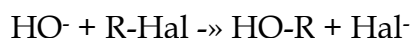


Nucleophilic substitution reactions at saturated carbon

Nucleophilic substitution reactions at a saturated carbon atom are most detailed studied reactions in organic chemistry are exemplified by the displacement reaction of an alkyl halide with an alcohol, in presence of an aqueous base



Kinetic measurements on reactions in which alkyl halides are attacked by a wide variety of different nucleophiles, Nu:, have revealed two, essentially extreme, types : one in which,

$$\text{Rate} = k_2 [\text{RHal}][\text{Nu}:] \quad [1]$$

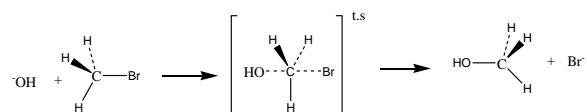
and another in which,

$$\text{Rate} = k_1 [\text{RHal}] \quad [2]$$

i.e. the rate is independent of [Nu:]. In some cases the rate equations are found to be 'mixed' or are otherwise complicated, but examples are known which exactly follow the simple relations above.

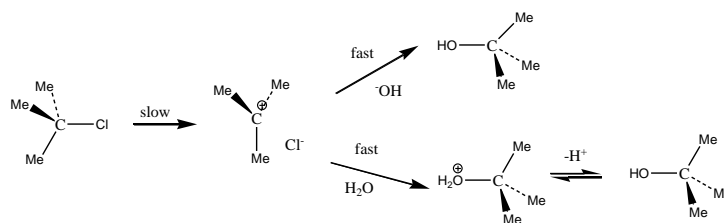
RELATION OF KINETICS TO MECHANISM

Hydrolysis of the primary halide bromomethane (methyl bromide) in aqueous base has been shown to proceed according to equation [1] which shows that both the alkyl halide and hydroxyl ion are involved in the rate-limiting (i.e. slowest) step of the reaction. Ingold has suggested a transition state in which the attacking hydroxyl ion becomes partially bonded to the reacting carbon atom before the incipient bromide ion has become wholly detached from it; thus part of the energy necessary to effect the breaking of the C–Br bond is then supplied by that produced in forming the HO–C bond. Quantum mechanical calculation shows that an approach by the hydroxyl ion along the line of centers of the carbon and bromine atoms is that of lowest energy requirement. This can be represented as below:



The negative charge is spread in the transition state and the hydrogen atoms attached to the carbon atom, all lie in one plane (at right angles to the plane of the paper as drawn above). The initially sp^3 hybridized carbon atom becomes sp^2 hybridized in the transition state, the HO and Br being associated with the two lobes of the unhybridized p orbital that is thereby made available. This type of mechanism has been designated by Ingold as SN_2 : Substitution Nucleophilic bimolecular.

Consider another example, hydrolysis of the tertiary halide 2-chloro-2-methylpropane(3-*t*-butyl chloride) in base. This reaction is found kinetically to follow equation [2], i.e. as the rate is independent of $[\text{OH}^-]$, so this can play no part in the rate-limiting step.



This has been interpreted as indicating that the halide undergoes slow ionization as the rate-limiting step to yield the ion pair R^+Cl^- ; followed by rapid, non rate-limiting attack by OH^- .

This type of mechanism has been designated $\text{S}_{\text{N}}1$: Substitution Nucleophilic unimolecular. The energy necessary to effect the initial ionization is largely recovered from the energy evolved through solvation of the resultant ion pair. The entropy of activation, ΔS^* for such a dissociative process is also advantageous; thus ΔS^* for the hydrolysis of Me_3CCl is found to be $+51 \text{ J K}^{-1} \text{ mol}^{-1}$ compared with $-17 \text{ J K}^{-1} \text{ mol}^{-1}$ for hydrolysis of CH_3Cl . The cation in the ion pair, in which the central carbon atom carries the +ve charge, is of course a carbocation intermediate, and during its formation the initially sp^3 hybridized carbon atom collapses to a more stable planar (sp^2) state, in which the three methyl groups are as far apart from each other as they can get. Attack by OH^- or solvent can then take place from either side of this planar intermediate. If attainment of this planar state is inhibited by steric or other factors, the carbocation intermediate will be formed only with difficulty then reaction by the $\text{S}_{\text{N}}1$ pathway, may not take place.

