Journal of Chromatography, 462 (1989) 458–460
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 21 071

Note

Resolution of *rac*-1,2-halohydrins by chiral complexation gas chromatography

N. N. JOSHI and M. SREBNIK*

H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, IN 47907 (U.S.A.)

(First received July 12th, 1988; revised manuscript received October 25th, 1988)

One of the important requisites in asymmetric synthesis is the determination of enantiomeric excess (ee) by a simple and suitable analytical technique. During the course of our studies aimed at the asymmetric synthesis of 1,2-halohydrins[1], we required a rapid and reliable method to determine %ee of the synthesized compounds. In this regard, capillary gas chromatography (GC) affords a high degree of precision and reproducibility. Surprisingly, there is no report in the literature describing the resolution of 1,2-halohydrins by GC[2].

Initially we attempted the resolution on capillary GC through the standard chiral derivatizing agents, (+)- or (–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA)[3], (–)-menthyl chloroformate (MCF)[4] and (–)-N-(trifluoroacetyl) prolyl chloride (TPC)[5], on the following columns of increasing polarity: methyl silicone (50 m × 0.25 mm I.D.), SPB-35 (30 m × 0.25 mm I.D.) and Supelcowax (15 m × 0.25 mm I.D.). However, only a few chlorohydrins could be moderately resolved and most compounds did not resolve at all. In addition, retention times for the iodo derivatives were excessively long with concommitant peak broadening. Recently, chiral metal complexation chromatography has emerged as an efficient method for resolving various classes of compounds[6]. Roush has further extended the scope of this method to include homoallylic alcohols as their methyl ethers[7]. We, therefore, decided to investigate the feasibility of separating, 1,2-halohydrins by complexation GC.

EXPERIMENTAL

Separations were performed on a 25 × 0.25 mm I.D. fused-silica Ni-R-Cam column purchased from Capillary Columns Complexation Chromatography (Kirchentellinsfurt, F.R.G.), with a Hewlett-Packard Model 5890 gas chromatograph and monitored with a Hewlett-Packard Model 3392A integrator. Helium was used as the carrier gas.

A microscale procedure for the derivatization was performed as follows: to a solution of acetyl chloride (0.15 mmol, 1.0 *M* in carbon tetrachloride) the halohydrin (0.1 mmol) was added, followed by pyridine (0.15 mmol, 1.0 *M* in carbon tetrachloride). After stirring at room temperature for 1 h, the reaction mixture was diluted with diethyl ether (20 ml) and washed successively with 2 *M* hydrochloric acid, water,

0021-9673/89/$03.50 © 1989 Elsevier Science Publishers B.V.

saturated aqueous $NaHCO_3$ and water. After drying over sodium sulfate the solution was filtered through a short pad of neutral alumina (grade I), and an aliquot (0.2–0.4 μl) was injected in the column.

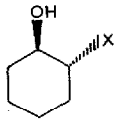
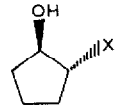
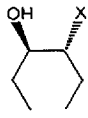
RESULTS AND DISCUSSION

We first examined underivatized chlorohydrins on an Ni-R-Cam column (25 m × 0.25 mm I.D.). Unfortunately the resolution was marginal, and the retention times were unacceptably long. In addition, thermally labile bromo- and iodohydrins could not be analysed directly. It is generally known that the introduction of π-donor systems (aromatic, carbonyl and nitrogen containing groups) enhances the chiral recognition on metal complex chiral columns. We therefore examined the corresponding acetates. Gratifyingly, the results were impressive (Table I). Excellent resolutions were obtained for all the halohydrins (Cl, Br, I) examined, cyclic as well as acyclic. In general, the separation factor (α) was greater in the case of cyclic compounds than for the corresponding acyclic analogues. Also for each series of halohydrins, resolution was in the order, Cl < Br < I. An important finding was the fact that the (1*R*,2*R*) enantiomers always eluted first on the Ni-R-Cam column[1]. A typical chromatogram is shown in Fig. I.

TABLE I

RESOLUTION OF 1,2-HALOHYDRINS (AS THEIR ACETATES) ON NI-R-CAM

Entries 1–6: carrier gas, helium; head pressure, 207 kPa. Entries 7–12; carrier gas, helium; head pressure, 137 kPa.

Entry	*Compound*	*X*	*Temperature (°C)*	t_R *(min)**	*Absolute configuration*[1]	α**
1		Cl	100	11	1*R*,2*R*	1.16
2		Br	105	11.8	1*R*,2*R*	1.18
3		I	110	12.3	1*R*,2*R*	1.19
4		Cl	85	9.9	1*R*,2*R*	1.14
5		Br	95	10.7	1*R*,2*R*	1.15
6		I	100	11.9	1*R*,2*R*	1.17
7		Cl	80	10.97	1*R*,2*R*	1.06
8		Br	85	10.7	1*R*,2*R*	1.10
9		I	90	12.7	1*R*,2*R*	1.11
10		Cl	85	12.47	1*R*,2*R*	1.04
11		Br	90	16.4	1*R*,2*R*	1.07
12		I	95	17.5	1*R*,2*R*	1.07

* Retention time for the first eluting enantiomer.

** Defined as $[(t_{R2}-t_0)/(t_{R1}-t_0)]$, where t_{R1} is the retention time for the first eluting enantiomer, t_{R2} for the second, and t_0 for the unretained solvent.

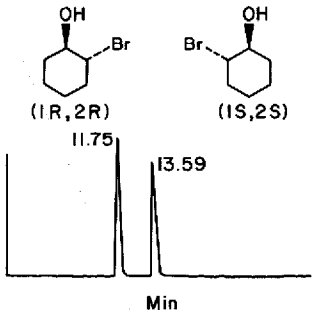


Fig. 1. Enantiomeric resolution of (±)-*trans*-1-bromocyclohexanol (as the acetate) on an Ni-R-Cam column (25 m × 0.25 mm I.D.) at 100°C and 207 kPa. Carrier gas: helium.

Thus, we have demonstrated the efficacy of complexation GC for the enantiomeric analysis of 1,2-halohydrins. Since optically active halohydrins are potentially important synthons, the present method, which is both rapid and unequivocal, should find wide applicability.

ACKNOWLEDGEMENTS

We would like to thank the National Institutes of Health (Grant No. GM 10937-25) for financial support of this work, and Professor H. C. Brown for fruitful discussions.

REFERENCES

1 N. N. Joshi, M. Srebnik and H. C. Brown, *J. Am. Chem. Soc.*, 110 (1988) 6246.
2 W. A. König, *The Practice of Enantiomer Separation by Capillary Gas Chromatography*, Hüthig Verlag, Heidelberg, 1987.
3 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 34 (1969) 2543.
4 J. W. Westley and B. Halpern, *J. Org. Chem.*, 33 (1968) 3978.
5 E. A. Hoopes, E. T. Peltzer and J. L. Bada, *J. Chromatogr. Sci.*, 16 (1978) 556.
6 V. Schurig, *Kontakte (Darmstadt)*, 1 (1986) 3.
7 R. L. Halterman, W. R. Roush and L. K. Hoong, *J. Org. Chem.*, 52 (1987) 1152.