

CHAPTER 8

Electrophilic Aromatic Substitution

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General

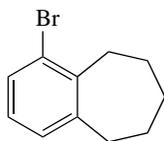
Methyl cation affinities of benzene and some substituted benzenes have been calculated. These follow a simple additivity rule and the value for benzene shows good agreement with the experimental estimate. Conclusive evidence is presented that these values are linearly related to the corresponding proton affinities.¹ The competition between deuteration and alkylation in the reaction of radiolytically formed perdeuterio ethyl cations with *N*-methylpyrrole and with thiophene has been studied. Deuteration, the Brønsted acid pathway, predominates and intramolecular selectivities have been determined for each reaction.²

Examples have been given where high and unusual reactivity with electrophiles is seen when simple, monocyclic benzene rings are bent by short bridges into a boat-shaped conformation, as in small para- and meta-cyclophanes.³ For example, bromination of [5]metacyclophane occurs at -75°C without a catalyst to give the bromobenzocycloheptene (**1**). *Ab initio* calculations suggest⁴ that chloro and bromo substituents deactivate a benzene ring to electrophilic substitution not, as commonly quoted, by the inductive effect but because the energy levels of the valence *p*-orbitals of these elements, are higher than that of the π -molecular orbital (π_1) of benzene. For chlorobenzene, π_1 is then at a lower energy and electron density at the 4-position is significantly reduced, causing deactivation.

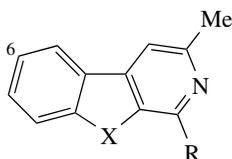
Changes in intramolecular selectivity in the bromination and nitration of alkylbenzenes in acidic media have been attributed⁵ to changes in medium polarity or changes in electrophile solvation. Mass spectrometric studies of the first stage in the gas-phase reactions of halobenzenes, furan, thiophene and pyrrole with alkyl cations have been rationalized in terms of co-existing σ - and π -complexes.⁶ The extent of

π -complex formation decreases as the capability of the aromatic to donate electron density increases. Alkyl group isomerization can occur within the lifetime of the π -complex. Complete isomerization occurs in the loosely bound π -complexes formed between halobenzenes and carbenium ions.

Electrophilic substitution in benzo[*b*]thieno- and benzo[*b*]furo-[2,3-*c*]pyridines (**2**) occurs mainly at the 6-position, although when this position is blocked by Cl in a related structure 5-,7-, and 8-substituted products are formed.⁷ The usefulness of trifluoromethanesulfonic acid as a new solvent with CFCl_3 for the reaction of fluorine with aromatics has been explored.⁸ Fluorobenzene gives 1,4-difluorobenzene (31%) and 1,2-difluorobenzene (7%) instead of the addition products mainly observed when the acid is absent; 1,2- and 1,3- but not 1,4-difluorobenzene undergo further substitution at appropriate acidity.

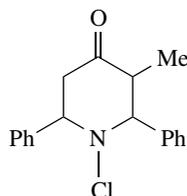


(1)



(2)

X = S, R = Et
X = O, R = Me



(3)

Halogenation

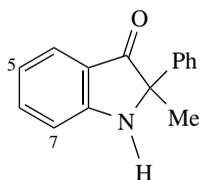
Kinetic results on the chlorination of aniline by *N*-chloro-3-methyl-2,6-diphenylpiperidin-4-one (**3**) suggest that the protonated reagent is reactive and that the initial site of attack is at the amino nitrogen.⁹ The effects of substituents in the aniline have been analysed but product studies were not reported. Zinc bromide supported on acid-activated montmorillonite K-10 or mesoporous silica (100 Å) has been demonstrated¹⁰ to be a fast, selective catalyst for the regioselective *para*-bromination of activated and mildly deactivated aromatics in hydrocarbon solvents at 25 °C. For example, bromobenzene yields around 90% of dibromobenzenes with an *ortho/para* ratio of ~0.12.

The regioselectivity of chlorination and bromination of *N,N*-dialkylbenzamides in aqueous acetic acid is strongly influenced by the alkyl groups.¹¹ *Ortho* and *para* orientation results fairly selectively from substrates with large alkyl substituents. For example, *N,N*-diisopropylbenzamide gives *o*-, *m*- and *p*-chloro derivatives in the proportion 47:11:42.

