

On the Optical Activity of Bromochlorofluoromethane

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Abstract: A simple method for the partial resolution of CHBrClF (**1**), one of the simplest possible chiral molecules, is reported. The determination of its maximum or absolute rotation makes it possible to assess the validity of earlier attempts to calculate the molar rotations of conformationally simple molecules. Knowledge of the absolute rotation of **1** has a bearing on the configurational stability of haloform carbanions. The resolution of **1** on short contact with brucine is nondestructive. Inclusion compound formation rather than kinetic resolution accounts for the results. An interpretation of the low efficiency of the process in the case of **1** is given.

Bromochlorofluoromethane, CHBrClF (**1**), is one of the simplest possible chiral molecules. Several unsuccessful attempts to prepare it in optically active form since the turn of the century²⁻⁵ culminated in the preparation of both enantiomers by Hargreaves and Modarai by a route involving the difficult resolution of α -, α -, α -bromochlorofluoroacetone (**2**) followed by base-promoted degradation.⁶ In recent years, spectroscopists and theoretical chemists have expressed interest in chiral methanes and in **1**, in particular,⁷⁻¹⁵ but little progress has been made in meeting their needs for samples of optically active compound in order to study its chiroptical properties, to compare the measured rotation with calculated values, and to establish its configuration.

A simple method for the partial resolution of CHBrClF has been available for some time,¹⁶ but publication of this fact has been deferred due to our inability to determine the enantiomeric purity of the samples obtained in spite of numerous trials. This

information has now been provided by Canceill, Lacombe, and Collet (preceding paper)¹⁹ through application of an ingeniously contrived chiral shift reagent. We are thus able to make the following report and observations:

(1) An optically active sample of **1**²¹ obtained by a single batch heterogeneous reaction of racemic **1** with brucine in the absence of solvent¹⁷ and having $\alpha_D^{25} +0.128^\circ$ (neat, 1 dm)²⁴ has an enantiomeric purity (or ee) of 4.3% ($\pm 1\%$) as determined by Canceill, Lacombe, and Collet.¹⁹ This measured rotation corresponds to $\alpha_D^{25} +3.0^\circ$, $[\alpha]_D^{25} +1.6^\circ$ ($D^{25} 1.91$), and $[\phi]_D^{25} +1.7 \pm 0.5 \text{ deg}\cdot\text{cm}^2\cdot\text{dmol}^{-1}$ for enantiomerically pure compound.

It is noteworthy that the sample whose enantiomeric purity was measured had been stored in a sealed vial for 10 years. The optical activity of the sample was unchanged from that measured at the time the resolution was carried out (in 1975).²⁵

Mosher et al.⁹ have called attention to the utility of conformationally simple chiral molecules in theoretical studies of optical activity in relation to molecular structure. To the best of our knowledge, **1** is the first compound totally devoid of conformational mobility for which absolute rotation data have been established experimentally. The theoretical treatment of chiral methanes based on polarizability theory involving pairwise interaction of groups predicts zero rotation for chiral methanes whose substituents possess C_∞ symmetry.^{26,27} The observed (extrapolated)

(1) Undergraduate research participant.

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(3) Berry, K. L.; Sturtevant, J. M. *J. Am. Chem. Soc.* **1942**, 64, 1599-1600.

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(6) Hargreaves, M. K.; Modarai, B. *J. Chem. Soc. D* **1969**, 16, 458; Hargreaves, M. K.; Modarai, B. *J. Chem. Soc. C* **1971**, 1013-1015.

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(10) Diem, M.; Burow, D. F. *J. Chem. Phys.* **1976**, 64, 5179-5185; **1977**, 81, 476-479. Diem, M.; Nafie, L. A. Burow, D. F. *J. Mol. Spectrosc.* **1978**, 71, 446-457.

(11) Marcott, C.; Faulkner, T. R.; Moscovitz, A.; Overend, J. *J. Am. Chem. Soc.* **1977**, 99, 8169-8175.

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(15) Evans, M. W. *J. Chem. Soc., Faraday Trans. 2* **1983**, 79, 1811-1815. Evans, M. W. *J. Mol. Liq.*, **1983**, 26, 211-228; **1983**, 27, 11-18. Evans, M. W.; Evans, G. J. *Ibid.* **1984**, 29, 11-35.

(16) Wilen, S. H.; Bunding, K. A.; Kascheres, C. M.; Wieder, M. J., unpublished results. See: Wilen, S. H. *Top. Stereochem.* **1971**, 6, 122. Wilen, S. H. In "Tables of Resolving Agents and Optical Resolutions"; Eliel, E. L., Ed.; University of Notre Dame Press: Notre Dame, Indiana, 1972; p 299. Our original and successful resolution experiments, begun in 1967, were based on the contemporary prevalent view that reaction of halogen compounds with brucine involved asymmetric destruction (kinetic resolution).¹⁷ Only (-)-**1** was isolated in these experiments. Following the appearance of the paper by Skell et al.,¹⁸ we repeated the resolution and isolated both (-) and (+) enantiomerically enriched samples of **1**. One of the referees has suggested that resolution of **1** by interaction with brucine is conceptually derivative of resolution by formation of tri-*o*-thymotide (TOT) inclusion complexes of **1** which was reported in 1969 by Hargreaves and Modarai.⁶ This view is not supported by the facts outlined above. We observe further that the evidence supporting the assertion of success in the resolution of **1** by inclusion in TOT is tenuous (see ref 19, note 7). In this connection, it has been found that the complex of TOT with haloethane (**4**) is racemic.²⁰

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(18) Skell, P. S.; Pavlis, R. R.; Lewis, D. C.; Shea, K. J. *J. Am. Chem. Soc.* **1973**, 95, 6735-6745. Pavlis, R. R.; Skell, P. S. *J. Org. Chem.* **1983**, 48, 1901-1902.