Thus the salient difference between reaction by the $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}1$ pathways is that $\text{S}_{\text{N}}2$ proceeds in one step only, via a transition state; while $\text{S}_{\text{N}}1$ proceeds in two steps, via an actual (carbocation) intermediate.

The order is an experimentally determined quantity, the overall order of a reaction being the sum of the powers of the concentration terms that appear in the rate equation.

$$\text{Rate} = k_3[\text{A}][\text{B}][\text{C}] \text{ Third order overall}$$

$$\text{Rate} = k_3[\text{A}]^2[\text{B}] \text{ Third order overall}$$

$$\text{Rate} = k_2 [\text{A}]^2 \text{ Second order overall}$$

Generally, however, it is the order with respect to a particular reactant (or reactants) that is of more interest and significance than the overall order, i.e. that the above

reactions are first order, second order, and second order, respectively, with respect to A.

The molecularity refers to the number of species (molecules, ions, etc.) that are undergoing bond-breaking and/or bond-making in one step of the reaction, usually in the rate-limiting step. It is important to realize that the molecularity is not an experimentally determined quantity, and has significance only in the light of the particular mechanism chosen for the reaction.

The molecularity of the reaction as a whole only has meaning if the reaction proceeds in a single step as is believed to be the case with the hydrolysis of bromo methane above; order and molecularity then coincide, the reaction being second order overall (first order in each reactant) and bimolecular. However, order and molecularity do not always have the same value.

Factors effecting S_N2 versus S_N1 reactions

1) Effect of solvent

Change in solvent effects the rate and even the mechanistic path way of the reaction. Thus **an increase in polarity (dielectric constant) and also in ion solvating ability cause an increase in the rate of reaction** for example the rate of solvolysis of tertiary halide Me₃C Br can be increased 3 x10⁴ times faster in 50 % aqueous ethanol than in ethanol alone. This is because in S_N1 mode, charge is developed in T.S as compared to reactants.

Such processes are more facilitated by increasing the ion salvation as well as polarity because increased polarity make this process less energy demanding.

However for S_N2 reactions, increasing polarity have very less effect and actually the rate of reaction is somewhat decreased. This is due to the reason that in transition phase, no charge is developed and existing charge is dispersed as compared with starting materials.

A very marked effect is observed by transferring the S_N2 reaction from Protic solvents e.g. methanol to non Protic solvents e.g. N,N-dimethylformamide (DMF). As the Protic solvents solvate the nucleophile and reduce its attacking power. However the non Protic solvents cannot make hydrogen bonding with nucleophile and it can be more powerful and the reaction rate increases. e.g. reaction rate of primary halide MeI with N₃ at 0 °C increase 4.5X10⁴ on transferring from MeOH to DMF.

So we can conclude that as for as the solvent is concerned, the S_N2 mode can be changed to S_N1 by increasing the ion solvating ability. Similarly changing solvent from Protic to non Protic can change the mechanism from S_N1 to S_N2.

2) Effect of structure

On going from primary alkyl halide to tertiary alkyl halide, S_N2 mechanism changes to S_N1 .



There are two important factors electronic and steric factors which decide about the mechanism of the reaction.

