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Intrinsic Asymmetry and Diastereotopism

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Abstract: The term "intrinsic asymmetry", as applied to the time-averaged anisochrony of geminal groups in systems of the type $[R^*]CU_2V$ (where R* is a chiral perturbing group), is critically discussed against the background of symmetry criteria for chemical shift nonequivalence. It is concluded that continued use of the term is no longer justified. The symmetry requirements for time-averaged anisochrony under conditions of equipopulation of conformers are extended to the general case of an *n*-fold barrier to internal rotation. Chemical shift nonequivalence of geminal methyl groups in a compound of the type $XYZC-C{\equiv}C-CH(CH_3)_2$ is demonstrated and the adequacy of the free rotation (windmilling) model for such a system is discussed. It is noted that for NMR purposes, the distinction between groups diastereotopic by internal and external comparison is more a matter of convenience than of principle.

The structural criteria for magnetic shielding (or chemical shift) equivalence (isochrony) and nonequivalence (anisochrony) of nuclei have previously been discussed in terms of the symmetry relationships between molecular subunits.[2] Against the backdrop of this analysis, the present paper addresses the theme of "intrinsic asymmetry", which continues to be the subject of lively interest even though it has been under debate for 20 years.

Symmetry Criteria for Anisochrony

The symmetry equivalence of two or more nuclei is a sufficient but not a necessary condition for isochrony; conversely, the symmetry nonequivalence of such nuclei is a necessary but not a sufficient condition for anisochrony.[3] We consider two or more nuclei symmetry equivalent if they are permutable under an operation of the appropriate molecular symmetry (MS) group.[4] This group consists not only of the set of permutations and permutation-inversions which are feasible under the conditions of measurement, i.e., which occur on the time scale of the NMR experiment, but also of the products of these operations with rotatory reflections, since we are here concerned with measurements in achiral media. For a rigid molecule this reduces to an MS group which is isomorphic to the molecular point group.[5] It follows that symmetry nonequivalent nuclei are not permutable under the operations of the appropriate group.

Thus expressed, the symmetry criteria for isochrony and anisochrony are independent of bonding connectivity (constitution). The pairwise bonding connectedness of atoms, as conventionally expressed by an adjacency matrix or, more commonly, by a constitutional graph, while admittedly a powerful and often indispensable symbolic tool, is fundamentally irrelevant to the question of chemical shift equivalence or nonequivalence, except insofar as it bears upon the magnitude of the effect.

For our purposes the most important consequence of this analysis is that the anisochronies of diastereotopic and constitutionally heterotopic[6] groups stem from a single source: symmetry nonequivalence of nuclei. Stated otherwise, it is impossible to distinguish between diastereotopic and constitutionally heterotopic nuclei solely on the basis of the observation that the nuclei are anisochronous, i.e., in the absence of ancillary information.

Accordingly, the differences in screening constants between diastereotopic groups (e.g., the geminal fluorines in $ClBrFCCF_2Br$) are dealt with by precisely the same theory as those between constitutionally heterotopic groups (e.g., the vicinal fluorines in the same molecule).[7] Specifically, the total Hamiltonian of an isolated molecule and the associated wave functions reflect the symmetry properties of this molecule. If two nuclei are homotopic (or enantiotopic) for symmetry reasons, the electronic distributions around these nuclei are identical up to reflection. On the other hand, if two nuclei are constitutionally heterotopic or diastereotopic, they are characterized by different electronic distributions.

The symmetry properties of a molecule can of course be modified by an external perturbation, such as interaction with other molecules or with external electric or magnetic fields. The well-known transformation of isochronous enantiotopic nuclei into anisochronous nuclei by interaction with chiral solvent molecules or shift reagents exemplifies the first kind of perturbation. The modification of the symmetry properties of a molecule by a crystal lattice as observed in an external magnetic field, obviously very important in an NMR experiment, is illustrated by the work of Pausak et al.[9] on the high-resolution ^{13}C NMR spectra of single-crystal durene (1,2,4,5-tetramethylbenzene), in which distinct signals were observed for the CH_3 groups, the chemical shift difference between these signals being a function of the orientation of the crystal with respect to the magnetic field.[10]

Although the screening tensor components[10] are in principle accessible by quantum mechanical calculations,[11,12] no molecules of the type $[R^*]CU_2V$ (where R* is a chiral grouping and U is an NMR-active nucleus) have yet been studied by these methods. However, screening tensor components of diastereotopic and constitutionally heterotopic nuclei have been calculated for 1,1-difluoro-, *cis*-1,2-difluoro-, and *trans*-1,2-difluoroethylene,[12] and are in reasonable agreement with

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the experimental values. In this work no distinction was made between constitutionally heterotopic and diastereotopic nuclei since, from the point of view of screening constant theory (as for all quantum mechanical calculations), nuclei are either symmetry equivalent or not.

