

Regioselectivity of the Nitration of Phenol by Acetyl Nitrate Adsorbed on Silica Gel

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Abstract: The reaction of phenol with acetyl nitrate in chloroform gives nitrophenol with an *ortho/para* ratio of 1.8. This ratio increase to 13.3 when the reaction was carried out with acetyl nitrate pre-adsorbed on dry silica gel. Silica may be acting as a template to bring phenol close to acetyl nitrate by hydrogen bonds forming a ternary complex, which undergoes a six-center rearrangement to *o*-nitrophenol. The formation of this ternary complex is evaluated by *ab initio* molecular orbital calculation. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords : Nitration; Nitric acid and derivatives; Phenols; Regioselection.

Introduction

The distribution of the *ortho/para* isomer ratio in electrophilic aromatic substitution of activated monosubstituted benzenes continues to challenge organic chemists. The regioselectivity is governed by steric hindrance, interaction between the substituent and the reagent, electronic effects, and solvent effects.¹ Aromatic nitration of benzene derivatives with electron donating substituent leads to substitution at the *o*- and *p*-positions according to a statistical distribution. Steric bulkiness of reagent and/or substrate usually provides high concentrations of the *p*-products.² The use of supported reagents³ and catalysts are known to favor the *para* substitution.⁴ One alternative to increase the production of *o*-nitroderivatives is to employ laterally functionalized compounds together with the *chaperon* effect initially described by Strazzoloni *et al.*⁵ A similar approach has been used in ozone-mediated nitration of phenylalkyl ethers, phenylacetic esters and related compounds with nitrogen dioxide to achieved high proportions of *ortho* nitro derivatives.⁶

Phenol can be nitrated with a mixture of nitric acid and sulfuric acid in 61% yield giving 2-nitrophenol and 4-nitrophenol in a ratio 1.4.⁷ In a recent paper, Lazslo demonstrated that phenol can be nitrated in a system called *claycop* (trihydrated cupric nitrate supported on montmorillonite/acetic anhydride/CCl₄) in 92% yield with an *o/p* ratio of 13.3.⁸ Very high regioselective nitration of phenol was achieved with a surfactant suspended in acetonitrile treated with nitronium tetrafluoroborate which gave a ratio *o/p* of 19.0.⁹ The authors attributed the regioselectivity to the hydrogen bond interaction between the phenol and the oxygen of the acetyl group forming a six member ring complex. Halvarson and Melander found a high *o/p* ratio (3.0) in the nitration of anisole with benzoyl nitrate in acetonitrile.¹⁰ They suggested that the regioselectivity could be due to the interaction of the reagent with the oxygen atom of the ether which results in a subsequent six-center

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rearrangement, as was suggested by De La Mare and Ridd for the nitration of acetanilide with acetyl nitrate.¹¹ 2-Nitrophenol is an important starting material used in multiple step syntheses of valuable compounds.¹² In order to get more insight on these mechanistic pathways and to explore the *ortho*-regioselectivity, we decide to study the reaction of phenols with acyl nitrates under neutral conditions.

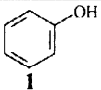
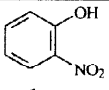
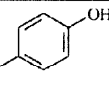
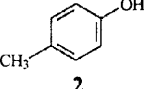
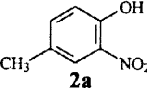
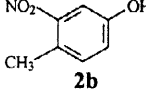
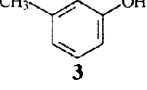
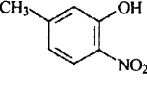
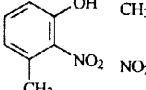
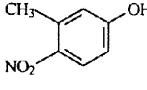
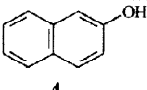
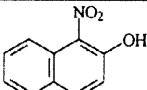
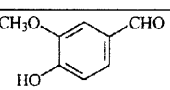
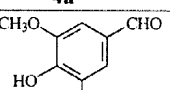
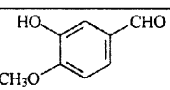
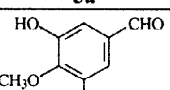
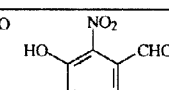
Results and discussion