As we can see that primary alkyl halide gives us cation which is not stabilized by any electronic effect. However the cation formed from tertiary alkyl halide is stabilized by hyper conjugation as nine protons are present on tertiary carbocation. Similarly tertiary alkyl halide on going from halide to cation reduces the crowding a lot. In neutral alkyl halide four groups are attached in sp^3 hybridized carbon which is converted to three groups with sp^2 planar hybridization in a radical. So in tertiary alkyl halide, attack by a nucleophile via S_N2 mode, will have five groups around it in T.S which makes it more and more crowded as the size of original substituents increases (from H to Me). This more crowded state will have higher energy, and it is formed slower. As a result $sn2$ reaction rate is decreased.

3) Effect of entering and leaving group

Changing the attacking nucleophile, i.e. entering group will not have any effect on S_N1 reactions as this will not appear in the rate limiting step. However for S_N2 reactions, more strongly nucleophilic the reagent more will be the reaction promoted. A strong nucleophile will favor S_N2 while weak nucleophile will favor $sn1$ route. E.g. a reaction which is $sn1$ with H_2O , HCO_3^- , MeCO_2^- etc., may become S_N2 with $-\text{OH}$ or EtO^- .

However changing the leaving group will have effect on both S_N1 as well as S_N2 reactions as breaking the bond to the leaving group occurs in slow step. A leaving group which is a strong base is very difficult to displace, e.g. $-\text{OH}$, $-\text{OR}$, $-\text{NH}_2$ cannot normally be displaced directly by other nucleophiles.

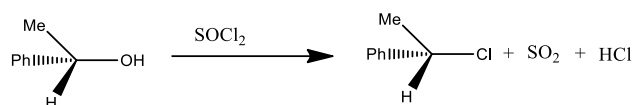
S_Ni Mode

The S_Ni Mechanism

In a few reactions, nucleophilic substitution proceeds with retention of configuration, even where there is no possibility of a neighboring-group effect. In the S_Ni mechanism (substitution nucleophilic internal), part of the leaving group must be able to attack the substrate, detaching itself from the rest of the leaving group in the process. The IUPAC designation is DN_iPANDe . The first step is the same as the very first step of the S_N1 mechanism dissociation into an intimate ion pair.²¹⁰ But in the second step part of the leaving group attacks, necessarily from the front since it is unable to get to the rear, which results in retention of configuration.

There are some reactions which nor follows S_N1 (no racemization) neither S_N2 mechanism (no inversion). It comes for the fact that a number of reactions are

reported which proceed via retention of configuration i.e. starting material and the product have the same configuration. One of the reaction is replacement of OH by Cl though the use of thionyl chloride SOCl_2 .



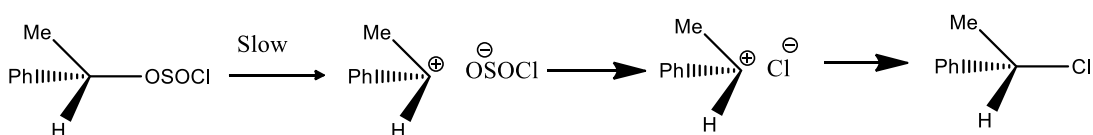
The reaction follows a second order rate equation.

$$\text{Rate} = k_2[\text{ROH}][\text{SOCl}_2]$$

Clearly it does not proceed via $\text{S}_{\text{N}}2$ mode because there is no inversion of configuration in the product.

Mechanism:

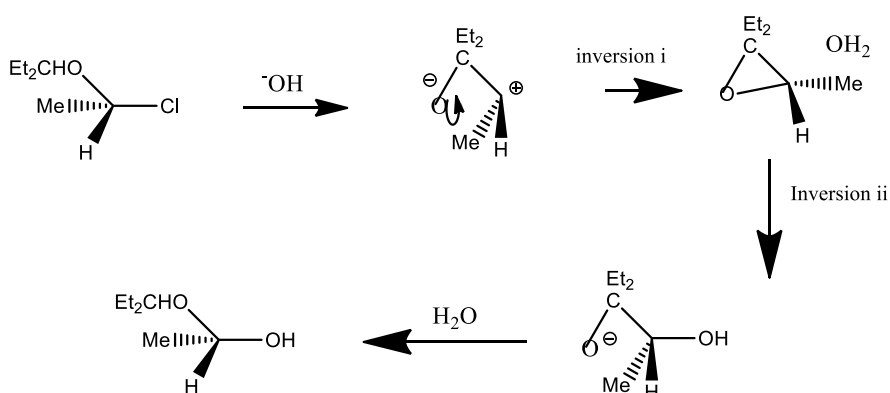
When the reaction is carried out in milder conditions, then we can isolate alkyl chlorosulphite ROSOCl and this can be true intermediate. It is formed by reaction of R-OH with SOCl_2 with the removal of HCl . The rate at which ROSOCl breaks down to product increases with an increase in polarity of the solvent and also with increasing stability of the carbocation R^+ . It means that an ion pair $\text{R}^+\text{-OSOCl}$ is certainly involved which then collapse down to products rapidly. It means that the suggested ion pair $\text{PhCMeH}^+ \text{-Cl}$ within the solvent cage is formed on which Cl^- can attack on the same side from which -OSOCl is departed, i.e. with retention of configuration.



However the question that C-O bond or S-Cl bond breaking takes place simultaneously or one before other is still answer able.

Neighbouring group participation

When an atom or group close to the carbon under attack have electron pair, then its participation will lead to the overall retention of configuration.

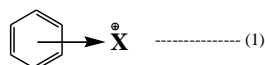


ELECTROPHILIC SUBSTITUTION REACTIONS IN BENZENE

ELECTROPHILIC ATTACK ON BENZENE

π complex

Pi (π) complex is formed by the interaction between the electrophile and the delocalized pi orbitals of benzene ring. In fact, so-called π complexes such as (1) are formed as below:



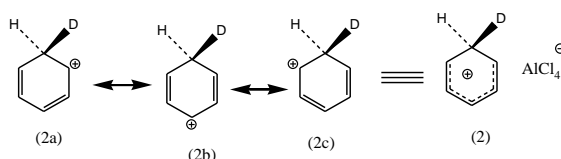
Thus methylbenzene (toluene) forms a 1:1 complex with hydrogen chloride at -78° .

- 1) The reaction being **readily reversible**. It means that no actual bond is formed between a ring-carbon atom and the proton from HCl. It is confirmed by repeating the reaction with DCl; this also yields a π complex, but its formation and decomposition do not lead to the exchange of deuterium with any of the hydrogen atoms of the nucleus, showing that no C–D bond has been formed in the complex.
- 2) Aromatic hydrocarbons have also been shown to form π complexes with species such as the **halogens, Ag^+ and, better known, with picric acid, $2,4,6\text{-(O}_2\text{N)}_3\text{C}_6\text{H}_2\text{OH}$** , to form stable colored crystalline adducts whose melting points may be used to characterize the hydrocarbons. These adducts are also known as **charge transfer complexes**.
- 3) In the complex that benzene forms with bromine, it has been shown that the halogen molecule is located centrally, and at right angles to the plane of the benzene ring.

Sigma (δ) complex

However in the presence of an electron deficient compound such as AlCl_3 , a different complex is formed.

- 1) If DCl is now employed in place of HCl, rapid exchange of deuterium with the hydrogen atoms of the nucleus takes place indicating the formation of a complex called Sigma δ complex or arenium or arenonium ions (2), or Wheland intermediate. In this sigma complex, H^+ or D^+ , as the case may be, has actually become covalently bonded to a ring-carbon atom.
- 2) The positive charge is shared over the remaining five carbon atoms of the nucleus via the π orbitals and the deuterium and hydrogen atoms are in a plane at right angles to that of the ring in the carbocation intermediate:



Difference between pi and sigma complex

Both the Π and δ complexes with, e.g. methylbenzene and HCl, really differ in behavior.