Nevertheless, one finds in the literature numerous discussions (see below) of the "origin" of the anisochrony between diastereotopic nuclei, with the clear implication that the source of this anisochrony differs from the one which exists for constitutionally heterotopic nuclei. This misconception arises from the semiempirical description of the screening constant which has been used in discussing anisochrony between diastereotopic groups. In this semiempirical description, derived from the Saika-Slichter[13] theory, the molecule is partitioned into sets of atoms which are either bonded or not bonded to the atom containing the nucleus of interest. The bonded atoms are considered to contribute to the local diamagnetic and paramagnetic components of the screening constant, while the other atoms are able to contribute only by long-range effects.[14] With this kind of description, it is tempting to consider that the "origins" of the screening constant differences between constitutionally heterotopic groups and diastereotopic groups differ in a fundamental way: the former appear to be characterized by different local diamagnetic and paramagnetic contributions to the screening constant, while for the latter, characterized by the same connectivity, long-range effects seem to be the only contributions to the difference. However, the apparent distinction between the two situations is an artifact of the model used to describe the physical system, and the temptation should be resisted.

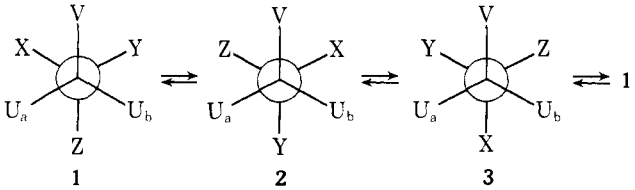
Intrinsic Asymmetry

The term "intrinsic asymmetry" has not been used with consistency since its introduction into the chemical literature; in order to provide a meaningful perspective for our discussion, it is therefore necessary to review briefly the origins and connotations of this still widely used phrase.

Twenty years ago, Drysdale and Phillips[15] observed that molecules such as $ClBrFCCF_2Br$ exhibit geminal ^{19}F chemical shift nonequivalence even at elevated temperatures. After an initial period of some confusion, during which various interpretations were advanced for this and similar observations,[15-18] Waugh and Cotton[19] pointed out that for structures of the type $[R^*]CU_2V$, the anisochrony of the U's "can in principle still persist when the isomers are all accidentally of *equal* energy, or even when the internal rotation is *free*. (This statement depends entirely on a symmetry argument. . .)." Acknowledging the distinctness of the methylene protons in molecules of the type $R_1R_2R_3CCH_2X$ "even assuming equal populations and rapid interconversion of the three conformers", Whitesides et al.[20] stated that the " 'intrinsic asymmetry' of the methylene group might also be the cause of the observed magnetic nonequivalence of the methylene protons" (as indeed was later found to be the case for related structures[21]). In a subsequent study, Gutowsky showed[22] that it is possible to partition the time-averaged total anisochrony of the U's ($\langle \nu_a - \nu_b \rangle$) in a mobile equilibrium mixture of **1**, **2**, and **3** into population-dependent and independent terms:

$$\langle \Delta\nu_U \rangle = \sum_n \left(x_n - \frac{1}{3}\right) \Delta\nu_n + \sum_n \frac{1}{3} \Delta\nu_n \qquad (1)$$

where x_n is the mole fraction of the nth rotamer (n = 1, 2, 3)



and $\Delta\nu_n$ is the chemical shift between the two U's (e.g., two protons) in a given rotamer.

