Chemical Shift Nonequivalence in Prochiral Groups†

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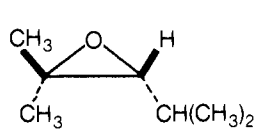
Contents

I. Introduction

The purpose of this report is to consider the chemical shift nonequivalence of geminal groups in NMR spectra. The phenomenon which was first recognized in 1957 has aroused much interest and debate, and indeed it often appears to have been associated with some mystique. This article describes the symmetry considerations underlying the observation of geminal nonequivalence in both chiral and achiral media and reviews the various stereochemical and environmental factors involved.

The author has been stimulated to write this review because of the considerable confusion that often arises in this area. Most of the examples cited are concerned with acyclic moieties as these are inherently more interesting and this is where confusion can most readily arise.

Thus in the oxirane (**1**) it can be clearly recognized that the two methyl groups attached to the ring should give rise to separate signals in the ^1H or ^{13}C NMR spectrum as one is cis to the isopropyl moiety whereas the other is trans. However, it may not be immediately evident that the two acyclic isopropyl methyl groups are also nonequivalent and can give rise to separate NMR signals. In the author's experience, observations of this type are often incorrectly rationalized in terms of a proposed "restricted rotation" around the isopropyl-ring bond. Indeed, it is often not made clear as to whether the proposed restricted rotation is in the kinetic sense (i.e., slow on the NMR time scale) or in the thermodynamic sense (i.e., unequal population of the various conformations around the isopropyl-ring bond). Neither of these explanations is required as the isopropyl methyl groups are nonequivalent for symmetry reasons; i.e., they occupy different environments in space even when rotation around the isopropyl-ring bond is free (in both the kinetic and thermodynamic senses). We will show that this phenomenon can be simply rationalized by combining the prochirality concept of Hanson[1] with the nomenclature of Mislow and Raban.[2] Cases will also be considered where geminal groups reside in mirror image (enantiotopic) environments and can show chemical shift nonequivalence only in chiral media.



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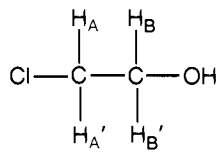

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A source of possible confusion in the past has been the use of the term "magnetic nonequivalence" to describe cases where geminal groups have different chemical shifts. We reinforce the view expressed by Mislow and Raban[2] that this term should not be used in this context without further clarification as it has also been employed to describe a completely different phenomenon in NMR spectroscopy. Thus in 2-chloroethanol (**2**) the geminal protons H_A and H'_A (also H_B and H'_B) can be termed magnetically nonequivalent even though they have identical chemical shifts (in achiral or racemic media). This type of magnetic nonequivalence arises entirely in the coupled spin system, as H_A and H'_A both couple differently to a given adjacent proton, e.g., H_B (i.e., $J_{AB} \neq J_{AB'}$). It is therefore necessary to state whether the magnetic nonequivalence refers to chemical shift or spin coupling or to use the terms "chemical shift nonequivalence" and "spin coupling nonequivalence." The latter phenomenon will not be considered further here as it is more appropriately dealt with in connection with complex spin–spin coupling. Groups which are nonequivalent in chemical shift (e.g., the methyl groups in **1**) may be termed "anisochronous," and spin coupling nonequivalent nuclei (e.g., H_A and H'_A in **2**) may be said to be "anisogamous."[3]

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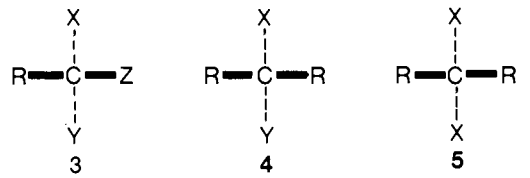
Finally it should be pointed out that, although this article is concerned with NMR spectroscopy, similar considerations apply to chemical reactivity of geminal groups.[4]

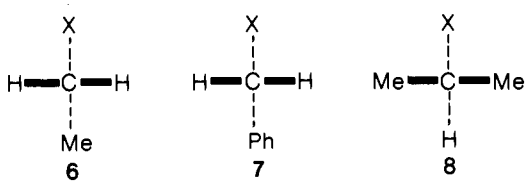
II. Stereochemical Aspects

A. Prochiral and Related Assemblies

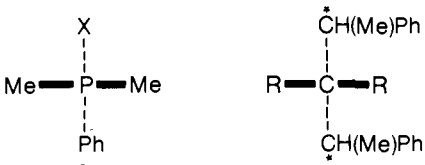
Consider an assembly of point ligands around a tetrahedral center denoted by C. If all four ligands are different in constitution as in **3**, the center is said to be "chiral" and the stereochemical significance of these centers is well established. However, a second type of tetrahedral assembly (**4**) also has considerable importance in stereochemistry and NMR spectroscopy. These centers (**4**) where two ligands are identical have been recognized by Hanson[1] and named "prochiral centers". A third type of assembly (**5**) is also pertinent to this discussion; here the center bears two pairs of identical ligands (R and X) and lies on a C_2 molecular symmetry axis. We will classify these as "C2 centers". In a prochiral assembly (**4**), the paired ligands can be equivalent (isochronous) or nonequivalent in chemical shift (anisochronous) depending on the nature of the remaining ligands X and Y. Commonly encountered acyclic prochiral groups are ethyl (**6**), benzyl (**7**), isopropyl (**8**), and the phosphino moiety (**9**), where X denotes the rest of the molecule (a metal-containing moiety in the case of **9**).



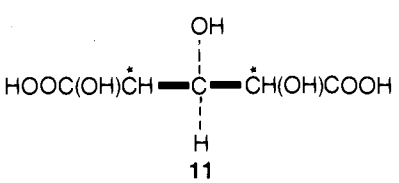
3 **4** **5**



6 **7** **8**



9 **10**



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The case should also be considered where two of the ligands differ only in that they are enantiomeric. Hanson[1] has proposed the following general definition of prochirality: "If a chiral assembly is obtained when a point ligand in a finite nonchiral assembly is replaced by a new point ligand, the original assembly is prochiral." The term "chiral assembly" refers to the center in question and not to any overall molecular chirality. In (**10**) the central carbon is clearly not C2 if the α-methylbenzyl ligands differ in configuration, nor is it strictly prochiral according to the above definition since replacement of one of the paired R ligands by a new ligand generates a pseudo-asymmetric center rather than a chiral center. The above definition of a prochiral center could be widened to include these cases, or alternatively the term "pseudo-prochiral" might be used to describe centers of this type. The central carbon in **10** is a C2 center if the chiral ligands have the same configuration. The R substituents in **4** may also be chiral as in the pentaric acids (**11**). Here the central carbon is prochiral if the CH(OH)COOH groups have the same configuration but pseudo-asymmetric if they differ in configuration.

B. Stereochemical Relationship of the Paired Ligands

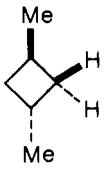
In their authoritative publication dealing with stereochemical relationships in general, Mislow and Raban[2] have pointed out that intramolecular group relationships may be determined by a substitution test. This involves the replacement of each of the two groups in question by an achiral test group that is not already present in that assembly, and then inspecting the intermolecular relationship between the two resulting structures. If they are superimposable the two groups in the original assembly were stereochemically equivalent (i.e., homotopic); if they are enantiomeric the two original groups were enantiotopic; and if they are diastereomeric the original groups were diastereotopic. Equivalent groups always have identical chemical shifts (isochronous). Enantiotopic groups are equivalent in chemical shift in achiral or racemic media but can be nonequivalent (anisochronous) in chiral solvents. Diastereotopic groups are potentially anisochronous even in achiral or racemic solvents, though the degree of chemical shift nonequivalence may not always be large enough to lead to observable signal splitting under certain conditions. In these cases a change of solvent or an increase in the spectrometer frequency may serve to remove the accidental degeneracy. Although the above procedure is a most general method of elucidating intramolecular relationships, in the case of the inexperienced stereochemist it requires the construction of molecular models. In complex cases such as the relationships of the methyl groups in **27**, the method is very tedious owing to the large number of molecular conformations. Considering the paired ligands at a prochiral or C2 center, the following method provides a simple alternative.

(i) Pick out the relevant prochiral or C2 tetrahedral centers in the molecule.

(ii) If a center is C2 the paired ligands will be equivalent (homotopic)

(iii) If the center is prochiral the paired ligands will be either enantiotopic or diastereotopic. Inspect the molecule for a molecular symmetry plane (σ plane) *bisecting the angle RCR* in **4**. If such a plane exists, the R groups are enantiotopic; otherwise they are diastereotopic. Note that for acyclic prochiral centers there is usually fast rotation (on the NMR time scale) around the bonds connecting the prochiral center to the rest of the molecule. In these cases a sufficient condition for enantiotopicity is that a molecular symmetry plane bisects the angle RCR in any conformation.

In the past some oversimplified statements have been made regarding the conditions required for geminal nonequivalence to be observed. Even in a recent review it has been stated that it is sufficient that there is no symmetry plane between geminal species.[5] This is not strictly correct since, for example, compound **12** has no such plane but the geminal methylene protons are clearly equivalent. It is first necessary to see if the center is C2. In the oxirane (**1**), the cyclic CMe_2 carbon atom and the acyclic methine carbon atom are both prochiral. There is no molecular σ plane bisecting the cyclic Me–C–Me angle or passing through the acyclic methine carbon atom; thus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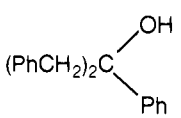
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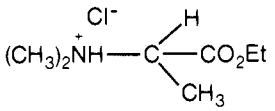
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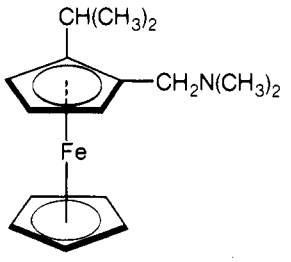
the geminal methyl groups at both these centers are diastereotopic. Indeed, a chiral molecule cannot possess any symmetry plane; therefore, it is a general rule that the paired ligands attached to a prochiral center in a chiral compound are always diastereotopic. The converse is not true; for example, the carbinol **13** is achiral but the geminal methylene hydrogens are diastereotopic as the symmetry plane does not pass through the prochiral carbon centers. Chemical shift nonequivalence has been observed in these and related compounds, but there is no guarantee that the chemical shift difference between diastereotopic groups will be large enough to be observable. Cases of accidental equivalence are very common; thus, for example, compound **13** shows nonequivalent geminal methylene protons in carbon tetrachloride solution, but not in deuteriomethanol.[6] Similarly, mercaptals of type $(PhCH_2S)_2CXPh$ show geminal nonequivalence when X = H or COPh in a variety of solvents, but not if X = Me even though the hydrogens are diastereotopic in all of these compounds.[7] Dabrowski et al.[8a] have reported that the methyl groups attached to the prochiral nitrogen atom in the ester **14** are accidentally isochronous in the ^1H spectrum (in $CDCl_3$) but are anisochronous by 0.84 ppm in the ^{13}C spectrum.

