Tetrahedron. Vol 33, pp 2981 to 2986. Pergamon Press 1977. Printed in Great Britain

ON THE INTRINSIC ANISOCHRONY OF DIASTEREOTOPIC NUCLEI IN CHIRAL ETHANES AND BUT-2-YNES

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(*Received in the UK 25 May 1977; Accepted for publication 2 June 1977*)

Abstract—A theory for intrinsic magnetic shielding non-equivalence of the geminal nuclei U_a and U_b in ethanes $CXYZ\text{-}CU_aU_bV$ and but-2-ynes $CXYZ\text{-}C{\equiv}C\text{-}CU_aU_bV$ is developed and illustrated with the aid of symmetry arguments and mechanistic models. Special attention is given to mechanisms which survive when internal rotation is free and to the attenuation of intrinsic anisochrony with increasing separation between the chiral perturbing group and the sensor nuclei.

It has been known for over a century that intermolecular forces enable a chiral molecule to discriminate between the enantiomers of a second chiral species.[1] More recently it became recognised[2] that a chiral molecule can even distinguish atoms such as the two fluorines in bromodifluoromethane at enantiotopic[3] sites of an achiral species. Such atoms become diastereotopic[3] in the presence of a chiral perturbing group. In 1957 Drysdale and Phillips[4] found that the diastereotopic fluorine nuclei in $CHBrPh\text{-}CF_2Br$ exhibited different chemical shifts in the room temperature NMR spectrum. Further studies showed that magnetic shielding non-equivalence or *anisochrony* of nuclei in atoms U_a and U_b in substituted ethanes of the type $CXYZ\text{-}CU_2V$ in which the prochiral $\text{-}CU_aU_bV$ moiety is perturbed by the chiral $CXYZ$-group is a regular feature of NMR spectra.[5] The observed anisochrony was recognised by Waugh and Cotton[6] and by Gutowsky[7] to be the sum of an intrinsic component which survives when the three rotamers in each enantiomer of $CXYZ\text{-}CU_aU_bV$ are equally populated and another component which can be attributed to unequal rotamer populations. Waugh and Cotton were the first to realize that the intrinsic anisochrony persists even when internal rotation about the *C-C* bond is completely free.

At low temperatures the interconversion of rotamers is sometimes so slow that the individual spectra of all three rotamers can be identified in the experimental spectrum.[8] Raban[9] and others[10] have used this technique to deduce the intrinsic anisochrony expected when rotamer populations are equal.

Direct routes to intrinsic anisochrony for special classes of molecules have been devised by Mislow and Raban[3] and by Binsch and Franzen.[11] Mislow and Raban suggested replacing the prochiral $\text{-}CU_aU_bV$ group with planar symmetry by a C_{3v} group such as bicyclopentyl in which the three prochiral methylene groups are symmetrically disposed about the threefold axis. Because the bicyclopentyl group has C_{3v} symmetry the three conformers of *CXYZ-bicyclopentyl* are equally populated and the anisochrony of the geminal protons is completely intrinsic. Related experiments were successfully executed by McKenna, McKenna and Wesby[12] and by Franzen and Binsch.[11b] A second ingenious route to the intrinsic component was devised by Binsch and Franzen[11] who replaced the asymmetric $CXYZ$-group of $CXYZ\text{-}CU_2V$ by a chiral group of C_3 symmetry. All rotamers are then equally populated so the observed and intrinsic anisochronies are identical.

Despite considerable experimental progress[5] few advances have been made in recent years on the theory of intrinsic anisochrony and its relationship to chirality.† Questions of fundamental importance include:

(i) How is the intrinsic anisochrony related to *chiral properties of the perturbing group* and to *the local chiral environments of the sensor nuclei*

(ii) How rapidly does the intrinsic anisochrony fall away when the distance between the prochiral sensor group and the chiral perturbing group is increased? How, for example, does the intrinsic anisochrony in $CXYZ\text{-}CU_2V$ compare with that in $CXYZ\text{-}C{\equiv}C\text{-}CU_2V$?

