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The highly stereoselective decarboxylation of (+)-1-bromo-1-chloro-2,2,2-trifluoropropanoic acid to give (+)-1-bromo-1-chloro-2,2,2-trifluoroethane [(+)-halothane] with retention of configuration

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This article is dedicated to Dr. Leonid Rozov on the occasion of his 65th birthday and retirement

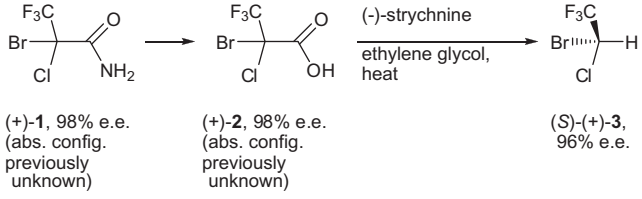
ABSTRACT

The absolute configuration of the title acid **2** has been determined to be *S* by X-ray crystallography. Thus, decarboxylation of **2** produces (*S*)-(+)-halothane with 99% retention of configuration. This behavior is compared to other stereoselective decarboxylation reactions of α-haloacids from the literature that also gave high degrees of retention of configuration when in the form of their quaternary ammonium salts, which contain one proton. The proton of the ammonium salt is necessary in order to protonate the anionic intermediate formed from decarboxylation. In the absence of this relatively acidic proton, we had previously found that using triethylene glycol (TEG) as both the solvent and proton source for the decarboxylation reaction of acid **2** caused poor stereoselectivity. This was in contrast to 1,2,2,2-tetrafluoro-1-methoxypropionic acid **6**, which showed a high degree of retention of configuration in TEG. In order to rationalize this differing behavior, we report DFT studies at PCM-B3LYP/6-31++G** level of theory (the results were additionally confirmed with 6-311++G** and aug-cc-pVDZ basis sets). The energy barrier to inversion of configuration of the anionic reaction intermediate **11** of acid **2** is 10.23 kcal/mol. However, we find that the anionic intermediate **10** from acid **6** would rather undergo β-elimination instead of inversion of configuration. Thus the planar transition state required for inversion of configuration is never reached, regardless of the rate of proton transfer to the anion.

1. Introduction

Halothane **3** (1-bromo-1-chloro-2,2,2-trifluoroethane) was one of the first halogenated non-flammable inhaled anesthetics to replace diethyl ether.[1] Efforts have been made to synthesize halothane and other chiral fluorinated anesthetics in enantiomerically enriched form, with the anticipation that one enantiomer may have improved pharmacological properties over the other or over the racemate.[2a] Thus far, only three studies of the pharmacology of halothane enantiomers have appeared, which contradict each other. [2b–d] It is possible that this lack of studies is due to the lack of availability of large amounts of the enantiomers.

Edamura and Larsen[3] described the first synthesis of halothane in enantiomerically enriched form, although the ee was not high. Pearson[4] improved upon this procedure, isolating halothane with a high ee and also determining its absolute configuration. Our approach to an enantiomer of halothane relied on the stereoselective decarboxylation of the title carboxylic acid **2** (Scheme 1).[5] This approach is a part of our program to synthesize chiral non-racemic halogenated inhaled anesthetics.[6] The stereoselective decarboxylation of halogenated carboxylic acids has been highly successful in the synthesis of enantiomers of theoretically interesting halogenated molecules[7,8] and an intermediate in the synthesis of fluoroether anesthetics.[9] The resolution of the enantiomers of halothane and other highly halogenated molecules by enantioselective gas chromatography (GC) has become a commonplace[10] since the first report by Meinwald et al.[11] It is unlikely that preparative GC will be able to supply the amounts needed for testing of anesthetic enantiomers in humans, so efforts at their preparation by synthesis should continue.



Scheme 1. Stereoselective decarboxylation of (+)-**2** giving (*S*)-(+)-halothane.

