

# A NOTATION FOR THE STUDY OF CERTAIN STEREOCHEMICAL PROBLEMS

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FOR many years the Fischer projection formulas have been used to represent the stereochemistry of molecules with multiple asymmetric centers. These formulas are adequate if one is dealing only with the classical aspects of stereoisomerism. Recently, however, the investigations involving conformational analysis have required other notations for visualization of the fine points. The author has been using a different kind of notation for several years for problems involving compounds containing two adjacent asymmetric carbons (1). Recently this notation has been extended to cover similar problems in cyclohexane and related compounds. This article describes some applications of the notation to various stereochemical problems.

To be specific, let us consider the isomers of a 1,2-dibromide having two similar asymmetric carbons,  $\text{RCHBrCHBrR}$ . The projection formula written is that envisioned when the eye is placed along the extension of the bond joining the two asymmetric carbons. As a convention the carbon farthest from the eye is called carbon 2, and that nearest, carbon 1. Carbon 2 is designated by a circle with three equally spaced radial extensions to locate the three other atoms to which it is attached. Carbon 1 is designated by equally spaced radii, as shown in Figure 1.

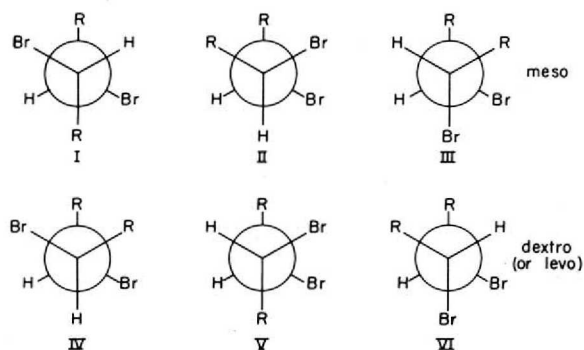


Figure 1. Rotamers of Diastereomeric Dibromides

If one bears in mind the fact that the valence bonds to carbon 1 are viewed as one views the spokes of an umbrella when the eye is at the handle, and the valence bonds to carbon 2 are viewed as though the eye were at the tip, it is simple to write a *meso* form. One writes the three different groups in the same clockwise order for each carbon; *i. e.*, in the present example, R, Br, H. This assures one that the configuration at the two carbons is opposite, and hence a *meso* form is at hand.

To write a *d* or an *l* form one has merely to interchange any two groups on either atom.

The structures in Figure 1 are written in staggered forms corresponding to the three low-energy conformations. For convenience these forms will be called rotamers (2). By inspection of these structures it is possible to make predictions as to the stereochemistry and rate of a number of reactions as shown below.

## PREDICTION OF GEOMETRIC ISOMERS OBTAINED ON DEBROMINATION OF VICINAL DIBROMIDES

Consider the rotamers of a *meso* dibromide I, II, III, and those of the corresponding *d* or *l* dibromide, IV, V, and VI.

Assuming that the two bromine atoms are *trans* eliminated it can readily be seen that a *trans* olefin will result from rotamer I, *meso* form, and that a *cis* olefin will result from rotamer IV, *dextro* (or *levo*) form. Of course, rotamers II and III will yield the same product as I, and V and VI the same as IV.

## PREDICTION AS TO RELATIVE RATES OF FORMATION OF PRODUCT FROM DIASTEREOMERS

Three methods may be used to predict the relative rates of reaction of diastereoisomers. Each method is offered here as being empirical. It should be emphasized that in the application of any method an assumption must be made as to whether the reaction under consideration requires a *cis* or *trans* involvement of the groups undergoing reaction. In this case, for example, the assumption is made that the two bromine atoms are removed (using either zinc and alcohol or sodium iodide in acetone) when in the *trans* position.