(19) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.*, preceding paper in this issue.

(20) Arad-Yellin, R.; Green, B. S.; Knosow, M.; Tsoucaris, G. *J. Am. Chem. Soc.* **1983**, 105, 4561-4571 (see note 19 therein).

(21) Compound **1** (bp 35.5-36.7 °C (lit.³ bp 36.11-36.18 °C)) was prepared from CHBr₂Cl by reaction with HgF₂²² or with SbF₃ + Br₂.²³ The precursor was commercially available or synthesized by photochlorination of CH₂Br₂ (300 W clear bulb; the resulting mixture was fractionally distilled in a spinning band column, bp 113.0-113.8 °C). The purity of **1** as found by GC was 99% (6-ft column containing 10% SE-30 on Chromosorb W; carrier gas N₂; column temperature 68 °C).

(22) Hine, J.; Dowell, A. M., Jr.; Singley, J. E., Jr. *J. Am. Chem. Soc.* **1956**, 78, 479-482.

(23) Jacobsen, O.; Neumeister, R. *Ber.* **1882**, 15, 599-602.

(24) Compound **1** (18.4 g, 0.125 mol) was mixed and allowed to stand with brucine (17.2 g, 0.044 mol; molar ratio 1:0.35) at 30 \pm 2 °C. After 55 min, unreacted **1** (3.1 g) was recovered by pumping (at 17 mm for 20 s) into a liquid nitrogen cooled trap. Two other fractions were recovered by pumping at intervals of 25 min (3.1 and 3.0 g, respectively). The optical activity of the fractions increased in magnitude with increasing contact time with brucine: Fraction 1, $\alpha_D^{25} -0.054^\circ$; fraction 2, $\alpha_D^{25} -0.089^\circ$ (both neat, 1 dm). The residual brucine was treated with 50% H₂SO₄ (16 mL) at 0 °C for 3 h. Steam distillation (bp 32.6-34.8 °C) of the mixture afforded 6.1 g (94% of the amount required for 1:1 complex formation with brucine) of **1**. Distillation was halted before water condensed. The distillate, $\alpha_D^{25} +0.128^\circ$ (neat, 1 dm), was dried and stored in a sealed ampule with 4A molecular sieves. The purity of the sample, as determined by DSC 10 years later, was found to be 99.5 mol % (see ref 19).

(25) At one time, it was assumed that compounds such as **1** would be easily racemized "... in accord with the conception of extreme mobility of groups attached to isolated atoms" (quoted from ref 4).

(26) Kirkwood, J. G. *J. Chem. Phys.* **1937**, 5, 479-491.

(27) Boys, S. F. *Proc. R. Soc. London, Ser. A* **1934**, 144, 655-692.

molar rotation is of the correct order of magnitude relative to that calculated by Applequist, $[\phi]_D +2$ to $+16^\circ$, on the basis of an atom-dipole refinement requiring fivefold interactions.⁸

(2) The enantiomeric purities of the samples prepared by Hargreaves and Modarai⁶ are approximately three times greater than ours. Their findings have been cited repeatedly as evidence for the pyramidal stability and high barrier to inversion of the :CBrClF anion that is expected to intervene in the haloform reaction of the optically active ketone **2**.²⁸ The revelation that their samples are of low enantiomeric purity (ca. 13%) suggests that the haloform reaction may have been attended by a large degree of racemization. At the very least, the new findings tend to weaken the case for a configurationally very stable haloform carbanion. However, a full interpretation must await an assessment of the enantiomeric purity of the precursor ketone **2**.

(3) Our resolution procedure furnishes both enantiomers with the more strongly bound and more highly enriched (+) enantiomer freed from the recovered brucine by reaction of the latter with acid.²⁴ This is in accord with the operation of a nondestructive mechanism for the resolution of halogen compounds that is consistent with the results and interpretation of Skell et al.¹⁸ on *rac*-2,3-dibromobutane (**3**) and at variance with those of Tanner et al., who isolated only (-)-**3** on interaction of the racemate with brucine.²⁹ Resolution of **1** and kindred compounds³⁰ with brucine under heterogeneous conditions is thus not a kinetic resolution process as had been originally proposed.¹⁷ The amount of the more highly retained enantiomer associated with brucine is consistent with the formation of a 1:1 complex.³¹ Such complex formation had been suggested as a possible route to the resolution of chiral haloforms by Hassel.³³ Either surface adsorption or formation of an inclusion compound fit the results nicely.

