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THE DETERMINATION OF OPTICAL PURITY BY NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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We wish to call attention to a convenient method for the determination of optical purities.

There are two approaches to the problem of determining the optical purity of a mixture of enantiomers A and $\bar{A}$. The first approach involves partial or total separation of A and $\bar{A}$. The isotope dilution method (1), the kinetic resolution method of Horeau (2), and the enzymatic methods (3) fall into this category. This category also includes the "methods of total resolution" which involve (a) physical separation of the enantiomers, or (b) conversion of the mixture of enantiomers A and $\bar{A}$ into a mixture of diastereomers AB and $\bar{A}B$ by complete reaction with a dissymmetric reagent B, or (c) complete conversion of a mixture of diastereomers AB and $\bar{A}B$ into a mixture of enantiomers A and $\bar{A}$. In cases (b) and (c), the diastereomeric composition is determined by separation of the diastereomers and, from the ratio R of diastereomers $AB/\bar{A}B$, which equals the ratio of precursor or product enantiomers $A/\bar{A}$, the optical purity $(R-1)/(R+1)$ is readily calculated. Such an estimation of diastereomeric ratios is achieved with particular convenience by gas-liquid chromatography (g.l.c.) (4). The same ratio might be estimated more directly, if less conveniently, by chromatography of the mixture of enantiomers A and $\bar{A}$ on an optically active substrate (5); in this case

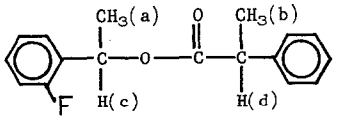
one deals with diastereomeric interactions rather than with diastereomeric compounds.

In the second approach, the enantiomers A and $\bar{A}$ are not separated. For example, polarimetry (as well as optical rotatory dispersion and circular dichroism) and correlative methods (6) provide a measure of optical purity which does not involve the physical separation of A and $\bar{A}$. It should now be pointed out that the determination of optical purities may also be achieved by the measurement of ratios R of precursor or product diastereomers AB and $\bar{A}B$ without physical separation of the diastereomers. In principle, this method requires the measurement of two associated parameters. One corresponds to a structure-dependent intensive property and must give distinguishable values for the two diastereomers. The other is an extensive parameter which must be structure-independent and which must provide a measure of the relative quantities of the two diastereomers. Nuclear magnetic resonance chemical shifts and integrated intensities suggest themselves as two convenient parameters for this purpose. It is well known that diastereomers differ in their n.m.r. spectra (7).

Because a physical separation is not necessary when n.m.r. is used to analyze diastereomeric mixtures, this approach may be successful even in those cases in which bulk properties (e.g. boiling point, solubility, etc.) are not different enough to effect a significant difference in g.l.c. retention times. Fluorine n.m.r. may be especially useful for N-trifluoroacetyl derivatives of amino acids and peptides.

To illustrate the correspondence between analytical results obtained by g.l.c. and those obtained by n.m.r. we have examined a mixture of diastereomers of compound 1, prepared from 1-(o-fluorophenyl)-ethanol and 2-phenylpropanoyl chloride (liquid, distilled [Kugelrohr] at ca. 85°/0.40 torr. Found: C, 75.02; H, 6.49; F, 6.71. Calcd. for $C_{17}H_{17}FO_2$:

C, 74.97; H, 6.29; F, 6.98).



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Analysis by g.l.c. on a 2 m. column of 10% Apiezon on Chromosorb-W at 180°C revealed the presence of two nicely separated components with retention times of 41 and 47 min., in a ratio of 67/33.

