Electrophilic aromatic substitution

21

Connections

Building on

- Structure of molecules ch4
- Conjugation ch7
- Mechanisms and catalysis ch12
- Electrophilic addition to alkenes ch19
- Enols and enolates ch20

Arriving at

- Phenols as aromatic enols
- Benzene and alkenes compared: what is special about aromatic compounds?
- Electrophilic attack on benzene
- Activation and deactivation of the benzene ring
- Position of substitution
- Elaborating aromatic structures: competition and cooperation
- Problems with some aromatic substitution reactions and how to solve them

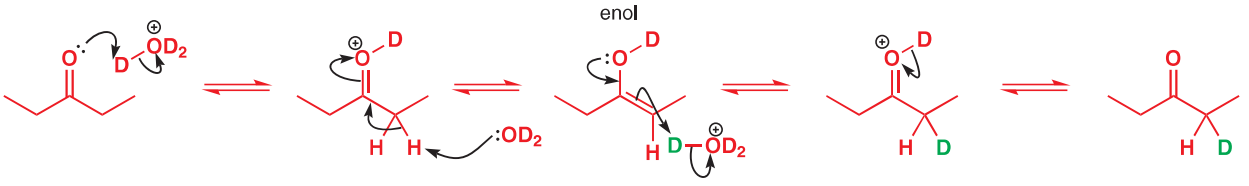
Looking forward to

- Nucleophilic aromatic substitution ch22
- Oxidation and reduction ch23
- Regioselectivity and ortholithiation ch24
- Retrosynthetic analysis ch28
- Aromatic heterocycles ch29 & ch30
- Rearrangements ch36
- Transition-metal catalysed couplings to aromatic compounds ch40

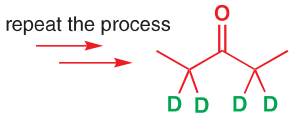
Introduction: enols and phenols

In the last chapter you saw that many ketones have a nucleophilic 'alter ego' known as an enol tautomer. Formation of the enol tautomer is catalysed by acid or by base, and because the ketone and enol are in equilibrium, enolization in the presence of D_2O can lead to replacement of the protons in the α positions of ketones by deuterium atoms. This is what happens to pentan-3-one in acidic D_2O:

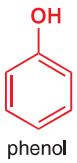
■ If you haven't just read Chapter 20, look back at p. 451 to remind yourself of how this works.



Because the enolization and deuteration process can be repeated, eventually all of the α-protons are replaced by deuterium.

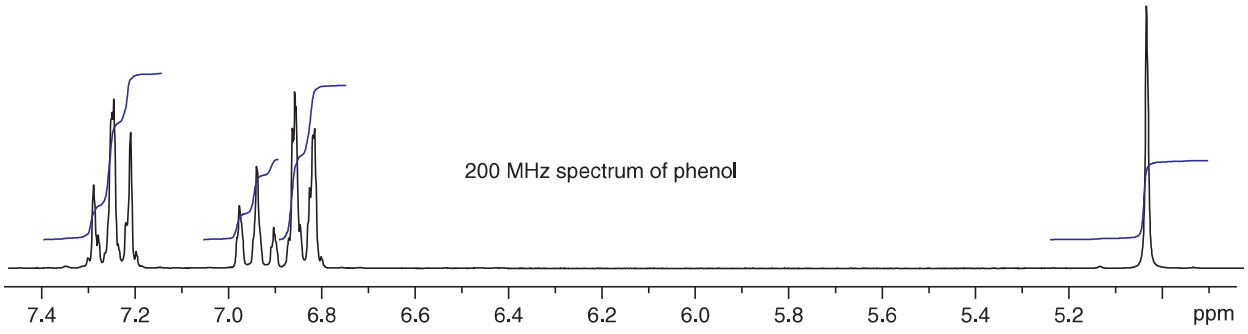


The way this ketone is deuterated provides evidence that its enol form exists, even though the keto/enol equilibrium greatly favours the ketone form at equilibrium. In this chapter we shall be discussing similar reactions of a compound that exists entirely in its enol form. That very stable enol is phenol and its stability is a consequence of the aromaticity of its benzene ring.

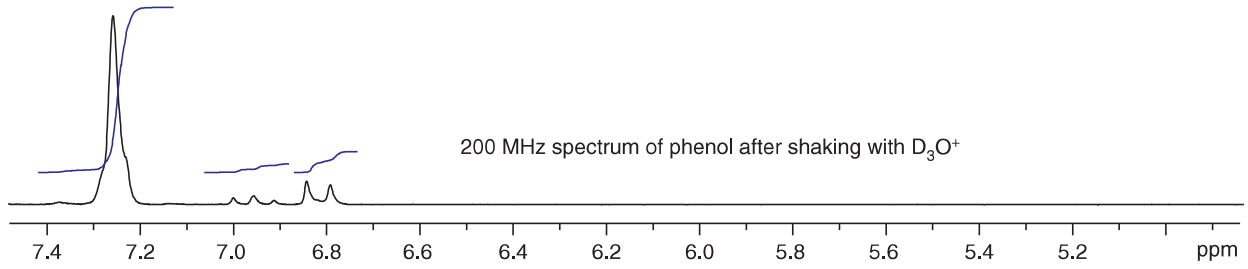


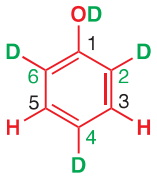
phenol

The proton NMR spectrum for phenol is shown below. Before reading any further cover up the rest of this page and make sure you can assign the spectrum.



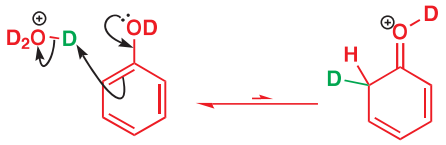
The next spectrum is the proton NMR after shaking phenol with acidic D_2O. Most of the peaks have almost disappeared because the H atoms have been replaced with D. Only one signal remains the same size, and even that is simplified because it has lost any coupling to adjacent protons it may have had previously.



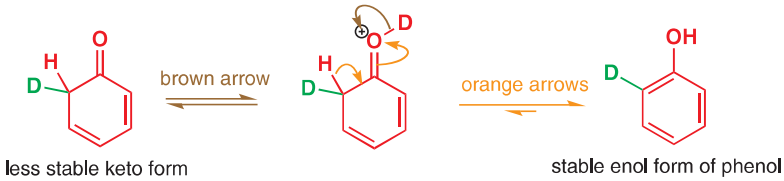


The signal that remains is the 2H signal for the protons in the 3 and 5 positions of the aromatic ring, so the product must be the one shown in the margin. We can explain why by using the same mechanism we used with the ketone on the previous page. Phenol is deuterated in the same way as other enols, except that the final product remains in the very stable, aromatic, enol form rather than reverting to the keto form. The first step (after initial replacement of the OH with OD) is addition of D_3O^+ to the enol.

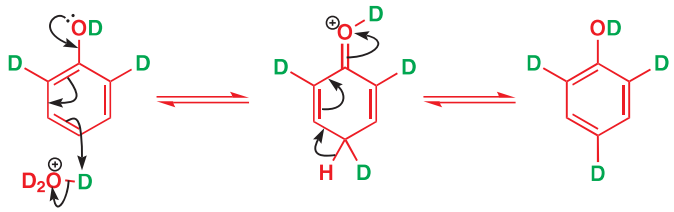
This equilibrium was discussed on p. 456.



Now this cation could lose the D from oxygen to leave a ketone (brown arrow below), or it could lose the proton from carbon to leave the phenol (orange arrows below). Alternatively, it could just lose the D and go back to the starting material, which is why there is an equilibrium arrow in the scheme above.



Our spectrum tells us that *three* ring protons are replaced by D—the ones at the 2, 4, and 6 positions. It's not hard to see how the same process on the other side of the OH group replaces the proton at C-6. But how does the D at position 4 get there? The enol of phenol is conjugated, and we can push the curly arrows one stage further, like this:

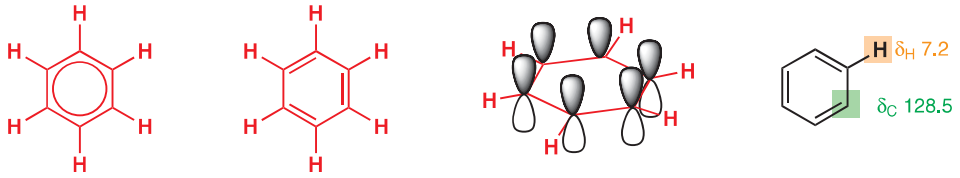


The end product on treating phenol with D_3O^+ has the protons in the 2, 4, and 6 positions (that is, the *ortho* and *para* positions) substituted by deuterium. D_3O^+ is an electrophile, and the overall process is called *electrophilic substitution*. It is a reaction characteristic of not only phenol but of other aromatic compounds, and it forms the subject of this chapter.

● **When aromatic compounds react with electrophiles they generally do so by electrophilic aromatic substitution.**

Benzene and its reactions with electrophiles

We'll start with the most straightforward aromatic compound: benzene. Benzene is a planar symmetrical hexagon with six trigonal (sp^2) carbon atoms, each having one hydrogen atom in the plane of the ring. All the bond lengths are 1.39 Å (compare C–C 1.47 Å and C=C 1.33 Å). All the ^{13}C shifts are the same (δ_C 128.5).

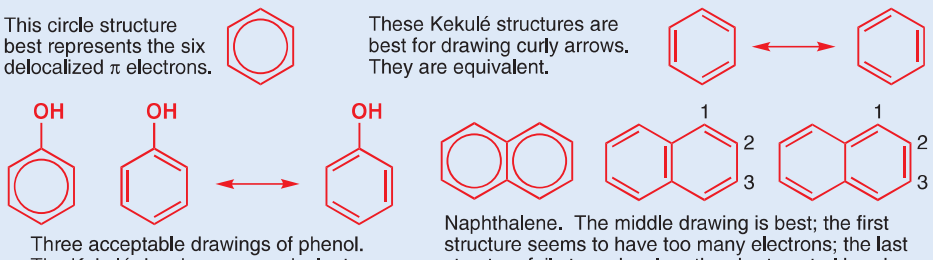


two ways of drawing benzene | the π system | NMR data

The special stability of benzene (aromaticity) comes from the six π electrons in three molecular orbitals formed by the overlap of the six atomic p orbitals on the carbon atoms. The energy levels of these orbitals are arranged so that there is exceptional stability in the molecule (a notional 140 kJ mol^{-1} over a molecule with three conjugated double bonds), and the shift of the six identical hydrogen atoms in the NMR spectrum (δ_H 7.2) is evidence of a ring current in the delocalized π system.

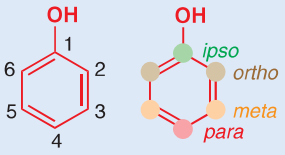
Drawing benzene rings

Benzene is symmetrical and the structure with a circle in the middle best represents this. However, it is impossible to draw curly arrow mechanisms using this representation so we shall usually make use of the Kekulé form with three double bonds. This does not mean that we think the double bonds are localized! It makes no difference which Kekulé structure you draw—any mechanism can be equally well drawn using either.



Aromatic substituents

A reminder (see pp. 36 and 416) of the names we give to the positions around a benzene ring relative to any substituent:



Ortho, *meta*, and *para* are sometimes abbreviated to *o*, *m*, and *p*.

■ The concept of *aromaticity* is central to this chapter: we will elaborate considerably on the introduction to aromatic compounds we presented in Chapter 7.

➡ The orbitals of benzene were discussed in Chapter 7.

In substituted aromatic molecules such as phenol, the C–C bond lengths in the ring are no longer exactly the same. However, it is still all right to use either representation, depending on the purpose of the drawing. With some aromatic compounds, such as naphthalene, it *does* matter which Kekulé structure you use as there is some alternation of bond lengths. Only the first Kekulé representation shows that the central bond is the strongest and shortest in the molecule and that the C1–C2 bond is shorter than the C2–C3 bond. And if a circle in a ring indicates six π electrons, then two circles suggests 12, even though naphthalene has only 10, making this representation less satisfactory too.