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2. Results and discussion

Herein we report that we have determined the absolute configuration of acid **2**, and that the decarboxylation proceeds with the retention of configuration. Suitable crystals of acid **2** could not be grown, so amide **1**, the immediate precursor of acid **2** in the synthetic sequence[5] giving (*S*)-(+)-**3**, was used. Slow crystallization of (+)-amide **1** from its solution in hexane/dichloromethane gave crystals suitable for X-ray analysis. The structure of **1** was solved by direct methods in the space group $P2_1$. There are two molecules in the asymmetric unit (Fig. 1). The two independent molecules in the asymmetric unit are connected in an infinite chain of hydrogen bonds involving one amine hydrogen atom and the carbonyl oxygen atom (see Table 1). Both molecules in the asymmetric unit are disordered (Fig. 2). One is only slightly disordered (labeled without primes) while the other (labeled using primes and double primes) is disordered by a rotation around C(2′) so that all three groups attached to it occupy two positions. As can be seen in Figure 2, the disordering does not significantly change the size, shape, or volume occupied by the groups attached to C(2) or C(2′). A separate occupancy factor was refined for each of the independent molecules in the asymmetric unit. In the molecule which is only slightly disordered, two positions for the chlorine and bromine atoms are displaced by about half an Angstrom [0.71(3) and 0.29(3) occupancy factors]. However, while the disorder in this trifluoromethyl group could not be resolved, it could be observed in the large thermal ellipsoids for the atoms in this group. The trifluoromethyl group is held in position by hydrogen bonding between the amine hydrogen atom and one of the fluorine atoms. In the other molecule, the greater rotation about C(2′) results in the chlorine and bromine atoms occupying the same site as well as the chlorine atom and trifluoromethyl group and the bromine atom and trifluoromethyl group sharing a site [0.683(10) and 0.317(10) occupancy factors]. Disordering in molecules which contain both chlorine and bromine atoms in which both atoms partially occupy the same position is common.[12] During the refinement, the C–F distances were constrained to be 1.34(2) Å. The bond distances are presented in Table 2. As can be observed, the distances in the two molecules are very similar. The largest deviations are found in the C(2′)–C(3′), C(2′)–C(3″), C(2′)–Cl″ and the C(2′)–Br″ bond lengths. These differences are all due to the disordering. C(3′) is 0.722 Å from Cl″ while C3″ is 0.780 Å from Br′. In order to achieve this separation, the two atoms move away from each other in the refinement resulting in C(2′)–C(3′) becoming too short while the C(2′)–Cl″ bond becomes too long. The same is true for C(2′)–C(3″) and C(2′)–Br′, only in this case the effect is less because of the smaller difference between the length of a C–C and a C–Cl versus a C–C and a C–Br bond. The C(2′)–Br″ bond appears to be too short because Cl′ and Br″ share a common site due to the disorder and refined as a Cl and a Br with occupancy factors of 0.683(10) and 0.317(10), respectively. As a result, the bond distance is a weighted average of that of a carbon–chlorine and a carbon–bromine bond. Close intramolecular contacts due to this disordering also result in distorted thermal ellipsoids for some of the atoms such as F(3″), C(3″), and Br*.

The Friedel parameter is 0.01(9), however, in the collection of the data Friedel pairs were not collected meaning that the correct configuration of the molecule was also determined using the Hamilton *R* value test.[13] At the end of the refinement the (*R*)-configured amide was refined to an *R* value of 0.0715. The ratio of the *R* value for the (*R*)-configured amide (0.0715) to the (*S*)-configured amide (0.0711) was 1.006, which is greater than the $R_{1,1024,\ 0.005}$ of 1.003. This result indicates that we can reject the hypothesis that at the 0.005 level, amide **1** has the (*R*)-configuration. Therefore, the dextrorotatory isomer of amide **1**, and by correlation, acid (+)-**2**, have the (*S*)-absolute configuration.

Since both acid **2** and its product halothane are of the same configuration, the stereochemistry is retained to a very high degree.

