133. L.N.Yakhontov, D.M.Krasnokutskaya, E.M.Peresleni, Yu.N.Sheinker, and M.V.Rubtsov, Dokl.Akad.Nauk SSSR, 172, 118 (1967).
134. M.M.Robison, F.P.Butler, and B.L.Robison, J.Amer. Chem.Soc., 79, 2573 (1957).
135. J.von Braun, O.Bayer, and G.Blessing, Ber,, 57, 392 (1924).
136. H.Adkins and H.L.Conradt, J.Amer.Chem.Soc., 63, 1563 (1941).
137. B.Witkop, J.Amer.Chem.Soc., 78, 2873 (1956).
138. B.Witkop, J.Amer.Chem.Soc., 76, 5597 (1954).
139. B.Witkop, Experientia, 10, 420 (1954).
140. L.N.Yakhontov and M.V.Rubtsov, "Biologicheski Aktivnye Soedineniya" (Biologically Active Compounds), Sbornik Zhur.Obshch.Khim., 1965, p.83.
141. A.P.Terent'ev and M.N.Preobrazhenskaya, Dokl.Akad. Nauk SSSR, 118, 302 (1958).
142. A.P.Terent'ev and M.N.Preobrazhenskaya, Dokl.Akad. Nauk SSSR, 121, 481 (1958).
143. A.P.Terent'ev, Ko Pang-lun, and M.N.Preobrazhenskaya, Zhur.Obshch.Khim., 32, 1335 (1962).
144. A.P.Terent'ev, M.N.Preobrazhenskaya, and G.M.Sorokina, Zhur.Obshch.Khim., 29, 2875 (1959).
145. L.N.Yakhontov and M.V.Rubtsov, Zhur.Obshch.Khim., 34, 2603 (1964).
146. M.M.Robison and B.L.Robison, J.Amer.Chem.Soc., 78, 1247 (1956).
147. M.V.Rubtsov and L.N.Yakhontov, USSR P. 162535 (1962); Byul.Izobr., No.10 (1964).
148. A.Butenant and H.Helmann, Z.phys.Chem., 289, 175 (1949).
149. W.R.N.Williamson, J.Chem.Soc., 8233 (1962).
150. L.N.Yakhontov, M.Ya.Uritskaya, and M.V.Rubtsov, Zhur. Org.Khim., 1, 2040 (1965).
151. L.N.Yakhontov and M.V.Rubtsov, Khim.Geterotsikl. Soedinenii, 141 (1967).
152. G.Stevens, Record Chem.Progr., 23, 105 (1962).
153. L.N.Yakhontov and M.V.Rubtsov, Khim.geterotsikl. Soedinenii, 80 (1966).
154. E.R.B.Sundaram and P.S.Sarma, Current Sci., 26, 13 (1957).
155. G.W.Kidder and V.C.Dewey, Biochim.Biophys.Acta, 17, 288 (1955).
156. A.B.Pardee, V.G.Shore, and L.S.Prestidge, Biochim. Biophys.Acta, 21, 406 (1956).
157. A.B.Pardee and L.S.Prestidge, Biochim.Biophys.Acta, 27, 330 (1958).
158. R.V.Thimann, Plant Physiol., 33, 311 (1958).
159. L.Velluz, G.Muller, and A.André, French P. 1261179 (1961).

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Chromatographic Resolution of Racemates on Dissymmetric† Sorbents

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The review discusses the use of natural sorbents (proteins, carbohydrates, and optically active quartz) and also artificial dissymmetric sorbents (based on silica gel and activated carbon) for the chromatography of racemates. Gas chromatography is very effective for the separation of diastereomers, but is less suitable for the direct separation of optical isomers. On the other hand, dissymmetric ion-exchange sorbents, which are considered in detail in the review, may find wider practical application. The list of references contains 197 items.

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I. INTRODUCTION

In connection with the vigorous development of research on the production of synthetic medicines, animal feeds, and food products, the problem of resolving various racemic compounds into optically active components has now become urgent. Chemical synthesis produces a racemic mixture of enantiomorphs, but usually only one form can be used for biological purposes.

A foreign dissymmetric agent is necessary for the resolution of a racemic compound‡. Use can be made of differences between the enantiomorphs in—(1) interaction with a dissymmetric environment (sorption on dissymmetric phases, diffusion through a medium containing dissymmetric centres, dissolution in optically active solvents, interaction with circularly polarised radiation or with polarised elementary particles, etc.); (2) rate of chemical interaction with optically active substances, and physical and chemical properties of pairs of diastereomers formed as a result of such interaction; and (3) interaction with a

† The term dissymmetric is to be applied to sorbents containing dissymmetric structural units possessing optical activity of definite sign (positive or negative). We recall that a structure is said to be dissymmetric if it contains no rotation-reflection axis of symmetry (an axis rotation about which, followed by reflection in a plane perpendicular to the axis, yields a structure identical with the original structure). Dissymmetry of structure is the necessary and sufficient condition for the appearance of optical activity in a substance. In determining the dissymmetric character of a molecule it is necessary to take into account all the conformations which the molecule can adopt under the given conditions. The selective absorption by a dissymmetric sorbent of one of the enantiomorphs of a racemate is to be termed stereoselective sorption.

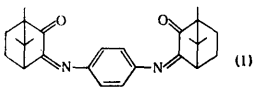
‡ The "spontaneous" resolution of racemates during crystallisation generally requires the introduction of a seed of an optically active substance.

living cell or its enzymes, which are capable of selectively assimilating or modifying one of the enantiomorphs of the racemic mixture.

Among all the methods enumerated[1], the resolution of racemates by chromatography on a dissymmetric sorbent is favourably distinguished by the theoretical possibility of quantitatively isolating both components of the racemate in optically pure form even if the dissymmetric sorbent used does not possess 100% optical purity[2]. This fact, coupled with the well known merits of the chromatographic method, suggests that the chromatographic resolution of racemates is quite promising for use on an industrial scale.

The possibility of resolving racemic compounds by stereoselective sorption of one of the enantiomorphs on a dissymmetric sorbent was first suggested by Willstätter in 1904.[3] By simulating dyeing processes for animal fibres, he tried unsuccessfully to detect the appearance of optical activity in a solution of a racemic alkaloid (tropacocaine, atropine, homatropine) in contact with the fibres. In such a case optical activity in the solution would have indicated preferential sorption of one of the enantiomorphs on the fibres. A difference in the sorbability of the optical isomers of a dye on wool was detected only in 1919 by Porter, first colorimetrically[4] and then by a polarimetric method[5].

In 1938 Henderson and Rule[6] first applied Tswett's chromatographic method to the resolution of racemic *NN'*-bis-2-oxoborn-3-ylidene-*p*-phenylenediamine


(I)

on a (+)–lactose column. In this case, the resolution of the racemate was due to the differing stabilities of the labile diastereomeric adducts formed with the enantiomorphs on the surface of the sorbent. The chromatographic method enabled these small differences in sorbability of the enantiomorphs to be clearly revealed, and showed the suitability of chromatography for the partial resolution of racemates.

Much research has been done during recent years on the problem of stereoselective sorption, these investigations having been partly surveyed in several review papers[7-14]. Therefore, while giving a full bibliography on these questions, we have discussed in greater detail only the most recent work in this field, and also the general features of the stereoselective sorption and the chromatography of racemates.

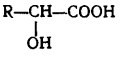
II. CHROMATOGRAPHY OF RACEMATES ON NATURAL AND INORGANIC DISSYMMETRIC SORBENTS

Natural proteins constituted the first dissymmetric sorbent used in studying the stereoselective sorption of enantiomorphs. In several cases some difference was confirmed in the sorbability of the enantiomorphs of racemic azo-dyes on the proteins of wool[4,5,15,16] or a difference in sorbability between the racemate and one of the enantiomorphs[17,18]. However, the effect observed under conditions of static sorption was extremely small, and the results obtained[4,5,15,16] could not be repeated on more careful checking[18-20]. Several workers report the absence of stereoselectivity in the sorption of azo-dyes on wool[20-22].

It was only in 1941 that Martin and Kuhn[23] demonstrated a separation of enantiomorphs sufficient for accurate observation in the case of mandelic acid, using an original device having a moving endless wool top. The optical activity observed in the acid solution in these experiments reached −0.35° and +1.0° at opposite ends of the apparatus.

A more detailed study of the sorption of racemic α-hydroxy-acids on wool was made during the 1950s by Bradley and his coworkers[8,24-28], who reached the conclusion[24,26] that an important part in this process is played by the free basic groups of L-lysine and L-arginine, which are present in considerable quantities in wool (the exchange capacity of wool with respect to acids reaches 0.45 mg-equiv. g^{-1}). This is supported by the sharp decrease in adsorption and in degree of resolution of mandelic acid when wool is used whose basic groups have previously been blocked by the radicals of some other acid[28]. It is indicated also by the inability of silk, which contains only minute quantities of diamino-carboxylic acids, to sorb selectively the enantiomorphs of racemic acids[17,18,22,24].

