Equivalence of Nuclei in High-resolution Nuclear Magnetic Resonance Spectroscopy

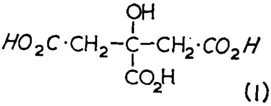
By M. van Gorkom
UNILEVER RESEARCH LABORATORY, VLAARDINGEN, NETHERLANDS
and G. E. Hall
UNILEVER RESEARCH LABORATORY, SHARNBROOK, BEDFORD

Since free rotation about a single bond is generally easy, two identical atoms or groups attached to a common atom (*e.g.*, the protons of a CH_2 group) are often assumed to be indistinguishable. In practice they may be chemically or magnetically distinguishable. A proper three-dimensional consideration of molecular structure allows an understanding of otherwise unexpected non-equivalence.[1] The aim of this Review is to reduce the confusion surrounding the concept of equivalence of nuclei. The principles involved are of value to organic and inorganic chemists in appreciating stereochemical subtleties and in interpreting even the simplest high-resolution nuclear magnetic resonance (n.m.r.) spectra in terms of chemical structures; to the physical chemist investigating barriers to chemical changes or the interaction forces between groups; and to the biochemist requiring to distinguish two similar groups and trying to understand the niceties of enzymic action.

1 Definitions

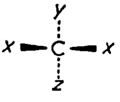
A. Chemical Non-equivalence.—Two atoms of the same isotopic species in a molecule are chemically non-equivalent if there is no molecular symmetry axis of rotation relating the two atoms.

Citric acid (1) has been shown to react enzymically in such a way that the two indicated carboxyl groups are distinguishable. The 'three-point attachment' theory, which attributes the enzyme with special features, was suggested[2] as an explanation of this observation. These features are, however, not a unique[3]

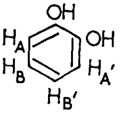


$$HO_2C{\cdot}CH_2{-}\overset{OH}{\underset{CO_2H}{C}}{-}CH_2{\cdot}CO_2H$$

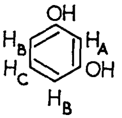
(1)



(2)



(3)



(4)

---

[1] K. Mislow and M. Raban in 'Topics in Stereochemistry', ed. N. L. Allinger and E. L. Eliel, John Wiley, New York, vol. I, ch. I.
[2] A. G. Ogston, *Nature*, 1948, **162**, 963.
[3] G. Popják and J. W. Cornforth, *Biochem. J.*, 1966, **101**, 553.

condition for a stereospecific reaction. Consider[4,5] a molecule C*xxyz* (2). Looking from the 'left-hand' *x* group towards the rest of the molecule, the clockwise sequence is *y*–*x*–*z*. From the right-hand *x* group the clockwise sequence is *y*–*z*–*x*. The *x*-groups are enantiotopic[1] because they are situated in enantiomeric environments.[6] Consequently the approach of an asymmetric reagent will be affected by the direction of approach and the *x* groups may react at different rates. With a highly asymmetric reagent such as an enzyme, the differentiation may be complete. Further consideration shows[5] that for two otherwise identical groups to be chemically non-equivalent (distinguishable) the relevant criterion is one of rotational symmetry. Chemically non-equivalent atoms require an optically active reagent for their chemical differentiation only if the molecule has a rotation–reflection axis, such as a plane of symmetry relating these atoms, as in (2).

B. Isochronous Nuclei.—Nuclei which experience equal magnetic shielding have identical chemical shifts; such nuclei are termed[7] isochronous. Chemically equivalent nuclei are isochronous but the reverse is not necessarily true. For example, the two *x* nuclei of (2) are isochronous, since a plane of symmetry relates them.

C. Magnetic Non-equivalence.—Two atoms (or groups of atoms) are magnetically equivalent if they are isochronous and if the constants (J) for the coupling to any other atom are identical. In catechol (3) the nuclei labelled B are chemically shifted (non-isochronous) from those labelled A. They are magnetically non-equivalent in the chemical-shift sense. Also the coupling between A and B is through three bonds whilst between A′ and B it is through four bonds; the coupling constants must therefore be expected to be different. Consequently A and A′ are magnetically non-equivalent in the spin-coupling sense (this is an example of isochronous magnetic non-equivalence[7]). The aromatic ring proton spin system is described in the usual convention[8] as AA′BB′. On the other hand, the atoms labelled B in resorcinol (4) are isochronous and do have identical values for the coupling constants with either nuclei C or A. They are therefore magnetically equivalent and this spin system is described as AB_2C. This analysis ignores any coupling between the ring protons and the hydroxyl protons.

D. Accidental Magnetic Equivalence.—The above arguments are based simply on considerations of symmetry without recourse to experimental data. If in (3) by some quirk of fate it had transpired that $J(\mathrm{AB}) = J(\mathrm{A'B})$ and $J(\mathrm{AB'}) = J(\mathrm{A'B'})$,

---

[4] P. Schwartz and H. E. Carter, *Proc. Nat. Acad. Sci. U.S.A.*, 1954, **40**, 499.

[5] H. Hirschmann, *J. Biol. Chem.*, 1960, **235**, 2762.

[6] K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, and G. H. Wahl, *J. Amer. Chem. Soc.*, 1964, **86**, 1710.

[7] (*a*) A. Abragam, 'The Principles of Nuclear Magnetism', Oxford University Press, 1961, p. 480; (*b*) E. I. Snyder, *J. Amer. Chem. Soc.*, 1963, **85**, 2624.

[8] *E.g.*, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, 'High Resolution Nuclear Magnetic Resonance Spectroscopy', Pergamon Press, Oxford, 1965, p. 283.

then A and A′ would be said to be accidentally magnetically equivalent. Two atoms may appear to be equivalent if the operating conditions are insufficient to resolve the appropriate peaks. For example the acetylenic and methyl protons in propyne[9] are accidentally isochronous at 60 Mc./sec., and produce a one-line spectrum.

E. Time-averaged Equivalence.—If a configurational or conformational change occurs rapidly[10] compared with the inherent time scale of the n.m.r. experiment, then two atoms may become equivalent, by averaging, if each spends the same time in each particular environment.

