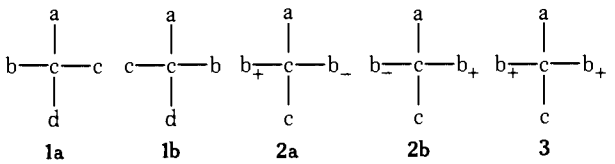
Pseudoasymmetry as a Means for Distinguishing Meso and *dl* Diastereomers[1]

Morton Raban,*[2a] Sanford K. Lauderback,[1d] and Daniel Kost[2b]

Contribution from the Department of Chemistry, Wayne State University, Detroit, Michigan 48202. *Received August 20, 1974*

Abstract: Meso and *dl* diastereomers of compounds containing two constitutionally equivalent chiral units can be distinguished by using NMR spectroscopy to demonstrate the creation of pseudoasymmetry. In suitable compounds, a new configurational unit, a unit of pseudoasymmetry, can be constructed in the meso diastereomer but not the *dl* diastereomer. Two examples are presented and analyzed, using cyclic and acyclic examples and featuring both a configurationally stable pseudoasymmetric center and a configurationally labile pseudoasymmetric axis. In the first example, a pseudoasymmetric center was introduced into *cis*-2,6-dimethylcyclohexanone by reduction to the carbinol, and the configurations of the two diastereomers were assigned on the basis of their NMR spectra. The corresponding trans ketone furnished only a single diastereomer. Chemical-shift nonequivalence in the benzyl ether of the *dl*-carbinol also permitted its assignment. In the second example, the 2,4-dinitrobenzenesulfenamides of *meso*- and *dl*-bisphenylethylamine were prepared. The sulfenamide bond in the meso sulfenamide is an axis of pseudoasymmetry, and the presence of two meso isomers is evident in the NMR spectrum. The free energy of activation at the coalescence temperature for rotation about the S–N bond in the *dl* sulfenamide (T_c = 91°; $\Delta G_c^{\ddagger}$ = 19.6 kcal/mol) was intermediate between those for forward and reverse interconversions of the two meso diastereomers (T_c = 86°; $\Delta G_c^{\ddagger}$(forward) = 19.5 kcal/mol; $\Delta G_c^{\ddagger}$(reverse) = 20.5 kcal/mol), although the stereochemical descriptions of the processes associated with coalescence in the two cases are different.

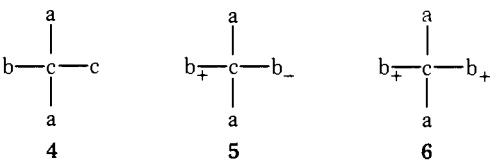
When four ligands with different constitutions, or ligands of the same constitution which are diastereomeric, are attached to the tetrahedral framework of a tetrasubstituted carbon atom (**1a**), a configurational unit is formed, a center of chirality or an asymmetric center. Interchange of any two ligands will produce a new stereoisomer (**1b**), an enantiomer if all of a,b,c, and d are achiral, or a chiral diastereomer if one or more of the ligands are chiral. If two of the ligands have the same constitution but are related as nonsuperposable mirror images (**2a**), a slightly different situation applies. Interchange of two groups still produces a new stereoisomer (**2b**) which is a diastereomer of **2a**. In this, the situation for **2** parallels that for **1**. However, both of the stereoisomers **2a** and **2b** are achiral, while at least one of **1a** and **1b** must be chiral. Since there is no question of molecular asymmetry for either stereoisomer of **2**, the configurational unit is referred to as a pseudoasymmetric center.[3-8] Application of the Cahn-Ingold-Prelog rules[7] for specification of configuration reinforces this distinction. While designations *R* and *S* are used for specifying configuration at centers of asymmetry, the lower case letters *r* and *s* are the configurational designations for pseudoasymmetric centers.[6] If, on the other hand, the two chiral ligands b have the same configurations (**3**), the central carbon atom



1a **1b** **2a** **2b** **3**

is not a configurational unit since interchange of two ligands results in a structure which is superposable with the original structure.

A parallel series of structures can be considered within the framework of prochirality.[9,10] In **4**, which has two constitutionally different or diastereomeric ligands b and c in addition to the paired ligands a, the paired ligands are enantiotopic[11] if the ligands are all achiral. The carbon atom is termed prochiral since the substitution of an arbitrary ligand d for one of the enantiotopic groups leads to a chiral array (**1**).[12] The two a ligands in **5** are diastereotopic. Here application of the substitution criterion[11] results in the creation of a model with a center of pseudoasymmetry (**2**). The relationship between **4** and **5** is analogous to that between **1** and **2**, and the central carbon atom in **5** was originally[9] included within the set of prochiral atoms,[13] in the same way that the pseudoasymmetric carbon atom of **2** can be considered as a part of the set of generalized asymmetric carbon atoms.[3] The two a ligands in **6**, which is analogous to **3**, are equivalent. The central carbon atom in **6** is not a



4 **5** **6**

center of prostereoisomerism just as the central carbon atom in **3** is neither a chiral center nor a center of pseudoasymmetry.

The concepts of pseudoasymmetry and prochirality can be extended to include systems which correspond to axial and planar chirality.[8] Thus, systems with planar and axial pseudoasymmetry are possible, and molecules bearing such structural features have been prepared.[1b,14,15]

Nuclear magnetic resonance (NMR) spectroscopy can be used as a tool for making configurational assignments. The creation of a unit of pseudoasymmetry can play an important role in using NMR to distinguish between meso and *dl* isomers. Two examples are presented in this paper, one using central and the other axial pseudoasymmetry.

