# Absolute Configuration of Bromofluoroiodomethane after Preparative Gas Chromatographic Separation

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*Abstract*

The enantiomers of bromofluoroiodomethane (CHBrFI) were separated on a preparative scale using gas chromatography (GC). The collected single enantiomers were analysed by vibrational circular dichroism spectroscopy and polarimetry in combination with *ab initio* calculations to determine the respective absolute configuration. We determined (S)(+)- and (R)(-)-CHBrFI with specific optical rotatory power $[\alpha]_D^{26}$ of (5.51±0.39) and (-5.39±0.23) $^\circ$ cm$^3$ g$^{-1}$ dm$^{-1}$, respectively.

In order to achieve the enantio-separation, a new chiral stationary phase (CSP) has been synthesized. This CSP, based on $\alpha$-cyclodextrine, is capable of separating a number of halomethanes and their derivatives on a preparative scale and thus opens the way to collect enantiomers pure or enriched up to a gram-scale within weeks in an efficient automated manner.

## Introduction

Space missions are equipped with chiral columns to investigate chiral (large) molecules in outer space (see[1] and refs. therein). It is expected that the analysis will shed some light on the formation of the solar system and the origin of life.[2–4] This underlines the importance of chiral molecules in many areas related to chemistry and biology,[5] however, these molecules are more likely large compared to the small molecules which are of particular interest here.

Small chiral halomethanes and oxiranes are ideal prototype molecules for the investigation of chiroptical properties (rotational angle,[6] (vibrational) circular dichroism,[7] photo-electron circular dichroism,[8,9] etc.). The synthesis of small, halogen containing chiral molecules ($C_1$ and $C_2$) is difficult and has not been performed with high versatility in the past, however, we devised a versatile and efficient synthetic route to achieve this for chiral halogenated acetic acids.[10] Similarly difficult is the separation of enantiomers of such small compounds, where it is still a great challenge to crystallize the target molecules.

Chiral derivatization and measurement of NMR anisotropy between two diastereomers can be used to determine the absolute configuration,[11] as well as enzymatic methods which rely on the enantio-preference of enzymes.[12] Recent developments explore three-wave mixing techniques in the microwave spectral region to distinguish both enantiomers and the racemic in a mixture.[13] Except $X$-ray crystallography, such methods are 'indirect' methods: they require some additional 'input' (reference material, empirical rules, *ab initio* calculations, etc.) to resolve the absolute configuration.

Pitzer et al.[14] used a laser to ionize and fragment target molecules (Coulomb Explosion Imaging, CEI)[15] to determine the spatial structure of gas-phase chiral molecules. In contrast to $X$-ray crystallography, this method works also for target compounds which do not crystallize but require rather large quantities at present. Similarly, one can use ionization and immediate fragmentation upon sending the target molecule through a thin foil,[16] however, this technique is limited to rather light atoms. Those CEI techniques are 'direct' methods because one 'observes' the structure in a direct way.

Small chiral molecules ($C_1$ and $C_2$) are suited for high-quality computational methods, appear as gases or have at least a relatively high vapour pressure.

This allows to study them in the gas-phase as 'isolated' molecules where intermolecular interactions are suppressed or absent; this in turn facilitates spectroscopic investigations and analysis.[17]

Some recent fundamental research dealing with enantio-pure or enantio-enriched samples of small chiral molecules concern the measurement of molecular parity violating effects.[18,19] Particularly for the measurement of frequency shifts, one relies on enantio-pure target molecules containing heavy nuclei[18,20–22] and a thorough understanding of high-resolution rovibrational spectra.[17,23,24] Table 1 shows chiral halomethanes and derivatives

| Target | Yield | Selectivity; Abs. Config., $[\alpha]^{25}_{589}$ |
|---|---|---|
| CHClFCOOH[25,26] | 9 to 16 % | ee 73 to 88 % (f.c., DHB) $(S)(+), (R)(-)$ |
| $CH_3CHXCOOR'$[27] (X=Br,Cl; R′=n-butyl) | 72 % | ee > 94 % (enzymatic) |
| CHClFI[28,29] | 33 to 42 % | ee 63 (2[illegible]) % (f.c., strychnine); $(S)(+), (R)(-)$; $\pm 2.5\,^\circ$ cm$^3$/(g dm) |
| CHBrFCOOH[30] | 52 % | ee 84 % (f.c., strychnine); $(S)(+), (R)(-)$ |
| CHBrClF[31–34] | 52 % | ee 56-72 % (f.c., strychnine); $(S)(+), (R)(-)$; $\pm 1.6\,^\circ$ cm$^3$/(g dm) |