Table 1 *The possible combinations of chemical and magnetic equivalence*

Relationship of the two (groups of) nuclei			*Example*	*Spectrum type*	*Ref.*
CE	IS	ME	Fluorine nuclei in 1,1-difluoroallene	A_2X_2	*a*
CE	IS	MNE	Fluorine nuclei in 1,1-difluoroethylene	$AA'XX'$	*a*
CNE	IS	ME	Protons in chlorofluoromethane	A_2X	*b*
CNE	IS	MNE	Protons in tetraethyl-lead	$A_3A_2'X$	*c*
CNE	NIS	MNE	α and β Protons in pyridine	$A\,A'\,B\,B'C$	*d*

C(N)E ≡ chemical (non-)equivalence
(N)IS ≡ (non-)isochronous
M(N)E ≡ magnetic (non-)equivalence

[a] H. M. McConnell, A. C. McLean, and C. A. Reilly, *J. Chem. Phys.*, 1955, **23**, 1152; [b] Ref. 8; [c] E. B. Baker, *J. Chem. Phys.*, 1957, **26**, 960; [d] W. G. Schneider, H. J. Bernstein, and J. A. Pople, *Ann. New York Acad. Sci.*, 1958, **70**, 806.

Table 1 lists all the possible combinations of chemical and magnetic equivalence, with examples. Further examples are given both later and elsewhere.[11,12]

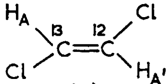
2 Temperature-independent Magnetic Non-equivalence

Any factor which locks two nuclei in different magnetic environments will cause them to be magnetically non-equivalent. In the isotopically unusual form (5) of *trans*-1,2-dichloroethylene, the protons exhibit[13] magnetic non-equivalence which, since there is no reaction causing exchange, should be temperature-

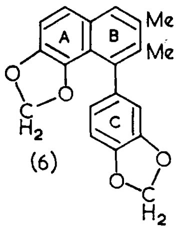
---

[9] N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, 'N.M.R. Spectra Catalog', National Press, New York, 1962, vol. 1, Spectrum 16.
[10] J. E. Anderson, *Quart. Rev.*, 1965, **19**, 426.
[11] F. A. Bovey, *Pure Appl. Chem.*, 1966, **12**, 525.
[12] M. L. Martin and G. J. Martin, *Bull. Soc. chim. France*, 1966, 2117.
[13] A. D. Cohen, N. Sheppard, and J. J. Turner, *Proc. Chem. Soc.*, 1958, 118.

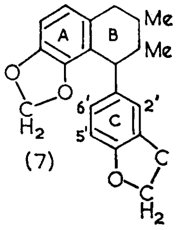
independent. Similarly the two methylenedioxy rings of the tetradehydro-otobain (6) have sharp proton n.m.r. lines.[14] The plane of the molecule evidently bisects the <HCH angle of the two methylene groups, and the two protons in each



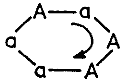
(5)



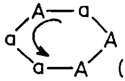
(6)



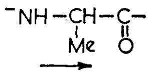
(7)



(8)



(9)



$$^{-}NH-\underset{Me}{CH}-\underset{O}{\overset{}{\underset{\|}{C}}}- \longrightarrow$$

A = *S*-alanyl residue
a = *R*-alanyl residue

group are equivalent. This is not so for otobain (7) itself; the methylenedioxy-group on ring C shows a singlet, but the two protons of the other methylenedioxy ring (attached to ring A) exhibit non-equivalence as an AB quartet. It is also interesting that the protons at 2′, 5′, and 6′ of otobain are accidentally magnetically equivalent and have a single proton n.m.r. signal. The corresponding protons of the dehydro-compound (6) are non-equivalent.

Diastereoisomers may also have sufficiently different magnetic environments at particular atoms for distinguishable spectra to be observed. As an example, the proton n.m.r. spectra of L-[Co(en)$_2$-L-ala]Cl$_2$ and D-[Co(en)$_2$-L-ala]Cl$_2$ are different. These complexes involve cobalt(III), ethylenediamine (en), and alanine (ala). On the other hand, the n.m.r. spectra of L-[Co(en)$_2$-L-ala]Cl$_2$ and D-[Co(en)$_2$-D-ala]Cl$_2$ should be identical[15] because they are enantiomeric compounds (*i.e.*, mirror images). Cycloenantiomers[16] must also have the same n.m.r. spectra. The cyclohexapeptides (8) and (9) are mirror images of each other; although they have the same distribution of chiral[17] (*i.e.*, asymmetric) centres they differ by virtue of the ring direction, which is indicated by the arrows. Such compounds are termed cycloenantiomers. As expected their n.m.r. spectra are identical and their optical rotations are equal and opposite. On the other hand, each methyl group of either compound 'sees' a different sequence of *R*- and *S*-chiral centres from those 'seen' by the other five, and the proton spectrum contains six methyl doublets. Cyclodiastereoisomers,[16] which have an identical

---

[14] T. Gilchrist, R. Hodges, and A. L. Porte, *J. Chem. Soc.*, 1962, 1780.

[15] D. A. Buckingham, S. F. Mason, A. M. Sargeson, and K. R. Turnbull, *Inorg. Chem.*, 1966, **5**, 1649.

[16] V. Prelog and H. Gerlach, *Helv. Chim. Acta*, 1964, **47**, 2288; H. Gerlach, J. A. Owtschinnikow, and V. Prelog, *ibid.*, p. 2294.

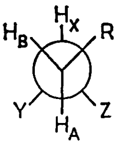
[17] R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Internat. Edn.*, 1966, **5**, 385.

sequence of chiral centres and differ only in the ring direction, but are not mirror images, are expected to give distinguishable n.m.r. spectra.

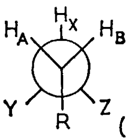
3 Magnetic Non-equivalence with Both Temperature-dependent and -independent Contributions. The 'Ethane Type'

The substituted ethanes form the basis of the following discussion not only for historical reasons; the principles involved can be clearly demonstrated and then used for the understanding of related instances of magnetic non-equivalence.

