which must be added to its unused co-ordination site, comes last in the sequence of groups, and hence, by the conversion rule, prescribes the aspect from which the pattern of the other groups is classified. This may be illustrated by the α-*iso*sparteine represented[12] by formula (XXXVI). Both ring junctions are *trans*, with the tertiary H atoms at C_6 and C_{11} on the side of the methylene bridge C_8, and therefore the imaginary atoms at N_1 and N_{16} are on the opposite side, i.e., that at N_1 approximately towards C_{14}, and at N_{16} towards C_3. The sequence of groups about N_1 is C_6, C_{10}, C_2, o; and since this must be viewed from the side away from the imaginary atom o, the configuration of N_1 is *R*. That of N_{16} is similarly *R*. The sequence about C_6 is N_1, C_7, C_5, H; and this must be viewed from the side away from H; hence C_6 is *R*. Similarly, C_{11} is *R*. The sequence about C_7 is C_6, C_{17}, C_8, H; this must be viewed from the neighbourhood of C_9; and hence C_7 is *S*. Similarly C_9 is *S*. Therefore the α-*iso*-compound represented may be given the fully descriptive title (1*R*:6*R*:7*S*:9*S*:11*R*:16*R*)-sparteine.

Second Part.
Generalization of the Sequence Rule and More Special Applications

Though the centre-piece of the sequence rule is described in the preceding Part, certain additions to it are necessary in order to cope with the full degree of generalization we wish to cover. Asymmetry can arise when some of the four groups are only stereochemically different, or only isotopically different, or even when they are not different at all if suitable differences characterize their spatial relations to each other. Obviously we must supplement the criterion of atomic number by some auxiliary criteria for the purpose of ordering such groups as these. Formally, we deal with this situation by describing the rule of atomic numbers as sub-rule 1 of the sequence rule. In note form, it is as follows[7]:

Higher atomic number precedes lower
(Sub-rule 1)

We can now add other sub-rules, as far as is necessary for dealing with the types of case indicated above. Such sub-rules are introduced in the following three Sections.

(3) *Asymmetry and Pseudo-asymmetry dependent on Stereochemical Differences between Groups*

(3.1) *Types of Stereochemical Difference.* In a molecule Xaa'bc, if a and a' are identical but for a stereochemical difference, X will have properties of asymmetry or pseudo-asymmetry, which increase the total number of forms of the molecule.

If a and a' are not enantiomeric, then X will be asymmetric in essentially the ordinary sense. It will be associated with optical activity, and its presence will lead to additional isomers under the same general rules as would apply to any asymmetric tetrahedral atom. We shall be able to specify all isomers of Xaa'bc, if we can completely order the groups aa'bc, and thus classify the asymmetric atom X as *R* or *S*.

If a and a' are enantiomeric then X will be only pseudo-asymmetric. It cannot lead to, or even be associated with, optical activity; but since there are two possible arrangements of the surrounding groups, it will produce an increased number of optically inactive isomers. We can specify all the inactive forms, if we can completely order the groups aa'bc, and can thus classify the pseudo-asymmetric atom as *r* or *s* (cf. Section 2.2).

Sub-rule 1 will not distinguish between a and a'. These groups must therefore be ordered by means of their stereochemical differences, which may be (i) geometrical, (ii) enantiomeric, or (iii) that combination of these characters which appears in alicyclic structures.

(3.2) *Geometrical Differences.* The sub-rule we shall introduce in order to take care of stereochemical differences of a geometrical kind between a and a' is simply

cis procedes trans (Sub-rule 2)

This sub-rule encounters the problem that no sufficiently general rule for assigning *cis* and *trans* labels to the geometrical relations between two pairs of groups,

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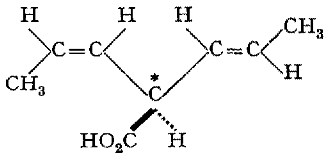
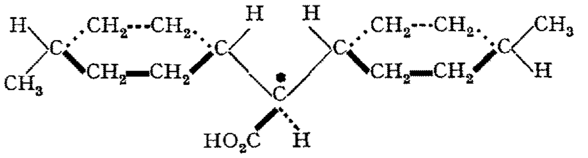
[12] M. Przybylska and W. H. Barnes, Acta Cryst. *6*, 377 (1953).

kj and lm, has yet been given. We therefore propose to make this assignment for our purposes by allowing the sequence rule itself to select its preferred group k from the pair kj, and its preferred group l from the pair lm: then, according as the sequence-rule-selected groups k and l are *cis-* or *trans-*related in the usual sense, we can describe the configuration of the whole assembly, kjlm, as *cis* or *trans*. It is to be emphasized that this procedure is adopted only as a working tool of temporary use in the application of sub-rule 2: its geometrical labels do not appear in our final stereochemical assignments, and need not have any effect on the standard nomenclature of geometrical isomers[13].