The interplay of geometric, kinetic and thermodynamic factors which can influence isochrony of geminal nuclei in chiral molecules is indicated in Table 1.

A preliminary reconnaissance

The detailed mechanisms that permit the perturbing group to discriminate between the diastereotopic sensor nuclei are clearly implicit in any rigorous theory for the chemical shift. No practical *ab initio* quantum-mechanical scheme is yet available to estimate shieldings to the precision with which anisochronies can be measured experimentally. It therefore seems useful to expound a simple mechanistic model based on the assumption that a molecule of interest can be separated into electronically independent sensor and perturbing groups. Such an approach considers through-space interactions but neglects through-bond interactions which may be significant. Similar models have proved most useful in understanding other phenomena, such as the carbonyl octant rule in natural optical activity,[14a] which also rely on the interactions between groups in polyatomic molecules.

We show in the following section that the phenomenon of geminal anisochrony is determined solely by average spatial symmetry on the *NMR* time scale. Anisochrony that relies on differential rotamer populations is readily understandable in terms of well known long-range electrostatic,[15] dispersive,[16] and magnetic anisotropy[17] shielding mechanisms[18] but the magnitude of the intrinsic component, particularly when internal rotation is com-

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†The early observation by Nair and Roberts[13] that achiral molecules such as diethylsulphoxide display geminal anisochrony effectively dispelled the erroneous view that chirality of the whole molecule is a relevant factor.

Table 1. Dependence of nuclear anisochrony on structural, kinetic and thermodynamic factors

MOLECULE	SENSOR NUCLEI	SLOW ROTATION	RAPID ROTATION	
			HINDERED	FREE
$CHClBr{-}CH_3$	methyl protons	anisochronous	isochronous	isochronous
$CHClBr{-}NO_2$	nitro oxygens	anisochronous	isochronous	isochronous
$CHClBr{-}CH_2F$	methylene protons	anisochronous	anisochronous	anisochronous

pletely free, is more difficult to interpret. A simple explanation for intrinsic anisochrony in such cases can be based on a chiral shielding mechanism which may be viewed in the following way. The enantiotopic nuclei U_a and U_b in the prochiral sensor group $-CU_aU_bV$ are located at chiral sites of opposite handedness. This point is illustrated below.

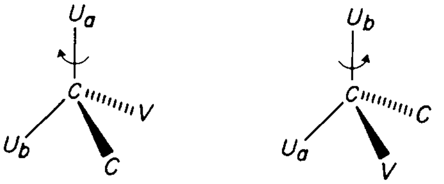


Fig. 1.

Any scalar quantity dependent on site chirality must be equal in magnitude and opposite in sign for the two nuclei. Such quantities are called pseudo-scalars. Discriminatory shielding mechanisms which survive regardless of the mutual positions and orientations of the sensor and perturbing groups must depend on the product of two pseudo-scalars—one of which describes the site chirality of the nucleus, the other, the chirality of the perturbing group. We recently reported a universal dispersive shielding mechanism of this type.[19] It falls away as the sixth power of the distance R between the nucleus and the carbon atom of the $CXYZ$ perturbing group but, being about ten thousand times weaker than normal dispersive shielding,[16] is too small to account for intrinsic anisochronies previously reported.[5]

In molecules of the type $CXYZ{-}CU_2V$ the relative positions and orientations of the sensor and perturbing groups are constrained by the sigma bond between them. Under geometric constraints of this type group properties that do not depend on the intrinsic chirality of the perturbing group or the site chiralities of the sensor nuclei can be invoked to interpret the observed anisochrony. Mechanisms discussed in subsequent sections fall into this category.

