Determination of rate constants for H-abstraction by 4-fluorophenyl radicals from fatty acid methyl esters by F-19 NMR

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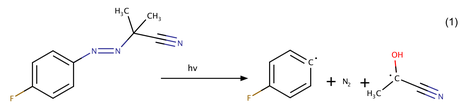
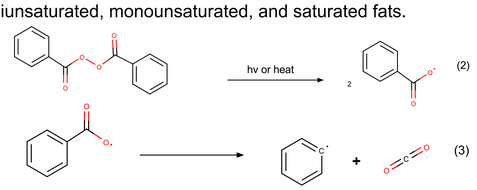
Introduction

Phenyl radicals (Ph·) are very reactive intermediates known to rapidly abstract hydrogens and add to double bonds.[1] Rate constants for H-abstraction by Ph· from various types of substances have been determined and are generally in the range of k=3.3 x 10^4 to 3.3 x 10^5 M^{-1} s^{-1}. [1,2] Kenttamaa and coworkers used mass spectrometry to examine the rate of gas-phase reactions of Ph· with lipids, using Ph· with cationic ammonium substituents.[3] However, solution phase rate constants for H-abstraction by uncharged phenyl radicals from lipids remains, in large part, unknown. Thus, this research is attempting to measure k for H-abstraction from fatty acid methyl esters (FAME) by uncharged Ph· using 4-fluorophenyl radicals (Ar·) generated from the visible photolysis of 4-fluorophenylazoisobutyronitrile (FPAIN) (eq 1). The research may provide insight as to the types of effects phenyl radicals from benzoyl peroxide (BPO) may have on the human body.



BPO is an over the counter medication widely used as a treatment for acne and is on the list of World Health Organization's list of essential medicines.[4] BPO is also known to break down to form free Ph· (eq 2,3), and is accordingly frequently used as an initiator for radical polymerization.[1] Previous work has shown that BPO can act as a tumor promoter in mice skin; however, there was not enough evidence to suggest that BPO is a tumor initiator.[1] This research project is aiming to provide information relevant to the possible effects of free radicals formed from BPO on human skin. Specifically, we are measuring the rate constants of H-abstraction by Ph· from fatty acid methyl esters (methyl linoleate, methyl oleate, and methyl stearate) as respective models for diunsaturated, monounsaturated, and saturated fats.



References

(1) Slaga, T. J; Klein-Szanto, A. J. P; Triplett, L. L; Yotti, L. P; Trosko, J. E. Skin Tumor-Promoting Activity of Benzoyl Peroxide, a Widely Used Free Radial-Generating Compound. *Science* **1981**,*213,* 1023-1025.
(2) Kryger, R. G; Lorand, J, P; Stevens, N. R; Herron, N. R. Radical and Scavengers. 7. Diffusion Controlled Scavenging of Phenyl Radicals and Absolute Rate Constants of Several Phenyl Radical Reactions. *J. Am. Chem. Soc.* **1977,** *99:23*, 7589-7600.
(3) Heidbrink, J. L; Thoen, K. K; Kenttamaa, H. I; Ramirez-Arizemendi, L. E; Guler, L. Polar Effects Control Hydrogen-Abstraction Reactions of Charged, Substituted Phenyl Radicals. *J. Org. Chem.,* **2000**, *65 (3),* 645–65.1
(4) WebMD. http://www.webmd.com/drugs/2/drug-1344/benzoyl-peroxide-topical/details
(5) Marousek, V. 1. A contribution to the study of unsymmetrical azo nitriles. V. Thermal decomposition of 2-phenylazoisobutyronitrile derivatives. *Polymery—Chemie, Vlastnosti a Zpracovani* **1978**, *S1*, 101-111.
(6) Tanner, D.D. ; Reed, D. W. ; Setiloane, B. P. *J. Am. Chem. Soc.* **1982,** *104,* 3917-3923.

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Results

Figure 1: Preparation of 4-fluorophenylazoisobutyronitrile (FPAIN)