Consider the examples (XXXVII) and (XXXVIII):



(XXXVII)



(XXXVIII)

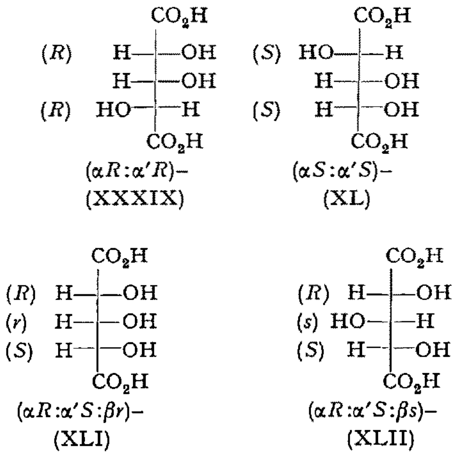
In both, the carbon atom marked with an asterisk (i.e., the atom X of Xaa'bc) is asymmetric, inasmuch as the propenyl or 4-methyl *cyclo*hexyl groups on either side of it (the a and a' of Xaa'bc) are geometrically different, that to the left being *cis*, and that to the right *trans*, according to our procedure for assigning these labels. It follows by sub-rule 2 that the group to the left precedes the group to the right; and then it follows by the conversion rule that the carboxyl-bearing carbon atom in these examples is *R*.

(3.3) *Enantiomeric Differences.* For the treatment of such differences we introduce the sub-rule

R precedes S (Sub-rule 3).

This sub-rule is required only when a pseudo-asymmetric configuration is being considered.

The classic case is that of αα'β-trihydroxyglutaric acid. There are four forms. In two of them [the enantiomers (XXXIX) and (XL) below], the α- and the α'-carbon atom (a and a') are either both *R* or both *S*, so that the β-carbon atom is not asymmetric or pseudo-asymmetric. In the other two [the irresolvable compounds (XLI) and (XLII)], one of the atoms α and α' is *R* and the other *S*, so that the β-atom is pseudo-asymmetric. Its configuration can be assigned by sub-rule (3).



(αR:α'R)-(XXXIX) (αS:α'S)-(XL)

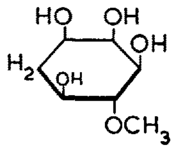
(αR:α'S:βr)-(XLI) (αR:α'S:βs)-(XLII)

αα'β-Trihydroxyglutaric acids

Application to more complicated open-chain cases of pseudo-asymmetry is straightforward. Thus in (XLIII) the configuration of the CHMe group, when pseudo-asymmetric, will be determined by those of the two CH(OH) groups.

$$HO_2C\,CHClCH(OH)\,CH_2CHMeCH_2CH(OH)\,CHClCO_2H$$

(XLIII)



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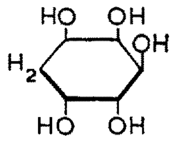

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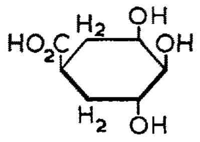
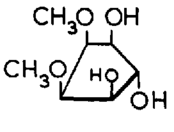


(XLVI)



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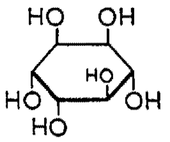

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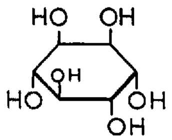
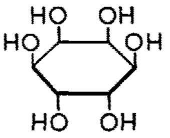
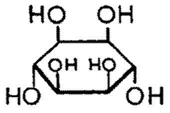


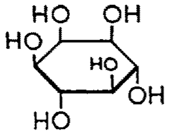
(XLIX)



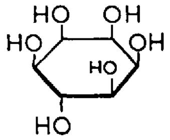
(L)



(LI)



(LII)



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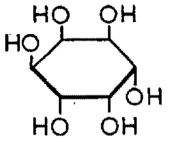
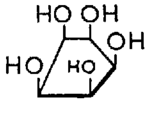


(LIV)



(LV)

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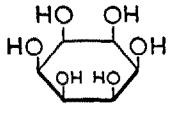
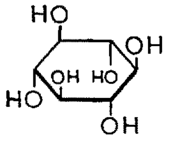
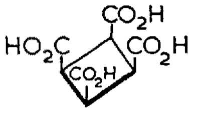
[13] On the other hand, there is no generally accepted, comprehensive principle for the nomenclature of *cis-trans*-isomers, but one could be developed by using the sequence rule as indicated, if that were thought desirable.