The classical criterion for distinguishing between the meso and *dl* isomers of molecules containing two chiral units[16] involves the resolvability of such *dl* isomers. Such a configurational assignment rests upon a symmetry argument and, for this reason, avoids the ambiguity which is often inherent in configurational assignments which rely upon analogies in chemical and physical properties.[17]

This assignment is unambiguous only when both isomers are available or when it is applied successfully to the *dl* isomer. If only a single isomer is available and it can be made optically active, it must be the *dl* isomer. However, if only a single isomer is available, which resists all efforts to induce optical activity, it may either be the meso isomer, or the efforts to induce optical activity may fail for chemical rea-

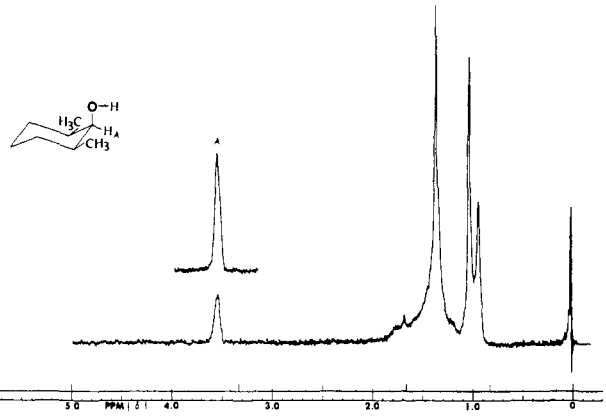


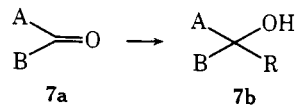
Figure 1. NMR spectrum of 1-*s*-*meso*-2,6-dimethylcyclohexanol (**9a**).

sons. This criterion is also inapplicable to molecules which suffer stereomutation rapidly on the isolation time scale and is often tedious to carry out.

NMR spectra can also be used in symmetry arguments to make configurational assignments. Thus, Hill and Chan have shown that it is possible to differentiate between *cis*-2,5-dimethylpyrrolidine (a meso diastereomer) and *trans*-2,5-dimethylpyrrolidine (a *dl* diastereomer), and related α,ω-disubstituted cyclic amines, by conversion to their *N*-benzyl derivatives and examination of their NMR spectra.[19,20] The benzyl methylene protons in the meso isomer are enantiotopic and appear as a singlet, while those in the *dl* isomer are diastereotopic and appear as an AB quartet. This method like the method of resolution serves only to distinguish the *dl* isomer. A single isomer which exhibits chemical-shift equivalence for the benzyl methylene protons, like a single isomer which resists resolution, might be either the meso isomer or might be a *dl* isomer which exhibits a chemical-shift difference which is too small to be resolved (apparent or accidental equivalence).

The creation of pseudoasymmetry can be used as a criterion which serves to distinguish the meso isomer and thus serve as a useful alternative or supplement to the resolution method and the method of Hill and Chan. This approach has been used only occasionally, for example, in the assignment of the meso configuration to cuskhygrine.[21] When NMR spectroscopy is used, it is possible to employ either a stable pseudoasymmetric unit or one which is configurationally labile but exhibits slow configurational change on the NMR time scale. Examples of both are described below.

Let us consider a meso isomer which possesses a structural feature which is a "potential configurational unit", which lies on the mirror plane. A "potential configurational unit" is a site of chemical reactivity which can be readily transformed chemically into a configurational unit. Such a "potential configurational unit" may be associated with a unit of prochirality but need not be. The carbonyl group in **7a** represents such a unit; reduction or reaction with a nucleophile results in the formation of a chiral unit if A differs from B constitutionally. In this case, the carbonyl carbon can be regarded as prochiral, and the two faces of the carbonyl group are enantiotopic. If A and B are enantiomeric ligands, the unit formed is a center of pseudoasymmetry, and **7b** represents two diastereomers while, if A and B are superposable chiral ligands, no new configurational unit is



7a **7b**

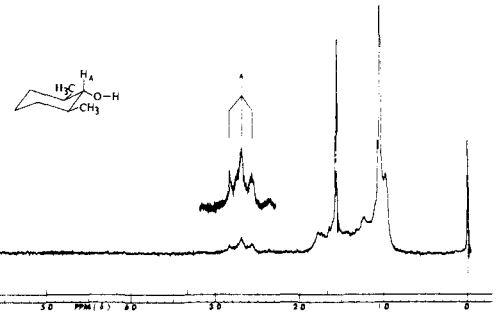
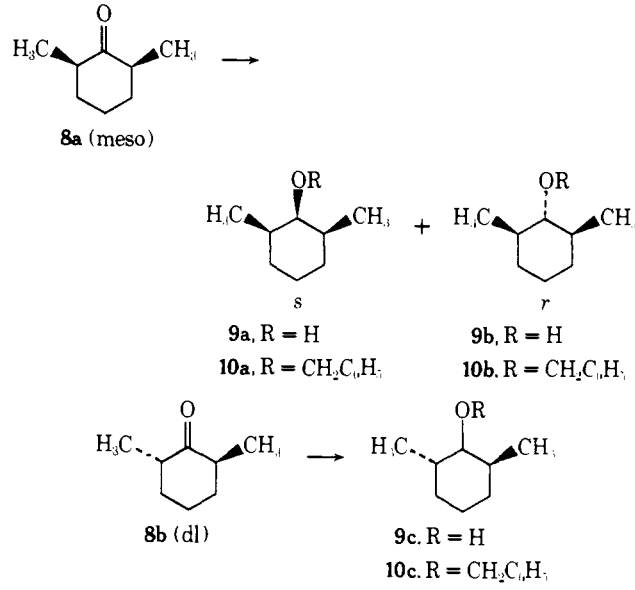