By studying the separation on wool of the isomers of a large number of racemic α-substituted glycollic acids



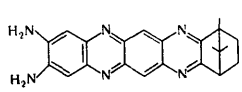
Bradley showed[24,26-28] that substituents R which are too large promote non-selective adsorption, and thus impair resolution of the racemic acid. Thus on passing in α-substituted glycollic acids from phenyl, substituted phenyl, and naphthyl radicals to *p*-hexadecyloxyphenyl and anthr-9-yl radicals the degree of separation of the isomeric acids is appreciably diminished. These facts make clear the reason for the failure of earlier attempts to detect the selective sorption of the large molecules of azo-dyes[18,20,21].

According to Bradley, important factors for the development of the selective sorption of α-hydroxy-acid enantiomorphs on wool are the presence of a free carboxyl and of an aromatic ring in the α-position[26,27].

It is interesting that, in all cases studied by Bradley[8,24-28] and by other workers[5,23,29], the dextrorotatory isomers of α-arylglycollic acids were more strongly retained by wool than were the laevorotatory isomers. It may be supposed that L-mandelic acid and its analogues containing substituted phenyl radicals and even other aromatic and heterocyclic substituents in place of the phenyl radical will possess a greater affinity for wool protein. Thus the accumulation and systematisation of experimental data on the chromatography of racemates may lead to the establishment of empirical rules for the assignment of dissymmetric compounds to known configurational series.

Slight selectivity of sorption for racemic azo-dyes[30], and to a greater extent for tryptophan[31], was observed with proteins of the serum albumin type. In contrast to mandelic acid[8], no separation of the enantiomorphs of α-bromopropionic acid was observed on casein[32].

There are indications of the non-selective sorption of the product (II) of the interaction of tetra-aminophenazine with camphorquinone isomers on protein tissues of living organisms[33].


(II)

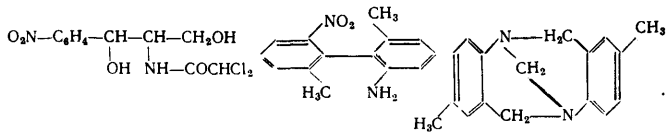
Grubhofer and Schleith[34] made successful use of a product obtained by coupling a protein with diazotised poly-*p*-aminostyrene for the partial resolution of racemic alanine.

Natural carbohydrates (lactose, cellulose, starch, sucrose) have been used in a considerable amount of work on the resolution of racemates. Carbohydrates contain no functional groups capable of electrolytic dissociation in

neutral media, and therefore the resolution of racemates on them is a consequence of intermolecular forces, an important part in these processes probably being played by hydrogen bonds.

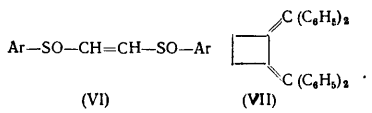
It has already been mentioned above that the chromatographic method was first used for the resolution of *NN'*-bis-2-oxoborn-3-ylidene-*p*-phenylenediamine (I) on a (+)-*lactose* column[6]. The resolving effect was very considerable. When the initial fractions of the eluate, enriched with the laevorotatory enantiomorph, were repeatedly passed through the column, the optically pure isomer was isolated after four cycles[19].

Lactose columns have been used for the partial separation of the isomers of chloromycetin (III)[35] and 1-amino-6,6'-dimethyl-1'-nitrobiphenyl (IV)[36], as well as Tröger's base (V)[37], which could not be resolved by other methods owing to its instability in acid media. The use of (+)-tartaric acid columns and those containing its potassium hydrogen salt gave a smaller effect[37].



(III) (IV) (V)

The molecules (IV) and (V) contain no asymmetric carbon atoms, their dissymmetry being due in the former to the non-coplanarity of the molecule and in the latter to the asymmetry of the rigid pyramidal structure of tervalent nitrogen attached to three different substituents. The similar pyramidal structure of sulphoxides is responsible for the existence of enantiomers in the *cis*- and *trans*-forms of 1,2-bisarylsulphoxyethylenes (VI), which also have been separated by means of (+)-lactose[38].



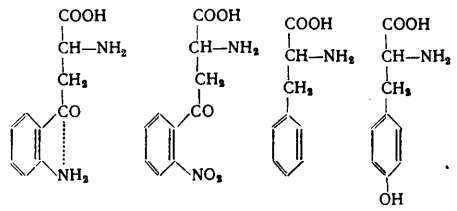
(VI) (VII)

Partial resolution on (+)-lactose has been observed with racemic lysine, its methyl ester and dihydrochloride, proline, tryptophan, glutamic acid[39], quaternary arsonium salts[40], and also the trisacetylacetonates of chromium and cobalt[41], yttrium and gadolinium[42], but not of iron, gallium, and indium[41]. Failure attended attempts to resolve the racemates of 1,2-bisdiphenylmethylenecyclobutane (VII) and its analogues[43], although the molecules of these compounds are non-coplanar.

In contrast to calcium (+)-tartrate, emulsin, maltose, glucose, and sucrose, (+)-lactose is able to resolve *m*-naphth-2'-ylazomandelic acid[21]. In some cases lactose can nevertheless be replaced by sucrose[39].

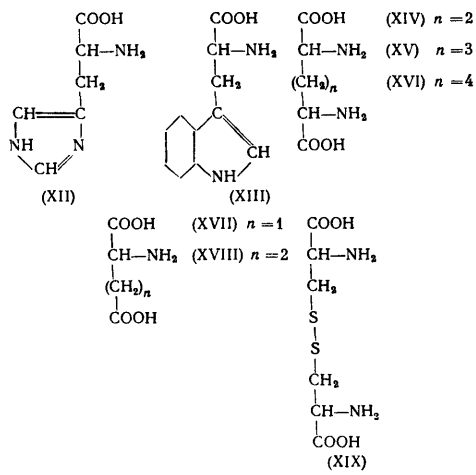
During the 1950s considerable progress was made in the resolution of racemates by chromatography on *cellulose* (paper). The first attempts to resolve racemic sugars were unsuccessful[44]. It was then found that preliminary treatment of the paper with (+)-camphorsulphonic acid[45] enabled the enantiomorphs of phenylglycine to be separated. In the presence of (+)-tartaric acid the isomers of 1-benzylamino-2-naphthol[46] and phenylalanine[47] are separated on paper. Some Japanese workers have subsequently found[48-51] that tyrosine, glutamic acid, and especially well tyrosine-3-sulphonic acid are resolved into two components even in the absence of foreign optically active substances. It was concluded that the reason was selective adsorption of the enantiomorphs on the paper, which was soon confirmed by the resolution of several other racemic amino-acids—kynurenine[52,53], α-hydroxytryptophan[54], tryptophan[52,55,56], histidine[56,57]—although Fujisawa[52] found that tyrosine (see, however, Refs. 49 and 50), leucine, phenylalanine, *N*-benzoyltyrosine, acetyltryptophan, and phenylalanine-*p*-sulphonic acid are not resolved on paper. In this connection it should be noted that the first worker to observe the resolution of a racemate by paper chromatography was obviously Dent[58], who as early as 1948 described the unexpected splitting of chromatographic spots of aspartic and glutamic acids.

An important contribution to elucidating the fundamental laws governing the resolution of racemates by paper chromatography was made by the work of Dalgliesh[59-61], who concluded that paper chromatography did not involve partition chromatography, as had previously been assumed[62], but represented a method of adsorption chromatography. Hydrogen bonds play an important part in the process of adsorption.



(VIII) (IX) (X) (XI)

Dalgliesh observed that racemic kynurenine (VIII) and 3-hydroxykynurenine[59] are successfully resolved on paper, but kynurenine which has been acetylated at either of the amino-groups, and also α-amino-β-benzoylpropionic acid and its *o*-nitro-derivative (IX), are not resolved[59,60]. Among phenylalanine (X) derivatives the 2,3-diol and the 2-methyl-3,4-diol are resolved, but phenylalanine itself, its 3,4-diol and 5-methyl-3,4-diol, and also tyrosine (XI) are not resolved (see, however, Refs. 49 and 50, which report partial resolution of tyrosine in the presence of amines). From these results Dalgliesh concludes that, for successful resolution of the racemate of an amino-acid, its molecule should contain a free carboxyl and a free amino-group. A planar aromatic ring having a small *ortho*-substituent can serve as third functional group to ensure three-point adsorption. The presence of a hydrogen bond between the amino-group and carbonyl in the kynurenine molecule (VIII) provides also a planar ring system in the β-position. However, whereas the L-series of isomers are more strongly sorbed among phenylalanine and tryptophan derivatives, the opposite situation is found for kynurenine derivatives.



(XII) (XIII) (XIV) $n=2$ (XV) $n=3$ (XVI) $n=4$ (XVII) $n=1$ (XVIII) $n=2$ (XIX)

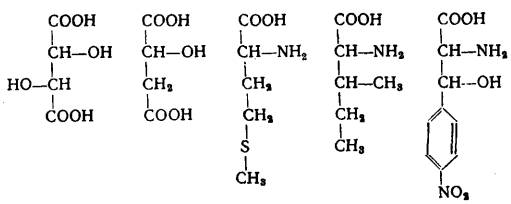
Dalgliesh's rules concerning three-point sorption are only approximate. They are consistent with the above resolution of histidine (XII) and tryptophan (XIII), but they cannot explain the fact that, among the dihydroxy-derivatives of phenylalanine, the 2,3-, 2,4-, 2,5-, and 3,5-diols are resolved, while the 3,4- and 2,6-isomers are not resolved[61,63]. Furthermore, it is obvious that the presence of an aromatic ring is not essential, since resolution on paper is observed for racemic $\alpha\delta$-diaminoadipic (XIV), $\alpha\epsilon$-diaminopimelic (XV), and $\alpha\zeta$-diaminoazelaic (XVI) acids[64], as well as partial resolution of aspartic (XVII)[58] and glutamic (XVIII) acids[48-51,58] and of cystine (XIX)[65].

