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Enantiomer Separations

Kurt Günther
Industriepark Wolfgang GmbH, Hanau, Germany
Klaus Möller
MACHEREY-NAGEL GmbH & Co. KG, Dueren, Germany

I. INTRODUCTION

Because of different biological activities on enantiomers of active ingredients, the preparation of highly enantio-pure compounds is of utmost importance (1–10). Frequently, only one of the two antipodes is pharmaceutically active, while the other may be at best inactive or even toxic.

Only about 20% of the optically active pharmaceuticals are sold as pure enantiomers (11). This has resulted in an increasing interest in stereoselective syntheses based on chiral intermediates. The production of these so-called auxiliaries ultimately requires enantiomerically pure natural substances, with optically active amino acids playing an important part as a chiral pool. Consequently, efficient analytical procedures for control of optical purity are needed to supplement modern procedures for asymmetric synthesis.

Polarimetry is used in many laboratories for control of optical purity. However, this method suffers from some well-known specific drawbacks. Furthermore, calculation of the enantiomeric excess from optical rotation is often impossible because the specific rotation of the pure enantiomer is not known precisely, or calculated enantiomeric excess values may be incorrect owing to impurities. For these reasons direct chromatographic analytical procedures are preferred.

Because simple separation techniques are not known, gas chromatographic (8,12–16) and high-pressure liquid chromatographic (8,17–26) and capillary electrophoresis (27) procedures are generally used for direct determination of enantiomeric composition. These systems require costly equipment; sometimes sample derivatization is necessary; and for routine applications, standardized stationary phases must be commercially available.

Application of thin-layer chromatography (TLC) separation techniques is desirable, especially with large test series. Furthermore, TLC allows simple reaction control of a synthesis—on the spot—by laboratory personnel.

The present review discusses the versatile applicability and separation mechanisms of thin-layer chromatographic enantiomeric separations. R_f values and separation conditions for numerous classes of racemic compounds are summarized in tabular form. More detailed descriptions are given for practical applications—separations of underivatized samples—on commercially available, ready-to-use plates, focusing on the thin-layer chromatographic racemate separation based on ligand exchange that was introduced in 1983 by Günther et al. (28) and on the use of a densitomer for determination of antipode distributions at trace level.

This chapter does not discuss the numerous and interesting diastereomeric separations by paper and thin-layer chromatography. We refer to the literature on amino acids (29–35), peptides, diketopiperazines (36–45), and other classes of compounds (46–55). In this context the work of Palamareva and coworkers (52–55) should be mentioned. They investigated the thin-layer chro-