(4) A recent X-ray crystallographic study by Gould and Walkinshaw³⁴ has revealed the common basis for the ability of brucine to complex with and to act as resolving agent for a wide variety of organic compounds. In contrast to other alkaloids such as strychnine, the packing arrangement in brucine crystals permits channel-type inclusion compounds to be formed in which guest ions and molecules and brucine host molecules interact through hydrogen bonds as well as through weaker intermolecular forces.

(28) See, for example: Rauk, A.; Allen, L. C.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 400-414. Roux-Schmitt, M.-C.; Seyden-Penne, J.; Wolfe, S. *Tetrahedron*, **1972**, *28*, 4965-4979. Normant, J.-F.; Sauvetre, R.; Villieras, C. R. C. R. *Hebd. Seances Acad. Sci. Ser. C*, **1973**, *277*, 469-471.

(29) Tanner, D. D.; Blackburn, E. V.; Kosugi, Y.; Ruo, T. C. S. *J. Am. Chem. Soc.* **1977**, *99*, 2714-2723. Tanner, D. D.; Ruo, T. C. S.; Meintzer, C. P. *J. Org. Chem.* **1985**, *50*, 2573-2575.

(30) We have successfully applied the same resolution process to CF₃CHBrCl (**4**) (the anesthetic halothane) and to CBrF₂CHClF. Both (-) and (+) enantiomers of each of these compounds were isolated.

(31) Compound **3** apparently also forms a 1:1 complex with brucine.³²

(32) Pavlis, R. R. Ph.D. Dissertation, Pennsylvania State University, 1969, p 93, and personal communication from Dr. Pavlis.

(33) Hassel, O. *Science (Washington, D.C.)* **1970**, *170*, 497-502 (see p 501).

(34) Gould, R. O.; Walkinshaw, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 7840-7842.

Our results may be contrasted with other nondestructive and more efficient brucine-mediated resolutions, in particular, those of acetylenic alcohols^{35a} and cyanohydrins.^{35b} The ability of guest molecules to hydrogen bond to brucine through its amine nitrogen and its carbonyl oxygen helps to hold the included guest molecules in one position in the crystal lattice and to enhance the stereoselectivity of inclusion. The overall shape and size of guest molecules contribute to their ability to form complexes even in the absence of hydrogen bonds.³⁶ Hydrogen bonding between the carbonyl hydrogen of **1** and the amine nitrogen of brucine may be possible. Yet the small relative size of **1** and the small difference in the van der Waals radii of bromine and chlorine³⁷ may be responsible for the low stereoselectivity of inclusion in spite of the fact that the size of the chiral cavity of the host can adjust itself somewhat to that of the guest.³⁹

There remains the question of the absolute configuration of **1**. Brewster has predicted the (*S*) configuration for the dextrorotatory enantiomer on the basis of an additivity model of atom polarizabilities with the order of Br > Cl > H > F.⁴¹ While Applequist has also predicted the (*S*)-(+)-configuration,⁸ there is disagreement between the two predictions since the relative magnitudes of H and F atom polarizabilities are reversed in his calculations.^{8,42} The experimental determination of the absolute configuration of **1** remains a challenge. However, the way is now open to meaningful chiroptical studies of **1** and its analogues.

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Registry No. (±)-**1**, 88987-26-2; (+)-**1**, 22611-58-1; (-)-**1**, 31747-37-2; brucine, 357-57-3.

(35) (a) See, for example: Toda, F.; Tanaka, K.; Ueda, H. *Tetrahedron Lett.* **1981**, *22*, 4669-4672. Toda, F.; Tanaka, K.; Ueda, H.; Oshima, T. *J. Chem. Soc., Chem. Commun.* **1983**, 743-744. (b) Toda, F.; Tanaka, K. *Chem. Lett.* **1983**, 661-664.

(36) Hart, H.; Lin, L.-T. W.; Ward, D. L. *J. Am. Chem. Soc.* **1984**, *106*, 4043-4045.

(37) The van der Waals radii (Å) of the relevant atoms are the following: hydrogen, 1.2; fluorine, 1.35; chlorine, 1.80; bromine, 1.95.³⁸

(38) Pauling, L. "The Nature of the Chemical Bond", 3rd ed., Cornell University Press: Ithaca, NY, 1960; p 260.

(39) The chiral ethane **4** (see note 30) is another example of a small and weakly interacting molecule that exhibits low stereoselectivity of inclusion in brucine. The maximum rotation of the more strongly included enantiomer recovered from the brucine is $\alpha_D^{25} -0.08^\circ$ (neat, 1 dm). This corresponds to ca. 3% ee (see ref 40).

(40) Edamura, F. Y.; Larsen, E. R.; Peters, H. M. "Abstracts of Papers", 159th National Meeting of the American Chemical Society, Houston, TX, Feb. 23-27, 1970; American Chemical Society: Washington, D.C., 1970; Abstract ORGN 84. Also personal communication from Dr. Larsen (1973).

(41) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5475-5483.

(42) Applequist, J.; Carl, J. R.; Fung, K.-K. *J. Am. Chem. Soc.* **1972**, *94*, 2952-2960.