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STEREOLABILE CONFIGURATIONAL UNITS
TORSIONAL AND INVERSIONAL STEREOCHEMISTRY IN SULFENAMIDES AND HYDROXYLAMINES

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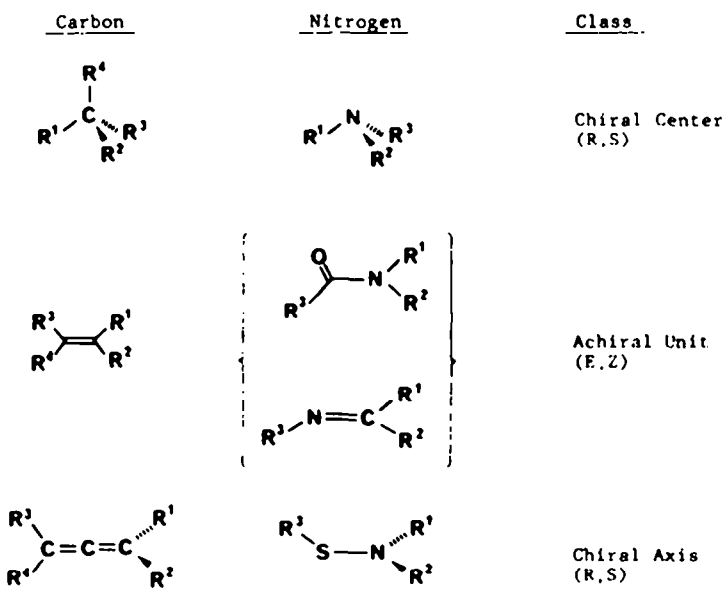
CONTENTS

I. STEREOSTABLE AND STEREOLABILE CONFIGURATIONAL UNITS

In order to appreciate the unique stereochemical properties of sulfenamides and hydroxylamines, it is necessary to recognize the essential similarities and differences between stereostable and stereolabile configurational units. The development of the field of stereochemistry over the period of more than a century since the postulation of the tetrahedral carbon atom has been focused on the stereostable configurational units associated with carbon, especially the asymmetric carbon atom and the achiral olefin configurational unit. The importance of methods and concepts based on optical activity has derived from the resolvability of enantiomers which owe their chirality to the carbon asymmetric center, the allene chiral axis and other stereostable configurational units. By contrast, investigation of the stereochemistry of the nitrogen chiral center could not be developed using the classical methods based on chiroptical properties. Instead, NMR spectroscopy provided a new means for investigation of this and other stereolabile chiral units. While there are differences between the methodology applied to stereostable and stereolabile chiral units, it is possible to apply many of the classical stereochemical concepts to phenomena which are best investigated using NMR spectroscopy.[1]

In this section we will try to define the analogies between carbon and nitrogen configurational units (Scheme 1), and to show the parallels between the chiroptical methods used for carbon stereochemistry and the NMR methods employed to study stereochemistry of trivalent N compounds.



Scheme 1. The analogy between carbon and nitrogen configurational units.

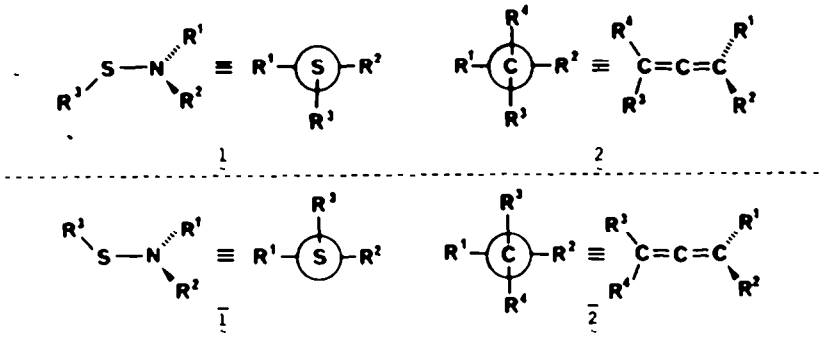
The N chiral center parallels the asymmetric carbon center, and can be assigned *R* and *S* chiralities using the Cahn, Ingold, Prelog (CIP) rules.[2] Since the only stereochemical difference between these two systems lies in the magnitude of the barrier to stereomutation, we consider both to be configurational units and refer to invertomers of chiral amines as having opposite configurations.

Similarly, the achiral olefin configurational unit has a stereolabile parallel in the amide functionality. For amides of the form $RC{=}ONR^1R^2$ we can use the *E*, *Z* nomenclature[3] to distinguish between the two diastereomers. It seems appropriate to extend the definition of configuration to include also this system, and to refer to the amide group as the framework for an achiral configurational unit. To describe one system as configurational and one as conformational simply on the basis of barrier heights can lead to confusion, especially since in some compounds C−C double bond barriers are lower than amide barriers. In general, we advocate the use of the term configuration in all cases where the ordering of ligands about a geometrical framework can be specified as *R/S* or *E/Z*, regardless of barriers to stereomutation. Accordingly, we reserve the term conformation for a quantitative description of dihedral angles.† The imine configurational unit also parallels the olefin unit, in a more straightforward fashion. Clearly all compounds having C=N and N=N double bonds (e.g. oximes, azo compounds, etc.) can be assigned *E/Z* configurations.

Allenes exemplify a third stereochemical class of carbon compounds, featuring a stereostable configurational unit, the chiral axis. There are several groups of nitrogen analogues to this class, all with an N-heteroatom single bond. These include sulfenamides ($RS{-}NR^1R^2$), hydroxylamines ($RO{-}NR^1R^2$), hydrazines ($R^1R^2N{-}NR^3R^4$), and selenenamides ($RSe{-}NR^1R^2$). We use as an example of this class a model sulfenamide with (hypothetical) planar geometry at nitrogen. The sulfenamide ground state is one in which the $R^3{-}S{-}N$ plane is perpendicular to the R^1NR^2 plane, as shown in Scheme 2.

Stereoformulae **1** and $\bar{\mathbf{1}}$ are enantiomeric and are related by a mirror plane indicated by the dotted line in Scheme 2. In order to assign *R/S* configurations to **1** and $\bar{\mathbf{1}}$ we need to perform a "ligancy complementation", as specified in the CIP method. A second ligand at sulphur, a

†An important difference between the concepts of configuration and conformation can be understood by referring to the variables which are used to describe each. Configuration is represented by a variable with a finite number of values (generally a two-valued variable). On the other hand, conformational information is expressed with a continuous variable (generally a dihedral angle). Even when we use terms such as eclipsed or staggered to describe conformations, these descriptors are different in principle from configurational descriptors and are really shorthand ways of defining particular values or ranges of values of a continuous variable.



Scheme 2. Comparison between sulfenamide and allene chiral axes.

phantom atom of lowest priority, is introduced in an orientation analogous to R^4 in the allene **2**. Then if R^1 has a higher priority than R^2, the overall priority will be R^3 > phantom > R^1 > R^2 and **1̄** can be assigned the *R*-configuration using the sequence rule as applied to chiral axes.

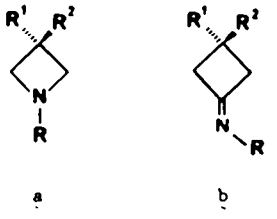
II. MECHANISMS FOR STEREOMUTATION

The stereochemistry of carbon compounds has dealt mainly with resolution of racemates into enantiomers, stereospecificity of reactions, configurational assignments and chiroptical properties. Because the carbon units are stereostable, stereomutations generally require the breaking and making of bonds, usually σ bonds, and most often are catalytically or photochemically induced. Many of these phenomena do not apply to nitrogen stereochemistry, due to its stereolability. Rather, mechanisms for thermal (uncatalyzed) stereomutation play a central role in investigations of stereochemistry of nitrogen and other stereolabile configurational units.

These mechanisms, which involve geometry changes rather than bond making or bond breaking, can be conveniently categorized according to the type of geometry change and the symmetry consequences of the stereomutation (Scheme 3). Thus we can differentiate between changes in bond angles (Inversion) and dihedral angles (Torsion) and between stereomutations at chiral and achiral configurational units. When a single configurational unit is present in the molecule, these stereomutations interconvert enantiomers and diastereomers, respectively. Scheme 3 provides examples of these four types of processes, which we term: I_C (Inversion, Chiral); I_A (Inversion, Achiral); T_C (Torsion, Chiral); T_A (Torsion, Achiral).†

Both mechanisms I_C and I_A are characterized by changes in bond angles at nitrogen, from *ca* 109° in the ground state (GS) to *ca* 120° in the transition state (TS) in I_C, and from *ca* 120° in GS to *ca* 180° in TS in I_A. We note that there is an introduction of a σ-plane in transition state I_C while the symmetry remains C_S throughout the I_A process (when $R^1 \neq R^2$). Thus for I_C, the chirality of GS is lost in TS, and interconversion of enantiomers results. By contrast, there is no introduction of a new σ plane in I_A, and consequently the process interconverts diastereomers.

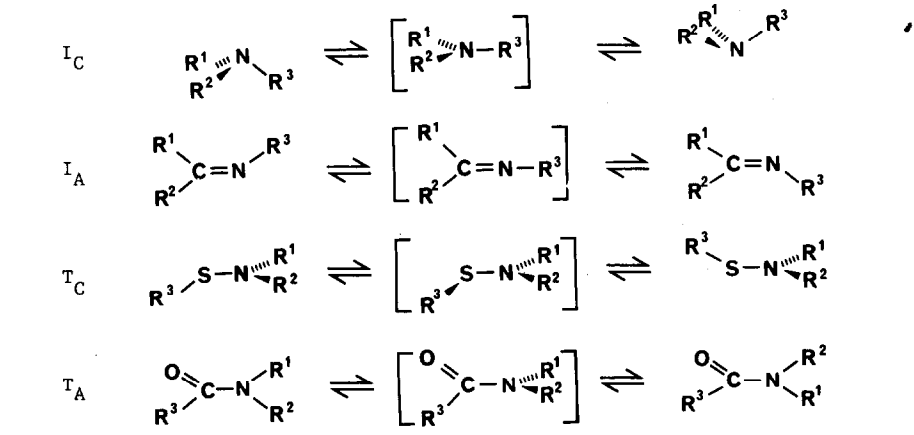
†The categorization of the amine configurational unit as chiral and the imine unit as achiral is a convenient one and is generally accurate. However, we do not mean to imply that the amine pyramid cannot generate an achiral configurational unit or that the imine functionality cannot generate a chiral unit in suitably substituted compounds. In fact, in compounds of the form G_sNHG_R, where G_R and G_S represent dissymmetric substituents of opposite chiralities, the amine pyramid generates an achiral unit, the well-known pseudoasymmetric center, and the invertomers are diastereomers. Similarly, in imines of the form $G_RC(=NH)G_S$ stereomutation interconverts enantiomers, a situation termed geometrical enantiomerism. Compounds *a* and *b* also represent examples of situations where amine inversion interconverts diastereomers and imine stereomutation interconverts enantiomers. Although pairs of antipodal chiral ligands are not present in these examples, they represent close parallels to pseudoasymmetry and geometrical enantiomerism. In both compounds the ring carbon C_3 plays the same role as *both* G_R and G_S in the previous example.



a b

	Chiral	Achiral	
Inversion	I_C	I_A	Bond Angle Change
Torsion	T_C	T_A	Dihedral Angle Change
	Enantiomers	Diastereomers	

Mechanism Type — Example



Scheme 3. Types of stereomutation at stereolabile configurational units.

This symmetry distinction can be expressed by referring to I_A as planar inversion and I_C as nonplanar inversion (pyramidal inversion).

The torsional mechanisms, T_A and T_C, can also be described as planar and nonplanar, respectively, since C_S symmetry is present in the ground state of T_A and is only introduced at the T_C transition state. Both mechanisms involve changes in dihedral angles, from 90° in GS–T_C to 0° (or 180°) in TS–T_C, and from 0° (or 180°) in GS–T_A to 90° in TS–T_A. The I and T processes, as defined above, are the primitive processes associated with changes in bond angles and dihedral angles, respectively. There are more complex stereomutations of both types which are excluded from our analysis. It is clear, for example, that the Berry mechanism for pseudorotation, which interconverts various substitution patterns at pentavalent atoms which adopt the trigonal bipyramid geometry, involves changes in bond angles and might be included in the I category. Similarly, the interchanges involving ring geometries, such as chair–chair interconversion in cyclohexanes (ring reversal) and pseudorotation of 5-membered rings, belong to the T category.[4] The stereomutations in propeller type triarylmethanes exemplified by the one-ring flip mechanism also can be placed into the T category. While it is clear that the one-ring flip can be described as torsional stereomutation, it is not always possible to define a configurational unit which is generated by slow one-ring flip. This situation, which has been termed "residual stereoisomerism" is clearly not covered by our categorization. We stress that the analysis summarized in Scheme 3 is applicable only to the primitive processes. Although it will be applicable in most situations, there are many complex systems for which such an approach is not valid.

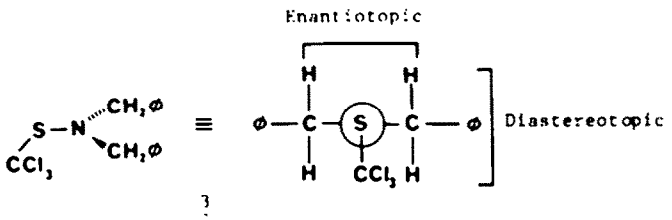
The reader may have noticed the similarity between examples used for the stereolabile configurational units in Scheme I and the examples of mechanisms for stereomutations in Scheme 3. This correspondence emphasizes that stereolabile configurational units can be usefully characterized by their mechanisms for interconversion. Since stereolabile configurational units are generally observed under conditions of dynamic equilibrium, dynamic concepts play a more important role as opposed to the static concepts which are of primary importance in carbon stereochemistry.

III. NMR CONSEQUENCES OF STEREOMUTATION AND TOPOMERIZATION

As we have indicated above, NMR spectroscopy has been the most effective tool for investigating nitrogen stereochemistry. This method plays a central role in the study of stereolabile compounds, just as chiroptical methods have been crucial in the development of carbon stereochemistry. Since NMR spectroscopy can probe individual groups in a molecule rather than simply properties of the entire molecule, NMR studies often focus on the stereochemical relationships between groups in the same molecule. These stereochemical relationships are between paired groups whose environments can be indistinguishable, enantiomeric or diastereomeric, and such paired groups are described as homotopic, enantiotopic or diastereotopic groups, respectively.[5]

The chiral configurational units T_C and I_C can be differentiated from the achiral ones, T_A and I_A, on the basis of these relationships. In order to do so a prochiral[6] group of the form $-CX_2Y$ (e.g. $-CH_2CH_3$, $-CH_2Ph$, $-CH(CH_3)_2$, $-C(CH_3)_2CH_2OCH_3$, etc.) is incorporated in the molecule. Such a prochiral group in a molecule of the form RCX_2Y can serve as a probe for the chirality or lack of chirality of the radical R (Scheme 4). When R is an achiral group (R_A) which may contain either a T_A or I_A configurational unit, the molecule has a plane of symmetry (σ) in the plane of the paper, which interchanges the two X substituents. As a result these groups are enantiotopic and will have the same NMR chemical shifts.† However, when a chiral group (R_C) is present, this plane is no longer a symmetry plane, and hence the X groups are diastereotopic and will, in principle, exhibit different chemical shifts. Thus, the observation of chemical shift nonequivalence of the X groups in a prochiral probe provides unequivocal evidence for the chirality of the group R_C. The observation of chemical shift equivalence of the X groups is not as conclusive for the lack of chirality, since the magnitude of the chemical shift nonequivalence might have been too small to be observed. The probability of such apparent equivalence can be decreased by introducing more than one prochiral probe group in the molecule, or by examining a series of molecules with different probe groups.

Our statement that molecules of the form R_CCX_2Y exhibit chemical shift nonequivalence since R_C is a chiral radical, does *not* imply that R_CCH_2Ph must be a chiral molecule. For example, N,N-dibenzyltrichloromethanesulfenamide, compound **3**, exhibits chemical shift nonequivalence (AB quartet) of the benzyl methylene protons.[7] Although the molecule as a whole is achiral, the radical CCl_3SNCH_2Ph is chiral. We note that the molecule possesses a σ plane (the CSN plane).



