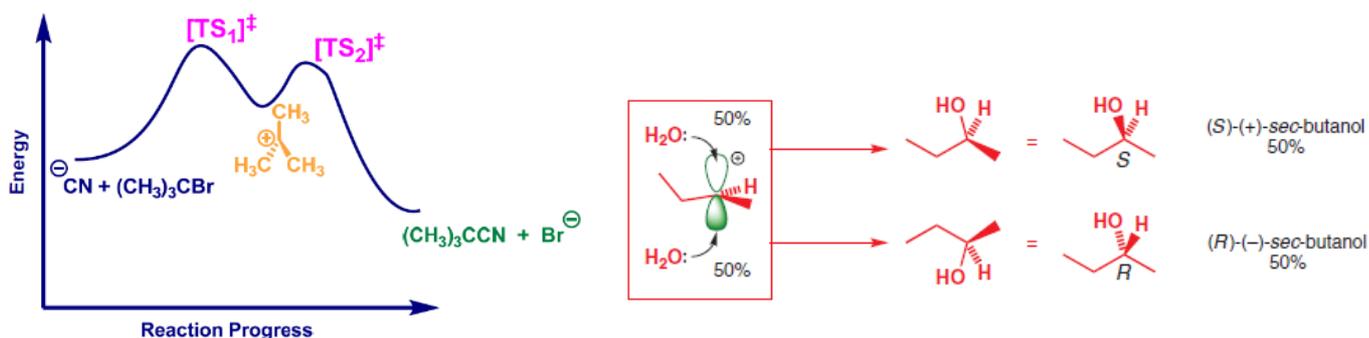


# Lecture 5: Nucleophilic Substitution Reactions

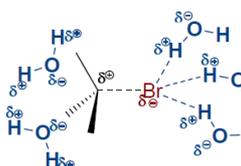
**Substitution unimolecular (S<sub>N</sub>1):** substitution nucleophilic, unimolecular. It is first order. The rate is dependent upon one molecule, that is the substrate, to form the carbonocation intermediate. The rate determining step is the formation of this carbonocation because it is an unstable species so it will form slowly from a stable neutral organic molecule. However, after it is formed, it is very reactive and the proceeding reactions will be very fast regardless of the strength of the nucleophile. The nucleophile will thus attack the carbonocation by donating electrons to the empty p-orbital and form a bond. From either side of the carbonocation empty p-orbital.



Because we know that the first step, the formation of the carbonocation is slow, that in an energy diagram, that step must be the step with the higher energy transition barrier. The energy of that transition state which determines the overall rate for the reaction, is closely linked to the stability of the carbonocation intermediate (Hammond's postulate) and it is for this reason that the most important factor in determining the efficiency of an S<sub>N</sub>1 reaction is the stability of the carbonocation intermediate. The 4 factors will affect its reactivity:

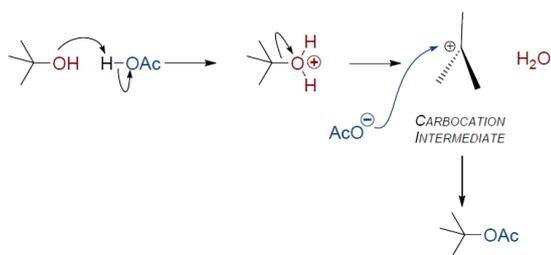
- **L.G.:** it needs to be a good leaving group. The ability for a molecule to be a leaving group increases down a group in the periodic table in case of halogens.
- **Substrate:** a secondary and tertiary carbonocation can form depending whether the leaving group is bonded to a secondary or tertiary carbon. However, if it is a secondary, then other reactions will compete and depending on the solvent it can promote carbonocation formation.
- **Nucleophile:** the strength of the nucleophile nor the concentration of it matters. However, we use poor nucleophiles for S<sub>N</sub>1. These needs to be relatively small in size so they experience low steric effects as they approach the substrate.
- **Solvent:** polar protic solvents can solvate both negatively and positively charged species, it can thus promote S<sub>N</sub>1 by stabilising the intermediate and spreading the localised positive charge around the molecule. This will also stabilize the transition state (Hammond's postulate) lowering the activation energy and increasing the rate of the reaction. However, using polar aprotic solvents, although it can solvate positively charged species, it does it poorly, and so this is not enough to promote carbonocation formation (this only applies for secondary because a tertiary carbonocation is stable enough to exist even though the solvent is not aiding in its formation) and thus cannot increase the rate of an S<sub>N</sub>1 reaction, it rather slows it down because the energy of the transition state is much greater than compared to a stabilized transition state (Hammond's postulate).

