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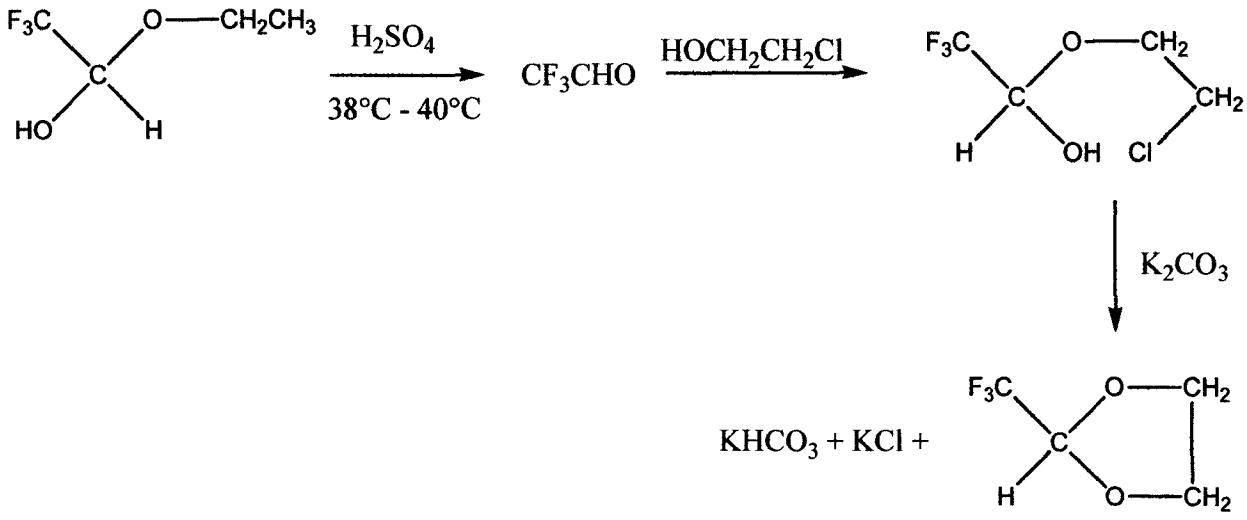
Ring fluorination of some substituted 1,3-dioxalanes, successful deactivation of the 2-hydryl group by 2-trifluoromethyl relative to 2-methyl

Kashif Saleem

Background

Aerosol direct fluorination of 2-methyl-1,3-dioxolane resulted in the formation of products with many different isomers, listed in Appendix B. There was instability in the fluorination products and an increased degree of ring opening. The ring was easily fluorinated and the low fluorination procedure produced products that were comparable to the high fluorination procedure of 2,2-dimethyl-1,3-dioxlane system. Significantly there was almost always fluorination at the 2-hydryl, an undesirable occurance. There was also ring opening which produced perfluorinated diethyl ether in amounts comparable to the perfluorinated analog. Small quantities of fluorinated material did not survive the sodium carbonate hydrolysis step and four other compounds, one major, were not stable to dehydrofluorination over several weeks.

Therefore, the synthesis and fluorination of a 2-trifluoromethyl-1,3-dioxalane system was pursued for this project. It is hoped that that this process will allow the isolation of samples which are not mixtures. Furthermore, the electron-withdrawing nature of the trifluoromethyl may allow for preservation of the 2-hydryl grouping, which is important in this compound as it may help in allowing it to become a usable anesthetic. The trifluoromethyl group may be a source of instability, but it is hoped it will cause the 2-hydryl group to be less reactive.



Trifluoracetaldehyde is not stable as it polymerizes easily and must be generated each time the synthesis is run. It is hoped that the electronic deactivation by the trifluormethyl group along with its steric bulk will render the 2-hydryl group less reactive to elemental fluorine.

Reactor Background

Aerosol direct fluorination is a process by which an organic vapor is absorbed onto the surface of many microscopic (17 Å) sodium fluoride preaerosol nucleating particles in a helium carrier gas at low (-196°C) temperatures. The particulates so formed are carried into a low-temperature (-20°C) region consisting of a tubular microporous walled (2 μm) reactor where fluorine diffuses into the reactor the reactor stream through porous walls. As the adsorbed molecules are fluorinated, they are carried down the tubular reactor into regions of higher fluorine concentration and higher temperatures, where they undergo higher degrees of fluorination.

Relevant conditions that contribute to the high-yield fluorination include the following:

(1) The fluorination of molecules adsorbed on sodium fluoride and held in a crystalline state has many different effects. First, it allows for a heat sink which in turn allows for the release of energy into the lattice by radiationless relaxation processes. Second, it allows for a template on which a molecule subjected to skeletal bond scission may recombine instead of fragment. Third, it is a means of immobilizing two radicals formed by hydrogen abstraction so that their interactions remain at minimal levels. Fourth, it allows for the protection of one side of the molecule from attack by gaseous fluorine. Fifth, it is a catalyst which involves the effects of the fluoride ion on some substrates. Sixth, it allows for the interaction of sodium fluoride with elemental fluorine. Seventh, the interaction as a base will absorb the hydrogen fluoride that is generated throughout the process. Eighth, it allows for a base that will react with any carbocations produced in the process.

