Electronic Factors Affecting the Rate and Regioisomeric outcome of the Friedel-Crafts Acylation Reaction

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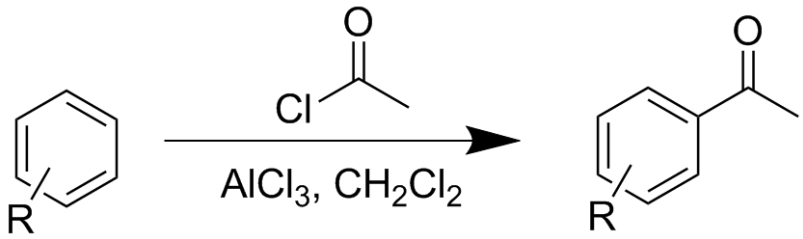


ABSTRACT

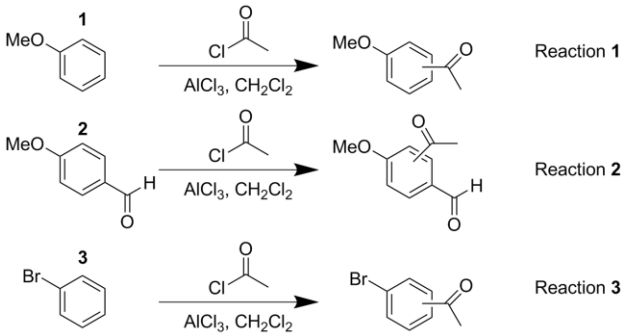
Using Thin Layer Chromatography and ^{1}H NMR spectroscopy, various reaction metrics, including relative reactivity and regioselective preferences, were determined for three differentially substituted aromatic substrates in the Freidel-Crafts acylation reaction. Our results suggest that activating groups, such as an electron-donating methoxy group, increase the reaction rate, while deactivating groups substantially decrease the relative reactivity. Furthermore, our results are consistent with previous literature, revealing that activating groups direct substitution to the ortho/para position, while deactivating groups are meta directors. Lastly, we propose an additional set of experiments involving additional rate measurements and acyl chlorides with various sterochemical/electronic properties to gain further insight into the Friedel-Crafts acylation reaction.

Since its discovery in 1877, the Friedel-Crafts acylation (FCA), developed by the chemists Charles Friedel and James Craft, has become a commonly used method for the construction of carbon-carbon bonds, and thus it is a useful reaction in the synthesis of larger, more complex molecules from smaller ones[1]. Carried out under anhydrous conditions, the FCA reaction utilizes a strong Lewis acid catalyst, typically aluminum chloride, for the acylation (addition of acyl group) of nucleophilic aromatic rings using an electrophilic acyl chloride. From a mechanistic standpoint, the initial step, aided by the aluminum chloride catalyst, consists of the dissociation of a chloride ion to form a positively charged, resonance stabilized carbon electrophile, termed an acylium ion, which is then subject to nucleophilic addition by the arene. Since the product retains a trigonal planar, sp^2 – hybridized carbon at the site of substitution, stereochemical considerations are not of particular interest to this study; however, it is known that the regioselectivity of the FCA reaction is strongly influenced by the electronic properties of the arene substituents. In general, through inductive and/or resonance effects, substituent groups either increase or decrease electron density in the benzene ring, affecting the course of

[1] Smith, J.; *Organic Chemistry*. Ed. 3; McGraw-Hill New York, **2011**

electrophilic aromatic substitution (EAS). Specifically, a substituent group that donates electrons into the benzene ring, designated as an activating group, directs substitution to the ortho/para position. In contrast, deactivating groups, which withdraw electron density from the benzene ring, have been shown to direct meta. Furthermore, it is also known that substituent groups influence the rate of reaction, with activating groups increasing the rate of reaction and deactivating groups reducing the reaction rate[1]. Lastly, this EAS reaction, whose product contains a carbonyl and ketone group, maintains several advantages over the related Friedel-Crafts alkylation reaction since neither multiple acylations nor carbocation rearrangements can occur. Overall, Friedel Crafts reactions exhibit considerable diversity, and many important industrial processes such as the production of high-octane gasoline, synthetic rubber, plastics and detergent alkylates are based on Friedel-Crafts Chemistry[2].