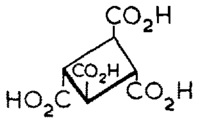
(LVI)



(LVII)



(LVIII)



(LIX)

(3.4) *Alicyclic Structures.* Consider the examples (XLIV)–(LIX), in the formulae of which tertiary hydrogen atoms are omitted.

In (XLIV), all the ring atoms can be labelled *R* or *S* with the aid of sub-rule (1) alone; but this is not true of the other examples. For (XLV) and (XLVI) sub-rules (1) and (2), and for (XLVII) sub-rules (1) and (3) are required. After this, sub-rule (1) does not help, but (XLVIII) and (XLIX), which are enantiomers, and likewise (L), can be labelled on the basis of sub-rule (2) alone, whilst (LI)–(LIV) require sub-rules (2) and (3). However, (LV)–(LIX) cannot be labelled by any of the preceding sub-rules.

This inability of certain stereoisomers in the alicyclic series to receive distinctive labels from the sequence rule is peculiar to monocyclic rings $(\mathrm{Xab})_n$, e.g., to alicyclic rings $(\mathrm{Cab})_n$ composed *entirely* of identical units Cab. If in this case *n* is odd, then one isomer, e.g., (LV), in general, that having all like-groups *cis*, and thus having an *n*-fold axis of symmetry, cannot be labelled; and if *n* is even, two isomers, e.g., (LVI) and (LVII) or (LVIII) and (LIX), in general, the isomer with all like-groups *cis* and with an *n*-fold axis, and the isomer with all nearest-neighbour like groups *trans* and thus with an *n*-fold alternating axis, cannot be labelled. The reason is that, in these particular isomers of $(\mathrm{Cab})_n$, the symmetry has become so high that they have no asymmetric, nor even a pseudo-asymmetric atom. Indeed, their configurations, which might, unlike any of those of the other isomers, be quite unambiguously described as *cis* or *trans*, belong wholly to the domain of geometrical isomerism, without even a vestigial connexion with optical, exactly as in the only isomers of the limiting case of the ethylene compounds to which the general formula applies with $n = 2$: in such isomers, we pass outside the field of stereochemistry for which the sequence rule is intended to provide a system.

It is not necessary to resort to the general system furnished by the sequence rule in substitution for established local systems of sufficient convenience within their own range of application. And in the series $(\mathrm{Cab})_n$, which overflows the limits of asymmetry and pseudo-asymmetry, a local notation, independent of these limits, is available in the so-called "fractional" system, now used for the inositols and other groups of isomers belonging to the special case $(\mathrm{CaH})_n$. This notation can easily be extended to the series CaH–CbH. Some examples, belonging to either case, of the fractional and sequence-rule stereochemical symbols are contained in the names here listed corresponding to the set of formulae already given:

(XLIV)	(1:2:3:5/4)- or (1*R*:2*R*:3*R*:4*R*:5*S*)-4-methoxy-*cyclo*hexane-1:2:3:5-tetraol
(XLV)	(1:2:3/4:5)- or (1*R*:2*R*:3*S*:4*R*:5*R*)-*cyclo*hexane-1:2:3:4:5-pentaol
(XLVI)	(1:3:4/5)- or (1*R*:3*R*:4*S*:5*R*)-3:4:5-trihydroxy-*cyclo*hexane-1-carboxylic acid[14]
(XLVII)	(1:3:4:5/2)- or (1*S*:2*s*:3*R*:4*R*:5*S*)-4:5-dimethoxy-*cyclo*pentane-1:2:3-triol
(XLVIII)	(1:2:4/3:5:6)- or (1*R*:2*S*:3*S*:4*S*:5*S*:6*R*)-inositol
(XLIX)	(1:2:5/3:4:6)- or (1*R*:2*S*:3*S*:4*R*:5*R*:6*R*)-inositol
(L)	(1:2:3:4/5:6)- or (1*R*:2*R*:3*S*:4*S*:5*S*:6*R*)-inositol
(LI)	(1:2:4:5/3:6)- or (1*R*:2*S*:3*s*:4*R*:5*S*:6*s*)-inositol
(LII)	(1:2:3:5/4:6)- or (1*R*:2*s*:3*S*:4*S*:5*r*:6*R*)-inositol
(LIII)	(1:2:3:4:5/6)- or (1*R*:2*R*:3*s*:4*S*:5*S*:6*s*)-inositol
(LIV)	(1:2:3/4:5:6)- or (1*R*:2*s*:3*S*:4*S*:5*s*:6*R*)-inositol
(LVI)	(1:2:3:4:5:6/–)- or *cis*-inositol
(LVII)	(1:3:5/2:4:6)- or *trans*-inositol