Electrophilic attack on benzene and on cyclohexene

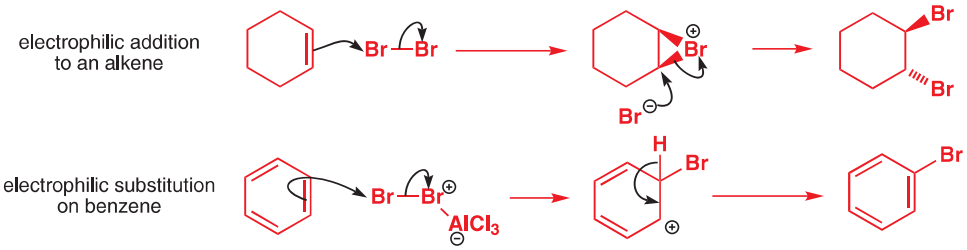
Simple alkenes, including cyclohexene, react rapidly with electrophiles such as bromine or peroxy-acids (Chapter 19). Bromine gives the product of *trans* addition, peracids give epoxides by *cis* addition. Under the same conditions benzene reacts with neither reagent.

➡ Lewis acids were described on p. 180.

Benzene can, however, be persuaded to react with bromine if a Lewis acid catalyst such as $AlCl_3$ is added. The product contains bromine but is not from either *cis* or *trans* addition.

The bromine atom has replaced an atom of hydrogen, so this is a substitution reaction. The reagent (Br_2) is electrophilic and benzene is aromatic so the reaction is **electrophilic aromatic substitution**, the subject of this chapter.

We can compare the bromination of cyclohexene and of benzene directly.



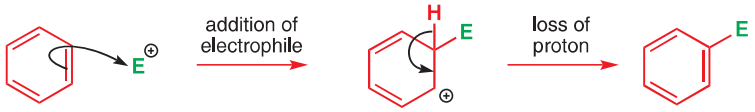
The intermediate in both reactions is a cation but the first (from cyclohexene) adds an anion while the second (from benzene) loses a proton so that the aromatic system can be restored. Notice also that neutral bromine reacts with the alkene but the cationic $AlCl_3$ complex is needed to get reaction with benzene. Bromine itself is a very reactive electrophile. It is indeed a dangerous compound and should be handled only with special precautions. Even so it does not react with benzene. It is difficult to get benzene to react with anything.

- **Benzene is very unreactive**
  - **It combines only with very reactive (usually cationic) electrophiles.**
  - **It gives substitution and not addition products.**

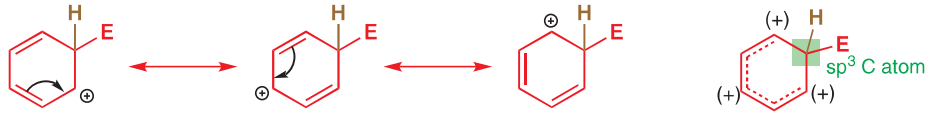
The intermediate in electrophilic aromatic substitution is a delocalized cation

We will return again and again to this mechanism of electrophilic aromatic substitution during this chapter. In its most general form the mechanism has two stages: attack by an electrophile to give an intermediate cation and loss of a proton from the cation to restore the aromaticity.

General mechanism for electrophilic aromatic substitution



The cationic intermediate is, of course, unstable compared with the starting materials or the product. But it is nonetheless stabilized by delocalization. The arrows below show how the positive charge can be delocalized to the two *ortho* positions and to the *para* position, or can be drawn as a single delocalized structure with partial (dotted) bonds and about one-third of a positive charge (+) at three atoms.

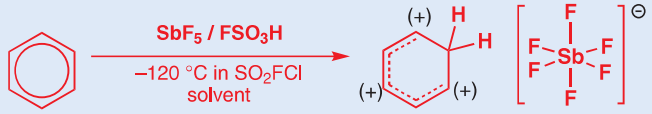


the brown H is drawn in to emphasize the non-aromaticity of this delocalized cation

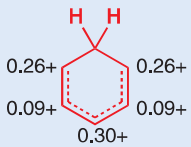
It's very important to note that although it is delocalized, this cation is not aromatic: there is no cyclic array of p orbitals because the ring contains a single tetrahedral (sp^3 hybridized) carbon atom. We have emphasized this tetrahedral atom by drawing in the hydrogen atom at the point of substitution—the one that will be lost when aromaticity is regained. We suggest that when you write mechanisms for electrophilic aromatic substitution you do the same. Given this loss of aromaticity, it is not surprising that formation of the cationic intermediate is the rate-determining step of an electrophilic aromatic substitution.

How do we know the cationic intermediate exists?

In strong acid, the electrophile is a proton and it is actually possible to observe this cationic intermediate. The trick is to pick a non-nucleophilic and non-basic counterion X^-, such as SbF_6^-. In this octahedral anion, the central antimony atom is surrounded by the fluorine atoms with the negative charge spread over all seven atoms. The protonation is carried out using FSO_3H and SbF_5 at –120 °C. A similar trick was described in Chapter 15 as a means to show the existence of simple carbocations as intermediates in the S_N1 mechanism.



Under these conditions it is possible to record the ^1H and ^{13}C NMR spectra of the cation. The shifts show that the positive charge is spread over the ring but is greatest (i.e. the electron density is least) at the *ortho* and *para* positions. Using the data for the ^1H and ^{13}C NMR shifts (δ_H and benzene δ_C, respectively), a charge distribution can be calculated that closely matches the predictions of the curly arrows.



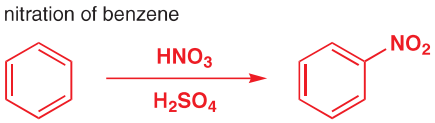
position	δ_H	δ_C
1	5.6	52.2
2,6	9.7	186.6
3,5	8.6	136.9
4	9.3	178.1
benzene (for comparison)	7.33	129.7

Nitration of benzene

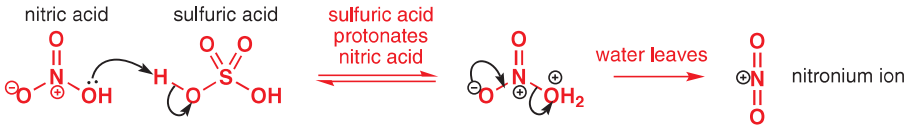
Now we've introduced to you the general principles of electrophilic aromatic substitution we need to delve into the details a little more and show you some real reactions of benzene. In each case, a powerful cationic electrophile is needed to persuade the unreactive benzene to act as a nucleophile.

■ The delocalized structure of the nitro group was discussed in Chapter 2.

We'll start with nitration, the introduction of a nitro (NO_2) group. Nitration requires very powerful reagents, the most typical being a mixture of concentrated nitric and sulfuric acids.



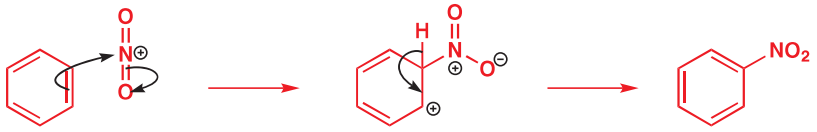
Sulfuric acid is the stronger acid and it produces the powerful electrophile NO_2^+ by protonating the nitric acid so that a molecule of water can leave.



The nitronium ion (NO_2^+) is linear—it's isoelectronic with CO_2, with an sp-hybridized nitrogen atom at the centre. It's this nitrogen that is attacked by benzene, breaking one of the N=O bonds to avoid a five-valent nitrogen.

Interactive mechanism for nitration of benzene

■ A reminder: electrophilic aromatic substitution mechanisms are easier to follow if you draw in the H at the point of substitution.

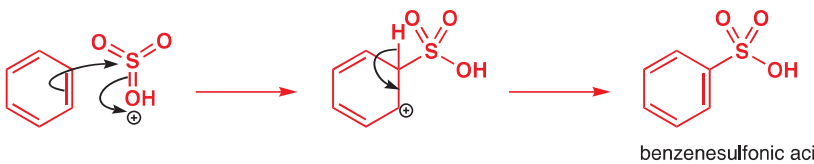


● **Nitration converts aromatic compounds (ArH) into nitrobenzenes ($ArNO_2$) using NO_2^+ from $HNO_3 + H_2SO_4$.**

Sulfonation of benzene

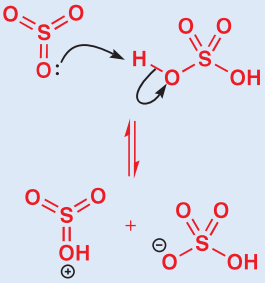
Benzene reacts slowly with sulfuric acid alone to give benzenesulfonic acid. One molecule of sulfuric acid protonates another and loses a molecule of water. Notice the similarity with the first step of the nitration above.

The cation produced is very reactive and attacks benzene by the same mechanism we have seen for bromination and nitration—slow addition to the π system followed by rapid loss of a proton to regenerate aromaticity.



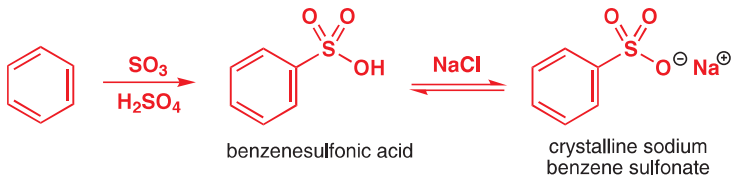
The product contains the sulfonic acid group $-SO_2OH$. Sulfonic acids are strong acids, about as strong as sulfuric acid itself. They are stronger than HCl, for example, and can be isolated

The cationic intermediate can also be formed by the protonation of sulfur trioxide, SO_3, and another way to do sulfonations is to use concentrated sulfuric acid with SO_3 added. These solutions have the industrial name **oleum**. It is possible that the sulfonating agent in all these reactions is not protonated SO_3 but SO_3 itself.



Interactive mechanism for sulfonation of benzene

from the reaction mixture as their crystalline sodium salts if an excess of NaCl is added. Not many compounds react with NaCl!

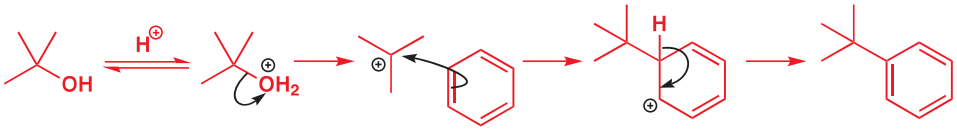


You met a related sulfonate anion in the guise of the excellent tosylate leaving group in Chapter 15.

● **Sulfonation with H_2SO_4 or SO_3 in H_2SO_4 converts aromatic compounds (ArH) into aromatic sulfonic acids ($ArSO_2OH$). The electrophile is SO_3 or SO_3H^+.**

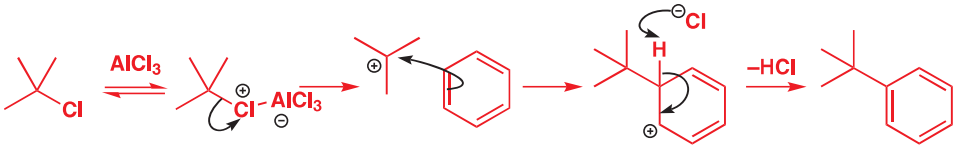
Alkyl and acyl substituents can be added to a benzene ring by the Friedel–Crafts reaction

So far we have added heteroatoms only—bromine, nitrogen, or sulfur. Adding a carbon substituent to a reluctant aromatic nucleophile requires reactive carbon electrophiles and that means carbocations. In Chapter 15 you learned that any nucleophile, however weak, will react with a carbocation in the S_N1 reaction: benzene rings are no exception. The classic S_N1 electrophile is the *t*-butyl cation, which is generated from *tert*-butanol with acid.



This is, in fact, an unusual way to carry out such reactions. The **Friedel–Crafts alkylation**, as this is known, usually involves treating benzene with a tertiary alkyl chloride and the Lewis acid $AlCl_3$. Rather in the manner of the reaction with bromine, $AlCl_3$ removes the chlorine atom from *t*-BuCl and releases the *t*-Bu cation for the alkylation reaction.

