Highly Stereoselective Decarboxylation of (+)-1-Bromo-1-chloro-2,2,2-trifluoropropanoic Acid gives (+)-1-Bromo-1-chloro-2,2,2-trifluoroethane ((+)-Halothane) with Retention of Configuration

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Supporting Information

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1. Computational Methodology

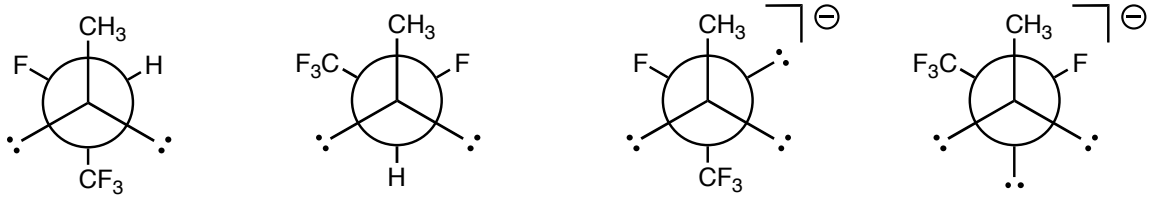
In this study, calculations were carried out using B3LYP[1] hybrid functional in Gaussian09[2] software package using 6-31++G** basis set. Results were confirmed with 6-311++G** and aug-cc-pVDZ basis sets. Pople's[3] 6-31++G** and 6-311++G** basis sets have been shown to well reproduce experimental geometries in a range of molecules.[4] Due to the presence of two sets of diffuse valence basis atomic orbitals, they satisfy the requirement for calculating anions, which calls for a use of more diffuse functions, as well as high computational efficiency.[5] For comparison, the results were confirmed using Dunning's[6] aug-cc-pVDZ that was shown to overestimate the bond lengths and energies,[4] but has been chosen for its consistency in anionic systems.

All stationary points were characterized as being either minima or maxima by harmonic frequency analysis. All first-order saddle points had one imaginary frequency and the local minima had zero negative frequencies. The reaction pathways were confirmed by the internal reaction coordinate (IRC)[7] analysis. Reported enthalpies include unscaled zero-point energy (ZPE) corrections that were calculated with the same method and basis set. Structures reported in the manuscript were visualized using GaussView[8] software.

In attempt to reproduce experimental reactions carried out in this work, we used Polarizable Continuum Model (PCM)[9] for introducing solvents. In the case of the DMPU/TEG mixture, solvent mixture was specified by using *generic* command alongside with *PCMDoc* followed by the experimental parameters, which were combined assuming linearity.[10] Additionally, we included a temperature parameter in accordance with the experiment.

There exist multiple rotamers of anion **10** which differ by the position of the OMe group relative to the lone pair. In our theoretical study we considered two major conformers **10A** and **10B** (Fig S1) in which the position of the OMe group differs by approximately 180º. Analysis determined that **10A** conformer is more stable than **10B** by 3.8 kcal/mol, which is in agreement with findings of Polavarapu *et al.*[11] who used vibrational circular dichroism for studies of 1,2,2,2,-tetrafluoroethyl methyl ether **7**. They determined that *trans*-conformer corresponding to conformation of **10A** is dominant by 78%, while the *g*- conformer, is less stable and is present at 22% at B3LYP/6-31G* level of theory.

Figure S1. Conformers of **2**[11] and anion **10**.



2. References for Computational Methodology

1. (a) Becke, A. D. *J. Chem. Phys.* **1993,** *98,* 1372-1377. (b) Becke, A. D. *J. Chem. Phys.* **1993,** *98,* 5648-5652. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988,** *37,* 785-789. (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* 1994, *98,* 11623-11627.

2. Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G.,

Sonnenberg, J. L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, Jr., J. A., Peralta, J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Rega, N., Millam, N. J., Klene, M., Knox, J. E., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Martin, R. L., Morokuma, K., Zakrzewski, V. G., Voth, G. A., Salvador, P., Dannenberg, J. J., Dapprich, S., Daniels, A. D., Farkas, Ö., Foresman, J. B., Ortiz, J. V., Cioslowski, J., Fox, D. J. (2009) Gaussian, Inc., Wallingford CT.