Chemical shift nonequivalence is also commonly encountered in metallocene chemistry; for example, the isopropyl methyl groups and the methylene protons in **15** are anisochronous by 0.13 and 0.77 ppm, respectively, in toluene solution at 28°.[8b] It should be noted that the *N*-methyl groups are isochronous since the potentially prochiral nitrogen center is inverting in configuration rapidly on the NMR time scale (see section VII) and therefore does not constitute a stable tetrahedral assembly. Similarly, the methylene protons in the o-ethylacetophenone tricarbonylchromium complex (**16**) are anisochro-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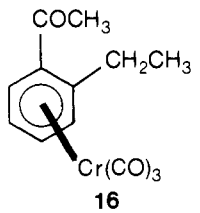
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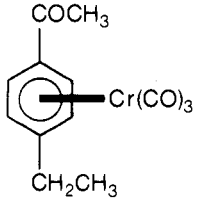
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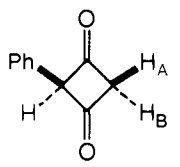
nous by 0.78 ppm in carbon tetrachloride.[9] However the para isomer (**17**) possesses a molecular symmetry plane (orthogonal to the plane of the ring) which passes through the prochiral methylene carbon atom; hence the methylene hydrogens are enantiotopic and isochronous in achiral solvents. The meta isomer provides another example of accidental chemical shift equivalence as, like the ortho compound, the methylene protons are diastereotopic, but only a single methylene signal (quartet) was observed in carbon tetrachloride solution at 100 MHz.[9] The geminal protons in the free ligands are, of course, isochronous since a symmetry plane exists (in the plane of the ring) containing the prochiral methylene carbon.

Structures of type **18** may cause some confusion since the cyclic methylene carbon is clearly not a C2 center as it does not lie on a C_2 symmetry axis, nor is it strictly a prochiral center according to the definition in section II.A. Fortunately, the relationship of H_A and H_B can be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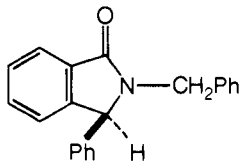
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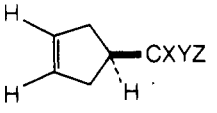
clearly seen to be diastereotopic as the former is cis to the phenyl group and the latter is trans. However, for the purist, centers of this type should be treated as if they were prochiral and rule iii applied. This also applies to centers of types **10** and **11** where the chiral substituents differ in configuration. Another possible source of confusion is the suggestion made in a previous review[10a] that there is asymmetry associated with planar nitrogen. However, the conformational argument used to support this view is incorrect, and the chemical shift nonequivalence of the benzyl methylene protons in compound **19**, which was used as an illustration, is due to the chiral carbon center and not to any asymmetry at planar nitrogen.[10b]

Although this review is concerned with geminal nonequivalence, the concept of diastereotopic and enantiotopic groups is of course quite general. Thus, for example, the vicinal alkene hydrogens in **20** are diastereotopic, and the trans-vicinal hydrogens in the oxirane **21** are homotopic, but the cis-vicinal hydrogens and the geminal hydrogens in **21** are enantiotopic. Further examples and discussion can be found in the article by Mislow and Raban.[2]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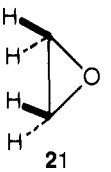
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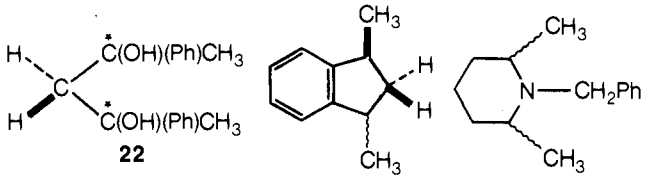
III. Chemical Shift Nonequivalence in Diastereotopic Groups

A. Meso Compounds

The meso and racemic isomers of compounds of type **22** may be identified by NMR spectroscopy.[11-20] In the meso isomer the two chiral centers (C*) differ in absolute configuration. The methylene carbon is not C2 and the molecular symmetry plane does not bisect the angle H–C–H; hence the methylene protons are diastereotopic and potentially anisochronous. On the other hand, the methylene center in the racemic compound is C2, and the methylene protons will show as a singlet. Similarly, in the cyclic hydrocarbon **23** the methylene protons are anisochronous in the cis (meso) compound and isochronous in the trans (±) compound.[18] These observations have important consequences in tacticity analysis of polymers; the geminal methylene protons are diastereotopic in an isotactic sequence and equivalent in the syndiotactic form.[12,13,15,19,20] The amine **24** provides an interesting



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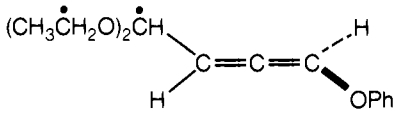
use of a prochiral benzyl probe to elucidate molecular stereochemistry. The benzyl methylene hydrogens are diastereotopic in the trans 1,3-dimethyl compound and give an AB system in the ^1H NMR spectrum, whereas they are enantiotopic in the cis isomer and occur as a singlet.[21]

B. Multiple Nonequivalence

The allenic compound **25** shows four different methylene signals in the NMR spectrum, and Martin et al.[22] have suggested the term "double nonequivalence" to describe situations of this type. A useful way of seeing how this arises is to apply prochiral factorization and the above rules. Thus the CH carbon atom (•) is prochiral and, as it does not lie in a molecular σ plane, the two ethoxy moieties are diastereotopic and are in different environments. However, the methylene carbon atoms (•) in each ethoxy moiety are also prochiral, and the geminal hydrogens are diastereotopic because of the absence of a symmetry plane through these centers. Therefore, all



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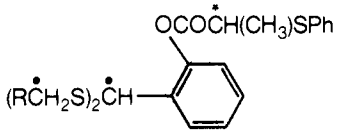

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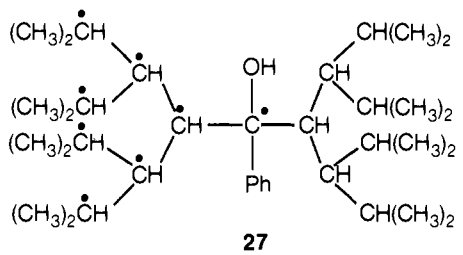
four methylene hydrogens in **25** reside in different positions in space and give rise to separate NMR signals (each is split further by geminal and vicinal coupling). Brink[23,24] has extensively investigated double nonequivalence in thioacetals, e.g., **26.** These compounds show four different methylene signals for the same reason as the allene **25,** and a large amount of data has been acquired on the effect of structure and solvent on the magnitude of the chemical shift nonequivalence. The concept is not limited to double nonequivalence; thus compound **27** should show quadruple nonequivalence of the methyl groups in achiral solvents and hence (ideally) eight methyl signals (doublets).



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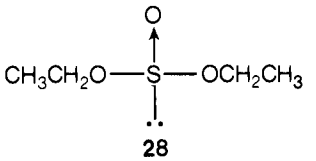
Applying prochiral factorization, the carbinol carbon is prochiral and lies in a molecular symmetry plane; therefore the two attached alkyl moieties are enantiotopic. Additionally, all seven methine carbon atoms within each alkyl moiety are also prochiral but do not lie in the molecular σ plane. Thus all eight methyl groups are mutually diastereotopic. In chiral media the two enantiotopic alkyl moieties attached to the carbinol carbon would in principle become nonequivalent and ideally 16 methyl signals would occur in the ^1H or ^{13}C NMR spectrum. Although no compounds of this type appear to have been studied, it is likely that many signals would be accidentally coincident, though lanthanide shift reagents might be used to remove some degeneracies.

C. Sulfinyl Compounds

The sulfur atom in sulfinyl compounds normally constitutes a stable tetrahedral center on the NMR time scale,[25] and the dissymmetry at these centers commonly leads to chemical shift nonequivalence within attached prochiral groups. Indeed, one of the earliest reports of geminal nonequivalence in acyclic compounds was that observed for the methylene hydrogens in diethyl sulfite (**28**) by Finegold,[26] though at that time the phenomenon caused some confusion. The spectrum was eventually interpreted correctly by Waugh and Cotton[27] and oth-



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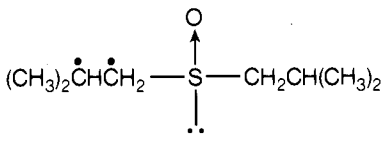

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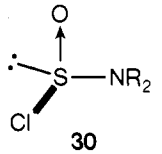
ers.[28,29] Geminal nonequivalence has been reported in many related compounds, e.g., $(PhCH_2O)_2SO$, $CH_3CH_2OS(O)Ph$, and $PhCH_2OS(O)Ph$, though it is worth noting that both sets of diastereotopic methylene hydrogens in ethyl ethanesulfinate, $CH_3CH_2OS(O)CH_2CH_3$, are accidentally isochronous (in CCl_4).[30] Similar considerations apply to sulfoxides where a prochiral alkyl group is directly bonded to the sulfur atom. Thus there have been numerous reports of anisochronous geminal methylene protons or methyl groups in ethyl, benzyl, and isopropyl sulfoxides.[31-37] Diisobutyl sulfoxide (**29**) is a particularly good example as the (enantiotopic) isobutyl groups each possess two prochiral centers (•), neither of which lies in the molecular symmetry plane. The geminal methylene protons and methyl groups have indeed been reported to be anisochronous in deuteriobenzene solution.[37] Alkylsulfinyl chlorides,[38,39] e.g., $PhCH_2S(O)Cl$, $CCl_3CH_2S(O)Cl$, and $(CH_3)_2CHS(O)Cl$, and sulfinamides,[40,41] e.g., $CH_3CH_2S(O)N(CH_3)_2$, $CH_3S(O)N(CH_2CH_3)_2$, and $CCl_3S(O)N(CH_3)CH_2Ph$, have anisochronous geminal methylene protons or methyl groups. In the latter two examples the prochiral methylene center is linked to the asymmetric sulfur atom through nitrogen. In view of this it is surprising that aminosulfinyl chlorides of type **30,** where R = $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2Ph$, and $-CH_2CH(CH_3)_2$, do not show chemical shift nonequivalence of the diastereotopic geminal NCH_2 or $CH(CH_3)_2$ hydrogens.[39,42] Although this could be due to accidental equivalence,[39] it seems unlikely that this could be true only in cases where a chlorine is attached to the sulfur atom but not for other sulfinamides. Jackson et al.[43] have suggested that the sulfur atom in **30** may be inverting in configuration rapidly in solution at ambient temperature by a bimolecular chlorine exchange mechanism. This process would lead to a symmetry plane on the NMR time scale containing the prochiral methylene or



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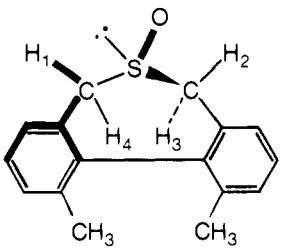
methine carbons; hence the attached hydrogens or methyl groups would be enantiotopic (on the NMR time scale) and isochronous in achiral solvents.