- Rate depends on stability of transition state 1 ([TS1]‡)
  - Charge separation increases in [TS1]‡.



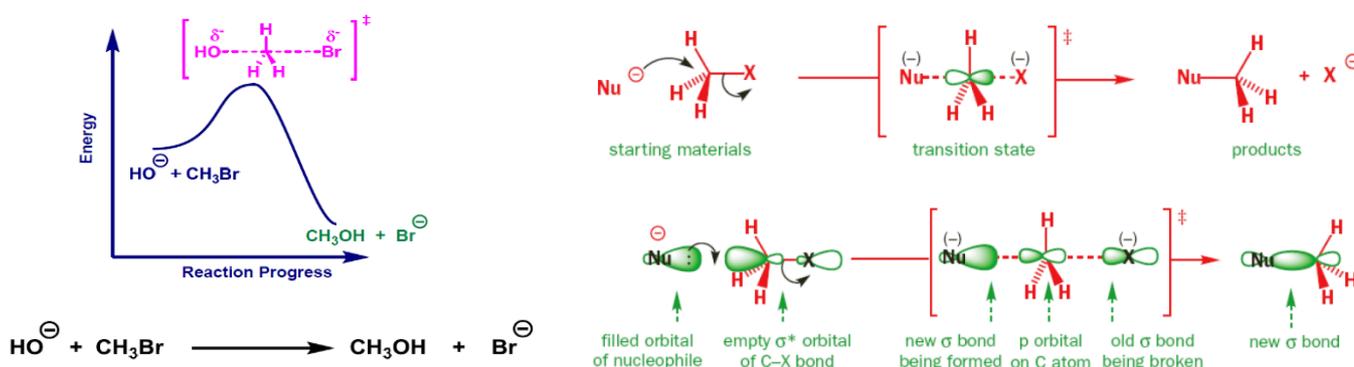
- Polar protic solvents solvate both positive and negative charge.
- Stabilises [TS1]‡ and increases reaction rate.

Note: Using acidic solvents can also promote  $S_N1$  by increasing the rate of carbocation formation.



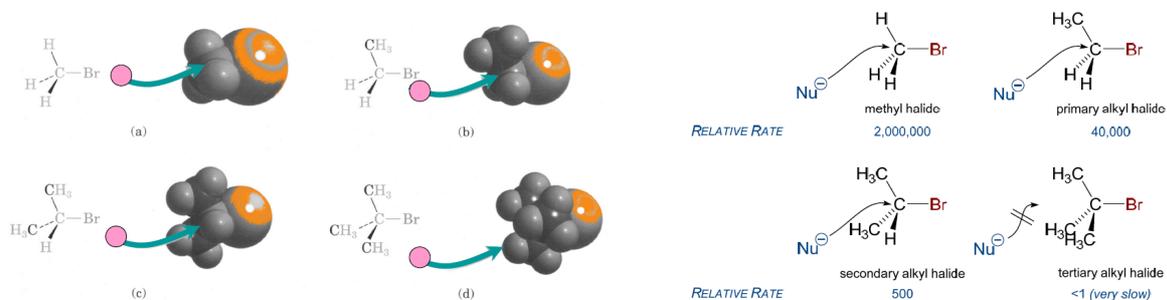
- $S_N1$  reactions can occur under acidic conditions,
  - converts a poor leaving group  $\text{OH}^-$  (conjugate acid  $\text{pK}_a$  is 14)
  - into a good one  $\text{H}_2\text{O}$  (conjugate acid  $\text{pK}_a$  is -1.7)

**Substitution bimolecular ( $S_N2$ ):** substitution nucleophilic, bimolecular and second order. The rate of the reaction is dependent upon the strength of nucleophile and the substrate. Thus it is dependent upon 2 molecules (bimolecular). There is no carbocation formation so the nucleophile will directly attack the carbon bonded to the L.G. it will donate a pair of electrons into the antibonding molecular orbital of the C-Br bond, this is at  $180^\circ$ . In the transition state, the nucleophile and the 3 hydrogens and the Br atom are all bonded. However, the bond between the nucleophile and the carbon is not fully formed, and the bond between the carbon and Br atom is not yet completely broken. These are partial bonds. The nucleophile will then completely donate the pair of electrons into the antibonding molecular orbital of the C-Br bond and the sigma bonding molecular orbital between C-Br is broken and thus the L.G. leaves.