### Method 1. Estimation of the Steric Factors on the Stability of the Products Formed

The essence of this method is to predict a greater rate of reaction for that isomer which yields the more stable final product. Ordinarily the *trans* olefin is presumed to be more stable than the *cis* olefin, hence the *meso* form should react more rapidly than the *dl* form. Furthermore, the larger the groups which end up *cis* or *trans*, the greater should be the ratio of rates. Experimentally the following relative rates have been determined for the debromination using iodide ion: *meso*-2,3-dibromobutane, 0.065, *dl*-2,3-dibromobutane (3), 0.035; *meso*-dibromohexane, 0.154, *dl*-2,3-dibromohexane (4), 0.044; and *meso*-dibromooctane, 0.183, *dl*-dibromooctane (4), 0.060. A qualitative comparison of the isomeric stilbene dibromides indicated that the

*meso* form reacted at least 100 times as rapidly as the *dl* form. Thus it is seen that there is a larger ratio of rates in the molecules where larger groups produce the major steric effects than in the molecules where methyl groups provide the interference.

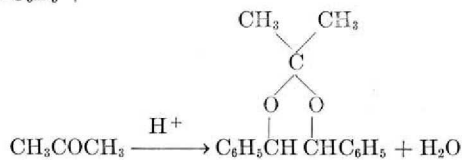
#### Method 2. Comparison of the Relative Abundance of the "Reactive" Rotamers

*Example 1.* The essence of this method of prediction is to compare rotamers I and IV with respect to their relative abundance in the rotamer mixture. In the *meso* form, I, the rotamer containing the bromine atoms in the *trans* position also has the R groups distant from each other. In the racemate, IV, the rotamer containing the bromine atoms in the *trans* position has the R groups close together and in close juxtaposition to the bromine atoms also. Hence one could argue that the *meso* form on the time average approximates I more nearly than the racemate approximates IV. Therefore the *meso* form should react more rapidly than the racemate (which is the case). It is realized that this argument may be based on unsound principles. Nevertheless, the predictions based on it have been correct in every case examined to date.

It is interesting to note that the Br—Br distances in *meso* and racemic dibromostilbene (solid state) have been determined by X-ray diffraction (5). The distance for the *meso* form is 4.50 Å., corresponding to the geometry of rotamer I (R = C<sub>6</sub>H<sub>5</sub>), whereas the distance for the racemic form is 3.85 Å., which is about as close as the van der Waals radius for bromine will allow two bromines to approach. On the other hand, measurements on the *meso* and racemic forms of 2,3-dibromobutane (liquid state) show that the bromines are essentially *trans* in both forms (6), as the Br—Br distance is about 4.60 Å. in each.

In cases where the stability of the two possible products is not known, Method 1 of predicting the relative rates for diastereoisomers cannot be applied unless one makes an assumption about the stabilities of the end products. However, Method 2 can still be applied as shown below.

*Example 2. Prediction of Relative Rates of Reaction of Diastereomeric Glycols to Form Cyclic Ketals.* Consider the rotamers of the *meso* and racemic forms of hydrobenzoin, (see Figure 2). The reaction under consideration is the formation of a cyclic ketal using acetone:



The assumption is made that the reaction involves a *cis* arrangement of hydroxyl groups because the final ketal contains a five-atom heterocycle involving the two oxygens. On the time average rotamer IX of the

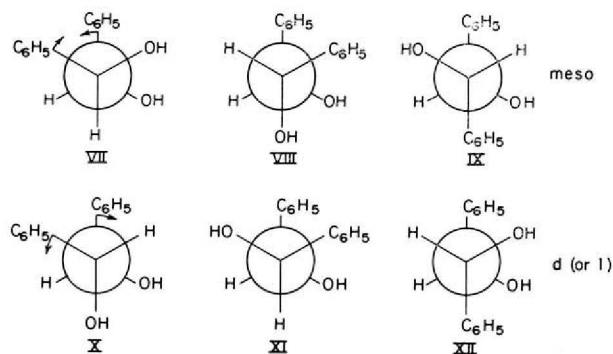


Figure 2. Stereoisomeric Hydrobenzoin

*meso* form would be favored because of steric factors, and rotamer XII of the *d* (or *l*) form. Since XII has the favored *cis* location of hydroxyl groups whereas IX does not, it would be predicted that the racemate would react more rapidly than the *meso* form. The relative experimental rates are: racemate 38.8; *meso*, 4.4 (7).