(2) The resulting high surface area exposed to gaseous fluorine greatly increases the reactivity of molecules. This can be seen in examples where material such as grain, which is seemingly harmless, whose dust can have explosive reactivity under certain conditions.

(3) The equal exposure of all the molecules to gaseous fluorine throughout the whole process allows for a high yield of unfragmented fluorocarbon. Once a molecule is approximately 40% fluorinated, its skeletal integrity seems to be enhanced, thus allowing the molecule to undergo more vigorous attack.

(4) The high initial dilution of gaseous fluorine has several beneficial effects. First, it reduces the overall rate of reaction resulting in a lower heat flux. Second, it

reduces the chances of multiple simultaneous reactions on a single molecule. Multiple simultaneous reactions can result in fragmentation. Third, it reduces the changes of adjacent molecules forming radicals in proximity close enough for coupling to occur.

(5) Initial low temperatures have the effect of lowering the overall kinetic energy of the molecules, resulting in the reduction of the frequency of collisions between molecules. Lower temperature also assists in the removal of excess heat of reaction.

(6) The adsorbed molecules lose heat directly to the aerosol particulate, and both the molecules and aerosol particulate lose heat via helium mediated thermal conduction to the reactor walls. This allows for an efficient cooling system within the reactor.

Procedure

Preparation of 2-Trifluoromethyl-1,3-dioxalane

Prepare two reaction vessels each containing magnetic stir bars. Note tare weight of both vessels. Add 20 mL of sulfuric acid to one vessel, weigh amount of sulfuric acid put in, and de-gas. Add 5 mL of trifluoroacetaldehyde ethyl hemiacetal 90% to the other vessel, weigh amount of trifluoroacetaldehyde ethyl hemiacetal, and de-gas. Put both reaction vessels on vacuum line and transfer trifluoroacetaldehyde ethyl hemiacetal into reaction vessel with sulfuric acid. Keep under liquid nitrogen to prevent mixing. Calculate amount of 2-chloroethanol that must be added to the reaction in order to have a

1:1 of trifluoroacetaldehyde ethyl hemiacetal and 2-chloroethanol. Add this amount of 2-chloroethanol along with 10 mL of n-pentane into the empty reaction vessel and de-gas. Once this is done, keep liquid nitrogen trap around reaction vessel with the 2-chloroethanol/n-pentane mixture. Allow the reaction vessel with the sulfuric acid and trifluoroacetaldehyde ethyl hemiacetal to warm up slowly. Put warm water bath around reaction vessel on top of a stirrer. Allow stir bar to stir contents and heat water bath up slowly. When the sulfuric acid/ trifluoroacetaldehyde ethyl hemiacetal mixture mixes into one layer, slowly open stopcock to allow product that is formed (CF_3CHO) to transfer into reaction vessel with the 2-chloroethanol/n-pentane mixture. When contents of sulfuric acid/trifluoroacetaldehyde ethyl hemiacetal mixture stop vigorously bubbling, reaction is complete. Allow reaction vessel with 2-chloroethanol/n-pentane mixture with new product to stir overnight. The following day, add enough potassium carbonate to allow for a 2:1 of potassium carbonate to $C_4H_6F_3O_2Cl$ and allow to stir overnight.

Fractionate mixture at -20°C, -40°C, -60°C, -80°C, and -196°C. The -40°C, -60°C, and -80°C traps contain 2-trifluoromethyl-1,3-dioxolane. Purify product on a gas chromatograph and put on molecular sieve to dry.

Aerosol Fluorination of 2-Trifluromethyl-1,3-dioxalane

The aerosol fluorinator design and a description of the process are presented elsewhere [1,2]. Details of the parameters are given in Table 1. The 2-trifluoromethyl-1,3-dioxolane is fed into the evaporater/sublimator unit through a 10 mL Precision Sampling Corp, "Pressure Lock" syringe. Once the reactant is run through the reactor, the sodium fluoride loaded product trap is warmed overnight to remove any hydrogen

fluoride, the product is transferred from the product trap on the vacuum line, and fractionated through -20°C, -40°C, -60°C, -80°C, -196°C traps set up on the vacuum line. The product condenses in the -40°C, -60°C, and -80°C traps. The liquid in these traps is combined, hydrolyzed with a 10% aqueous solution of sodium carbonate, and is run through a gas chromatograph. Following the gas chromatographic separation, the products is characterized by vapor phase infrared spectrometry and by ^{1}H and ^{19}F nuclear magnetic resonance spectrometry in $CDCl_3$ with 1% $CFCl_3$ internal standard.

Table 1.