Anisochrony and group symmetry

Nuclear isochrony is a symmetry based phenomenon. The essential point is that nuclei in a molecule are anisochronous unless required by symmetry constraints to be isochronous.[3,6]

Nuclear magnetic shielding is defined by a second rank polar tensor.[20] The sum of its diagonal components and hence the shielding constant therefore transforms under proper and improper spatial symmetry operations as a true scalar and in rigid molecules the isotropic shieldings of two nuclei which are interconverted by any molecular symmetry operation must be identical. All nuclei of an asymmetric rigid molecule are therefore anisochronous. Because the staggered rotamer of $CXYZ{-}CH_3$ is asymmetric the proton shieldings are inequivalent when internal rotation is slow on the NMR time scale. However, as Hirschmann[21] and Mislow and Raban[3] have pointed out, the local three-fold symmetry axis of the methyl group is sufficient to ensure chemical reactivity and NMR shielding equivalence of the three protons, provided that the internal rotation is rapid. The observed anisochrony $\overline{\Delta\sigma_{ab}} = \overline{\sigma^{(a)}} - \overline{\sigma^{(b)}}$ for any two of the three methyl protons is a temporal average involving all thermally populated conformations. If the residence time in each conformation is short on the NMR time scale the temporal averaging can usually be replaced by classical Boltzmann averaging and we find

$$\overline{\Delta\sigma_{ab}} = \frac{\int_0^{2\pi} \Delta\sigma_{ab}(\phi)\, e^{-V(\phi)/kT} d\phi}{\int_0^{2\pi} e^{-V(\phi)/kT} d\phi} \tag{1}$$

where $\Delta\sigma_{ab}(\phi) = \sigma^{(a)}(\phi) - \sigma^{(b)}(\phi)$ is the anisochrony, and $V(\phi)$ the conformational energy, when the torsional angle is ϕ. We assume here and throughout this article that both the sensor and perturbing groups have rigid nuclear frameworks that are unaffected by joining the two moieties. The torsional angle ϕ, conveniently regarded as the Newman angle between the substituents X and U_a, then completely specifies the molecular conformation.

The three-fold rotational axis of the methyl group ensures that $V(\phi + 2\pi/3) = V(\phi + 4\pi/3) = V(\phi)$ and that the anisochronies $\Delta\sigma_{ab}(\phi + 2\pi/3) = \Delta\sigma_{bc}(\phi)$ and $\Delta\sigma_{ab}(\phi + 4\pi/3) = \Delta\sigma_{ca}(\phi)$. By resolving the integral in the numerator of eqn (1) into three components with limits separated by $2\pi/3$ and employing the preceding equalities we find the average anisochrony,

$$\begin{aligned}\overline{\Delta\sigma_{ab}} &= \frac{\int_0^{2\pi/3} [\Delta\sigma_{ab}(\phi) + \Delta\sigma_{bc}(\phi) + \Delta\sigma_{ca}(\phi)]\, e^{-V(\phi)/kT} d\phi}{\int_0^{2\pi} e^{-V(\phi)/kT} d\phi} \\ &= 0,\end{aligned} \tag{2}$$

since by definition $\Delta\sigma_{ab}(\phi) + \Delta\sigma_{bc}(\phi) + \Delta\sigma_{ca}(\phi) = 0$. Because the particular choice of protons a and b is immaterial all three protons in our model of $CXYZ{-}CH_3$ must be isochronous. An exactly analogous argument

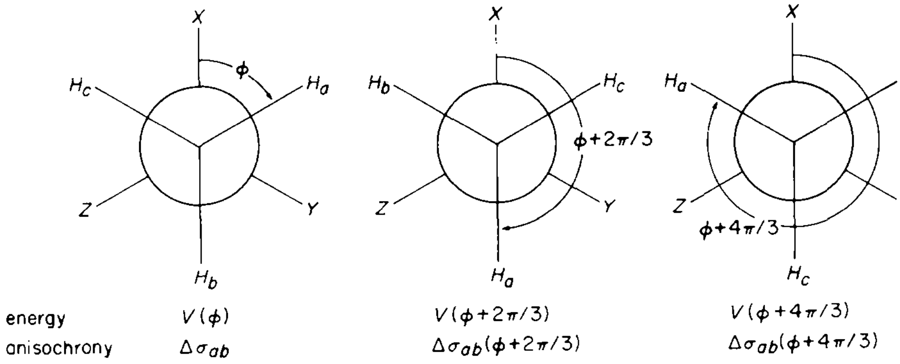


Fig. 2.

