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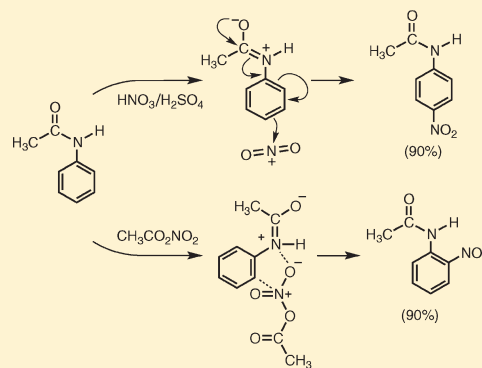
Electric Hindrance and Precursor Complexes in the Regiochemistry of Some Nitrations

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ABSTRACT: There are still gaps in the theory of supposedly well-known chemical reactions. For example, there is no explanation why there is a notorious preponderance of one of the expected isomers in some electrophilic aromatic substitutions. The preferred ortho orientation of acetyl nitrate has been used widely to obtain ortho nitro compounds; however, there is not causal explanation of this phenomenon. In this communication, an explanatory discussion is given to provide a complete theory on the regiochemistry of some of the mentioned reactions. To illustrate our theory, acetanilide, toluene, and anisole have been chosen as substrates in nitrations performed with nitric/sulfuric acid mixture and with acetyl nitrate.

KEYWORDS: Second-Year Undergraduate, Organic Chemistry, Inquiry-Based/Discovery Learning, Aromatic Compounds, Electrophilic Substitution, Mechanisms of Reactions, Noncovalent Interactions, Reactive Intermediates, Resonance Theory



Scheme 1. Nitration of Acetanilide by Two Different Paths

Nitration of acetanilide **1**, also known as antifebrin,^{1,2} with $\text{HNO}_3/\text{H}_2\text{SO}_4$ (sulfonitric mixture) yields 90% of colorless *p*-nitroacetanilide and 10% of the yellow ortho isomer (Scheme 1). Acetic acid or sulfuric acid can be used as the solvents for this reaction.^{3–5} The preponderance of the para isomer can be explained, at first glance, by steric hindrance at the ortho position owing to the acetamido group. However, when acetanilide **1** is nitrated with acetyl nitrate **2**, the reaction product yields are inverted and the ortho isomer is completely favored,^{6–9} indicating that steric hindrance is not the determining factor. Because the results from these two reactions have not been explained, we provide a theory regarding the regiochemistry in both cases.

First, we must consider the amide resonance in **1** (Scheme 2). The resonance dipole structure, **3**, explains the low nucleophilicity of this anilide, as is the case with other amides. Thus, we do not expect electron contribution at the ortho and para positions prior to reaction with an electrophile. Benzene aromaticity is not altered until a π -complex is formed. Our proposal (Scheme 3) is that the nitronium ion reacts at the farther double bond to avoid electric repulsion (Coulombic type) with the positive-charged nitrogen atom in dipole structure **4**. The electronic contribution from the substituent chain generates a semiquinone structure **5**. The positive charge in the iminium ion is neutralized via deprotonation and the aromaticity is restored, **6**. Thus, electric hindrance can explain why the para position is preferred and the ortho isomer is the byproduct.

Now let us turn our attention to the reaction of acetanilide **1** with acetyl nitrate **2** (acetonitric anhydride). Acetyl nitrate is prepared by adding nitric acid to acetic anhydride.¹⁰ When the addition order is incorrect, the system becomes potentially shock

sensitive.¹¹ Acetyl nitrate must be distilled in vacuo because it explodes at 60 °C at atmospheric pressure. Its boiling point is 295 K at 0.09 bar.^{12,13}

Acetyl nitrate reactivity is clearly shown in the reaction with furan, yielding 2-acetoxy-5-nitro-2,5-dihydrofuran (Figure 1).^{14–16} Acetyl nitrate has reacted as nitronium acetate, without participation of acetyl and nitrate ions. An interesting question is: are nitronium ions formed previously by reagent dissociation? We do not think that this happened because, in the reaction with acetanilide **1**, we would have the same reactive species (NO_2^+) as with sulfonitric mixture. Then we would obtain the

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Scheme 2. Resonance of Acetanilide

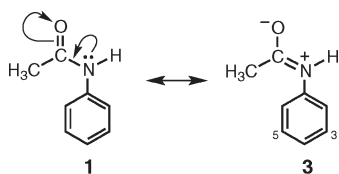
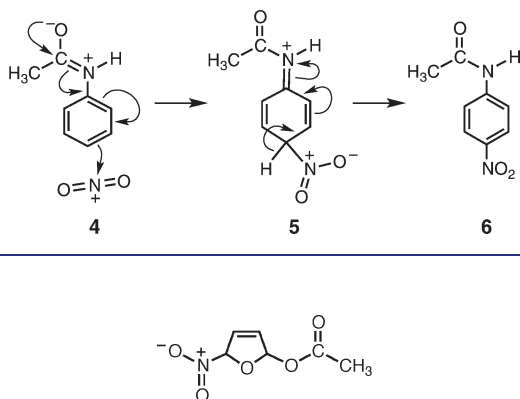
Scheme 3. Proposed Mechanism of Acetanilide Nitration with NO_2^+ 