Compound **31** is an interesting example of a cyclic sulfoxide which shows double nonequivalence. Owing to the twisted biphenyl structure, the molecule lacks a symmetry plane through the prochiral sulfur atom; thus the two methylene moieties are diastereotopic. Furthermore there is no symmetry plane through the prochiral methylene carbons; hence the geminal methylene hydrogens are also diastereotopic. The compound does indeed show four methylene signals in the NMR spectrum (Table I); chemical shift assignments were established by the clever use of nuclear–nuclear Overhauser effects.[44] Additionally, since the four methylene hydrogens are diastereotopic they can show different chemical reactivities; the relative rates of deuterium exchange determined by Fraser et al.[44] are given in Table I.



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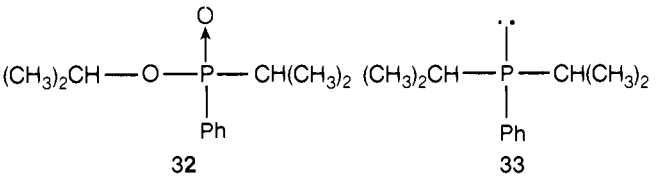
Geminal nonequivalence has been observed in sulfonium salts and sulfonium ylides containing prochiral groups.[45] For example, the geminal methylene hydrogens in $(CH_3CH_2)_2{}^+SPh\ ClO_4{}^-$ and $(CH_3CH_2)_2S{=}CHCOPh$ are anisochronous by 0.12 ppm and 60 Hz (magnetic field strength not specified but probably 60 MHz), respectively, in deuteriochloroform solution. These observations indicate that the sulfur atoms in sulfonium salts and ylides are nonplanar and inverting slowly on the NMR time scale (cf. sulfoxides).

D. Organophosphorus Compounds

Chemical shift nonequivalence of geminal groups is commonly observed in tetracoordinate phosphorus compounds which possess a prochiral group directly bonded to an asymmetric phosphorus atom as in $(CH_3)_2CHP(O)(Ph)OCH_3$,[46] or bonded through oxygen to phosphorus as in $(CH_3CH_2O)_2P(S)CH_3$.[47] Compound **32** combines both of these features and shows anisochronous methyl groups in both isopropyl moieties.[48] Trivalent phosphorus is normally a configurationally stable tetrahedral center on the NMR time scale;[25] hence dissymmetric phos-



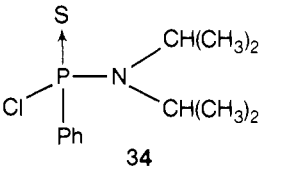
32 33

phines which contain prochiral alkyl groups can also show chemical shift nonequivalence. Anisochronous geminal methyl groups have been observed in the ^1H NMR spectrum of phosphine **33** ($\Delta\delta$ = 0.17 ppm),[49] and the geminal methylene protons in $(CH_3CH_2O)_2P{\cdot}Ph$[48] and the geminal fluorine atoms in $(CF_3CF_2CF_2)_2PI$[50] are anisochronous. There have been several reports of chemical shift nonequivalence in aminophosphorus compounds; for example, the methylene protons in $ClCH_2P(O)(Cl)N(CH_3)_2$,[51] $ClCH_2P(S)(Cl)N(CH_3)_2$,[51] and $ClCH_2P(Cl)N(CH_3)_2$[52] are anisochronous as are the geminal fluorine atoms in $CHCl_2CF_2P(F)N(CH_3)_2$[53] and $CHF_2CF_2P(Cl)N(CH_3)_2$[53] and the isopropyl methyl groups in $(CH_3)_2CHP(O)(Cl)N(CH_3)_2$.[51] Nonequivalence has also been reported in aminophosphorus compounds where the prochiral moiety is bonded to the nitrogen atom;[54,55] for example, the geminal methyl groups in **34** are anisochronous in both the ^1H[55] and ^{13}C[56] NMR spectra at ambient temperature owing to the absence of a molecular σ plane containing the prochiral methine carbon. At higher temperatures the phosphorus atom in

TABLE I. Chemical Shifts and Relative Exchange Rates at 30° for the Benzyl Hydrogens in the Cyclic Sulfoxide 31[44]

Proton	δ^a	Relative rates of exchange in $CD_3OD/CD_3O^-Na^+$	Relative rates of exchange in $(CH_3)_3COD/(CH_3)_3CO^-K^+$
H_1	4.12	1	1
H_2	3.63	200	1100
H_3	3.29	7600	300
H_4	2.98	30	1300

[a] In deuteriochloroform solution.



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some chlorophosphorus compounds may undergo rapid chlorine exchange with concomitant inversion in configuration at phosphorus and loss of geminal nonequivalence in attached prochiral alkyl substituents.[57] Di(isopropylamino)phenylphosphine sulfide, $PhP(S)[NHCH(CH_3)_2]_2$, shows an unusual effect in the ^1H NMR spectrum. Thus the geminal methyl groups are anisochronous by 0.02 ppm in deuteriochloroform solution at ambient temperature, but the magnitude of the nonequivalence increases on passing gaseous hydrogen chloride into the solution. When the resulting solution was allowed to stand, the nonequivalence decreased to zero. Cowley et al.[58] have suggested that in these solutions the phosphine is in rapid equilibrium (on the NMR time scale) with a protonated form, and that the observed nonequivalence is a weighted average of that in these two compounds. Evidently the sense of the nonequivalence is opposite in these two forms; otherwise the net effect could not be zero at a certain concentration of hydrogen chloride.

E. Nonequivalence at Prochiral Heteroatoms

The previous examples have generally involved diastereotopic geminal ligands attached to a prochiral carbon atom. However, other elements with tetrahedral geometry can readily be prochiral.

Chiral compounds of type **14** possess a prochiral nitrogen center, and the geminal methyl groups have been reported to be nonequivalent in the ^1H and ^{13}C spectra.[8a] McFarlane and Nash[59] have investigated salts of type **35** where M–X = N–Ph, P–Ph, S–:, and Se–: by ^1H NMR and found the paired methyl ligands to be anisochronous by 0.20, 0.24, 0.38, and 0.19 ppm, respectively, in deuteriochloroform solution. The geminal methyl groups in the organometallic compound **36** have been reported to be anisochronous by 0.36 ppm because of the prochiral phosphorus and the chiral iron centers.[60] Shaw et al.[61]

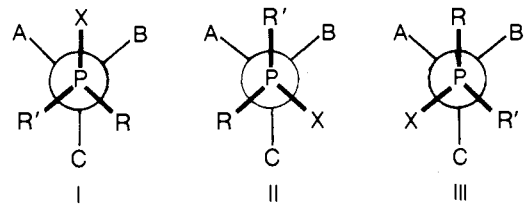
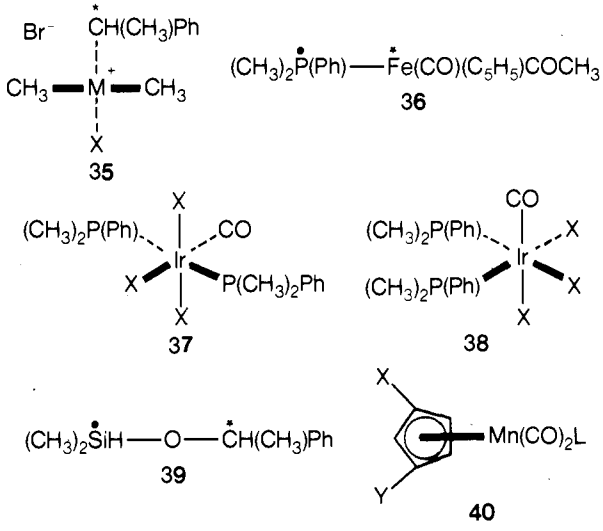


Figure 1.

have used prochiral phosphorus moieties to elucidate the stereochemistry of octahedral complexes. For example, the geminal methyl groups in the trans iridium complex **37** are isochronous as the prochiral phosphorus atoms lie in a molecular σ plane, whereas they are anisochronous in the cis isomer **38** as the molecular σ plane does not pass through the phosphorus atoms. Geminal nonequivalence has also been observed at prochiral silicon in several chiral compounds of type **39**.[62] Prochiral metal atoms can also be envisaged; for example, the organometallic complexes of type **40**, where X differs from Y, contain prochiral manganese in a distorted tetrahedral assembly. The molecule lacks a symmetry plane through the metal atom; thus the paired carbonyl ligands are diastereotopic. With the advent of routine ^{13}C NMR facilities it is important to realize that compounds of this type can give rise to two carbonyl carbon resonances.



IV. Factors Affecting the Magnitude of Geminal Nonequivalence

The symmetry rules discussed in section II.B enable it to be established whether geminal chemical shift nonequivalence should be observed in principle. However, these rules do not afford any guide as to whether the nonequivalence will be large enough in practice to be observable under any given conditions. The factors affecting the magnitude of $\Delta\delta$ are discussed below, but it should be pointed out that it is very difficult to predict a priori even qualitatively what the magnitude of $\Delta\delta$ will be in a given case.

A. Conformational Aspects

Consider a compound of the type $R_2P(X)$-M(A)(B)C where a prochiral center (P) is bonded to an atom (M) which bears three different substituents (A, B, and C). The three possible staggered conformations around the P–M bond are depicted in Figure 1. The paired R ligands are diastereotopic by the symmetry rules; i.e., the prochiral center (P) does not lie in a molecular σ plane. The observed chemical shifts of the paired R ligands (arbitrarily labeled R and R′) will be time averaged over the residence time in each conformation, i.e.

$$\delta(R)_{obsd} = \delta(R)_I p_I + \delta(R)_{II} p_{II} + \delta(R)_{III} p_{III}$$

$$\delta(R')_{obsd} = \delta(R')_I p_I + \delta(R')_{II} p_{II} + \delta(R')_{III} p_{III}$$

where $\delta(R)_I$ is the chemical shift of R in conformer I and p_I is the fractional population of conformer I. Therefore, the magnitude of the observed nonequivalence ($\Delta\delta$) between R and R′ is given by

$$\Delta\delta = p_I[\delta(R)_I - \delta(R')_I] + p_{II}[\delta(R)_{II} - \delta(R')_{II}] + p_{III}[\delta(R)_{III} - \delta(R')_{III}] = \sum_n p_n(\Delta\delta)_n \quad (1)$$

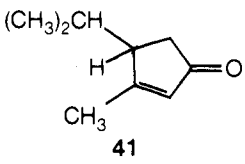
Hence the magnitude of $\Delta\delta$ depends on the relative populations of the various conformations, but it is important to realize that even if all three conformations are equally populated (i.e., $p_I = p_{II} = p_{III} = 1/3$), chemical shift nonequivalence would still be observed (as demanded by the symmetry rules). This arises because none of the $\delta(R)_n$ terms are equal to any of the $\delta(R')_n$ terms, except, of course, by accident. Thus, for example, $\delta(R)_I$ does not equal $\delta(R')_{III}$ even though the R group in both cases lies between ligands B and C (Figure 1). Closer inspection reveals that in conformer I, R "sees" C partly overshadowed by R′, but in conformer III, R′ "sees" C partly overshadowed by an X moiety.

Nair and Roberts[63] (1957) appear to have been the first workers to observe acyclic geminal nonequivalence and rationalize the phenomenon in terms of conformational preference. Waugh and Cotton[27] pointed out in 1961 that nonequivalence would still persist in the absence of a conformational preference, and this aspect has been considered more fully by Gutowsky.[64] However, because this point was not always fully appreciated, readers should be warned that some conclusions of early investigators into this phenomenon may be incorrect.