Scheme 1. FCA reactions under investigation in this study.



In this study, we investigated how the electronic nature of the substituents on aromatic compounds **1-3** (scheme **1)** affect the relative rate and regiochemistry the FCA reaction. To address the question regarding the FCA reaction rate, we monitored reaction progress via thin layer chromatography (TLC) samples taken at 5 minute intervals and characterized the reaction rate by the time interval necessary for the reaction to go to completion. Using ^{1}H NMR spectroscopy, we determined the ratio of isomeric substitution products by taking the ratio of peak integrations for non-overlapping signals located in the aromatic region (7-8 ppm) and accounting for differences in the number of hydrogen atoms represented in the compared signals. From these data, we extracted the molar ratio of isomeric substitution products.

Monitoring reaction rates of reactions **1-3** by TLC revealed that the properties of the aromatic substituents strongly influence the time interval required for the reactions to go to completion (Table 1). Since the identity and quantity of catalyst, solvent and non-aromatic reagent (acyl chloride) remained constant throughout all three reactions, we attributed differences in reaction rate to the arene substituents. As predicted, the electron-donating methoxy group on compound **1** functioned as an activating group and produced the most rapid reaction, with reaction completion occurring within 5 minutes of the aluminum chloride catalyst addition. Activation of the benzene ring can be explained in terms of the methoxy group's effect on the rate-determining step (first step) of the EAS mechanism. By the Hammond postulate, the stability of the resonance stabilized carbocation intermediate formed during the first step of the EAS mechanism is a predictor of the energy of the transition state, and thus the relative reaction rate[1]. The resonance effects of activating groups such as the methoxy group dominate over its electron withdrawing inductive effects, and the net effect is electron donation through the pi system, which stabilizes the carbocation intermediate and increases the reaction rate. In contrast, halogenation of a benzene ring as in compound **3** was shown to significantly decrease the reaction rate, with reaction completion requiring well over 1 h. Although halogens, such as Br, maintain lone pair electrons which can be donated through the pi system, an electron withdrawing inductive effect dominates due their high degree of electronegativity. As a result, the reaction was slowed because the stability of the carbocation is reduced. Finally, as expected, a reaction involving a benzene ring with both activating and deactivating groups took approximately 10 min to reach completion, slower than the activated benzene but faster than the deactivated benzene. Interestingly, the mixed activated/deactivated benzene reacted on a timescale more similar to the activated benzene than the deactivated one, which suggests that, in this case, the methoxy group was more strongly activating than the bromine was deactivating.

Table 1. The influence of various substituent groups on the rate of the FCA reaction.

Reaction	Substituent(s) and Type(s)	Rate - Time to Completion (min)
1	–OMe - Strongly Activating	< 5
2	–OMe : Strongly Activating –CHO : Moderately Deactivating	5 – 10
3	–Br : Weakly Deactivating	> 60

Examination of the ^{1}H NMR spectra of the concentrated products produced by reactions **1-3** revealed the relative amounts of each regioisomer. ^{1}H NMR spectroscopy, in general, allows the investigator to determine the number and type of hydrogen atoms present in a molecule. An NMR spectrum plots the intensity of a signal against its chemical shift, typically measured in parts per million (ppm), and the chemical shift of any

[2] Olah, G.A.; Reddy, V.P.; Prakash, G.K.; Friedel-Crafts Reactions. *Kirk-Othmer Encyclopedia of Chemical Technology* **2000**

given proton depends on its electronic environment. Since the properties and position of substituent groups influence the protons' electronic environments in predictable ways, by donating or withdrawing electrons, one can determine the position of the substituent, and thus the regioisomer formed. Furthermore, the area under and NMR signal (peak integration) is proportional the number of absorbing protons, and this fact can be exploited to compute the ratio of isomeric substitution products[1]. In this study, we identified a clean signal corresponding to each constitutional isomer based on differences in chemical shifts and comparisons to NMR spectra of previously identified compounds and computed peak integrations (shown in in Table 2).

Table 2. Chemical shifts and peak integrations of signals corresponding to each constitutional isomer produced in FCA reactions **1-3** determined using ^{1}H NMR spectroscopy.