Figure 2. NMR spectrum of 1-*r*-*meso*-dimethylcyclohexanol (**9b**).

formed on reduction, and **7b** represents a single diastereomer. Thus, if A and B are chiral ligands which are either enantiomeric or equivalent, **7a** represents a set of meso and *dl* diastereomers which can be differentiated by reduction. NMR spectroscopy provides a useful means for examining and differentiating the reduction products **7b**.

The two diastereomeric ketones, *cis*- and *trans*-2,6-dimethylcyclohexanone[22] (**8**), are a pair of meso and *dl* diastereomers of the form **7a**. One which exhibits a shorter gas chromatography retention time and a methyl doublet at δ 1.00 was assigned the meso configuration; the methyl doublet of the other diastereomer, assigned the *dl* configuration, appears at δ 1.08. The faces of the carbonyl group in **8a** are diastereotopic, and reduction to the carbinol pro-



8a (meso)

s *r*

9a, R = H **9b**, R = H

10a, R = $CH_2C_6H_5$ **10b**, R = $CH_2C_6H_5$

8b (dl) **9c**, R = H

10c, R = $CH_2C_6H_5$

duces two diastereomers **9a** and **9b** which have the *s* and *r* configurations, respectively, at the pseudoasymmetric carbinol carbon atom. The carbonyl group of the *dl* ketone has equivalent faces, and reduction yields a single diastereomer **9c**.

Reduction of the isomer of **8** with the shorter GC retention time with either lithium aluminum hydride or sodium borohydride afforded two isomers which could be separated by gas chromatography in a ratio of 54:46 ($LiAlH_4$) or 73:27 ($NaBH_4$), confirming that it is the meso isomer **8a**. Reduction of the other isomer afforded a single diastereomer confirming its assignment as the *dl* isomer.

The NMR spectra of the resulting alcohols (Figures 1-3) provide confirmation of the assignments and allow assignment of configuration at the pseudoasymmetric atom in **9a** and **9b**. The two meso alcohols **9a** and **9b** are conformationally locked by the *cis*-methyl groups. As a result, the carbinol methine proton must be equatorial in **9a** and axial in **9b**,

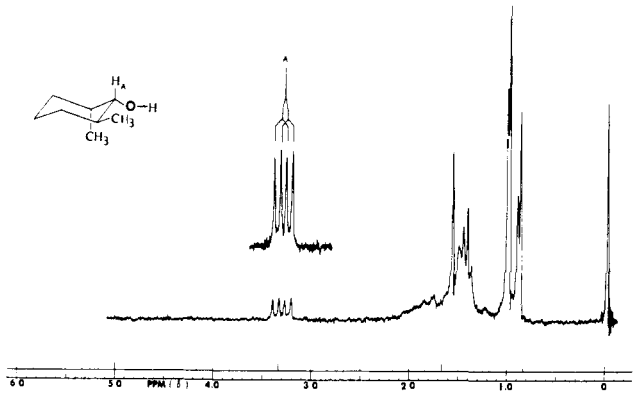


Figure 3. NMR spectrum of *dl*-2,6-dimethylcyclohexanol (**9c**).

while the methine protons in the 2- and 6-positions must be axial in both isomers. The methine carbinol proton in **9a** thus exhibits gauche coupling to the two other methine protons and appears as a broadened singlet at δ 3.5 (Figure 1). The methine–methine coupling in the *r* alcohol **9b** is trans diaxial, and a triplet (J = 8.1 Hz) is observed. The chemical shift is also further upfield, δ 2.7, characteristic of an axial proton (Figure 2). In the *dl* alcohol, both cis and trans couplings are present, and a doublet of doublets (J_{AB} = 7.8, J_{AC} = 4.2 Hz) is observed at an intermediate chemical shift, δ 3.30 (Figure 3).

Chemical-shift nonequivalence of diastereotopic protons can also be used to reach the same conclusions. This requires the attachment of a probe for chirality of the form $-CA_2Y$. If the remainder of the molecule is chiral, the two A groups will be diastereotopic and should exhibit chemical-shift nonequivalence while, if the remainder of the molecule is achiral, they will be enantiotopic and isochronous.

Incorporation of a suitable probe was accomplished by conversion of the carbinols **9** to their benzyl ethers. Since the meso carbinols, and their ethers, **9a** and **9b,** possess planes of symmetry and are thus achiral, the benzylmethylene protons are enantiotopic and appear as singlets (Figures 4 and 5). By contrast, the *dl*-carbinol and its ether are chiral, and the diastereotopic benzylmethylene protons appear as an AB quartet (Figure 6). The use of a probe for chirality is a useful complement to the use of pseudoasymmetry since chemical-shift nonequivalence points unequivocally to the *dl* isomer, while the creation of a pseudoasymmetric center provides unambiguous evidence of the meso isomer. Thus, the combination can be used to make unambiguous assignments when only a single isomer is available. A ketone of the type **7a** (where A and B are equivalent or enantiomeric chiral ligands) which gives rise to two isomers upon reduction must be a meso isomer, while a ketone which gives only a single isomer upon reduction, which exhibits chemical-shift nonequivalence upon conversion to the benzyl ether, must be a *dl* isomer.