A detailed study of the effect of the conditions of chromatography on the degree of resolution of racemic amino-acids has shown[65] that the best medium is 90% aqueous methanol without any addition of electrolytes. It has been found also that the separation of the enantiomorphs is appreciably improved by lowering the temperature to +2° and −15°C, a fact which was not explained[65]. Lowering the temperature to +4°C has an analogous effect also in the thin-layer chromatography of tryptophan and its derivatives on cellulose[66].

Partial resolution on paper has been reported for racemic catechin and epicatechin[67], complex cobalt(III) salts of glycine, alanine, and oxalic acid[68], pteridines[69], and also several alkaloids of the berberine[70,71]. Alessandro and Caldarera[72] described the resolution of the racemates of several physiologically active amines of the adrenaline group, but these results could not be repeated by other workers[73].

Chromatography on cellulose can be conducted also on a preparative scale in columns[67,69,71], but the degree of separation of the enantiomorphs then drops sharply[67,71].

The successful work of Krebs and his collaborators[74-82] has added yet another carbohydrate, *starch*, to the store of natural dissymmetric sorbents suitable for the resolution of racemates. This sorbent has proved capable of partly resolving into fractions having opposite optical rotation a large number of dissymmetric complex salts of cobalt and chromium containing two or three bidentate ligands such as glycine, dithiocarbamic acid, *p*-methylaminophenol, ethylenediamine, oxalic acid, etc.[74-77]. The resolution of these complexes was more effective on starch than on lactose, cellulose, sucrose, or wool[75,77].

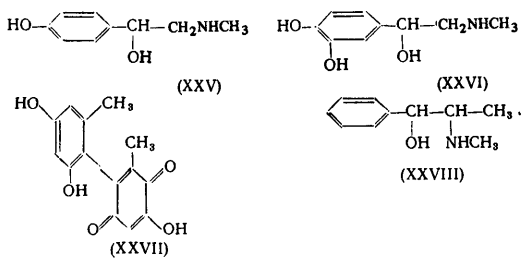


(XX) (XXI) (XXII) (XXIII) (XXIV)

Among organic substances the racemates of racemic acid (XX), malic acid (XXI) (optical purity 8%), and aspartic acid (XVII) (13%) are resolved on starch, but alanine, phenylalanine (X), methionine (XXII), isoleucine (XXIII), tryptophan (XIII), and β-hydroxy-β-*p*-nitrophenylalanine (XXIV) are not resolved[78-80]. These results agree well with Dalgliesh's rule on three-point adsorption established for paper chromatography. However, Krebs considers it valid only for flexible aliphatic molecules. The resolution of mandelic acid (optical purity 64.5%), phenylglycine (42%), phenylchloroacetic acid (50%), *O*-alkyl and *O*-acyl derivatives of mandelic acid, and also its esters shows that, with all these aromatic compounds having rigid molecules, the presence of two or even one functional group capable of forming hydrogen bonds with the hydroxyls of the starch is sufficient for successful resolution. Krebs regards molecular rigidity as the decisive condition for the successful resolution of isomers of such compounds[78-82]. This can be artificially increased by introducing additional bulky groups. Thus alanine, valine, and isoleucine are not resolved on starch, but their benzoyl derivatives are resolved. To resolve phenylalanine it proved sufficient to introduce into its molecule an acetyl or even a formyl group.

Krebs made the interesting observation that the best medium for chromatography on starch was water. The use of water–alcohol mixtures always diminishes the efficiency of the separation of isomers[78-80]. This fact has been confirmed by other investigators[83].

Ohara and his coworkers[84-86] have pointed out that, in all pairs of enantiomorphs of mandelic acid and its derivatives, the D-series of isomers—D(−)-mandelic acid $C_6H_5CH(OH)COOH$, (−)-methyl ester of D-mandelic acid, D(+)-acetylmandelic acid, D(+)-β-phenyl-lactic acid $C_6H_5CH_2CH(OH)COOH$, D(−)-tropic acid $C_6H_5CH(CH_2OH)COOH$—are the more weakly sorbed on starch. In the chromatography of atrolactic acid $C_6H_5C(OH)(CH_3)COOH$, on the other hand, the L(+)-isomer is eluted first. In view of this, these workers conclude that either the generally accepted assignment of (+)-atrolactic acid to the L-series is incorrect or else starch begins to develop a greater affinity for isomers of the D-series—not of the L-series—on passing from mandelic to atrolactic acid[85]. The latter hypothesis seems to us entirely plausible, because in mandelic acid and its derivatives the smallest substituent attached to the asymmetric carbon atom is a hydrogen atom, whereas in atrolactic acid the smallest substituent is a hydroxy-group. This marked change in molecular structure is fully able to explain the reversal in the order of sorption of these compounds.



(XXV) (XXVI) (XXVII) (XXVIII)

Partial resolution on starch has been reported for trichloroacetyl derivatives of α-amino-acids[83], phenylglycine[87], sympathol (XXV), adrenaline (XXVI), Henrich's quinone (XXVII)[88], and allylethylmethylphenylphosphonium bromide[89].

Reference has been made[90] to the possibility of resolving ephedrine (XXVIII) and 1-phenylethylamine by means of a copolymer of styrene and maleic acid which has been treated with thionyl chloride and then with glucose.

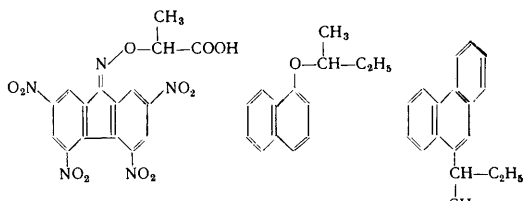
Finely ground crystals of *optically active quartz*, among inorganic dissymmetric sorbents, have been used for resolving racemates. Quartz is inert towards *m*-naphth-2′-ylazomandelic acid[19], *NN′*-bis-2-oxoborn-3-ylidene-*p*-phenylenediamine[6,19], and quaternary phosphonium salts[89], but several racemic complexes have been separated by means of quartz into fractions having opposite rotations. A partial separation has been effected of the oxahedral complex salts of cobalt(III) and chromium(III) with two or three bidentate ligands such as ethylenediamine, dimethylglyoxime, oxalate[91-96], and pentane-2,4-dione[97], and with

hexadentate ethylenediaminetetra-acetate[98], the tetrahedral complex of beryllium with benzoylacetone[99], and also potassium dinitro-*N*-methyl-*N*-ethylglycineplatinate[100] containing an asymmetric nitrogen atom.

Very little selectivity has been detected, during sorption on optically active quartz, of racemates of such neutral compounds as butan-2-ol[101], cyclic hydroperoxides[102], and quaternary arsonium salts[40,103]. The use[104] of this property of quartz for establishing molecular dissymmetry in compounds has been proposed. It has also been suggested[105] that the stereoselectivity of sorption can be determined by measuring the quantities of isomers sorbed from the vapour phase.

Sodium chlorate, like quartz, is able to form enantiomorphous optically active crystals. This property has been used by Ferroni and Cini[106] for the partial resolution of beryllium bisbenzoylacetonate. These workers report the possibility of resolving this complex directly on a commercial aggregate of sodium chlorate, which is a mechanical mixture of enantiomorphous crystals. They explain this phenomenon by the non-equivalent sorption of (+)- and (−)-forms of the complex on the corresponding forms of the crystals, which appears to us doubtful.

Methods have been described for preparing *silica gels* capable of the stereoselective sorption of optical enantiomorphs. Such silica gels contain "imprints" of the molecules of an optically active isomer of a substance which had been present in the reaction mixture during formation of the gel and then removed by extraction[107]. The presence of these "imprints" is due to the greater sorption capacity of the gel for the same isomer of this substance or of a structurally related substance than for their enantiomorphs. Thus silica gels have been prepared in the presence of optically active mandelic acid, (+)-camphorsulphonic acid[107,108], quinine and its enantiomorph quinidine[109], and also by hydrolysing optically active tetrakis-2-methylbutoxysilane, tetramenthyloxysilane, and tetrabornyloxysilane[110]. A silica gel containing "imprints" of quinine possessed greater affinity for quinine, cinchonidine, and other alkaloids of the same steric series than did silica gel having "imprints" of quinidine[109]. The selectivity of such sorbents falls with time.



(XXIX) (XXX) (XXXI)

Ordinary silica gel can also be given the properties of a stereoselective sorbent, by impregnating it with a solution of (+)-α-(2,4,5,7-tetranitrofluoren-9-ylideneamino-oxy)propionic acid (XXIX). Racemates of esters and ethers, e.g. 1-s-butoxynaphthalene (XXX)[111], and even of hydrocarbons such as 9-s-butylphenanthrene (XXXI)[112] can be partly resolved on such a sorbent. In this case the adsorbent and adsorbate molecules form adducts of the picrate type, with the aromatic rings arranged parallel.