The second (population independent) term in eq 1, described[22] as the "asymmetry effect", represents the quantitative expression of Whitesides' "intrinsic asymmetry"; in both cases explicit reference is made to chemical shift nonequivalence of geminal protons at the *fast* exchange limit and under the artificial constraint of equal conformer populations. However, it does not seem to have been generally appreciated that Gutowsky's use[22] of "intrinsic asymmetry" had quite another meaning: the relative values of the chemical shifts of the three U's in the parent molecule $XYZCCU_3$ at the *slow* exchange limit were taken to reflect the " 'intrinsic asymmetry' of the three nonequivalent sites."[22] But the U's in this molecule are diastereotopic (and therefore expected to be anisochronous) only at the slow exchange limit;[23] at the fast exchange limit they become equivalent and therefore isochronous. "Intrinsic asymmetry" therefore has quite a different significance in these two usages.[20,22]

Yet a third definition of "intrinsic asymmetry", advanced by Anderson,[24] requires brief mention. Anderson's "intrinsic asymmetry shifts" refer to the anisochrony of groups which are diastereotopic by external comparison at the *slow* exchange limit. For example, in terms of structures **1-3**, this "intrinsic asymmetry shift" could have any one of three values, ($\nu_1^a - \nu_3^b$), ($\nu_2^a - \nu_1^b$), or ($\nu_3^a - \nu_2^b$), where ν_n^a and ν_n^b are the chemical shifts of the diastereotopic nuclei in the nth rotamer. Since Gutowsky's "asymmetry effect", conventionally expressed as in eq 1, can alternatively be written as $\frac{1}{3}((\nu_1^a - \nu_3^b) + (\nu_2^a - \nu_1^b) + (\nu_3^a - \nu_2^b))$, the "intrinsic asymmetry shift" is seen to be precisely one term—arbitrarily chosen—of the three terms which constitute the "asymmetry effect". The substance of this paper[24] having recently been withdrawn,[25] no further comment is required.

The profusion of terminology descending from "intrinsic asymmetry" ("intrinsic diastereotopism", "intrinsic nonequivalence", "intrinsic anisochrony", "asymmetry effect", "inherent magnetic asymmetry", etc.) has not served to lessen "the considerable confusion that often arises in this area".[26] The problem derives in part from the lack of agreement on what is meant by this phrase (as described above), and in part from the artificiality of partitioning $\langle \Delta\nu_U \rangle$ into two terms (eq 1) when $x_n \neq \frac{1}{3}$, i.e., when the components of the mixture differ in energy (as they do in **1-3**). In such a case, it is doubtful whether any physical significance can be attached to either one of the terms.

The phenomenon under discussion is the time-averaged anisochrony of geminal groups which remain symmetry nonequivalent (i.e., diastereotopic) under conditions of rapid conformational interconversion, and under the constraint that all conformers are equally populated.[27] The underlying concept is well understood,[19] and requires no special theoretical interpretation: the observed phenomenon merely provides another example of the generalization that anisochrony is expected as a result of nuclear symmetry nonequivalence on the time scale of the experiment.[28] We therefore believe that the time has come to abandon the use of "intrinsic asymmetry" and allied terminology. The usefulness of such phrases lies in the past, and there is no longer any justification for the use of a term which, as we have shown, mystifies rather than enlightens and thus serves as an impediment to understanding.

In the next section we discuss the effects of symmetry on the distribution of conformations available to a mobile system, and the concomitant effects on anisochrony.

Time-Averaged Anisochrony of Geminal Groups in Conformationally Mobile Systems

Conformational Homogeneity. The need for partitioning $\langle \Delta\nu_U \rangle$ into population-dependent and independent terms

disappears when $x_n = 1/3$, i.e., when all conformers are equally populated. For the basic structural type $[R^*]CU_2V$, this condition is achieved by introducing three-fold rotational symmetry (1) into the moiety containing the sensor group (CU_2V), or (2) into the moiety containing the chiral perturber group ($[R^*]$), or (3) into both. Although no example of the third class (e.g., $R_3^*CC(CU_2V)_3$, which has C_3 symmetry)[30] is known, representatives of the two less symmetrical—in fact asymmetric—classes have been proposed and realized.[2,31,32] As first pointed out by Franzen and Binsch[32] in their critical and incisive analysis of this problem, the key difference between these two classes lies in their behavior under conditions of slow and fast site exchange. For representatives of the first class[2,31] (e.g., $XYZCC(CU_2V)_3$), there are six different chemical shifts for the U's in the frozen conformer; these average to two under conditions of fast internal rotation. In contrast, for representatives of the second class[32] (e.g., $R_3^*CCU_2V$) the number of chemical shifts is the same at the slow and fast exchange limits, i.e., $\langle \Delta\nu_U \rangle = \Delta\nu_U$ (the same would be true for representatives of the third class).