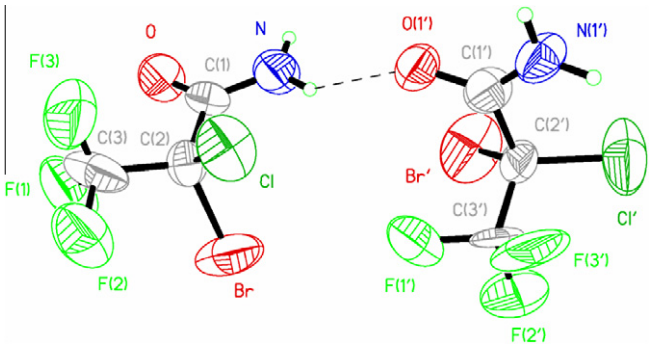


Figure 1. ORTEP (50% thermal ellipsoids) plot of the molecules in the asymmetric unit of **1**.

Table 1
Hydrogen bonds for 1 [Å and deg.]

D–H…A	d(D–H)	d(H…A)	d(D…A)	<(DHA)
N–H(11)…O(1′)[a]	0.88	2.15	3.011(16)	166.6
N–H(12)…O(1′)	0.88	2.46	3.253(13)	150.1
N–H(12)…F(1″)	0.88	2.53	3.22(2)	135.5
N–H(12)…Cl*	0.88	2.56	3.01(3)	112.3
N(1′)–H(11′)…O[b]	0.88	2.12	2.987(17)	169.9
N(1′)–H(12′)…Br″	0.88	2.55	2.995(13)	111.9
N(1′)–H(12′)…F(1)[c]	0.88	2.58	3.264(14)	135.5
N(1′)–H(12′)…O[c]	0.88	2.64	3.457(14)	155.3

Symmetry transformations used to generate equivalent atoms:
[a] $-x+1, y+1/2, -z+2$.
[b] $-x+1, y-1/2, -z+2$.
[c] $x, y, z+1$.

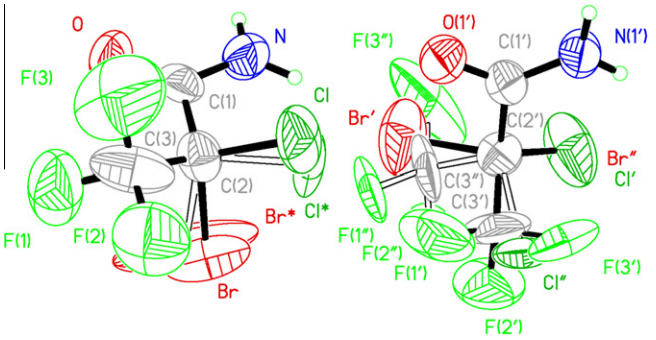
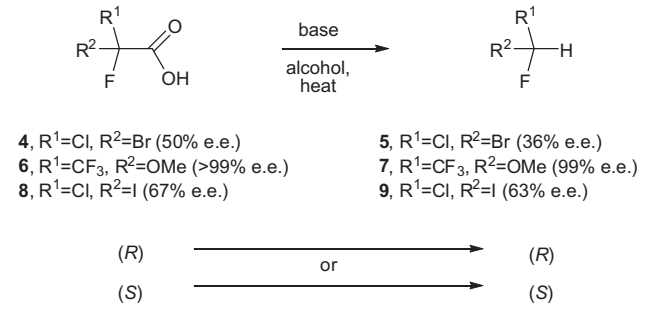


Figure 2. The two disordered molecules in the asymmetric unit of **1**.