B. Structural Effects

Although it is not generally possible to relate the magnitude of $\Delta\delta$ to the molecular structure, a few aspects deserve mention. Thus in Figure 1 if two of the groups, say A and B, are very similar (e.g., hydrogen and deuterium), the magnitude of the observed nonequivalence will be very small. Indeed $\Delta\delta$ becomes zero if A is identical with B by the symmetry rules. It can be readily verified from Figure 1 that if A and B are hydrogen and deuterium, respectively, $\delta(R)_I$ is approximately equal to $\delta(R')_I$; $\delta(R)_{II}$ is approximately equal to $\delta(R')_{III}$; $\delta(R_{III})$ is approximately equal to $\delta(R')_{II}$; and p_{II} is approximately equal to p_{III}. Therefore, from eq 1, $\Delta\delta$ is close to zero. Conversely if groups A, B, and C are very different in size and in magnetic anisotropy, there is a good chance that $\Delta\delta$ will be fairly large. Thus, for example, $\Delta\delta$ = 0.35 ppm for the isopropyl methyl groups in the cyclopentenone (**41**) in carbon tetrachloride solution.[65] This fairly large nonequivalence has been ascribed to a preferred conformation around the bond linking the prochiral methine carbon to the chiral center. Furthermore, it was suggested that the anisotropy of the alkene bond serves to selectively shield the more proximate isopropyl methyl group.[65] Similarly, a combination of conformational preference and selective anisotropic effects probably contribute to the remarkably large nonequivalence of the isopropyl methyl groups in **42** where $\Delta\delta$ = 0.91 ppm,[66] and of the benzyl methylene hydrogens in **19** and **43** where $\Delta\delta$ = 1.75 and 1.99 ppm, respectively.[67,68]

It is interesting to consider the effect of increasing the



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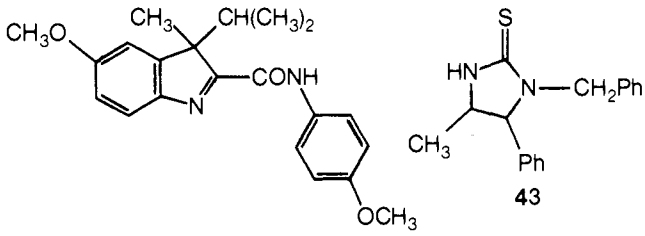

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TABLE II. Effect of Distance between the Prochiral and Chiral Centers on the Observed Geminal Methyl Nonequivalence ($\Delta\delta$) in Compounds of Type 44[69]

$(CH_3)_2\dot{C}H—(X)—\overset{*}{C}H(CH_3)Ph$

44

X	$\Delta\delta$ ppm (CCl_4 soln)	$\Delta\delta$ ppm (benzene soln)
—	0.182	0.133
-O-	0.067	0.013
$-OCH_2-$	0.005	0.008
$-OCH_2CH_2-$	0.042	0.030
$-OCH_2CH_2O-$	0.000	0.013
$-OCH_2CH_2OCH_2-$	0.000	0.000

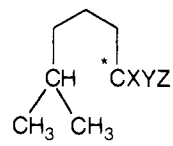
TABLE III. Effect of Distance between the Prochiral and Chiral Centers on the Observed Geminal Methyl Nonequivalence ($\Delta\delta$) in Sulfoxides of Type 45[35]

$(CH_3)_2\dot{C}(OH)—(CH_2)_N—\overset{*}{S}(O)Ph$

45

N	$\Delta\delta$ ppm (CCl_4 soln)	N	$\Delta\delta$ ppm (CCl_4 soln)
1	0.257	3	0.044
2	0.032	4	0.00

distance between the prochiral center and the asymmetric or dissymmetric center in the molecule. One would expect the magnitude of $\Delta\delta$ for the paired substituents to decrease with distance since both the conformational interactions between the centers and the anisotropic effects of the substituents attached to the asymmetric center should become less important at longer distance. The few investigations that have been carried out are in agreement with this view. Whitesides et al.[69] have investigated this effect in a series of isopropyl ethers and some of their results are given in Table II. Recently, Taddei[35] has carried out a similar investigation for the geminal methyl nonequivalence in sulfoxides (Table III). In both these cases $\Delta\delta$ tends to fall off rapidly with distance, but it is interesting to note that the nonequivalence again becomes significant when three atoms separate the prochiral and chiral centers. It has been suggested that this may be in accord with the Newman "rule of six"; therefore, the geminal methyl groups may reside part of the time reasonably close to the substituents on the chiral center as depicted in **46**.[69] The nonequivalence of the isopropyl methyl groups in the indole derivatives (**47**) has been reported to be 0.063, 0.032, and 0.00 ppm for N equal to 0, 1, and 2, respectively (in dimethyl sulfoxide solution).[70] In sulfinates of the type $(CH_3)_2CH(CH_2)_NO-S(O)CH_3$, $\Delta\delta$ for the geminal methyl group is 0.04 ppm



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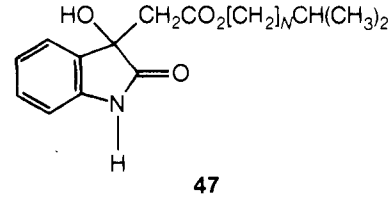

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when N = 0 and 0.00 ppm when N = 1 or 2 (in CCl_4).[30b]

Dabrowski et al.[71] have investigated geminal nonequivalence in compounds of type $R^1R^2C(OH)CH_2OR^3$ (R^1 or R^3 = $CH(CH_3)_2$) using both ^1H and ^{13}C NMR spectroscopy. The magnitude of $\Delta\delta$ for the methyl groups tended to be smaller when the isopropyl moiety (R^3) was remote from the chiral carbinol center. These authors have also investigated esters of the type $R^1CH(Ph)CH(COOR^2)_2$ which contain diastereotopic carbethoxy moieties. It appears that $\Delta\delta$ for ^{13}C spectra is more sensitive to structural changes in these compounds than the corresponding proton data. Although $\Delta\delta$ usually tends to decrease with increasing distance, this "rule" should be treated with caution as exceptions are likely to be encountered.

It can be seen from eq 1 that the chemical shift nonequivalence parameter ($\Delta\delta$) contains a great deal of structural information in both the p_n and δ_n terms; however, the problems of extracting this information are enormous. There appears to be little possibility at present of being able to calculate $\Delta\delta$ accurately by ab initio molecular orbital methods. The problems are formidable as it would require conformational energies to be determined to great precision together with small chemical shift effects. Perhaps a semiempirical molecular orbital procedure might be feasible, but the problem remains of extrapolating from the gas phase into solution. An empirical approach would appear to offer the best hope of attempting to relate $\Delta\delta$ to molecular structure. Gutowsky et al.[72] pioneered this area by attempting to derive conformer populations and δ_n terms by a multiparameter fit to the observed temperature dependence of $\Delta\delta$ for the geminal fluorine nuclei in $BrCF_2CFClBr$. However, this method also used the variation in the vicinal fluorine coupling constants as additional information, and even then the results are of questionable validity.[73-75] Investigations into the conformation of acyclic ethane systems have generally been concerned with the utility of observed time-averaged vicinal coupling constants.[76,77] This procedure has met with considerable success, but it is limited to systems containing vicinal hydrogen or fluorine nuclei. The best method of conformational analysis by NMR is to cool the sample until bond rotation has become slow and measure the relative conformer populations (and chemical shifts) directly.[74,75,78] However, because of the low barrier to rotation in ethanes and the complexity of the spectra, this method is of limited use.

In a recent notable paper, Binsch[79] has attempted to relate the magnitude of geminal nonequivalence to the molecular structure by developing an empirical heuristic model. In this novel approach, parameters were assigned to the substituents in halogenated ethanes of the type $BrCF_2CXYZ$. A least-squares method was used to fit the mathematical model to the observed ambient temperature values of $\Delta\delta$ for the geminal fluorine nuclei. The calculated conformer populations were in close agreement with those extrapolated from experimental measurements at low temperatures where CC bond rotation was slow on the NMR time scale.[80] One of the assumptions involved in determining the conformer populations is that the intrinsic anisochronism can be neglected. However, the results are encouraging for the compounds considered in this initial investigation.

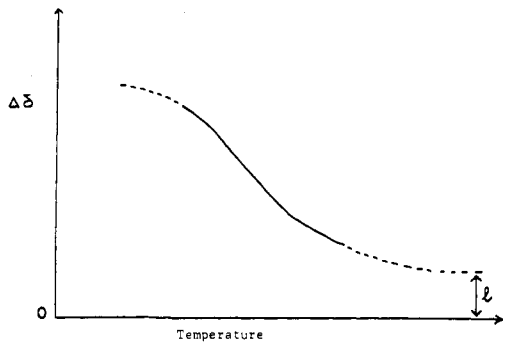
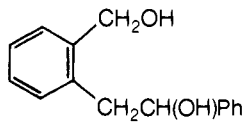


Figure 2.

C. Temperature Effects

Temperature can affect the magnitude of the chemical shift nonequivalence of geminal groups either by altering the relative conformer populations (p_n) or the individual chemical shift terms (δ_n) in eq 1. However, in relatively inert solvents such as cyclohexane or carbon tetrachloride, it is reasonable to suppose that any major change in $\Delta\delta$ with sample temperature is probably due to changes in the conformer populations. However, if any of the substituents A, B, or C at the dissymmetric center (M in Figure 1) are not axially symmetrical, conformational population changes *within* these substituents could affect the δ_n terms. In aromatic solvents, which are often known to induce marked solvent shifts of proton signals, it is quite possible that solvent–solute interactions could lead to significant temperature effects on the δ_n terms and hence on $\Delta\delta$. From the data available to date, it seems that $\Delta\delta$ normally decreases with increasing temperature. Thus in $BrCF_2CFClBr$, $\Delta\delta$ for the diastereotopic geminal fluorine nuclei decreases from 2.13 ppm at −49° to 1.15 ppm at 193°.[72] Jakobsen et al.[81] have reported that for the geminal methyl groups in $(CH_3)_2CHCH(CN)COOCH_2CH_3$, $\Delta\delta$ (CCl_4) decreased from 0.09 ppm at −40° to 0.02 ppm at 70°, and Cowley et al.[58] have observed that $\Delta\delta$ for the methyl groups in $[(CH_3)_2CHNH]_2P(S)Ph$ steadily decreased from 0.14 ppm at −58° to ca. 0 ppm at 60° in deuteriochloroform solution. A similar effect has been observed for the diastereotopic methyl groups in the following isopropyl compounds: **41**,[65] **42**,[66] $[(CH_3)_2CHO]_2P(O)R$,[48] $(CH_3)_2CHS(O)Cl$,[38] $(CH_3)_2CHOC(O)CH(OR)R$,[82] $(CH_3)_2CHN{=}NCH(CH_3)Ph$,[83] and 1-(*N*,*N*-diisopropylthiocarbazoyl)imidazole.[84] In the following compounds containing diastereotopic geminal methylene hydrogens, the magnitude of the nonequivalence has also been observed to decrease on raising the temperature: $RCH_2OC(O)CH(OR)R'$,[82] $PhCH_2Si(CH_3)(OCH_3)Ph$,[85] $PhCH_2P^+XYZ\ Br^-$,[86] $PhCH_2As^+XYZ\ Br^-$,[86] $p\text{-}NO_2C_6H_4OP(O)(CH_3)OCH_2COPh$,[87] and ethyl and benzyl analogs of compound **42**.[66] Both sets of diastereotopic methylene protons in **48** and related compounds show a similar inverse temperature effect.[88] In compounds of the type