In these applications, the numbering, on which the fractional symbols fundamentally depend, is determined by the disposition of the substituents other than hydrogen. It would obviously be possible to make it similarly depend generally on the sequence-rule-preferred substituents of pairs, and thus to extend fractional notation to the successively more general series

$(\mathrm{Cab})_n$, Cab—Ccd and Xab—Ycd

The fractional notation, having no basis in the theory of optical isomerism, gives no indication of which isomers are optically active, and of which among them are enantiomers. Sequence-rule prefixes give this information. If, and only if, the (Capital) *R*'s and *S*'s do *not* balance in the configurational symbol, as for (XLIV), (XLV), (XLVI), (XLVIII), and (XLIX), the molecules represented will be optically active. Provided that the numbers of the atoms are not changed when we pass over from an optically active molecule to its enantiomer, the configurational symbol of the latter follows from that of the former by replacing each *R* by *S* and each *S* by *R*. The fact that such a relation of mutual replacement is not apparent for (XLVIII) and (XLIX) until the *R*'s and *S*'s are arranged round a ring, is due, not to any departure from the principle that, for any atom, the same configuration always receives the same symbol, but to the irregularity of the present custom of numbering, inasmuch as in the

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[14] This is (—)-hydroshikimic acid, which K. FREUDENBERG and W. LWOWSKI cited as an example of a compound which cannot be stereochemically specified on the basis of sub-rule 1 alone [Ann. Chem. *594*, 76 (1955)]. Actually sub-rules 1 and 2 are required.

series $(Cab)_n$, we change the numbers of the carbon atoms, when we go over to an enantiomer.

Every pseudo-asymmetric atom, indicated by a (lower-case) *r* or *s*, lies on a plane of symmetry. Therefore, in a stereochemical symbol which contains an *r* or *s*, the (Capital) *R*'s and *S*'s *must* balance (for the molecule must be optically inactive). In odd-membered rings, such planes must pass through just one *r* or *s* atom. In even-membered rings, they may pass either through no atom, when, despite the absence of an *r* or *s*, the *R*'s and *S*'s will still balance as in (L), or through two atoms, each of them *r* or *s*, as in (LI)–(LVII). The recognition of planes of symmetry aids the construction of models from sequence-rule symbols.

(4) *Asymmetry dependent on Isotopic Differences between Groups*

It is easy to provide the machinery for dealing with the asymmetry which arises when some of the groups, on whose differences it depends, are alike in their constitution, and in their stereochemistry, but are different isotopically with respect to one or more of their constituent atoms. Our proposal for dealing with this situation is to order those groups, which cannot be ordered on the basis of sub-rules 1, 2, and 3, by means of another sub-rule, which follows exactly the lines of sub-rule 1, except that mass-number is read in place of atomic number[7]:

Higher mass-number precedes lower (Sub-rule 4)

Asymmetry of this class seems likely to attain considerable chemical and biochemical importance, especially in view of its potential uses in the study of reaction mechanism, and the accumulating evidence that some enzymes exhibit stereo-specificity in forming or destroying enantiomers which differ only in the reversed positions of isotopic hydrogen atoms[15].

(5) *The General Asymmetric Frame*

(3.1) *Types of Asymmetric Frame.* So far our discussion has been confined to asymmetric atoms. The dissymmetry of by far the largest class of optically active molecules can be completely factorized into the asymmetry of atoms. However, there exist classes of optically active molecules, whose dissymmetry cannot be so factorized. The conditions in which this situation can arise may be deduced as follows.