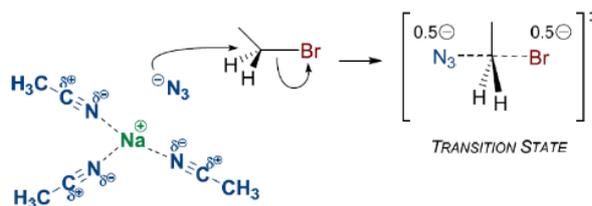


Thus the highest energy barrier that this reaction encounters in the reaction is the formation of the transition state. Thus if we can stabilise the intermediate or we can increase the nucleophilicity of the nucleophile we can increase the rate of the reaction. The 4 factors will affect its reactivity:

- **L.G.:** it needs to be a good leaving group. The ability for a molecule to be a leaving group increases down a group in the periodic table in case of halogens.
- **Nucleophile:** the strength and concentration of the nucleophile is very important. We generally use strong and good nucleophiles. They need to be small in size so that the steric effects experience when it approaches the molecule are minimized and thus it can directly attack the electrophile attached to the leaving group.
- **Substrate:** it needs to be unhindered, the leaving group can be attached to a secondary or primary carbon. However, if it is tertiary, it is too hindered  $S_N2$  will not proceed as the groups block the antibonding molecular orbital of the C-X bond and thus the nucleophile cannot donate its electrons into it.

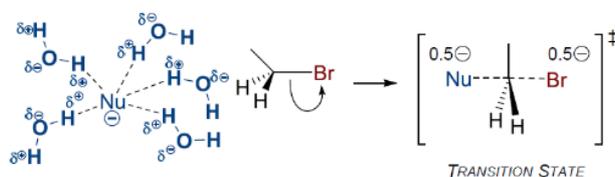


- **Solvent:** if we use polar and aprotic solvent, this will be able to solvate positive charged species, however poorly as compared to a protic solvent, but will not be able to solvate the nucleophile effectively and thus it makes it more reactive creating 'naked ions'. This increases the energy of the starting materials, decreases the activation energy and thus increases the reaction rate. The transition state is also less polar than a localised negative charge (or positive charge like in  $S_N1$ ) since the charge is spread between the nucleophile and substrate, thus the transition state is less in need for solvation as in  $S_N1$ , so the polar aprotic solvent can be used.



<b>PROTIC SOLVENT</b>	DMSO	DMF	CH <sub>3</sub> CN	CHCl <sub>3</sub>	hexane
<b>DIELECTRIC POLARISATION</b>	48	38	38	5	2

However, if we use polar and protic solvent, this can solvate both positive and negatively charged species and thus will solvate and stabilise the nucleophile via hydrogen bonding, and thus decrease its strong nucleophilicity required for an S<sub>N</sub>2 and so the reaction slows down. This will lower the energy of the reactants more than the transition state energy thus increasing the activation energy barrier.



<b>PROTIC SOLVENT</b>	H <sub>2</sub> O	CH <sub>3</sub> OH	CH <sub>3</sub> CH <sub>2</sub> OH
<b>DIELECTRIC POLARISATION</b>	80	33	24

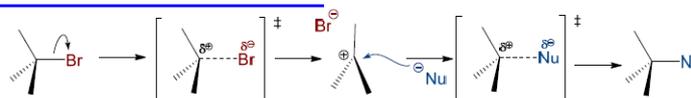
The ability of nucleophiles to participate in hydrogen bonding decreases as we go down the periodic table. Hence fluoride is the strongest hydrogen bond acceptor, and iodide is the weakest. This means that the lone pairs of iodide ion will be considerably more "free" than those of fluoride, resulting in higher rates

**The product obtained S<sub>N</sub>1 and S<sub>N</sub>2:** for S<sub>N</sub>1 it will produce a racemic mixture of products because the nucleophile can attack from above or below the molecules. the stereochemistry for S<sub>N</sub>2 of the molecule will be reversed. If it was S, now it is R, because the nucleophile needs to attack at 180 degrees to the leaving group.