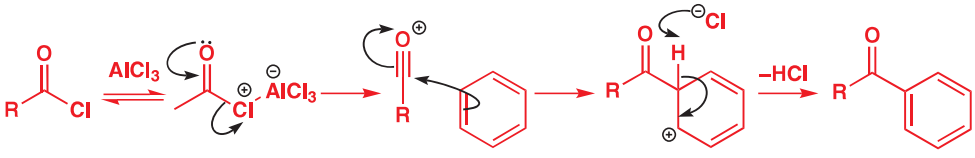
Charles Friedel (1832–1899), a French chemist, and James Crafts (1839–1917), an American mining engineer, both studied with Wurtz and then worked together in Paris, where in 1877 they discovered the reaction which now carries their names.



Interactive mechanism for Friedel–Crafts alkylation

We have not usually bothered with the base that removes the proton from the intermediate. Here it is chloride ion as the by-product is HCl, so you can see that even a very weak base will do. Anything, such as water, chloride, or other counterions of strong acids, will do this job well enough and you need not in general be concerned with the exact agent.

A more important variation of this reaction is the **Friedel–Crafts acylation** with acid chlorides and $AlCl_3$. Aluminium chloride behaves with acyl chlorides much as it does with alkyl chlorides—it removes chloride to leave behind a cation. In this case the cation is a linear acylium ion, with the carbocation stabilized by the adjacent oxygen lone pair. When the acylium ion attacks the benzene ring it gives an aromatic ketone: the benzene ring has been acylated.



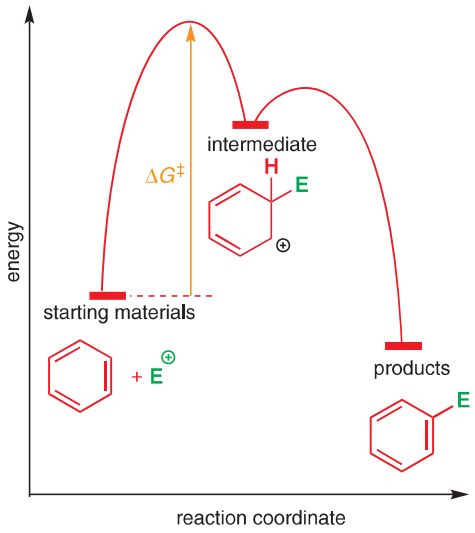
Interactive mechanism for Friedel–Crafts acylation

We'll come back (on p. 492) to why this is and what can be done about it.

The acylation is better than the alkylation because it does not require any particular structural feature in the acyl chloride—R can be almost anything. In the alkylation step it is essential that the alkyl group can form a cation, otherwise the reaction does not work very well. In addition, for reasons we are about to explore, the acylation stops cleanly after one reaction whereas the alkylation often gives mixtures of products.

● Friedel–Crafts reactions

Friedel–Crafts alkylation with *t*-alkyl chlorides and Lewis acids (usually $AlCl_3$) gives *t*-alkyl benzenes. The more reliable Friedel–Crafts acylation with acid chlorides and Lewis acids (usually $AlCl_3$) gives aryl ketones.



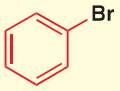
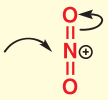
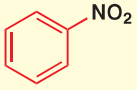
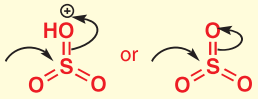
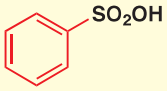
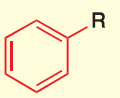
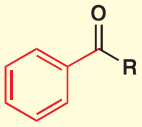
Summary of electrophilic substitution on benzene

This completes our preliminary survey of the most important reactions in aromatic electrophilic substitution. We shall switch our attention to the benzene ring itself now and see what effects various types of substituent have on these reactions. During this discussion we will return to each of the main reactions and discuss them in more detail. Meanwhile, we conclude this introduction with an energy profile diagram for a typical substitution.

Since the first step involves the temporary disruption of the aromatic π system, and is therefore rate determining, it must have the higher-energy transition state. The intermediate is unstable and has a much higher energy than either the starting material or the products, close to that of the transition states for its formation and breakdown. The two transition states will be similar in structure to the intermediate and we shall use the intermediate as a model for the important first transition state.

■ This argument is based on the **Hammond postulate**, which suggests that structures close in energy that transform directly into each other are also similar in structure. For more on this, see Chapter 39.

● Summary of the main electrophilic substitutions on benzene

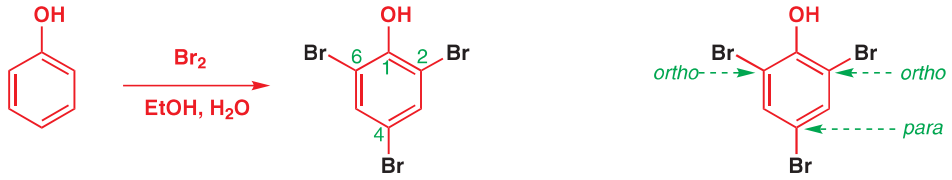
Reaction	Reagents	Electrophile	Product
bromination	Br_2 and Lewis acid, e.g. $AlCl_3$, $FeBr_3$, Fe powder		
nitration	$HNO_3 + H_2SO_4$		
sulfonation	concentrated H_2SO_4 or $H_2SO_4 + SO_3$ (oleum)		
Friedel–Crafts alkylation	RX + Lewis acid usually $AlCl_3$		
Friedel–Crafts acylation	RCOCl + Lewis acid usually $AlCl_3$		

Electrophilic substitution on phenols

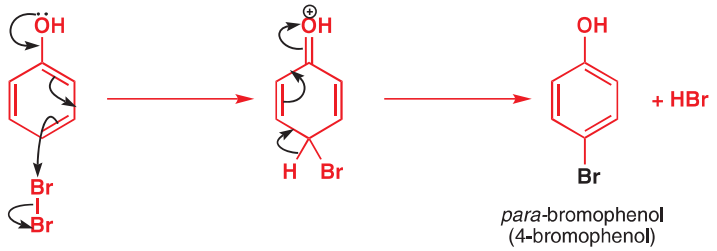
We started this chapter by comparing phenols with enols and now we return to phenols and look at electrophilic substitution in full detail. You will find that the reaction is much easier than it was with benzene itself because phenols are like enols and the same reactions (bromination, nitration, sulfonation, and Friedel–Crafts reactions) occur more easily. There is a new question too: the positions round the phenol ring are no longer equivalent—so where does substitution take place?

Phenols react rapidly with bromine

Benzene does not react with bromine except with Lewis acid catalysis. Phenols react in a very different manner: no Lewis acid is needed, the reaction occurs very rapidly, and the product contains three atoms of bromine in specific positions. All that needs to be done is to add bromine dropwise to a solution of phenol in ethanol. Initially, the yellow colour of the bromine disappears but if, when the colour just remains, water is added, a white precipitate of 2,4,6-tribromophenol is formed.



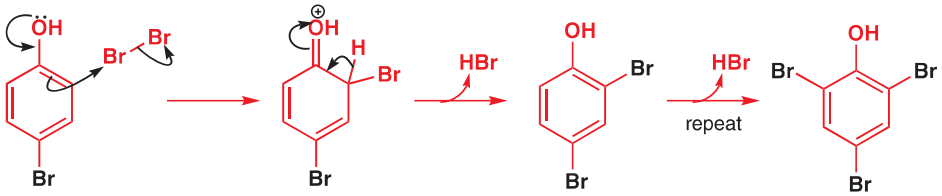
The product shows that bromination has occurred at the *para* position and at both *ortho* positions. What a contrast to benzene! Phenol reacts three times, without catalysis, at room temperature. Benzene reacts once, and needs a Lewis acid to make the reaction go at all. The difference is, of course, the enol nature of phenol. The non-bonding lone pair of electrons at oxygen contribute to a much higher-energy HOMO than the low-energy bonding electrons in a benzene ring. We should let our mechanism show this. Starting in the *para* position:



para-bromophenol
(4-bromophenol)

Notice that we start the chain of arrows with the lone pair electrons on the OH group and push them through the ring so that they emerge at the *para* position to attack the bromine molecule. The benzene ring is acting as a conductor, allowing electrons to flow from the OH group to the bromine molecule.

Now the reaction is repeated, but this time at one of the two equivalent *ortho* positions:

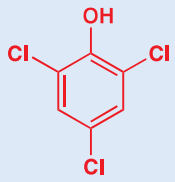


Again the lone pair electrons on the OH group are fed through the benzene ring to emerge at the *ortho* position. A third bromination in the remaining *ortho* position—you could draw the mechanisms for this as practice—gives the final product 2,4,6-tribromophenol.

Why do we use numbers for some descriptions, such as 2,4-dibromophenol, but also use *ortho* and *para* in others? The numbers are best in naming compounds but we need *ortho* and *para* to describe the relationship between substituents. Phenol brominates in both *ortho* positions. In this molecule they happen to be positions 2 and 6. In other molecules, where the OH group is not at C1, they will have other numbers, but they will still be *ortho* to the OH group. Use whichever description suits the point you are making.

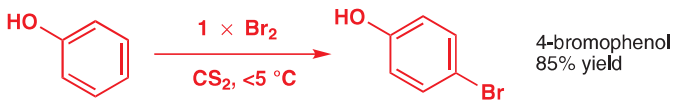
This mechanism should remind you of the bromination of enols in Chapter 20.

A similar reaction with chlorine is used to make the well-known antiseptic TCP (2,4,6-trichlorophenol). The characteristic smell of TCP is typical of the smell of many other phenols.

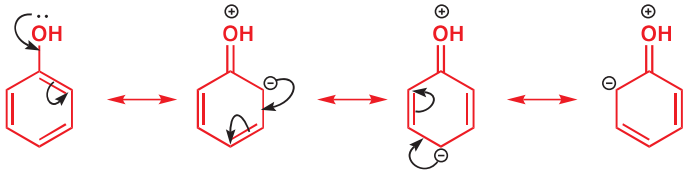


2,4,6-trichlorophenol (TCP)

If you want to put just one bromine atom into a phenol, you must work at low temperature (<5 °C) and use just one equivalent of bromine. The best solvent is the rather dangerously inflammable carbon disulfide (CS_2), the sulfur analogue of CO_2. Under these conditions, *para*-bromophenol is formed in good yield as the main product (which is why we started the mechanism for bromination of phenol in the *para* position). The minor product is *ortho*-bromophenol.



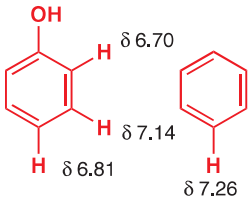
The OH group is said to be ***ortho*, *para*-directing** towards electrophiles. No substitution occurs in either *meta* position. We can understand this by looking at the curly arrow mechanisms or by looking at the molecular orbitals. In Chapter 20 (p. 453) we looked at the π system of an enolate and saw how the electron density is located mainly on the end atoms (the oxygen and the carbon). In phenol it is the *ortho* and *para* positions that are electron-rich (and, of course, the oxygen itself). We can show this using curly arrows.



The curly arrows actually give an indication of the electron distribution in the HOMO of the molecule. The reason is that the HOMO has large coefficients at *alternate atoms*, just as the allyl anion had large coefficients at its ends but not in the middle (Chapter 7).

NMR can give us some confirmation of the electron distribution

^{1}H NMR shifts in phenol and benzene



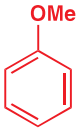
The ^{1}H NMR shifts of phenol give us an indication of the electron distribution in the π system. The more electron density that surrounds a nucleus, the more shielded it is and so the smaller the shift (see Chapter 13). All the chemical shifts for the ring protons in phenol are smaller than those for benzene (7.26 ppm), which means that overall there is greater electron density in the ring. There is little difference between the *ortho* and the *para* positions: these are where the electron density is greatest and hence these are the sites for electrophilic attack. The chemical shift at the *meta* positions is not significantly different from those in benzene—this is where the electron density is lowest.

● Electrophilic attack on phenols

OH groups on benzene rings are *ortho*, *para*-directing and activating.

You will get the right product if you start your arrows at a lone pair on the OH group.

