

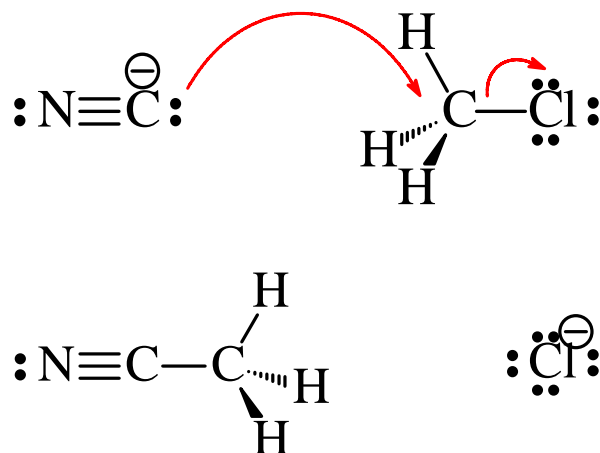
## We can use bonding theories to explain reactions and reactivity

- **Lewis structures** allow us to “push electrons” but explain little
- **Valence bond theory** allows us to use Lewis structures in a natural way, bringing in “resonance,” “hybridization” and “orbital overlap.”
- **Molecular orbital theory** allows us to explain how bonds are formed and broken by donation of electrons from a HOMO to a LUMO

## How do we explain this?

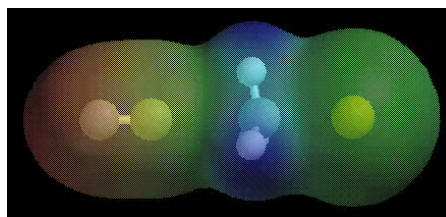
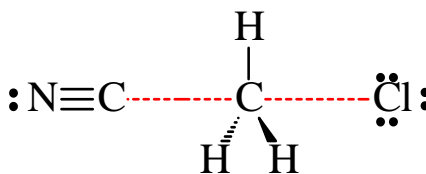
- Lewis/Valence-bond theory does not allow an explanation but does allow us to “push the electrons” to provide a convenient picture.
- “Frontier MO theory” allows us to explain this in terms of the donation of electrons from the HOMO of the nucleophile to the LUMO of the alkyl halide electrophile.

## Molecular orbitals: Lewis picture of the $S_N2$ reaction



Transition state for the  $S_N2$  reaction can be explained with valence-bond theory

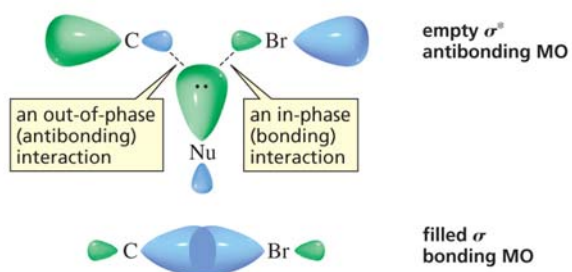
- Bond to chlorine breaks as the bond to cyanide forms.
- Notice that **negative charge** is spread “evenly” between the nucleophile and the leaving group.
- But why must attack be from the backside?



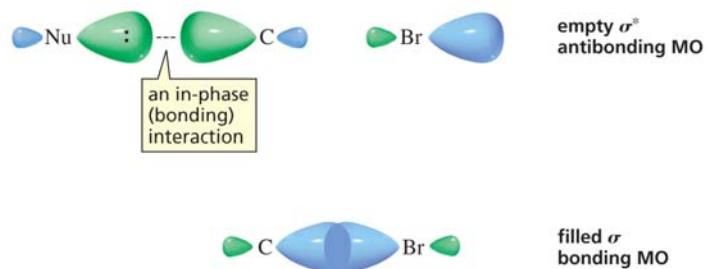
[animation](#)

