Article

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An "*Ortho Effect*" in Electrophilic Aromatic Nitrations: Theoretical Analysis and Experimental Validation

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Usually, a π-donor substituent acts as an *ortho*/*para* directing group in an electrophilic aromatic substitution reaction, and a π-acceptor substituent acts as a *meta* directing group. Interestingly, when a π-acceptor substituent is *meta* to a π-donor substituent, certain electrophilic aromatic nitration occurs *ortho* to the π-acceptor substituent rather than *para*. The "*ortho effect*", highlighted in various textbooks, has been tentatively analyzed here based on *ab initio* calculations. The reliability of the calculations was verified by the corresponding experimental data, including a newly-designed electrophilic aromatic nitration that also gave reasonable product distributions.

Keywords: Electrophilic aromatic nitration; Positional selectivity; *Ortho effect*; *Ab initio* calculation.

INTRODUCTION

Electrophilic aromatic nitrations are important and widely studied chemical reactions since aromatic nitro compounds are fundamental synthetic precursors in the production of dyes, plastics, perfumes, agrochemicals, explosives, and pharmaceuticals.[1–3] Usually, an electrophilic aromatic nitration is considered to occur *via* a stepwise mechanism (Figure 1). A π complex[4] or a radical ion pair[5] may or may not be directly involved in an electrophilic aromatic nitration mechanism and its rapidly reversible formation is usually not the rate-determining step.[1] However, for an electrophilic aromatic nitration to occur, a cationic reaction intermediate called an arenium ion, known as a σ complex or Wheland intermediate,[6] is usually formed.[1a] In this arenium ion, the carbon at the site of substitution is bonded both to the electrophile and the hydrogen that is being displaced. As proton removal is usually faster than the loss of the electrophile, the deprotonation of the arenium ion to afford the substituted aromatic product is usually not the rate-determining step.[7] In contrast, the formation of the arenium ion is difficult due to the loss of the inherent stability associated with aromaticity and is usually the rate-determining step, in which the transition state comes later on the reaction coordinate and is closer in energy to the arenium ion. According to the Hammond postulate,[8] the rate-determining transition state resembles the arenium ion, so that factors stabilizing the arenium ion also stabilize the transition state and lower the activation energy, and thereby usually favour the electrophilic aromatic nitration.

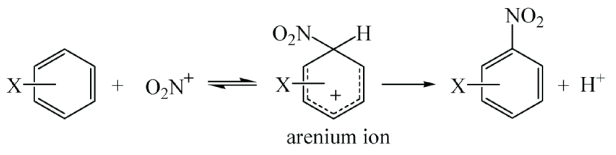

Fig. 1. Electrophilic aromatic nitration.

As mentioned in Carey & Sundberg's book,[1a] substituents can influence the product distribution by favouring the formation of one arenium ion over another. Based on Hückel molecular orbital theory, the positive charge of arenium ion **A** is equally delocalized at the positions that are *ortho* and *para* to the site of the substitution (Figure 2). Therefore, a π-donor substituent at one of these positions stabilizes the arenium ion and also stabilizes the transition state and lowers the activation energy necessary for the electrophilic aromatic nitration, and thus acts as an *ortho*/*para* directing group. In contrast, a π-acceptor substituent at one of these positions destabilizes the arenium ion and increases the activation energy necessary to attain the transition state, and thus acts as a *meta* directing group. The resulting principles,[1] known as the Holleman rules,[9] have already been described with Hückel molecular orbital theory in Carey & Sundberg's book.[1a] They are in good agreement

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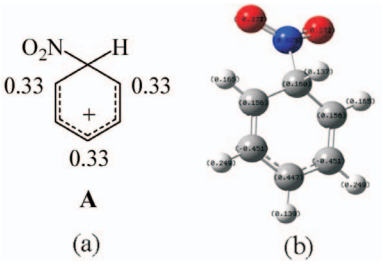
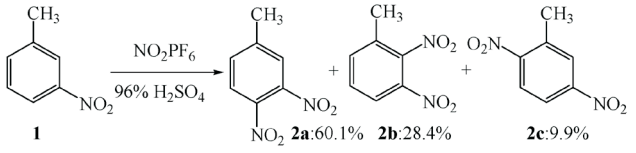