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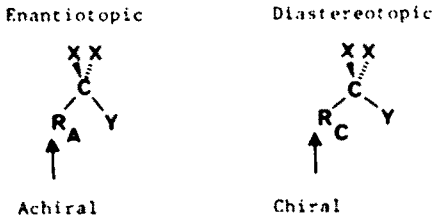
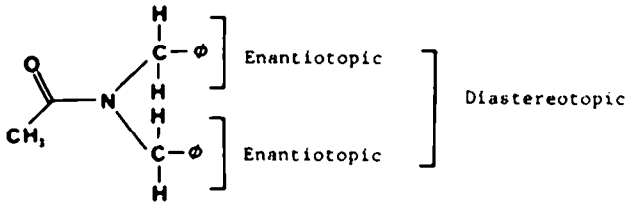
While this plane interchanges the benzyl groups as a whole (and renders them enantiotopic) it does not interchange the two methylene protons in each individual benzyl group and they are diastereotopic. Thus the spectrum features a single AB quartet.



Scheme 4. Prochiral groups as chirality sensors.

†Here and elsewhere in this discussion we assume that achiral solvents are used, unless otherwise stated. If a chiral solvent is used, of course, the X groups are diastereotopic even when R is achiral, and thus chirality of the medium, rather than that of the molecule, is sensed by the prochiral probe.



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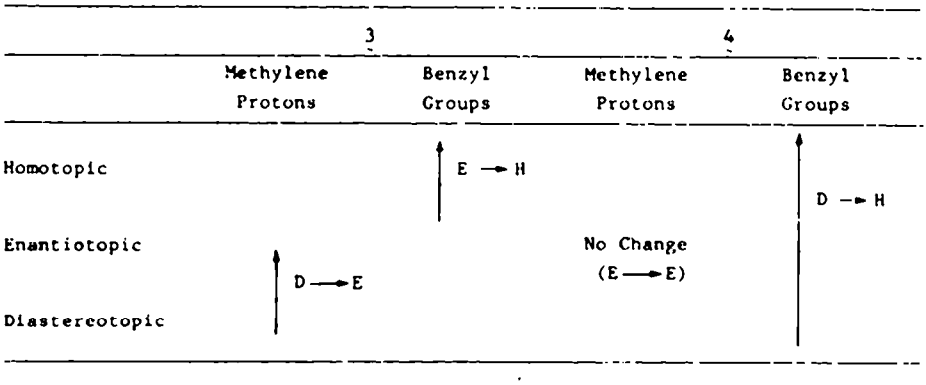
The difference in NMR spectra of molecules with chiral and achiral configurational units can be illustrated by comparing the spectrum of 3,[8] which belongs to class T_C, with that of 4 which belongs to class T_A. In 4 the two methylene hydrogens in each benzyl group are enantiotopic, while the two benzyl groups, each taken as a whole, are diastereotopic. As a result the benzyl groups appear as two singlets in the NMR spectrum of 4.

The spectral characteristics described above are only observed when the rate of torsion is slow on the NMR time scale. When the rate of torsion increases relative to the NMR time scale, typical exchange phenomena are observed, as the result of averaged stereochemical relationships involving the benzyl methylene protons. This averaging of stereochemical relationships is termed topomerization.[9] In 3, when the sample temperature is increased, torsion about the S–N bond becomes rapid on the NMR time scale, and the benzyl methylene protons become enantiotopic on time average. As a result, the NMR spectrum changes gradually from an AB quartet characteristic of diastereotopic methylene protons, to a singlet characteristic of enantiotopic protons (A_2 spin system). The same process also effects a topomerization of the whole benzyl groups, which become homotopic, on time average, rather than enantiotopic. However, this is without consequence in the NMR spectrum, since both homotopic as well as enantiotopic groups are isochronous (i.e. chemical shift equivalent).

In compound 4 the topomerization, resulting from rapid rotation about the amide bond, renders the diastereotopic benzyl groups homotopic on time average, and the two benzyl singlets coalesce to one singlet. It may be noted that rapid rotation does *not* affect the stereochemical relationship between protons in each methylene group, which remain enantiotopic. Thus, the topomerization of these two compounds, 3 and 4, illustrates the four possibilities for averaging of stereochemical environments of groups in molecules (Scheme 5). Since topomerization can only lead to increased average symmetry, the arrows in Scheme 5, pointing from less symmetrical to more symmetrical situations represent the three types of topomerization, viz. D→E, E→H in 3 and D→H in 4.† The scheme also emphasizes that the *same* physical process can lead to topomerization of one pair of groups while at the same time leaving the stereochemical relationship of another pair unchanged (compound 4). It is equally possible to have two different types of topomerization in the same molecule as the result of a single process (compound 3). We may note that only

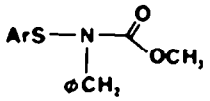


Scheme 5 Types of topomerizations in compounds 3 and 4.

†Binsch *et al.*,[9] refer to these three types as "stereoheterotopomerizations" and divide them into only two categories. Thus, both D→E and D→H topomerizations are referred to as diastereotopomerizations in their scheme.

topomerizations which render diastereotopic groups either enantiotopic or homotopic on time average (D→E, D→H) lead to coalescence and can be investigated using NMR spectroscopy.

Compounds **3** and **4** do not contain time configurational units since the presence of two benzyl graphs as R^1 and R^2 introduces added symmetry. Nevertheless they may be grouped in the same categories: T_C and T_A, since the same types of processes with similar NMR consequences are involved. Compound **5** exemplifies a molecule in which true configurational units are present.[10] It also illustrates that when T_C and T_A units are present in the same molecule, the stereomutations which affect these units are readily differentiable. Rotation about the S—N bond represents a T_C process while rotation about the amide bond constitutes a T_A process. The T_C stereomutation interchanges the benzyl methylene protons in essentially the same manner as in **3** (D—E topomerization) leading also to the coalescence of an AB quartet to a singlet. While the T_C process in **5** (but not in **3**) is also stereomutation (degenerate racemization) at the sulfenamide chiral axis, this does not have any effect on the appearance of the NMR spectra. There is also a difference between the stereochemical descriptions of the T_A process, amide rotation, in **4** and **5**. In **4** the process is a topomerization (D—H), while in **5** it is a true interconversion of diastereomers (Z⇌E).



5a Ar = 2,4-Dinitrophenyl
5b Ar = 3-Nitrophenyl

The benzyl groups in the *E* and *Z* diasteromers have different chemical shifts and should give rise to two signals of different intensities due to the unequal concentrations of the isomers at equilibrium. The benzyl groups in the *E* and *Z* isomers of **5** may be described as diastereotopic by external comparison in order to differentiate this situation from that of **4** where the benzyl groups are diastereotopic by internal comparison.

Four different situations may be envisaged for **5** in terms of the rates of the T_A and T_C processes relative to the NMR time scale: (a) both fast; (b) T_C slow, T_A fast; (c) T_C fast, T_A slow; and (d) both slow. At high temperatures situation (a) prevails and the benzyl methylene protons appear as a singlet in the NMR spectrum. When the temperature is lowered either situation (b) or (c) may occur. In fact, in compound **5a** the S–N torsional barrier is higher than the amide barrier and situation (b) occurs at intermediate temperatures. Under such conditions only nonequivalence due to the sulfenamide chiral unit (T_C) is in evidence, i.e. a symmetrical AB quartet is observed (Fig. 1, T = 38°). Upon further cooling both processes become slow [situation (d)]; the single AB quartet further splits into two unequally intense AB quartets, one for each of the amide diastereomers (Fig. 1, T = −51°).

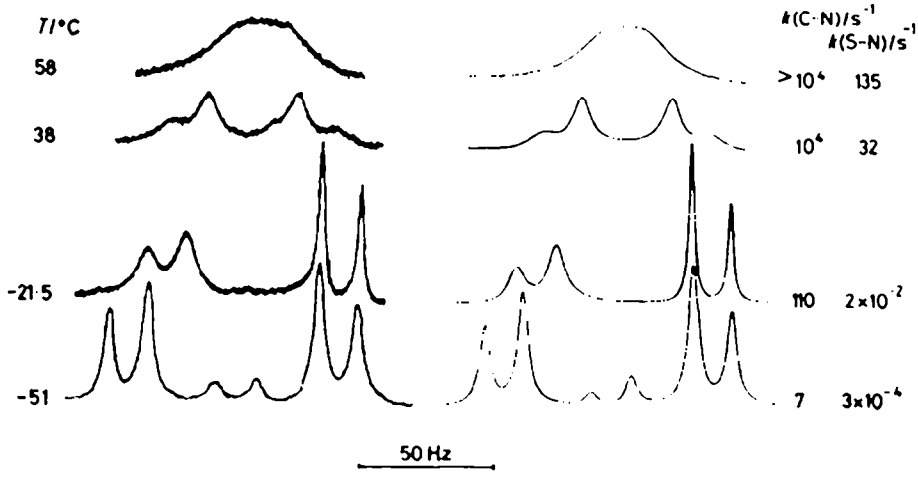
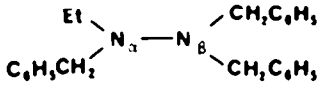


Fig. 1. Dynamic NMR spectra of the benzyl methylene protons of (5a); left: experimental; right: computed.[10]

The other possibility [situation (c)] is observed at intermediate temperatures in the spectrum of **5b**. The singlet observed at the fast exchange limit broadens upon cooling and splits in an asymmetrical fashion into two unequal singlets characteristic of the T_A (amide) configurational unit (Fig. 2, T = −49°). Upon further cooling these singlets broaden and eventually split into a pattern of two unequal AB quartets typical of situation (d) as in compound **5a**. Because of the different stereochemical consequences of stereomutations corresponding to T_A and T_C both first order rate constants (and torsional barriers) can be obtained by complete line shape analysis and can be unambiguously assigned to each of the processes. The examples above employ T_C and T_A processes as characteristic of chiral and achiral processes. Similar NMR consequences obtain for the inversional stereomutations I_C and I_A and need not be separately illustrated.

While the distinction between chiral and achiral processes can be made on symmetry grounds, this is not generally possible for differentiation of T_C from I_C or T_A from I_A. In fact, the similarity between T_C and I_C (or T_A and I_A) leads to some ambiguities which are discussed in the following section. Nevertheless, in some special cases, there are symmetry differences between these processes.

The NMR spectral behavior of tribenzylethylhydrazine (**6**) represents one such case.[11] Two types of labile configurational units were considered, resulting from either slow inversion of both



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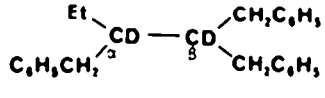

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nitrogen pyramids (I_C), or slow rotation about the N–N bond (T_C). If I_C were slow and T_C were fast on the NMR time scale, **6** would have the same symmetry and topomeric relationships as **7**, the stereostable carbon analogue (deuterated to avoid additional coupling) the analysis of which may be more straightforward. Since C_α is an asymmetric carbon atom the two benzyl groups attached to the prochiral carbon atom, C_β, are diastereotopic. In addition, the two methylene protons within each benzyl group are diastereotopic and we would expect to observe three AB quartets in the NMR spectrum. By extension, we would expect to observe the same type of spectral pattern for **6** if it belonged to class I_C, with slow inversion at both nitrogen atoms. The consequence of rapid nitrogen inversion but slow torsion about the N—N bond can be understood by reference to the hypothetical (time averaged) structure **8** which features planar nitrogen atoms. It is clear that **8** is achiral, as a result of the σ plane which passes through N_α and its three ligands. Consequently, the two benzyl groups attached to N_β are enantiotopic, as are the two methylene

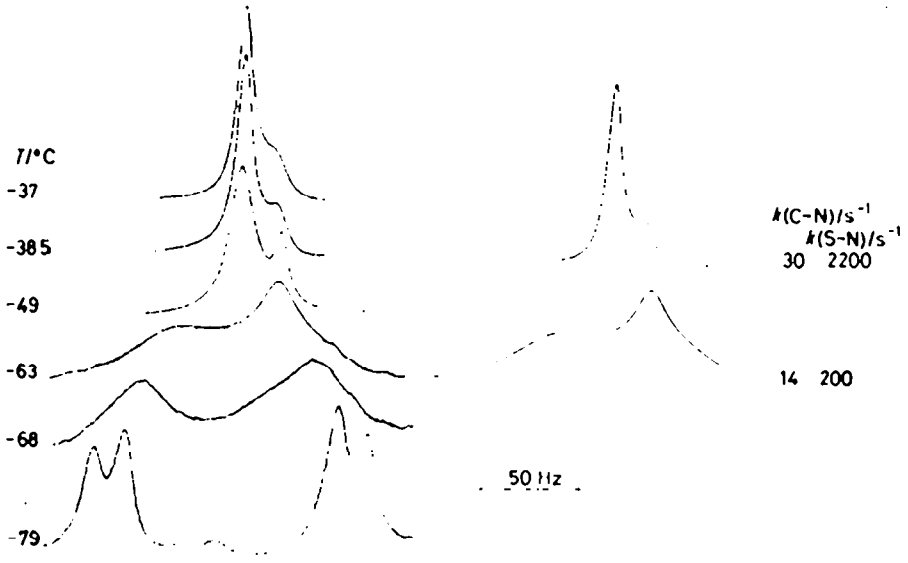
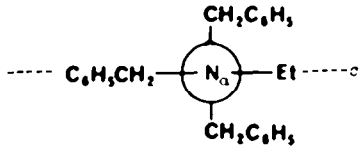


Fig. 2. Dynamic NMR spectra of the benzyl methylene protons of (5b); left: experimental; right: computed.[10]

protons in the benzyl group at N_α. The σ plane lies between and does *not* pass through the benzyl groups at N_β. Thus, while the two benzyl groups as a whole are enantiotopic, the two methylene hydrogens within each group are diastereotopic. If **6** belonged to class T_C (fast inversion and slow rotation), we would expect to observe a singlet for the benzyl methylene group at N_α, and a single AB quartet for the other two benzyl groups. The latter pattern was observed experimentally, and it was concluded that slow torsion about the hydrazine bond was responsible for the nonequivalence.



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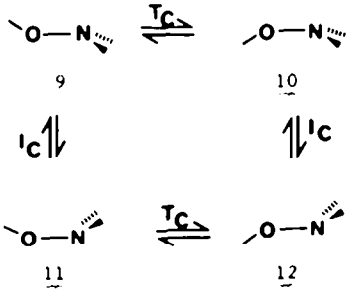
IV. TORSION–INVERSION AMBIGUITY

We have shown above that the four types of stereomutations and their associated configurational units can be divided into chiral and achiral subgroups which can be readily distinguished using NMR spectroscopy. By contrast, there is often a problem in distinguishing T_C from I_C and T_A from I_A. In fact, the mechanism for stereomutation of a single compound often involves both processes. As we shall see, the mode of combination can be described using the logical descriptors AND/OR. Alternatively, we shall draw an analogy between these two modes of combination and series and parallel electrical circuits. Both of these situations can best be understood by considering experimental examples. We exemplify the AND mode of combination using stereomutations of sulfenamides and hydroxylamines (T_C AND I_C). The OR mode will be illustrated using imine stereomutation (I_A OR T_A).

The hydroxylamine system provides an example for the T_C AND I_C mechanistic dichotomy (Scheme 6). In order to bring about an interconversion of one ground state structure **9** into its antipode **12** (degenerate racemization), *both* N inversion (I_C) *and* O–N bond torsion (T_C) must take place. Inversion at oxygen via a structure with linear substitution would have the same effect as O–N torsion but we expect this process to be much higher in energy and need not consider it in this situation.

We have good grounds for supposing that inversion and torsion are sequential, and that the combined process of torsion and inversion would require a higher energy transition state. In the first place, if the two processes were independent, we would expect energy of activation for the combined process to be on the order of the sum of the individual activation energies, since both destabilizing geometric distortions are present. In the present examples the two processes, I_C and T_C, are not entirely independent and their interaction provides further exaltation of the activation energy for the combined process. Experimental and theoretical evidence discussed in a subsequent section indicates that the torsional barrier is increased at the inversion transition state, and that the inversion barrier increases at the transition state for torsion.