#### Method 3

Perhaps the best method of predicting relative rates in this and similar cases is to note whether the large groups approach each other or move farther away in going from reactant to the activated state. By observation of any one of the rotamers VII, VIII, or IX, it can be seen that in going to the cyclic ketal the phenyl groups must approach each other rather closely. In the case of rotamers X, XI, and XII, it is seen that the phenyl groups move to a position farther apart. Note particularly the small arrows in rotamers VII and X, which indicate the direction in which the phenyl groups move during approach to the activated state. The prediction in such cases is that the isomer in which the large groups move away from each other in going from reactant to product will react more rapidly than that in which the large groups move toward each other. In other words, that isomer which forms the most strained activated state will be the one which reacts at the slower rate.

#### PREDICTION OF MIGRATING GROUP IN THE CASE OF DIASTEREOMERIC AMINO ALCOHOLS

In semipinacolic deaminations an amino alcohol,

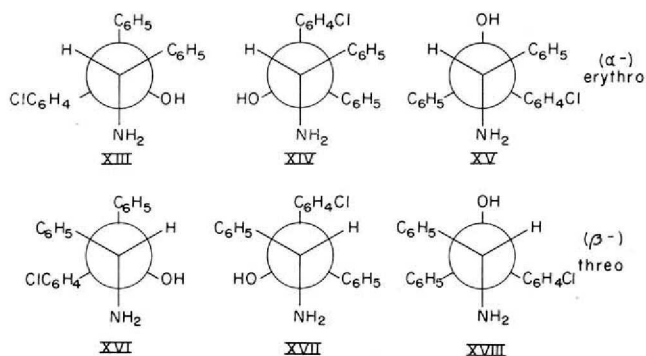


Figure 3. Stereoisomeric Amino Alcohols

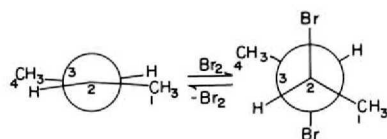


Figure 4. Addition of Bromine to *Trans*-2-butene

$RR'COHCHR''NH_2$ , on treatment with nitrous acid may yield either or both of two ketones,  $R'COCHR''R$  and  $RCOCHR'R$ . From certain studies (8) on "migration aptitudes" it might be supposed that the ratio of these two ketones would depend on the migration aptitudes of R and R'. However, recent studies

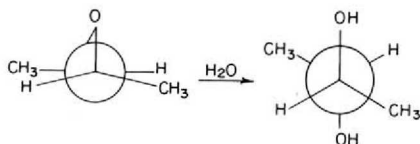


Figure 5. Hydration of *Trans*-2-butene Oxide

(9) have shown that the ketone formed depends mainly on the stereochemical configuration of the amino alcohols and not on the electronic nature of the migrating group. Results like these are readily understood by a study of the rotamers shown in Figure 3.

In the rearrangement that occurs when the amino alcohol is treated with nitrous acid, it is assumed that the group which displaces the amino group does so with inversion. This assumption has been proved correct

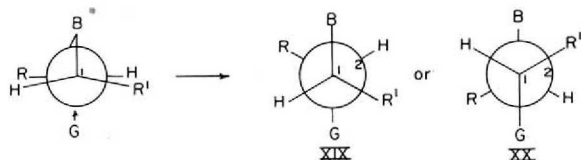


Figure 6. Cyclic Intermediate Reactions

in one case (10) and is probably generally valid. Curtin and his co-workers (9) showed that the  $\alpha$ -isomer of 1,2-diphenyl-1-*p*-chlorophenyl-2-aminoethanol yielded *p*-chlorophenyl benzhydryl ketone almost exclusively (phenyl migration), whereas the  $\beta$ -isomer yielded only  $\alpha$ -*p*-chlorophenyldesoxybenzoïn (*p*-chlorophenyl migration). Of the rotamers XIII, XIV, and XV: XIII would lead to phenyl migration; XIV would lead to *p*-