Acyl nitrates (CAUTION) are not used in routine procedures since they show low stability at room temperature and should be prepared *in situ*.¹³ A simple stabilization procedure was used by adsorption of the acyl nitrates on minerals such as montmorillonite, silica and alumina. With this condition, it is possible to work at room temperature for long periods of time (3–4 h). The results are summarized in Table 1. The reaction of phenol with acetyl nitrate in chloroform is rapid and quantitative giving an *ortho/para* ratio of 1.8 (entry 1) which is slightly superior to the classical method using H₂SO₄-HNO₃ (1.4).⁵ When the reaction was carried out with acetyl nitrate pre-adsorbed on chrysotile or alumina, the *o/p* ratio increase to 2.3–2.5 (entries 2 and 3). In the presence of montmorillonite K10, the *ortho* selectivity went up to 2.9 (entry 4). High proportion of the 2-nitrophenol (93%) was obtained with the reagent previously adsorbed on dry silica which gave an *o/p* ratio of 13.3 (entry 5). This selectivity is equivalent to the best result reported by the literature.^{5–6} By increasing the polarity of the solvent, the regioselectivity decrease to 1.3 for a mixture of chloroform-dioxane which suggests that acetyl nitrate was less adsorbed on the support leaving more reagent in solution than in less polar solvent⁵ like chloroform (entry 6). We concluded that in order to obtain high *ortho* selectivity, it is necessary to have all of the reagent adsorbed on the support and the best support tested was silica gel. Under the conditions of the reaction, 3-nitrophenol is non-reactive but compete⁵ with acetyl nitrate for the adsorption sites on the surface of the silica. In the presence of a 5:1 mixture of chloroform and 3-nitrophenol, the *o/p* ratio decreases to 1.1 (entry 7). Increasing the amount of 3-nitrophenol to 1:1 in relation to chloroform, decreases the *o/p* ratio to 0.4 (entry 8). This supports our conclusion that the reagents must be adsorbed on the support in order to obtain high *ortho*-selectivity. Similar results were achieved with benzoyl nitrate (entries 9 and 10) and with trimethylsilyl nitrate (entries 11 and 12). The regioselectivities were inferior which indicate that the bulky trimethylsilyl group may interfere in the reaction selectivity. To evaluate the role of the hydrogen bond between phenol and silica or phenol and acetyl nitrate on the regioselectivity, the nitration of anisole in acetyl nitrate-silica was carried out, which afforded 70% of 2-nitroanisole and 30% of 4-nitroanisole giving an *o/p* ratio of 2.3. On the other hand, the nitration of *para*-cresol with acetyl nitrate-silica gave 2-nitro-4-methylphenol and 3-nitro-4-methylphenol in 93% and 6% yield respectively (ratio of 15.5). For nitration of *meta*-cresol with the same reagent, 5-methyl-2-nitrophenol, 3-methyl-2-nitrophenol and 3-methyl-4-nitrophenol were isolated in 50%, 30% and 20% respectively, and without silica, the reaction gave 37%, 30% and 35%, respectively. 2-Naftol was nitrated in the presence of silica to give only 1-nitro-2-naftol (see Table 2).

Table 1. Nitration of phenol with acyl nitrates in the presence of various supports.

Entry	Reagent	Solvent	Ratio o/p
1	AcONO ₂	CHCl ₃	1.8
2	AcONO ₂ -chrys	CHCl ₃	2.3
3	AcONO ₂ -Al ₂ O ₃	CHCl ₃	2.5
4	AcONO ₂ -K10	CHCl ₃	2.9
5	AcONO ₂ -SiO ₂	CHCl ₃	13.3
6	AcONO ₂ -SiO ₂	CHCl ₃ -dioxane	1.3
7	AcONO ₂ -SiO ₂	1:5 CHCl ₃ : 3-nitrophenol	1.1
8	AcONO ₂ -SiO ₂	1:1 CHCl ₃ : 3-nitrophenol	0.4
9	BzONO ₂	CHCl ₃	1.8
10	BzONO ₂ -SiO ₂	CHCl ₃	9.0
11	TMSONO ₂	CHCl ₃	1.1
12	TMSONO ₂ -SiO ₂	CHCl ₃	2.3