MO explanation: the nucleophile fills the unoccupied, antibonding orbital

b. Front-side attack

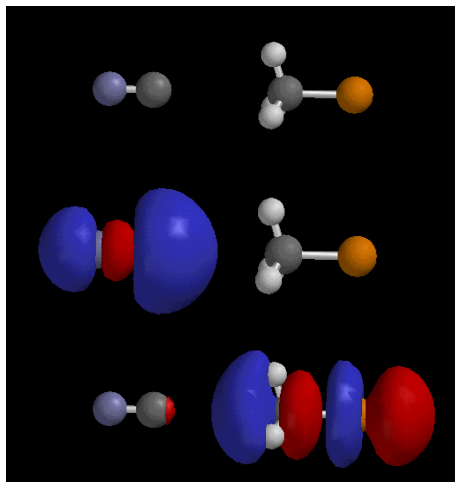
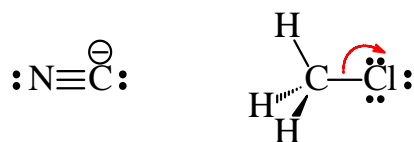
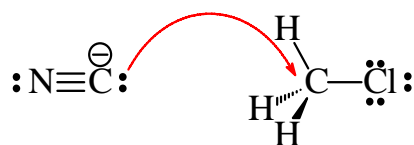


a. Back-side attack



MO explanation: the nucleophile fills the unoccupied, antibonding orbital

## Molecular orbitals are required to explain backside attack!

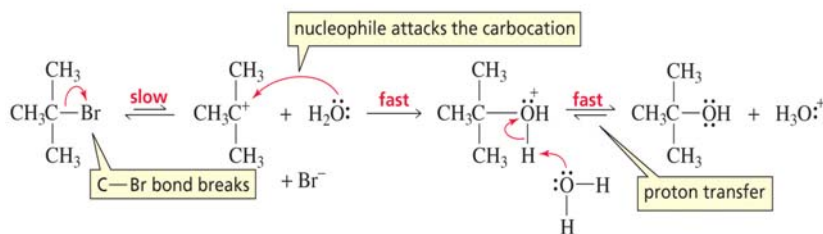


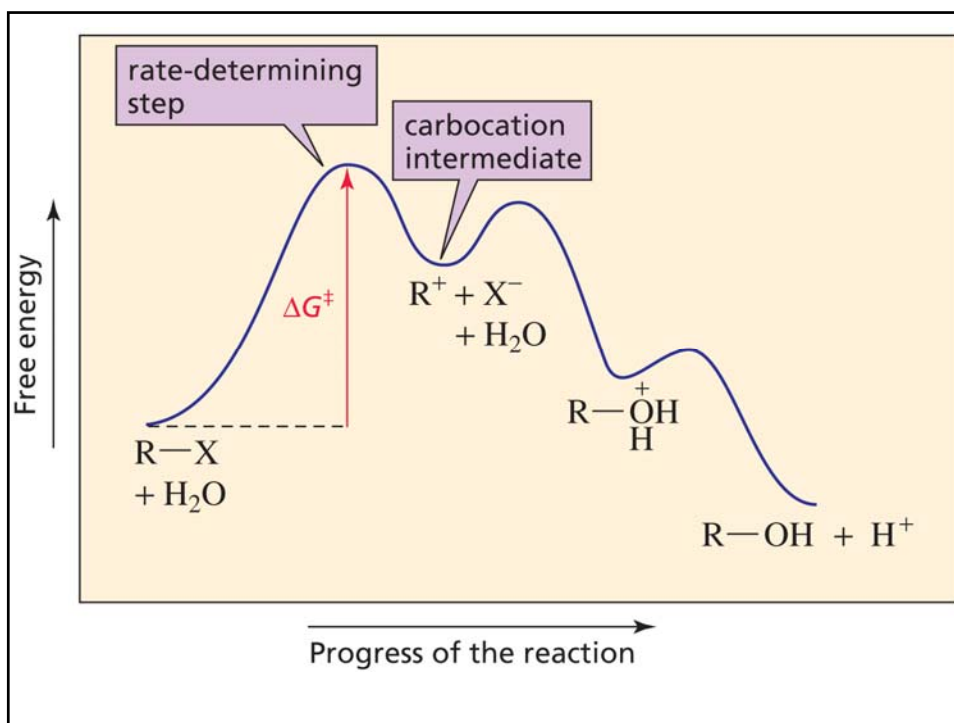
## Mechanism of the $\text{S}_{\text{N}}1$ reaction