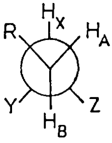
(i) *Ethanes.* In 1957 the 30 Mc./sec. room-temperature fluorine-19 n.m.r. spectrum of $CF_2Br.CHBr.C_6H_5$ was reported.[18] It was clear that the fluorine atoms are magnetically non-equivalent on two counts; they are chemically shifted and they couple with the vicinal proton to different extents. The fluorine spectrum of $CF_2Br.CBrCl_2$ on the other hand is, down to −30°c, a single[19] sharp line. It is thus unlikely[20] that restricted rotation is the cause of the observed non-equivalence, the origin of which can be understood in the following way. Consider a compound of the general formula $H_XYZC.CH_AH_BR$. In general the energy barriers to rotation will be sufficiently small that at ordinary temperatures free rotation occurs. The eclipsed forms[21] correspond to potential maxima, have very short residence times, and may be ignored. There are then three distinguishable rotational forms, represented[22] as (10)—(12). The environment of H_A in (11) is such that it is 'opposite' Z and has Y and R to one side and H_B and H_X to the other. Magnetic anisotropy in the bonds can[23] cause significant differences in magnetic shielding. In none of the conformers (10)—(12) does H_B have exactly that same environment. In (10) H_B is opposite Z but it has R and H_X to one side and Y and H_A to the other. Even if H_A and H_B spent equal times in each of the three possible conformations, the average environments can never be exactly identical and a chemical shift can therefore be expected. This possibility has not been recognised by some authors.[24,25] (It should be noted that either Y or Z may be the same as $RCH_2\cdot$ in which case the two $RCH_2\cdot$ groups are chemically, and the two protons within each group magnetically, non-



(10)



(11)



(12)

---

[18] J. J. Drysdale and W. D. Phillips, *J. Amer. Chem. Soc.*, 1957, **79**, 319.

[19] P. M. Nair and J. D. Roberts, *J. Amer. Chem. Soc.*, 1957, **79**, 4565.

[20] E. O. Bishop, *Ann. Reports,* 1961, **58**, 67.

[21] D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, 1956, **10**, 44.

[22] M. S. Newman, 'Steric Effects in Organic Chemistry', John Wiley, New York, 1956.

[23] L. M. Jackman and N. S. Bowman, *J. Amer. Chem. Soc.*, 1966, **88**, 5565.

[24] H. Finegold, *J. Amer. Chem. Soc.*, 1960, **82**, 2641; R. Freymann, *Compt. rend.*, 1965, **261**, 2637.

[25] K. Deutsch and I. Deutsch, *Ann. Physik*, 1965, **16**, 30.

equivalent. If neither Y nor Z is $RCH_2\cdot$ then optical isomerism arises.) The non-equivalence within one group arises by its interaction with another of low symmetry (in this case a carbon atom with either three or four different substituents). Although magnetic non-equivalence always arises by virtue of some form of low symmetry in the molecule, the term *intrinsic asymmetry*[26] is reserved for this special case. Two atoms (or groups) such as H_A and H_B, which reside in diastereomeric environments and cannot be interchanged by symmetry operations, are said to be diastereotopic.[1]

Since populations of excited vibrational and solvation states probably influence chemical shifts and coupling constants only slightly, the intrinsic asymmetry effect is generally assumed to be temperature-independent. The temperature-dependent effect which results from unequal populations (*i.e.*, residence times) of the conformers must however be allowed for. As we have already seen, the environments of H_A and H_B in any one of the conformers (10)—(12) are different. Consequently, if the populations are unequal, a weighted average must be computed. Since the populations will vary with temperature, there results a temperature-dependent contribution. At ordinary temperatures this is normally more important than the intrinsic asymmetry effect. Various simplified mathematical treatments[27–29] have been given. In one method, a least-mean-square analysis allows an estimation of the rotamer populations and of all the coupling constants. These calculations have been made for several compounds,[29] and in the case of protons the *gauche* and *trans* coupling constants (about 2 and 16 c./sec. respectively) compare favourably with those obtained[28] by the analysis of the carbon-13 satellite proton spectra. All methods agree that as the temperature is raised the chemical shift differences should approach a limiting value, owing to the intrinsic asymmetry. At infinite temperature the populations of all three rotamers will be equal, and so this limiting value should be the average of the chemical shifts within each rotamer. For the geminal fluorine atoms in $CF_2Br.CFBrCl$ the limiting value was found[29] to be 0·11 p.p.m. At very low temperatures, the three possible (±)-rotamers can be frozen out,[30] and the fluorine-19 spectrum is the superposition of the spectra of these three forms. Analysis of these spectra gives the chemical shift between the geminal fluorine atoms for each rotamer, and their average (0·09 p.p.m.)[31] agrees well with the above figure.

An interesting compound is the phthalide (13), for which the measured temperature-independent chemical shift (0·73 p.p.m.) between the methyl groups is said[32] to be due to intrinsic asymmetry. A temperature-independent spectrum

---

[26] G. M. Whitesides, F. Kaplan, K. Nagarajan, and J. D. Roberts, *Proc. Nat. Acad. Sci. U.S.A.*, 1962, **48**, 1112.

[27] J. N. Shoolery and B. Crawford, *J. Mol. Spectroscopy*, 1957, **1**, 270; J. A. Pople, *Mol. Phys.*, 1958, **1**, 3.

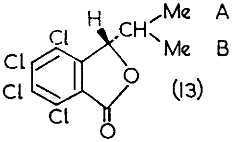
[28] N. Sheppard and J. J. Turner, *Proc. Roy. Soc.*, 1959, *A*, **252**, 506.

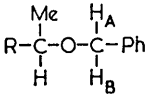
[29] H. S. Gutowsky, *J. Chem. Phys.*, 1962, **37**, 2196; H. S. Gutowsky, G. G. Belford, and P. E. McMahon, *ibid.*, 1962, **36**, 3353.

[30] R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, 1963, **39**, 3131; 1965, **43**, 602.

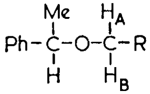
[31] M. Raban, *Tetrahedron Letters*, 1966, 3105.

