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A NEW METHOD FOR RESOLVING ENANTIOMERS BY GAS CHROMATOGRAPHY
I. RESOLUTION OF SOME BICYCLIC ALCOHOLS AND KETONES

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It has been shown that racemic modifications of enantiomers may be resolved gas chromatographically by co-injection of the racemate and an appropriate, volatile resolving agent onto a non-optically active column.

For more than a decade the possibility of resolving optical isomers by gas chromatography has been studied.[2] During this time two techniques have been developed: (1) conversion of the enantiomers to diastereomers with an optically active resolving agent followed by chromatographic separation of the resulting diastereomers, and (2) direct resolution of the enantiomer pair on an optically active stationary phase. Method 1 has been used in a variety of resolutions but has the drawback that a given resolution requires at least two steps beyond the separation itself: bonding the resolving agent to the racemic substrate and cleaving the resolving agent from the separated diastereomers. In a synthetic scheme, extra steps may also have to be included to provide functionality appropriate for reaction with the resolving agent. Method 2 has been developed into an elegant and well studied procedure for resolving certain amino acid derivatives[3] but attempts to expand the method to other classes of compounds have been only partially successful.[4] Even the optimum case, in which N-TFA-amino acid esters are resolved, requires forming a derivative of the amino acid prior to the resolution thus diminishing the value of the method for preparative scale synthesis of the amino acids themselves.

It has been established that the interaction of each antipode of an enantiomer pair with an optically active solvent may be different,[5] a difference which no doubt depends on non-bonded interactions occurring between the solvent and the solute molecules. If relatively weak bonding, such as hydrogen bonding, can occur between the solute and solvent molecules, it is reasonable that the bonding strength of each antipode with the optically active solvent may be quite different.[6] If, on the other hand, the bond strengths are comparable for the complex formed by interaction of each antipode with the solvent, the complexes are still diastereomeric and, therefore, theoretically separable by ordinary physical methods. This reasoning led us to postulate that it would be possible to resolve an enantiomer pair by co-injecting it onto a gas chromatography column along with a volatile, optically active resolving agent. The resolving agent should provide the diastereomeric interaction with the enantiomers necessary to resolve them while the two compounds are in contact during the early part of passage through the

column, but the bonding between the resolving agent and the enantiomer pair would be sufficiently weak that the resolving agent would be separated from both antipodes prior to reaching the end of the column. Once separated from each other and from the resolving agent the enantiomers should move at identical rates on an achiral stationary phase and remain separated for the remainder of their passage through the column.

We have now established that resolutions may, in fact, be effected by co-injection of a mixture of a racemic modification and a volatile, optically active resolving agent onto a gas chromatography column which is not itself optically active.

Thus, for example, upon injecting a 1:3 mixture of d,ℓ-isoborneol, and pure d-camphor, onto a 10 ft. by 1/4 in. column of 5% of QF-1 on Chromosorb W, three peaks were observed in the gas chromatogram. The peaks corresponding to the first two compounds eluted (the levo- and dextrorotatory isomers of isoborneol respectively) partially overlapped but the peak corresponding to camphor was well separated from them. To verify that resolution of the enantiomers had in fact occurred, the eluent corresponding to each of the first two peaks was collected and its optical rotation determined. The eluent from the first peak (retention volume = 930 ml) had $[\alpha]_D^{25}$-27° (C=0.026, alcohol) while the eluent from the second peak (retention volume = 1060 ml) had $[\alpha]_D^{26}$+27° (C=0.051, alcohol). By comparison to specific rotations determined at 20° and C=5.0[7] this represents an optical purity of 79% in each case.[8] To verify that the observed rotations were indeed caused by the isoborneol enantiomers and were not artifacts from unseparated camphor, the combined eluent from the first two peaks was collected and shown by ir to be identical with the starting d,ℓ-isoborneol and to be free to any absorption in the carbonyl region of the spectrum.

To explore the scope of this method for separating optical isomers, a number of pairs of compounds were examined. The results of this survey are given in Table 1. For each positive result in Table 1, the apparent resolution was chromatographically observed as two distinct but overlapping peaks in the chromatogram for the resolved enantiomers and a third peak separated from the first two for the resolving agent.

During the course of this preliminary study a number of interesting observations were made concerning the chromatographic parameters which affect the resolution. Not surprisingly, the enantiomers were most readily resolved at low column temperatures. This result is consistent with the postulate that resolution would be effected by weak diastereomeric interactions between the antipodes and the resolving agent. A consequence of the requirement for low column temperatures is that the resolving agent and substrate be poorly retained by the column. This was shown to be true during an attempted resolution of d,ℓ-isoborneol with ℓ-borneol. Though the isoborneol peak was partially resolved into two peaks when isoborneol was co-injected with ℓ-borneol, failure of column (A) to fully separate the isoborneol and the borneol prevented this from offering a practical resolution. When the resolution was attempted on a diethyleneglycol adipate (DEGA) column which would separate borneol from isoborneol, resolution of the dextro- and levo-isoborneol isomers was no longer observed at the higher temperature required. The possibility of overcoming this difficulty by using two columns in succession with temperature programming is being explored. While resolution of enantiomers was chromatographically observed at racemate:resolving agent ratios of 1:1, better results were generally obtained when the ratio was 1:3 to 1:6.