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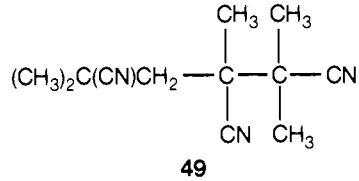
$XCH(Ph)CH(CO_2R)_2$, the paired CO_2R moieties attached to the prochiral methine carbon are diastereotopic. The magnitude of the nonequivalence of the various proton signals in the two diastereotopic R groups (R = CH_3, $CH(CH_3)_2$, or $C(CH_3)_3$; X = CH_3 or CN) was found to decrease at higher temperature.[71] In most of these cases a graph of $\Delta\delta$ vs. temperature has the form shown in Figure 2. This "normal" behavior is to be expected from the gradual equalization of conformer populations at high temperature provided that the intrinsic contribution to $\Delta\delta$ is relatively small. The gradient and exact form of the curve will depend on the various terms in the above equations. An essentially constant value of $\Delta\delta$ over a limited temperature range can arise if this gradient is small, or if only one conformer is significantly populated, or if the conformer populations have attained their limiting value (ℓ in Figure 2). It is also possible for $\Delta\delta$ to *increase* on raising the temperature owing to an interplay of the various δ_n and p_n terms. Thus the sense of the nonequivalence (i.e., the relative signs of the individual $\Delta\delta_n$ terms in eq 1) can differ in each conformer. For example, at low temperature the preferred conformation may only have a very small $\Delta\delta$ value. On raising the temperature the $\Delta\delta_n$ terms of the other conformations could contribute and increase the observed $\Delta\delta$ value. At even higher temperatures $\Delta\delta$ could decrease again as the conformer populations reach their limiting value which may be small (see section V).

It has been reported that $\Delta\delta$ for the geminal methylene protons in **49** increases with increasing temperature in several solvents.[89] Similarly in the silane, $(CH_3)_2Si(Ph)CH_2CH(CH_3)Ph$, $\Delta\delta$ for the diastereotopic methylene protons increases with temperature whereas $\Delta\delta$ for the diastereotopic methyl groups shows the more usual decrease with temperature.[62] Fantazier[90,91] has investigated geminal nonequivalence in several esters of 2,2,4-trimethylpentan-1,3-diol (**50**). These compounds



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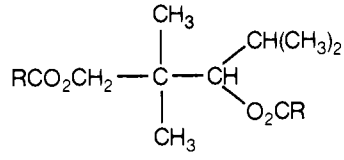

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contain at least three prochiral sites, and examples were studied where group R was itself a prochiral isopropyl moiety. It was found that $\Delta\delta$ decreased on raising the temperature for most of the paired ligands in these compounds. However, the nonequivalence of the methyl groups at the 2 position was observed to increase at higher temperature in the neat liquid but showed "normal" behavior in *o*-dichlorobenzene solution. Dabrowski et al.[92] have reported that the magnitude of $\Delta\delta$ in a series of carbinols of the type $(CH_3)_2C(NO_2)CH(OH)R$ increases on raising the temperature. This "abnormal" temperature effect was observed in all nine compounds studied (R = alkyl or aryl) in several solvents. A similar effect was also observed in formyl esters of the carbinols, showing that it was not associated with hydrogen bonding.[92]

The chiral ferrocene **15** shows another unusual temperature effect as $\Delta\delta$ for the isopropyl methyl groups decreased to zero and then increased again on raising the temperature as shown in Figure 3.[8b] It is interesting that $\Delta\delta$ for the diastereotopic methylene protons showed the normal decrease at higher temperature. An apparent discontinuity at $\Delta\delta$ = 0 (Figure 3) results from a change in

the sense of the nonequivalence; i.e., the signals "cross over" and $\Delta\delta$ changes sign. The behavior is normal if the curve is plotted to accommodate the change in sign as shown by the dotted line in Figure 3.[8b]

In summary, owing to the number of conformations available in flexible molecules, the curve of $\Delta\delta$ vs. temperature for a given diastereotopic geminal moiety can be very complex. It must be realized that temperature can effect the $\Delta\delta_n$ values in each conformer in addition to the relative conformer populations (p_n). Therefore, one must be very cautious in interpreting the temperature dependence of geminal nonequivalence ($\Delta\delta$) in terms of any particular conformational behavior.

D. Solvent Effects

The magnitude of geminal chemical shift nonequivalence is often significantly solvent dependent because of medium effects on the δ_n and p_n terms in eq 1. Numerous investigators have noted solvent effects on $\Delta\delta$ (see ref 7, 22–24, 37, 38, 59, 62, 70, 83–93), but there have been few systematic studies. Whitesides et al.[94] have extensively investigated the solvent dependence of the methylene nonequivalence in chiral benzyl ethers of the type $PhCH_2OCH(R)CH_3$. In the case where R = phenyl, the magnitude of $\Delta\delta$ showed an approximate inverse relation to the dielectric constant of the medium. The solvent effect was much less pronounced in cases where R was an alkyl moiety. These observations were rationalized in terms of the solvent affecting the orientation of the phenyl ring and thus altering the various δ_n terms.[94] In the case of an asymmetric phosphorus compound, $PhCOCH_2OP(O)(CH_3)OC_6H_4$-*p*-$NO_2$, the degree of nonequivalence of the methylene protons has also been reported to decrease with increasing dielectric constant of the medium.[87] Snyder[77,95] has investigated the effect of the solvent $\Delta\delta$ for a number of compounds. In a series of 1,1,2-trisubstituted ethanes of the type RCH_2CHXY, the methylene proton nonequivalence showed a marked solvent dependence. However, the variation in the vicinal coupling constants was relatively small, indicating that the solvent does not greatly alter the conformer populations around the CC bond.[77] Thus it would appear that in these compounds the solvent effect on $\Delta\delta$ is mainly due to alterations in the various chemical shift terms (δ_n in eq 1).

Aromatic solvents often have a particularly marked effect on $\Delta\delta$. Presumably this arises mainly from an aromatic solvent induced shift (ASIS) on the various δ_n terms of the component conformers.[96] The direction of the selective ASIS may be such that $\Delta\delta$ either increases or decreases (ref 23, 24, 30b, 37, 38, 40, 83, 84, 93), but a useful application of the ASIS is to render the nonequivalence observable under conditions where diastereotopic signals are accidentally degenerate in aliphatic solvents. Another method of achieving this might be to add a lanthanide shift reagent to the solution.[6]

V. Intrinsic Nonequivalence

The residual chemical shift nonequivalence which remains when all three conformations are equally populated (Figure 1, section IV.A) is known as the "intrinsic nonequivalence" or the "intrinsic anisochronism" ($\Delta\delta_i$), i.e.

$$\Delta\delta_i = 0.333[\delta(R)_I - \delta(R')_I] + 0.333[\delta(R)_{II} - \delta(R')_{II}] + 0.333[\delta(R)_{III} - \delta(R')_{III}] \quad (2)$$

Gutowsky[64] has pointed out that the observed nonequivalence ($\Delta\delta$) can therefore be partitioned into an intrinsic term ($\Delta\delta_i$) and a second term ($\Delta\delta_c$) which depends on the relative conformer populations, i.e.

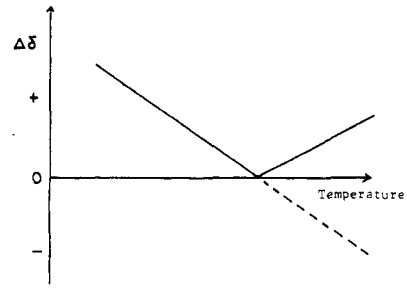


Figure 3.

$$\Delta\delta_{obsd} = \Delta\delta_c + \Delta\delta_i \quad (3)$$

There has been great interest in attempting to evaluate the relative importance of these two components in particular cases. One suggested approach to this problem has been to record the effect of increasing the temperature on $\Delta\delta$ and then extrapolate the curve to a limit (ℓ in Figure 2).[10,83,85,92] This limiting value of the nonequivalence has been equated with the intrinsic term ($\Delta\delta_i$). However, this procedure is unreliable as it assumes that all three conformers will be equally populated at high temperature. This will only be true if the entropy differences between the conformers are zero. In simple molecules with axially symmetrical substituents (e.g., halogen) at the chiral and prochiral centers, conformational entropy differences will probably be small in weakly solvating media. It should be noted, however, that an entropy preference of only 1 eu for one of the three conformers corresponds to a limiting population ratio of 0.45:0.27:0.27 which could possibly be a sufficient departure from 0.33 to mask the intrinsic term. A second criticism of this procedure is that the intrinsic term may be temperature dependent owing to variation in the various chemical shift terms in eq. 2; therefore, a true limit may not be attained. Finally, the limited temperature range available to current spectrometers can make extrapolation inaccurate. However, in favorable cases this method might afford a guide to the magnitude of the intrinsic term. The only reliable method of estimating the intrinsic term is to use the procedure suggested by Gutowsky[64] and first applied by Raban[97] to the geminal fluorine nonequivalence in $BrCF_2CFBrCl$ and $BrCF_2CHBrCl$. The NMR spectrum of these compounds had been previously investigated by Newmark and Sederholm[74] at low temperature where rotation around the CC bond had become slow on the NMR time scale, enabling the spectrum of each individual conformer to be observed. Thus the chemical shifts of the fluorine nuclei in each conformer could be obtained, and also (by integration) the relative conformer populations. These δ_n and p_n terms can then be substituted into eq 1 to give $\Delta\delta$, or alternatively $\Delta\delta_i$ may be estimated by setting all the p_n terms equal to one-third (eq 2). Norris and Binsch[80] have recently extended this approach to a wider range of halogenated ethanes. A selection of their results is presented in Table IV. It is clear from their data that the intrinsic term is by no means negligible for this type of compound. Additionally, the intrinsic and conformational components of $\Delta\delta$ sometimes differ in sign. This could cause the nonequivalence to decrease to zero and change sign on increasing the temperature and afford a plot of the type shown in Figure 3, though an interplay of the conformer populations could possibly cause a similar effect. It would be interesting to have comparable data for proton nonequiv-

TABLE IV. Total ($\Delta\delta$) and Intrinsic ($\Delta\delta_i$) Nonequivalence of the Geminal Fluorine Nuclei in Asymmetric Ethanes of the Type RCF_2CXYZ[80]

R	X	Y	Z	$\Delta\delta$ (ppm)[a]	$\Delta\delta_i$ (ppm)[b]
Br	H	F	Cl	3.83	0.9
Br	H	F	Br	4.18	1.1
Br	H	Cl	Br	3.30	0.52
Br	H	Cl	Ph	4.92	−0.37
Cl	H	Br	Ph	6.28	−0.07
Cl	H	Cl	Ph	3.13	−0.30
Cl	H	F	I	2.44	1.3
Br	H	F	Ph	−1.73	−0.63
Br	Cl	Br	Ph	0.0	0.34
Cl	F	Cl	Ph	0.62	0.54
Br	F	Cl	Ph	0.46	0.38
Br	F	Cl	Br	1.65	0.23

[a] Measured in vinyl chloride solution at ambient temperature. [b] Estimated from low-temperature data (−120 to −160°) in vinyl chloride solution.

alence, but the experimental problems are much greater owing to the relatively small chemical shift differences and the low barriers to rotation around most CC bonds.