[32] G. C. Brumlik, R. L. Baumgarten, and A. I. Kosak, *Nature*, 1965, **201**, 388.


(13)


(14)

$$R-\underset{H}{\overset{Me}{C}}-O-\underset{H_B}{\overset{H_A}{C}}-Ph$$


(15)

$$Ph-\underset{H}{\overset{Me}{C}}-O-\underset{H_B}{\overset{H_A}{C}}-R$$

can actually be observed[27] in three circumstances: (1) if one rotamer has a much lower energy than the others; (2) if all possible rotamers have almost equal energies; (3) if the energy barriers between the rotamers are high. Some interesting spectral types are shown in Table 2.

Table 2 *Some possible spectral types for substituted ethanes*

		Proton spectrum type	
Substituted ethane	*Slow rotation*[a]	*Fast rotation, unequal populations*[b]	*Fast rotation, equal populations*[a]
CH_3–$\overset{*}{C}XYZ$	ABC[c]	A_3	A_3
CH_2U–$\overset{*}{C}HXY$	3 × ABC[d]	ABC	ABC
CH_2U–$\overset{*}{C}XYZ$	3 × AB[d]	AB	AB
$\overset{*}{C}HUV$–$\overset{*}{C}HXY$	3 × AB[d]	AB	AB

[a] Not temperature-dependent; [b] Temperature-dependent; [c] Not yet reported; [d] Three overlapping spectra; * Indicate possible asymmetric carbon atoms. Enantiomers of each formula give identical spectra.
Table 2 is based upon that given by J. A. Pople, *Mol. Phys.*, 1958, **1**, 3.

In the case of longer substituted chains many conformational isomers become possible. An example is 2,3,5-tricyano-2,3,5-trimethylhexane, all five methyl groups of which can be magnetically non-equivalent. More interestingly, though, the chemical shift between the methylene protons increases[33] in many solvents on increase in temperature. This presumably means that a low temperature favours a conformation in which these protons experience almost identical shieldings.

It is now possible to generalise the conditions which must be satisfied in order that magnetic non-equivalence may be observed: (*a*) There must be no molecular symmetry operation which relates the nuclei concerned but not those nuclei to which they are spin-coupled. The plane of symmetry which relates A and A′

---

[33] P. Smith and J. J. McLeskey, *Canad. J. Chem.*, 1965, **43**, 2418.

in catechol (3) also relates B and B′ to which the protons A are coupled; A and A′ are thus magnetically non-equivalent. (*b*) Any molecular motions which are occurring rapidly compared with the n.m.r. time scale must not both correspond to such a symmetry operation and allow the nuclei to reside in the same environments for comparable times. (*c*) There must be a field gradient between the nuclei. In other words, the previous two conditions having been satisfied, if the (average) environments are insufficiently dissimilar then no magnetic non-equivalence will yet be observed.

The effect leading to satisfying condition (*c*) appears to be transmitted mainly spatially. The number of bonds is in itself not significant and the interacting sites may be quite far apart and not necessarily involve carbon atoms. In other words, non-equivalence of geminal nuclei can always be expected if there is present somewhere in the molecule a carbon atom with three different substituents. A selection of examples[25] is given in the following sections.

(ii) *Oxygen-containing compounds.* The two interacting groups may be separated by a bivalent atom such as oxygen[34] as in (14) and (15). The difficulties encountered in studying the various conformations of such compounds are considerably increased by the oxygen; the ether linkage has been insufficiently studied in this respect[35] for the possible conformers confidently to be predicted. The compounds (14) and (15) were however studied to help determine the manner in which an asymmetric centre exerts its influence. In (14) the chemical shift between A and B appears to increase the larger the group R which is a saturated alkyl chain; in the compounds (15) this is not so. Steric size at the chiral centre therefore plays some part. Roberts and his co-workers[34,36] considered that the shielding differences between A and B would result from two general effects. These are electronic differences in the two carbon–hydrogen bonds concerned, and differences in shielding by more distant parts of the molecule and solvent.

Now the protons in the methylene groups of diethyl sulphoxide[37] and diethyl sulphite[38] exhibit magnetic non-equivalence. The constants for the coupling between the methylene carbon-13 and each of the protons are said[34] to be equal in these cases. But for acetaldehyde diethyl acetal there are two distinct[39] such coupling constants, which are a sensitive indication of the bond character. They may therefore provide a new criterion for non-equivalence, since they should be[39] largely unaffected by the magnetic shielding contributions which complicate the interpretation of chemical shifts. They therefore probably reflect the first of the two effects considered by Roberts and his co-workers, and indicate that there are electronic differences in the two carbon–hydrogen bonds concerned.

Of the various factors considered possibly to affect shielding differences, (the

[34] G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1964, **86**, 2628.

[35] S. C. Abrahams, *Quart. Rev.*, 1956, **10**, 407.

[36] G. M. Whitesides, J. J. Grocki, D. Holtz, H. Steinberg, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1965, **87**, 1058.

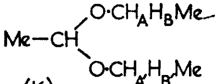
[37] K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, *J. Amer. Chem. Soc.*, 1965, **87**, 1958.

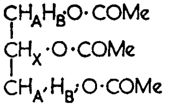
[38] F. Kaplan and J. D. Roberts, *J. Amer. Chem. Soc.*, 1961, **83**, 4666.

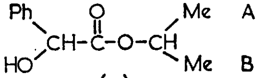
[39] L. S. Rattot, L. Mandel, and J. H. Goldstein, *J. Amer. Chem. Soc.*, 1967, **89**, 2253.

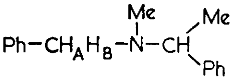
second effect), interactions with the solvent are significant. Chemical shift differences therefore form an unreliable measure of conformational equilibria.[7b] It has been shown[40] that for substituted ethanes the energy differences between the rotamers are not constant but are a function of both the dielectric constant and the temperature of the medium. A change of solvent may therefore affect the observed non-equivalence by altering conformer populations. However, the ring current[41] of the aromatic ring attached to the methylene group in (14) was considered the most important factor. This would mean that the chiral centre affects the conformation of the benzyl group in such a way that the two protons are in different positions relative to the aromatic ring. The experimental data do not suffice to decide whether the effects discussed are altering conformer populations or the intrinsic asymmetry contribution[6] or both.