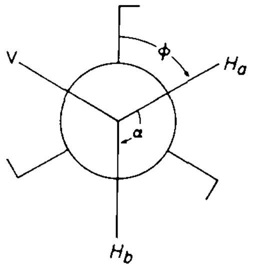
can be used to demonstrate that the isochrony of the oxygen nuclei in $CXYZ{-}NO_2$ is a direct consequence of the two-fold rotational symmetry of the nitro group. If one of the methyl hydrogens, H_c say, is replaced by a different atomic species V symmetry arguments no longer require the proton anisochrony, $\Delta\sigma_{ab}$ as defined by eqn (1), to vanish. Thus the protons H_a and H_b which are anisochronous when internal rotation is slow remain anisochronous when internal rotation is rapid.

Mechanisms for intrinsic anisochrony

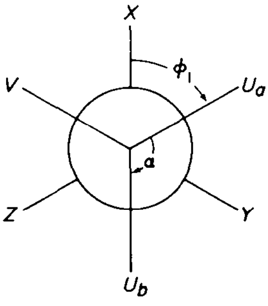
Non-ideal conformational geometry. Intrinsic anisochrony can be divided into a contribution that relies on geometric non-ideality and another which survives even if the molecular geometry is ideal. We deal first with the former. In $CXYZ{-}CU_2V$ (U, V, X, Y, Z are assumed to be monatomic) anisochrony of the nuclei U in the $-CU_aU_bV$ sensor group relies exclusively on perturbation by the $CXYZ$ group. When internal rotation is hindered geometric non-idealities of conformational origin produce intrinsic anisochrony through all long-range shielding mechanisms. This point was first noted by Jackman and Sternhell.[22] It can be examined in some detail if we further restrict the substituted ethane to possess three rotamers as depicted below. For this model the torsional angle ϕ uniquely defines the structure of each rotamer and hence the positions of both protons in the $CXYZ$-frame of reference. If the three rotamers are equally populated and internal rotation is rapid the observed shielding of nucleus U_a is the average of the shieldings associated with its three angular positions ϕ_1, ϕ_2 and ϕ_3. Nucleus U_b occupies positions $\phi_1+\alpha$, $\phi_2+\alpha$ and $\phi_3+\alpha$ where α is angle $U_a\hat{C}U_b$ in Newman projection. Its shielding too is an average over these three positions. *We define the molecular geometry to be ideal if the angle α between the diastereotopic nuclei is equal, in Newman projection, to the common angular separation of the rotamers*, i.e. if $\phi_2-\phi_1=\phi_3-\phi_2=\phi_1-\phi_3=\alpha$. Even when the four bonds about each carbon atom are disposed towards the apices of a regular tetrahedron, thus ensuring that $\alpha = 120°$, the ideality criterion is not normally satisfied[23] and the diastereotopic nuclei occupy mutually exclusive points in space within the frame of reference of the $CXYZ$-group. Their shieldings are therefore, on average, unequal. In real molecules the angular separation of the rotamers depicted in I is not constant, nor is $\alpha = 120°$.[24] The bonds CU_a and CU_b are also of unequal length.

Intrinsic anisochrony of this type has very long range components in R^{-3} from the magnetic dipolar anisotropy[17] and from the permanent electric dipole moment[15] of the $CXYZ$-group. Order of magnitude calculations based on angular inequalities of less than 10° suggest that intrinsic anisochronies of at least 10^{-2} ppm for geminal protons and 10^{-1} ppm for carbon, fluorine and heavier nuclei can be expected from this source. Until more precise data on the detailed geometries of all three rotamers become available estimates of this important component of the intrinsic anisochrony will be of little value.