Aluminium oxide modified with optically active alanine, lactose, glucose, tartaric acid, sodium glutamate, menthan-3-ol, and fenchone was used by Karagounis[113,114], which enabled him to observe the weak resolution of mandelic acid, phenylglycine, camphor, etc.[114]. However, he was unable to resolve the free biphenylnaphth-1-ylphenylmethyl radical on these sorbents or on several other sorbents, undoubtedly owing to its planar structure[113].

Carbon modified with alkaloids has been used to separate the isomers of mandelic acid[115], and aluminium oxide modified with (+)-tartaric acid for separating chromium and cobalt acetylacetonates[97].

Thus, beginning in the 1920s, a large number of attempts have been made to resolve various racemic compounds on naturally occurring dissymmetric sorbents (proteins, carbohydrates, and optically active quartz) and also on silica gel, aluminium oxide, and activated carbon modified with optically active substances. The best results were obtained by using carbohydrates. In several cases it was possible to achieve quantitative resolution of a racemate by paper chromatography. However, on passing from purely analytical chromatography to the preparative separation of enantiomorphs on cellulose columns, the degree of separation fell sharply. On (+)-lactose and starch columns it has sometimes been possible to obtain fractions of isomers of optical purity ~ 50%, but an immense excess of the sorbent had to be used.

III. RESOLUTION OF RACEMATES BY GAS CHROMATOGRAPHY

Attempts have been made during recent years to apply the method of gas chromatography to the resolution of racemates.

The considerable advances made in the separation of various diastereomeric pairs by gas–liquid chromatography[116–135] have enabled highly sensitive methods to be developed for determining the degree of optical purity of optically active compounds, based on chromatography of the diastereomers formed by coupling these compounds with some other dissymmetric compound[130,131,135]. These methods have proved to be far more accurate than traditional measurements of specific rotation. The rapidity of an analysis and the great reliability of the results have permitted the use of gas–liquid chromatography for solving such complex problems as, for example, racemisation in peptide synthesis[136,137].

Here, however, we are more interested in direct separation of the components of a racemate by gas chromatography on an optically active phase. The first results in this field were obtained in 1959 by Karagounis and Lippold[138], who used (−)-ethyl tartrate or starch as adsorbent, and observed slight splitting of the peaks corresponding to racemic butan-2-ol, 2-bromobutane, ethyl α-bromobutyrate, and α-bromopropionic acid. However, in 1962 Japanese workers reported[84] that they were unable to repeat Karagounis' experiments on the separation of butan-2-ol by gas chromatography on columns containing starch, (−)-ethyl tartrate, or other optically active sorbents. Goldberg and Ross[139] also reported unsuccessful attempts to separate butan-2-ol, 2-chlorobutane, and 2-bromobutane on starch, (+)-1-methylheptyl sebacate, and methyl (+)-tartrate. They were unable to establish even partial separation of the enantiomorphs by measuring the optical activity of the fractions obtained by a preparative method of gas–liquid chromatography. Here these workers showed—what is extremely important—that racemisation of the optically active components does not take place under

analytical conditions. A paper[140] on the gas-chromatographic separation of the n-pentyl esters of *N*-acetyl-α-amino-acids on L-glutamic acid and sodium L-glutamate also does not report the splitting of peaks due to racemic compounds.

A detailed investigation of the possibility of separating by gas chromatography fifteen different racemates (carbohydrates, alcohols, alkyl halides, alkenes) on a series of optically active phases (sucrose octapropionate, heptamethylsucrose, menthyl stearate, and poly(propylene oxide)) was made by Goeckner[141]. In no single experiment was he able to observe splitting of the chromatographic peaks, in spite of his varying the temperature and the speed of the carrier gas between wide limits.

Nevertheless, Karagounis published a second paper[142] on the resolution of racemates by gas-adsorption chromatography on starch, sucrose, camphor-β-sulphonic acid, sorbitol, and (+)-trisethylenediaminecobalt(III) chloride, and also by gas–liquid partition chromatography on the optically active phases—(+)-dipentyl phthalate, ethyl (+)-tartrate, (+)-heptamethylsucrose, and (+)-heptamethyllactose—the racemates used being *trans*-1,2-dichlorohexafluorocyclobutane, 2-methoxybutane, and 3-hydroxybutan-2-one. In all cases the degree of separation of the enantiomorphs was extremely small. Nevertheless, in the preparative chromatography of *N*-methylpiperidine on sucrose two fractions of volume 0.3 and 0.5 ml were isolated, their optical rotations being respectively +0.100° and −0.120°.

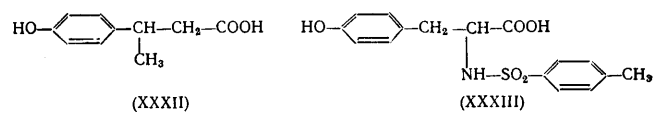
Complete separation of the isomers of racemic esters of the *N*-trifluoroacetyl derivatives of valine, alanine, and isoleucine was achieved only in 1966,[143] a capillary column of efficiency 75 000 theoretical plates being used. The optically active phase was the dodecyl ester of *N*-trifluoroacetyl-L-isoleucine. It was established that the degree of separation of the enantiomorphs increased with increase in the size of the alcoholic radical in the ester of the amino-acid. However, this was accompanied by an increase in the retention time, which reached 300–400 min, with almost complete blurring of the chromatographic zones. Besides this, the high temperature of the experiment (210°C) casts doubt on the lasting configurational stability either of the optically active phase or of the compounds undergoing separation.

Thus available information suggests that gas chromatography holds little promise for the resolution of racemates. On the other hand, the chromatography of diastereomers may prove of inestimable value as a rapid and accurate method of analysis.

The ineffectiveness of gas chromatography for the separation of optical isomers is explained, in our opinion, by the high temperature necessary for the analysis. The stereoselectivity of the sorption of enantiomorphs is determined by the difference in their energies of interaction with the dissymmetric phase. This interaction is characterised by weak intermolecular forces (induction, dispersion forces, hydrogen bonds, etc.), the effect of which falls rapidly with rise in temperature. Attempts to strengthen this interaction by introducing additional polar or bulky groups inevitably entail a rise in the boiling point of the racemate, and hence in the temperature of the chromatographic process. This difficulty cannot be removed within the limits of gas chromatography, but it does not arise in liquid chromatography. Such an explanation is consistent with the increase in degree of separation of enantiomorphous amino-acids noted above[65,66] with drop in the temperature of their chromatography on paper. The influence of temperature should appear especially clearly in paper chromatography, since here the process of sorption is not complicated by the temperature-dependent process of diffusion.

IV. DISSYMMETRIC ION-EXCHANGE SORBENTS§

In order to resolve racemic alcohols Macbeth and his coworkers[144] esterified them with dicarboxylic acids, and then prepared diastereomeric salts of the resulting acid esters with optically active alkaloids, an example being brucine 1-methylheptyl phthalate. Instead of the usual crystallisation, however, these workers successfully used a chromatographic method to separate the diastereomeric salts on a column filled with brucine. Although separation of the diastereomers takes place here mainly as a consequence of the difference in their solubilities in the solvent mixture employed, these workers correctly pointed out the theoretical possibility of ion-exchange reactions between the acid component of the salt and the brucine. This enabled them to propose the possibility of resolving racemates by means of synthetic dissymmetric ion-exchangers.



(XXXII) (XXXIII)

In 1952 Bunnett and Marks[145,146] synthesised dissymmetric ion-exchangers by the polycondensation of formaldehyde with optically active (+)-β-*p*-hydroxyphenylbutyric acid (XXXII) or *N*-toluene-*p*-sulphonyl-L-tyrosine (XXXIII). They showed in separate experiments that these compounds undergo no considerable racemisation under the conditions of polycondensation. However, all attempts to resolve racemic amines (*N*-methylpiperidine, 1-phenylethylamine, and γ-dimethylamino-αα-diphenylvaleronitrile) by means of these ion-exchangers in water and in ethanol were unsuccessful. Yet the accuracy of the measurements would have enabled even a slight (3%) enrichment of the eluate with one of the enantiomorphs to be detected. Discussing their results, Bunnett and Marks reject the possibility of the resolution of racemates by means of ion-exchangers containing in the macromolecule considerable aliphatic portions and only one ionogenic group for interaction with the ions of the substance to be separated.

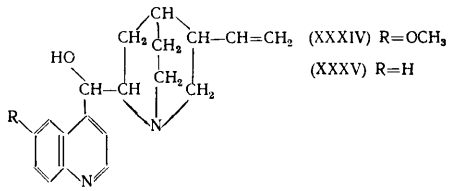
Failure attended an attempt to separate the isomers of mandelic acid on an anion-exchanger obtained by detaching the acetyl groups from the D-glucosamine units in the chitin macromolecule[147].

The successful resolution of racemic mandelic acid on a dissymmetric anion-exchange resin was first reported by Grubhofer and Schleith[34,148]. They converted the carboxyls in the cation-exchange resin Amberlite XE 64 (polyacrylic acid) into chlorocarbonyl groups, and esterified them with the secondary alcoholic groups of quinine (XXXIV). The exchange capacity of the resulting anion-exchange resin was low, 0.7 mg-equiv. g^{-1}. The isomers of mandelic acid did not separate on a column of the anion-exchange resin in aqueous and alcoholic media. On passing a 0.036 *N* solution of the acid in chloroform through the column, however, the percentage optical purity of the first

§ It has already been mentioned that naturally occurring proteins, e.g. wool, also contain ionogenic groups, which, perhaps, play an important part in the processes of sorption and chromatography.

few fractions, containing 4, 7, 16, 26, 34, and 43 micromoles of the acid, was found to be 100, 70, 44, 34, 31, and 30 respectively. The great defect of this exchanger is partial hydrolysis of the ester bonds even during its regeneration.