Fig. 2. Charge distribution of arenium ion **A** based on (a) Hückel molecular orbital theory and (b) the *ab initio* calculations via GAUSSIAN 09 program package. Values on C and H atoms in (b) indicate the atomic charge assignments (the positive or negative sign implies that the atom donates or accepts charges).

with the experimental observations that are easily explained by comparison of the corresponding resonance structures.[1b]

Interestingly, the electrophilic aromatic nitration of 1-methyl-3-nitrobenzene (**1**, Scheme 1) affords 4-methyl-1,2-dinitrobenzene (**2a**) and 1-methyl-2,3-dinitrobenzene (**2b**) in 60.1% and 28.4% yields, respectively.[10] In contrast, 2-methyl-1,4-dinitrobenzene (**2c**) is isolated in only 9.9% yield.[10] As witnessed in the above example, when a π-acceptor substituent (πAS) is *meta* to a π-donor substituent (πDS), the S_EAr nitration occurs *ortho* to the πAS rather than *para* (Scheme 1). The "*ortho effect*", highlighted in various books such as Smith & March's book, is not the same as the usual *ortho effect* in electrophilic aromatic substitutions.[1,11] To understand this "*ortho effect*", theoretical calculations are required. Herein, *ab initio* calculations are used for a tentative analysis of this positional selectivity.

Scheme 1 Electrophilic aromatic nitration of 1-methyl-3-nitrobenzene

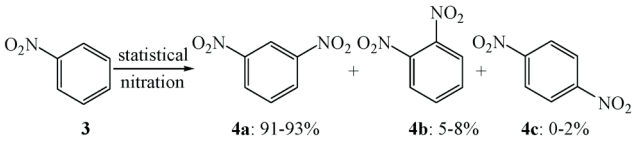


RESULTS AND DISCUSSION

That *ab initio* calculations are being available thanks to advances in computational technology, which can provide higher-level computational results in a reasonable time-scale without the need for concerns about the approximations and parameterization of semi-empirical one-electron based methods.[12] Accordingly, *ab initio* calculations usually provide chemists with relatively reliable quantitative information. Indeed, calculating the charge distribution in arenium ion **A** by the *ab initio* calculations via GAUSSIAN 09 program package[13] did provide some insightful quantitative information. The atomic charge assignments on the C and H atoms of the arenium ion are shown in Figure 2b, where the positive or negative sign implies that the atom donates or accepts charges. The calculations indicated that the overall magnitude of the electron deficiency of the arenium ion over the various positions follows the order of *para* > *ortho* > *meta*. Without influence of any other factors, a πDS would direct an electrophilic aromatic nitration to the position in the preferential order of *para* > *ortho* > *meta*, whereas a πAS would direct an electrophilic aromatic nitration to the position in the preferential order of *meta* > *ortho* > *para*.

Statistical experimental results supported the principle that a πAS normally directs an electrophilic aromatic nitration to the positions *meta* > *ortho* > *para* in a preferential order[1b,14] As shown in Scheme 2, nitration of nitrobenzene statistically affords the expected ratios of products.[1a] Although direct comparison is not always valid due to the different reaction conditions, the tendency is nevertheless quite clear.