The potential energy surface (Fig. 3) depicts the results of one such theoretical investigation of a system ($HSCH_2^-$) closely related to the hydroxylamines and sulfenamides.[12] Examination of the surface indicates that the lowest energy pathway involves sequential inversion and torsion. It is evident that the combined torsion–inversion pathway (corresponding to direct **9** ⇌ **12**



Scheme 6. Inversion rotation combination in hydroxylamines (and sulfenamides). T_C AND I_C.

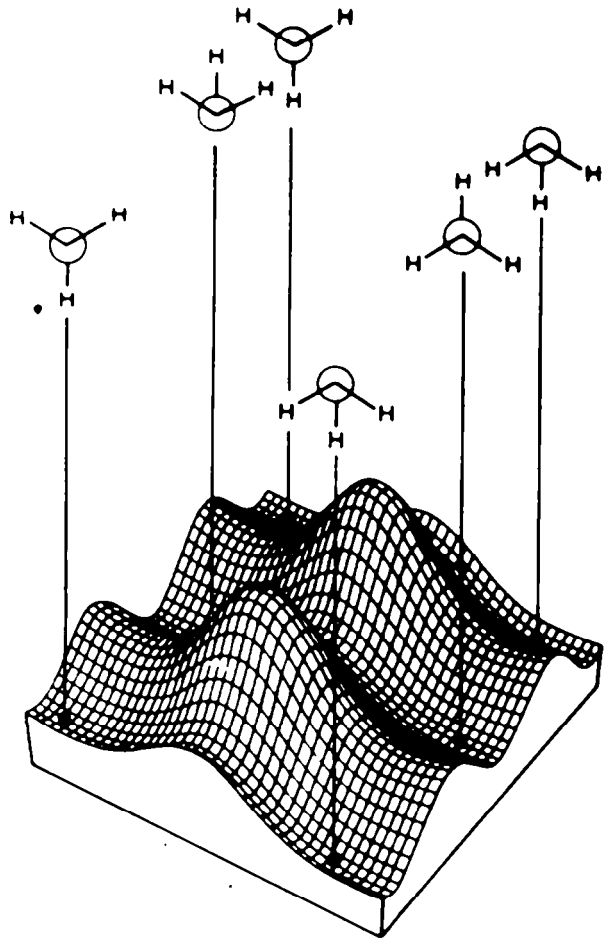
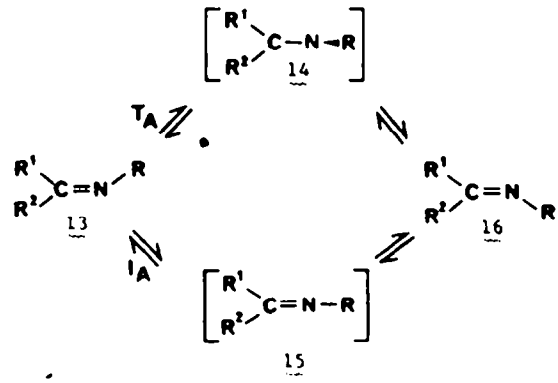


Fig. 3. The rotation–inversion surface of $^{-}CH_2OH$. The rotation and inversion barriers (Y to W) are 10.6 and 20.5 kcal/mol, respectively. The W conformation is 6.67 kcal/mol higher than the Y conformation.[12]

interconversion) would require passage over the highest peak, in the center of the potential surface.

Because I_C and T_C are related in an AND fashion, the process with the higher activation energy represents the rate determining step for stereomutation. Thus, the barrier measured by coalescence in a prochiral probe group provides information only concerning the process which has the higher barrier. No information about the fast step can be obtained by the NMR method, as long as only coalescence due to degenerate racemization (**9** $\rightleftharpoons$ **12**) is observed. If the minor diastereomer (**10, 11**) were sufficiently populated to permit detection by NMR, the coalescence associated with interconversion of diastereomers (**9, 12** $\rightleftharpoons$ **10, 11**) would provide the second of the two first order rate constants. However, such a situation has not been observed in studies on acyclic sulfenamides, hydroxylamines or hydrazines. The inability to observe the minor diastereomer could result from either one of these reasons: an unfavorable equilibrium constant ($K = [9]/[10] \gg 10$), or a free energy of activation for the fast step below the lower limit of the DNMR method (i.e. $\Delta G^{*} < 5$ kcal/mol), or accidental coincidence of signals due to the two diastereomers. In those cases where the rate determining step is I_C, the overall process can be called inversion dominant. We may assign the chiral unit in the molecule to I_C, and refer to a center of chirality as the origin of the observed nonequivalence. Similarly, we may term the mechanism rotation dominant when T_C is the slow step, and focus on the axial chirality of the T_C configurational unit.

The imine stereomutation depicted in Scheme 7 exemplifies the OR mode (T_A OR I_A). This mode of combination differs from the AND mode (Scheme 6) in that stereomutation can be accomplished via either of two different pathways: by torsion (T_A, transition state **14**) or by planar inversion (I_A, transition state **15**). In the general case we may suppose that the free energies of activation for the two alternative processes are different. If they differ substantially, stereomutation will take place



Scheme 7. Inversion rotation combination in imines, T_A OR I_A.

only via the lower energy transition state. Thus we may refer to the mechanism as inversion dominant (I_A) when **15** is lower in energy than **14**, or rotation dominant (T_A) if **14** is the lower in energy. It may be noted that our definitions of rotation–inversion dominance in the OR combination focus on the lower energy transition state, while in the AND combination the higher energy transition state is the determining factor. In fact, no experimental information can be obtained in the OR mode concerning the higher energy transition state. This is also in contrast to the AND situation, where information about the *lower* energy transition state is often inaccessible. These two situations also differ in that in the AND case there are exceptions where both processes can be studied (when K_{eq} is not very different from 1), whereas in the OR case the inaccessibility of the slower rate process is required by transition state theory. Such "forbidden" processes can, however, be studied using MO calculations, and this is an example where calculations can provide information about processes which are in principle prohibited from being studied experimentally.

An interesting contrast between the OR and AND combinations relates to the shapes of "broken" Hammett plots, which are potentially obtainable in linear free energy relationships of stereomutations. Let us consider a hypothetical situation in which the free energy of activation for inversion correlates linearly with Hammett substituent constants (σ) and is characterized by a positive reaction constant (ρ), where torsion is similarly characterized by a negative ρ (Fig. 4), and the two lines cross within the range of accessible σ values. Since only the higher barrier is measured for the AND combination, the observed correlation for this mode will be V shaped when a crossover in the rate determining step occurs (Fig. 4a). By contrast, an inverted V characterizes the change from a rotation dominant to an inversion dominant mechanism in the OR situation (Fig. 4b). Of course, the reaction constants need not be of opposite signs. In the

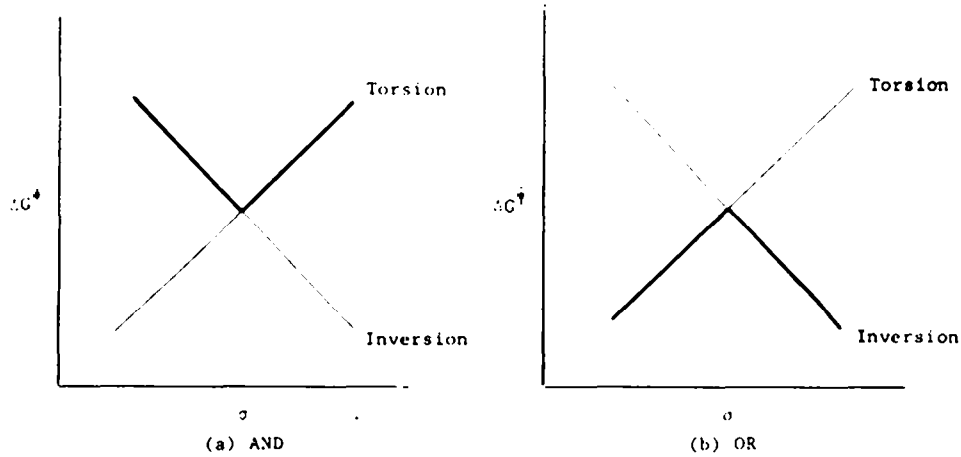


Fig. 4. Hypothetical Hammett plots for (a) AND and (b) OR mechanistic combinations. The heavy line represents the observable free energies of activation.

general case, a positive change in the slope will be observed for the AND combination when a cross over in the rate determining step occurs, while a negative change in slope would be observed for the OR combination.

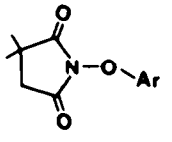
One way of visualizing the difference between the AND and OR combinations is by analogy to series and parallel combinations of resistors in electrical circuits. When their resistances differ by several orders of magnitude, it is clear that the overall resistance in a series arrangement essentially equals that of the larger resistor, and that of the smaller resistor can be neglected. This is like the AND situation, where resistance is analogous to free energy of activation and the larger resistor corresponds to the rate determining step. Conversely, the parallel arrangement is a model for the OR combination: here the overall resistance is essentially equal to the lesser of the two resistors. Here the bulk of the current passes through the smaller resistor just as most of the molecules pass through only the lower energy transition state in an OR combination.

V. THE ROTATION–INVERSION DICHOTOMY IN SUBSTITUTED HYDROXYLAMINES

The ambiguity between the I_C and T_C processes within the AND mode of combination discussed in the previous section is well manifested in a long literature controversy concerning the dominance of the barrier in hydroxylamines.[13] Experimental evidence indicates that comparable barriers have been measured for both processes. Thus the rotation–inversion ambiguity does not involve assigning either I_C or T_C mechanism for the entire class of substituted hydroxylamines, but rather determining to which of these classes individual compounds or sets of closely related compounds belong.

A. *Unambiguous* T_C *and* I_C *barriers*

In some cases it is clear which step is rate determining and which type of chirality should be assigned to the molecule. For example, the barrier to nitrogen inversion can be lowered by attachment of a substituent which can conjugate with the N lone pair and render it planar or nearly planar. Compounds **17–20** represent cases in point where we are confident in attributing non-equivalence of diastereotopic groups to the axial chirality at the oxygen–nitrogen bond and attributing the experimentally measured free energy of activation to the T_C process.[14–16]



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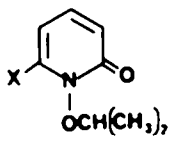
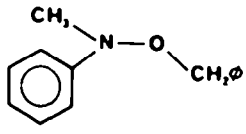


18

(a) X = H

(b) X = Cl



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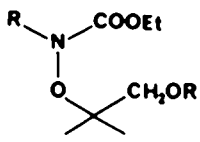

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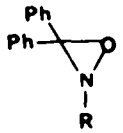

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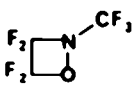

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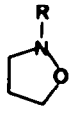
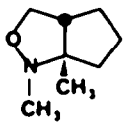


23

(a) R = CH_3

(b) R = $CH(CH_3)_2$



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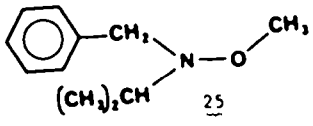


25

Incorporation of the O and N atoms into a small, (3-, 4- or 5-membered), ring increases the barrier to N inversion and at the same time fixes the CONC dihedral angle at or near the geometry of the torsional transition state. In such compounds, e.g. **21**,[17] **22**,[18] **23**[19] and **24**,[20] the barrier must

be an inversion barrier (I_C), and nonequivalence is due to central chirality at N. The increase in the inversion barrier is great enough in oxaziridines to permit isolation of optical isomers which are stereostable at room temperature.[17]

Compounds **17–24** represent extreme cases, in which one of the two processes (I_C or T_C) can be excluded. The situation in simple trialkyl hydroxylamines is more ambiguous. In fact, the rotation–inversion dichotomy in acyclic substituted hydroxylamines has been the subject of considerable controversy in the literature. Three criteria have been applied to indicate whether a stereomutation of acyclic N,N-dialkylhydroxylamines is rotation or inversion dominant. These make use of conjugative, steric and solvent effects.

B. *Conjugation effects*

The first criterion involves comparison of barriers with those of compounds where N inversion may be excluded, viz **17–20**. The comparison with N-acylhydroxylamines would ignore the considerable steric and electronic differences between acyl and alkyl groups and as a result cannot be regarded as definitive. Nevertheless, the fact that barriers in **17** and **20** are in the range 12–15 kcal/mol, and are comparable to those of typical trialkylhydroxylamines, provides *prima facie* evidence that torsional barriers cannot be ignored. A more meaningful comparison is between **19**[15] and **25**,[21] in which the essential difference is replacement of a phenyl by an isopropyl group. The barrier in **25** is 4.3 kcal/mol higher than in **19**, which is clearly rotation dominant. This suggests that the barrier in **25** is inversion dominant.

C. *Steric effects*

The second criterion makes use of the difference in steric effects on rotation and inversion. The change from the pyramidal ground state to the planar transition state during N inversion involves an increase in the distances between ligands on nitrogen. Thus, relief of strain due to steric interactions in the ground state will be manifest in steric acceleration of inversion when the steric requirements of the ligands are increased. This effect is apparent in the comparison of the nitrogen inversion barriers in the isoxazolidines **23a**, **23b** and **24**, in which the bulkiest ligand at nitrogen changes from primary through secondary to tertiary (**23a**, $\Delta G^{\ddagger}$ = 15.6 kcal/mol;[19a] **23b**, 14.8 kcal/mol;[19b] **24**, 13.7 kcal/mol[20]). By contrast, the torsional transition state involves eclipsing of substituents at oxygen and nitrogen and as a result torsional barriers increase with increasing steric bulk of the ligands. An example is provided by **18a** and **18b**: replacement of H by Cl is occasioned by an increase in the torsional barrier from 9.3 to 10.0 kcal/mol.[15] The very large barriers in compounds **20** are also a manifestation of steric deceleration.[16]

While these effects are clearly displayed by the model systems, where the I_C and T_C mechanisms can be unambiguously assigned, their application to N,N-dialkylhydroxylamines has led to conflicting results. In some series, steric acceleration is found, while in others deceleration is observed. Table 1 includes the experimental data relevant to the problem of steric effects in trialkylhydroxylamines.

Two kinds of comparisons can be made: (a) between alkyl groups of different sizes, and (b) between hydrogen and alkyl groups. Comparison of the data for **25**, **26** and **27** (in $CDCl_3$ solvent) indicates a small increase in barrier (0.5 kcal/mol) upon replacement of the Me group by the more bulky i-Pr. The direction of this effect is in accord with the T_C mechanism, although some workers have argued that the magnitude of this effect is small.[22a] Other workers have based their assignment of an inversion dominated mechanism on even smaller steric effects on the barriers. Thus, Hall *et al.* noted a slight decrease in the barrier of **28**, the *o*-tolyl analogue of **26**, although it is difficult to argue that this change (0.1 kcal/mol) is outside the range of experimental error.[23] A larger decrease (0.7 kcal/mol) is observed upon introduction of an *ortho* chlorine (**29**), which might have been expected to have a steric effect similar to the *ortho* methyl in **28**.