Kinetic studies of the iodination of benzene and acetanilide by iodine, diiodine pentoxide, and sulfuric acid in acetic acid indicate that benzene is involved in an equilibrium reaction prior to the rate-limiting σ -complex formation.¹² It is proposed that this equilibrium involves the formation of a π -complex between iodine adsorbed on diiodine pentoxide and the benzene as it is adsorbed. In the case of acetanilide the σ -complex is formed directly with activated iodine adsorbed on the diiodine pentoxide.

The kinetics of iodination of aniline and *p*-toluidine by iodine in acidified aqueous methanol have been determined¹³ at various solvent compositions and temperatures. It was deduced that HOI was the effective electrophile under the reaction conditions.

1,2-Dihydro-2-methyl-2-phenyl-3*H*-indol-3-one [the indoxyl (**4**)] gives 5- and/or 7-substitution on reaction with *N*-chlorosuccinimide, *N*-bromosuccinimide, or *N*-chlorobenzotriazole.¹⁴ Reactions either involved conventional electrophilic substitution or the intermediate formation of the *N*-haloindoxyl, which then rearranged via a nitrenium ion.



(4)

Nitration

An authoritative review¹⁵ on homogeneous nitration reactions involving NO^+ , NO_2^* , NO_3^* and N_2O_5 has appeared. Evidence on the electron-transfer reaction mechanism under thermal conditions for nitrous acid-catalysed nitration, on nitration by $\text{NO}_2^*/\text{N}_2\text{O}_4$ in organic solvents, on nitration by N_2O_5 and on ozone-mediated $\text{NO}_2^*/\text{N}_2\text{O}_4$ nitration is assembled. There has also been a comprehensive review of the last of these systems, kyodai nitration.¹⁶ Theoretical studies¹⁷ of the $\text{NO}_2^+ - \text{NO}$ electron transfer and related systems show that the activity of NO_2^+ as an oxidizing reagent in aromatic nitration is lowered owing to a high activation barrier resulting mainly from the change in the ONO bond angle. Nitrous acid and 4-fluorophenol react in trifluoroacetic acid to form 4-fluoro-2-nitrophenol by a mechanism involving reaction of an intermediate phenoxy radical with NO_2^* such as that occurring for similar substrates in media of lower acidity.¹⁸ A review¹⁹ covering reactions of phenols with nitrogen dioxide also describes reactions of nitrodienones, which may be intermediates under other nitration conditions.

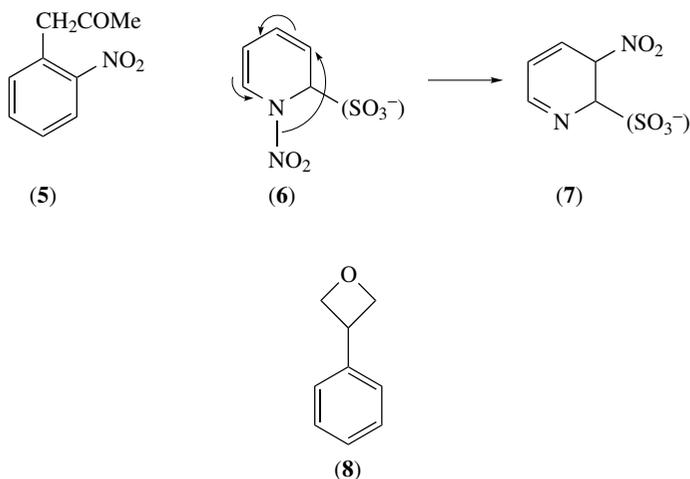
Vanadium(V) oxytrinitrate [$\text{VO}(\text{NO}_3)_3$] has been established as a powerful but moisture-sensitive reagent which nitrates a range of substituted aromatic compounds in good yield in dichloromethane at room temperature.²⁰ The hydrated triflates $\text{Hf}(\text{OTf})_4$ and $\text{Zr}(\text{OTf})_4$ are excellent recyclable catalysts for the mononitration of *o*-nitrotoluene with 1 equiv. of concentrated nitric acid.²¹

Examples of the so-called chaperon effect involving interaction between the electrophile and an appropriate substituent at the α -position in an alkyl chain prior to ring substitution at the *ortho*-position have been explored in nitrations involving dilute solutions of nitric acid in dichloromethane.²² Aldehydic or ketonic carbonyl groups are most effective, but carboxyl, alkoxycarboxyl, and amide groups also work well. 1-Phenylpropan-2-one, for example, forms 85% of 1-(2-nitrophenyl)propan-2-one (**5**).

