

Variation of isomer distribution in electrophilic nitration of toluene, anisole, and *o*-xylene: Independence of high regioselectivity from reactivity of reagent*

(nitration/toluene/anisole/*o*-xylene/selectivity)

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ABSTRACT The nitration of toluene and anisole was studied with nitrating systems of varying reactivity. High regioselectivity of *ortho-para* over *meta* substitution was maintained in all nitrations, regardless of the reactivity of the nitrating system. At the same time, the amount of *meta* substitution stayed low (3% or less), even when the fast reactions may have reached the encounter-controlled limit. Because the nitration of *o*-xylene, in which both ring positions are activated by the effect of a methyl group, also does not show any diminishing of regioselectivity, the possibility of a dual mechanistic pathway, in which the activated position would react by a fast, encounter-controlled path, whereas the nonactivated *meta* position by a slower σ -type path, can be ruled out. The data unambiguously prove that the high regioselectivity of electrophilic aromatic nitration is independent of the reactivity of the reagent, because no significant increase of *meta* substitution of toluene or anisole was observed, regardless of the activity of the nitrating system. No selectivity-reactivity relationship is thus evident and the *ortho-para* directing effect of primary substituents over *meta* substitution is always maintained. The variation in the amount of the *meta* isomer, up to the observed limit of about 3% in the case of toluene and <2% for anisole, is probably significant but, at the present time, cannot be quantitatively evaluated with the $\pm 0.5\%$ overall reproducible accuracy of the nitrations. Steric factors, such as increasing bulkiness of the nitrating agent, also can affect the *ortho-para* isomer ratios but are not considered to be the only reason for the observed variations, which reflect the specific nitrating systems, affecting the nature and position of the transition state of highest energy on the reaction pathway.

Electrophilic aromatic nitration has been shown by Ingold's classical studies (2) to proceed via the formation of the nitronium ion (NO_2^+). The nitration of toluene and other substituted benzenes by different nitrating systems is generally accepted to show little variation in isomer distribution. This constancy of isomer distribution has been interpreted (3-5) as indicative of a common nitrating agent—i.e., the nitronium ion. Although there is a good evidence that reagents other than the nitronium ion, such as acetyl nitrate, can act in their own right as nitrating agents (4), Ingold's view that the NO_2^+ ion is indeed the common and only nitrating agent generally prevails. Solvation of this very reactive ion by the reaction medium should modify its reactivity, depending primarily upon the nucleophilicity of the solvent.

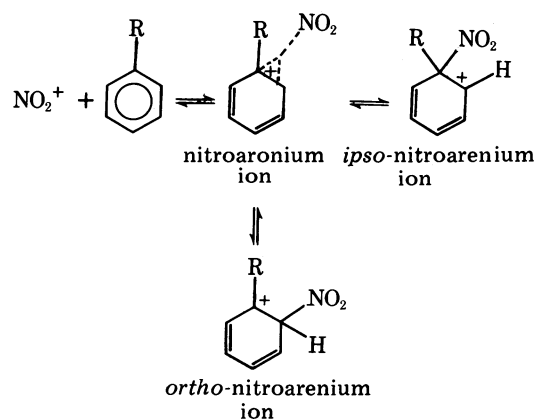
We now report that, contrary to discussed general belief (2), the isomer distribution, particularly the *ortho/para* ratios, in the nitration of the studied substituted benzenes (e.g., toluene,

anisole, *o*-xylene) shows a significant variation, depending upon the nature of the specific nitrating system used. The high *ortho-para* regioselectivity of these substrates, however, seems to be independent of the reactivity of the reagent, because no significant increase of *meta* substitution is observed in any instance, even when reactions with highly reactive reagents may reach the encounter-controlled limiting rates.

Results and discussion

We selected toluene, anisole, and *o*-xylene as representative examples of substituted benzenes for our studies. Table 1 summarizes data of nitration with various nitrating systems, as well as some relevant data from the literature for comparison. Reactions were carried out at 25°, under homogeneous conditions (if not otherwise indicated). Products were analyzed, after the usual quenching and work-up, by gas/liquid chromatography. Dinitro products, if present, were generally less than 2% and thus could have no significant effect on the results. Isomer distributions are given to $\pm 0.5\%$ (absolute) accuracy, rounded to the next significant number, which is considered to be the overall reproducibility of isomer distributions in nitration experiments.