Table 2. Mononitration of aromatics with acetyl nitrate adsorbed on silica gel

Starting Materials	Main products Isolated	Yields
 1	 1a  1b	1a 93% 1b 7%
 2	 2a  2b	2a 93% 2b 6%
 3	 3a  3b  3c	3a 50% 3b 30% 3c 20%
 4	 4a	4a only
 5	 5a	5a 88%
 6	 6a  6b	6a 54% 6b 36%

The nitration of 4-hydroxy-3-methoxybenzaldehyde (vanillin) gave 88% yield of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde, and the reaction with 3-hydroxy-4-methoxy-benzaldehyde (*iso*-vanillin) gave 90% yield of 3-hydroxy-4-methoxy-5-nitrobenzaldehyde and 3-hydroxy-4-methoxy-2-nitrobenzaldehyde in a ratio of 3:2. These results suggest that the acidic hydrogen of phenol participates in the formation of a phenol-acetyl nitrate-silica complex. We assume that silica acts as a template by first forming hydrogen bonds between acetyl

nitrate with the silanol groups and then phenol approach to this system forming the complex phenol-acetyl nitrate (see Figure. 1.a). This complex collapses to the intermediate that undergoes a six-center rearrangement to *o*-nitrophenol (Figure 1.b).

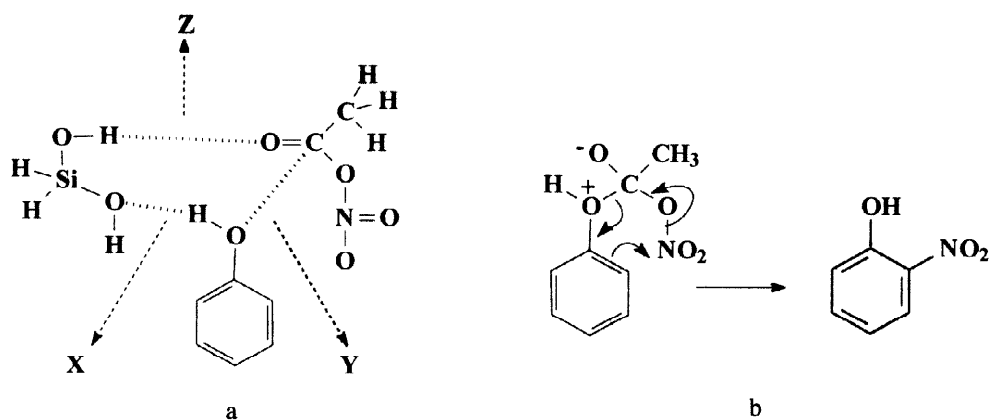


Figure 1. (a) Optimized model for the interaction of phenol, silanodiol and acetyl nitrate. The distances for hydrogen bonds are: X=1.75Å; Y=2.99Å; Z=2.05Å. (b) a six-center rearrangement to *o*-nitrophenol.

To test the hypothesis, *ab initio* calculations were performed at the Hartree-Fock level of theory with 6-31G basis set. The calculations were carried out with the Gaussian 94 program.¹⁴ A reasonable representation of the silica surface should present many atoms in order to provide a realistic investigation of the possible interactions of the adsorbed reactants. However, due to the computational nature of the *ab initio* methods only an approximation of the silica surface was possible.¹⁵ The phenol and acetyl nitrate molecules can be adsorbed on the silica surface through hydrogen bonds. The hydrogen bonds can be formed by the interactions of hydroxyl of the reactants with the hydroxyl groups present on the silica surface. Statistically, it would be expected that the hydrogen bonds of the reactants would occur at neighbor hydroxyls on the surface. Therefore, one of the smallest silicon compounds able to represent this situation is the silanodiol. The structures were then fully optimized and the minimum energy obtained. Fig. 1a is the most stable structure obtained with the three molecules. In this structure, the bond distances X, Y and Z correspond to 1.75Å, 2.99Å and 2.05Å, respectively. The X and Z distances are characteristic of hydrogen bonds and Y distance is the smallest distance between the oxygen of phenol with the carbon of the carbonyl group of the acetyl nitrate. The HOMO and LUMO molecular orbitals for this system present energies of -8.60eV and 1.39eV, respectively. The HOMO orbital is concentrated on the phenolic molecule while the LUMO is on the acetyl nitrate. Fig.2 shows that the HOMO of the phenolic oxygen is in-phase with the LUMO carbonyl of acetyl nitrate. This suggests a favorable but weak interaction between these two centers. However, calculations on the complex phenol-acetyl nitrate also shows a small charge distribution in the bonds connecting both molecules. The charge distributions between the carbon of the carbonyl and the oxygen atom of the phenol and of the nitrate group are almost zero. These results suggest that the weak interaction between the molecules favor the mechanism for the migration of the nitrate group to the aromatic ring and further dissociation of both products.