The terms "asymmetric atom" and "atomic asymmetry" must be understood to involve a considerable ellipsis: the reference is always to asymmetry in the *occupation of the space about* an atom. The same is to be understood, when we refer, in similarly abbreviated terms, to asymmetry with respect either to some more general material frame than an atom, or to a geometrical abstraction from possible frames.

Three-dimensional space can in principle be occupied asymmetrically about the zero-, one-, or two-dimensional elements of symmetry, that is, the point (or centre), the line (or axis), and the plane. We have already dealt with the centre; for, although in the abstract, a centre of asymmetry need not be occupied by an atom, in organic molecules whose dissymmetry can be factorized in terms of centres, it is always possible so to choose these that they are thus occupied; and so, for organic molecules, asymmetric centre and asymmetric atom become effectively synonymous. There remain for consideration the asymmetric axis, and the asymmetric plane.

We shall always select these elements of asymmetry as a line or plane containing atoms, indeed, as many as possible, and after that with the widest distribution possible. If a choice should still remain, we should select that line or plane which contains the atom most preferred by the sequence rule.

These elements of asymmetry involve a new feature; because of the distinction between the ends of an axis, or the sides of a plane, fewer differences between groups are needed to produce asymmetry about an axis or a plane, than are required to give asymmetry about a centre: what is lost in differences between groups can be compensated by distinctions of position with respect to the axis or plane.

On the other hand, although we may have fewer groups to order by the already-given sub-rules, we shall need a new sub-rule to deal with the distinctions of position. It is suggested that, with respect to an external point, groups at the near end of an axis, or on the near side of a plane, should be give precedence over groups at the far end or side. In note form, this sub-rule is:

Near groups precede far groups (Sub-rule 0)

Keeping in mind the possibility that groups may be bound in intermediate positions along an axis, we shall interpret this sub-rule in that case as referring with greatest emphasis to nearest and furthest groups. The sub-rule is numbered zero, because, although it has no application to atomic asymmetry, in more general asymmetric structures, it is the sub-rule to be applied first (even before sub-rule 1).

As to the ordering of constitutionally different groups by sub-rule 1, etc., we shall, just as we did for groups about an asymmetric atom, order them primarily by reference to the atom in each group adjoining (but not occupying) the element of asymmetry, i.e., the axis or the plane, thereafter working outwards to more remote atoms as far as necessary.

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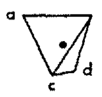
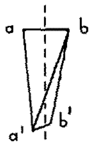
[15] C. Martius and G. Schorre, Ann. Chem. *570*, 140, 143 (1950). – P. E. Wilcox, C. Heidelberger, and V. R. Potter, J. Amer. chem. Soc. *72*, 5019 (1950). – F. A. Loewus, F. H. Westheimer, and B. Vennesland, J. Amer. chem. Soc. *75*, 5018 (1953). – A. Streitwieser, J. Amer. chem. Soc. *77*, 1117 (1955).

(5.2) *Axial Asymmetry.* This form of asymmetry is well known in allenes, methylenecyclanes, spirans, and diphenyls.

The way in which axial asymmetry can be derived from central asymmetry by "pulling out" the point into a line, is shown in (LX) and LXI). As explained above, so many differences between the groups as are required to produce asymmetry about a centre are not needed to give asymmetry about an axis. In the axial case, it is enough that a and b are different, and that a′ and b′ are different; and it is not necessary that a′ should be different from a, or b′ from b.

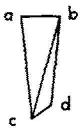


Centre of asymmetry
(LX)

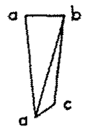


Axis of asymmetry
(LXI)

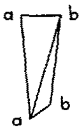
In its application to axial asymmetry, sub-rule 0 requires that, with respect to an external point, groups at the near end of the axis are given precedence over groups at the far end. Let a, b, c, d, be the sequence-rule order of any four different groups, and consider first the structure (LXII). It would seem natural to choose the external point towards that end of the axis which is marked by the leading group, a. But, if we consider simultaneously the special cases, represented by (LXIII) and (LXIV), in which identities have been introduced, without, as noted already, any loss of axial asymmetry, such a choice becomes ambiguous. However, it is a property of axial asymmetry, that the end of the axis towards which the external point is taken is immaterial. For, first, let the point lie below the figure in (LXII), (XLIII), or (XLIV): then in all three cases, the sub-rules will give the groups the priorities shown in (XLV). Alternatively, let it lie above the figure: then in all cases, the priorities will be as in (XLVI). If now, in accordance with the conversion rule, the model is viewed, either as (XLV), or as (XLVI), from the side remote from the group last in sequence (4), it is seen to have the same configuration (*R*).