Fluorine Flow, cc/min					
Evaporator	Top of Reactor Tube		Middle of Reactor Tube	Bottom of Reactor Tube	
1.2	30.0		30.0	12.0	
Helium Diluent, mL/min					
Furnace	Evaporator		Main	Window	
80	130		30	30	
Reaction Temperature, °C					
Preaerosol Furnace	Hydrocarbon Evaporator	Injector Heat	Main Coolant Supply	Module 1 Cooler	Module 2 Cooler
985	99	45	-41	-23	5

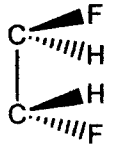
Results and Discussion

	A	B	C
Trial 1	27.32%	26.91%	12.92%
Trial 2	63.08%	19.85%	1.15%
Trial 3	35.43%	34.47%	9.77%

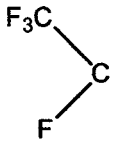
*Compounds A, B, and C are defined later

The yields for Trial 2 are off due to the fact that we had a leak in the reactor while running the experiment. Infrared Fourier spectra along with ^{1}H and ^{19}F NMR spectra are used to analyze the structures of the three compounds. See Appendix C for the GC graph.

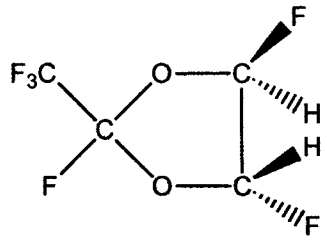
For Compound A (see Appendix D), the ^{1}H NMR spectrum shows major peaks between the ranges of δ=5.963 ppm and δ=6.272 ppm. The two doublet peaks show H-H splitting. The two triplet peaks show H-F splitting. The shift of one doublet peak and one triplet peak downfield is due to that fact that we have a molecule with a trans configuration. Looking at the ^{19}F NMR, there are peaks found in between φ=-132.597 and φ=-131.698. The two doublets correspond F-F splitting, while the triplets corresepond to H-F splitting. Again, the two sets of doublet and triplet peaks correspond to a trans configuration.



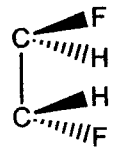
We can also see a major singlet peak at φ=-86.056 ppm. This corresponds a trifluoromethyl group. The peaks at φ=-85.0 ppm correspond to a lone fluorine. The splitting is due to shielding effects from the trifluoromethyl group and fluorines on the other side of the molecule. The 2-trifluoromethyl and 2-fluorine usually have coupling constants of less than 1 Hz and it is not observed in this spectrum.



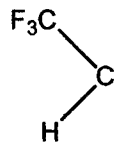
The IR spectrum shows that the compound is an ether. Therefore, it is safe to say that Compound A is *trans*-2-trifluoromethyl-2,4,5-trifluro-1,3-dioxalane.



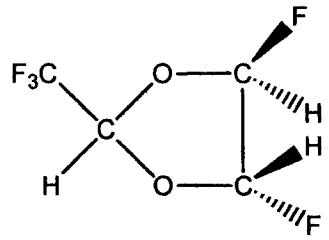
Looking at the ^{1}H NMR spectrum for Compound B (see Appendix E), we see that it similar to Compound A with a few exceptions. The peaks found between δ=5.86 ppm and δ=6.16 ppm correspond to the trans configuration of the hydrogens, just like in Compound A. The heptet at δ=5.723 ppm corresponds to a lone hydrogen. Looking at the ^{19}F NMR spectrum, there is a set of peaks between φ=-128.574 ppm and φ=-133.239 ppm. These peaks, when looked at closer, correspond to a trans configuration of fluorines. Therefore, the Compound B has a trans H-F configuration exactly like Compound A.



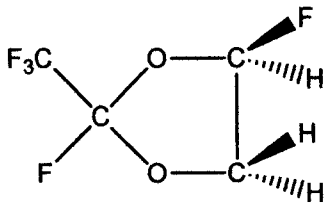
There is a major peak at φ=-83.97 ppm, which corresponds to a trifluoromethyl group. The doublet splitting of the trifluoromethyl by the 2-hydrl group indicates the presence of the 2-hydryl group. From this data, it is safe to assume that we have the 2-hydrogen preserved compared to Compound A, and from the data, it is safe to assume that it is found in Compound B in the 2 position.

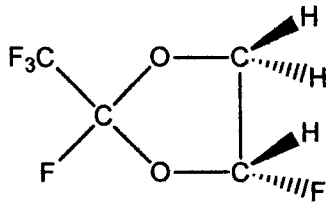


Again, from the IR spectra we know that we have an ether, so it is safe to assume that our compound is *trans*-2-trifluoromethyl-4,5-difluoro-1,3-dioxalane.



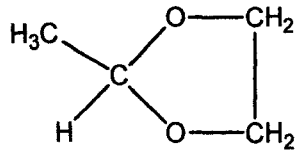
Compound C is still under analysis and it is yet to be determined what the compound is but appears to be a mixture of two compounds.



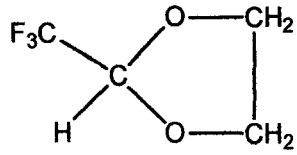


It is safe to say that from the given results, we did end up getting a fair amount of the desired material, which was Compound B (*trans*-2-trifluoromethyl-4,5-difluoro-1,3-dioxalane). The 2-hydryl group remained on the molecule after fluorination indicating that we did indeed see significant deactivation of the 2-hydryl with respect to attack by elemental fluorine. The 2-hydryl group is important in allowing this molecule to have usable anesthetic qualities. Further analysis of this compound will determine whether it can be used in future anesthetics.

