# Correlation of the Absolute Configuration of α-Alkylphenylacetic Acids by Gas–liquid Chromatography

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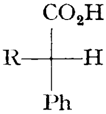
A recent Communication on the asymmetric transformation of α-alkylphenylacetic acids (I) with *S*-(+)-2-methylamino-1-phenylpropane concludes that (+)-alkylphenylacetic acids (R = Me, Et, $\text{Pr}^n$, $\text{Bu}^n$) and (−)-alkylphenylacetic acids (R = $\text{Pr}^i$, $\text{Bu}^i$) have the same absolute (*S*)-configuration.[1]



$$\begin{array}{c} \text{CO}_2\text{H} \\ \text{R}-\!\!\!-\!\!\!\!+\!\!\!\!-\!\!\!-\text{H} \\ \text{Ph} \end{array}$$

(I)

These assignments, however, are not in agreement with results derived from optical rotatory dispersion (o.r.d.) measurements of the *N*-methylthionamide derivatives[2,3] and experimental evidence[3] based on Freudenberg's "rule of shift",[4] which suggest that all (+)-alkylphenylacetic acids have the same absolute (*S*)-configuration.

The steric course of the asymmetric transformation is based on the assumption that *S*-(+)-2-methylamino-1-phenylpropane reacts with an excess of the racemic acid in such a way that one (A) of the two possible diastereoisomeric intermediates is formed preferentially. (Figure.)

Since the experimental evidence for such a conclusion is entirely based on the measurement of a small rotation of some of the re-isolated unreacted acid, we have re-examined this reaction, but with gas–liquid-chromatographic (g.l.c.) separation of the diastereoisomeric amides for the steric analysis of the products.

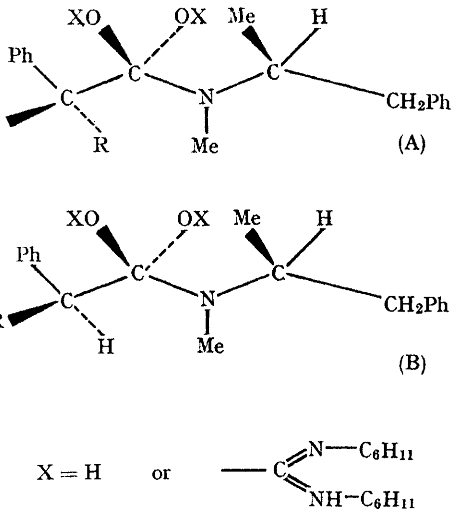
In a typical experiment, the alkylphenylacetic acid (1·5 mmole) was treated with dicyclohexylcarbodi-imide (1 mmole) in tetrahydrofuran. After cooling, *S*-(+)-2-methylamino-1-phenylpropane (1 mmole) was added and the suspension stirred for 24 hr. at room temperature. The mixture was then diluted with ethyl acetate and the dicyclohexylurea formed was filtered off. The unchanged acid was isolated for optical analysis (alkali extraction) and a part of the dried organic layer (~2μl. containing approximately 5μg.) injected into the gas chromatograph.

TABLE. *Gas-chromatographic analysis of diastereoisomeric α-alkylphenylacetyl derivatives of* S-(+)-*2-methylamino-1-phenylpropane*

| α-Alkylphenylacetic acid (I; R=) | Ratio of concentration of diastereoisomers $\frac{(-)\text{acid}(+)\text{amide}}{(+)\text{acid}(+)\text{amide}}$ | Sign of optical rotation of unchanged acid | Retention time of diastereoisomers (min)*† (+)-(+) | (−)-(+) |
|---|---|---|---|---|
| Methyl | 1·13 | + | 9·2 | 10·5 |
| Ethyl | 1·06 | + | 9·5 | 10·7 |
| n-Propyl | 1·10 | + | 11·8 | 13·0 |
| Isopropyl | 1·01 | + | 9·0 | 10·2 |
| n-Butyl | 1·03 | + | 15·6 | 17·2 |
| Isobutyl | 1·06 | + | 12·2 | 12·8 |
| t-Butyl | 1·82 | 0 | 8·9 | 10·2 |
| Cyclopentyl | 1·04 | 0 | 12·0 | 13·6 |

* G.l.c. analyses were carried out on a Varian Aerograph Series 1200 gas chromatograph using a 5 ft. × ⅛ in. column (1% HI-EFF-8AP on gas chrom Q). During the analyses the nitrogen flow was 35 ml./min. and the separation temperature 200° (cyclopentyl derivative 220°).

† G.l.c. retention time assignments were made on the basis of the g.l.c. analyses of optically pure (+)-(+)-amides prepared from (+)-α-alkylphenylacetic acids obtained by resolution *via* the 1-1′-Naphthylethylamine salts (ref. 4).



FIGURE

Our results (Table) show that for all α-alkylphenylacetic acids (I; R = Me, Et, $\mathrm{Pr}^n$, $\mathrm{Bu}^n$, $\mathrm{Pr}^i$, $\mathrm{Bu}^i$, $\mathrm{Bu}^t$, cyclopentyl) the diastereoisomer derived from the (−)-acid is formed preferentially. However, g.l.c. analysis shows that the reaction is only slightly stereospecific (diastereoisomer product ratio 1 : 1·01 to 1 : 1·13), except in the case of the derivative (R = $\mathrm{Bu}^t$) where significantly more of (−)-acid (+)-amide is formed (product ratio 1 : 1·82).

In the *homologous* series (R = Me, Et, $\mathrm{Pr}^n$, $\mathrm{Bu}^n$, $\mathrm{Pr}^i$, $\mathrm{Bu}^i$) slightly dextrorotary acids were obtained by alkali extraction. For the more sterically hindered acids (R = $\mathrm{Bu}^t$, cyclopentyl), amide formation proceeds in such a low yield, that optical analysis of the unreacted acids showed no observable rotation (Zeiss polarimeter, mean error 0·01°).

Finally it has already been demonstrated in the case of α-amino-acids,[5,6] alkylamines,[7] α-hydroxy-acids,[8] and α-chloro-acids,[9] that the retention volumes of diastereoisomers derived from a *homologous* series could be used for the correlation of absolute configuration. Our g.l.c. data (Table) show that all (+)-acid-*S*(+)-amides consistently have the shorter retention volume and since the absolute configuration of (+)-hydratropic acid (I; R = Me) is known to have the *S*-configuration, we conclude that all (+)-acids have the *S*-configuration. This further confirms the assignment indicated by o.r.d., Freudenberg's "rule of shift", and the now corrected asymmetric transformation reaction.

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[1] O. Červinka and L. Hub, *Chem. Comm.*, 1966, 761.
[2] J. V. Burakevich and C. Djerassi, *J. Amer. Chem. Soc.*, 1965, **87**, 51.
[3] H. S. Mosher, private communication.
[4] B. Halpern and J. W. Westley, forthcoming publication.
[5] B. Halpern and J. W. Westley, *Biochem. Biophys. Res. Comm.*, 1965, **19**, 361.
[6] E. Gil-Av, R. Charles-Sigler, G. Fischer, and D. Nurok, *J. Gas Chromatog.*, 1966, **4**, 5.
[7] B. Halpern and J. W. Westley, *Chem. Comm.*, 1966, 34.
[8] E. Gil-Av and D. Nurok, *Proc. Chem. Soc.*, 1962, 146.
[9] B. Halpern and J. W. Westley, *Chem. Comm.*, 1965, 246.
[10] E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill Co., 1962, p. 120.