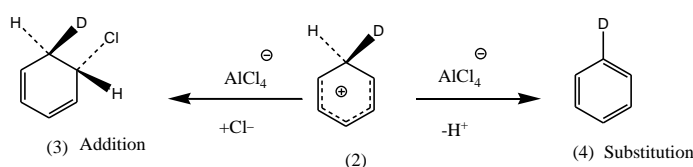
- 1 Thus the formation of Π complex leads to a solution that is a non-conductor of electricity,
- 2 to no color change,
- 3 and to little difference in U. V. spectrum,

indicating that there has been little disturbance of electron distribution in the original methylbenzene;

while if AlCl₃ is present,

- 1 the solution becomes green,
- 2 will conduct electricity
- 3 and the U. V. spectrum of the original methylbenzene is modified,

Indicating the formation of a sigma complex such as (2) as there is no evidence that aluminum chloride forms complexes of the type, H⁺AlCl₄⁻.



The reaction may be completed by AlCl₄⁻ removing a proton from the δ complex (2) to (4). This can lead only to exchange of hydrogen atoms when HCl is employed but to some substitution of hydrogen by deuterium with DCl, i.e. the overall process is electrophilic substitution.

In theory, (2) could, as an alternative, react by removing Cl⁻ from AlCl₄ resulting in an overall electrophilic addition reaction (2) to (3) as happens with a simple carbon-carbon double bond; **but this would result in permanent loss of the stabilization due to loss of aromaticity**. So we consider that by expelling H⁺ this reaction will undergo overall substitution rather than addition and completely filled, delocalized Π orbitals are re attained in the product (4) and characteristic aromatic stability recovered. The gain in stabilisation in going from (2) – (4) helps to provide the energy required to break the strong C–H bond and for expulsion of H⁻; in the reaction of, for example, HCl with alkenes there is no such factor promoting substitution and addition reactions are therefore the rule.

It might perhaps be expected that conversion of benzene into sigma complex (2), due to loss of its aromatic stabilisation, must need a considerable amount of energy, i.e. the activation energy for the process would be high and the reaction rate

correspondingly low: **in fact, many aromatic electrophilic substitutions are found to proceed quite rapidly at room temperature.**

This is because there are two factors that serve to reduce the energy barrier in formation of (2)

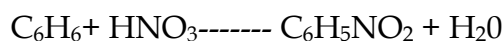
- 1 first, the energy liberated by the complete formation of the new bond to the attacking electrophile, and,
- 2 second, the fact that the positively charged δ^+ complex can stabilize itself, i.e. lower its energy level, by delocalization, as shown by its structure (2).

This type of electrophilic substitution of aromatic species commonly involves **initial addition followed by subsequent elimination.**

NITRATION

Nitration is a reaction provides the most detailed picture about its mechanism. Preparative nitration is most frequently carried out with a mixture of concentrated nitric and sulphuric acids, the so-called **nitrating mixture.**

First it was thought that the **presence of the sulphuric acid is important because it absorbs the water formed in the nitration** and so prevents the reverse reaction from proceeding.

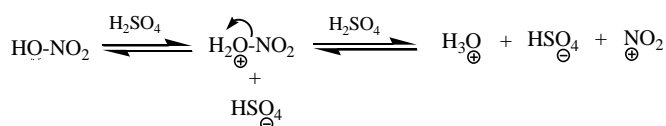


This explanation is unsatisfactory because nitro benzebe once formed appears not to be attacked by water under the conditions of the reaction.

However there are two important clues in this regard:

- i) One important clue is that the nitration is slow in the absence of sulphuric acid,
- ii) Secondly sulphuric acid by itself has virtually no effect on benzene under the conditions normally employed.