The steric effects observed upon replacement of hydrogen attached to oxygen or nitrogen by an alkyl group are also problematical. Comparison of the barriers for **31** and **25** in $CDCl_3$ indicates that the barrier does not significantly change upon replacement of H by a Me group. A similar comparison between **30** and **26** suggests a small decrease in barrier (< 0.5 kcal/mol) for the same change, although the exact magnitude is uncertain since R^2 is Me in **26** and $PhCH_2$ in **30**. Furthermore, the comparison of **30** and **31** indicates only a negligible change upon replacement of benzyl by the bulkier isopropyl. While these results do not exhibit the steric deceleration

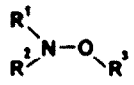


Table 1. Barriers in selected substituted hydroxylamines

Compound	R^1	R^2	R^3	$\Delta G^{\ddagger}$ kcal/mol	Solvent	Reference
26	$PhCH_2$	CH_3	CH_3	9.9	Acetone-d_6	22
				12.3	$CDCl_3$	21
				12.7	Toluene-d_8	23
25	$PhCH_2$	$(CH_3)_2CH$	CH_3	12.8	$CDCl_3$	21
27	$PhCH_2$	CH_3	$(CH_3)_2CH$	12.8	$CDCl_3$	21
28	o-$CH_3C_6H_4CH_2$	CH_3	CH_3	12.6	Toluene-d_8	23
29	o-$ClC_6H_4CH_2$	CH_3	CH_3	12.0	Toluene-d_8	23
30	$PhCH_2$	$PhCH_2$	H	12.8	$CDCl_3$	24
				12.2	CD_3OD	24
31	$PhCH_2$	$(CH_3)_2CH$	H	12.9	$CDCl_3$	24
				12.3	CD_3OD	24
32	$PhCH_2$	CH_3	H	12.4	Acetone-d_6	22
33	$(CH_3)_2CH$	H	CH_3	10.7	CD_3OD	25
34	$PhCH_2$	H	CH_3	$<8.7^a$	CD_3OD	25

[a]The low temperature limit was not reached, but the barrier could be estimated on the basis of differential line broadening of the benzyl-methylene and N-methyl resonances.

characteristic of the T_C mechanism, they also fail to demonstrate the steric acceleration expected for the I_C mechanism. In fact, the latter comparison may be best accommodated within the T_C framework, since the torsional transition state involves eclipsing of the O-ligand (R^3) with *the smaller* of the N-ligands (R^1, R^2). In both **30** and **31** the smaller N-ligand is a benzyl group; thus no change in barrier is expected.

On first glance the comparison of **32** and **26** measured in acetone-d_6 might seem to provide strong evidence of steric acceleration. However, comparison of the three values reported for the barrier in **26** in different solvents indicates that the large effect may be associated with a dramatic and unexplained solvent effect. It may be noted that change of solvent from $CDCl_3$ to methanol-d_4 results in relatively small change in the barriers for **30** and **31**, although the OH group might be expected to interact more strongly with polar solvents than does OMe. It is for these reasons that we cannot regard the comparison of **32** and **26** as definitive evidence for the I_C process.

The final evidence in Table 1 concerns **33** and **34**. The low barriers for both compounds as well as the difference between them was given as evidence for the T_C mechanism. Here, too, possible effects of methanol solvent interacting with the polar NH group might make one reluctant to compare these barriers with barriers measured in other solvents.

While individual pieces of evidence in Table 1 might be taken to support either one or the other of the mechanisms, when we consider all of the data taken together we must conclude that steric effects fail to provide a useful criterion for distinguishing between the mechanisms.†

D. *Solvent effects*

The initial paper on stereomutation of hydroxylamines suggested that the barrier to nitrogen inversion is lowered in nonpolar solvents, although the authors did not consider the possibility of a torsional mechanism.[22b] This conclusion was based on the judgement that the planar transition state for nitrogen inversion would be more polar than the pyramidal ground state. Alternatively, one might argue that the ground state might be more strongly solvated, especially by protic

†The reader may wonder why this lengthy analysis of Table 1 is provided in view of our conclusion that the analysis of steric effects in this system is not meaningful. It is because we and other workers have come to conflicting conclusions on the basis of individual comparisons without considering the evidence in full.

solvents. Indeed, a rate retardation for inversion was observed for isoxazolidine **24** in methanol solvent.[20]

The N,N-dialkylhydroxylamines **30** and **31** exhibit rate enhancements in methanol (Table 1). While this might have been regarded as evidence for the T_C mechanism, the authors preferred an I_C mechanism, because they considered the substituent at oxygen (hydrogen) to be too small to produce a significant rotational barrier.[24] Since solvent effects have been neither extensively investigated nor well understood, most workers have been reluctant to attribute great significance to conclusions based on solvent effects.

We have examined three criteria for resolving the I_C–T_C ambiguity in acyclic trialkylhydroxylamines. As we have seen, the solvent and steric effects do not permit reliable conclusions to be made. Seemingly, the strongest evidence derives from the conjugative criterion, the comparison of N-phenyl- and N-isoproyl-hydroxylamines **19** and **25** which favors inversion dominance (I_C). The evidence accumulated thus far indicates that both I_C and T_C barriers are substantial. Since substituent and solvent effects can change the shape of the energy surface, it seems reasonable to suppose that subtle changes in structure or medium should be capable of shifting the mechanism for topomerization from I_C to T_C or *vice versa*.

VI. THE ROTATION–INVERSION DICHOTOMY IN SUBSTITUTED SULFENAMIDES

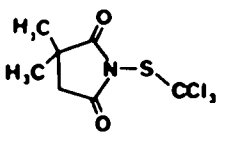
The stereomutation of sulfenamides also represents a T_C AND I_C combination and can be represented by the transformations depicted in Scheme 6 if the O atom is replaced by S. We may consider the sulfenamide functionality as the site of either a chiral center (at N) or a chiral axis (along the S–N bond) depending upon which of the two processes corresponds to the rate determining step.

In contrast to the situation for substituted hydroxylamines discussed in the previous section, the experimental evidence permitting assignment of individual compounds to either the I_C or T_C categories is straightforward and consistent. As in the case of the hydroxylamines, some compounds can be unambiguously assigned to one of the categories. In addition to the criteria based upon steric and conjugative effects, which give consistent results, evidence based upon electronic effects and X-ray crystallographic study support the conclusion that the rate determining step in the stereomutation of acyclic N,N-dialkylsulfenamides is torsion about the N–S bond (category T_C).

A. *Unambiguous* T_C *and* I_C *barriers*

When the sulfenamide nitrogen atom bears an acyl or aryl substituent, the inversion barrier is lowered substantially.[7,10] Thus we can make unambiguous assignment of **5**, **35** and **36** to the T_C category since the rate determining step for degenerate racemization must involve torsion about the S–N bond. The barriers in these compounds are quite substantial and suggest that comparable torsional barriers might be expected in N,N-dialkylsulfenamides as well.

When the N atom is incorporated into a 3-membered ring the rate of nitrogen inversion is lowered.[26-28] Thus it becomes reasonable to suppose that the barriers associated with coalescence of the ring methylene protons and/or the geminal Me groups in **37** and **38** correspond to the I_C barrier. That this is the case is demonstrated by the difference in polar substituent effects between **37** and **38** and analogous acyclic sulfenamides. These substituent effects, which are discussed in Section D, indicate that there is a change of mechanism in going from sulfenylaziridines to acyclic sulfenamides. A similar comparison of substituent effects and trends in barriers for sulfenylaziridines, sulfenylazetidines and acyclic sulfenamides also allowed the conclusion that the I_C process was rate determining for sulfenylaziridines but that the other compounds should be assigned to the T_C category.[28]



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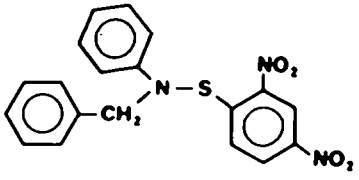

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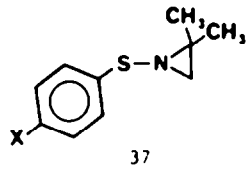

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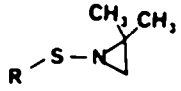
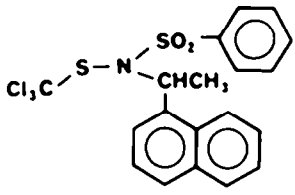
X = OCH_3, CH_3, H, Cl, Br, NO_2



38

a. R = CCl_3
b. R = CF_3
c. R = CH_3
d. R = $C(CH_3)_3$

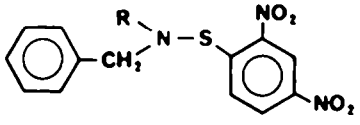
A final case in which an unambiguous assignment can be made involves **39**, the crystal structure of which has been determined by X-ray diffraction.[29] The geometry at nitrogen in this compound did not differ greatly from planarity. The sum of bond angles at nitrogen equaled 356.5° compared with the values of 328° and 360°, which correspond to sp^3 and sp^2 hybridization, respectively. Since the geometry at nitrogen in this molecule is so close to planarity in the ground state, we can be sure that the substantial barrier measured for stereomutation ($\Delta G^* = 18.3$ kcal/mol)[48] cannot be a barrier to nitrogen inversion.



39

B. *Conjugation effects*

The criterion for mechanistic assignment based on conjugation effects can be applied to the sulfenamides just as it has been applied to the substituted hydroxylamines. Thus, the barrier for the N-phenylsulfenamide **36** can be compared with that of the N-isopropyl analogue **40**. While the



36 R = C_6H_5
40 R = $CH(CH_3)_2$

barrier for the N-phenylhydroxylamine **19** is somewhat smaller than that in the N-isopropyl analogue **25**, the opposite trend is observed in the sulfenamide series. The N-phenylsulfenamide **36** actually exhibits a slightly higher barrier than that in **40**: **36**, $\Delta G^* = 17.8$ kcal/mol; **40**, $\Delta G^* = 16.5$ kcal/mol.[7] This strongly suggests that the N–S torsional barrier is greater than the barrier to inversion of the nitrogen pyramid, and that **40**, as well as **36**, should be assigned to the T_C category.

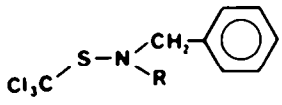
C. *Steric effects*

In contrast to the situation for hydroxylamines, the interpretation of steric effects on barriers to stereomutation of sulfenamides is straightforward. Compounds **41a–d** represent a series of sulfenamides with ligands of increasing size at nitrogen. As the size of the substituent is increased, the magnitude of the observed barrier becomes greater (Table 2). This steric deceleration is characteristic of T_C barriers. The alkanesulfenylaziridines **38c** and **38d** show the opposite trend. Here the barrier decreases with increasing steric bulk consistent with the I_C barrier observed for these compounds. These are not the only compounds for which such a steric comparison can be

Table 2. Steric effects on T_C and I_C barriers in sulfenamides

Compound	R	ΔG^* kcal/mol	Solvent	Ref.
41a	CH_3	14.4	$CDCl_3$	7b
41b	CH_2CH_3	15.6	$CDCl_3$	7b
41c	$CH(CH_3)_2$	16.0	$CDCl_3$	7b
41d	1-Adamantyl	16.9	C_6H_5Br	7b
38c	CH_3	13.3	$CDCl_3$	28
38d	$C(CH_3)_3$	12.2	$CDCl_3$	28

made. However, in all cases except for the sulfenylaziridines,[28] the same trend is observed: steric deceleration typical of T_C barriers.[7] Not surprisingly, **42** with the highest reported sulfenamide torsional barrier has very bulky substituents at nitrogen ($\Delta G^* = 21.4$ kcal/mol).[30] The barrier in **43** is apparently even higher (> 23 kcal/mol) since coalescence could not be observed up to 160°.[28]



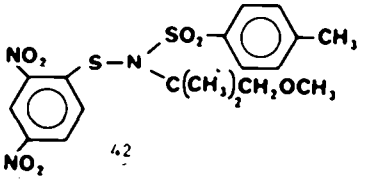
41

a. R = CH_3

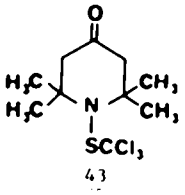
b. R = CH_2CH_3

c. R = $CH(CH_3)_2$

d. R = 1-Adamantyl



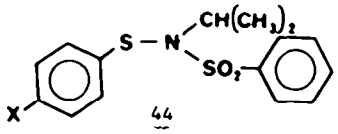
42



43

D. *Polar substituent effects*

Comparison of the effects of polar substituents on observed barriers to stereomutation of sulfenylaziridines and acyclic sulfenamides can also be used to provide information concerning the torsion–inversion dichotomy. One comparison utilizes the Hammett reaction constants for the *para*-substituted benzenesulfenylaziridines **37**[27] (I_C), N-arenesulfenyl-N-benzylurethanes **5**[10] (T_C) and the acyclic sulfenylsulfonamides **44**.[31] The two systems with unambiguous T_C and I_C barriers (**5** and **37**, respectively) provide benchmarks against which the acyclic sulfenylsulfonamides **44** can be evaluated.



44

a. X = OCH_3

b. X = CH_3

c. X = H

d. X = Cl

e. X = NO_2

The effect of polar substituents on the sulfenyl phenyl rings in **37** and **44** is best analyzed by using the plots of the free energy of activation (ΔG^*) as a function of the Hammett substituent constants (σ) and the free energy form of the Hammett equation (eqn 1). It may be noted that the slope of the linear least squares line (i.e. the coefficient of σ) contains two variables, namely the temperature and ρ, the Hammett reaction constant. Since the product of ρ and the absolute

temperature is constant, this equation implies that ρ should be temperature dependent. Equation (1) may be modified by replacement of $T\rho$ by a modified, temperature independent Hammett reaction constant ρ' to yield eqn (2).[31]

This approach is well suited to the analysis of kinetic data obtained using dynamic NMR spectroscopy. The most reliable kinetic data are free energies of activation obtained at, or near, the coalescence temperature. Since these generally correspond to different temperatures for a series of compounds, the use of eqn (2) obviates the need for conversion of data to a common temperature. Such conversions often involve extrapolations of rates over a large enough range that errors can be introduced. In general, the use of eqn (2) requires that free energies of activation be temperature independent (or very nearly so) over the temperature range of measurement. This is normally the case since most stereomutations are known to exhibit entropies of activation close to zero. For purposes of comparison with Hammett reaction constants in the literature, it is useful to use a hypothetical reaction constant corresponding to a temperature of 300°K (eqn 3). It is this ρ_{300} which is used in the following discussions.

$$\Delta G^{\ddagger} = 2.3\,RT\rho\sigma + \Delta G_0^{\ddagger} \tag{1}$$

$$\Delta G^{\ddagger} = 2.3\,R\rho'\sigma + \Delta G_0^{\ddagger} \tag{2}$$

$$\rho_{300} = \frac{\rho'}{300}. \tag{3}$$

Hammett plots for series **37** and **44** are presented in Figs. 5 and 6. Linear least squares analysis using eqn (2) afforded the reaction constants: **37**,[27c] $\rho' = -49 \pm 37$, $\rho_{300} = -0.16 \pm 0.11$; **44**,[31] $\rho' = -582 \pm 55$, $\rho_{300} = -1.9 \pm 0.2$; **5**,[10] $\rho' = -275 \pm 29$, $\rho_{300} = -0.9 \pm 0.1$. It is clear that a substantial negative reaction constant is observed for the T_C barriers in **5** as well as those in the