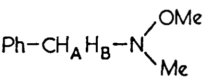
Various families of optically inactive compounds may contain nuclei which meet the conditions for observable magnetic non-equivalence. Diethyl acetals such[42] as (16) and triglycerides such as triacetin (17) have a molecular symmetry plane and consequently are optically inactive. However, this plane does not bisect the connecting line of the geminal protons, which are magnetically non-equivalent. This is manifested by the relative complexity of the AA′BB′X type proton spectrum of the glyceryl moiety of triacetin (Figure). Similar magnetic non-equivalence can be induced across an ester bond; *e.g.*, the two methyl groups of the isopropyl ester (18) are[43] non-equivalent.


(16)


(17)


(18)


(19)


(20)

(iii) *Nitrogen-containing compounds.* The asymmetry effect in a molecule can be transmitted across a nitrogen atom similarly to the way it is transmitted across an oxygen. The methylene protons of (19) are[44] non-equivalent, probably for this reason. However, non-equivalence may be caused by the nitrogen atom itself. One cause may be a sufficiently slow inversion of a trigonal nitrogen atom. The two methylene protons of the substituted hydroxylamine (20) are non-equivalent at low temperatures, and this can be explained on the assumption of

---

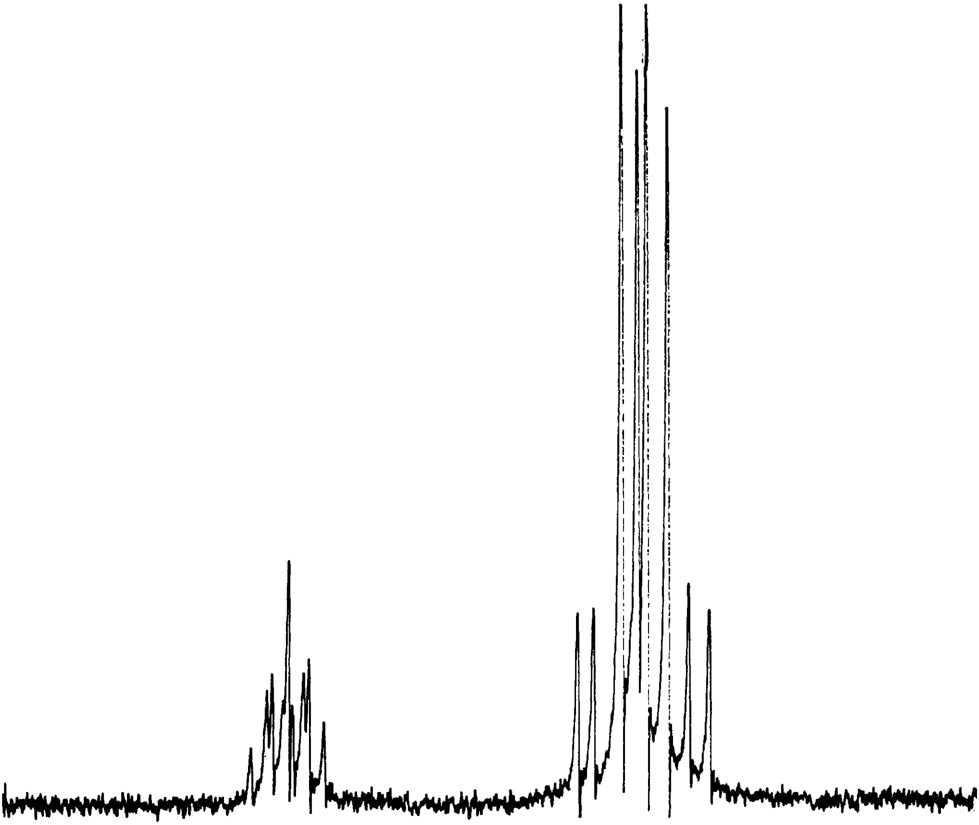
[40] R. J. Abraham, L. Cavalli, and K. G. R. Pachler, *Mol. Phys.*, 1966, **11**, 471; R. Freeman and N. S. Bhacca, *J. Chem. Phys.*, 1966, **45**, 3795.

[41] H. P. Figeys, *Tetrahedron Letters*, 1966, 4625; J. I. Musher, *J. Chem. Phys.*, 1965, **43**, 4081.

[42] P. R. Shafer, D. R. Davis, M. Vogel, K. Nagarajan, and J. D. Roberts, *Proc. Nat. Acad. Sci. U.S.A.*, 1961, **47**, 49.

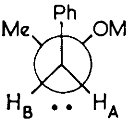
[43] N. S. Bowman, D. E. Rice, and B. R. Switzer, *J. Amer. Chem. Soc.*, 1965, **87**, 4477; C. van der Vlies, *Rec. Trav. chim.*, 1965, **84**, 1289.

[44] T. H. Siddall, *J. Phys. Chem.*, 1966, **70**, 2249.

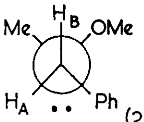


The 100 *Mc./sec. spectrum of the glyceryl protons of triacetin.*

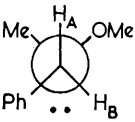
a non-planar nitrogen atom, as in the conformers (21)—(23). The energy barrier to umbrella inversion was found[45] to vary inversely with the dielectric constant of the medium.



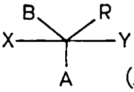
(21)



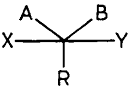
(22)



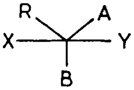
(23)



(24)



(25)

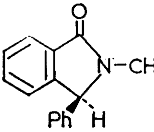


(26)

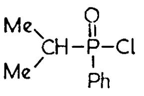
[45] D. L. Griffith and J. D. Roberts, *J. Amer. Chem. Soc.*, 1965, **87**, 4089.