Appendix A



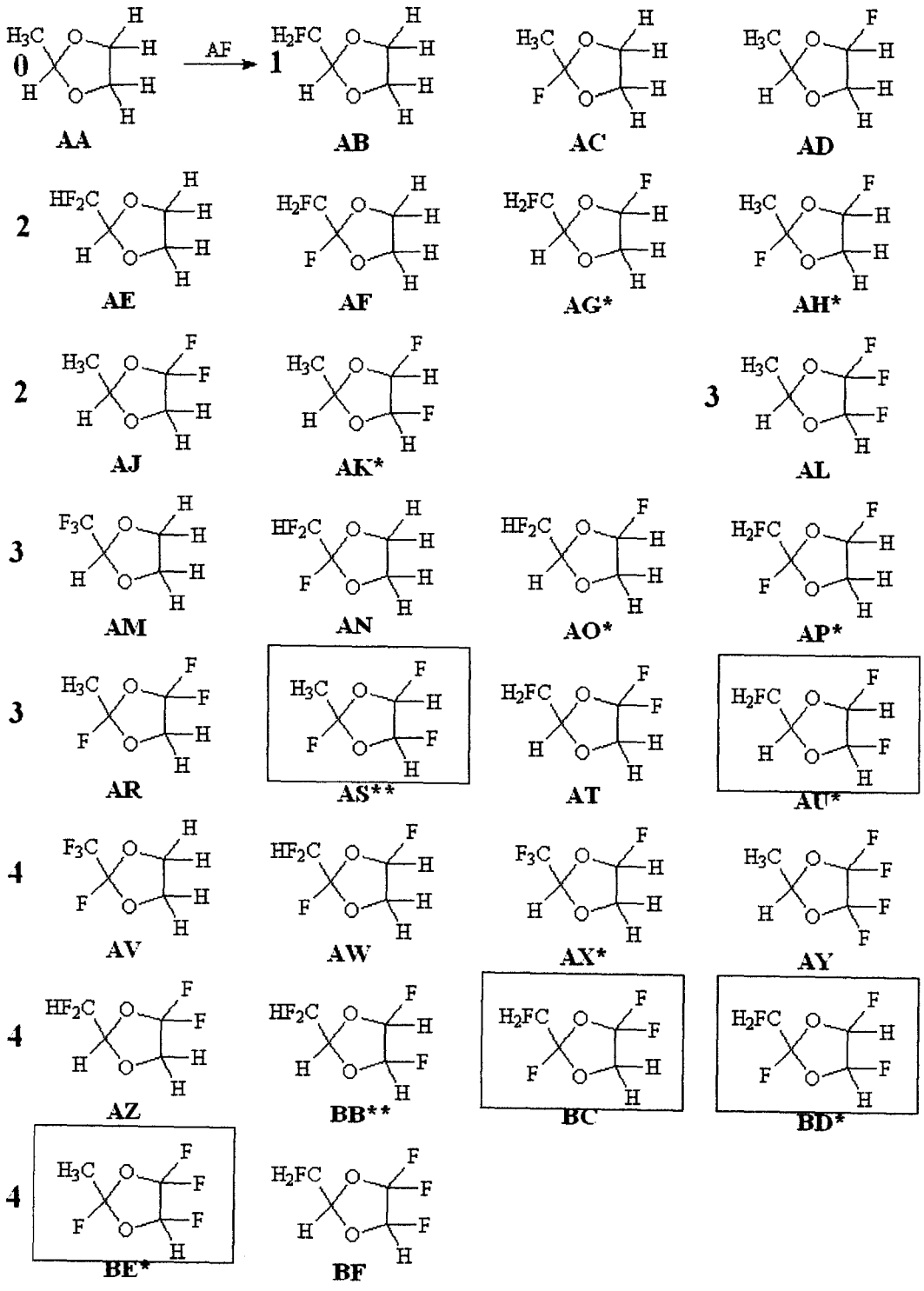
2-methyl-1,3-dioxolane



2-trifluoromethyl-1,3-dioxalane

Appendix B

#F's



