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# Gas Chromatographic Enantiomer Separation of Bromochlorofluoromethane

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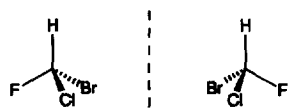
**Abstract:** Analytical enantiomer separation of bromochlorofluoromethane, one of the simplest chiral molecules, has been achieved by capillary gas chromatography on a Chirasil-Dex-type stationary phase.

Numerous attempts to prepare the enantiomers of bromochlorofluoromethane have been made, because the experimental determination of its maximum rotation and absolute configuration are of great interest in the context of the modern theories of optical activity[1]. Due to the lack of a suitable analytical method, the enantiomeric composition of weakly optically active CHFClBr samples prepared by different groups[2,3] remained elusive until 1985, when Collet *et al.* synthesized a cryptophane host, which was tailor-made for enantioselective inclusion of CHFClBr and could be used as a chiral NMR shift-reagent[4]. The completely separated haloform proton resonances of the resulting diastereomeric host-guest complexes permitted for the first time the determination of the enantiomeric purity. A dextrorotatory sample obtained by Wilen *et al.*[3] showed an enantiomeric excess of ee = 4.3 ± 1 % and the expected maximum specific rotation of CHFClBr could consequently be calculated to be $\alpha_D^{25}$ +3 (± 0.5, neat, 1 dm). This conclusion was recently supported by the preparation of a sample of higher ee[5].




(*S*)- (*R*)-
bromochlorofluoromethane

In this account we report a further, convenient and rapid, analytical method which requires only minute amounts of the analyte. Enantiomer separation of CHFClBr by capillary gas chromatography (GC) on an immobilized cyclodextrin stationary phase proved successful. The cyclodextrin derivative, octakis(3-*O*-butanoyl-2,6-di-*O*-*n*-pentyl)-γ-cyclodextrin, has been introduced into enantioselective GC by König *et al.*[6] and was recently[7] adapted to a Chirasil-Dex-type stationary phase[8], *i.e.*, the cyclodextrin derivative was chemically linked *via* one 6-*O*-octamethylene spacer to a dimethylpolysiloxane. The resulting stationary phase can be crosslinked and/or immobilized onto the surface of fused-silica capillaries and shows all advantages inherent to apolar polysiloxanes, such as high chromatographic efficiency, high temperature stability and long column lifetime. Furthermore, this kind of stationary phases may be operated under cryogenic conditions without loss in column efficiency. This fact may be crucial in the case of difficult separations, because in the enthalpy-controlled temperature region the enantioselectivity $-\Delta\Delta G$ increases with decreasing temperatures[9]. As shown in Fig. 1, temperatures even below -20 °C were necessary to achieve a baseline-resolution of CHFClBr. The sample injected was the original sample of Wilen[3], and the peak integration yielded an enantiomeric excess of ee = 4.5 ± 1 %, thus confirming the quantitative NMR results mentioned above and proving that no racemization has occurred since the preparative resolution by Wilen's group 19 years ago.

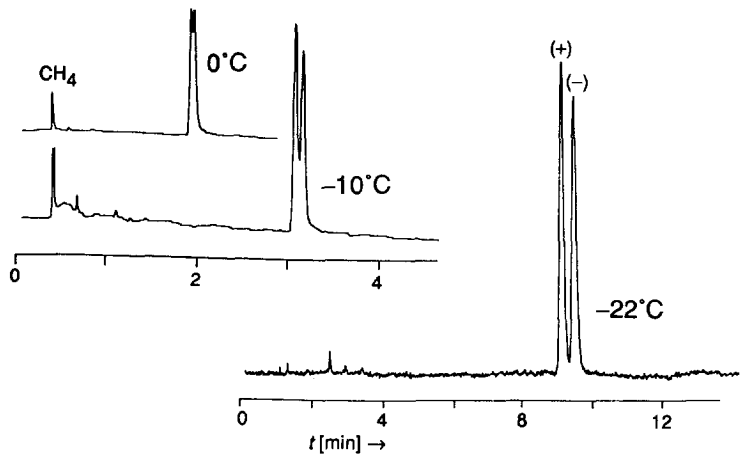



**Fig. 1.** Gas chromatographic enantiomer separation of CHFClBr at different column temperatures. Fused-silica capillary column (10 m, i.d. = 0.25 mm) coated with immobilized polysiloxane-bonded octakis(3-*O*-butanoyl-2,6-di-*O*-*n*-pentyl)-γ-cyclodextrin (film thickness 0.18 μm). Carrier gas hydrogen (50 cm/sec), split injection (100 ml/min), flame-ionization detection (FID). CHFClBr was injected as vapour-air mixture, a trace of methane was added.

To our knowledge, CHFClBr is the smallest chiral (non-isotopically labelled) molecule that has ever been resolved by chromatography. As the cyclodextrin cavity is clearly too large for this molecule, it is likely that the observed enantioselectivity is due to averaged diastereomeric dipole/dipole and/or H-bonding interactions between the substrate and the chiral force field of the cyclodextrin, rather than to enantioselective inclusion. The chromatographic method described here will allow an easy and rapid analysis of samples obtained by enantioselective synthetic approaches aiming at establishing the absolute configuration of this molecule[10].

## References

[1] P. H. Anderson, B. Stephenson and H. S. Mosher, *J. Am. Chem. Soc.* **1974**, *96*, 3171-3177; J. Applequist, *Acc. Chem. Res.* **1977**, *10*, 79-85; C. Marcott, T. R. Faulkner, A. Moscowitz and J. Overend, *J. Am. Chem. Soc.* **1977**, *99*, 8169-8175; K. R. Sundberg, *J. Chem. Phys.* **1978**, *68*, 5271-5276 and references therein; L. D. Barron and B. P. Clark, *Molecular Physics* **1982**, *46*, 839-851.

[2] M. K. Hargreaves and B. Modarai, *J. Chem. Soc. D* **1969**, 16; M. K. Hargreaves and B. Modarai, *J. Chem. Soc. C* **1971**, 1013-1015.

[3] S. H. Wilen *et al.*, 1975, unpublished work, *cf.* S. H. Wilen, K. A. Bunding, C. M. Kascheres and M. J. Wieder, *J. Am. Chem. Soc.* **1985**, *107*, 6997-6998. Wilen's sample exhibited $[\alpha]_D^{25}$ +0.129 (neat). We are particularly grateful to S. H. Wilen for providing us with this sample.

[4] J. Canceill, L. Lacombe and A. Collet, *J. Am. Chem. Soc.* **1985**, *107*, 6993-6996.

[5] T. R. Doyle and O. Vogl, *J. Am. Chem. Soc.* **1989**, *111*, 8510-8511.

[6] W. A. König, R. Krebber and P. Mischnick, *J. High Resolut. Chromatogr.* **1989**, *12*, 732-738.

[7] H. Grosenick and V. Schurig, unpublished results.

[8] V. Schurig, D. Schmalzing, U. Mühleck, M. Jung, M. Schleimer, P. Mussche, C. Duvekot and J. C. Buyten, *J. High Resolut. Chromatogr.* **1990**, *13*, 713-717.

[9] V. Schurig, J. Ossig and R. Link, *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 194-196.

[10] J. Costante, C. Garcia and A. Collet, work in progress.

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