3. Hehre, W. J.; Random, L.; Schleyer, P. v. R.; Pople, J. A. Ab Initio Molecular Orbital Theory; Wiley: New York, 1986.

4. Wiberg, K. B. *J. Comput. Chem.* **2003**, *25,* 1342–1346.

5. Simmons, J. *J. Phys. Chem. A* **2008,** *112,* 6401–6511.

6. Dunning, T. H., Jr. J Chem Phys **1989**, 90, 1007.

7. (a) Fukui, K. *Acc. Chem Res*. **1981,** *14,* 363-368 (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990,** *94,* 5523-5527.

8. GaussView, Version 5, Dennington, R.; Keith, T.; Millam, J. *Semichem Inc.*, Shawnee Mission KS, 2009.

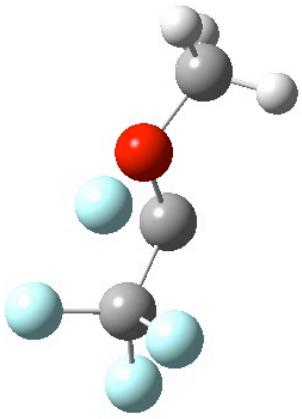
9. Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.*, **2005**, *105*, 2999-3093.

10. Fox, J.; Scalmani, G. Gaussian, Inc, private communication, 2011.

11. Polavarapu, P. L.; Zhao, C.; Ramig, K. *Tetrahedron: Asymmetry* **1999**, *10*, 1099-1106.

3. Cartesian coordinates, number of imaginary frequencies and energies for the structures involved in the inversion of anion 10 at PCM-B3LYP/6-31++G**

Reactant 10



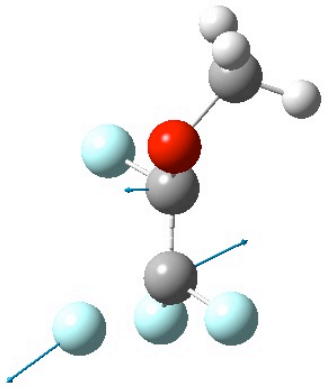
0 imaginary frequencies

Zero-point correction= 0.061651 (Hartree/Particle)
Thermal correction to Energy= 0.079033
Thermal correction to Enthalpy= 0.080531
Thermal correction to Gibbs Free Energy= 0.001318
Sum of electronic and zero-point Energies= -590.762612
Sum of electronic and thermal Energies= -590.745231
Sum of electronic and thermal Enthalpies= -590.743732
Sum of electronic and thermal Free Energies= -590.822945

-1 1

C	0.47053500	0.31816300	-0.48326100
O	1.36956700	-0.32876000	0.37367200
C	2.69065700	-0.44731900	-0.15160700
H	3.16008800	0.53703700	-0.26784100
H	3.26746800	-1.03625600	0.56734200
H	2.67838800	-0.95562300	-1.12296700
C	-0.88791000	-0.17306500	-0.06366700
F	-1.05729900	-1.48933700	-0.39719000
F	-1.89426200	0.51454600	-0.68171400
F	-1.21425900	-0.11367800	1.28850400
F	0.42113400	1.74383100	0.01543300

Transition State 10 – β-elimination
(Displacement vectors show direction of atom movement during elimination)



1 imaginary frequency

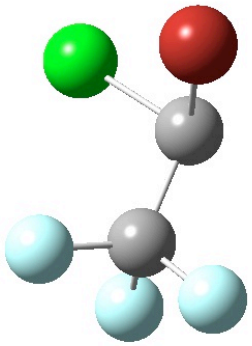
Zero-point correction= 0.060735 (Hartree/Particle)
Thermal correction to Energy= 0.077861
Thermal correction to Enthalpy= 0.079359
Thermal correction to Gibbs Free Energy= 0.000022
Sum of electronic and zero-point Energies= -590.751326
Sum of electronic and thermal Energies= -590.734199
Sum of electronic and thermal Enthalpies= -590.732701
Sum of electronic and thermal Free Energies= -590.812038

-1 1

C	0.48574000	0.35301600	-0.20944300
F	-1.66377200	-0.22483400	1.33909300
F	-1.75220300	0.59293600	-0.84359400
F	-0.95957300	-1.44600300	-0.53116500
F	0.53328400	1.74832000	0.06572900
O	1.42458300	-0.32460400	0.51943300
C	2.68486800	-0.50411100	-0.15013100
H	3.15500200	0.46278000	-0.35903700
H	3.31901200	-1.07793700	0.52925800
H	2.54441800	-1.05452100	-1.08642900
C	-0.80972900	-0.14344700	-0.22539600