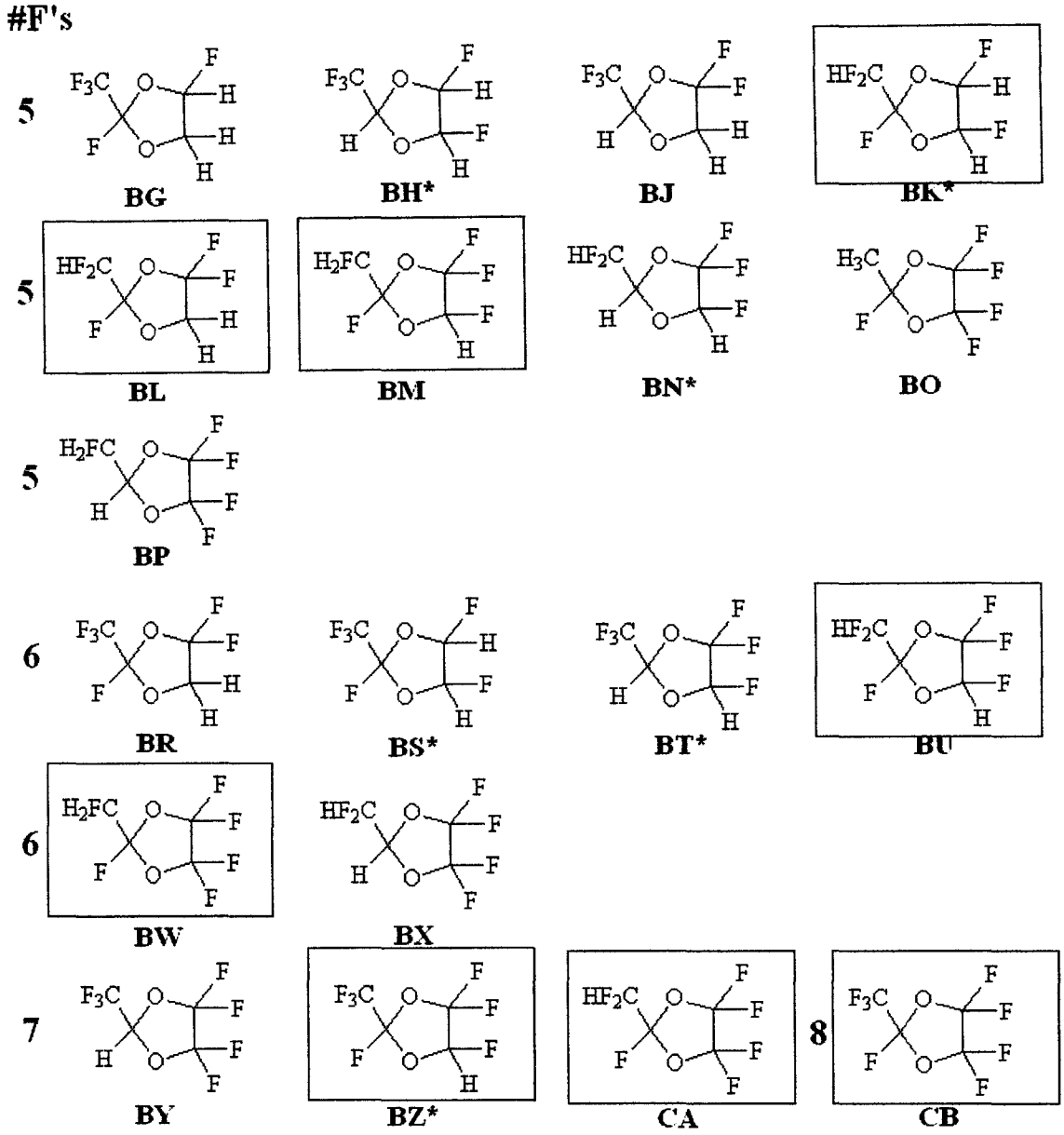


Figure 1. Different products that can be formed with aerosol fluorination of 2-methyl-1,3-dioxolane