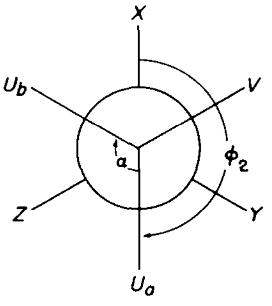
Molecules with Newman projections of type II exhibit



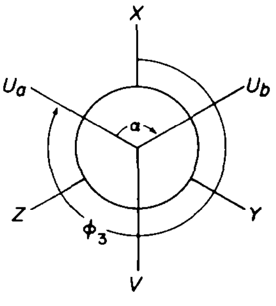
II



Ia



Ib



Ic

proton anisochrony that is entirely intrinsic.[11] The C_3 symmetry of the perturbing group ensures that the three identical rotamers have a common separation of 120° but because the sensor group has only a plane of symmetry the angle α usually deviates from 120°, thus rendering the conformational geometry non-ideal. Long-range shielding mechanisms in R^{-3} invoked in the case of $CXYZ$–CU_2V cannot discriminate between the protons of the Binsch–Franzen species. However, a mechanism in R^{-4} relying on quadrupolar terms[17b] in the magnetic anisotropy of the chiral perturbing group produces anisochrony in this case. If the rotamer geometry is defined by the angle ϕ the associated anisochrony is

$$\Delta\sigma_{ab} = \frac{-30\sin(3\alpha/2)\sin^3\theta}{R^4}[A_{33}\sin 3(\phi-\alpha/2) - B_{33}\cos 3(\phi-\alpha/2)] \quad (3)$$

where A_{33} and B_{33} are quadrupolar susceptibility anisotropies[17b] of the perturbing group and θ is the angle subtended at the $CXYZ$-group by either C–U bond of the sensor group. There is no discriminatory electric shielding mechanism of equally long range.

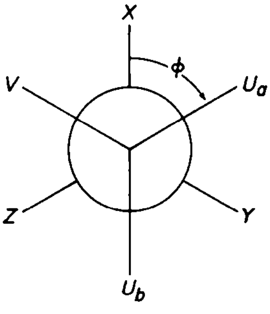
Anisochrony that relies on non-ideal conformational geometry vanishes when internal rotation is completely free. We also note that many of the mechanisms associated with non-ideal conformational geometry remain relevant even if the local $CXYZ$ and CU_2V geometries become planar and trigonal rather than tetrahedral.

Rapid rotation in molecules with ideal geometry. The through-space electric-field contribution[15] to the shielding constant depends on both the nuclear position and the orientation of the sensor group with respect to the perturbing group. Because the sensor group has *different* orientations with respect to the electric field of the perturbing group when the nuclei U_a and U_b have the *same* angular position (see illustration below) electric polarisation of the CU_2V group by the $CXYZ$-perturbing group results in differential shielding of the two nuclei even when the molecular geometry is ideal. The magnetic anisotropy mechanism[17b] on the other hand depends only on the positions of the sensor nuclei in the frame of reference of the perturbing group and cannot contribute to intrinsic anisochrony if the conformational geometry is ideal. Although we have been unable to find simple mechanisms which distinguish between intrinsic anisochrony when internal rotation is rapid and hindered as opposed to rapid and free the magnitudes of these two types of intrinsic anisochrony are clearly different. In the former case intrinsic anisochrony is approximated by a finite sum

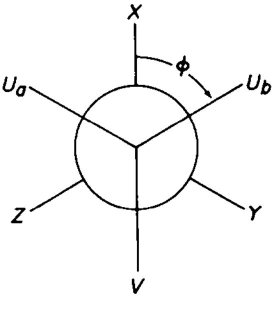
$$\overline{\Delta\sigma_{ab}} = \frac{1}{3}\sum_{i=1}^{3}\Delta\sigma_{ab}(\phi_i), \quad (4)$$

where the ϕ_i represent the dihedral angles of the three potential minima in $V(\phi)$; in the latter limit equation (1) reduces to

$$\overline{\Delta\sigma_{ab}} = \frac{1}{2\pi}\int_0^{2\pi}\Delta\sigma_{ab}(\phi)\,\mathrm{d}\phi. \quad (5)$$