The classifications described above are by no means restricted to structures with an ethane skeleton, but are readily extended to systems with other than three-fold torsional barriers. As a hypothetical example, given a two-fold barrier for the aminoborane (H_2NBH_2) skeleton,[33] the three classes are represented by (1) $XR^*NB(CU_2V)_2$, (2) $R_2^*NB(X)CU_2V$, and (3) $R_2^*NB(CU_2V)_2$. In general, introduction of n-fold rotational symmetry in (1) the sensor moiety, (2) the perturber moiety, and (3) both may be illustrated by the representative structures (1) $X_{n-1}R^*MN(CU_2V)_n$, (2) $R_n^*MN(X_{n-1})CU_2V$, and (3) $R_n^*MN(CU_2V)_n$, respectively.

Class 3 above can be generalized by considering $R_m^*MN(CU_2V)_n$ ($m \neq n$). Either m and n have no common factors, resulting in an nm-fold barrier, or they do share at least one common factor, resulting in an nm/G-fold barrier, where G is the largest common factor of m and n. In the first case, the molecule will display $2n$ and two chemical shifts for the U groups at the slow and fast exchange limits, respectively, whereas in the second the molecule will display $2n/G$ shifts for the U groups at the slow exchange limit and two shifts at the fast exchange limit. It is recognized that for the special case of $m = n$, and for the special case of $1 = n \neq m$ (which is described by class 2 above and which effectively includes the system studied by Franzen and Binsch[32]) two signals will be seen at both the slow and fast exchange limits.

Toward the Limit of Free Rotation. The time-averaged geminal anisochrony in molecules of type $[R^*]CU_2V$ is adequately expressed by eq 1. This applies as well to the case of $XYZC(C{\equiv}C)_mCU_2V$ (**4**) and $R_3^*C(C{\equiv}C)_mCU_2V$ (**5**) when $m = 0$. However, when $m = 1$ the torsional barrier is expected to decrease by as much as three orders of magnitude.[34] As m increases further, the barrier is expected to decrease until, in the limit, a state of barrier-free rotation is reached. This limit is of course unattainable, for, in order to have a barrier identically equal to zero, at least one of the groups joined by the torsional axis must have local $C_{\infty v}$ symmetry, a condition which is incompatible with the structures of **4** and **5**. By the same token, barrier-free rotation precludes the possibility of geminal anisochrony since a perturbing group with local $C_{\infty v}$ symmetry is necessarily achiral, and the U's in the sensor moiety therefore cannot be diastereotopic. Nevertheless, although we are barred from examining cases where the barrier is zero, compounds of type **4** and **5** are expected to exist largely in torsionally unbound states, i.e., states above the barrier. One might thus imagine that it would be permissible to speak of free rotation, at least for the large proportion of the molecules occupying these states under the condition of observation. Before we pursue this point further, we briefly digress to present the theoretical formalism which states the relation between the anisochrony of sensor groups U_a and U_b ($\Delta\nu = \nu_a - \nu_b$) and the spatial position of these groups relative to the perturbing group.

The theoretical treatment for a system in which the CU_2V group undergoes perfectly free rotation relative to the chiral perturbing group ("windmilling"[37]) is quite general and has been applied previously in various other contexts.[38] The formalisms described below have been independently derived by Stiles.[29]

In the case of windmilling, all conformations attainable by internal rotation about the torsional axis are equally probable, and the time-averaged chemical shift $\langle \Delta\nu \rangle$ between U_a and U_b is given by the equation

$$\langle \Delta\nu \rangle = \frac{1}{2\pi} \int_0^{2\pi} \Delta\nu(\theta) d\theta \qquad (2)$$

where $\Delta\nu(\theta) = \nu_a(\theta) - \nu_b(\theta)$, and $\nu(\theta)$ expresses ν as a function of the dihedral angle between the two rotors. If torsional barriers are present, $\Delta\nu(\theta)$ is appropriately weighted by a periodic and continuous function of the potential energy V which is in general described by a Fourier series.[36] Under conditions of fast exchange:

$$\langle \Delta\nu \rangle = \frac{\int_0^{2\pi} \Delta\nu(\theta) \exp[-V(\theta)/RT]\, d\theta}{\int_0^{2\pi} \exp[-V(\theta)/RT]\, d\theta} \qquad (3)$$

The general expression in eq 3 reduces to eq 2 for the case of free rotation (i.e., $\exp[-V(\theta)/RT] = 1$). On the other hand, for systems of the type described by Franzen and Binsch[32] (**5**, $m = 0$), $V(\theta)$ is taken to be discontinuous, and $\exp[-V(\theta)/RT] = 1$ for three discrete values of θ separated by $2\pi/3$, and zero elsewhere. Equation 3 then reduces to Gutowsky's eq 1, with $x_n = 1/3$.