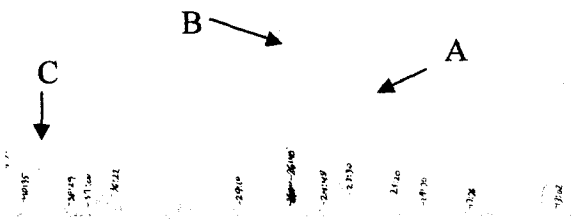


Figure 2. Gas chromatograph graph of Trial 1

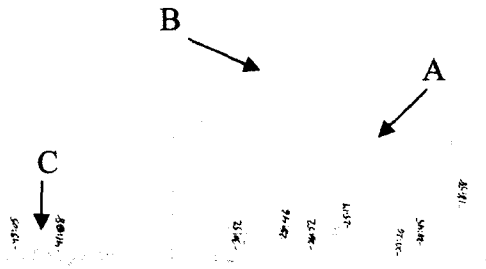


Figure 3. Gas chromatograph graph of Trial 2

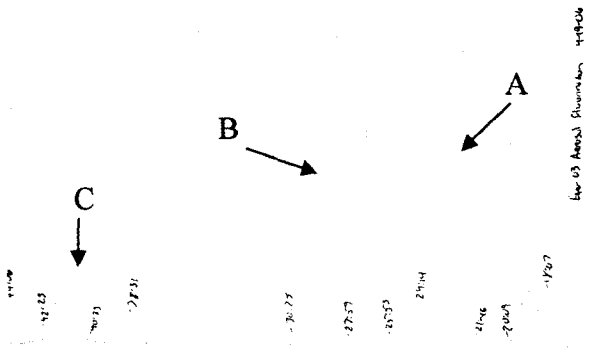


Figure 4. Gas chromatograph graph of Trial 3

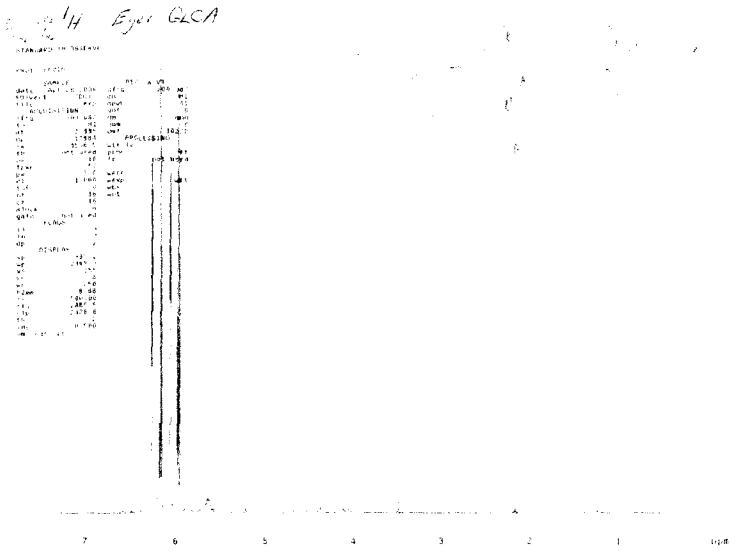


Figure 5. ^{1}H NMR spectrum of Compound A

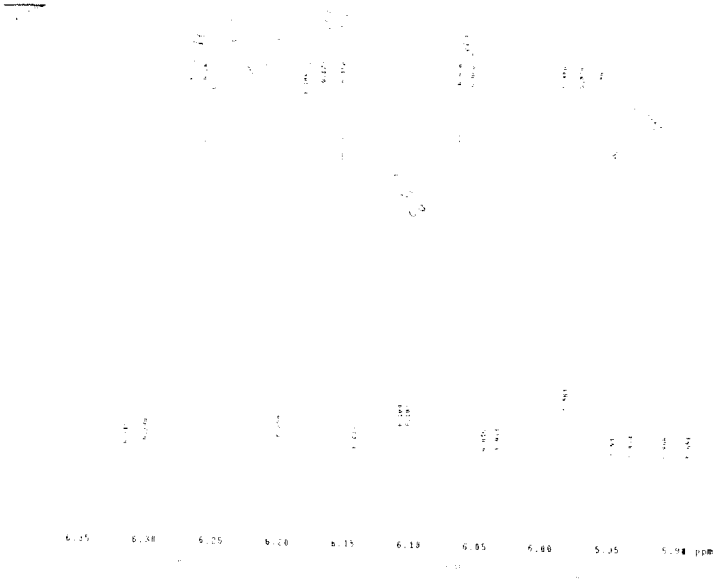


Figure 6. ^{1}H NMR spectrum of Compound A magnified

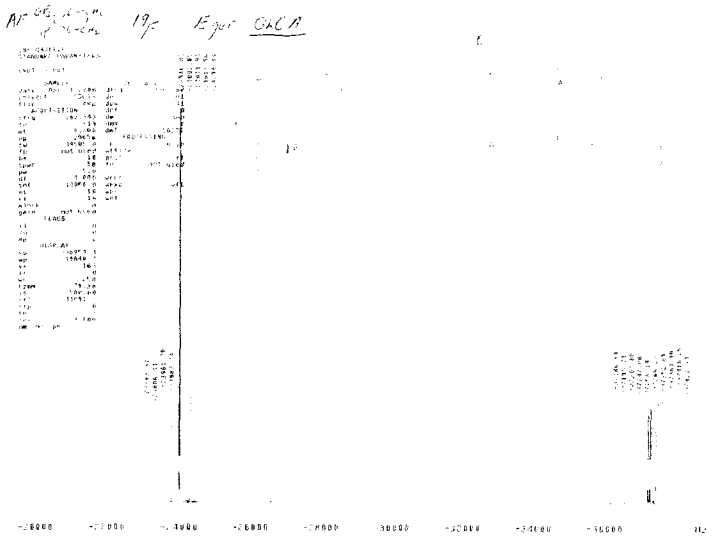


Figure 7. ^{19}F NMR spectrum of Compound A