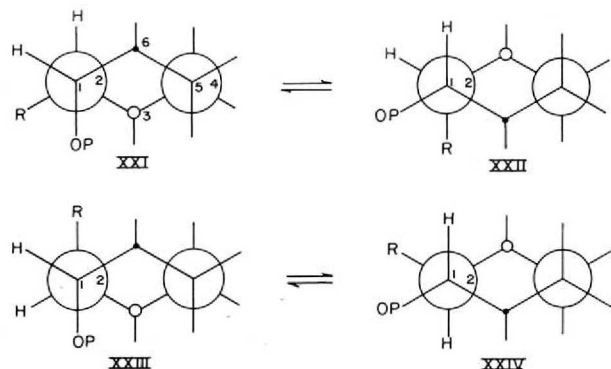


Figure 7. Rotamers of *Cis*- and *Trans*-2-alkylcyclohexanols

chlorophenyl migration; and XV would probably lead to products other than the rearranged ketones. Since rotamer XIII should be favored for steric reasons over XIV, the  $\alpha$ -isomer should react mainly with phenyl migration (as it does). By similar reasoning it is seen that the favored rotamer, XVII, should lead to *p*-chlorophenyl migration in the  $\beta$ -series (as it does). The configurations for the  $\alpha$ -(erythro) and  $\beta$ -(threo) isomers were established unequivocally (9).

In order to allow for the representation of stereospecific additions to olefinic linkages the notation shown in Figure 4 is recommended. Here the eye is looking at carbons 2 and 3 of *trans*-2-butene from the plane containing the doubly bonded atoms. The bonds connecting the  $CH_3$  and H groups to these carbons are bent slightly to allow both sets to be seen. The final dibromide is recognized as *meso* since the clockwise order of groups is the same ( $CH_3, H, Br$ ) on both carbons from the eye position (*vide infra*). Similarly it can be shown that *d* (or *l*) and *l* (or *d*) forms result from *trans* addition of bromine to *cis*-2-butene according to the direction, above or below the plane, of approach of bromine to carbon 2.

By a modification it also is possible to follow the course of other stereospecific reactions involving three atom ring compounds, such as ethylene oxides, ethylenimines, and ethylene sulfides, or bridged ions, such as those postulated in reactions with neighboring group participation, *e. g.*, acetoxy, methoxy, phenyl, etc. In Figure 5 the hydration of *trans*-2-butene oxide to yield *meso*-2,3-butanediol is illustrated.

The problem of notation for hypothetical reaction intermediates involving bridged ions is more difficult. However, if one breaks down this problem into two parts, each may be solved in a satisfactory manner. The first part is the indication of the nature of the bridged intermediate. The second part is the indication of the stereochemical relationships of the products formed when the bridged intermediate is attacked by some reagent at each carbon respectively. Different representations for bridged ions have been used by Winstein (11), Cram (12), Curtin (9), and Roberts (13) depending upon the species at hand. The type of notation illustrated by Figure 6 is recommended for explanation or prediction of the products formed from such bridged intermediates. The only bond not seen when this notation is used is that joining the two carbons that are connected by the bridging group. Since the unseen bond is not affected during reaction one is not sacrificing much. As before, the circle represents the carbon farthest from the eye, and the radii meeting in the center, the carbon nearest the eye. *B* represents any bridging structure and *G* any attacking group. If desired more detailed (slightly perspective) drawings for *B* are possible. If the attack is on carbon 2 isomer XIX is obtained, whereas attack at carbon 1 produces isomer XX.