Oxygen substituents activate a benzene ring

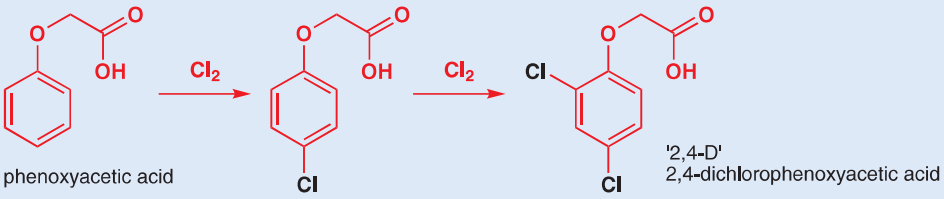


anisole

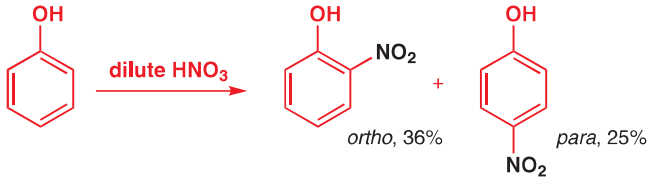
To brominate phenol, all we had to do was to mix bromine and phenol—if we do this with benzene itself, nothing happens. We therefore say that, relative to benzene, the OH group in phenol *activates* the ring towards electrophilic attack. The OH group is both activating and *ortho, para*-directing. Other groups that can donate electrons also activate and direct *ortho, para*. Anisole (methoxybenzene) is the 'enol ether' equivalent of phenol. It reacts faster than benzene with electrophiles.

2,4-D

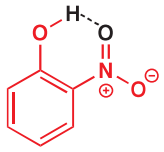
The multiple chlorination of another oxygen-substituted compound, phenoxyacetic acid, leads to a useful product. Chlorination with two equivalents of chlorine provides 2,4-dichlorophenoxy acetic acid, which is the herbicide 2,4-D. The oxygen substituent again activates the ring and directs the chlorination to the *ortho* and *para* positions.



Nitration of phenol is also very fast and can be problematic under the usual nitration conditions (conc. HNO_3, conc. H_2SO_4) because concentrated nitric acid oxidizes phenols. The solution is to use dilute nitric acid. The concentration of NO_2^+ will be small but that does not matter with such a reactive benzene ring.

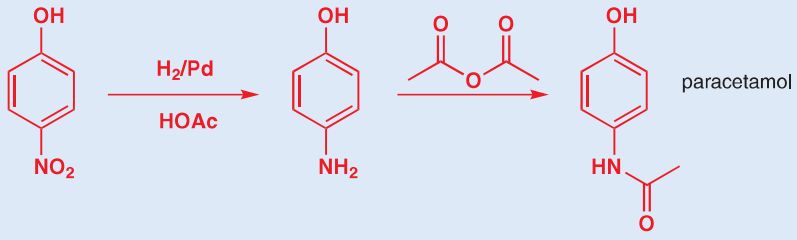


The product is a mixture of *ortho*- and *para*-nitrophenol from which the *ortho* compound can be separated by steam distillation. A strong intramolecular hydrogen bond reduces the availability of the OH group for intermolecular hydrogen bonding so the *ortho* compound has a lower boiling point.


strong intramolecular H bond

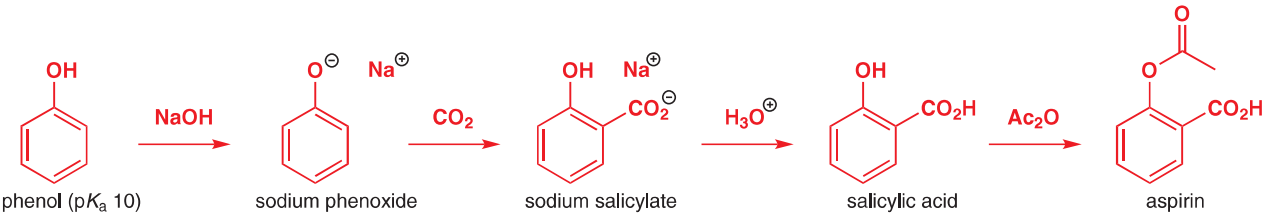
Paracetamol from a phenol

The remaining *para*-nitrophenol is used in the manufacture of the painkiller paracetamol (also known as acetaminophen).

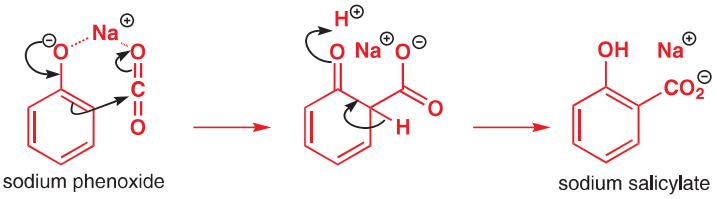


The phenoxide ion is even more reactive towards electrophilic attack than phenol. It manages to react with such weak electrophiles as carbon dioxide. This reaction, known as the **Kolbe–Schmitt process**, is used industrially to prepare salicylic acid (2-hydroxybenzoic acid), a precursor in making aspirin.

■ Salicylic acid is 2-hydroxybenzoic acid and is named after the willow trees (genus *Salix*) from which it was first isolated.

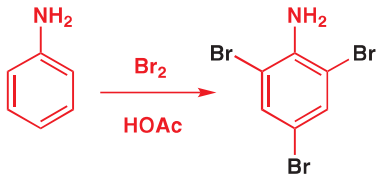


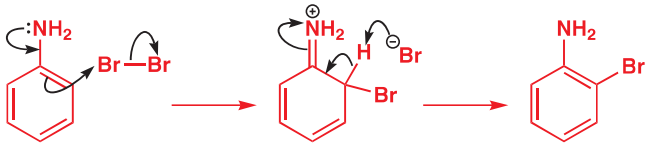
The O^- substituent is *ortho, para*-directing but the electrophilic substitution step with CO_2 gives mostly the *ortho* product. There must be some coordination between the sodium ion and the oxygen atoms of both the phenoxide and CO_2 that delivers the electrophile to the *ortho* position.



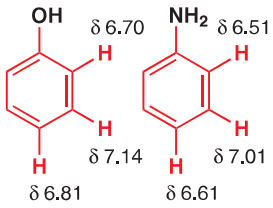
A nitrogen lone pair activates even more strongly

Aniline (phenylamine) is even more reactive towards electrophiles than phenols, phenyl ethers, or phenoxide ions. Because nitrogen is less electronegative than oxygen, the lone pair is higher in energy and so even more available to interact with the π system than is the lone pair on oxygen. Reaction of aniline with bromine is very vigorous and rapidly gives 2,4,6-tribromoaniline. The mechanism is very similar to the bromination of phenol so we show only one *ortho* substitution to remind you of how it goes.



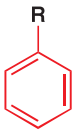


^{1}H NMR shifts in phenol and aniline



The ^{1}H NMR spectrum of aniline supports the increased electron density in the π system—the aromatic protons are even less deshielded than those of phenol as a result.

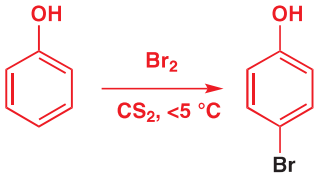
Just how good nitrogen is in donating electrons into the π system is shown by comparing the relative rates for the bromination of benzene, methoxybenzene (anisole), and *N,N*-dimethylaniline.

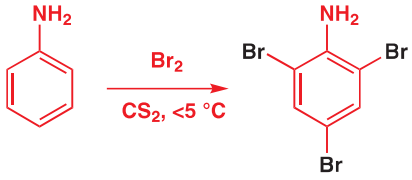


Compound	R	Relative rate of bromination
benzene	H	1
methoxybenzene (anisole)	OMe	10^9
N,N-dimethylaniline	NMe_2	10^{14}

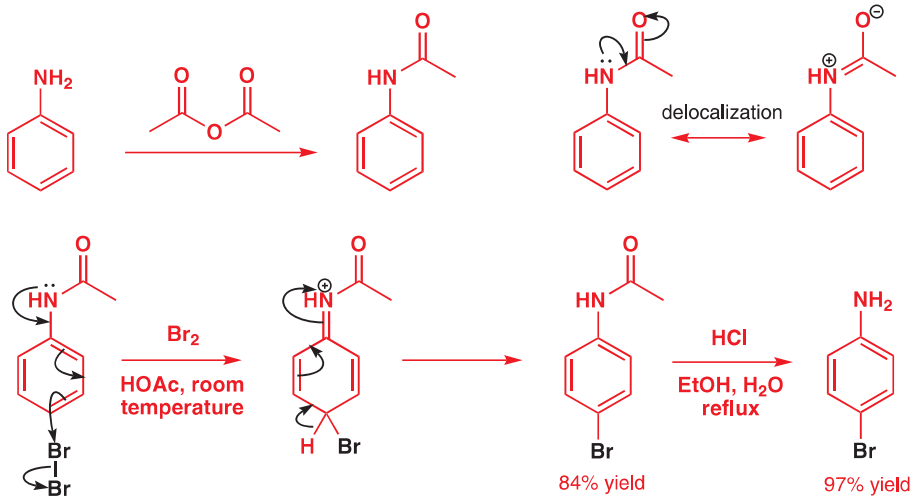
Making aromatic amines less reactive

The high reactivity of aniline can actually be a problem. Suppose we wanted to put just one bromine atom onto the ring. With phenol, this is possible (p. 480)—if bromine is added slowly to a solution of phenol in carbon disulfide solution and the temperature is kept below 5 °C, the main product is *para*-bromophenol. Not so if aniline is used—the main product is the triply substituted product.





How then could we prevent oversubstitution from occurring? What we need is a way to make aniline less reactive by preventing the nitrogen lone pair from interacting so strongly with the π system of the ring. Fortunately, it is very simple to do this. In Chapter 8 (p. 175) we saw how the nitrogen atom in an amide is much less basic than a normal amine because it is conjugated with the carbonyl group. This is the strategy that we will use here—simply acylate the amine to form an amide. The lone pair electrons on the nitrogen atom of the amide are conjugated with the carbonyl group as usual but their delocalization into the benzene ring is weaker than in the amine. The amide nitrogen donates less electron density into the ring, so the electrophilic aromatic substitution is more controlled. The lone pair is still there, but its power is tamed. Reaction still occurs in the *ortho* and *para* positions (mainly *para*) but it occurs once only.



After the reaction, the amide can be hydrolysed (here, with aqueous acid) back to the amine.

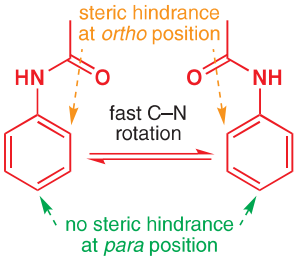
■ Amides formed by the acylation of anilines are sometimes called *anilides*. If they are acetyl derivatives they are called *acetanilides*. We shall not use these names but you may meet them elsewhere.

● **Anilines react rapidly with electrophiles to give polysubstituted products. Their amide derivatives react in a more controlled manner to give *para*-substituted products.**

Selectivity between *ortho* and *para* positions

Phenols and anilines react in the *ortho* and/or *para* positions for electronic reasons. These are the most important effects in deciding where an electrophilic substitution will occur on a benzene ring. When it comes to choosing between *ortho* and *para* positions we need to consider steric effects as well. You will have noticed that we have seen one *ortho* selective reaction—the formation of salicylic acid from phenol—and several *para* selective reactions such as the bromination of an amide just discussed.

If the reactions occurred merely statistically, we should expect twice as much *ortho* as *para* product because there are two *ortho* positions. However, we should also expect more steric hindrance in *ortho* substitution since the new substituent must sit closely beside the one already there. With large substituents, such as the amide, steric hindrance will be significant and it is not surprising that we get more *para* product.