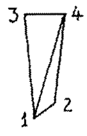
(LXII)



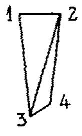
(LXIII)



(LXIV)

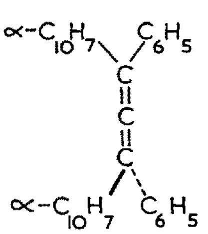


(LXV)



(LXVI)

The molecules (LXVII)–(LXXVIII) are all represented in their *R*-forms. The first seven are historically notable examples of optical activity in their respective molecular types. The spirans (LXX) and (LXXIII) are axially asymmetric molecules, even though the asymmetric axis is occupied by only one atom in either case, viz., the spiran carbon atom. Owing to the presence of a tercovalent axial atom in the oxime (LXXII), an imaginary atom must here be added, as usual in such cases, for the purposes of the sequence and conversion rules. Examples (LXXIII) and (LXXIV) are introduced in order to illustrate our choice of nearest and furthest groups along the axis in classifying the configurations. The two diphenyl compounds (LXXV) and (LXXVI) have been assigned absolute configurations, such that the forms represented would be laevo rotatory towards visible light[16]. Examples (LXXVII) and (LXXVIII) illustrate the problem of choosing an asymmetric axis among several



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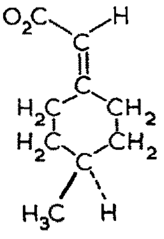
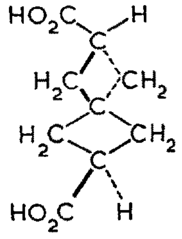


(LXVIII)



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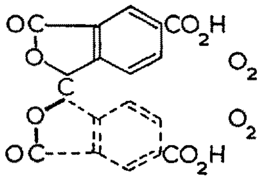
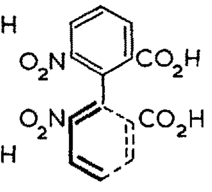


(LXX)



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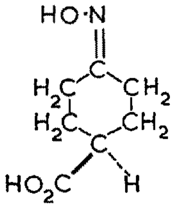

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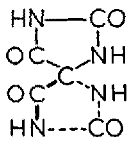
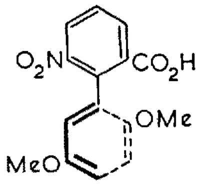
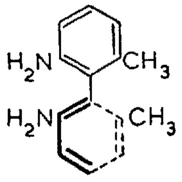


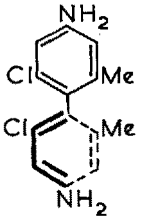
(LXXIII)



(LXXIV)



(LXXV)



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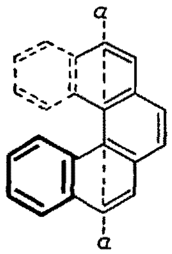
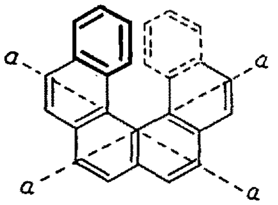


(LXXVII)



(LXXVIII)

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[16] W. Kuhn and R. Rometsch, Helv. chim. Acta *27*, 1346(1944).

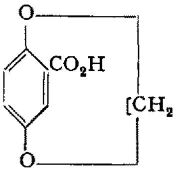
alternatives. In (LXXVII), there are three diphenyl axes, but the sequence rule, applied as explained to secure inclusion of most favoured atoms on the axis, selects that marked aa. In (LXXVIII) the four diphenyl axes form two symmetry-related pairs, of which the sequence rule selects one pair, the two axes each marked aa, either of which may be used (with identical results) for the purpose of classifying the configuration.

(5.3) *Planar Asymmetry.* A number of molecules having planar asymmetry, not reducible to axial or central asymmetry, are already known, some of them in optically active forms.