However, although a non-planar nitrogen atom probably introduces a greater asymmetry, a planar nitrogen (or a nitrogen atom pseudo-planar owing to rapid inversion) may introduce sufficient asymmetry for observable magnetic non-equivalence. There is confusion in the literature[46,47] as to the conformations in which a compound containing a planar trisubstituted atom exists. However, by arguments similar to those used to demonstrate that the average environments of A and B in (10)—(12) are not identical it may be seen that A and B in the conformers (24)—(26) have differing average environments. The compound (27), in which the methylene protons are[48] magnetically non-equivalent, may be an example of such a situation. It appears that before invoking a slow nitrogen inversion on the basis of magnetic non-equivalence, some independent evidence ought to be obtained.

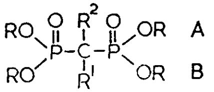
(iv) *Phosphorus-containing compounds.* Other multivalent atoms may introduce the requisite degree of low symmetry into a molecule. For example, the tetraco-ordinated, approximately tetrahedral phosphorus atom can induce magnetic non-equivalence. Proton n.m.r. spectra[49] of (28) and its analogues show that the two methyl groups are non-equivalent. In compounds (29) if R = 2-propyl the



(27)



(28)

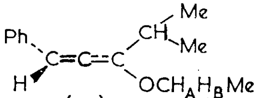


(29)

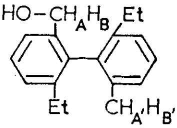
two methyl groups may similarly[44] be non-equivalent even if $R^2 = R^1$ [since the phosphorus atom has three different groups attached to it; see Section 3 (i)]. If $R^2 \neq R^1$ then the two R groups can also be distinguishable, as there is then no symmetry plane relating these two groups on each phosphorus.

A trico-ordinated phosphorus atom may[50] also introduce magnetic non-equivalence in a molecule.

(v) *Allenes, biphenyls, and other aromatic compounds.* The examples discussed so far have been concerned with compounds in which the required low order of symmetry is related to a chiral centre. Other types of chirality[17] may cause



(30)



(31)

---

[46] Ref. 21, p. 50; J. A. Elvidge, in 'Nuclear Magnetic Resonance for Organic Chemists', ed. D. W. Mathieson, Academic Press, London, 1967, p. 39; I. S. Showell, *Progr. Chem. Fats and Other Lipids*, 1965, **8**, 275.

[47] E. L. Eliel, 'Stereochemistry of Carbon Compounds', McGraw-Hill, New York, 1962, p. 155.

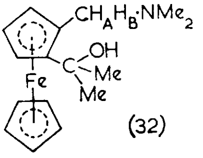
[48] A. H. Lewin, J. Lipowitz, and T. Cohen, *Tetrahedron Letters*, 1965, 1241.

[49] T. H. Siddall and C. A. Prohaska, *J. Amer. Chem. Soc.*, 1962, **84**, 2502, 3467.

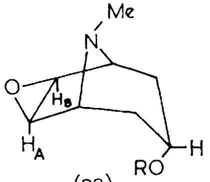
[50] T. H. Siddall, C. A. Prohaska, and W. E. Shuler, *Nature*, 1961, **190**, 903.

magnetic non-equivalence. The allenes (30) serve as examples of axial chirality, the methylene protons of the ethyl group being[51] non-equivalent. The (hydroxy) methylene protons of the biphenyl (31) are[52a] similarly non-equivalent. If the stable biphenyl conformers occur with the aromatic rings at right-angles to one another, then such magnetic non-equivalence can only be observed if rotation around the bond between the rings is slow since a rotation through 180° exchanges the environments of the two protons in the methylene groups. This rotation is the process by which an optically active biphenyl would be racemised. Consequently, a temperature study of the spectra of a compound such as (31) can yield information on the racemisation process[52b] without recourse to optical resolution.

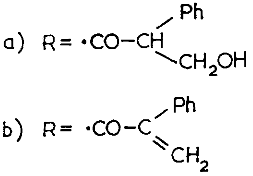
The protons of the unsubstituted ring in monoacetyl-ferrocene, -ruthenocene, and -osmocene produce a sharp[53] singlet. This is due to the fast rotation of the five-membered ring, as is typical[54] for metallocenes. However, non-equivalence of the methylene protons in the side-chain of the ferrocene derivative (32) is[55] observed. This observation is presumably related to the non-equivalence of the methylene protons of *NN*-dimethylbenzylamines[56] with *ortho* or *meta* substituents lacking symmetry. A similar example is the non-equivalence of the two methyl groups of an isopropyl residue[57] attached to a highly substituted naphthalene nucleus. The exact cause of such magnetic non-equivalence has not been established, but may be explicable in terms of conformers such as (24)—(26) in which X–Y would represent the asymmetrically substituted aromatic nucleus. However, not only interspatial effects but also the influence[56] of asymmetry induced in the molecular electronic system might be important.



(32)



(33)



(vi) *Vicinal atoms.* The previous examples have been concerned with demonstrating that some low order of symmetry may cause two geminal (groups of) nuclei to be magnetically non-equivalent. Similar effects can be observed with two vicinal groups. One example of this is the non-equivalence of protons A and B in (33a) and their equivalence in (33b).[58]

---

[51] M. L. Martin, R. Mantione, and C. J. Martin, *Tetrahedron Letters*, 1965, 3185.

[52] (*a*) W. L. Meyer and R. B. Meyer, *J. Amer. Chem. Soc.*, 1963, **85**, 2170; (*b*) D. M. Hall and T. M. Poole, *J. Chem. Soc.* (*B*), 1966, 1034.

[53] M. D. Rausch and V. Mark, *J. Org. Chem.*, 1963, **28**, 3225.

[54] M. Rosenblum and R. B. Woodward, *J. Amer. Chem. Soc.*, 1958, **80**, 5443.

[55] P. Smith, J. J. McLeskey, and D. W. Slocum, *J. Org. Chem.*, 1965, **30**, 4356.

[56] J. C. Randall, J. J. McLeskey, P. Smith, and M. E. Hobbs, *J. Amer. Chem. Soc.*, 1964, **86**, 3229.

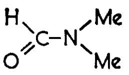
[57] F. Conti, C. H. Eugster, and W. von Philipsborn, *Helv. Chim. Acta*, 1966, **49**, 2267.