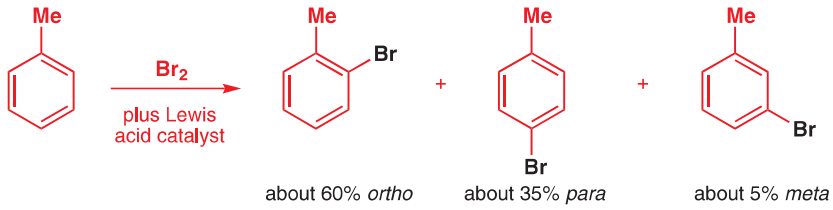


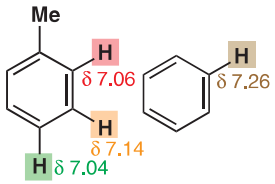
There is another effect that decreases the amount of *ortho* substitution, and that is the *inductive* electron-withdrawing effect of an electronegative substituent. As you've seen, oxygen and nitrogen, although they are electronegative, activate the ring towards attack by donating π electron density from their lone pairs. At the same time, the C–O or C–N σ bond is polarized back towards the O or N atom—in other words, they *donate* electron density to the π system but *withdraw* electron density from the σ framework. This is *inductive* electron withdrawal—it affects the atoms nearest the O or N atom the most, and has the effect of decreasing the likelihood that attack will happen in the *ortho* positions.

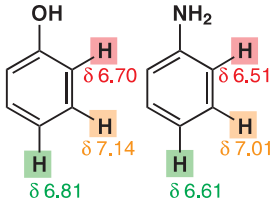
➡ Inductive effects were introduced on p. 135.

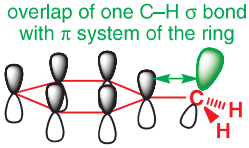
Alkyl benzenes also react at the *ortho* and *para* positions

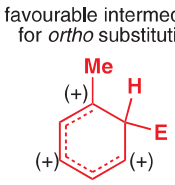
This is what happens when toluene (methylbenzene) meets bromine:







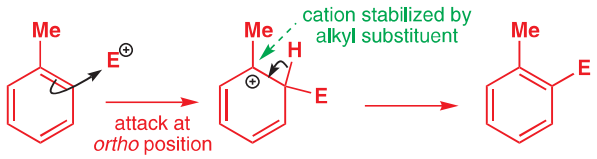




Toluene reacts 4000 times faster than benzene (this may sound like a lot, but the rate constant for *N,N*-dimethylaniline is 10^{14} times greater), and the electrophile attacks mostly the *ortho* and *para* positions. These two observations together suggest that the methyl groups may be increasing the electron density in the π system of the benzene ring, specifically in the *ortho* and *para* positions, rather like a weaker version of an OR group. The ^{1}H NMR chemical shifts for toluene (see margin) do suggest that there is slightly more electron density in the *para* position than in the *meta* positions. All the shifts are smaller than those of benzene (but not by much) and the shielding is much less than it is in phenols or anilines.

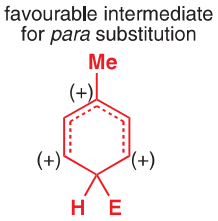
The methyl group donates electrons weakly by conjugation. In phenol, a lone pair on oxygen is conjugated with the π system. In toluene there is no lone pair but one of the C–H σ bonds can still interact with the π system in a similar way. This interaction is known as σ **conjugation**. Just as the conjugation of the oxygen lone pair increases the electron density at the *ortho* and *para* positions, so too does σ conjugation, but far less so.

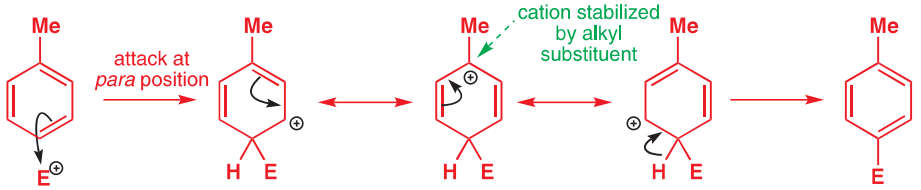
σ conjugation also means toluene's π electrons—its HOMO—become slightly higher in energy than those of benzene. It is best to regard alkyl benzenes as rather reactive benzenes, and to draw mechanisms using their π electrons as the nucleophile, like this:



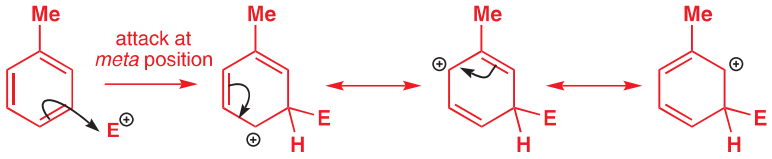
Electrophilic attack occurs on alkyl benzenes so that the positive charge ends up on the carbon bearing the alkyl group. This carbon is tertiary, making the cation there more stable. This condition is fulfilled if toluene is attacked at the *ortho* position, as shown above, but also at the *para* position, because in both cases the positive charge is delocalized onto the same three carbons atoms.

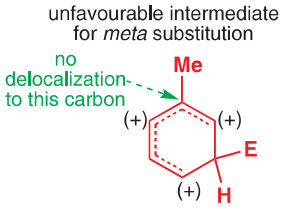
■ You are familiar with the idea that more substituted cations are more stable (Chapter 15, p. 335) and that more substituted alkenes are more stable (Chapter 17, p. 394). The effect we are discussing here is the same.





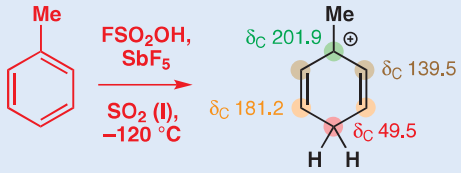
If, on the other hand, the electrophile were to attack at the *meta* position, the charge would end up delocalized over three carbon atoms, none of which are tertiary, so no stabilization by the alkyl group is possible. The situation is no worse than that of benzene, but given that toluene reacts some 10^3 times faster than benzene at the *ortho* and *para* positions these reactions win out. Nonetheless, unlike phenol, toluene does give trace amounts of *meta*-substituted products.





Protonating toluene with a superacid

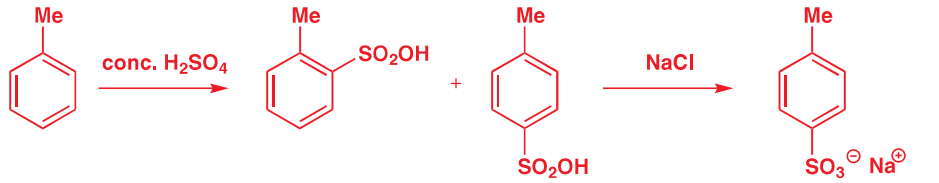
On p. 475 we described how to observe the cationic intermediate in electrophilic substitution reactions of benzene by protonation in an NMR tube using a superacid. In benzene the cation which forms is symmetrical. Doing the same experiment with toluene leads to protonation in the *para* position.



The *ortho* (to the Me group) carbon has a shift (δ 139.5) only 10 ppm greater than that of benzene (δ 129.7) but the *ipso* and *meta* carbons have the very large shifts that we associate with cations. The charge is mainly delocalized to these carbons but the greatest charge is at the *ipso* carbon.

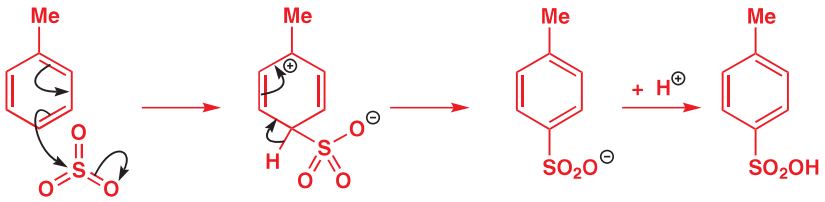
The sulfonation of toluene

Direct sulfonation of toluene with concentrated sulfuric acid gives a mixture of *ortho* and *para* sulfonic acids from which about 40% of toluene *para* sulfonic acid can be isolated as the sodium salt.



about 40% *para* product
isolated as sodium salt

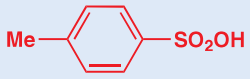
We shall use SO_3 as the electrophile in this case and draw the intermediate with the charge at the *ipso* carbon to show the stabilization from the methyl group.



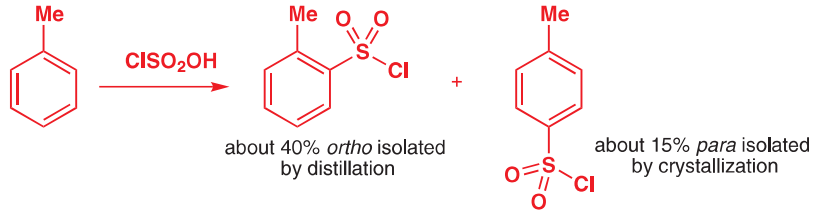
You met the *para*-toluenesulfonate group (tosylate, OTs) as an important leaving group if you want to carry out an S_N2 reaction on an alcohol (Chapter 15, p. 349) and the acid chloride (tosyl chloride, TsCl) needed to make tosylates can be made from the acid in the usual way (p. 215) with PCl_5. It can also be made directly from toluene by sulfonation with chlorosulfonic acid $ClSO_2OH$. This reaction favours the *ortho* sulfonyl chloride, which is isolated by distillation.

Toluenesulfonic acid

The product *para*-toluenesulfonic acid is important as a convenient solid acid, useful when a strong acid is needed to catalyse a reaction. Being much more easily handled than oily and corrosive sulfuric acid or syrupy phosphoric acid, it is useful for acetal formation (Chapter 11) and eliminations by the E1 mechanism on alcohols (Chapter 17). It also gets called tosic acid, TsOH, or PTSA, and its sulfonyl chloride derivative is tosyl chloride, TsCl (Chapter 15).

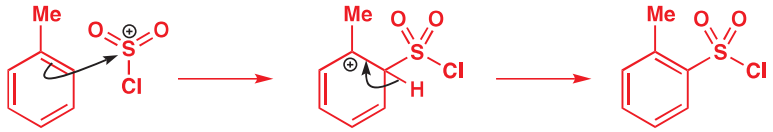


p-toluenesulfonic acid
= tosic acid = TsOH = PTSA

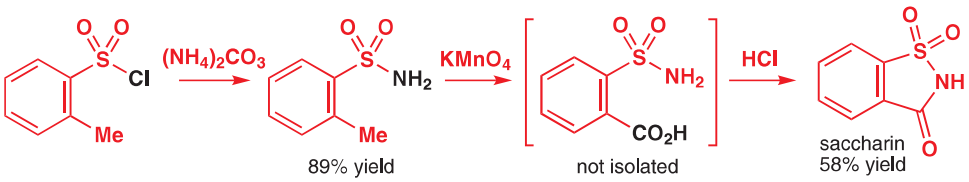


No other acid is needed because chlorosulfonic acid is a very strong acid indeed and protonates itself to give the electrophile. This explains why OH is the leaving group rather than Cl and why chlorosulfonation rather than sulfonation is the result.

In drawing the mechanism we can again get the positive charge onto the tertiary *ipso* atom. No treatment with NaCl is needed in this reaction as the major product (the *ortho* acid chloride) is isolated by distillation.



It is fortunate that the *ortho* acid chloride is the major product in the chlorosulfonation because it is needed in the synthesis of saccharin, the first of the non-fattening sweeteners. The formation of the sulfonamide is like that of an ordinary amide, but the oxidation of the methyl group with potassium permanganate is probably new to you. It's a rather vigorous reaction, but one which very usefully turns toluene derivatives into benzoic acid derivatives.



■ The preference for *para* product in the sulfonation and *ortho* product in the chlorosulfonation is the first hint that sulfonation is reversible. This point is discussed, and exploited, in Chapter 24 (p. 566).

■ As you will see in the next section, the substitution reactions of benzoic acid derivatives show different selectivity from the substitution reactions of toluene itself.

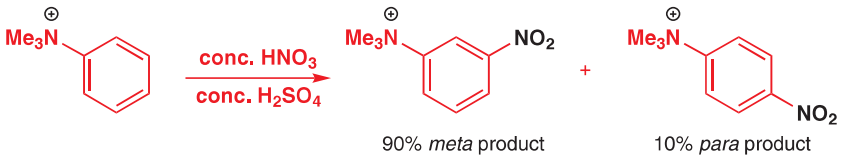
● **Alkylbenzenes react with electrophiles faster than benzene and give mixtures of *ortho*- and *para*-substituted products.**

Electron-withdrawing substituents give *meta* products

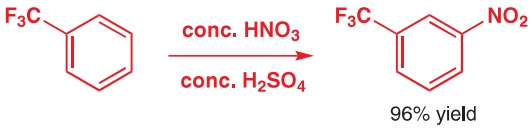
So far, all of the substituted benzene rings we have considered have carried substituents capable of donating electron density to the ring: despite being electronegative atoms, oxygen and nitrogen have lone pairs which conjugate with the ring's π system; a similar but weaker effect results from σ conjugation from a methyl group. Two consequences arise from these substituents: the ring becomes more reactive than benzene, and substitution takes place in the *ortho* and *para* positions.