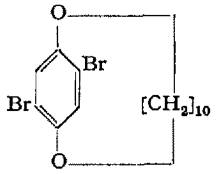
For the classification of a molecular model of such a type, we first locate, as the plane of asymmetry, what would be a plane of symmetry if certain different groups were made identical; and we select this plane so that it contains (or is accessible to) the greatest number and distribution of atoms, including, if a choice of plane remains, the atom most preferred on the sequence rule. Then, on a side of the plane which we shall call the near side, that on which lies the group most preferred by the sequence rule if possible, and among the atoms there bound directly to the plane, we pass from the most preferred of them, to the most preferred of those next it, and similarly on, until a path is traced to which the conversion rule can be applied. In applying it we view the path from an external point on the near side; and according as its curvature appears right- or left-handed, we classify the model as *R* or *S*.

Two points in this procedure may be emphasized. First, the atoms among which the path is to be traced are all adjacent to the reference plane, and are on one side of it: no atom *of* the plane itself is included among the set of atoms to be ordered (just as in central asymmetry the asymmetric atom is not included, and in axial asymmetry the atoms of the axis are not). Secondly, we have not necessarily to order *all* atoms of the set: having found the most preferred, we use the sequence rule to distinguish between its immediate neighbours, and to select one of them, and then to select a nearest neighbour to that neighbour, and so on, a step at a time, as far as necessary.

One group of illustrations is furnished by LÜTTRINGHAUS and GRALHEER's quinol polymethylene ethers[17], several of which have been obtained in optically active forms, for example, (LXXIX) and (LXXX). Particular enantiomers of these molecules are shown in (LXXXI) and (LXXXII), each a representation of an aspect of the molecule from a point in the asymmetric plane, outside its defining polymethylene loop. The representations are somewhat formal, inasmuch as it is convenient (since conformations are not in question) to consider planar rings without re-entrant angles. In (LXXXI) the relevant set of atoms are the ring carbon atoms marked *a* and *b*, together with one hydrogen atom of each methylene group. Our procedure traces the path a → b → c, which has to be viewed from the right; and hence the represented form is *R*. In (LXXXII) the sides of the plane are equivalent, and thus our path is either *a* → *b* → *c*, to be viewed from the right, or *a'* → *b'* → *c'*, to be viewed from the left: by either criterion the classification is *R*.



(LXXIX)



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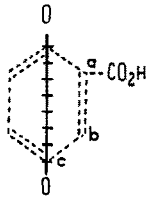
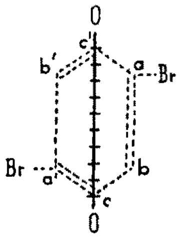
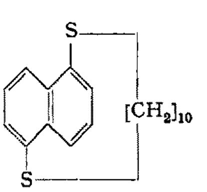


(LXXXI)

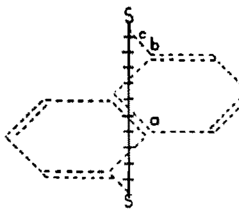


(LXXXII)

The same authors prepared the compound (LXXXIII), one enantiomer of which is diagrammatically represented in (LXXXIV). Here no aromatic carbon atom lies on the asymmetric plane, again defined by the polymethylene loop, but two adjacent to it, together with the nearest methylene hydrogen, on the same side of the plane, can constitute the path, *a* → *b* → *c*, which, on application of the conversion rule, shows that an (*S*)-form is being represented.



(LXXXIII)



(LXXXIV)

The bis-*p*-phenylenepolymethylenes form a second group of examples. The acid (LXXXV) has been resolved[18]. The anhydride (LXXXVI) has been partly resolved[19]. In either case the diagnostic pattern starts with the substituted aromatic carbon atom (or one of them), then passes through the next aromatic carbon on the same side of the plane of the methylene groups, and then through methylene hydrogen atoms towards

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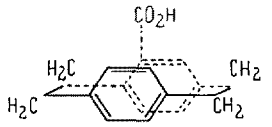
[17] A. LÜTTRINGHAUS and H. GRALHEER, Ann. Chem. *550*, 67 (1941); *557*, 108, 112 (1947).

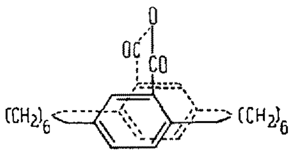
[18] Personal communication from Dr. D. J. CRAM.

[19] D. J. CRAM and J. ABELL, J. Amer. chem. Soc. *77*, 1179 (1955).

the second benzene ring. The forms represented are evidently both *R*.