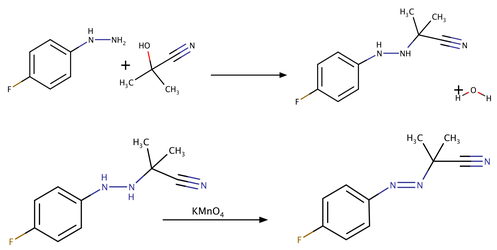


Figure 2: ^{1}H NMR of 4-fluorophenylhydrazinoisobutyronitrile

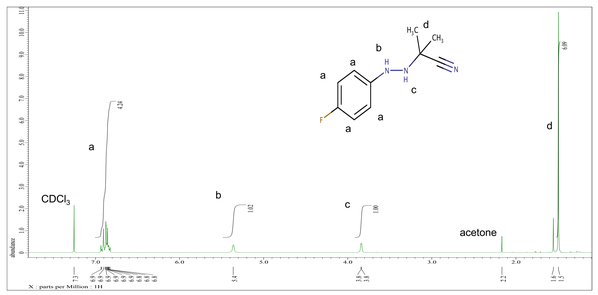


Figure 3: ^{1}H NMR of purified FPAIN

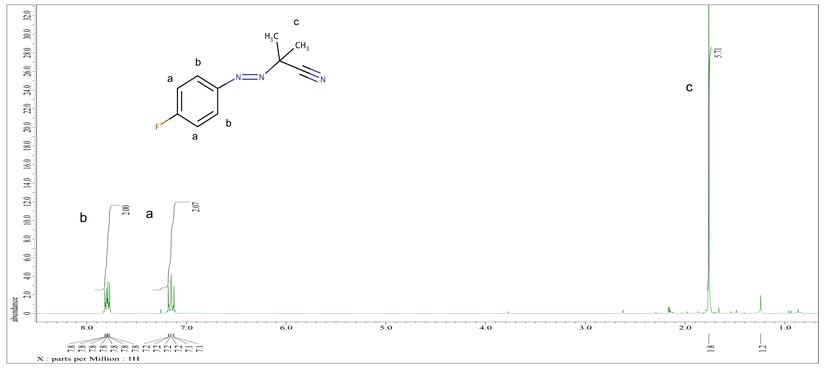


Figure 4: Photolysis of FPAIN in the presence of a FAME and iodobenzene

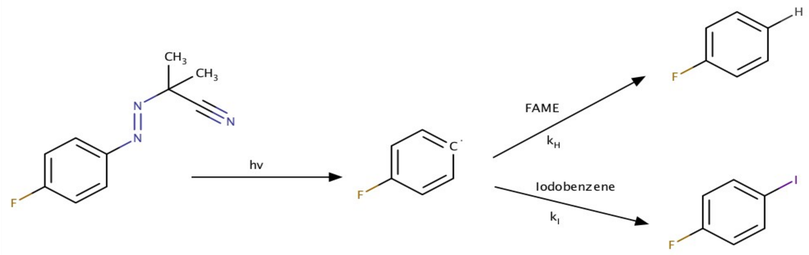


Figure 5: k_H calculation

$$\frac{[ArH]}{[ArI]} = \frac{kH[Ar\cdot][FAME]}{kI[Ar\cdot][PhI]}$$

k_H= ArH/ArI x [PhI]/[FAME] x k_I
ArH/ArI= 0.629 [PhI]/[FAME]=2.09
k_I=1.05 x 10^8 [1,2]
k_H=3.17 x 10^7

Figure 7: F-19 NMR of FPAIN

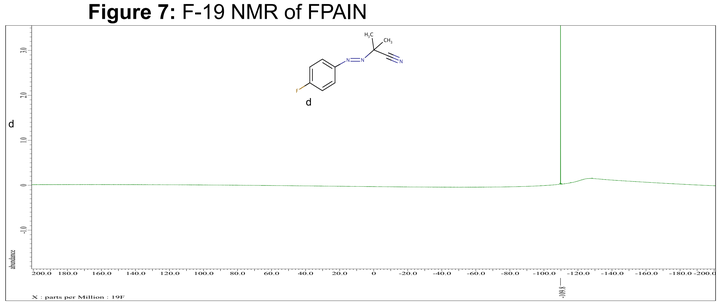
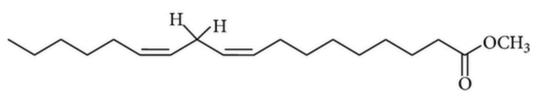


Figure 9: Methyl Linoleate



https://www.researchgate.net/figure/Structure-of-methyl-linoleate-ML-and-its-peroxyl-radical_fig4_273663520

Figure 6: F-19 NMR of fluorobenzene

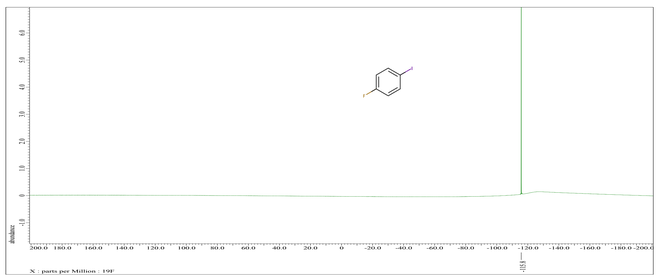
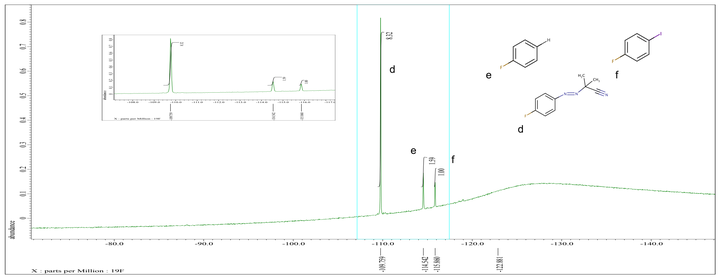