*Ips*o substitution, under our reaction conditions involving nonaqueous, low nucleophilicity media and substituents forming extremely poor electrophilic leaving groups (methyl, methoxy), is not considered to affect regioselectivity because there is no suitable nucleophile present to quench the *ip*so-nitronium ion, which can only reverse or rearrange to the *ortho* ion.



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Table 1. Nitration of substituted benzenes with various nitrating systems*

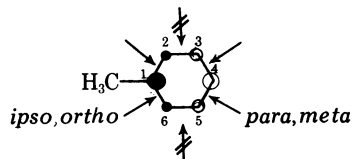
Nitrating agent	Solvent	Distribution, %			
		<i>Ortho</i>	<i>Meta</i>	<i>Para</i>	<i>Ortho/para</i>
Toluene					
NO ₂ ⁺ PF ₆ ⁻	CH ₃ NO ₂	67	3	30	2.23
NO ₂ ⁺ BF ₄ ⁻	Sulfolane	66	3	31	2.13
CH ₃ ONO ₂ /BF ₃	CH ₃ NO ₂	64	3	33	1.94
HNO ₃	Ac ₂ O (or AcOH)	57	3	40	1.42
HNO ₃	CCL ₄	53	3	44	1.20 (6)
NO ₂ Cl/TiCl ₄	Toluene	53	2	45	1.18
CH ₃ ONO ₂ /PPA	CH ₃ NO ₂	50	3	47	1.06
Anisole					
NO ₂ ⁺ BF ₄ ⁻	Sulfolane	72	<1	27	2.67
NO ₂ ⁺ PF ₆ ⁻	CH ₃ NO ₂	70	<1	29	2.41
HNO ₃	Ac ₂ O, 10°	71	2	27	2.64 (7)
CH ₃ ONO ₂ /BF ₃	CH ₃ NO ₂	57	<1	43	1.33 [†]
CH ₃ COCl/AgNO ₃	CH ₃ CN	56	<1	44	1.27
HNO ₃	AcOH, 65°	44	1	55	0.80 (9, 10) [‡]
HNO ₃ /H ₂ SO ₄	AcOH, 45°	31	2	67	0.46 (9, 10) [‡]
		3-NO ₂	4-NO ₂	3-/4-	
<i>o</i> -Xylene					
NO ₂ ⁺ BF ₄ ⁻	Sulfolane	72	28	2.57	
NO ₂ ⁺ PF ₆ ⁻	CH ₃ NO ₂	64	36	1.78	
CH ₃ ONO ₂ /CH ₃ OSO ₂ F	Methyl fluorosulfate/ <i>o</i> -xylene	61	39	1.56	
CH ₃ ONO ₂ /BF ₃	CH ₃ NO ₂	65	35	1.86	
HNO ₃	CH ₃ NO ₂	58	42	1.38	
HNO ₃ /H ₃ PO ₄ -BF ₃	CH ₃ NO ₂	57	43	1.33	
CH ₃ ONO ₂ /H ₃ PO ₄ -BF ₃	CH ₃ NO ₂	52	48	1.08	
NO ₂ Cl/BF ₃	<i>o</i> -Xylene	49	51	0.96	
Fuming HNO ₃	CH ₃ NO ₂	47	53	0.89	

* All nitrations, if otherwise not stated, were carried out at 25°.

[†] Previously with this system, a lower *ortho/para* ratio was found (8).

[‡] Nitrosation-oxidation could be a competing reaction in these experiments.

Bonding interactions of NO₂⁺ with the aromatics involve initial interaction with the highest occupied molecular orbital and can be achieved only at bonds bearing the same sign. In the case of toluene, these are the C1—C2, C1—C6, C3—C4, and C4—C5 but not the C2—C3 and C5—C6 bonds.



Attack on the C1—C2 and C1—C6 bonds can lead to *ortho* or *ipso* substitution, whereas attack on the C3—C4 and C4—C5

bonds will lead to *para* or *meta* substitution (11). The direction of electrophilic attack thus, in fact, can be reflected in the (*ipso* + *ortho*)/(*meta* + *para*) ratio, and overall *ortho* substitution is not affected in comparison to *meta* + *para* by formal *ipso-ortho* "interconversion".