Table 1: Various synthesized halomethanes and derivatives for use in enantio-separation with corresponding yield, enantiomeric excess (f.c.: fractional crystallization, DHB: dehydroabietylamine), absolute configuration and specific optical rotatory power, $[\alpha]^{25}_{589}$.

tives so far synthesized in racemic form and enantio-separated. CHClFI is the only target which has been prepared on 'large scale' (about 250 mg[28]). As can be seen from Table 1, enantio-separation was achieved almost exclusively by fractional crystallization. More often than not, no crystals are obtained and therefore, other separation methods are required. An elegant but also difficult route would be the asymmetric synthesis of the respective targets since every single class of targets would need a new reaction scheme for asymmetric synthesis.[35] However, a rather universal method for enantio-separation or enantio-enrichment of our target molecules is gas chromatography (GC).[5] The small target compounds are liquids with an appreciable vapour pressure and are sufficiently thermally stable (below 70

°C) to separate them on a chiral stationary phase (CSP). Since we are interested in a rather large amount, preparative columns are needed. It is well known that scale-up from an analytical to a preparative column does not work in general, there is no guarantee that a CSP which separates enantiomers on an analytical column also separates on a preparative column.[36] Therefore, synthesis of new CSPs which are capable to separate the target compounds on a preparative scale are required.

After extensive exploring and testing, we were able to synthesize a suitable CSP based on alkylated $\alpha$-cyclodextrine.[37–40] A wide variety of larger molecules were separated successfully by cyclodextrine derived CSPs on an analytical scale[36] in the past. Our CSP, however, is able to separate a wide variety of our $C_1$ and $C_2$ target compounds very efficiently either at room temperature or at temperatures slightly below 0 °C on a preparative scale.[38] Depending on how well the peaks are separated on the retention time scale, a very high enantiomeric excess can be achieved and the production of enantiopure samples with preparative GC is faster than fractional crystallization. Until now, GC resolution of CHBrClF, $CHClF_1$, and $CHBrClCF_3$ has been achieved only on an analytical scale with capillary columns.[39, 41]

## Experimental Section

The synthesis of bromofluoriodomethane, CHBrFI, was performed following the procedure described by Li et al.[42] Hexakis(2,3,6-tri-*O*-butyl)-$\alpha$-cyclodextrine, was obtained from $\alpha$-cyclodextrine (1,4-glycocidic connection of $D(+)$-glucose) with 1-bromobutane as the only alkylation reagent following the description for similar compounds.[39] An early synthesis of hexakis(2,3,6-tri-*O*-butyl)-$\alpha$-cyclodextrine was reported[40] to investigate its reductive cleavage, but it has never been used as chiral stationary phase in GC. We dissolved it in polysiloxane and packed a column (length about 2 m, 5.3 mm inner diameter), CHBrFI was separated by GC and collected with a home-built fraction collector. This CSP separates a large variety of halomethanes and derivatives (e.g. amines and esters) of the corresponding acetic acids.[10] The VCD spectra were recorded on a BioTools Chiral*IR* *2X* spectrometer. For detailed experimental procedures, see the Supporting Information.