Another ingenious method of investigating intrinsic nonequivalence, first suggested by Mislow and Raban,[2] is to consider the intrinsically diastereotopic cyclic methylene hydrogens in compounds of type **51** where all three conformer populations are equal by symmetry. Binsch and Franzen[98] and McKenna et al.[99] have synthesized some suitable compounds of this type: **52, 53,** and **54.** A selection of their data is given in Table V. It can be seen that the intrinsic nonequivalence in these compounds is of the same order of magnitude as the total observed nonequivalence of methylene protons in ordinary acyclic systems. However, it has been suggested that the intrinsic anisochronism in these compounds might be amplified in comparison with acyclic systems due to the geometric constraint.[98] It must be emphasized that this view has not yet been confirmed, and therefore it is dangerous to neglect $\Delta\delta_i$ in acyclic systems.

Binsch and Franzen[98] have also suggested the novel propeller-shaped compound **55** as a model for investigating intrinsic anisochronism in attached acyclic prochiral R moieties. In the benzyl derivative (**55,** R = CH_2Ph) the intrinsically diastereotopic benzyl methylene hydrogens were found to be isochronous even at 220 MHz or in the presence of added europium shift reagent. However, in the derivative with R = $-C(CH_3)_2OH$, the intrinsically diastereotopic methyl groups were found to be anisochronous by 0.007, 0.020, and 0.038 ppm in deuterium oxide, deuteriodimethyl sulfoxide, and pyridine, respectively. The fluorine analog (**55,** R = $-C(CF_3)_2OH$) exhibits a much larger intrinsic nonequivalence for the trifluoromethyl groups, $\Delta\delta_i$ = 0.28 ppm in dimethyl sulfoxide solution.[98] The latter observation is in line with the much greater sensitivity of fluorine chemical shifts to environmental factors.

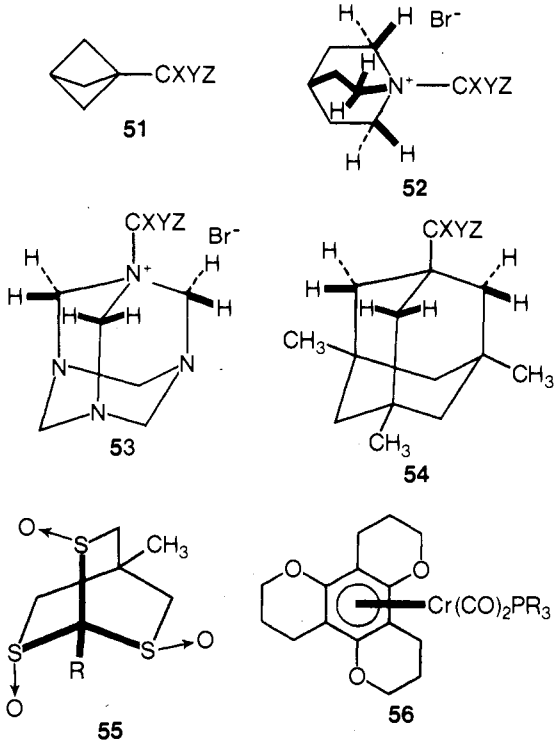


TABLE V. Intrinsic Nonequivalence ($\Delta\delta_i$) of the Intrinsically Diastereotopic Cyclic Methylene Protons in Model Compounds[98,99]

Compd	X	Y	Z	Solvent	$\Delta\delta_i$(ppm)
52	H	CH_3	Ph	$(CD_3)_2SO$	0.10
52	H	CH_3	$CO_2CH_2CH_3$	$(CD_3)_2SO$	0.09
53	H	CH_3	Ph	$(CD_3)_2SO$	0.21
54	H	Cl	CO_2H	$CDCl_3$	0.17
54	H	Cl	CO_2H	C_6D_6	0.20
54	H	Cl	CO_2Ph	$CDCl_3$	0.23
54	H	Cl	CO_2Ph	C_6D_6	0.25
54	H	Cl	$CON(CH_3)_2$	$CDCl_3$	0.29
54	H	Cl	$CON(CH_3)_2$	C_6D_6	0.38
54	H	Cl	Br	$CDCl_3$	<0.06
54	H	Cl	Br	C_6D_6	<0.06

The fluorine analog (**55,** R = $-C(CF_3)_2OH$) exhibits a much larger intrinsic nonequivalence for the trifluoromethyl groups, $\Delta\delta_i$ = 0.28 ppm in dimethyl sulfoxide solution.[98] The latter observation is in line with the much greater sensitivity of fluorine chemical shifts to environmental factors.

Franzen and Binsch[98] have also reported that the intrinsic anisochronism of the cyclic methylene hydrogens in the adamantane (**54,** X = H, Y = Cl, Z = CO_2H) is temperature dependent. Thus in benzene solution $\Delta\delta_i$ decreased from 0.20 ppm at 40° to 0.18 ppm at 100°. The intrinsic nonequivalence was also found to be solvent dependent with values ranging from 0.14 ppm in dichloromethane solution to 0.21 ppm in pyridine solution. These observations further emphasize the general remarks made earlier in this section when considering the extrapolation procedure.

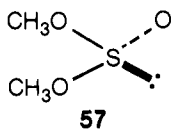
The organometallic compound **56** is of some interest as the carbonyl ligands are intrinsically diastereotopic and should (in principle) show separate signals in the ^{13}C NMR spectrum.[100]

VI. Chemical Shift Nonequivalence in Enantiotopic Groups

Geminal groups attached to a prochiral center are enantiotopic if the center lies in a molecular symmetry plane which bisects the angle between the paired geminal substituents (section II.B). Enantiotopic groups reside in "mirror image" environments and are isochronous in achiral or racemic media.

However, in a chiral environment the internally enantiotopic groups become "diastereotopic by external comparison" and hence anisochronous in the NMR spectrum.[2] Chemical shift nonequivalence should therefore be observed in principle for enantiotopic geminal groups in optically active solvents. However, the effect relies on solvent–solute interactions which are often weak; hence the degree of signal splitting is often too small to be observed.

Pirkle et al.[101,102] have reported that the internally enantiotopic methyl groups of dimethyl sulfite (**57**) and *N,N*-dimethylaniline oxide (**58**) are anisochronous by 0.06 and 0.038 ppm, respectively (^1H spectrum), in optically



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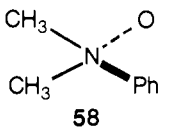

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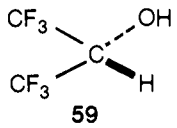

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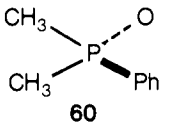

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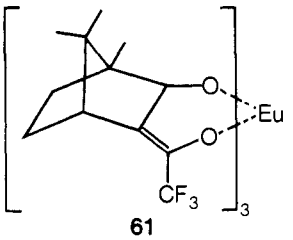
active 2,2,2-trifluorophenylethanol solution. It is interesting that, in the same solvent, the internally enantiotopic methyl groups of dimethyl sulfoxide are nonequivalent by 0.02 ppm in the ^1H NMR spectrum, but signal splitting was not observed in the ^{13}C NMR spectrum ($\Delta\delta < 0.02$ ppm).[103] Nonequivalent trifluoromethyl groups in 1,1,1,3,3,3-hexafluoro-2-propanol (**59**) and nonequivalent methyl groups in phenyldimethylphosphine oxide (**60**) and sulfide have been observed in optically active solvents.[104] In all of these cases there is probably a strong interaction between the polar solute and the polar alcohol solvent.

The advent of chiral lanthanide shift reagents, e.g., tris[3-trifluoromethylhydroxymethylene-*d*-camphorato]europium(III) (**61**), has enabled chemical shift nonequivalence of enantiotopic groups to be observed in common achiral NMR solvents.[103,105] Interactions between a



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donor site on the substrate and the chiral lanthanide reagent cause internally enantiotopic groups to become diastereotopic by external comparison. Thus using carbon tetrachloride solution 0.1 *M* in substrate and 0.05 *M* in **61**, the methyl groups in dimethyl sulfoxide were observed to be anisochronous by 0.06 ppm in the ^1H spectrum and by 0.20 ppm in the ^{13}C spectrum.[103] Similar observations were reported for the enantiotopic methyl groups in 2-propanol and 2-propylamine and 2-methyl-2-butanol, and the methylene protons in 2,2-dimethylpropanol and 2-methyl-2-butanol in the presence of a chiral shift reagent.[103] Fraser et al.[105] have reported on elegant application of chiral lanthanide shift reagents to investigate the magnitude of geminal coupling constants in substituted benzyl alcohols. Thus the internally enantiotopic geminal methylene hydrogens could be rendered sufficiently anisochronous by the lanthanide reagent to allow ^2J(HCH) to be measured directly. Their results are given in Table VI. The geminal coupling constants were shown to be independent of the lanthanide reagent concentration up to 0.06 *M*. Therefore, it was concluded that the shift reagent was not significantly perturbing the magnitude of the coupling constants. Undoubtedly this technique will find further use in the study of spin coupling.

VII. Application of Prochiral Groups to Investigate Dynamic Molecular Stereochemistry

Owing to the large amount of literature, a few illustrative examples have been selected in each area; more detailed discussion can be found in certain key references

TABLE VI. Chemical Shift Nonequivalence ($\Delta\delta$) and Geminal Coupling Constants (J) of the Enantiotopic Methylene Protons of Alcohols of the Type RCH_2OH in the Presence of Chiral Tris[3-heptafluoropropylhydroxymethylene-*d*-camphorato]praseodymium(III)[105]

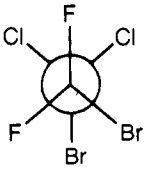
R	Mole ratio lanthanide: substrate	$\Delta\delta$ (ppm)[a]	J (Hz)
C_6H_5	0.15	0.13	13.0
C_6H_5	0.28	0.22	12.9
4-CNC_6H_4	0.30	0.12	14.5
4-$CF_3C_6H_4$	0.27	0.15	14.0
4-FC_6H_4	0.26	0.08	13.2
4-$CH_3C_6H_4$	0.23	0.15	12.8
4-$CH_3OC_6H_4$	0.22	0.11	13.0
4-$N(CH_3)_2C_6H_4$	0.22	0.09	12.5
$(CH_3)_3C$	0.27	0.12	12.0

[a] Spectra were determined using 0.2 *M* solutions of the alcohol in carbon tetrachloride.

and in some review articles on dynamic NMR spectroscopy.[106,107]

A. Bond Rotation

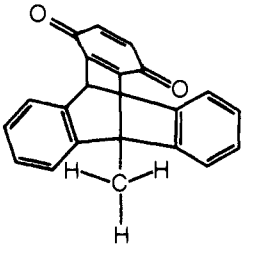
Intramolecular rate processes (e.g., bond rotation and ring inversion) can affect the stereochemical relationship of the paired ligands at a prochiral center. For example, in the rotamer **62** of $BrCF_2$–CCl_2Br the geminal fluorine nuclei are diastereotopic and anisochronous. However, at



62

ambient temperature rotation around the CC bond is fast on the NMR time scale and the time-averaged environments of the fluorine ligands are enantiotopic. Thus at ambient temperature only a single fluorine signal is observed.[74] This is in accord with rule iii in section II.B which allows for time-averaging processes around mobile acyclic bonds.