- Two-step reaction
- Requires good leaving group
- Requires nucleophile that is a poor base

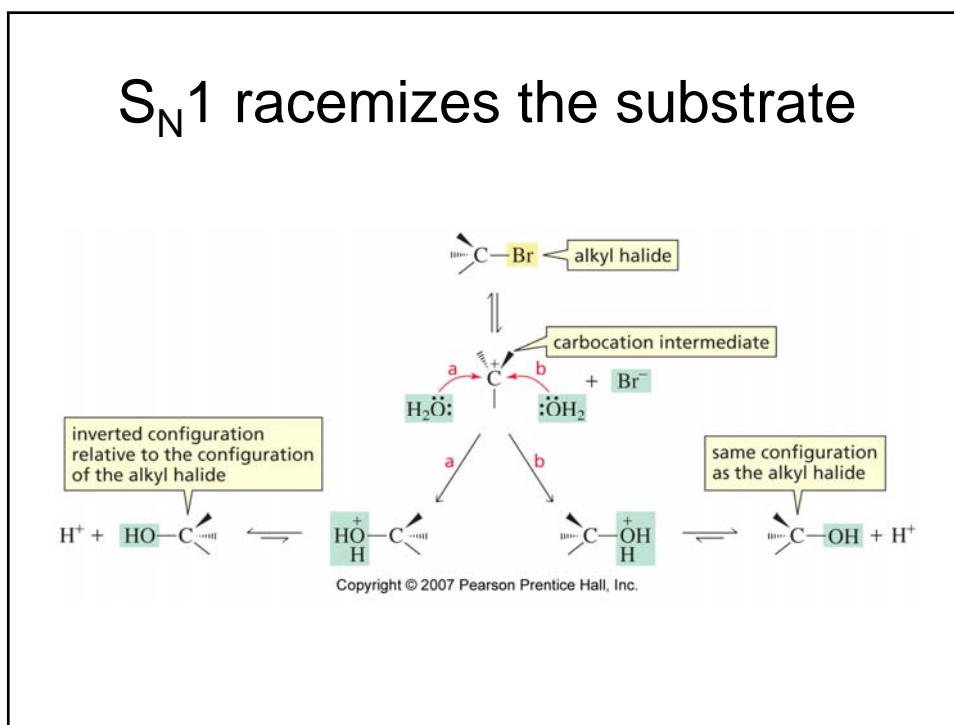
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mechanism for the  $\text{S}_{\text{N}}1$  reaction of an alkyl halide