Although **8a** and **9b** are meso and *dl* isomers of the type **5** and **6,** the fact that they are cyclic may appear to simplify the problem of differentiating between them. Indeed, the arguments based on coupling constants would not have been as straightforward in an acyclic system. For this reason, we have chosen an acyclic system as a second example. In addition, this second example makes use of axial pseudoasymmetry.

The secondary amines **11a** and **11b** represents an acyclic pair of meso and *dl* diastereomers which can be conveniently separated by fractional crystallization of the benzoate salts. The nitrogen atom also represents a "potential configurational unit". While various methods are available for creating a configurational unit, we have chosen conversion into the sulfenamide. Secondary amines (RR′NH) can be easily converted into the corresponding sulfenamides (RR′NSR″) by reaction with sulfenyl chlorides in the presence of base. Slow rotation about the sulfur–nitrogen bond renders the sulfenamide unit an axis of chirality in sulfenamides (RR′NSR″), where R and R′ are achiral ligands which differ in constitution.[23] Torsion about the N–S bond represents the rate-determining step in the interconversion of enantiomers, which can be conveniently studied by NMR spectroscopy. When one of R and R′ is chiral, torsional diastereomerism is possible and is manifest in NMR[24] and ORD–CD spectra.[24c] If R and R′ are both chiral ligands which are enantiomeric, the sulfenamide bond becomes an element of axial pseudoasymmetry. Torsion about the S–N bond interconverts two meso diastereomers. If R and R′ are

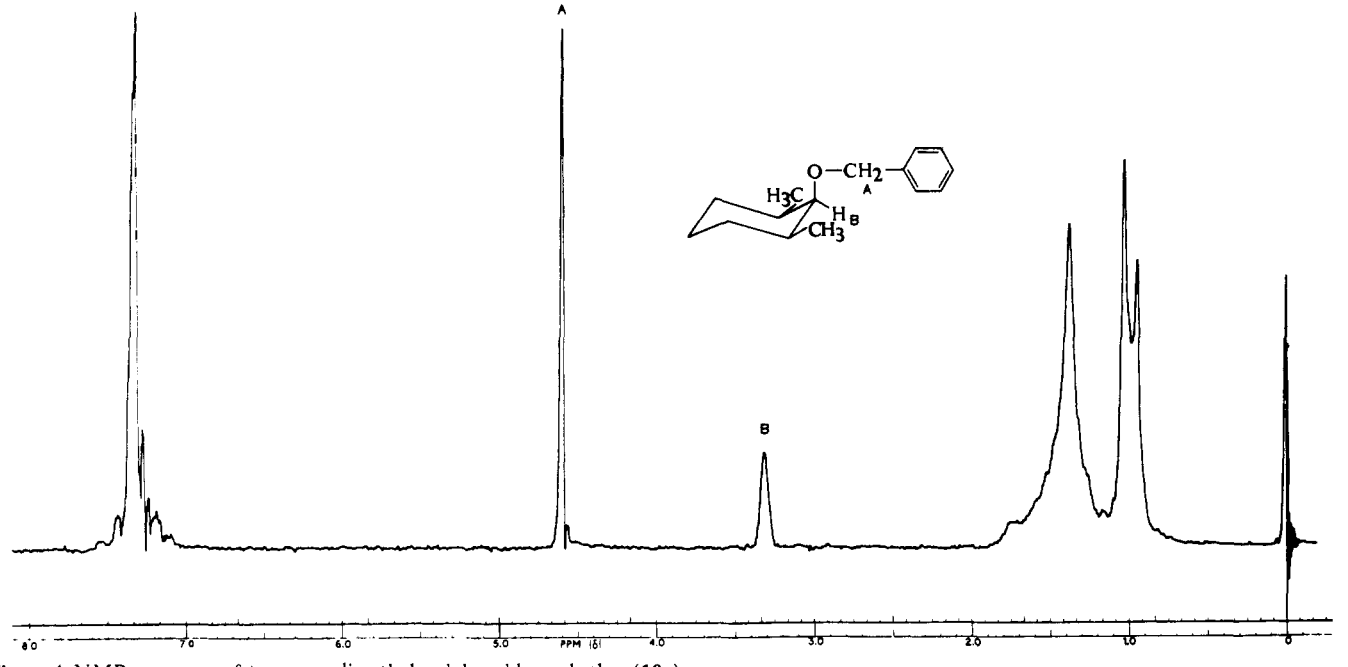


Figure 4. NMR spectrum of 1-*r*-*meso*-dimethylcyclohexyl benzyl ether (**10a**).