TABLE I

ATTEMPTED RESOLUTIONS OF BICYCLIC KETONE AND ALCOHOL ENANTIOMERS

Racemate	Resolving Agent	Column[a]	Ratio[b]	Temperature	Results[c]
d,ℓ-isoborneol	d-borneol	A	1:1	82°	+
d,ℓ-isoborneol	d-camphor	A	1:3, 1:6	85°	+
d,ℓ-exo-norborneol	d-camphor	B	1:3	88°	+
d,ℓ-exo-norborneol	ℓ-borneol	A,B	1:3, 1:6	72°, 60°	-
d,ℓ-exo-norborneol	d-limonene	A	1:3	70°	-[d,e]
d,ℓ-exo-norborneol	ℓ-amphetamine	B	1:3	55°, 75°	-
d,ℓ-camphor	ℓ-borneol	A,B	1:3	82°	+
d,ℓ-camphor	d-camphor	A	1:1	89°	-
d,ℓ-norcamphor	d-camphor	B	1:3	83°	-
d,ℓ-norcamphor	ℓ-borneol	B	1:3	65°	-
d,ℓ-norcamphor	ℓ-menthol	B	1:3	90°	+
d,ℓ-[3.2.0]heptenone[f]	ℓ-menthol	B	1:3	81°	+
d,ℓ-[3.2.0]heptenone[f]	d-camphor	A,B	1:1	82°, 71°	-
d,ℓ-[3.2.0]heptenone[f]	ℓ-borneol	A	1:1	90°	-
d,ℓ-[3.2.0]heptenone[f]	d-limonene	A	1:3	76°, 90°	-[d,e]
d,ℓ-ethyl-2-bromopropionate	d-limonene	B	1:3	71°	-[d,e]

a. Column A: 5% QF-1 on Chromosorb W, 45/60, AW, 10 ft. X 1/4 in.
Column B: 5% QF-1 on Chromosorb W, 45/60, AW, 5 ft. X 1/4 in.

b. Weight ratio of racemate to resolving agent in the injected mixture.

c. A (+) indicates that resolution was observed chromatographically by partial splitting of the peaks corresponding to the racemate into two peaks. A (-) indicates no such splitting was observed.

d. The peak corresponding to the resolving agent partially split.

e. Resolving agent eluted ahead of the racemate peaks.

f. d,ℓ-endo-7-methylbicyclo[3.2.0]hept-2-en-6-one, kindly provided by Dr. R. W. Holder of this Department. The sample contained a small percentage of the exo isomer.

Several other observations are less readily understood. First, it was found that the resolution is generally improved (and in some cases only occurs) with very high loadings of the substrate-resolving agent mixture on the column. Second, it was found that in those cases (Table I) where the resolving agent eluted ahead of the racemate there was generally no resolution of the racemate. (The single exception was the apparent resolution of d,ℓ-camphor with ℓ-borneol.) Instead, it was sometimes observed in these cases that the peak corresponding to the resolving agent was partially split. Apparently the desired diastereomeric interaction was occurring between the enantiomers of the racemate and the resolving agent, but the effect was to slow passage of part of the resolving agent through the column rather than resolve the enantiomers. The implication of this observation is that with a properly chosen resolving agent these compounds should also be resolvable by this method--a significant point because included

in this category is the splitting of d-limonene by d,ℓ-ethyl-2-bromopropionate, an acyclic racemate. Finally, it was felt that if a more strongly retained resolving agent such as d-ca was injected first as a slug comparable to the loading used in the co-injection procedure and this was followed by injection of a racemic substrate such as d,ℓ-isoborneol which moves through the column more rapidly, resolution of the enantiomers should occur while the racemate is passing through the resolving agent slug on the column. It has not yet been possible to effect a resolution in this way, however, even using pairs of compounds which give successful results in the co-injection method. Thus it appears that the diastereomeric interaction of the enantiomers with the resolving agent is established in solution, prior to injection, and survives the vaporization step or that the resolution occurs at the very beginning of the column when it is overloaded. Investigation of these questions as well as a systematic study of the chromatographic parameters affecting a given resolution is underway.

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References

1. American Chemical Society Project SEED Participant, Highland High School, Albuquerque, New Mexico.
2. For reviews see E. Gil-Av and D. Nurok in Advances in Chromatography, J. C. Giddings and R. A. Keller, eds., Marcel Dekker, New York (1974). S. J. Rogozhin and V. A. Davankov, Russ. Chem. Rev., 37, 565 (1968). B. L. Karger, Anal. Chem., 39, 24A (1967).
3. P. Y. Howard and W. Parr, Chromatographia, 7, 283 (1974) and references therein. W. Parr, C. Yang, E. Bayer, and E. Gil-Av, J. Chromatogr. Sci., 8, 591 (1970) and references therein. J. A. Corbin, J. E. Rhoad, and L. B. Rogers, Anal. Chem., 43, 327 (1971).
4. G. Karagounis and G. Lippold, Naturwiss., 46, 145, (1959). N. A. Goeckner, Ph.D. Dissertation, State University of Iowa, (1959) [Diss. Abstr., 19, 3127 (1959)]. G. Goldberg and W. A. Ross, Chem. and Ind. (London), 657 (1962). J. Houche, M. Moreau, R. Longeray, and J. Dreux, Chromatographia, 7, 306 (1974). J. A. Corbin and L. B. Rogers, Anal. Chem., 42, 974 (1970). B. Feibush and E. Gil-Av, J. Gas Chromatogr., 5, 257 (1967).
5. T. S. Patterson and C. Buchanan, J. Chem. Soc., 290 (1940).
6. B. Feibush, Ph.D. Thesis, The Weizmann Institute of Science, Rehovoth, Israel (1967).
7. CRC Handbook of Chemistry and Physics, 52nd Ed., Chemical Rubber Co., Cleveland (1971) p. C-345.
8. Since the observed optical puritics represent the result of collecting parts of two overlapping peaks, the observation of identical values of 79% is, of course, fortuitous. Repeating this experiment gave the following results: first peak $[\alpha]_D^{22}$ -19° (C = 0.076, alcohol) 55% optically pure. Second peak $[\alpha]_D^{22}$ +5° (C = 0.137, alcohol) 15% optically pure.