[58] S. R. Johns and J. A. Lamberton, *Chem. Comm.*, 1965, 458.

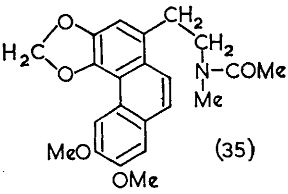
4 Temperature-dependent Magnetic Non-equivalence in other than Ethane-type Molecules

Any process which effectively exchanges the environments of two nuclei will cause time-averaged equivalence of the nuclei if the process is fast on the n.m.r. time scale. If the rate of the process is temperature-dependent and comparable with the n.m.r. time scale (which is a function of the magnetic field strength employed) the spectra and any magnetic non-equivalence observed will be a function of temperature.

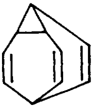
A. Intramolecular Processes.—Owing to the partial double bond between, and hence the restricted rotation around, the carbonyl–nitrogen bond of *NN*-dimethylformamide (34), two methyl signals may be observed. These correspond to methyls *cis* and *trans* to the carbonyl group. As the temperature is raised the rate[10,59] of the relevant rotation increases, the spectra alter, and finally no non-equivalence is observed. The phenanthrene derivative (35) exists as two distinct molecular species which give[60] overlapping spectra. These species, one of which has the methyl group *cis* to the carbonyl and the other the methyl *trans*, are interconverting by rotation. There is thus an important difference between this example and dimethylformamide, in which non-equivalence of the two methyl groups occurs within the single molecular species.



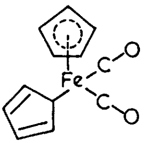
(34)



(35)



(36)



$(\pi-C_5H_5)Fe(CO)_2C_5H_5$

(37)

Valence isomerisation can cause similar effects. The proton spectrum[61] of bullvalene, one form of which is shown in (36), at low temperatures consists of two bands, corresponding to the six olefinic and the four allylic protons. As the temperature is raised, the Cope rearrangements become easier and at room temperature only a single resonance, close to the weighted average of the other two, is observed. Organometallic compounds also undergo processes which can affect the appearance of the n.m.r. spectra. An *X*-ray crystallographic analysis

---

[59] L. W. Reeves, in 'Advances in Physical Organic Chemistry', ed. V. Gold, Academic Press, London, 1965, vol. 3, p. 196; W. D. Phillips, *Ann. New York Acad. Sci.*, 1958, **70**, 817.

[60] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Chem. Comm.*, 1966, 480.

[61] G. Schröder, *Angew. Chem.*, 1963, **75**, 722.

of (37) has shown[62] the structure to be that given; the second C_5H_5 group is present as a normal σ-bonded 2,4-cyclopentadienyl group. In solution at room temperature, the proton spectrum consists of two singlets. The five protons of this second C_5H_5 group are evidently all equivalent. A study of this resonance as a function of temperature has led to the conclusion that a rapid intramolecular reorientation process occurs, possibly by repeated 1,2-shifts. Such organometallic compounds ('sterically non-rigid') are thus phenomenologically related to the 'fluxional' structures typified by bullvalene. Similar averaging processes have also been postulated[63] to occur in trisallylrhodium to account for some otherwise fortuitous magnetic equivalences.

B. Intermolecular Processes.—If a molecule containing two or more equivalent nuclei interacts with the solvent or with some third material, magnetic non-equivalence may arise either by conversion into a new species or by conformational changes. Clearly the reverse may also occur. Since the extent of interaction is ordinarily a function of temperature the spectra observed will change with temperature.

(i) *Solvent effects.* There has been considerable interest recently in inducing non-equivalence by the use of a suitable solvent. The magnetic anisotropy of aromatic compounds such as benzene, pyridine,[64] and quinoline[65] is normally exploited for this purpose. The technique has been frequently employed in the steroid field.[64] Orientation occurs[66] in the collision complex and so different parts of the molecule may experience different shielding effects. For example, the C(12) axial and equatorial protons in 2β-epoxy-5α-androstan-11-one have practically identical chemical shifts in deuteriochloroform, but in benzene[64] solution are non-equivalent.

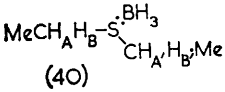
The method has been extended to distinguish two enantiomers. Racemic 2,2,2-trifluoro-1-phenylethanol (38) gives two overlapping spectra[67] in an optically active base. The two types of collision complex formed between the base and the two forms of the alcohol are diastereomeric, and consequently

$PhCH(OH)\cdot CF_3$

(38)

$Ph\cdot CH_AH_B\cdot \overset{+}{N}HMe\cdot CH_{A'}H_{B'}Ph$

(39)



$MeCH_AH_B-\overset{\cdot BH_3}{S}-CH_{A'}H_{B'}Me$

(40)

---

[62] M. J. Bennett, F. A. Cotton, A. Davison, J. W. Faller, S. J. Lippard, and S. M. Morehouse, *J. Amer. Chem. Soc.*, 1966, **88**, 4371; P. von R. Schleyer, J. J. Harper, G. L. Dunn, V. J. DiPasquo, and J. R. E. Hoover, *J. Amer. Chem. Soc.*, 1967, **89**, 698.

[63] J. K. Becconsall and S. O'Brien, *Chem. Comm.*, 1966, 720.

[64] N. S. Bhacca and D. H. Williams, 'Applications of N M R Spectroscopy in Organic Chemistry', Holden-Day, San Francisco, 1964, ch. 7.

[65] A. P. Tulloch, *J. Amer. Oil Chemists' Soc.*, 1966, **43**, 670.

[66] J. Ronayne and D. H. Williams, *Chem. Comm.*, 1966, 712.

[67] W. H. Pirkle, *J. Amer. Chem. Soc.*, 1966, **88**, 1837; J. C. Jochens, G. Taigel, and A. Selinger, *Tetrahedron Letters*, 1967, 1901.

the trifluoromethyl groups are in different environments. This means that the presence of optical isomers can be established without optical resolution, and the optical purity checked by the relative intensity of the overlapping spectra.