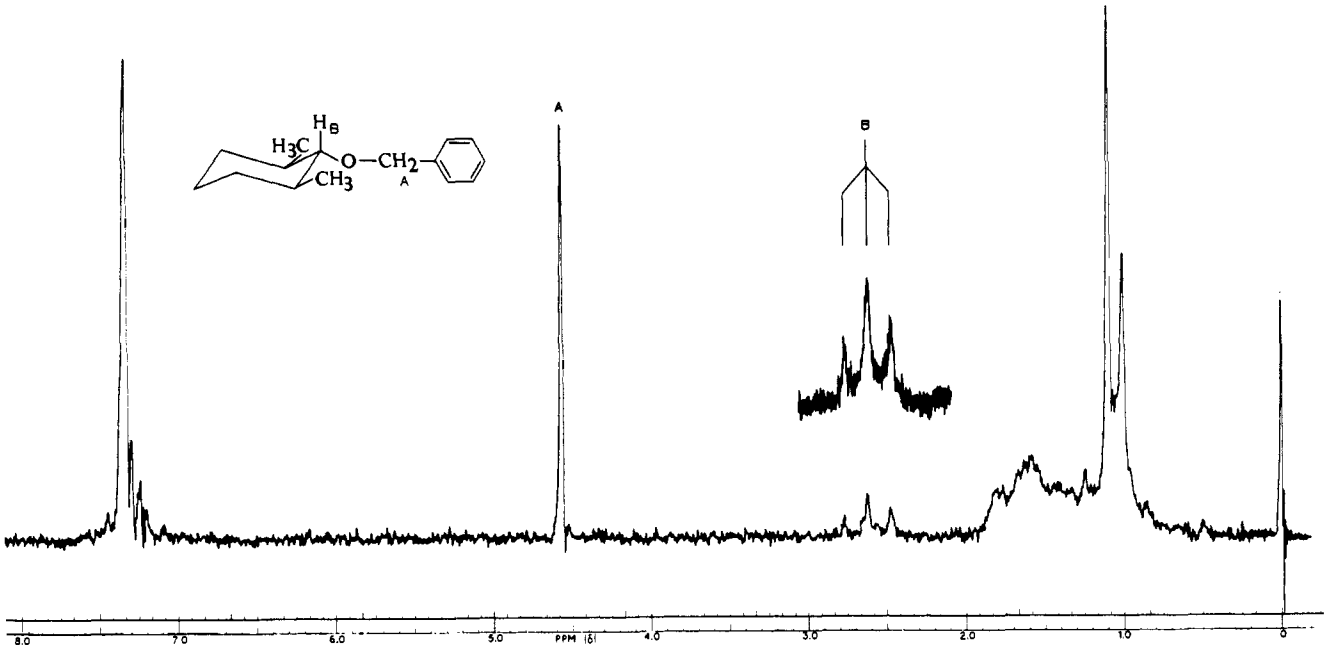
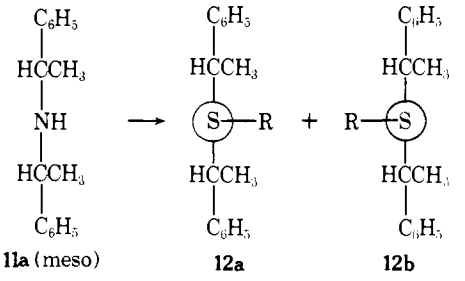
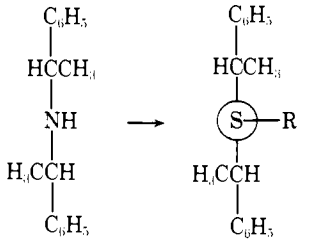


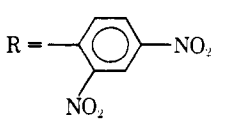
Figure 5. NMR spectrum of 1-*s*-*meso*-dimethylcyclohexyl benzyl ether (**10b**).

identical chiral ligands, however, the sulfenamide grouping is not a configurational element, neither an asymmetric nor a pseudoasymmetric axis.

Reaction of one of the diastereomers of bis(phenylethyl)amine (shown to be **11a**) with 2,4-dinitrobenzenesulfenyl chloride produced a product sulfenamide whose NMR spectra indicated that it was a mixture of two diastereomers which could be interconverted by rotation about the S–N bond. At 50°, the spectrum features two doublets with a ratio of integrated intensities of 4.5:1, the equilibrium constant for interconversion of the *r* and *s* meso isomers (Figure 7). The meso isomers **12a** and **12b** each give rise to a







single *C*-methyl doublet. Since the two methyl groups in each molecule lie on opposite sides of the σ plane which passes through the sulfur–nitrogen bond, they are enantiotopic and must have the same chemical shift. The NMR spectrum of the sulfenamide prepared from the *dl* amine is consistent with the presence of the single diastereomer **12c**. Again two *C*-methyl doublets are present but now in a ratio of 1:1. The two doublets arise from the two *C*-methyl groups in a single molecule.[25] Since **12c** is asymmetric, the two *C*-methyl groups cannot be interchanged by any symmetry operation and must be diastereotopic. While rotation about the S–N bond does not generate a new stereoisomer, it does effect a topomerization, that is an interchange of the environments of the two *C*-methyl groups. While the sulfenamide bond is not a unit of stereoisomerism in **12c**, it might be considered a unit of prostereoisomerism.[10]

When the temperature is increased, torsion about the sulfur–nitrogen bond becomes rapid on the NMR time scale. As this happens, the pair of doublets observed for either the mixture of two meso isomers **12a** and **12b** or the *dl* sulfenamide **12c** broaden and coalesce. Above the coalescence temperature, 86° for the mixture of **12a** and **12b** and 91° for **12c**, a single doublet is observed for either sample. The free energies of activation at the coalescence point were calculated using first-order rate constants obtained using approximate equations or calibration curves which have been shown to yield reliable free energies of activation.[27] While a single coalescence rate constant and associated free energy of activation is obtained for **12c** ($\Delta\nu$ = 5.6 Hz; T_c = 91°; $\Delta G_c^{\ddagger}$ = 19.6 kcal/mol), two rate constants are obtained for the reversible interconversion of **12a** and **12b**, corresponding to forward and reverse reactions ($\Delta\nu$ = 4.6 Hz; T_c = 86°; $\Delta G_c^{\ddagger}$(forward) = 19.5 kcal/mol; $\Delta G_c^{\ddagger}$(reverse) = 20.5 kcal/mol).