It is, of course, not necessary for a center to be prochiral in order for geminal chemical shift nonequivalence to be observed if rotation around the bond linking the center to the rest of the molecule is slow on the NMR time scale. Thus, for example, Anderson and Rawson[108] have observed two anisochronous methyl proton signals (intensity ratio 2:1) in the spectrum of **63** at −141°. Simi-

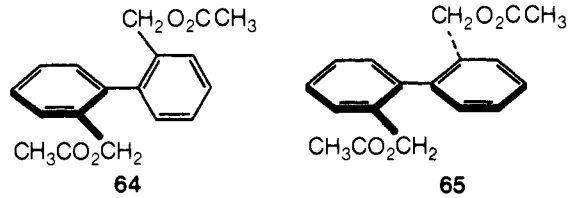


63

lar observations of geminal nonequivalence of methyl group hydrogens at low temperature have been reported by Oki et al.,[109] and nonequivalence of the methyl groups in *tert*-butyl groups at low temperature due to slow bond rotation is well established.

In the above examples the prochiral or methyl groups are involved directly in the conformational change. However, a more subtle and general approach is to substitute

an acyclic prochiral group (e.g., isopropyl) into a molecule at a site that is not directly involved in the dynamic process. The prochiral moiety can then respond to changes in molecular symmetry on the NMR time scale and provide useful information on molecular conformation and rate processes in solution. One of the earliest applications of this technique is that of Meyer and Meyer[110] who used a methylene ester moiety to study central CC bond torsion in the twisted biphenyl **64**. In the ground state (**64**) the geminal methylene hydrogens are diastereotopic owing to the absence of a symmetry plane through the prochiral methylene center. Rotation through 180° to give **66** renders these hydrogens enantiotopic and isochronous. This may be verified readily by observing that the transition state **65** possesses a symmetry plane containing the prochiral centers. The rotation process **64** $\rightleftharpoons$ **66** corresponds to a racemization as the two rotamers are enantiomeric. However, as the NMR investigation is carried out using racemic material and there is no net change in the bulk properties of the sample, the observed process is best described as a "degenerate racemization."[111] The rate of the process can be determined from the spectrum in the temperature range where the methylene AB system collapses to a singlet.



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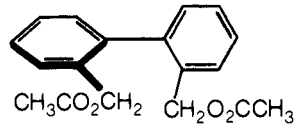

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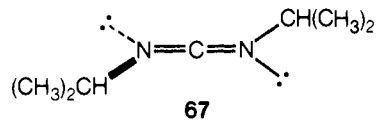
Another example that deserves mention is the use of the prochiral isopropyl group by Anet et al.[112] to investigate the degenerate racemization of carbodimides. Interconversion of **67** and **68** was monitored by observing the collapse of the geminal methyl signals at ca. −140°. In-



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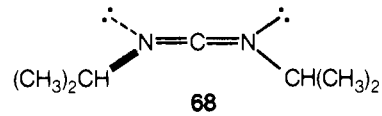
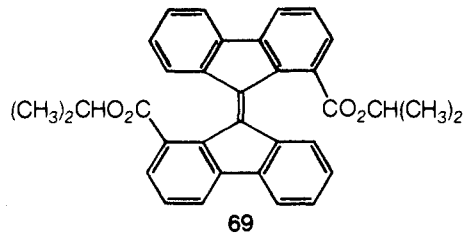


68

terconversion can take place either by rotation around the C=N bonds or by a lateral shift of the nitrogen substituent. Ollis et al.[113] have employed prochiral probes in an elegant study of the conformational mobility of bisfluorenylidenes (**69**). The observed nonequivalence of the geminal methyl groups at ambient temperature results from nonplanarity at the alkene bond. The skillful use of



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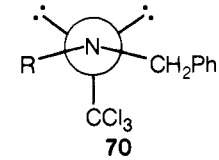

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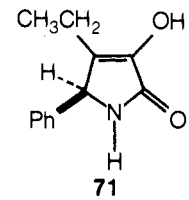
prochiral substituents has also greatly facilitated conformational studies around formal single bonds connecting elements of groups V and VI.[106] For example, the observation of anisochronous methylene hydrogens in *N,N*-dialkylsulfenamides at ambient temperature indicates that **70** is the preferred conformation and that the barrier to rotation around the SN bond is remarkably high.[111]

The observed chemical shift nonequivalence of the geminal methylene protons in the pyrrolin-2-one derivative **71** up to 175° has recently led to the surprising suggestion that "internal rotation about the CH_2-ring linkage is impossible owing to steric hindrance between 5-phenyl and 4-alkyl groups."[114] However, it should be

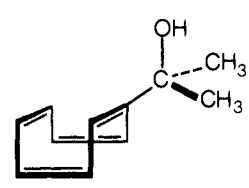


71

noted that the methylene hydrogens in **71** are diastereotopic even if rotation is completely free (in both the kinetic and thermodynamic senses) around this bond. It has also been reported that in chloro(tri-*n*-propyl)silane, $(CH_3CH_2CH_2)_3SiCl$, and in the germanium analog, the NMR signals of the α-methylene protons at 220 MHz deviate from an "anticipated triplet absorption."[115] It was suggested that the observed spectrum may contain the superimposition of the spectra of the three conformations around the CH_2–Si bond. In this example also, it is very unlikely that bond rotation would be slow on the NMR time scale at ambient temperature; therefore, the α-methylene hydrogens are enantiotopic by rule iii (section II.B) and isochronous in achiral media. However, the α-methylene protons are nonequivalent in the spin coupling sense (anisogamous), and therefore a simple triplet absorption would *not* be anticipated, particularly if there is some conformational preference around the CH_2–CH_2 bond (rather than the CH_2–Si bond).

B. Ring Inversion

Anet et al.[116] used an acyclic prochiral probe in their early study of cyclooctatetraene ring inversion. The rate of the inversion process **72** $\rightleftharpoons$ **73** which corresponds to a degenerate racemization was determined from the collapse of the anisochronous geminal methyl signals of the hydroxyisopropyl moiety. Rapid ring inversion renders the



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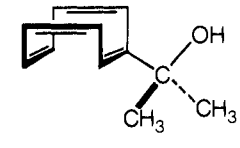

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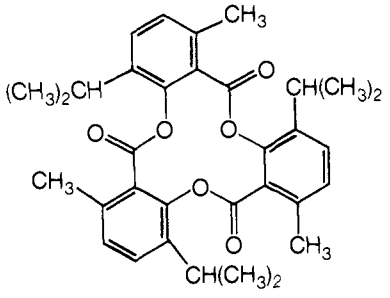
diastereotopic methyl groups enantiotopic on the NMR time scale and isochronous. The rate of double bond shift was also determined by observing collapse of the alkene proton signals in partly deuterated material and shown to be slower than ring inversion. Similarly, Ollis et al.[117] have made skillful use of the prochiral isopropyl groups

to investigate conformational changes in tri-*o*-thymotide (**74**) and related compounds. The geminal methyl groups are diastereotopic at ambient temperature as the molecule is restricted to nonplanar conformations, and inversion through the plane is slow on the NMR time scale. Other examples may be found in certain review articles on ring inversion.[106,118,119]



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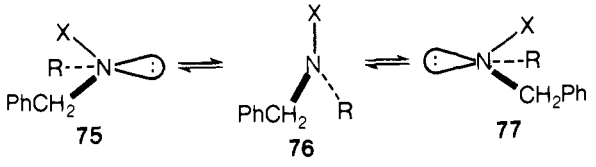
C. Pyramidal Inversion

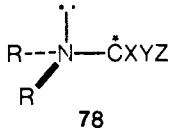
Prochiral probes have provided valuable data on the barriers to "umbrella" inversion of trivalent acyclic compounds of group V.[25,120] For example, the geminal methylene hydrogens of the prochiral benzyl group in **75** are diastereotopic provided that group R is not identical with X as the molecule then lacks a σ plane through the methylene center. Rapid inversion of the nitrogen atom, i.e., **75** $\rightleftharpoons$ **77**, renders the methylene hydrogens enantiotopic and isochronous in achiral solvents. This may be simply ra-



75 **76** **77**

tionalized by observing that the transition state **76** for inversion has a σ plane through the prochiral methylene center. The inversion process corresponds to a degenerate racemization if R $\neq$ X $\neq$ CH_2Ph. However, if either R or X is a benzyl group, **75** and **77** are superimposable structures and the inversion process corresponds to an identity reaction. The term "topomerization" has been suggested for processes of this type, and **75** and **77** may be referred to as "topomers."[3]

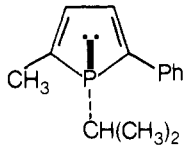
Another way of investigating pyramidal inversion is to observe the NMR spectra of chiral compounds which contain a prochiral element of group V. Thus in a compound of type **78** the nitrogen atom will constitute a stable prochiral tetrahedral assembly only if inversion at this center is slow on the time scale of the observation. The



78

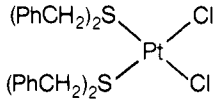
paired R moieties are then diastereotopic and potentially anisochronous since the molecule does not possess the relevant symmetry plane through the prochiral nitrogen center. Rapid nitrogen inversion inverts the prochiral assembly and renders the R groups homotopic and isochronous. This method has been less popular than the former but has been used, for example, by Johnson et al.[121] to study α,α'-bis(difluoroamino)bibenzyl (**78**, R = F, X = H, Y = Ph, Z = $CH(NF_2)Ph$). The geminal fluorine nuclei were found to be anisochronous even at 140°. This remarkably high stability of the nitrogen pyramid is probably due to the electronegativity of the fluorine substituents.[120]

In contrast to most nitrogen compounds, trivalent phosphorus and sulfur are normally configurationally stable on the NMR time scale up to 200° (the upper limit of current NMR probes).[25] However, in certain circumstances the barrier may be low enough for dynamic NMR studies. Thus, for example, the phosphorus atom in the phosphole **79** inverts sufficiently rapidly to enable to process to be monitored by the collapse of the anisochronous geminal methyl signals at ca. 50°.[122] The planar



79

transition state for inversion may be stabilized by possessing some aromatic character.[122] Similarly the sulfur atoms in the bis(dibenzyl sulfide)platinum(II) complex **80** invert rapidly on the NMR time scale above 35° as the diastereotopic geminal methylene protons were observed to be anisochronous below this temperature but collapsed to a singlet on raising the temperature.[123] The