IIIa



IIIb

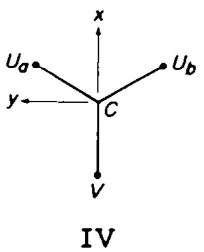
Two electric shielding mechanisms which fall away as R^{-7} give experimentally significant contributions to the intrinsic anisochrony in cases of ideal conformational geometry. These have their origins in reaction field inductive and dispersive interactions. The reaction field mechanism utilises the permanent electric dipole moment of the sensor group which has a component μ_x perpendicular to the C–C axis. This electric moment produces an electrostatic field at the perturbing group and induces local electric dipole and quadrupole moments *via* skew-symmetric components of the group's dipole-quadrupole polarisability.[14] Four of the six skew-symmetric components of this polarisability tensor have non-zero mean values $\overline{a_{x,yz}} = \overline{a_{x,zy}} = -\overline{a_{y,zx}} = -\overline{a_{y,xz}} = \frac{1}{2}(a_{x,yz} - a_{y,zx})$ that survive free rotation about the C–C bond and change sign but remain unaltered in magnitude when the chirality of the $CXYZ$-perturbing group is reversed. The electric dipoles and quadrupoles thereby induced create a reaction field back at the sensor group which discriminates between the nuclei U_a and U_b through the linear electric shielding mechanism described by Buckingham.[15] The associated anisochrony has a free rotation limit

$$\overline{\Delta\sigma_{ab}} = -\frac{\mu_x\overline{a_{x,yz}}}{R^7\cos^4\theta}[\surd(3)A_x^{(a)}(3\text{–}5\cos^2\theta)\sin^2\theta + 5A_y^{(a)}(1\text{–}3\cos^2\theta)\sin^2\theta + \surd(3)A_z^{(a)}(4\text{–}5\cos^2\theta)\sin 2\theta] \quad (6)$$

where the $A_\alpha^{(a)}$ are linear shielding coefficients in the expansion[15]

$$\sigma^{(a)} = -A_\alpha^{(a)}E_\alpha - B_{\alpha\beta}^{(a)}E_\alpha E_\beta + \cdots \quad (7)$$

for the electric field dependence of isotropic nuclear magnetic shielding at nucleus U_a in the isolated sensor group. All cartesian suffices in (6) refer to a right handed axis system fixed in the sensor group as indicated below. More direct mechanisms come from shielding at the sensor nucleus which is quadratic in the electric field strength **E**. There is an inductive component from the electrostatic field and a dispersive component which is attributed in semi-classical theories[16a] to fluctuations in the field strength. When internal rotation is completely



IV

free the general expression for this component reduces to

$$\overline{\Delta\sigma_{ab}} = \frac{\overline{4Q_{x,yz}}}{R^7}[\tfrac{1}{2}\surd(3)(B_{xx}^{(a)} - B_{yy}^{(a)}) \sin 2\theta + B_{xy}^{(a)} \sin 2\theta + (\surd(3)B_{xz}^{(a)} - B_{yz}^{(a)}) \cos 2\theta] \sin \theta \quad (8)$$

where $Q_{x,yz}$ is the expectation value of the skew-symmetric product of the electric dipole operator μ_x and electric quadrupole operator Θ_{yz} of the perturbing group in its electronic ground state. The horizontal bar over $\overline{Q_{x,yz}} = \frac{1}{2}(Q_{x,yz} - Q_{y,xz})$ denotes an unweighted classical average over all values of the torsional angle defining the orientation of the perturbing group with respect to axes fixed in the sensor group.