Figure 8. ^{19}F NMR spectrum of Compound A magnified

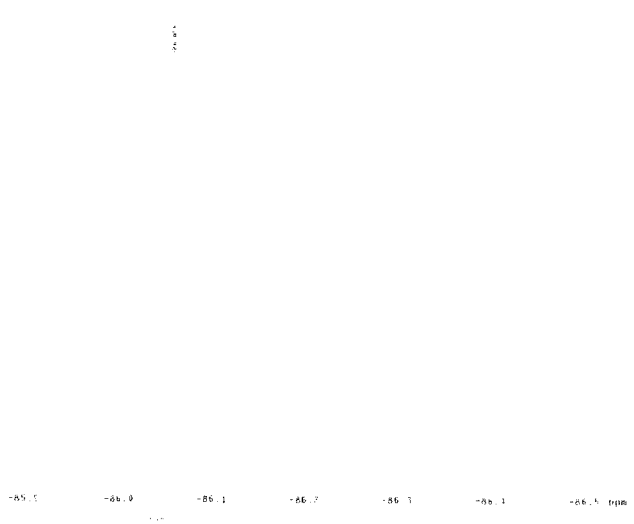


Figure 9. ^{19}F NMR spectrum of Compound A magnified

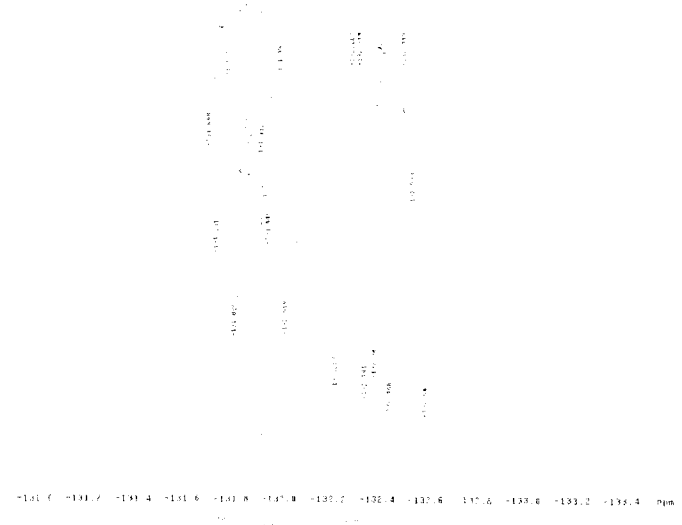


Figure 10. ^{19}F NMR spectrum of Compound A magnified

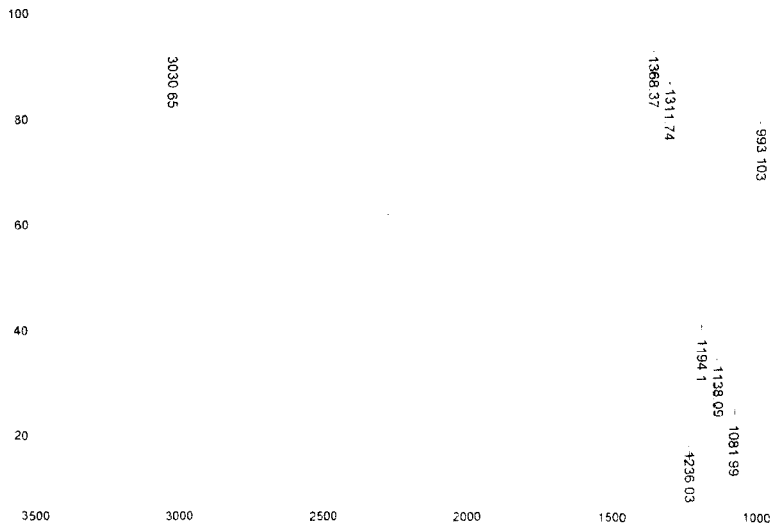


Figure 11. Gaseous Infrared Fourier spectrum of Compound A at 2 Torr

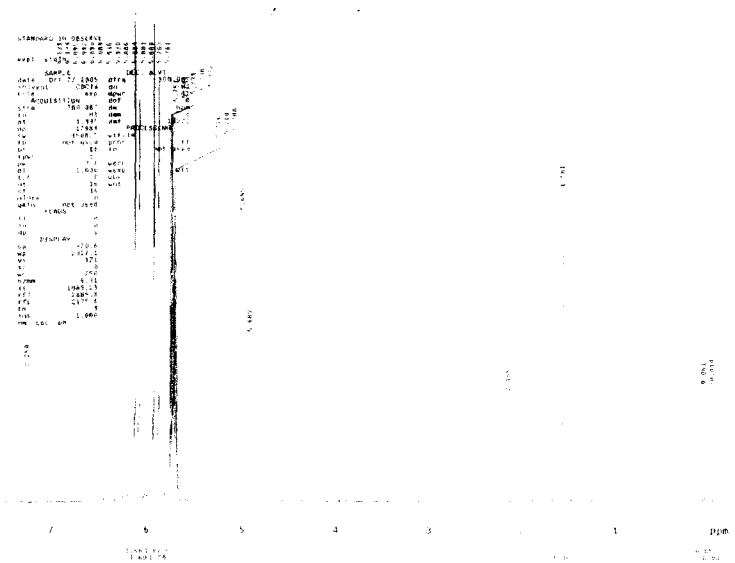


Figure 12. ^{1}H NMR spectrum of Compound B

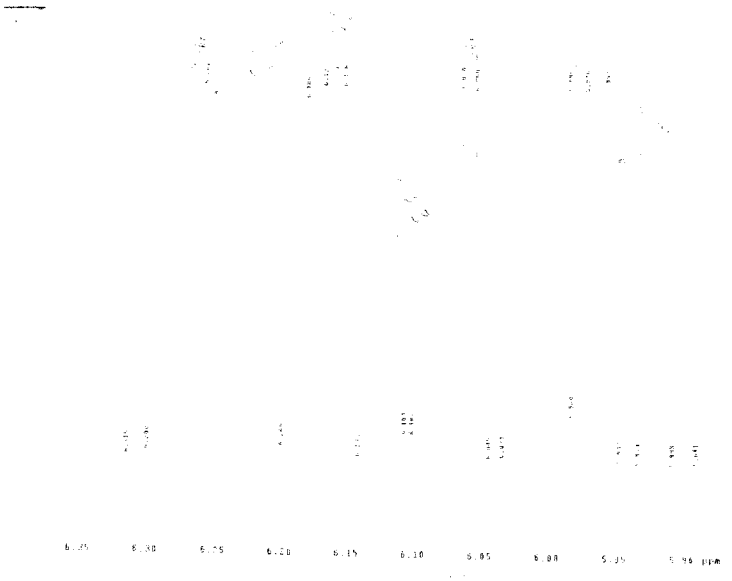


Figure 13. ^{1}H NMR spectrum of Compound B magnified

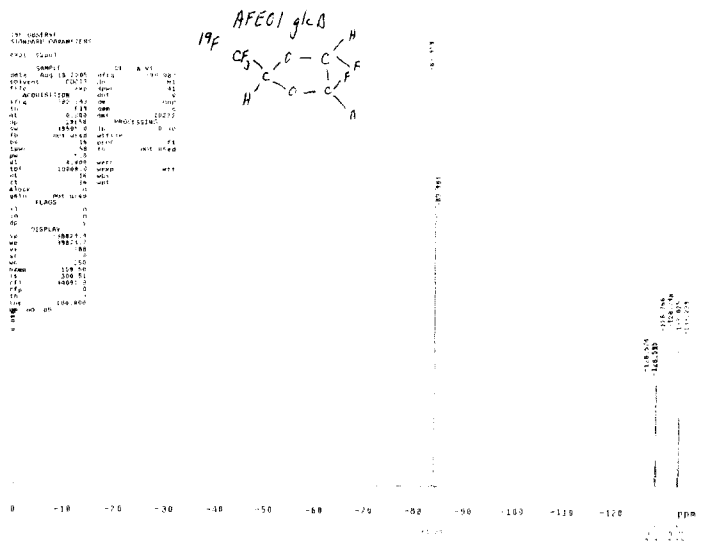