So what happens with groups which pull electron density away from the ring? Such a group is the trimethylammonium substituent: the nitrogen is electronegative but unlike in aniline this electronegativity is not offset by donation of a lone pair—the nitrogen is tetrahedral and no longer has one to donate. Nitration of the phenyltrimethyl ammonium ion yields mainly

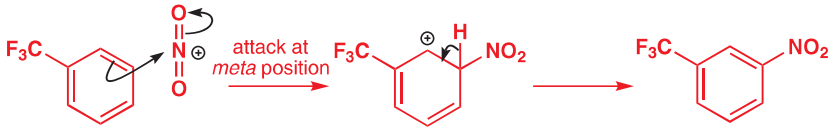
the *meta* product. And it does so slowly too—this nitration proceeds about 10^7 times more slowly than that of benzene.



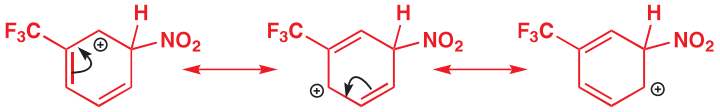
The same thing happens with the CF_3 group. The three very electronegative fluorine atoms polarize the C–F bonds so much that the Ar–C bond is polarized too. Nitration of trifluoromethylbenzene gives a nearly quantitative yield of *meta* nitro compound.



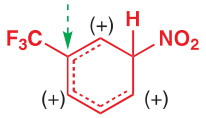
Draw the mechanism for this reaction and you see the reason for the switch to *meta* selectivity.



The intermediate cation is again delocalized over three carbons, but importantly none of these carbons is the one next to the CF_3 group.

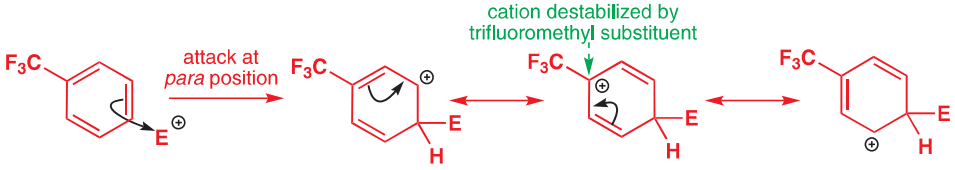


charge can avoid being delocalized to this carbon

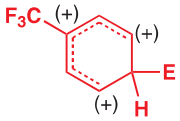


favourable intermediate for *meta* substitution

If, on the other hand, the electrophile were to attack the *ortho* or *para* position (the hypothetical reaction *para* to CF_3 is shown below) then the carbon next to CF_3 would *have* to carry a positive charge, which would be destabilized by the electron withdrawal, making this a high-energy intermediate.



unfavourable intermediate for *para* substitution



Think of it this way: the electron-deficient ring would really rather not react with an electrophile (hence the slower rate) but if it has to (because the electrophile is so reactive) then it takes the least bad course of keeping the positive charge away from the electron-withdrawing groups—and that means *meta* substitution.

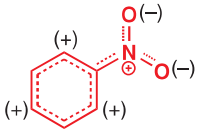
Some substituents withdraw electrons by conjugation

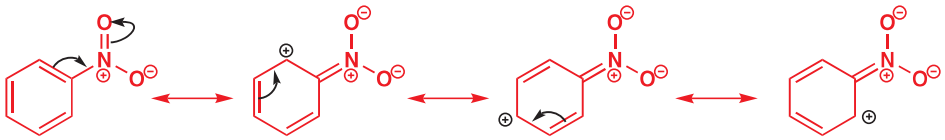
Aromatic nitration is important because it is a convenient way of adding a nitrogen substituent to the ring and because it stops cleanly after one nitro group has been added. Double nitration of benzene is possible but stronger conditions must be used—fuming nitric acid instead of normal concentrated nitric acid—and the mixture must be refluxed at around 100 °C.

75% yield *meta*-dinitrobenzene

The second nitro group is introduced *meta* to the first: evidently the nitro group is deactivating and *meta*-directing.

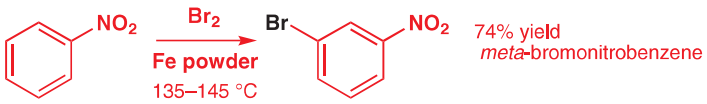
The nitro group is conjugated with the π system of the benzene ring and is strongly electron *withdrawing*—and it withdraws electrons specifically from the *ortho* and *para* positions. We can use curly arrows to show this:



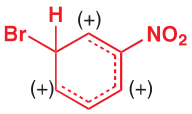


The nitro group withdraws electron density from the π system of the ring thereby making the ring less reactive towards an electrophile. Since more electron density is removed from the *ortho* and *para* positions, the least electron-deficient position is the *meta* position. Hence the nitro group is *meta* directing. In the nitration of benzene, it is much harder to nitrate a second time and, if we insist, the second nitro group goes in *meta* to the first.

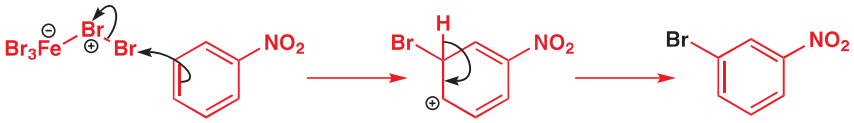
Other reactions go the same way: bromination of nitrobenzene gives *meta*-bromonitrobenzene in good yield. The combination of bromine and iron powder provides the necessary Lewis acid catalyst ($FeBr_3$) while the high temperature needed for this unfavourable reaction is easily achieved as the boiling point of nitrobenzene is over 200 °C.



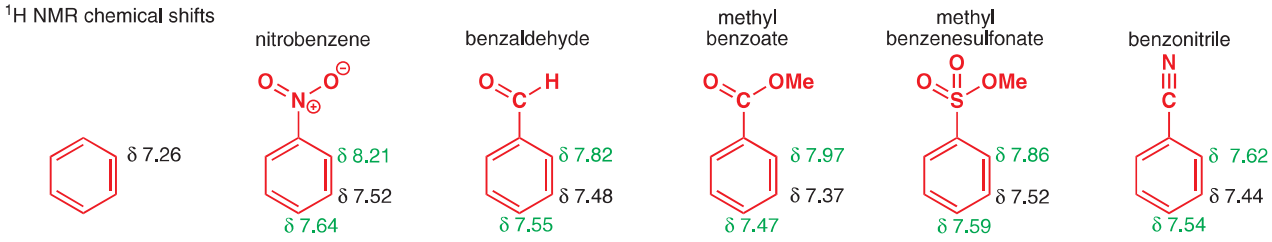
In drawing the mechanism it is best to draw the intermediate and to emphasize that the positive charge must not be delocalized to the carbon atom bearing the nitro group.



delocalization of intermediate cation



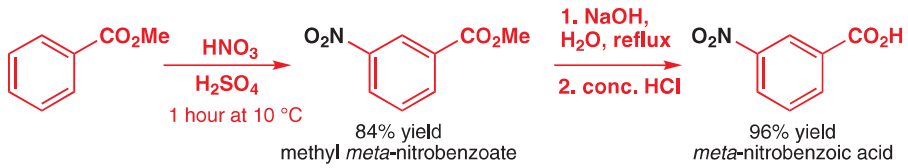
Nitro is just one of a number of groups that are also deactivating towards electrophiles and *meta* directing because of electron withdrawal by conjugation. Others include carbonyl groups (aldehydes, ketones, esters, etc.), nitriles, and sulfonates. The ^{1}H NMR shifts of rings carrying these substituents confirm that they remove electrons principally from the *ortho* and *para* positions.



Points to note:

- Each of the compounds contains the unit Ph–X=Y, where Y is an electronegative element, usually oxygen.
- In each compound, *all* the protons have larger chemical shifts than benzene because the electron density at carbon is less.
- The protons in the *meta* position have the smallest shift and so the greatest electron density.

Nitro is the most electron-withdrawing of these groups and some of the other compounds are nearly as reactive (in the *meta* position, of course) as benzene itself. It is easy, for example, to nitrate methyl benzoate and the *m*-nitro ester can then be hydrolysed to *meta*-nitrobenzoic acid very easily.

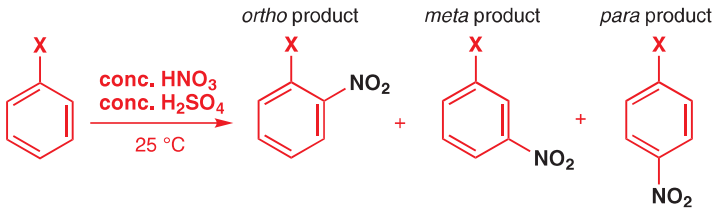


● **Electron-withdrawing groups make aromatic rings more reluctant to undergo electrophilic substitution, but when they do react, they react in the *meta* position.**

One group of substituents remains and they are slightly odd. They are *ortho, para*-directing but they are also *deactivating*. They are the halogens.

Halogens show evidence of both electron withdrawal and donation

So far we have steered clear of the reactions of halogenated derivatives of benzene. Before we explain their reactions, have a look at the table, which shows the rates of nitration of fluoro, chloro, bromo, and iodobenzene relative to benzene itself, and also gives an indication of the products formed in each case.



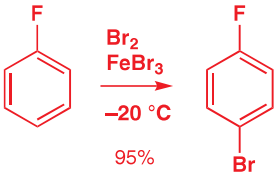
Compound	Products formed (%) *ortho*	*meta*	*para*	Nitration rate (relative to benzene)
PhF	13	0.6	86	0.18
PhCl	35	0.9	64	0.064
PhBr	43	0.9	56	0.060
PhI	45	1.3	54	0.12

We'll come back to this table a few times in the next page or so, but the first thing to note is that **all the halobenzenes react more slowly than benzene itself**. Evidently, electron withdrawal by the electronegative halogen deactivates the ring towards attack. But the second thing that should strike you is that, unlike the deactivating groups we have just been discussing, **halogens are *ortho, para* directing**—very few *meta*-nitrated products are formed.

The only way this makes sense is if there are two opposing effects: electron donation by conjugation and electron withdrawal by induction. The halogen has three lone pairs, one of which may conjugate with the ring just like in phenol or aniline. Yet the conjugation is much less good than in phenol or aniline, for one of two reasons. When Cl, Br, or I is the substituent, the problem is size: the 2p orbitals from the carbon atoms overlap poorly with the bigger p orbitals from the halogen (3p for chlorine, 4p for bromine, and 5p for iodine). This size mismatch is clearly illustrated by comparing the reactivities of aniline and chlorobenzene:

chlorine and nitrogen have approximately the same electronegativity, but aniline is much more reactive than chlorobenzene because of the better overlap between the carbon and nitrogen 2p orbitals. Fluorine 2p orbitals are the right size to overlap well with the carbon 2p orbitals, but now there is another problem: the orbitals of fluorine are much lower in energy than the orbitals of carbon since fluorine is so electronegative.

So, all four halogens are less good at donating electrons to the ring than an OH or NH_2 group, but not only are the halobenzenes less reactive than phenol or aniline, they are even less reactive than benzene itself. Now, when we looked at aniline and phenol, we didn't worry about any electron withdrawal by induction, even though both oxygen and nitrogen are of course rather electronegative. Electron donation from their N and O lone pairs is evidently much more important. But with the conjugation in the halobenzenes already weak, inductive electron withdrawal takes over as the dominant factor in determining reactivity.