The mechanism for conformational change, torsion about the sulfur–nitrogen bond, is the same for *dl*-**12** and *meso*-**12** as are the consequences in the NMR spectra, namely coalescence of two doublets to one doublet. The similarity between the two systems is reflected in the comparable energies of activation obtained; that for **12c** is intermediate between those for the forward and reverse interconversions of the meso diastereomer. Nevertheless, the stereochemical descriptions of the events associated with coalescence are different. Coalescence of the doublets of unequal intensity, observed in the spectrum of *meso*-**12**, is associated with rapid reversible epimerization at the pseudoasymmetric axis, and the peaks which coalesce derive from methyl

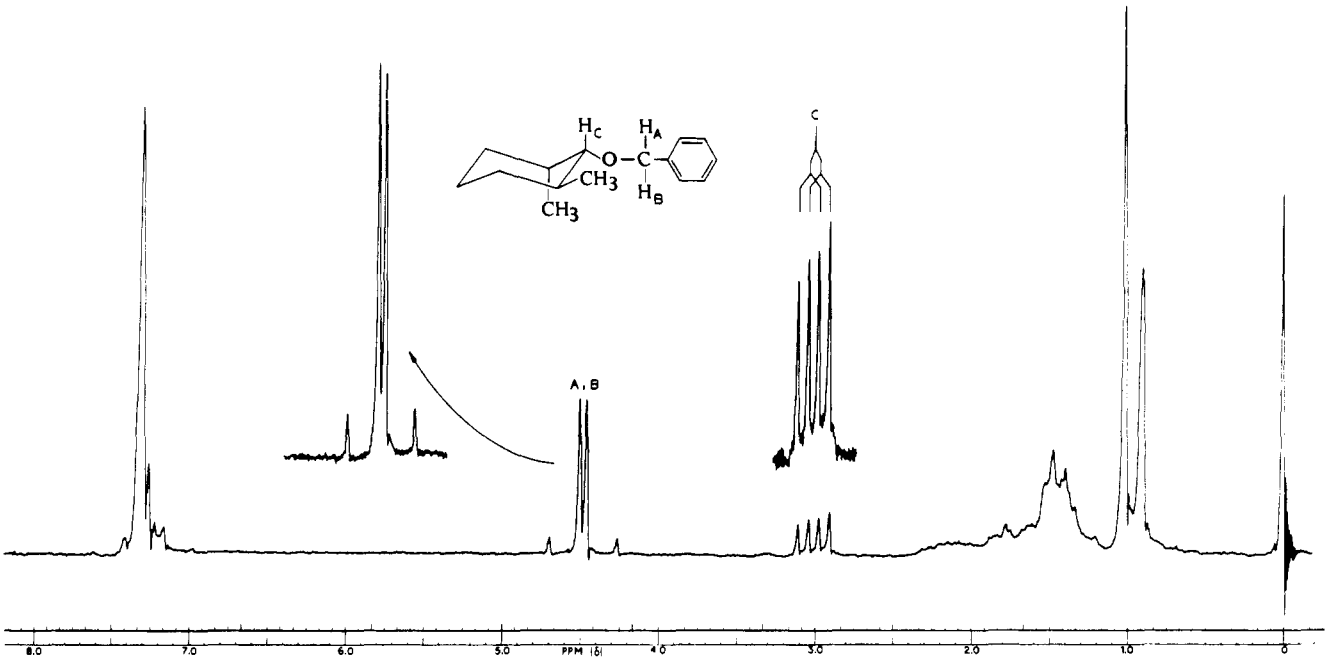


Figure 6. NMR spectrum of *dl*-2,6-dimethylcyclohexyl benzyl ether (**10c**).

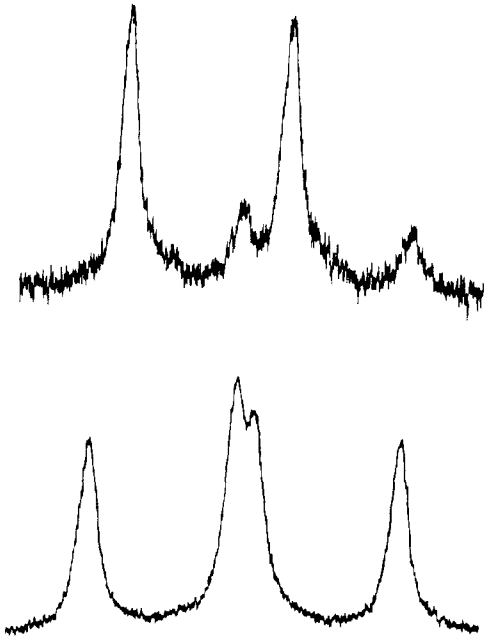


Figure 7. Portions of the NMR spectra ($CDCl_3$, 50°) of *N,N*-bis-1-phenylethyl-2,4-dinitrobenzenesulfenamide (**12**) featuring resonances of the *C*-methyl groups. Upper curve: equilibrium mixture of *meso*-sulfenamides **12a** and **12b**. Lower curve: *dl*-sulfenamide **12c**.

groups in two different diastereomers. By contrast, the process which results in the coalescence of the pair of doublets in the spectrum of **12c** is not a stereomutation but a topomerization, and the coalescing peaks are associated with two diastereotopic methyl groups in the same molecule, which become equivalent on time average as torsion becomes rapid on the NMR time scale.