When eqn (7) is applied to nuclei in a polyatomic group the vector $\mathbf{A}^{(a)}$ is usually assumed to lie along the straight line joining nucleus U_a to its nearest neighbor. It is also customary to assume that this line is a principal axis of the quadratic shielding tensor $B_{\alpha\beta}^{(a)}$. These assumptions are not usually valid when the polyatomic group has low symmetry. Both $A_\alpha^{(a)}$ and $B_{\alpha\beta}^{(a)}$ should strictly be regarded as property tensors characteristic of the entire group containing nucleus U_a rather than properties of the bond connecting atom U to its neighbour. Because the group $-CU_aU_bV$ has only a plane of symmetry the bond direction U_a–C defines neither the direction of the vector $\mathbf{A}^{(a)}$ nor a principal direction of $B_{\alpha\beta}^{(a)}$. In groups such as $-CU_aU_bV$ the direction of $\mathbf{A}^{(a)}$ and the principal longitudinal axis of $B_{\alpha\beta}^{(a)}$ are likely to be inclined at least several degrees from the bond axis. Anisochrony described by eqn (8) vanishes if this point is overlooked.

Mechanisms described in this section also contribute to anisochrony in molecules of type II.

Attenuation of anisochrony with increasing sensor-perturber separation

The various mechanisms for intrinsic anisochrony reported in the previous section exhibit differential sensitivities to changes in the sensor-perturber separation R. It would therefore be interesting to compare intrinsic anisochronies of the ethanes $CXYZ$–CU_2V with those of the corresponding but-2-ynes $CXYZ$–$C{\equiv}C$–CU_2V. Barriers to internal rotation in substituted ethanes are typically an order of magnitude larger than kT at room temperature whereas those of the corresponding but-2-ynes are of order kT or smaller. It follows that internal rotation in substituted but-2-ynes is much closer to the free rotation limit in which the anisochrony is effectively attenuated by terms in R^{-7} and shorter range. In substituted ethanes the interacting groups are so close to each other that truncated expansions of external fields in inverse powers of R are extremely crude[26] and terms in R are not necessarily much less significant than those of longer range in R^{-3}.

The first observations of geminal anisochrony in substituted but-2-ynes of type $CXYZ$–$C{\equiv}C$–CU_2V have been made in this laboratory[27] and independently by a team from Brussels and Princeton.[28]

CONCLUSION

A theoretical framework has been outlined for interpreting intrinsic anisochrony in substituted ethanes and related molecules in terms of long range through-space interactions between sensor and perturbing groups. Symmetry arguments alluded to by Waugh and Cotton[6] and by Mislow and Raban[3] have been amplified. A condition for intrinsic anisochrony based on non-ideal conformational geometry and first recognised by Jackman and Sternhell[22] has been extended. Several hitherto unrecognised mechanisms have been discussed in some detail.

It is well known[13] that the phenomenon of geminal anisochrony can be observed in achiral species such as diethylsulphoxide. Nevertheless, geminal anisochrony is most frequently encountered in chiral molecules of the type $CXYZ$–CU_2V in which the $CXYZ$-perturbing group is chiral and the nuclei U_a and U_b in the isolated sensor group are enantiotopic. Anisochrony in such species contains a minute contribution that relies on the intrinsic chiralities of both the perturbing group and the sensor sites.[19] The sign of the total anisochrony can sometimes be deduced if the absolute configuration of the perturbing group is known.[10a,11b,29]

Mechanisms that produce intrinsic anisochrony when internal rotation is completely free also produce intrinsic anisochrony when internal rotation is hindered but the converse is not always true. With the notable exception of chiral dispersive shielding[19] which is extremely weak, the mechanisms described in this article seem strong enough to account for extant data.

Acknowledgements—I thank Prof. D. P. Craig and Mr. R. W. Rickards for useful discussions and Prof. K. Mislow for illuminating correspondence and constructive criticisms of the manuscript.

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