## Results and Discussion

Some fundamentals of the infrared spectrum of CHBrFI have been measured before[42,43] and can be compared to *ab initio* calculations.[44] Table 2 shows the measured and the corresponding calculated frequencies, which were obtained from Moller-Plesset perturbation theory (MP2) and coupled cluster singles-doubles calculations including noniterative triple contributions (CCSD(T)). Schwerdtfeger et al.[44] applied scalar relativistic pseudopotentials for the heavy I and Br atoms and correlation-consistent valence double-zeta (cc-pVDZ) basis sets. Column 4 shows MP2 calculations with a larger (L) basis set of triple-zeta quality (cc-pVTZ) to assess the influence of the basis set size. The values from CCSD(T) show best agreement with the experimental data, however, the calculated frequencies were obtained in the harmonic approximation, which is strictly not comparable to observed anharmonic values. We should note that these calculations and ours presented in Table 3 do not provide frequencies in the range of 735 to 909 $cm^{-1}$ and therefore, it is likely that the observed bands[42,43] do not belong to fundamentals of CHBrFI.

| | Exp. | | | | Calc.[44] | | |
|---|---|---|---|---|---|---|---|
| No. | This work[a] | Exp.[42] | Exp.[43] | Exp.[45] | MP2 | MP2/L | CCSD(T) |
| 2 | 1291 | | | | | | |
| 3 | 1141 | 1132 | | 1139.35 | 1204 | 1195 | 1179 |
| 4 | 1061 | 1044 | | 1060.85 | 1102 | 1106 | 1100 |
| | | 909[b] | 908.6[b] | | | | |
| | | 735[b] | 735.3[b] | | | | |
| 5 | 687 | 673 | 673.2 | 686.5 | 683 | 718 | 654 |
| 6 | 565 | | | | 568 | 589 | 552 |
| 7 | | | | | 334 | 347 | 326 |

Table 2: Experimental band centres and earlier *ab initio* calculated harmonic fundamentals (both in $cm^{-1}$). [a] With our setup we cannot measure below 400 $cm^{-1}$; two weak bands around 2975 and 3125 $cm^{-1}$ are observed and might be the CH-stretching perturbed by (Fermi) resonance interaction. An additional peak at 2104 $cm^{-1}$ is likely due to a CF-stretch overtone ($p$(CHBrFI) = 6 mbar, resolution 0.5 $cm^{-1}$, see Supporting Information). [b] indicates that the assignment as a fundamental is probably incorrect.

This is also supported by our measurements of the infrared band centers between 400 and 4200 $cm^{-1}$ (reproduced in the Supporting Information).
In order to determine the absolute configuration, we need to measure the VCD spectrum and compare the relative signs of the signals with those from calculations of the respective enantiomers. For the measurement of the VCD spectra, it is necessary to obtain enantio-separated CHBrFI and as an example, Figure 1 shows a chromatogram of the successful separation. Two fractions appear between 80 and 110 min and are baseline separated

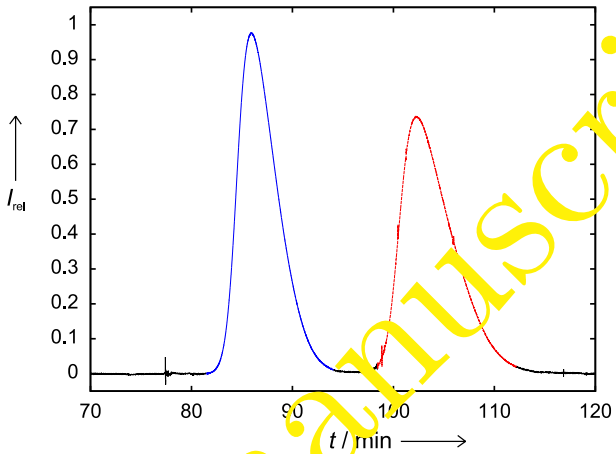


Figure 1: Chromatogram of CHBrFI between 70 and 120 minutes retention time. One can distinguish an early Fraction 1 (blue) and a later Fraction 2 (red) on our CSP. CHBrFI was injected dissolved in $CCl_4$. The chromatogram for the preparative collection is reproduced in the Supporting Information.