From above mentioned two facts it appears that the sulphuric acid is acting on the nitric acid rather than the benzene in the system. This is also supported by the fact that **solutions of nitric acid in pure sulphuric acid show an almost four-fold molecular freezing-point depression which has been interpreted as being due to formation of the four ions:**



There are certain evidences for the presence of nitronium ions:

i) **The presence of $^+\text{NO}_2$, the nitronium ion,** both in this solution and in a number of salts (some of which, e.g. $^+\text{NO}_2 \text{ClO}_4^-$ have actually been isolated) has been **confirmed spectroscopically** : there is a line in the Raman spectrum of each of them at 1400 cm^{-1} which can only originate from a species that is **both linear and triatomic**.

ii) It means that Nitric acid itself is converted in concentrated sulphuric acid virtually entirely into $^+\text{NO}_2$, and there can be little doubt left that this is the effective electrophile in nitration under these conditions.

iii) If the purpose of the sulphuric acid is merely to function as a highly acid medium in which $^+\text{NO}_2$ can be released from $\text{HO}-\text{NO}_2$, it would be expected that other strong acids, e.g. HClO_4 , would also promote nitration. This is indeed found to be the case, and HF plus BF_3 are also effective.

iv) The poor performance of nitric acid by itself in the nitration of benzene is thus explained for it contains but little $^+\text{NO}_2$; the small amount that is present is obtained by the two-stage process in which nitric acid is first converted rapidly into its conjugate acid, and that then more slowly into $^+\text{NO}_2$.

v) The rate of nitration of aromatic species more reactive than benzene itself is often found to be independent of $[\text{Ar}-\text{H}]$, indicating that here it is the actual formation of $^+\text{NO}_2$ that is the slow, and hence rate -limiting, step in the overall nitration reaction. That $^+\text{NO}_2$, once formed, is a highly effective nitrating agent is borne out by the rapid nitration that may be effected, of even relatively unreactive aromatic species, by the salt $^+\text{NO}_2\text{BF}_4^-$ at room temperature or below.

vi) Many nitration reactions with nitrating mixture are, however, found to follow an 'idealised' rate equation of the form,

$$\text{Rate} = k [\text{Ar}-\text{H}][^+\text{NO}_2]$$

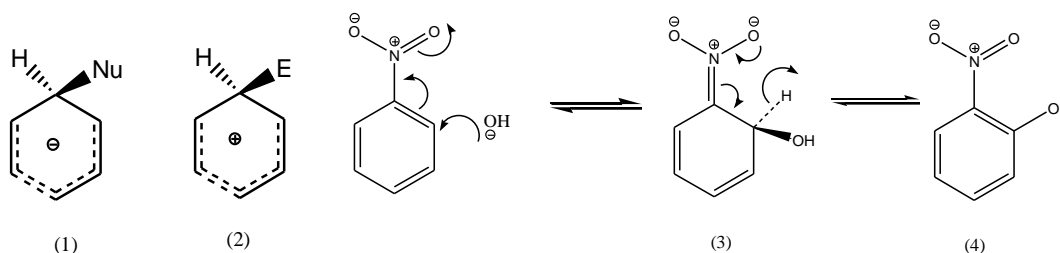
but, in practice, the actual kinetics are not always easy to follow or to interpret for a variety of reasons. Thus the solubility of, for example, benzene itself in nitrating mixture is sufficiently low for the rate of nitration to be governed by the rate at which the immiscible hydrocarbon dissolves in the acid layer. With nitrating mixture, $[^+\text{NO}_2]$ is related directly to $[\text{HNO}_3]$ added, as HNO_3 is converted rapidly and completely into $^+\text{NO}_2$, but with nitration in other solvents complex equilibria may be set up. The relation of the concentration of the effective electrophile (nearly always NO_2^+) to the concentration of HNO_3 , or other potential nitrating agent, actually added may then be far from simple.

NUCLEOPHILIC ATTACK ON AROMATIC SPECIES

Substitution of hydrogen

It is to be expected that attack by nucleophile on an unsubstituted benzene ring will be much more difficult as compared to the electrophile due to the two reasons:

- 1 First the negative charge on the ring will repel the incoming nucleophile and
- 2 secondly the pi electron system of the benzene ring will not be able to stabilize the extra two electrons of the coming nucleophile in the negatively charged complex (1) as compared to the positively charged Wheland intermediate (2).