Interestingly enhanced *para* substitution results from the nitration of 3-phenylpropanenitrile. It is suggested that in these dilute solutions the NO_2^+ donor is some adduct of lower reactivity than free NO_2^+ .

Although the intermolecular selectivity of the nitration of alkylbenzenes by nitric acid in trifluoroacetic acid is controlled by both electronic and steric factors, it is argued²³ that intramolecular selectivity is controlled by steric effects on transition state solvation.

The formation of 3-nitropyridines by reaction of *N*-nitropyridinium nitrates with aqueous sodium hydrogen sulfite solution has been further studied²⁴ with particular attention to the rearrangement of 1,2-dihydropyridines [e.g. (6) from pyridine]. The activation parameters, response to medium effects, and regioselectivity of the rearrangement here and with related compounds are better explained by a [1,5]-sigmatropic shift, (6) \rightarrow (7), than by formation of a radical pair intermediate. In contrast to the reaction with nitric acid, 3-phenyloxetane (8) reacts with dinitrogen pentoxide in dichloromethane to yield quantitatively 3-(2-nitrophenyl)oxetane (10%) and 3-(4-nitrophenyl)oxetane (90%), with oxetane-ring opening occurring subsequent to the aromatic nitration.²⁵

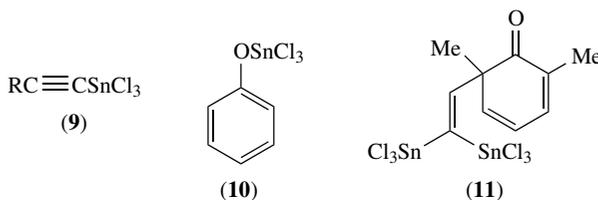


Alkylation, Acylation, and Related Reactions

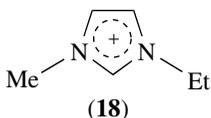
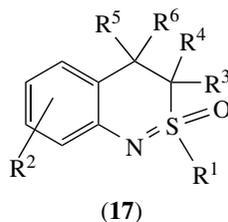
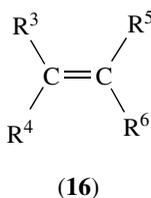
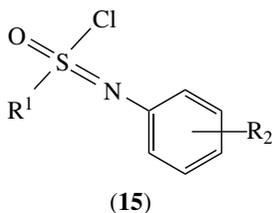
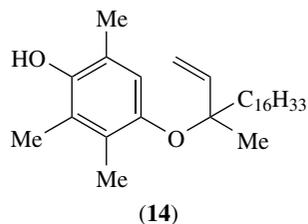
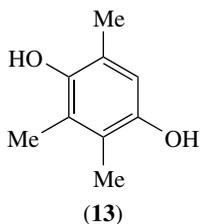
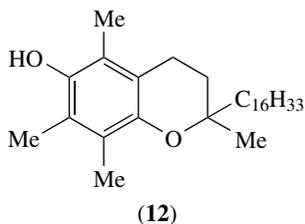
The lifetimes of typical ion–neutral complexes $\text{CH}_3\text{C}_6\text{H}_5\cdot\text{C}_2\text{Y}_4\text{X}^+$ ($\text{X} = \text{H}, \text{Y} = \text{D}$; $\text{X} = \text{D}, \text{Y} = \text{H}$) in the alternative mechanism of gas-phase electrophilic alkylation which has been reported over the last 3 years (*Organic Reaction Mechanisms 1995*, p. 252, ref. 31; *1996*, p. 168, ref. 40; *1997* p. 259, ref. 3) have been estimated ($\sim 10^{-11}$ s at 393 K) by a kinetic approach which uses the rate of H/D scrambling in $\text{C}_2\text{H}_4\text{D}^+$ or C_2HD_4^+ as an internal clock.²⁶ The addition of various promoters (Br_2 , $\text{C}_2\text{H}_5\text{Cl}$, CCl_4 , Ph_3CCl) to aluminium chloride or aluminium chloride–silica in the alkylation of benzene with pentane and 2-methylbutane gives a 1.5–4.4-fold increase in alkylbenzene yield.²⁷