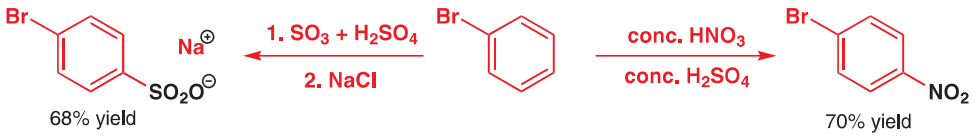
With all this in mind, how would you expect fluorobenzene to react? Most electron density is removed first from the *ortho* positions by induction, then from the *meta* positions, and then from the *para* position. Any conjugation of the lone pairs on fluorine with the π system would increase the electron density in the *ortho* and *para* positions. Both effects favour the *para* position and this is where most substitution occurs. But is the ring more or less reactive than benzene? This is hard to say and the honest answer is that sometimes fluorobenzene is more reactive in the *para* position than benzene (for example, in proton exchange and in acetylation—see later) and sometimes it is less reactive than benzene (for example, in nitration, as shown by the table above). In all cases, fluorobenzene is significantly more reactive than the other halobenzenes. We appreciate that this is a rather surprising conclusion, but the evidence supports it. For example, fluorobenzene reacts with bromine and an iron catalyst (it does need a catalyst: it is not as reactive as phenol) at only –20 °C to give the *para*-bromo derivative.

Let's now look back in bit more detail at the table above. We can now also explain two other features of the results:

We mentioned inductive effects as a factor controlling *ortho* vs *para* reactivity on p. 483.

- The percentage of the *ortho* product increases from fluorobenzene to iodobenzene. We might have expected the amount to decrease as the size of the halide increases because of increased steric hindrance at the *ortho* position but this is clearly not the case. Instead the greater inductive effect of the more electronegative atoms (F, Cl) withdraws electron density mostly from the *ortho* positions, lessening their reactivity.
- The rates of the reactions fall into two pairs and follow a 'U-shaped' sequence: fluorobenzene nitrates most quickly, followed closely by iodobenzene; chloro-, and bromobenzene nitrate at around half these rates. Chlorine and bromine suffer because both are quite electronegative and neither has good lone pair overlap: in fluorine, overlap is good; in iodine, electronegativity is much less.

In practical terms, it is usually possible to get high yields of *para* products from electrophilic substitution reactions of halobenzenes. Both nitration and sulfonation of bromobenzene give enough material to make the synthesis worthwhile. Although mixtures of products are always bad in a synthesis, electrophilic aromatic substitution is usually simple to carry out on a large enough scale to make separation of the major product, ideally by crystallization, a workable method. A 68% yield of sodium *p*-bromobenzenesulfonate can be achieved by recrystallization of the sodium salt from water and a 70% yield of *p*-bromonitrobenzene by separation from the *ortho* isomer by recrystallization from EtOH.



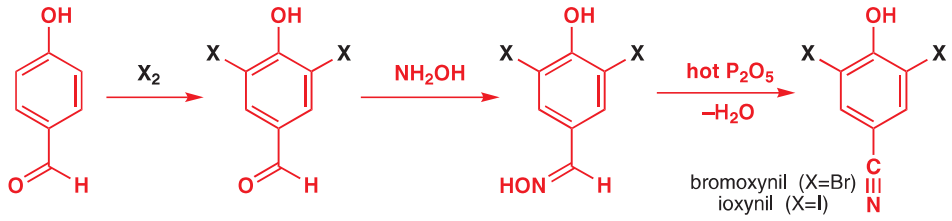
● **Summary of directing and activating effects**

Now we can summarize the stage we have reached in terms of *activation* and *direction*.

Electronic effect	Example	Activation	Direction
donation by conjugation	$-NR_2$, $-OR$	very activating	*ortho*, *para* only
donation by inductive effect	alkyl	activating	mostly *ortho*, *para* but some *meta*
donation by conjugation *and* withdrawal by inductive effect	F, Cl, Br, I	deactivating	*ortho* and (mostly) *para*
withdrawal by inductive effect	$-CF_3$, $-NR_2^+$	deactivating	*meta* only
withdrawal by conjugation	$-NO_2$, $-CN$, $-COR$, $-SO_3R$	very deactivating	*meta* only

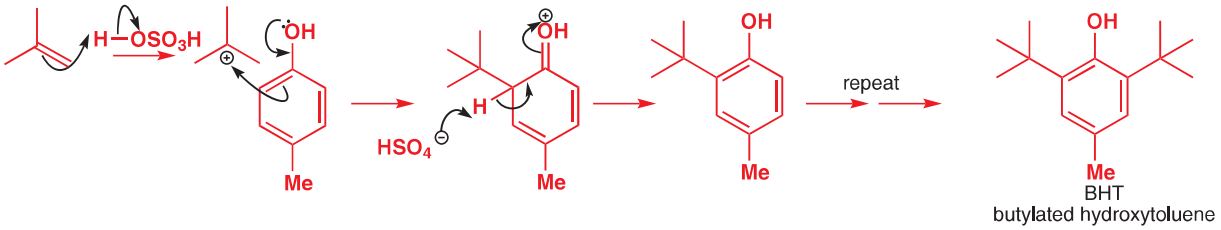
Two or more substituents may cooperate or compete

The directing effects of two or more substituents can work with or against one another. Bromoxynil and ioxynil are contact herbicides especially used in spring cereals to control weeds resistant to other weedkillers, and both are synthesized from *p*-hydroxybenzaldehyde by double halogenation. The aldehyde directs *meta* and the OH group directs *ortho*: both effects work together to promote bromination or iodination at the same two positions.



■ The reaction with NH_2OH is the formation of an oxime from the aldehyde and hydroxylamine and was dealt with in Chapter 11. The reaction with P_2O_5 is a dehydration—phosphorus is used to form the nitrile by removing water from the oxime.

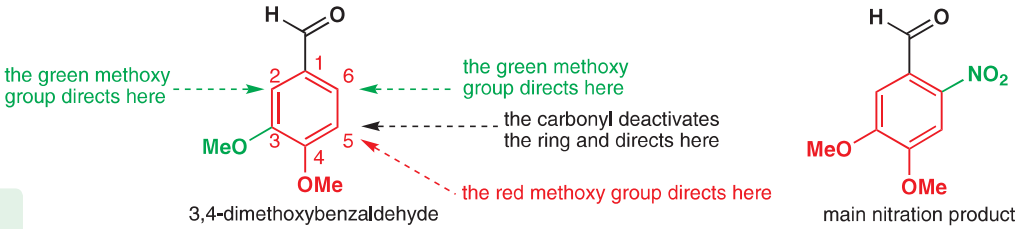
In other cases substituents compete by directing to different positions. The antioxidant BHT (p. 58) is made from 4-methylphenol (known as *p*-cresol) by a Friedel–Crafts alkylation. Usually, both the methyl and OH groups are *ortho, para* directors. The *para* positions are obviously both blocked, but the positions *ortho* to each of the groups are different. Since the –OH group is much more powerfully directing than the methyl group it 'wins' and directs the electrophile (a *t*-butyl cation) *ortho* to itself.



In this case the *t*-butyl cation is made from the alkene and protic acid; alternative reagents would be *t*-butanol with protic acid or *t*-butyl chloride with $AlCl_3$.

Even a 'watered-down' activating group like the amide –NHCOMe, which provides an extra pair of electrons, will 'win' over a deactivating group or an activating alkyl group. Bromination of this amide goes *ortho* to the –NHCOMe group but *meta* to the methyl group.

When looking at any compound where competition is an issue it is sensible to consider electronic effects first and then steric effects. For electronic effects, in general, any activating effects are more important than deactivating ones. For example, the aldehyde below has three groups—two methoxy groups that direct *ortho* and *para* and an aldehyde that directs *meta*.



■ If you are in a bar and someone picks a fight with you, it is no help that an inoffensive little man in the corner would prefer not to pick a fight. Aggressive –NR_2 and –OR groups are not much affected by inoffensive –Br or carbonyl groups in another corner of the molecule.

Despite the fact that the aldehyde group withdraws electron density from positions 2 and 6, C6 is still the position for nitration. The activating methoxy groups dominate electronically and the choice is really between C2, C5, and C6. Now consider steric factors: reaction at C2 or C5 would lead to three adjacent substituents. Substitution occurs at position 6.

Some problems and some opportunities

You've seen plenty of electrophilic aromatic substitution reactions in this chapter that are reliable and widely used—bromination and nitration, for example. But others pose problems:

- Friedel–Crafts alkylation works only when the intermediate cation is stable, so how do we add an *n*-alkyl chain to an aromatic ring?
- There is no good way of introducing an oxygen electrophile to an aromatic ring, so how do we make Ar–O bonds?
- Electron-donating groups always direct *ortho, para*, so how do we put in a group *meta* to, for example, an amino group?

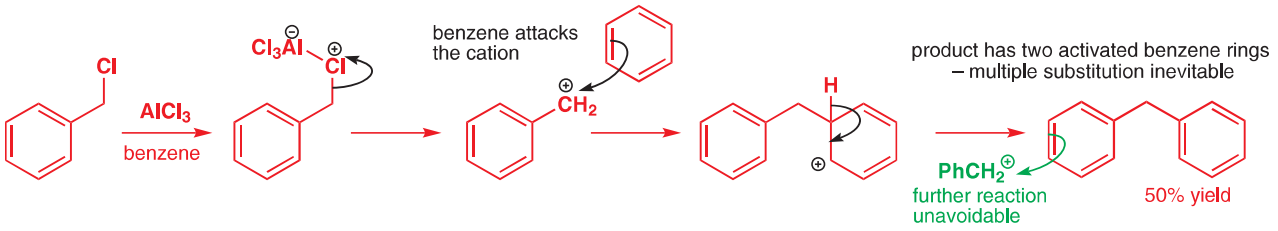
We will consider some answers to these questions in this last section of this chapter.

A closer look at Friedel–Crafts chemistry

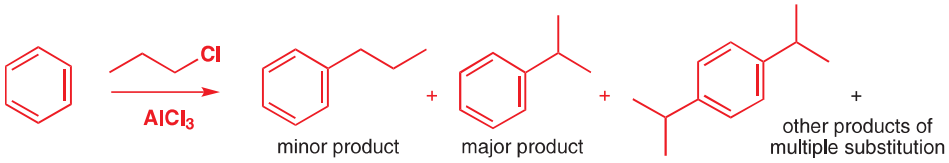
Reactions such as nitration and sulfonation add a very deactivating substituent. They usually stop cleanly after a single substitution unless there is also a strongly activating substituent. Even then it may be possible to stop after a single substitution. Weakly electron-withdrawing substituents like the halogens can be added once, but multiple substitution is common when the starting arene carries strongly activating substituents like OH and NH_2.

Two reasons to avoid a Friedel–Crafts alkylation

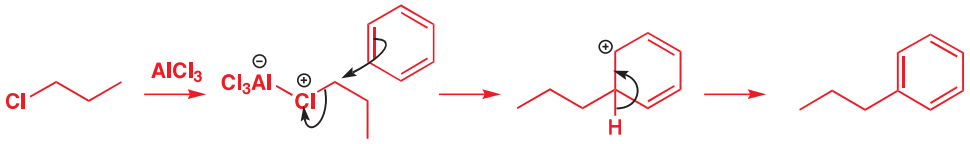
When electron-donating substituents are added, multiple substitution is always a threat. The principal reaction where multiple substitution is a genuine problem is the Friedel–Crafts alkylation reaction. Here's an example: preparation of diphenylmethane from benzene and benzyl chloride is a useful reaction but the product has two benzene rings, each more reactive than benzene itself. A 50% yield is the best we can do and that requires a large excess of benzene to ensure that it competes successfully for the reagent with the reactive, electron-rich product.



Multiple substitution is just one of the potential pitfalls of Friedel–Crafts alkylations. The other is important to be aware of too: **Friedel–Crafts alkylations work well only with stable cations.** This is what happens when we try a Friedel–Crafts reaction with *n*-propyl chloride.



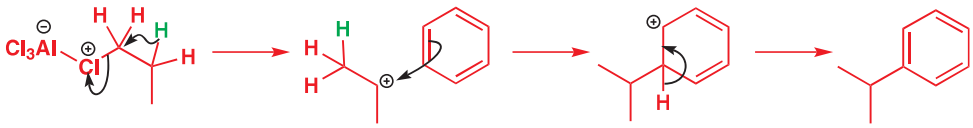
Recall from Chapter 15 that primary halides don't form cations easily, so the Friedel–Crafts reaction with *n*-propyl chloride has to go via an S_N2 mechanism.