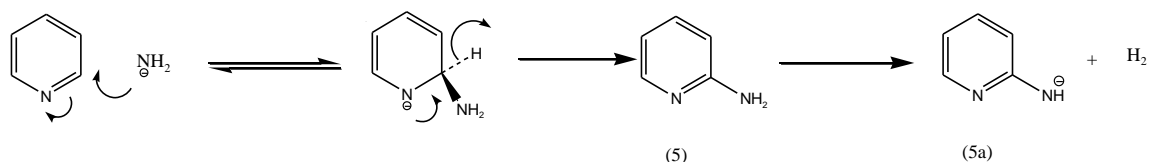


All these problems can be overcome if a strong electron withdrawing group is attached with the benzene nucleus. It is found in practice that nitrobenzene can be fused with KOH, in the presence of air, to yield o- (plus a little p-) nitrophenol (4).

Other canonical states can be written for the anionic species (3, cf. Wheland intermediates), but the most important one is that shown above in which the charge is accommodated (and stabilised) by an oxygen atom of the nitro group. This can occur only if the attacking OH^- enters the positions o- and p- to the NO_2 group. The species (3) can regain the aromatic condition by either OH^- (a) or H^- (b) acting as a leaving group: the former resulting in recovery of the starting material (nitrobenzene), the latter resulting in the formation of product (4). H^- is a poor leaving group (contrast the very much better leaving group H^+ in electrophilic attack) so the equilibrium tends to lie over to the left, OH^- , being a better leaving group, is lost a lot more often than H^- , unless an oxidizing agent, e.g. air, KNO_3 , or $\text{K}_3\text{Fe}(\text{CN})_6$, is present to encourage the elimination of hydride ion, and to destroy it as formed. Some conversion does occur in the absence of any added oxidizing agent because nitrobenzene can act as its own oxidizing agent (being reduced to azoxy benzene in the process), but the yield of nitro phenol is then very poor.

As we might have expected, the electron-withdrawing substituent, NO_2 , that we have already seen to direct electrophilic attack m- to itself (p. 151), directs nucleophilic attack into the o- and p-positions.

Pyridine (76) requires no more than its own in-built capacity for electron withdrawal and is itself attacked by powerful nucleophiles, e.g. by NH_2^- (sodamide, NaNH_2) in *N,N*-dimethylaniline as Solvent, the **Tschitschibabin reaction**:

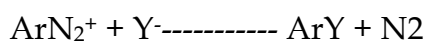


The leaving group, H^- , subsequently removes a proton from the introduced NH_2 group, thereby evolving H_2 and converting the amino group into its anion (5 a). This anion may ultimately be inverted, on treatment with H_2O , into the desired 2-aminopyridine (5), which is a useful starting material for further synthetic activity.

Substitution of atoms other than hydrogen

H^- is, in contrast to H^+ , a very poor leaving group indeed, with the result that in simple aromatic nucleophilic substitution, **ipso** attack is the rule rather than the exception. Cl^- , Br^- , N_2 , SO_3^{2-} , NR_2^- , etc., are found to be among the more effective leaving groups and, with them, certain nucleophilic substitution at a saturated carbon atom may now be observed.

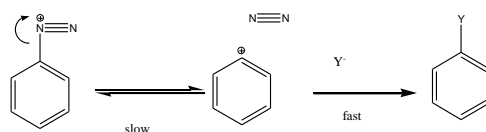
One very common example is the displacement of N_2 in the reactions of diazonium salts, ArN_2^+ , a very useful preparative series:



This is found to follow the rate law, $\text{Rate} = k[\text{ArN}_2^+]$

i.e. the rate is independent of $[\text{Y}^-]$, and analogies to $\text{S}_{\text{N}}1$ immediately spring to mind.