The above formalism is quite independent of any particular theory which deals with the magnitudes of screening constants. Such theoretical models have been discussed by Stiles,[29] and we now turn to a description of experimental results which have a bearing on the problem of geminal anisochrony under conditions of free rotation, since Snyder has suggested[39] that examination of the NMR spectrum of a compound of type **4** ($m = 1$) would provide an "unambiguous test for the origin of magnetic nonequivalence", and that any observed geminal anisochrony "must necessarily arise from magnetic asymmetry".

We have found that a compound of type **4** ($m = 1$), 2-(2-naphthyl)-5-methylhex-3-yn-2-ol (**6**), exhibits two methyl doublets in the 300-MHz ^1H NMR spectrum in pyridine at ambient temperature. Previous attempts by Ejchart et al.[40] to detect anisochrony in similar compounds ($ArCH(OH)C{\equiv}CCH(CH_3)_2$) at 100 MHz were unsuccessful. The present result therefore represents one of the first observations of anisochrony in a system of this type.[41,43]

The time-average symmetries[5] of **4** and **5** are isomorphic to C_1 and C_3, respectively. Accordingly, the sensor groups U are symmetry nonequivalent in both types of molecules, and the necessary condition for anisochrony is therefore met. The small magnitude of the observed effect in **6** ($\Delta\delta = 1.3 \times 10^{-3}$ ppm) is unsurprising in view of the considerable distance which separates the sensor (isopropyl) and chiral perturbing groups.[40] The question now remains as to what extent the observed anisochrony can be associated with a freely rotating species.

We have seen that any attempt to observe geminal anisochrony in a species undergoing completely free rotation is certain to be frustrated since, for symmetry reasons, there will *inevitably* be at least one barrier.[44] Reference to such a species in the present context is therefore meaningful only if it is assumed that in compounds of type **4** and **5** ($m \geq 1$) the barriers

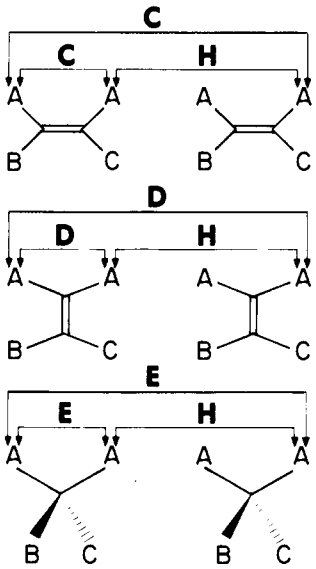


Figure 1. Internal and external topic relationships are shown in boldface: H = homotopic, C = constitutionally heterotopic, D = diastereotopic, E = enantiotopic.

are at least one and perhaps two orders of magnitude smaller than RT,[34] that under normal conditions of measurement the partitioning of molecules in a given sample between the bound and unbound torsional states will therefore result in the placement of a great preponderance of molecules into the latter, and, finally, that rotation in the unbound states is completely free.

It can be shown by first-order perturbation theory that if the free-rotor energy levels are perturbed by imposition of a small n-fold symmetric barrier (V_n) to internal rotation, the energy ϵ_0 of the ground torsional state equals $\frac{1}{2} V_n$. Consequently, at least one state lies below the top of the barrier. In the classical picture, we might imagine the NMR spectrum of a system with a very low barrier to be dominated by the contribution of freely rotating molecules in unbound states. However, the presence of *any* barrier has the effect of perturbing *all* rotational states, including the unbound ones. In each such state, the density of conformations corresponding to a given angle ϕ is always at an extremum wherever the underlying potential function has one. Thus, while the perturbation on each state falls off rapidly both with an increase in the energy of the state and with a decrease in the barrier height, so that for very low barriers the angular probability distribution for any state is almost flat, it is never absolutely so. As a result, we can never speak of "free rotation", even for unbound states, so long as any finite barrier is present.