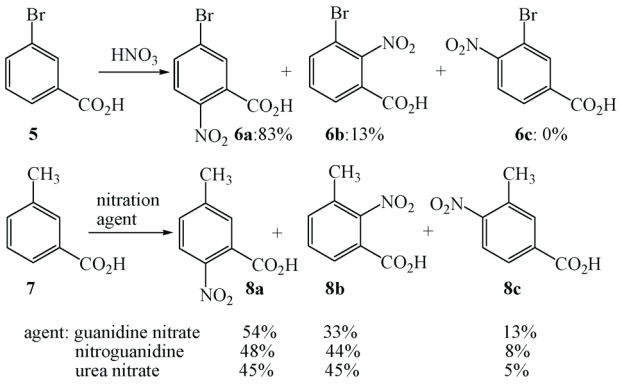
Scheme 2 Positional selectivity in statistical nitration of nitrobenzene



These positional selectivity tendencies mentioned above are also in good agreement with other related experimental results.[15] For example, the nitration of 3-bromobenzoic acid (**5**) gives 5-bromo-2-nitrobenzoic acid (**6a**, 83% yield) and 3-bromo-2-nitrobenzoic acid (**6b**, 13% yield) and the potential isomer of 3-bromo-4-nitrobenzoic acid (**6c**) is not detected (Scheme 3).[16] Similarly, the nitration of 3-methylbenzoic acid (**7**) affords 5-methyl-2-nitrobenzoic acid (**8a**) and 3-methyl-2-nitrobenzoic acid (**8b**) as the major mononitrated isomers, in which 3-methyl-4-nitrobenzoic acid (**8c**) is just a minor mononitrated isomer.[17]

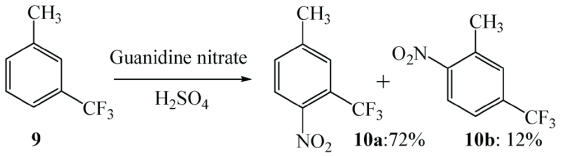
As the stability of the possible six-member ring tran-

Scheme 3 Electrophilic aromatic nitrations of 3-bromobenzoic acid and 3-methylbenzoic acid



sition state, resulting from the hydrogen bonding interaction between -CO_2H and -NO_2, might be part of reasons in the above examples, herein we would like to report an additional experiment to eliminate the interference of such hydrogen bonds. By treating 1-(trifluoromethyl)-3-methylbenzene (**9**) with guanidine nitrate in concentrated sulfuric acid, 2-(trifluoromethyl)-4-methyl-1-nitrobenzene (**10a**) was obtained (72% yield) as the major isomer and 4-(trifluoromethyl)-2-methyl-1-nitrobenzene (**10b**) are obtained in only 12% yield (Scheme 4). This experimental observation agrees well with the results based on *ab initio* calculations.

Scheme 4 Electrophilic aromatic nitration of 1-(trifluoromethyl)-3-methylbenzene (**9**)



The structures of these isomers have been confirmed from their IR, MS and NMR spectra (see supporting information). For example, isomers **10a** and **10b** have the same aryl hydrogen system (ABX system), but they can be differentiated each other from their ^{1}H NMR, ^{13}C NMR and HSQC spectra. The C-F coupling constants can be used to determine the –CF_3 group (δ = 122.1 ppm, quadruple peak, $^1J_{CF}$ = 271.6 Hz), atom C-1 (δ = 123.5, quadruple peak, $^2J_{CF}$ = 34.3 Hz), and atoms C-2 and C-6 (δ = 128.4 ppm, quadruple peak, $^3J_{CF}$ = 5.9 Hz; δ = 145.9 ppm, quadruple peak, $^3J_{CF}$ = 2.1 Hz, see supporting information). The HSQC diagram of three aryl hydrogen atoms in the major isomer of compounds **10** was elucidated in Figure 3a. It was found that atom C-2 was connected with atom H-2 based on this HSQC diagram (Figure 3a). However, atom C-6 was not connected with an aryl hydrogen atom and the rest two aryl hydrogen atoms were all connected with other carbon atoms (Figure 3a). Thus, the major isomer is compound **10a**.