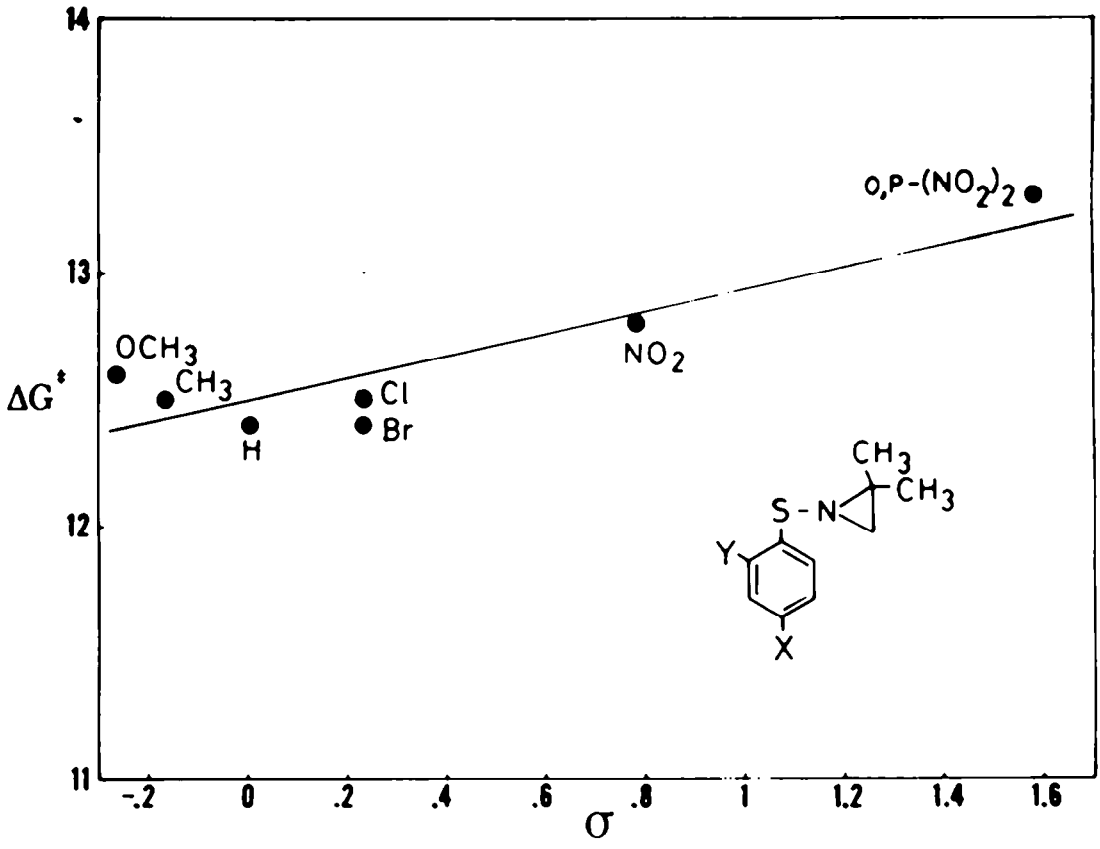


Fig. 5. Hammett plot of free energies of activation for degenerate racemization in **37**.[27c]

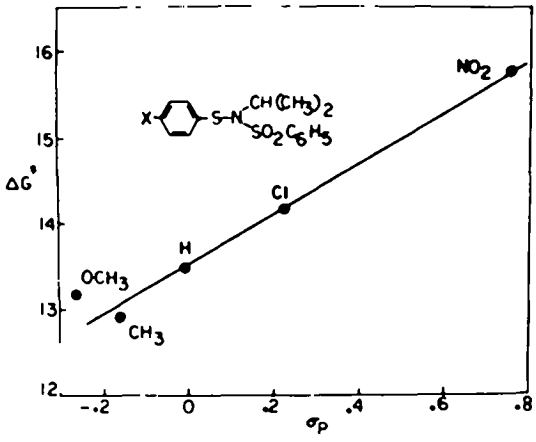


Fig. 6. Hammett plot for series **44**.[31]

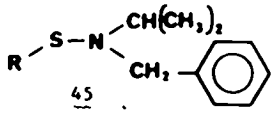
Table 3. Free energies of activation for T_C and I_C barriers in trihalomethanesulfenamides

Compound	R	$\Delta G^{\ddagger}$ kcal/mol	Solvent	Class	Ref.
38a	CCl_3	9.2	$CH_2Cl_2/CHFCl_2$	I_C	27c
38b	CF_3	10.4	CH_2Cl_2	I_C	27c
45a	CCl_3	16.0	$CDCl_3$	T_C	7b
45b	CF_3	13.3	$CDCl_3$	T_C	7b

acyclic system **44**, while that for the I_C system **37** is close to zero. Thus, **44a–e** are assigned to the T_C category.

Another difference in substituent effects involves comparison of barriers in trihalomethanesulfenylaziridines, **38**, with those in the acyclic N,N-dialkyltrihalomethanesulfenamides **45a** and **45b**. In the case of the sulfenylaziridines, the trichloro **38a** has the lower barrier, while it is the trifluoro compound which has the lower barrier in the acyclic series **45** (Table 3). It is clear from these comparisons that the measured barriers in the acyclic series, which are larger, must be associated with the T_C process since it is not conceivable that the N inversion barriers in the acyclic compounds are higher than those in their aziridine counterparts. These phenonema may be best understood in terms of steric substituent effects. It is the relative steric bulk of the trichloromethyl and trifluoromethyl groups rather than their relative polar effects that cause the change in trends of barriers in the cyclic and acyclic sulfenamides. Thus, steric acceleration of nitrogen inversion is observed in **38a** relative to **38b**, and deceleration of S–N torsion due to the bulky CCl_3 group is responsible for the opposite trend in barriers in **45a** and **45b**.

The data in Table 3 also indicate that the presence of the 3-membered ring is associated with a decrease in the T_C barrier as well as an increase in the I_C barrier since the observed barrier corresponds to the higher of the two in a T_C AND I_C system. For this reason, one of the assignments in Table 3 may not be definitive. It seems that the CCl_3 group lowers the I_C (N inversion) barrier (relative to CF_3) in **38a** to such an extent that the measured barrier could conceivably correspond to the T_C process.[27]



45

a, R = CCl_3

b, R = CF_3

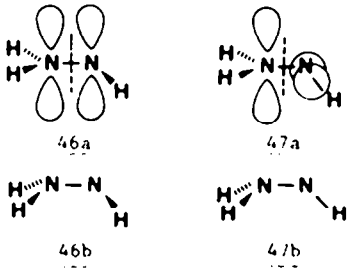
VII. MOLECULAR ORBITAL CONSIDERATIONS

In a previous section we have discussed the fundamental stereochemical distinctions between the amide and sulfenamide (T_A and T_C) torsional processes. This stereochemical distinction may be derived by examination of the molecular orbital (MO) descriptions of the two types of molecular systems. In this section we shall develop a simple PMO model, which illustrates how the barrier type derives from orbital populations. This analysis will also make clear the relationship between inversional and torsional processes and indicate the effects of two- and four-electron interactions on I_A and I_C as well as T_A and T_C processes. In a subsequent discussion we review some of the theoretical work based on SCF-MO calculations.

A. *Perturbational molecular orbital* (PMO) *analysis*[32]

We have chosen to use the hydrazyl species H_2NNH as a convenient model since this constitution can give rise to models for all four categories: I_A, I_C, T_A and T_C.[33c]

Let us first examine the torsional processes, T_A and T_C, using structures **46a** and **47a**, which have planar geometry at the $-NH_2$ group. The hydrazyl cation H_2NNH^+ belongs to class T_A, and will have a ground state geometry **46a** and a torsional transition state **47a**. Conversely, the hydrazyl



anion ground state will be the nonplanar structure **47a** and **46a** will represent the torsional transition state. Thus, the anion belongs to the T_C class.

We begin the PMO analysis of this molecular system by dissecting it conceptually into two fragments, the planar $-NH_2$ fragment and $-NH$. These fragments can now be combined to form either structure **46a** or **47a**. The major fragment orbitals of the NH_2 and NH fragments are the N p-lone pair orbitals. The NH fragment has also an in-plane, hybrid lone pair orbital of substantial s character and hence lower energy than the p-orbital. Since we consider π overlap as the main interaction between the fragments, the latter hybrid orbital can be neglected. When the two fragments are combined in geometry **46a**, overlap between the two fragment p-orbitals is at a maximum, and the orbitals mix to form π and π^* MO's (Fig. 7). In the hydrazyl cation only the lower bonding level is populated (two-electron interaction). This corresponds to a π bond and strongly stabilizes this geometry. This situation is like that in imines and amides in which the ground state is planar. In amides the effective π bonding is between the nitrogen lone pair and the low lying CO π^* orbital. In general, two-electron π interactions lead to T_A configurational

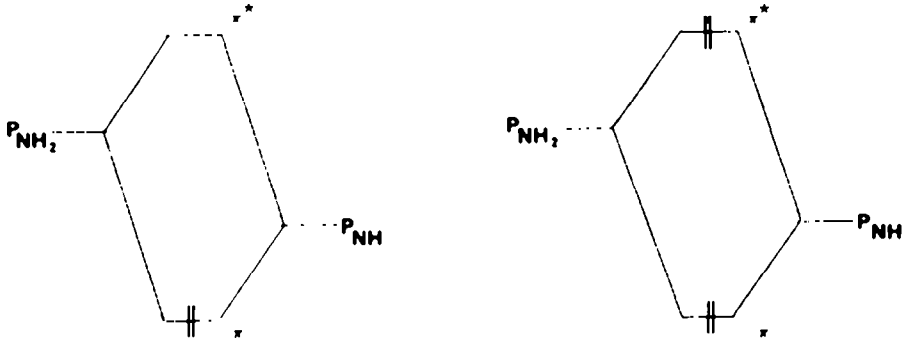


Fig. 7. Schematic representation of π interaction in the hydrazyl (a) cation and (b) anion.

units with planar ground states like **46a**. When the two fragments are arranged as in **47a**, the two p-orbitals are perpendicular to each other and their mutual overlap is reduced to a minimum. Consequently the two-electron stabilization is lost, and geometry **47a** corresponds to the T_A transition state. Such two-electron interactions can occur between two non-bonding p-orbitals as in aminoboranes and imines, or between n and π^* orbitals as in amides, nitrosamines, and enamines.

In the hydrazyl anion model, both π and π^* levels are populated when the fragments are combined in geometry **46a**. Since the antibonding π^* orbital is raised in energy more than the π orbital is lowered, this four-electron interaction results in net destabilization.[32] As a result, geometry **46a** corresponds to the transition state for torsion in the hydrazyl anion, a T_C process. Thus, the change from a two-electron interaction to a four-electron interaction interchanges the roles of **46a** and **47a** as ground and transition states, and switches the mechanism from T_A to T_C. We note that both two-electron and four-electron interactions operate only in **46a** and are turned off in **47a**. Whether **47a** is ground or transition state depends on whether the interaction in **46a** is destabilizing or stabilizing. In general, only four-electron interactions between nonbonded electron pairs are substantial enough to give rise to T_C barriers which can be measured by NMR methods. However, there are numerous classes of molecules which bear this kind of functionality and give rise to T_C configurational units. These include, besides the sulfenamides and hydroxylamines which are the major subjects of this review, hydrazines, peroxides, disulfides, selenenamides, sulfenates, and other compounds with heteroatom–heteroatom single bonds.

In order to consider the effect of two-electron and four-electron interactions on N inversion, we shall consider the pyramidalization of the NH_2 group in structures **46a** and **47a** in both the hydrazyl cation and anion to produce structures **46b** and **47b**. As we have indicated above, both conjugative interactions are minimized in structures **47a** and **47b** since the two p-oribtals are perpendicular. Since simple amines are pyramidal with small inversion barriers, we might expect **47b** to be more stable than **47a** in both the cation and the anion. In both cases, we would expect the inversion barriers to be small. Both two- and four-electron interactions will be greater in **46a** than **46b** since the NH_2 lone pair has more p-character and π-overlap will be greater in **46a**. In the cation, the two-electron interaction will stabilize **46a** (more than **46b**), and we expect it to be the gound state. In the anion, however, the four-electron interaction will destabilize **46a** more than **46b** and we would expect **46b** to be more stable and feature an inversion barrier which is higher than that expected for **47b**.

Our model allows a number of predictions. The two-electron systems should prefer geometries which are planar at the NH_2 group (or only slightly pyramidal with only very small inversion barriers) but should adopt geometry **46a** and exhibit substantial barriers for the T_A process and the I_A process (inversion at the NH). This corresponds to the situation in imines which are certainly planar but can exhibit T_A or I_A barriers, as well as amides, which are nearly planar and feature high T_A barriers and very low I_C barriers. We may note that while the ground state for the two-electron systems is most closely represented by the planar structure **46a**, the transition state for torsion is most likely close to the pyramidal structure **47b**.

The four-electron systems should adopt structure **47b** as their ground state structures, and we might suppose that the four-electron interactions will give rise to high T_C barriers but will not contribute as much to the I_C barriers, since the four-electron interactions are minimized in both **47a** and **47b**. If, however, the geometry could be constrained by incorporation of both atoms in a small ring we might consider **46b** to represent the ground state for a cyclic four-electron system, e.g. the oxaziridines. In this case we can see that the geometry is appropriate for the four-electron interaction to make a major contribution to the I_C barrier. Indeed, such an effect was found in MO calculations of eclipsed N,N-dimethylhydroxylamine.[33a,b] In summary, acyclic four-electron systems are expected to exhibit substantial T_C barriers and cyclic four-electron systems should exhibit substantial I_C barriers.

If we consider the effect of the second hybridized lone pair in the four-electron systems, we can conclude that there may be a small increase in the I_C barrier but this should be substantially less than the effect on inversion barriers in cyclic systems. We note that consideration of four-electron interactions indicates that the effect on the inversion barrier should be greatest at the torsional transition state (**46b**) and the effect on the torsional barrier should be greatest at the inversional transition state (**47a**). For this reason, we may conclude that the transition state for simultaneous

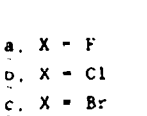
inversion and torsion **46a** should be higher than those for sequential inversion **47a** and torsion (**46b**) and that stereomutation will involve two steps: I_C AND T_C.†

One type of two electron interaction requires separate consideration, that involving interaction between a lone pair and an antibonding σ^* orbital. This kind of interaction has often been referred to as anionic or negative hyperconjugation.[34] If we consider an analogue of the hydrazyl system in which the NH moiety has been replaced by NX (where X is an electronegative atom or group) such an interaction becomes possible in **47a** or **47b**. In this geometry the nonbonding orbital on the NH_2 fragment can overlap with the antibonding σ^* orbital associated with the N–X σ-bond. This kind of interaction, which can be represented for the anion using canonical structure **48a** and

48a **48b**

48b, will have different effects on the T_C and I_C barriers. Since **47a** will be stabilized more than **47b** the I_C barrier will be decreased but since both structures **47** will be stabilized relative to the counterpart structures **46** the torsional barrier T_C will be increased.

An interesting case in which both n-σ^* and n-π^* 2-electron interactions have been proposed involves the effect of halogen atoms and aryloxy groups, X, on the amide torsional barriers (T_A barriers) in **49**.[35,36] There are two effects associated with X which can lower the barrier. The initial



49

a. X = F
b. X = Cl
c. X = Br
d. X = OPh
e. X = p-$NO_2C_6H_4O$

explanation focused on the possibility of stabilization of the T_A transition state by overlap of the N lone pair with the C–X σ^* orbital.[35] The alternative explanation[36,37] which has been supported by experiment, attributes the barrier lowering to overlap of the nonbonded electrons on X with the C–O π^*-orbital which diminishes amide conjugation and ground state stabilization.

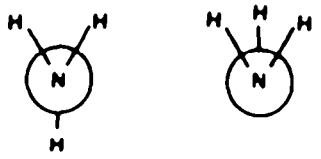
As we have seen, n–n four-electron interactions and n–σ^* two-electron interactions (negative hyperconjugation) can both increase T_C torsional barriers. It is not surprising that there has been considerable controversy concerning which of the effects is responsible (or which is more important) for the anomeric effect, which is related to the T_C barriers discussed here.[38]

While the n–n four electron interactions increase both T_C and I_C barriers, negative hyperconjugation has opposite effects on the T_C and I_C barriers and this provides one means of distinguishing between them. This is illustrated in Section VI–D by the effect of trihalomethyl groups on I_C barriers in sulfenylaziridines and T_C barriers in acyclic sulfenamides. While the trihalomethanesulfenyl group is associated with high T_C barriers in one system, it is associated with low I_C barriers in the other, as compared with other sulfenyl groups for which negative hyperconjugation should be less important.

B. *Molecular orbital calculations*

Several MO calculations on hydroxylamine and related compounds have been published. From the earliest of these reports[39,40] it has become evident that hydroxylamine and its analogues (e.g. CH_2–OH anion, which is isoelectronic with hydroxylamine)[12,41] have two torsional ground states, the so called "Y" and "W" shaped conformations (corresponding to **9** and **10** in Section iii, respectively, depicted here in Newman projection). The conformations of these compounds are determined mainly by the tendency of the lone pair orbitals to avoid mutual overlap, resulting in the gauche effect.[42] Eclipsing the lone pairs with bond-pairs is less destabilizing than is overlap of adjacent lone pairs,[13] in accord with the four electron hydrazyl anion model discussed above.