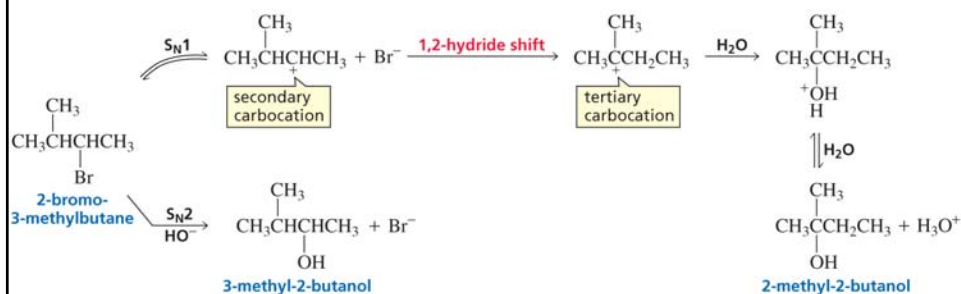




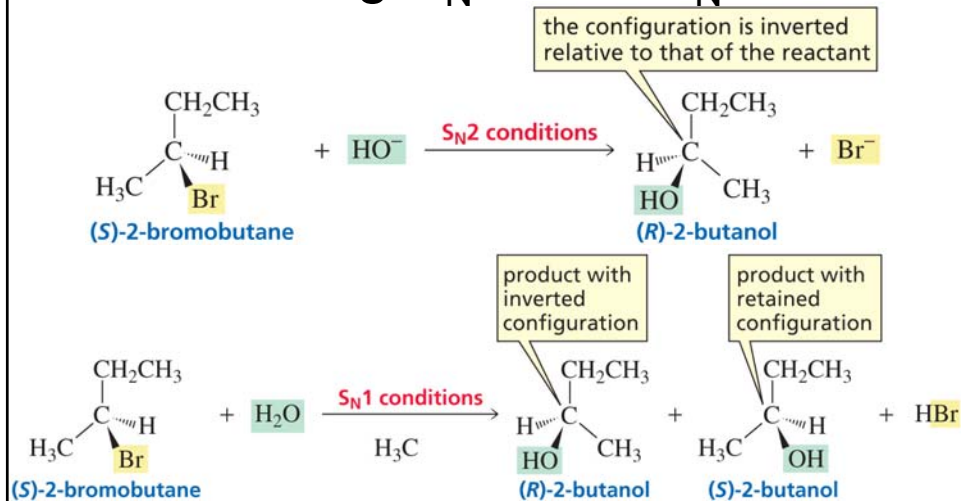
## $S_N1$ racemizes the substrate



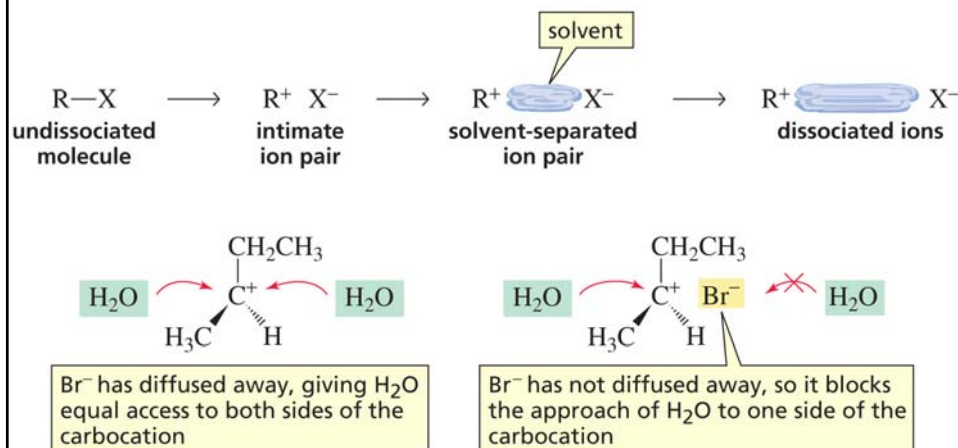
## S<sub>N</sub>1 can lead to rearranged product



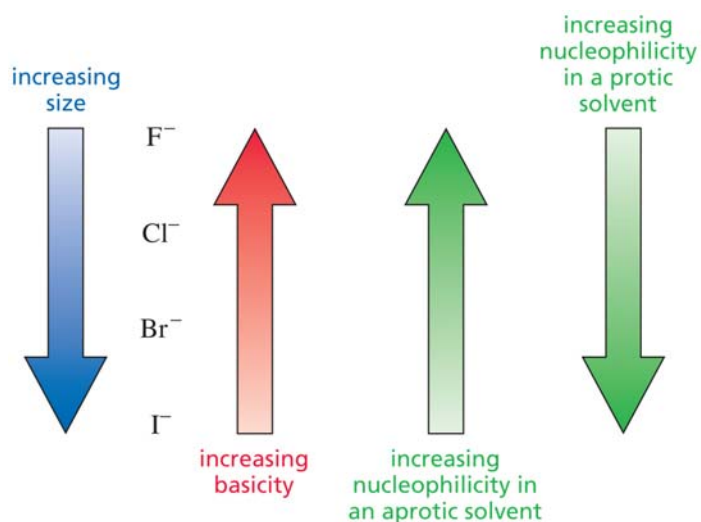
## Telling S<sub>N</sub>1 from S<sub>N</sub>2