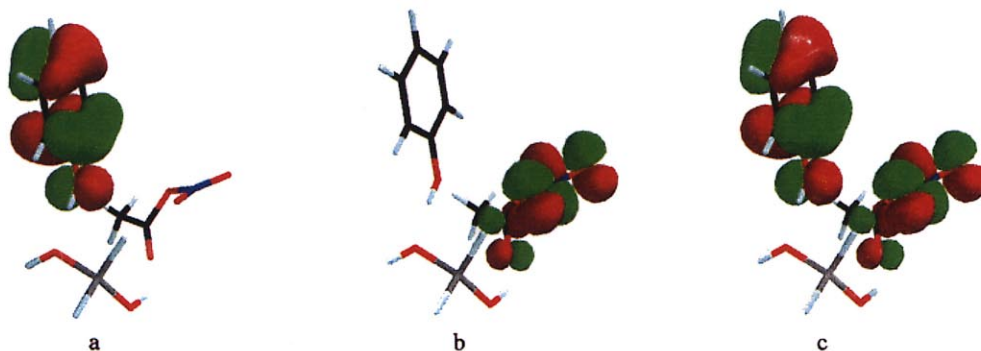


Figure 2. Molecular orbitals of the system phenol-acetyl nitrate-silanodiol: a) HOMO; b) LUMO and c) HOMO and LUMO.

In conclusion, we have described a highly regioselective procedure for nitration of phenol using acetyl nitrate pre-adsorbed on silica gel giving an *o/p* ratio of 13.3. We postulate the formation of a ternary complex between silica, acetyl nitrate and phenol stabilized by hydrogen bonds. This complex collapses to the intermediate that undergoes a six-center rearrangement to *o*-nitrophenol. *Ab initio* calculations were performed and showed that HOMO of the phenolic oxygen is in-phase with the carbonyl's LUMO of acetyl nitrate suggesting a favorable interaction between these two centers.

Experimental Section

Gas chromatograms was recorded on a Hewlett Packard model HP5890-A with flame detector and a HPI-dimethylsiloxane capillary column, and an internal standard was used. The oven temperature was raised at a rate of 2 °C min⁻¹ to 150 °C. For quantification, the same response factor was assumed for all compounds. The identity of the peaks was verified by analysis in a HP-5890 II gas chromatograph coupled to a mass detector (HP-9070B) at 70 eV using the same column. Reagents were of analytical grade (Aldrich) and we employed Merck grade 7754, 70-320 mesh silica gel.

Acyl nitrates (CAUTION) were prepared from the corresponding acyl chlorides with silver nitrate, following the literature method,¹⁵ at -20 °C in dry chloroform. This stock solution is stable for a week or two at this temperature. The solution obtained was used directly and quantities were based on the amount of acyl nitrate used in the preparation. Trimethylsilyl nitrate (TMSONO₂) was prepared from trimethylsilyl chloride and silver nitrate.¹⁶ For each 10 mmol of acyl nitrate in 30 ml of dry chloroform at -20 °C, we added 0.20g of dry silica or montmorillonite, under magnetic stirring during one hour at the same temperature. Then, 10 mmol of the substrate were added and after one hour the temperature was slowly increased to room temperature. After the reaction was completed, the support was filtered off and washed with ether. After the solvent was evaporated, the products were quantified by GC and were identified by comparison (TLC, GC-MS, mp, IR, or NMR) with authentic samples. We have carried out reactions in a scale from 1 to 50 mmol.

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