It follows that any interpretation of the magnitude of the observed geminal anisochrony in **6**, or in any molecule of the type $[R^*]CU_2V$ no matter how low the torsional barrier, will therefore be physically meaningless without an extensive quantum mechanical calculation coupled with an assignment of differential shieldings for each conformation. At present, this task seems to be beyond the capacity of shielding effect theory.[45] Snyder's original suggestion[39] is therefore of dubious significance.

Diastereotopism by Internal and External Comparison. As has been repeatedly emphasized here and elsewhere,[32] the time-averaged chemical shift difference between geminal groups in structures of the type $[R^*]CU_2V$ is an ultimate consequence of their diastereotopic relationship. In defining spatial relationships of molecular substructures (i.e., of atoms or groups of atoms), we had previously[2] pointed to a distinction between internal and external comparisons: "In the former, the comparison takes place between portions of the same molecule, whereas in the latter the comparison takes place between corresponding portions which are parts of different molecules." Now while substructures which are related by external comparison are not necessarily related by internal comparison (e.g., the enantiotopic methyl groups in (R)- and (S)-alanine, and the diastereotopic fluorine atoms in *cis*- and *trans*-1,2-difluoroethene), *substructures which are related by internal comparison are always relatable by external comparison.* Consider two molecules of the same kind, M_1 and M_2, composed of corresponding sets of atoms $\{x_1, y_1, \ldots\}$ and $\{x_2, y_2, \ldots\}$. Since the models of the two molecules are properly congruent, corresponding atoms are pairwise homotopic by external comparison, i.e., $x_1 \sim x_2$, $y_1 \sim y_2$, etc. Therefore any internal relation $x_1 \sim y_1$ in M_1 and $x_2 \sim y_2$ in M_2 is also an external relation $x_1 \sim y_2$ and $x_2 \sim y_1$ between M_1 and M_2 (cf. Figure 1). In the context of the present discussion, the internally diastereotopic relationship $U_a \sim U_b$ and $U_a' \sim U_b'$ in the two molecules $[R^*]CU_aU_bV$ and $[R^*]CU'_aU_b'V$ is therefore the same as the externally diastereotopic relationships $U_a \sim U_b'$ and $U_a' \sim U_b$. Consequently, *the geminal anisochrony in such molecules is precisely the same whether reference is made to diastereotopism by internal or external comparison.*[46] Failure to recognize this point may lead to serious misunderstanding.[25]

Experimental Section[47]

2-(2-Naphthyl)-5-methylhex-3-yn-2-ol. A solution of 0.1 mol of isopropylacetylene in 20 mL of tetrahydrofuran was added to a solution of 0.075 mol of methylmagnesium bromide in 50 mL of THF. The resulting solution was heated under reflux for 3 h, a solution of 0.05 mol of 2-acetylnaphthalene in 20 mL of THF was added, and the mixture was refluxed for 1 h further. The mixture was then cooled, poured into a mixture of ice and ammonium chloride, diluted with water (ca. 500 mL), and extracted thrice with ether. The combined ethereal extracts were washed with water and saturated NaCl solution, and then dried over $MgSO_4$. Filtration followed by concentration under reduced pressure yielded an oil which was chromatographed on silica gel using as eluting solvent a mixture of petroleum ether and ether, with increasing proportion of Et_2O. The material collected (after evaporation of solvent) was crystallized several times from pentane, then sublimed to give colorless crystals, mp 64 °C, in 35% final yield. The IR spectrum (KBr pellet) showed absorptions at 2230, 1605, 1080, 1050, 860, and 820 cm^{-1}. The 60-MHz ^1H NMR spectrum ($CDCl_3$) featured resonances at δ 1.24 (d, 6 H, isopropyl methyls, J = 7.0 Hz), 1.80 (s, 3 H, CH_3), 2.20 (bs, 1 H, OH), 2.65 (heptuplet, 1 H, isopropyl methine, J = 7.0 Hz), and 7.3–8.2 (7 H, aromatic). The noise-decoupled 15.08-MHz ^{13}C NMR spectrum ($CDCl_3$) featured resonances at (ppm downfield from Me_4Si) 20.6 (methine of isopropyl), 23.0 (isopropyl methyls, not resolved at 15.08 MHz), 33.5 (CH_3), 70.1 (COH), 83.2 (C≡), 91.3 (C≡), 123.4, 123.8, 126.2 (indication of second peak as apparent shoulder), 127.6, 128.1, 128.4, 132.9, 133.2, and 143.8 (all resonances from 123.4 through 143.8 are aromatic C).