for entire 5 min. This facilitated the preparative collection by an algorithm that controls switching between two cold traps of our home-built fraction collector for both enantiomers. The resolution obtained is $R = 1.07$ and the separation factor is $\alpha = 1.23$. A separation factor $\alpha > 1.3$ is often considered a prerequisite for the preparative application of racemic separations based on selective guest-host interactions, for which cycledextrines are representatives.[46]
The experimental VCD spectrum in the range between 1000 and 1200 $cm^{-1}$ is shown in Figure 2 and can be compared to our *ab initio* calculated VCD

spectrum. Figure 2(a) shows the two VCD raw signals of both collected enantiomers which are mirror images of each other (solid blue line and dotted red line). This shows that the occurring peaks are truly due to enantioseparation. The calculated VCD spectrum of (*S*)-CHBrFI is shown in Figure 2(b), it was obtained using DFT (convoluted to guide the eye). From the relative sign of the main peaks it can be inferred that Fraction 1 of the chromatogram corresponds to (*S*)-CHBrFI (solid line, blue) and consequently Fraction 2 to (*R*)-CHBrFI (dotted line, red). Figure 2(c) reproduces the experimental IR spectrum of the racemate. The calculated IR spectrum considering anharmonic corrections[48] are shown in Figure 2(d), which represents a gas-phase spectrum; however, no pronounced effects caused by the solvent are expected other than broadening and minor shifts.

We used MP2 and density functional theory (DFT) with the B3LYP functional, the latter is capable to provide also VCD intensities.[48] We used the same basis set (Stuttgart-Dresden-Bonn cc-pVTZ basis set with pseudopotentials for the heavy atoms Br and I) for both methods. The geometries were fully optimized both for MP2 and DFT calculations. The harmonic frequencies, $\tilde{\omega}$, and the corresponding anharmonically corrected values, $\tilde{\nu}$, which were obtained perturbatively from the quartic force field are reproduced in Table 3 and given in parenthesis. The calculated infrared intensities and the VCD signal intensities are also tabulated. The intensities are obtained in the double harmonic approximation. More details on the computations can be found in the Supporting Information. The agreement between the calculated MP2 harmonic frequencies shown in Tables 2 and 3 are good. One would expect the CCSD(T) results of better quality, but this is difficult to judge by comparison with experiment, because no anharmonically corrected frequencies were calculated.[44] Our anharmonically corrected band centers are sufficiently close to experiment and could serve as a basis for the detailed understanding of the vibrational dynamics of CHBrFI in the fundamental region. From our experience with halomethanes carrying an isolated CH-chromophore, we rather expect strong multi-dimensional anharmonic resonance interactions which would alter the band positions as well as the intensities. This has been shown in the past for CHBrClF and CDBrClF up to very high overtone excitation as well as for such tiny effects like the computed parity violating contributions.[22,49,50]