4. Cartesian coordinates, number of imaginary frequencies and energies for the structures involved in the inversion of anion 11 at PCM-B3LYP/6-31++G**

Reactant 11



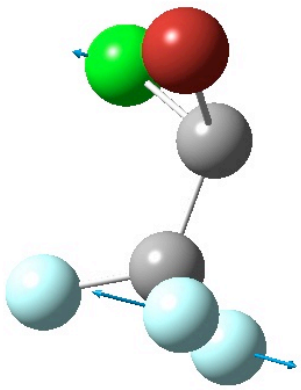
0 imaginary frequencies

Zero-point correction= 0.018647 (Hartree/Particle)
Thermal correction to Energy= 0.028576
Thermal correction to Enthalpy= 0.029735
Thermal correction to Gibbs Free Energy= -0.024691
Sum of electronic and zero-point Energies= -3407.760724
Sum of electronic and thermal Energies= -3407.750795
Sum of electronic and thermal Enthalpies= -3407.749636
Sum of electronic and thermal Free Energies= -3407.804062

-1 1

C	-0.14916900	0.34727100	-0.70214700
Cl	-0.43009800	2.03573600	0.01542000
Br	1.64029100	-0.27960400	0.00727800
C	-1.17023600	-0.54295800	-0.05068300
F	-1.24831700	-0.60972100	1.33417300
F	-1.00642500	-1.83783800	-0.45009900
F	-2.43215400	-0.17991600	-0.43961700

30º Rotamer of Anion 11
(Displacement vectors show direction of atom movement during rotation of CF_3)



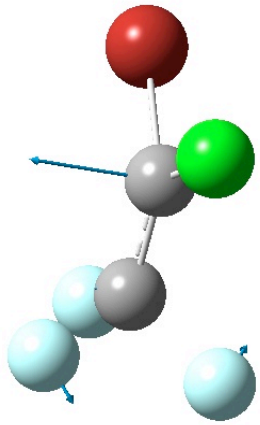
0 imaginary frequencies

Zero-point correction= 0.018462 (Hartree/Particle)
Thermal correction to Energy= 0.030531
Thermal correction to Enthalpy= 0.031838
Thermal correction to Gibbs Free Energy= -0.033827
Sum of electronic and zero-point Energies= -3407.754169
Sum of electronic and thermal Energies= -3407.742101
Sum of electronic and thermal Enthalpies= -3407.740793
Sum of electronic and thermal Free Energies= -3407.806458

-1 1

C	-0.12908300	0.35813000	-0.62868500
Cl	-0.38261000	2.05116100	0.01791700
Br	1.65899500	-0.30654100	0.00520900
C	-1.19844800	-0.52849500	-0.05897900
F	-0.81305200	-1.82741100	0.06118700
F	-2.31564100	-0.51853100	-0.86015400
F	-1.71522700	-0.22279500	1.20330700

Transition State – inversion of asymmetric carbon in anion 11
(Displacement vectors show direction of atom movement during inversion)



1 imaginary frequency

Zero-point correction= 0.017755 (Hartree/Particle)
Thermal correction to Energy= 0.027240
Thermal correction to Enthalpy= 0.028399
Thermal correction to Gibbs Free Energy= -0.025456
Sum of electronic and zero-point Energies= -3407.743089
Sum of electronic and thermal Energies= -3407.733605
Sum of electronic and thermal Enthalpies= -3407.732446
Sum of electronic and thermal Free Energies= -3407.786301

-1 1

Cl	0.27481000	2.07284700	0.00003200
C	0.06940400	0.32187900	0.00043800
Br	-1.70193300	-0.35262600	0.00001500
C	1.20674100	-0.48797600	-0.00006000
F	2.15271800	-0.30416300	-1.08604500
F	2.15291000	-0.30527400	1.08625300
F	0.94315200	-1.82388700	-0.00057700

5. Enthalpies of activation for anions 10 and 11 at PCM-B3LYP/6-31++G, PCM-B3LYP/6-311++G** and PCM-B3LYP/aug-cc-pVDZ including Temperature parameter.**

	B3LYP /6-31++G**	B3LYP/6-311++G**	B3LYP/aug-cc-pVDZ
10 $\Delta H^{\neq}_{elimination}$	6.35 kcal/mol	5.29 kcal/mol	6.24 kcal/mol
11 $\Delta H^{\neq}_{inversion}$	10.23 kcal/mol	10.01 kcal/mol	11.24 kcal/mol