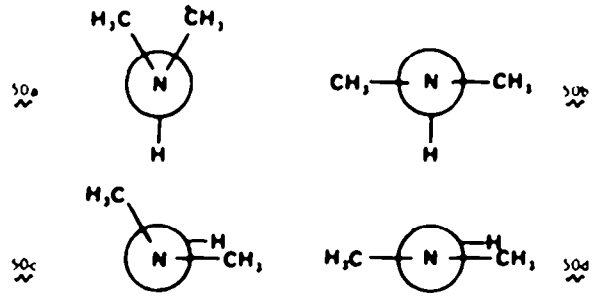
† These qualitative PMO conclusions are fully borne out in *ab-initio* SCF-MO calculations on the hydrazyl system.[14]



9. Y conformation 10. W conformation

The torsional process in hydroxylamine and its substituted derivatives has been analyzed by Radon *et al.* in terms of a Fourier component analysis of the torsional potential functions, and compared with numerous other "ethane like" molecules.[43] While ethane itself is characterized by a pure three-fold barrier, with zero contributions from one- and two-fold potential barriers, the torsion of hydroxylamine is best described by strong and essentially equal one-fold and two-fold potential functions, with only a minor contribution of a three-fold component. The one-fold barrier is taken to represent a dipole moment effect which is minimized at the Y conformation and reaches a maximum at the W structure. The two-fold barrier contribution, which dominates the torsional process in NH_2OH, was interpreted as a two-electron effect, n to σ^* (or n to pseudo-π^*) hyperconjugative stabilization of both the Y and W conformations.[43] A similar approach focusing mainly on two-electron interactions was used by Brunk and Weinhold.[44] Within the PMO framework elaborated above, we can ascribe the two-fold component to four-electron as well as two-electron interactions. No attempt to resolve the rotation–inversion ambiguity was made in these theoretical studies.

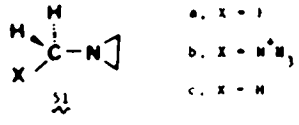
Such an attempt was undertaken in a semiempirical (CNDO/2 and INDO) study on N,N-dimethylhydroxylamine (**50**).[33]† Nitrogen inversion barriers were calculated for the relaxed acyclic **50a**, as well as for the eclipsed molecule, **50c**, which represents a model for 4- or 5-membered ring cyclic hydroxylamines. The I_c barrier for the cyclic compound was found to be 2.1 kcal/mol higher than that for the acyclic compound (14.8 and 12.7 kcal/mol, respectively), in excellent



agreement with experiment. It was concluded that observed barriers in acyclic trialkylhydroxylamines represent I_c stereomutations. The torsional potential profiles for **50** at the inversional ground state (pyramidal N) as well as at the corresponding transition state (planar N) were calculated (Fig. 8).[33]

It is evident from Fig. 8 that the torsional barrier is lower at the relaxed, pyramidal N structure than at planar N, indicating, as discussed earlier, that simultaneous rotation–inversion can be excluded.

The importance of negative hyperconjugation and its effect on aziridine inversion barriers was demonstrated recently and analyzed in detail, using nonempirical SCF–MO calculations.[47] Reduced barriers due to n-σ^* two-electron interactions at the inversional transition states in **51a,b**,



51

†Despite severe doubts that have been cast on the ability of CNDO and INDO to reproduce nonbonded interactions,[45,46] the study described here yielded excellent agreement with experiment and provided a satisfying qualitative picture of hydroxylamine topomerizations. This could be a result of either implicit inclusion of the effects of nonbonded interactions in the semi-empirical parameters, or could be due to the fact that most arguments based on repulsive lone pair interaction can be rationalized also in terms of lone-pair antibond hyperconjugation.[47,48]

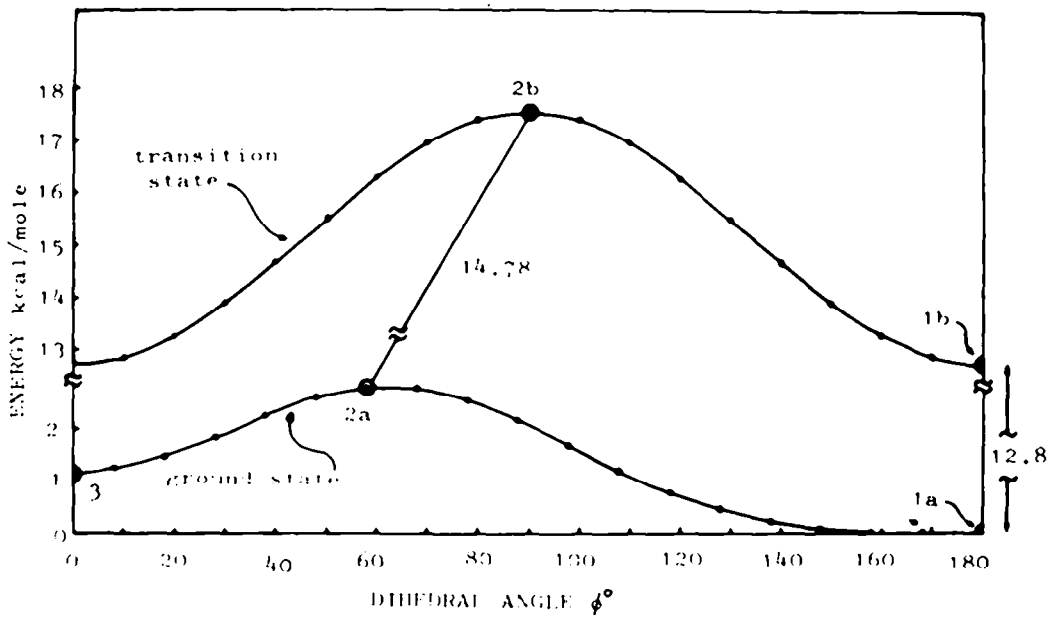


Fig. 8. CNDO/2 calculated energy profiles for N–O torsion for the pyramidal and planar states of dimethylhydroxylamine (**50**).[33]

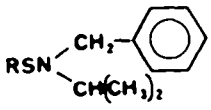
relative to **51c**, were associated with substantial N–C bond shortening and C–X bond lengthening, as required by the hyperconjugative model. This model is further discussed in Section VIII. Compounds **51** serve as models for sulfenylaziridines **38**, and the calculations agree well with experiments and provide additional evidence for the importance of negative hyperconjugation in the latter system.

VIII. POLAR SUBSTITUENT EFFECTS

Polar substituents have a significant effect on T_C barriers in sulfenamides, as well as in hydroxylamines and hydrazines.[1e] These substituent effects are particularly remarkable since only torsional barriers are involved and no formal charges are developed in the torsional transition state. This section will summarize the observed polar substituent effects, focusing mainly on sulfenamides, and we will discuss them in terms of steric factors and the electronic effects discussed in Section VII. We can distinguish two kinds of polar substituent effects. The σ-effects, or inductive effects operate by electron withdrawal from a σ-orbital at sulfenyl sulfur, while the π-effects, or resonance effects, involve withdrawal from a nonbonding orbital at sulfur.

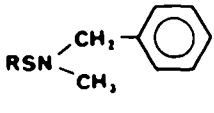
A. *Inductive (σ) effects*

The attachment of inductively withdrawing groups at sulfenyl sulfur is associated with increased torsional (T_C) barriers. Partly for this reason, many studies of sulfenamide torsional barriers have involved trichloromethanesulfenamides and trifluoromethanesulfenamides which exhibit much higher barriers than their alkane sulfenyl analogs.[7,48] This effect can be clearly seen in comparisons of the barriers in the sulfenamides **52**, **53** and **54** which have atoms of quite different electronegativities attached to S (Table 4).[49-51] Clearly, the sulfenamides bearing the more electronegative



52

a. R = Cl
b. R = $OCH(CH_3)_2$
c. R = $N(CH_3)_2$
d. R = $N(CH_2C_6H_5)CH(CH_3)_2$
e. R = $SCH(CH_3)_2$



53

a. R = Cl
b. R = $OCH(CH_3)_2$
c. R = $N(CH_3)CH_2C_6H_5$
d. R = $SSN(CH_3)CH_2C_6H_5$

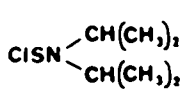


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Table 4. Torsional (T_C) barriers in sulfenamides with heteroatoms at sulfur[a]

Compound	Heteroatom	Electro-negativity	Coalescence Temp. (°C)	$\Delta G_c^{\ddagger}$ kcal/mol	Ref.
52a	Cl	3.16	31	15.1	49
53a	Cl	3.16	39	15.5	50
54	Cl	3.16	5	14.5[b]	51
52b	O	3.44	48	16.0	49
53b	O	3.44	15	14.3	50
52c	N	3.04	-51	10.9	49
52d	N	3.04	-55	10.7	49
53c	N	3.04	-55	10.7	50
52e[a]	S	2.58	-62	10.1	49
53d	S	2.58	-46	10.1	50

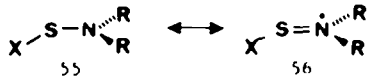
[a]All spectra except for that of 52e were measured in deuterated toluene. The barrier for 52e was measured in deuterated acetone.

[b]The barrier was reported as 60.8 kJ/mol.

O and Cl atoms attached to S feature much higher barriers than those with the less electronegative N and S atoms. The data for compounds **52** indicated a monotonic increase with the atomic (Pauling–Allred) electronegativity,[52] while for **53** the values for the Cl and O compounds are reversed. It should be noted that the data for chlorosulfenyl compounds can be considered as less reliable than those for other compounds in Table 4 since they can undergo topomerization via mechanisms which involve chlorine exchange as well as by torsion.[50,51] Such mechanisms which can involve bimolecular exchange as well as heterolysis of the S—Cl bond are thought to be less important in toluene as solvent but cannot be ruled out. Experimental evidence indicates that such mechanisms can effectively compete with torsion in chloroform.[50]

Inductively withdrawing groups have a different effect on the inversion (I_C) barriers in sulfenylaziridines. Here, the presence of a trichloromethyl or a trifluoromethyl group at sulfenyl sulfur is associated with a lowered barrier. Based upon an analysis of the effect of steric factors upon the I_C barriers in sulfenylaziridines, it was estimated that the electron withdrawing capability of the trihalomethyl groups lowered the inversion barrier by about 2–2.5 kcal/mol.[27]

Both effects, the raised T_C barriers and the lowered I_C barriers are readily interpreted in terms of the two-electron interaction discussed in Section VII. Overlap of the nitrogen lone pair with the σ^*-orbital associated with the S—X σ-bond leads to greater stabilization when the X group is electronegative. This stabilization raised the T_C barrier since overlap is possible in the torsional ground state but not in the torsional transition state. The two electron stabilization has an opposite (barrier-lowering) effect on the I_C barrier since overlap and stabilization are increased in the inversion transition state as the p-character of the nitrogen lone pair is increased. The effects on both I_C and T_C barriers can be expressed using canonical structures **55** and **56**. The contribution



55 56

of negative hyperconjugation expressed by structure **56** is associated with increased S–N double bond character which is reflected in increased torsion and decreased inversion barriers.

B. *Resonance (π) effects*

The effects of para substituents in arenesulfenamides on I_C and T_C barriers provided one of the criteria for resolving the rotation–inversion dichotomy discussed above in Section VI. The acyclic arenesulfenamides exhibit a substantial enhancement of the torsion (T_C) barrier when electron withdrawing groups are present,[31] while the inversional (I_C) barriers in arenesulfenylaziridines are essentially insensitive to electron withdrawing groups as illustrated in Figs. 5 and 6. While this

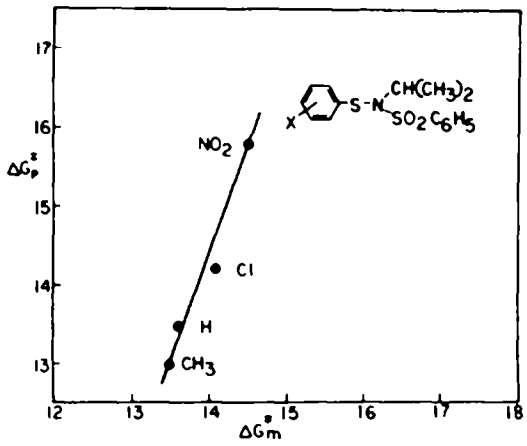


Fig. 9. Free energies of activation for compounds with para substituents as a function of those for compounds with the same substitution in the meta position (Exner plot).[31]

comparison is sufficient to characterize the two systems as exhibiting different barrier types, it does not provide an explanation for the remarkable dependence of the T_C barrier on the electron withdrawing ability of the sulfenyl phenyl ring.

The effect of electron withdrawing groups in *para*-substituted benzenesulfenamides does not derive from an interaction with σ or σ^* orbitals at the sulfenyl sulfur as do the effects discussed in Section VIIIA above. Rather it has been shown that π-overlap between the aromatic ring and an orbital S is involved. This is evident in the Exner plot (Fig. 9).[31] This is a plot of free energies of activation of *para*-substituted compounds as a function of those of compounds with the same substituents in the *meta*-position. Exner has shown that such plots feature slopes near unity (< 1.2) when inductive effects only are involved.[53] A much greater slope as in the present case is an indication that a "thorough resonance" interaction is involved.

While the initial explanation of the π-effect involved d-orbital conjugation, a number of subsequent experimental studies ruled out this explanation. For example, an explanation based upon d-orbital conjugation is not consistent with the trends in amide and sulfenamide barriers in the N-benzyl-N-arenesulfenylurethanes, **5** discussed above in Section III. In that system it was found that electron withdrawing substituents did not affect the amide (T_A) barrier although they led to significant enhancements of the sulfenamide (T_C) barriers.[10] This indicates that the electron withdrawing substituents do not interact with the nitrogen lone-pair orbital as required by the explanation based upon d-orbital conjugation. Subsequent experiments have suggested two possible explanations for the resonance effect, one based upon changes in 4-electron interactions[10] and a second which has been termed the "electrosteric effect".[30]

The "four-electron interaction" model is a discussion of lone pair repulsion in terms of simple PMO concepts. It provided an explanation for the intuitively disturbing observation that sulfenamide rotational barriers *increase* when electron withdrawing substituents are attached to the sulfenyl phenyl ring in **44**, **5** and similar compounds. This observation meant that the lone pair repulsive interaction, which is responsible for the T_C barriers (as discussed above using the hydrazyl model) increases when electron density is withdrawn away from the S–N bond. The model focuses on the π interaction between the sulfur p-lone pair and the N lone pair (Fig. 10). Interactions involving the in-plane lone pair on sulfur are less important due to lack of suitable symmetry, and can be ignored. The interaction shown in Fig. 10 involves four electrons, and is, therefore, repulsive and responsible for the high energy of the torsional transition state. The effect of an electron withdrawing substituent is to lower the energy of the sulfur p-lone pair orbital by way of conjugation across the phenyl ring (Fig. 10b). As a result, the two interacting orbitals are closer in energy, and the π interaction is more intense. This is a repulsive π-interaction, and this means that in the substituted case the destabilizing interaction at the T_C transition state is greater and, hence, the barrier measured is higher.†

† The four-electron repulsion is not directly related to the energy ΔE but to the mean energy, E°, of the interacting orbitals. However, changes in ΔE bring about indirect changes in overlap and matrix elements, which may operate to increase overall repulsion.[10]

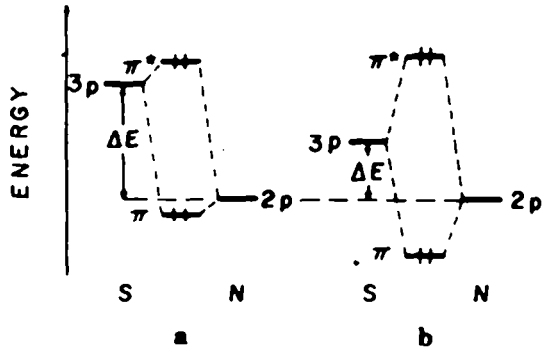
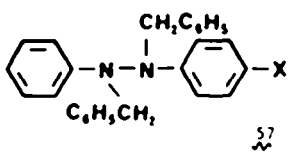


Fig. 10. Schematic diagram of the four electron interaction between lone pairs on S and N at the transition state for rotation about the N–S bond: (a) without substituent; (b) with an electronegative substituent: smaller ΔE and greater interaction.