To understand the high positional selectivity in the above electrophilic aromatic nitration of **9**, the atomic charge of reactant **9** has been calculated based on *ab initio* calculations. As shown in Figure 4, the charge of reactive carbon atoms at the C-2, C-4, C-5, and C-6 sites are -0.185, -0.184, -0.171, -0.188, respectively, showing that the C-2, C-4, and C-6 sites could accept more electrons than the C-5 site. Accordingly, the C-2, C-4, or C-6 cite has higher reactivity than the C-5 site, and thereby may be much more favourable site to react with NO_2^+ than the C-5 site.

The energy of transition-states associated with the isomers **10** has been also calculated based on *ab initio* calculations. As shown in Figures 4-5, the transition states show the smallest energy was obtained when the NO_2^+ attaches to the benzene ring at the C-4 site, while it is the least

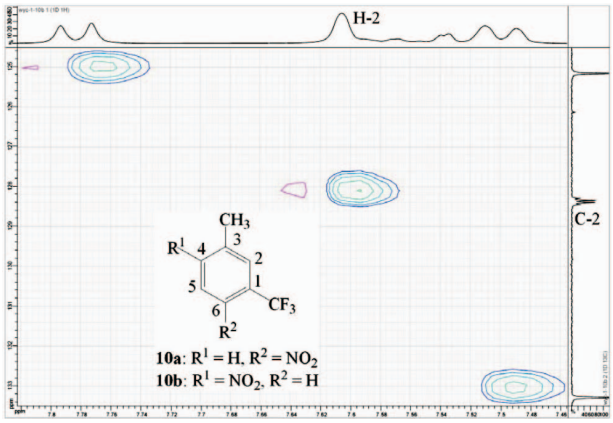


Fig. 3. The differentiation between isomers **10a** and **10b**.

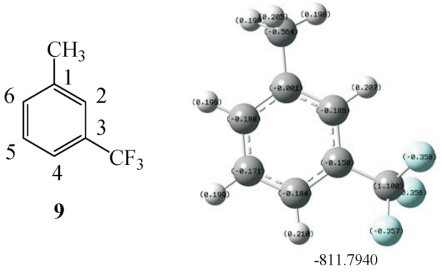


Fig. 4. Charge distribution and total of electronic energy of 1-(trifluoromethyl)-3-methylbenzene (**9**).

stable state if the NO_2^+ attaches to the benzene ring at the C-5 site. For the barrier energies for reactant **9** to reach the four transition states **B** (C-2 site), **C** (C-4 site), **D** (C-5 site), and **E** (C-6 site) are 0.2268, 0.2250, 0.2301, and 0.2256 Hartree, respectively, reflecting that the transition states **C** and **E** can transfer to both the reactant and product states. The regioisomer with respect to the transition state **C** should be the major regioisomer (**10a**) as changes in the barrier energies result in exponential changes in the relative rates of reaction at different sites,[18] which supports the aforementioned experimental observations (Scheme 4). These results are consistent with the regioselectivity deduced from the viewpoint of the charge distribution of arenium ion **A** (Figure 2).

To explain the positional selectivity in an electrophilic aromatic nitration, valence bond theory, resonance theory and frontier molecular orbital theory have been used, and the related electrostatic potentials, charge distribution, electrophile affinity and local ionization energy have been calculated.[3] Moreover, various calculation methods and reaction pathways have also been proposed.[3] Although the accurate positional selectivity in an electrophilic aromatic nitration is unclear at this time, more and more related endeavours would complement each other to lead to a better understanding of the controlling elements behind the corresponding experimental results. The electrophilic aromatic nitration could be driven toward the desired product if each individual factor is turned the right way.