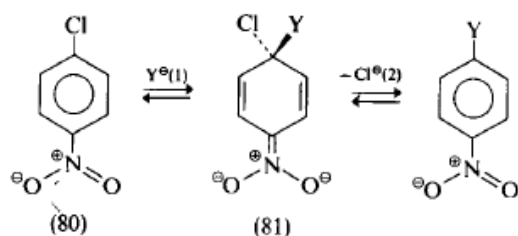
The observed rate law has been interpreted in terms of the slow, rate-limiting, formation of an aryl cation, followed by its rapid reaction with any nucleophile present. The $\text{S}_{\text{N}}1$ analogy is reinforced by the fact that added nucleophiles, Cl^- , MeOH , etc., are found to affect the product composition but not the rate of reaction – just as the above rate law would require.



The formation of the highly unstable phenyl cation (the (+) charge cannot be delocalized by the n orbital system) is at first sight somewhat surprising, but the driving force is provided by the extreme effectiveness of N_2 as a leaving group [$\text{N}=\text{N}$ bond energy = 946 kJ (226kcal) mol^{-1}]. It is significant that this appears to be the only reaction by which simple aryl cations can be generated in solution.

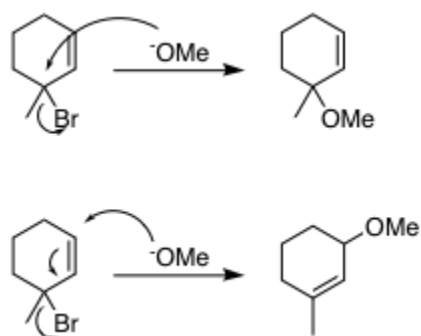
A particularly useful displacement reaction on ArN_2 is the introduction of F into the benzene nucleus (not possible by direct reaction with F_2):

The fluoroborates are unusual among diazonium salts in being relatively stable. They may be isolated, and then heated in the dry state to yield pure ArF ; the other products being lost as gases. A number of the reactions of diazonium salts, particularly in less polar solvents, may proceed via the initial generation of an aryl radical, however (cf. p. 334). Probably the most common aromatic nucleophilic displacement reactions involve the displacement of Hal from a halide activated by electron-withdrawing groups, e.g. (80)



S_{N}' ($\text{S}_{\text{N}}1'$ and $\text{S}_{\text{N}}2'$)

The primed version of $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ can only occur if there is a double bond in the vicinity of the leaving group as in your example. I have drawn both possibilities for the $\text{S}_{\text{N}}2$ case in the scheme below.



Scheme 1: Comparison of the reaction products in an $\text{S}_{\text{N}}2$ (top) and $\text{S}_{\text{N}}2'$ (bottom) pathway.

The $\text{S}_{\text{N}}2$ reaction is as you expect it to be. The $\text{S}_{\text{N}}2'$ reaction uses the double bond as an electron relay system. Instead of the nucleophile (here: OMe^-) directly interacting with the $\sigma^*(\text{C}-\text{Br})$ orbital, the π system interacts with the σ^* orbital. The nucleophile then interacts with the π system's LUMO (corresponding to the middle orbital of the allyl π system) to perform the attack. Since the nucleophilic attack and the leaving group are on different carbon atoms, relayed by the π system, this is not a direct $\text{S}_{\text{N}}2$ but a derivative of it ($\text{S}_{\text{N}}2'$).

The same logic can be applied to $\text{S}_{\text{N}}1'$: here, the intermediate carbocation is not a localised one but an allyl cation.

The primed versions here are observed because not only the bimolecular attack on the highly substituted tertiary carbon (SN2) is unlikely – this carbon is tertiary which usually already implies no SN2 – but also the capturing of the carbocation under SN1 conditions is more likely to happen at the sterically much less hindered carbon atom.

As to why methanol predominantly attacks according to an SN1-type mechanism while methanolate predominantly follows an SN2-type mechanism I will refer you back to your textbook; the reasons are stated pretty often.