## lecture 6: Hammond's Postulate

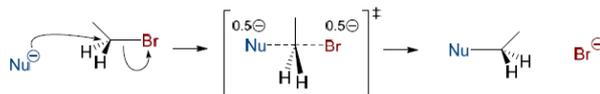
**Comparison between S<sub>N</sub>1 and S<sub>N</sub>2 mechanisms:** if conditions will favour one particular type of reactions then the product formation will be dependent upon the mechanism favoured. However, there are instances where both reactions will compete

### S<sub>N</sub>1: Summary Overview



- **Mechanism** (how):
  - LG departs to give a *carbocation intermediate* (RDS)
  - Nu approaches planar carbocation from either face
    - So proceeds with *racemisation* of stereochemistry
- **Rate** (how fast) is effected by three factors -
  1. **Leaving group:** more stable anions are better leaving groups
    - More stable leaving group means lower activation energy to form intermediate, which increases reaction rate.
  2. **Substrate:** stable carbocation intermediates are favoured.
    - i.e. tertiary, allylic and benzylic halides.
  3. **Solvent:** polar solvents stabilise the intermediate, increasing rate
    - Protic or aprotic okay, so long as solvent is polar
- **Nucleophile:** does not feature in the rate equation

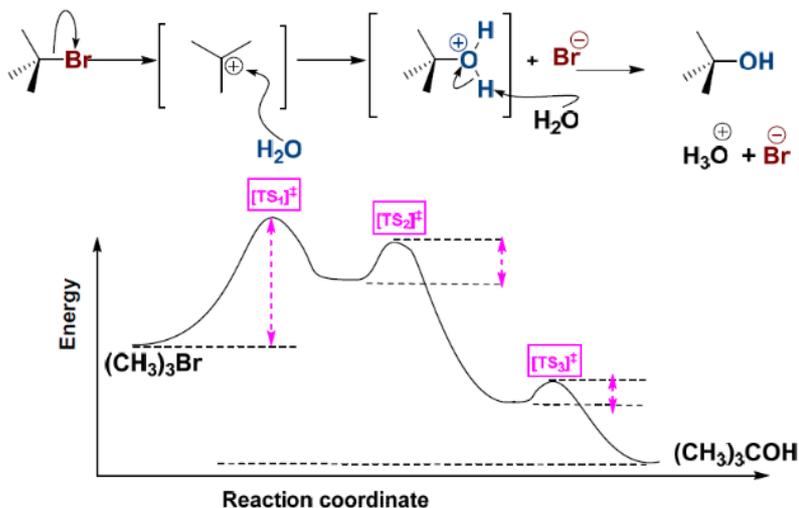
## S<sub>N</sub>2: Summary Overview



- **Mechanism** (how):
  - Nu<sup>⊖</sup> attacks from backside (180° to LG) interacting with σ\*
  - Single *transition state* (highest energy point of reaction profile)
  - Proceeds with *inversion of stereochemistry*
- **Rate** (how fast) is effected by four factors -
  1. **Nucleophile**: follows basicity (for same attacking atom); anions better nucleophiles; increases going down group Periodic Table.
  2. **Leaving group**: more stable anions are better LGs (as for S<sub>N</sub>1)
  3. **Substrate**: steric hindrance can slow Nu approach.
    - bulky substrates increase activation energy and slow the rate
  4. **Solvent**: polar aprotic are go
    - polar aprotic solvents stabilise cations (i.e. counterions to Nu) which destabilises Nu and increases the rate.
    - polar protic solvents stabilise Nu (therefore increase the rate)

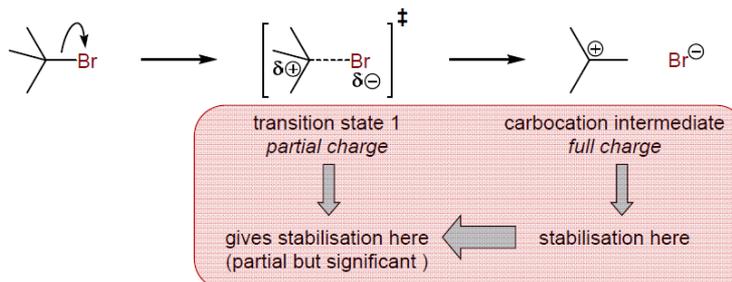
**Hammond's postulate:** if 2 states are directly linked on an energy profile and are close to each other in energy, then they are also close to each other in structure. That is the structure of the transition state resembles the structure of the nearest stable species in energy. For example:

- The first transition state is more similar to the first intermediate
- The second transition state is more similar to the first intermediate.
- The third transition state is more similar to the second intermediate



As already discussed, for S<sub>N</sub>1 reaction, the rate determining step is the formation of the carbocation and thus it is strongly endothermic reaction. Since the first T.S. resembles the first intermediate in energy, stabilizing the first intermediate will also stabilize the first T.S.

- So [TS1]<sup>‡</sup> is a *late TS* and resembles the carbocation intermediate

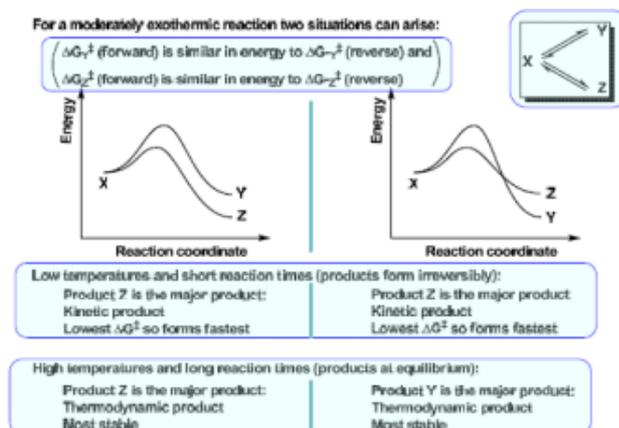


- So a more stable carbocation intermediate ...
  - ⇒ lower energy TS<sup>‡</sup> 1 ⇒ lower ΔG<sup>‡</sup> ⇒ faster reaction

**Kinetic vs Thermodynamic product:** reactions under thermodynamic control have outcomes that depend on the position of the equilibrium and therefore it will produce the lowest energy products. Reactions under kinetic control have outcomes that depend on the rate at which the reaction proceeds, and therefore the relative energies of the transition states. This leads to the production of products with the lowest energy pathway.

- **Kinetic product:** if the system is not allowed to reach equilibrium, the product with the lowest energy pathway will be the major product.
- **Thermodynamic product:** if the system reaches equilibrium, the lowest energy product will be the major product.

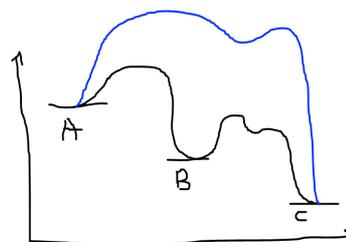
**Case 1:** consider the following reaction:



- At low temperatures, product Z for both cases is preferred because the reverse reaction is too slow (there is not enough energy and time for the reaction to reach equilibrium, the products do not have time to reverse and overcome the bigger energy barrier to form the other product). However, if we had a longer reaction time, the molecules can reverse and rather form the most stable product even though it is under low temperature conditions
- At high temperatures and long reaction time, product Z and Y (thermodynamic products) are preferred because the reverse reaction also proceeds (in this condition, all these reactions will occur until equilibrium is achieved where the most thermodynamically stable product will form). The molecules have enough energy to reverse and overcome the bigger energy barrier.

**Case 2:** consider the following reaction:

- Heat + long reaction time = C
- Heat + short reaction time = C
- Cold + long reaction time = C
- Cold + short reaction time = B



Although the conditions are cold, and left for a long reaction time, we would obtain product C because it is the most stable. The molecules although they are in low temperatures, will reverse back and form the most stable product or like in this case, the molecules B can either reverse back or proceed through a different pathway to form product C. Once molecules of A turn to B, and if given enough time, molecules B will turn to C.

**Case 3:** When the reaction is highly exothermic and is irreversible since the reverse reaction requires massive amounts of energy, the reaction that forms the fastest, whether it is the thermodynamic or kinetic product, will be the major product.