Various experimental observations are accounted for by this model, including the Hammett relationships discussed above,[10,31] as well as the insensitivity of amide rotational barriers in 5[10] and nitrogen inversion barriers in aziridines 37 to changes in substitution.[27] The model suggests that in cases where the interacting lone pair orbitals are degenerate, any substitution that removes the orbital degeneracy will result in weaker repulsion and a lower barrier. However, this expectation was not borne out experimentally: the T_C barriers measured for a series of para-substituted dibenzylhydrazobenzenes 57,[34] increased linearly with increasing substituent constants σ^-(57,



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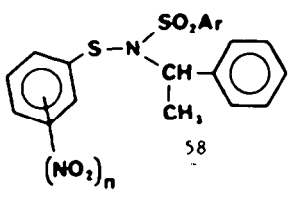
a, X = OCH_3 d, X = Cl
b, X = CH_3 e, X = CN
c, X = H

$\rho_{300} = -1.09$), rather than displaying a "broken" Hammett plot with its maximum point at $\sigma^- = 0$ for X = H (Table 6).

The major evidence supporting the alternate explanation, the electrosteric effect, derived from studies on the T_C barriers in trinitrobenzenesulfenamides.[30] While the increase in the number of nitro groups in sulfenamides 58 from zero to two increases the T_C barrier, incorporation of a third nitro group (to form a 2,4,6-trinitrobenzenesulfenamide) is accompanied by a barrier decrease (Table 5).



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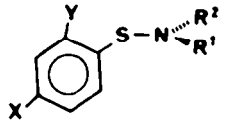

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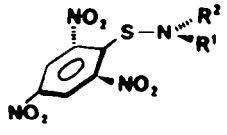

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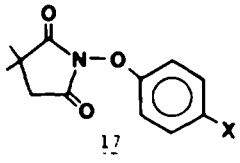
Table 5. Equilibrium constants and torsional barriers in nitrobenzenesulfenamides, 58[30]

Compound	n(position)	Ar=	K	$\Delta G^{\ddagger}$
58a	0	phenyl	1	13.0
58b	1(4)	p-tolyl	1.8	14.7
58c	1(2)	p-tolyl	1.9	18.4
58d	2(2.4)	phenyl	2.5	19.7
58e	3(2.4.6)	p-tolyl	1.1	13.8

The interruption of the trend to higher barriers with increasing number of electron withdrawing substituents was ascribed to steric inhibition of resonance, which led to a change in the ground state conformation of the sulfenamide from one in which the arene ring is coplanar with the CSN plane **59** to one in which the two planes have a considerable dihedral angle **60**. The geometry which is necessary for observation of the electrosteric effect, i.e. **59**, is one in which the aromatic π-system can conjugate with the p-lone pair on S. This conjugation which stabilizes the sulfenamide ground state geometry is lessened or removed in the transition state, since steric interactions with the eclipsing substituent on nitrogen become much more severe. The conjugation can be viewed as adding to the stiffness of the arene–sulfur bond and consequently changing the effective steric bulk of the phenyl ring. The more electron withdrawing the aryl ring, the more difficult it is to accomodate the close approach of eclipsing groups at nitrogen by twisting about the aryl–sulfur bond.

In support of this interpretation, it was noted that the magnitude of the decrease in the torsional barrier upon introduction of the third nitro group was not a constant but was related to the steric bulk of the substituents at nitrogen. The barrier decrease was smallest when one of the substituents at nitrogen was a small (primary) substituent. A second argument was based upon the thermodynamic asymmetric induction[55] which is observed for sulfenamides **58** and is represented by the diastereomer equilibrium constants in Table 5. The induction is due to differences in the steric interactions in the two diastereomers between the substituents at the asymmetric C atom and the substituent at the sulfenyl sulfur. As the data in Table 5 indicate, the effects of nitro substitution on the barrier and equilibrium constant are similar suggesting a similar (steric) explanation for both. The interruption of the electrosteric effect is noted in both the barrier and equilibrium constants when two *ortho* nitro groups are present.

Resonance effects of the type discussed in this section have also been observed in substituted hydroxylamines and hydrazines. Hydroxylamines **17** belong to the T_C category, since N inversion



17

must be rapid in this system due to conjugation with both CO groups. The I_C mechanism may also be excluded for the N,N'-dibenzylhydrazobenzenes (**57**), since the N atoms are conjugated with the aromatic ring systems. The T_C barriers for both series are given in Table 6.

Despite the greater scatter in the results for **17**, both series of compounds exhibit polar substituent effects which are similar in trend to those measured for sulfenamides. This suggests that a common mechanism operates in all three analogous compound types centered around single bonds between heteroatoms (N–S, N–O and N–N). However, the results for hydrazines do not fully support the mechanisms based on observations in sulfenamides. On the one hand, no "broken" Hammett plot was found for **57**, as could have been predicted by the four-electron repulsion model,

Table 6. T_C Barriers for hydroxylamines and hydrazobenzes

Compound	X	$\Delta G^{\ddagger}$ kcal/mol	Reference
17a	CH_3	9.35	14
17b	H	9.5	14
17c	Cl	9.2	14
17d	NO_2	10.0	14
57a	CH_3O	13.1	54
57b	CH_3	13.9	54
57c	H	14.2	54
57d	Cl	14.4	54
57e	CN	15.8	54

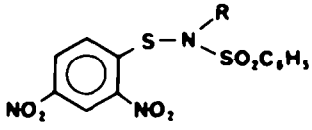
as discussed earlier in this section. On the other hand, the observation that led to the formulation of the electrosteric effect in sulfenamides is less dramatic in hydrazines. While the introduction of a third nitro group into a sulfenyl phenyl ring resulted in a large decrease in the T_C barrier in some sulfenamides, Dewar reported similar barriers for N,N-dibenzyl-N'-2,4-dinitrophenyl- and N,N-dibenzyl-N'-2,4,6-trinitrophenyl-hydrazines, 16.6 and 16.4 kcal/mol, respectively.[56]

IX. DIASTEREOMERIC SULFENAMIDES

The use of prochiral probe groups provides one way of demonstrating the chirality of labile chiral units and measuring barriers to stereomutation using NMR spectroscopy. Chiral probe groups can be used for the same purposes and, in addition, make possible a number of other experiments. In this section we shall compare the use of prochiral and chiral probe groups and illustrate some of these additional experiments using the sulfenamides as examples.

A. *Internal and external topomerism*

The incorporation of a chiral probe group, e.g. $Ph(CH_3)CH-$, into a molecule can be used to test for the chirality of the remaining portion of a molecule just as a prochiral probe group can. We use the two sulfenamides **61** and **62** as examples to illustrate the differences between these two kinds of probe groups.



61 R = $CH(CH_3)_2$

62 R = $CH(CH_3)C_6H_5$

When the prochiral isopropyl group is used, sulfenamide chirality is manifest in the chemical shift nonequivalence of the diastereotopic methyl groups. Since the two Me groups reside in the same molecule, we may describe them as being diastereotopic by internal comparison. The situation in **62** is somewhat different. Here, because of the chirality of the sulfenamide moiety, structure **62** will exist as an equilibrium mixture of two diastereomers. The two Me groups in the two diastereomers will be diastereotopic by external comparison and will exhibit chemical shift nonequivalence.

While the two Me doublets observed for **61** must be equal in intensity, the two Me doublets in the spectrum of **62** will have a ratio of intensities equal to the equilibrium constant relating to the two diastereomers. Thus, the use of chiral probe groups to test for chirality involves an ambiguity. If the equilibrium constant relating the two diastereomers is greater than *ca* 20 : 1, it is possible that the signal of the minor diastereomer will be too weak to be observed. On the other hand, there is an advantage to the use of chiral probe groups. Since the diastereotopic groups reside in different molecules the magnitude of the nonequivalence can be increased by differences in intermolecular interactions (e.g. solvation) which involve different degrees of complexation by the two diastereomers. This is not possible for groups which are diastereotopic by internal comparison although here, too, solvation can affect the magnitude of the nonequivalence.

Topomerization is observed for both **61** and **62** when torsion about the N–S bond becomes rapid on the NMR time scale. Internal topomerization occurs in **61**, while we will observe external topomerization for **62** since the coalescence is between corresponding groups in different molecules. The internal topomerization in **61** is a D→E topomerization while the external topomerization in **62** is a D→H topomerization (if we consider the interconversion of two diasteromeric molecules which have the same configuration at the asymmetric carbon atom and differ in configuration at the N–S chiral axis).

B. *Axial pseudoasymmetry in sulfenamides*

In sulfenamide **62**, which possesses a chiral ligand (the 1-phenethyl group) at N, torsion about the N–S bond interconverts two diastereomers and the sulfenamide moiety is axially chiral. When two constitutionally equal chiral groups are present as ligands at nitrogen, the situation is quite

different: the possibility of diastereomerism depends upon the relative configuration of the two chiral ligands. In this latter case, depending on the relative configurations of the ligands, the sulfenamide moiety may or may not generate a configurational unit, *viz.* a pseudoasymmetric (or pseudochiral) axis. This situation is best understood by considering an example.[57,58]

Bis-phenethyl amine can exist as two diastereomers, the *meso* diastereomer, **63a**, in which the two phenethyl groups have opposite configurations, and **63b**, the *dl*-diastereomer in which the two groups have the same configurations. When these two diastereomers are treated with 2,4-dinitrobenzenesulfenyl chloride, they are converted into the corresponding sulfenamides, **64**. The product obtained by reaction of **63b** is a single diastereomer, the *dl*-sulfenamide **64c**. In this compound the sulfenamide moiety does not contain a configurational unit. Since torsion about the S—N bond does not generate a new stereoisomer. On the other hand, reaction of the meso amine affords an equilibrium mixture of two diastereomeric sulfenamides, **64a** and **64b**, which can be interconverted by torsion about the S—N bond. Clearly, the sulfenamide moiety in **64a** and **64b** is a configurational unit, although it is not a chiral axis. Rather it is a unit of axial pseudoasymmetry (or axial pseudochirality). Application of the Cahn-Ingold-Prelog rules requires the subrule: R precedes S, in order to differentiate between the two enantiomeric ligands at nitrogen, and the two diastereomers are assigned configurational designations r and s. The lower case symbols signify that the configurational unit is not a chiral unit.†

The NMR spectra of the *meso* and *dl*-sulfenamides (Fig. 11) reflect the difference in stereochemistry discussed above. The signals corresponding to the methyl groups in the phenethyl ligands appear as two unequal doublets for the mixture of **64a** and **64b**, and as two equal doublets for the single *dl*-diastereomer **64c**. The two Me groups in each of the *meso* isomers are enantiotopic since they are interchanged by reflection in the C—S—N mirror plane, and each isomer gives rise to one doublet. Thus, the two unequally intense doublets arise from corresponding Me groups in diastereomeric molecules, i.e. Me groups which are diastereotopic by external comparison. By contrast, the *dl*-sulfenamide is asymmetric (point group C_1) and the two Me groups cannot be interchanged by any symmetry operation. As a consequence, they are diastereotopic (by internal comparison) and give rise to separate, equally intense doublets.

When either sample is heated, torsion about the N–S bond becomes rapid on the NMR time scale and coalescence to one Me doublet is observed. While the measured free energies of activation for torsion are comparable in the two systems, and the NMR behavior is similar (i.e. coalescence to a single doublet), the stereochemical descriptions of the events giving rise to coalescence are quite different. The coalescence of the doublets of unequal intensity, observed in the spectrum of *meso*-**64**, is associated with rapid reversible epimerization at the pseudoasymmetric axis, and the peaks which coalesce derive from methyl groups in two different diastereomers. By contrast, the process which results in the coalescence of the pair of doublets in the spectrum of **64c** is not a stereomutation but a topomerization, and the coalescing peaks are associated with two diastereotopic Me groups in the same molecule, which become homotopic on time average as torsion becomes rapid on the NMR time scale (D → H topomerization).

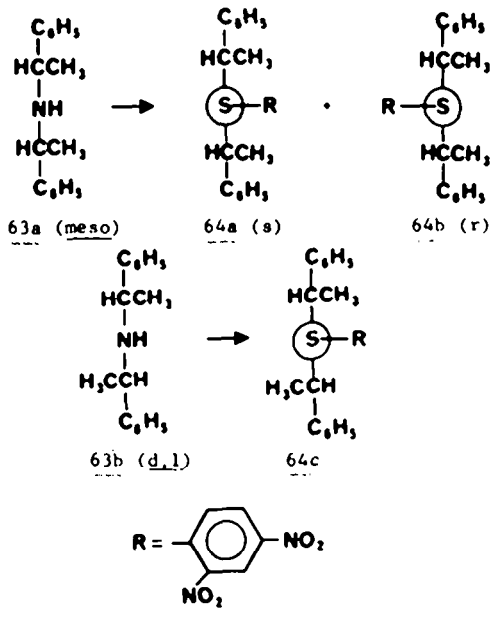
C. *Diastereomeric transformation*

The classical phenomena of asymmetric transformation and mutarotation[59] have their counterparts in the stereochemistry of stereolabile configurational units in what we term diastereomeric transformation.[60] However, rather than representing exceptional situations, diastereomeric transformation represents the usual situation when solid–liquid phase transition (i.e. crystallization and dissolution) occur in diastereomeric compounds which differ in configuration at stereolabile configurational units.[60,61]

Normally, the crystallization of a mixture of diastereomers from solution (or from the melt) results in the segregation of the diastereomers into different phases.‡ Typically, for stable chiral units, the solid is enriched in one diastereomer and the solution (or residual melt) is enriched in

†Cahn, Ingold and Prelog[2] point out an important difference between the upper case symbols, R and S for true chiral units (axes and centers) and the lower case symbols r and s, for pseudoasymmetric units. The upper case configurational designations are inverted upon mirror reflection of the molecular model, while the lower case designations for pseudoasymmetric units are invariant with respect to mirror reflection.

‡ We ignore the unusual situations where diastereomers form isomorphous crystals and co-crystallize in solid solutions.