Table 2
Selected bond lengths [Å] for the two independent molecules (atoms without primes and the atoms labeled with primes) and for the disordered part of each independent molecule (labeled with a star and a double prime)

		Starred (*)	Prime (′)	Double prime (″)
N–C(1)	1.351(17)		1.308(15)	
O–C(1)	1.197(13)		1.249(14)	
C(1)–C(2)	1.530(18)		1.552(19)	
C(2)–C(3)	1.50(2)		1.39(3)	1.44(5)
C(2)–Cl	1.772(15)	1.80(3)	1.835(11)	1.982(18)
C(2)–Br	1.960(14)	1.90(2)	1.988(15)	1.835(11)
C(3)–F(3)	1.268(16)		1.29(2)	1.34(2)
C(3)–F(1)	1.301(16)		1.330(19)	1.34(2)
C(3)–F(2)	1.335(14)		1.286(18)	1.33(2)



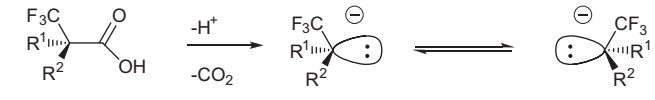
4, R^1=Cl, R^2=Br (50% e.e.)
6, R^1=CF_3, R^2=OMe (>99% e.e.)
8, R^1=Cl, R^2=I (67% e.e.)

5, R^1=Cl, R^2=Br (36% e.e.)
7, R^1=CF_3, R^2=OMe (99% e.e.)
9, R^1=Cl, R^2=I (63% e.e.)

Scheme 2. Decarboxylation of halogenated carboxylic acids from the literature.

This result is in line with the three previous stereoselective decarboxylations of α-halocarboxylic acids in the literature: Doyle and Vogl[7] obtained (+)-bromochlorofluoromethane **5** from (+)-bromochlorofluoroacetic acid **4** (Scheme 2); the ee of product **5** was estimated from the specific rotation. Koenig[14] was the first to separate the enantiomers of **5** by enantioselective GC, allowing the precise determination of the ee. The stereochemical outcome of the reaction was not known until it was shown that both the starting material and product had the same absolute configuration.[15] A second example was given by Ramig et al.[9] who decarboxylated acid (*R*)-(+)-**6** to obtain fluoroether (*R*)-(−)-**7**. The stereochemical course of this reaction was first reported to be inversion of configuration,[9b,c] but was subsequently amended to retention[16] after some reservations had been noted.[17] This came about because the absolute configuration of fluoroether **7** rested on conversion of it into fluoroether anesthetic desflurane, which had originally been assigned by Polavarapu et al.[18] as (*R*)-(+)/(*S*)-(−). The determination was found to be incorrect,[19] and had to be reversed.[20] Confirmation of this reversal came with the direct determination of the absolute configuration of fluoroether **7**.[21] The third example of stereoselective decarboxylation was shown by Crassous et al.[8] who converted chlorofluoroiodoacetic acid **8** into chlorofluoroiodomethane **9** with a high degree of stereoselectivity. Thus, the stereochemical inversion of the presumed anionic intermediates in all of these cases appears to be much slower than their capture by a proton.

The putative intermediate anion **10** formed from the decarboxylation of acid **6** appears to be more stable toward inversion of configuration than the anion **11** formed from acid **2** (Scheme 3). This assertion is based on the comparison of the decarboxylation behavior of the two acids under identical conditions. When acid **6** is treated with KOH in a solvent system of triethylene glycol (TEG)/DMPU, followed by heating to 200 °C, ether **7** is isolated in a 75% yield and is nearly enantiomerically pure.[9] However, when acid **2** is subjected to the same conditions, albeit at a lower temperature, the halothane **3** obtained in a 55% yield has an ee of only 20%, favoring retention of configuration.[5] The production of halothane and halocarbons **5** and **9** from Scheme 2 proceeds with good stereoselectivity when the base is a tertiary amine (either strychnine or triethylamine) and when the solvent is ethylene glycol. In these cases, the proton source for the protonation of the anionic intermediates would be the quaternary ammonium ion, which is much more acidic than the alcoholic solvent; therefore the anion is presumably more likely to be protonated than undergo inversion



6, R^1=F, R^2=OCH_3
2, R^1=Br, R^2=Cl

10, R^1=F, R_2=OCH_3
11, R^1=Br, R_2=Cl

Scheme 3. Stereochemical inversion of anions derived from acids **2** and **6**.

of configuration. The case of the conversion of acid **6** to ether **7** is unusual, in that using a less acidic alcoholic solvent still gives a high level of stereoselectivity. It was unclear to us why anion **10** should be so much more stable toward inversion of configuration than anion **11**.