Krebs confirmed[80] Grubhofer and Schleith's results and used their anion-exchange resin to resolve complex salts of cobalt[77].


(XXXIV) R=OCH_3
(XXXV) R=H

Grubhofer's work was repeated by Klabunovskii[149], who also used quinine and the carboxylate cation-exchange resin KMG as starting materials. It is true that the maximum degree of enrichment with mandelic acid reached only 39% in his experiments, and was zero on the quite similar anion-exchange resin containing cinchonidine (XXXV). Attempts to employ an analogous anion-exchange resin with optically active ephedrine (XXVIII) were also unsuccessful.

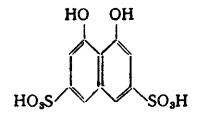
In 1959 Tsuboyama and Yanagita[150] described a dissymmetric anion-exchange resin of a different type: a styrene–divinylbenzene copolymer was subjected to chloromethylation and then to amination with (–)-1-phenylethylamine, which resulted in the introduction of secondary amino-groups into the copolymer. The capacity of the resulting anion-exchange resin was extremely small (0.43 mg-equiv. g^{-1}). On a column containing 10 g of this exchanger (4.3 millimoles) was sorbed 100 mg (0.66 millimole) of racemic mandelic acid, which was then eluted with 0.2 *N* aqueous ammonia. The resulting chromatogram consisted of two completely separate peaks, which were not equal in size. These workers state that the mandelic acid fraction corresponding to the second peak, and containing about 25% of the initial quantity of acid, consists of the practically pure dextrorotatory isomer. No explanation is given for the inequality of the chromatographic peaks.

We have tried to repeat Tsuboyama and Yanagita's results. However, no resolution of mandelic acid could be detected[2] on the high-capacity anion-exchange resin (3.36 mg-equiv. g^{-1}) which we have synthesised. The exchanger showed poor swelling in aqueous media, and retained practically no mandelic acid.

American workers have also been unable[151] to repeat the results of this work. Since Tsuboyama and Yanagita have published no further investigations on the chromatography of racemates, their results[150] must obviously be regarded as erroneous. Nevertheless, they aroused great interest in the ion-exchange chromatography of racemates.

A possible way of synthesising dissymmetric ion-exchangers is the polycondensation of optically active compounds containing basic or acidic groups. This method was used by Khromov-Borisov and Kozhevnikov[152], who effected the polycondensation of L-tyrosine with formaldehyde. They obtained insoluble polymers, since tyrosine reacted not only at the aromatic ring but also at the amino-groups, between which methylene bridges $NHCH_2NH$ or dimethyleneoxy-bridges $NHCH_2OCH_2NH$ were formed. The ability of the resulting exchangers to resolve racemates was not tested.

This was done by Losse et al.[153], who effected the polycondensation of formaldehyde with L-tyrosine in the presence of chromotropic acid

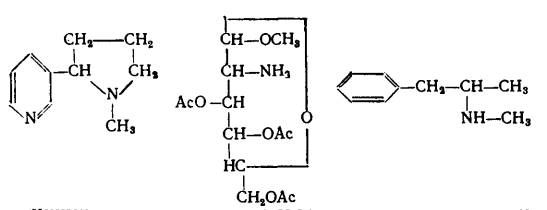

(XXXVI)

resorcinol, or *m*-toluidine. As a result, acidic or basic groups predominated in the polycondensate. The exchangers were tested for their ability to resolve racemic amino-acids—ornithine, lysine, valine, and glutamic and aspartic acids—for which purpose 1 g of the amino-acid in 10 ml of water (in the case of valine and the amino-dicarboxylic acids this could be assumed to be a suspension of the amino-acid in water) was sorbed on a column containing the exchanger, and eluted with 0.1 *N* hydrochloric acid or with water. In all cases the L-isomer of the amino-acid could be isolated from the eluate with an optical purity of 20–50%. The best results were given by the polymer obtained in the presence of resorcinol. The efficiency of separation of the isomers increased to a certain level with increase in the tyrosine content of the exchanger.

Another route has since been proposed for the synthesis of a dissymmetric cation-exchange resin containing residues of an optically active amino-acid[154]: cross-linked polyacrylic acid (Amberlite IRC-50) was converted into its acid chloride, and then treated with excess of L-aspartic or L-glutamic acid in boiling pyridine. The cation-exchange resins obtained in this way are capable of partly resolving racemates of diamino-carboxylic acids. By chromatographing lysine, for example, the D-isomer was isolated with an optical purity of 17%.

Analogous cation-exchange resins have been obtained by the radical polymerisation of optically active *N*-acryloyl-α-amino-acids or their esters[155]. In the latter case the carboxyl of the amino-acid is freed by heating the polymer with an acid (partial detachment of the amino-acid itself, bound to the polymer chain by an amide bond, is unavoidable).

A number of publications have described the synthesis of dissymmetric anion-exchange resins by the amination of chloromethylated styrene copolymers by means of various optically active amines, most often alkaloids. Thus Oda et al.[156] synthesised strongly basic anion-exchange resins, by using brucine and quinine. When a solution of mandelic acid was passed through a column containing the exchanger based on brucine, a fraction of the acid of optical purity 27% was isolated.

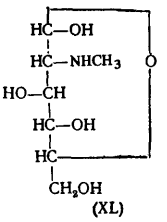

(XXXVII) (XXXVIII) (XXXIX)

Trochimczuk, Rabek, and Morawiec report an analogous synthesis of anion-exchange resins containing as dissymmetric components 1-phenylethylamine[157], cinchonidine (XXXV), nicotine (XXXVII), and ephedrine (XXVIII)[158,159]. Tsuboyama[160] used 3,4,6-triacetyl-1-methyl-D-glucosamine (XXXVIII) for the same purposes, and Selegny[161] has employed (–)-deoxyephedrine (XXXIX).

Lott and Rieman[151] used the laevorotatory isomer of *NN*-dimethyl-1-phenylethylamine for the amination of a

chloromethylated copolymer of styrene with divinylbenzene, and showed that the strongly basic anion-exchange resin formed possessed a greater affinity for (−)-mandelic acid than for its enantiomorph. Calculations based on a series of experiments with this exchanger indicate that a chromatographic column 2.3 km long would be required for complete separation of the isomers of mandelic acid.

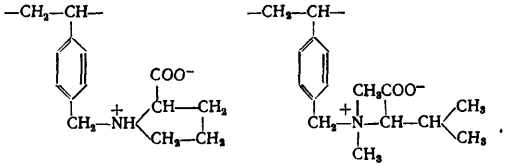
A patent[162] for the synthesis of ion-exchange resins based on cross-linked chloromethylated styrene copolymers proposes the use of a wide range of optically active amines and alkaloids—1-phenylethylamine, strychnine, ephedrine, *N*-methylglucosamine



(XL)

and also amino-carboxylic and amino-sulphonic acids or their esters.

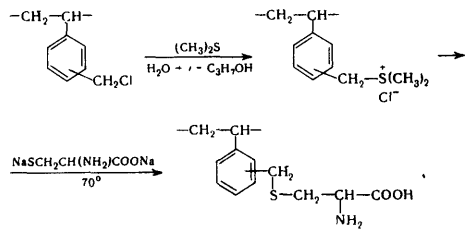
A series of dissymmetric ion-exchange sorbents based on α-amino-acids and copolymers of styrene with divinylbenzene has been synthesised by Davankov et al.[2,163,164]. Highly active bromo- and iodo-methylated copolymers were used for the synthesis, which enabled them to be aminated under mild conditions with amino-acids and their derivatives. Proline and *NN*-dimethylvaline readily undergo this reaction, forming amphoteric ion-exchange resins containing the units (XLI) and (XLII)



(XLI) (XLII)

It is advisable to use other α-amino-acids in the form of amides. Their interaction with halogenomethylated copolymers gives anion-exchange resins which can be converted into amphoteric exchangers by acid hydrolysis of the amide groups. Exchangers based on L-valineamide, L-leucineamide, and L-leucine have been prepared in this way. Chromatography of mandelic acid on these sorbents led to the isolation of small fractions of the optically pure dextrorotatory isomer of the acid. The isomers of proline undergo separation when its aqueous solution is run through a column of an exchanger based on L-proline.

Roberts and Haigh[165] synthesised an exchanger containing residues of optically active cysteine bound to a styrene copolymer by means of a sulphide bond:



The product possessed weak resolving power for racemic methionine.

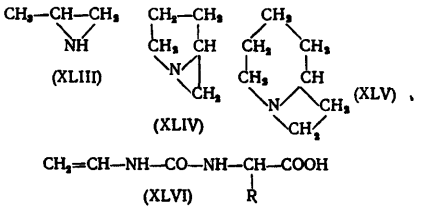
Papers by Manecke and his coworkers on the synthesis and examination of enzymatically active resins[166-168] have described nitrated copolymers of acrylic acid with its *m*-fluoroanilide, which, in virtue of the presence of a labile fluorine atom, could be combined with various enzymes or amines, in particular ephedrine. The anion-exchange resin obtained with L-ephedrine retained (+)-mandelic acid more firmly during chromatography, while the enantiomorph of the acid was eluted from the chromatographic column with optical densities up to 52.7%.[167]

Japanese workers[169] prepared a dissymmetric sorbent by the action of epichlorohydrin on chitosan, a product of the alkaline hydrolysis of chitin comprising oligomers of D-glucosamine. The sorbent obtained exhibited only very slight ability to resolve mandelic acid.