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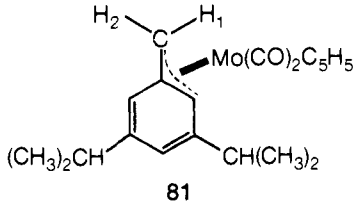
loss of geminal nonequivalence was not due to dissociation of the Pt–S bond as the coupling to ^{195}Pt in the satellites persisted above 35°. Presumably the sp^2 transition state for sulfur inversion is stabilized by overlap of the lone-pair p orbital with a vacant orbital on the metal. Unusually facile inversion has also been observed in other diselenide and ditelluride complexes of platinum and palladium which contain prochiral groups.[124]

D. Dynamic Stereochemistry of Organometallic Compounds

One of the earliest applications in this area was the elegant use of a prochiral isopropyl substituent by Cotton and Marks[125] to investigate π-benzyl derivatives of molybdenum and tungsten (**81**). At −17° the alkene hydrogens H_1 and H_2 were anisochronous in addition to the geminal methyl groups in each of the two different isopropyl moieties. When the temperature was raised, the methyl signals all became isochronous in the same temperature range as the ortho and alkene hydrogens. Thus face-exchange of the metal moiety was accompanying



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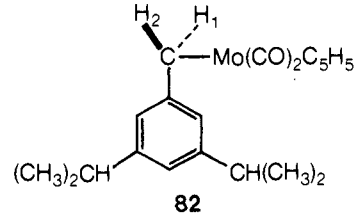
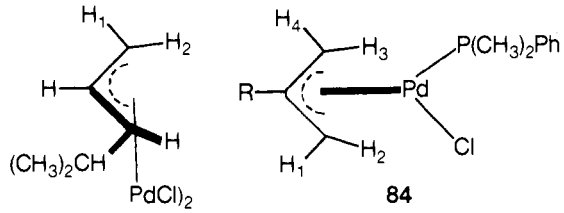


82

the edge-exchange process. These observations are consistent with a monohapto-benzyl intermediate (**82**). Prochiral isopropyl substituents have also been used to investigate the rate of exchange of a palladium moiety between the two faces of π-allyl palladium complexes **83** and **84** (R = isopropyl).[126,127]



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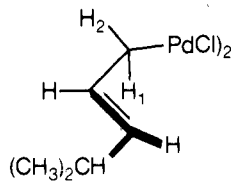
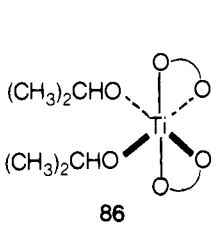


85

The face-exchange process becomes rapid on raising the temperature and renders the diastereotopic isopropyl methyl groups enantiotopic and isochronous. This process can also be investigated by observing the collapse of the signals from the diastereotopic methyl groups attached to the prochiral phosphorus atom in **84**.[128] The alkene hydrogens H_1 and H_2 in **83** were shown to become equivalent at a similar rate to the face-exchange process.[126] These observations were in agreement with a common σ-bonded intermediate **85** for both processes.

The degenerate racemization of octahedral complexes has also been investigated with the aid of prochiral substituents. The geminal methyl groups in compounds **86**–**89** and the geminal methylene hydrogens in **90** are diastereotopic at low temperature but are rendered isochronous at higher temperature by rapid intramolecular enantiomerization.[129-134]



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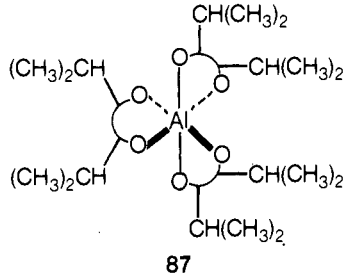

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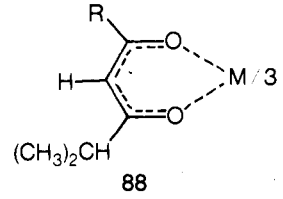

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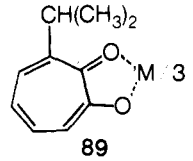

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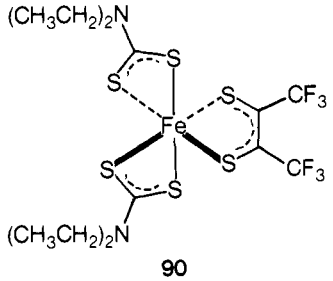

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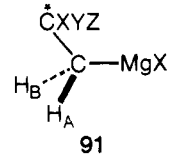

91

Inversion at the prochiral α-carbon center in organomagnesium compounds of type **91** has also been investigated by NMR spectroscopy.[135]

Acknowledgment. I wish to thank Professor W. R. Jackson (Monash University, Australia) and Dr. N. Baggett (University of Birmingham) for many stimulating discussions and, together with the referees, for helpful suggestions.

VIII. Addendum

Further attempts to correlate the magnitude of geminal nonequivalence in diastereotopic groups with molecular structure (section IV) have been reported recently. Hruska et al.[136] have carried out a detailed study of the anisochronous 5′-methylene hydrogens in some nucleosides and nucleotides. The magnitude of $\Delta\delta$ in a series of structurally related pyrimidine nucleosides was observed to correlate with the sum of the 4′–5′ vicinal proton coupling constants. The authors concluded that the variation in $\Delta\delta$ reflected conformational changes around the $C_{4'}$–$C_{5'}$ bond, and that the intrinsic term ($\Delta\delta_i$) was essentially invariant. Vigevani[137] has reported that the diastereotopic isopropyl methyl groups in some 10-isopropoxyergoline-8β-methanol derivatives show an usually large chemical shift nonequivalence ($\Delta\delta \simeq 0.9$ ppm) in the ^{1}H spectrum. The same methyl groups are anisochronous by 1.0 ppm in the carbon-13 spectrum (this value is not unusually large bearing in mind the greater spread of ^{13}C chemical shifts). Another large ^{1}H nonequivalence (0.8–0.9 ppm depending on solvent) had been previously observed for the isopropyl methyl groups in racemic 2,5-dimethyl-3,4-diphenyl-3,4-hexanediol, though the meso diastereomer showed a normal value of $\Delta\delta$ (0.0–0.24 ppm depending on solvent).[138] These large values of $\Delta\delta$ are probably due to a large conformational contribution ($\Delta\delta_c$) arising from a preferred conformation of the isopropyl group where the methyl hydrogens experience markedly different shielding. Other examples of large proton nonequivalence are discussed in section IV.B. Another recent paper deals with structural effects on the magnitude of $\Delta\delta$ for diastereotopic geminal methyl groups in the side chain of steroids.[139] In connection with structural effects on chemical shift nonequivalence (section IV.B), reference should be made to the study by Roberts et al.[140] of the ^{13}C NMR of compounds of the type $(CH_3)_2CHCH(OH)R$. In these compounds, $\Delta\delta$ for the diastereotopic methyl carbon nuclei was found to increase from 0.2 ppm when R = CH_3 to 6.9 ppm when R = $C(CH_3)_3$. It was suggested that increasing the steric bulk of R increased the conformational bias around the central bond. In compounds of the type $(CH_3)_2CH[CH_2]_nCH(CH_3)CH_2CH_3$, $\Delta\delta$ for the geminal carbon nuclei was found to attenuate with distance between the prochiral and chiral centers as normally observed for proton nonequivalence (see section IV.B.).[140]

Further investigations into structural, solvent, and temperature effects on the chemical shift nonequivalence of diastereotopic groups in sulfinates have been reported (see section III.C).[141] Nonequivalence of diastereotopic geminal groups in sulfonium and phosphonium salts has been investigated by Schiemenz and coworkers.[142] The magnitude of $\Delta\delta$ is dependent on the nature of the anion; for example, in the sulfonium salt $(CH_3CH_2)_2S^+$-$N(CH_2Ph)_2$, $\Delta\delta$ for the diastereotopic ethyl methylene hydrogens is 0.125 and 0.672 ppm for the chloride and tetraphenylborate, respectively (in CD_2Cl_2 solution). The onium ions form short-lived contact ion pairs with the anion; therefore, aromatic anions such as

tetraphenylborate or tris(2,2′-biphenylene) phosphate act as shift reagents owing to a differential ring current effect on the diastereotopic protons.[143] Lanthanide shift reagents can often be employed to increase $\Delta\delta$ for diastereotopic groups in neutral compounds.[6,144-146] A further investigation of intrinsic nonequivalence of geminal methylene protons has been reported for nortricyclene and adamantane compounds where the conformational contribution is absent by symmetry (see section V).[147] It was found that $\Delta\delta_i$ was close to zero in the absence of added shift reagent.

Goering et al.[148] have investigated the proton chemical shift nonequivalence of the enantiotopic methyl groups in dimethyl sulfoxide induced by a chiral shift reagent (see section VI). Changing the lanthanide reagent to substrate molar ratio from 0.32 to 3.12 caused $\Delta\delta$ to decrease to zero (at a ratio of 1.09) and then to increase ($\Delta\delta$ is of course zero in the absence of a chiral reagent). The authors suggest that at least two coordinated species contribute to $\Delta\delta$ and that the sense of the nonequivalence differs in the complexes.

Although this review is primarily concerned with chemical shift nonequivalence it is worth mentioning that since diastereotopic groups reside in different molecular environments they should in principle have different coupling constants to another magnetic nucleus present in the molecule. This aspect has been discussed recently by Cowley et al.[149] *N,N*-Dimethylchloromethylphosphonamidothioic fluoride, $ClCH_2P(S)F(NMe_2)$, serves as a good example as the diastereotopic geminal methylene protons show different coupling constants to the phosphorus nucleus, ^2J(HCP) = 7 and 9 Hz, respectively, and to fluorine, ^3J(HCPF) = 2.2 and 0.5 Hz respectively.[51] Similarly the diastereotopic methyl groups in diisopropylphenylphosphine (**33**) show different ^3J(HCCP) couplings,[49] and substituted ethanes of the type RCH_2CHXY and RCF_2CFXY commonly show different vicinal coupling constants.[64,72-74,76,77] However, although diastereotopic groups should in principle show this effect, in practice the difference in coupling constants may often be too small to be detected. Thus the diastereotopic geminal methyl groups in chloro(diisopropylamino)phenylphosphine sulfide (**34**) show identical coupling to phosphorus in the ^{13}C NMR spectrum at ambient temperature [^3J(CCNP) = 4 Hz], whereas in the corresponding phosphine these coupling constants are markedly different [^3J(CCNP) = 13 and 4 Hz]. It is not necessary for nuclei to be diastereotopic in order for them to show different coupling constants to a third nucleus. Enantiotopic groups should in principle show this effect in chiral media where they may be regarded as becoming diastereotopic by external comparison. Nuclei can also be nonequivalent in spin coupling (anisogamous) without being diastereotopic (either by internal or external comparison) or anisochronous. This is encountered when equivalent or enantiotopic nuclei are spin coupled to another set of equivalent or enantiotopic nuclei provided that a given nucleus in the first set couples differently to the nuclei in the second set as observed in $[AX]_2$ spin systems (see Introduction).

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