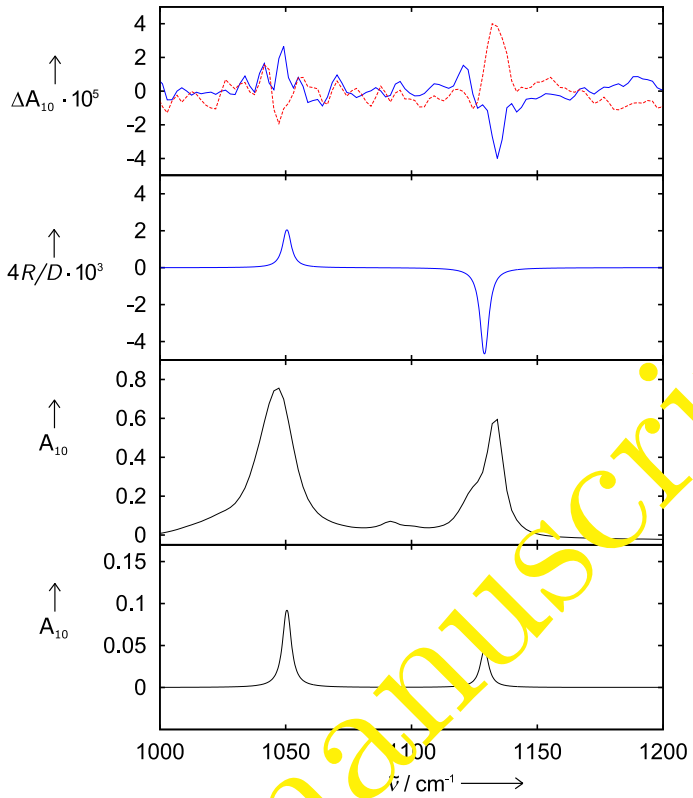


Figure 2: Part of the VCD and IR spectra between 1000 and 1200 $cm^{-1}$. The quantity $A_{10}$ or $A$ is the decadic absorbance.[47] $\Delta A_{10}$ is the VCD signal as difference in (decadic) absorbances of left and right circularly polarized light. (a) Experimental VCD spectrum of Fraction 1 (solid line, blue) and Fraction 2 (dotted line, red) dissolved in $CCl_4$ ($m$ = 0.251 mol/kg, about 9000 spectra (3 h) superimposed, baseline has been corrected against the racemate; resolution 4 $cm^{-1}$. See Supporting Information for more details on various baseline correction schemes.) (b) *Ab initio* calculated VCD spectrum of (*S*)-CHBrFI (B3LYP, SDB ccpVTZ P basis set, see Text). (c) Experimental IR spectrum dissolved in $CCl_4$ ($m$ = 0.251 mol/kg, resolution 4 $cm^{-1}$, 10 scans superimposed). (d) *Ab initio* calculated IR spectrum of (*S*)-CHBrFI (B3LYP, SDB ccpVTZ P basis set, see Text). The IR frequencies have been corrected anharmonically by using the quartic force field.[48]

| Mode | $\frac{\tilde{\omega}\,(\tilde{\nu})}{\mathrm{cm}^{-1}}$ | $\frac{G_{\mathrm{IR}}}{\mathrm{pm}^2}$ | $\frac{\tilde{\omega}\,(\tilde{\nu})}{\mathrm{cm}^{-1}}$ | $\frac{G_{\mathrm{IR}}}{\mathrm{pm}^2}$ | $\frac{D\cdot 10^{+40}}{\mathrm{esu}^2\,\mathrm{cm}^2}$ | $\frac{R\cdot 10^{+44}}{\mathrm{esu}^2\,\mathrm{cm}^2}$ | $\frac{10^4\cdot 4\,R}{D}$ |
|---|---|---|---|---|---|---|---|
| | (MP2) | | (DFT) | | | | |
| 1, $CH_{str}$ | 3185 (3052) | $6.\cdot10^{-4}$ | 3156 (3009) | $9.6\cdot10^{-4}$ | 0.23 | 0.26 | 4.57 |
| 2, $CH_{be}$ | 1328 (1298) | $1.54\cdot10^{-1}$ | 1315 (1284) | $1.52\cdot10^{-1}$ | 36.6 | -1.33 | -0.15 |
| 3, $CH_{be}$ | 1179 (1155) | 1.28 | 1156 (1129) | 1.41 | 339.7 | -12.7 | -0.15 |
| 4, $CF_{str}$ | 1103 (1075) | 2.5 | 1084 (1051) | 2.95 | 709.6 | 11.7 | 0.07 |
| 5, $CBr_{str}$ | 721 (709) | 3.21 | 668 (645) | 4.44 | 1066.6 | 16.4 | 0.06 |
| 6, $CI_{str}$ | 588 (582) | $5.05\cdot10^{-1}$ | 559 (554) | $7.50\cdot10^{-1}$ | 180.1 | -15.2 | -0.34 |
| 7, $CFBr_{be}$ | 346 (343) | $5.7\cdot10^{-3}$ | 332 (329) | $9.57\cdot10^{-3}$ | 2.3 | -0.95 | -1.64 |
| 8, $CFI_{be}$ | 275 (272) | $1.01\cdot10^{-2}$ | 264 (261) | $8.69\cdot10^{-3}$ | 2.09 | 0.51 | 0.98 |
| 9, $CBrI_{be}$ | 145 (144) | $1.44\cdot10^{-3}$ | 138 (137) | $9.7\cdot10^{-4}$ | 0.23 | -0.04 | -0.76 |