So where does the major product of the reaction come from? The three carbons are arranged not as an *n*-propyl group but as an *iso*-propyl group: a *rearrangement* has occurred. This is the mechanism:

➡ We'll deal with rearrangements in much greater detail in Chapter 36.

rearrangement (migration of green H) leads to isopropyl benzene

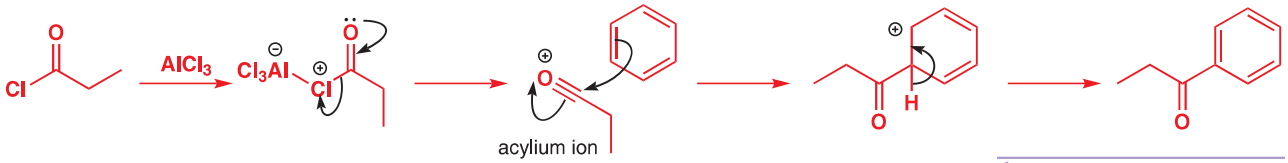


The green hydrogen migrates to allow a secondary rather than a primary alkyl cation to be formed, and *iso*-propylbenzene results. This leaves us with a problem: how can you add primary alkyl groups to benzene rings?

The solution: use Friedel–Crafts acylation instead

We can kill two birds with one stone here: both problems common to the Friedel–Crafts alkylation are solved when the acylation is used instead. Firstly, the product of the acylation is a ketone: the reaction introduces a deactivating, electron-withdrawing, conjugating carbonyl group to the ring, so the product is *less* reactive than the starting material. Reaction will stop cleanly after one acylation. Here's benzene reacting with propionyl chloride.

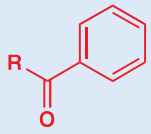
➡ We introduced the Friedel–Crafts acylation on p. 477.



Interactive mechanism for Friedel–Crafts acylation

If we want the ketone then all well and good. But a simple reduction also allows us to get the alkylated product—this compound (trivially called propiophenone) is reduced to

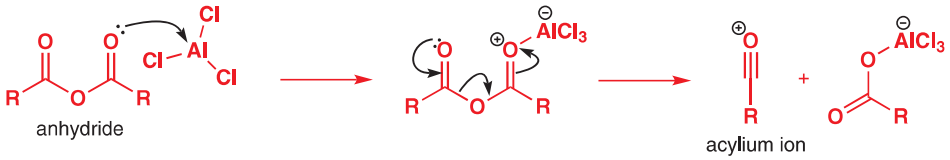
You may also meet the trivial names acetophenone and benzophenone.



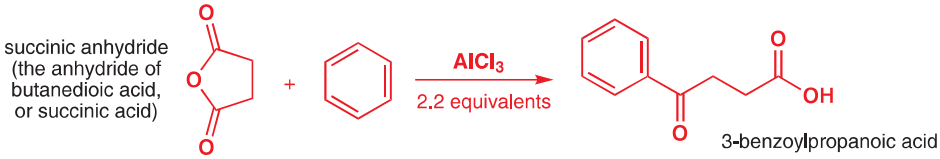
R = Me: acetophenone
R = Ph: benzophenone

propylbenzene using any of a number of reduction methods, for example zinc amalgam in hydrochloric acid.

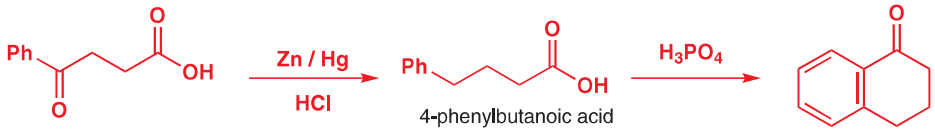
The reduction of a Friedel–Crafts acylation product like this always gives an *n*-alkylbenzene, exactly the sort of compound that causes the problems in Friedel–Crafts alkylation. Friedel–Crafts acylations also work well when anhydrides are used in the place of acid chlorides. The acylium ion is formed in the same way:



If a cyclic anhydride is used, the product is a keto-acid.



Reduction of the ketone can give a simpler carboxylic acid, but we can go one step further and do another acylation—because the reaction is intramolecular, it goes even with just a strong acid (phosphoric acid): the strong acid makes the OH into a good leaving group (water) and the acylium ion is again an intermediate.



● The advantages of acylation over alkylation

Two problems in Friedel–Crafts alkylation do not arise with acylation.

- **The acyl group in the product withdraws electrons from the π system, making multiple substitutions harder. Indeed, if the ring is too deactivated to start off with, Friedel–Crafts acylation may not be possible at all—nitrobenzene is inert to Friedel–Crafts acylation and is often used as a solvent for these reactions.**
- **Rearrangements are also no longer a problem because the electrophile, the acylium cation, is already relatively stable.**
- **The acyl groups of the products can be reduced to primary alkyl groups, which are impossible to introduce cleanly by Friedel–Crafts alkylation.**

Exploiting the chemistry of the nitro group

The nitro group is remarkably useful in a number of ways:

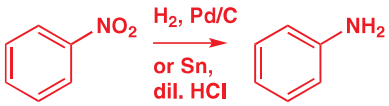
- It is easy to introduce by nitration chemistry (p. 476).
- Unlike most N- or O-based functional groups, it is a *meta* director (p. 488).
- It can be reduced to an amino group.
- It can be replaced with other substituents using diazonium chemistry.

➡ More reductions like this—which get rid of the carbonyl group completely—are discussed in Chapter 23.

■ Notice how much $AlCl_3$ is needed: in Friedel–Crafts alkylations using an alkyl chloride, the Lewis acid is used in catalytic quantities. In an acylation, however, the Lewis acid can also complex to any oxygen atoms present, to the carbonyl in the product, for example. As a result, in acylation reactions more Lewis acid is required—just over one equivalent per carbonyl group.

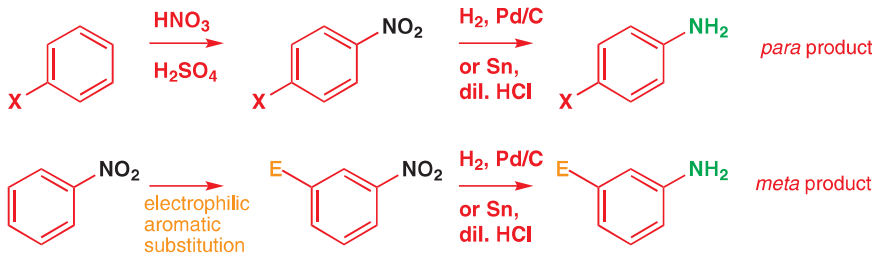
■ Make sure you can see how this reaction works.

You have met the first two of these features, but the last two may be new to you. An aromatic nitro group is easy to turn into an amino group—a number of reagents will do this, but the most common are tin in dilute HCl or hydrogenation with a palladium catalyst supported on charcoal (written as Pd/C).

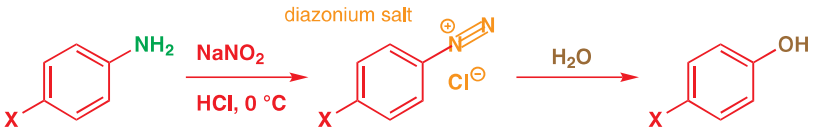


➡ There is more on these selective reducing agents in Chapter 23.

This simple transformation is extremely important because it turns the *meta*-directing nitro group into an *ortho, para*-directing amino group (although as you saw on p. 483, the amino group may need 'taming' to make its reactivity useful). The sequence of nitration–reduction allows us to introduce a useful NH_2^+ equivalent into an aromatic molecule, and can let us make otherwise difficult-to-form *meta*-substituted amino compounds.



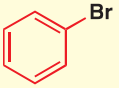
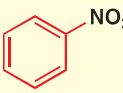
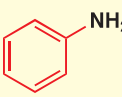
The reduction to an amino group also opens up the possibility of replacing the nitrogen substituent completely, by converting it first to a diazonium group. Treatment of an amine with nitrous acid converts it to an unstable diazonium salt, whose mechanism of formation and chemistry we will discuss in the next chapter. Not surprisingly, diazonium salts very readily lose nitrogen gas, and this substitution of N_2 by a nucleophile opens yet more opportunities to compounds derived from nitrobenzene derivatives. It also involves *nucleophilic* substitution at the aromatic ring, which forms the subject of the next chapter.



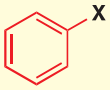
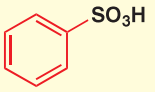
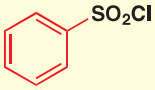
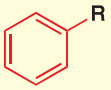
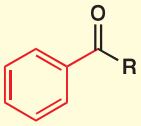
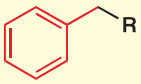
➡ Diazonium salts are discussed on p. 520. Chapter 40 introduces the idea of using transition metals in the formation of bonds to aromatic rings, while Chapter 24 revisits the methods available when control of regiochemistry (i.e. *ortho*, *meta*, or *para* selectivity) is needed.

Summary

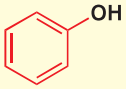
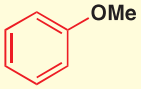
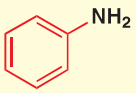
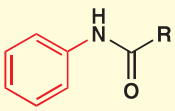
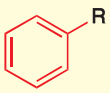
● Products from electrophilic substitution reactions

Product	Reaction	Reagents	Page
	bromination	Br_2 and Lewis acid, e.g. $AlCl_3$, $FeBr_3$, Fe powder	474
	nitration	$HNO_3 + H_2SO_4$	476
	reduction of nitro compounds	From $ArNO_2$: Sn, HCl or H_2, Pd/C	495

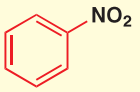
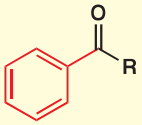
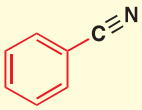
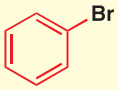
(*continued*) Products from electrophilic substitution reactions

Product	Reaction	Reagents	Page
	substitution of diazonium salts	From $ArNH_2$: 1. $NaNO_2$, HCl; 2. X^-	See Chapter 22, p. 520
X = OH, CN, Br, I...			
	sulfonation	concentrated H_2SO_4 or H_2SO_4 + SO_3 (oleum)	476
	chlorosulfonation	$ClSO_3H$	486
	Friedel–Crafts alkylation	RX + Lewis acid, usually $AlCl_3$	477
	Friedel–Crafts acylation	RCOCl + Lewis acid, usually $AlCl_3$	477
	Friedel–Crafts acylation and reduction	From ArCOR: Zn/Hg, HCl	493

● Reactions of aromatic compounds in this chapter

Starting material	Example	Activating/deactivating	Directing effect	Page
benzene, PhH		–	–	474
phenol, PhOH		activating	*ortho, para*	479
anisole, PhOMe		activating	*ortho, para*	480
aniline, $PhNH_2$		activating	*ortho, para*	482
ArNHCOR (anilides)		activating	*ortho, para*	483
toluene and alkylbenzenes, PhR		activating	*ortho, para*	484

(*continued*) Reactions of aromatic compounds in this chapter

Starting material	Example	Activating/deactivating	Directing effect	Page
nitrobenzene, $PhNO_2$		deactivating	*meta*	488*
acylbenzenes, PhCOR (acetophenone, benzophenone)		deactivating	*meta*	489
benzonitrile, PhCN		deactivating	*meta*	488
halobenzenes, PhX		deactivating	*ortho, para*	489

*For methods of converting nitro substituents to other groups by reduction, diazotization and substitution, see pp. 520 and 567, and Chapters 22 and 24.

Further reading

Every big organic chemistry text has a chapter on this topic. One of the best is: F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry A, Structure and Mechanisms*, 5th edn, Springer, 2007, chapter 9 and B, *Reactions and Synthesis*, chapter 11. B. S. Furniss, A. J. Hannaford, P. W. G. Smith, and A. T. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Longman, 5th edn, 1989, sections 6.1–6.4 and 6.10–6.13 gives many practical examples of the reactions in this chapter.

Check your understanding

To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at http://www.oxfordtextbooks.co.uk/orc/clayden2e/