Figure 14. ^{19}F NMR spectrum of Compound B

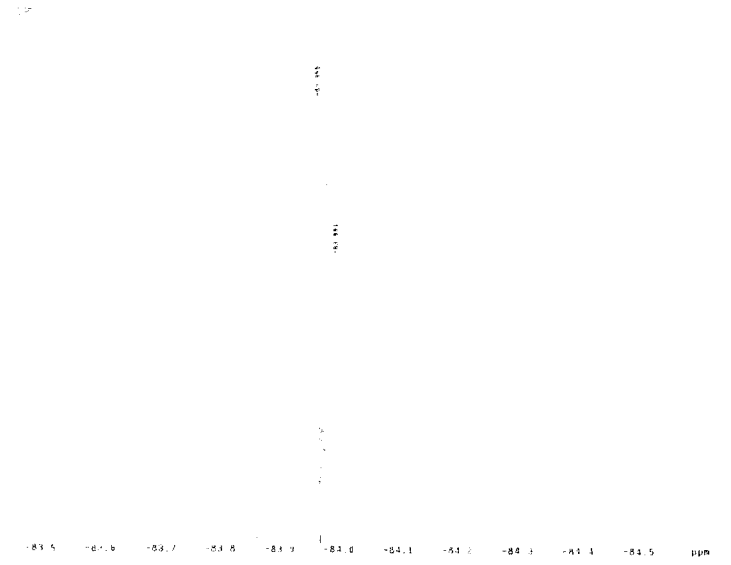


Figure 15. ^{19}F NMR spectrum of Compound B magnified

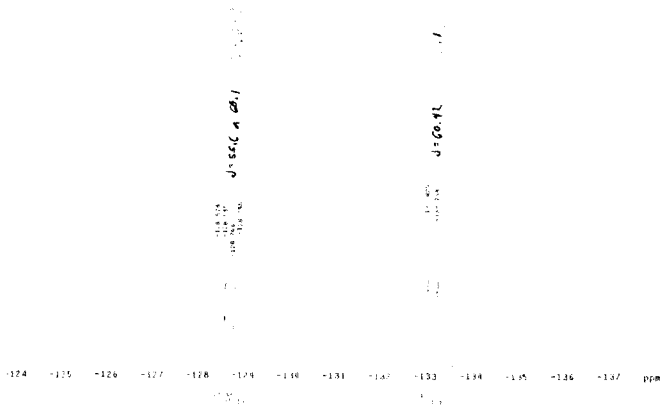


Figure 16. ^{19}F NMR spectrum of Compound B magnified

Figure 17. Gaseous Infrared Fourier spectrum of Compound A at 2 Torr

References

1. J. L. Adcock and M.L. Cherry, Industrial & Engineering Chemistry Research, 26 (1987) 208.
2. J.L. Adcock, K. Horita and E.B. Renk, J. Am. Chem. Soc., 103 (1981) 6937.
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