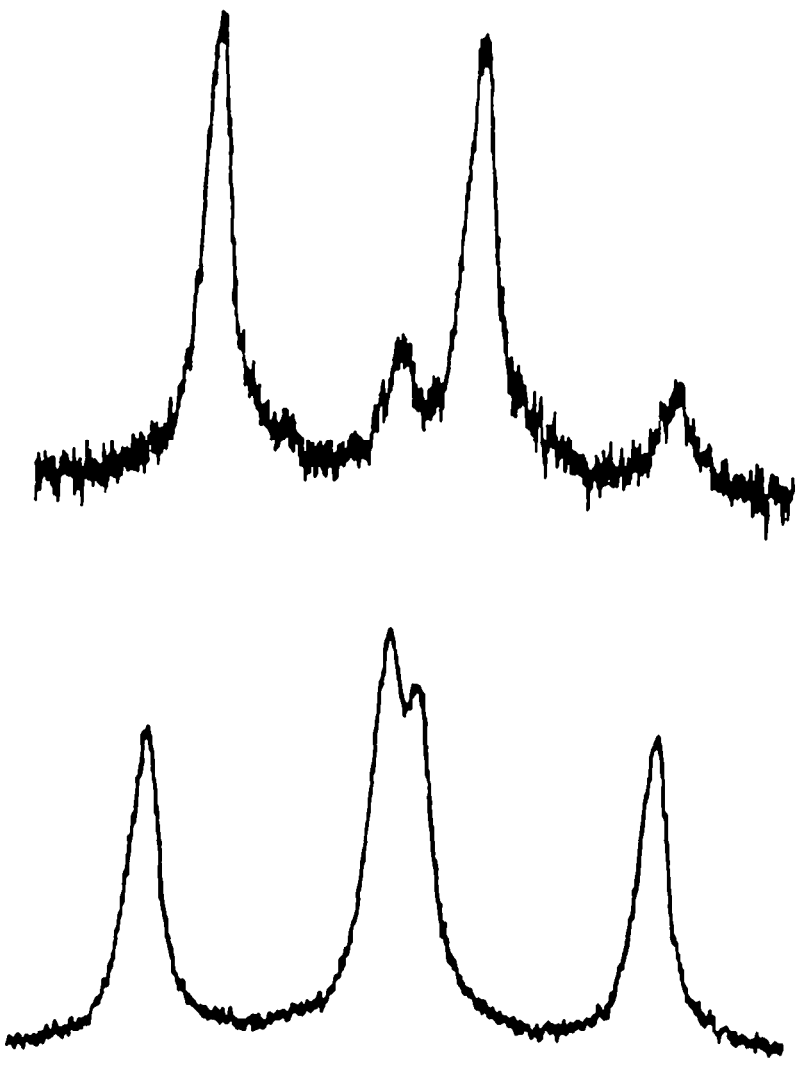


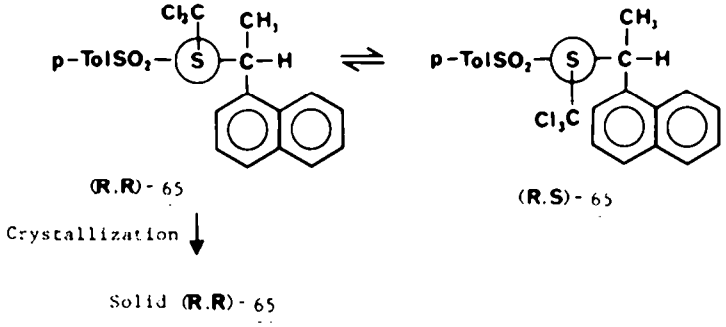
Fig. 11. Portions of the NMR spectra of N,N-bis-1-phenethyl-2,4-dinitrobenzene-sulfenamides **64** featuring resonances of the C-methyl groups. Upper curve: equilibrium mixture of *meso*-sulfenamides **64a** and **64b**. Lower curve: *d,l*-sulfenamide **64c**.[57]

the other. The composition of the solution begins to approach that of the eutectic mixture of diastereomers. When this composition is reached, the diastereomers both begin to crystallize, and the newly formed solid has the eutectic composition.

However, when the two diastereomers are in equilibrium and interconvert rapidly with respect to the time scale for crystallization, the enrichment of the solid phase in one diasteromer will not be accompanied by the enrichment of the solution phase in the other diastereomer. The composition of the liquid phase will be maintained at the equilibrium diastereomeric ratio. When crystallization of such a system has been allowed to proceed to completion, we may expect that the entire sample has been converted from a mixture of diastereomers into a single diastereomer. The identity of the diastereomer in the crystal phase is not directly predictable from the position of equilibrium, since it is not determined by the stability in solution but rather by the relative facility of crystallization.

This phenonemon occurs in the crystallization of glucose. In solution, the two anomers of glucose (the epimers which differ in configuration at C-1) are in mobile equilibrium. The crystallization of this mixture of α and β diastereomers leads to a solid composed only of a single diastereomer. The identity of the isomer obtained in the solid depends on the conditions of crystallization. This phenomenon has been termed asymmetric transformation. We prefer the term diastereomeric transformation since the phenomenon is not restricted to diastereomers which differ in configuration at a labile chiral unit, but is also observed for diastereomers which differ in configuration at a stereolabile achiral configurational unit, such as the C—N double bond in imines.[60]

The phenomena associated with diastereomeric transformation in sulfenamides can be exemplified using the diastereomeric sulfenamides corresponding to formula **65**.[62] Because of the



presence of an asymmetric carbon atom (which has the absolute *R*-configuration) **65** exists in solution as a mixture of diastereomers (*R,R*)-**65** and (*R,S*)-**65**, which differ in configuration at the sullfenamide chiral axis. This is reflected in the NMR spectrum which features two unequally intense doublets corresponding to the two C-Me groups in the 1-naphthylethyl moieties of the two diastereomers (Fig. 12, lower curve). Upon crystallization, a sharp melting solid is obtained which has been shown by X-ray crystallography to have the (*R,R*)-configuration.[63]

When crystallization of the mixture begins, the formation of the (*R,R*) crystal is more favorable and remains so since torsion about the N–S bond is rapid on the crystallization time scale (isolation time scale) and the equilibrium composition of the mother liquors is continually being reestablished. If the solid is redissolved at a temperature at which torsion is rapid (i.e. room temperature for **65**) the equilibrium is reestablished and the spectrum of the equilibrium mixture is observed. However, if the crystalline **65** is placed into solution at a temperature low enough that torsion about the N—S bond is slow on the isolation time scale, and the spectrum is measured without warming of the sample, the spectrum of the single isomer in the solid is observed (Fig. 12, upper curve). In the present case it is the more abundant diastereomer which is obtained upon crystallization. However, this need not be so. When the equilibrium mixture of the *E/Z* isomers of imine **66** is crystallized, it is the *less* abundant isomer which is obtained in the crystal.[60]

After dissolving the crystals at low temperature, the sample can now be warmed up to some convenient temperature and the growth of the second isomer monitored using NMR spectroscopy as the system approaches equilibrium. This latter experiment is quite analogous to the mutarotation

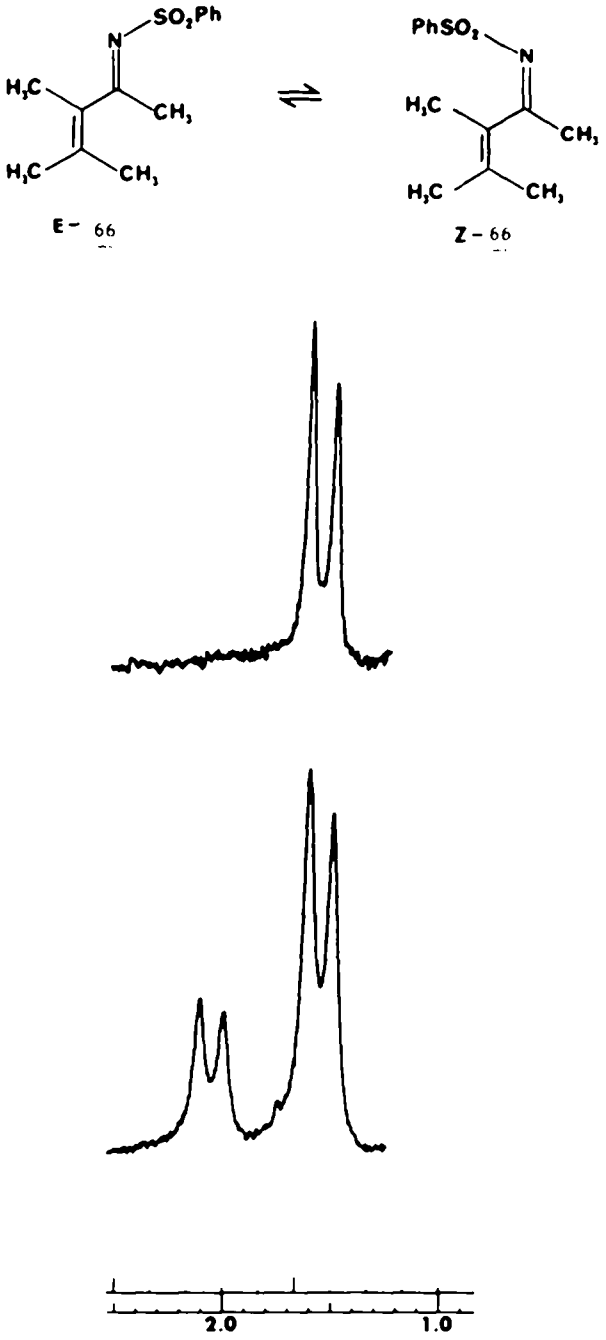


Fig. 12. NMR spectra of 65 in methylene chloride. The upper spectrum was measured at −50° after dissolution at *ca* −70°. The lower spectrum was measured at −50° after dissolution at room temperature.[62]

of glucose in which the approach of the epimer ratio to equilibrium, after dissolution of a pure diastereomer, is monitored using optical rotation.

Consideration of the difference between NMR and isolation time scales indicates that convenient temperatures for measuring the approach to equilibrium should be about 100° below the coalescence temperature (the temperature at which stereomutation becomes rapid on the NMR time scale). The use of diastereomeric transformation is a useful adjunct to coalescence measurements of rate constants, since it allows measurements over a temperature range greater than 100°. This can result in activation enthalpies and entropies which are more reliable than those obtained using either method alone. In conjunction with X-ray crystallography, diastereomeric transformation can afford unambiguous assignment of the configurations of the major and minor isomers in solution.

Thus, assignment of the (*R*,*R*)-configuration to the diastereomer in solid **65** and the comparison between the two NMR spectra in Fig. 12 allow the unambiguous assignment of the (*R*,*R*)-configuration to the isomer which is most abundant in solution. The relation between isolation and NMR time scales can also serve as a rough guide to the minimum temperature at which diastereomeric transformation will take place upon crystallization. If one can induce rapid crystallization at temperatures much more than 100° below the coalescence temperature, the continual establishment of the diastereomeric equilibrium will not occur and the composition of the solution will approach that of the eutectic composition. This occurs during the crystallization of the equilibrium mixture of axial and equatorial forms of chloro-cyclohexane at low temperature and permitted the partial segregation of the two species.[64]

D. *Thermodynamic asymmetric induction*

Asymmetric synthesis and kinetic resolution which play very important roles in the stereochemistry of stereostable chiral units, obviously have little importance in stereochemical investigations of stereolabile configurational units. We shall, in this section, compare thermodynamic asymmetric induction[55,65] which can be easily observed for stereolabile chiral units, with kinetic asymmetric induction, which results in asymmetric synthesis and kinetic resolution. Here, too, we shall use sulfenamides as examples, although our conclusions are equally applicable to other stereolabile configurational units.

Thermodynamic asymmetric induction occurs when a stereolabile chiral unit is present in a molecule along with a stereostable chiral unit. The sulfenamide chiral axis represents a useful stereolabile chiral unit for studies of thermodynamic asymmetric induction since many sulfenamides exhibit torsional barriers in the range of about 15–20 kcal/mol. Barriers within this range correspond to stereomutation which is rapid on the isolation time scale, at or near room temperature, but slow on the NMR time scale. Thus, it is easy to set up and maintain an equilibrium, while, at the same time, it is possible to measure the relative amounts of the two stereoisomers using NMR spectroscopy.

In the absence of a stable chiral unit, compounds containing labile chiral units (e.g. sulfenamides $R^1SNR^2R^3$ such as **61**, which do not possess additional chiral units) exist as mixtures of rapidly interconverting enantiomers. Because of the symmetry present, the two stereoisomers must have the same free energies of formation and the equilibrium constant must be unity (Fig. 13). When a stable chiral unit (CHML) is introduced as a substituent at N, as in **62**, this symmetry is destroyed and the stereoisomers which interconvert by torsion about the S–N bond are diastereomers and must, in principle, have different free energies of formation (Fig. 13). Thus, the equilibrium constant must differ from unity and this difference (or the associated difference in free energies of formation of the stereoisomers) is a quantitative measure of the thermodynamic asymmetric induction. In effect, the presence of the stable chiral unit is responsible for a preference for one or the other configuration at the labile chiral unit. The stereostable chiral unit represents the inducing configurational unit, and the labile chiral unit is analogous to the newly formed chiral unit in asymmetric synthesis.

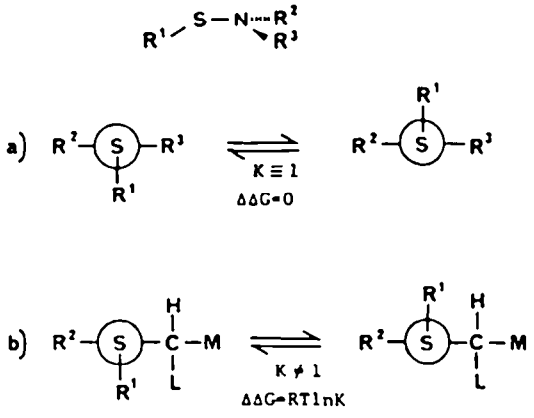


Fig. 13. Comparison of stereomutations in sulfenamides (a) lacking and (b) containing a stable chiral unit.

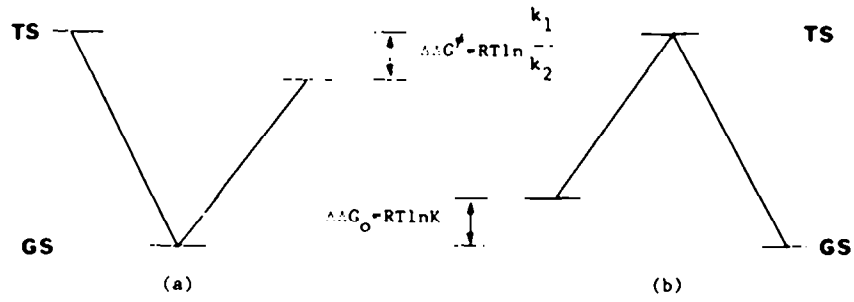


Fig. 14. Energy diagrams for asymmetric induction: (a) Kinetic asymmetric induction (Asymmetric synthesis), (b) Thermodynamic asymmetric induction.

This situation can be compared with the asymmetric induction which takes place in asymmetric synthesis (Fig. 14). Asymmetric synthesis, or kinetic resolution, can be represented by a schematic energy diagram of the type used by Mislow[66] in which a single ground state is involved (or two enantiomeric and isoenergetic ground states, in the case of kinetic resolution). The stereoisomeric products of reaction are produced via diastereomeric transition states and the ratio of stereoisomeric products, which is a measure of kinetic asymmetric induction, is related to the difference in free energy of these two diastereomeric transition states. In thermodynamic asymmetric induction, this energy diagram is reversed: A single transition state connects two diastereomeric ground states. The ratio of diastereomers is now an equilibrium constant and is related to a difference in free energies of formation.

In both cases, diastereomeric interactions are responsible for an energy difference which is expressed in a ratio of stereoisomers, and the stereochemical treatments are analogous. However, the difference between the two situations is an important one. Much more information can be obtained about thermodynamic asymmetric induction since direct spectroscopic and structural measurements can be made upon ground state diastereomers. By contrast, the only direct information which can be obtained about diastereomeric transition states is the difference in free energies of activation. Other structural parameters must be inferred from energy differences or obtained from theoretical calculations.

Thermodynamic asymmetric induction in diastereomeric sulfenamides can be quantitatively studied by integration of corresponding signals in the NMR spectra of the equilibrium mixture of the two diastereomers.[65] The results obtained show similarities to comparable experiments employing kinetic asymmetric induction. The magnitude of the asymmetric induction depends upon the relative size of the three ligands at the inducing chiral unit. Table 7 illustrates the increase in the equilibrium constant K which follows increasing size of largest ligand (L) at the asymmetric center in a series of trichloromethanesulfenamides **67**. This trend corresponds to improved kinetic asymmetric induction which is obtained when a better inducing chiral unit is used. The magnitude

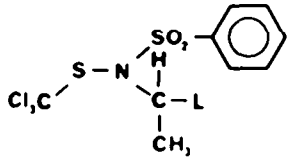


Table 7. Relation between inducing chiral unit and equilibrium constants in sulfenamides 67[55]

Compound	L	K
67a	phenyl	1.2
67b	2-naphthyl	1.3
67c	o-tolyl	1.6
67d	1-naphthyl	2.0
67e	t-butyl	5.7

of the asymmetric induction is also affected by the ligand at sulfur. This dependence corresponds to the susceptibility of a system to asymmetric induction expressed by ρ in the Ruch–Ugi[68] approach to asymmetric synthesis. Table 5 illustrates such a dependence. The magnitude of the induction in substituted benzenesulfenamides changes as increasing numbers of nitro groups are placed on the sulfenyl phenyl ring. This dependence has been ascribed to changes in the energy required for deformation at the C—S and S—N bonds. In effect, the presence of electron withdrawing groups in the para position changes the effective steric bulk of the phenyl ring. This is one expression of the "electrosteric effect" which is discussed in Section VIII.

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