A continuous procedure for the alkylation of mesitylene and anisole with supercritical propene, or propan-2-ol in supercritical carbon dioxide, with a heterogeneous polysiloxane-supported solid acid Deloxan[®] catalyst has been reported²⁸ giving 100% selectivity for monoalkylation of mesitylene with 50% conversion at 250 °C and 150 bar by propan-2-ol in supercritical carbon dioxide. *p*-Toluenesulfonic acid monohydrate has been demonstrated as an efficient catalyst for the clean alkylation of aromatics using activated alkyl halides, alkenes or tosylates under mild conditions.²⁹ Cyclohexene, for example, reacts with toluene to give 100% cyclohexyltoluenes (*o*:*m*:*p*-29:18:53) under these circumstances.

Various phenols with electron-donating or -withdrawing substituents were vinylated at the *ortho*-position with ethyne using an SnCl₄-Bu₃N reagent.³⁰ Trichlorostannyloethynes (**9**) and phenoxytins [e.g. (**10**)] are suggested as intermediates, the latter then undergoing electrophilic substitution by attack of the β-carbon of the former. *Ortho* attack is much favoured and 2,6-dimethylphenol reacts via the *ipso* cyclohexadienone intermediate (**11**). The results from hydroxymethylation of monocyclic aromatics with formaldehyde in benzene-aqueous sulfuric acid depend³¹ on the phase-transfer catalyst, sodium tetra-perfluorophenylborate, (C₆F₅)₄B⁻Na⁺, or dimethylstearyltaurobetaine, C₁₈H₃₇(CH₃)₂N⁺CH₂CH₂SO₂⁻, being studied. Results are interpreted in terms of an 'early' transition state for reactions with the former reagent and a 'late' transition state for the latter.



A review has appeared³² of the mechanism of synthesis of α-tocopherol (**12**) from trimethylhydroquinone (**13**). This suggests that the reaction in the presence of a Lewis acid differs from that in the presence of Brønsted acids and involves intermediate formation of an ether (**14**), which undergoes Claisen rearrangement and then ring closure. The stereoselectivity of reaction of *N*-arylsulfonimidoyl chlorides (**15**) with alkenes (**16**) to form benzothiazines (**17**) has been investigated.³³ With trisubstituted alkenes steric effects seem definitely to cause a reaction pathway involving a carbocationic intermediate which may also precede σ-complex formation. The ionic liquid system 1-methyl-3-ethylimidazolium (**18**) chloride-aluminium(III) chloride is an excellent medium for the acetylation using acetyl chloride of a range of aromatic substrates.³⁴ Excellent yields and selectivities are observed. In the case of anthracene the reaction is reversible and the 9-acetylanthracene initially formed undergoes a slow disproportionation to anthracene and mainly 1,5-diacetylanthracene. The acetylation of 2-methylnaphthalene by acetyl chloride with various catalysts has been studied, changing solvent, mode of addition, concentration and the catalyst.³⁵ Under appropriate conditions the formation of mainly either 1-acetyl-2-methyl- or 2-acetyl-6-methyl-naphthalene can be achieved, accompanied by other minor products.

