Stereochemistry of Organic Compounds

ERNEST L. ELIEL
Department of Chemistry
The University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

SAMUEL H. WILEN
Department of Chemistry
The City College of the City University of New York
New York, New York

With a Chapter on Stereoselective Synthesis by

LEWIS N. MANDER
Research School of Chemistry
Australian National University
Canberra, Australia

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was ascribed to conformational rigidity and to the presence of isotactic helical blocks of a preferred helical sense in the copolymer. A similar example of such a cooperative phenomenon (with a resulting high optical rotation) involving a copolymer consisting of mostly achiral poly(*n*-hexyl isocyanate) incorporating as little as 0.12 mol% of a nonracemic chiral isocyanate [(*S*)-(−)-2,2-dimethyl-1,3-dioxolane-4-methylene isocyanate] has been described (Green et al., 1989).

> Attachment of achirotopic chromophoric groups such as dehydrophenylalanine and azobenzene to polypeptides [e.g., poly(L-glutamic acid)] generates synthetic macromolecules whose CD spectra reflect the presence of inherently chiral chromophores. This spectral feature results because the pendant side chains serve as chirality reporters of the secondary structure of the peptides (Ciardelli and Pieroni, 1980).

In subsequent studies on dimethyloctene–styrene and similar copolymers, the CD could be measured deeper into the UV spectral region. Other CD bands typical of isolated benzenoid electronic transitions (^1B and ^1L_a) signaling the chirotopicity of the benzene ring were observed. In contrast to model compounds, such as the conformationally restricted 2-phenyl-3,3-dimethylbutane (Salvadori et al., 1972), the copolymer exhibits, in addition, an exciton-like couplet centered at about 190 nm. The latter was attributed to a helical conformation in which benzene rings in the same chain are sufficiently close to couple. The enantiomer exhibiting negative chirality incorporates a right handed helix (Ciardelli et al., 1972). The CD of such helical copolymers can be calculated by means of a classical theory developed by DeVoe (DeVoe, 1969, 1971; see Hug et al., 1974 and Section 13-4.a).

It is only since the 1980s that CD studies have permitted the observation of CEs in the vacuum UV region of hydrocarbon polymers devoid of aromatic groups. The CD spectra of films of poly-(*S*)-4-methyl-1-hexene and poly-(*R*)-3,7-dimethyl-1-octene exhibit a CD band at 158 nm that is ascribed to conformations containing helical segments having a common helix sense (Ciardelli and Salvadori, 1985).

13-5. APPLICATIONS OF OPTICAL ACTIVITY

a. Polarimetry

The actual measurement of optical activity may be carried out with either manual or photoelectric polarimeters. Manual polarimeters have changed relatively little since the first instruments were developed some 140 years ago (Lowry, 1964, p. 180). Photoelectric polarimeters, the type nowadays commonly found in research laboratories, have greatly reduced the tedium formerly associated with the measurement of optical rotation with manual instruments. Moreover, photoelectric polarimeters are much more accurate and sensitive, permitting the rapid and meaningful recording of quite small absolute rotation values α to about $\pm 0.002°$ and, consequently, the use of smaller samples. Polarimeters fitted with microcells may even serve advantageously as detectors in HPLC resolutions (Mannschreck,

Eigelsperger, and Stühler, 1982; Mannschreck, 1992; Pirkle, Salvadori, et al., 1988; Lloyd and Goodall, 1989). A laser-based polarimetric HPLC detector has been shown to be sensitive to as little as 12 ng of sample (Yeung et al., 1980). For the advantages of the use of CD detectors in HPLC, see Salvadori, Bertucci, and Rosini (1991); Mannschreck (1992).

The laser polarimetric detector has been adapted to HPLC analysis not only of optically active samples but also, in a different way, as a universal detector for *achiral*, that is, optically inactive, substances. In this technique, termed "indirect polarimetry," the mobile phase is optically active, containing, for example (−)-2-methyl-1-butanol or (+)-limonene, and the detector output due to the optically active solvent is zeroed. Under these conditions, any optically inactive fraction passing through the detector cell is sensed since the concentration of the optically active solvent is thereby reduced. The response of the detector is universal, like that of a refractive index detector, but is more sensitive than the latter (Bobbitt and Yeung, 1984, 1985; Yeung, 1989). The simultaneous measurement of absorbance and optical rotation during the liquid chromatographic resolution of chiral substances on enantioselective stationary phases make possible the determination of the enantiomer composition in spite of extensive peak overlap (Mannschreck et al., 1980; Mannschreck, Eigelsperger, and Stühler, 1982; compare Drake, Gould, and Mason, 1980).

For a brief discussion of polarimetry and its instrumentation, see the review by Lyle and Lyle (1983); for a more extensive treatment, see Heller and Curmé (1972).