In the electrophilic nitration of toluene, as shown by the data of Table 1, a significant variation in isomer distribution is observed, depending upon the reaction conditions and nitrating agent used. This is particularly apparent when considering the *ortho/para* isomer ratio, which varies from 2.23 to 1.06, a variation of >100%. The amount of *meta* isomer, however, is generally ~3%, even with the most reactive nitrating agents studied, the nitronium salts.

In the nitration of anisole, the variation of isomer distribution, in terms of the *ortho/para* ratio, is again significant. Increased *ortho* substitution of anisole has been previously rationalized in terms of an initial interaction between the nitronium ion and the n-donor oxygen atom (12). In our view, however, there is no foundation for such so-called linear coordination effect (13) causing increased *ortho* substitution of anisole. If the initial attack were on oxygen, the intermediate methylphenylnitro-

troxonium ion, C₆H₅(CH₃)ONO₂⁺, would transfer its nitro group only intermolecularly, because the intramolecular process is symmetry forbidden and would necessitate a strained four-center transition state. Whereas the methylphenylnitroxonium ion so far could not be observed or isolated, in related work we previously isolated the phenyldimethyloxonium ion, C₆H₅O(CH₃)₂⁺, and found that it transfers its methyl group exclusively intermolecularly (14). Beak (15) and Dewar (16) reached similar conclusions. Thus, the isomer distribution in the nitration of anisole also should properly reflect the electronic effects of the strongly electron-donating methoxy group.

With the reactive nitronium salts, the isomer distribution of the nitration of anisole shows the highest *ortho/para* ratio (2.7–2.4), reflecting the "early" (i.e., starting aromatic-like) nature of the transition state of highest energy. Indeed, the calculated electron density in the ground state of anisole is the highest around the *ortho* positions, even higher than in the case of toluene. As the reactivity of the nitrating system decreases (e.g., with CH₃ONO₂/BF₃ or acetyl nitrate), the amount of *para* substitution increases. Because the *para*-methoxy substituent can stabilize the arenium ion intermediate better than a *para* methyl group, these reactions seem to show increasing intermediate ion-like nature of the transition state. Steric effects can also be of significance with bulkier or more solvated nitrating agents in causing preferential *para* over *ortho* substitution but, in the homogeneous nitrations studied, these effects are not considered to be excessive.

In the nitration of anisole with nitric acid or mixed acid at somewhat elevated temperatures, as studied by Griffith (9) and Bunton (10), particularly low *ortho/para* isomer ratios were obtained. It could be argued, however, that these lower ratios are a consequence of nitration via nitrosation (2). If this is the case, it reflects the much weaker electrophilic nature of NO⁺ (as compared to NO₂⁺) and its reaction through an intermediate arenium ion-like transition state of highest energy.

The data of nitration of toluene and anisole consistently show that there is a significant variation in the *ortho/para* regioselectivity without, however, any significant observable change in *meta* substitution. (In order to evaluate the relatively small variation of the amount of *meta* substitution, the reproducibility of isomer distributions in nitration experiments would have to be much improved over the present level of ±0.5%.) Present data thus provide additional and independent evidence for the

previous suggestion that substrate and regioselectivity are determined in separate steps and thus are not interrelated (17). We have concluded, as Moodie *et al.* (18) did independently, that, on the reaction path of nitrations with reactive nitrating agents, two distinct intermediates are involved and are separated by an energy maximum. According to the Brown–Stock selectivity relationship (19), substrate and regioselectivity are directly correlated and thus must be determined in the same step. Even with very reactive nitrating systems when nitrations reach the encounter-controlled rate limit, high regioselectivity is always maintained whereas substrate selectivity disappears. According to the selectivity principle, however, under such conditions the monosubstituted benzenes should give statistical 40% *ortho*, 40% *meta*, and 20% *para* substitution. Thus, we must conclude that the Brown–Hammett type relationship, expectedly, is applicable only to systems in which both substrate and positional selectivity are determined in the same “late” or intermediate arenium ion-like step. Alternatively, as Moodie *et al.* (18) have suggested, the electronically activated *ortho* and *para* positions in toluene (or, for that matter, in anisole) could react in fast, encounter-controlled fashion with reactive nitrating agent, whereas the *meta* positions, lacking such activation, would react in a different, slower reaction, thus accounting for the observed predominant *ortho-para* directing effects.