The 300-MHz ^1H NMR spectrum (0.21 M, pyridine) shows two overlapping doublets (for each, J = 6.9 Hz) in the isopropyl CH_3 region, one centered at 1.1205 ppm, the other at 1.1192 ppm, $\Delta\delta = 1.3 \times 10^{-3}$ ppm ($\Delta\nu$ = 0.4 Hz).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.91; H, 7.45.

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$$\sigma_{iso} = \tfrac{1}{3}(\sigma_{xx} + \sigma_{yy} + \sigma_{zz})$$

where σ_{xx}, σ_{yy}, and σ_{zz} are the three principal components of the tensor. σ_{iso} is a scalar, which can be positive or negative. Therefore, for a freely rotating molecule the induced field acting on the nuclei is antiparallel or parallel to the external magnetic field. When a molecule has a fixed orientation with respect to the external field, the anisotropy of the screening tensor can produce anisochrony between nuclei which could be described as symmetry equivalent in a field-free space. For a molecule with a fixed orientation with respect to the external magnetic field, the induced field acting on the nuclei can a priori take any orientation with respect to this external magnetic field.
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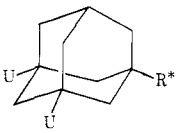
(27) The restriction of geminality is imposed by the context in which the term "intrinsic asymmetry" has been historically employed. This restriction is clearly an artifact of usage, and is rooted in the notion of connectivity (see above). For example, in structure i, the adamantane framework represents



i

a pseudoatom fully equivalent to the C atom in $[R^*]CU_2V$.
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(38) See, for example, V. Tabacik, *Tetrahedron Lett.*, 555 (1968); L. Salem, *J. Am. Chem. Soc.*, **95**, 94 (1973).
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(41) After our experimental work had been completed, we learned that Jones and Stiles[42] had independently observed geminal methyl anisochrony in the ^{13}C NMR spectrum of 2-chloro-5-methylhex-3-yne, a representative of type **4** ($m = 1$).
(42) A. J. Jones and P. J. Stiles, *Tetrahedron Lett.*, 1965 (1977).
(43) We found that another compound of type **4** ($m = 1$), 1-(1-naphthyl)-1-phenyl-4-methylpent-2-yn-1-ol, also exhibits two methyl doublets (in $CDCl_3$, $\Delta\delta = 1.17$ Hz at 60 MHz). However, because of difficulties encountered in the purification, we have been unable to characterize this compound to our complete satisfaction.
(44) This situation had been clearly envisaged by Waugh and Cotton:[19] "It seems unlikely that in practice the asymmetry with respect to internal rotation required to produce magnetic non-equivalence would not also be reflected in some angular dependence of potential energy."
(45) Geminal anisochrony was observed for the isopropyl methyls of **6** in pyridine but not in benzene or $CDCl_3$. The observed solvent dependence of the anisochrony reinforces our view that an interpretation of the magnitude of the effect is beyond the power of the present theory.
(46) It is interesting to realize, for example, that although the geminal anisochrony often observed in the ^{13}C NMR spectra of compounds of the type $[R^*]CH(CH_3)_2$ is normally considered to refer to groups which are diastereotopic by internal comparison, it is highly improbable that two $^{13}CH_3$ groups reside in the same molecule of a sample of natural isotopic composition. The measurement therefore actually compares $^{13}CH_3$ groups which are diastereotopic by external comparison. We also note that a convenient heuristic[2] for distinguishing between two diastereotopic atoms involves substitution of each in turn by a test group, such as an isotopic atom, to form diastereomers. The heuristic thus effectively converts internal into external diastereotopism.
(47) ^1H NMR spectra (60 MHz) were recorded on a Bruker WP 60 spectrometer, as were 15.08-MHz ^{13}C NMR spectra. The 300-MHz ^1H NMR spectra were recorded on a Varian HR 300 spectrometer. Isopropylacetylene was purchased from K&K Laboratories and distilled just before use.