Figure 8: F-19 NMR of Preliminary Expt with FAME = Methyl Linoleate



Discussion

The preparation of FPAIN was accomplished by adapting a literature method for phenylazoisobutyronitrile (BPAIN)[5]. FPAIN was then used as a radical initiator. (Figure 4)

Preparation of 4-fluorophenylazoisobutyronitrile (FPAIN) (Figure 1). The ammonium salt, 4-fluorophenylhydrazine hydrochloride was deprotonated with NaOH in order to form the free amine which was then reacted with acetone cyanohydrin to give a 49.9% yield of the derived hydrazine compound. The product was large yellow/orange gem-like crystals and the ^{1}H NMR showed no impurity peaks (Figure 2). This compound was then oxidized with excess $KMnO_4$ to give a 46.6% yield of FPAIN, as a viscous yellow liquid after purification by flash chromatography. The product showed excellent purity by ^{1}H NMR and mass spectrometry verified the expected molecular weight of 191. UV/Vis spectroscopy revealed the wavelength of maximum absorption as 387 nm.

Determination of k for H-abstraction (k_H) for methyl linoleate (Figure 4). We only recently completed the synthesis of FPAIN, so as of now we only have one preliminary experiment to report. However, the results are quite promising. Specifically visible irradiation of a solution of FPAIN (0.12 M), methyl linoleate (0.13 M), and iodobenzene (0.064 M) by a 65W CFL light (4 h) led to two new peaks in the F-19 NMR (Figure 8). In addition to the starting material peak at -109.8 ppm (FPAIN) (Figure 7), were product peaks at -114.5 ppm and -115.9 ppm assigned to the expected products fluorobenzene and fluoroiodobenzene respectively (Figure 6). Through integration, the ratio of fluorobenzene to fluoroiodobenzene was determined to be 1.59:1.00. Using this ratio and the known rate constant for iodine abstraction by phenyl radicals from iodobenzene (k_I = 1.05 x 10^8 $M^{-1}s^{-1}$), we are able to calculate k for H abstraction by phenyl radicals as k_H = 3.2 x 10^7 M^{-1} s^{-1} (Figure 5). This would place linoleate as one of the fastest hydrogen donors in reactions with phenyl radicals, which is not completely surprising due to the doubly allylic hydrogens as seen in Figure 9.

Experimental

4-Fluorophenylhydrazinoisobutyronitrile

4-Fluorophenylhydrazine hydrochloride (10 g, 0.062 mol, Sigma Aldrich) was suspended in water with NaOH in a separatory funnel. It was tested with litmus paper to confirm basicity. The solution was then extracted 3X with diethyl ether and dried over Na_2SO_4. the solution was pipetted into a r.b.f. and acetone cyanohydrin (5.8 mL) was added. The solvent was then evaporated in *vacuo* (2 hours) on a lukewarm bath. The solution formed crystals upon storage in a freezer (1 week), which were washed with ice cold ether and collected to give 49.9% yield. ^{1}H NMR (300MHz, $CDCl_3$) δ 1.5 (6H, s), 3.8 (1H, s), 5.4 (1H, s), 6.9 (4H, m)

4-Fluorophenylazoisobutyronitrile (FPAIN)

The hydrazine compound was dissolved in acetone and $KMnO_4$ (1.96 g) was added and the solution was left to stir at r. t. for 4 days). ^{1}H NMR revealed that oxidation was complete. The solution was then filtered to remove the $KMnO_4$ and dried over Na_2SO_4 and pipetted into a r.b.f. where it was evaporated in *vacuo* (30 min) to give product as a yellow, viscous liquid in 46.6% yield ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8 (6H, s), 7.2 (2H, m), 7.8 (2H, m) ppm. F-19 NMR (282 MHz) -109.7 ppm, APCI-MS M + H at m/z = 192.0 , calcd for $C_{10}H_{11}FN_3$ = 192.1. UV/Vis λmax = 387 nm , ε = 179 cm^{-1} M^{-1}

Preliminary Expt with FAME = Methyl Linoleate

Equimolar amounts of FPAIN (0.1 mmol) and methyl linoleate (0.1 mmol) as well as 0.5 equiv iodobenzene (0.05 mmol) were dissolved in acetone-d_6 in a dry Pyrex tube and placed on a merry go round apparatus under a 65 W CFL light (4 h). F19 NMR (283 MHz) FPAIN: δ -109.8 ppm, fluoroiodobenzene: δ -114.4 ppm, iodobenzene: δ -115.9 ppm. (Figure 8). Products were identified by their chemical shifts (PhF = -113.15 ppm (lit), FPhI = -115.7 ppm (pure sample)) .