Chemical-shift nonequivalence can also be used to differentiate between **11a** and **11b**. Using the approach of Hill and Chan,[19] the *dl* isomer **11b** was converted into the *N*-benzylamine **14** via the corresponding benzamide **13**. The NMR spectrum features an AB quartet for the diastereotopic benzylmethylene protons ($\Delta\nu_{AB}$ = 0.45 ppm; J_{AB} = 15 Hz), reflecting the asymmetry of parent secondary amine.

Experimental Section

NMR spectra were measured on a Varian A60-A equipped with a V-6040 temperature controller. Melting points were taken on a Thomas-Hoover apparatus. Elemental analyses were performed by Midwest Microlab, Inc.

2,6-Dimethylcyclohexanol (9). (a) Lithium Aluminum Hydride Reduction. An ethereal solution of *meso*-2,6-dimethylcyclohexanone or *dl*-2,6-dimethylcyclohexanone (1.0 g, 0.008 mol) was added dropwise to 0.15 g of lithium aluminum hydride (0.004 mol) in dry ether and the mixture allowed to react at room temperature for 20 hr. After treatment with saturated aqueous ammonium chloride and filtration, the solvent was removed in vacuo. The meso alcohols could be separated by gas chromatography on an 8 ft column of 25% NMPM on Chromosorb P: 54% **9a** (*s*); 46% **9b** (*r*).

(b) Sodium Borohydride Reduction. Solid sodium borohydride was added to a cooled (0°) methanolic solution of 1.0 g of 2,6-dimethylcyclohexanone (either meso or *dl*). After being stirred for 2 hr at 0° and 20 hr at room temperature, the solvent was removed in vacuo. The residue was partitioned between 15% aqueous KOH and pentane and the pentane dried over anhydrous magnesium sulfate and removed in vacuo. Gas chromatographic analysis of the product of reduction of the meso ketone indicated that it was composed of 73% **9a** and 27% **9b**.

Benzyl 2,6-Dimethylcyclohexyl Ether (10). 2,6-Dimethylcyclohexanol (0.64 g, 0.005 mol) was added to a solution of sodium amide (0.20 g, 0.005 mol) in dry tetrahydrofuran. Benzyl chloride (0.7 g, 0.005 mol) was added dropwise and the reaction temperature increased to reflux for 20 hr. The reaction mixture was cooled and filtered and the solvent removed in vacuo. The residue was extracted with 2-methylbutane which was removed in vacuo. The product was purified by gas chromatography on a 12 ft column of 10% versamide on Chromosorb W.

Bis-1-phenylethylammonium Benzoate (15). Bis-1-phenylethylamine (20 g, 0.09 mol) and benzoic acid (11 g, 0.09 mol) were mixed in cold isopropyl alcohol, and the precipitate was collected. Recrystallization from benzene afforded needle-shaped crystals of what was shown to be the *dl*-ammonium benzoate, mp 135–136°. Upon standing, the concentrated mother liquors deposited two types of crystals, needles and cubes. The mixture of crystals was treated with benzene which dissolved the needles. The cube-shaped crystals were collected and recrystallized from hexane to afford the *meso*-ammonium benzoate, mp 103–105.5°. The free amines **11** could be obtained by treatment with 10% NaOH, extraction with ether, and removal of solvent in vacuo.

***N,N*-Bis-1-phenylethyl-2,4-dinitrobenzenesulfenamides (12).** A

solution of 2,4-dinitrobenzenesulfenyl chloride (0.84 g, 0.0036 mol) in benzene was added dropwise to a benzene solution of **11a** or **11b** (1.6 g, 0.0072 mol) in benzene and allowed to react for 20 hr. The reaction mixture was filtered, washed with water, 5% aqueous HCl, saturated, aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over magnesium sulfate, and the solvent was removed in vacuo. The residue was recrystallized from benzene (meso sulfenamides) or benzene–methanol (*dl* sulfenamide): *meso*-**12**, mp 187–188°; *dl*-12, mp 133.5–134.5°.

***dl*-*N*-Benzyl-*N*,*N*-bis-1-phenylethylamine (14).** A suspension of *dl*-bis-1-(phenylethyl)amine in 5% aqueous sodium hydroxide was treated with benzoyl chloride. The precipitated benzamide (**13**) which formed was recrystallized from ethanol, mp 124–126°. The benzamide (3.3 g, 0.01 mol) was suspended in dry ether, treated with an excess of lithium aluminum hydride (0.4 g, 0.01 mol), and allowed to react at room temperature for 20 hr. The reaction mixture was treated with wet tetrahydrofuran and filtered through a Celite pad. Evaporation of the solvent and recrystallization furnished the *N*-benzylamine **10c**, mp 75–77°.

Acknowledgment. We thank Dr. Francis Johnson, Eastern Research Laboratory, Dow Chemical Co., for providing us with *meso*- and *dl*-2,6-dimethylcyclohexanone.