Rxn	Chemical Shift of Identifying Peaks (ppm)	Multiplicity	Integration	Ratio (with H Correction)
1	**Ortho:** 7.30	Singlet	0.0166	Para : Ortho
	Para: 7.90	Doublet	1.000	120.4 : 1.000
	Meta: N/A	N/A	N/A	
2	**3,4 - benzaldehyde:** 7.26	Triplet	1.000	3,4 : 2,4
	2,4 - benzaldehyde: 7.51	Doublet	0.266	3.759 : 1.000
3	**Ortho:** 7.2	Sextet	2.134	Para : Ortho
	Para: 7.4	Doublet	1.000	0.937 : 1.000
	Meta: N/A	N/A	N/A	

The regiochemistry of the FCA reaction also appeared to be sensitive to the electronic properties of the substituents in a manner consistent with our previous understanding, and regioisomeric outcomes are shown in Figure 1. The FCA reaction with the activated benzene 1 significantly favored para substitution (**4**), producing para and ortho substituted products in a ratio of 120.4: 1.000. Meta substituted products could not be detected in the ^{1}H NMR spectrum. In general, it has been found that activating groups ortho/para substitution because ortho/para attack allows for more stabilized carbocation intermediate. In particular, ortho/para attack allows the positive charge associate with electrophilic addition to be positioned on the carbon atom bonded directly to the activating group, which ultimately stabilizes the adjacent positive charge[1]. Additionally, we explained the prevalence of the para substituted product over the ortho product, in the case of an activated, monosubstituted benzene ring such as compound **1**, using a steric argument. Product stability increases as energy is reduced, and steric interactions increase the energy of a molecule, thus, the preferred product is typically the one that minimizes steric interactions.

In terms of regiochemistry, reaction **2** did not exhibit unexpected behavior. The benzaldehyde **2** maintained an activating methoxy group in the para position. Since the directing effects of these two groups reinforce, it was predicted that the 3,4-substitution pattern (**5**) would be strongly favored (i.e. substitution would be directed ortho to the activating methoxy group and meta to the deactivating aldehyde group). Furthermore, the 3,4 product (**5**) is sterically favored as well, so it did not come as a surprise that we observed almost 4 times as much 3,4-substituion product as 2,4-substituion product.

Lastly, in reaction **3**, we observed approximately equal amounts of ortho and para products (**6** and **7**), with no meta products detected in the ^{1}H NMR spectrum. Since the bromine substituent is not sterically "bulky," the steric argument in favor of the para substituted product cannot be easily made. Thus, the distribution of products aligned with our current understanding. Additionally, we suspected that slight preference for the ortho product can be explained using probabilities of ortho and para attack. Brief examination of a monosubstituted benzene ring reveals twice as many positions for ortho attack (2 positions) as for para attack (1 position), although this property seemed to have only a minor effect on isomeric product distribution.

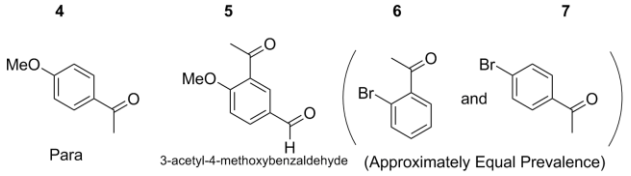


Figure 1. Major regioisomeric products of FCA reactions **1-3** as determined by ratios of peak integrations corresponding to each constitutional isomer.

To further characterize the rate and regioselectivity of the FCA reaction, we would like to propose additional experiments. In this paper, we have identified fairly large time intervals during which reactions were found to conclude; however, it may be useful to decrease the TLC sampling interval as the reaction nears completion, which would allow for more precise statements about the reaction rates. Additionally, taking multiple ^{1}H NMR samples as the reaction nears completion and computing % conversions for each sample would provide another reaction metric/property and more conclusive evidence that the reaction has complete (e.g. the % conversion converging to a specific value would suggest completion). Lastly, we imagine that introducing additional acyl chlorides with various

stereochemical and electronic properties may provide additional insight into the regiochemisty of the FCA reaction.

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Supporting Information Available: General experimental procedures, specifc experimental procedures and copies of ^{1}H NMR. This material is available free of charge in the attached documents.