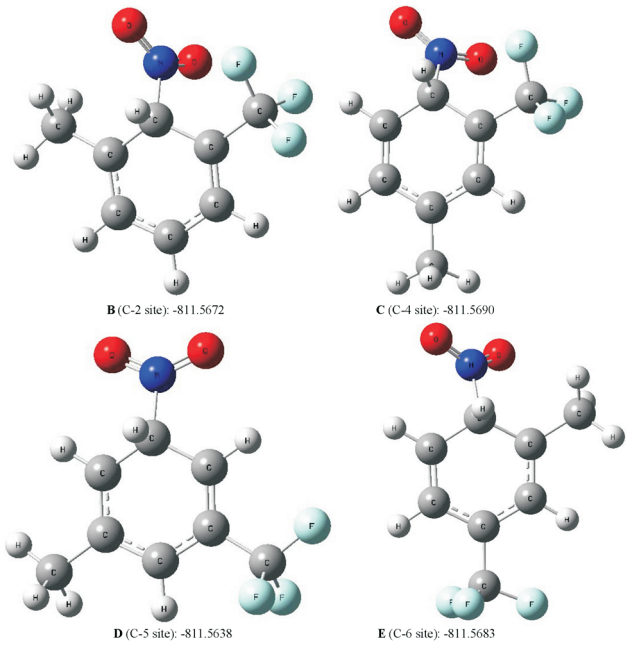


Fig. 5. Total of electronic energies of the transition-states of the isomer products in the electrophilic aromatic nitration of 1-(trifluoromethyl)-3-methylbenzene (**9**).

In summary, the results based on *ab initio* calculations provide a clear indication for the positional selectivity tendencies in an electrophilic aromatic nitration. Results illustrated that without considering any other factors, a π-donor substituent would direct an electrophilic aromatic nitration to the position in the preferential order of *para* > *ortho* > *meta*, whereas a π-acceptor substituent would direct an electrophilic aromatic nitration to the position in the preferential order of *meta* > *ortho* > *para*. The analysis based on *ab initio* calculations indicated that the "*ortho effect*" mentioned previously is likely to be inherent to a π-acceptor substituent that tends to obviate the *para* electrophilic aromatic nitration. Although direct comparison is not always valid due to the different reaction conditions, the tendency is nevertheless quite clear. The present results would provide a valuable guidance for organic chemists in their related researches.

EXPERIMENTAL

Calculations: The *ab initio* calculations of arenium ion A in electrophilic aromatic nitrations have been performed via GAUSSIAN 09 program package.[13] The calculations were carried out within the framework of MP2 methodology using 6-311++G (*d*, *p*) basis set. The vibration frequency is calculated for all structures involved to examine the structural stability. Charge densities were calculated from the electrostatic potential by the method of Merz-Kollman[19] and illustrated in Figures 2b and 4. The sign of the charges illustrated in these figures indicates whether the atom is a donor (a cation with positive value) or an acceptor (an anion with negative value).

Electrophilic aromatic nitration of compound 9: Compound **9** (97%, 165.09 mg, 1.0 mmol) was dissolved in concentrated sulfuric acid (1 mL) and cooled to -10 °C in a low-temperature reactor. Guanidine nitrate (98%, 249.14 mg, 2.0 mmol) was added slowly to the above mixture with rapid stirring. The resulting mixture was allowed to warm slowly to room temperature, and stir at room temperature overnight. The solutions were then quenched with cold water (20 mL) and then extracted with ethyl acetate (30 mL ×3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatogra-

phy to afford compound **10a** (147.7 mg) in 72% yield. White form; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 1H, J = 8.4 Hz), 7.61 (s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 2.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9 (q, $^3J_{CF}$ = 2.1 Hz); 144.2, 133.3, 128.4 (q, $^3J_{CF}$ = 5.9 Hz), 126.1, 125.1, 123.5 (q, $^2J_{CF}$ = 34.3 Hz), 21.2; FTIR (film): 3122, 2931, 1599, 1539, 1413, 1360, 1319, 1277, 1209, 1177, 1142, 1051, 896.7, 796.6, 759.2, 661.8, 635.1 cm^{-1}. Anal. calcd for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83. Found: C, 46.98; H, 2.99; N, 6.96. For more details, see supporting information.

ACKNOWLEDGEMENTS

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