References and Notes

(1) (a) Stereochemistry in Trivalent Nitrogen Compounds. XXVI. Part XXV: M. Raban, D. A. Noyd, and L. Bermann, *J. Org. Chem.*, **40**, 752 (1975). (b) A portion of the work described herein has appeared in a preliminary account: D. Kost and M. Raban, *J. Am. Chem. Soc.*, **94**, 2533 (1972). (c) We are grateful to the National Science Foundation and the Edmond de Rothschild Foundation for support. (d) Taken in part from a thesis submitted by S. K. Lauderback in partial fulfillment of the requirements for the Ph.D. degree, Wayne State University, 1974.

(2) (a) A. P. Sloan Fellow; (b) Ben Gurion University of the Negev, Beersheva, Israel.

(3) Mislow[4] defines an asymmetric carbon atom as "a carbon atom attached to four substituents which differ in the sense that exchange of any two gives a new stereoisomer". Within this framework, pseudoasymmetric carbon atoms may be considered as a subset of asymmetric carbon atoms.[4b] We have used the term configurational unit to encompass both centers in **1** and **2**. Hirschmann and Hanson[5] use the term "center of stereoisomerism" in the same sense. They regard both **1** and **2** as similar in that both have "chiral configurations" since, in each case, four different ligands are present. However, the configuration of the center in **1** but not in **2** changes upon reflection of the model, which distinguishes true asymmetric centers from pseudoasymmetric centers.[6]

(4) (a) K. Mislow, "Introduction to Stereochemistry", W. A. Benjamin, New York, N.Y., 1966, p 25; (b) *ibid.*, p 91.

(5) H. Hirschmann and K. R. Hanson, *J. Org. Chem.*, **36**, 3293 (1971).

(6) Cahn, Ingold, and Prelog[7] point out an important difference between the upper case symbols, *R* and *S* for true asymmetric centers, axes, and planes and the lower case symbols, *r* and *s*, for pseudoasymmetric centers, axes, and planes. The uppercase 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.[8]

(7) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem.*, **78**, 413 (1966); *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).

(8) V. Prelog and G. Helmchen, *Helv. Chem. Acta*, **55**, 2581 (1972).

(9) K. R. Hanson, *J. Am. Chem. Soc.*, **88**, 2731 (1966).

(10) H. Hirschmann and K. R. Hanson, *Eur. J. Biochem.*, **22**, 301 (1971).

(11) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

(12) The paired ligands a at a center of prochirality are enantiotopic if all of the ligands are achiral. They are diastereotopic if any of the ligands is chiral.

(13) While the term propseudoasymmetric for the central carbon atom in **5** reinforces the analogy between **5** and **2**, it suffers from awkwardness. Hirschmann and Hanson[5] have recently described **5** as a "proachiral center of prostereoisomerism with prochiral assembly".

(14) G. Helmchen and V. Prelog, *Helv. Chim. Acta*, **55**, 2599 (1972).

(15) S. J. Goldberg and W. D. Bailey, *J. Am. Chem. Soc.*, **93**, 1046 (1971).

(16) We refer to molecules in which the two chiral units can be interchanged by a symmetry operation, rotation about a C_n axis in the *dl* diastereomer and a rotation–reflection operation in the meso isomer.

(17) As an example, the von Auwers–Skita rule[18] can be used to assign configuration to *dl* and meso isomers of 1,3-disubstituted cyclohexanes. Such assignments are based upon generalizations about the differences between meso and *dl* isomers, and their application often involves some ambiguity.

(18) E. L. Eliel, "The Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 216–219.

(19) R. K. Hill and T.-H. Chan, *Tetrahedron*, **21**, 2015 (1965).

(20) This method is applicable to acyclic amines as well as cyclic amines as indicated by our results discussed below and in our preliminary account.[1b] For a similar application to ketones, see J. F. Pazos and F. D. Greene, *J. Am. Chem. Soc.*, **89**, 1030 (1967).

(21) (a) K. Hess and R. Bappert, *Justus Liebigs Ann. Chem.*, **141**, 137 (1925); (b) F. Galinovsky and H. Zuber, *Monatsh. Chem.*, **84**, 798 (1953); (c) cf. also ref 18, p 275.

(22) F. Johnson and L. G. Duquette, *Chem. Commun.*, 1448 (1969).

(23) (a) M. Raban, D. W. J. Kenney, Jr., and F. B. Jones, Jr., *J. Am. Chem. Soc.*, **91**, 6677 (1969); (b) M. Raban and F. B. Jones, Jr., *ibid.*, **93**, 2692 (1971).

(24) (a) J. Kay, M. D. Glick, and M. Raban, *J. Am. Chem. Soc.*, **93**, 5224 (1971); (b) M. Raban, E. H. Carlson, S. K. Lauderback, J. M. Moldowan, and F. B. Jones, Jr., *ibid.*, **93**, 2781 (1971); (c) M. Raban and S. K. Lauderback, *ibid.*, **93**, 2781 (1971).

(25) A similar situation applies in the meso and *dl* sulfites[26] prepared by reaction of chiral alcohols with thionyl chloride. In the meso sulfites, the sulfite sulfur atom is a center of pseudoasymmetry, and the two alcohol moieties are enantiotopic. In the *dl* sulfites, the sulfur atom is not a unit of pseudoasymmetry, but here the two alcohol residues are diastereotopic and exhibit chemical shift nonequivalence.

(26) R. E. Lack and L. Tarasoff, Jr., *J. Chem. Soc. B*, 1095 (1969).

(27) D. Kost, E. H. Carlson, and M. Raban, *Chem. Commun.*, 656 (1971).