Table 3: *Ab initio* calculated (MP2 and DFT, Stuttgart-Dresden-Bonn cc-pVTZ basis set with pseudopotentials for Br and I) fundamental (str: stretch, be: bend) harmonic ($\tilde{\omega}$) and anharmonically corrected ($\tilde{\nu}$) frequencies, the latter are given in parenthesis. $G_{\mathrm{IR}}$ denotes the infrared band strength (in $\mathrm{pm}^2$), $D$ the dipole strength (in $10^{-40}$ $\mathrm{esu}^2$ $\mathrm{cm}^2$), $R$ the rotatory strength (in $10^{-44}$ $\mathrm{esu}^2$ $\mathrm{cm}^2$); $4R/D$ signifies the VCD signal[48,51] (for more details, see the Supporting Information).

The absolute configuration requires the determination of the specific optical rotatory power, $[\alpha]_{\mathrm{D}}^{26}$. This quantity if often called "specific rotation" and quoted without units; here we follow the IUPAC terminology (see Section 2.7.1 in[47]). The specific optical rotatory power assigns a plus or minus sign to the $R$ or $S$ configurational label. For Fraction 1, $[\alpha]_{589}^{26}$ is equal to $(5.51 \pm 0.38)^\circ$ cm$^3$ g$^{-1}$ dm$^{-1}$ ($c = 0.341$ g cm$^{-3}$, $CCl_4$, $d = 0.05$ dm, $n = 10$, 99 % confidence interval) and the corresponding value for Fraction 2 is equal to $(-5.39 \pm 0.23)^\circ$ cm$^3$ g$^{-1}$ dm$^{-1}$ ($c = 0.326$ g cm$^{-3}$, $CCl_4$, $d = 0.05$ dm, $n = 10$, 99 % confidence interval). Those values have been obtained by taking the separately determined different enantiomeric excess (ee) for Fraction 1 and 2 into account. The values for the specific optical rotatory power are equal in magnitude within experimental uncertainty (see Supporting Information for details). We calculated the specific optical rotatory power at different wavelength by DFT (with B3LYP functional) for various basis sets at four different wavelength, details are provided in the Supporting Information.

| | 589 nm | 546 nm | 436 nm | 405 nm |
|---|---|---|---|---|
| *Theory* | 5.0 | 6.7 | 19.8 | 30.9 |
| Exp. | 5.51±0.38 | 7.02±0.38 | 20.02±0.60 | 32.20±0.60 |

Table 4: Specific optical rotatory power of ($S$)-CHBrFI calculated at four different wavelengths. All geometries were fully optimized at the DFT/B3LYP level (cc-pVTZ-PP basis). More results for different basis sets with and without pseudo-potential are collected in the Supporting Information.

Independent of the basis sets used, the specific optical rotatory power is always positive for the $S$-configuration of CHBrFI and increases with decreasing wavelength; the basis cc-pVTZ-PP compares best with the experimentally determined values (see Table 4 and Table 3 of the Supporting Information). We can conclude from our experiments and the theoretical analysis that the absolute configuration of bromofluoroiodomethane is therefore ($S$)(+)-CHBrFI and ($R$)(−)-CHBrFI, as is the case for similar compounds, collected in Table 1.

We demonstrated efficient enantio-separation of CHBrFI by preparative GC with our CSP and determined the absolute configuration to be ($S$)(+)-

CHBrFI and (*R*)(−)-CHBrFI with the aid of VCD spectroscopy and *ab initio* calculations. An enantio-separation of a halomethane on a preparative scale with a chiral stationary phase in gas-chromatography was not reported before. We should mention that with our autosampler and home-built fraction collector system, we are able to collect 200 to 400 mg per week in an automated fashion. This is an enormeous improvement over current techniques towards enantio-separation of halomethanes on a large scale.

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