This notation may advantageously be extended to illustrate stereochemical points in cyclic structures as shown in Figure 7. For example, differences in the

rates of alkaline hydrolysis of the half phthalates of *cis*- and *trans*-2-alkylcyclohexanols (14) may be rationalized rather easily. Structures XXI through XXIV represent stereoisomeric and rotameric forms of the half phthalates (OP) of 2-alkylcyclohexanols. Carbon 1 of the cyclohexanols is represented by the three radii, and carbon 2 (containing the alkyl groups R) is represented by the circle with the three radial extensions. The other atoms in the ring are designated by the small numbers 3, 4, 5, and 6 in structure XXI. There are four bonds which are not seen in this notation: One is an equatorial bond pointing directly at the reader from carbon 6; a second is an equatorial bond on carbon 3 pointing directly away from the reader. The convention adopted for these cases uses  $\text{Y}$  for an unseen bond pointed toward the eye and  $\text{V}$  for an unseen bond pointed away from the eye. The fact that both of these unseen bonds are equatorial partly overcomes the objectionable feature of this notation. The other two bonds not seen are those connecting carbon 1 with 2, and 4 with 5.

If one makes the assumption that the saponification step always occurs when the ester bond is equatorial, one can readily see that the steric relationship be-

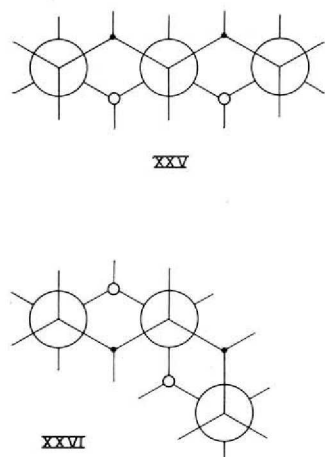


Figure 8. *Trans*-decalin (Above) and *Cis*-decalin (Below)

tween the ester group and the alkyl group on carbon 2 is the same (approximately) in both the *cis* form, XXII, and the *trans* form, XXIV. However, form XXIV has R in an equatorial position whereas form XXII has R in an axial position. Hence one would expect to find a greater energy difference between the ground state and the activated state for XXII than for XXIV and hence the *cis* isomer should be saponified more slowly than the *trans* (as is the case) (14).

Finally, the utility of this notation can be illustrated by inspection of the formulas for *trans*-decalin, XXV, *cis*-decalin, XXVI, the steroid nucleus with A-B rings *trans*, XXVII and XXVIII (two views), and *cis*, XXIX and XXX (two views). With a little practice it becomes a simple matter to see whether a bond is  $\alpha$  or  $\beta$ , equatorial or axial.

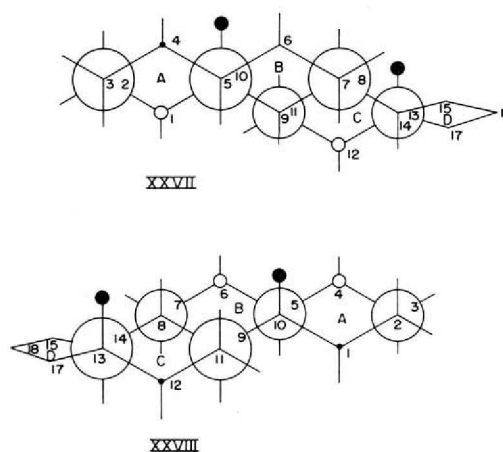


Figure 9. Steroid Nucleus A-B Rings *Trans*

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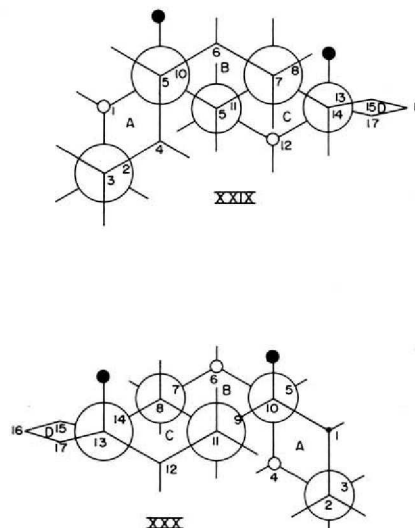


Figure 10. Steroid Nucleus A-B Rings *Cis*