Figure 1. 2-Acetoxy-5-nitro-2,5-dihydrofuran, the product from the reaction of acetyl nitrate with furan.

same product mixture, and this is not the case. Thus, acetyl nitrate must react with **1** without previous dissociation. This theoretical deduction is sustained by experimental evidence (^{14}N NMR) indicating the nonexistence of nitronium ions by dissociation of acetyl nitrate.¹⁷

We invoke the possibility of reagent-substituent coordination. This can occur because the electric charges, both in the reagent and in the substrate, are pincers, or *chelas*, capable of forming a chelate. This can explain the regiochemical change with acetyl nitrate. In the proposed chelate (Figure 2), there are five atoms at a one-bond distance. Electrons are transferred from the enolate to the ortho position and then to the positive nitrogen atom in acetyl nitrate, yielding *o*-nitroacetanilide. Thus, this electron displacement results in the ortho configuration of *o*-nitroacetanilide.

When the above-mentioned electrostatic arrangement does not occur, acetyl nitrate can form a π -complex with the C3–C4 double bond in compound **3** (Scheme 2), giving 4-nitroacetanilide as byproduct. The C5–C6 double bond does not react because it is not conjugated with the electronic contribution from the enolate.

Both explanations are supported in similar reactions: reactions with toluene and with anisole. With toluene, there cannot be an iminium ion to control the regiochemistry. Thus, nitration with sulfonitric mixture gives rise to significant quantities of both nitro isomers: 58% ortho and 37% para.^{18–20} The yield of the para isomer can be increased to 66% if only nitric acid is used.²⁰ Acetyl nitrate nitration of toluene gives the ortho nitro compound in 90% yield.^{18,20} In this case, the residual electric charges in the methyl group are paramount. A σ -complex can be formed and the Baker–Nathan effect (hyperconjugation)²¹ enhances the synthesis of *o*-nitrotoluene, as indicated in Scheme 4. With anisole, nitration with sulfonitric mixture gives rise to the ortho and para isomers, 35% and 65%, respectively,²² whereas nitration

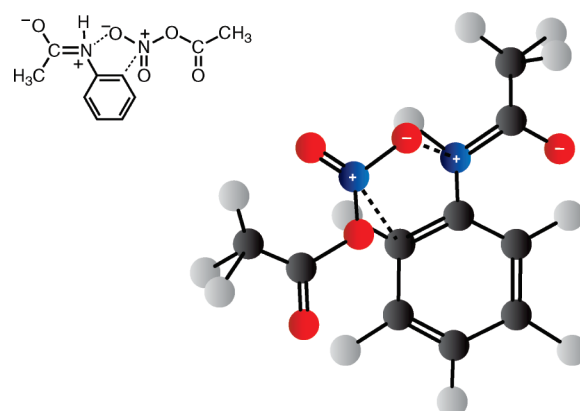


Figure 2. Precursor complex between acetanilide and acetyl nitrate (two representations).

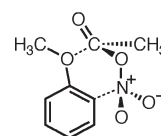
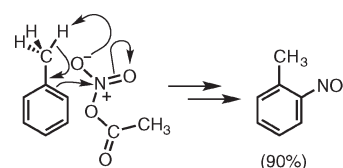


Figure 3. Complex of anisole and acetyl nitrate.

Scheme 4. Reaction of Toluene and Acetyl Nitrate To Form *o*-Nitrotoluene

with acetyl nitrate occurs at the ortho position. In the last reaction, interaction between the ether and the carbonyl group in the acetanilic anhydride is postulated (Figure 3), thus inducing nitration at the ortho position with a 90% yield.²³

In a very recent study on directing effects in nitration of aromatic ketones, complexation of nitrating agent has been suggested.²⁴ However, our substrates are an amide, an arene, and an ether, and our precursor complexes are quite different.

■ CONCLUSIONS

Starting from experimental data, we have deduced and provided a theory explaining the observed regiochemistry in the six reactions here considered.

- Acetanilide's dipolar structure explains its reactivity with nitric/sulfuric acid mixture and with acetyl nitrate.
- Electronic contribution from the acetamido group only occurs after the nitronium ion has formed the π -complex at the double bond farther to the substituent chain (oriented π -complex).
- Undissociated acetyl nitrate forms a precursor complex with acetanilide (oxyphilic interaction).
- With toluene and sulfonitric mixture, both ortho- and para nitro derivatives are formed because there is no iminium ion present.

- In the reaction of toluene with acetyl nitrate, residual electric charges intervene, as well as hyperconjugation. A six-membered concerted mechanism is proposed.
- With anisole and nitric/sulfuric acid mixture, both nitro isomers are formed, as with toluene. Acetyl nitrate can form a chain-reagent complex, giving *o*-nitroanisole.

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NOTE ADDED AFTER ASAP PUBLICATION

There was an error in the figure 1 caption in the version published on 5/6/2011. This has been fixed in the version published on 5/26/2011.