The use of carboxycellulose has been proposed[170] for the resolution of propylenediamine, and the product of the interaction of alkali cellulose with (−)-epoxypropyldeoxyephedrine for resolving racemic α-hydroxy-acids[171].

Attempts to resolve racemates by means of products of the reaction of poly-*p*-lithiumstyrene with nicotine, camphor, and camphorsulphonic acid have been unsuccessful[172].

Among the large number of optically active polymers which have been synthesised during recent years (for reviews see Refs. 173–175), a series of polyelectrolytes have been described which could in principle serve as foundation for dissymmetric ion-exchangers. Among them are the optically active polymers of 2-methylaziridine (XLIII),[176] 1-azabicyclo[3,1,0]hexane (XLIV),[177] and conidine (XLV).[178]



(XLIII) (XLIV) (XLV)

(XLVI)

Besides polypeptides (reviews[179,180]) we must include here polymers containing α-amino-acid fragments linked to the polymer chain by amide bonds at the amino-groups[181-183] or by ester bonds at the carboxy-groups[184], and also polymers of *N*-(vinylcarbamoyl)-L-amino-acids (XLVI)[185]. (Ionogenic groups in the polymers described in Refs. 182 and 184 can be freed by splitting off the protective groups.)

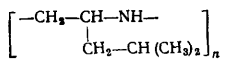
From our point of view the practical application of stereoselective sorption on a dissymmetric ion-exchanger is complicated by the fact that, in contrast to such sorbents as quartz, wool, starch, and cellulose, where we are dealing with dissymmetric active centres rigidly fixed on a solid surface, ion-exchangers when functioning have mobile solvated polymer chains. On the one hand, this tends to hinder formation of an adduct with the molecule undergoing sorption, which makes it necessary to impose specially rigorous requirements on the active centres of such a sorbent. On the other hand, it ensures that the sorbent shall operate throughout its bulk, which is shown in a considerably larger exchange capacity of the exchangers in comparison with other sorbents. This property makes dissymmetric ion-exchangers quite promising for the preparative resolution of racemates.

In our opinion the most suitable for these purposes are chromatographic systems having continuous circulation of the separable mixture through one or more columns. The initial and final fractions of a chromatographic zone are automatically withdrawn, and fresh portions of the mixture

are introduced into the middle of the zone, during each cycle. Such systems make even minute separation effects appreciable[186-188].

In connection with this problem it is interesting to mention the work of Toy et al.[189,190], who, foreseeing the need in the near future to convert amino-acids of the D-series into L-amino-acids, have synthesised resins which effect racemisation of optically active α-amino-acids. The desired isomer could be isolated from the racemic mixture, and the less valuable enantiomorph again subjected to racemisation. The process of racemisation is catalysed by resins containing units of the salicylaldehyde type, at pH 10.5 in the presence of copper ions.

Dissymmetric ion-exchangers can be used not only for the resolution of racemates but also as catalysts in asymmetric organic synthesis. This aspect of their application is shown by the work of Tsuboyama[160,191], who conducted a cyanohydrin synthesis in the presence of optically active polyisobutylethyleneimine

 (XLVII).

The benzaldehyde cyanohydrin (mandelonitrile) obtained in this way was laevorotatory, its optical purity reaching 11–19%. If a proportion of the amino-groups in the polymer were treated with isocyanate, the resulting polymer would catalyse the formation of the dextrorotatory cyanohydrin[191]. This phenomenon was explained by supposing that asymmetric catalysis was determined in this case not so much by the configuration of the asymmetric carbon as by the conformation of the whole polymer chain, which changed on passing from amine to amide nitrogen atoms in the chain.

Finally, dissymmetric sorbents may find application also in elucidating the mechanisms of chemical reactions and establishing the three-dimensional structure of compounds. Quite often only partial resolution of a racemate by a chromatographic method is sufficient for this purpose[91,100,192].

In conclusion we note the appearance of the first communications on the chromatographic *resolution of polymers*, containing asymmetric carbon atoms in the main chain[193,194] or in side-chains[195,196], into fractions of opposite rotation. Thus the separation of the crystalline polymer of 2-methyloxiran by means of polymeric (–)-menthyl glycidyl ether[193], and also by means of components containing sucrose, menthol, or borneol[194], has shown that the polymer consists mainly of enantiomorphous chains, and is not a stereo-block-copolymer. The analogous separation of poly-4-methylhex-1-ene adsorbed on optically active stereoregular poly-3-methylpent-1-ene[195] suggests that the polymerisation of racemic alkenes can be conducted not only as a stereospecific but also as a stereoselective process. Such separation of polymers differs, of course, from the chromatography of racemates of substances of low molecular weight in the fact that the polymeric product must in general be regarded not as a racemic mixture of enantiomeric chains but as a mixture of diastereomers[197]. It is noteworthy that, in contrast to poly-4-methylhex-1-ene, the monomeric analogue of its chain unit, 3-methylhexane, is not resolved on poly-3-methylpent-1-ene[196].

REFERENCES

1. R.M.Secor, Chem.Rev., 63, 297 (1963).
2. V.A.Davankov, Candidate's Thesis, Institute of Inorganic and Organoelementary Compounds of the USSR Academy of Sciences, Moscow, 1966.
3. R.Willstätter, Ber., 37, 3758 (1904).
4. C.W.Porter and C.Hirst, J.Amer.Chem.Soc., 41, 1264 (1919).
5. C.W.Porter and H.K.Ihrig, J.Amer.Chem.Soc., 45, 1990 (1923).
6. G.M.Henderson and H.G.Rule, Nature, 141, 917 (1938).
7. L.Zechmeister, Ann.N.Y.Acad.Sci., 49, 220 (1948).
8. W.Bradley and G.C.Easty, J.Chem.Soc., 499 (1951).
9. L.Ya.Yanovskaya, Priroda, No.10, 95 (1952).
10. E.I.Klabinovskii, Priroda, No.2, 88 (1955).
11. A.P.Terent'ev and V.M.Potapov, Uspekhi Khim., 26, 1152 (1957).
12. E.I.Klabunovskii, Uspekhi Khim., 27, 949 (1958).
13. E.Lederer, "Chromatographie en Chimie organique et biologique", Paris, Vol.1, 1959, p.607.
14. L.J.Smit, Chem.Tech.(Amsterdam), 17, 339 (1962).
15. A.W.Ingersoll and R.Adams, J.Amer.Chem.Soc., 44, 2930 (1922).
16. G.T.Morgan and D.G.Skinner, J.Chem.Soc., 127, 1731 (1925).
17. W.R.Brode and R.Adams, J.Amer.Chem.Soc., 46, 2032 (1924).
18. W.R.Brode and R.Adams, J.Amer.Chem.Soc., 48, 2193 (1926).
19. G.M.Henderson and H.G.Rule, J.Chem.Soc., 1568 (1939).
20. W.R.Brode and R.Adams, J.Amer.Chem.Soc., 48, 2202 (1926).
21. W.R.Brode and R.E.Brooks, J.Amer.Chem.Soc., 63, 923 (1941).
22. A.Korolev and I.Bilik, Dokl.Akad.Nauk SSSR, 29, 585 (1940).
23. H.Martin and W.Kuhn, Z.Elektrochem., 47, 216 (1941).
24. W.Bradley and G.C.Easty, J.Chem.Soc., 1519 (1953).
25. W.Bradley and R.A.Brindley, Chem. and Ind., 579 (1954).
26. W.Bradley, R.A.Brindley, and G.C.Easty, Discuss.Faraday Soc., No.16, 152 (1954).
27. W.Bradley and R.A.Brindley, Nature, 173, 312 (1954).
28. W.Bradley and R.A.Brindley, J.Chem.Soc., 1622 (1956).
29. R.De Vrecker and R.Lontie, Colloq.St.Jans.Hosp., Brugge (Belg) 3 Colloq., 1955, p.185; Chem.Abs., 51, 14554 (1957).
30. F.Karush, J.Phys.Chem., 56, 70 (1952).
31. R.H.McMenamy and J.L.Oncley, J.Biol.Chem., 233, 1436 (1958).
32. H.Euler and B.Bucht, Z.anorg.Chem., 126, 267 (1922).
33. F.Kögl, J.G.Faber, and Z.C.DeBoer, Rec.Trav.chim., 69, 482 (1950).
34. N.Grubhofer and L.Schleith, Naturwiss., 40, 508 (1953).
35. G.di Modica and E.Angeletti, Atti R.Accad.Sci.Torino, 87, 164 (1952–1953).
36. G.di Modica and E.Angeletti, Ricerca sci., 22, 715 (1952).
37. W.Prelog and P.Wieland, Helv.Chim.Acta, 27, 1127 (1944).
38. G.Farina, F.Montanari, and A.Negrini, Gazzetta, 89, 1548 (1959).
39. D.L.Garmaise and J.Colucci, U.S.P. 2957886 (1960); Chem.Zentr., 302 (1962).
40. G.Kamai and Yu.F.Gatilov, Zhur.Obshch.Khim., 34, 782 (1964).
41. T.Moeller and E.Gulyas, J.Inorg.Nuclear Chem., 5, 245 (1958).
42. T.Moeller, E.Gulyas, and R.H.Marshall, J.Inorg.Nuclear Chem., 9, 82 (1959).
43. F.B.Kipping and J.J.Wren, J.Chem.Soc., 3246 (1957).
44. A.E.Flood, E.L.Hirst, and J.K.L.Jones, J.Chem.Soc., 1679 (1948).