## The FULL S<sub>N</sub>1 mechanism, or, why the isomer distribution isn't always 50:50

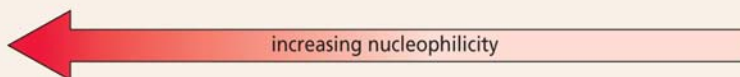


## Effect of size and solvent on nucleophile strength



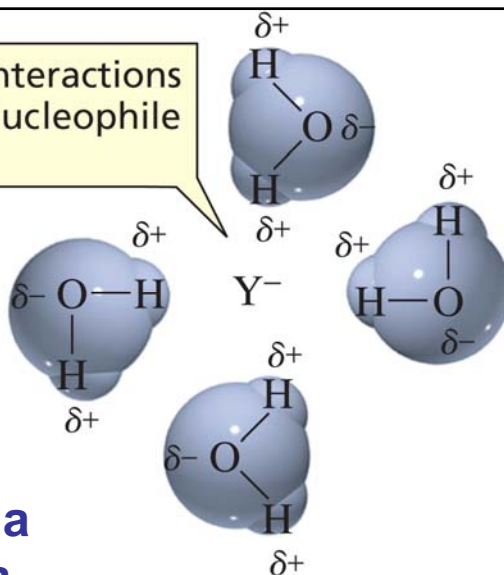
## Nucleophilicity as function of solvation

Table 8.2 Relative Nucleophilicity Toward  $\text{CH}_3\text{I}$  in Methanol



- Larger nucleophiles are more poorly solvated in protic solvents
- Better solvation makes a poorer nucleophile
  - Stabilizing the reactants makes the activation energy larger

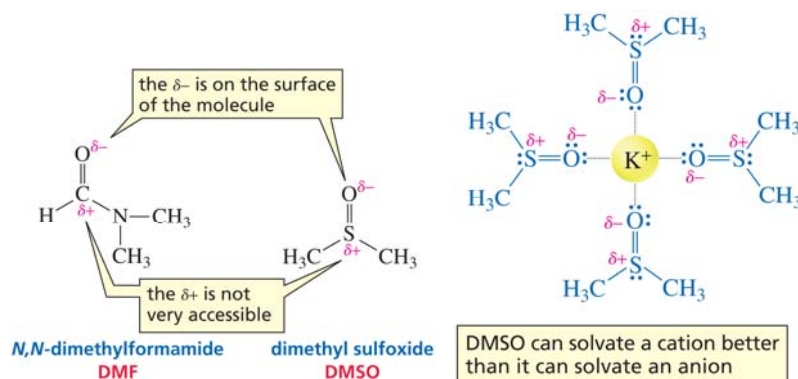
ion-dipole interactions between a nucleophile and water



**Stabilization of a nucleophile in a protic solvent**



## DMSO and DMF are polar aprotic solvents that don't solvate anions well

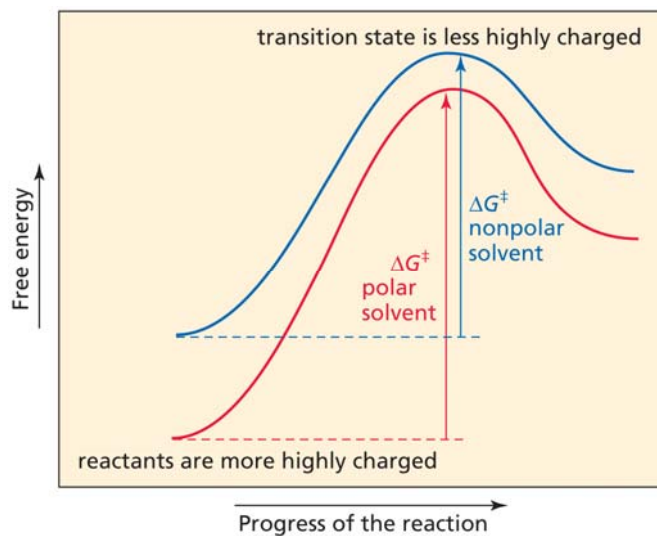


- Poorer solvation makes a better nucleophile
  - Destabilizing the reactants makes the activation energy smaller