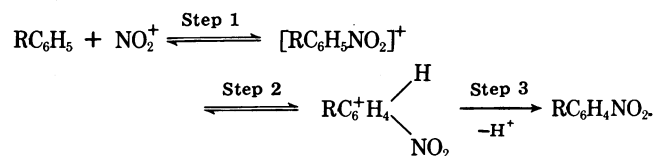
In order to study the possibility of different reaction paths for methyl group-activated *ortho* and *para* positions, compared with the nonactivated *meta* positions, we undertook a study of the nitration of *o*-xylene. In this case, both available ring positions are activated by an *ortho* or *para* methyl group. Therefore, both positions would react very rapidly—i.e., under encounter-controlled conditions. According to the selectivity relationship, this should also result in diminished regioselectivity between the two positions. The data summarized in Table 1, however, are to the contrary. Although the 3-/4- (i.e., *ortho/para*) isomer ratio shows significant changes up to ~250%, depending on the nature of the nitrating system, there is no indication of a tendency for a leveling off corresponding to the statistical 50%/50% value. These observations are in line with those made by Moodie *et al.* (18) on the nitration of pseudocumene. They observed that high positional selectivity is maintained even when the molecule is reacting under encounter control. These results clearly show that encounter control has no effect on the regioselectivity of the reactions.

On the basis of the present studies, we reconfirm our conclusion that, in aromatic substitutions with reactive electrophiles, substrate and regioselectivity indeed are not determined in the same reaction step and thus are independent of each other. This conclusion can now be reached independently of the question of whether the rates of the very fast reactions reach the diffusion- or encounter-controlled limit.

Regardless of the activity of the nitrating systems, toluene and anisole remain predominantly *ortho-para* directing, and no unusual increase in *meta* substitution occurs. At the same time, the *ortho/para* isomer ratios show significant changes, depending on the nature of the systems, reflecting changes in the relative position and nature of the transition state (more intermediate ion or starting aromatic-like) and/or steric factors.

The overall mechanistic picture of nitration of reactive aromatics with the nitronium ion (or other related reactive nitrating agents) can thus be depicted in the following with the significant change from the original Ingold scheme in that two distinct steps are involved in reaching the arenium ion-like intermediates which then give the product nitroarenes *via*

proton elimination.



Step 1 determines the overall rate (substrate selectivity) and step 2, the regioselectivity (isomer distribution).

It was Coombes *et al.* (20) who pointed out that the fast, first step can reach the encounter-controlled limit, and thus substrate selectivity can become meaningless. The nature of the first intermediate, which they call the “encounter pair,” was not defined by these authors. We tend, however, to agree with Ridd’s view (21)

... The product composition is independent of the position of the rate determining stage, providing that the formation of the encounter-pair is considered to involve the aromatic molecule as a whole, not a particular carbon atom within it. This concept of the encounter pair, as implied in the discussion of Coombes, Moodie and Schofield, is, in some ways, similar to the concept of an intermediate π -complex suggested in a different context by Olah, Kuhn, and Flood [ref. 22 in this paper].

We think that there is no discrepancy between our original suggestion of two separate steps determining substrate and regioselectivity and conclusions of Schofield and associates (20), including encounter control of the first step.

EXPERIMENTAL

All solvents, methyl nitrate, toluene, *o*-xylene, anisole, and their nitro derivatives were commercially available highest purity materials, purified by the usual methods before use. Nitronium salts (Cationics) were thoroughly purified from possible nitrosonium ion impurities (23) or were prepared from methyl nitrate free of nitrite.

General Procedure for Nitration. All nitrations were carried out at 25° (unless stated otherwise). The nitrating agent was dissolved in an appropriate solvent to give a 5–10% solution and added dropwise to a 10-fold molar excess of the aromatics in the same solvent, while the temperature was maintained at 25°. The reaction mixture was stirred at this temperature for 30 min, quenched successively with ice water and aqueous sodium bicarbonate, extracted with ether, dried, concentrated, and analyzed by gas chromatography. The data shown in Table 1 are the means of three separate experiments.

Analytical Procedure. Analyses of nitroaromatic products were carried out by using a Perkin–Elmer model 226 gas chromatograph equipped with a hydrogen flame ionization detector and either an open tubular column or a packed column. Areas of peaks were determined with an Infotronics model CRS-100 electronic printing integrator.

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