45. S.Berlingozzi, G.Serchi, and G.Adembri, Sperimentale, Sez.Chim.biol., 2, 89 (1951).
46. G.B.Bonino and V.Carassiti, Nature, 167, 569 (1951).
47. S.Berlingozzi, G.Adembri, and G.Bucci, Gazzetta, 84, 393 (1954).
48. M.Kotake, T.Sakan, N.Nakamura, and S.Senoh, J.Amer. Chem.Soc., 73, 2973 (1951).
49. T.Sakan, N.Nakamura, and S.Senoh, J.Inst.Polytechnics, Osaka City Univ.Ser.C, 2, No.1, 33 (1951); Chem.Abs., 46, 7075h
50. T.Sakan, N.Nakamura, and S.Senoh, J.Chem.Soc.Japan, 72, 745 (1951).
51. N.Nakamura, J.Chem.Soc.Japan, 72, 789 (1951).
52. Y.Fujisawa, J.Osaka City Med.Center, 1, 7 (1951); Chem. Abs., 48, 13550d (1954).
53. M.Mason and C.P.Berg, J.Biol.Chem., 195, 515 (1952).
54. T.Miwa, A.Ohsuka, and T.Sakan, J.Chem.Soc.Japan, 74, 113 (1953).
55. K.Closs and C.M.Haug, Chem. and Ind., 103 (1953).
56. V.Klingmüller and L.Maier-Sihle, Z.phys.Chem.(Leipzig), 308, 49 (1957).
57. R.Weichert, Acta Chem.Scand., 8, 1542 (1954); 9, 547 (1955).
58. C.E.Dent, Biochem.J., 43, 169 (1948).
59. C.E.Dalgliesh, J.Chem.Soc., 137 (1952).
60. C.E.Dalgliesh, Biochem.J., 52, 3 (1952).
61. C.E.Dalgliesh, J.Chem.Soc., 3940 (1952).
62. R.Consden, A.H.Gordon, and A.J.P.Martin, Biochem.J., 38, 224 (1944).
63. J.P.Lambrooy, J.Amer.Chem.Soc., 76, 133 (1954).
64. L.E.Rhuland, E.Work, R.F.Denman, and D.S.Hoare, J. Amer.Chem.Soc., 77, 4844 (1955).
65. C.L.DeLigny, H.Neiboer, J.J.M.DeVijlder, and J.H.Van Villingen, Rec.Trav.chim., 82, 213 (1963).
66. S.F.Contractor and J.Wragg, Nature, 208, 71 (1965).
67. W.Meyer and F.Merger, Annalen, 644, 65 (1961).
68. E.Buchar and K.Suchy, Magyar Kém.Folyóirat, 64, 45 (1958); Chem.Abs., 52, 11518f (1958).
69. A.Albert and E.P.Serjeant, Nature, 199, 1098 (1963).
70. I.Kikkawa, Yakugaku Zasshi, 81, 732 (1961); Chem.Abs., 55, 26005c (1961).
71. M.Tomita and M.Sugamoto, Yakugaku Zasshi, 82, 1141 (1962); Chem.Abs., 58, 6873c (1963).
72. A.Alessandro and C.M.Caldarera, Boll.chim.farm., 93, 404 (1954); Chem.Abs., 49, 4235d (1955).
73. J.Kisbye, B.E.Nielsen, and I.L.Handler, Dansk Tidsskr. Farm., 35, 121, 141 (1961); Chem.Abs., 56, 1376a (1962).
74. H.Krebs and R.Rasche, Naturwiss., 41, 63 (1954).
75. H.Krebs and R.Rasche, Z.anorg.Chem., 276, 236 (1954).
76. H.Krebs, R.Rasche, A.J.Wagner, and J.Diewald, Angew. Chem., 66, 329 (1954).
77. H.Krebs, J.Diewald, H.Arlitt, and J.A.Wagner, Z.anorg. Chem., 287, 98 (1956).
78. H.Krebs, J.Diewald, and J.A.Wagner, Angew.Chem., 67, 705 (1955).
79. H.Krebs, J.A.Wagner, and J.Diewald, Chem.Ber., 89, 1875 (1956).
80. H.Krebs, "Die Trennung von Racematen auf chromatographischem Wege", Westdeutscher Verlag, 1956.
81. H.Krebs and J.Diewald, German P. 1013655 (1956); Chem.Zentr., 4625 (1958).
82. H.Krebs and J.Diewald, German P. 1016713 (1958); Ref.Zhur.Khim., 72201 (1959).
83. W.Lautsch and D.Heinicke, Kolloid.Z., 154, 1 (1957).
84. M.Ohara, I.Fujita, and T.Kwan, Bull.Chem.Soc.Japan, 35, 2049 (1962).
85. M.Ohara, K.Ohta, and T.Kwan, Bull.Chem.Soc.Japan, 37, 1 (1964).
86. M.Ohara, C.J.Chen, and T.Kwan, Bull.Chem.Soc.Japan, 39, 137 (1966).
87. H.Krebs and A.Wagner, German P. 1013637 (1957); Chem. Abs., 54, 329a (1960).
88. H.Musso, Chem.Ber., 91, 349 (1958).
89. G.Kamai and G.M.Rusetskaya, Dokl.Akad.Nauk SSSR, 143, 596 (1962).
90. K.H.König, Thesis, 1956; see R.C.Schulz and E.Kaiser, Adv.Polymer Sci., 4, 301 (1965).
91. R.Tsuchida, M.Kobayashi, and A.Nakamura, J.Chem.Soc. Japan, 56, 1339 (1935).
92. R.Tsuchida, M.Kobayashi, and A.Nakamura, Bull.Chem. Soc.Japan, 11, 38 (1936).
93. G.Karagounis and G.Coumoulos, Nature, 142, 162 (1938).
94. M.Henderson and H.Rule, Nature, 142, 163 (1938).
95. G.Karagounis and G.Coumoulos, Praktika, 13, 414; Chem.Zentr., 1, 4740 (1939).
96. G.K.Schweitzer, C.K.Talbott, and J.Tennes, Acad.Sci., 25, 143 (1950); Chem.Abs., 46, 11004e (1952).
97. T.S.Piper, J.Amer.Chem.Soc., 83, 3908 (1961).
98. D.H.Busch and J.C.Bailar, J.Amer.Chem.Soc., 75, 4574 (1953).
99. D.H.Busch and J.C.Bailar, J.Amer.Chem.Soc., 76, 5352 (1954).
100. J.R.Kuebler and J.C.Bailar, J.Amer.Chem.Soc., 74, 3535 (1952).
101. E.I.Klabunovskii and V.V.Patrikeev, Dokl.Akad.Nauk SSSR, 78, 485 (1951).
102. Y.Ykeda, Bull.Liberal Arts Coll., Nakayama Univ.(Nat. Sci.), 4, 27 (1954); Chem.Abs., 49, 9583i (1955).
103. G.Kamai, E.I.Klabunovskii, Yu.F.Gatilov, and G.S.Khodakov, Dokl.Akad.Nauk SSSR, 139, 1112 (1961).
104. V.V.Patrikeev, N.I.Shuikin, and E.I.Klabunovskii, USSR P. 95526 (1953).
105. E.I.Klabunovskii, USSR P. 150528 (1963); Byul.Izobr., No.16, 13 (1963).
106. E.Ferroni and R.Cini, J.Amer.Chem.Soc., 82, 2427 (1960).
107. R.Curti, U.Colombo, and F.Clerici, Gazzetta, 82, 491 (1952).
108. R.Curti and U.Colombo, J.Amer.Chem.Soc., 74, 3961 (1952).
109. A.H.Beckett and P.Anderson, Nature, 179, 1074 (1957).
110. E.I.Klabunovskii, L.M.Volkova, and A.E.Agronomov, Izv.Akad.Nauk SSSR, Otd.Khim.Nauk, 2101 (1961).
111. L.H.Klemm and D.Reed, J.Chromatog., 3, 364 (1960).
112. L.H.Klemm, K.B.Desai, and J.R.Spooner, J.Chromatog., 14, 300 (1964).
113. G.Karagounis, Helv.Chim.Acta, 32, 1840 (1949).
114. G.Karagounis, E.Charbonnier, and E.Flöss, J.Chromatog., 2, 84 (1959).
115. H.Fischgold and R.Ammon, Biochem.Z., 234, 39 (1931).
116. I.Elphimoff-Felkin and H.Felkin, Bull.Soc.chim.France, 450 (1957).
117. Y.Gault and H.Felkin, Bull.Soc.chim.France, 742 (1965).
118. P.S.Fredricks and J.M.Tedder, Proc.Chem.Soc., 9 (1959); R.Stern and E.R.Atkinson, Chem. and Ind., 1758 (1962).
119. C.L.Arcus, L.A.Cort, T.J.Howard, and Le Ba Loc, J.Chem.Soc., 1195 (1960).
120. D.R.Moore and A.D.Kossoy, Analyt Chem., 33, 1437 (1961).
121. P.J.Porcaro and V.D.Johnston, Analyt.Chem., 33, 1748 (1961).
122. W.Doering and W.R.Roth, Tetrahedron, 18, 67 (1962).
123. F.Weygand, B.Kobl, A.Prox, M.A.Tilak, and I.Tomida, Z.phys.Chem.(Leipzig), 322, 38 (1960).
124. J.Casanova and J.Corey, Chem. and Ind., 1664 (1961).
125. E.Gil-Av and D.Nurok, Proc.Chem.Soc., 146 (1962).
126. E.Gil-Av, R.Charles, and G.Fischer, J.Chromatog., 17, 408 (1965).