The measurement of optical activity has traditionally been the method of choice to establish the nonracemic character of a sample of a chiral compound and, when quantitatively expressed as a ratio $[\alpha]/[\alpha]_{max}$, of its enantiomeric composition (optical purity). In contemporary practice, chiroptical measurements have to a large extent been replaced by NMR and by chromatographic analyses for the purpose of determining enantiomeric compositions (cf. Chapter 6). Nevertheless, the use of $[\alpha]$ for this and other purposes continues. The reasons are that the measurement is easy to carry out and one may wish to compare experimental values of $[\alpha]$ with those in the literature. While substantial collections of optical rotation data exist, for example those in various handbooks and chemical supplier catalogs, it should not be assumed that values of $[\alpha]$ provided are those of enantiomerically pure compounds. A consistent set of specific rotation data for amino acids including temperature coefficients has been compiled by Itoh (1974).

Optical activity has been used (*a*) to determine if a given unknown substance is chiral or achiral; (*b*) to ascertain the enantiomeric composition of chiral samples, either qualitatively or quantitatively; (*c*) to study equilibria; the mutarotation or change in rotation of equilibrating stereoisomers as a function of time is one such phenomenon (Eliel, 1962; for a recent example, see Arjona, Pérez-Ossorio, et al., 1984); and (*d*) to study reaction mechanisms. Other chiroptical techniques, namely, ORD and CD, have increasingly replaced polarimetry in these applications, especially in the past 20 years. For reviews of applications of polarimetry, see Lowry (1964), Eliel (1962), Legrand and Rougier (1977), and Purdie and Swallows (1989).

Polarimetric methods remain useful for quality control in pharmacology and

food-related industries (Lowman, 1979; Chafetz, 1991); there are also numerous applications in forensic, clinical, pharmaceutical, and agricultural chemistry (Purdie and Swallows, 1989). The percentage of sucrose in commercial samples is still being determined by polarimetry (saccharimetry); in the trade this is called "direct polarization". The cost of raw sugar is based on the results of the polarimetric analysis; if the analyte solution is dark, the raw sugar is first clarified by precipitation of the dark side products with basic lead acetate (Cohen, 1988). An example of application *d* (above) is the methanolysis of the tosylate of (R)-(+)-$C_6H_5CH_2SCH_2CH(CH_3)CH_2OH$ that leads to a partially racemized methyl ether. The intervention of a cyclic (symmetrical, and hence achiral) intermediate, via neighboring group participation, was inferred (Eliel and Knox, 1985).

The magnitude of rotation α, in degrees, fundamentally depends on the number of molecules of the sample being traversed by the linearly polarized light as well as on their nature, hence optical activity is not a colligative property. Values of α are affected by many variables, among which are wavelength, solvent, concentration, temperature, and presence of soluble impurities. It must also be mentioned that large molecules, such as proteins, may spontaneously orient themselves in solution, and consequently no longer be isotropic. The measurement of the rotatory power of such substances may then be complicated by the occurrence of linear dichroism (see Heller and Curmé, 1972, p. 67).

As already pointed out in Section 1-3 (q.v.), rotation magnitudes are usually normalized to a quantity called the *specific rotation* $[\alpha]$ that was introduced by Biot in 1835 (Biot, 1835; cf. Lowry, 1964, p. 22), Eq. 13.28,

$$[\alpha] = \alpha/\ell\rho = \alpha/\ell c \tag{13.28}$$

where ℓ is the length of the cell in decimeters, ρ (for undiluted liquids) is the density in grams per milliliter ($g\,mL^{-1}$) and c is the concentration also in grams per milliliter. The units of $[\alpha]$ are $10^{-1}\,deg\,cm^2\,g^{-1}$ (see also Eq. 1.1 and Section 1-3).

Comparison of specific rotations of homologues, and of organic compounds generally, is more significant if a modified Biot equation is used in which the quantity called the *molar rotation* $[\Phi]$ depends on the number of moles of substance traversed by the linearly polarized light, Eq. 13.29.

$$[\Phi] = [\alpha]M/100 \tag{13.29}$$

where M is the molecular weight. The units of $[\Phi]$ are $10\,deg\,cm^2\,mol^{-1}$ (see also Eq. 1.2) (IUPAC, 1986).

The cumulative effect of the above-mentioned variables on $[\alpha]$ or $[\Phi]$ is potentially very large. A practical consequence is that precise reproduction of published rotation values, from laboratory to laboratory, or even from day to day in the same laboratory, is difficult to achieve (Lyle and Lyle, 1983). This sensitivity to numerous variables (Schurig, 1985) and the absence of major tabulations of critically evaluated absolute rotation data is responsible for the decreasing reliance on optical activity as a measure of enantiomeric composition.

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