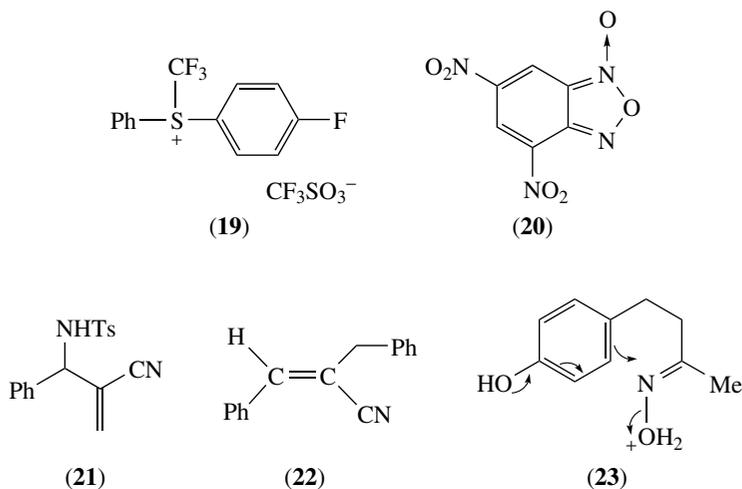


Other Reactions

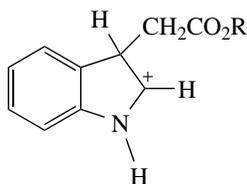
Ab initio calculations have been performed on the *ipso* protonation of toluene and mainly disubstituted derivatives and suggest³⁶ that a simple scheme of additivity of substituent effects is operative. The results suggest that protonation *ipso* to methyl is not thermodynamically the most favourable pathway provided that there is a single unsubstituted position on the ring. Radiolytic studies³⁷ of H/D exchange between substituted arenium ions and various bases together with NMR analysis provide information about the site of protonation. This is found to involve the most basic ring positions *ortho/para* for alkyl substituents and *ortho/meta* for electron-withdrawing substituents.

The kinetics of the diazo coupling of aryldiazo phenyl sulfides with 2-naphthol in acidic media have been reported and indicate that the sulfides are fully protonated in a pre-equilibrium stage of the reaction.³⁸ Synthetic routes to four stable trifluoromethylating agents have been established.³⁹ These reagents, substituted *S*-(trifluoromethyl)diphenylsulfonium triflates [e.g. (19)], react with a range of reactive aromatics to give, for example, 2- and 4-trifluoromethylaniline from aniline. The ability of these reagents to transfer a CF₃ group is enhanced by electron withdrawal in the phenyl groups. Rates of reaction of 4,6-dinitrobenzofuroxan (20) with a series of activated substituted benzenes have been reported;⁴⁰ (20) is more reactive and less selective than H₃O⁺ towards these substrates. In the case of 1,3,5-trimethoxybenzene

a primary kinetic isotope effect is observed, indicating that reversion to reactants and proton loss from the Wheland intermediate occur at comparable rates. The compound **(20)** reacts with 3-methoxythiophene but here the first step is rate limiting.⁴¹ The solvent effect suggests a highly polar transition state where the development of negative charge on the dinitrobenzofuroxan moiety and of a partial positive charge on the thiophene ring occur together. The results allow the estimation of the carbon basicity of the thiophene and support the view that it exhibits some vinyl ether behaviour. The aluminium chloride and antimony pentafluoride-catalysed reaction of *p*-toluenesulfonyl chloride with benzene and toluene in dichloromethane gave higher toluene/benzene rate ratios and proportions of *meta* sulfone products than in the literature.⁴² The probable electrophile for the former reactions is a molecular complex between *p*-toluenesulphonyl chloride and aluminium chloride with coordination through oxygen. The reaction of benzene and substituted benzenes with the Baylis–Hillman adducts of *N*-tosylimine derivatives [e.g. **(21)**] in the presence of sulfuric acid gives stereochemically defined substituted benzylalkenes [e.g. **(22)**] in moderate yields, the stereochemistry depending on the electron-withdrawing group present in the adduct.⁴³ *Ab initio* calculations on the intramolecular nucleophilic displacement of a protonated oxime oxygen with an aryl ring to give a spiro intermediate demonstrated that the substitution on the *sp*² nitrogen atom is a low-energy process.⁴⁴ Experimental results on the effects of changing the acid catalyst on such a reaction of **(23)** and the competing Beckmann rearrangement were reported.



The formation of 2-(indolin-2-yl)indole dimers from indole-3-acetic acid and its propyl ester in trifluoroacetic acid and phosphoric acid has been studied.⁴⁵ The reaction involves electrophilic attack of the protonated species **(24)** on the free substituted indole to give the *trans* stereochemistry at the C(2)–C(3) bond.



(24)

R = H, Pr

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