Normally, high-resolution n.m.r. experiments are deliberately obtained under conditions in which both the solute and solvent molecules are tumbling rapidly. In this way, direct dipole–dipole interactions are averaged. However a new field may be opened up if liquid crystals[68] are used as the anisotropic solvent. Such nematic phases as *pp'*-di-n-hexyloxyazoxybenzene cause large-scale ordering of the solute molecules, and[69] additional lines, due to intramolecular dipole–dipole interactions, are observed.

(ii) *Reaction with a third material.* If the solute reacts with some other compound in the solution, the molecular symmetry may be altered. For example, the methylene protons of the benzylamines are generally equivalent. However, in the presence of trifluoroacetic acid the protonated species (*e.g.*, 39) is formed,[70] and the protons A and B are magnetically non-equivalent. Again, diethyl sulphide gives a normal 1 : 3 : 3 : 1 quartet for the methylene protons, but it reacts with borane to give an addition compound (40) of reduced symmetry[71] and the methylene protons A and B of this adduct are magnetically non-equivalent. If dimerisation of a compound occurs in solution[72] similar spectral changes may be observed. As an example, the *meso* protons of certain[72] porphyrin tetramethyl esters give the expected singlet signals in dilute solution, but in concentrated solutions extra signals owing to dimerisation.

(iii) *Exchange reactions.* The copper-63 resonance of a mixture of the copper(I) and copper(II) ions in water consists[73] of a single peak. This is due to a rapid electron-transfer reaction between the two types of ion, which then appear to be equivalent. On the other hand, the rate of exchange between bulk water molecules and water molecules bound to cobalt(II) ions may be slow at certain temperatures. In this case two signals may be observed for the oxygen-17 resonance of the water molecules[74] and the relative areas of the resonances give an indication of the hydration number of the cobalt(II) ion.

5 Interpretation of Spectra

Before concluding it is worth drawing attention to some pitfalls that can be met in certain circumstances. The concept of magnetic equivalence is not absolute but is briefly an observational property. In this way it is a somewhat negative

---

[68] G. W. Gray, 'Molecular Structure and the Properties of Liquid Crystals', Academic Press, London, 1962; D. Chapman, *Science Journal*, 1965, Oct. 1, 32.

[69] A. Saupe, *Z. Naturforsch.*, 1964, **19a**, 161; S. Meiboom and L. C. Snyder, *J. Amer. Chem. Soc.*, 1967, **89**, 1038; R. A. Bernheim and B. J. Lavery, *ibid.*, p. 1279; J. I. Musher, *J. Chem. Phys.*, 1967, **46**, 1537.

[70] W. F. Reynolds and T. Schaefer, *Canad. J. Chem.*, 1964, **42**, 2119.

[71] T. D. Coyle and F. G. A. Stone, *J. Amer. Chem. Soc.*, 1961, **83**, 4138.

[72] R. J. Abraham, P. A. Burbidge, A. H. Jackson, and D. B. Macdonald, *J. Chem. Soc. (B)*, 1966, 620.

[73] H. M. McConnell and H. E. Weaver, *J. Chem. Phys.*, 1956, **25**, 307.

[74] J. A. Jackson, J. F. Lemons, and H. Taube, *J. Chem. Phys.*, 1960, **32**, 553; I. R. Lantzke and D. W. Watts, *Austral. J. Chem.*, 1967, **20**, 173.

feature, since its validity may depend on the experimental conditions such as the operating magnetic field strength and homogeneity. As an example, the aromatic protons of toluene and cumene give an unsplit singlet at 60 Mc./sec., but well-resolved[75] analysable resonance lines at 200 Mc./sec. It is therefore dangerous to rely on negative n.m.r. evidence; apparent equivalence must not be interpreted as proving the nuclei involved to be identical.

It is also dangerous to assume that measured splittings necessarily correspond to the coupling constants involved, since the first-order interpretation rules[76] may only be applied to groups of magnetically equivalent nuclei. The ABX system has been fully discussed[77] in this respect. Failure of first-order rules is sometimes manifested by virtual coupling.[78] When in three sets of nuclei the first set is coupled to the second which is also coupled to the third, the spectrum of the first set of nuclei may appear more complicated owing to virtual coupling with the third set even if the real coupling is zero.

6 Conclusion

The magnetic non-equivalence which has been the main concern of this Review arises from quite subtle differences in (average) environment or conformer populations. The existence of these differences does not necessarily lead to observable non-equivalence. So far, most workers have attempted to accentuate such potential differences by means of a magnetically anisotropic group such as cyano or phenyl. Any resulting magnetic non-equivalence can normally be qualitatively explained on topological grounds after observation, but quantitative prediction is virtually impossible. More research is required regarding interaction between groups. An awareness of the possibility of otherwise unexpected magnetic non-equivalence is important in spectral interpretation.

When two atoms (or groups) are distinguishable in an n.m.r. spectrum they may sometimes be differentiated chemically. For example, the methylene protons of methyl benzyl sulphoxide[79] are magnetically non-equivalent, and on reaction with sodium deuteroxide the resonances due to the lower-field proton disappear more rapidly than those of the higher-field proton. The fact that the two protons of a methylene group in biologically important materials such as triglycerides can be distinguished may assist in showing enzymic preference for one particular proton.

[75] F. A. Bovey, F. P. Hood, E. Pier, and H. E. Weaver, *J. Amer. Chem. Soc.*, 1965, **87**, 2060.
[76] E. D. Becker, *J. Chem. Educ.*, 1965, **42**, 591.
[77] J. D. Roberts, 'An Introduction to the Analysis of Spin–Spin Splitting in High Resolution Nuclear Magnetic Resonance Spectra', W. A. Benjamin, New York, 1962, p. 71.
[78] J. I. Musher and E. J. Corey, *Tetrahedron*, 1962, **18**, 791; D. L. Hooper, N. Sheppard, and C. M. Woodman, *J. Chem. Phys.*, 1966, **45**, 398.
[79] A. Rauk, E. Buncel, R. Y. Moir, and S. Wolfe, *J. Amer. Chem. Soc.*, 1965, **87**, 5498.