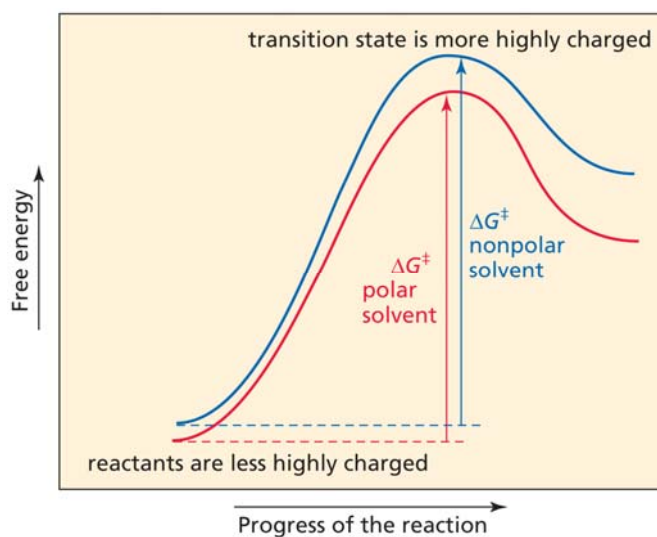
Table 8.7 The Dielectric Constants of Some Common Solvents				
Solvent	Structure	Abbreviation	Dielectric constant ( $\epsilon$ , at 25 °C)	Boiling point (°C)
<i>Protic solvents</i>				
Water	H <sub>2</sub> O	—	79	100
Formic acid	HCOOH	—	59	100.6
Methanol	CH <sub>3</sub> OH	MeOH	33	64.7
Ethanol	CH <sub>3</sub> CH <sub>2</sub> OH	EtOH	25	78.3
<i>tert</i> -Butyl alcohol	(CH <sub>3</sub> ) <sub>3</sub> COH	<i>tert</i> -BuOH	11	82.3
Acetic acid	CH <sub>3</sub> COOH	HOAc	6	117.9
<i>Aprotic solvents</i>				
Dimethyl sulfoxide	(CH <sub>3</sub> ) <sub>2</sub> SO	DMSO	47	189
Acetonitrile	CH <sub>3</sub> CN	MeCN	38	81.6
Dimethylformamide	(CH <sub>3</sub> ) <sub>2</sub> NCHO	DMF	37	153
Hexamethylphosphoric acid triamide	[(CH <sub>3</sub> ) <sub>2</sub> N] <sub>3</sub> PO	HMPA	30	233
Acetone	(CH <sub>3</sub> ) <sub>2</sub> CO	Me <sub>2</sub> CO	21	56.3
Dichloromethane	CH <sub>2</sub> Cl <sub>2</sub>	—	9.1	40
Tetrahydrofuran		THF	7.6	66
Ethyl acetate	CH <sub>3</sub> COOCH <sub>2</sub> CH <sub>3</sub>	EtOAc	6	77.1
Diethyl ether	CH <sub>3</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub>	Et <sub>2</sub> O	4.3	34.6
Benzene		—	2.3	80.1
Hexane	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	—	1.9	68.7

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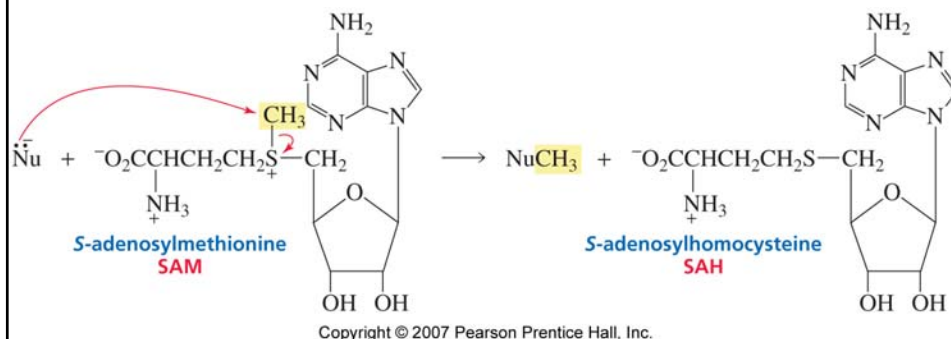
## Effect of solvent polarity on reaction rate for ionic nucleophiles



## Effect of solvent polarity on reaction rate for neutral nucleophiles



## Why is SAM such a good methylating agent?



## Why is N<sup>5</sup>-methyltetrahydrofolate such a good methylating agent?