127. E.Gil-Av, R.Charles-Sigler, G.Fischer, and D.Nurok, J.Gas Chromatog., 4, 51 (1966).
128. B.Halpern and J.W.Westley, Biochem.Biophys.Res.Comm., 361 (1965).
129. B.Halpern and J.W.Westley, Chem.Comm., 246 (1965).
130. B.Halpern and J.W.Westley, Biochem.Biophys.Res.Comm., 710 (1965).
131. B.Halpern and J.W.Westley, Chem.Comm., 34 (1966).
132. G.E.Pollock, V.I.Oyama, and K.D.Johnson, J.Gas. Chromatog., 3, 174 (1965).
133. G.E.Pollock and V.I.Oyama, J.Gas Chromatog., 4, 126 (1966).
134. H.C.Rose, R.L.Stern, and B.L.Karger, Analyt.Chem., 38, 469 (1966).
135. S.V.Vitt, M.B.Saporowskaya, I.P.Gudkova, and V.M.Belikov , Tetrahedron Letters, 2575 (1965).
136. F.Weygand, A.Prox, L.Schmidhammer, and W.König, Angew.Chem., 75, 282 (1963).
137. H.C.Beyerman, Maassen van den Brink, F.Weygand, A.Prox, W.König, L.Schmidhammer, and E.Nintz, Rec. Trav.chim., 84, 213 (1965).
138. G.Karagounis and G.Lippold, Naturwiss., 46, 145 (1959).
139. G.Goldberg and W.A.Ross, Chem. and Ind., 657 (1962).
140. A.Murai and Y.Tachikawa, J.Chromatog., 14, 100 (1964).
141, N.A.Goeckner, Diss.Abs., 19, 3127 (1959).
142. G.Karagounis and E.Lemperle, Z.analyt.Chem., 189, 131 (1962).
143. E.Gil-Av, B.Feibusk, and R.Charles-Sigler, Tetrahedron Letters, 1009 (1966).
144. A.K.Macbeth, J.A.Mills, and R.Pettit, J.Chem.Soc., 3538 (1950).
145. J.F.Bunnett and J.L.Marks, J.Amer.Chem.Soc., 74, 5893 (1952).
146. J.F.Bunnett, U.S.P. 2750347 (1956); Chem.Abs., 50, 12552g (1956).
147. A.Santoro, Baskerville Chem.J., City Coll.N.Y., 4, No.1, 8 (1953); Chem.Abs., 48, 4448i (1954).
148. N.Grubhofer and L.Schleith, Z.phys.Chem.(Leipzig), 296, 262 (1954).
149. E.I.Klabunovskii, Thesis, Institute of Organic Chemistry of the USSR Academy of Sciences, 1966, p.102.
150. S.Tsuboyama and M.Yanagita, Sci.Papers Inst.Phys.Chem. Res., Tokyo, 53, 245 (1959).
151. J.A.Lott and W.Rieman, J.Org.Chem., 31, 561 (1966).
152. N.V.Khromov-Borisov and S.P.Kozhevnikov, Zhur.Obshch. Khim., 31, 2926 (1961).
153. G.Losse, H.Jeschkeit, G.Fickert, and H.Rabe, Z.Naturforsch., 170b, 419 (1962).
154. Belg.P. 621135 (1962); Chem.Abs., 60, 661f (1964).
155. German P.Application 1211397 (24.2.1966); Literaturschenelldienst, 12, 2172 (1966).
156. H.Suda and R.Oda, Mem.Fac.Tech.Kanazawa Univ., 2, 215 (1960).
157. T.I.Rabek and J.Morawiec, Polimery Tworzywa, 11, 251 (1966).
158. W.M.Trochimzcuk and T.I.Rabek, Internat.Symp.Macromol.Chem., Prague, 1965; Abstracts, A567.
159. W.Trochimczuk, Polimery Tworzywa, 11, 279 (1966).
160. S.Tsuboyama, Bull.Chem.Soc.Japan, 35, 1004 (1962).
161. E.Selegny, N.Thoal, and M.Vert, Compt.rend., 262c, 189 (1966).
162. A.Rieche and H.Gross, East German P. 20475 (1958); Chem.Abs., 36, 1610g (1962).
163. V.V.Korshak, S.V.Rogozhin, and V.A.Davankov, USSR P. 176064 (1965); Byul.Izobr., No.21, 47 (1965).
164. V.V.Korshak, S.V.Rogozhin, V.A.Davankov, and S.G.Vyrbanov, Izv.Akad.Nauk SSSR, Ser.Khim., 544 (1966).
165. C.W.Roberts and D.H.Haigh, J.Org.Chem., 27, 3375 (1962).
166. G.Manecke and S.Singer, Makromol.Chem., 39, 13 (1960).
167. G.Manecke and G.Gunzel, Makromol.Chem., 51, 199 (1962).
168. G.Manecke and H.J.Förster, Makromol.Chem., 91, 136 (1966).
169. J.Noguchi, S.Tokura, M.Inomata, and C.Asano, J.Chem. Soc.Japan, Ind.Chem.Sect., 68, 904 (1965).
170. D.L.Garmaise, U.S.P. 2957917 (1960); Chem.Abs., 55, 5349d (1961).
171. E.Selegny, J.Huguet-Luzaic, and Y.Merle, Compt.rend., 262c, 71 (1966).
172. D.Braun, "Anomalien bei Ionenaustausch-Vorgängen", Berlin, 1961.
173. R.C.Schulz, Kolloid Z., 197, 55 (1964).
174. R.C.Schulz and E.Kaiser, Adv.Polymer Sci., 4, 236 (1965).
175. I.N.Topchieva, Uspekhi Khim., 35, 1788 (1966) [Russ. Chem.Rev., 741 (1966)].
176. Y.Minoura, M.Takebayashi, and C.C.Price, J.Amer. Chem.Soc., 81, 4689 (1959).
177. R.Buyle, Chem. and Ind., 195 (1966).
178. M.S.Toy and C.C.Price, J.Amer.Chem.Soc., 82, 2613 (1960).
179. V.V.Korshak, S.V.Rogozhin, V.A.Davankov, Yu.A.Davidovich, and T.A.Makarova, Uspekhi Khim., 34, 777 (1965) [Russ.Chem.Rev., 329 (1965)].
180. M.Szwarc, Adv.Polymer Sci., 4, 1 (1965).
181. R.K.Kulkarni and H.Morawetz, J.Polymer Sci., 54, 491 (1961).
182. R.C.Schulz, P.Elzer, and W.Kern, Makromol.Chem., 42, 197 (1961).
183. T.Ida, K.Noda, S.Takahashi, and I.Umsumi, Makromol. Chem., 73, 215 (1964).
184. Y.Minoura and N.Sakota, J.Chem.Soc.Japan, 83, 912 (1962).
185. R.C.Schulz and H.Hartmann, Makromol.Chem., 65, 106 (1963).
186. F.H.Spedding, J.E.Powell, and H.J.Svec, J.Amer.Chem. Soc., 77, 1265 (1955).
187. G.Dickel and K.Becker, Chem.-Ing.-Tech., 28, 529 (1956).
188. S.E.Bresler, A.I.Egorov, and B.P.Konstantinov, Izv. Akad.Nauk SSSR, Otd.Khim.Nauk, 1938 (1960).
189. K.Toy, Y.Izumi, and S.Akabori, Bull.Chem.Soc.Japan, 35, 1422 (1962); 36, 743, 829 (1963).
190. K.Toy, Bull.Chem.Soc.Japan, 36, 739 (1963).
191. S.Tsuboyama, Bull.Chem.Soc.Japan, 38, 354 (1965); 39, 698 (1966).
192. N.J.Leonhard and W.J.Middleton, J.Amer.Chem.Soc., 74, 5114 (1952).
193. T.Tsuruta, S.Inoue, and I.Tsukuta, Makromol.Chem., 84, 298 (1965).
194. J.Furukawa, S.Akutsu, and T.Saegusa, J.Chem.Soc.Japan, Ind.Chem.Sect., 68, 909 (1965); Makromol.Chem., 94, 68 (1966).
195. P.Pino, F.Ciardelli, G.P.Lorenzi, and G.Natta, J.Amer. Chem.Soc., 84, 1487 (1962).
196. B.P. 914569 (1963); Chem.Abs., 58, 6943 (1963).
197. P.Pino, G.Montagnoli, F.Ciardeli, and E.Benedetti, Makromol.Chem., 93, 158 (1966).

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