(LXXXV)



(LXXXVI)

(6) *Summary of the Generalized Scheme*

It may be convenient to bring together in note form the explanations and procedures set out and illustrated in the foregoing sections.

Classification of Asymmetry. Atomic covalencies up to four are to be covered. The elements of asymmetry are the centre, in practice identified with the asymmetric atom, the axis, and the plane.

Sequence Rule. In order to classify configuration about an element of asymmetry, we order the groups about it by an application in turn of the following sub-rules:

(0) Near end or side precedes far (inapplicable to the asymmetric atom).
(1) Higher atomic number precedes lower.
(2) *Cis* precedes *trans*.
(3) *R* precedes *S* (for pseudo-asymmetry only).
(4) Higher mass-number precedes lower (among isotopes only).

Conversion Rule. Among the groups of highest priority follow the right- or left-handed pattern of their sequence from the side of the model remote from the group of lowest priority.

Labelling Rule. According as the pattern is right- or left-handed, label the element of asymmetry *R* or *S*, or, in the case of a pseudo-asymmetric element, *r* or *s*.

Zusammenfassung

Ein früherer Vorschlag[4] für die Spezifizierung der asymmetrischen Konfiguration organischer Verbindungen wurde modifiziert und erweitert. In der vorliegenden Abhandlung wird mehr Nachdruck auf Beispiele gelegt, welche das Verfahren erläutern, als auf eine formelle Darlegung der Prinzipien in allgemeiner Form. Die prinzipiellen und praktischen Gründe, welche für ein allgemeines Verfahren zur Spezifizierung der absoluten asymmetrischen Konfigurationen sprechen, werden diskutiert. Da ein solches Verfahren nur auf wenigen eindeutigen Regeln beruhen soll, muss es folgende Bedingungen erfüllen: 1. die Reste, welche die Asymmetrie bedingen, müssen auf Grund einer permanenten, internen Eigenschaft geordnet werden; 2. das dreidimensionale Muster, welches so erhalten wird, muss direkt als Klassifikationsgrundlage dienen.

Ebenso wie in der früheren Mitteilung wird auch in der vorliegenden Abhandlung als ordnende Eigenschaft von Gruppen, welche sich in ihrer chemischen Konstitution unterscheiden, die Atomnummer verwendet. Darüber hinaus wird gezeigt, wie die feineren Unterschiede, welche Asymmetrie verursachen, wie die Atommasse sowie Konfiguration und Position der Gruppen, berücksichtigt werden können.

Das Verfahren wurde soweit ausgebaut, dass man es auf alle bekannten Typen der optischen Isomerie organischer Verbindungen anwenden kann. Zur Spezifizierung der Konfiguration werden neue Symbole vorgeschlagen, welche ausschliesslich die absolute Konfiguration darstellen sollen.

Formation of the Resting Condition in Plants

Environmental Factors Causing the Onset of Rest

By A. VEGIS[1], Uppsala

The question concerning the formation of resting condition, i.e., of quiescence of plants, has not yet been solved in spite of its great theoretical and practical importance. The formation of resting condition before the onset of the season unfavourable for the growth has been known for some time[2]. But, inspite of all efforts made, it has, however, not been possible to achieve any success in establishing the environmental factors which under natural conditions are responsible for the formation of resting state. This circumstance has been the cause of considering the rest period as an unalterable peculiarity in plants, which is hereditary and does not come about by the influence of environmental conditions[3]. Such a conception is even now advocated by some investigators[4].

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[1] Institute of Physiological Botany, University of Uppsala.

[2] E. ASKENASY, Bot. Ztg. *35*, 793 (1877).

[3] M. TREUB, Bull. Soc. roy. Bot. Belgique *26*, 182 (1877). – G. HABERLANDT, *Eine botanische Tropenreise* (Engelmann, Leipzig 1893). – A. F. W. SCHIMPER, *Pflanzengeographie auf physiologischer Grundlage* (Fischer, Jena 1898). – G. VOLKENS, *Laubfall und Lauberneuerung in den Tropen* (Gebr. Borntraeger, Berlin 1912). – S. SIMON, Jb. wiss. Bot. *54*, 71 (1914).

[4] E. BÜNNING, Naturwissenschaften *31*, 493 (1943); *Entwicklungs- und Bewegungsphysiologie der Pflanzen* (Springer, Berlin, Göttingen und Heidelberg, 1948).