The 60 mc p.m.r. spectrum in carbon tetrachloride featured an aromatic multiplet at τ 3.0 p.p.m. (fluorophenyl) and a singlet at τ 2.8 p.p.m. (phenyl). The A portions of two AX_3 systems appeared as quartets centered at τ 3.89 p.p.m. (J = 6.7 c.p.s.) and τ 6.30 p.p.m. (J = 7.1 c.p.s.) and were assigned to methine protons H_c and H_d respectively (Figure 1). Evidently the chemical shifts and coupling constants of H_c as well as of H_d in the two components of the diastereomeric mixture are almost equal in that solvent, although the H_d quartet exhibits shoulders indicative of a similar but less intense quartet displaced about 0.8 c.p.s. toward higher fields. The methyl resonances appeared as two doublets (Figure 1). The weaker doublet, centered at τ 8.63 p.p.m., was assigned to H_a in the minor component of the diastereomeric mixture since J = 6.6 c.p.s. The high-field member of the stronger doublet, centered at about 8.54 p.p.m. (J = 7.1 c.p.s.), evinced a shoulder indicative of a superimposed doublet with a slightly smaller coupling constant. These superimposed doublets were assigned to H_a in the major component of the diastereomeric mixture and to H_b in <u>both</u> components. Integration of the methyl resonances indicated a diastereomeric ratio of 68/32, in good agreement with the result of the g.l.c. analysis. Integration of the entire p.m.r. spectrum showed that the weak pair of signals centered at τ 8.63 p.p.m. was not due to a contaminant.

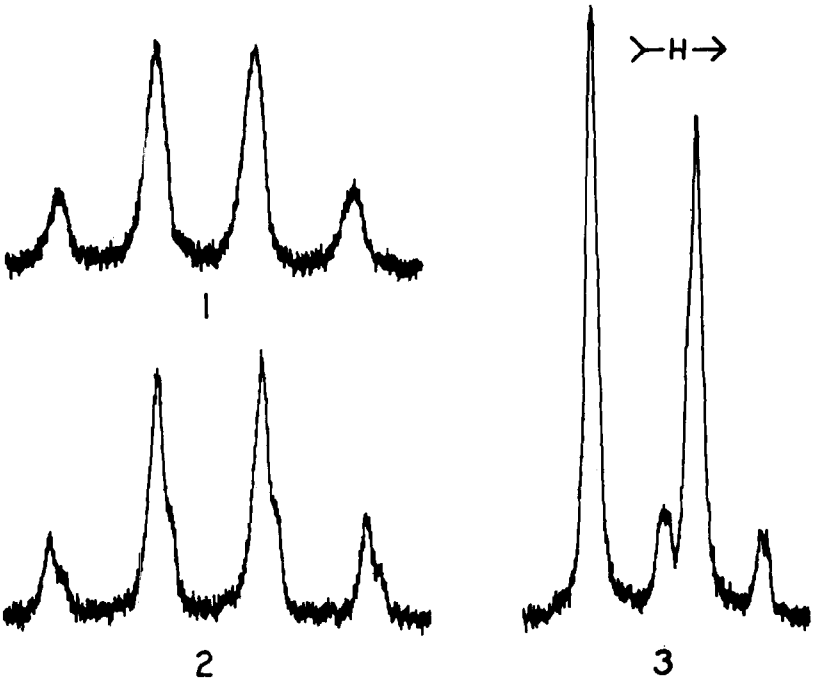

FIG. 1

Portions of the p.m.r. spectrum of 1 showing methine proton $H_c(1)$, methine proton $H_d(2)$ and methyl protons H_a and $H_b(3)$.

Optical purity might in principle be determined more directly by an examination of the n.m.r. spectrum of a mixture of enantiomers A and $\bar{A}$ in an optically active solvent; here again one deals with diastereomeric interactions rather than with diastereomeric compounds. However, no examples of this phenomenon have yet come to our attention.

It must be emphasized that, of the methods discussed above, only the isotope dilution method, chromatography of mixtures of enantiomers on optically active substrates, and n.m.r. spectroscopy of mixtures of

enantiomers in optically active solvents are "absolute" in the sense that only they are capable of providing a direct measure of the optical purity without recourse to a standard whose optical purity is already known.

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