In order to investigate the reasons for the unusual stability, experimental conditions for anions **10** and **11** were modeled with Gaussian09[22] using PCM-B3LYP/6-31++G** level of theory which included a temperature parameter. The results were confirmed by two additional basis sets, 6-311++G** and aug-cc-pVDZ which were in good agreement. In order to determine the energy barrier to inversion of configuration, anions **10** and **11** were modeled in a DMPU/TEG solvent mixture with TEG as the proton source. The barrier to enantiomerization for anion **11** is 10.23 kcal/mol. Before inversion of the anionic carbon atom in **11** can occur, the CF_3 group has to rotate by 30 degrees. This process is endothermic by 5.43 kcal/mol. For anion **10** however, our DFT studies showed that it undergoes β-elimination rather than enantiomerization, with a barrier of 6.34 kcal/mol. This explains the higher degree of retention of configuration in this species.

3. Conclusion

We have shown that the inhaled anesthetic halothane is produced from the decarboxylation of acid **2** with retention of configuration. It appears that halogenated carboxylic acid salts will generally decarboxylate to give halohydrocarbons with retention of configuration, when a relatively acidic proton source is available. A computational study indicated that intermediate anion **11** has a barrier to enantiomerization of 10.23 kcal/mol. When the proton source is sufficiently acidic, proton transfer to anion **11** yielding halothane results in a high level of retention of configuration. The anionic intermediate **10** from acid **6** does not undergo inversion of configuration even in the presence of a less acidic proton source. Intermediate **10** is predicted to undergo β-elimination instead. This is a relatively minor process however, as the yield of the product formed from proton transfer to anion **10**, namely ether **7**, is reasonably high.

4. Experimental

4.1. General

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Biospin-Avance 1 instrument, at 400.1, 100.6, and 199.7 MHz, respectively.

4.2. (*S*)-(+)-1-Bromo-1-chloro-2,2,2,-trifluoropropanamide 1

(*S*)-(+)-1-Bromo-1-chloro-2,2,2,-trifluoropropanamide **1** was obtained as described previously,[5] mp = 81–82 °C, $[\alpha]_D^{25} = +20$ (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 6.62 (br s, 1H, NH), 6.38 (br s, 1H, HN). ^{13}C NMR ($CDCl_3$) δ 162.4 (s, C=O), 121.1 (q, J_{CF} = 283 Hz, CF_3), 65.61 (q, J_{CF} = 34.4 Hz, CBrCl). ^{19}F ($CDCl_3$) δ −73.62 (s). HRMS: $[M-H]^-$ 237.8887 (calcd for $C_3HBrClF_3NO$ 237.8888). X-ray crystal structure, $C_3H_2BrClF_3NO$: To a crystal (0.07 × 0.13 × 0.50 mm) of (*S*)-(+)-**1**, a very thin coating of Vaseline was applied, and the crystal was mounted inside a glass capillary and then transferred to an Enraf Nonius CAD4 diffractometer using Cu radiation for the collection of diffraction data at a temperature of 200 K; *M* = 240.42, monoclinic, space group $P2_1$, *a* = 10.8410(10), *b* = 6.1514(7), *c* = 10.9177(6) Å, β = 102.986(7)°, *V* = 709.45(11) Å^3, *Z* = 4, μ = 11.435 mm^{-1}, D_{calcd} = 2.251 g cm^{-3}; the structure was solved by direct methods. A face indexing absorption correction was used. In the least-squares refinement, anisotropic temperature parameters were used for all the non-hydrogen atoms resulting in a model

with $R_1 = 0.0711$, $wR_2 = 0.2305$ for all data (1479 independent reflections) and 247 parameters; Flack parameter $x = 0.01(9)$.

CCDC 852346 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Role of the funding source

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